CHEMISTRY OF 1,2,3-TRIAZINES AND 1,2,4-TRIAZINES, TETRAZINES, AND PENTAZINES

This is the Thirty-Third Volume in the Series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER and EDWARD C. TAYLOR

Editors

CHEMISTRY OF 1,2,3-TRIAZINES AND 1,2,4-TRIAZINES, TETRAZINES, AND PENTAZINES

Hans Neunhoeffer
TECHNISCHE HOCHSCHULE DARMSTADT

Paul F. Wiley
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To MARGARET
ELLEN and HENRIK

The Chemistry of Heterocyclic Compounds

The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocyclic compounds.

A field of such importance and intrinsic difficulty should be made as readily accessible as possible, and the lack of a modern detailed and comprehensive presentation of heterocyclic chemistry is therefore keenly felt. It is the intention of the present series to fill this gap by expert presentations of the various branches of heterocyclic chemistry. The subdivisions have been designed to cover the field in its entirety by monographs which reflect the importance and the interrelations of the various compounds, and accommodate the specific interests of the authors.

In order to continue to make heterocyclic chemistry as readily accessible as possible new editions are planned for those areas where the respective volumes in the first edition have become obsolete by overwhelming progress. If, however, the changes are not too great so that the first editions can be brought up-to-date by supplementary volumes, supplements to the respective volumes will be published in the first edition.

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Preface

This volume presents, with the exception of the 1,3,5-triazines, the chemistry of all six-membered nitrogen heterocycles containing more than two nitrogen atoms in the ring. It also covers all condensed systems containing these rings.

The first volume discussing the chemistry of these ring systems was originally published in 1956, covering the whole literature through *Chemical Abstracts*, 1950. The large growth of research in these different areas has led to many new reactions and the synthesis of formerly unknown systems. Many new and important pharmaceutical and agricultural chemicals are heterocycles with more than two nitrogen atoms in a six-membered ring. Therefore it is felt that a new review of the chemistry of 1,2,3-triazines, 1,2,4-triazines, 1,2,4,5-tetrazines, 1,2,3,4-tetrazines, 1,2,3,5-tetrazines, and pentazines is justified.

This volume attempts to cover all the literature on these heterocyclic systems from the earliest references through those appearing in *Chemical Abstracts* in 1974, we have tried to list in the tables all compounds known during this period. As far as possible every article was consulted in the original, and we are grateful to all those colleagues who sent us reprints or copies of articles published in journals not available in our libraries.

For the convenience of practitioners in this area of chemistry and other users of this volume, the order is maintained as far as possible as in the original. For each heterocyclic system the aromatic compounds are considered first, followed by progressive degrees of hydrogenation. After the condensed systems a chapter discussing the uses and biochemical aspects of the mentioned class was added. For every group of compounds methods of preparation are described first, followed by tables containing all known compounds, a discussion of the physical properties, and finally the chemical properties.

We trust that this volume will prove readable and useful to those engaged in research or development on the different heterocyclic systems discussed. We also hope that it will stimulate additional research in the chemistry of triazines, tetrazines, and pentazines.

We want to thank Mrs. Gilian Peters for her kindness in reading portions of the manuscript and offering valuable criticisms and suggestions and Mrs. Susan

Bliss for secretarial assistance. We want especially to thank our wives, Margaret Neunhoeffer and Veronica Wiley, for their assistance in the preparation of the manuscript.

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August 1977

Contents

CHEMISTRY OF 1,2,3-TRIAZINES AND 1,2,4-TRIAZINES, TETRAZINES, AND PENTAZINES

This is the Thirty-Third Volume in the Series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

1,2,3-Triazines

HANS NEUNHOEFFER

Chemistry of Heterocyclic Compounds, Volume 33
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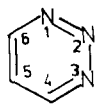
I

Introduction

Of the three possible systems of triazine compounds the 1,2,3-triazines, also called *v*-triazines, are by far the least-studied class. A comprehensive review on the 1,2,3-triazines was given in 1956 (1) covering the whole literature through *Chemical Abstracts* 1950. Five years later a second review was published by J. P. Horwitz (2).

The number of publications on the chemistry of 1,2,3-triazines has increased during the last 20 years, especially during the last 5 years, and it is felt that a review covering the whole literature on 1,2,3-triazines through 1974 (*Chemical Abstracts*, Volume 81) should be given together with the review of the chemistry of 1,2,4-triazines that follows. The chemistry of 1,2,3-triazines and condensed 1,2,3-triazines is reviewed completely, but those publications dealing with the biochemical properties or the uses of 1,2,3-triazines are listed in a separate chapter without a detailed discussion.

The parent compound of the 1,2,3-triazine series has structure **1a** and is numbered as indicated. In *Chemical Abstracts* it is called 1,2,3-triazine or *v*-triazine. In *The Ring Index* it is number RRI 210 and is called *v*-triazine or 1,2,3-triazine. In the older literature the name *β*-triazine (205) can also be found. Throughout this discussion the term 1,2,3-triazine is used.



1a

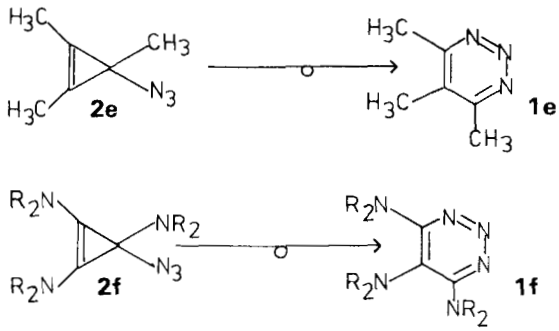
Only a few papers dealing with uncondensed, aromatic or hydrogenated 1,2,3-triazines have been published and most of them present physical considerations on this system; only a small number report the synthesis or reactions of the uncondensed 1,2,3-triazine system. No attempts to prepare the unsubstituted 1,2,3-triazine (**1a**) have been reported, but from theoretical calculations some degree of electron delocalization should be expected and it may be assumed from the stability of the 4,5,6-trimethyl-1,2,3-triazine that **1a** will be a relatively stable compound.

Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

1,2,3-Triazines

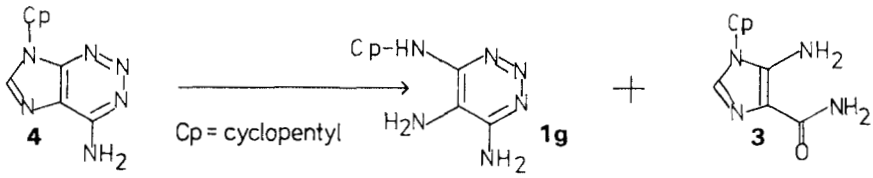
HANS NEUNHOEFFER

4,5,6-tris(*tert*-butyl)-1,2,3-triazine through rearrangement of 1,2,3- tris(*tert*-butyl)cyclopropenyl azide failed (9, 10).

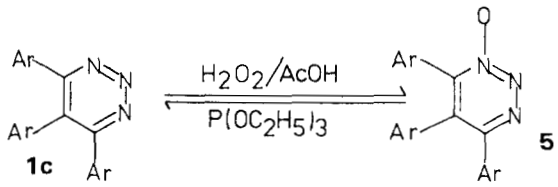


As was shown by PMR spectroscopy cyclopropenyl azides with two different substituents form a mixture of the possible isomers. Rearrangement of this mixture yields a single 1,2,3-triazine, the structure of which was determined by mass spectrometry (4). By these studies it was found that the substituent with the highest electron-donating power is located in position 5 of the 1,2,3-triazine system.

Montgomery and Thomas (303) isolated 4,5-diamino-6-(cyclopentylamino)-1,2,3-triazine (**1g**) as well as 4-amino-3-cyclopentylimidazole-5-carboxamide (**3**) when they hydrolyzed 4-amino-1-cyclopentylimidazo[4,5-*d*] 1,2,3-triazine (**4**).



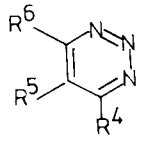
Oxidation of 4,5,6-triaryl-1,2,3-triazines (**1c**) with hydrogen peroxide in acetic acid affords 1,2,3-triazine *N*-oxides, the structure of which was established as the 1,2,3-triazine 1-oxides (**5**), due to a M^+-28 fragment in the mass spectra of these *N*-oxides (8). Reduction of **5** with triethyl phosphite yields **1c**.

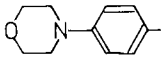
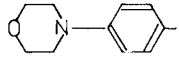
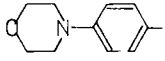
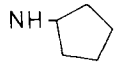


II. COMPOUND SURVEY

The uncondensed aromatic 1,2,3-triazines reported in the literature are listed in Tables II-1 and II-2.

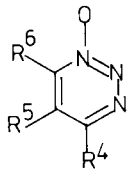
TABLE II-1. 1,2,3-TRIAZINES



R^4	R^5	R^6	m.p. (°C)	Refs.[a]
CH_3	CH_3	CH_3	146–147	5
C_6H_5	C_6H_5	H	176–177	4
C_6H_5	C_6H_5	C_6H_5	276 (dec.)	3
			280	4
C_6H_5	C_6H_5	4-Cl–C_6H_4	206	4
C_6H_5	4-CH_3–C_6H_4	C_6H_5	222	4
C_6H_5	4-CH_3O–C_6H_4	C_6H_5	227	4
C_6H_5	4-CH_3–C_6H_4	4-CH_3–C_6H_4	188	4
C_6H_5	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	177–178	4
4-CH_3–C_6H_4	4-CH_3–C_6H_4	4-CH_3–C_6H_4	216	4
4-CH_3–C_6H_4	4-CH_3O–C_6H_4	4-CH_3–C_6H_4	180	4
4-CH_3–C_6H_4	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	193	4
4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	192–193	4
4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	4-Cl–C_6H_4	197–198	4
			110–112	7
$(CH_3)_2N$	$(CH_3)_2N$	$(CH_3)_2N$	93	8/6
CH_3–N–C_6H_5	CH_3–N–C_6H_5	CH_3–N–C_6H_4	170–171	8
			138	8
			275 (dec.)	303

[a]No melting points were published in references separated by a line, but a method for preparation is reported.

TABLE II-2. UNCONDENSED AROMATIC 1,2,3-TRIAZINE 1-OXIDES (8)



R^4	R^5	R^6	m.p. (°C)
C_6H_5	C_6H_5	C_6H_5	213
C_6H_5	4-CH_3–C_6H_4	C_6H_5	198
4-CH_3–C_6H_4	4-CH_3–C_6H_4	4-CH_3–C_6H_4	223
4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	219
C_6H_5	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	163
or			
4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	C_6H_5	
4-CH_3–C_6H_4 *or*	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	223
4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	4-CH_3–C_6H_4	

III. PHYSICAL PROPERTIES AND THEORETICAL CONSIDERATIONS

The known alkyl and aryl-1,2,3-triazines are white, stable, crystalline compounds with melting points greater than 145°C. The triamino-1,2,3-triazines show a yellow color.

The structure of 4,5,6-tris(4-methoxyphenyl)-1,2,3-triazine (**1h**) was determined by X-ray crystallographic analysis (11). By this method it was shown that the 1,2,3-triazine ring is planar, as one expects for a molecule with some degree of electron delocalization. The experimental bond distances and angles are given in Table II-3; the experimental bond distances are in reasonable agreement with calculated values (12).

The electronic spectra of most known 1,2,3-triazines have been published. Chandross and Smolinsky report the following ultraviolet spectrum for the 4,5,6-triphenyl-1,2,3-triazine (**1b**): $\lambda_{max}(\epsilon) = 262$ (21.400), 278 sh (15.500), and 297 nm sh (8.100) (3), whereas Neunhoeffer and his group (4) observed only two absorption maxima for triaryl-1,2,3-triazines (**1c**) between 260 to 286 nm and 301 to 325 nm sh with an absorptivity (log ϵ) between 4.1 and 4.4 for the first maximum. The 4,5-diphenyl-1,2,3-triazine (**1d**) has a maximum at 251 nm and a shoulder at 270 nm, whereas for the 4,5,6-trimethyl-1,2,3-triazine (**1e**) two absorption maxima were reported at 278 (610) and 217 nm (4.300) with the given absorptivities (5). For 4,5-diamino-6-cyclopentylamino-

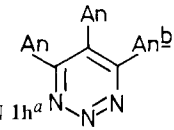


TABLE II-3. EXPERIMENTAL BOND DISTANCES AND ANGLES IN 1h[a]

Bond	Experimental bond distances (Å)	Calculated bond distances PPP	Calculated bond distances SPO	Experimental bond angle	(°)
N_1-N_2	1.319(7)	1.302	1.302	$C_6-N_1-N_2$	120.2(4)
N_2-N_3	1.314(6)			$N_1-N_2-N_3$	122.8(4)
N_3-C_4	1.368(6)	1.328	1.331	$N_2-N_3-C_4$	119.3(4)
C_4-C_5	1.406(6)	1.399	1.399	$N_3-C_4-C_5$	120.6(4)
C_5-C_6	1.388(6)			$C_4-C_5-C_6$	116.2(4)
C_6-N_1	1.363(7)	1.328	1.331	$C_5-C_6-N_1$	120.4(4)

[a]The standard deviations are given in parentheses.

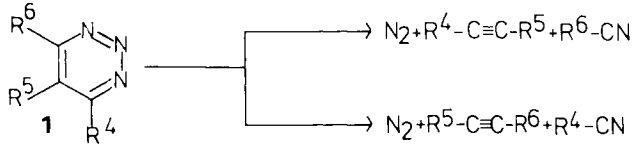
[b]An = 4-$CH_3O-C_6H_4$.

1,2,3-triazine (**1g**) the following ultraviolet spectra were recorded (303). At pH 2: $\lambda_{max}(\epsilon)$ = 374 (5.720), 289 (9.300), 252 (18.800), and 204 nm (13.800). At pH 7: 318 (4.850), 286 (7.060), and 235 nm (25.400). At pH 13: 318 (4.900), 286 (7.120), and 236 nm (25.700).

At present the only infrared spectrum published is for the 4,5,6-trimethyl-1,2,3-triazine (**1e**) (5), and the following absorption bands are reported: 3000, 1548, 1433, 1399, 1386, 1366, 1241, 1137, 1102, 1033, 991, 898, 769, and 668 cm^{-1}.

NMR spectra have been published for only a few 1,2,3-triazines. The heteroaromatic proton in the 4,5-diphenyl-1,2,3-triazine (**1d**) gives a signal at 0.92τ (4). The PMR spectrum of the 4,5,6-trimethyl-1,2,3-triazine (**1e**) has two signals at 7.34 and 7.68τ and the relative intensities are 2 and 1 (5); in the PMR spectrum of the 4,5,6-tris(dimethylamino)-1,2,3-triazine two signals were observed at 7.10 and 7.25τ (6).

The mass spectra of most known 1,2,3-triazines (1) have been reported. From the given data it follows that a fragmentation into nitrogen, a nitrile, and an acetylene (4) occurs.

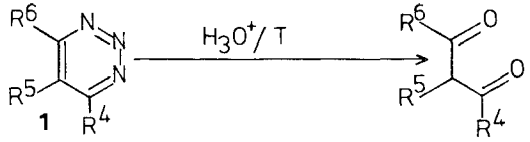


A large number of theoretical calculations on the 1,2,3-triazine system have been reported. These publications include calculations of the resonance energy (12, 13), π-binding energies (12), dipole moment (14–16), ionization

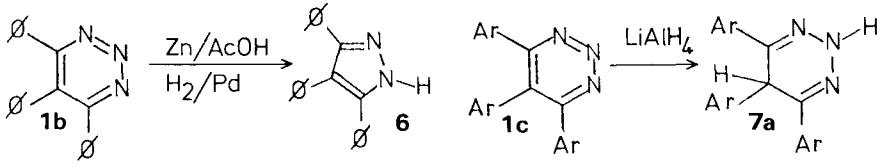
potential (15, 17, 19), singlet and triplet transitions in the electronic spectra (13, 15–23), bond length (12), molecular energy levels (24, 375), electron affinities (15), electron distribution (15, 25), bond orders (26), electron densities (16, 27), second moments (14), localized atom charges and nonlocalized atom and bond charges (17), atom–atom, atom–bond, and bond–bond polarizabilities (28), proton chemical shifts (25), and ^{14}N chemical shifts (29). Palmer and Findlay (23) have shown that diamagnetic susceptibility anisotropy is not related to aromaticity of these molecules.

IV. REACTIONS

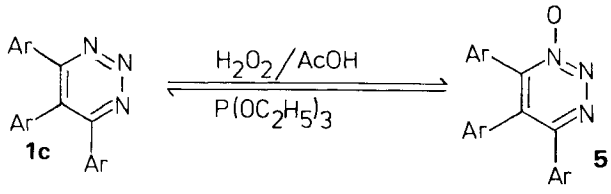
At present only a few reactions of 1,2,3-triazines (**1**) have been reported. They are stable to acids at room temperature but are easily hydrolyzed at higher temperatures, yielding 1,3-dicarbonyl compounds or products of further degradation of the initially formed 1,3-dicarbonyl compounds (3, 8).



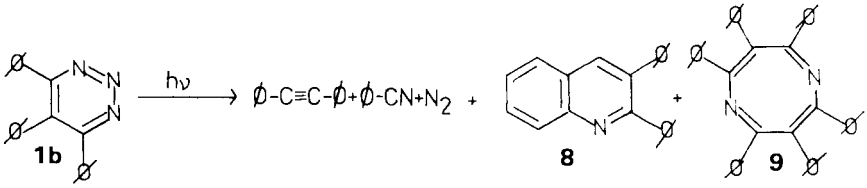
Reduction of the 4,5,6-triphenyl-1,2,3-triazine (**1b**) with zinc in acetic acid or with hydrogen over palladium affords 3,4,5-triphenylpyrazole (**6**) (3), while reduction of 4,5,6-triaryl-1,2,3-triazines (**1c**) with lithium aluminium hydride yields dihydro-1,2,3-triazines, which are best formulated as the 2,5-dihydro-1,2,3-triazines (**7a**) (8).



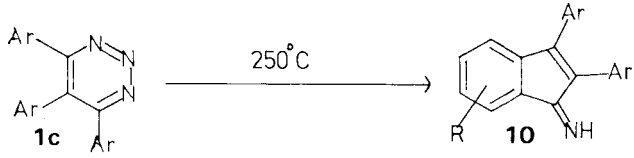
As was already mentioned, triaryl-1,2,3-triazines (**1c**) can be oxidized by hydrogen peroxide in acetic acid, yielding 1,2,3-triazin-1-oxides (**5**), which can be reduced to give the starting 1,2,3-triazines (**1c**) by treatment with triethyl phosphite (8).



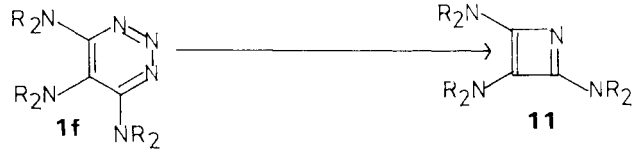
Photolysis of 1,2,3-triazines was reported by different groups (3, 5, 8, 33, 34). In most cases an acetylene, a nitrile, and nitrogen are formed (3, 5, 8). Burgess and Sanchez (33, 34) observed the formation of tolane and benzonitrile when 4,5,6-triphenyl-1,2,3-triazine (**1b**) was irradiated; 3,4-diphenylchinoline (**8**) and 2,3,4,6,7,8-hexaphenyl-1,5-diazocine (**9**) were also formed.



The pyrolysis of 1,2,3-triazines is the most intensively studied reaction of these compounds. Pyrolysis of 4,5,6-trimethyl- (**1e**) and 4,5,6-triphenyl-1,2,3-triazine (**1b**) was reported to yield nitrogen, an acetylene, and a nitrile (3, 5, 30). Heating the 4,5,6-triaryl-1,2,3-triazines (**1c**) without a solvent at 250°C yields mainly the indenone imines (**10**) (31).



Flash pyrolysis of 4,5,6-triamino-1,2,3-triazines (**1f**) affords products that can be formulated as 2,3,4-triaminoazacyclobutadienes (**11**) (6, 8, 32).



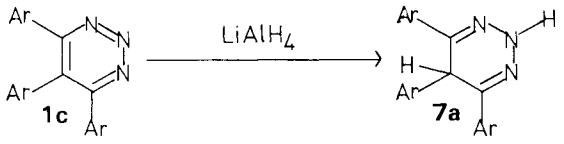
Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

III

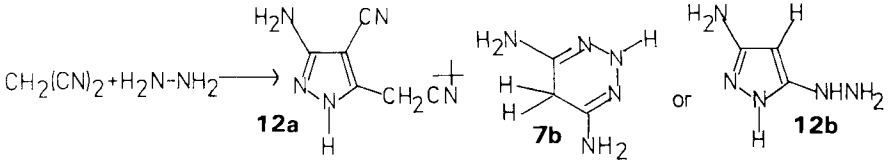
Uncondensed Reduced Systems

I. DIHYDRO-1,2,3-TRIAZINES

At present only a small amount of data on dihydro-1,2,3-triazines is available. Reduction of triaryl-1,2,3-triazines (**1c**) with lithium aluminum hydride afforded dihydro-1,2,3-triazines which are best formulated as the 2,5-dihydro isomers (**7a**) (18).

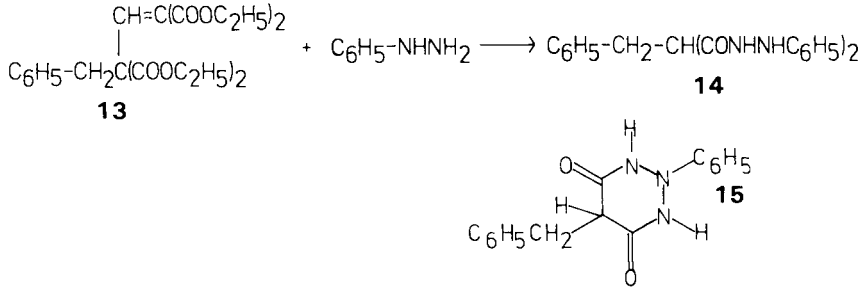


Sato in 1959 reported the reaction of malodinitrile with hydrazine and obtained, besides 3-amino-4-cyano-5-cyanomethylpyrazole (**12a**), a second compound that could be formulated, from its analytical and spectroscopic properties, as 4,6-diamino-2,5-dihydro-1,2,3-triazine (**7b**) (35). Reaction of this compound with benzoyl chloride gave a tribenzoyl derivative. The structure of **7b** is not fully established and the second structure discussed, a 3-amino-5-hydrazinopyrazole (**12b**), seems much more probable to us.



Ruhemann and Morrell (734) heated the ethyl ester of benzyldicarboxyglutaconic acid (**13**) with phenylhydrazine and isolated several products from this reaction. One of these, obtained in very low yield, was a solid of melting point 259°C and soluble in alkali. On the basis of its nitrogen analysis

(14.97% N), they decided that this compound was either benzylmalonic acid bis(phenylhydrazide) (**14**) or 5-benzyl-2-phenyl-2,5-dihydro-1,2,3-triazine-4,6-dione (**15**). Compound **14** was prepared in a different manner and was found to have a different melting point and to be insoluble in alkali. Accordingly they assigned structure **15** to the isolated solid, but this structure is not the only possible one.

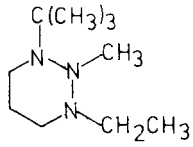


13 **14** **15**

II. HEXAHYDRO-1,2,3-TRIAZINES

In a number of Russian publications, the use of 1-*tert*-butyl-3-ethyl-2-methyl-hexahydro-1,2,3-triazine (**16**) as a corrosion inhibitor for steel is reported (36–48). No further information on this compound could be found in the literature.

16



Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

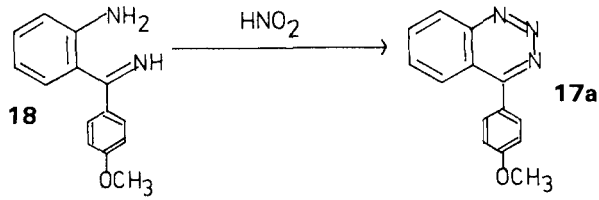
IV

1,2,3-Triazine Rings Condensed with Carbocycles

I. CONDENSED WITH THE BENZENE RING

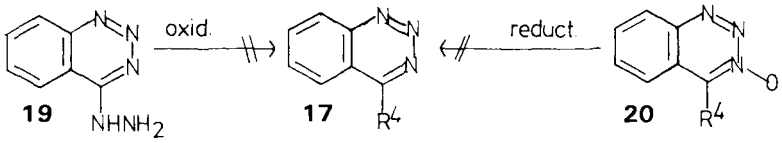
A. 4-Alkyl- and 4-Aryl-Substituted 1,2,3-Benzotriazines

Not only the uncondensed 1,2,3-triazines, but also 1,2,3-benzotriazines with alkyl or aryl substituents in the 4-position are rare at present. The first compound of this class was reported in 1953 by Nunn and Schofield (49), who obtained the 4-(4-methoxyphenyl)-1,2,3-benzotriazine (**17a**) through diazotization of 2-amino-α-(4-methoxyphenyl)benzylidenamine (**18**)



This route for the synthesis of 1,2,3-benzotriazines (**17**) has generally not been explored, presumably because of the instability of the imines.

Parnell (50) in 1961 published unsuccessful attempts to synthesize the unsubstituted 1,2,3-benzotriazine (**17b**) (R^4 = H) through oxidation of 4-hydrazino-1,2,3-benzotriazine (**19**). The same result was reported by Stanovnik and Tišler (51) and by Rees and his group (52). Attempts to prepare **17** by reduction of the known 1,2,3-benzotriazine 3-oxides (**20**) (50, 52–54) were also unsuccessful.



Recently five methods for the synthesis of 4-alkyl- and 4-aryl-1,2,3-benzotriazines (**17**) and the unsubstituted compound (**17b**) were reported by Rees and his group. These methods are as follows:

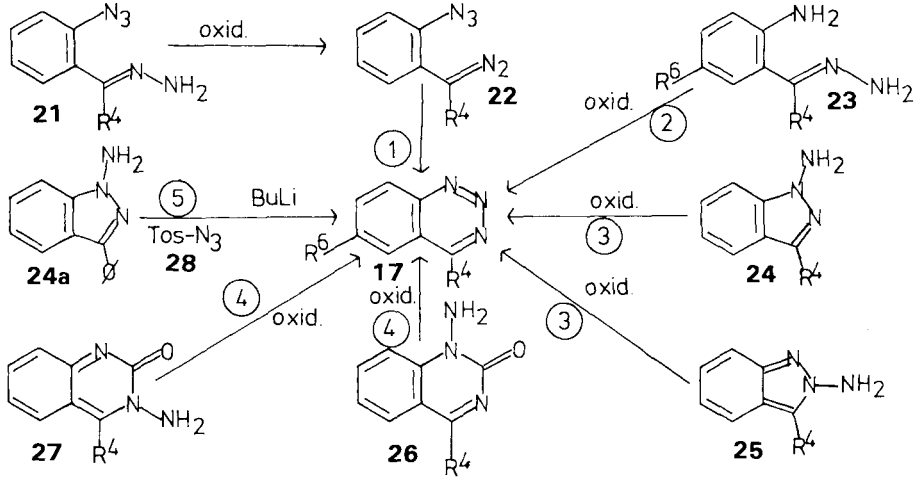
1. Oxidation of the hydrazones of *o*-azidophenyl ketones (**21**) and thermal cyclization of the resulting *o*-azidophenyldiazoalkanes (**22**) (52, 55).

2. Oxidative cyclization of the hydrazones of *o*-aminophenyl ketones (**23**) (52, 55).

3. Oxidation of 1-amino- (**24**) or 2-aminoindazoles (**25**) (52, 56).

4. Oxidation of *N*-aminoquinazolin-2-ones (**26, 27**) (52).

5. Conversion of 1-amino-3-phenylindazole (**24a**) into 4-phenyl-1,2,3-benzotriazine (**17c**) ($R^4 = C_6H_5$, $R^6 = H$) by reaction with butyllithium and 4-toluenesulfonyl azide (**28**) (57).



1,2,3-Benzotriazines (**17**) reported in the Literature are listed in Table IV-1.

The known 1,2,3-benzotriazines (**17**) are colorless to pale-yellow compounds. The mass spectra of these compounds show intense parent peaks and also intense fragment peaks corresponding to losses of nitrogen and a nitrile. The infrared spectra of the 4-methyl-, 4-phenyl-, and 6-chloro-4-phenyl-1,2,3-benzotriazine were reported (52); the infrared spectrum of the 4-methyl derivative shows absorption at 1608, 1570, 1250, 1208, 1141, 1018, 916, 825, 800, 762, and

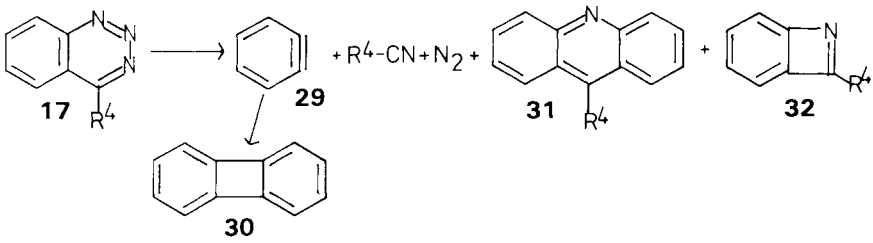
TABLE IV-1. 1,2,3-BENZOTRIAZINES (17)

R^4	R^6	m.p. (°C)	Refs.
H	H	119–120	52, 56
CH_3	H	120–121	52/55, 56
C_6H_5	H	153–154	57
		159–160	52/55, 56
C_6H_5	Cl	126–127	52
4-CH_3O–C_6H_4	H	138–139	49
		141.5–142.5	52/55

711 cm^{-1}. Electronic spectra were reported for the 4-methyl (207, 227, 275 nm; log ϵ = 3.58, 4.0, 2.83) and the 4-phenyl derivatives (206, 232, 293 nm; log ϵ = 3.86, 4.1, 2.95) (52, 57). The signal for the 4-methyl group in the PMR spectrum of the 4-methyl derivative is found at τ = 6.95 (52). Calculations on this system were reported by Wait and Wesley (59), using the Hückel method.

The unsubstituted 1,2,3-benzotriazine (**17b**), and especially its conjugate acid, react very easily with nucleophiles, such as water, acetic acid, or *N*-aminoindazole, to give derivatives of *o*-aminobenzaldehyde (52, 56). 4-Substituted 1,2,3-benzotriazines are less reactive toward attack of nucleophiles at the 4-position. However, 4-phenyl-1,2,3-benzotriazine gave *o*-aminobenzophenone and its hydrazone quantitatively with aqueous acid and hydrazine (52).

The most intensively studied reaction of 1,2,3-benzotriazines (**17**) is their vapour-phase pyrolysis, which leads, depending on the reaction conditions and the structure, to nitrogen, a nitrile, benzyne (**29**), biphenylene (**30**), 9-substituted acridines (**31**), and benzazetes (**32**) (30, 52, 58, 60).

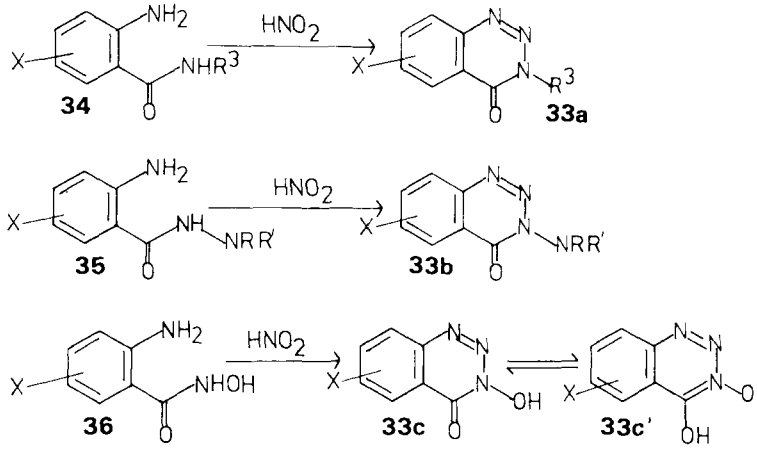


B. 1,2,3-Benzotriazin-4-ones (4-Hydroxy-1,2,3-benzotriazines)

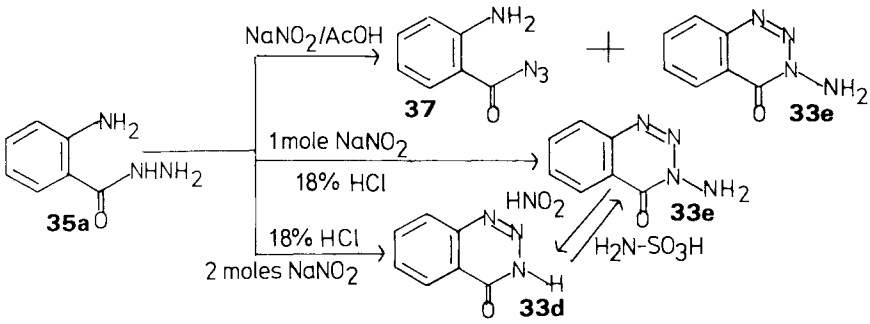
1. *Preparation*

1,2,3-Benzotriazin-4-ones (**33**), also called benzazimides (61), are the most intensively studied class of 1,2,3-benzotriazine derivatives (61–211), and effective methods for their synthesis are known.

The most frequently used method for the synthesis of **33** is the reaction of an 2-aminobenzamide (**34**), 2-aminobenzohydrazide (**35**), or an 2-aminobenzohydroxamic acid (**36**) with nitrous acid, which affords 1,2,3-benzotriazin-4-ones (**33a**) (61–102, 129, 226, 381), 3-amino-1,2,3-benzotriazin-4-ones (**33b**) (84, 93, 103–116, 123), and 3-hydroxy-1,2,3-benzotriazin-4-ones (**33c**) (117, 118, 242–244), respectively. The 3-hydroxy-1,2,3-benzotriazin-4-ones (**33c**) can also be formulated as the tautomeric 4-hydroxy-1,2,3-benzotriazine 3-oxides (**33c'**), a formulation which is sometimes found in the literature. In this discussion we always use the tautomeric structure (**33c**).

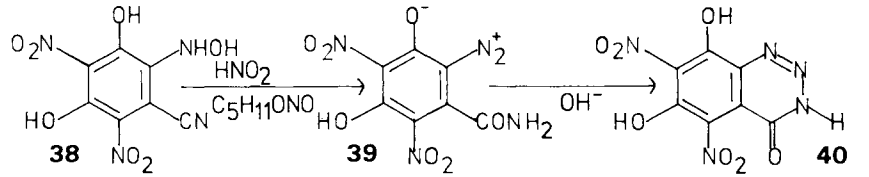


Thode (119) claimed to have obtained 1,2,3-benzotriazin-4-one (**33d**) from anthranilohydrazide (**35a**) and nitrous acid. This reaction was intensively studied by Heller and Siller (114), who found that the reaction of **35a** and nitrous acid could give any of three products, depending on the reaction conditions. Treatment of **35a** with sodium nitrite in dilute acetic acid gives a 45% yield of anthraniloylazide (**37**) and a 40% yield of 3-amino-1,2,3-benzotriazin-4-one (**33e**), whereas treatment of **35a** with 1 mole of sodium nitrite in 18% hydrochloric acid gives only **33e**. Reaction of **35a** with 2 moles of sodium nitrite in 18% hydrochloric acid yields 1,2,3-benzotriazin-4-one (**33d**), which is presumably

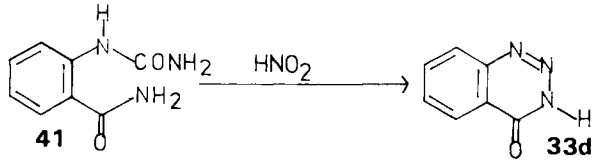


formed from **33e**. **33e** can be obtained by reaction of **33d** with sulfamic acid (103).

Reaction of isopurpuric acid (**38**) with nitrous acid or amyl nitrite yielded a diazonium compound (**39**), in which a cyano group had been hydrolyzed to an amide group. The diazonium compound, when dissolved in alkali, gave a new explosive compound which is formulated as **40** (120, 121).

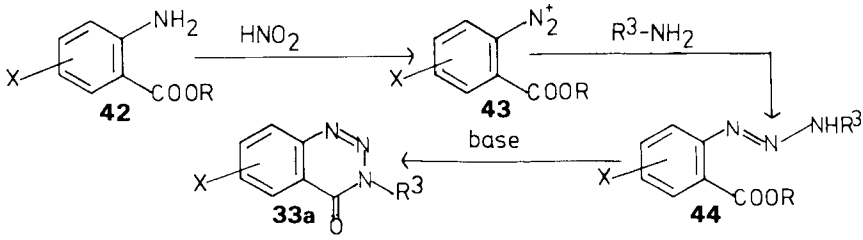


A method similar to the first discussed reaction is reported by Jacini (122), who obtained 1,2,3-benzotriazin-4-one (**33d**) through reaction of isatoic diamide (**41**) with nitrous acid.

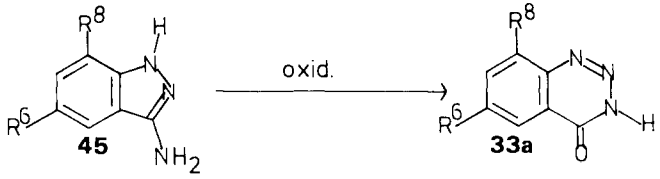


The second method frequently used for the synthesis of 1,2,3-benzotriazin-4-ones (**33a**) is the reaction of anthranilates (**42**) with nitrous acid and reaction of the formed diazonium compound (**43**) with an amine (67, 79–85, 93, 124–129, 136, 157, 180, 206, 209, 210, 229). As was meanwhile shown the primary reaction product is a triazene (**44**), which then cyclizes to the isolated 1,2,3-benzotriazin-4-one (**33a**).

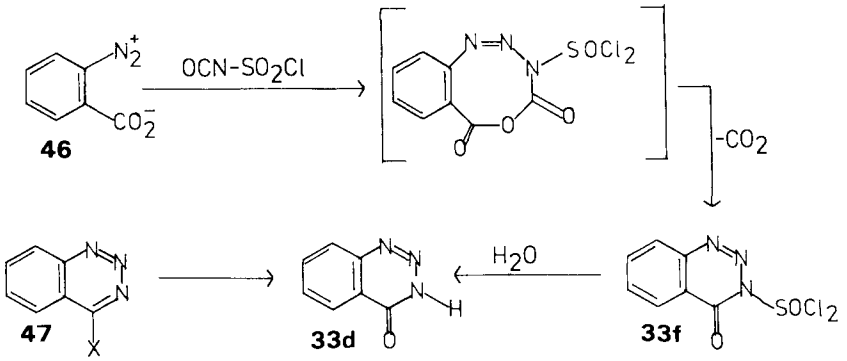
A third method for the preparation of **33a** was reported by Bamberger and Goldberger (130, 131), who isolated 1,2,3-benzotriazin-4-ones (**33a**) from the



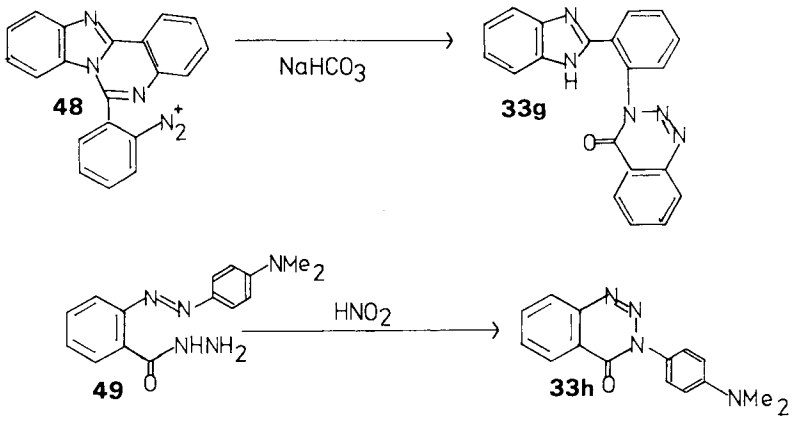
oxidation of 3-aminoindazoles (**45**) with hydrogen peroxide, permanganate, bichromate, or persulfate.



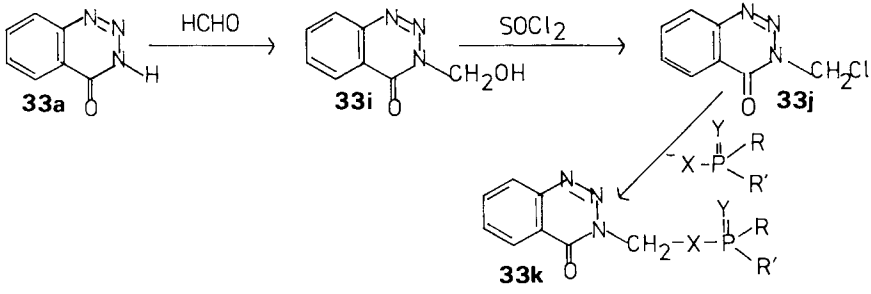
Besides these methods a number of reactions leading to 1,2,3-benzotriazin-4-ones (**33**) were reported but until now have been used in only a few cases (132–134, 136). These reactions include interaction of benzenediazonium carboxylate (**46**) with chlorosulfonyl isocyanate (132), *N,N*-bis(chlorosulfonyl)urea (132), or phosphinimines (133); exchange of other groups in the 4-position of 1,2,3-benzotriazines (**47**) by a "hydroxy" group (134, 204, 230); formation of 3-[*o*-(2-benzimidazolyl)phenyl]-1,2,3-benzotriazin-4-one (**33g**) on treatment of **48** with a cold saturated aqueous sodium hydrogen carbonate solution (136); and reaction of 2-([4-(dimethylamino)phenyl]-azo)benzohydrazide (**49**) with nitrous acid (224).



Finally a large number of substituted 1,2,3-benzotriazin-4-ones were prepared by alkylation or acylation of 3*H*-1,2,3-benzotriazin-4-ones or by modification of



substituents already bound to the 1,2,3-benzotriazine nucleus (63, 64, 67–70, 74, 129, 138–176, 178, 207, 211, 227, 376–380). Of these reactions the following reaction sequence is of special interest, since the compounds finally obtained (**33k**) are useful as insecticides, nematocides, and acaricides, (X, Y = O, S; R, R′ = alkyl, *O*-alkyl, *S*-alkyl, aryl, NH_2) (139, 142, 143, 150,154, 162, 164, 165, 169, 170, 173, 178, 207, 211, 376–380, 697).



2. *Compound Survey*

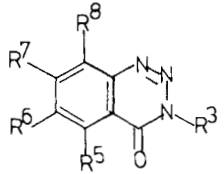
1,2,3-Benzotriazin-4-ones reported in the literature are listed in Table IV-2.

3. *Physical Properties*

All known 1,2,3-benzotriazin-4-ones (**33**) are colorless or yellow crystalline compounds with high melting points. Alkylation or acylation at nitrogen or oxygen generally lowers the melting point.

TABLE IV-2. 1,2,3-BENZOTRIAZIN-4-ONES

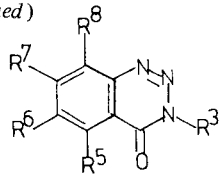
A. 3*H*-1,2,3-Benzotriazin-4-ones



R^3	R^5	R^6	R^7	R^8	m.p. (°C)	Refs.
H	H	H	H	H	207	122
					210 (dec.)	176
					210–211 (dec.)	132
					210–212	108
					211–212	128
					211–212 (dec.)	61
					212–213 (dec.)	134, 361
					213	131
					213 (dec.)	66, 130
					216	61
					217–218	138
					220 (dec.)	87
					222–225	230/119
H	H	H	H	CH_3		728
H	H	H	H	C_2H_5		728
H	H	H	H	Cl	202–203	65
H	H	H	CH_3	H	226 (dec.)	100
H	H	H	Cl	H	213 (dec.)	82
					215–216	129
					219–220 (dec.)	204
H	H	H	NO_2	CH_3		728

TABLE IV-2. (*continued*)

A. 3*H*-1,2,3-Benzotriazin-4-ones (*continued*)



R^3	R^5	R^6	R^7	R^8	m.p. (°C)	Refs.
H	H	H	NO_2	Cl		728
H	H	H	OCH_3	H	218–219 (dec.)	82
					220–221 (dec.)	204
H	H	CH_3	H	H	228	130, 131
H	H	CH_3	H	CH_3	219–220 (dec.)	130, 131
H	H	C_2H_5	H	H		728
H	H	*t*-C_4H_9	H	H		728
H	H	NO_2	H	H	185 (dec.)	98
					189–190	103
					194 (dec.)	82
H	H	Cl	H	H	205–206 (dec.)	82
					210–211	129
H	H	Cl	H	CH_3		728
H	H	Cl	H	Cl	195–196	129
H	H	Br	H	H	198	67
H	H	Br	H	Br		728
H	H	OCH_3	H	H	232–233 (dec.)	82
H	H	OCH_3	H	OCH_3		381
H	H	OCH_3	OCH_3	OCH_3	204–205	64
H	H	SO_2NH_2	Cl	H	270–272	84, 91, 93, 376

	CH_3	H	H	H	728
H	NO_2	H	H	H	728
H	NO_2	CN	NO_2	OH	120
H	Cl	H	H	H	728
K	H	Cl	H	Cl	450 65
CH_3	H	H	H	H	119 161
					120–122 210
					121–122 124
					122–123 138
					123 61, 66, 94
					123–124 79/62
CH_3	H	H	H	Cl	147.5–148 65
CH_3	H	H	Cl	H	145–146 80
CH_3	H	NO_2	H	H	199 (dec.) 98
CH_3	H	Cl	H	H	135.5–136.5 80
CH_3	H	Cl	H	Cl	131.5–132.5 80
CH_3	H	OCH_3	OCH_3	H	381
CH_3	H	SO_2NH_2	Cl	H	246–249 93
					247–250 84
CH_3	H	N=NR	H	H	(39 comp.) 732
C_2H_5	H	H	H	H	70 61
					70–71 79, 210
					51, 62, 161
C_2H_5	H	H	H	Cl	99–100 65
C_2H_5	H	H	Cl	H	99–100 80
C_2H_5	H	NO_2	H	H	105 98
C_2H_5	H	Cl	H	H	75.5–76.5 80
C_2H_5	H	Cl	H	Cl	45.5–47.5 65
C_2H_5					89.5–90.5 80
	H	OCH_3	OCH_3	H	381
C_2H_5	H	SO_2NH_2	Cl	H	186–187 84, 93
C_2H_5	H	N=NR	H	H	732
C_2H_5					

TABLE IV-2. (*continued*)

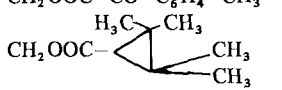
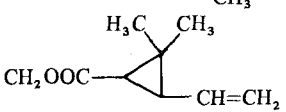
A. 3*H*-1,2,3-Benzotriazin-4-ones (*continued*)

R^3	R^5	R^6	R^7	R^8	m.p. (°C)	Refs.
n-C_3H_7	H	H	H	H	56–56.5	124
					61–62	67, 90
n-C_3H_7	H	H	H	Cl	81.5–82	65
i-C_3H_7	H	H	H	H	55.5–56	124
					60–61	67, 90/62
i-C_3H_7	H	H	H	Cl	106	65
i-C_3H_7	H	OCH_3	OCH_3	H		381
i-C_3H_7	H	OCH_3	OCH_3	OCH_3		381
CH_2=CH–CH_2	H	H	H	H	75–76	80
					b.p. 105°C/1.1 torr	210
CH_2=CH–CH_2	H	H	Cl	H	87.8	80
CH_2=CH–CH_2	H	Cl	H	H	67–68	80
CH_2=CH–CH_2	H	Cl	H	Cl	81–82.5	80
n-C_4H_9	H	H	H	H	22–23	67
n-C_4H_9	H	H	Cl	H	87–88	80
n-C_4H_9	H	Cl	H	H	47–48	80
n-C_4H_9	H	Cl	H	Cl	78.5–79.5	80
i-C_4H_9	H	H	H	H	53–54	67
t-C_4H_9	H	H	H	H	69–70	83
C_6H_{13}	H	H	H	H	b.p. 135–136/0.05	67
Cyclohexyl	H	N=NR	H	H		732

trans-2-Methylcyclohexyl	H	H	H	H	145–148	86
1-Adamantyl	H	H	H	H	116–117	78/76
$C_6H_5-CH_2$	H	H	H	H	114–116	79
					115	86
					120–121.5	124
					122–123	67
$C_6H_5-CH_2$	H	Cl	H	Cl	157.5–158	65
$C_6H_5-CH_2$	H	SO_2NH_2	Cl	H	193–194	93, 84
$C_6H_5-CO-CH_2$	H	H	H	H	134	157/227
4-Br$-C_6H_4-CO-CH_2$	H	H	H	H		227
CH_2Cl	H	H	H	H	125	207, 211, 376
CH_2Cl	H	NO_2	H	H	125–127	72
CH_2Cl	H	Cl	H	H	125–126	72
CH_2Cl	H	Cl	H	Cl	132–134	160
CH_2Cl	H	Br	H	Br	172–174	160
CH_2Br	H	H	H	H	126	207, 376
CH_2SCN	H	H	H	H	118–120	379
CH_2OH	H	H	H	H	134–135	211, 376
$\cdot CF_3COCF_3$					90	185
CH_2OH	H	H	H	CH_3	160–162	156
CH_2OH	H	H	Cl	H	144–146	156
CH_2OH	H	C_3H_7	H	Br		156
CH_2OH	H	NO_2	H	H	136–138	156
CH_2OH	H	NO_2	H	NO_2		156
CH_2OH	H	Cl	H	Cl	162–168 (dec.)	156
					165–166	65
CH_2OH	H	Cl	Cl	Cl		156
CH_2OH	H	Br	H	H	143–146	156
CH_2OH	H	I	H	H	163–165	156
CH_2OH	H	OCH_3	H	H	93–102	156
CH_2OH	Cl	H	H	H	125–128	156
CH_2OCH_3	H	Cl	H	H	105–107	160

TABLE IV-2. (*continued*)

A. 3*H*-1,2,3-Benzotriazin-4-ones (*continued*)

R^3	R^5	R^6	R^7	R^8	m.p. (°C)	Refs.
CH_2OCH_3	H	Cl	H	Cl	110–110.5	160
CH_2OCH_3	H	Br	H	Br	119–121	160
$CH_2OC_4H_9$	H	Cl	H	Cl		160
$CH_2-CO-CH_3$	H	H	H	H		227
$CH_2O-CO-CH_3$	H	Cl	H	H	108–109	160
CH_2OOCCH_3	H	Cl	H	Cl	115–116	160
CH_2OOCCH_3	H	Br	H	Br	133–134	160
$CH_2OOC-i\text{-}C_4H_9$	H	Cl	H	H	48–49	160
$CH_2OOC-i\text{-}C_4H_9$	H	Cl	H	Cl	75	160
$CH_2OOC-C_7H_{15}$	H	Cl	H	Cl	62	160
$CH_2OOC-CH_2C_6H_5$	H	Cl	H	Cl	141	160
					142–143	160
$CH_2OOC-COOC_2H_5$	H	Cl	H	Cl	167–168 (dec.)	160
$CH_2OOC-CO-C_6H_4-CH_3$	H	Cl	H	Cl	145.5–147	160
	H	H	H	H		163
	H	H	H	H	79–81	171/148

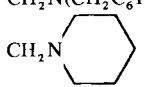
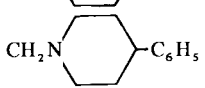
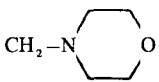
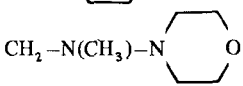
CH_2OOCNH_2	H	H	H	H	180–185	156
$CH_2OOCNHCH_3$	H	H	H	H	150–152	156
$CH_2OOCNHCH_3$	H	H	H	CH_3	152–154	156
$CH_2OOCNHCH_3$	H	H	H	Cl	186–188	156
$CH_2OOCNHCH_3$	H	H	*sec*-C_4H_9	H		156
$CH_2OOCNHCH_3$	H	H	Cl	H	198–200	156
$CH_2OOCNHCH_3$	H	NO_2	H	H	205–207 (dec.)	156
$CH_2OOCNHCH_3$	H	Cl	H	H	170–172	156
$CH_2OOCNHCH_3$	H	Br	H	H	180–182	156
$CH_2OOCNHCH_3$	H	I	H	H	178–180	156
$CH_2OOCNHCH_3$	Cl	H	H	H	168–170	156
$CH_2OOCN(CH_3)_2$	H	H	H	H	83–85	156
					117–117.5	156
$CH_2OOCNHC_2H_5$	H	H	H	H	140–141	156
$CH_2OOCNHC_2H_5$	H	H	Cl	H	187–189	156
$CH_2OOCNHC_2H_5$	H	Cl	H	H	193–195	156
$CH_2OOCNHC_3H_7$	H	H	H	H	102–104	156
CH_2OOCNH–*i*-C_3H_7	H	H	H	H	140–142	156
CH_2OOCNH–*i*-C_3H_7	H	Cl	H	H	165–167	156
$CH_2OOCNHC_4H_9$	H	H	H	H	104–106	156
$CH_2OOCNHC_4H_9$	H	Cl	H	H	145–147	156
$CH_2OOCNHC_4H_9$	H	Cl	H	Cl	151–153	156
$CH_2OOCNHC_6H_{11}$	H	H	H	H	144–146	156
$CH_2N(C_3H_7)_2$	H	Cl	H	Cl	93–94	160
$CH_2N(C_3H_7)_2$	H	Br	H	Br		160
$CH_2N(i\text{-}C_3H_7)CH_2C_6H_5$	H	Br	H	Br	84–85	160
$CH_2N(CH_2C_6H_5)_2$	H	Cl	H	H	118	160
	H	Cl	H	Cl	125–126	160
	H	Cl	H	Cl	150–152	160

TABLE IV-2. (*continued*)

A. 3*H*-1,2,3-Benzotriazin-4-ones (*continued*)

R^3	R^5	R^6	R^7	R^8	m.p. (°C)	Refs.
	H	Cl	H	Cl	83–84.5	65
	H	Cl	H	Cl	132.5–134	160
$CH_2SCH_2CH_2Cl$	H	H	H	H		92
$CH_2SCH_2CH_2OH$	H	H	H	H	76	92
$CH_2SCH_2CH_2S–PO(C_2H_5)OC_2H_5$	H	H	H	H		92
$CH_2SCH_2CH_2S–PO(OC_2H_5)_2$	H	H	H	H		92
$CH_2SCH_2CH_2S–PS(C_2H_5)OC_2H_5$	H	H	H	H		92
$CH_2SCH_2CH_2S–PS(C_6H_5)OC_2H_5$	H	H	H	H		92
$CH_2SCH_2CH_2S–PS(OC_2H_5)_2$	H	H	H	H	Oil	92
$CH_2S–COOCH_3$	H	H	H	H	62–63.5	152
$CH_2S–PS(CH_3)_2$	H	H	H	H	160	165
			H		166	170, 178
$CH_2S–PS(CH_3)OCH_3$	H	H	H	H	103–104	165
$CH_2S–PS(CH_3)OC_2H_5$	H	H	H	H	104	377
$CH_2S–PS(CH_3)O–i\text{-}C_3H_7$	H	H	H	H	Oil	165
$CH_2S–PS(C_2H_5)OC_2H_5$	H	H	H	H	Oil	377
$CH_2S–PS(CH{=}C(CH_3)_2)OC_2H_5$	H	H	H	H	Oil	377

$CH_2S-PO(C_6H_5)OC_2H_5$	H	H	H	H	Oil	377
$CH_2S-PO(OCH_3)_2$	H	H	H	H	81–83	376
$CH_2S-PO(OC_2H_5)_2$	H	H	H	H	Oil	207, 211, 376
$CH_2S-PO(OC_2H_5)_2$	H	H	Cl	H	Oil	154
$CH_2S-PO(OC_2H_5)_2$	H	Cl	H	H	Oil	154
$CH_2S-PO(OC_2H_5)_2$	H	Cl	H	Cl	88–90	154
$CH_2S-PO(OC_2H_5)_2$	H	Br	H	H	74–75.5	154
$CH_2S-PO(OC_2H_5)_2$	H	CH_3S	H	H		150
$CH_2S-PO(OC_3H_7)_2$	H	H	H	H	Oil	207, 211
$CH_2S-PO(O-i-C_3H_7)_2$	H	H	H	H	55	207, 211
$CH_2S-PO(OC_4H_9)_2$	H	H	H	Cl		150
$CH_2S-PO(OCH_3)O-i-C_3H_7$	H	H	H	H		173
$CH_2S-PO(OCH_3)O-\underset{\displaystyle CH_3}{\overset{\displaystyle |}{CH}}-C(CH_3)_2$	H	H	H	H	73–74	173
$CH_2S-PO(OCH_3)OC_6H_{11}$	H	H	H	H		173
$\underset{\displaystyle CH_3}{\overset{\displaystyle |}{CHS}}-PO(OC_2H_5)_2$	H	H	H	H	56	169
$CH_2S-PO(OCH_3)SCH_3$	H	H	H	H		646
$CH_2S-PO(OCH_3)S-n-C_3H_7$	H	H	H	H	Oil	143
$CH_2S-PO(OCH_3)SCH_2CH_2OC_2H_5$	H	H	H	H		142
$CH_2S-PO(OC_2H_5)SC_2H_5$	H	H	H	H		646
$CH_2S-PO(OC_2H_5)S-n-C_3H_7$	H	H	H	H	Oil	143
$CH_2S-PO(OC_2H_5)S-n-C_4H_9$	H	H	H	H	Oil	143
$CH_2S-PO(OC_2H_5)S-i-C_4H_9$	H	H	H	H	Oil	143
$CH_2S-PO(OC_2H_5)S-CH_2CH_2OCH_3$	H	H	H	H	Oil	142
$CH_2S-PO(OC_2H_5)SCH_2CH_2OC_2H_5$	H	H	H	H	Oil	142
$CH_2S-PO(OC_2H_5)SCH_2CH_2SC_2H_5$	H	H	H	H	Oil	142
$CH_2S-PO(O-n-C_3H_7)S-n-C_3H_7$	H	H	H	H		646
$CH_2S-PO(SCH_3)OCOO-i-C_3H_7$	H	H	H	H		162
$CH_2S-PS(OCH_3)_2$	H	H	H	H	63–66	165
					70–72	139, 164
					72	207, 211

TABLE IV-2. (*continued*)

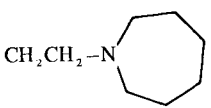
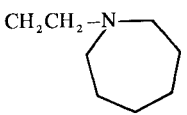
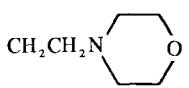
A. 3*H*-1,2,3-Benzotriazin-4-ones (*continued*)

R^3	R^5	R^6	R^7	R^8	m.p. (°C)	Refs.
$CH_2S-PS(OCH_3)_2$	H	H	H	Cl	110–112	154
$CH_2S-PS(OCH_3)_2$	H	H	Cl	H	79–80	154
$CH_2S-PS(OCH_3)_2$	H	Cl	H	H	57–58.5	154
$CH_2S-PS(OCH_3)_2$	H	Cl	H	Cl	102–104	154
$CH_2S-PS(OCH_3)_2$	H	Cl	Cl	H	Oil	154
$CH_2S-PS(OCH_3)_2$	H	Cl	Cl	Cl	117–119	154
$CH_2S-PS(OCH_3)_2$	H	Br	H	H	70–72	154
$CH_2S-PS(OCH_3)_2$	H	Br	H	Br	132–134	154
$CH_2S-PS(OCH_3)_2$	H	Br	Br	Br		154
$CH_2S-PS(OCH_3)_2$	H	CH_3S	H	H		150
$CH_2S-PS(OCH_3)_2$	Cl	H	H	H	99–101	154
$CH_2S-PS(OC_2H_5)_2$	H	H	H	H	45–47	139, 164
					49	165
					49–50	207, 211
$CH_2S-PS(OC_2H_5)_2$	H	H	H	Cl	73–75	154
$CH_2S-PS(OC_2H_5)_2$	H	H	Cl	H	64–65	154
$CH_2S-PS(OC_2H_5)_2$	H	H	Cl	Cl	90–92	154
$CH_2S-PS(OC_2H_5)_2$	H	H	CH_3SO_2	H		150
$CH_2S-PS(OC_2H_5)_2$	H	Cl	H	H	56–58	154
$CH_2S-PS(OC_2H_5)_2$	H	Cl	H	Cl	105–106.5	154
$CH_2S-PS(OC_2H_5)_2$	H	Cl	Cl	H	86–87	154

$CH_2S-PS(OC_2H_5)_2$	H	Cl	Cl	Cl	85–87	154
$CH_2S-PS(OC_2H_5)_2$	H	Br	H	Cl		154
$CH_2S-PS(OC_2H_5)_2$	H	Br	H	Br	130–132	154
$CH_2S-PS(OC_2H_5)_2$	H	$(CH_3)_2CHS$	H	H		150
$CH_2S-PS(OC_2H_5)_2$	H	$(CH_3)_2CHSO_2$	H	H		150
$CH_2S-PS(OC_2H_5)_2$	Cl	H	H	H	86–88	154
$CH_2S-PS(OC_2H_5)_2$	Cl	H	H	Cl	130–131	154
$CH_2S-PS(OC_2H_5)_2$	Cl	Cl	H	H	100–101.5	154
$CH_2S-PS(OC_2H_5)_2$	Cl	Cl	Cl	H	111–113	154
$CH_2S-PS(OC_2H_5)_2$	Cl	Cl	H	Cl	119–120	154
$CH_2S-PS(OC_2H_5)_2$	Cl	Cl	Cl	Cl	142–144	154
$CH_2S-PS(OC_3H_7)_2$	H	H	H	H	53	207, 211
$CH_2S-PS(O-i-C_3H_7)_2$	H	H	H	H	56	211
$CH_2S-PS(O-i-C_3H_7)_2$	H	H	Cl	H	77–79	154
$CH_2S-PS(O-i-C_3H_7)_2$	Cl	H	H	Cl	55–57	154
$CH_2S-PS(OCH_3)O-i-C_3H_7$	H	H	H	H	64	165
					68	173
$CH_2S-PS(OCH_3)O-sec-C_4H_9$	H	H	H	H		173
$CH_2S-PS(OCH_3)OC_6H_{11}$	H	H	H	H	78	173
$CH_2S-PO(OC_2H_5)NH_2$	H	H	H	H	118	378
$CH(CH_3)-S-PS(OCH_3)_2$	H	H	H	H	94	169
$CH(CH_3)-S-PS(OCH_3)OC_3H_7$	H	H	H	H	70–71	169
CH_2-COOH	H	H	H	H	193–194	210
$CH_2-COOC_2H_5$	H	H	H	H	98–100	210
$CH_2CH_2C_6H_5$	H	H	H	H	111–113	79
					113–115	67
CH_2CH_2Cl	H	H	H	H	68–70	67, 90
CH_2CH_2OH	H	H	H	H	116–118	210/62
$CH_2CH_2O-CO-CH_3$	H	OCH_3	OCH_3	H		381

TABLE IV-2. (*continued*)

A. 3*H*-1,2,3-Benzotriazin-4-ones (*continued*)

R^3	R^5	R^6	R^7	R^8	m.p. (°C)	Refs.
$CH_2CH_2N(CH_3)_2$	H	H	H	H	61–62	210/62
					· HCl 222–224	210
					267–270	129
$CH_2CH_2N(CH_3)_2$	H	OCH_3	OCH_3	H		381
$CH_2CH_2N(CH_3)_2$	H	OCH_3	OCH_3	OCH_3		381
$CH_2CH_2N(CH_3)_2$	H	H_2N-SO_2	Cl	H	280–283	93
					· HCl 286–287	93, 84
$CH_2CH_2N(C_2H_5)_2$	H	H	H	H	b.p. 176/1.6	210
					· HCl 226 (dec.)	210
	H	H	H	H		62
	H	OCH_3	OCH_3	H		381
	H	H	H	H	99	210

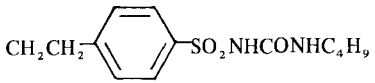
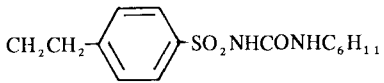
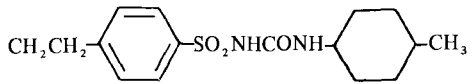
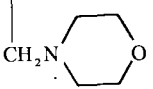
					·HCl 230–232	210
	H	H	H	H	211–213	98
	H	H	H	H	213–215	98
	H	H	H	H	212–214	98
$C_6H_5-CH_2-CH(COOH)$	H	H	H	H	152–154	79
$C_6H_5-CH_2-CH(COOC_2H_5)$	H	H	H	H	60–62	79
4-$HO-C_6H_4-CH_2-CH(COOH)$	H	H	H	H	150–152	79
4-$HO-C_6H_4-CH_2-CH(COOC_2H_5)$	H	H	H	H	122–123	79
3,5-$(CH_3O)_2C_6H_3HCOOCH-CH_2$ 	H	CH_3O	CH_3O	CH_3O	·HCl 125	153
3,4,5-$(CH_3O)_3C_6H_2-COOCH(CH_2N(C_2H_5)_2)-CH_2$	H	CH_3O	CH_3O	H	·HCl 195	153
3,4,5-$(CH_3O)_3C_6H_2-COOCH(CH_2N(C_2H_5)_2)-CH_2$	H	CH_3O	CH_3O	CH_3O	·HCl 208–210	153

TABLE IV-2. (*continued*)

A. 3*H*-1,2,3-Benzotriazin-4-ones (*continued*)

R^3	R^5	R^6	R^7	R^8	m.p. (°C)	Refs.
3,4,5-$(CH_3O)_3C_6H_2$–COOCH(–$CH_2N(CH_3)CH_2CH{=}CH_2$)–CH_2	H	CH_3O	CH_3O	H	·HCl 180	153
3,4,5-$(CH_3O)_3C_6H_2$–COOCH(–$CH_2N(CH_3)CH_2CH{=}CH_2$)–CH_2	H	CH_3O	CH_3O	CH_3O	·HCl 85	153
3,4,5-$(CH_3O)_3C_6H_2$–COOCH(–$CH_2N(CH_3)(CH_2)_3OCH_3$)–CH_2	H	CH_3O	CH_3O	CH_3O	·HCl 130	153
3,4,5-$(CH_3O)_3C_6H_2$–COOCH(–$CH_2N(CH_3)(CH_2)_3N(C_2H_5)_2$)–$CH_2$	H	CH_3O	CH_3O	H	·2HCl 165	153
3,4,5-$(CH_3O)_3C_6H_2$–COOCH(–$CH_2N(CH_3)(CH_2)_3N(C_2H_5)_2$)–$CH_2$	H	CH_3O	CH_3O	CH_3O	·2HCl 75	153
3,4,5-$(CH_3O)_3C_6H_2$–COOCH(–$CH_2N(CH_3)$(cyclopropyl)–CH_2	H	CH_3O	CH_3O	CH_3O	·HCl 95	153

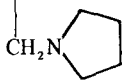
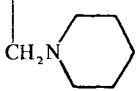
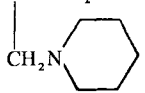
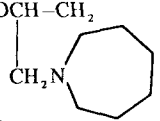
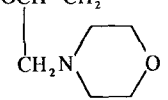
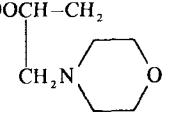
3,4,5-$(CH_3O)_3C_6H_2$–COOCH–CH_2 $CH_2N(CH_3)C_6H_{11}$	H	CH_3O	CH_3O	CH_3O	·HCl	85	153
3,4,5-$(CH_3O)_3C_6H_2$–COOCH–CH_2 $CH_2N(CH_3)CH_2C_6H_5$	H	CH_3O	CH_3O	CH_3O	·HCl	75	153
3,4,5-$(CH_3O)_3C_6H_2$–COOCH–CH_2 	H	CH_3O	CH_3O	CH_3O	·HCl	80	153
3,4,5-$(CH_3O)_3C_6H_2$–COOCH–CH_2 	H	CH_3O	CH_3O	H	·HCl	220	153
3,4,5-$(CH_3O)_3C_6H_2$–COOCH–CH_2 	H	CH_3O	CH_3O	CH_3O	·HCl	190	153
3,4,5-$(CH_3O)_3C_6H_2$–COOCH–CH_2 	H	CH_3O	CH_3O	CH_3O	·HCl	125	153
3,4,5-$(CH_3O)_3C_6H_2$–COOCH–CH_2 	H	CH_3O	CH_3O	H	·HCl	136–138	153
3,4,5-$(CH_3O)_3C_6H_2$–COOCH–CH_2 	H	CH_3O	CH_3O	CH_3O	142–144		153

TABLE IV-2. (*continued*)

A. 3*H*-1,2,3-Benzotriazin-4-ones (*continued*)

R^3	R^5	R^6	R^7	R^8	m.p. (°C)		Refs.
3,4,5-$(CH_3O)_3C_6H_2$–COOCH–CH_2 CH_2N N–CH_3	H	CH_3O	CH_3O	CH_3O	·2HCl	160	153
3,4,5-$(CH_3O)_3C_6H_2$–COOCH–CH_2 3,4,5-$(CH_3O)_3C_6H_2COOCH_2CH_2$–N N–$CH_2$	H	CH_3O	CH_3O	H	·2HCl	192	153
3,4,5-$(CH_3O)_3C_6H_2$–COOCH–CH_2 CH_2N N–C_6H_5	H	CH_3O	CH_3O	CH_3O	·2HCl	163	153
3,4,5-$(CH_3O)_3C_6H_2$–COOCH–CH_2 3,4,5-$(CH_3O)_3C_6H_2$–$COOCH_2CH_2$–N N–CH_2	H	CH_3O	CH_3O	CH_3O	·2HCl	150 (dec.)	153
3,4,5-$(C_2H_5O)_3C_6H_2$–COOCH–CH_2 $CH_2N(C_2H_5)_2$	H	CH_3O	CH_3O	CH_3O	·HCl	200–202	153

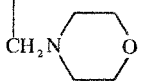
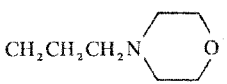
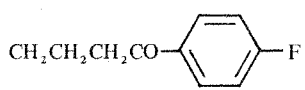
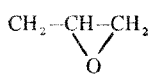
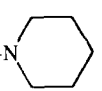
3,5-$(CH_3O)_2$-4-C_4H_9O-C_6H_2-COOCH-CH_2 	H	CH_3O	CH_3O	CH_3O		
					·HCl 115	153
$CH_2CH_2CH_2OCH_3$	H	H	H	H	45–47	67
$CH_2CH_2CH_2N(CH_3)_2$	H	H	H	H	b.p. 178/2.4	210
Hydrochloride					208–210	210
$CH_2CH_2CH_2N(CH_3)_2$	H	H	Cl	H		
					·HCl 262–263	129
					269–270	129
$CH_2CH_2CH_2N(CH_3)_2$	H	Cl	H	H		
					·HCl 230–232	129
$CH_2CH_2CH_2N(CH_3)_2$	H	H	Cl	H		
					·HCl 232–233	129
$CH_2CH_2CH_2N(C_2H_5)_2$	H	Cl	H	H		
					·HCl 185–186	129
	H	OCH_3	OCH_3	H		381
$CH(CH_2OH)_2$	H	H	H	H	b.p. 117–120/3.3	210
$CH-CH_2CH_2CH_2N(C_2H_5)_2$	H	H	H	H	b.p. 185/1.1	210
CH_3					·HCl 130–131	210
	H	Cl	H	Cl		147
	H	CH_3O	CH_3O	CH_3O	123–125	64

TABLE IV-2. (*continued*)

A. 3*H*-1,2,3-Benzotriazin-4-ones (*continued*)

R^3	R^5	R^6	R^7	R^8	m.p. (°C)	Refs.
$CH_2-CH(OH)-CH_2Cl$	H	H	H	H	103–105	64
$CH_2-CH(OH)-CH_2-N(CH_3)CH_2CH=CH_2$	H	CH_3O	CH_3O	H	154	64
$CH_2-CH(OH)-CH_2-N(CH_3)CH_2CH=CH_2$	H	CH_3O	CH_3O	CH_3O	Oil	64
$CH_2-CH(OH)-CH_2-N$ 	H	CH_3O	CH_3O	CH_3O	Oil	64
$CH_2-CH(OH)-CH_2-N(CH_3)C_6H_{11}$	H	CH_3O	CH_3O	CH_3O	Oil	64
$CH_2-CH(OH)-CH_2-N(CH_3)CH_2C_6H_5$	H	CH_3O	CH_3O	CH_3O	Oil	64
$CH_2-CH(OH)-CH_2-N(CH_3)(CH_2)_3OCH_3$	H	CH_3O	CH_3O	CH_3O	Oil	64
$CH_2-CH(OH)CH_2-N(CH_3)(CH_2)_3N(C_2H_5)_2$	H	CH_3O	CH_3O	H	120	64
$CH_2-CH(OH)CH_2-N(CH_3)(CH_2)_3N(C_2H_5)_2$	H	CH_3O	CH_3O	CH_3O	Oil	64
$CH_2-CH(OH)-CH_2-N(C_2H_5)_2$	H	CH_3O	CH_3O	H	164	64
$CH_2-CH(OH)-CH_2-N(C_2H_5)_2$	H	CH_3O	CH_3O	CH_3O	73	64
$CH_2-CH(OH)-CH_2-N$ 	H	CH_3O	CH_3O	CH_3O	126	64
$CH_2-CH(OH)-CH_2-N$ 	H	CH_3O	CH_3O	H	168	64

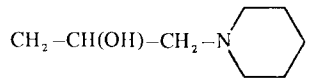
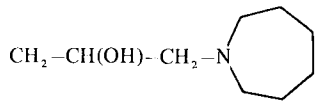
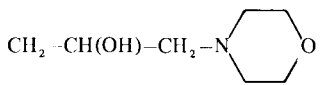
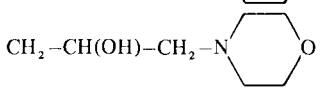
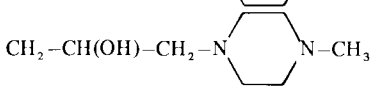
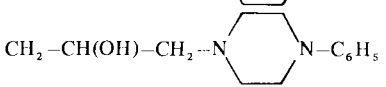
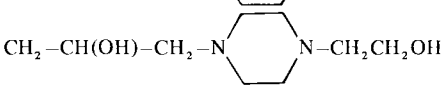
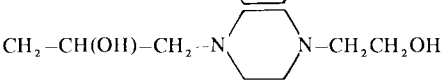
	H	CH_3O	CH_3O	CH_3O	101–103	64
	H	CH_3O	CH_3O	CH_3O	75–77	64
	H	CH_3O	CH_3O	H	195	64
	H	CH_3O	CH_3O	CH_3O	135–136	64
	H	CH_3O	CH_3O	CH_3O	102	64
	H	CH_3O	CH_3O	CH_3O	157–158	64
	H	CH_3O	CH_3O	H	196	64
	H	CH_3O	CH_3O	CH_3O	·2HCl 182	64
β-D-Glucopyranosyl	H	H	H	H	218–221	159
Tetraacetyl-β-D-glucopyranosyl	H	H	H	H	113–115	159
C_6H_5	H	H	H	H	149–150	133
					150–151	68, 97
					151	126, 127, 180
					151.5	81
					151–152	79

TABLE IV-2. (*continued*)

A. 3*H*-1,2,3-Benzotriazin-4-ones (*continued*)

R^3	R^5	R^6	R^7	R^8	m.p. (°C)	Refs.
3-^{15}N					151	102
C_6H_5	H	NO_2	H	H	190	98
2-CH_3–C_6H_4	H	H	H	H	166	127
					167	86, 180
3-CH_3–C_6H_4	H	H	H	H	150	127
4-CH_3–C_6H_4	H	H	H	H	142–143	133
					143	127, 180
					143–144	138
2-C_2H_5–C_6H_4	H	H	H	H	134–135	86
2-C_6H_5–C_6H_4	H	H	H	H	183	180
2,4-$(CH_3)_2C_6H_3$	H	H	H	H	132	127
2,4,6-$(CH_3)_3C_6H_2$	H	H	H	H	142	180
2-NO_2–C_6H_4	H	H	H	H	184	180
					187–189	229
3-NO_2–C_6H_4	H	H	H	H	238	127
					240–242 (dec.)	227
					243	180
					252 (dec.)	180
4-NO_2–C_6H_4	H	H	H	H	252–254	127
					254–255 (dec.)	227
					271–272	68
					275	180

2-F–C_6H_4	H	H	H	H	142	86, 89
2-Cl–C_6H_4	H	H	H	H	115–116	73
					122	180
3-Cl–C_6H_4	H	H	H	H	144	180
4-Cl–C_6H_4	H	H	H	H	185–186	68
					186	180
2-Br–C_6H_4	H	H	H	H	120–120.5	73, 77
4-Br–C_6H_4	H	H	H	H	196	206
					198–199	68
2-I–C_6H_4	H	H	H	H	189–190	73
2,3-$Cl_2C_6H_3$	H	H	H	H	177–178	73
2,4-$Cl_2C_6H_3$	H	H	H	H	125.5–126.5	73
2,5-$Cl_2C_6H_3$	H	H	H	H	165–166	73
2,6-$Cl_2C_6H_3$	H	H	H	H	169–170	73
2,4-$Br_2C_6H_3$	H	H	H	H	136	206
2-CH_3O–C_6H_4	H	H	H	H	153	180
4-CH_3O–C_6H_4	H	H	H	H	157	68, 180
4-C_2H_5O–C_6H_5	H	H	H	H	186–187	86
2-H_2N–C_6H_4	H	H	H	H	174–175	125
2-CH_3CO–NH–C_6H_4	H	H	H	H	246	180
3-H_2N–C_6H_4	H	H	H	H	194–196	125
4-H_2N–C_6H_4	H	H	H	H	210–211	125
4-$(CH_3)_2N$–C_6H_4	H	H	H	H	246–247	224
					249–250	226
4-CH_3CO–NH–C_6H_4	H	H	H	H	242	180
2-$(C_6H_5)_2N$–C_6H_4	H	H	H	H	237–238	101
2-HOOC–C_6H_4	H	H	H	H	192 (dec.)	96
2-(2-HOOC–C_6H_4)–NH–CO–C_6H_4	H	H	H	H	201 (dec.)	96
4-NC–C_6H_4	H	H	H	H	230–232	83
4-H_2O_3As–C_6H_4	H	H	H	H		95
2-$HOCH_2$–C_6H_4	H	H	H	H	165–166	69
2-$HOCH_2$–C_6H_4	H	H	Cl	H	168–169	69
2-$HOCH_2$–C_6H_4	H	Cl	H	H	129–130	69

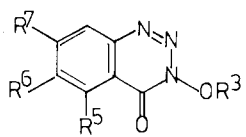
TABLE IV-2. (*continued*)

A. 3*H*-1,2,3-Benzotriazin-4-ones

R^3	R^5	R^6	R^7	R^8	m.p. (°C)	Refs.
2-CH_3COOCH_2–C_6H_4	H	H	H	H	92–93	69
2-CH_3COOCH_2–C_6H_4	H	H	Cl	H	131–132	69
2-CH_3COOCH_2–C_6H_4	H	Cl	H	H	120–120.5	69
2-$C_2H_5COOCH_2$–C_6H_4	H	H	H	H	68–69	69
2-$(CH_3)_2CHCH_2COOCH_2$–C_6H_4	H	H	H	H	50	69
2-HOOC–$CH_2CH_2COOCH_2$–C_6H_4	H	H	H	H	134–135	69
2-C_6H_5–$COOCH_2$–C_6H_4	H	H	H	H	142–143	69
2-C_2H_5NH–$COOCH_2$–C_6H_4	H	H	H	H	113.5–115	69
2-(*n*-C_4H_9NH–$COOCH_2$)–C_6H_4	H	H	H	H	87–89	69
2-[4,6-$(H_2N)_2$-1,3,5-triazin-2-yl]–C_6H_4	H	H	H	H	303–305	83
4-[4,6-$(H_2N)_2$-1,3,5-triazin-2-yl]–C_6H_4	H	H	H	H	324–326	83
2-(2-benzimidazolyl)–C_6H_4	H	H	H	H	254	136
4-Cl-2-CH_3–C_6H_3	H	H	H	H	113–114	86
					130–134	88
2-CH_3-4-CH_3O–C_6H_3	H	H	H	H	131	88
2-CH_3-4-$(C_2H_5)_2N$–C_6H_3	H	H	H	H	153–154	86, 88
2-CH_3-5-Cl–C_6H_3	H	H	H	H	136–137	86
2-CH_3-5-CH_3O–C_6H_3	H	H	H	H	131	86
2-Cl-6-CH_3–C_6H_3	H	H	H	H	127–128	73
2-Cl-3-CF_3–C_6H_3	H	H	H	H	155–155.5	73
4-Cl-2-$HOCH_2$–C_6H_3	H	H	H	H	147–148	69

5-Cl-2-$HOCH_2$–C_6H_3	H	H	H	H	132–133	69
2-$HOCH_2$-4,6-$Cl_2C_6H_2$	H	H	H	H	181–182	69
2-Pyridyl	H	H	H	H	189–190	210
3-Pyridyl	H	H	H	H	133	209
3-Quinolyl	H	H	H	H	188–189	210
CH_3CO	H	H	H	H	165	94, 176
C_6H_5CO	H	H	H	H	132	176
					132–133	94
$COOC_2H_5$	H	H	H	H	65–66	94
$COOC_2H_5$	H	Cl	H	H	94–95	65
$COOC_2H_5$	H	Cl	H	Cl	88.5	160
$COOC_2H_5$	H	Br	H	Br	91–93	160
$COOC_4H_9$	H	Cl	H	Cl	58	160
$COOCH_2C_6H_5$	H	Cl	H	Cl	106–108	160
$COOC_6H_5$	H	Cl	H	Cl	116–117	160
CO–NHC_6H_5	H	H	H	H	114–115 (dec.)	117

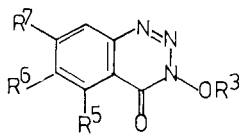
B. 3-Hydroxy-1,2,3-benzotriazin-4(3*H*)-ones

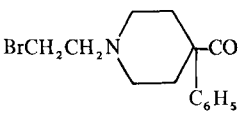
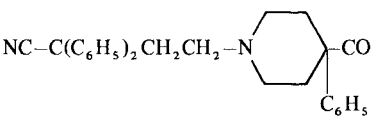
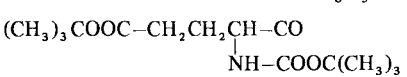


R^3	R^5	R^6	R^7	m.p. (°C)	Refs.
H	H	H	H	180–181 (dec.)	244
H	H	H	NO_2	154	243
H	H	Br	H	178 (dec.)	117
H	Cl	H	Cl	184	243
H	OCH_3	OH	H		242
2-H_2N–C_6H_4–CO	H	H	H	202–204	118

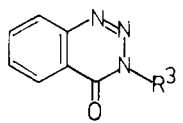
TABLE IV-2. (*continued*)

B. 3-Hydroxy-1,2,3-benzotriazin-4(3*H*)-ones (*continued*)



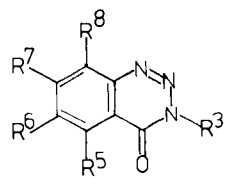
R^3	R^5	R^6	R^7	m.p. (°C)	Refs.
$2\text{-}N_3\text{-}C_6H_4\text{-}CO$	H	H	H	131–134	155
	H	H	H		146
	H	H	H	208–210 (dec.)	146
	H	H	H	136.5–138	203

C. 3-Mercapto-1,2,3-benzotriazin-4-(3*H*)-ones



R^3	m.p. (°C)	Refs.
$SCCl_3$	125 (dec.)	166
	150 (dec.)	168
$SCFCl_2$		167
$SCCl_2-CHCl_2$		167
$SCCl=CHCl$		167
$SCCl=CCl_2$		167
$SCF_2-CHFCl$		167
$SOCl_2$	113–116 (dec.)	132
$4\text{-}CH_3-C_6H_4-SO_2$		157

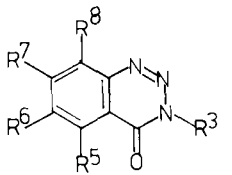
D. 3-Amino-1,2,3-benzotriazin-4(3*H*)-ones



R^3	R^5	R^6	R^7	R^8	m.p. (°C)	Refs.
NH_2	H	H	H	H	152–153 (dec.)	107, 115
					154–155 (dec.)	103
NH_2	H	H	NO_2	H	191–192	103

TABLE IV-2. (*continued*)

D. 3-Amino-1,2,3-benzotriazin-4(3*H*)-ones (*continued*)



R^3	R^5	R^6	R^7	R^8	m.p. (°C)	Refs.
NH_2	H	H	Cl	H	184–185	103
NH_2	H	CH_3	H	H	140–140.5	103
NH_2	H	NO_2	H	H	188–190	103
NH_2	H	Cl	H	H	163–164	103
NH_2	H	SO_2NH_2	Cl	H	230–231	84
C_6H_5–NH	H	H	H	H	135 (dec.)	116
CH_3CO–NH	H	H	H	H	199–200	107
					206 (dec.)	115
C_6H_5–CO–NH	H	H	H	H	205–206	115
CH_3O–CO–NH	H	H	H	H	149	113
					153–154	175
C_2H_5O–CO–NH	H	H	H	H	147	143
					150–151	176
C_2H_5O–CO–NH	H	H	CH_3	H	172–173	176
C_2H_5O–CO–NH	H	H	SO_2NH_2	H	223–225	176
C_2H_5O–CO–NH	H	$NHCOOC_2H_5$	H	H	191–192	107
C_2H_5O–CO–NH	Cl	H	H	H	148–149	175
C_2H_5O–CO–NH	SO_2NH_2	H	H	H	224–225	175
C_3H_7O–CO–NH	H	H	H	H	101–102	175

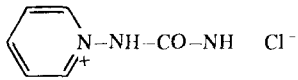
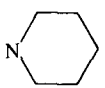
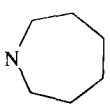
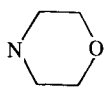
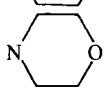
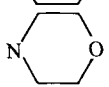
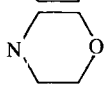
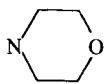
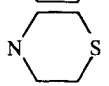
CH_2=CH–CH_2O–CO–NH	H	H	H	H	98–99	107
CH_2=CH–CH_2O–CO–*NH*	H	Br	H	H	102–103	107
$HOCH_2CH_2O$–CO–NH	H	H	H	H	137–138	107
					138	106, 110
$CH_3OCH_2CH_2O$–CO–NH	H	H	H	H	84–86	107
4-Pyridyl–CO–NH	H	H	H	H	225	107
	H	H	H	H	230 (dec.)	107
C_2H_5O–CS–NH	H	H	H	H	150–152	107
CH_2=CH–CH_2NH–CS–NH	H	H	H	H	173	107
C_6H_5–SO_2–NH	H	H	H	H	220–222	107
4-CH_3–C_6H_4–SO_2–NH	H	H	H	H	204–206 (dec.)	104
4-CH_3–C_6H_4–SO_2–*NH*	H	Cl	H	H	170–172 (dec.)	104
C_2H_5O–CO–NNa	H	H	H	H		175, 177
C_2H_5O–CO–NK	H	H	H	H		177
C_2H_5O–CO–NNa	H	H	CH_3	H		175, 177
$N(CH_3)_2$	H	H	H	H	116	108
					117	107
$N(CH_3)_2$	H	NO_2	H	H	168	108
$N(CH_3)_2$	Br	H	H	H	160	108
$N(CH_3)C_6H_5$	H	H	H	H	110–111	105
	H	H	H	H	146–147	107
	H	H	H	H	118–119	107, 108

TABLE IV-2. *(continued)*

D. 3-Amino-1,2,3-benzotriazin-4(3*H*)-ones *(continued)*

R^3	R^5	R^6	R^7	R^8	m.p. (°C)	Refs.
	H	H	H	H	199–200 (dec.)	108, 109, 107
	H	H	CH_3	H	149–150	107, 108
	H	NO_2	H	H	189	108
	H	Br	H	H	214–215	108
	H	OCH_3	OCH_3	H		381
	H	H	H	H	180–181	107, 108

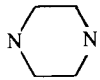
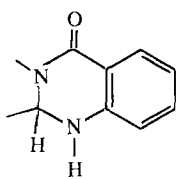
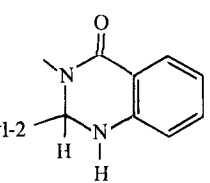
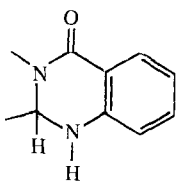
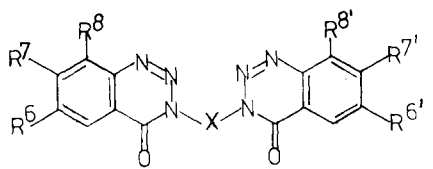
	H	H	H	H	158–159	107
$N(CH_3)COOC_2H_5$	H	H	H	H	95–96	174, 107
$CH_3-N-COOCH_2CH=CH_2$	H	H	CH_3	H	78–80	174
$C_2H_5-N-COOCH_2CH=CH_2$	H	H	CH_3	H	62–64	174
$C_6H_5CH_2-N-COOC_2H_5$	H	H	H	H	66–67	174
$C_6H_5CH_2-N-COOCH_2CH=CH_2$	H	H	CH_3	H	85–86	174
$C_2H_5O-CO-N-CH_2COOC_2H_5$	H	H	H	H	111–112	107
					112–113	175
$CH_2=CHCH_2O-CO-N-CH_2COOC_2H_5$	H	H	CH_3	H	64–66	174
$C_2H_5O-CO-N-COOC_2H_5$	H	H	H	H	126–127	174
$C_6H_5-CH=N$	H	H	H	H	174–175	114
$C_6H_5(CH_3)C=N$	H	H	H	H	168.5	115
$C_6H_5(CH_3)C=N$	H	H	NO_2	H	191–193	103
$C_6H_5(CH_3)C=N$	H	SO_2NH_2	Cl	H	237–240	84, 93
$CH_3SO_2-N-CH_3$	H	H	H	H	158–159	107, 174
$C_6H_5SO_2-N-CH_3$	H	H	H	H	175–176	174
$CH_3SO_2-N-CH_2CH=CH_2$	H	H	H	H	143	174
$C_6H_5SO_2-N-CH_2CH=CH_2$	H	H	H	H	125–126	174
4-$CF_3-C_6H_4$ 	H	NO_2	H	H	200	123
5-NO_2-furyl-2 	H	NO_2	H	H	278	123

TABLE IV-2. (*continued*)

D. 3-Amino-1,2,3-benzotriazin-4(3*H*)-ones

R^3	R^5	R^6	R^7	R^8	m.p. (°C)	Refs.
5-NO_2-furyl-2 	H	Cl	H	H	291 (dec.)	123

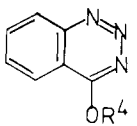
E. Compounds with more than one 1,2,3-Benzotriazin-4(3*H*)-one system



X	R^6	R^7	R^8	$R^{6'}$	$R^{7'}$	$R^{8'}$	m.p. (°C)	Refs.
–	H	H	H	H	H	H	240 (dec.) 249 (dec.)	123 112

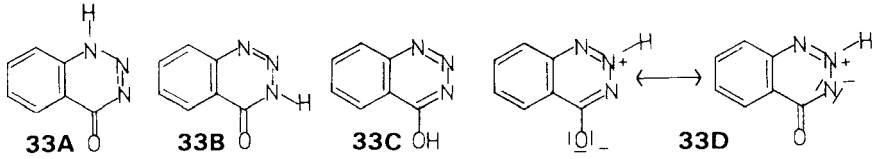
–	H	Cl	H	H	Cl	H	245	111, 112
–	Cl	H	H	H	H	H	241	123
–	Cl	H	Cl	H	H	H	236 (dec.)	123
–	H	NO_2	H	H	H	H	234 (dec.)	123
–	NO_2	H	H	H	H	H	225 (dec.)	123
–	NO_2	H	H	NO_2	H	H	254 (dec.)	123
CH_2–CH_2	H	H	H	H	H	H	213–215	210
							216	99
CH_2–CH_2	NO_2	H	H	NO_2	H	H	>290	98
N-C_4H_9	Cl	H	Cl	Cl	H	Cl	143–145	160
	H	H	H	H	H	H		726
			50 other compounds mentioned					727

F. 4-Hydroxy-1,2,3-benzotriazines



R^4	m.p. (°C)	Refs.
CH_3	Unstable	161
C_2H_5		51
4-CH_3–C_6H_4	145–147.5	138
Tetraacetyl-β-D-glucopyranosyl	142–145	159

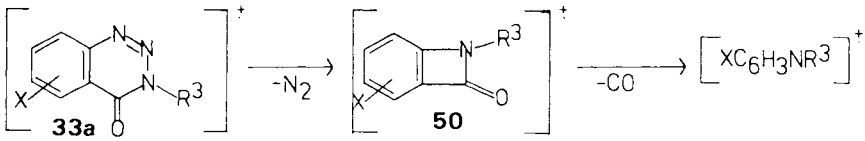
Four tautomeric structures can be discussed for these compounds, two 1,2,3-benzotriazin-4-one structures (**33A**, **33B**), the 4-hydroxy tautomer (**33C**), and the zwitterionic structure **33D**. Derivatives of structures **33B** to **33D** are known (derivatives of **33D** are discussed in Section **I-C**). Owing to an intensive band in the infrared spectra between 1700 and 1667 cm^{-1} the 4-hydroxy form (**33C**) could be excluded. Hjortas (179) has shown by X-ray crystallographic analysis that the unsubstituted 1,2,3-benzotriazin-4-one crystallizes as the 3*H*-tautomer (**33B**). The length of the double bond between N-1 and N-2 is 1.274 Å. The molecules in the crystal are bonded together by almost linear N–H···O hydrogen bonds; the N···O distance is 2.828 Å. Some crystallographic data on the 3-phenyl-1,2,3-benzotriazin-4-one was published by Grabowski (374).



Spectroscopic data on the 1,2,3-benzotriazin-4-ones (**33**) are reported in a number of publications (72, 80, 132, 138, 159, 186, 187, 189, 190, 200). As was already mentioned, in the infrared spectrum of **33** an intensive band for the CO–NH group is observed between 1700 and 1667 cm^{-1} (132, 138, 180, 184). For the unsubstituted 1,2,3-benzotriazin-4-one (**33d**) the following UV spectrum was published (138): $\lambda_{max}(\log \epsilon) = 307$ (3.42), 296 (3.63), 278 (3.80), 250 (3.71), 224 (4.28), and 211 nm (4.15). The 3-methyl-1,2,3-benzotriazin-4-one has the following UV spectrum (138): $\lambda_{max}(\log \epsilon) = 316$ sh (3.61), 300 sh (3.79), 285 (3.89), 252 sh (3.69), 225 (4.35), and 214 nm (4.31). For many other 1,2,3-benzotriazin-4-ones (**33**) only two absorption maxima, between 290 and 300 nm and between 226 and 244 nm, were reported.

The PMR spectrum of the unsubstituted 1,2,3-benzotriazin-4-one shows the signal for the N–H proton at -1.00τ and a multiplet for the four aromatic protons between 1.90 and 2.40τ (132).

The mass spectrometric fragmentation of 1,2,3-benzotriazin-4-ones (**33a**) was studied by various groups (72, 161, 186, 189, 190). The fragmentation starts with the loss of nitrogen, as was shown by high-resolution mass spectrometry (72). Labeling with ^{15}N shows that the nitrogen in the 3-position remains in the molecule. Although Rigterink (72), Stevens (189) and Eckroth (190) formulate the first product of the fragmentation as benzazetone (**50**), Ege (186) excludes this structure but makes no other suggestion for the structure of this fragment. The loss of nitrogen is followed by loss of carbon monoxide.



The preferred conformation of 3-(tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-benzotriazin-4-one was determined by Wagner and his group (187), using the PMR technique.

A large number of papers were published dealing with the isolation and determination of derivatives of 1,2,3-benzotriazin-4-ones, especially of the phosphorylated compounds of type **33k** (181–183, 188, 366, 367, 663–696). Studies on the hydrolysis (365, 657) or determination of the half-lives of these compounds (655, 656) were also reported (see also Chapter IX).

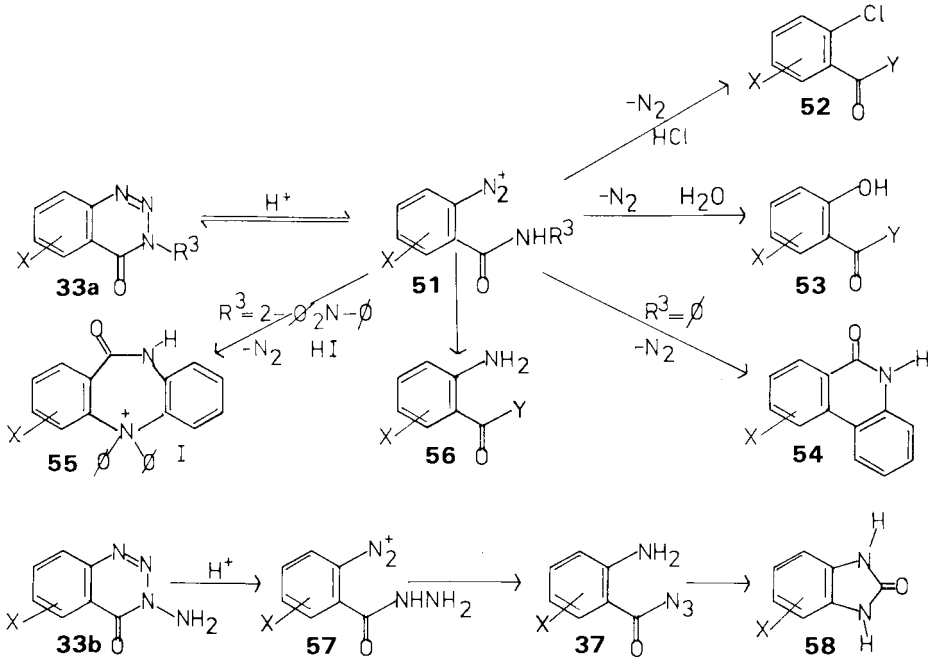
3-Hydroxy-1,2,3-benzotriazin-4-one forms stable complexes with hexafluoroacetone (185); palladium complexes of phosphorylated 1,2,3-benzotriazin-4-ones were reported by Bidleman and Frei (184).

4. *Reactions*

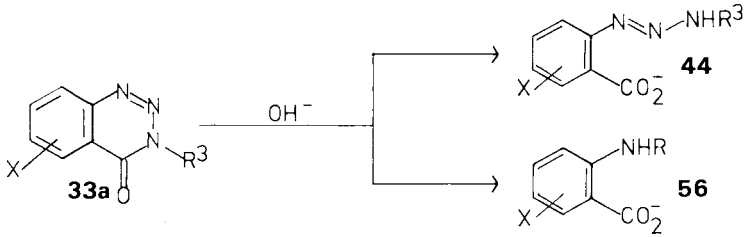
1,2,3-Benzotriazin-4-ones (**33a**) are slightly acidic compounds and easily soluble in aqueous or alcoholic bases; addition of acid to these solutions reprecipitates them unchanged. The preparation of sodium, potassium, silver, or copper salts is reported by various groups (61, 65–66, 94, 98, 176, 177). A number of 1,2,3-benzotriazin-4-ones are soluble in concentrated hydrochloric acid and reprecipitate on addition of water.

Heating 1,2,3-benzotriazin-4-ones (**33a**) in acidic media affords several products, depending on the structure of **33a** and the reaction conditions. Most products can be explained by a reversible ring scission between N-2 and N-3 in strongly acidic media yielding the diazonium ion **51** (68), which can be transformed into the isolated products as 2-chlorobenzoic acid derivatives (**52**) (61, 98, 99, 127), derivatives of salicylic acid (**53**) (61, 79, 96, 98, 112, 194), phenanthridones (**54**) (68, 194), and 4,4-diphenyl-7-oxodihydrodibenzo-1,4-diazepinium iodide (**55**) (101). The isolation of derivatives of anthranilic acid (**56**) from the acidic degradation of **33a** is reported by Kratz (98). The influence of copper bronze on acidic decomposition of **33a** is discussed by Mair and Stevens (79).

3-Amino-1,2,3-benzotriazin-4-ones (**33b**) are primarily transformed by acid into the diazonium ion **57** which then gives anthraniloylazide (**37**) (105, 114, 115). Longer reaction time leads to a Curtius degradation of **37** and benzimidazolones (**58**) were isolated (105, 115).

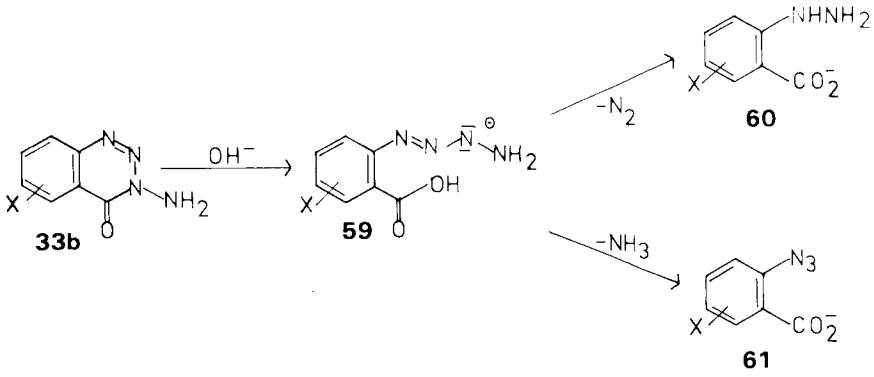


Alkaline degradation of **33a** affords either the triazenes (**44**) (127) or anthranilic acids (**56**) (61, 98, 202).

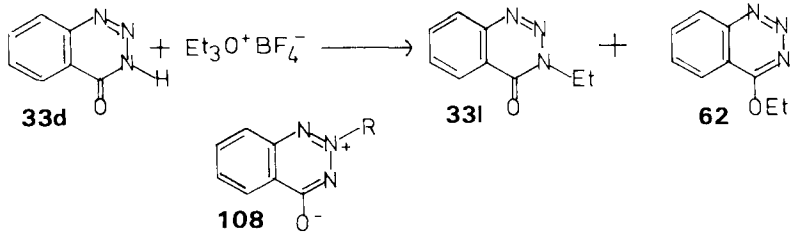


3-Amino-1,2,3-benzotriazin-4-ones (**33b**), hydrolyzed in alkaline solution, decompose by two mechanisms depending on the structure of the compound used (105). Attack of a hydroxyl ion at the carbonyl group of **33b** affords the intermediate **59**, which gives the 2-hydrazinobenzoate (**60**) by a prototropic shift and loss of nitrogen or 2-azidobenzoic acid (**61**) by loss of an amide ion (ammonia) (105, 113, 114).

Alkylation (61, 62, 65–67, 85, 94, 98, 138, 139, 147, 151, 157, 159, 161, 227) and acylation (94, 123, 157, 167) of 1,2,3-benzotriazin-4-ones (**33a**) is reported by many groups. In general substitution occurs at the nitrogen in



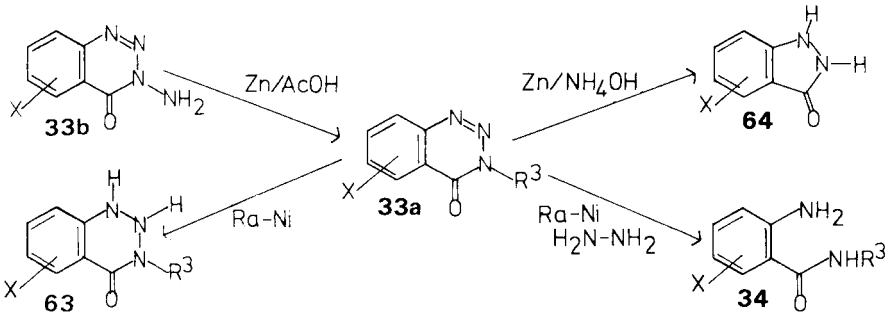
position 3; only a few *O*-alkylated products are known. Alkylation of the unsubstituted 1,2,3-benzotriazin-4-one (**33d**) with triethyloxonium tetrafluoroborate led to a 3:1 mixture of 3-ethyl-1,2,3-benzotriazin-4-one (**33l**) and 4-ethoxy-1,2,3-benzotriazine (**62**) (51). For the formation of 2-alkyl-1,2,3-benzotriazinium betaines (**108**), see Section I-C.



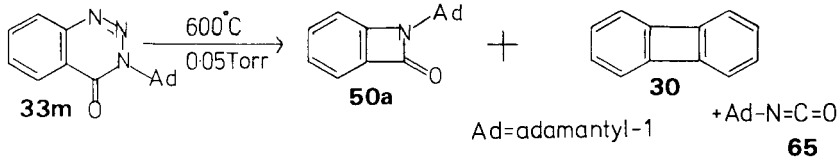
Reduction of 1,2,3-benzotriazin-4-ones (**33a**) with Raney nickel in 95% ethanol at 60°C affords 1,2-dihydro-1,2,3-benzotriazin-4-ones (**63**) (91); Raney nickel and hydrazine in ethanol transform **33a** into anthranilamides (**34**) (79, 125). Stannous chloride in hydrochloric acid converts **33a** into anthranilic acids (127) or anthranilamides (120, 121), or is ineffective (79). Boiling titanous chloride solution converts **33a** into benzamides (96). Reduction of 1,2,3-benzotriazin-4-ones (**33a**) with zinc and ammonia was reported to afford indazolin-3-ones (**64**), but these experiments were not reproducible (94). 3-Substituted 1,2,3-benzotriazin-4-ones seem to be stable to sodium amalgam (127); they are also stable to Adams catalyst (79, 125).

Reduction of 3-amino-1,2,3-benzotriazin-4-one (**33b**) with zinc/acetic acid afforded 1,2,3-benzotriazin-4-one (**33d**) (115) (R^3 = H).

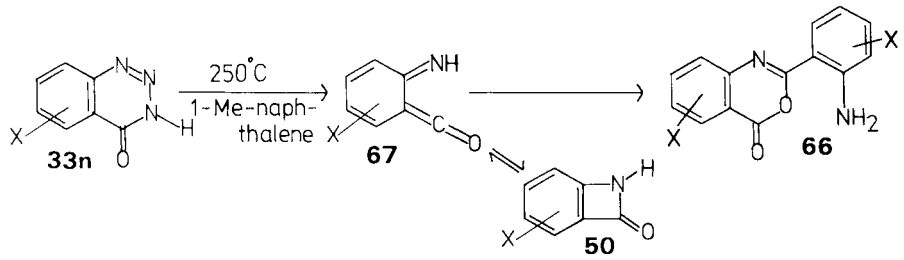
Pyrolysis of 1,2,3-benzotriazin-4-ones (**33a**) is an intensively studied reaction since the intermediate formation of benzazetones (**50**) can be expected. The formation of this intermediate is proved by isolation of the 1-adamantylbenzazetone (**50a**) in addition to biphenylene (**30**) and adamantylisocyanate (**65**) on



vacuum flash pyrolysis of 3-adamantyl-1,2,3-benzotriazin-4-one (**33m**) at 600°C and 0.05 torr (78). The 1-*tert*-butylbenzazetone could not be isolated, but was detected by infrared spectroscopy of the pyrolysate of 3-*tert*-butyl-1,2,3-benzotriazin-4-one (78).

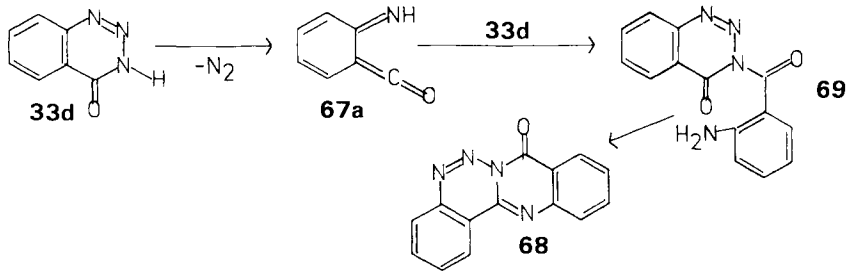


Heating 1,2,3-benzotriazin-4(3*H*)-ones (**33n**) in 1-methylnaphthalene at 250°C led to the isolation of 2-(2-aminophenyl)-3,1-benzoxazin-4-ones (**66**) as the major product (82, 158, 196). The benzoxazinones (**66**) are considered to arise via a Diels–Alder type of cycloaddition of the iminoketenes (**67**) formed by loss of nitrogen from the triazinones (**33n**) across the double bond of a second molecule of the ketene **67**. The postulated imino ketenes (**67**) may be regarded as valence tautomers of the benzazetones (**50**) and could be trapped by reaction with other dienophiles, such as benzine (158), 4-methoxybenzaldehyde (158, 196), or isocyanates (192).

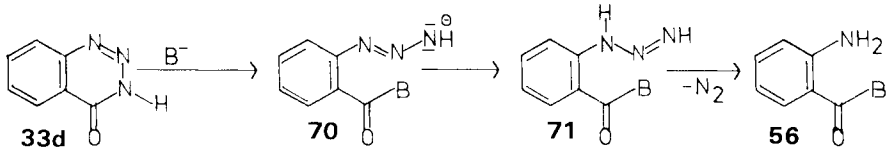


When a solution of 1,2,3-benzotriazin-4-one (**33d**) in diethylene glycol dimethyl ether was heated under reflux for periods of up to 2 hr it yielded

quinazolino[3,2-*c*]1,2,3-benzotriazin-8-one (**68**) in 70% yield (198). For its formation the following mechanism is suggested: addition of one molecule of the starting triazinone (**33d**) to the imino ketene **67a** yields the 3-(2-aminobenzoyl)-1,2,3-benzotriazin-4-one (**69**) which cyclizes to the isolated **68**.

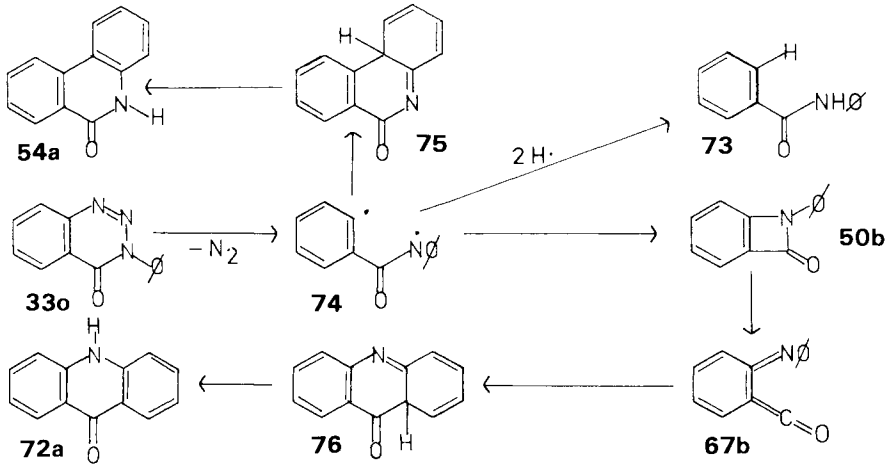


When 1,2,3-benzotriazin-4-one (**33d**) is heated with high-boiling amines, alcohols, phenol, mercaptans, or other nucleophiles, loss of nitrogen is observed and anthranilic acid derivatives or products formed from them are isolated. Since this reaction occurs at temperatures lower than that of the decomposition of **33d** the best explanation is a nucleophilic attack at the carbonyl carbon atom leading to **70** and **71** and loss of nitrogen, affording the anthranilic acid derivatives **56** (198).

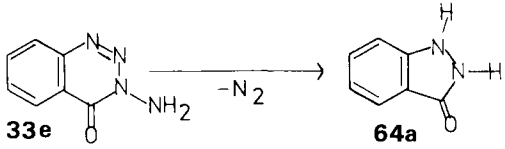


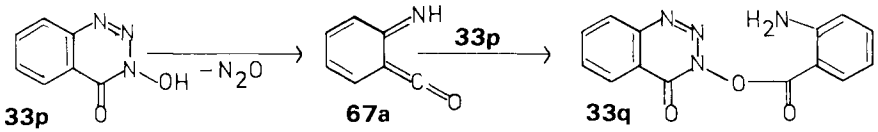
Heating 3-phenyl-1,2,3-benzotriazin-4-one (**33o**) alone up to 285 to 320°C yields 9-acridone (**72a**) and phenanthridin-6-one (**54a**) (81, 195). Heating the same compound in liquid paraffin led to a different, somewhat faster reaction and benzanilide (**73**) was isolated in good yield (81, 195). For this reaction the following general mechanism is suggested: loss of nitrogen from **33o** gives the diradical **74** which may abstract two hydrogens from the solvent to form the benzanilide (**73**) or may cyclize to **75** or the 1-phenylbenzazetone (**50b**). Tautomerization of **75** yields **54a**, whereas ring opening of **50b** and ring closure of the imino ketene **67b** affords **76**, which tautomerizes to the isolated **72a** (81).

Vapour-phase pyrolysis of 3-amino-1,2,3-benzotriazin-4-one (**33e**) affords indazolin-3-one (**64a**) in 80% yield (78). Thermolysis of 3-hydroxy-1,2,3-benzotriazin-4-one (**33p**) led to the isolation of 3-[(2-aminobenzoyl)-oxy]-1,2,3-benzotriazin-4-one (**33q**), the formation of which is explained by the intermediate formation of the imino ketene (**67a**) and its reaction with the



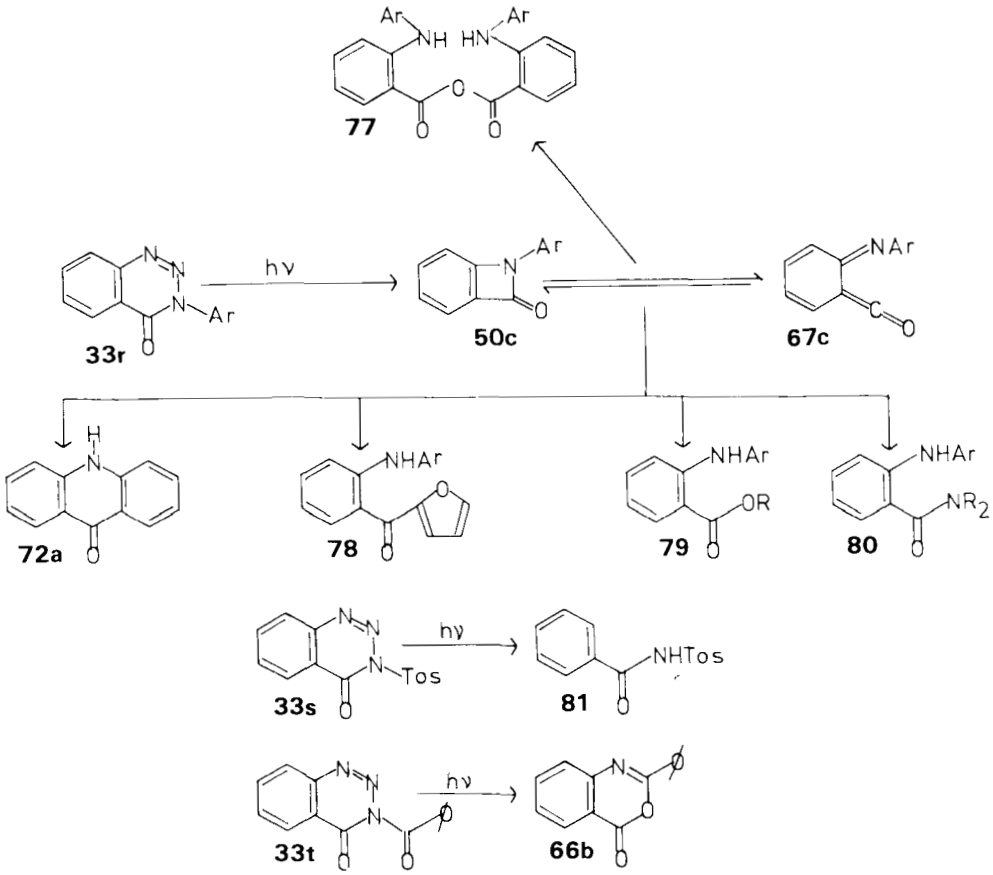
starting material. The intermediate formation of **67a** was proved by trapping it with phenyl isocyanate, *n*-amyl alcohol, or aniline (118).



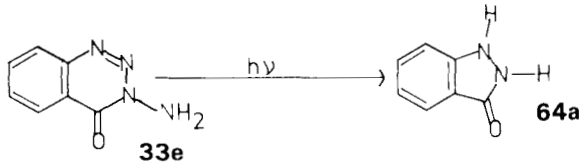


Photolysis of 1,2,3-benzotriazin-4-ones (**33a**) was most intensively studied by Ege and his group (102, 126, 157, 212). Owing to their work and the studies of other groups (78, 79, 82, 197, 202, 213) 3H- and 3-alkyl-1,2,3-benzotriazin-4-ones were found to be stable to irridiation with ultraviolet light. 3-Aryl-1,2,3-benzotriazin-4-ones (**33r**) lose nitrogen and form 1-arylbenzazetones (**50c**), which are valence tautomers with the imino ketenes **67c**. As was shown by photolysis of labeled 1,2,3-benzotriazin-4-ones the nitrogens of positions 1 and 2 are eliminated (126). All isolated products (**72a** and **77–80**) are formed from the intermediates **50c** or **67c**, which could not be isolated but could be shown to exist by spectroscopic measurements (157, 213).

Photolysis of 3-tosyl-1,2,3-benzotriazin-4-one (**33s**) affords *N*-tosylbenzamide (**81**); 2-phenyl-4*H*-3,1-benzoxazin-4-one (**66b**) is isolated from the photolysis of 3-benzoyl-1,2,3-benzotriazin-4-one (**33t**) (157, 212).

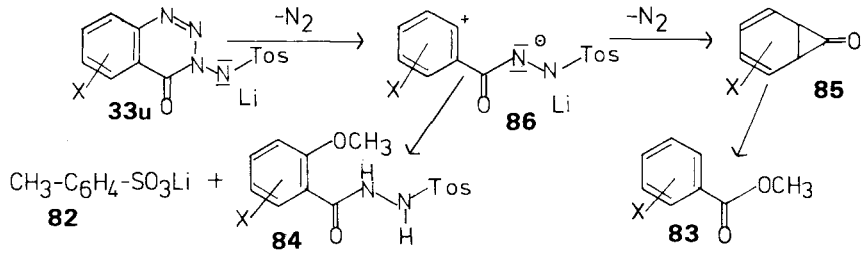


Photolysis of 3-amino-1,2,3-benzotriazin-4-one (**33e**) in acetonitrile resulted in a rapid evolution of nitrogen and the formation of a precipitate, which was shown to be indazolin-3-one (**64a**) (78). When the photolysis was stopped before all the nitrogen had been evolved, only starting material and indazolin-3-one could be detected.

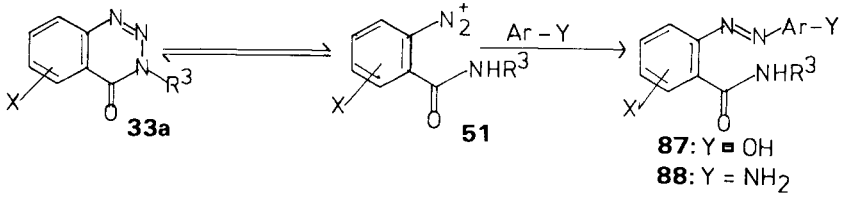


Photolysis of lithium 3-[(4-toluenesulfonyl] amino)-1,2,3-benzotriazin-4-ones (**33u**) in methanol at 40°C gave lithium 4-toluenesulfonate (**82**), methyl

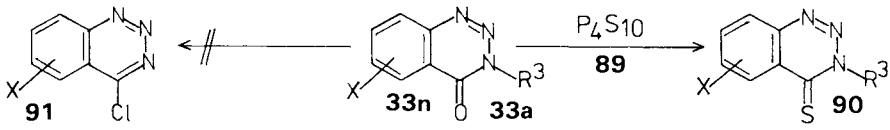
benzoates (**83**), and 2-methoxybenzoic acid 4-toluenesulfonohydrazides (**84**) (104). From these results it was concluded that benzocyclopropenones (**85**) are intermediates in this photochemical process.



1,2,3-Benzotriazin-4-ones (**33a**) behave as masked diazonium compounds (**51**) and couple with phenols or amines (79, 92, 96, 183, 131, 191, 193, 198, 361, 366, 367), to give azo dyes (**87**) (Y = OH) or **88** (Y = NH_2) (Bamberger–Goldberger reaction).

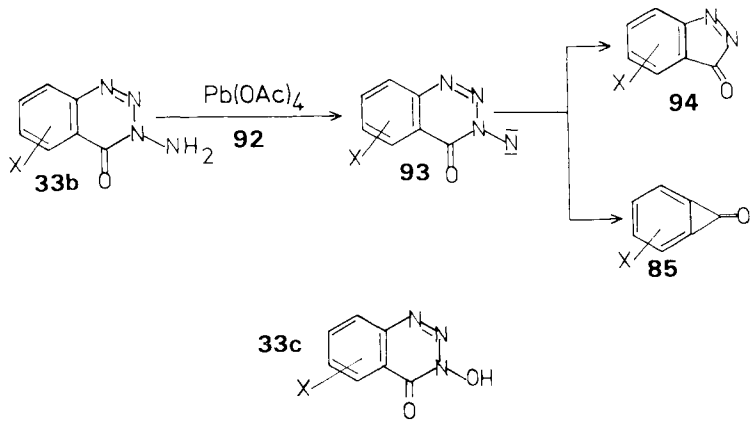


Treatment of 1,2,3-benzotriazin-4-ones (**33a**) with phosphorus pentasulfide (**89**) was used for the synthesis of 1,2,3-benzotriazin-4-thiones (**90**) (159, 161, 201). Attempts to prepare 4-chloro-1,2,3-benzotriazine (**91**) from **33n** (R^3 = H) were unsuccessful (61, 361).

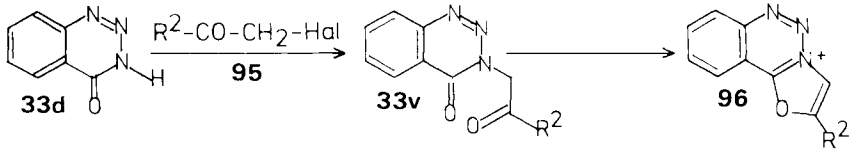


Oxidation of 3-amino-1,2,3-benzotriazin-4-ones (**33b**) with lead tetraacetate (**92**) proceeds by two simultaneous independent routes, which involve the loss of one molecule of nitrogen from the nitrene **93** to form indazolones (**94**) and the loss of two molecules of nitrogen from **93** to form benzocyclopropenones (**85**) (103, 208). These suggested mechanisms were supported by ^{15}N-labeling experiments.

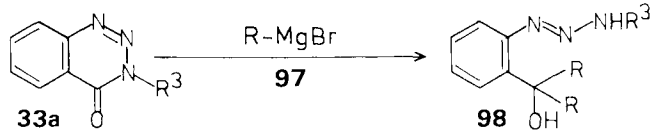
The use of 3-hydroxy-1,2,3-benzotriazin-4-ones (**33c**) in peptide synthesis to prevent racemization is reported by König and Geiger (117, 155, 387, 388), by Jäger (203), and by Heidemann (389).



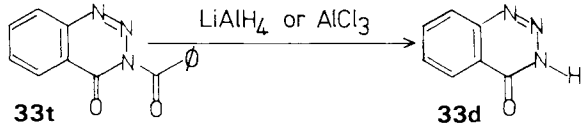
Treatment of the 3-(β-oxoalkyl) derivatives of 1,2,3-benzotriazin-4-ones (**33v**), prepared from **33d** and α-halo ketones (**95**), with cold concentrated sulfuric acid yields the oxazolo[3,2-*c*]1,2,3-benzotriazinium salts (**96**), which were isolated as their fluoroborates and chlorides (227).



Action of Grignard reagents (**97**) upon 3-substituted 1,2,3-benzotriazin-4-ones (**33a**) leads to opening of the heterocyclic ring with formation of the triazenylcarbinols (**98**) (358).



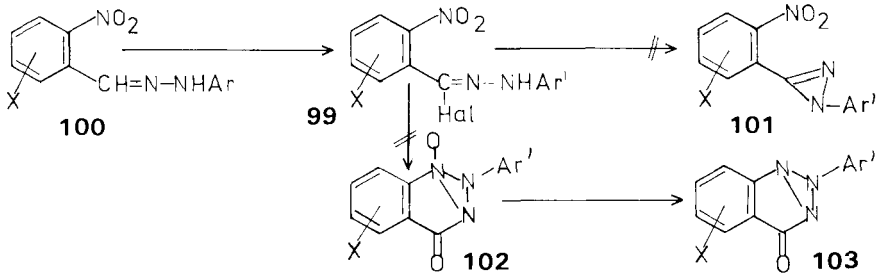
Reaction of 3-benzoyl-1,2,3-benzotriazin-4-one (**33t**) with lithium aluminum hydride or aluminum chloride removes the benzoyl group and the unsubstituted 1,2,3-benzotriazin-4-one (**33d**) is isolated (358).



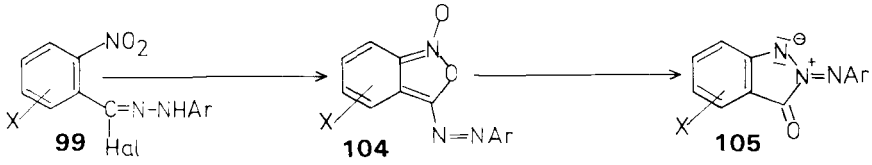
C. 1,2,3-Benzotriazin-4(2*H*)-ones, 1,2,3-Benzotriazinium Betaines

1. *Preparation*

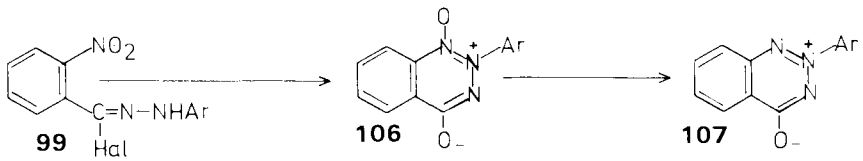
In a series of papers from 1925 to 1935 Chattaway and his co-workers (206, 214–219) reported that halogenation of *o*-nitrobenzaldehyde arylhydrazones (**100**), followed by treatment with base, gives a series of compounds to which they assigned first the isodiazomethane structure (**101**) and later the structure **102**. Reduction of **102** with stannous chloride or heating them in ethanol gave a series of compounds to which they assigned the triaziridine structure, **103**. A compound of structure **102** was also prepared by Parkes and Burney (220).



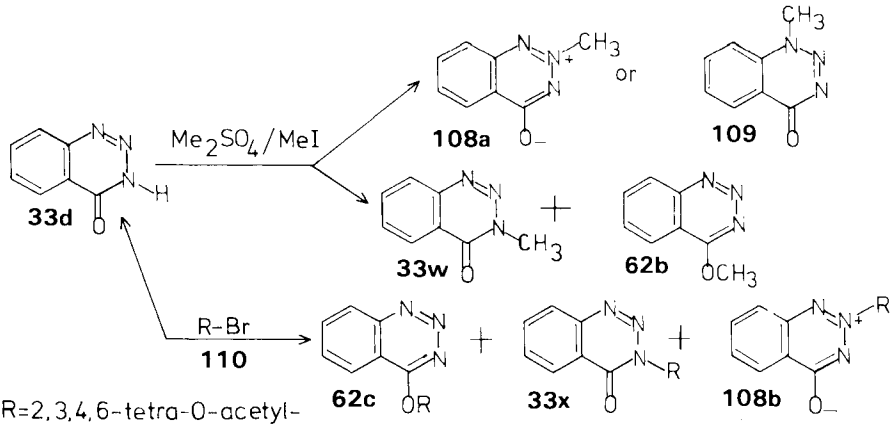
The mentioned reactions were reinvestigated in 1962 by Gibson (221, 222), who proposed the new structures **104** and **105** for the compounds prepared by Chattaway and his group and by Parkes and Burney. The proposal for the new structures were based mainly on the theory of 1,3-dipolar cycloaddition reactions and infrared spectroscopic studies.



From new spectroscopic data Kerber (223, 224) in 1972 showed that the discussed compounds have neither the proposed triaziridine structures **102** and **103** nor the structures **104** and **105** suggested by Gibson, but are in fact the azimines **106** and **107** (1,2,3-benzotriazinium betaines). The conclusions of Kerber were unambiguously confirmed in 1974 by McKillop and Kobylecki (138), who were able to prepare the 1,2,3-benzotriazinium betaines by an alternative route.

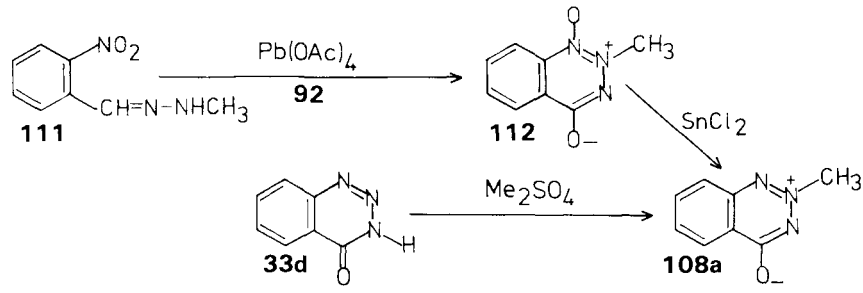


Wagner and Gentzsch (161) in 1968 reported the alkylation of 1,2,3-benzotriazin-4-one (**33d**) with dimethyl sulfate or methyl iodide and isolated besides 4-methoxy-1,2,3-benzotriazine (**62b**) and 3-methyl-1,2,3-benzotriazin-4-one (**33w**) a third product which they formulated as the 2-methyl-1,2,3-benzotriazinium betaine (**108a**) but were not able to exclude the possibility of the 1-methyl-1,2,3-benzotriazin-4-one structure (**109**). Reaction of **33d** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**110**) again gave three products, the *O*-alkylated compound (**62c**), the *N*-3-alkylated product (**33x**), and the 1,2,3-benzotriazinium betaine **108b** (159).

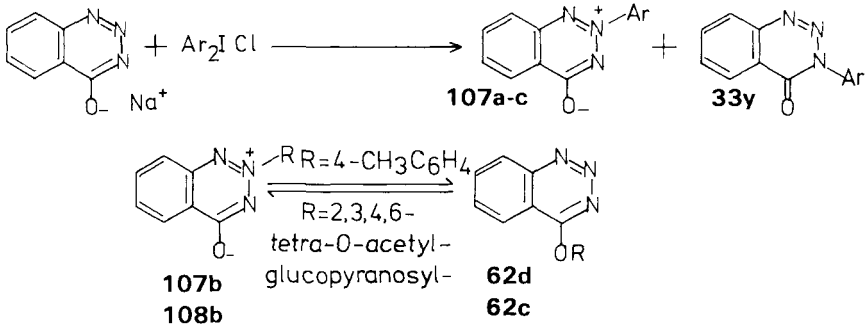


McKillop and Kobylecki (138) found that the 2-methyl-1,2,3-benzotriazinium betaine (**108a**) could be prepared in 71% yield from **33d** and dimethyl sulfate when the reaction conditions used by Wagner and Gentzsch were modified slightly. That the methylation occurs at N-2 was demonstrated by synthesizing **108a** through oxidation of 2-nitrobenzaldehyde methylhydrazone (**111**) with lead(IV) acetate (**92**) and reduction of the formed 2-methyl-1,2,3-benzotriazinium betaine *N*-oxide (**112**) with stannous chloride.

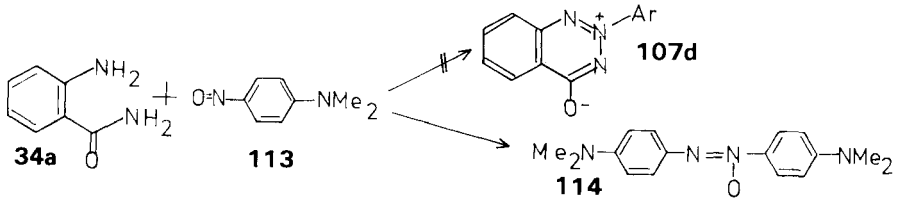
McKillop and Kobylecki (138) also prepared three 2-aryl-1,2,3-benzotriazinium betaines (**107a** to **107c**) by reaction of the sodium salt of **33d** with diaryliodonium chlorides. In these reactions arylation occurred exclusively or mainly at N-2; only in one case was arylation at N-3 observed. Heating the 2-(*p*-tolyl)-1,2,3-benzotriazinium betaine (**107b**) for 1 hr at 120°C/0.1 mm gave

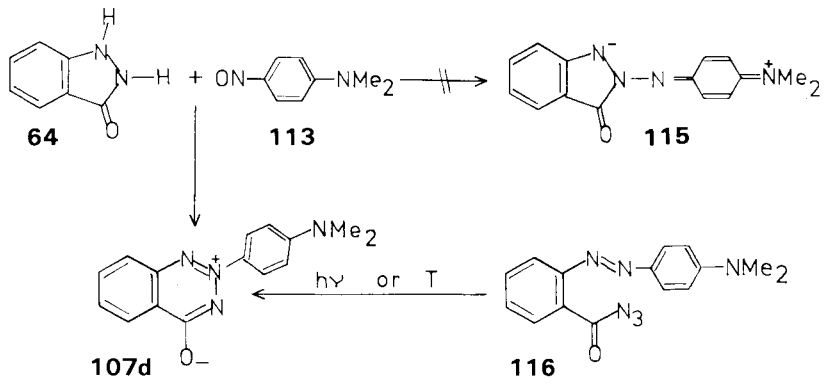


a 50% yield of the 4-(*p*-tolyloxy)-1,2,3-benzotriazine (**62d**). This result is contrary to the observation of Wagner and Gentzsch (159), who were able to rearrange the compound **62c** into the betaine **108b** by heating it in toluene.



In 1956 Jennen (226) claimed to have prepared the betaine **107d** (Ar = 4-Me_2N-C_6H_4) by reaction of anthranilamide (**34a**) with *p*-nitroso-*N*,*N*-dimethylaniline (**113**), but Kerber (223) later showed that the given structure was incorrect and the isolated product was in fact the 4,4′-bis(dimethylamino)-azoxybenzene (**114**). On the other hand, Jennen (225, 226) condensed indazolinone (**64**) with **113** and isolated a product formulated as **115**. Kerber has shown (223) that this product should be formulated as **107d** instead of **115**. He also tried to prepare **107d** through photolysis or thermolysis of 2-{[4-(dimethylamino)phenyl]azo}benzazide (**116**) but the yields were very low (3.5%) (223, 224).





2. *Compound Survey*

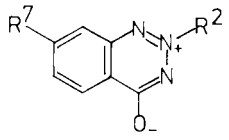
Table IV-3 lists the compounds in this class that have been reported in the literature.

3. *Physical Properties and Reactions*

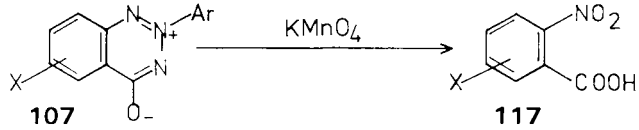
The known 1,2,3-benzotriazinium betaines (**107, 108**) are colorless or pale yellow, relatively inert, crystalline compounds with high melting points. Only the 2-[4-(dimethylamino)phenyl]-1,2,3-benzotriazinium betaine (**107d**) is reported to be blue. Infrared, ultraviolet, PMR, and mass spectroscopic data have been reported by various groups (138, 159, 161, 221–224). Studies by McKillop and Kobylecki (138) have shown that neither infrared nor PMR spectroscopy can be used for the structural assignment of these compounds. In the very complex infrared spectra a band is observed in the CO double bond region between 1630 and 1675 cm^{-1}. In the mass spectra of **107** and **108** a prominent parent peak and intensive peaks for $M^+ - 28$ (N_2 or CO) and $M^+ - 56$ (N_2 + CO) were observed. The following ultraviolet spectrum is reported for the 2-methyl-1,2,3-benzotriazinium betaine (**108a**) (138): $\lambda_{max}(\log \epsilon) = 335$ (3.86), 276 sh (3.43), 266 sh (2.53), 250 sh (3.82), 238 (4.00), 231 (4.01), and 212 nm (4.02).

1,2,3-Benzotriazinium betaines (**107, 108**) seem to be stable toward irridation with ultraviolet light (224); they are not affected by treatment with hydrogen peroxide in acetic, trifluoroacetic, or concentrated sulfuric acid, with peracetic acid, or with *m*-chloroperbenzoic acid (138). Oxidation with potassium permanganate led to the isolation of 2-nitrobenzoic acids (**117**) (206).

TABLE IV-3. 1,2,3-BENZOTRIAZIN-4(2*H*)-ONES, 1,2,3-BENZOTRIAZINIUM BETAINES



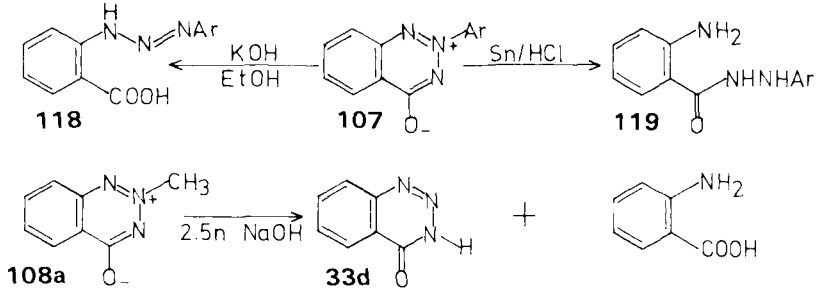
R^2	R^7	m.p. (°C)	Refs.
CH_3	H	122–123 (fast)	138
		139–140	161
		143–145 (slow)	138
β-D-Glucopyranosyl	H	230	159
Tetra-*O*-acetyl-β-D-glucopyranosyl	H	178–181	159
C_6H_5	H	116–118.5	138
4-CH_3–C_6H_4	H	165–167	138
4-Br–C_6H_4	H	197	206
		199–200	223
		199–201	138
4-O_2N–C_6H_4	H	244–245	138
4-CH_3O–C_6H_4	H	193–194	138
4-$(CH_3)_2N$–C_6H_4	H	198	226
		199–200	223, 224
2-CH_3–4-Br–C_6H_3	H	181	216
4-CH_3–2-Cl–C_6H_3	H	173	215
4-CH_3–2,6-$Cl_2C_6H_2$	H	202	215
4-CH_3–2-Br–C_6H_3	H	166	214
4-CH_3–2-Br–C_6H_3	NO_2	250	217
4-CH_3–2,6-$Br_2C_6H_2$	H	190 (dec.)	214
4-CH_3–2,6-$Br_2C_6H_2$	NO_2	279	217
2,4-$Cl_2C_6H_3$	H	157 (labile)	206
		167 (stable)	206
2,4,6-$Cl_3C_6H_2$	H	258	206
2,4-$Br_2C_6H_3$	H	178	206
		181–182	222



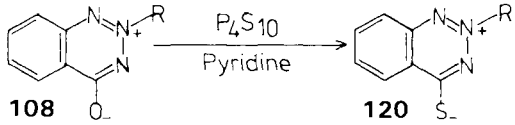
107 **117**

1,2,3-Benzotriazinium betaines are stable toward acids, halogens, and acetic anhydride (206); they show feebly basic properties and form salts that are very easily hydrolyzed. Treatment with potassium hydroxide leads to the formation of *N*-arylazoanthranilic acids (**118**) (206). Hydrolysis of the 2-methyl deriv-

ative (**108a**) with 2.5 *N* NaOH is reported to give 1,2,3-benzotriazin-4-one (**33d**) and anthranilic acid (161). Reduction of **107** with tin in hydrochloric acid affords anthraniloyl arylhydrazides (**119**) (206, 223).



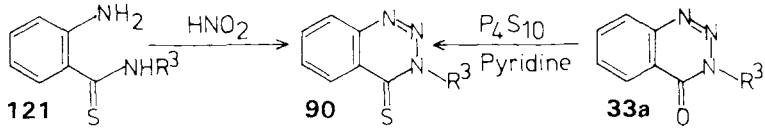
Rearrangement of **107b** into **62d** is reported by McKillop and Kobylecki (Ref. 138, p. 63/64). Transformation of two 1,2,3-benzotriazinium betaines (**108**) into their thio analogues (**120**) by reaction with phosphorus pentasulfide in pyridine is reported by Wagner and Gentzsch (159, 161).



D. 1,2,3-Benzotriazine-4-thiones, 4-Mercapto-1,2,3-benzotriazines, and Related Betaines

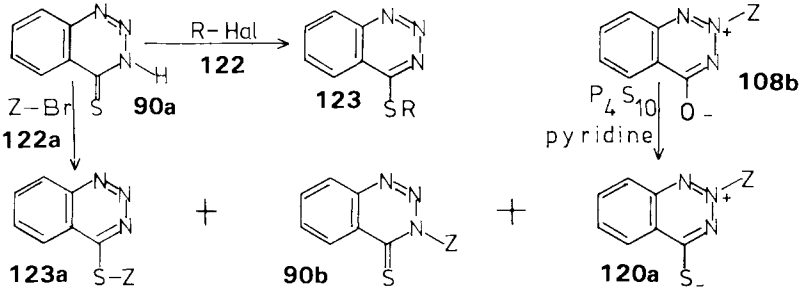
1. *Preparation*

Just as reaction of anthranilamide with nitrous acid is used for the synthesis of 1,2,3-benzotriazin-4-ones, diazotization of anthranilthioamides (**121**) affords 1,2,3-benzotriazine-4-thiones (**90**) in good yields (51, 134, 204). The second method for the preparation of **90** is the thionation of 1,2,3-benzotriazin-4-ones (**33a**) with phosphorus pentasulfide in pyridine (159, 161, 201).



Alkylation of 1,2,3-benzotriazine-4(3*H*)-thiones (**90a**) with alkyl halides (**122**) in alkaline media is used for the synthesis of 4- (alkylmercapto)-

1,2,3-benzotriazines (**123**) (51, 134, 159, 161, 227, 230). Reaction of **90a** with tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**122a**) in acetone/water in the presence of sodium hydroxide affords three products, the *S*-substitution product (**123a**), the *N*-3-substitution product (**90b**), and the 1,2,3-benzotriazinium betaine **120a** (159). **120a** was also prepared by reaction of the benzotriazinium betaine **108b** with phosphorus pentasulfide in pyridine (161).

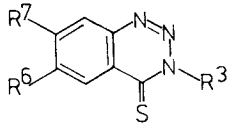


2. *Compound Survey*

The compounds of this group that have been reported in the literature are listed in Table IV-4.

TABLE IV-4. 1,2,3-BENZOTRIAZINE-4-THIONES

A. 1,2,3-Benzotriazine-4(3H)-thiones



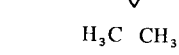
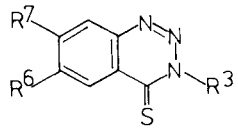
R^3	R^6	R^7	m.p. (°C)	Refs.
H	H	H	187.5	134
			195–196	161
			205–206	51
H	H	Cl	205 (dec.)	227
			215–217 (dec.)	204
H	Cl	H	207 (dec.)	227
CH_3	H	H	107–108	161
β-D-Glucopyranosyl	H	H	128–130	159
Tetra-*O*-acetyl-β-D-glucopyranosyl	H	H	141–143	159
CH_2OOC—  —$CH{=}CMe_2$	H	H	Syrup	171

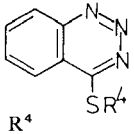
TABLE IV-4. (*continued*)

A. 1,2,3-Benzotriazine-4(3*H*)-thiones



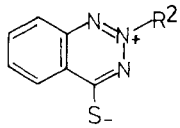
R^3	R^6	R^7	m.p. (°C)	Refs.
$CH_2-S-P(S)(CH_3)_2$	H	H		201
$CH_2-S-P(S)C_2H_5(OC_2H_5)$	H	H		201
$CH_2-S-P(S)(OCH_3)_2$	H	H	102–103	201
$CH_2-S-P(S)(OC_2H_5)_2$	H	H	84	201
CH_3-CO	H	H	144 (dec.)[a]	134
C_6H_5-CO	H	H	163 (dec.)[a]	134

B. 4-Mercapto-1,2,3-benzotriazines



R^4	m.p. (°C)	Refs.
CH_3	100–101	51
	101–103	134, 161
$CH_2-CH=CH_2$	85–87	230
$CH_2-CO-CH_3$		227
$CH_2-CO-C_6H_5$	175	51/227
$CH_2-CO-C_6H_4-Br(4)$		227
CH_2-COOH	163–165 (dec.)	51
$CH_2-COOC_2H_5$	139	51
$CH_2-C_6H_5$	109–110	51
Tetra-*O*-acetyl-β-D-glucopyranosyl	149–150	159
$2,4,6-(O_2N)_3C_6H_2$	185 (dec.)	51

C. 1,2,3-Benzotriazinium betaines

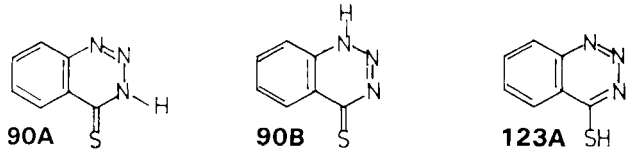


R^2	m.p. (°C)	Refs.
CH_3	197–199	161
C_2H_5	190–192	161
β-D-Glucopyranosyl	188–190	159
Tetra-*O*-acetyl-β-D-glucopyranosyl	156–159	159

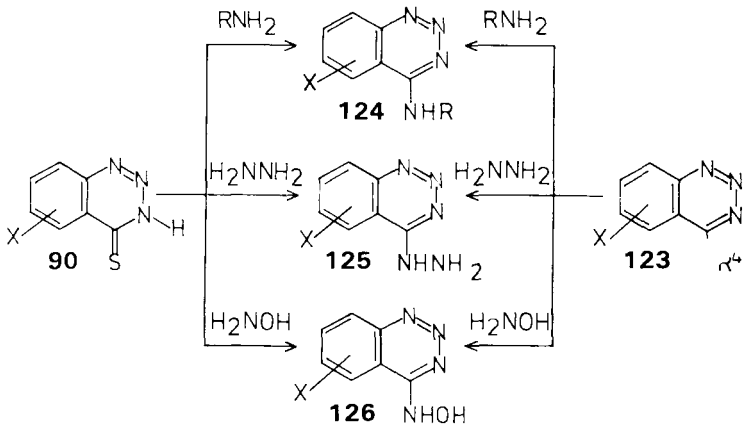
[a]Structure not fully established.

3. *Physical Properties and Reactions*

1,2,3-Benzotriazine-4-thiones (**90**) and 4-mercapto-1,2,3-benzotriazines (**123**) are mostly colored compounds (yellow, orange, red) of acidic character. Compounds **90** are soluble in bases and give deeply colored solutions. At present only a few spectroscopic data are available (159, 161, 187, 228–229). The solid-state infrared spectrum of **90a** shows absorption at 3100 cm^{-1}, which suggests that in the solid state the thiono form **90A** or **90B**, not the thiol form, **123A**, predominates. The ultraviolet spectrum of 4-(methylmercapto)-1,2,3-benzotriazine shows the following absorption maxima: $\lambda_{max}(\log \epsilon) = 316$ (3.92), and 261 nm (3.65) (229). The preferred conformation of 3-(tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-benzotriazine-4-thione was determined by Wagner and his group, using the PMR technique (187).

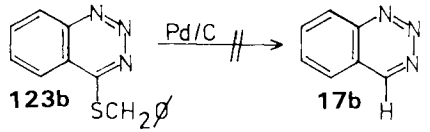


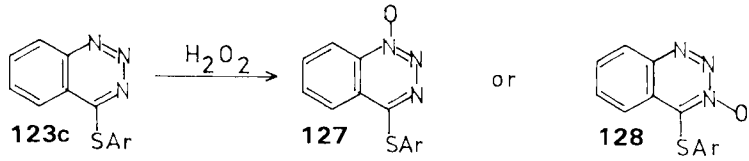
Alkylation of **90** has been discussed already. Rearrangement of an *S*-substituted compound (**123a**) in benzene in the presence of mercury bromide into the two *N*-substituted compounds **90b** and **120** is reported by Wagner and Gentzsch (159). 1,2,3-Benzotriazine-4-thiones (**90**) and 4-mercapto-1,2,3-benzotriazines (**123**) can be transformed into 4-amino- (**124**) (50, 204, 228), 4-hydrazino- (**125**) (50, 51, 204, 228), or 4-(hydroxylamino)-1,2,3-benzotriazines (**126**) (50) by reaction with amines, hydrazine, or hydroxylamine, respectively.



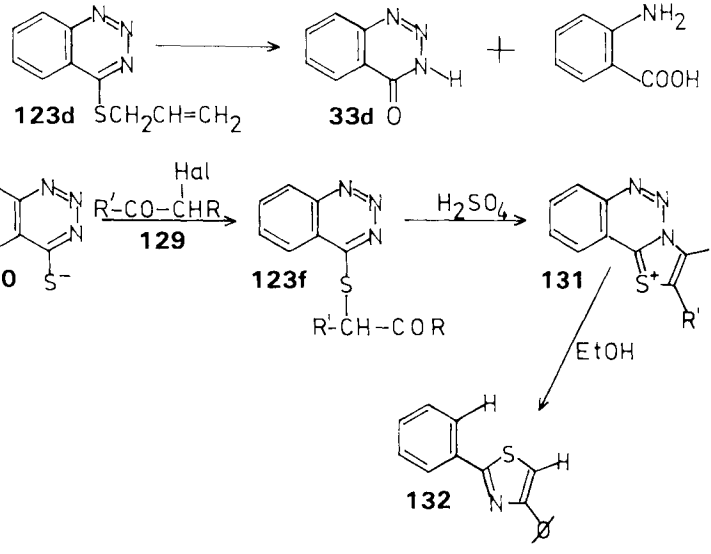
Attempts to prepare the unsubstituted 1,2,3-benzotriazine (**17b**) through

treatment of 4-(benzylmercapto)-1,2,3-benzotriazine (**123b**) with palladium on charcoal failed (51). Several attempts to oxidize *S*-substituted derivatives (**123**) failed to give identifiable products, an exception being the 4-[(2,4,6-trinitrophenyl)thio]-1,2,3-benzotriazine (**123c**) which afforded a product with hydrogen peroxide, which is formulated as one of the two possible *N*-oxides (**127** or **128**) from infrared and mass spectroscopic studies (51).





Treatment of 4-(allylmercapto)-1,2,3-benzotriazine (**123d**) with Claisen alkali led to the isolation of 1,2,3-benzotriazin-4-one (**33d**) and anthranilic acid (230). The keto sulfides (**123f**) prepared by the reaction of α-halo ketones (**129**) with the anion of 4-mercapto-1,2,3-benzotriazine (**130**) were cyclized by cold concentrated sulfuric acid treatment to the thiazolo[3,2-*c*]triazinium salts (**131**) (227). Prolonged treatment of the monophenyl compound (**131a**) ($R' = H$, $R = C_6H_5$) under reflux with aqueous ethanol afforded 2,4-diphenylthiazole (**132**), unambiguously demonstrating that the original alkyl derivatives were *S*-alkyl compounds (**123**) and not *N*-alkyl derivatives (227).



E. 4-Amino-1,2,3-benzotriazines, 4-Imino-1,2,3-benzotriazines, and Related Betaines

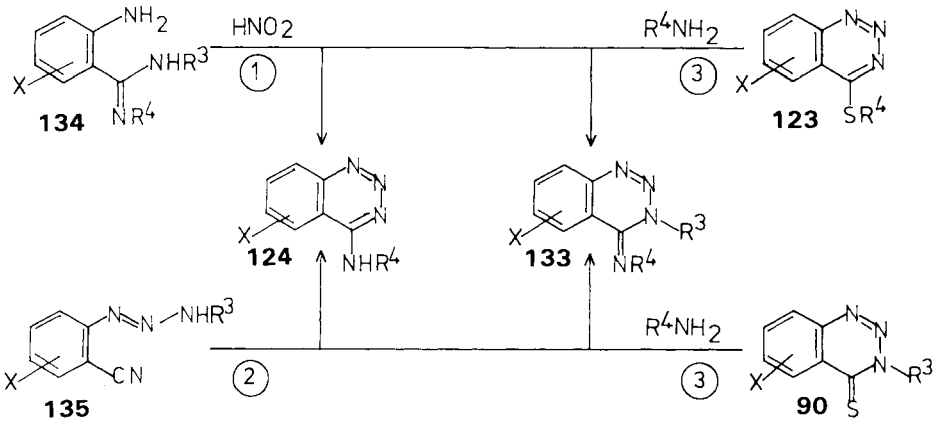
1. *Preparation*

Three methods were reported for the synthesis of 4-amino-1,2,3-benzotriazines (**124**) and their isomeric 4-imino-1,2,3-benzotriazines (**133**) (50, 83, 125, 200, 204, 228, 229, 231–233, 235):

1. Cyclization of 2-aminobenzamidines (**134**) with nitrous acid (50, 125, 231, 232).

2. Cyclization of 1-aryl-3-(2-cyanophenyl)triazenes (**135**) in boiling aqueous ethanol, ethanol/piperidine, or aqueous acid (83, 200, 229, 232, 235).

3. Reaction of 1,2,3-benzotriazines-4-thiones (**90**) or 4-mercapto-1,2,3-benzotriazines (**123**) with amines (50, 204, 228, 229).

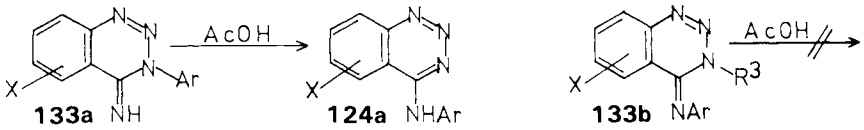


Depending on the structure of the starting materials (**90, 123, 134, 135**) and the reaction conditions, either **124** or **133** or both compounds were isolated.

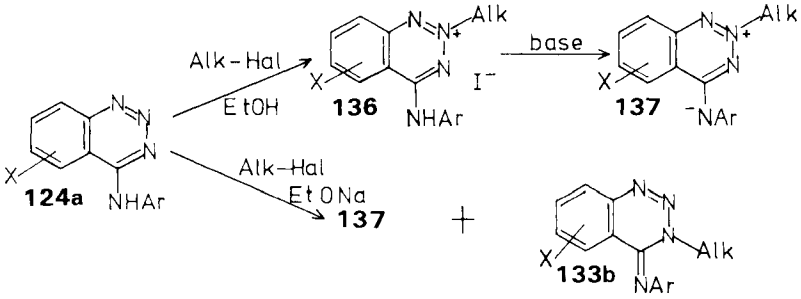
If R^3 in **135** is an electron-donating or a mildly electron-withdrawing substituent **133** is obtained, whereas compounds **135** in which R^3 is a strongly electron-withdrawing group afford **124**. Rearrangement of **133a** to the isomeric **124a** has been effected by heating in 95% ethanol, hydrochloric acid, or preferably, in acetic acid (235). 3-Substituted 4-(arylamino)-1,2,3-benzotriazines (**133b**) are stable in acetic acid.

1,2,3-Benzotriazine-4-thiones (**90**) react only with alkylamines; for reactions with arylamines the use of **123** is necessary.

Alkylation of 4-(arylamino)-1,2,3-benzotriazines (**124a**) with alkyl iodines in ethanol affords the 2-alkyl-4-(arylamino)-1,2,3-benzotriazinium iodides (**136**)



which on basification yield the deep red 2-alkyl-4-(arylamino)-1,2,3-benzotriazinium betaines (**137**) (200). In contrast alkylation of **124a** with alkyl iodides in sodium ethoxide solution affords a mixture of the isomeric 2-alkyl-4-(arylimino)-1,2,3-benzotriazinium betaines (**137**) and 3-alkyl-4-(arylimino)-1,2,3-benzotriazines (**133b**) (200).

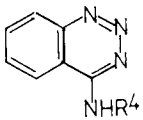


2. *Compound Survey*

Table IV-5 lists the compounds of this type that have been reported in the literature.

TABLE IV-5. 4-AMINO- AND 4-IMINO-1,2,3-BENZOTRIAZINES AND RELATED BETAINES

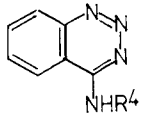
A. 4-Amino-1,2,3-benzotriazines

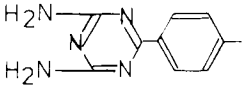


R^4	m.p. (°C)	Refs.
H	266 (dec.)	50
	284–285	204
Hydrochloride	160–163 (dec.)	204
Picrate	237–238 (dec.)	50
Methiodide	216–217 (dec.)	50
$C_6H_5-CH_2$	207–209 (dec.)	229, 235
$C_6H_5-CH_2CH_2$	202–204 (dec.)	229, 235

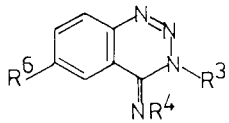
TABLE IV-5. (*continued*)

A. 4-Amino-1,2,3-benzotriazines



R^4	m.p. (°C)	Refs.
C_6H_5	200–201 (dec.)	229, 235
	201 (dec.)	232
2-CH_3–C_6H_4	163–164 (dec.)	229, 235
4-CH_3–C_6H_4	207–208 (dec.)	235
4-C_2H_5–C_6H_4	176–177 (dec.)	235
2-Cl–C_6H_4	168–169 (dec.)	229, 235
2-O_2N–C_6H_4	207–209 (dec.)	229
3-O_2N–C_6H_4	244–245 (dec.)	229, 235
4-O_2N–C_6H_4	237–238 (dec.)	229
3-NC–C_6H_4	242–243 (dec.)	229, 235
4-NC–C_6H_4	229–230 (dec.)	229
2-H_2N–C_6H_4	194–195 (dec.)	229
3-H_2N–C_6H_4	206–207 (dec.)	229
4-H_2N–C_6H_4	216–218 (dec.)	229
	259–260 (dec.)	83, 235

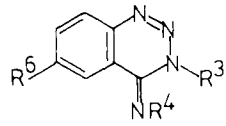
B. 4-Imino-1,2,3-benzotriazines

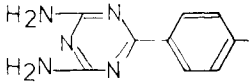


R^3	R^4	R^6	m.p. (°C)	Refs.
H	*n*-C_4H_9	H	153–155	228
H	*n*-C_4H_9	Cl	198	228
H	$CH_2CH_2N(C_2H_5)_2$	H	130–132	228
H	$CH_2CH_2N(C_2H_5)_2$	Cl	181–182	228
H	$CH_2CH_2CH_2OC_2H_5$	H	112–114	228
H	$CH_2CH_2CH_2O$-*n*-C_6H_{13}	H	95–97	228
H	C_6H_5–CH_2	H	204–205	228
H	C_6H_5–CH_2	Cl	201–204	228
H	4-CH_3O–C_6H_4–CH_2	H	205–207	228
H	4-Cl–C_6H_4–CH_2	H	213–214	228
H	C_6H_5–CH_2CH_2	H	200–202	228
H	C_6H_5–$CH_2CH_2CH_2$	H	145–147	228
CH_3	C_6H_5	H	130–131	200
			131–132[a]	232

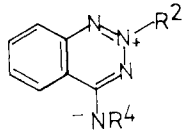
TABLE IV-5. (*continued*)

B. 4-Imino-1,2,3-benzotriazines (*continued*)



R^3	R^4	R^6	m.p. (°C)	Refs.
CH_3	2-Cl–C_6H_4	H	99–101	200
CH_3	2-O_2N–C_6H_4	H	147–148	200
C_2H_5	C_6H_5	H	83–84[a]	232/200
C_2H_5	2-Cl–C_6H_4	H	112–114	200
C_2H_5	2-O_2N–C_6H_4	H	123–124	200
i-C_3H_7	C_6H_5	H	76–77[a]	232/200
C_6H_{11}	C_6H_5	H	94–95[a]	232
C_6H_5–CH_2	H	H	119–120	229, 232 235
C_6H_5	H	H	112–114	229, 232
C_6H_5	C_6H_5	H	139–140	231
2-CH_3–C_6H_4	H	H	100–101	229
4-CH_3–C_6H_4	H	H	103–104	235
4-CH_3–C_6H_4	4-CH_3–C_6H_4	CH_3	145	231
4-C_2H_5–C_6H_4	H	H	112–113	235
2-Cl–C_6H_4	H	H	137–138	229
3-O_2N–C_6H_4	H	H	230–231 (dec.)	229
3-NC–C_6H_4	H	H	224–226 (dec.)	229
4-CH_3O–C_6H_4	4-CH_3O–C_6H_5	H	123–124	232
4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	CH_3O	122–123	231
		H	214–215 (dec.)	83

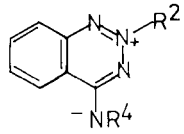
C. 1,2,3-Benzotriazinium betaines



R^2	R^4	m.p. (°C)	Refs.
CH_3	C_6H_5	130–131	200
·HI		219–220 (dec.)	200/236
CH_3	4-CH_3–C_6H_4 ·HI		236
CH_3	2-Cl–C_6H_4	157–158	200
·HI		196–198	200
CH_3	2-O_2N–C_6H_4	199–200	200
·HCl		202–203 (dec.)	200

TABLE IV-5. (*continued*)

C. 1,2,3-Benzotriazinium betaines



R^2	R^4	m.p. (°C)	Refs.
CH_3	2-NC–C_6H_4	180–181	200
CH_3	4-NC–C_6H_4	202–203	200
·HI		212–214	200
CH_3	C_6H_5–CH_2 ·HI		236
CH_3	C_6H_5–CH_2CH_2 ·HI		236
C_2H_5	C_6H_5	64–65	200
·HI		199–200	200/236
C_2H_5	4-CH_3–C_6H_4 ·HI		236
C_2H_5	2-Cl–C_6H_4	101–102	200
·HI		197–198 (dec.)	200
C_2H_5	2-O_2N–C_6H_4	125–126	200
·HI		184–186 (dec.)	200
·HCl·H_2O		172–173 (dec.)	200
C_2H_5	2-NC–C_6H_4	134–135	200
C_2H_5	C_6H_5–CH_2 ·HI		236
C_2H_5	C_6H_5–CH_2CH_2 ·HI		236
n-C_3H_7	C_6H_5 ·HI		236
n-C_3H_7	4-CH_3–C_6H_4 ·HI		236
n-C_3H_7	2-O_2N–C_6H_4	112–113	200
n-C_3H_7	C_6H_5–CH_2 ·HI		236
n-C_3H_7	C_6H_5–CH_2CH_2 ·HI		236
i-C_3H_7	C_6H_5 ·HI		236
i-C_3H_7	4-CH_3–C_6H_4 ·HI		236
i-C_3H_7	2-O_2N–C_6H_4	86–87	200
i-C_3H_7	C_6H_5–CH_2 ·HI		236
i-C_3H_7	C_6H_5–CH_2CH_2 ·HI		236
n-C_4H_9	C_6H_5 ·HI		236
n-C_4H_9	4-CH_3–C_6H_4 ·HI		236
n-C_4H_9	C_6H_5–CH_2 ·HI		236
n-C_4H_9	C_6H_5–CH_2CH_2 ·HI		236
n-C_5H_{11}	C_6H_5 ·HI		236
n-C_5H_{11}	4-CH_3–C_6H_4 ·HI		236
n-C_5H_{11}	C_6H_5–CH_2 ·HI		236
n-C_5H_{11}	C_6H_5–CH_2CH_2 ·HI		236

[a]Structure given is incorrect (200).

3. *Physical Properties*

Most known 4-amino-1,2,3-benzotriazines (**124**) and 4-imino-1,2,3-benzotriazines (**133**) are crystalline, colored (yellow, ochre, brown) compounds; the 1,2,3-benzotriazinium betaines (**137**) are red. Infrared, ultraviolet, PMR, and mass spectroscopic data are reported for the three classes of compounds (83, 189, 200, 228, 229, 232).

The infrared spectra of all 4-anilino-1,2,3-benzotriazines (**124a**) show a strong absorption at $1145 \pm 10\ cm^{-1}$ which is absent in the 3-aryl-4-imino isomers (**133a**) and represents a useful aid in identification (229). Less helpful are the PMR spectra. The ultraviolet and visible spectra of **124**, **133**, and **137** are quite different. **133a** show characteristic double peaks in the ranges 260 to 270 and 305 to 320 nm whereas **124** have only one absorption in each region (229). The following spectra are given for 3-phenyl-4-imino-1,2,3-benzotriazine: $\lambda_{max}(\log \epsilon) = 318$ (3.77), 307 (3.76), 268 (3.96), and 260 nm (3.97). For 4-anilino-1,2,3-benzotriazine: 333 (4.00) and 273 nm (3.76) (229). 3-Alkyl-4-(arylimino)-1,2,3-benzotriazines (**133b**) have only one absorption maximum in the 305 to 320 nm region (200).

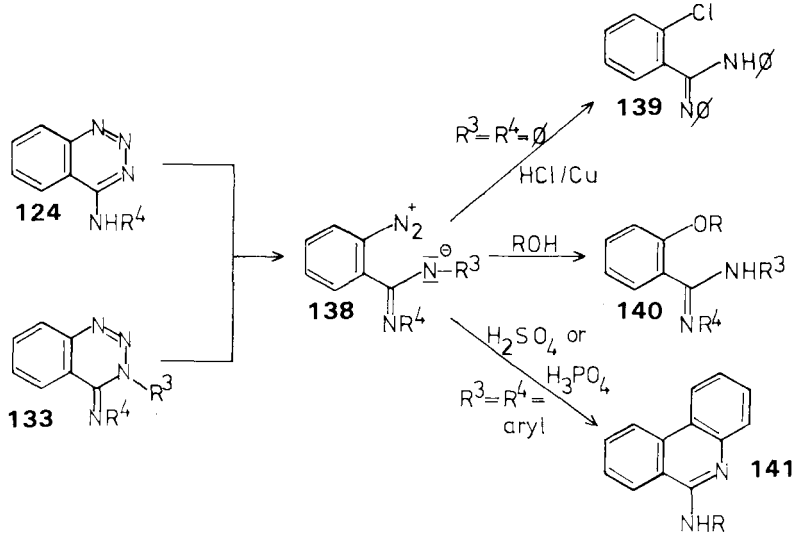
Gilbert and Veldhuis (228) used infrared spectroscopy to distinguish between 4-(alkylamino)-1,2,3-benzotriazines and 4-(alkylimino)-1,2,3-benzotriazines and came to the conclusion that most of their compounds have the imino structure in the solid state.

Ultraviolet and visible spectra of the 1,2,3-benzotriazinium betaines (**137**) are reported by Stevens and Stevens (200). They show up to six absorption maxima; the third and sixth are not observed in all compounds. The following spectra is published for the 2-methyl-4-[(2-chlorophenyl)imino]-1,2,3-benzotriazinium betaine: $\lambda_{max}(\log \epsilon) = 392$ (3.65), 340 (3.76), 328 (3.76), 296 (3.98), 253 sh (3.96), and 245 nm (4.00).

The mass spectra of **124**, **133**, and **137** have been intensively studied (189). The fragmentation of 3-aryl-4-imino-1,2,3-benzotriazines (**133a**) starts with the loss of nitrogen followed by ejection of a neutral particle after rearrangement. The 3-alkyl-4-(arylimino)-1,2,3-benzotriazines (**133b**) show in addition to the $(M^+ - N_2)$ peak an intensive peak corresponding to loss of N_2H from the molecular ion. The 4-(arylamino)-1,2,3-benzotriazines (**124a**) show a peak due to loss of nitrogen and cleavage of the arylamino group to give the intense ion at $m/e = 130$. The fragmentation of 2-alkyl-4-(arylimino)-1,2,3-benzotriazinium betaines (**137**) starts either with the loss of the ortho substituent of the aryl group or with the elimination of alkyl-N_2.

4. *Reactions*

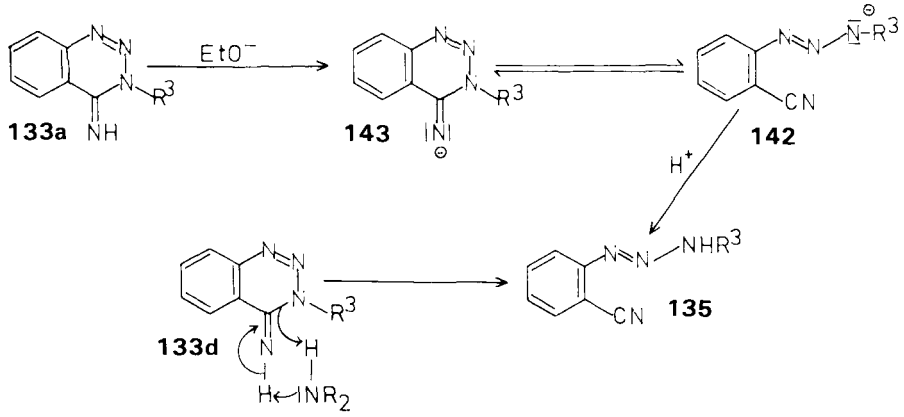
Like most other 1,2,3-benzotriazine derivatives, 4-amino-1,2,3-benzotriazines (**124**) and 4-imino-1,2,3-benzotriazines (**133**) behave as masked diazonium compounds, and products isolated by hydrolysis or pyrolysis can be explained by transient formation of the diazonium compounds (**138**) (50, 83, 231, 232). The intermediate diazonium compounds can be trapped by coupling with naphthols (235).



Shah (231) reported to have isolated a compound of formula $C_{19}H_{15}N_2Cl$ from the treatment of 3-phenyl-4-(phenylimino)-1,2,3-benzotriazine (**133c**) ($R^3 = R^4 = C_6H_5$) with dilute hydrochloric acid at room temperature in the presence of copper bronze. This compound can perhaps be better formulated as **139**. Heating a number of 4-anilino-1,2,3-benzotriazines (**124a**) in high-boiling alcohols, Mackenzie and Stevens (83) isolated 2-alkoxy-*N*-arylbenzamidines (**140**). 6-Aminophenanthridines (**141**) were isolated when 4-imino-1,2,3-benzotriazines (**133a**) or 4-anilino-1,2,3-benzotriazines (**124**) were decomposed in 30% sulfuric acid with copper powder or in 100% phosphoric acid (232).

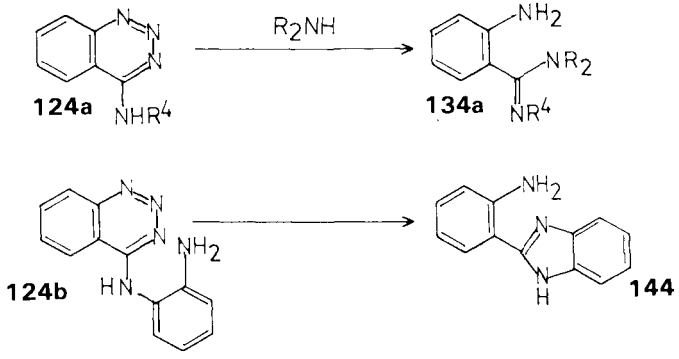
4-Imino-1,2,3-benzotriazines (**133a**) undergo ring fission in sodium ethoxide solution to form the red triazene anions (**142**) from which the free triazenes (**135**) can be obtained by acidification (233).

3-Substituted 4-imino-1,2,3-benzotriazines (**133d**) undergo ring opening in secondary amines to afford the 1-(2-cyanophenyl)triazenes (**135**) (199). Attack by amines at the exocyclic imino substituent is implicated in these isomeri-

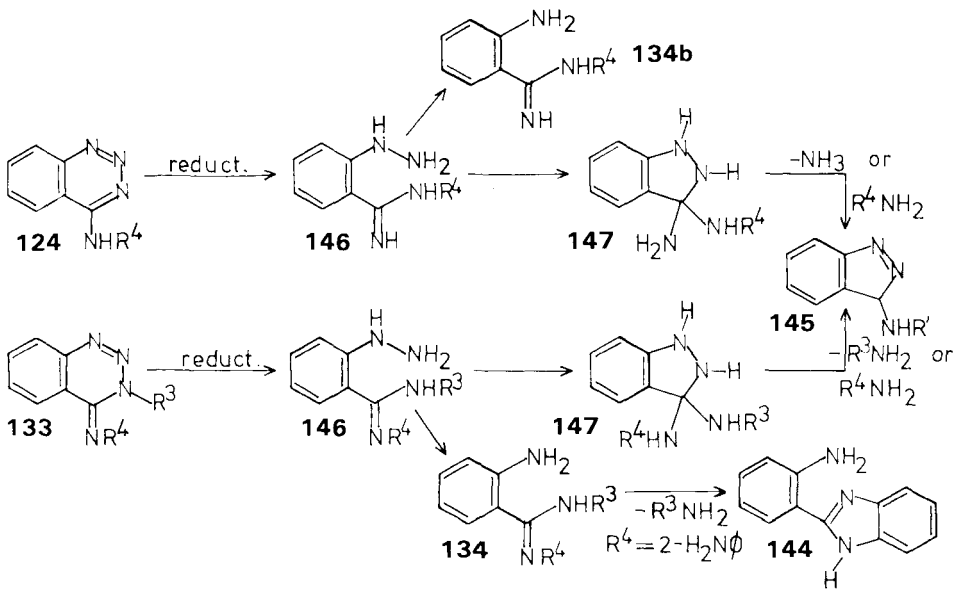


zations since the 3-benzyl-4-imino-1,2,3-benzotriazine and the 3-substituted 4-(arylimino)-1,2,3-benzotriazines (**133e**) are all unreactive.

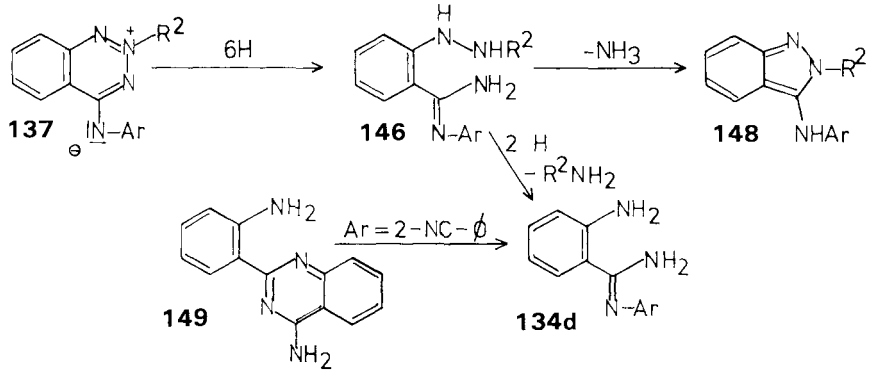
4-(Arylamino)-1,2,3-benzotriazines (**124a**) decompose in secondary amines to afford *N,N,N'*-trisubstituted 2-aminobenzamidines (**134a**). 4-(2-Aminoanilino)-1,2,3-benzotriazine (**124b**) yields 2-(o-aminophenyl)benzimidazole (**144**) when heated in ethylene glycol or piperidine (234), Nucleophilic attack by the amines at C-4 of the benzotriazine ring is implicated in these transformations.



Reduction of 4-amino-1,2,3-benzotriazines (**124**) or 4-imino-1,2,3-benzotriazines (**133**) with stannous chloride in ethanol furnished 3-aminoindazoles (**145**) in high yield (232). Reduction of the same compounds with Raney nickel and hydrazine affords a 3-aminoindazoles (**145**) and 2-aminobenzamidines (**134**) as the major products (125). In a few cases benzimidazoles (**144**) were also isolated; these are formed from **134**. The 4-amino-1,2,3-benzotriazines (**124**) were more resistant to the later reduction than the isomeric **133**. The following mechanisms were suggested for the reductions of **124** and **133**.



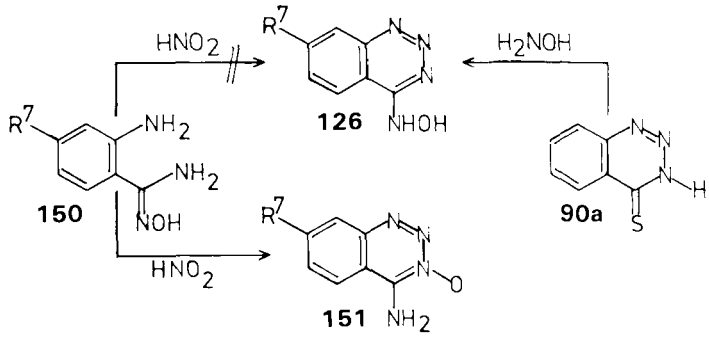
Reduction of 2-alkyl-4-imino-1,2,3-benzotriazinium betaines (**137**) with Raney nickel and hydrazine affords 3-amino-2*H*-indazoles (**148**) and 2-amino-benzamidines (**134d**) or products (**149**) formed from **134d** (200).



F. 4-(Hydroxylamino)-, 4-Hydrazino-, and 4-Azido-1,2,3-benzotriazines

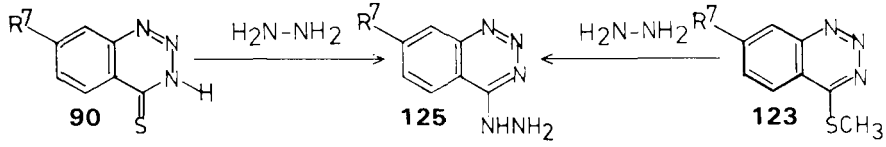
In 1898 Pinnow and Sämann (237) claimed to have obtained the 4-(hydroxylamino)-1,2,3-benzotriazine (**126a**) ($R^7 = H$) through reaction of 2-aminobenzamidoxime (**150a**) with nitrous acid. The same reaction was repeated by

Gabriel in 1903 (238). Grundmann and Ulrich (204) claimed to have isolated the 7-chloro- (**126b**) (R^7 = Cl) and 7-methoxy-4-(hydroxylamino)-1,2,3-benzotriazine (**126c**) (R^7 = CH_3O) from the reaction of the appropriate 2-aminobenzamidoximes (**150b,c**) with nitrous acid.

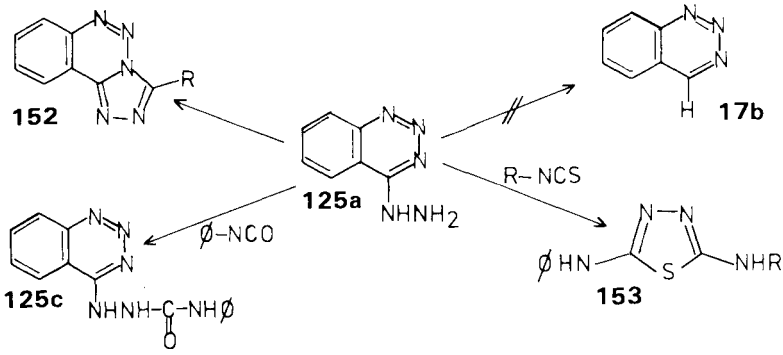


In 1961 Parnell (50) prepared the 4-(hydroxylamino)-1,2,3-benzotriazine (**126a**) (R^7 = H) by reaction of 1,2,3-benzotriazine-4-thione (**90a**) with hydroxylamine and showed that this compound has properties quite different from the compound obtained by Pinnow and Sämann. Because of the reactions of the substance prepared by Pinnow and Sämann he suggested that the 4-amino-1,2,3-benzotriazine 3-oxide structure (**151**) might be the best for this compound. In analogy the substances prepared by Grundmann and Ulrich should have the same structure.

4-Hydrazino-1,2,3-benzotriazine (**125a**) (R^7 = H) was prepared by reaction of 1,2,3-benzotriazine-4-thione (**90a**) (50) or 4-(methylmercapto)-1,2,3-benzotriazine (**123e**) (204) with hydrazine; the 7-chloro derivative (**125b**) (R^7 = Cl) was obtained by interaction of 7-chloro-1,2,3-benzotriazine-4-thione (**90c**) with hydrazine (204).



Attempts to synthesize the parent 1,2,3-benzotriazine (**17b**) from 4-hydrazino-1,2,3-benzotriazine (**125a**) were unsuccessful (50, 51). Reaction of **125a** with triethyl orthoformate or cyanogen bromide afforded the tricyclic compounds **152a** (R = H) and **152b** (R = NH_2) (51). The semicarbazide **125c** was isolated from interaction of **125a** with phenylisocyanate, and reaction of **125a** with arylisothiocyanates afforded the thiadiazoles **153a** (R = C_6H_5) and **153b** (R = 4-CH_3O–C_6H_4) (51).



Treatment of **125a** with nitrous acid gave the diazonium compound **154** which was coupled with resorcinol to give **155**. 4-Azido-1,2,3-benzotriazine (**156**) was obtained through reaction of **125a** with amyl nitrite in glacial acetic acid (51). The azido compound revealed a strong azide band in its infrared spectrum and the azido–tetrazolo equilibrium (**156** ⇄ **157**) is completely on the azide side. The azido group could be displayed in a nucleophilic reaction with sodium thioglycolate to give **123f**. When the azide **156** is irradiated it is transformed into a colorless compound which is best represented by structure **158** (51).

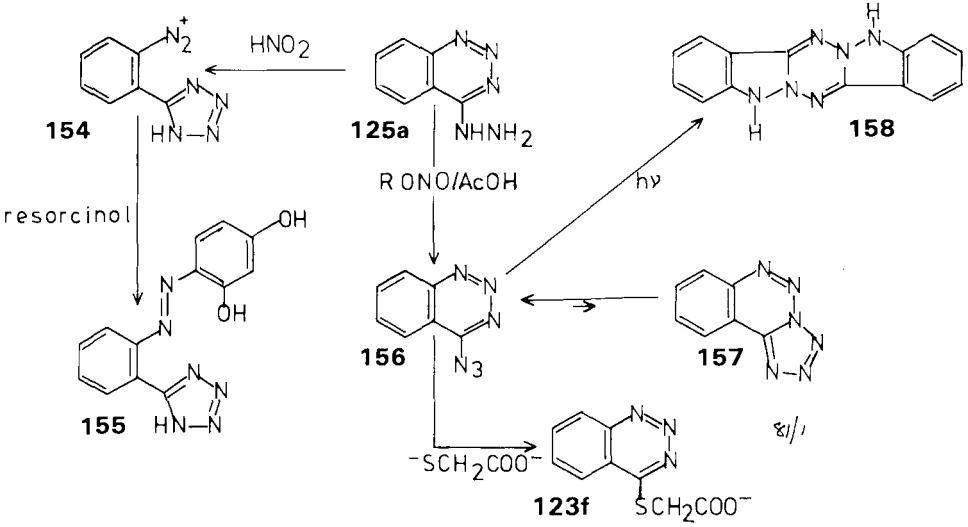
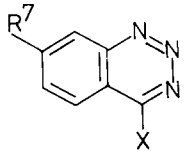


Table IV-6 lists the compounds of this type that have been reported in the literature.

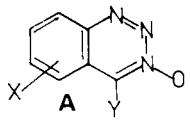
TABLE IV-6. 4-(HYDROXYLAMINO)-, 4-HYDRAZINO-, AND 4-AZIDO-1,2,3-BENZOTRIAZINES



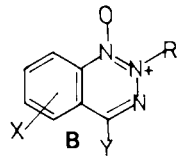
R^7	X	m.p. (°C)	Refs.
H	NHOH	175 (dec.)	50
H	$NHNH_2$	188 (dec.)	50
		191–192 (dec.)	204
		195–196 (dec.)	51
Methanesulfonate		166–167 (dec.)	50
H	NH—N=CHØ	180	51
H	NH—N=$C(CH_3)$COOH	104–105	51
H	NH—N=CH—COOH	144–146 (dec.)	51
H	NH—NHCONHØ	204–205	51
H	N_3	118 (dec.)	51
Cl	$NHNH_2$	195–198 (dec.)	204

G. 1,2,3-Benzotriazine *N*-Oxides

The chemistry of 1,2,3-benzotriazine *N*-oxides has not yet been studied in detail and only a few compounds of this class are known. Two types of 1,2,3-benzotriazine *N*-oxides have been prepared so far, 1,2,3-benzotriazine 3-oxides (**A**) and 2-substituted 1,2,3-benzotriazinium betaine 1-oxides (**B**). The types are discussed separately.



A

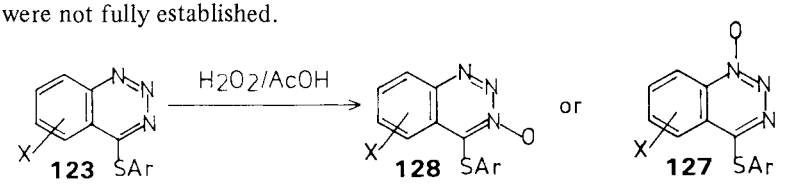


B

1. *1,2,3-Benzotriazine 3-Oxides*

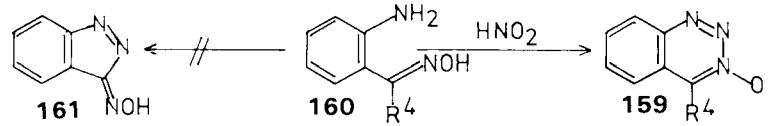
a. PREPARATION. Stanovnik and Tisler (51) reported experiments to oxidize a number of 4-mercapto-1,2,3-benzotriazines (**123**) with strong oxidizing agents, such as hydrogen peroxide in acetic acid, but isolated, with one exception, only the starting material. The exception was the 4-[(2,4,6-trinitrophenyl)mercapto]-1,2,3-benzotriazine (**123c**), which gave a compound character-

ized by the uptake of one oxygen atom and which is formulated as either the 3-oxide (**128a**) or the 1-oxide (**127**). These structures seem to be the best ones but were not fully established.

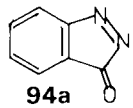


Ar=2,4,6 -$(O_2N)_3C_6H_2$

All other known 1,2,3-benzotriazine 3-oxides were prepared by diazotization of appropriate precursors, but in many cases the isolated compounds were not formulated as 1,2,3-benzotriazine 3-oxides. Reaction of 2-(aminophenyl)-aldoximes (**160**) (R^4 = H) or 2-(aminophenyl)ketoximes (**160**) ($R^4 \neq$ H) with nitrous acid affords 1,2,3-benzotriazine 3-oxides (**159**), from ketoximes in good yield and from aldoximes in poor yield (53, 135, 239, 240, 247, 249).



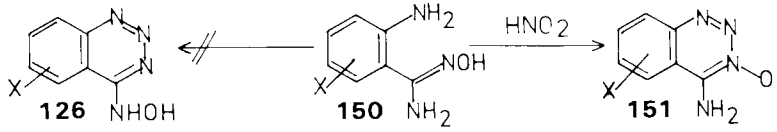
Bamberger and his co-workers (135, 239) formulated the products obtained by this reaction to be indazolone oxime (**161**), but since it is known that indazolone (**94a**) is a very unstable compound (103, 241) this structure seems



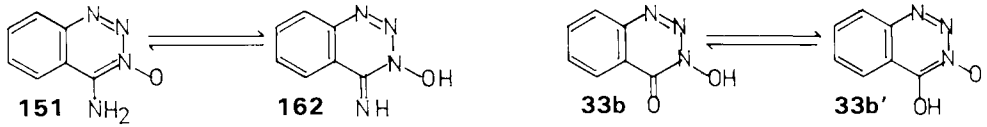
very unlikely. Meisenheimer, Senn, and Zimmermann (53) suggested the 1,2,3-benzotriazine 3-oxide structure (**159**) for these compounds, a suggestion that is accepted in later work and confirmed by the fact that PMR, and mass spectra of these compounds are in agreement only with the 1,2,3-benzotriazine 3-oxide structure (240).

As was discussed in the preceding section, reaction of 2-aminobenzamidoximes (**150**) with nitrous acid yields compounds (204, 237, 238) that were formulated for a long time as 4-(hydroxylamino)-1,2,3-benzotriazines (**126**) but that should be formulated as 4-amino-1,2,3-benzotriazine 3-oxides (**151**), as indicated by the work of Parnell (50).

Besides structure **151**, the tautomeric structure **162** may be given for these compounds; in this case the substances should be called 3-hydroxy-4-imino-1,2,3-benzotriazines. Owing to the statement of Horspool and his group that the spectroscopic data are in agreement only with the structure **151** (240), we have formulated all compounds as the 3-oxides.

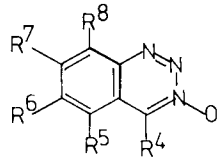


The oxygen analogues of **151** or **162** are the 3-hydroxy-1,2,3-benzotriazin-4-ones (**33b**) or their tautomers **33b'**. In the literature both structures were published but since derivatives of the 3-hydroxy tautomer (**33b**) are known and all compounds with a similar structure should be discussed together, we always use the 3-hydroxy-1,2,3-benzotriazin-4-one structure (**33b**); see Section B.



b. COMPOUND SURVEY. The 3-oxides reported in the literature are listed in Table IV-7.

TABLE IV-7. 1,2,3-BENZOTRIAZINE 3-OXIDES

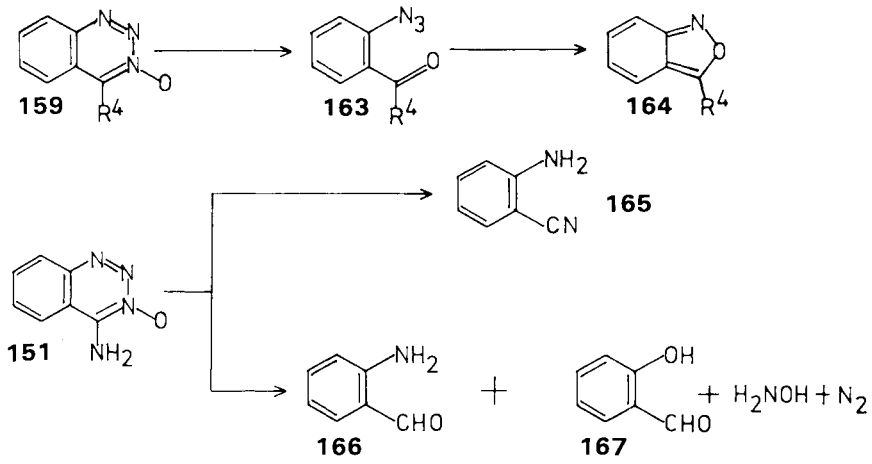


R^4	R^5	R^6	R^7	R^8	m.p. (°C)	Refs.
H	H	H	H	H	158–159	53
					160–160.5	135
H	H	CH_3	H	CH_3	181.5–182.5	238
H	Cl	H	H	H	168.5	135
		H_2Br_2			182 (dec.)	135
CH_3	H	H	H	H	185–188	53
C_2H_5	H	H	H	H		239
C_6H_5	H	H	H	H	154 (dec.)	53
C_6H_5	H	Cl	H	H		239
4-Cl–C_6H_4	H	H	H	H		239
4-CH_3O–C_6H_4	H	H	H	H		239
NH_2	H	H	H	H	180	247
$\cdot C_2H_5OH$					181	237
$\cdot$HCl					151	237
NH_2	H	H	Cl	H	205–206 (dec.)	204
NH_2	H	H	CH_3O	H	215–216 (dec.)	204
2,4,6-$(O_2N)_3C_6H_2$–S	H	H	H	H	275	51

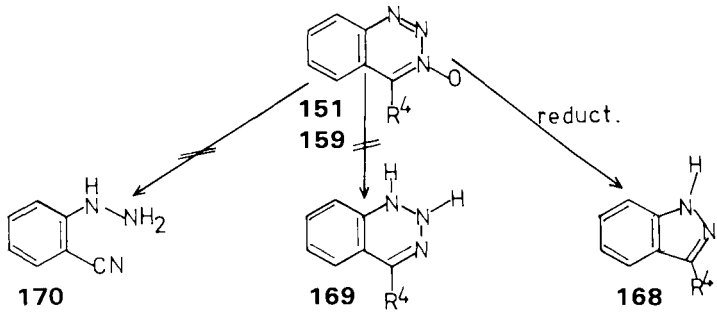
c. PHYSICAL PROPERTIES AND REACTIONS. At present only a little information on the physical properties of 1,2,3-benzotriazine 3-oxides is available. Most isolated compounds seem to be yellow, crystalline compounds. 4-Amino-1,2,3-benzotriazine 3-oxides (**151**) are soluble in bases and mineral acids and can be reprecipitated by addition of acetic acid or ammonia. Longer treatment with diluted acids leads to the opening of the 1,2,3-triazine ring.

Very few spectroscopic data on 1,2,3-benzotriazine 3-oxides have been published (51, 240, 247). The 4-methyl-1,2,3-benzotriazine 3-oxide has the following ultraviolet spectrum: $\lambda_{max}(\epsilon) = 395$ (1.200), 310 (6.800), and 302 nm (8.200) (240). The 4-phenyl derivative has two absorption maxima, at 407 (1.700) and 306 nm (7.100) (240). The following spectrum for 4-amino-1,2,3-benzotriazine 3-oxide is reported: $\lambda_{max}(\epsilon) = 390$ (1.850), 325 (4.500), 258 sh (9.300), and 232 nm (23.000) (247).

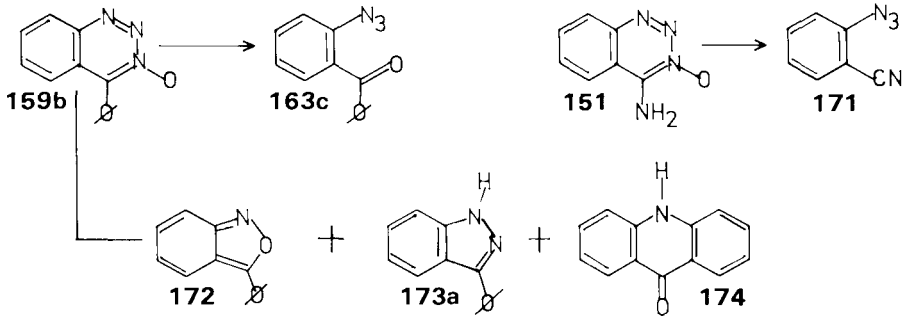
Treatment of 1,2,3-benzotriazine 3-oxides (**159**) with base or diluted mineral acids affords 2-azidobenzaldehydes (**163a**) (R^4 = H) or 2-azidophenyl ketones (**163b**) (R^4 = alkyl, aryl) (35, 53, 135, 240) which can be transformed into anthranils (**164**) (53, 250). Treatment of 4-amino-1,2,3-benzotriazine 3-oxides (**151**) with bases was reported to yield 2-aminobenzonitriles (**165**) (204) or 2-aminobenzaldehydes (**166**) and salicylaldehydes (**167**) (239).



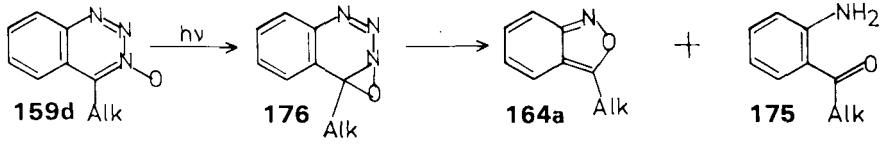
Reduction of 1,2,3-benzotriazine 3-oxides (**151, 159**) with different reducing agents affords 3-alkyl- (**168a**) (R^4 = alkyl), 3-aryl- (**168b**) (R^4 = aryl), or 3-aminoindazoles (**168c**) ($R^4 = NH_2$) (53, 207, 238, 247, 248). The 3-aminoindazoles (**168c**) formed were tentatively formulated as dihydro-1,2,3-benzotriazines (**169**) (237) or 2-hydrazinobenzonitrile (**170**) (238) but Aron and Elvidge (247) as well as Cooper (248) have shown that the isolated compounds were in fact the 3-aminoindazoles (**168c**).

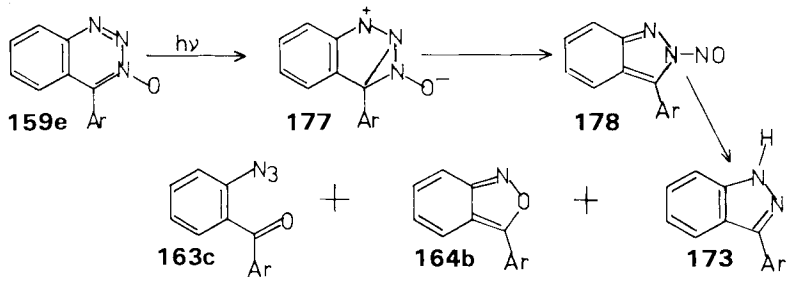


Heating 4-phenyl-1,2,3-benzotriazine 3-oxide (**159b**) affords 2-azidobenzophenone (**163c**) (240), and heating 4-amino-1,2,3-benzotriazine 3-oxide (**151**) in the presence of ammonium acetate affords 2-azidobenzonitrile (**171**) (53). Interaction of **151** with secondary bases also gives 2-azidobenzonitriles (**171**) (199). Pyrolysis of 4-phenyl-1,2,3-benzotriazine 3-oxide (**159b**) at 420°C gave 3-phenylbenzisoxazole (**172**), 3-phenylindazole (**173a**), and acridone (**174**) (30).

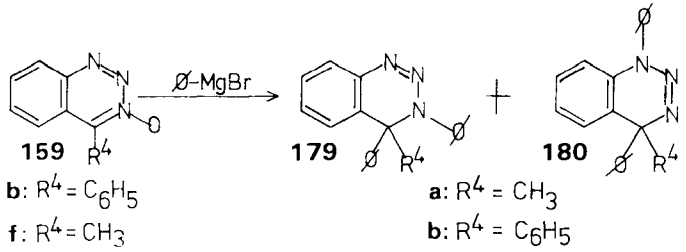


Irradiation of 4-alkyl-1,2,3-benzotriazine 3-oxides (**159d**) in methanol, ethanol, or benzene affords the 3-alkylanthranils (**164a**) and a small amount of a 2-aminophenyl ketone (**175**) (240). Irradiation of 4-aryl-1,2,3-benzotriazine 3-oxides (**159e**) yields mainly 3-arylindazoles (**173**) plus 3-phenylbenzisoxazole (**164b**) and 2-azidobenzophenone (**163c**) if the 4-phenyl derivative is used (240). In the photolysis of 4-alkyl-1,2,3-benzotriazine 3-oxides (**159d**) the oxaziridine (**176**) is postulated as the intermediate but for the photolysis of **159e** a different mechanism is suggested (240).





Reaction of 4-methyl- (**159f**) and 4-phenyl-1,2,3-benzotriazine 3-oxide (**159b**) with phenylmagnesium bromide is reported by Japanese chemists (245). They obtained a complex reaction mixture from which they isolated and identified five (R^4 = Me) or six products (R^4 = C_6H_5). The dihydro-1,2,3-benzotriazines **179a**, **179b**, and **180a** were found among the isolated products.

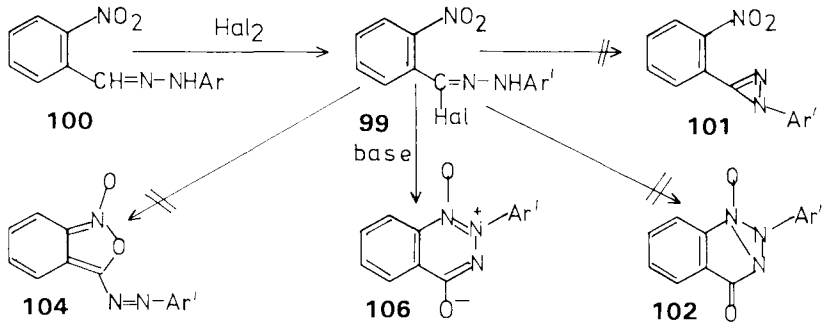


2. *1,2,3-Benzotriazinium Betaine 1-Oxides*

a. PREPARATION. In a series of papers from 1925 to 1935 Chattaway and his co-worker (206, 214–219) reported that halogenation of 2-nitrobenzaldehyde arylhydrazones (**100**), followed by treatment with base, gave a series of compounds to which they assigned first the isodiazomethane structure (**101**) and later structure **102**. A compound with the same structure was also prepared by Parkes and Burney (220) (see also Section I-C-1).

The reactions were reinvestigated in 1962 by Gibson (221, 222), who proposed the new structure **104** for the isolated compounds. The proposal for the 3-(arylazo)anthranil 1-oxide structure (**104**) was based mainly on the theory of 1,3-dipolar cycloaddition reactions and infrared spectroscopic studies. The 3-(arylazo)anthranil 1-oxide structure (**104**) is also used by Gladstone, Aylward, and Norman (735) for the substances obtained by lead tetraacetate oxidation of **100**.

By new spectroscopic studies Kerber (223) in 1972 showed that the discussed compounds have neither the proposed triaziridine structure **102** nor the structure **104** but are in fact the azimines **106**. The conclusions of Kerber were confirmed by McKillop and Kobylecki in 1974 (138).



b. COMPOUND SURVEY The 1-oxides reported in the literature are listed in Table IV-8.

c. PHYSICAL PROPERTIES AND REACTIONS. 1,2,3-Benzotriazinium betaine 1-oxides (**106**) are easily crystallized, yellow compounds which can be kept indefinitely without change at room temperature but explode with great violence when heated.

A number of spectroscopic studies on **106** have been published since these data were used to determine the structure of these compounds. The following ultraviolet spectrum is reported for the 2-methyl-1,2,3-benzotriazinium betaine 1-oxide: $\lambda_{max}(\log \epsilon) = 384$ (3.76), 278 (3.89), and 226 nm (4.29) (138). The ultraviolet spectra of other derivatives are very similar. In the infrared spectra a band in the 1628 to 1660 cm^{-1} region is observed (138). All compounds of this class underwent fragmentation in the mass spectra giving prominent ions at *m/e* values corresponding to $M - O$, $M - N_2$ or CO, $M - O$–(N_2 or CO) ($M - 16$, $M - 28$, $M - 44$, $M - 72$) (138).

1,2,3-Benzotriazinium betaine 1-oxides (**106**) are stable toward acids and show feebly basic properties, dissolving in concentrated hydrochloric acid, for example, and being reprecipitated on dilution. When hydrogen chloride is passed into their dry ethereal solution colorless addition products are precipitated which readily lose hydrogen chloride. They are all rapidly decomposed by alcoholic potash or alcoholic ammonia, yielding as one of the products a halogen-substituted benzene (206). On oxidation with potassium permanganate they yield 2-nitrobenzaldehydes and they are reduced by boiling ethanol or stannous chloride to the 1,2,3-benzotriazine betaines (**107**) (214–218).

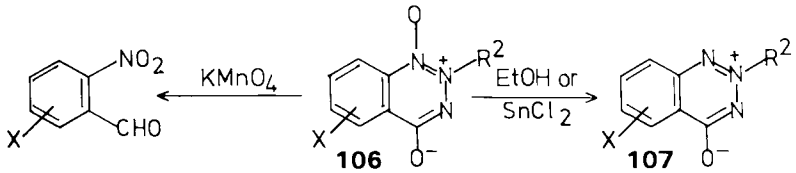
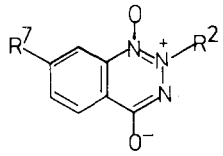


TABLE IV-8. 1,2,3-BENZOTRIAZINIUM BETAINE 1-OXIDES



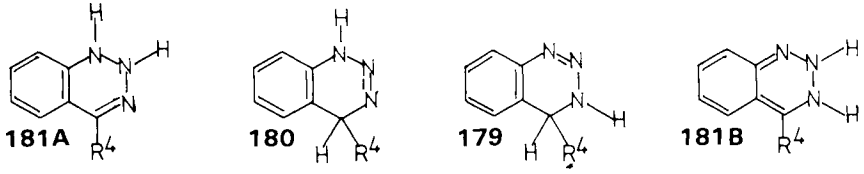
R^2	R^7	Explosion point (°C)	Refs.
CH_3	H	145–157	138
C_6H_5	H	145	
		147–149	138
4-CH_3–C_6H_4	H	142–143	138
		143	214
4-Cl–C_6H_4	H	147	219
4-Br–C_6H_4	H	138	223
		144	219
		144–146	138
4-O_2N–C_6H_4	H	145–146	138
		159	
4-CH_3O–C_6H_4	H	141	138
2,4-$Cl_2C_6H_3$	H	140	219
2,4-$Br_2C_6H_3$	H	145–146	219, 222
2-CH_3-4-Br–C_6H_3	H	151	216
4-CH_3-2-Cl–C_6H_3	H	134	215
4-CH_3-2-Br–C_6H_3	H	139	214
4-CH_3-2-Br–C_6H_3	NO_2	133	217
2-NO_2-4-Br–C_6H_3	H	142	216
2,4,6-$Cl_3C_6H_2$	H	163	219
3,4,5-$Cl_3C_6H_2$	H	151	219
2-CH_3-4,6-$Br_2C_6H_2$	H	145	216
4-CH_3-2,6-$Cl_2C_6H_2$	H	155	216
4-CH_3-2,6-$Br_2C_6H_2$	H	167	214
4-CH_3-2,6-$Br_2C_6H_2$	NO_2	142	217
5-CH_3-2,4-$Br_2C_6H_2$	H	126	220
2,3,4,5-Br_4C_6H	H	155	218
C_6Cl_5	H	128	218
C_6Br_5	H	157	218

H. Dihydro-1,2,3-benzotriazines

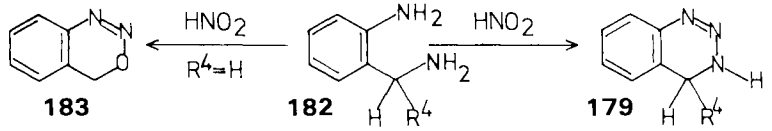
1. *Preparation*

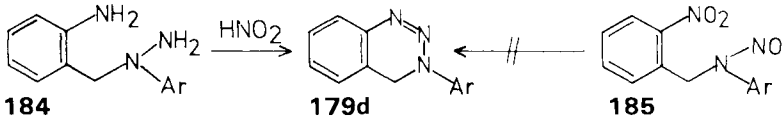
Four different dihydro-1,2,3-benzotriazine tautomers can be discussed: the 1,2-dihydro structure (**181A**), the 1,4-dihydro form (**180**), the 3,4-dihydro

structure (**179**), and the 2,3-dihydro form (**181B**). Derivatives of the first three tautomers seem to be known; the fourth structure (**181B**) is a very unlikely one because of the orthoquinoid structure of the benzene ring.

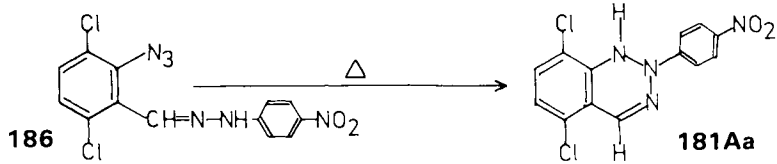


Reaction of (2-aminobenzyl)amines (**182**) with nitrous acid is widely used for the synthesis of compounds formulated as 3,4-dihydro-1,2,3-benzotriazines (**179**) (250–258). The use of amyl nitrite instead of nitrous acid may give better yields (255). Attempts to prepare the unsubstituted 3,4-dihydro-1,2,3-benzotriazine (**179c**) (R^4 = H) by this method failed. Instead of **179a** an amorphous powder was obtained for which the 3,1,2-benzoxadiazine structure (**183**) was discussed (251). Reaction of 1-(2-aminobenzyl)-1-arylhydrazines (**184**) with nitrous acid affords 3-aryl-3,4-dihydro-1,2,3-benzotriazines (**179d**) (250, 253). Attempts to prepare **179d** (Ar = C_6H_5) by the action of oxidizing agents on **184** (Ar = C_6H_5) or by the action of reducing agents on *N*-(2-nitrobenzyl)-*N*-nitrosoaniline (**185**) failed (250).





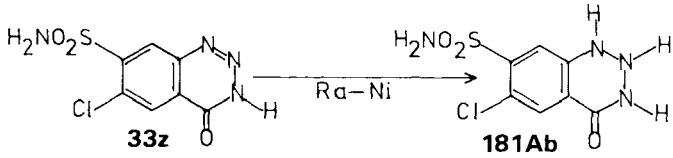
Bamberger and Demuth (135) obtained a golden-yellow, crystalline compound when they heated the 4-nitrophenylhydrazone of 2-azido-3,6-dichlorobenzaldehyde (**186**). For the isolated substance they discussed the 5,8-dichloro-2-(4-nitrophenyl)-1,2-dihydro-1,2,3-benzotriazine structure (**181Aa**) (m.p. 234 to 235°C).



Reduction of the so-called 4-(hydroxylamino)-1,2,3-benzotriazine (**126**), which is in fact the 4-amino-1,2,3-benzotriazine 3-oxide (**151**), with zinc and acetic acid yielded a compound which was formulated as a dihydro-1,2,3-benzotriazine (**169**) by Pinnow and Sämann (237) and as 2-hydrazinobenzonitrile (**170**) by Gabriel (238), but which is in fact the 3-aminoindazole (**168c**) as was shown by Aron and Elvidge (247) and by Cooper (248).

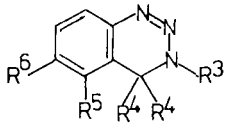
Reaction of 4-methyl (**159f**) or 4-phenyl-1,2,3-benzotriazine 3-oxide (**159b**) with phenylmagnesium bromide afforded complex mixtures from which, beside other products, the following compounds were isolated: 4-methyl-1,4-diphenyl-1,4-dihydro-1,2,3-benzotriazine (**180a**) (3%) (m.p. 187 to 188°C), 4-methyl-3,4-diphenyl-3,4-dihydro-1,2,3-benzotriazine (**179a**) (3%) and 3,4,4-triphenyl-3,4-dihydro-1,2,3-benzotriazine (**179b**) (6%), respectively (245).

Reduction of 7-chloro-6-sulfamoyl-1,2,3-benzotriazin-4-one (**33z**) with Raney nickel in ethanol affords a compound which is said to be 7-chloro-6-sulfamoyl-1,2,-dihydro-1,2,3-benzotriazin-4-one (**181Ab**) (m.p. 229 to 230°C) (91).



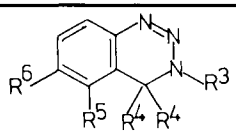
33z **181Ab**

TABLE IV-9. 3,4-DIHYDRO-1,2,3-BENZOTRIAZINES



R^3	R^4	R^4	R^5	R^6	m.p. (°C)	Refs.
CH_3	H	H	H	H	72–73 (dec.)	251
·HCl					146–147 (dec.)	251
$\cdot H_2PtCl_6$					163 (dec.)	251
·Picrate					172 (dec.)	251
CH_3	C_6H_5	C_6H_5	H	H	162–163	245
C_2H_5	H	H	H	H	Oil	251
·HCl					141	251
·HBr					151	251
$\cdot H_2SO_4$					150	251
$\cdot H_2PtCl_2$					70 (dec.)	251
·Picrate					150 (dec.)	251
C_6H_5–CH_2	H	H	H	H	91 (dec.)	251
$\cdot H_2PtCl_6$					101 (dec.)	251
·Picrate					167 (dec.)	251
2-H_2N–C_6H_4–CH_2	H	H	H	H		254

TABLE IV-9 *(continued)*



R^3	R^4	R^4	R^5	R^6	m.p. (°C)	Refs.
2-$^+N_2$–C_6H_4–CH_2	H	H	H	H		254
2-(2-OH–$C_{10}H_7$)–N=N–C_6H_4–CH_2	H	H	H	H	185 (dec.)	254
C_6H_5	H	H	H	H	128 (dec.)	250
· H_2PtCl_6					130 (dec.)	250
· Picrate					111 (dec.)	250
C_6H_5	H	H	NO_2	H	153–154 (dec.)	258
C_6H_5	C_6H_5	C_6H_5	H	H	233	245
4-CH_3–C_6H_4	H	H	H	H	151 (dec.)	250
· H_2PtCl_6					190 (dec.)	250
· Picrate					132 (dec.)	250
4-CH_3–C_6H_4	H	H	H	CH_3	173 (dec.)	255
· HCl						255
· H_2PtCl_6					180	255
· Picrate					138 (dec.)	255
3-Cl–C_6H_4	H	H	H	H	146–147 (dec.)	253
4-Cl–C_6H_4	H	H	H	H	134	253
· HCl					103 (dec.)	253
· H_2PtCl_6					130 (dec.)	253
· H_2AuCl_5					105 (dec.)	253
· Picrate					109 (dec.)	253
4-Br–C_6H_4	H	H	H	H	164	253
· HCl					105–106	253
· H_2PtCl_6					191 (dec.)	253
· H_2AuCl_5					108–109 (dec.)	253
· Picrate					106 (dec.)	253
4-CH_3O–C_6H_4	H	H	H	H	139 (dec.)	253
· HCl					91 (dec.)	253
· H_2PtCl_6					>100 (dec.)	253
· Picrate					125 (dec.)	253
4-C_2H_5O–C_6H_4	H	H	H	H	144 (dec.)	253
· HCl					>115 (dec.)	253
· HBr					104	253
· H_2PtCl_6					100 (dec.)	253
· H_2AuCl_5						253
· Picrate					120 (dec.)	253
CH_3–CO	H	H	H	H	138 (dec.)	252
· H_2PtCl_6					~90 (dec.)	252
C_6H_5–CO	H	H	H	H	114–115 (dec.)	252
· H_2PtCl_6					85 (dec.)	252
C_6H_5–SO_2	H	H	H	H	130 (dec.)	256, 257

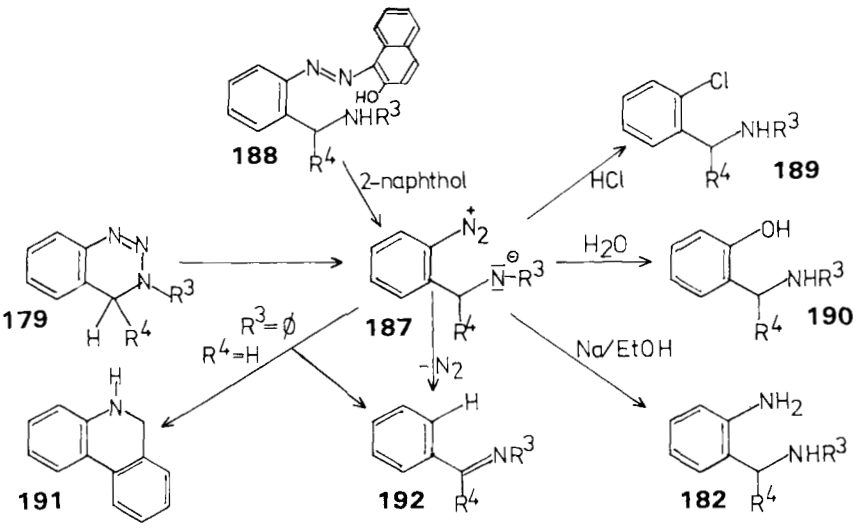
2. *Compound Survey*

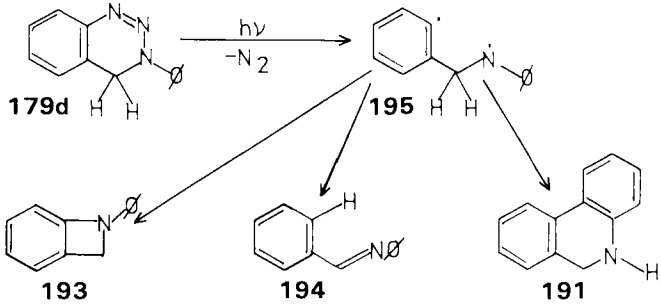
Table IV-9 lists the compounds of this class that have been reported in the literature.

3. *Physical Properties and Reactions*

Most known 3,4-dihydro-1,2,3-benzotriazines (**179**) are yellow crystalline compounds; the 3-ethyl derivative is a yellow oil. Only a small amount of spectroscopic data on 3,4-dihydro-1,2,3-benzotriazines (**179**) has been published so far (245, 259). For the 4-methyl-3,4-diphenyl-3,4-dihydro-1,2,3-benzotriazine four absorption maxima at 317, 268, 259, and 252 nm were reported (245).

The reactions of 3,4-dihydro-1,2,3-benzotriazines (**179**) are best explained by the intermediate formation of the diazonium ion **187**, which can be coupled with 2-naphthol to give the azo compound **188** and which reacts with hydrochloric acid to afford the 2-chlorobenzylamine (**189**) (254). Heating **179** in dilute acids or in water yields the 2-hydroxybenzylamines (**190**), and reduction with sodium in ethanol leads to the isolation of 2-aminobenzylamines (**182**). 3,4-Dihydro-1,2,3-benzotriazines (**179**) are stable at room temperature but heating leads to the elimination of nitrogen and the imines (**192**) can be isolated. In the case of 3-phenyl-3,4-dihydro-1,2,3-benzotriazine, 5,6-dihydrophenanthridine (**191**) was also obtained. The diazonium ion (**187**) formulated as the

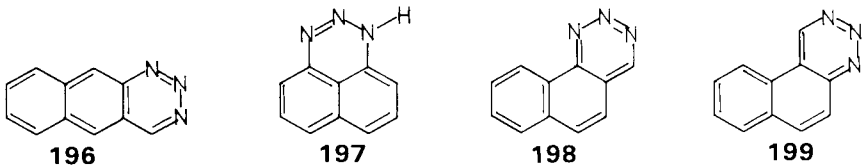




intermediate in these reactions was isolated in one case, namely, from 3-acetyl-3,4-dihydro-1,2,3-benzotriazine (**179c**) ($R^3 = CH_3CO$, $R^4 = H$). Photolysis of 3-phenyl-3,4-dihydro-1,2,3-benzotriazine (**179d**) in benzene affords 1-phenylbenzazetine (**193**), benzalaniline (**194**), and 5,6-dihydrophenanthridine (**191**) (260). For the photolysis the 1,4-diradical (**195**) is reported as an intermediate.

II. CONDENSED WITH THE NAPHTHALENE SYSTEM

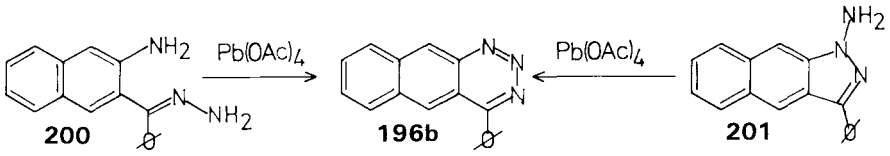
At present, derivatives of only two of the four possible naphtho-1,2,3-triazines (**196** to **199**) are known, namely, the naphtho[2,3-*d*]1,2,3-triazine (**196**) and naphtho[1,8-*de*]1,2,3-triazine (**197**).



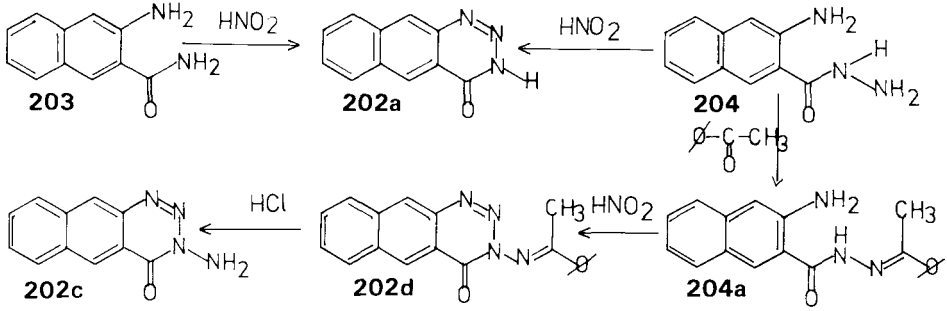
A. Naphtho[2,3-*d*]1,2,3-triazines

The unsubstituted naphtho[2,3-*d*]1,2,3-triazine (**196a**) has not yet been reported. Owing to the high reactivity of the unsubstituted 1,2,3-benzotriazine one may expect that **196a** will also be a very reactive and unstable compound. The 4-phenylnaphtho[2,3-*e*]1,2,3-triazine (**196b**) was prepared by Rees and his group (52) through oxidation of either 2-amino-3-benzoylnaphthalene hydrazone (**200**) or 1-amino-3-phenylbenz[*f*]indazole (**201**) with lead tetraacetate. It forms yellow needles and has a melting point of 194 to 195°C.

The first derivative of the naphtho[2,3-*d*]1,2,3-triazine system, the naphtho-[2,3-*d*]1,2,3-triazin-4-one (**202a**) was prepared by Fries, Walter, and Schil-

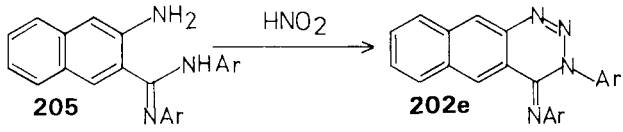


ling (261) by reaction of either 3-aminonaphthalene-2-carboxamide (**203**) or 3-aminonaphthalene-2-carbohydrazide (**204**) with nitrous acid. It is obtained as colorless needles and has a melting point of 250°C (dec.). Ege and Beisiegel (263) prepared the 3-phenyl-naphtho[2,3-*d*]1,2,3-triazin-4-one (**202b**) (m.p. 226°C), but they did not publish any details on the method they used for the synthesis.



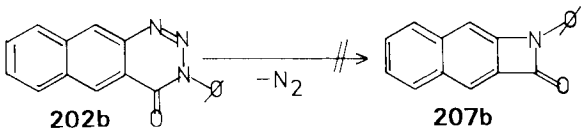
3-Aminonaphtho[2,3-*d*]1,2,3-triazin-4-one (**202c**) (yellow crystal of m.p. 208 to 209°C) was prepared by the following reaction sequence: 3-aminonaphthalene-2-carbohydrazide (**204**) was reacted with acetophenone to give the α-phenylethylene derivative of the hydrazide (**204a**), which was diazotized with nitrous acid to yield the red 3-[(α-phenylethylidene)amino]naphtho[2,3-*d*]1,2,3-triazin-4-one (**202d**) (m.p. 215 to 217°C). The removal of the protecting group was achieved by treating **202d** with ice-cold concentrated hydrochloric acid for 30 min (103).

Four 3-aryl-4-(arylimino)naphtho[2,3-*d*]1,2,3-triazines (**202e**) (Ar = C_6H_5, 184.5 to 185°C; Ar = 2-CH_3–C_6H_4, 130.5 to 131°C; Ar = 3-CH_3–C_6H_4, 155.5 to 156°C; Ar = 4-CH_3–C_6H_4, 186°C) were synthesized by Burmistrov and Belykh (262) through diazotization of 3-amino-2-naphthoic acid *N,N'*-diarylamidines (**205**).

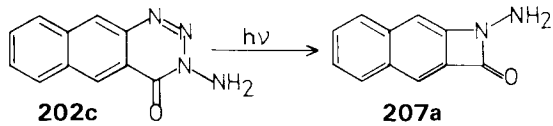


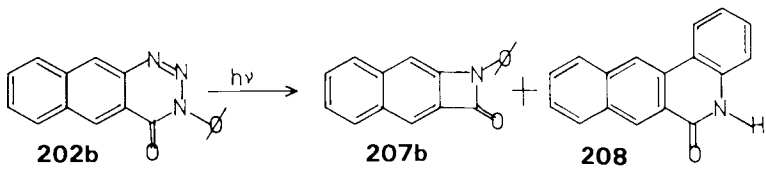
At present only a few spectroscopic data on naphtho[2,3-*d*]1,2,3-triazines have been published (52, 103, 263, 264). In the infrared spectrum of

4-phenylnaphtho[2,3-*d*]1,2,3-triazine (**196b**) the following absorption bands were observed (52): 1620, 1600, 1580, 1270, ,1250, 940, 900, 760, and 700 cm^{-1}. The 2-phenylnaphtho[2,3-*d*]1,2,3-triazin-4-one shows the following absorption maxima in the electronic spectrum: $\lambda_{max}(\epsilon)$ = 365 (6.800), 348 (8.500), 265 (44.500), and 246 nm (28.300) (263). The following spectroscopic data were given for 3-aminonaphtho[2,3-*d*]1,2,3-triazine (**202c**): ν_{max} = 3310, 3200, 1678, and 1630 cm^{-1}; $\lambda_{max}(\epsilon)$ = 345 (3.500), 258 (20.000), and 242 nm (18.000) (103). Mass spectrometric fragmentation of 3-phenylnaphtho[2,3-*d*]-1,2,3-triazin-4-one (**202b**) was studied by Ege and his group (264). The fragmentation starts with the loss of nitrogen and appearance potential measurements have shown that the formed ion does not have a four-membered ring structure (**207b**).

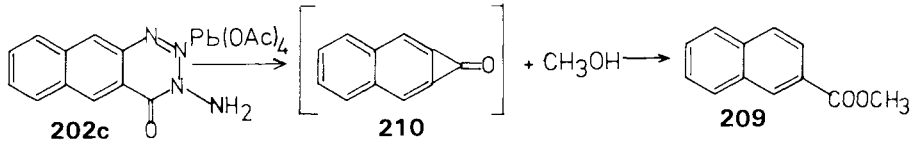


Pyrolysis of 4-phenylnaphtho[2,3-*d*]1,2,3-triazine (**196b**) at 470°C yields the orange 2-phenylnaphth[2,3-*b*]azete (**206**), which is quite stable at room temperature (30, 58). Photolysis of 3-aminonaphtho[2,3-*d*]1,2,3-triazin-4-one (**202c**) in acetonitrile with a Pyrex filter resulted in the evolution of nitrogen and yellow crystals identified as *N*-aminonaphth[2,3-*d*]azet-2(1*H*)-one (**207a**) were isolated (78). Photolysis of 3-phenylnaphtho[2,3-*d*]1,2,3-triazin-4-one (**202b**) in tetrahydrofuran also resulted in the evolution of nitrogen and two compounds, identified as *N*-phenylnaphth[2,3-*b*]azet-2(1*H*)-one (**207b**) and benz[*d*]acridon (**208**) (5%), were isolated (263).



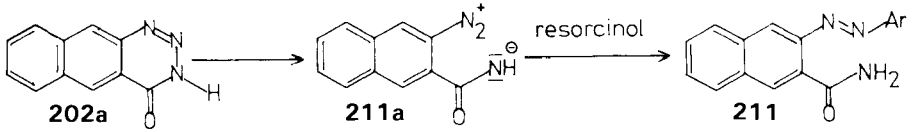


Oxidation of 3-aminonaphtho[2,3-*d*] 1,2,3-triazin-4-one.(**202c**) with lead tetraacetate in methanol gave a rapid evolution of gas which appeared to be complete in about 1 min, and methyl 2-naphthoate (**209**) was isolated (103). The intermediate formation of a naphthocyclopropenone (**210**) in this reaction was discussed.



202c **210** **209**

Heating naphtho[2,3-*d*] 1,2,3-triazin-4-one (**202a**) with resorcinol yields a red azo compound (**211**), the formation of which is best explained by intermediate formation of the diazonium ion (**211a**) from **202a** (261).



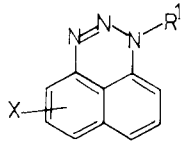
202a **211a** **211**

B. Naphtho[1,8-de]triazines

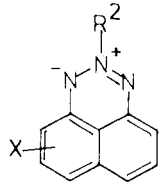
1. *Preparation*

This ring system has been known for a long time and several names have been suggested for this condensed 1,2,3-triazine system, such as the azimide of 1,8-diaminonaphthalene, 1,8-aziminonaphthalene, 1,2,3-triazaperinaphthindene, α-perinaphthotriazole, or perinaphthotriazine. In this discussion we always use the term naphtho[1,8-*de*]triazine, which is the name given in *The Ring Index* (RRI 3249) and also normally used by *Chemical Abstracts*.

Two types of naphtho[1,8-*de*]triazines are known, the red (orange, brown, violet), 1*H*-naphtho[1,8-*de*]triazines (**197**) and the blue (black, blue-green) derivatives of 2*H*-naptho[1,8-*de*]triazines (**212**).



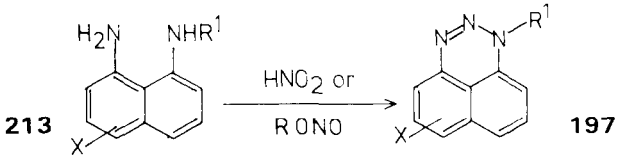
197



212

De Aguiar (292) was the first to prepare the unsubstituted 1*H*-napththo-

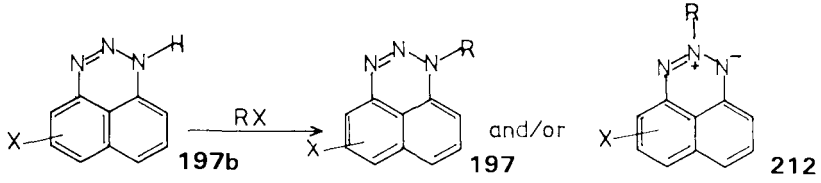
[1,8-*de*]triazine (**197a**) (R^1 = X = H) through reaction of 1,8-diaminonaphthalene (**213a**) (R^1 = X = H) with nitrous acid, but since he didn't know the structure of the starting diamine, he was not able to give the correct structure of the isolated compound. Erdmann(293) in 1888 suggested structure **197a** for the compound prepared by de Aguiar and reported that it is reasonably stable. Reaction of 1,8-diaminonaphthalenes (**213**) with nitrous acid or nitrosodiarylamines (87) is used not only for the synthesis of the unsubstituted naphtho[1,8-*de*]triazine (**197a**) (87, 264–265, 272–274, 276, 277, 294,) but also for the preparation of compounds substituted at the nitrogen (N–1) or in the naphthalene ring (87, 257, 265–267, 269–271, 275–277, 282). The best yields were obtained from the method described by Tavs, Sieper, and Beecken (96% **197a**) (277).



213 **197**

1,8-Diaminonaphthalenes (**213**) were coupled with diazonium salts and the formed substances were diazotized with nitrous acid, but the structure of the formed compounds was not fully established (266, 269).

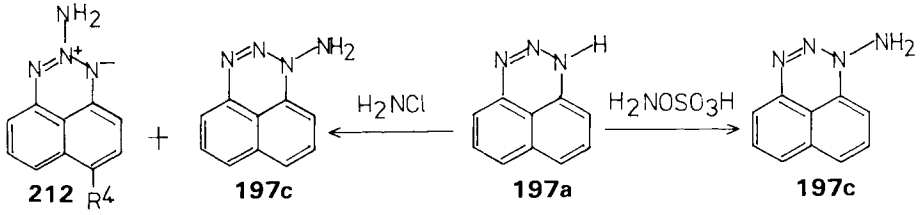
Alkylation or arylation of 1*H*-naphtho[1,8-*de*]triazines (**197b**) affords, depending on the structure of the starting material, the reaction conditions and the alkylating or arylation agent 1-substituted naphtho[1,8-*de*]triazines (**197**) and/or 2-substituted naphtho[1,8-*de*]triazines (**212**) (294, 275–277, 284). The two classes of naphtho[1,8-*de*]triazines can easily be differentiated since 1-substituted naphtho[1,8-*de*]triazines (**197**) are normally red whereas the 2-substituted naphtho[1,8-*de*]triazines (**212**) were reported to be blue. The correct structure of the blue compounds were determined by Perkins (276).

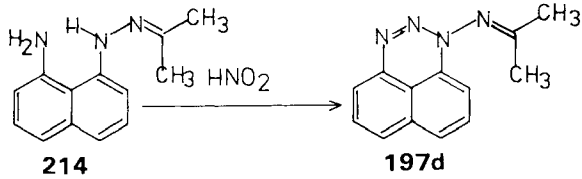


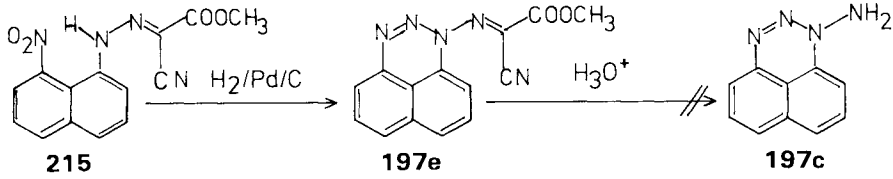
197b **197** **212**

1-Aminonaphtho[1,8-*de*]triazine (**197c**) was isolated from the interaction of 1*H*-naphtho[1,8-*de*]triazine (**197a**) with hydroxylamine-*O*-sulfonic acid in aqueous alkali (279–281). Amination of **197a** with ethereal chloramine gives a mixture of 1-amino- (**197c**), 2-aminonaphtho[1,8-*de*]triazine (**212a**) (R^4 = H), and 2-amino-4-chloronaphtho[1,8-*de*]triazine (**212b**) (R^4 = Cl) (280). Reaction of the acetone 8-amino-1-naphthylhydrazone (**214**) with nitrous acid yielded

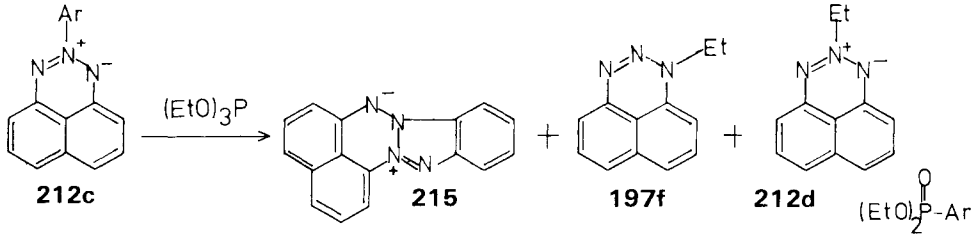
the 1-[(isopropylidene)amino]naphtho[1,8-*de*]triazine (**197d**) (282). Methyl-(naphtho[1,8-*de*]triazin-1-ylimino)cyanacetate (**197e**) was prepared by hydrogenation of methyl 8-nitro-1-naphthylhydrazonocyanacetate (**215**) over 5% palladium on carbon at 0 °C (281). It could not be used for the synthesis of **197c** through acid hydrolysis, which is in agreement with the finding that **197c** is decomposed by acid.



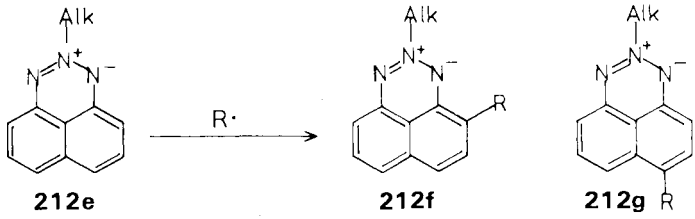




Heating the 2-arylnaphtho[1,8-*de*]1,2,3-triazines (**212c**) with 2 moles of triethyl phosphite affords besides benzotriazolo[2,1-*d*]naphtho[1,8-*de*]1,2,3-triazines (**215**), 1-ethyl- (**197f**), and 2-ethylnaphtho[1,8-*de*]1,2,3-triazine (**212d**) (278). A mechanism for this reaction is suggested.



Reaction of 2-alkylnaphtho[1,8-*de*]1,2,3-triazines (**212e**) with radicals affords 4- (**212f**) and/or 6-substituted 2-alkylnaphtho[1,8-*de*]1,2,3-triazines (**212g**) (290, 291).



212e **212f** **212g**

2. *Compound Survey*

Table IV-10 lists the naphtho[1,8-*de*]triazines reported in the literature.

3. *Physical Properties*

As mentioned, all naphtho[1,8-*de*]triazines (**197**) and (**212**) are deeply colored, crystalline compounds, which are stable at room temperature. 1-Substituted naphtho[1,8-*de*]triazines (**197**) are more basic than the isomeric 2-substituted derivatives (**212**) and can therefore be precipitated as salts from solutions in nonpolar solvents by addition of mineral acids (277). This difference in basicity can be used for the separation of a mixture of **197** and **212** (277), the mixtures can also be separated by chromatography. **197** are soluble in concentrated sulfuric acid, giving a colored (yellow, red-brown) solution (265).

A large amount of infrared, ultraviolet, visible, and PMR spectroscopic data has been reported for both classes of compounds (87, 276, 277, 279–281, 283, 289–291). The following electronic spectra are published: for 1*H*-naphtho[1,8-*de*]triazine (**197a**), $\lambda_{max}(\epsilon) = 452$ (750), 338.5 (10.000), and 232.5 nm (31.000), for 1-methylnaphtho[1,8-*de*]triazine (**197g**), 451 (950), 338 (10.200), and 231.5 nm (32.000) (276)· and for 2-methylnaphtho[1,8-*de*]triazine (**212a**), 655 (570), 603 (820), 559 (820), 355 (12.900), and 231.5 nm (33.000) (276) or 700 (2.53), 602 (2.94), and 556 nm (2.94) (277). The first spectrum of **212a** is measured in ethanol and the second is recorded in methanol.

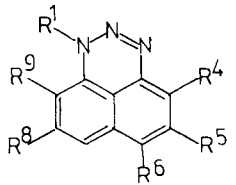
π-Bond orders, π-electron densities, energies of the highest occupied molecular orbital, total π-electronic energies, and energies of the first π-π^*-transition were calculated by a Russian chemist, using the Hückel MO approximations (283).

4. *Reactions*

Alkylation of 1-methylnaphtho[1,8-*de*]triazine (**197g**) with dimethyl sulfate yields the 1,3-dimethylnaphtho[1,8-*de*]triazinium methylsulfate (**216**) of

TABLE IV-10. NAPHTHO[1,8-*de*]1,2,3-TRIAZINES

A. 1*H*-Naphtho[1,8-*de*]1,2,3-triazines

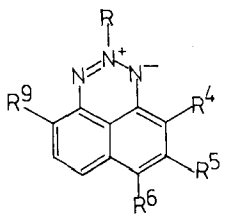


R^1	R^4	R^5	R^6	R^8	R^9	m.p. (°C)	Refs.
H	H	H	H	H	H	230 (dec.)	276
						235–237 (dec.)	280
						236–237 (dec.)	265, 274
						258–262 (dec.)	273, 277
						260–262 (dec.)	87
							268, 292–294
H	H	H	SO_3H	H	H		271
H	H	SO_3H	H	SO_3H	H		271
H	CH_3	H	H	H	CH_3	204–206	277
						206–208	87
H	CH_3	CH_3	H	H	H	196–200 (dec.)	87/277
H	Br	Br	H	H	Br	216–218 (dec.)	275
CH_3	H	H	H	H	H	86–87	277
						91–92	276

CH_3	CH_3	H	H	H	CH_3	113–115	277
CH_3	CH_3	CH_3	H	H	H	140–141	277
C_2H_5	H	H	H	H	H	73–74	276
						77–78	277/278
$(CH_3)_3C-CH_2$	H	H	H	H	H	71–72	277
$C_{12}H_{25}$	H	H	H	H	H	50–52	277
$CH_2-COOC_2H_5$	H	H	H	H	H	91–94	277
$C_6H_5-CH_2$	H	H	H	H	H	126–130	277
$C_6H_5-CH_2$	CH_3	CH_3	H	H	H	158–160	277
$2,4,6-(CH_3)_3C_6H_2-CH_2$	H	H	H	H	H	160–162	277
C_6H_5	H	H	H	H	H	131–133	87
						134	265
$2-O_2N-C_6H_4$	H	H	H	H	H	170–172	277
$2,4-(O_2N)_2C_6H_3$	H	H	H	H	H	163 (dec.)	265
						167–170 (dec.)	87, 277
$2,6-(O_2N)_2C_6H_3$	H	H	H	H	H	164–165	277
$C_6H_5-SO_2$	H	H	H	H	H		259, 267
NH_2	H	H	H	H	H	135–140 (dec.)	279
						154.5–155.5	280
						158	281
Picrate						124	281
Tos–NH	H	H	H	H	H	153–155 (dec.)	281
$(Tos)_2N$	H	H	H	H	H	185 (dec.)	281
$(CH_3)_2C=N$	H	H	H	H	H	115	282
$N=C(CN)COOCH_3$	H	H	H	H	H	135 (dec.)	281
$C_6H_5-CH=N$	H	H	H	H	H	151–152	280

TABLE IV-10 (*continued*)

B. 2*H*-Naphtho[1,8-*de*]triazines

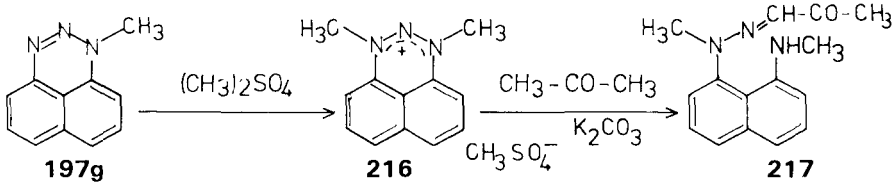


R^2	R^4	R^5	R^6	R^9	m.p. (°C)	Refs.
CH_3	H	H	H	H	129–130	277
					132	276/294
1,3,5-$(O_2N)_3C_6H_3$					154	276
CH_3	H	H	–)$_2$	H	270 (dec.)	291
CH_3	H	H	$(CH_3)_2CCN$	H	153–154	290
CH_3	H	H	C_6H_5–CO	H	169–170	291
CH_3			$H_4(C_6H_5–CO)_2$		280–281	291
CH_3			H_2Br_4		212–213 (dec.)	276
CH_3	CH_3	H	H	CH_3	135–137	277
CH_3	CH_3	H	–)$_2$	CH_3	260 (dec.)	291
CH_3	CH_3	H	$(CH_3)_2CCN$	CH_3	224–225	290

CH_3	CH_3	CH_3	H	H	103–105	277
CH_3	$(CH_3)_2CCN$	H	H	H	153–154	290
CH_3	C_6H_5-CO	H	H	H	176–177	291
C_2H_5	H	H	H	H	84–85	276
					87–88	277/278
$1,3,5\text{-}(O_2N)_3C_6H_3$					108–109	276
C_2H_5	CH_3	H	H	CH_3	76–77	277
$(CH_3)_3C-CH_2$	H	H	H	H	98–99	277
$C_{12}H_{25}$	H	H	H	H	52	277
$C_{12}H_{25}$	CH_3	H	H	CH_3	68–69	277
$CH_2COOC_2H_5$	H	H	H	H	130	277
$C_6H_5-CH_2$	H	H	H	H	136	277
$C_6H_5-CH_2$	CH_3	CH_3	H	H	144–145	277
$2,4,6\text{-}(CH_3)_3C_6H_2-CH_2$	H	H	H	H	142–144	277
$C_6H_5-CH=CH$	H	H	H	H	168	276
$C_6H_5-CH=CH-CH=CH$	H	H	H	H	~165[a]	276
$2\text{-}O_2N-C_6H_4$	H	H	H	H	168–170	277
$2\text{-}O_2N-C_6H_4$	CH_3	H	H	CH_3	153–154	277
$2\text{-}O_2N-C_6H_4$	CH_3	CH_3	H	H	167–169	277
$2,4\text{-}(O_2N)_2C_6H_3$	H	H	H	H	174–175	277
$2,6\text{-}(O_2N)_2C_6H_3$	H	H	H	H	252–253	277
NH_2	H	H	H	H	179–181	280
NH_2	Cl	H	H	H	197–198	280

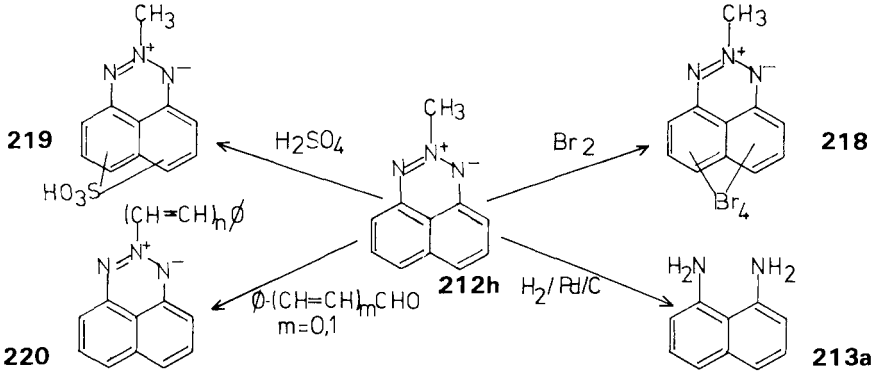
[a] Structure not fully established.

melting point 263 to 265 °C (277, 284). **216** reacts with acetone in the presence of potassium carbonate to give the hydrazone **217** (284). Under similar reaction conditions 2-methylnaphtho[1,8-*de*]triazine (**212h**) can not be further alkylated (277, 284).



197g **216** **217**

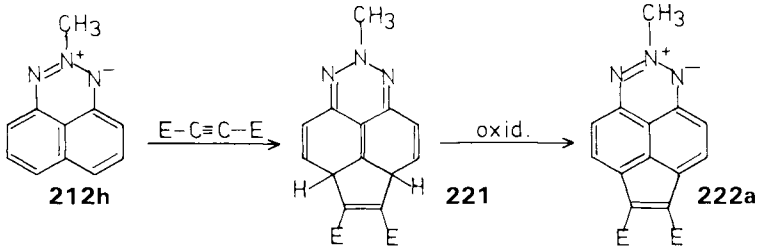
2-Methylnaphtho[1,8-*de*]triazine (**212h**) can be brominated very readily to give a tetrabromo derivative (**218**), the structure of which is not fully established (276). **212h** is also soluble in cold concentrated sulfuric acid to give a water-soluble blue product, presumably a sulfonic acid (**219**) (276). The methyl group of **212h** undergoes base-catalyzed condensations with benzaldehyde and cinnamaldehyde· the structure of the condensation products is considered to be **220a** (n = 1) and **220b** (n = 2) (276). Hydrogenation of **212h** with 10% palladium on charcoal at room temperature affords 1,8-diaminonaphthalene **213a** and methylamine (276), this is in agreement with the structure of the starting material.



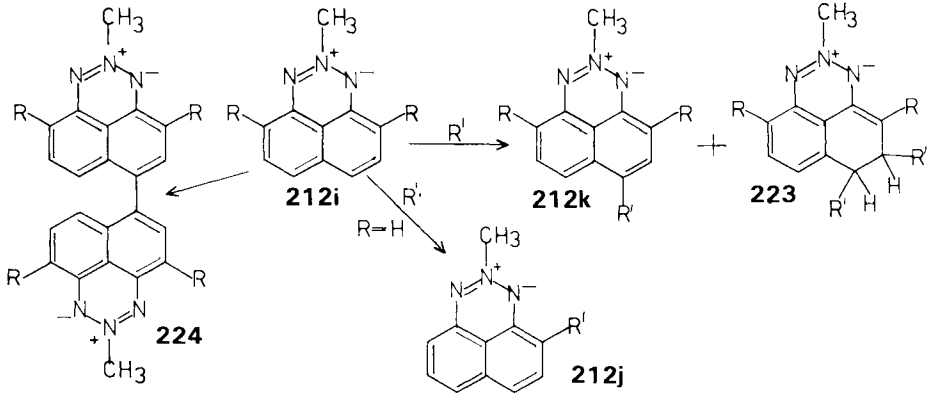
219 **218** **212h** **220** **213a**

Reaction of **212h** with dimethyl acetylene dicarboxylate on refluxing with *o*-dichlorobenzene yields, via a thermally allowed 1,11-dipolar cycloaddition, the compound **221**, which is dehydrogenated under the reaction conditions to give the red acenaphtho[5,6-*de*]triazine (**222a**) (288). Better yields were obtained when sulfur was added as a dehydrogenating agent.

2-Methylnaphtho[1,8-*de*]triazines (**212i**) react with α-cyanoisopropyl radicals to give substitution (**212j**, **212k**) and addition products (**223**) (290). Reaction of



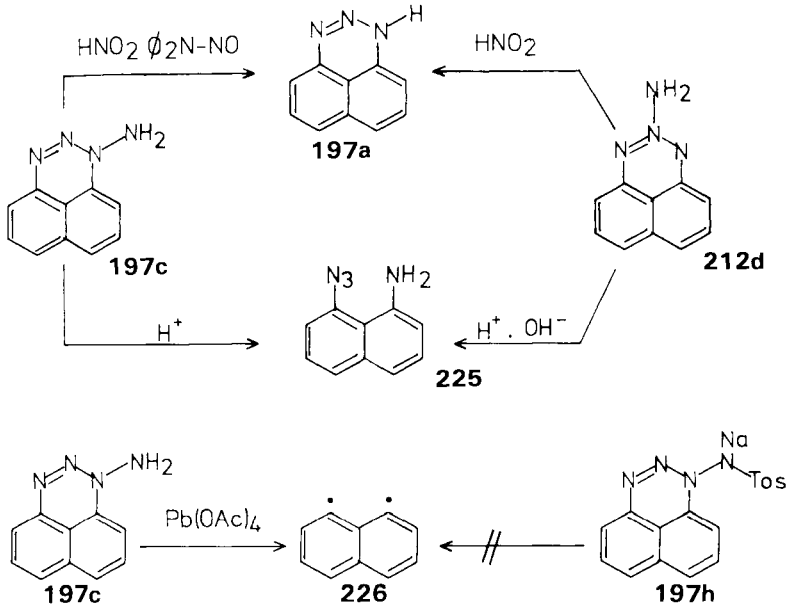
212i with benzoyloxy radicals affords only substitution products (**212j, 212k**) while reaction of **212i** with diphenylpicrylhydrazyl yields the dimerized 2-methylnaphtho[1,8-*de*]triazines (**224**) (291).



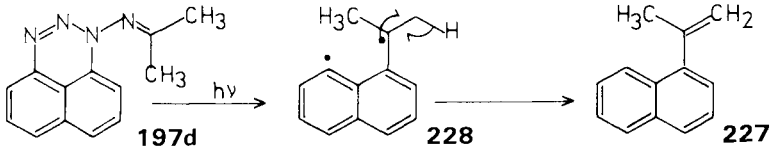
Treatment of 2-(2-nitrophenyl)naphtho[1,8-*de*]triazines (**212c**) with triethylphosphite led to the isolation of the new heterocyclic system (**215**), 1-ethylnaphtho[1,8-*de*]triazine (**197f**), and 2-ethylnaphtho[1,8-*de*]triazine (**212d**) (278, 289).

1-Amino- (**197c**) and 2-aminonaphtho[1,8-*de*]triazine (**212d**) can be deaminated by nitrous acid or diphenylnitrosamine to give 1*H*-naphtho[1,8-*de*]triazine (**197a**) (280). Both compounds rearrange smoothly with acids to 1-amino-8-azidonaphthalene (**225**), under basic conditions **197c** is stable but **212a** also yields **225** (280).

Oxidation of 1-aminonaphtho[1,8-*de*]triazine (**197c**) with lead tetraacetate results in the evolution of nitrogen and 1,8-didehydronaphthalene (**226**) is formed, which can be trapped by olefins, acetylenes, hydrogen, or benzene (279, 281, 286, 287). The 1,2-addition of 1,8-didehydronaphthalene (**226**) to olefins is stereospecific and the overall reactions can be explained by a singlet diradical structure. Attempts to prepare 1,8-didehydronaphthalene (**226**) through pyrolysis or photolysis of the sodium salt of 1-[(4-toluenesulfonyl)-amino]naphtho[1,8-*de*]triazine (**197h**) failed (281).

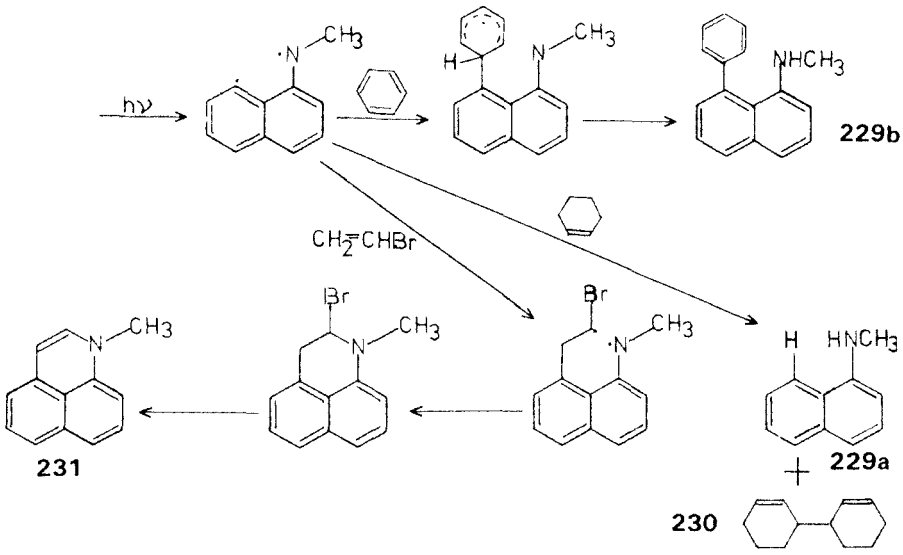


Photolysis of 1-(isopropylidenamino)naphtho[1,8-*de*]triazine (**197d**) in benzene provided a 60% yield of 1-isopropenylnaphthalene (**227**) (282). The formation of **227** is explained by a 1,6-hydrogen shift in the initially formed 1,4-diradical **228**.



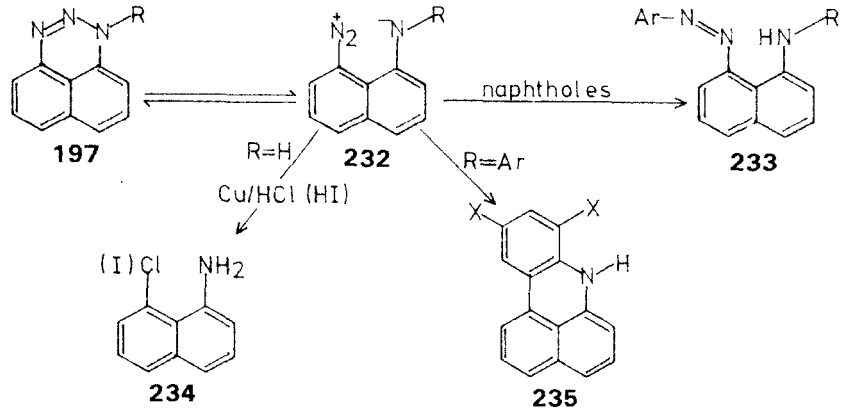
Photolysis of 1-methylnaphtho[1,8-*de*]1,2,3-triazine (**197g**) in cyclohexene yields 1-(methylamino)naphthalene (**229a**) and bicyclohexyl (**230**), while the photolysis of **197g** in benzene affords 1-(methylamino)-8-phenylnaphthalene (**229b**) as the sole detectable product, suggesting the following mechanism (285, 364). Photolysis of **197g** in the presence of vinyl bromide led to the isolation of 1-methyl-1-azaphenalene (**231**).

A number of reactions of naphtho[1,8-*de*]triazines (**197**) are known, which are best explained by intermediate formation of the diazonium compound **232**, a reaction well-known for 1,2,3-benzotriazines. Heating **197a** with hydrochloric acid (271) or hydriodic acid (268) in the presence of copper powder affords 1-amino-8-chloronaphthalene (**234a**) and 1-amino-8-iodonaphthalene (**234b**), respectively. Heating 1-phenyl- (**197i**) or 1-(2,4-dinitrophenyl)naphtho[1,8-*de*]-



triazine (**197j**) in nitrobenzene affords benzacridines (**235**) (265). Coupling of **197a** with naphthols to give azo dyes (**233**) (267, 294) and also with diazonium compounds is reported (270).

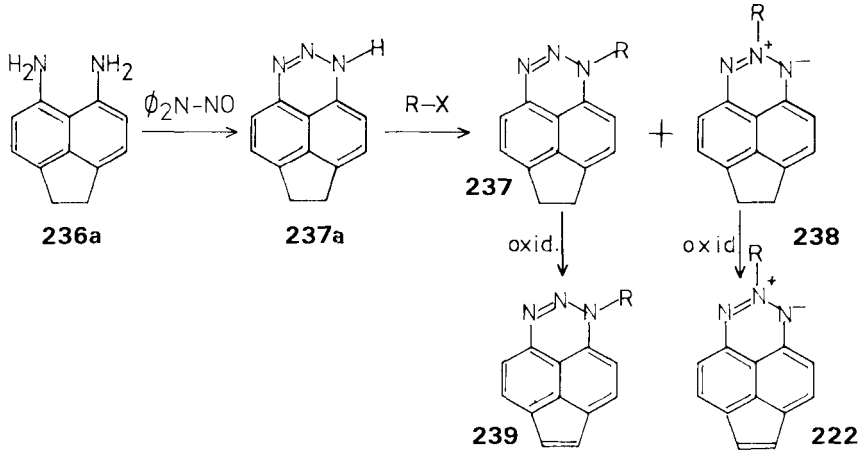
On reaction with dichlorobenzoquinone chloroimide **197a** forms an indophenol the structure of which was not given (272).



III CONDENSED WITH THE ACENAPHTHYLENE SYSTEM

A. Acenaphtho[5,6-*de*]triazines

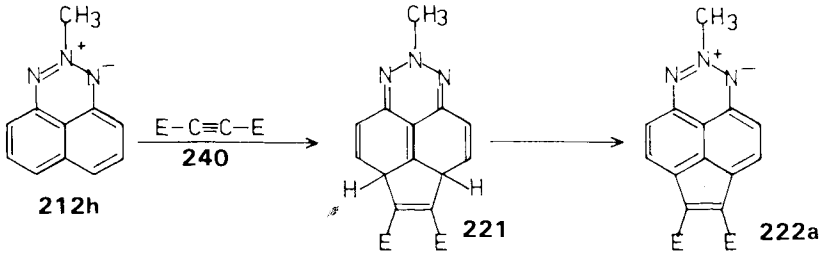
Diazotization of 5,6-diaminoacenaphthene (**236a**) with nitrous acid or diphenylnitrosamine affords 6,7-dihydroacenaphtho[5,6-*de*]triazine (**237a**) of m.p. 195 to 200 °C (277, 295 296). Alkylation or arylation of **237a** yields a mixture of red 1-substituted (**237**) and blue 2-substituted 6,7-dihydroacenaphtho[5,6-*de*]triazines (**238**), which can be separated by chromatography. Oxidation of **237** or **238** with *o*-chloranil affords the aromatic yellow 1-substituted acenaphtho[5,6-*de*]triazines (**239**) and red 2-substituted acenaphtho[5,6-*de*]triazines (**222**) (295, 296).



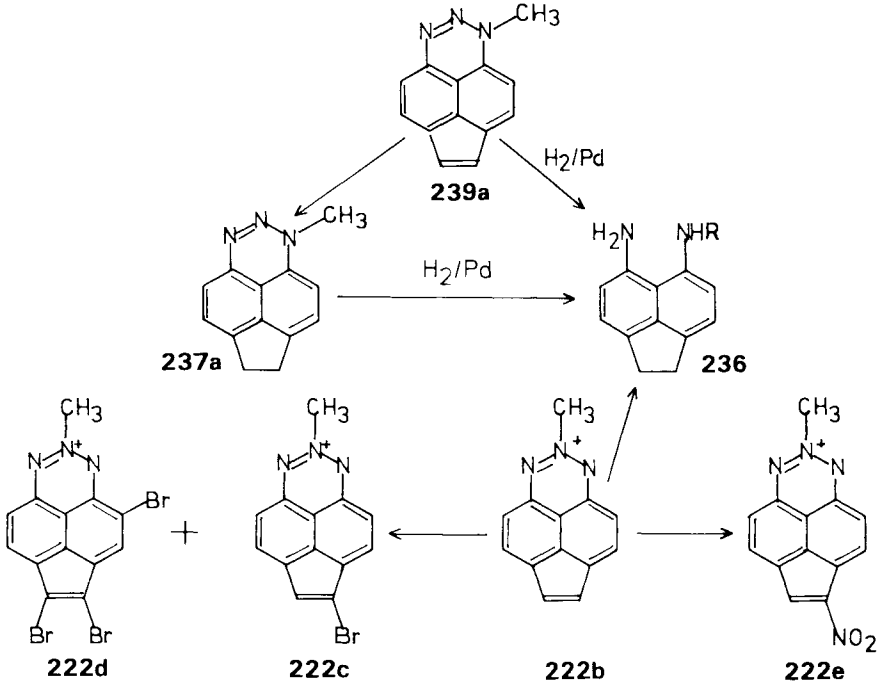
Interaction of 2-methylnaphtho[1,8-*de*]triazine (**212h**) with dimethyl acetylene dicarboxylate (**240**) gives, via a 1,11-dipolar cycloaddition and subsequent dehydrogenation the red 2-methyl-6,7-bis(methoxycarbonyl)acenaphtho[5,6-*de*]triazine (**222a**) (m.p. 233 °C) (288). The reaction was cleaner and the best yield was obtained in the presence of three equivalents of sulfur as dehydrogenating agent. Analogous cycloadditions were observed with diethyl acetylene dicarboxylate, methyl propiolate, and 2-(2,4-dinitrophenyl)naphtho[1,8-*de*]triazine instead of **212h**, but no experimental details were published (288).

The following electronic spectrum is recorded for the blue 2-methylacenaphtho[5,6-*de*]1,2,3-triazine (**222b**) in ethanol: λ_{max} (ϵ) = 464 (1.470), 337 (35.300), 330 (25.400), 322.5 (24.400), and 248 nm (18.800) (360).

Reduction of 1-methyl-6,7-dihydroacenaphtho[5,6-*de*]1,2,3-triazine (**237a**)



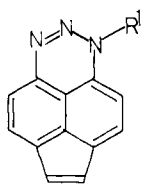
or 1-methylacenaphtho[5,6-*de*] 1,2,3-triazine (**239a**) with hydrogen and palladium as the catalyst yields 5-amino-6-methylaminoacenaphthene (**236b**) (R = CH_3) (296, 300); the reduction of **239a** to give **237a** is also reported. Reduction of 2-methylacenaphtho[5,6-*de*] 1,2,3-triazine (**222b**) yields 5,6-diaminoacenaphthene (**236a**) (R = H) (296). Bromination of **222b** led to the isolation of a mono- and a tribromo derivative, which were formulated as 6-bromo- (**222c**) and 4,6,7-tribromo-2-methylacenaphtho[5,6-*de*] 1,2,3-triazine (**222d**) (296); the compound obtained by nitration of **222b** is formulated as the 6-nitro-2-methylacenaphtho[5,6-*d*] 1,2,3-triazine (**222e**) (296).

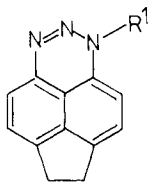


Photolysis of 1-methylacenaphtho[5,6-*de*] 1,2,3-triazine (**239a**) in the presence of vinyl bromide was used for the synthesis of *N*-methylacenaphtho-

TABLE IV-11 ACENAPHTHO[5,6-*de*]1,2,3-TRIAZINES

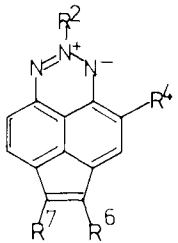
A. 1*H*-Acenaphtho[5,6-*de*]1,2,3-triazines and 6,7-Dihydro-1*H*-acenaphtho[5,6-*de*]1,2,3-triazines

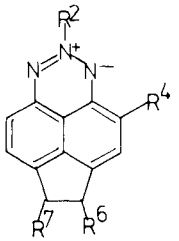




R^1	m.p. (°C)	Refs.	m.p. (°C)	Refs.
H		295	195–200 (dec.)	277/295
CH_3	114–115	295	108–109	295, 296
	114.5	296	115–116	277
$C_{12}H_{25}$			83–85	277
2,4,6-$(CH_3)_3C_6H_2$			190–192	277

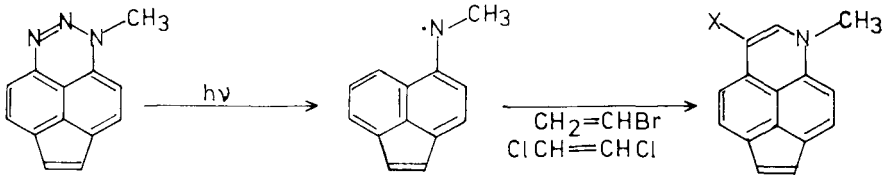
B. 2*H*-Acenaphtho[5,6-*de*]1,2,3-triazines and 6,7-Dihydro-2*H*-acenaphtho[5,6-*de*]1,2,3-triazines





R^2	R^4	R^6	R^7	m.p. (°C)	Refs.	m.p. (°C)	Refs.
CH_3	H	H	H	178–179	295, 296	167–168	295, 296
						168–170	277
CH_3	H	Br	H	300	296		
CH_3	H	NO_2	H	230–236	296		
CH_3	H	$COOCH_3$	$COOCH_3$	233	288		
CH_3	Br	Br	Br	290–295 (dec.)	296		
$C_{12}H_{25}$	H	H	H			67–68	277
2,4,6-$(CH_3)_3C_6H_2$	H	H	H			209–211	277

[5,6-*bc*]pyridine (**241a**) (X = H) (285, 364); photolysis of **239a** in the presence of 1,2-dichloroethene afforded the chloro derivative **241b** (X = Cl) (285). The diradical **242** is formulated as the intermediate in these reactions.



239a **242** **241**

The compounds reported in the literature are listed in Table IV-11.

Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

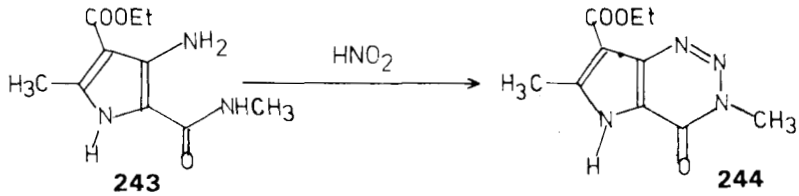
V.

1,2,3-Triazine Rings Condensed with Heterocycles through Carbon Atoms

I. CONDENSED WITH THE PYRROLE RING

A. Pyrrolo[3,2-*d*]1,2,3-triazines

Treatment of the pyrrole derivative (**243**) with nitrous acid afforded the 7-(ethoxycarbonyl)-3,6-dimethylpyrrolo[3,2-*d*]1,2,3-triazin-4-one (**244**) of melting point 242 to 244 °C (297). It has two absorption maxima in the ultraviolet spectrum, at 277 (3.68) and 234 nm (4.53).



243 **244**

II. CONDENSED WITH THE INDOLE SYSTEM

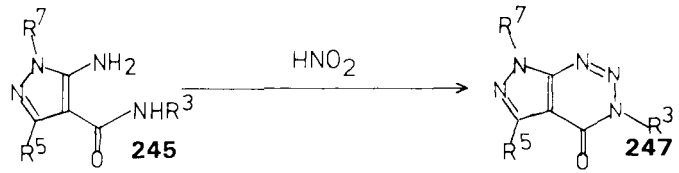
A. 1,2,3-Triazino[5,6-*b*]indoles

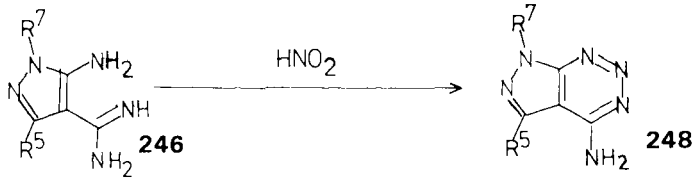
Three derivatives of this system are listed in the subject index of *Chemical Abstracts*, Volume 76, but this seems to be a mistake; the compounds in question are in fact 1,2,4-triazino[5,6-*b*]indoles.

III. CONDENSED WITH THE PYRAZOLE RING

A. Pyrazolo[3,4-*d*]1,2,3-triazines

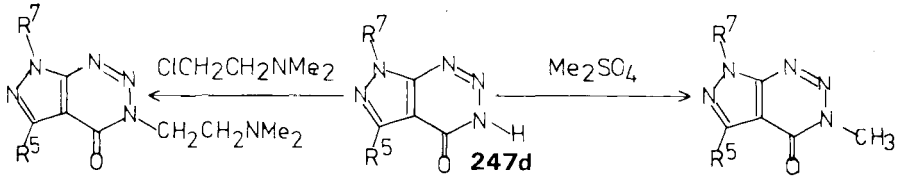
All known compounds of this system (RRI 1160) were prepared either by treatment of 3-aminopyrazole-4-carboxamides (**245**) or of 3-aminopyrazole-4-carboxamidines (**246**) with nitrous acid yielding either pyrazolo[3,4-*d*] 1,2,3-triazin-4-ones (**247**) or 4-aminopyrazolo[3,4-*d*] 1,2,3-triazines (**248**) (298–303).





The isolated pyrazolo[3,4-*d*] 1,2,3-triazines **247** and **248** are crystalline, mostly yellow compounds. Only a few properties of these compounds have been reported so far. Justoni and Fusco (298) said that the 5,7-diphenylpyrrolo-[3,4-*d*] 1,2,3-triazin-4-one (**247b**) (R^3 = H, $R^5 = R^7 = C_6H_5$) undergoes only slight decomposition when heated for a long time in diluted or concentrated hydrochloric acid and does not dissolve in this medium. **247a** ($R^3 = R^5 = R^7$ = H) is soluble in bases but its 3-methyl analogue is insoluble. The 7-methylpyrazolo[3,4-*d*] 1,2,3-triazin-4-one (**247c**) ($R^3 = R^5$ = H, $R^7 = CH_3$) has an absorption maximum in the ultraviolet spectrum at 284 nm (ϵ = 5.300) at pH = 1 and at 300 nm (7.600) at pH = 11 (302).

3*H*-Pyrazolo[3,4-*d*] 1,2,3-triazin-4-ones (**247d**) can be methylated at N-3 by treatment with dimethyl sulfate and alkylated by reaction with dimethylamino-ethyl chloride in the presence of sodium ethoxide (299, 300).



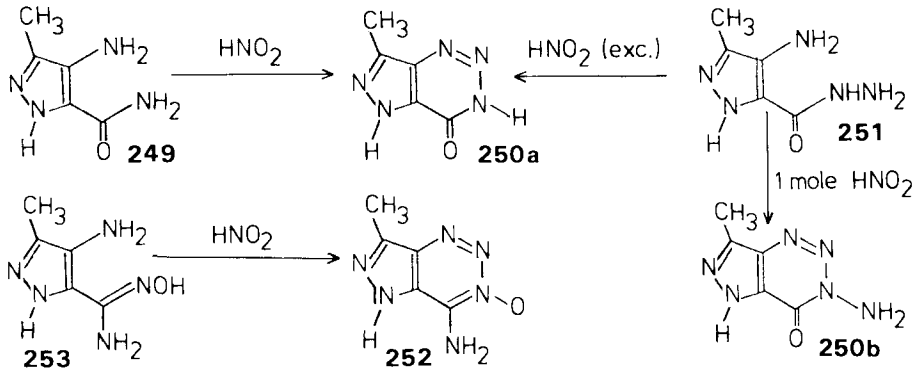
In Table V-1 are listed the compounds of this class that have been reported in the literature.

TABLE V-1. PYRAZOLO[3,4-*d*]1,2,3-TRIAZINE DERIVATIVES

R^3	R^5	R^7	m.p. (°C)	Refs.
Compound **247**				
H	H	H		301
H	H	CH_3	150 (dec.)	302
H	H	C_6H_5	136 (dec.)	299, 300
H	H	4-Cl–C_6H_4	160 (dec.)	299, 300
H	C_6H_5	C_6H_5	160 (dec.)	298
Na	C_6H_5	C_6H_5	230–240 (dec.)	298
CH_3	H	C_6H_5	136–137	299, 300
CH_3	C_6H_5	C_6H_5	155.5	298
$(CH_3)_2N-CH_2CH_2$	H	C_6H_5	103–105	299, 300
Compound **248**				
	H	β-D-Ribofuranosyl	207–208	303

B. Pyrazolo[4,3-*d*]1,2,3-triazines

Reaction of 4-amino-3-methylpyrazole-5-carboxamide (**249**) with nitrous acid affords 7-methylpyrazolo[4,3-*d*]1,2,3-triazin-4-one (**250a**) (m.p. 215 °C) in 83.5% yield (304). The same compound is obtained when 4-amino-5-methylpyrazole-5-carboxhydrazide (**251**) is treated with excess nitrous acid, and **251** affords the 3-amino-7-methylpyrazolo[4,3-*d*]1,2,3-triazin-4-one (**250b**) (m.p. 174 to 177 °C) with 1 mole of nitrous acid. 4-Amino-7-methylpyrazolo-[4,3-*d*]1,2,3-triazine 3-oxide (**252**) (m.p. 252 °C, expl.) is isolated when 4-amino-3-methylpyrazole-5-carboxamidoxime (**253**) is reacted with nitrous acid (304).



The following UV spectra were published for the three known pyrazolo[4.3-*d*]1,2,3-triazines:

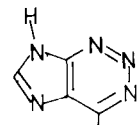
250a:			pH = 1: 272.5	(7.250);	pH = 11: 285	(6.950);	
250b:	MeOH: 280 nm	(6.310);	pH = 1: 243	(11.390);	pH = 11: 312	(4.650);	
						229	(17.200);
252:	MeOH: 355 nm	(2.490);	pH = 1: 302	(3.660);	pH = 11: 355	(3.660);	
	299 nm	(3.660);	235 sh	(16.920);	295	(3.320);	
			220	(19.900);	244	(38.500);	
	244 nm	(24.200);					

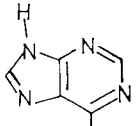
IV. CONDENSED WITH THE IMIDAZOLE RING

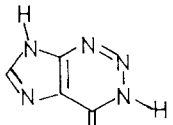
A. Imidazo[4,5-*d*]1,2,3-triazines

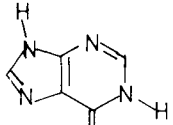
1. Preparation

Since the first synthesis of a member of this heterocyclic system in 1951 (315) a large number of papers on the chemistry of derivatives of imidazo[4,5-*d*]1,2,3-triazine (RRI 1159) have been published as 4-aminoimidazo[4,5-*d*]1,2,3-triazine (**255a**) is the 2-aza analogue of adenine (**254**) and imidazo[4,5-*d*]1,2,3-triazin-4-one (**257a**) is the 2-aza analogue of hypoxanthine (**256**). Therefore some biochemical reactivity can be expected for compounds of this system. Probably prior to Wooley and Shaw (315) Stetten and Fox (323) had already prepared (**257a**) but since they assumed an incorrect structure for their starting material (324) they were not able to give the correct structure of the isolated compound.


255a

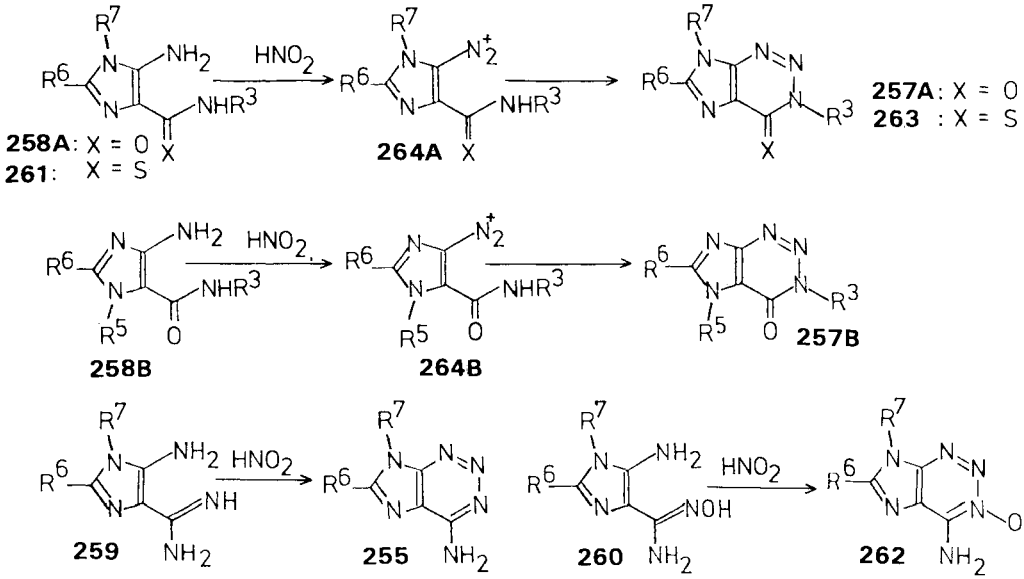

254


257a


256

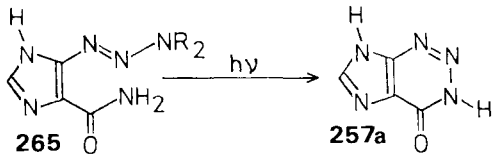
The methods for the synthesis of imidazo[4,5-*d*]1,2,3-triazine derivatives are the same as already used for other condensed 1,2,3-triazine systems, that is, starting from an imidazole derivative and construction of the 1,2,3-triazine ring. Reaction of 4-aminoimidazole-5-carboxamides (**258**), 4-aminoimidazole-5-carboxamidines (**259**), 4-aminoimidazole-5-carboxamidoximes (**260**), or 4-aminoimidazole-5-thiocarboxamides (**261**) with nitrous acid affords imidazo[4,5-*d*]-1,2,3-triazin-4-ones (**257**) (306–315, 322, 359, 382), 4-aminoimidazo[4,5-*d*]-1,2,3-triazines (**255**) (303, 314–318), 4-aminoimidazo[4,5-*d*]1,2,3-triazine 3-

oxides (**262**) (305, 313, 314), or imidazo[4,5-*d*] 1,2,3-triazine-4-thiones (**263**) (319), respectively.

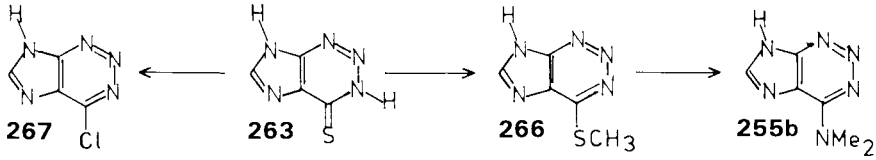


The first step in these reactions should be the formation of a diazonium salt, which cyclized to the isolated imidazo[4,5-*d*] 1,2,3-triazine derivatives. 5-Diazoimidazole-4-carboxamide (**264**) was isolated and was shown to be a stable compound that can be stored under anhydrous conditions for long periods of time. It cyclizes readily in aqueous solutions, over a wide range of pH values, to imidazo[4.5-*d*] 1,2,3-triazin-4-one (**257a**) (310).

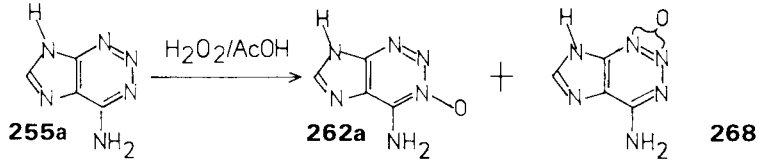
Most 4-(dialkyltriazeno)-imidazole-5-carboxamides (**265**) are stable in water and 0.1*N* hydrochloric acid in the absence of light. Exposure of these solutions to light resulted in the formation of imidazo[4,5-*d*] 1,2,3-triazine-4-one (**257a**) (308).



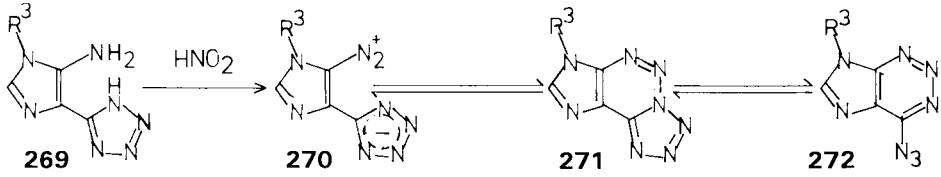
Imidazo[4,5-*d*] 1,2,3-triazine-4-thione (**263**) can be methylated to yield the 4-(methylmercapto)imidazo[4,5-*d*] 1,2,3-triazine (**266**), which reacts with dimethylamine to afford the 4-(dimethylamino)imidazo[4,5-*d*] 1,2,3-triazine (**255b**) (319). Chlorination of **263** was used for the synthesis of 4-chloroimidazo[4,5-*d*] 1,2,3-triazine (**267**) (320).



Oxidation of 4-aminoimidazo[4,5-*d*] 1,2,3-triazine (**255a**) with hydrogen peroxide in acetic acid affords a 3:1 mixture of two 4-aminoimidazo[4,5-*d*] 1,2,3-triazine *N*-oxides (313). The major component was identified as the 4-aminoimidazo[4,5-*d*] 1,2,3-triazine 3-oxide (**262a**) but the position of the *N*-oxide group in the second compound (**268**) could not be fully established (313).



Diazotization of 5-(4-amino-5-imidazolyl)tetrazoles (**269**) may afford three different compounds, namely, **270**, **271** and **272** (321). From spectroscopic studies the 4-azidoimidazo[4,5-*d*] 1,2,3-triazines (**272**) seem to be the least favored product.



2. *Compound Survey*

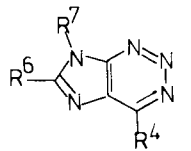
In Table V-2 are listed the compounds of this class that have been reported in the literature.

3. *Physical Properties and Reactions*

Imidazo[4,5-*d*] 1,2,3-triazines are crystalline, colored (yellow, brown) compounds, which very often decompose or explode at their melting point. A number of spectroscopic studies were reported for these compounds. Owing to a strong band at 1690 cm^{-1} in the infrared spectra of **257**, the imidazo[4,5-*d*]-1,2,3-triazin-4-one structure is thought to be the predominant tautomeric

TABLE V-2. IMIDAZO[4,5-*d*]1,2,3-TRIAZINES

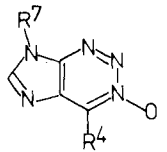
A. 7*H*-Imidazo[4,5-*d*]1,2,3-triazines



R^4	R^6	R^7	m.p. (°C)	Refs.
Cl	H	H		320
SH	H	H (tautomer)		319
SCH_3	H	H		319
NH_2	H	H	350–355	326
			>350	313/315
NH_2	H	H 1- or 2-oxide	>350	313
NH_2	H	Cyclopentyl	212–215	303
NH_2	H	β-D-Ribofuranosyl	240–241	303
			260	317
NH_2	H	2-Desoxy-β-D-ribofuranosyl	203–204	303
NH_2	H	β-D-Ribofuranosyl-3′,5′-cyclophosphate		386
NH_2	H	β-D-Arabinofuranosyl	236–238	303
NH_2	H	β-D-Xylofuranosyl	234–235	303
NH_2	OH	H		318
$N(CH_3)_2$	H	H		319

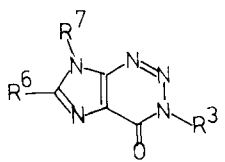
TABLE V-2 (*continued*)

B. 7*H*-Imidazo[4,5-*d*]1,2,3-triazine 3-oxides



R^4	R^7	m.p. (°C)	Refs.
CH_3	H	230 (dec.)	313
NH_2	H	>350	313, 326/305
NH_2	β-D-Ribofuranosyl	165–170	313
		195–200 (dec.)	313/305
NH_2	β-D-Ribofuranosyl-3′,5′-cyclophosphate		386

C. 7*H*-Imidazo[4,5-*d*]1,2,3-triazin-4(3H)-ones

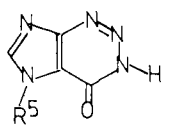


R^3	R^6	R^7	m.p. (°C)	Refs.
H	H	H	204–208 (expl.)	308/315
$\cdot H_2O$			210 (dec.)	310
			>260	310

H	H	CH_3	205–206 (expl.)	311
H	H	β-D-Ribofuranosyl	173–175 (expl.)	382
			176–177 (expl.)	311/306, 316
H	H	2-Desoxy-β-D-ribofuranosyl		316
H	H	2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl-	79–80	382
			84–86	311/306
H	H	2,3-*O*-Isopropyliden-α-D-ribofuranosyl-	175 (dec.)	312
H	H	5-*O*-Phosphono-β-D-ribofuranosyl-Na_2-salt	92–94	382/306
H	H	β-D-Ribofuranosyl-3′,5′-cyclophosphate·$\frac{1}{2}H_2O$		386
H	CH_3	NH_2	>360	309
H	CH_3	NHC_6H_5	190 (dec.)	309
H	CH_3	$N(CH_3)_2$	161 (dec.)	309
H	C_6H_{11}	CH_3	180 (dec.)	307
H	Br	β-D-Ribofuranosyl	95–995	359
H	Br	2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl-	Amorphous	359
H	N_3	2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl-	Amorphous	359
H	NH_2	2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl	173–176	359
H	OCH_3	β-D-ribofuranosyl-	114–116	359
H	OH	β-D-ribofuranosyl-	Amorphous (tautom.)	359
H	SH	β-D-ribofuranosyl-	228–231 (tautom.)	359
CH_3	CH_3	CH_3	197	307
CH_3	CH_3	NH_2	139	309
CH_3	CH_3	NHC_6H_5	108–109	309
$HOOC-CH_2CHCOOH$	H	5-*O*-Phosphono-β-D-ribofuranosyl-		307

TABLE V-2. *Continued*

D. 5*H*-Imidazo[4,5-*d*]1,2,3-triazin-4(3H)-ones



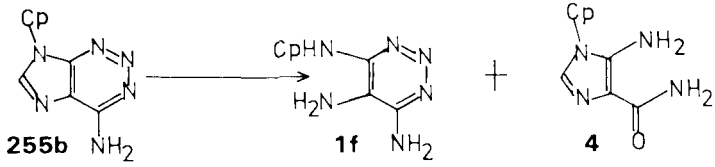
R^5	m.p. (°C)	Refs.
CH_3	199–200 (expl.)	311
β-D-ribofuranosyl	184–185 (expl.)	311

form (310). The following ultraviolet spectra were reported for 5-methylimidazo[4,5-*d*] 1,2,3-triazin-4-one. λ_{max} (log ϵ): in MeOH, 275 (3.51) and 253 nm (4.46) (311); at pH = 11, sh 285 (5.27) and 264 nm (6.05) (311). For 7-methylimidazo[4,5-*d*] 1,2,3-triazin-4-one: in MeOH, 287 (5.48) and sh 245 (4.32) (311), at pH = 11, 292 (7.41), and 250.5 nm (5.88). For 3,6,7-trimethylimidazo-[4,5-*d*] 1,2,3-triazin-4-one: at pH = 7, 297 and 245 nm (307); at pH = 12, 298 and 247 nm (307). For 4-methylimidazo[4,5-*d*] 1,2,3-triazine 3-oxide: at pH = 6, 330, 278, and 240 nm; at pH = 12, 330, 283, and 244 nm (313).

Calculations on the electronic structure of 4-aminoimidazo[4,5-*d*] 1,2,3-triazine (**255a**) were reported by Pullmann and Pullmann (325), and attempts were made by these authors to formulate correlations between the electronic structure and antitumor activity of this compound.

4-Aminoimidazo[4,5-*d*] 1,2,3-triazine 1-oxide (**262a**) can be reduced electrochemically and 4-aminoimidazo[4,5-*d*] 1,2,3-triazine (**255a**) was identified as the reduction product (326).

Hydrolysis of 4-amino-7-cyclopentylimidazo[4,5-*d*] 1,2,3-triazine (**255b**) led to the isolation of 4,5-diamino-6-(cyclopentylamino)-1,2,3-triazine (**1f**) and 4-amino-3-cyclopentylimidazole-5-carboxamide (**4**) (303).

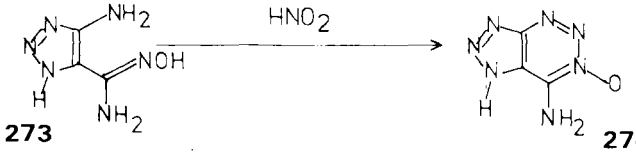


255b **1f** **4**

V. CONDENSED WITH THE 1,2,3-TRIAZOLE RING

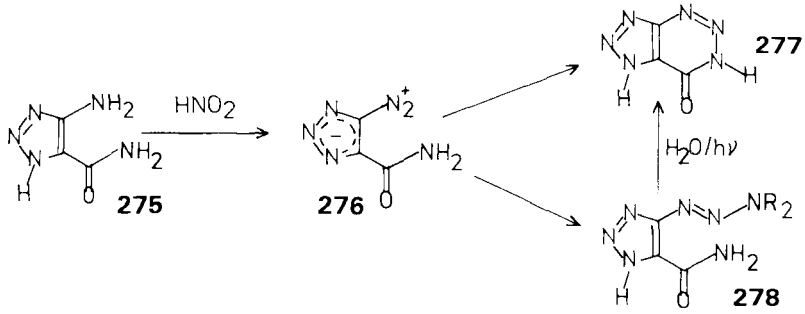
A. 1,2,3-Triazolo[4,5-*d*]1,2,3-triazines

Reaction of 5-amino-1,2,3-triazole-4-carboxamidoxime (**273**) affords 4-amino-1,2,3-triazolo[4,5-*d*] 1,2,3-triazine 3-oxide (**274**) (2,8-diazaadenine 1-oxide) as unstable crystals which decompose explosively on heating to 206 °C (313). The following ultraviolet spectra were recorded for this compound: at pH = 12.5, 370, 280–285 sh, 240–245 sh, and 221 nm; at pH = 5, 348, 276, 241, and 225 nm; and at pH = 2.0, 362, 277, 245, and 218 nm.

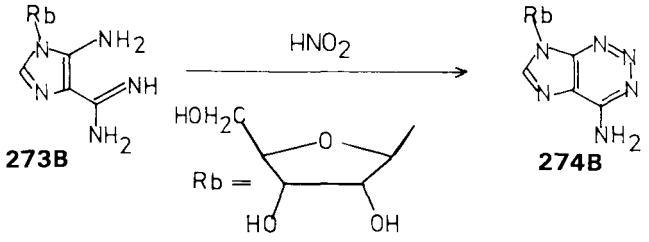


273 **274**

5-Amino-1,2,3-triazole-5-carboxamide (**275**) on treatment with nitrous acid yields the diazonium compound **276**, which can be cyclized to 1,2,3-triazolo-[4,5-*d*] 1,2,3-triazin-4-one (**277**) (m.p. 270 to 275 °C) in aqueous solution, slowly in acidic solution and rapidly at pH 7 (310, 327). **276** reacts with amines to give the triazenes **278**, which can be transformed into the triazolo[4,5-*d*]-1,2,3-triazin-4-ones (**277**) in aqueous solution in the presence of light (327). 1,2,3-Triazolo[4,5-*d*] 1,2,3-triazin-4-one (**277**) (2,8-diazahypoxanthine) was isolated as the dihydrate and decomposed explosively at 270 °C. When **277** is heated gradually it begins to darken near 200 °C and does not melt below 290 °C. Owing to an absorption at 1740 cm^{-1} in the infrared spectrum it was concluded that the given tautomeric amide structure is the predominant form (310).



Diazotization of 4-amino-3-(β-D-ribofuranosyl)-1,2,3-triazole-5-carboxamidine (**273B**) yields 4-amino-7-(β-D-ribofuranosyl-1,2,3-triazolo[4,5-*d*] 1,2,3-triazine (**274B**)(m.p. 193 to 195 °C) (303).

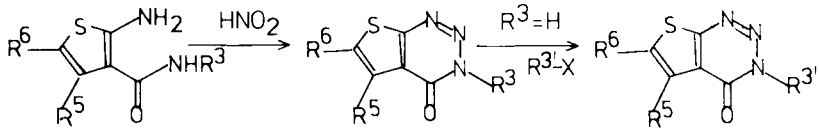


VI. CONDENSED WITH THE THIOPHENE RING

A. Thieno[2,3-*d*]1,2,3-triazines

Reaction of 2-aminothiophene-3-carboxamides (**279**) with nitrous acid is used for the synthesis of thieno[2,3-*d*] 1,2,3-triazin-4-ones (**280**) which are colorless crystalline compounds, mostly decomposing at their melting points. 3-Unsubsti-

tuted derivatives ($R^3 = H$) can be alkylated and since it was shown that alkylation with dimethyl sulfate affords the 3-methyl derivative ($R^{3'} = CH_3$), it is assumed that in all cases alkylation proceeds in the 3-position (328, 329).

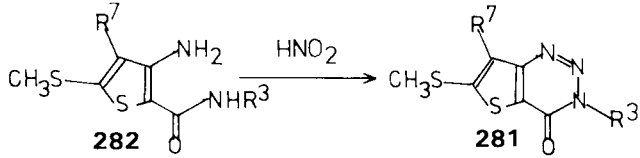


279 **280** **280**

R^3	R^5	R^6	m.p. (°C)	Refs.
H	H	H	180–185 (dec.)	328, 329
H	H	CH_3	180 (dec.)	328, 329
H	CH_3	CH_3	185 (dec.)	329
			185–195 (dec.)	328
H	$-(CH_2)_4-$		175–180 (dec.)	328, 329
CH_3	$-(CH_2)_4-$		118–119	328, 329
$(CH_3)_2N-CH_2CH_2$	$-(CH_2)_4-$			
		·HCl	254–256	329
		Maleate	159–160	329
$(C_2H_5)_2N-CH_2CH_2$	$-(CH_2)_4-$	·HCl	202–203	329
$C_6H_5-CO-CH_2$	$-(CH_2)_4-$		172–173	328, 329
$COOC_2H_5$	$-(CH_2)_4-$		113–114	329

B. Thieno[3,2-*d*]1,2,3-triazines

Five derivatives of thieno[3,2-*d*] 1,2,3-triazin-4-one (**281**) were prepared by reaction of 3-aminothiophene-2-carboxamides (**282**) with nitrous acid (330). The isolated compounds are colorless, crystalline compounds, which are acidic if the 3-position is unsubstituted ($pK_a \sim 6.6$). Because ultraviolet spectra of all derivatives are very similar, one has to conclude that the given amide structure is the predominant tautomeric form. The long-wavelength absorption maxima for these compounds is observed between 305 and 310 nm.

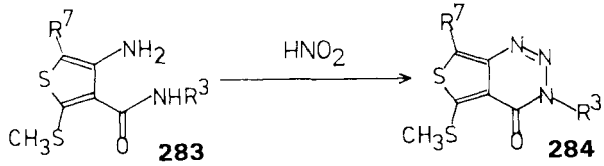


282 **281**

R^3	R^7	m.p. (°C)	Refs.
H	$COOC_2H_5$	170 (dec.)	330
H	$CONHCH_3$	225 (dec.)	330
H	CN	190 (dec.)	330
CH_3	$CONH_2$	302–305	330
CH_3	CN	179–180	330

C. Thieno[3,4-*d*]1,2,3-triazines

Interaction of 3-aminothiophene-4-carboxamides (**283**) with nitrous acid is used for the synthesis of the six known derivatives of thieno[3,4-*d*]-1,2,3-triazin-4-ones (**284**) (330). The isolated compounds are yellow, crystalline substances which are acidic if the 3-position is unsubstituted. The long-wavelength absorption maximum in the ultraviolet spectra is observed between 383 and 399 nm. Characteristic for these compounds is a strong yellow fluorescence which allows them to be observed at a very low concentration.



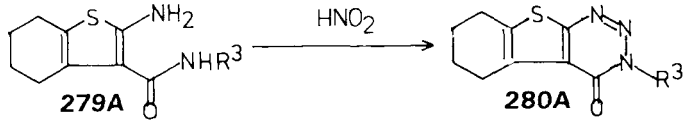
283 **284**

H	$CO-CH_3$	220 (dec.)	330
H	$CO-C_6H_5$	200 (dec.)	330
H	$COOC_2H_5$	210 (dec.)	330
H	$CO-NHCH_3$	260 (dec.)	330
CH_3	$COOCH_3$	228–229	330
CH_3	$CO-NH_2$	300–303	330

VII. CONDENSED WITH THE BENZO[*b*]THIOPHENE SYSTEM

A. Benzothieno[2,3-*d*] 1,2,3-triazines

At present only derivatives of the 5,6,7,8-tetrahydrobenzothieno[2,3-*d*]-1,2,3-triazin-4-one (**280A**) are known (328, 329). They are prepared by reaction of 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamides (**279A**) with nitrous acid or by alkylation of 3-unsubstituted derivatives (R^3 = H) (328, 329). All known compounds are listed in Section VI-A.

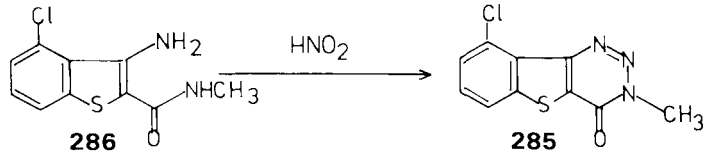


279A **280A**

B. Benzothieno[3,2-*d*]1,2,3-triazines

Only one member of the benzothieno[3,2-*d*]1,2,3-triazine system, the 9-chloro-3-methyl[1]benzothieno[3,2-*d*]1,2,3-triazin-4-one (**285**) (m.p. 269 to

271 °C) is known (383). It is prepared by diazotization of *N*-methyl-3-amino-4-chlorobenzothiophene-2-carboxamide (**286**).

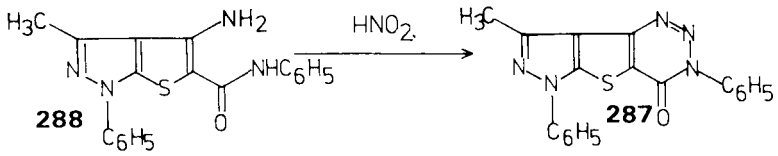


286 **285**

VIII. CONDENSED WITH THE THIENO[2,3-*d*]-PYRAZOLE SYSTEM

A. Pyrazolo[4′,3′:4,5]thieno[3,2-d]1,2,3-triazines

The 8-methyl-3,6-diphenylpyrazolo[4′,3′:4,5]thieno[3,2-*d*]1,2,3-triazine-4-one (**287**) was obtained by Zakharov, Kvitko, and El'tsov in 84% yield through diazotization of 4-amino-3-methyl-1,*N*-diphenylthieno[2,3-*c*]pyrazole-5-carboxamide (**288**) followed by cyclization of the initially formed diazonium compound (331) [m.p. 208 to 211 °C; ultraviolet spectrum (EtOH): λ_{max} (log ϵ) = 315 (3.80) and 275 nm (4.26)].

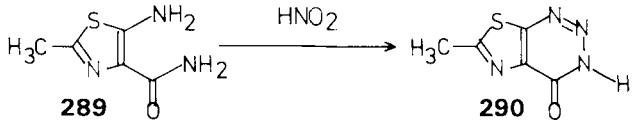


288 **287**

IX. CONDENSED WITH THE THIAZOLE RING

A. Thiazolo[5,4-*d*]1,2,3-triazines

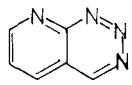
Weidel and Niemilowicz (332) treated 5-amino-2-methylthiazole-4-carboxamide (**289**) with nitrous acid and isolated yellow crystals (m.p. 270–280 °C, dec.) to which they assigned, on the basis of elemental analysis, the structure 2-methylthiazolo[5,4-*d*]1,2,3-triazin-7-one (**290**). 290 is the only known example of the thiazolo[5,4-*d*]1,2,3-triazine system (RRI 1130).



289 **290**

X. CONDENSED WITH THE PYRIDINE RING

Four pyrido-1,2,3-triazines are possible, the pyrido[2,3-*d*] 1,2,3-triazines (**291**), the pyrido[3,2-*d*] 1,2,3-triazines (**292**), the pyrido[3,4-*d*] 1,2,3-triazines (**293**), and the pyrido[4,3-*d*] 1,2,3-triazines (**294**). Of these four systems derivatives of only the pyrido[3,2-*d*] 1,2,3-triazine (RRI 10031) system are known. Calculations on the various pyrido1,2,3-triazines were reported by Wait and Wesley (59).



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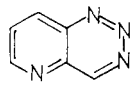

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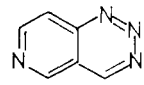

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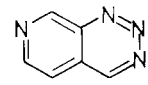
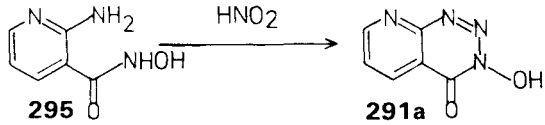


294

A. Pyrido[2,3-*d*] 1,2,3-triazines

At present no compound containing the pyrido[2,3-*d*] 1,2,3-triazine system is reported. Attempts to prepare 3-hydroxypyrido[2,3-*d*] 1,2,3-triazin-4-one (**291a**) through reaction of 2-aminonicotinhydroxamic acid (**295**) with nitrous acid failed (244). Wait and Wesley (59) published theoretical calculations on this system.



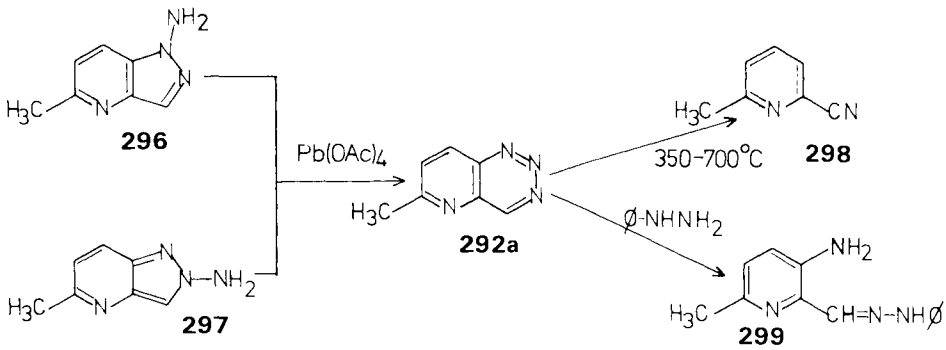
295 **291a**

B. Pyrido[3,2-*d*] 1,2,3-triazines

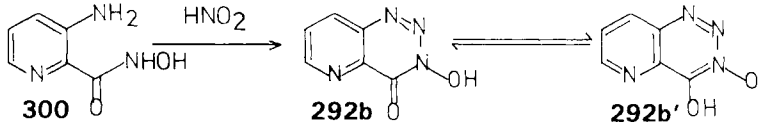
Oxidation of 1-amino-5-methylpyrazolo[4,3-*b*] pyridine (**296**) or 2-amino-5-methylpyrazolo[4,3-*b*] pyridine (**297**) with lead tetraacetate in the presence of calcium oxide gives 6-methylpyrido[3,2-*d*] 1,2,3-triazine (**292a**) as yellow crystals of melting point 146 to 147 °C in 62 to 65% yield (52). The following spectra are reported for this compound. Ultraviolet spectrum: λ_{max} (log ϵ) = 300 (3.63), 290 (3.67), and 218 nm (4.24). PMR spectrum: τ = 0.45 (1H, *s*,4-H), 1.47 (1H, *d*, 8-H), 2.17 (1H, *d*, 7-H) and 7.16 (3H, *s*, 6-CH_3).

Pyrolysis of **292a** between 350 and 700 °C always led to the isolation of 6-methylpyridine-2-carbonitrile (**298**) (60), reaction of **292a** with phenylhydrazine affords 3-amino-6-methylpyridine-2-carboxaldehyde phenylhydrazone (**299**) (52).

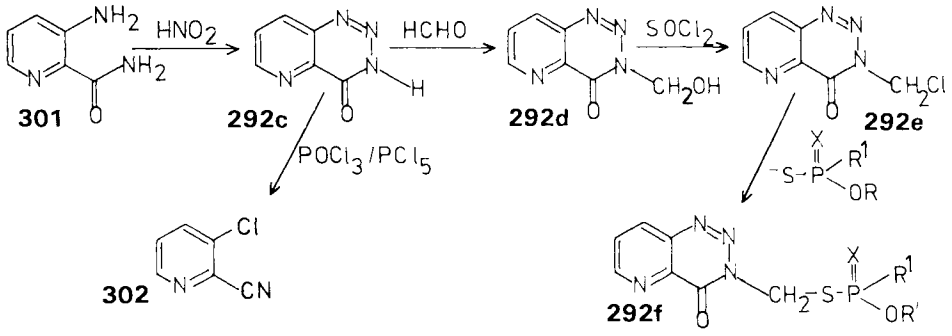
Treatment of 3-aminopicolinhydroxamic acid (**300**) with nitrous acid yields



the yellow 3-hydroxypyrido[3,2-*d*] 1,2,3-triazin-4-one (**292b**) or its tautomer (**292b'**), which explodes on heating to 195 °C and which gives a red color with ferric ions (244).



3-Aminopicolinamide (**301**) reacts with nitrous acid to give pyrido[3,2-*d*]-1,2,3-triazin-4-one (**292c**) (m.p. 230 °C) (333, 334). This reacts with formaldehyde to yield the 3-(hydroxymethyl)pyrido[3,2-*d*] 1,2,3-triazin-4-one (**292d**) [m.p. 140 °C (dec.)] (334) and affords 3-chloropicolino-nitrile (**302**) upon treatment with phosphorous chloride/phosphorus pentachloride (333). **292d** can be transformed into **292e** (m.p. 137 °C), which was reacted with phosphoric acid derivatives to give the phosphorylated pyrido[3,2-*d*] 1,2,3-triazin-4-ones (**292f**). These are useful as acaricides, insecticides, and nematocides (334). Melting points of **292f** are as follows: 43 to 45 °C for X = O, R = C_2H_5, R^1 = SCH_3; 68 to 70 °C for X = S, R = CH_3, R^1 = OCH_3; and 63 to 65 °C for X = S, R = C_2H_5, R_1 = OC_2H_5; 26 additional compounds with this structure were reported but no melting points were given (334).



C. Pyrido[3,4-*d*]1,2,3-triazines

No substance containing the pyrido[3,4-*d*] 1,2,3-triazine system could be found in the literature and no attempts to prepare this system have been reported. Wait and Wesley published theoretical calculations on this system (59).

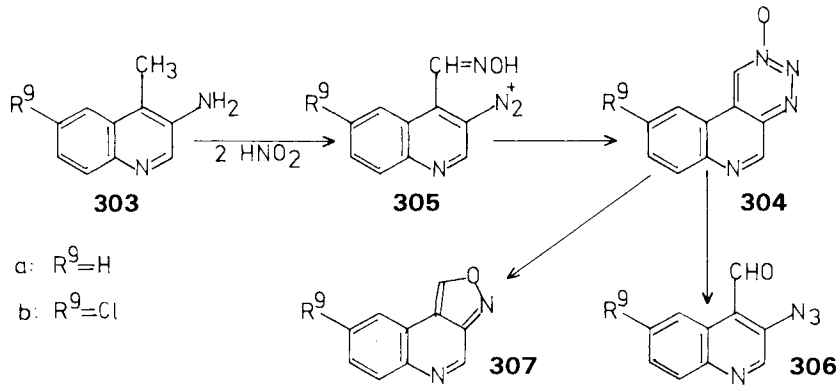
D. Pyrido[4,3-*d*]1,2,3-triazines

Compounds containing the pyrido[4,3-*d*] 1,2,3-triazine system have not yet been reported and no attempts to synthesize it could be found in the literature. Wait and Wesley published theoretical calculations on this system (59).

XI. CONDENSED WITH THE QUINOLINE SYSTEM

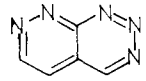
A. 1,2,3-Triazino[4,5-*c*]quinolines

When 3-amino-4-methylquinoline (**303a**) (3-aminolepidine) or its 6-chloro derivative (**303b**) were treated with 2 moles of sodium nitrite in concentrated hydrochloric acid 1,2,3-triazino[4,5-*c*]quinoline 2-oxide (**304a**) [m.p. 216° C (dec.)] or its 9-chloro derivative (**304b**) [m.p. 220 °C (dec.)] precipitated (335). The intermediate of this reaction should be the diazonium compound **305**. When the two *N*-oxides were left in contact with the acidic solution they slowly dissolved and on basification the 3-azidoquinoline-4-carbaldehyde (**306**) or the quinolino[3,4-*c*]isoxazoles (**307**) were isolated.



XII. CONDENSED WITH THE PYRIDAZINE RING

Three pyridazino-1,2,3-triazines are possible, the pyridazino[3,4-*d*] 1,2,3-triazines (**308**), the pyridazino[4,3-*d*] 1,2,3-triazines (**309**), and the pyridazino-[4,5-*d*] 1,2,3-triazines (**310**). Calculations on these three systems were published by Wait and Wesley (59). Only one derivative of the pyridazino[4,5-*d*]-1,2,3-triazine system has been reported.



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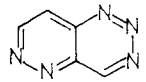

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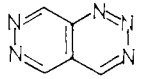
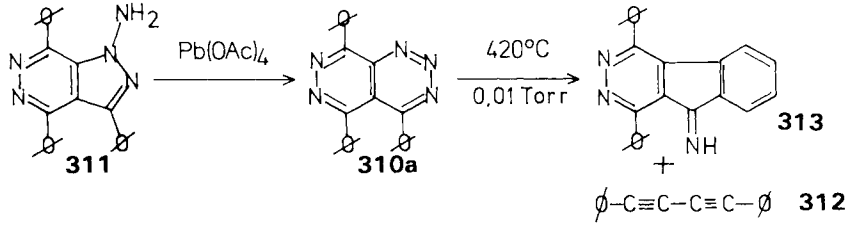


310

A. Pyridazino[4,5-*d*] 1,2,3-triazines

Oxidation of 1-amino-3,4,7-triphenylpyrazolo[3,4-*d*] pyridazine (**311**) with lead tetraacetate produced 4,5,8-triphenylpyridazino[4,5-*d*] 1,2,3-triazine (**310a**) of melting point 246 to 248 °C (336). Pyrolysis of **310a** at 420 °C and 0.01 mm Hg gave 1,4-diphenylbutadiyne (**312**) and 5-iminoindeno[1,2-*d*]-pyridazine (**313**).



311 **310a**

XIII. CONDENSED WITH THE PYRAZINE RING

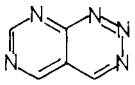
1. Pyrazino[2,3-*d*] 1,2,3-triazines

No compound containing this heterocyclic ring system could be found in the literature. Theoretical calculations on this system were published by Wait and Wesley.

XIV. CONDENSED WITH THE PYRIMIDINE RING

Two pyrimido-1,2,3-triazine systems are possible, the pyrimido[4,5-*d*]-1,2,3-triazines (**314**) and the pyrimido[5,4-*d*] 1,2,3-triazines (**315**). No

compound containing the pyrimido[4,5-*d*] 1,2,3-triazine system has been reported so far. Calculations on both systems were published by Wait and Wesley (59).



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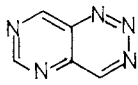
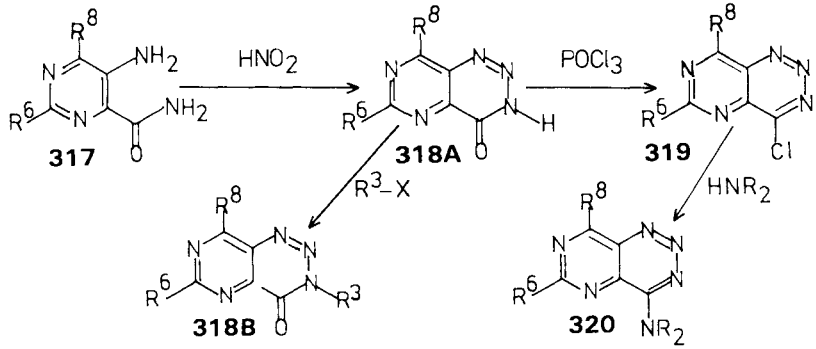


315

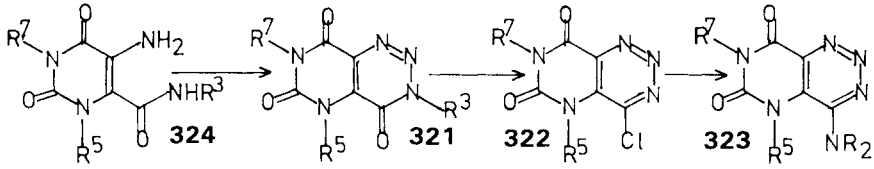
A. Pyrimido[5,4-*d*]1,2,3-triazines

1. *Preparation*

Reaction of 5-aminopyrimidine-4-carboxamides (**317**) with nitrous acid affords pyrimido[5,4-*d*] 1,2,3-triazin-4-ones (**318A**) which can be alkylated to give 3-alkylpyrimido] 5,4-*d*] 1,2,3-triazin-4-ones (**318B**) or transformed into the 4-chloropyrimido[5,4-*d*] 1,2,3-triazines (**319**) through reaction with phosphorus chloride. Reaction of the latter with amines yields 4-aminopyrimido[5,4-*d*]-1,2,3-triazines (**320**) (337, 338).

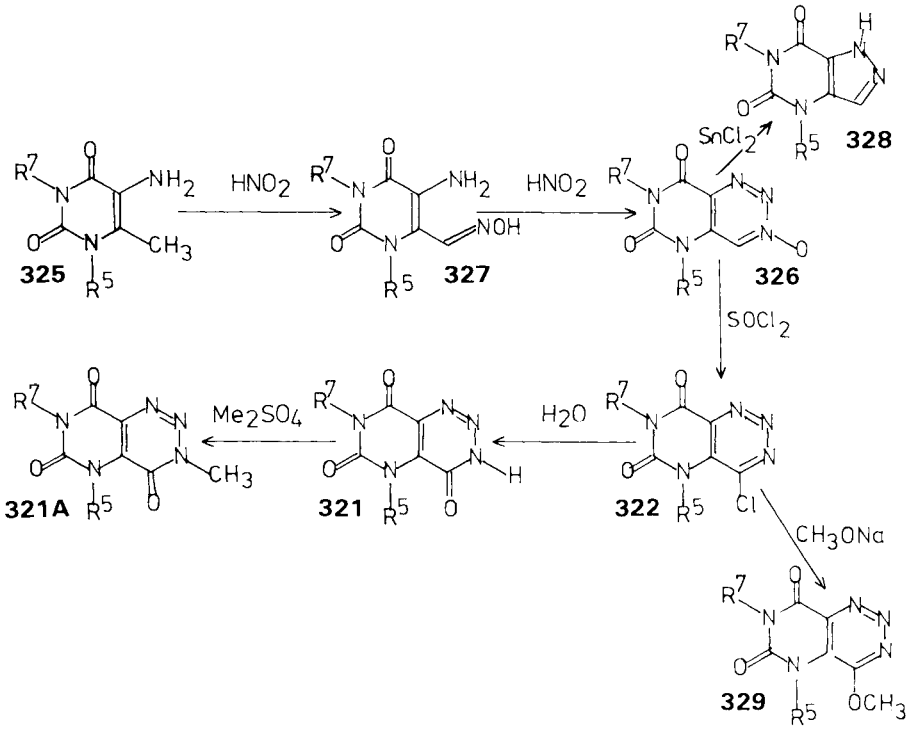


By the same reaction sequence pyrimido[5,4-*d*] 1,2,3-triazine-4,6,8-triones (**321**), 4-chloropyrimido[5,4-*d*] 1,2,3-triazine-6,8-diones (**322**), and 4-aminopyrimido[5,4-*d*] 1,2,3-triazine-6,8-diones (**323**) were prepared, starting from 5-amino-2,4-dioxo-pyrimidine-6-carboxamides (**324**) (337, 338).



Interaction of 5-amino-6-methylpyrimidine-2,4-diones (**325**) with excess

nitrous acid affords pyrimido[5,4-*d*]1,2,3-triazine-6,8-dione 3-oxides (**326**) (339–342), as shown by Papesch and Dodson. Behrend (344) as well as Rose (345) had already prepared these compounds but suggested incorrect formulas. An intermediate in the discussed reaction may be the 5-aminopyrimidine-2,4-dione-6-carbaldehyde oxime (**327**), which was prepared by Jones and his group (343) and transformed into **326** by treatment with nitrous acid.



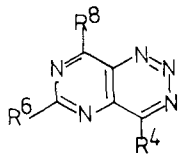
Compounds **326** can be reduced by stannous chloride to give pyrazolo-[4,3-*d*]pyrimidine-5,7-diones (**328**). Treatment of **326** with thionyl chloride affords the 4-chloropyrimido[5,4-*d*] 1,2,3-triazine-6,8-diones (**322**), which were transformed into the 4-methoxypyrimido[5,4-*d*] 1,2,3-triazine-6,8-diones (**329**) by reaction with sodium methoxide and hydrolyzed to give the pyrimido-[5,4-*d*] 1,2,3-triazine-4,6,8-triones (**321**) (339–342). The latter can be methylated by dimethyl sulfate in the presence of sodium hydroxide; the isolated compounds were formulated as the 3-methyl derivatives **321A**.

2. *Compound Survey*

Table V-3 lists the compounds of this class reported in the literature.

TABLE V-3. PYRIMIDO[5,4-*d*]1,2,3-TRIAZINES

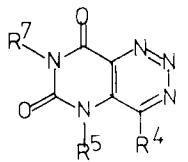
A. Pyrimido[5,4-*d*]1,2,3-triazines



R^4	R^6	R^8	m.p. (°C)	Refs.
OC_2H_5	4-Morpholino	4-Morpholino	257–258	337, 338
OC_6H_5	4-Morpholino	4-Morpholino	242–243	338/337
SH	4-Morpholino	4-Morpholino	249–253 (taut.)	337, 338
SC_2H_5	4-Morpholino	4-Morpholino	237–239	337, 338
$SCH_2C_6H_5$	4-Morpholino	4-Morpholino	268–269	337, 338
SC_6H_5	4-Morpholino	4-Morpholino	235–236	337, 338
Cl	4-Morpholino	4-Morpholino	179–180 (dec.)	337
NH_2	4-Morpholino	4-Morpholino	332–334	338
C_2H_5NH	1-Pyrrolidino	1-Pyrrolidino	202–204	338
i-C_3H_7NH	4-Morpholino	4-Morpholino	223–225	338
Allyl-NH	4-Morpholino	4-Morpholino	177–179	338
$HOCH_2CH_2NH$	1-Piperidino	1-Piperidino	216–219	337, 338
$(C_2H_5)_2NCH_2CH_2NH$	1-Pyrrolidino	1-Pyrrolidino	183–185	337
$C_6H_5CH_2NH$	4-Morpholino	4-Morpholino	221–222	338
C_6H_5NH	4-Morpholino	4-Morpholino	232–234	337, 338
$HOCH_2CH_2NCH_3$	$HOCH_2CH_2NCH_3$	$HOC_2CH_2NCH_3$	Oil	337, 338
$HOCH_2CH_2NCH_3$	4-Morpholino	4-Morpholino	197–198	338
$(HOCH_2CH_2)_2N$	4-Morpholino	4-Morpholino	234–236	338

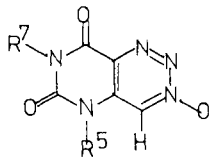
1-Piperidino	1-Piperidino	1-Piperidino	145–147	338
	4-Morpholino	4-Morpholino	205–206	337, 338
1-(3-Hydroxypiperidino)	1-Pyrrolidino	1-Pyrrolidino	208–209	338
Hexamethylenimino	Hexemethylenimino	Hexamethylenimino	146–147	338
4-Methylpiperazino	4-Morpholino	4-Morpholino	145–147	338
4-Morpholino	4-Morpholino	4-Morpholino	225–226	337, 338
4-(2-Methylmorpholino)	1-Pyrrolidino	1-Pyrrolidino	145–147	338
$(CH_3)_2N$–NH	1-Pyrrolidino	1-Pyrrolidino	189–191	338

B. Pyrimido[5,4-*d*]1,2,3-triazine-6,8-diones



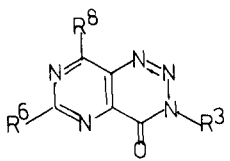
R^4	R^5	R^7	m.p. (°C)	Refs.
Cl	CH_3	CH_3	165–166 (dec.)	340, 342
Cl	C_2H_5	C_2H_5	137–138 (dec.)	340, 342
OCH_3	CH_3	CH_3	192–194 (dec.)	342
			197–199	340
$C_6H_5CH_2NH$	CH_3	CH_3	178–180 (dec.)	338
C_6H_5NH	CH_3	CH_3	>235 (dec.)	338
$(C_2H_5)_2N$	CH_3	CH_3	171–172	338
1-Piperidino	CH_3	CH_3	221–222	338
4-Morpholino	CH_3	CH_3	267–268 (dec.)	338

C. Pyrimido[5,4-*d*]1,2,3-triazine-6,8-dione 3-oxides



R^5	R^7	m.p. (°C)	Refs.
H	H	233 (dec.)	342
		239 (dec.)	345
$\cdot H_2O$		245 (dec.)	345
CH_3	CH_3	249–250	339, 342
C_2H_5	C_2H_5	244–245 (dec.)	339, 342

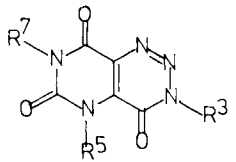
D. Pyrimido[5,4-*d*]1,2,3-triazin-4-ones



R^3	R^6	R^8	m.p. (°C)	Refs.
H	H	1-Piperidino	273–274	337, 338
H	Cl	1-Piperidino	227–228 (dec.)	337, 338
H	OC_2H_5	1-Piperidino	224–225	337, 338

H	$(C_2H_5)_2NCH_2CH_2O$	$N(CH_3)C_6H_5$	206–207	337, 338
H	OC_6H_5	1-Piperidino	227–228	337, 338
H	SC_2H_5	$N(CH_3)C_6H_5$	215–217	337, 338
H	$SCH_2C_6H_5$	1-Piperidino	166–168	337, 338
H	CH_3NH	Hexamethylenimino	255–257	337, 338
H	$C_6H_5CH_2NH$	1-Piperidino	258–259	338
H	C_6H_5NH	1-Piperidino	262–263	338
H	$(CH_3)_2N$	$(CH_3)_2N$	272–273	337, 338
H	$C_6H_5NCH_3$	C_2H_5O	147–149	337, 338
H	$C_6H_5NCH_3$	1-Pyrrolidino	256–258	337, 338
H	$C_6H_5NCH_3$	4-Morpholino	210–211	337, 338
H	$C_6H_5NCH_3$	C_6H_5S	230–231 (dec.)	337, 338
H	$(C_2H_5)_2N$	1-(3-Methylpiperidino)	290–292	337
H	$(HOCH_2CH_2)_2N$	1-(3-Methylpiperidino)	290–292	338
H	$HOCH_2CH_2NCH_3$	$HOCH_2CH_2NCH_3$	Oil	337, 338
H	1-Pyrrolidino	1-Pyrrolidino	295–296	337, 338
H	1-Piperidino	1-Piperidino	253–255	337, 338
H	1-Piperidino	4-Morpholino	262–263	337, 338
H	4-Methylpiperazino	4-Methylpiperazino	155–157	338
H	4-Morpholino	4-Morpholino	278–279	337, 338
H	4-Morpholino	1-Piperazino	264–265	338
CH_3	1-Piperidino	1-Piperidino	202–204	338
C_2H_5	1-Piperidino	1-Piperidino	177–179	338
C_2H_5	1-Piperidino	4-Morpholino	207–209	338
C_2H_5	4-Morpholino	1-Piperidino	234–235	338
C_3H_7	1-Pyrrolidino	1-Pyrrolidino	189–190	338
C_3H_7	1-Piperidino	1-Piperidino	109–111	338
i-C_5H_{11}	1-Piperidino	1-Piperidino	128–130	338
$CH_3OCH_2CH_2CH_2$	1-Piperidino	1-Piperidino	128–130	338

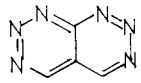
E. Pyrimido[5,4-*d*]1,2,3-triazine-4,6,8-triones



R^3	R^5	R^7	m.p. (°C)	Refs.
H	H	H	>350	337, 338
		NH_4 salt	250 (dark.)	337
		Na salt	>350	337
		K salt	>350	337
H	CH_3	CH_3	202–203 (dec.)	340, 342
H	C_2H_5	C_2H_5	190–191	340
			193–194	342
CH_3	CH_3	CH_3	174 (dec.)	340, 342
			178–179	337
CH_3	C_2H_5	C_2H_5	151–152 (dec.)	340
C_2H_5	H	H	254–256	337, 338
C_3H_7	H	H	240–241	337, 338
$CH_2=CH-CH_2$	H	H	231–233	337, 338
i-C_5H_{11}	H	H	238–239 (dec.)	338
$HOCH_2CH_2$	H	H	236–237 (dec.)	338
$CH_3OCH_2CH_2CH_2$	H	H	210–211 (dec.)	338
$C_6H_5CH_2$	H	H	243–245	337, 338
$C_6H_5CH_2$	$C_6H_5CH_2$	$C_6H_5CH_2$	166–168	337, 338
C_6H_5	H	H		338

XV. CONDENSED WITH THE 1,2,3-TRIAZINE RING

Two systems are possible in which two 1,2,3-triazine rings have one C-C bond in common, the 1,2,3-triazino[4,5-*d*] 1,2,3-triazines (**330**) and the 1,2,3-triazino-[5,4-*d*] 1,2,3-triazines (**331**). No compounds of either system have so far been reported, but Wait and Wesley have published some theoretical calculations on both systems (59).



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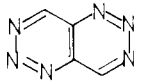
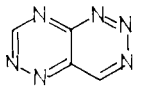


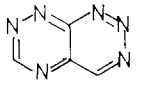
331

XVI. CONDENSED WITH THE 1,2,4-TRIAZINE RING

Two systems are possible in which one 1,2,4-triazine ring has one C-C bond in common with the 1,2,3-triazine ring, the 1,2,4-triazino[5,6-*d*] 1,2,3-triazines (**332**) and the 1,2,4-triazino[6,5-*d*] 1,2,3-triazines (**333**). Calculations on both systems were published by Wait and Wesley (59).



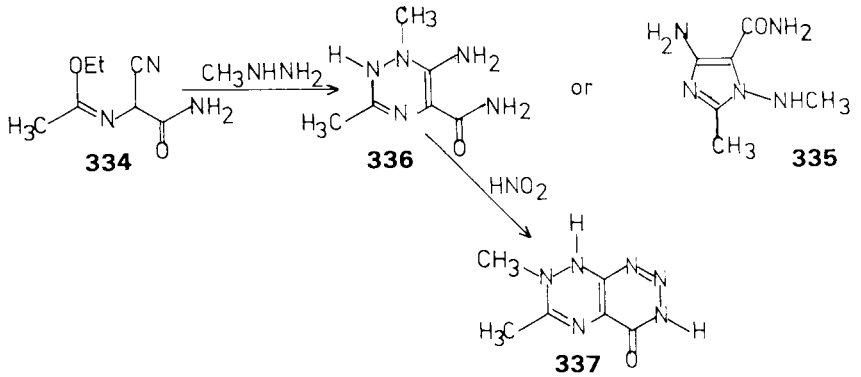
332



333

A. 1,2,4-Triazino[6,5-*d*]1,2,3-triazines

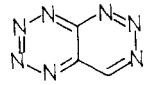
One compound that may contain the 1,2,4-triazino[6,5-*d*] 1,2,3-triazine system is reported in the literature (309). Treatment of the imidate **334** with methylhydrazine gave a compound which is formulated either as the



imidazole (**335**) or as 6-amino-2,3-dimethyl-1,2-dihydro-1,2,4-triazine-5-carboxamide (**336**). The latter structure is preferable. Diazotization of **335** or **336** yields a yellow crystalline compound of melting point 194 °C (dec.) which should be, if the starting material were in fact the 1,2,4-triazine **336**, the 6,7-dimethyl-7,8-dihydro-1,2,4-triazino[6,5-*d*] 1,2,3-triazin-4-one (**337**).

XVII. CONDENSED WITH THE 1,2,3,4-TETRAZINE RING

No derivatives of the 1,2,3-triazino[4,5-*e*] 1,2,3,4-tetrazine system (**338**) have been reported so far. Wait and Wesley published theoretical calculations on this system (59).



338

Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

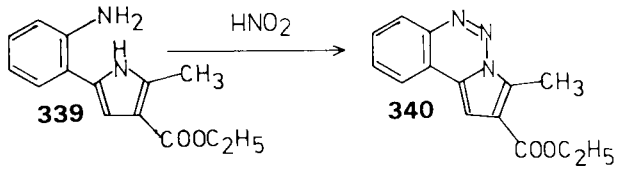
VI

1,2,3-Triazine Rings Condensed with Heterocycles Through a Carbon Atom and a Nitrogen Atom

I. CONDENSED WITH THE PYRROLE RING

A. Pyrrolo[1,2-*c*]1,2,3-benzotriazines

Diazotization of ethyl 2-methyl-5-(2-aminophenyl)-pyrrole-3-carboxylate (**339**) affords ethyl 4-methylpyrrolo[1,2-*d*] 1,2,3-benzotriazine-2-carboxylate (**340**) (384).



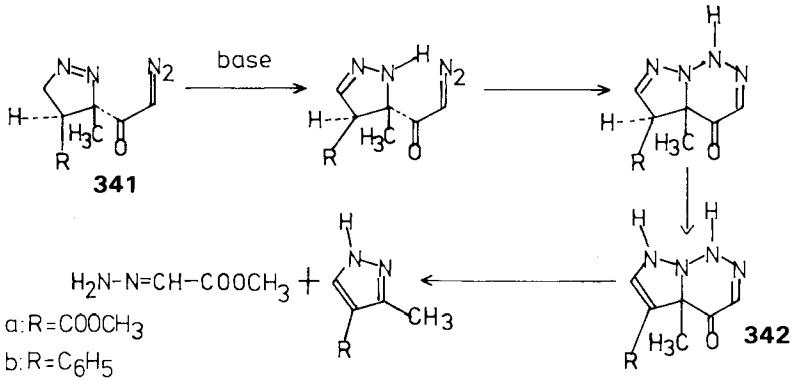
II. CONDENSED WITH THE PYRAZOLE RING

A. Pyrazolo[1,5-*c*]1,2,3-triazines

Culp, Nabeya, and Moore (346) isolated cream-colored crystals of melting point 140 to 142 °C when they tried to isomerize the 4-(methoxycarbonyl)-pyrazoline (**341a**) with base. On the basis of analytical and spectroscopic data the structure of the isolated compound was assigned as the methyl 1,4,4a,7-tetra-

hydro-4a-methyl-4-oxopyrazolo[1,5-*c*] 1,2,3-triazine-5-carboxylate (**342**). The yields of **342** are low when sodium methoxide is used as the base owing to the rapid further conversion of **342** to 4-(methoxycarbonyl)-3-methylpyrazole and methyl glyoxalate hydrazone.

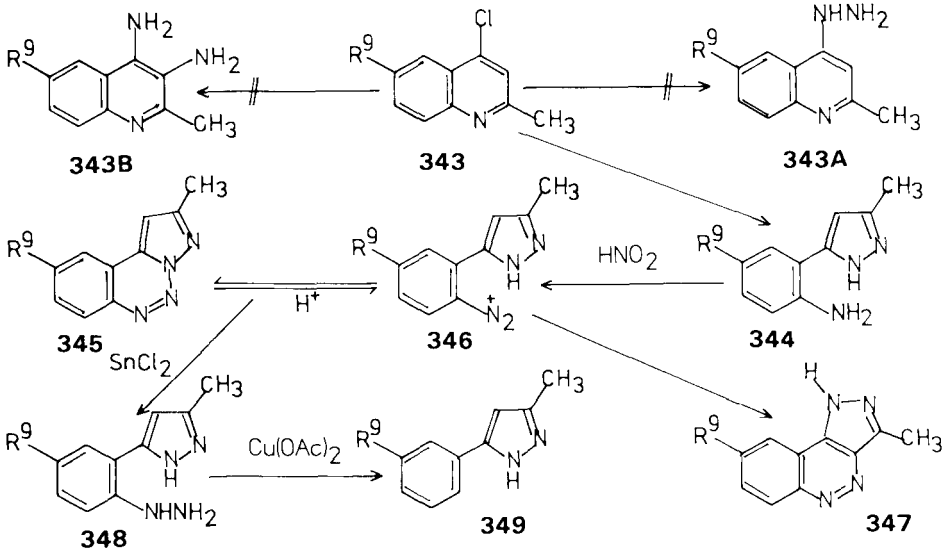
Better yields (70%) of **342** were obtained when trimethylamine was used as the base. The following mechanism for the formation of **342** from **341** is suggested. If the 4-phenylpyrazoline (**341b**) was treated with base, no pyrazolotriazine could be detected.



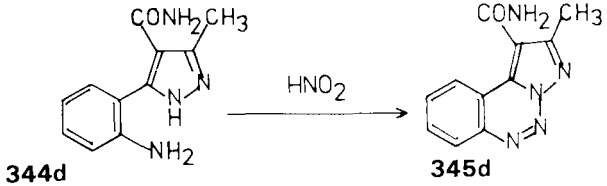
B. Pyrazolo[1,5-*c*]1,2,3-benzotriazines

At present only three compounds containing the pyrazolo[1,5-*c*]-benzotriazine system (RRI 2727) are known. When 4-chloroquinaldine (**343**) (R^9 = H) is heated with hydrazine at 150 °C 3-methyl-5-(2-amino-phenyl)pyrazole (**344a**) is formed (347). In earlier publications the formation of 4-hydrazinoquinaldine (**343A**) (348) or 3,4-diaminoquinaldine (**343B**) (349) in this reaction was discussed but shown by Koenigs and v. Loesch (350) to be incorrect. Reaction of **344a** with nitrous acid affords colorless needles of 2-methylpyrazolo[1,5-*d*] 1,2,3-benzotriazine (**345a**) of melting point 126 °C, which recrystallize at 240 °C and then melt at 300 °C. Heating the colorless needles with hydrochloric acid or sodium hydroxide yields yellow needles of melting point 342 °C, which are isomeric with the colorless needles and which form a sodium salt of decomposition point 230 °C (350). This rearrangement can be explained (194) by reversible protonation and ring scission of **345**, yielding the diazonium ion **346** which, by rotation through 180 ° about the central bond and recyclization, passes irreversibly with loss of a proton into the isomeric pyrazolo[3,4-*c*] cinnolines (**347a**). Similar results were obtained starting from 4-chloro-6-methoxyquinaldine (**343b**) and 4-chloro-6-ethoxyquinaldine (**343c**), leading to the colorless compounds **345b** and **345c** of melting point

186 °C ($R^9 = OCH_3$) and 212 °C ($R^9 = OC_2H_5$), which can be rearranged to yellow substances **347b** and **347c** of melting points 305 °C ($R = OCH_3$) and 292 °C (dec.) ($R = OC_2H_5$) (347).



Diazotization of 3-methyl-5-(2-aminophenyl)pyrazole-4-carboxamide (**344d**) affords 2-methylpyrazolo[1,5-*d*] 1,2,3-benzotriazine-1-carboxamide (**345d**) (385).



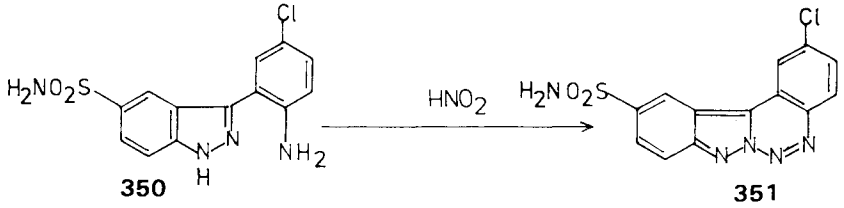
Reduction of **345a** with stannous chloride in hydrochloric acid affords 3-methyl-5-(2-hydrazinophenyl)pyrazole (**348**) which is oxidized by cupric acetate to yield 3-methyl-5-phenylpyrazole (**349**) (347).

III. CONDENSED WITH THE INDAZOLE SYSTEM

A. Benzo[5,6]1,2,3-triazino[3,4-*b*]indazoles

Addition of an aqueous solution of sodium nitrite to 3-(2-amino-5-chlorophenyl)-1*H*-indazole-5-sulfonamide (**350**) in dimethylformamide, acidified

with diluted hydrochloric acid, afforded 2-chlorobenzo[5,6] 1,2,3-triazine-[3,4-*b*] indazole-11-sulfonamide (**351**) (351).

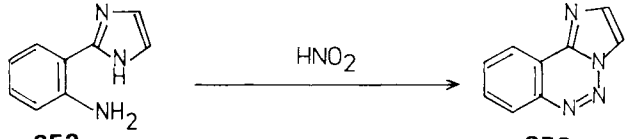


350 **351**

IV. CONDENSED WITH THE IMIDAZOLE RING

A. Imidazo[1,2-*c*]1,2,3-benzotriazines

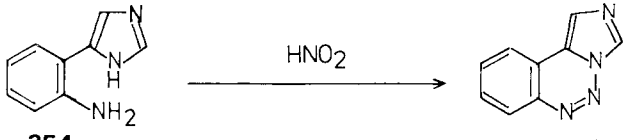
Reaction of 2-(2-aminophenyl)imidazole (**352**) with nitrous acid affords imidazo[1,2-*c*] 1,2,3-benzotriazine (**353**) (m.p. 113 to 114 °C), which is soluble in concentrated hydrochloric acid and insoluble in alkali, and does not couple with 2-naphthol (352).



352 **353**

B. Imidazo[3,4-*d*]1,2,3-benzotriazines

Treatment of 4-(2-aminophenyl)imidazole (**354**) with nitrous acid yields imidazo[3,4-*c*] 1,2,3-benzotriazine (**355**) (m.p. not given), which is insoluble in alkali and does not couple with 2-naphthol (352).



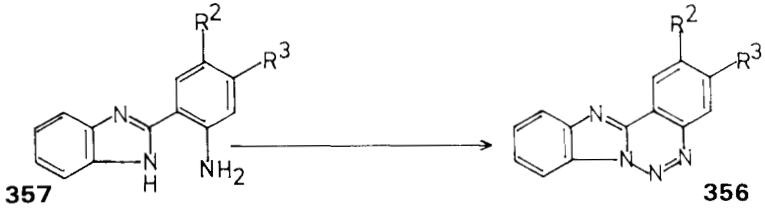
354 **355**

V. CONDENSED WITH THE BENZIMIDAZOLE SYSTEM

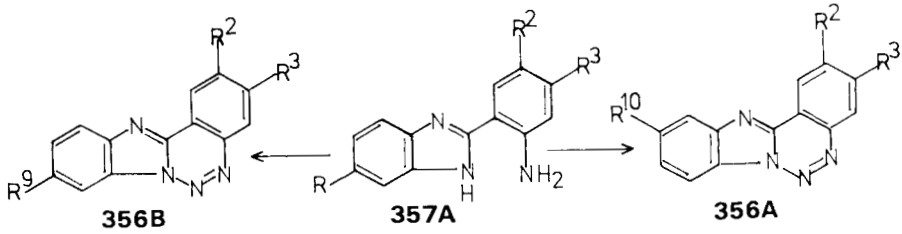
A. Benzimidazo[1,2-*c*]1,2,3-benzotriazines

1. *Preparation*

The benzimidazo[1,2-*c*] 1,2,3-benzotriazine system (**356**) (RRI 4419) was first synthesized and studied by v. Niementowski in 1898 (353, 370). The synthesis of **356** was achieved by diazotization of 2-(2-aminophenyl)-benzimidazoles (**357**), a method which was also used by Zaika and Joullie for the synthesis of **356** in 1966 (354). Substituents did not affect the ease of ring closure and the benzimidazo[1,2-*c*] 1,2,3-benzotriazines (**356**) were obtained in excellent yields.



4- or 5-substituted 2-(2-aminophenyl)-benzimidazoles (**357A**) may yield two isomeric benzimidazo[1,2-*c*] 1,2,3-triazines (**356A** and **356B**); the large melting-point range of the compounds obtained indicates the presence of the two isomers.



Reaction of 6-methylbenzimidazo[1,2-*c*]quinazoline (**358**) with nitrous acid is also said to yield benzimidazo[1,2-*c*] 1,2,3-benzotriazine (**356a**) (355). For this reaction one has to assume that **358** is first hydrolyzed to the 2-(2-aminophenyl)benzimidazole (**357a**) which is then cyclized by nitrous acid.

Davis and Mann (136) isolated benzimidazo[1,2-*c*] 1,2,3-benzotriazine (**356a**) when they treated the sodium salt **359** with hot acetic acid or hot mineral acids.

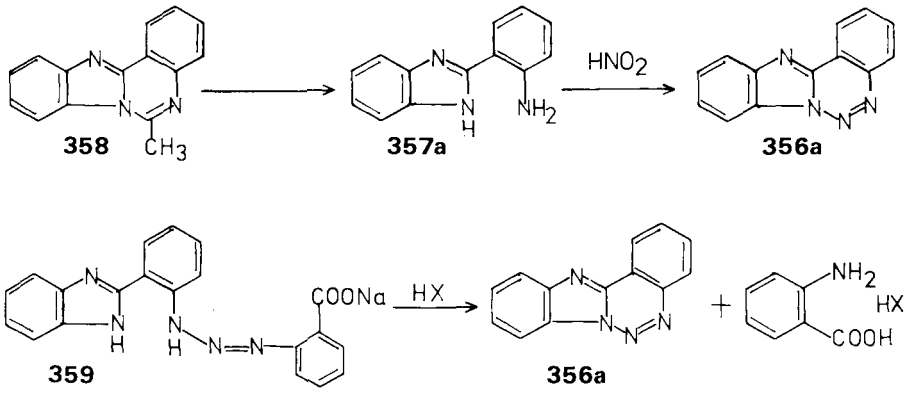
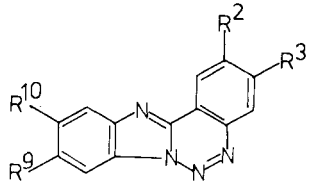


TABLE VI-1. BENZIMIDAZO[1,2-*c*]1,2,3-BENZOTRIAZINES



R^2	R^3	R^9	R^{10}	m.p. (°C)	Refs.
H	H	H	H	207–208	353/355
				210.5–211	354
				211	136
	·HCl			200 (dec.)	353
	·$HAuCl_4$·$2H_2O$			220 (dec.)	353
H	H	H,CH_3		167–168	354
				165–180	354
				192–195	354
				187–188	353
H	H	H,Cl		178–184	354
H	H	CH_3	CH_3	222–224.5	354
H	H	Cl	Cl	272–274	354
H	CH_3	H	H	178–179	354
				185	353
	·H_2PtCl_6			>290	353
H	CH_3	H,CH_3		197	353
H	F	H	H	158–159	354
H	Cl	H	H	215–216.5	354
Cl	H	H	H	211–212.5	354

2. *Compound Survey*

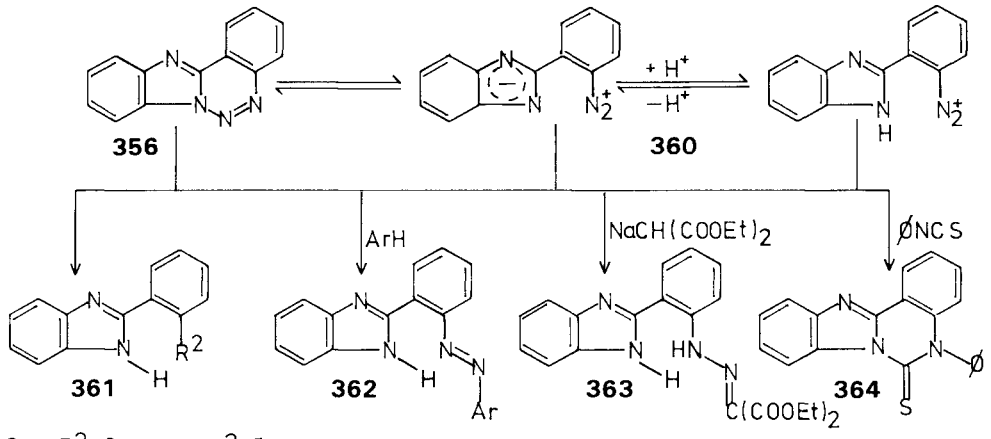
In Table VI-1 are listed the compounds of this class that have been reported in the literature.

3. *Physical Properties and Reactions*

Benzimidazo[1,2-*c*] 1,2,3-benzotriazines (**356**) are yellow crystalline compounds of weakly basic nature. They are soluble in most organic solvents, acetic acid, and mineral acids, although some 2-substituted derivatives tend to form insoluble salts when treated with acids. They are not attacked by boiling alkali or boiling piperidine, but decompose when heated above their melting points or when heated with mineral acids. The ultraviolet spectra of these compounds show three characteristic regions of absorption at 325, 280 to 300, and 230 nm (354). Substituents do not affect the intensities of the bands to any large degree. The following ultraviolet spectrum is reported for the unsubstituted benzimidazo[1,2-*c*] 1,2,3-benzotriazine: λ_{max} (log ϵ) = 320 sh (3.84), 287 (4.60), 281 (4.62) and 227 nm (4,51) (354). Only a small amount of information on the infrared spectra of **356** has been published: all absorb around 1620 to 1560 and 1160 to 1140 cm^{-1}. The mass spectrum of benzimidazo-[1,2-*c*] 1,2,3-benzotriazine (**356a**) is recorded by Stevens and others (189); it shows in addition to an intensive mass peak the peak at *M*-28 as the base peak. Stevens and Stevens (200) discussed the intermediate formation of benzimidazo-[1,2-*c*] 1,2,3-benzotriazines in the mass spectral fragmentation of 2-alkyl-4 amino-1,2,3-benzotriazinium betaines (**136**).

The reactions of benzimidazo[1,2-*c*] 1,2,3-benzotriazines (**356**) are best explained by the intermediate formation of diazonium ion **360**. Thus heating **356** in dilute sulfuric acid affords 2-(2-hydroxyphenyl)benzimidazoles (**361a**) (R^2 = OH) (136, 353, 369); hydrochloric acid yields mixtures of **361a** and the 2-(2-chlorophenyl)benzimidazoles (**361b**) (R^2 = Cl) (363, 369); hydrobromic acid gives the analogous bromo derivatives **361c** (R^2 = Br) (369); fluoroboric acid affords the 2-(2-fluorophenyl)benzimidazoles (**361d**) (R^2 = F) (369); hydrogen chloride in ethanol yields a mixture of **361b** and 2-phenylbenzimidazole (**361e**) (R^2 = H) (369); cuprous chloride and hydrochloric acid afford **361b**; cuprous bromide and hydrobromic acid give **361c**, both in excellent yields (369). The 2-(2-iodophenyl)benzimidazole (**361f**) (R^2 = I) is obtained on treatment of **356** with potassium iodide (363). Reduction of **356** with stannous chloride (125, 363) or zinc and acetic acid gave 2-(2-hydrazinophenyl)benzimidazole (**361g**) (R^2 = $NHNH^2$), whereas catalytic reduction or reduction with Raney nickel, sodium in ethanol, ammonium sulfide, sodium

hydrogen sulfite and hydrochloric acid, or sodium borohydride afforded 2-phenylbenzimidazole (**361e**) (R^2 = H) (363). The same compound is isolated when **356** is treated with sodium alkoxides (363). Reduction of **356** with Raney nickel and hydrazine led to the isolation of 2-(2-aminophenyl)-benzimidazole (**361h**) ($R^2 = NH_2$) (125). Azo compounds (**362**) were obtained upon reaction of **356** with phenols or amines (353, 363, 136), reaction of **356** with sodium malonate afforded the hydrazone **363** (363). Reaction of **356** with phenylisothiocyanate gives 5-phenylbenzimidazo[1,2-*c*]quinazoline-6-thione (**364**) (363) and photolysis of **356** in ethanol afforded a mixture of 2-(2-ethoxy-phenyl)benzimidazole (**361i**) ($R^2 = OC_2H_5$) and 2-phenylbenzimidazole (**361e**) (363).



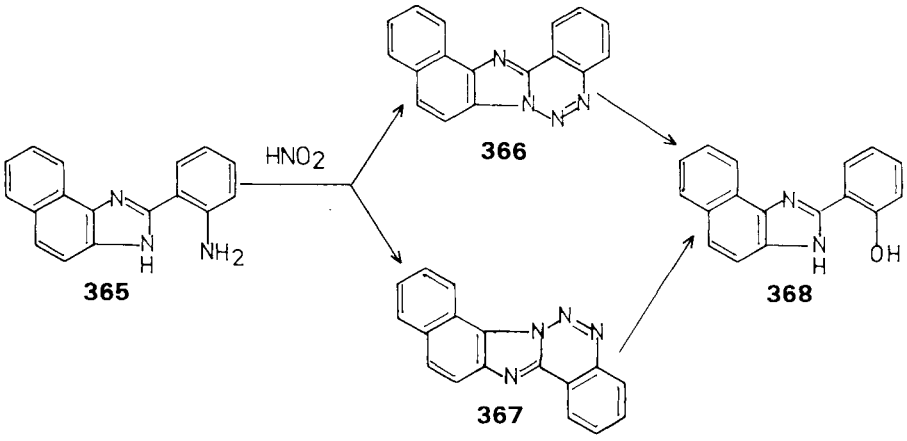
361a: R^2=OH 361f: R^2=I
361b: R^2=Cl 361g: R^2=$NHNH_2$
361c: R^2=Br 361h: R^2=NH_2
361d: R^2=F 361i: R^2=OEt
361e: R^2=H

VI. CONDENSED WITH THE NAPHTH[1,2-*d*]IMIDAZOLE SYSTEM

A. Naphth[1′,2′:4,5]imidazo[1,2-*c*]1,2,3-benzotriazines and Naphth[2′,1′:4,5]imidazo[1,2-*c*]1,2,3-benzotriazines

Diazotization of 2-(2-aminophenyl)naphth[1,2-*d*]imidazole (**365**) is said to give a crystalline solid which exhibits a large melting-point range, indicating it to

be a mixture of the two isomers naphth[1,2:4,5]imidazo[1,2-*c*]1,2,3-benzotriazine (**366**) and naphth[2,1:4,5]imidazo[1,2-*c*]1,2,3-benzotriazine (**367**) (354). In the experimental section of the same publication a melting point of 211 to 213 °C is given for the deep yellow plates obtained in 98% yield. The following ultraviolet spectrum is published: λ_{max} (log ϵ) = 341 sh (3.96), 293 (4.57), and 246 nm (4.42).

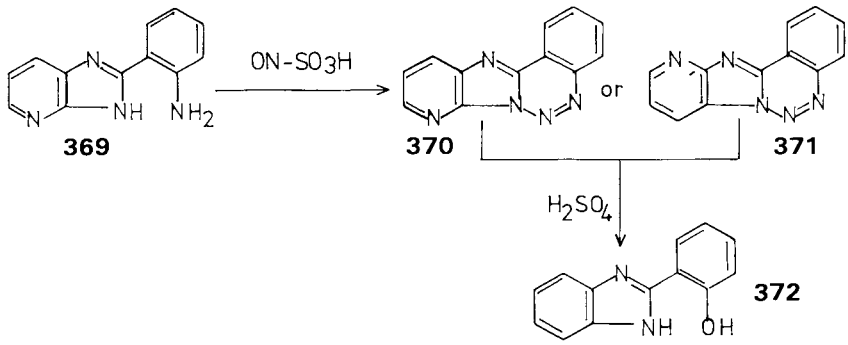


Treatment of **366/367** with dilute sulfuric acid affords 2-(2-hydroxyphenyl)-naphth[1,2-*d*]imidazole (**368**) (369).

VII. CONDENSED WITH THE IMIDAZO[4,5-*b*]PYRIDINE SYSTEM

A. Pyrido[2′,3′:4,5]imidazo[1,2-*c*]1,2,3-benzotriazines and Pyrido[3′,2′:4,5]imidazo[1,2-*c*]1,2,3-benzotriazines

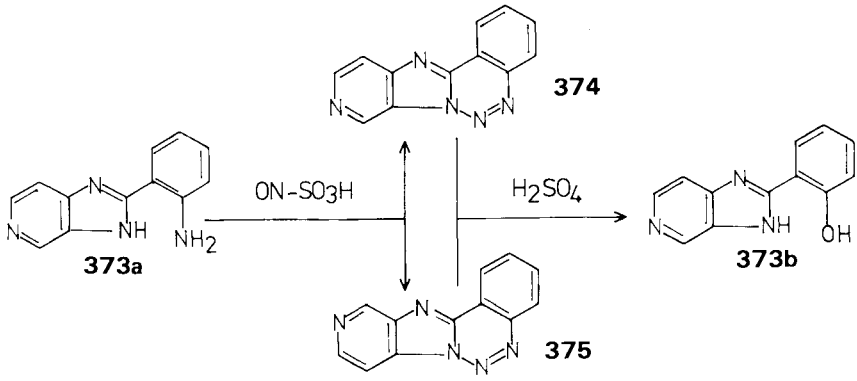
Addition of nitrosylsulfuric acid to a solution of 2-(2-aminophenyl)imidazo-[4,5-*b*]pyridine (**369**) in concentrated sulfuric acid gave after work-up a crystalline compound of melting point 228 to 229 °C which is either pyrido[2,3:4,5]imidazo[1,2-*c*]1,2,3-benzotriazine (**370**) or the isomeric pyrido-[3,2:4,5]imidazo[1,2-*c*]1,2,3-benzotriazine (**371**) (371). It has the following ultraviolet spectrum in methanol: λ_{max} (log ϵ) = 325 sh (13.155), 287 (68.000), 277 (59.022), and 223 nm (28.177) and is hydrolyzed by dilute sulfuric acid to give 2-(2-hydroxyphenyl)imidazo[4,5-*b*]pyridine (**372**).



VIII. CONDENSED WITH THE IMIDAZO[5,4-*b*]PYRIDINE SYSTEM

A. Pyrido[3′,4′:4,5]imidazo[1,2-*c*]1,2,3-benzotriazines and Pyrido[4′,3′:4,5]imidazo[1,2-*c*]1,2,3-benzotriazines

Treatment of 2-(2-aminophenyl)imidazo[4,5-*c*]pyridine (**373a**) with nitrosylsulfuric acid in concentrated sulfuric acid yields a crystalline substance of melting point 192 to 194 °C which is either pyrido[3,4:4,5]imidazo[1,2-*c*]-1,2,3-benzotriazine (**374**) or pyrido[4,3:4,5]imidazo[1,2-*c*] 1,2,3-benzotriazine (**375**) (371). The following ultraviolet spectrum is reported for the isolated compound: λ_{max} (log ϵ) = 315 sh (4.306), 280 (26.912), 272 (31.728), 264 sh (27.195), and 227 nm (20.226). Dilute sulfuric acid hydrolyzes this compound to 2-(2-hydroxyphenyl)imidazo[4,5-*c*]pyridine (**373b**) (363).

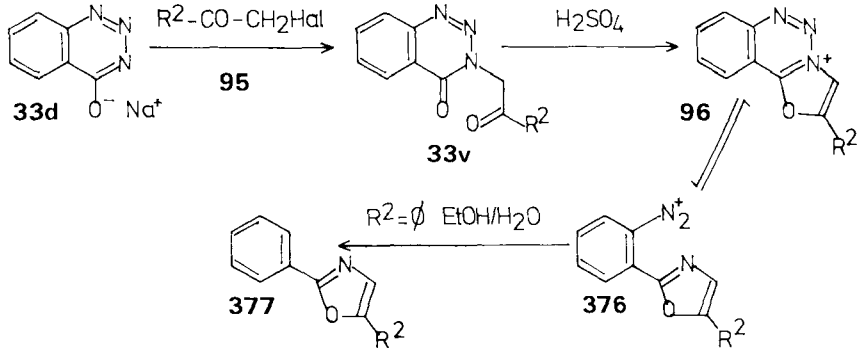


IX. CONDENSED WITH THE OXAZOLE RING

A. Oxazolo[3,2-*c*]1,2,3-benzotriazines

Treatment of the sodium salt of 1,2,3-benzotriazin-4-one (**33d**) with α-halo ketones (**95**) yielded *N*-(β-oxoalkyl)-1,2,3-benzotriazin-4-ones (**33v**), the cyclization of which with cold concentrated sulfuric acid yielded the oxazolo-[3,2-*c*] 1,2,3-benzotriazinium salts (**96**), which were isolated as their fluoroborates and chlorides in yields around 80% (227).

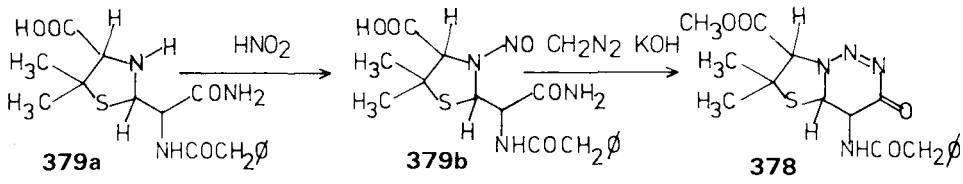
The infrared spectra of these salts show no significant absorption in the carbonyl region but the presence of a diazo band at 2300 cm^{-1} (KBr) indicates that the diazo form **376** is probably in equilibrium with the form **96**. Prolonged treatment of **96** under reflux with aqueous ethanol afforded 2,5-diphenyloxazole (**377**) (227).



X. CONDENSED WITH THE THIAZOLE RING

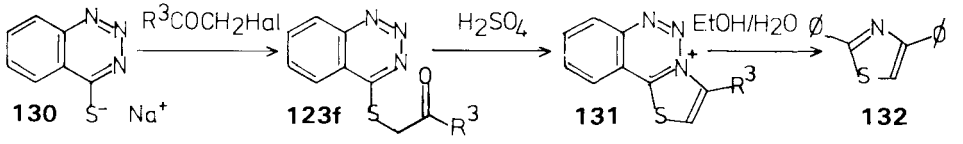
A. Thiazolo[3,2-*c*]1,2,3-triazines

One derivative of the thiazolo[3,2-*c*] 1,2,3-triazine system (RRI 1131) is reported by Cook and Heilbron (356). They obtained a compound (m.p. 133 to 134 °C), formulated as methyl 6,6-dimethyl-4-(2-phenylacetamido)-3-oxo-4,4a,6,7-tetrahydro-3*H*-thiazolo[3,2-*c*] 1,2,3-triazine-7-carboxylate (**378**) by the following reaction sequence: the α-amide of D-benzylpenicilloic acid (**379a**) was nitrosated to give the N_4-nitroso derivative (**379b**); esterification of **379b** with diazomethane followed by treatment of the formed ester with potassium hydroxide in methanol afforded **378**.



B. Thiazolo[3,2-*c*]1,2,3-benzotriazines

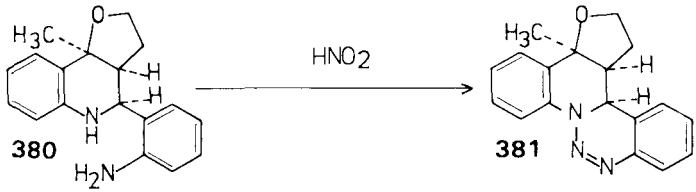
Treatment of the sodium salt of 1,2,3-benzotriazine-4-thione (**130**) with α-halo ketones gives the *S*-alkylated products **123f**, which were cyclized by cold concentrated sulfuric acid to give thiazolo[3,2-*c*] 1,2,3-benzotriazinium salts (**131**), which were isolated as their fluoroborates (227). Prolonged treatment of **131** ($R^2 = C_6H_5$) with aqueous ethanol yields 2,4-diphenylthiazole (**132**).



XI. CONDENSED WITH THE FURO[3,2-*c*]QUINOLINE SYSTEM

A. Furo[3′,2′:3,4]quino[1,2-*c*]1,2,3-benzotriazines

Treatment of *dl*-4-(2-aminophenyl)-2,3,3a,4,5,9b-hexahydro-9b-methylfuro-[3,2-*c*] quinoline (**380**) with aqueous nitrous acid gave, according to thin-layer chromatography, at least five products. Column chromatography, however, enabled the ready separation and isolation of *dl*-1,2,14b,14c-tetrahydro-3a-



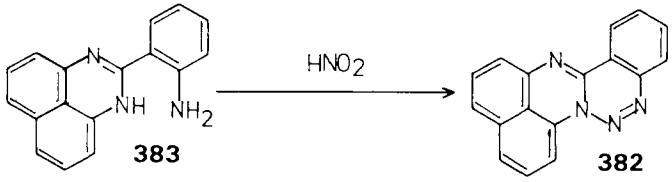
methyl-3a*H*-furo[3′,2′:3,4] quino[1,2-*c*] 1,2,3-benzotriazine (**381**) of melting point 133 to 134 °C in low yields (8%). Two absorption bands were recorded in the ultraviolet spectrum at 362 (10.900) and 235 nm (15.600) with the

absorptivities given in parentheses. One attempt to increase the yield of **381** by using nitrosylsulfuric acid instead of nitrous acid was unsuccessful (374).

XII. CONDENSED WITH THE PERIMIDINE RING

A. 1,2,3-Benzotriazino[3,4-*a*]perimidines

At present only the unsubstituted 1,2,3-benzotriazino[3,4-*a*]perimidine (**382**) (RRI 6129) is known. It was prepared by Sachs and Steiner (357) by reaction of 2-(2-aminophenyl)perimidine (**383**) with nitrous acid; it forms red-brown needles and has no melting point but explodes at 140 °C. It is soluble in most organic solvents and in hot diluted sulfuric acid and is insoluble in water. It is stable toward alkali and sulfuric acid at 50 to 60 °C. In concentrated sulfuric acid **382** gives a green color, on standing in dilute sulfuric acid a blue-violet color, and in dilute hydrochloric acid a blue color.



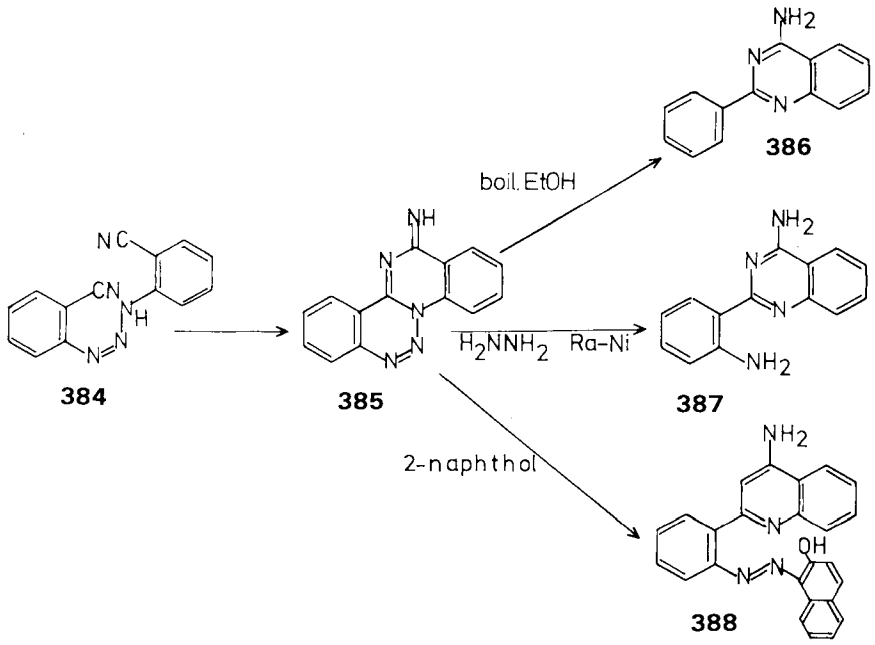
383 **382**

XIII. CONDENSED WITH THE QUINAZOLINE SYSTEM

A. Quinazolino[1,2-*c*]1,2,3-benzotriazines

Attempted chromatographic purification of the 1,3-bis(2-cyanophenyl)-triazene **384** in benzene on alumina furnished an unstable red solid which was identified as 13-iminoquinazolino[1,2-*c*]1,2,3-benzotriazine (**385**) on the basis of the following reactions: **385** underwent reduction in boiling ethanol evolving nitrogen and forming the 4-amino-2-phenylquinazoline (**386**); reduction with hydrazine and Raney nickel in ethanol afforded 2-(2-aminophenyl)-4-amino-quinazoline (**387**) and coupling with 2-naphthol gave the azo compound (**388**) (373).

Investigation of the conditions of the alumina-catalyzed cyclization of the triazene **384** showed that **385** is readily formed by absorption on alkaline alumina (pH = 9.6). The new compound forms crimson rosettes of melting point 135 to 136 °C (dec.) and has the following electronic spectrum: λ_{max} (log ϵ) = 355 (4.09), 324 (3.95), 306 (3.95), and 270 nm (3.94). The inter-

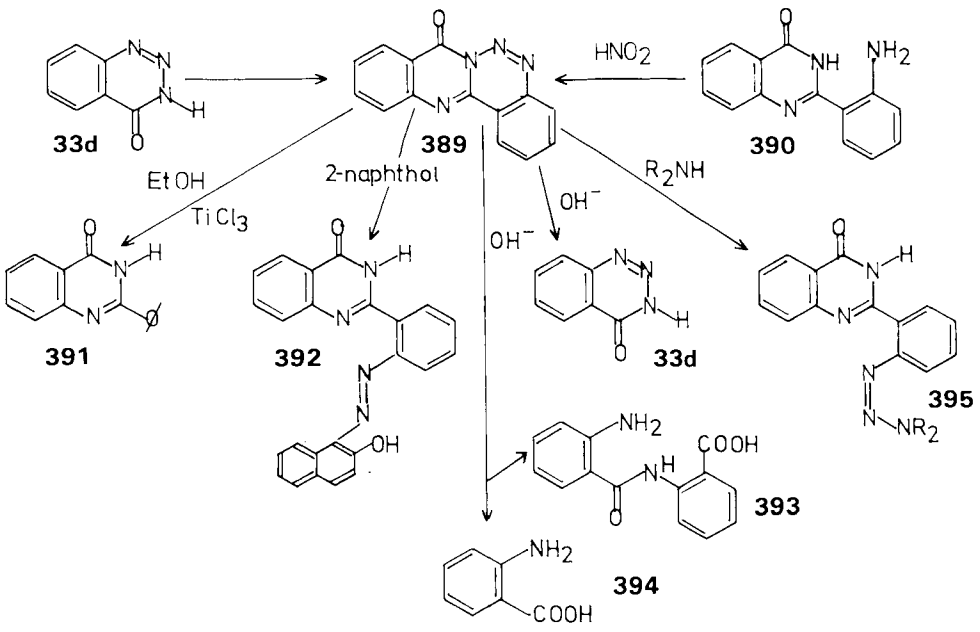


mediate formation of the tetracyclic system (**385**) during reactions of the triazene (**384**) is discussed in a number of papers (200, 229, 234, 372).

B. Quinazolino[3,2-*c*]1,2,3-benzotriazines

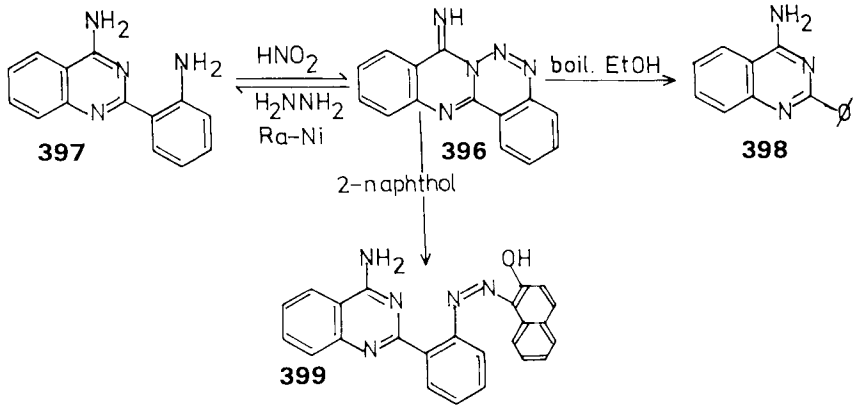
If a solution of 1,2,3-benzotriazin-4-one (**33d**) in diethylene glycol dimethyl ether is heated under reflux for periods up to 2 hr the quinazolino[3,2-*c*] 1,2,3-benzotriazin-8-one (**389**) is isolated in 70% yield (198). The same compound (**389**) was prepared by diazotization of 2-(2-aminophenyl)quinazolin-4-one (**390**) (198). **389** forms yellow prisms of melting point 214 to 216 °C and has the following ultraviolet spectrum: λ_{max} (log ϵ) = 325 (3.99), 311 (4.02), 287 (4.23), 275 (4.26), 249 (4.42), 232 (4.36), and 213 nm (4.29).

Prolonged heating of **389** in aqueous alcohol afforded 2-phenylquinazolin-4-one (**391**), the same compound was isolated by treating **389** with boiling titanium(III) chloride solution (198). Like most condensed 1,2,3-triazine systems, **389** behaves as a masked diazonium compound and forms the azo compound **392** upon reaction with 2-naphthol. Treatment of **389** with alcoholic sodium hydroxide yielded a small amount of 1,2,3-benzotriazin-4-one (**33d**) and anthraniloylanthranilic acid (**393**); prolonged treatment of **389** with alkali afforded anthranilic acid (**394**) (198). Heating **389** with pyrrolidine, piperidine, or morpholine gave the triazenes **395** (199).



The 8-iminoquinazolino[3,2-*c*]1,2,3-benzotriazine (**396**) was obtained on treatment of 4-amino-2-(2-aminophenyl)quinazoline (**397**) with nitrous acid (232). **396** forms brown prisms of melting point 148 to 150 °C (232, 373) and has the following ultraviolet spectrum: λ_{max} (log ϵ) = 364 sh (3.90), 350 (3.95), 340 sh (3.92), 320 (3.88), 296 (4.10), 268 (4.25), 254 sh (4.32), and 225 nm (4.58) (232, 373).

Reduction of **396** with boiling ethanol led to the isolation of 4-amino-2-phenyl-quinazoline (**398**), whereas reduction with ethanolic hydrazine and



Raney nickel gave 4-amino-2-(2-aminophenyl)quinazoline (**397**) (232, 373). Like many other condensed 1,2,3-triazines **396** can be coupled with 2-naphthol; leading to the azo compound **399**.

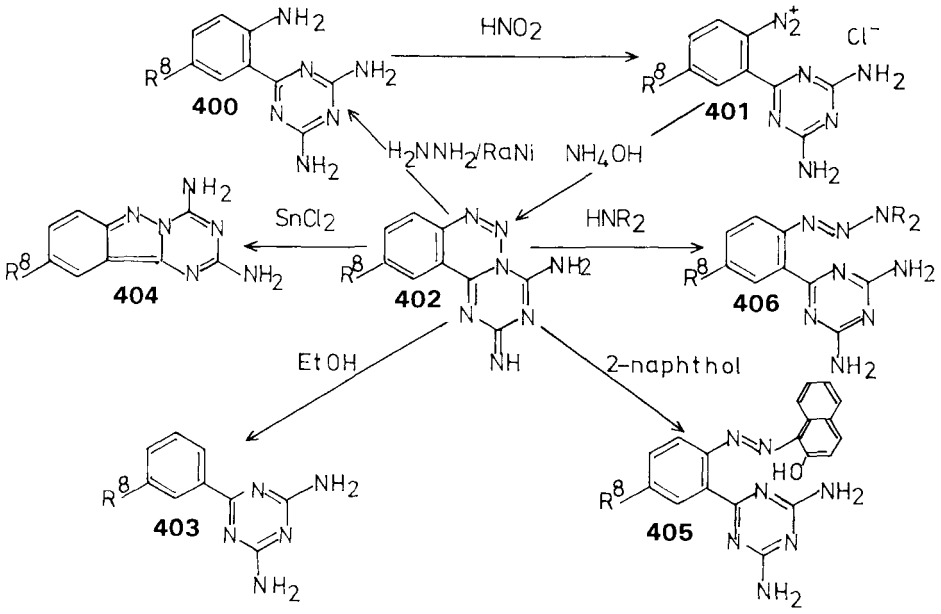
The intermediate formation of **396** in reactions of 1,3-bis(2-cyanophenyl)-triazene is discussed in a number of papers (200, 234, 229, 372).

XIV. CONDENSED WITH THE 1,3,5-TRIAZINE RING

A. 1,3,5-Triazino[1,2-*c*]1,2,3-benzotriazines

Diazotization of 2,4-diamino-6-(2-aminophenyl)-1,3,5-triazines (**400**) in 2*N* hydrochloric acid gave the diazonium chlorides (**401**), which on basification yielded the 2-imino-4-amino-1,3,5-triazino[1,2-*c*]1,2,3-benzotriazines (**402**). The isolated compounds are cream solids which decompose vigorously at their melting points, and in one instance (R = H) a slight explosion occurred when the compound was being gently powdered in a glass mortar (362). All attempts to recrystallize these compounds were unsuccessful; they were only sparingly soluble in nonpolar solvents and decomposed rapidly in polar solvents; the compounds failed to afford crystalline hydrochlorides, picrates, or 4-toluenesulfonates.

The 1,3,5-triazino[1,2-*c*]1,2,3-benzotriazines (**402**) were reduced by boiling



ethanol to give the 2,4-diamino-6-phenyl-1,3,5-triazines (**403**), by hydrazine and Raney nickel in ethanol to afford the 2,4-diamino-6-(2-aminophenyl)-1,3,5-tiazines (**400**) and by stannous chloride to yield the 1,3,5 triazino[1,2-*b*]indazoles (**404**) (362). Reaction of **402** in ethanol with 2-naphthol yielded the azo compounds **405** and treatment of **402** with secondary amines led to the isolation of the triazenes (**406**) (199).

Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

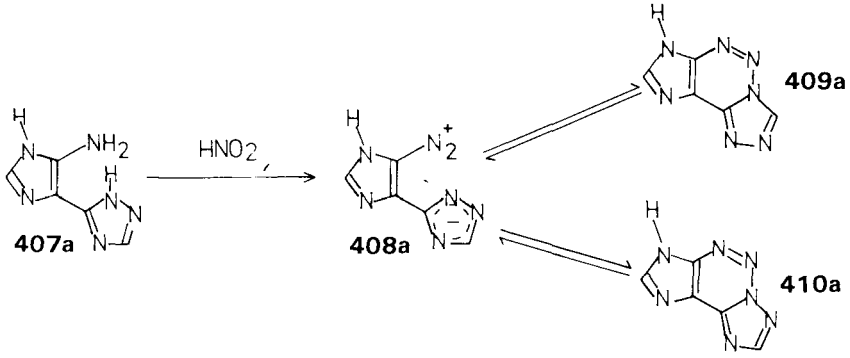
VII

1,2,3-Triazine Rings Condensed with Two Heterocycles

I. IMIDAZO[4,5-*e*]1,2,4-TRIAZOLO[4,3-*c*]1,2,3-TRIAZINES AND IMIDAZO[4,5-*e*]1,2,4-TRIAZOLO[1,5-*c*]1,2,3-TRIAZINES

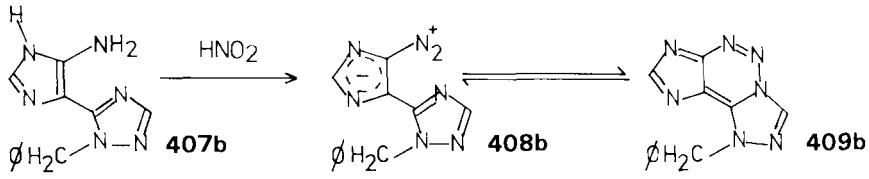
Temple, Kussner, and Montgomery (321) reacted the (5-amino-4-imidazol-2-yl)1,2,4-triazoles (**407**) with nitrous acid and studied the diazo-β-azomethine-1,2,3-triazine equilibrium of the formed compounds by spectroscopic methods. In all cases where the ring closure of the diazo group in **408** to the 1,2,4-triazole ring may proceed in two ways (to N-1 or N-4) the cyclization via N-1 of the 1,2,4-triazole ring is preferred by the authors because of the greater nucleophilicity of N-1.

From the nitrosation of **407a** they isolated mainly the diazo compound **408a**. On the other hand, the sodium salt of this compound has no absorption in the diazo region of the infrared spectrum; therefore it should be the sodium salt of **410a** (**409a**). Neutralization of an aqueous solution of the sodium salt deposited a mixture containing mainly the diazo compound **408a**. In trifluoroacetic acid the protonated form of **408a** predominates but in dimethyl sulfoxide only the

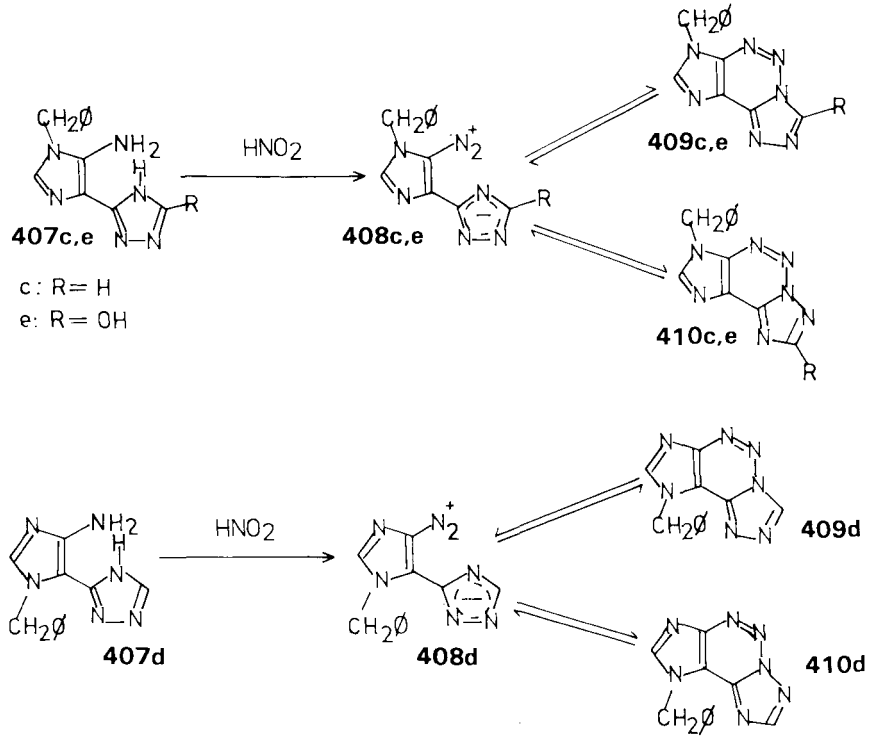


form **410a** (**409a**) was observed. Addition of trifluoroacetic acid to the DMSO-D_6 solution of **410a** (**409a**) led to the formation of **408a**, which was the only observable product in DMSO-D_6: CF_3COOH = 1:1.

Diazotization of **407b** gave a product which was mainly the diazo compound **408b** in the solid state, in DMSO-D_6 and acetic acid solution; the cyclized form **409b** was the only substance to be detected in trifluoroacetic acid.



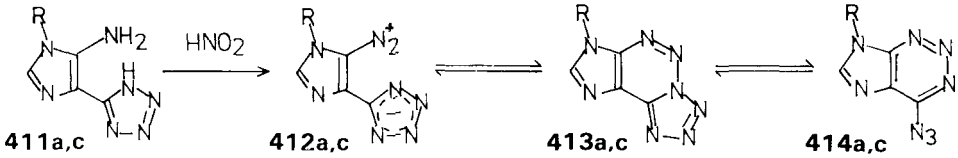
The nitrosation of **407c**–**407e** gave mainly the cyclized products **410c**–**410e**, identified by the absence of the diazo absorption in the solid-state infrared spectra. Similarly only the 1,2,3-triazine forms were detected in DMSO-D_6: CF_3COOH = 1:1 and CH_3COOH solutions. In CF_3COOH, however, only the protonated forms of the diazo compounds **408c**–**408e** were observed.



All reported compounds could be coupled with 2-naphthol to yield azo compounds.

II. IMIDAZO[4,5-*e*]TETRAZOLO[1,5-*c*]1,2,3-TRIAZINES

Diazotization of the 5-(5-amino-4-imidazoyl)tetrazoles (**411**) may yield the diazo compounds **412**, which can cyclize to the imidazo[4,5-*e*]tetrazolo[1,5-*c*]-1,2,3-triazines (**413**), which can undergo ring opening of the tetrazole ring to give the azidoimidazo[4,5-*e*]1,2,3-triazines (**414**) (311). Spectroscopic data showed that, starting from **411a** the diazo (**412a**) and the azido form (**414a**) predominate in the isolated product. The compound isolated from diazotization of **411b** exists mainly in the diazoimidazole structure (**412b**) in the solid state and in DMSO-D_6–acetic acid and trifluoroacetic acid solutions, whereas the substance obtained by nitrosation of **411c** exists mainly as the tricyclic compound **413c** in the solid state and in DMSO-D_6 solution, and as the diazoimidazole **412c** in trifluoroacetic acid.



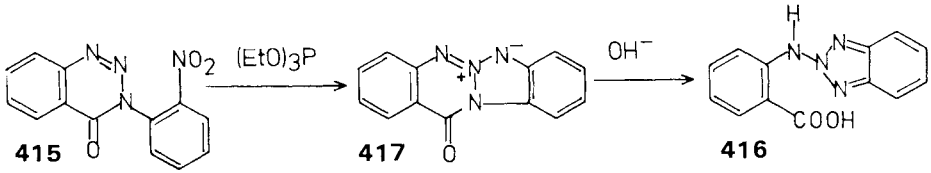
Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

VIII

1,2,3-Triazine Rings Condensed with Heterocycles through Two Nitrogen Atoms

I. BENZOTRIAZOLO[2,1-*b*]1,2,3-BENZOTRIAZINES

Reaction of 3-(2-nitrophenyl)-1,2,3-benzotriazin-4-one (**415**) with triethyl phosphite afforded a yellow crystalline compound of melting point 261 to 262 °C (368). This compound displayed an absorption at 1715 cm^{-1} in the infrared spectrum but no bands characteristic of nitro group absorption. The following ultraviolet spectrum was recorded: λ_{max} (log ϵ) = 404 (17.000), 369 (17.600), 358 (17.200), 304 (3.080), 295 (3.290), 267 (10.900), 240 (18.900), and 228 nm (17.600) (368). On the basis of the spectroscopic data and the alkaline hydrolysis which afforded 2-(2-carboxyphenylamino)benzotriazole (**416**) the isolated compound is formulated as the benzotriazolo[2,1-*b*]1,2,3-benzotriazinium betaine **417**. **417** can be brominated with bromine in glacial acetic acid to give a dibromo derivative and can be nitrated with 75% nitric acid to give a dinitro derivative, respectively. The structures of the derivatives are not established.

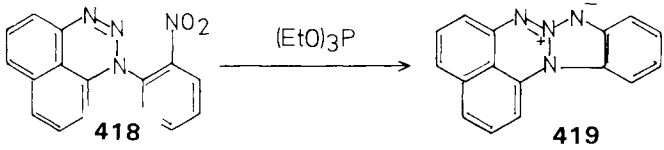


415 **417** **416**

II. BENZOTRIAZOLO[1,2-*a*]NAPHTHO[1,8-*de*]1,2,3-TRIAZINES

Reduction of 1-(2-nitrophenyl)-naphtho[1,8-*de*]1,2,3-triazine (**418**) with excess triethyl phosphite at 100 °C led to the isolation of the red benzotri-

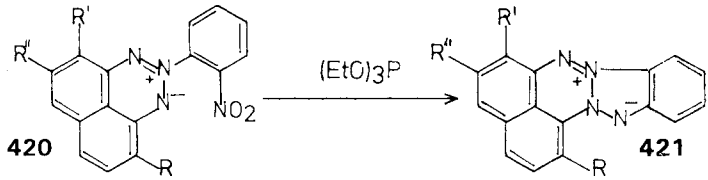
azolo[1,2-*a*]naphtho[1,8-*de*]1,2,3-triazine (**419**) (m.p. 230.5 to 232 °C) in 7.5% yield (289). The following ultraviolet spectrum is recorded for **419**: λ_{max} (log ϵ) = 515 (3.71), 486 (3.75), 396 (3.88), 376 (3.91), 337 (4.10), and 252 nm (4.02).



418 **419**

III. BENZOTRIAZOLO[2,1-*a*]NAPHTHO[1,8-*de*]-1,2,3-TRIAZINES

Heating the three 2-(2-nitrophenyl)naphtho[1,8-*de*]1,2,3-triazines (**420a** to **420c**) with 2 moles of triethyl phosphite at 140 °C afforded the blue benzotriazolo[2,1-*a*]naphtho[1,8-*de*]1,2,3-triazines (**421a** to **421c**) in yields between 49 and 60% (289). The new compounds have the following melting points and ultraviolet spectra. **421a**: 214–215 °C; 626 (3.44), 580 (3.44), 358 (4.51), and 285 nm (4.20). **421b**: 200–202 °C; 660 (3.36), 610 (3.37), 364 (4.34), 287 (4.24), 255 (4.24), and 225 nm (4.64). **421c**: 193–195 °C; 649 (3.48), 601 (3.48), 366 (4.53), and 287 nm (4.26).



420 **421**

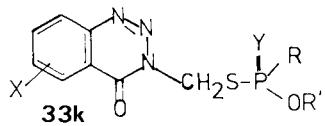
a: R = R' = H
b: R'' = H, R = R' = CH_3
c: R = H, R' = R'' = CH_3

Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

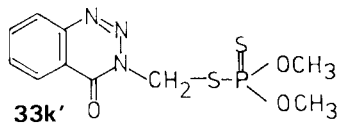
IX

Uses and Biochemical Aspects of 1,2,3-Triazine Derivatives

Most papers discussed here deal with the use of compounds of the general formula **33k** as insecticides, nematocides, or acaricides, their toxicity, their determination, and their properties. The synthesis of compounds of formula **33k** is discussed in Section I-B of Chapter IV. The most widely used compound seems to be the substance **33k′** (Bayer 17147, Guthion, azinphos methyl); a review on this compound with 112 references was published in 1974 by Anderson et al. (390).



33k



33k′

Owing to the high biochemical activities of these compounds tests have been carried out with the aim of controlling numerous insects or fungal diseases by these substances or to test their toxicities to insects or animals (391–652), such as the boll weevil (391–418), bollworms (391–396, 419–430), thrips (flower thrips, onion thrips) (391, 461–465), moths (diamondback moth, codling moth, tomato tuber moth, etc.) (436–453), leafhoppers (grape, white apple, potato, cotton leafhopper) (422, 504–506), mites (spider mite, two-spotted mite, bud mites, etc.) (391, 413, 414, 429–436, 454–461), leafworms (cotton leafworms) 391, 392, 423–425, 467–471), leaf rollers (red-banded leaf roller) (397, 422, 444–446, 507), beetles (Colorado beetle, potato beetle, and others) (506, 516–519, 540, 550), leaf miners (cabbage, vegetable, tobacco leaf miners) (461, 482, 508–510), borers (sugar cane borer, paddy borer, and others) (415, 484, 494–503, 548), caterpillers (cabbage, coconut, salt-marsh caterpillars) (414, 495, 538, 539, 549), aphids (cotton, cabbage, alfalfa, woolly apple aphids) (391,

414, 415, 471, 472, 487–493, 548), worms (leafworms, armyworms, cabbage worms and many others) (414, 429, 438, 439, 472–485), weevils (alfalfa, pecan, pine weevil, etc.) (466, 487–495), bugs (pineapple mealybug, grape mealybug, root mealybug, spittlebug, tarnished plant bug) (436, 520–524), loopers (cabbage) (438, 439, 535–537), fleahoppers (cotton) (391, 409, 465), as well as horses, birds, rats, cattle, sheep, guinea pigs, pheasants, mice, fish (553–565), and men (566–569).

The inhibition of choline esterase (570–577) and malathionase (578), and of mitochondrial electron transport (579) was studied by various groups. Effects of these substances on the germination and growth of plants and on the yield and quality of plant products or on the nitrification of soil were also studied (580–586). Special compositions of these compounds for enhanced penetration were claimed in two patents (587, 588). Numerous further tests were reported (589–652) but a detailed enumeration of all published tests is far beyond the scope of this book.

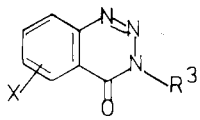
Properties and reactions such as deactivation by potassium permanganate (653), dissipation (654), half-life (655, 656), hydrolysis (365, 657), persistence and degradation (658), disappearance from cotton leaves (659), translocation (660), or the influence of temperature, light, and pH on the breakdown of these substances (661, 662) were studied by various groups.

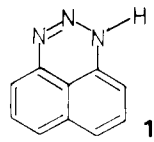
A large number of papers were published dealing with the isolation and determination of these substances. Very important are the attempts to isolate and determine residues of these substances and to correlate the isolated amounts with the tolerances or limits given by different organizations (181–183, 188, 366, 367, 663–696).

The synthesis of Guthion (**33k'**) labeled with carbon-14 in the benzene ring is reported by White, Al-Adil, Winterlin, and Kilgore (137).

A large number of 1,2,3-benzotriazin-4-ones of the general formula **33a** were prepared and found to have some biochemical properties, and their use as diuretics, inflammation inhibitors, sedatives, tranquilizers, etc. were claimed, (64, 65, 67, 74–77, 85, 88–91, 106–110, 123, 129, 144, 146, 148, 149, 151–153, 156, 160, 163, 167, 168, 171, 172, 174, 185, 204, 243, 246, 595, 697–700).

33a

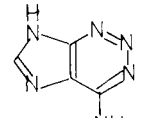




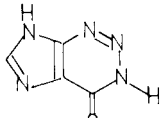
197a

In one paper it was reported that naphtho[1,8-*de*] 1,2,3-triazine (**197a**) is active against boll weevil (701).

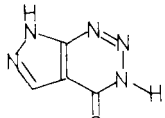
Imidazo[4,5-*d*] 1,2,3-triazines are azapurines and therefore high biochemical activities could be expected. Many experiments were reported to test the biochemical behavior of such compounds, especially that of 4-aminoimidazo-[4,5-*d*] 1,2,3-triazine (2-azaadenine) (**255a**) and imidazo[4,5-*d*] 1,2,3-triazin-4-one (2-azahypoxanthine) (**257a**) (315, 318, 702–722). Among the many reported activities are the following: they are inhibitors of xanthine oxidase (318, 702, 703), RNA polymerase (707), uricase (703, 704), phosphoribosyl transferase (703, 705, 706), formyl tetrahydrofolate synthetase (707), and of cell growth (708). They are active in the transport of potassium through membranes (709–710); their toxicity to carcinoma cells (711–714) and their effect on the multiplication of tobacco mosaic virus (715) were also tested.



255a



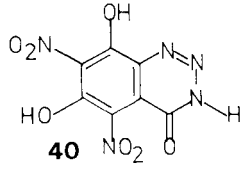
257a



247a

In one publication the biochemical properties of pyrazolo[3,4-*d*] 1,2,3-triazin-4-one (**247a**) were tested (703).

Besides the uses of 1,2,3-triazines which were based upon their biochemical properties some further uses were reported or claimed (725–735), such as the use of 1,2,3-benzotriazin-4-ones as additives to photographic layers (725), as foaming or blowing agents in polymers (726–728), as stabilizers for polymers (729, 730); 1,2,3-benzotriazine-4-thione is used as an antifoggant in photographic emulsions and as a blue-black toning agent in the solvent transfer process (731) or as a photosensitizer (733). The use of 1,2,3-benzotriazin-4-ones for the synthesis of azo dyes is claimed by different groups (92, 191, 193, 732), and the use of the 1,2,3-benzotriazine (**40**) or its monopotassium acid salt in pyrotechnic detonators or sensitizing percussion detonators is reported in two patents (723, 724)



40

The use of 3-hydroxy-1,2,3-benzotriazin-4-ones in peptide synthesis was already mentioned, as was the use of 1-tert-butyl-3-ethyl-2-methyl-hexahydro-1,2,3-triazine (**16**) as a corrosion inhibitor for steel.

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Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

1,2,4-Triazines

HANS NEUNHOEFFER

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I

Introduction

About 20 years ago a comprehensive review of the 1,2,4-triazines appeared (1), covering the whole literature through *Chemical Abstracts* 1950. Five years later a second review was published by Horwitz (2). A third review on the chemistry of 1,2,4-triazines was published by Hadacek and Slouka (3–5) in three volumes in 1965, 1966, and 1970. This review, written in German, is less known and is to our knowledge not mentioned in *Chemical Abstracts*. Finally, a short review of the 1,2,4-triazines was published by Jones and Kershaw (6) in 1971. Besides these reviews a number of discussions of special aspects of the chemistry of 1,2,4-triazines have been published. These publications are mentioned here where appropriate.

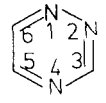
Because the number of publications on the chemistry of 1,2,4-triazines has increased tremendously during the last 10 years it is felt that a review covering the whole literature on 1,2,4-triazines through 1974 (*Chemical Abstracts*, Volume 81) is justified.

The increase in the literature on 1,2,4-triazines is mainly because of the following developments:

1. Owing to better synthetic methods nearly every required 1,2,4-triazine can be synthesized in good yield, leading to an intensive study of the chemical and physical properties of this class of heterocyclic compounds.
2. Interest in the biochemical properties of 1,2,4-triazines is high because a number of 3,5-disubstituted 1,2,4-triazines represent aza analogues of pyrimidine nucleo bases and a number of natural antibiotics are pyrimido-[5,4-e] 1,2,4-triazines.
3. 4-Amino-6-tert-butyl-3-(methylmercapto)-1,2,4-triazin-5-one is used as a herbicide.

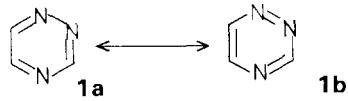
This review gives a complete discussion of the chemistry of 1,2,4-triazines, but those publications dealing only with the biochemical properties or with the uses of 1,2,4-triazines are listed separately without a detailed discussion.

The parent compound of the 1,2,4-triazine series has structure **1** and is numbered as indicated. In *Chemical Abstracts* it is called 1,2,4-triazine or



1

as-triazine. In *The Ring Index* it is called *as*-triazine (RRI 211). In the older literature the names α-triazine and isotriazine can also be found. In this review the term 1,2,4-triazine is used.



1a **1b**

For the 1,2,4-triazine **1** the two Kekulé structures **1a** and **1b** can be drawn. Theoretical calculations have shown that formula **1a** gives a higher contribution to the ground state of the molecule, for which considerable evidence for some degree of electron delocalization is given. Therefore formula **1a** is used in this review for all aromatic 1,2,4-triazines.

Besides the 1,2,4-triazines, condensed 1,2,4-triazine systems, dihydro-, tetrahydro-, and hexahydro-1,2,4-triazines are known. The material on 1,2,4-triazines is classified as follows:

1. Uncondensed 1,2,4-triazine systems (Chapters II and III)
2. Condensed 1,2,4-triazine systems (Chapters IV–IX)
3. Uses and biochemical aspects of 1,2,4-triazines (Chapter X)

The organization of the discussion of uncondensed 1,2,4-triazine systems is based on the degree of saturation of the 1,2,4-triazine ring and the compounds in each group are dealt with in the following order:

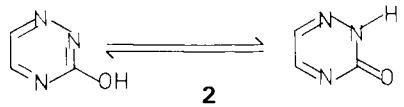
1. Parent heterocycles, their homologues, and aryl derivatives
2. Hydroxy or oxo derivatives
3. Mercapto or thioxo derivatives
4. Amines and hydrazines
5. Halogen derivatives
6. Compounds with two or three different hetero substituents
7. Ketones, carboxylic acids, and their derivatives
8. Carboxylic acids with hetero substituents directly attached to the 1,2,4-triazine nucleus
9. *N*-oxides and compounds with an ylidestructure

The condensed 1,2,4-triazine systems are discussed in the following order:

1. Condensed with carbocycles
2. Condensed with heterocycles without a bridgehead nitrogen

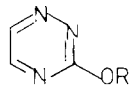
3. Condensed with heterocycles with bridgehead nitrogens

Owing to the organization of uncondensed 1,2,4-triazines by the degree of saturation of the 1,2,4-triazine ring a problem arises in the classification of the "hydroxy"-1,2,4-triazines such as **2**. In the literature three names are used for

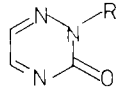


2

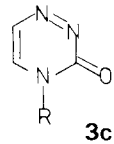
compound **2**: 3-hydroxy-1,2,4-triazine, 1,2,4-triazin-3-one, and 2,3-dihydro-1,2,4-triazin-3-one. We believe that compound **2** should be discussed together with its alkylation products **3a**, **3b**, and **3c**. Since **3a** represents a fully unsaturated 1,2,4-triazine system all 1,2,4-triazines with hetero substituents (oxygen, sulfur, selenium, nitrogen) directly bonded to the 1,2,4-triazine ring are discussed in the chapter to which the tautomer with the highest number of double bonds in the heterocyclic ring belongs. This is carried out strictly despite the fact that for most of these compounds it has been shown that this tautomer is the less predominant.



3a



3b



3c

Heterocyclic substituents that are attached by a carbon atom to a carbon atom of the 1,2,4-triazine system are considered as "aryl" substituents, and all heterocyclic substituents attached by a nitrogen atom to a carbon atom of the 1,2,4-triazine ring are considered as "amines."

At present only a few naturally occurring compounds having the 1,2,4-triazine system are known.

Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

II

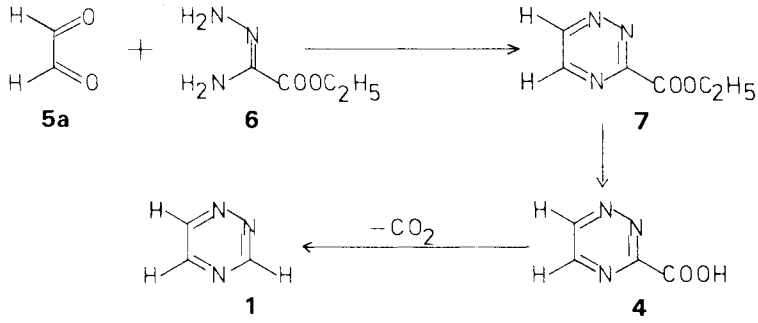
Uncondensed Aromatic Systems

I. ALKYL-, ARYL-, AND HETEROCYCLIC-SUBSTITUTED 1,2,4-TRIAZINES

A. Preparation

There are a large number of 1,2,4-triazines of this type reported in the literature. In this chapter all 1,2,4-triazines having substituents bound to the 1,2,4-triazine ring by a carbon atom are discussed, despite the fact that there may be functional groups in the substituents. Exceptions to this rule are carbonyl or carboxyl groups directly bound to the 1,2,4-triazine system.

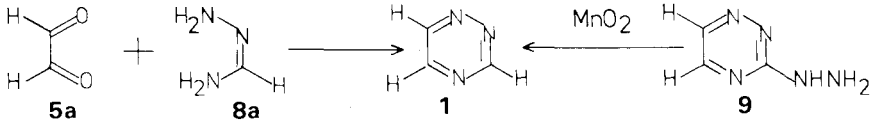
After a number of unsuccessful attempts (7–10, 158, 1019) to prepare the unsubstituted 1,2,4-triazine (**1**), the first synthesis of the parent compound of the 1,2,4-triazine series was reported in 1966 by Paudler and Barton (11). They synthesized this compound in 40% yield through decarboxylation of 1,2,4-triazine-3-carboxylic acid (**4**) which was prepared by reaction of glyoxal (**5a**) with ethyl oxalamidrazonate (**6**) (10% yield) and saponification of the formed ethyl 1,2,4-triazine-3-carboxylate (**7**). Meanwhile this method was improved (12) and seems now to be the best method for the synthesis of **1**. By decarboxylation of the deutero-compound **4a** the 1,2,4-triazine-*3-d* (**1c**) was synthesized (11).



4a **1c**

Besides this synthesis of **1**, two other methods for its preparation are reported.

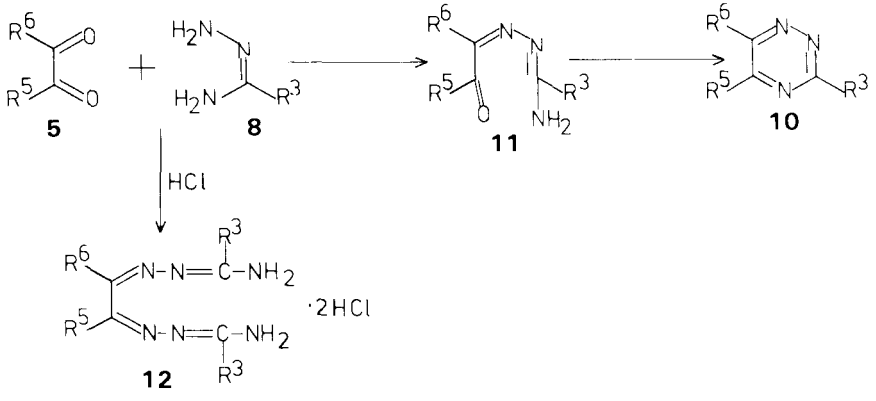
1. In 1968 the direct synthesis of **1** from formamidrazone (**8a**) and gyloxal (**5a**) was published (13).
2. In 1970 **1** was synthetized by oxidation of 3-hydrazino-1,2,4-triazine (**9**) with manganese dioxide (14).



5a **8a** **1** **9**

For the synthesis of 1,2,4-triazines (**10**) without a functional group directly bound to the 1,2,4-triazine ring a large number of methods are reported.

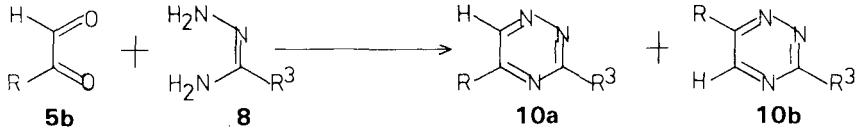
1. The most convenient method is the reaction of amidrazones (**8**) with 1,2-dicarbonyl compounds (**5**) (13, 15–40, 1068, 1069). No limitation of this reaction is reported if the right reaction conditions are observed. The best method is the addition of the 1,2-dicarbonyl compound to a solution of the free amidrazone or of the amidrazone hydrochloride in the presence of 1 mole of base and a reaction time of 12 hr (15). Since the ring closure of the intermediate (**11**) is sometimes slow, it can be isolated in a few cases. This method has also been used for the synthesis of compounds containing more than one 1,2,4-triazine nucleus.



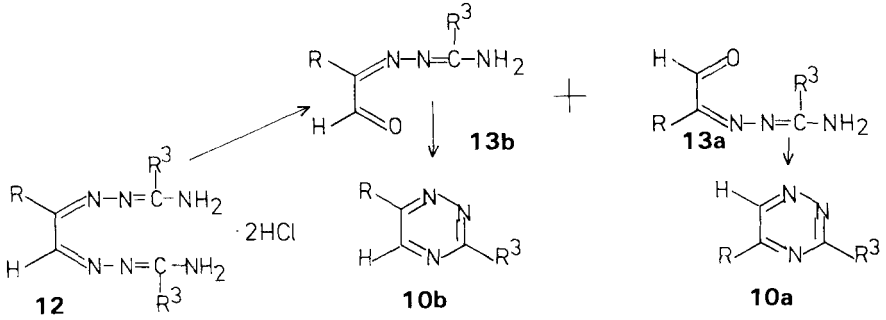
5 **8** **11** **10** **12**

If the reaction is run in the presence of free acid compounds of the osazone type **12** are formed, which are very stable if R^3 are aliphatic groups (37). For the preparation of 1,2,4-triazines from **12** see the next method.

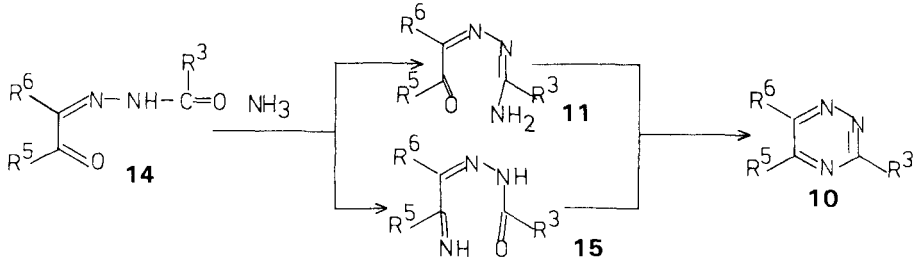
If a monosubstituted glyoxal (**5b**) is used as the 1,2-dicarbonyl compound two isomeric 1,2,4-triazines (**10a** and **10b**) can be formed. In all cases, that have so far been studied, **10a** is the predominant or the only isomer formed.



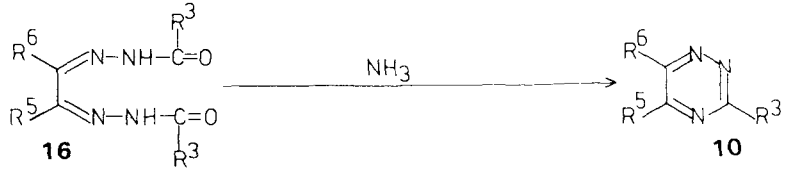
2. Mild hydrolysis of **12** with dilute acid (37) or aqueous copper sulfate (41) leads to the formation of 1,2,4-triazines in high yield. If the starting 1,2-dicarbonyl compound was a monosubstituted glyoxal (**5b**) the preferentially formed isomer was the 6-substituted 1,2,4-triazine (**10b**). This is best explained by preferential hydrolysis of **12** to **13b** and subsequent ring closure.



3. Metze and his group (42–49) and also Hasselquist (50) synthesized 1,2,4-triazines (**10**) by cyclization of the acylhydrazones of 1,2-dicarbonyl compounds (**14**) with ammonia. If the first step of this reaction is assumed to be the formation of **11**, this method is a special case of the reaction discussed 1. On the other hand the intermediate of this reaction could also be **15**.

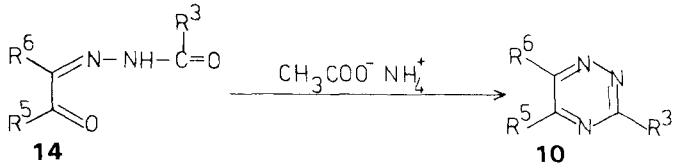


1,2-Bisacylhydrazones (**16**) can also be transformed into 1,2,4-triazines by a reaction with ammonia (56).



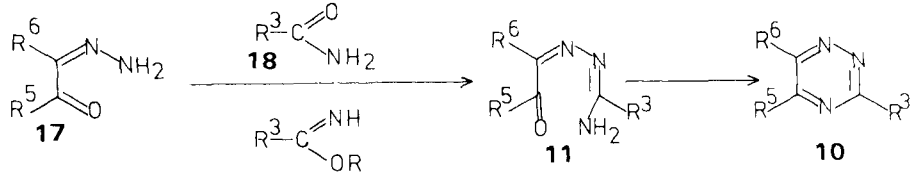
16 **10**

4. Laakso and co-workers (51) as well as other groups (52–54) synthesized 1,2,4-triazines (**10**) from the acylhydrazones of 1,2-dicarbonyl compounds (**14**) using ammonium acetate instead of ammonia for the cyclization reaction.



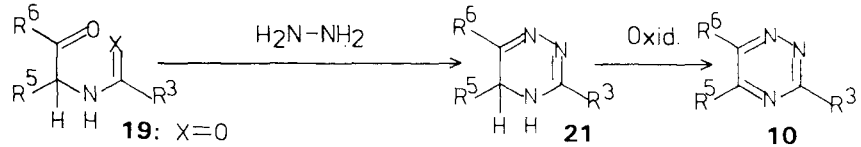
14 **10**

5. Cyclization of the monohydrazones of 1,2-dicarbonyl compounds (**17**) with amides (**18**) or imidates (40) is another method for the preparation of 1,2,4-triazines (55). The first reaction product should be the same intermediate (**11**) as in the reaction of amidrazones with 1,2-dicarbonyl compounds (method 1).



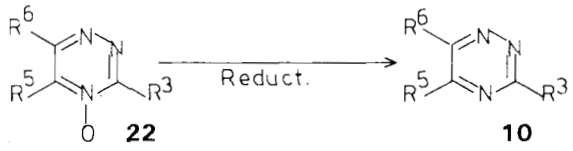
17 **18** **11** **10**

6. Cyclization of 2-(acylamino)-ketones (**19**) (52, 56, 58) or 2-[(thioacyl)amino]-ketones (**20**) (57) with hydrazine yields dihydro-1,2,4-triazines (**21**) (or tautomers of **21**) which are oxidized to 1,2,4-triazines (**10**).



19: X=O
20: X=S
21 **10**

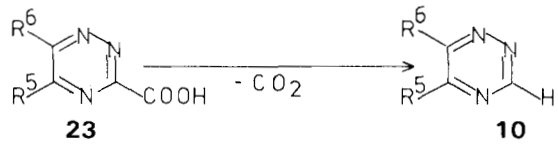
7. A large number of 1,2,4-triazines were synthesized by reduction of the 1,2,4-triazine 4-oxides (**22**) with trivalent phosphorus compounds (59, 60) or other reducing agents (61).



22 **10**

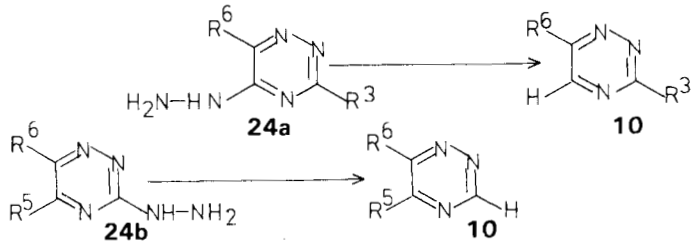
Since it is possible to specifically synthesize 6-substituted 1,2,4-triazine 4-oxides this is an elegant method for the synthesis of 6-substituted 1,2,4-triazines (**10b**).

8. The decarboxylation of 1,2,4-triazine-3-carboxylic acids (**23**) leads to 1,2,4-triazines with a hydrogen in the 3-position (11, 12, 62). Since it is possible to synthesize these compounds by the reaction of formamidine acetate with hydrazine in the presence of 1,2-dicarbonyl compounds (17), this method is especially useful for the synthesis of the unsubstituted 1,2,4-triazine (11, 12).



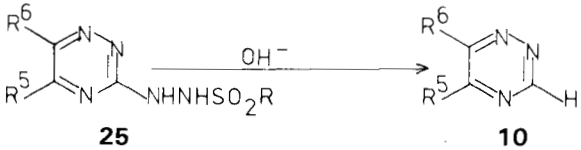
23 **10**

9. Oxidation of hydrazino-1,2,4-triazines (**24**) with manganese dioxide or silver oxide is used for the synthesis of 1,2,4-triazines with a hydrogen in the 5-position (51, 63, 64) or in the 3-position (14, 57).



24a **10** **24b** **10**

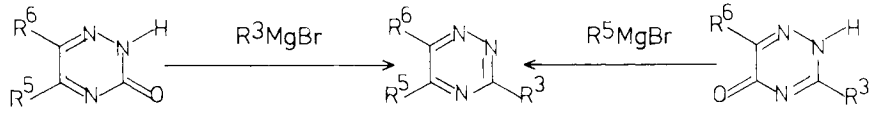
10. A method similar to the preceding method is the alkaline degradation of 3-(sulfonylhydrazino)-1,2,4-triazines (**25**) (57).



25 **10**

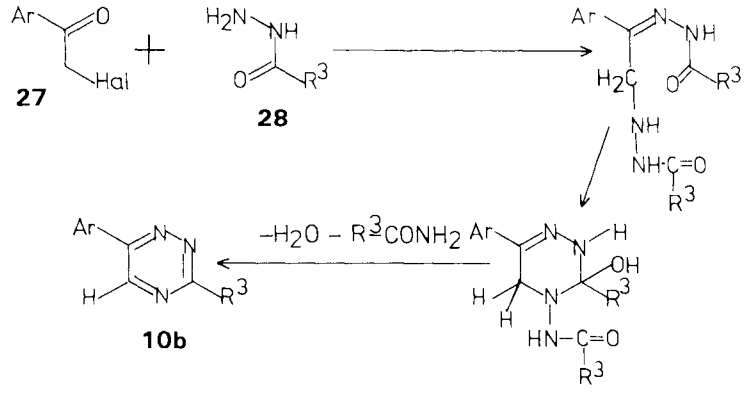
11. The reaction of 1,2,4-triazin-3-ones (**26a**) or 1,2,4-triazine-3,5-diones with Grignard reagents led, in a few cases, to the formation of 1,2,4-triazines in low yield (65, 66). Daunis and Jarquier reported the formation of 1,2,4-triazines by

reaction of 1,2,4-triazin-5-ones (**26b**) or 5-methoxy-1,2,4-triazines with Grignard reagents (1077).

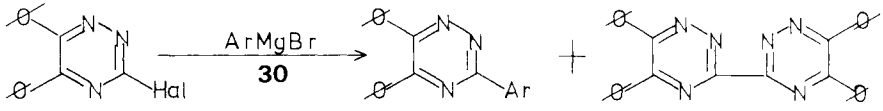


26a **10** **26b**

12. The formation of 1,2,4-triazines of type **10b** by reaction of phenacyl bromides or chlorides (**27**) with acylhydrazides (**28**) is reported in one publication (67). The following mechanism is proposed for this reaction.



13. The reaction of 3-chloro-5,6-diphenyl-1,2,4-triazine (**29**) with arylmagnesium bromide (**30**) led to the formation of 5,6-diphenyl-3-aryl-1,2,4-triazines (**31**) in low yield (51, 66). Besides **31**, the 3,3′-bi-1,2,4-triazine (**32**) was also isolated.



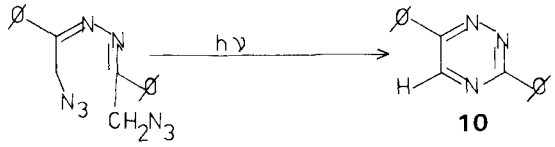
29 **31** **32**

14. The desulfuration of 3-mercapto-1,2,4-triazines (**33**) was used for the synthesis of 5,6-disubstituted 1,2,4-triazines (68).

33 **10**

15. Only in a few cases have 1,2,4-triazines been synthesized from other 1,2,4-triazines by modification of substituents in the different positions of the 1,2,4-triazine system (69–72).

16. The irradiation of 1,6-diazido-2,5-diphenyl-3,4-diazahexa-2,4-diene (**34**) in ether gave 3,6-diphenyl-1,2,4-triazine in 21.8% yield (73).



34 **10**

17. The pyrolysis of a compound formulated as **35** afforded a substance which is probably **32** (51).

35 **32**

B. Compound Survey

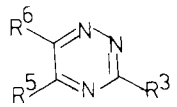
The compounds of this class that have been reported in the literature are listed in Table II – 1.

C. Physical Properties and Theoretical Considerations

Most 1,2,4-triazines discussed in this section are yellow compounds. The unsubstituted 1,2,4-triazine and its lower alkyl derivatives have a low melting point, are mostly liquid, and are reasonably stable. They can be stored at temperatures below 0°C, but in time become dark. After a long period in a refrigerator the unsubstituted 1,2,4-triazine became an amberlike solid, the constitution of which was 1 mole 1,2,4-triazine to 1 mole water (74). All these 1,2,4-triazines can be distilled under reduced pressure. They can be purified by vapor-phase chromatography, by which isomeric 1,2,4-triazines can be separated.

1,2,4-Triazines with aryl or heterocyclic substituents are crystalline and very stable compounds. All 1,2,4-triazines are soluble in most organic solvents. Owing to the basic character of the nitrogen 1,2,4-triazines form salts with mineral acids (13, 37, 55). Most 1,2,4-triazines with an aryl substituent form deep red

TABLE II-1. ALKYL, ARYL AND HETEROCYCLIC-SUBSTITUTED 1,2,4-TRIAZINES



A. 3-Substituted 1,2,4-triazines ($R^5 = R^6 = H$)

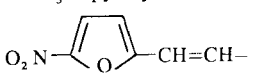
R^3	m.p. (°C)	b.p. (°C/torr)	Refs.
H	16–17	25–28/0.5 158/13	13
	16–17.5	156/740	11
			12, 14, 17
·HCl·H_2O	101–103 (dec.)		13
·$HClO_4$	74 (dec.)		13
·H_2SO_4	58–60 (dec.)		13
·Picrate	94–96 (dec.)		13
CH_3	7–8	64/4	15
C_6H_5	53–54		15
			10, 41
4-CH_3–C_6H_4	112–114		15
2-Thiazolyl	170–171		24
2-Pyridyl	86–87		24
4-CH_3-2-pyridyl	106–107		24
	220(dec.)		38

TABLE II-1. (*continued*)

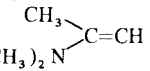
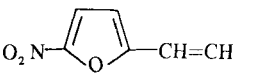
B. 5-Substituted 1,2,4-triazines ($R^3 = R^6 = H$)

R^5	m.p. (°C)	b.p. (°C/torr)	Refs.
CH_3	8–10	89–91/16 188–189	13, 37
		88–90/13	14
C_6H_5	98–99		57
	99.5–102		14
	102		17, 18
	103		13
4-HO–C_6H_4	206		57
4-Br–C_6H_4	136–137		18
2-Thienyl	116–118		18
2-(Dimethylamino)propenyl	112		70

C. 6-Substituted 1,2,4-triazines ($R^3 = R^5 = H$)

R^6	m.p. (°C)	b.p. (°C/torr)	Refs.
CH_3	5–7	74–76/15 180–182	13, 37
		67–69/14	59
C_6H_5	83		59
	85		17
	85–86		13
4-CH_3O–C_6H_4	147–148		59

D. 3,5-Disubstituted 1,2,4-triazines (R^6 = H)

R^3	R^5	b.p. (°C/torr)	m.p. (°C)	Refs.
CH_3	CH_3	82--84/22	−2–0	15, 37
CH_3			117–118	70
C_2H_5	C_6H_5		34	17
n-C_3H_7	C_6H_5		23	17
C_6H_5	CH_3		85–87	15, 37
C_6H_5	C_6H_5		98–99	15
4-CH_3–C_6H_4	CH_3		75–76	15, 37
	CH_3	(or isomer)	192 (dec.)	38
2-Pyridyl	C_6H_5		140.5–141	31, 32/30
2-Pyridyl	4-O_2N–C_6H_4		246–248	32
2-Pyridyl	4-HO–C_6H_4		211–213	32
4-CH_3-2-pyridyl	C_6H_5		111–112	21
4-C_6H_5-2-pyridyl	C_6H_5		183	21
6-(2-pyridyl)-2-pyridyl	C_6H_5		196	21
2-(1,10)phenanthrolyl	C_6H_5		254	21

E. 3,6-Disubstituted 1,2,4-triazines (R^5 = H)

R^3	R^6	m.p. (°C)	Refs.
CH_3	CH_3	55–56	15, 37
CH_3	C_6H_5	106–108	58
		107–109	37
		109	59
n-C_3H_7	C_6H_5	51–52	17

TABLE II-1. *(continued)*

E. 3,6-Disubstituted 1,2,4-triazines (R^5 = H)

R^3	R^6	m.p. (°C)	Refs.
C_6H_5	CH_3		37
C_6H_5	C_6H_5	155–157	61
		156	58
		156–157	52
		159–161	37
		160	59
			67
C_6H_5	4-CH_3–C_6H_4		67
4-CH_3–C_6H_4	CH_3		37
4-CH_3–C_6H_4	C_6H_5	168–170	37
			67
Trimethylgallyl	C_6H_5		67
2-Furyl	C_6H_5		67

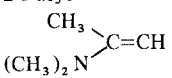
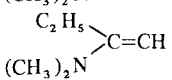
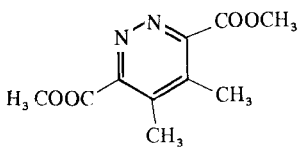
F. 5,6-Disubstituted 1,2,4-triazines (R^3 = H)

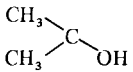
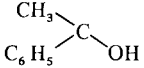
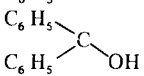
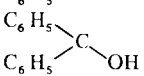
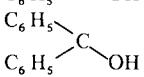
R^5	R^6	m.p. (°C)	b.p. (°C/torr)	Refs.
CH_3	CH_3	Oil		1077
		5–6		13, 47, 48
			83–85/13	14
			84–85/13	13
			87–88/14	47
			88/14	48
			90–92/15	37

CH_3	C_2H_5		96/14	48
CH_3	C_6H_5	60–61		1077
		68		59
C_2H_5	CH_3		96/14	47
C_2H_5	C_2H_5		105/14	47, 48
$(CH_3)_2N-C(CH_3)=CH$	CH_3	112–113		70
C_6H_5	CH_3	96		47, 48
		98–99		1077
C_6H_5	C_6H_5	110–111		62
		112–113		1077
		112–115		51
		116		17
		116–117		13
		116–118		14
		117		52, 55, 57, 59
		118		37
		119		68
·HCl		137		55
4-$CH_3-C_6H_4$	4-$CH_3-C_6H_4$	123		55
4-$CH_3O-C_6H_4$	4-$CH_3O-C_6H_4$	123		37, 55
		126–127		13
4-$(CH_3)_2N-C_6H_4$	4-$(CH_3)_2N-C_6H_4$	190–191		37/13
2-Furyl	2-Furyl	93–94		17
		96–97		13
2-Pyridyl	2-Pyridyl	130–131		17
		131–132		13

TABLE II-1. *(continued)*

G. 3,5,6-Trisubstituted 1,2,4-triazines

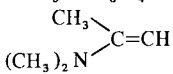
R^3	R^5	R^6	m.p. (°C)	b.p. (°C/torr)	Refs.
CH_3	CH_3	CH_3	48–50	94–96/14	15
			49–51	96/14	47, 48
			51		37
CH_3	CH_3	C_6H_5	60		59
			63		56/61
CH_3	C_2H_5	CH_3	11–12	102/14	47, 48
CH_3	C_2H_5	C_2H_5	19	109/14	47, 48
CH_3	C_6H_5	CH_3	102		47, 48
CH_3	C_6H_5	C_6H_5	90–92		15
			92		17, 45, 48
			92–94		52
·HCl			176–179		37
CH_3	2-Furyl	2-Furyl	152–153		15
CH_3		CH_3	111		70
CH_3		CH_3	68		70
CH_3		CH_3	134		70
C_2H_5		CH_3	−6 to −4	102/14	47, 48
				47/0.15	17
C_2H_5	C_2H_5	C_2H_5		118/14	47, 48

C_2H_5	C_2H_5	CH_3	11–12	110/14	47, 48
C_2H_5	C_6H_5	CH_3	64		47, 48
C_2H_5	C_6H_5	C_6H_5	52	160/01	17
n-C_3H_7	CH_3	CH_3		58/0.2	17
n-C_4H_9	CH_3	CH_3		65/0.1	17
CH_2OH	CH_3	CH_3	98		46, 48
	CH_3	CH_3	60–61		44
	CH_3	CH_3	74		44
	CH_3	CH_3	127		44
	CH_3	C_6H_5	126, 131		42
	C_6H_5	CH_3			
p-O_2N–C_6H_4–CH_2	CH_3	CH_3	91		46, 48
C_6H_5–CH_2–OCO–NH–CH_2	C_6H_5	C_6H_5	108		35
C_6H_5–CH_2–OCO–NH–CH_2	C_6H_5	p-$(CH_3)_2N$–C_6H_5	120–122 (dec.)		35
C_6H_5–CH_2–OCO–NH–CH_2	p-Cl–C_6H_4	p-Cl–C_6H_4	115–116 (dec.)		35

R^3	R^5	R^6	m.p. (°C)	Refs.
C_6H_5–CH_2–OCO–NH–CH_2	2-Furyl	C_6H_5	145 (dec.)	35
C_6H_5–CH_2–OCO–NH–CH_2	2-Thienyl	C_6H_5	120–121 (dec.)	35
C_6H_5–CH_2–OCO–NH–CH_2	2-Furyl	2-Furyl	105 (dec.)	35
C_6H_5–CH_2–OCO–NH–CH_2	2-Pyridyl	2-Pyridyl	152–153 (dec.)	35

TABLE II-1. *(continued)*

G. 3,5,6-Trisubstituted 1,2,4-triazines

R^3	R^5	R^6	m.p. (°C)	Refs.
C_6H_5	CH_3	CH_3	78–80	37
			79–80	15
			80	59
			81	17
			82	45, 47, 48
C_6H_5	C_2H_5	CH_3	122	47, 48
C_6H_5	C_2H_5	C_2H_5	56	47, 48
C_6H_5	CH_3	C_6H_5	119	59
			123–124	52
			125	42
			126	56
C_6H_5	C_6H_5	CH_3	104–106	47, 48
			109	42
			109–110	52
C_6H_5	C_6H_5	C_6H_5	142–143	51
			145	17, 52
			145–146	15
			148	56
			149	66
·HCl			105–106	37
C_6H_5	C_6H_5	4-$(CH_3)_2N$–C_6H_4	160–164	54
C_6H_5	4-$(CH_3)_2N$–C_6H_4	C_6H_5		
C_6H_5	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	164–165	54
C_6H_5		CH_3	139	70

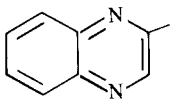
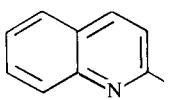
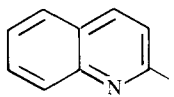
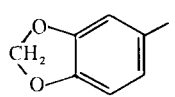
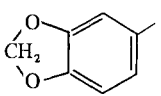
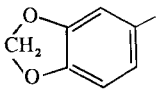
4-CH_3–C_6H_4	CH_3	CH_3	104	37
			104–105	15
4-CH_3–C_6H_4	C_6H_5	C_6H_5	136–137	51
			137.5–138	69
			138–140	15
			140	17
·HCl			116–118	37
4-CH_3–C_6H_4	2-Pyridyl	2-Pyridyl	163–164	15
4-CH_3–C_6H_4	 2-Quinoxalyl	C_6H_5	169	36
2-CH_3–C_6H_4	 2-Quinolyl	 2-Quinolyl	195–196	54
4-CH_3O–C_6H_4	CH_3	C_6H_5	169–170	52
4-CH_3O–C_6H_4	C_6H_5	CH_3	122–123	52
4-CH_3O–C_6H_4	C_6H_5	C_6H_5	159–160	52
			164	66
4-CH_3O–C_6H_4	C_6H_5	4-$(CH_3)_2N$–C_6H_4	175–177	54
4-CH_3O–C_6H_4	4-$(CH_3)_2N$–C_6H_4	C_6H_5		
4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	147–148	54
3-CH_3O–C_6H_4	C_6H_5	C_6H_5	129–130	51
2,4-$(CH_3O)_2C_6H_3$	C_6H_5	C_6H_5	167–168	51
3,4-$(CH_3O)_2C_6H_3$	C_6H_5	C_6H_5	177–178	51
	C_6H_5	C_6H_5	159–160	51

TABLE II-1. (*continued*)

G. 3,5,6-Trisubstituted 1,2,4-triazines

R^3	R^5	R^6	m.p. (°C)	Refs.
3,4,5-$(CH_3O)_3C_6H_2$	C_6H_5	C_6H_5	158–159	51
4-F–C_6H_4	C_6H_5	C_6H_5	144.5–145.5	19
4-Cl–C_6H_4	C_6H_5	C_6H_5	134–135	51
			152–153	52
4-Br–C_6H_4	C_6H_5	C_6H_5	140–141	52
2-O_2N–C_6H_4	C_6H_5	C_6H_5	194	52
3-O_2N–C_6H_4	C_6H_5	C_6H_5	195	52
4-O_2N–C_6H_4	C_6H_5	C_6H_5	194	52
			200–201	
4-HO–C_6H_4	C_6H_5	C_6H_5	254–255.5	51
			262–263	
2-HO–C_6H_4	C_6H_5	C_6H_5	174–175	53
2-HO–C_6H_4	4-CH_3–C_6H_4	4-CH_3–C_6H_4	179–180	53
2-HO–C_6H_5	4-Cl–C_6H_4	4-Cl–C_6H_4	178–179	53
2-HO–C_6H_5	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	176–177	53
2-HO–C_6H_5	2-CH_3O–C_6H_4	2-CH_3O–C_6H_4	151–152	53
2-HO–C_6H_5	2-HO–C_6H_4	2-HO–C_6H_4	225–226	53
2-HO–C_6H_5			210	53
2-HO–C_6H_5	2-Pyridyl	2-Pyridyl	164	53
2-HO-5-CH_3–C_6H_3	C_6H_5	C_6H_5	187–188	53
2-HO-5-CH_3–C_6H_3	4-CH_3–C_6H_4	4-CH_3–C_6H_4	178–179	53
2-HO-5-CH_3–C_6H_3	4-Cl–C_6H_4	4-Cl–C_6H_4	179	53
2-HO-5-CH_3–C_6H_3	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	163–164	53

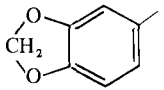
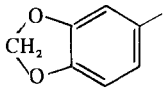
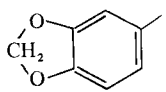
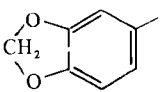
2-HO-5-CH_3–C_6H_3			175–176	53
2-HO-5-CH_3–C_6H_3	2-Pyridyl	2-Pyridyl	190–191	53
2-HO-3,5-Cl_2 C_6H_2	C_6H_5	C_6H_5	178–179	53
2-HO-3,5-Cl_2 C_6H_2	4-CH_3–C_6H_4	4-CH_3–C_6H_4	220–220.5	53
2-HO-3,5-Cl_2 C_6H_2	2-Pyridyl	2-Pyridyl	192.5–193	53
4-CH_3–COO–C_6H_4	C_6H_5	C_6H_5	175–176	51
4-H_2N–C_6H_4	C_6H_5	C_6H_5	218–219	51, 52
			219–220	54
4-H_2N–C_6H_4	2-Pyridyl	2-Pyridyl	224–225	54
2-H_2N–C_6H_4	C_6H_5	CH_3	144	46, 48
2-H_2N–C_6H_4	C_6H_5	C_6H_5	163–164	52
2-CH_3NH–C_6H_4	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	145–146	54
4-$(CH_3)_2N$–C_6H_4	C_6H_5	C_6H_5	196–198	54
4-$(CH_3)_2N$–C_6H_4	C_6H_5	4-CH_3O–C_6H_4	166	54
4-$(CH_3)_2N$–C_6H_4	4-CH_3O–C_6H_4	C_6H_5		
4-$(CH_3)_2N$–C_6H_4	C_6H_5	4-$(CH_3)_2N$–C_6H_4	217–218	54
4-$(CH_3)_2N$–C_6H_4	4-$(CH_3)_2N$–C_6H_4	C_6H_5		
4-$(CH_3)_2N$–C_6H_4	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	194–195	54
4-$(CH_3)_2N$–C_6H_4	4-C_2H_5O–C_6H_4	4-C_2H_5O–C_6H_4	196–197	54
4-$(CH_3)_2N$–C_6H_4	4-C_6H_5O–C_6H_4	4-C_6H_5O–C_6H_4	160–161	54
4-$(CH_3)_2N$–C_6H_4			244–245	54
4-$(CH_3)_2N$–C_6H_4	2-Furyl	2-Furyl	177–178	54
4-$(CH_3)_2N$–C_6H_4	2-Pyridyl	2-Pyridyl	189–190	54
4-$(CH_3)_2N$–C_6H_4	6-CH_3-2-pyridyl	6-CH_3-2-pyridyl	167–168	54
4-$(CH_3)_2N$–C_6H_4	2-Quinolyl	2-Quinolyl	231–232	54
4-$(C_2H_5)_2N$–C_6H_4	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	188–189	54

TABLE II-1. *(continued)*

G. 3,5,6-Trisubstituted 1,2,4-triazines

R^3	R^5	R^6	m.p. (°C)	Refs.
4-$(CH_3)C_6H_5N-C_6H_4$	4-$CH_3O-C_6H_4$	4-$CH_3O-C_6H_4$	151	54
4-$C_6H_5-C_6H_4$	C_6H_5	C_6H_5	204–205	54
4-$C_6H_5-C_6H_4$	2-Pyridyl	2-Pyridyl	178–180	54
p-$CH_3-CONH-C_6H_4$	C_6H_5	C_6H_5	264–265	51
			270	52
p-$(C_6H_5-CH=CH)-C_6H_4$	C_6H_5	C_6H_5	202.5–203.5	69, 72
p-$(C_6H_5-N=CH)-C_6H_4$	C_6H_5	C_6H_5		69
p-$[p-(C_6H_5)-C_6H_4-CH=CH]-C_6H_4$	C_6H_5	C_6H_5	264.5	72
			264–265	69
2-HO-3-naphthyl	2-Pyridyl	2-Pyridyl	209–211	54
1-Amino-2-anthraquinonyl	C_6H_5	C_6H_5	236–237.5	51
1-(Benzoylamino)-2-anthraquinonyl	C_6H_5	C_6H_5	275–277	51
1-Amino-4-bromo-2-anthraquinonyl	C_6H_5	C_6H_5	255 (dec.)	51
1,4-Diamino-2-anthraquinonyl	C_6H_5	C_6H_5	244–246	51
1-Amino-4-(benzoylamido)-2-anthraquinonyl	C_6H_5	C_6H_5	240–242 (dec.)	51
1,4-Dibenzoylamido-2-anthraquinonyl	C_6H_5	C_6H_5	270 (dec.)	51
2-Furyl	CH_3	CH_3	101	46, 48
2-Furyl	C_6H_5	C_6H_5	181–183	51
2-Furyl	*p*-$CH_3O-C_6H_4$	*p*-$CH_3O-C_6H_4$	155–156	54
5-O_2N-2-furyl	CH_3	CH_3	160.5–161	20
5-O_2N-2-furyl	C_6H_5	C_6H_5	198–199	40
5-O_2N-2-furyl	2-Furyl	2-Furyl	159–161	20
2-Coumary	CH_3	CH_3	177	46, 48
2-Pyrrolyl	CH_3	CH_3	216	46, 48
2-Pyridyl	CH_3	CH_3	92–93	24/39, 50
2-Pyridyl	C_2H_5	CH_3	82	46, 48

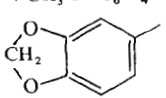
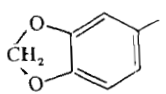
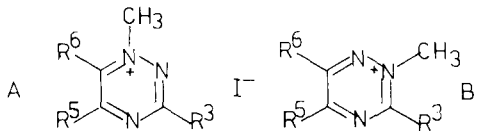
2-Pyridyl	C_6H_5	C_6H_5	189–190	28/39, 1068
2-Pyridyl	C_6H_5	2-Pyridyl	159–160	25
2-Pyridyl	C_6H_5	2-Quinoxalyl	187	36
2-Pyridyl	$4\text{-}HO_3S\text{–}C_6H_4$	$4\text{-}HO_3S\text{–}C_6H_4$		39, 1068
2-Pyridyl	2-Pyridyl	2-Pyridyl	186–187	28, 34
$4\text{-}CH_3$-2-pyridyl	CH_3	CH_3	147–148	24
$4\text{-}CH_3$-2-pyridyl	C_6H_5	C_6H_5	169–170	28
$4\text{-}CH_3$-2-pyridyl	C_6H_5	2-Pyridyl	205–206	25
$4\text{-}CH_3$-2-pyridyl	2-Pyridyl	2-Pyridyl	204–205	28
$6\text{-}CH_3$-2-pyridyl	CH_3	CH_3	154–155	25
$6\text{-}CH_3$-2-pyridyl	C_6H_5	C_6H_5	154–155	25
$4\text{-}C_2H_5$-2-pyridyl	C_6H_5	C_6H_5	150–151	28
$4\text{-}C_2H_5$-2-pyridyl	2-Pyridyl	2-Pyridyl	169–170	28
$4\text{-}C_6H_5$-2-pyridyl	CH_3	CH_3	112–113	24
$4\text{-}C_6H_5$-2-pyridyl	C_6H_5	C_6H_5	192–193	23/1069
$4\text{-}C_6H_5$-2-pyridyl	$4\text{-}HO_3S\text{–}C_6H_4$	$4\text{-}HO_3S\text{–}C_6H_4$		1069
$4\text{-}C_6H_5$-2-pyridyl	C_6H_5	2-Pyridyl	204–205	25
$4\text{-}C_6H_5$-2-pyridyl	2-Pyridyl	2-Pyridyl	171–172	28
$6\text{-}C_6H_5$-2-pyridyl	CH_3	CH_3	139–140	25
$6\text{-}C_6H_5$-2-pyridyl	C_6H_5	C_6H_5	163–164	25
6-(2-pyridyl)-2-pyridyl	CH_3	CH_3	149–150	23
6-(2-pyridyl)-2-pyridyl	C_6H_5	C_6H_5	184–185	27
6-(2-pyridyl)-2-pyridyl	2-Pyridyl	2-Pyridyl	164–165	27
3-Pyridyl	CH_3	CH_3	99	46, 48
3-Pyridyl	C_6H_5	C_6H_5	174–175	52
3-Pyridyl	$4\text{-}CH_3O\text{–}C_6H_4$	$4\text{-}CH_3O\text{–}C_6H_4$	163–164	54
3-Pyridyl			156–157	54
4-Pyridyl	CH_3	CH_3	123	46, 48
4-Pyridyl	C_6H_5	C_6H_5	161–162	52, 54
4-Pyridyl	$4\text{-}CH_3O\text{–}C_6H_4$	$4\text{-}CH_3O\text{–}C_6H_4$	155–156	28

TABLE II-1. (*continued*)

G. 3,5,6-Trisubstituted 1,2,4-triazines

R^3	R^5	R^6	m.p. (°C)	Refs.
4-Pyridyl	C_6H_5	4-$(CH_3)_2N-C_6H_4$	194–196	54
4-Pyridyl	4-$(CH_3)_2N-C_6H_4$	C_6H_5		
4-Pyridyl	2-Pyridyl	2-Pyridyl	181–182	54
2-Quinolyl	CH_3	CH_3	155	46, 48
2-Quinolyl	C_6H_5	C_6H_5	188–189	28
2-Quinolyl	2-Pyridyl	2-Pyridyl	176–177	28
2-C_6H_5-4-quinolyl	C_6H_5	C_6H_5	281–283	52
3-Isoquinolyl	C_6H_5	C_6H_5	198–199	29
3-Isoquinolyl	2-Pyridyl	2-Pyridyl	221–222	29
3-Pyridazyl	CH_3	CH_3	150	23
3-Pyridazyl	C_6H_5	C_6H_5	215–216	26
3-Pyridazyl	2-Pyridyl	2-Pyridyl	206–207	26
4-Pyrimidyl	CH_3	CH_3	116–117	23
4-Pyrimidyl	C_6H_5	C_6H_5	180–181	26
4-Pyrimidyl	2-Pyridyl	2-Pyridyl	198–199	26
2-Pyrazolyl	CH_3	CH_3	110–111	23
2-Pyrazolyl	C_6H_5	C_6H_5	179–180	26
2-Pyrazolyl	2-Pyridyl	2-Pyridyl	191–192	26
2-Thiazolyl	CH_3	CH_3	140–141	24
2-Thiazolyl	C_6H_5	C_6H_5	229–230	28
2-Thiazolyl	2-Pyridyl	2-Pyridyl	233–234	28
2,4-$(CH_3)_2$-5-thiazolyl	CH_3	CH_3	116	46, 48
2-(1,10)-phenanthrolyl	CH_3	CH_3	210–211	24
2-(1,10)-phenanthrolyl	C_6H_5	C_6H_5	215–216	28

H. *N*-Methyl-1,2,4-triazinium iodides



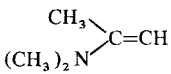
R^3	R^5	R^6	Isomer	Color	m.p. (°C)	Refs.
C_6H_5	C_6H_5	C_6H_5	A	Red	184	122
p-CH_3O–C_6H_4	C_6H_5	C_6H_5	A	Red	191, 198	122
p-Cl–C_6H_4	C_6H_5	C_6H_5	A	Red	200	122
p-Br–C_6H_4	C_6H_5	C_6H_5	A	Red	203–204	122
p-HO–C_6H_4	C_6H_5	C_6H_5	A	Red	230	122
p-CH_3CO–NH–C_6H_4	C_6H_5	C_6H_5	A	Red	203–204	122
CH_3	C_6H_5	C_6H_5	B	Colorless	168–169	122
CH_3	C_6H_5	C_6H_5	A	Red	165	122
H	C_6H_5	C_6H_5	B	Colorless	150–152	122
C_6H_5	C_6H_5	CH_3	A	Red	188	122
C_6H_5	CH_3	C_6H_5	A	Red	173–174	122
p-CH_3O–C_6H_4	C_6H_5	CH_3	A	Red	171–172	122
p-CH_3O–C_6H_4	CH_3	C_6H_5	A	Red	181–182	122

I. Labelled 1,2,4-triazines

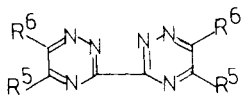
R^3	R^5	R^6		m.p. (°C)	b.p. (°C/torr)	Refs.
D	H	H				11, 101
D	CH_3	H				101
D	H	CH_3				101
D	CH_3	CH_3				101
D	C_6H_5	H				101
CH_3	H	H	4-^{15}N		56–58/2.5	16
CH_3	CH_3	CH_3	4-^{15}N	48–50		70

TABLE II-1. (*continued*)

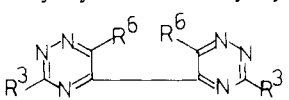
I. Labelled 1,2,4-triazines

R^3	R^5	R^6	m.p. (°C)	Refs.
CH_3		CH_3 4-^{15}N	110–111	70

J. Compounds with two 1,2,4-triazine rings directly attached



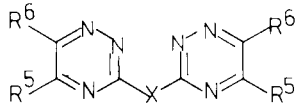
R^5	R^6	m.p. (°C)	Refs.
H	H[a]		33
CH_3	CH_3 $\cdot 2H_2O$	166	33
C_6H_5	H	244–246	31, 32
C_6H_5	C_6H_5	297	33
		298	66
p-O_2N–C_6H_4	H	342–344 (dec.)	32
2-Pyridyl	2-Pyridyl	278–279	28



R^3	R_6	m.p. (°C)	Refs.
H	H	210–212	109, 110

[a]May not be this structure.

K. Compounds with two 1,2,4-triazine rings separated by other groups



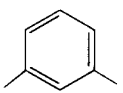
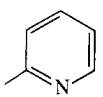
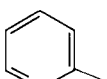
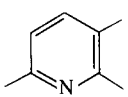
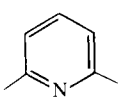
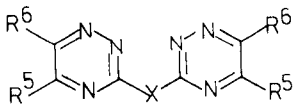
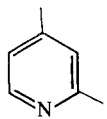
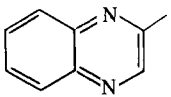
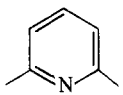
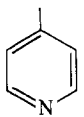
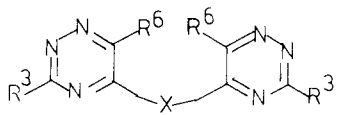
R^5	R^6	X	m.p. (°C)	Refs.
CH_3	CH_3	$(CH_2)_2$	149	49
CH_3	CH_3	$(CH_2)_3$	78	49
CH_3	CH_3	$(CH_2)_4$	65	49
CH_3	CH_3	$(CH_2)_5$	62	49
CH_3	CH_3	$(CH_2)_8$	61	49
CH_3	CH_3	$(CH_2)_{14}$	76	49
CH_3	CH_3		205	49
CH_3	CH_3		193–194	22
CH_3	CH_3		245–246	22
CH_3	CH_3		189	49
C_6H_5	C_6H_5	p-C_6H_4–CH=CH–C_6H_4	348.0–348.5	71
C_6H_5	C_6H_5		292–293	22

TABLE II-1. *(continued)*

K. Compounds with two 1,2,4-triazine rings separated by other groups

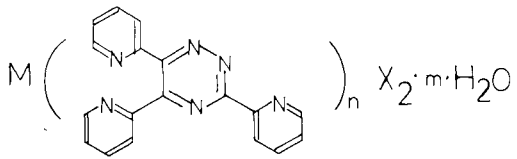


R^5	R^6	X	m.p. (°C)	Refs.
C_6H_5	C_6H_5		300–301	22
C_6H_5		p-C_6H_4	325–327	36
2-Pyridyl	2-Pyridyl		287–288	22
2-Pyridyl	2-Pyridyl		264–265	22



R^3	R^6	X	m.p. (°C)	Refs.
2-Pyridyl	H	p-C_6H_4	294–296 321–323	31 32/30

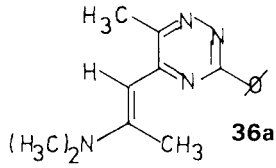
L. Metal complexes of 1,2,4-triazines



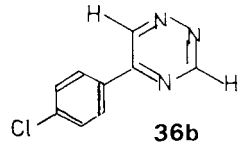
M	*n*	X	*m*	m.p. (°C)	Refs.
Zn	1	Cl	0	253–265	34
Zn	2	ClO_4	$\frac{1}{2}$	300	34
Cu	1	Cl	0	219–220	34
Cu	1	Br	0	300	34
Cu	2	ClO_4	2	215–220	34
Fe	2	ClO_4	0	254	34
Co	2	ClO_4	2	252–260	34
Ni	2	ClO_4	2	259–265	34

solutions in concentrated sulfuric acid. By addition of water the unchanged 1,2,4-triazine can be reprecipitated. Addition of concentrated hydrochloric acid to a solution of 5,6-diphenyl-1,2,4-triazine in concentrated sulfuric acid leads to the precipitation of the triazine hydrochloride (55).

Salts of other 1,2,4-triazines are prepared by addition of dry acids to a solution of the 1,2,4-triazine in an organic solvent (13).



36a



36b

The structure of 6-methyl-3-phenyl-5-[2-(dimethylamino)propenyl]-1,2,4-triazine (**36a**) (75) and 5-(4-chlorophenyl)-1,2,4-triazine (**36b**) (76) were determined by X-ray crystallographic analysis. In both cases it was shown that the 1,2,4-triazine ring is planar, as is expected for a molecule with some degree of electron delocalization. The bond lengths obtained in both cases are very similar and correlate remarkably with the bond length calculated by semi-empirical methods (77). The experimental and calculated bond distances are given in Table II–2. By comparison of these data with the bond lengths of other polyazabenzenes it follows that the canonical structure **1a** gives a greater contribution to the ground state than does canonical structure **1b** (76). The angles of the two molecules are given in Table II–3.

1a **1b**

The electronic spectra of the unsubstituted 1,2,4-triazine and a few of its lower alkyl derivatives have been measured in the gaseous phase (78). They show

TABLE II-2. BOND DISTANCES (Å)

	Experimental		Calculated for 1	
Bond	For **36a**	For **36b**	PPP	SPO
1–2	1.35	1.335	1.335	1.348
2–3	1.33	1.314	1.310	1.304
3–4	1.34	1.339	1.361	1.357
4–5	1.34	1.317	1.304	1.298
5–6	1.44	1.401	1.443	1.460
6–1	1.31	1.317	1.297	1.289

TABLE II-3. BOND ANGLES (Å) IN THE TRIAZINE RING

Angle	36a	36b
$C_6-N_1-N_2$	120	118.5
$N_1-N_2-C_3$	117	117.1
$N_2-C_3-N_4$	126	127.2
$C_3-N_4-C_5$	117	115.9
$N_4-C_5-C_6$	117	118.4
$C_5-C_6-N_1$	122	122.5

a number of absorption bands in the region of 410 to 380 nm which are due to $n \rightarrow \pi^*$ transitions. In solution the 1,2,4-triazines show an absorption in the region of 360 to 390 nm with an absorptivity of approximately 400 (13, 15–17, 69, 70, 79, 97). Most of the 1,2,4-triazines show a second absorption band in the region of 260 to 290 nm with an absorptivity of approximately 10^4 (13, 15–17, 52, 61, 70, 79, 80). The first absorption band is attributed to a $n \rightarrow \pi^*$ transition, whereas the other is a $\pi \rightarrow \pi^*$ transition (79, 80).

An interpretation of the electronic spectra of triazines by semiempirical methods is given by G. Favini (81).

The transition energies and intensities of the $\pi \rightarrow \pi^*$ transition have been calculated (82–86, 2307) for both the singlet and the triplet state. Goodman and Harrell (87) calculated the $n \rightarrow \pi^*$ transition energies for the singlet and triplet state. They have also calculated the orbital energy of the lowest unfilled π orbital by degenerate first-order perturbation theory.

The absorptions of the 1,2,4-triazines in the infrared region are those expected for this system. The infrared spectrum of unsubstituted 1,2,4-triazine (13) shows three absorption bands for the C–H stretching vibrations, at 3090, 3060, and 3035 cm^{-1}; five absorption bands for C=C and C=N stretching vibrations, at 1560, 1529, 1435, 1380, and 1295 cm^{-1}; three absorption bands for C–H in-plane deformation, at 1163, 1135, and 1113 cm^{-1}; two absorption bands for the characteristic ring skeletal vibrations, at 1050 and 995 cm^{-1}; and three absorption bands for the C–H out-of-plane deformation vibrations, at 851, 768, and 713 cm^{-1}. These values are in good agreement with similar bands for pyridine, pyridazine, pyrimidine, and pyrazine (88). Derivatives of 1,2,4-triazine show similar infrared spectra with additional bands for each substituent.

The NMR spectra of the 1,2,4-triazine nucleus have been reported for ^1H and ^{13}C. The parent compound (11) showed three signals at 0.37, 1.47, and 0.76τ (in CCl_4) which were attributed to H–3, H–5, and H–6. It is of special interest that the signal of proton H–6 is a doublet of a doublet but the signals for H–3 and H–5 are only doublets. Because a coupling constant between H–3

TABLE II-4. NMR SHIFTS OF 1,2,4-TRIAZINE IN DIFFERENT SOLVENTS AND PREDICTED CHEMICAL SHIFTS[8,9]

	Shifts (τ)		
Solvent	H-3	H-5	H-6
$CDCl_3$ (Ref. 11)	0.12	1.16	0.52
CCl_4	0.37	1.47	0.76
CD_3OD	0.14	1.07	0.48
$[D_6]$-DMSO	0.25	1.12	0.58
C_6D_6	0.55	2.08	1.32
Predicted shifts	0.26	1.26	1.02

and H—5 has never been observed, distinguishing between isomeric monosubstituted 1,2,4-triazines is easily carried out by pmr spectroscopy (15). As one would expect, the chemical shifts for the 1,2,4-triazine protons depend very much on the solvent (15), as shown in Table II–4.

The chemical shifts predicted by Nicholson (89) are in reasonable agreement with the observed values.

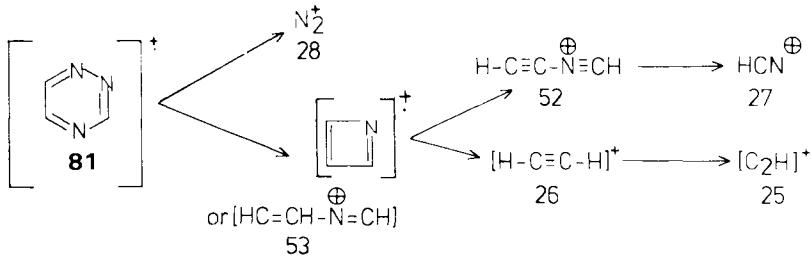
An interpretation of the chemical shifts is given by Veillard (90).

Braun, Frey, and Bachmann (91, 92) published an intensive study on the ^{13}C spectra of 1,2,4-triazines and the coupling constants in this system. The unsubstituted 1,2,4-triazine shows absorptions at 157.9 (C—3), 149.4 (C—5), and 150.6 ppm (C—6); the 3,5,6-trimethyl-1,2,4-triazine shows the following absorptions: 164.5 (C—3), 158.1 (C—5), 154.8 (C—6), 23.1 (3—CH_3), 21.6 (5—CH_3), and 19.2 ppm (6—CH_3). The C—H coupling constants for the 1,2,4-triazine are 207.1 (C_3—H_3), 9.1 (C_3—H_5), 1.3 (C_3—H_6), 188.0 (C_5—H_5), 7.5 (C_5—H_3). 9.0 (C_5—H_6), 187.5 (C_6—H_6), 9.5 (C_6—H_5), and 2.0 Hz (C_6—H_3); for the 3,5,6-trimethyl-1,2,4-triazine they are 7.1 (C_3—3—CH_3), 6.0 (C_5—5—CH_3), 3.5 (C_5—6—CH_3), 3.5 (C_6—5—CH_3), and 6.0 Hz (C_6—6—CH_3).

Until now no ^{14}N or ^{15}N spectra of 1,2,4-triazines have been reported; the ^{14}N shifts were predicted by Witanowski, Stefaniak, Januszewski, Grabowski, and Webb (93).

The mass spectra of a number of 1,2,4-triazines have been reported (16, 19, 70, 94). The mass spectrum of the unsubstituted 1,2,4-triazine (94) shows peaks at 81, 53, 52, 51, 40, 39, 38, 28, 27, 26, and 25, giving the following main fragmentation pattern, which is confirmed by the mass spectrum of the 1,2,4-triazine-*3-d* (94).

The mass spectra of 4-^{15}N-labelled 1,2,4-triazines (16, 70) show a similar fragmentation pattern.



The oscillator strengths and polarization directions for the lowest $\pi \rightarrow \pi^*$ transition were calculated by Michl et al. (84). The ionization potential was calculated to be 10.32 (83) or 10.84 eV (82).

Dewar and Gleicher (77) calculated the π-binding energies with fixed and variable β's.

Atom–atom, atom–bond, and bond–bond polarizabilities were calculated by De Giambiagi and Giambiagi (95). Dipole moments of 1,2,4-triazines were calculated by De Giambiagi and Giambiagi (2307) and by Palmer, Findlay, and Gaskell (1070), using the minimal basis set LCAO method.

Lofthus (360) calculated the bond orders of 1,2,4-triazines. The electron distribution of the 1,2,4-triazine was estimated from the observed pmr shifts by Black, Brown, and Heffernan (96).

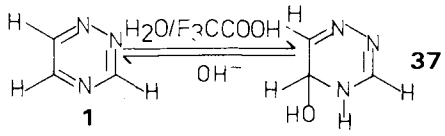
Maccoll (97) calculated the resonance energy of the 1,2,4-triazine to be 18 kcal/mole using the Forster approximation. The total energy and the binding energy were calculated by Palmer, Gaskell, and Findlay (98) using the ab initio method.

Wiberg and Lewis (99) measured the half-wave potential of 1,2,4-triazine by cyclic voltammetric reduction. They observed a value of −1.057 and a one-electron reduction forming the anion radical. The calculated values were 0.92 (CNDO), 0.66 (Nishimoto–Mataga), and 2.37 (Pariser–Parr). The half-wave potential of 1,2,4-triazine was also published by O'Reilly and Elving (1549).

Palmer and Findlay (100) found that there is no correlation between aromaticity of heterocyclic compounds, such as 1,2,4-triazine, and magnetic susceptibility anisotropy.

D. Reactions

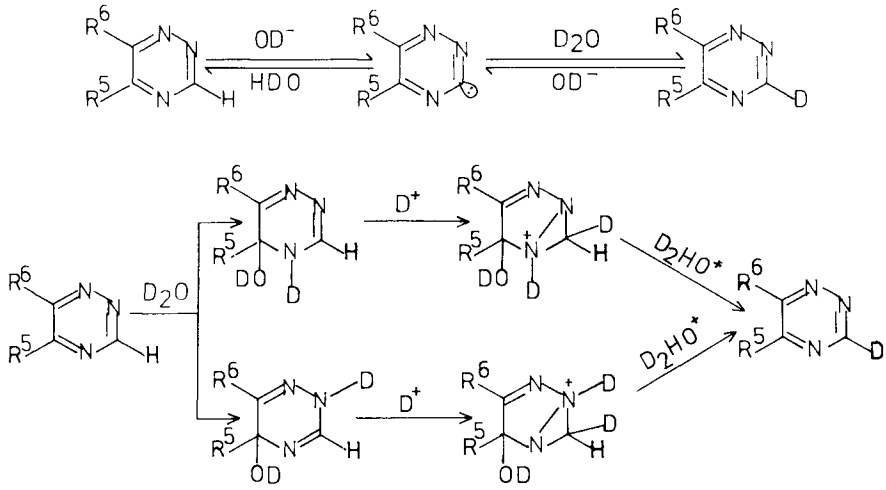
1,2,4-Triazines, including the unsubstituted 1,2,4-triazine and its lower alkyl derivatives, are stable to acid. The addition of water to a solution of 1,2,4-triazine in trifluoroacetic acid rapidly generates a new species the amount of which is directly proportional to the amount of water added to the acid solution. From the NMR spectra of this species it follows that compound **37** is



formed by covalent hydration of the N_4C_5 bond (14). Addition of base to a solution of this compound quantitatively regenerates the 1,2,4-triazine. Attempts to isolate the hydrated species have failed so far.

The 1,2,4-triazine and its lower alkyl derivatives are less stable to base. The half-life of 1,2,4-triazine in 0.5 *N* aqueous sodium hydroxide is 4.25 hr and that of 3-methyl-1,2,4-triazine is 168 hr (78). Products of the basic hydrolysis have not been identified.

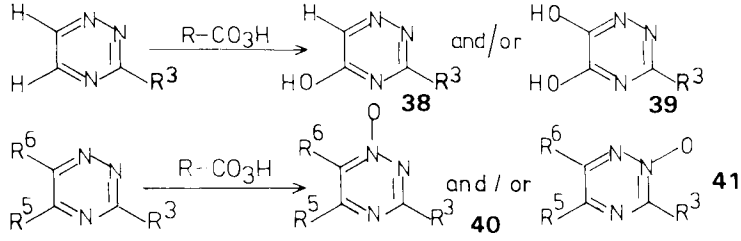
H—D exchange in neutral or basic media has been found for a number of 1,2,4-triazines (101). Two different mechanisms have been discussed for this H—D exchange, as given in the next scheme. In neutral media only those 1,2,4-triazines that undergo covalent hydration at C_5N_4 show H—D exchange.



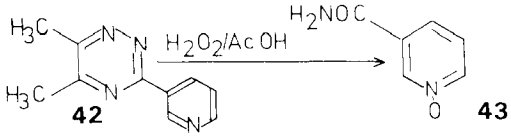
In methyl-1,2,4-triazines the 5-methyl group shows a rapid H—D exchange in basic media, whereas the other methyl groups show a very slow H—D exchange (102). Surprisingly no H—D exchange of the 5-methyl group in 5-methyl-1,2,4-triazine is reported by Paudler, Lee, and Chen (101).

1,2,4-Triazines with 2-pyridyl substituents in the 3- and/or 5-positions form stable complexes with metal ions (31, 34, 39, 1068, 1069, 2259–2268) such as iron(II), cobalt(II), nickel(II), zinc(II), and copper(II). Owing to the stability of these complexes the use of these 1,2,4-triazine derivatives was suggested for the determination of the mentioned ions, especially for iron(II) ions.

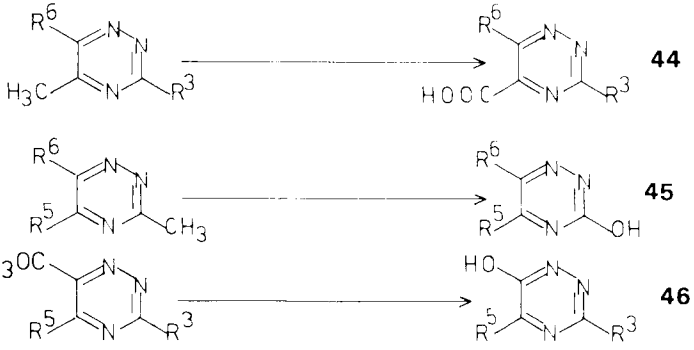
Oxidation of 1,2,4-triazines with peracids leads to three different products. In all cases where the 5 position was unsubstituted 1,2,4-triazin-5-ones (**38**) were isolated (103). If the 5-position of the 1,2,4-triazines is substituted, 1- and/or 2-oxides (**40**, **41**) are formed (104–106). Oxidation of 3-monoaryl substituted 1,2,4-triazines with peracids results in the formation of **38** and/or 5,6-di"hydroxy"-1,2,4-triazines (**39**) (103).



Oxidation of 5,6-dimethyl-3-(3-pyridyl)-1,2,4-triazine (**42**) with acetic acid/hydrogen peroxid led to the formation of nicotinamide *N*-oxide (**43**) (50).

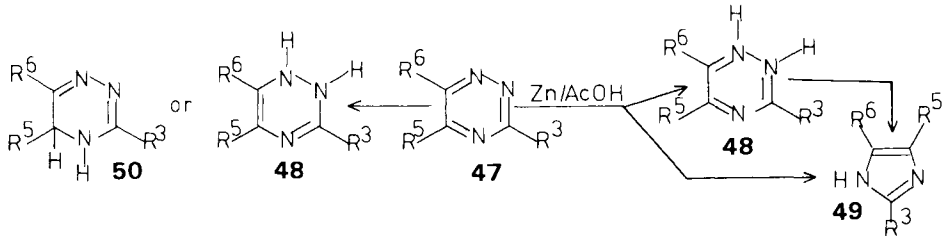


Metze and his group (44, 45) reported the oxidation of methyl groups directly bound to the 1,2,4-triazine nucleus. Whereas the oxidation of the 5-methyl group led to 1,2,4-triazine-5-carboxylic acids (**44**), the oxidation of the 3- or 6-methyl group gave 3- or 6-"hydroxy"-1,2,4-triazines (**45**, **46**).

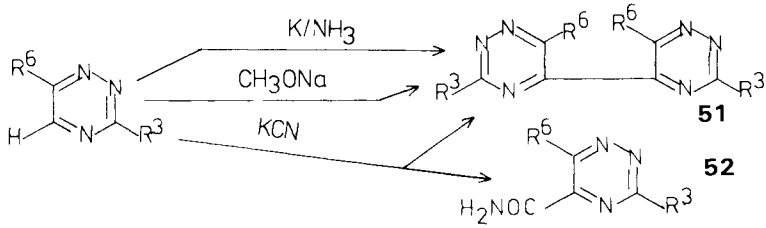


Reduction of 1,2,4-triazines (**47**) with zinc/acetic acid or Raney nickel leads to 1,2-dihydro-1,2,4-triazines (**48**) and imidazoles (**49**), which were formed from **48** (51, 107, 122). The reduction products of the electrochemical

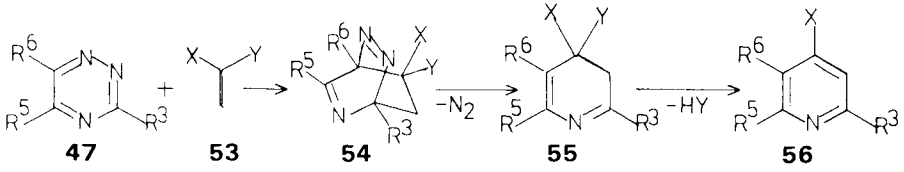
reduction of 1,2,4-triazines (**47**) are formulated as 1,2-dihydro- (**48**) and 4,5-dihydro-1,2,4-triazines (**50**) (73, 108).



Reaction of 1,2,4-triazines, with an unsubstituted 5-position, with sodium methoxide, potassium cyanide, or potassium in liquid ammonia leads to the formation of 5,5′-bi-1,2,4-triazines (**51**) (109, 110). Besides **51**, in the presence of potassium cyanide, 1,2,4-triazine-5-carboxamides (**52**) are formed. It is proposed that the sodium methoxide catalyzed dimerization occurs via a carbanionic intermediate, the aqueous potassium cyanide catalyzed reaction via a cyanide addition product, and the potassium in liquid ammonia reaction via a free radical dimerization process.

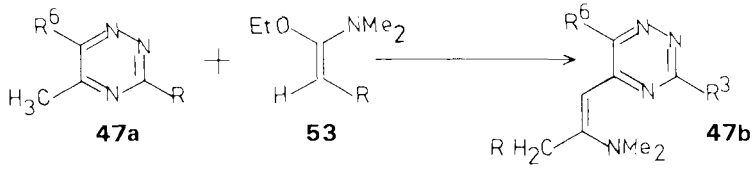


In the Diels–Alder reaction with inverse electron demand 1,2,4-triazines are reactive, electron-deficient dienes (111–119).* The reaction of 1,2,4-triazines (**47**) with electron-rich dienophiles (**53**) leads to dihydropyridines (**55**) which may aromatize to pyridines (**56**) by elimination of HX. The bicyclic intermediate **54** is postulated for the reaction mechanism.



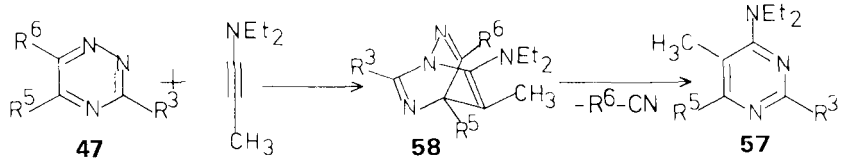
*References 115–119 do not strictly belong here, but are given for complete coverage of this reaction type.

Interaction of 5-methyl-1,2,4-triazines (**47a**) and 1-ethoxy-1-(dimethylamino)ethylene (**53a**) or -propene (**53b**) led to the formation of 5-[2-(dimethylamino)vinyl]-1,2,4-triazines (**47b**) (70).

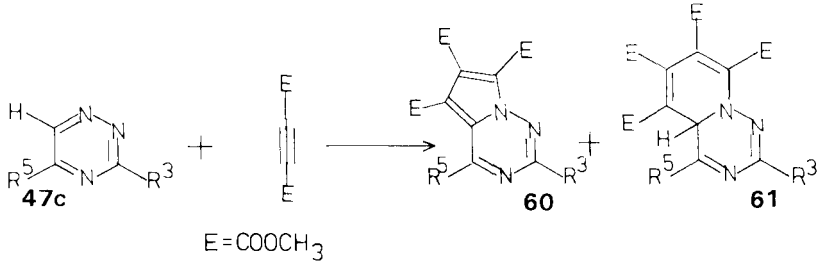


The following were used as electron-rich dienes and dienes with strained double bonds: ketene derivatives (111, 112), enamines (115), vinyl acetates (115), vinyl ethers (115), cyclopropenes (115, 117), norbornene and norbornadiene (115, 118, 119), bicyclo[2.2.2]octa-2,5-diene and -2,5,7-triene (118, 119) and dimethyl tricyclo[4.2.2.$0^{2,5}$]deca-3,7-diene-9,10-dicarboxylate and -3,7,9-triene-7,8-dicarboxylate (118).

The reaction of 1,2,4-triazines (**47**) with electron-rich acetylenes such as 1-(diethylamino)propyne mainly yields pyrimidines (**57**) (113, 114, 116), and pyridines (**56**) in only a few cases. As was shown by the reaction of 3-methyl-1,2,4-triazine-4-^{15}N, the isolated pyrimidines (**57**) are formed by a (4 + 2)-cycloaddition reaction and not by a (2 + 2)-cycloaddition reaction. For the reaction mechanism a bicyclic intermediate (**58**) is again postulated.

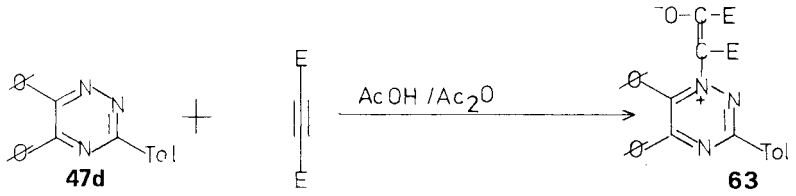


Reaction of 1,2,4-triazines (**47c**) with dimethyl acetylenedicarboxylate gives pyrrolo-1,2,4-triazines (**60**) and pyrido-1,2,4-triazines (**61**) (120).



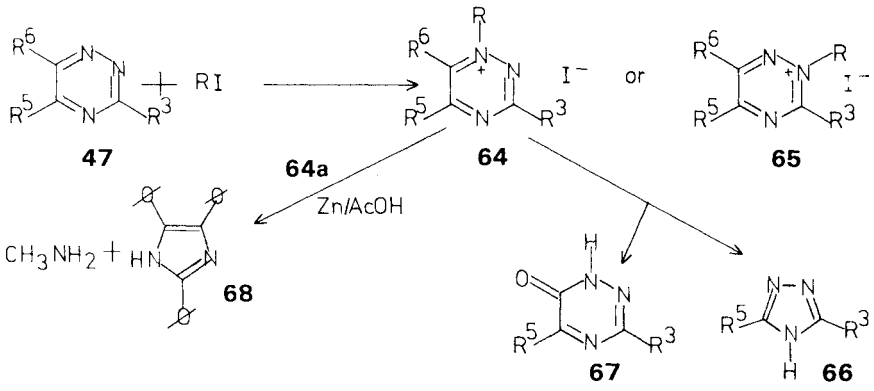
From the reaction mixture of 5,6-diphenyl-3-(*p*-tolyl)-1,2,4-triazine (**47d**) with dimethyl acetylenedicarboxylate in acetic acid/acetic anhydride a deep blue crystalline compound was isolated the structure of which was proved by X-ray

crystallographic analysis to be 1,2-bis(methoxycarbonyl)-2-[5,6-diphenyl-3-(p-tolyl)-1,2,4-triazin-1-io-1-yl]vinylate (**63**) (121). The mechanism for the formation of compound **63** could not be formulated.

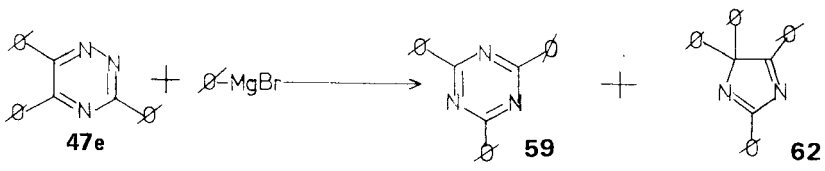


Alkylation of 1,2,4-triazines (**47**) with methyl iodide results in the formation of *N*-1- (**64**) or *N*-2-methylated (**65**) triazinium compounds (122). Best results were obtained in nitromethane. Although the *N*-1-methyl 1,2,4-triazinium iodides (**64**) are red, the *N*-2-methyl 1,2,4-triazinium iodides (65) are colorless. The formation of **64** or **65** depends on the nature of the substituent in the 3-position of the 1,2,4-triazine nucleus.

Basic hydrolysis of *N*-1-methyl 1,2,4-triazinium iodides (**64**) gives mainly 1,2,4-triazoles (**66**). The minor products were identified as 1-methyl-1,2.4-triazin-6-ones (**67**) (123). The reduction of *N*-1-methyl-3,5,6-triphenyl-1,2,4-triazinium iodide (**64a**) with zinc and acetic acid results in the formation of 2,4,5-triphenylimidazole (**68**) and methylamine (122).



Reaction of 3,5,6-triphenyl-1,2,4-triazine (**47e**) with phenylmagnesium bromide yielded 2,4,6-triphenyl-1,3,5-triazine (**59**) and 2,4,4,5-tetraphenylimidazole (**62**) (66).



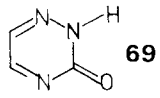
II. 1,2,4-TRIAZINONES (HYDROXY-1,2,4-TRIAZINES)

A. Introduction

1,2,4-Triazinones (hydroxy-1,2,4-triazines) are well-known compounds. In this section all compounds in which hydroxy tautomers have three double bonds in the 1,2,4-triazine ring and which have no other functional group directly bonded to the 1,2,4-triazine nucleus are discussed. Beside these compounds all substances that are derivatives of the different tautomers of the 1,2,4-triazinones (hydroxy-1,2,4-triazines) such as alkoxy-, aroxy-, and acyloxy-1,2,4-triazines or *N*-alkylated, *N*-arylated, or *N*-acylated 1,2,4-triazinones are discussed in this chapter.

Different names for the compounds of this section are used in the literature: 1,2,4-triazin-ones, hydroxy-1,2,4-triazines, or dihydro-1,2,4-triazin-ones. In this discussion we usually use the term 1,2,4-triazin-ones despite the fact that in some cases the hydroxy tautomer predominates in the solid state.

Three different 1,2,4-triazinones (monohydroxy-1,2,4-triazines) are possible: 1,2,4-triazin-3-one (**69**), 1,2,4-triazin-5-one (**70**) and 1,2,4-triazin-6-one (**71**) derivatives of which all are known.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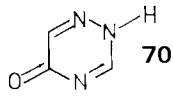
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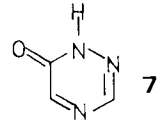
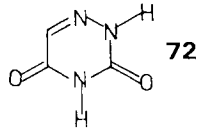
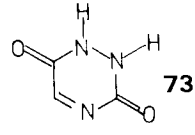

71

Three different 1,2,4-triazindiones (dihydroxy-1,2,4-triazines) are also known, of which the 1,2,4-triazine-3,5-diones (6-azauracils) (**72**) have been much more intensively studied than the 1,2,4-triazine-3,6-diones (**73**) and 1,2,4-triazine-5,6-diones (**74**).


72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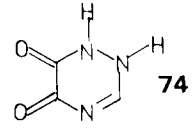
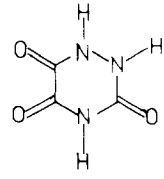

74

1,2,4-Triazine-3,5,6-trione (**75**) and its derivatives are less known compounds.

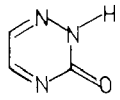

75

Despite the fact that 1,2,4-triazine-3,5-dione (**72**) and its derivatives are usually named in the literature as aza analogues of pyrimidine derivatives (6-azauracil, 6-azauridine, etc.), in this discussion all compounds are treated as 1,2,4-triazine derivatives. Furthermore, in all cases we use those tautomeric forms that are the predominant forms, as shown by physical methods, independent of which structure is used in the original papers.

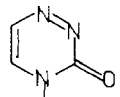
B. 1,2,4-Triazin-3-ones (3-Hydroxy-1,2,4-triazines)

1. *Preparation*

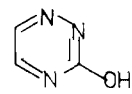
Three tautomeric forms can be discussed for the 1,2,4-triazin-3-ones **69a**, **69b**, and **69c**. Structure **69a** is the predominant form both in solution and in the solid state, derivatives of all three tautomeric forms are known.



69a

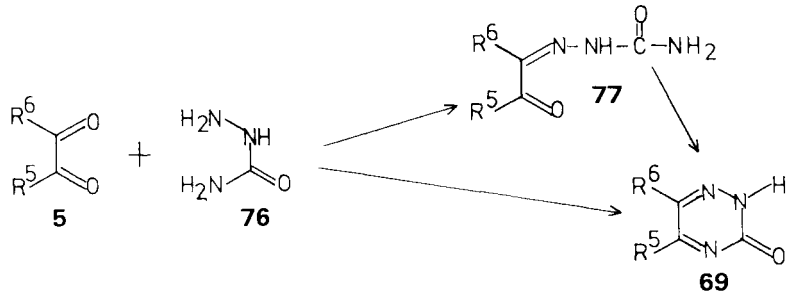


69b



69c

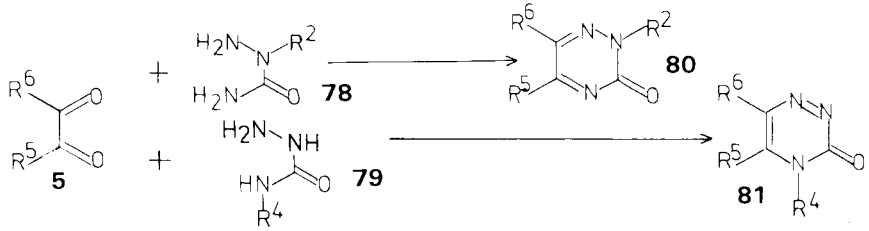
There are a great number of methods known for the synthesis of 1,2,4-triazin-3-ones (**69**). The best method which is widely used is the reaction of a 1,2-dicarbonyl compound (**5**) with semicarbazide (**76**) (124–151). The initially formed semicarbazones (**77**) can be isolated (124–134) but the direct formation of 1,2,4-triazin-3-ones (**69**) from the two starting compounds can easily be carried out (130, 133–151) by heating the two substances in acetic acid (133, 135, 136, 138, 142, 145, 148) or with a base in ethanolic solution (137–139). The cyclization of **77** is achieved by heating them in basic media (125, 129–134, 1072), in ethanol (137, 152) or in acetic acid (133, 134).



5 **76** **77** **69**

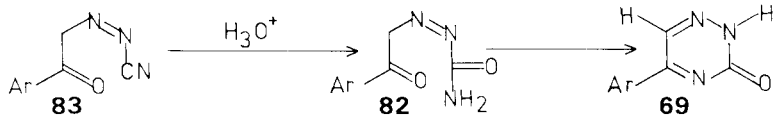
Diels (163) as well as Paudler (130) were not able to cyclize the semicarbazone of diacetyl, but Seibert (132) achieved this cyclization in 1947 by refluxing the semicarbazone in 2 *N* sodium hydroxide solution.

If *N*-2- or *N*-4-substituted semicarbazides (**78**, **79**) were used instead of semicarbazide in the cyclization reaction with 1,2-dicarbonyl compounds, *N*-2- or *N*-4-substituted 1,2,4-triazin-3-ones (**80**, **81**) are obtained (130, 144, 145).

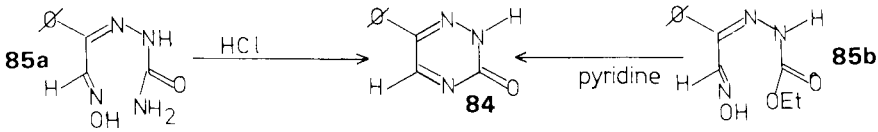


Biltz, Arndt, and Stellbaum (138) obtained 5,6-diphenyl-1,2,4-triazin-3-one by reaction of benzoin with semicarbazide.

Wolff (152) in 1902 reported the synthesis of 1,2,4-triazin-3-ones (**69**) by cyclization of α-carbamoylazoacetophenone (**82**) in hot sodium hydroxide solution. **82** were prepared from α-cyanoazoacetophenones (**83**) and are the tautomers of semicarbazones of arylglyoxales.

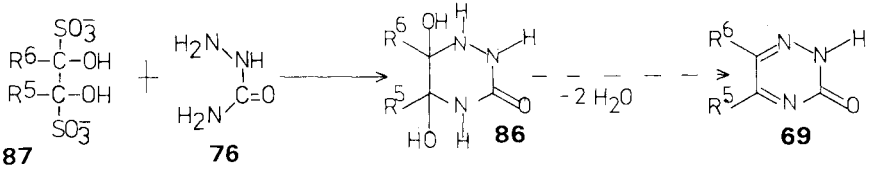


Lalezari and his group (153) reported the formation of 6-phenyl-1,2,4-triazin-3-one (**84**) by treatment of phenylglyoxal oxime semicarbazone (**85a**) with hydrochloric acid. The same compound is isolated by treatment of **85b** in dry pyridine (337).

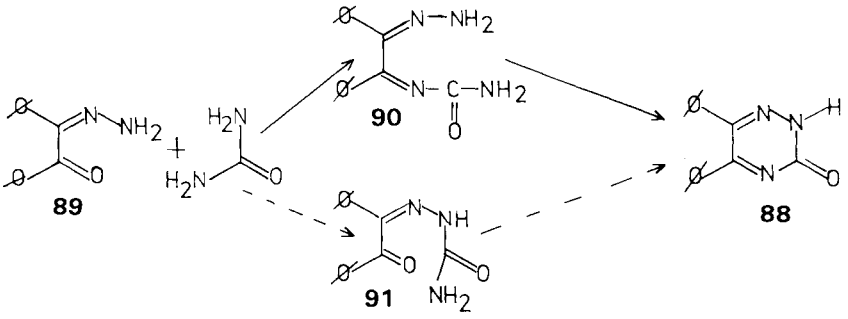


Ekeley and O'Kelly (150) as well as Jacquier and his co-workers (151) isolated compounds of structure **86** from the reaction of semicarbazide with the sodium bisulfite addition products of 1,2-dicarbonyl compounds (**87**). Compounds **86** can be considered as the dihydrated species of 1,2,4-triazin-3-ones (**69**).

Palazzo (162) described the synthesis of 5,6-diphenyl-1,2,4-triazin-3- one (**88**) by reaction of benzil monohydrazone (**89**) with urea in acetic acid/acetic

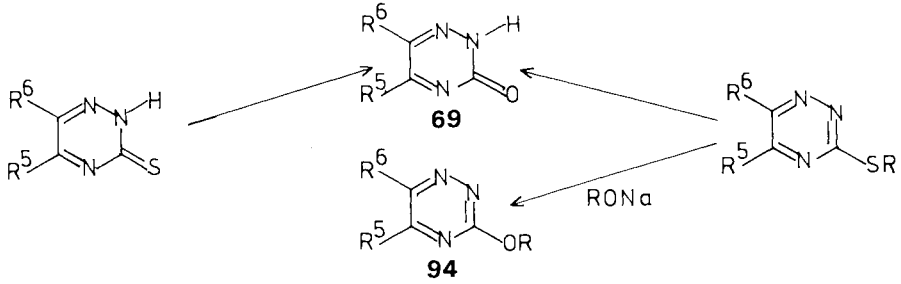


anhydride. The initially formed intermediate is formulated as **90**, not as **91**, which would be the semicarbazone of benzil.



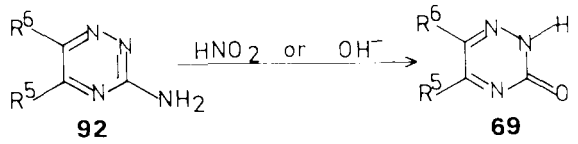
Besides these methods for the direct formation of the 1,2,4-triazin-3-one system, the replacement of other groups in the 3-position of the 1,2,4-triazine nucleus is widely used for the synthesis of **69**.

Replacement of the 3-thioxo group is carried out with acetic anhydride (68) or hydrogen peroxide in basic media (154, 156, 158, 576), whereas the 3-methylmercapto group is exchanged by treatment with base (130), hydrochloric acid, (157) or sodium alcoholates (159).



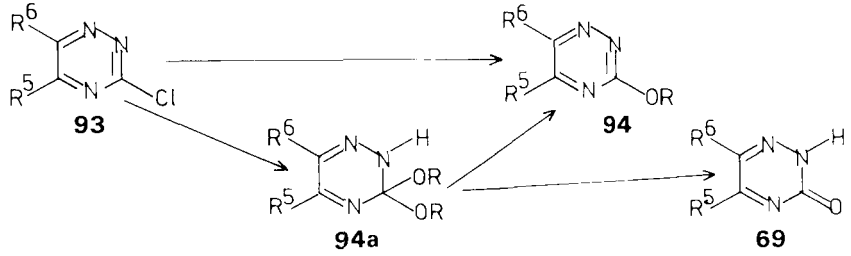
1,2,4-Triazin-3-ones (**69**) can be obtained from the much more easily prepared 3-amino-1,2,4-triazines (**92**) by reaction with nitrous acid (51, 131, 153, 605) or basic hydrolysis (130, 160, 189, 605).

Reaction of 3-chloro-1,2,4-triazines (**93**) with sodium alcoholates leads to the



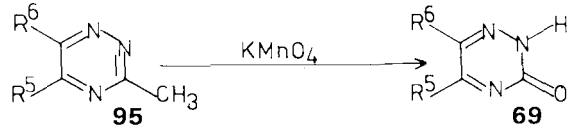
92 69

formation of 3-alkoxy-1,2,4-triazines (**94**) (51, 145, 146, 161). Laakso, Robinson, and Vandrewala mentioned the formation in this reaction of **94a**, which gave 1,2,4-triazin-3-ones (**69**) on heating (51).



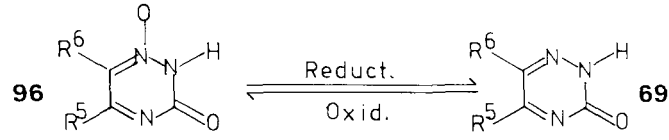
93 94 94a 69

Metze and Meyer (45) reported the oxidation of 3-methyl-1,2,4-triazines (**95**) with potassium permanganate, leading to the formation of 1,2,4-triazin-3-ones (**69**) in 66% yield.



95 69

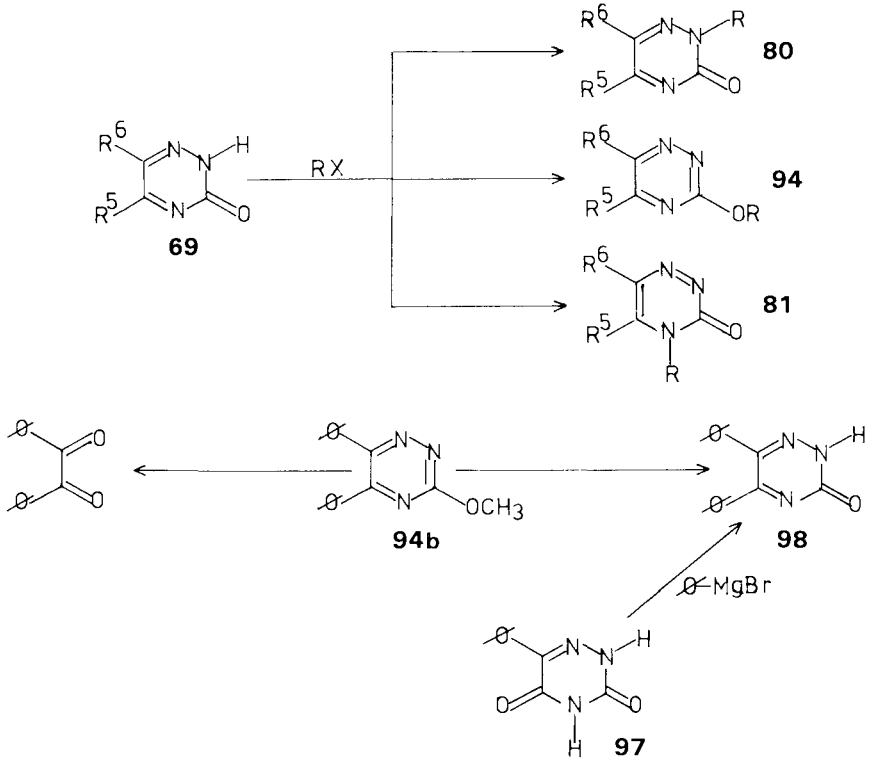
The reduction of 1,2,4-triazin-3-one *N*-oxides (**96**) (159, 160) cannot be treated as a special method for the synthesis of 1,2,4-triazin-3-ones (**69**), since the *N*-oxides (**96**) are prepared by oxidation of the 1,2,4-triazin-3-ones.



96 69

N-Alkylated 1,2,4-triazin-3-ones (**80**, **81**) or 3-alkoxy-1,2,4-triazines (**94**) can be prepared by alkylation of 1,2,4-triazin-3-ones (**69**). This reaction will be discussed below, under reactions of 1,2,4-triazin-3-ones.

3-Methoxy-5,6-diphenyl-1,2,4-triazin (**94b**) can be transformed into 5,6-diphenyl-1,2,4-triazin-3-one (**98**) by mild hydrolysis (145). Under stronger hydrolytic conditions benzil is formed.



Besides other products 5,6-diphenyl-1,2,4-triazin-3-one (**98**) was isolated from the reaction of 6-phenyl-1,2,4-triazin-3,5-dione (**97**) with phenylmagnesium bromide (66).

2. *Compound Survey*

Table II-5 lists the compounds of this class reported in the literature.

3. *Physical Properties*

As has already been mentioned three tautomeric forms **69a**, **69b**, and **69c** can be discussed for the 1,2,4-triazin-3-ones (**69**).

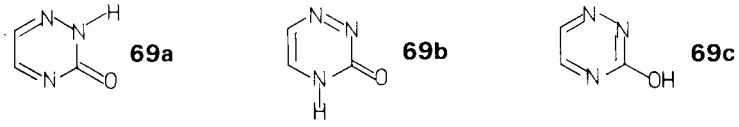
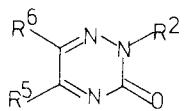


TABLE II-5. 1,2,4-TRIAZIN-3-ONES AND DERIVATIVES

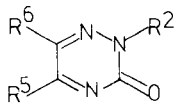
A. 1,2,4-Triazin-3(2H)-ones



R^2	R^5	R^6		m.p. (°C)	Refs.
H	H	H	K salt	262–265	130
H	H	C_6H_5		224–225	153
H	H	4-CH_3–C_6H_4		207	153
H	H	4-F–C_6H_4		217	153
H	H	4-Cl–C_6H_4		203	153
H	H	4-Br–C_6H_4		206	153
H	H	4-CH_3O–C_6H_4		215	153
H	H	4-CH_3S–C_6H_4		203	153
H	H	4-O_2N–C_6H_4		228	153
H	H	2-Naphthyl		208	153
H	CH_3	H		142	130
H	CH_3	CH_3		222–223 (dec.)	132
				224	130
H	C_2H_5	C_6H_5		216	133
				213 (methylene)	149
H	C_2H_5	4-CH_3O–C_6H_4		224	149
				200 (methylene)	130, 149
H	n-C_3H_7	n-C_3H_7		130	133
H	n-C_3H_7	C_6H_5		196	149
				148 (methylene)	133, 149

TABLE II-5. (*continued*)

A. 1,2,4-Triazin-3(2H)-ones



R^2	R^5	R^6	m.p. (°C)	Refs.
H	n-C_3H_7	4-CH_3O-C_6H_4	157 (methylene)	133, **149**
H	i-C_3H_7	C_6H_5	235 (dec.) (methylene)	133
H	C_6H_5	H	234	152, 158
			240	130
H	C_6H_5	CH_3	191–192	156
			192–194	147
H	C_6H_5	C_2H_5	172	133
H	C_6H_5	n-C_3H_7	148	133
H	C_6H_5	C_6H_5	218	45, 148
			222	66
			223	125
			224–225	136, 137
			224–226	51
			225	68
			225–226	145, 154, 576
			245	130
				140, 141, 155
				162
H	4-Cl–C_6H_4	H		1072
H	4-Br–C_6H_4	H		1072
H	4-Br–C_6H_4	4-Br–C_6H_4	253	135

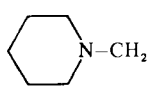
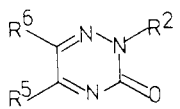
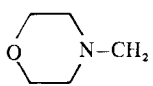
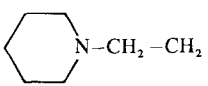
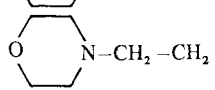
H	4-CH_3O–C_6H_4	CH_3	227	133
H	4-CH_3O–C_6H_4	C_2H_5	201	133
H	4-CH_3O–C_6H_4	n-C_3H_7	174	133
H	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	261–262	136, 138
			262	157
			262–264	578
H	2-CH_3O–C_6H_4	2-CH_3O–C_6H_4	212	142
H	2-HO–C_6H_4	2-HO–C_6H_4	239–240	142
H	4-(i-C_3H_7)–C_6H_4	4-(i-C_3H_7)–C_6H_4	250	136
			250–251	138
H	Fluorenyl	H	323–324	128
H	Phenanthryl	H	320 (dec.)	128
H	5-Br-2-HO–C_6H_3	5-Br-2-HO–C_6H_3	259–260	142
H	3,4-$CH_2O_2C_6H_3$	3,4-$CH_2O_2C_6H_3$	248	136, 138
H	5-O_2N-2-HO–C_6H_3	5-O_2N-2-HO–C_6H_3	276–277	143
H	2-Furyl	H	270–271	131
H	2-Benzofuryl	H	289	124/139
H	2-Selenienyl	H	264–265 (dec.)	134
H	2-Thienyl	H	273–275 (dec.)	129
H	5-Methyl-3-phenyl-4-isoxazolyl	H	241–242	127
CH_3	H	H	77.5	130
CH_3	CH_3	H	138	130
CH_3	CH_3	CH_3	86	130
CH_3	C_6H_5	H	158.5	130
			158–159	65
CH_3	C_6H_5	C_6H_5	152	130
			152–153	138
			153	145
			154	146/140
	C_6H_5	C_6H_5	179 (dec.)	170

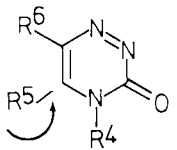
TABLE II-5. (*continued*)

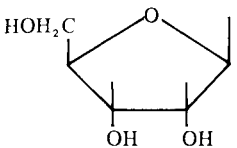
A. 1,2,4-Triazin-3(2H)-ones



R^2	R^5	R^6		m.p. (°C)	Refs.
	C_6H_5	C_6H_5		172 (dec.)	170
$Et_2N-CH_2-CH_2$	C_6H_5	C_6H_5	Oxalate	135–137	145
			HI·EtOH	165–166 (dec.)	145
	C_6H_5	C_6H_5	·HBr	184–187 (dec.)	145
	C_6H_5	C_6H_5	·HBr	183–185 (dec.)	145
CH_3CO	C_6H_5	C_6H_5		153–154	172
CH_3CO[a]	4-Br–C_6H_4	4-Br–C_6H_4		282	135

B. 1,2,4-Triazin-3(4H)-ones

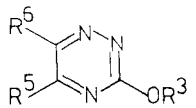


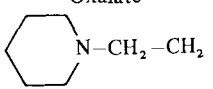
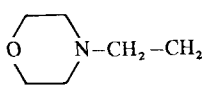
R^4	R^5	R^6	m.p. (°C)	Refs.
CH_3	CH_3	CH_3	154 (methylene)	130
CH_3	C_6H_5	C_6H_5	181	130
C_6H_5	C_6H_5	C_6H_5	170	144
	H	H	–	159

[a] Structure doubtful.

TABLE II-5. (*continued*)

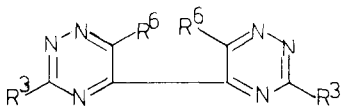
C. 3-Hydroxy-1,2,4-triazines



R^3	R^5	R^6		m.p. (°C)	Refs.
CH_3	H	H		44–46	14
CH_3	CH_3	H		89–90.5	14
CH_3	CH_3	CH_3		b.p. 67–68/0.15	14
CH_3	C_6H_5	H		76.5–78	14
				77–78	65
CH_3	C_6H_5	C_6H_5		75–77	161
				77	146, 174
				77.5	145
				77–79	14
C_2H_5	C_6H_5	C_6H_5		105	148
$C_6H_5-CH_2$	H	H		69–70	159
C_6H_5	C_6H_5	C_6H_5		133	161
$Et_2N-CH_2-CH_2$	C_6H_5	C_6H_5	·HBr	154–156	145
Oxalate				172	145
	C_6H_5	C_6H_5	·HBr		145
	C_6H_5	C_6H_5	·HBr	210–212	145

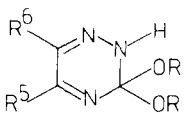
CH_3CO	C_6H_5	C_6H_5	154	154, 162
CH_3CO	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	157	138
CH_3CO	4-(i-C_3H_7)–C_6H_4	4-(i-C_3H_7)–C_6H_4	136–137	138
CH_3CO	3,4-$CH_2O_2C_6H_3$	3,4-$CH_2O_2C_6H_3$	208	138
Me_2N–CO	C_6H_5	C_6H_5	202	167

D. 5, 5′-Bi-1,2,4-triazines



R^3	R^6	m.p. (°C)	Refs.
OH	H	300	175
OCH_3	H	170–171	175
		175–176.5	109, 110
OCH_3	CH_3	159–161.5	110

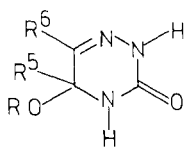
E. Derivatives formed by covalent addition to the C=O bond



R	R^5	R^6	m.p. (°C)	Refs.
CH_3	C_6H_5	C_6H_5	221–222	51
C_2H_5	C_6H_5	C_6H_5	220 221	51

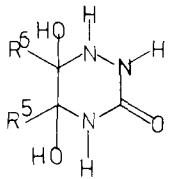
TABLE II-5. (*continued*)

F. Derivatives formed by covalent addition to the C_5N_4 bond



R	R^5	R^6	m.p. (°C)	Refs.
H	H	H	320 (dec.)	130
CH_3	CH_3	CH_3	219	130
CH_3	C_6H_5	C_2H_5	–	133
CH_3	C_6H_5	n-C_3H_7	–	133, 168
CH_3	C_6H_5	C_6H_5	–	133, 168
C_2H_5	C_6H_5	C_2H_5	–	168
C_2H_5	C_6H_5	C_6H_5	–	133, 168

G. Derivatives formed by covalent addition to the C_5N_4 and C_6N_1 bonds



R^5	R^6	Decomposition temp.	Refs.
H	H	265–270	150
H	CH_3	250–255	151
CH_3	H		
CH_3	H	250–255	150
CH_3	CH_3	240–245	150
CH_3	C_2H_5	230–235	150
CH_3	n-C_3H_7	240–245	150
CH_3	n-C_4H_9	230–235	150
CH_3	n-C_5H_{11}	100–105	150

By comparison of the ultraviolet (130, 131, 159, 161, 175), infrared (140, 163, 164) and PMR-spectra (130, 133, 149, 159) of the 1,2,4-triazin-3-ones with those of 2-alkyl-1,2,4-triazin-3-ones, 4-alkyl-1,2,4-triazin-3-ones, and 3-alkoxy-1,2,4-triazines it was shown that the tautomeric form **69a** predominates both in solution and in the solid state.

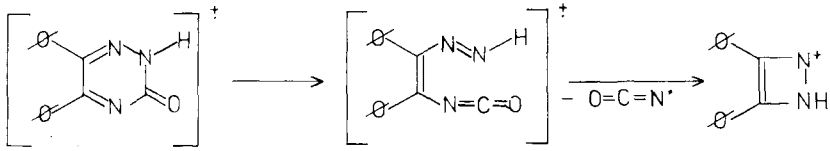
All 1,2,4-triazin-3-ones are white, stable crystalline compounds with melting points greater than 100 °C, mostly greater than 200 °C. Alkylation or acylation at N-2 or N-4 generally lowers the melting point as does alkylation or acylation at the oxygen. 1,2,4-Triazin-3-ones are stable to acid and base, in both of which they are soluble. They are weak acids but can not be titrated with bases (132). Sodium and potassium salts of 1,2,4-triazin-3-ones are reported (130, 139).

The electronic spectrum of 5,6-diphenyl-1,2,4-triazin-3-one shows the following absorption maxima and absorptivities: 335 sh (4.170), 295 sh (6.550), and 252 nm (14.880) (130). The 2-methyl-5,6-diphenyl-1,2,4-triazin-3-one has similar absorption maxima and absorptivities: 338 (4.970), 290 (6.160), and 254 nm (14.300), whereas the 4-methyl-5,6-diphenyl-1,2,4-triazin-3-one – 292 (10.720), 230 sh (10.920), 215 nm (15.430) – and the 3-methoxy-5,6-diphenyl-1,2,4-triazine – 328 (log ϵ 3.9), 257 (4.11) (161) – show a different absorption pattern.

In the infrared spectra of 1,2,4-triazin-3-ones no bands for an OH group were detected. The weak peak at 3450 cm^{-1} (KBr) or 3350 cm^{-1} (chloroform) is due to an N-H stretching vibration. A strong carbonyl absorption is observed at 1685 cm^{-1}, both in KBr and chloroform (140).

In the PMR spectra the methyl group of 2-methyl-5,6-diphenyl-1,2,4-triazin-3-one gives rise to a signal at $\tau = 6.10$ and the signal for the methyl group in 4-methyl-5,6-diphenyl-1,2,4-triazin-3-one is found at $\tau = 7.03$ (130).

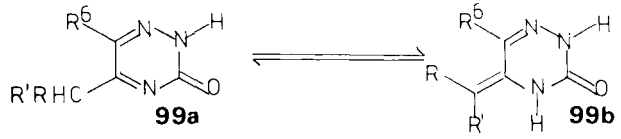
The mass spectrum of 5,6-diphenyl-1,2,4-triazin-3-one is recorded by Palmer and his group (165), the observed peaks indicate the following fragmentation pattern:



5-Alkyl-1,2,4-triazin-3-ones with a proton at C-1 of the alkyl group can occur in two tautomeric forms, the alkyl form (**99a**) and the structure with the alkylidene group (**99b**) (130, 133, 149).

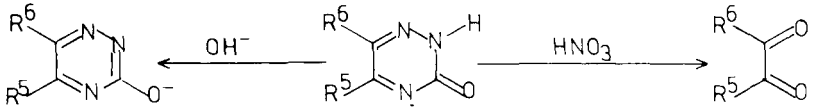
As was shown by PMR spectroscopy the ratio of the two tautomers depends on the solvent. In a few cases both tautomers were isolated.

5,6-Diphenyl-1,2,4-triazin-3-one forms stable complexes with 4,5-diphenyl-imidazole and 4,5-diphenyl-2-imidazolone (166, 222).

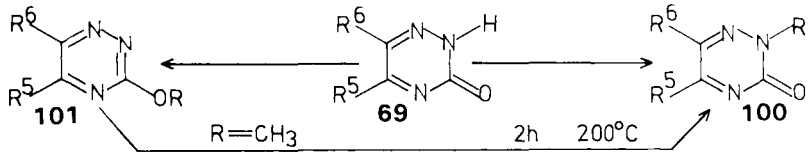


4. *Reactions*

1,2,4-Triazin-3-ones are stable to both acids and bases. They form salts equally as well with bases (130, 132, 139) and acids (138). Concentrated nitric acid destroys the whole system and 1,2-dicarbonyl compounds are isolated (156).

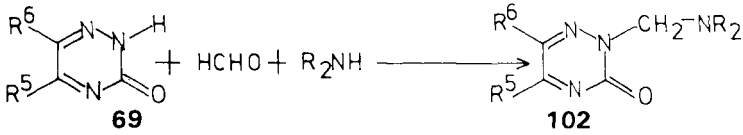


Alkylation of 1,2,4-triazin-3-ones occurs mainly at the nitrogen in the 2-position leading to 2-alkyl-1,2,4-triazin-3-ones (**100**) (65, 130, 138, 145, 146, 148, 160) but alkylation at the oxygen, leading to 3-alkoxy-1,2,4-triazines (**101**), is also reported (65, 148).



Polonovski and his collaborators (146) observed the rearrangement of 3-methoxy-1,2,4-triazine (**101a**) to a 2-methyl-1,2,4-triazin-3-one (**100a**) by heating **101a** for 2h at 200 °C.

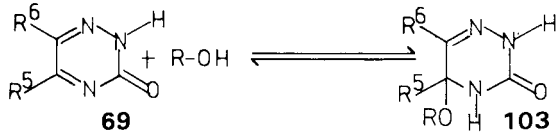
Reaction of 1,2,4-triazin-3-ones with formaldehyde and a secondary amine gives 2-substituted products (**102**) (170).



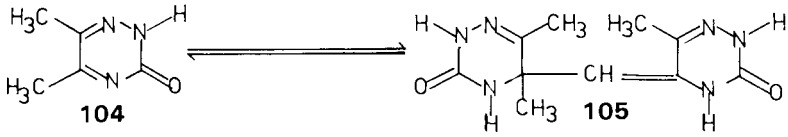
Acylation of 1,2,4-triazin-3-ones leads to *N*-2-acylated (172) and *O*-acylated (138, 167) products.

1,2,4-Triazin-3-ones (**69**) readily add water or alcohols at the *N*-4 and *C*-5

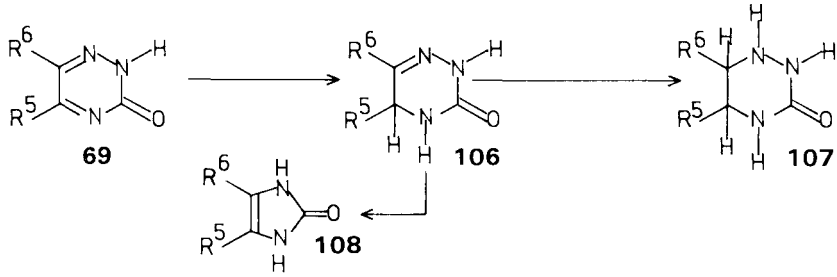
positions (51, 130, 133, 168) forming an equilibrium between the starting compound and the covalent addition product (**103**).



In altered solutions of 5,6-dimethyl-1,2,4-triazin-3-one (**104**) the dimeric compound (**105**) is observed, which is totally absent (130) in freshly prepared solutions. Formation of **104** from the dimer is achieved either by addition of base and then acid to the solution of **105** or by sublimation (130).

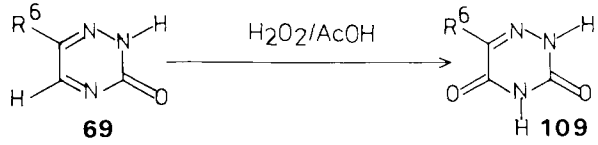


Hydrogenation (108, 133, 136, 138, 155, 157, 168, 171–174, 176) of **69** occurs at the 4,5 double bond of the 1,2,4-triazin-3-ones to give **106**. Further reduction of the dihydro compounds gives the tetrahydro-1,2,4-triazin-3-ones (**107**) (171, 172).



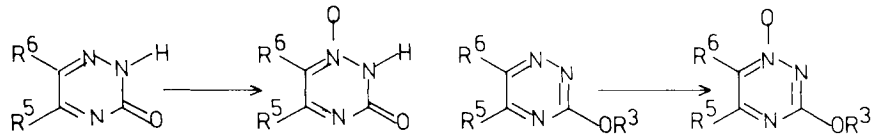
The following conditions were used for the reduction: Raney nickel (168, 172–174), zinc and acid (136, 138, 172), hydrogen with platinum catalyst (133, 168, 171–174), lithium aluminum hydride (157, 176), sodium borohydride (157), *p*-tolylmercaptan (157), or electrochemical means (108, 155). Reduction of **69** with HI/P at 180 °C leads to imidazoles (138). In alkaline media the dihydro-1,2,4-triazin-3-ones (**106**) rearranged to imidazolones (172) (**108**).

Lalezari and his co-workers (153) reported the oxidation of 1,2,4-triazin-3-ones (**69**) with unsubstituted 5-positions with hydrogen peroxide and acetic acid, leading to 1,2,4-triazine-3,5-diones (**109**).



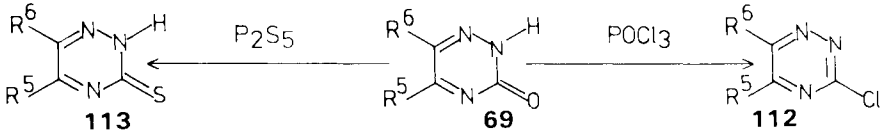
69 **109**

In all cases where the 5-position is substituted (104, 160, 161), 1,2,4-triazine-3-one 1-oxides (**110**) or 3-alkoxy-1,2,4-triazine 1-oxides (**111**) were isolated or ring-opened products were formed (180).



69 **110** **101** **111**

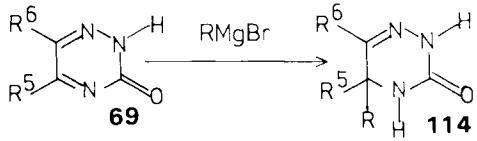
Reaction of 1,2,4-triazin-3-ones (**69**) with phosphorus oxychloride forms 3-chloro-1,2,4-triazines (**112**) in good yields (51,145, 146).



113 **69** **112**

1,2,4-Triazine-3-thiones (**113**) were obtained by reaction of 1,2,4-triazin-3-ones (**69**) with phosphorus pentasulfide (65, 68, 158, 189); this is the reverse reaction of the synthesis of 1,2,4-triazin-3-ones from **113**.

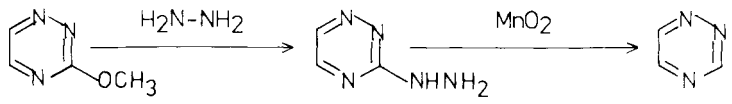
Similarly to hydrogen, Grignard reagents add to the 4,5-double bond of 1,2,4-triazin-3-ones (**69**) leading to 4,5-dihydro-1,2,4-triazin-3-ones (**114**) (65, 66, 157, 168, 175, 176). Besides the formation of **114**, the isolation of 1,2,4-triazines (65, 66) or imidazoles (65) from this reaction is reported.



69 **114**

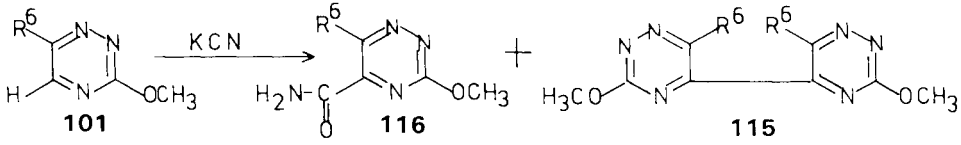
The reaction of 3-methoxy-1,2,4-triazine (**101a**) with hydrazine was used by Paudler and Chen (14) as part of their synthesis of the unsubstituted 1,2,4-triazine (**1**), since the formed 3-hydrazino-1,2,4-triazine (**9**) can be oxidized to **1**. The methoxy group can also be exchanged by amines (673).

Reaction of 3-methoxy-1,2,4-triazines (**101**) with unsubstituted 5-positions with sodium methoxide or potassium cyanide (109, 110) is a method for the



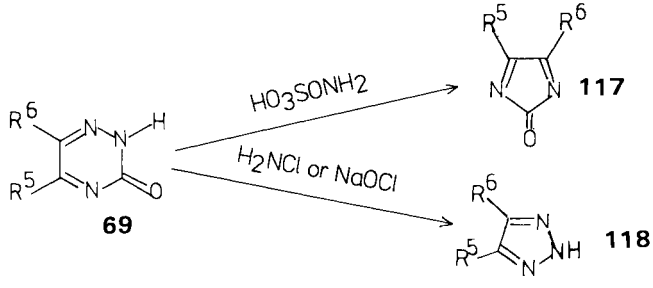
101a **9** **1**

synthesis of 5,5′-bi-1,2,4-triazines (**115**) and 3-methoxy-1,2,4-triazine-5-carboxamides (**116**).



101 **116** **115**

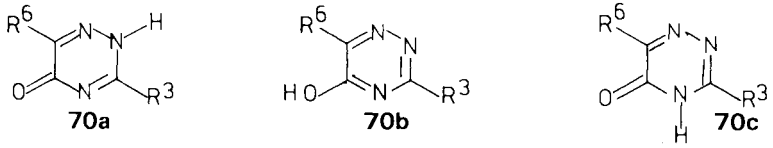
Rees and Sale (177–179) studied the reaction of 1,2,4-triazin-3-ones (**69**) with hydroxylamine-*O*-sulfonic acid (177, 179), chloroamine (177, 178) and sodium hypochloride (178). In the first reaction they isolated imidazolones (**117**) and the other reactions gave 1,2,3-triazoles (**118**).



C. 1,2,4-Triazin-5-ones (5-Hydroxy-1,2,4-triazines)

1. *Preparation*

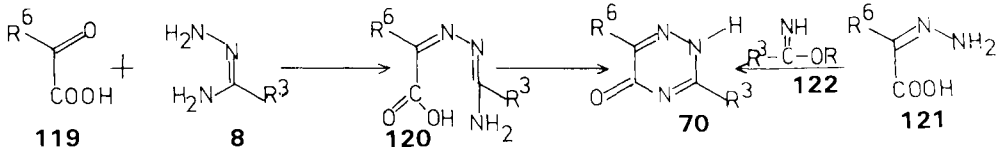
As for the 1,2,4-triazin-3-ones three tautomeric forms **70a**, **70b**, and **70c** can be discussed for the 1,2,4-triazin-5-ones. **70a** is the predominant tautomer in solution, while **70a** and **70b** were both established in the solid state. Derivatives



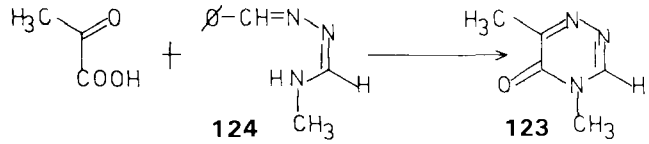
70a **70b** **70c**

of all three tautomers are known. For the synthesis of 1,2,4-triazin-5-ones (**70**) the following methods were reported.

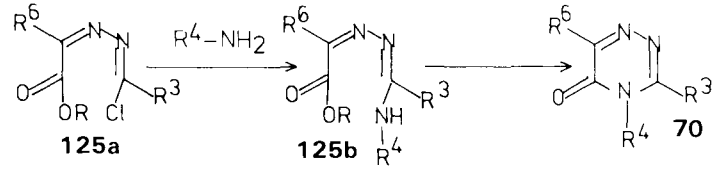
1. Reaction of amidrazones (**8**) with α-ketocarboxylic acids (**119**) is the most convenient method for the preparation of **70** (33, 38, 181–184). It is not necessary to isolate the initially formed condensation product (**120**) which can be cyclized by heating in dimethylformamide (184). Reaction of α-hydrazonocarboxylates (**121**) with imidates (**122**) also produces **70** (182).



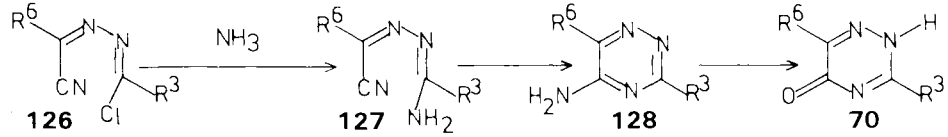
Gut and his collaborators (184) were able to synthesise 4,6-dimethyl-1,2,4-triazin-5-one (**123**) by reaction of N^1-benzal-N^4-methylformamidrazone (**124**) with pyruvic acid.



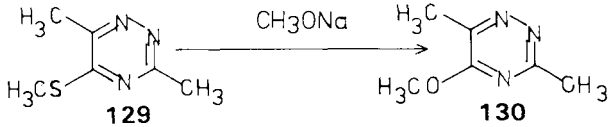
A synthesis of 1,2,4-triazin-5-ones (**70**) which is a modification of the reaction of amidrazones with α-ketocarboxylic acids is reported by Draber, Dickore, and Timmler (185). They obtained **70** by reacting amines with compound **125a**. The initially formed intermediate should be **125b**.



2. The reaction of the nitriles (**126**) with ammonia gives the compounds **127** which were cyclized to 5-amino-1,2,4-triazines (**128**), followed by hydrolysis of **128** to the 1,2,4-triazin-5-ones (**70**) (63, 64, 186, 187).

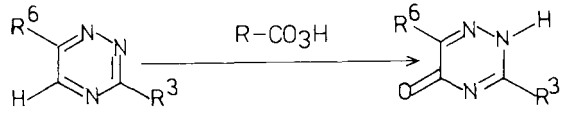


3. Lee and Paudler synthesized 5-methoxy-3,6-dimethyl-1,2,4-triazine (**130**) by reaction of 3,6-dimethyl-5-(methylmercapto)-1,2,4-triazine (**129**) with sodium methoxide (188).



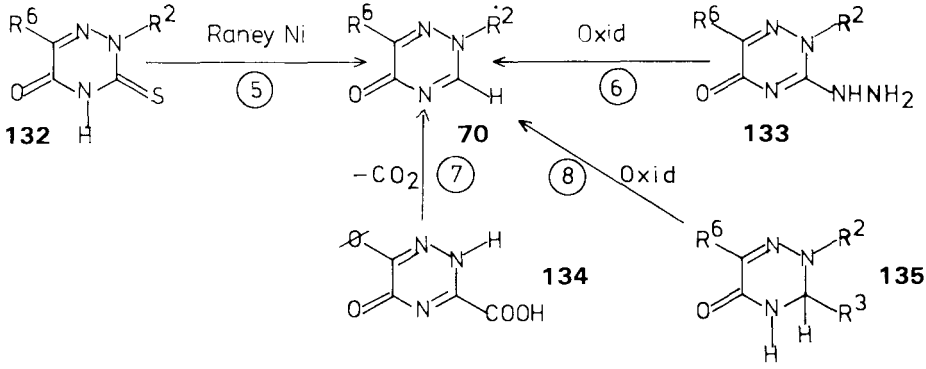
129 **130**

4. Neunhoeffer and Frühauf (103) obtained 1,2,4-triazin-5-ones (**70**) by oxidation of 1,2,4-triazines (**131**) with unsubstituted 5-positions with peracids.



131 **70**

5. Desulfuration of 3-thioxo-1,2,4-triazin-5-ones (**132**) with Raney nickel is another method for the synthesis of 1,2,4-triazin-5-ones (**70**) (182, 189, 190, 193, 489).



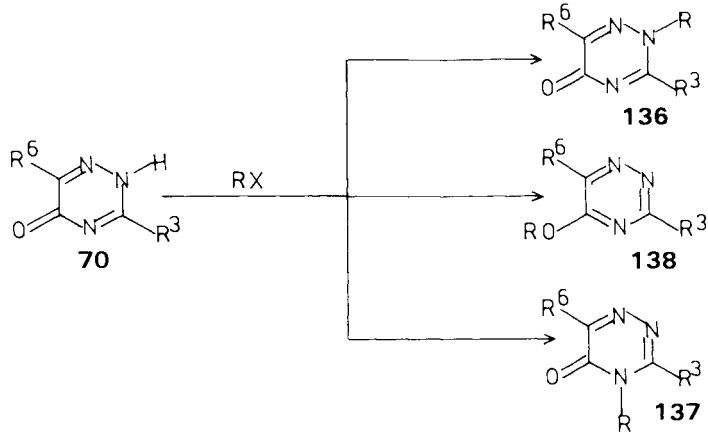
132 **70** **133** **134** **135**

6. Oxidation of 3-hydrazino-1,2,4-triazin-5-ones (**133**) with copper sulfate (189), silver oxide (192), or mercury oxide (57, 63, 188) gives 1,2,4-triazin-5-ones (**70**) in good yields (57, 63, 188, 189, 192).

7. Fusco and Rossi (63) reported the synthesis of 6-phenyl-1,2,4-triazine-5-one (**70**) ($R^6 = C_6H_5$, $R^2 = H$) by decarboxylation of 5-oxo-6-phenyl-1,2,4-triazine-3-carboxylic acid (**134**).

8. Dihydro-1,2,4-triazin-5-ones (**135**) can be transformed into 1,2,4-triazin-5-ones (**70**) by oxidation with bromine (1077) or *tert*-butyl hypochloride (193).

9. *N*-alkylated 1,2,4-triazin-5-ones (**136**, **137**) and 5-alkoxy-1,2,4-triazines (**138**) were obtained by alkylation of 1,2,4-triazin-5-ones (**70**). For further information see the section below on reactions.



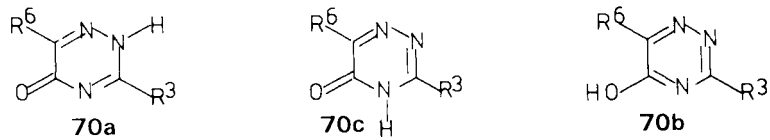
2. *Compound Survey*

The 1,2,4-triazin-5-ones reported in the literature are listed in Table II-6.

3. *Properties and Structure*

1,2,4-Triazin-5-ones (**70**) are white, crystalline compounds with high melting points. Alkylation or acylation generally lowers the melting point. They are soluble in bases, insoluble in water and most organic solvents.

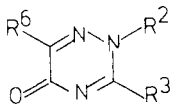
Theoretically 1,2,4-triazin-5-ones (**70**) may occur in three tautomeric forms, namely, the two 1,2,4-triazin-5-one forms **70a** and **70c** and the hydroxy form **70b**.



Determination of the predominant form was effected with the use of infrared, ultraviolet, and NMR spectroscopy (103, 181, 184, 188, 190, 191). In

TABLE II-6. 1,2,4-TRIAZIN-5-ONE AND DERIVATIVES

A. 1,2,4-Triazin-5(2H)-ones



R^2	R^3	R^6	m.p. (°C)	Refs.
H	H	H	190 (dec.)	192
			204–205	103
			212	188
H	H	CH_3	196	188
			205–206	189, 190
			205.5–207.5	489
			212	103
·HCl			192–193	189
H	H	C_2H_5	154.5–155.5	489
H	H	n-C_3H_7	144.5–145.5	489
H	H	C_6H_5	206–207	189, 190
			207–208	63, 103, 182
H	CH_3	H	203–205	103, 184
H	CH_3	CH_3	139–140	63
			245–247	182
			275–276	184
H	CH_3	C_6H_5	261–262	182
			263	103
H	$CH(CN)_2$	CH_3	dec. (3-methylene)	1078
H	C_6H_5	H	245	63
			249–250	182, 184
H	C_6H_5	CH_3	243–246	187
			245–247	181, 184
H	C_6H_5	CH_3CHCl	192–195	181

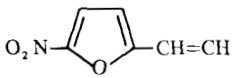
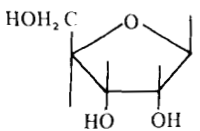
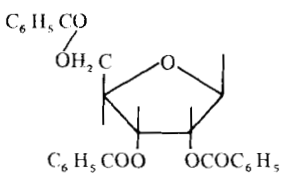
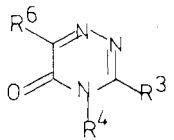
H	C_6H_5	C_6H_5	274–276	63, 103, 181, 182
			282–283	187
H	4-CH_3–C_6H_4	H	192	103
H	4-CH_3–C_6H_4	C_6H_5	299–301	103
H	4-O_2N–C_6H_4	4-O_2N–C_6H_4	335–340	188
			340–345 (dec.)	188
H	2-Pyridyl	CH_3		183
H	2-Pyridyl	C_6H_5		183
H		CH_3	280 (dec.)	38
CH_3	H	H	118	192
			125	188
CH_3	H	CH_3	146	188
			150–151	190
CH_3	H	C_6H_5	146–147	182, 190
CH_3	CH_3	H	66	103
CH_3	CH_3	CH_3	82	188
CH_3	CH_3	C_6H_5	164–165	182
CH_3	C_6H_5	H	134–135	182
CH_3	C_6H_5	CH_3	151–152	182
CH_3	C_6H_5	C_6H_5	181–182	182
	H	H	116–119	193
	H	H	117–119	193

TABLE II-6. *(continued)*

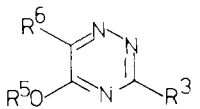
B. 1,2,4-Triazin-5(4H)-ones



R^3	R^4	R^6	m.p. (°C)	Refs.
H	CH_3	H	118.5	188
			128	192
H	CH_3	CH_3	105–108	184, 190
H	CH_3	C_6H_5	146–147	182
			147–148	190
H	C_2H_5	t-C_4H_9	154–155	185
H	i-C_3H_7	C_6H_5	197	185
H	t-C_4H_9	C_6H_5	256–258	185
CH_3	CH_3	H	100.5	188
CH_3	CH_3	CH_3	139	188
CH_3	CH_3	C_6H_5	146–147	182
			151	185
CH_3	CH_3	4-CH_3–C_6H_4	156	185
CH_3	C_2H_5	4-CH_3–C_6H_4	153	185
CH_3	n-C_3H_7	t-C_4H_9	67–68	185
CH_3	n-C_3H_7	C_6H_5	106	185
CH_3	i-C_3H_7	C_6H_5	101	185
CH_3	n-C_4H_9	t-C_4H_9	111–112	185
CH_3	i-C_4H_9	t-C_4H_9	60–63	185
CH_3	t-C_4H_9	t-C_4H_9	114	185
CH_3	CH_2CN	t-C_4H_9	212–213	185

CH_3	Cyclopropyl	t-C_4H_9	89–91	185
CH_3	Cyclopentyl	t-C_4H_9	93–94	185
C_2H_5	CH_3	t-C_4H_9	112–113	185
C_2H_5	CH_3	C_6H_5	181	185
C_2H_5	CH_2=CH–CH_2	4-CH_3–C_6H_4	101–102	185
CH_2CH_2OH	C_2H_5	C_6H_5	118.5	185
C_6H_5	CH_3	H	114–115	182
C_6H_5	CH_3	C_6H_5	124–125	182
C_6H_5	C_2H_5	C_6H_5	147–149	185
C_6H_5	C_6H_5	CH_3	169–170	182
4-O_2N–C_6H_4	CH_3	4-O_2N–C_6H_4	260	186
4-O_2N–C_6H_4	C_2H_5	4-O_2N–C_6H_4	274	186
4-O_2N–C_6H_4	H_3COOC–CH_2CH_2	4-O_2N–C_6H_4	200–201	186

C. 5-Hydroxy-1,2,4-triazines



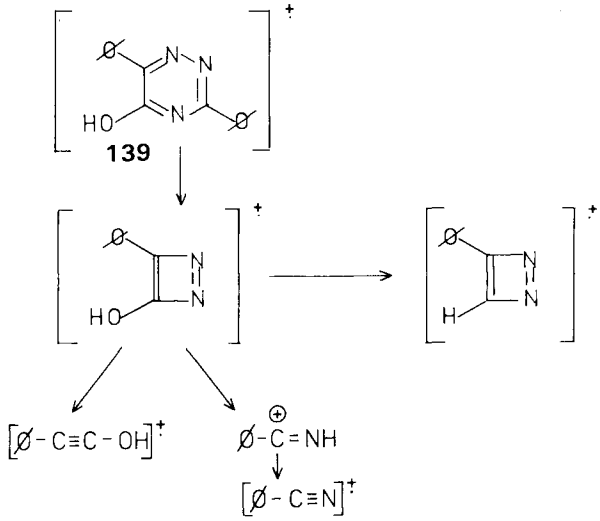
R^3	R^5	R^6	m.p. (°C)	Refs.
H	CH_3	CH_3	49–50	190
H	CH_3	C_6H_5	Oil	182, 190
H	$(CH_3)_3Si$	H		193
CH_3	CH_3	H	50	103
CH_3	CH_3	CH_3	81.5	188
CH_3	CH_3	C_6H_5	41–42	182
C_6H_5	CH_3	H	86–87	182
C_6H_5	CH_3	CH_3	115–116	182
C_6H_5	CH_3	C_6H_5	114–115	182

all cases it was shown that the paraquinoid tautomer **70a** predominates in solution, whereas Daunis, Jacquier, and Pigiere have shown that 3,6-diphenyl-1,2,4-triazin-5-one exists in the solid state mainly as the hydroxy tautomer (182).

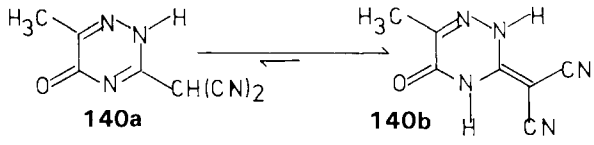
All 1,2,4-triazin-5-ones show N–H streching vibrations around 3170 cm^{-1} and C=O streching vibrations between 1640 and 1670 cm^{-1}. The C=O streching vibration of 2-methyl-1,2,4-triazin-5-ones is in the same region, whereas those of 4-methyl-1,2,4-triazin-5-ones occur around 1675 and 1690 cm^{-1}.

In the same way it was shown that the ultraviolet and NMR spectra of both 1,2,4-triazin-5-ones and 2-methyl-1,2,4-triazin-5-ones are very similar, but those of 4-methyl-1,2,4-triazin-5-ones and 5-methoxy-1,2,4-triazines show different absorption bands. The absorption region and the adsorptivity differ with the nature of the substituents in the 3- and 6-positions.

The mass spectrum of 3,6-diphenyl-1,2,4-triazin-5-one (**139**) has been published by Becker and co-workers (201). Contrary to the behavior of other 1,2,4-triazines the first fragmentation is not the elimination of nitrogen but elimination of benzonitrile. The main fragmentation pattern is given in the following scheme.



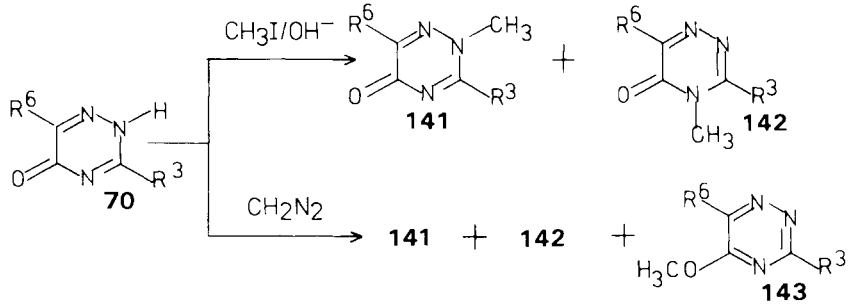
The 3-(dicyanomethyl)-6-methyl-1,2,4-triazin-5-one (**140**) is formulated as the methylene tautomer (**140b**) (1078).



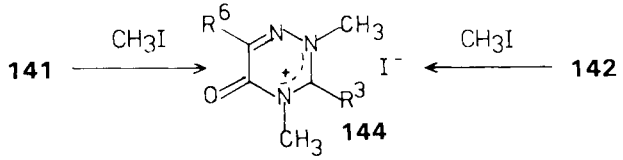
4. *Reactions*

1,2,4-Triazin-5-ones and their *N*-alkylation products seem to be stable both to acid and base. 5-Alkoxy-1,2,4-triazines can be hydrolyzed to 1,2,4-triazin-5-ones. 1,2,4-Triazin-5-ones (**70**) are weak acids and form salts with bases; the mercury salts are reported in a United States patent (1098).

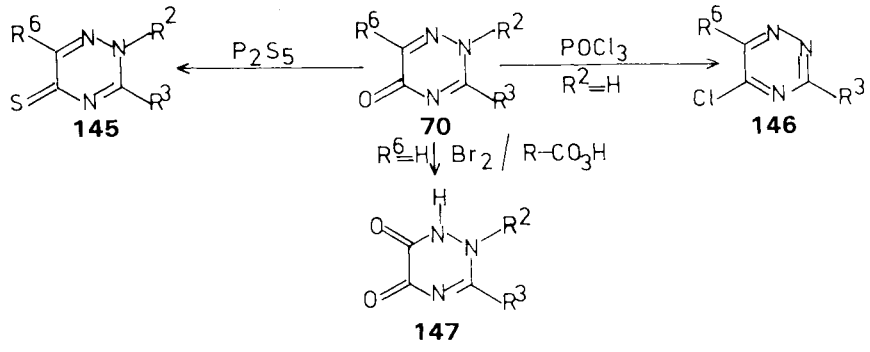
Alkylation of 1,2,4-triazin-5-ones (**70**) with methyl iodide occurs mainly at N-2 and N-4, with predominance of the 2-methylated product (182, 188, 190, 191). Alkylation of 1,2,4-triazin-5-ones with diazomethane gives the three possible products **141**, **142**, and **143**, the ratio of which depends on the solvent (103, 190, 191).



Further alkylation of the monomethylated 1,2,4-triazin-5-one leads to the isolation of a dimethylated iodide **144** (191).

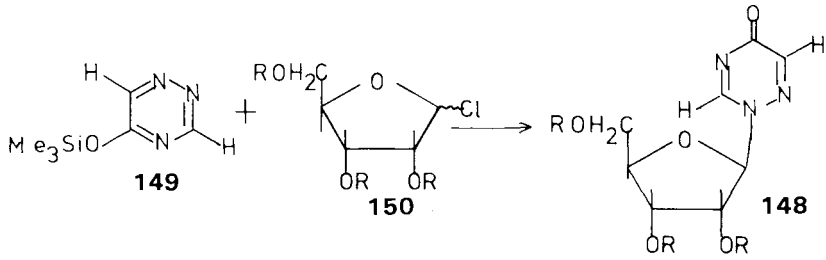


Reaction of 1,2,4-triazin-5-ones (**70**) with phosphorus pentasulfide leads to the isolation of 1,2,4-triazin-5-thiones (**145**) (188, 189).



Phosphorous chloride transforms 1,2,4-triazin-5-ones (**70**) into 5-chloro-1,2,4-triazines (**146**) (63, 64). Reaction of 1,2,4-triazin-5-ones (**70**) with unsubstituted 6-positions with bromine or peracids gives 1,2,4-triazine-5,6-diones (**147**) (103, 192).

The 2-(ribofuranosyl)-1,2,4-triazin-5-one (**148**) (R = H) was synthesized by reaction of 5-(trimethylsilyl)-1,2,4-triazine (**149**) with tribenzoylribofuranosyl chloride (**150**) (R = C_6H_5CO) and subsequent hydrolysis of the protecting groups (193).



Reaction of 1,2,4-triazin-5-ones or 5-methoxy-1,2,4-triazines with Grignard reagents affords 1,2,4-triazines and/or dihydro-1,2,4-triazin-5-ones and 5-methoxydihydro-1,2,4-triazines (1077).

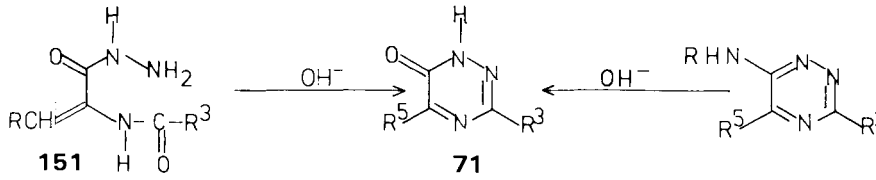
Reduction with lithium aluminum hydride transforms 1,2,4-triazin-5-ones into 1,4,5,6-tetrahydro-1,2,4-triazines or dihydro-1,2,4-triazin-5-ones (1077).

D. 1,2,4-Triazin-6-ones (6-Hydroxy-1,2,4-triazines)

1. *Preparation*

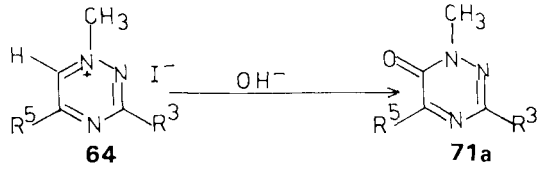
The 1,2,4-triazin-6-ones (**71**) are the less known monohydroxy-1,2,4-triazines. Until now only three methods for their synthesis have been published and it is still doubtful if one of these leads to 1,2,4-triazin-6-ones as stated or to 1,2,4-triazin-5-ones, as was shown in one case by Becker and his group (201).

The most common method for the synthesis of 1,2,4-triazin-6-ones (**71**) is the cyclization of α(acylamino)carboxhydrazides (**151**) (194–200), which are easily obtained by hydrazonolysis of azlactones, with sodium hydroxide.



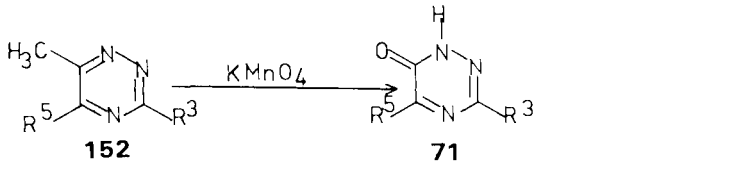
Amino or hydrazino groups in the 6-position as well as in other positions of the 1,2,4-triazine nucleus can be replaced by a hydroxyl group (201).

Lee and Paudler isolated 1-methyl-1,2,4-triazin-6-ones (**71a**) as the minor products of alkaline hydrolysis of 1-methyl-1,2,4-triazinium iodides (**64**) (123).

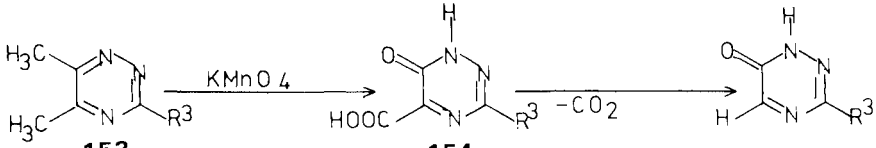


64 **71a**

Metze and his group (44, 45) reported the oxidation of 6-methyl-1,2,4-triazines (**152**) with potassium permanganate, claiming the isolation of 1,2,4-triazin-6-ones (**71**). 5,6-Dimethyl-1,2,4-triazines (**153**) were oxidized under the same conditions to 6-oxo-1,2,4-triazine-5-carboxylic acids (**154**) which were decarboxylated to 1,2,4-triazin-6-ones (**71**).



152 **71**



153 **154** **71**

At least in the case of the so-called 3,5-diphenyl-1,2,4-triazin-6-one it was shown by Becker and his group (201) that the isolated compound was 3,6-diphenyl-1,2,4-triazin-5-one. This result indicates the structure of the starting material must also have been incorrect.

2. *Compound Survey*

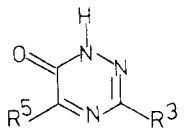
Table II-7 lists those 1,2,4-triazin-6-ones reported in the literature.

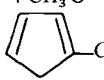
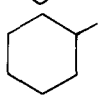
3. *Properties*

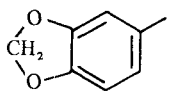
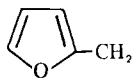
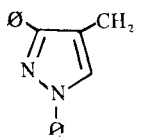
All isolated 1,2,4-triazin-6-ones are white crystalline compounds with high melting points. No detailed study of their structure has been reported until now.

TABLE II-7. 1,2,4-TRIAZIN-6-ONES

A. 1,2,4-Triazin-6(1H)-ones



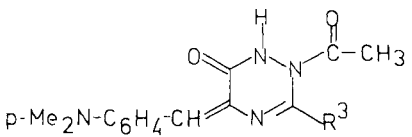
R^3	R^5	m.p. (°C)	Refs.
CH_3	C_6H_5	253 (dec.)[a]	45
CH_3	$C_6H_5-CH_2$	163–165	198
CH_3	4-$CH_3O-C_6H_4-CH_2$	140–142	197, 198
CH_3		195–197	198
C_6H_5		233–235	198
C_6H_5	C_6H_5	223	201
		272[a]	45
C_6H_5	$C_6H_5-CH_2$	175–176[b]	194, 195, 197
Acetyl deriv.		187–188	195
C_6H_5	2-$O_2N-C_6H_4-CH_2$	205–208	197
C_6H_5	3-$O_2N-C_6H_4-CH_2$	155–157	197
C_6H_5	4-$O_2N-C_6H_4-CH_2$	195–197	197
C_6H_5	2-$CH_3O-C_6H_4-CH_2$	202–203	198
C_6H_5	4-$CH_3O-C_6H_4-CH_2$	185–187	198

C_6H_5	$4\text{-}Cl\text{-}C_6H_4\text{-}CH_2$	225–227[b]	197
C_6H_5	$3,4\text{-}(CH_3O)_2C_6H_3\text{-}CH_2$	186–188	198
C_6H_5	$4\text{-}(CH_3)_2N\text{-}C_6H_4\text{-}CH_2$	170–172	198
C_6H_5	$C_6H_5\text{-}CH{=}CH\text{-}CH_2$	131–133	197
C_6H_5		185–187	197
C_6H_5		212–214	198
C_6H_5		243[b]	196
$4\text{-}O_2N\text{-}C_6H_4$	$C_6H_5\text{-}CH_2$	223–225	197
$4\text{-}O_2N\text{-}C_6H_4$	$4\text{-}CH_3O\text{-}C_6H_4\text{-}CH_2$	197–199	197
$4\text{-}CH_3O\text{-}C_6H_4$	$C_6H_5\text{-}CH_2$	[b]	197
$4\text{-}CH_3CO\text{-}NH\text{-}C_6H_4$	$C_6H_5\text{-}CH_2$	214–216	197
$4\text{-}CH_3CO\text{-}NH\text{-}C_6H_4$	$4\text{-}CH_3O\text{-}C_6H_4\text{-}CH_2$	172–175	197
$(C_6H_5)_2C(OH)$	H	178–180[a]	44
$(C_6H_5)_2C(OH)$	CH_3	207–208[a]	44
Hydrate		201–202[a]	44

[a] Structure doubtful, may be 1,2,4-triazin-5-ones.
[b] Partly 5-methylene structure.

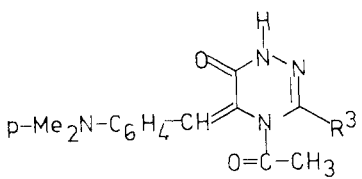
TABLE II-7. (*continued*)

B. 2-Acetyl-5-alkylidene-1,2,4-triazin-6-ones



R^3	m.p. (°C)	Refs.
C_6H_5	213–214	200
3-O_2N–C_6H_4	170–171	200

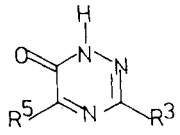
C. 4-Acetyl-5-alkylidene-1,2,4-triazin-6-ones



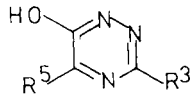
R^3	m.p. (°C)	Refs.
CH_3	215–216[c]	199
C_6H_5	199–201[c]	199

[c] Structure not fully established.

Because of the broad absorption band in the infrared spectra between 3200 and 2600 cm^{-1} and the intensive absorption at 1665 cm^{-1} Becker and his group (201) suggested that for 3,5-diphenyl-1,2,4-triazin-6-one the tautomeric form **71a** predominates.

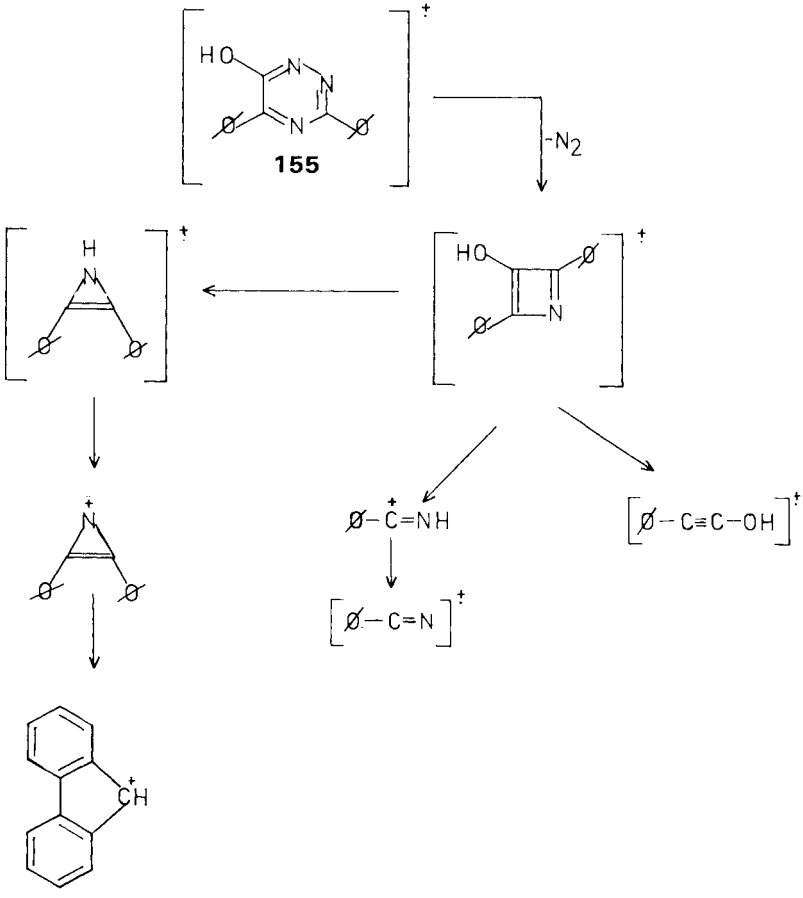


71a



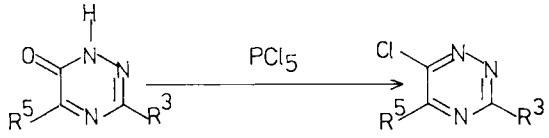
71b

The fragmentation pattern of the same compound is given in the following scheme; it shows that the fragmentation starts with the loss of nitrogen (201).



4. *Reactions*

So far only one reaction of 1,2,4-triazin-6-ones (**71**) has been published. Metze and Meyer (45) reported the synthesis of 6-chloro-1,2,4-triazines (**156**) by reaction of **71** with phosphorus pentachloride. But since the structure of the 1,2,4-triazin-6-ones synthesized by Metze and his group is doubtful, the structure of the 6-chloro-1,2,4-triazines must also be doubtful.



71 **156**

E. 1,2,4-Triazine-3,5-diones (3,5-Dihydroxy-1,2,4-triazines)

1. *Preparation*

1,2,4-Triazine-3,5-diones (**157**) are well-known compounds. This group of 1,2,4-triazine derivatives has been intensively studied since they are aza analogues of uracil and its derivatives, and biological activities can be expected.

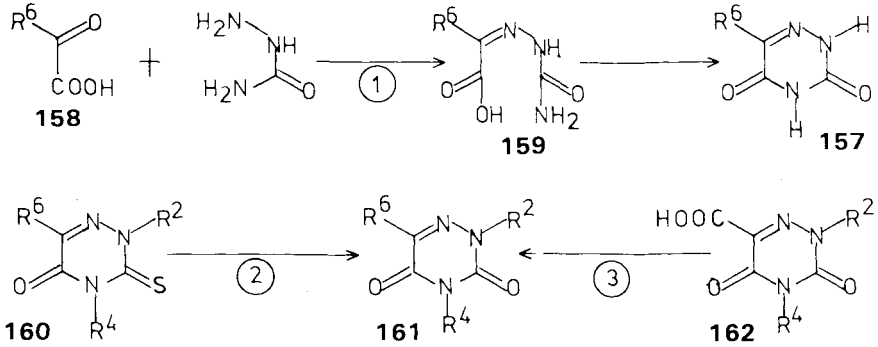
In this section all compounds are discussed in which hydroxy tautomers have three double bonds in the 1,2,4-triazine ring and which have no other functional group or hetero atom directly bonded to the 1,2,4-triazine nucleus. Furthermore all compounds are discussed which are derivatives of the different tautomers of the 1,2,4-triazine-3,5-dione system.

Publications that deal only with studies on the biological activities of 1,2,4-triazine-3,5-diones are no discussed here but are listed separately for the sake of complete literature coverage.

A review on the chemistry of 1,2,4-triazine-3,5-diones was published by Gut (202) in 1963.

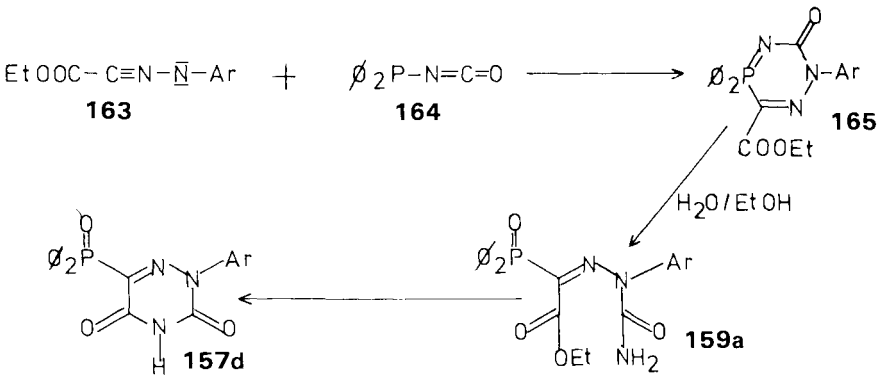
Owing to the intensive studies on the 1,2,4-triazine-3,5-diones a number of effective methods for the synthesis of these compounds and their derivatives are known. The most frequently used methods are (1) the reaction of a α-ketocarboxylic acid (**158**) or its derivatives with semicarbazide, (2) transformation of 3-thioxo-1,2,4-triazin-5-ones (**160**) into 1,2,4-triazine-3,5-diones (**161**), and (3) the decarboxylation of 3,5-dioxo1,2,4-triazin-6-carboxylic acids (**162**).

The direct cyclization of α-ketocarboxylic acids (**158**) or their derivatives with semicarbazide hydrochloride is achieved by heating the two components in ethanol (203, 206, 223, 241, 242, 244, 250).

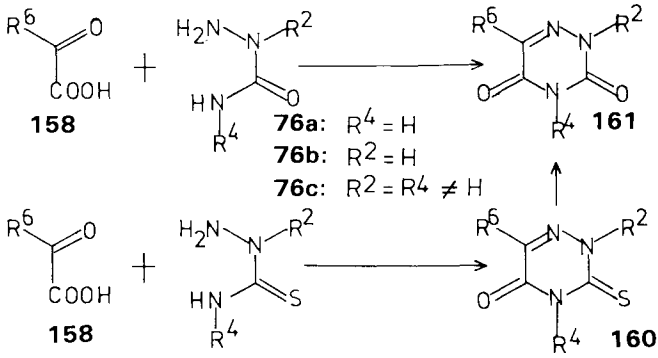


In most cases the initially formed semicarbazone (**159**) is isolated (204–211, 213–221, 225–228, 230–239, 243, 245–249, 277, 321) and cyclized in a second step, mostly under basic conditions. For the cyclization the following conditions were used: aqueous base (204, 206–214, 227, 232, 235, 237, 238, 245–249), sodium hydroxide in alcohols (234, 236, 243), or a sodium alkoxide, mainly sodium ethoxide (205, 215, 216, 218, 220, 226, 231, 233, 277). Besides these basic conditions the cyclization of **159** with thionyl chloride in the presence of pyridine is also reported (217, 219, 221).

A method that uses the intermediacy of a semicarbazone of an α-keto-carboxylic acid is published by Petrov and his collaborators (224). Reaction of the nitrilimines (**163**) with the isocyanate (**164**) forms the 1,2,4,5-phosphatri-azines (**165**) by a [3 + 3]-cycloaddition reaction. These were hydrolyzed to the semicarbazones (**159a**) which cyclized to the phosphorus-substituted 1,2,4-tri-azine-3-,5-diones (**157d**).



By reaction of α-ketocarboxylic acids (**158**) with *N*-2- and/or *N*-4-substituted semicarbazides (**76a**, **76b**, **76c**) N^2- and/or N^4- substituted 1,2,4-triazine-3,5-diones (**161**) can be prepared.



A method that is even more frequently used for the synthesis of 1,2,4-triazine-3,5-diones is the reaction of α-ketocarboxylic acids with thiosemicarbazide instead of semicarbazide followed by transformation of the initially formed 3-thioxo-1,2,4-triazin-5-one **160** into the desired compounds (227, 237, 248, 249, 252–263, 265–321). The reason for this method is the observation that the thiosemicarbazones can be cyclized much more easily than the semicarbazones (**159**), as Bougault (259, 322) and Cattelain (264) have already mentioned.

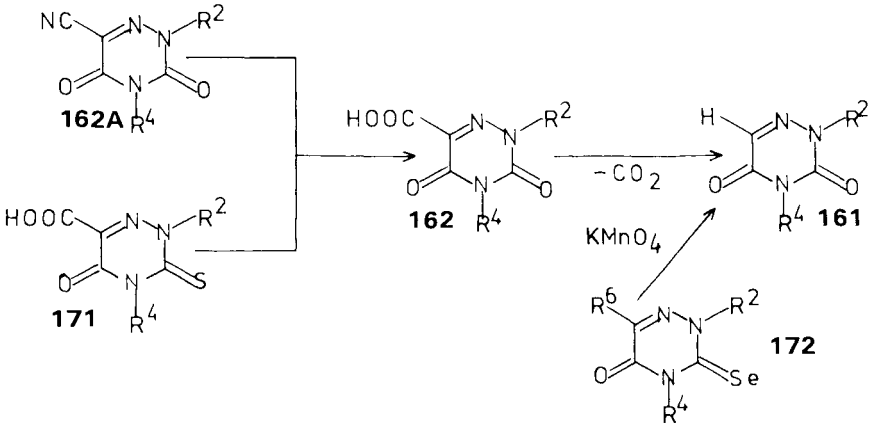
For easy achievement of the transformation the thioxo group is frequently alkylated and the alkylmercapto group is hydrolyzed in acidic media (237, 248, 249, 252–258, 260–263, 265, 267, 268, 270, 274, 275, 280–283, 289–291, 293, 294, 299–302, 304, 306–311, 314, 316, 317, 744, 1084, 1385, 1564). In many cases chloroacetic acid is used as the alkylating agent (251, 276, 286–288, 296, 297).

The thioxo group is replaced by an oxo group by reaction with sodium hypobromide (227, 237, 259, 272), potassium permanganate (189, 248, 278, 292, 298, 300, 303, 312, 316, 321, 324, 1294), hydrogen peroxide in the presence of a base (291, 305, 320), basic hydrolysis (189, 1385, 1564), or iodine and sodium hydroxide (266, 273).

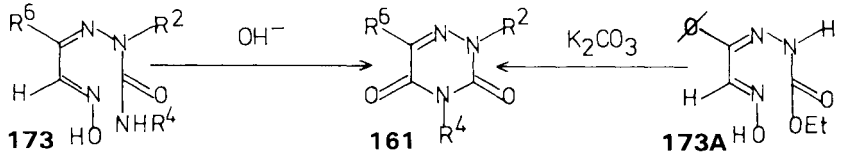
The hydrolytic transformation of 5-mercapto-1,2,4-triazin-3-ones (279, 289, 1385) or 1,2,4-triazine-3,5-dithione derivatives (279, 304, 1564) into 1,2,4-triazine-3,5-diones is also reported.

3,5-Dioxo-1,2,4-triazine-6-carboxylic acids (**162**), which give 1,2,4-triazine-3,5-diones (**161**) by decarboxylation (251, 323–335, 1081), were synthesized by saponification of 6-cyano-1,2,4-triazine-3,5-diones (**162A**) or 5-oxo-3-thioxo-1,2,4-triazine-6-carboxylic acids (**171**).

A method that is quite similar to the synthesis of 1,2,4-triazine-3,5-diones (**161**) from 3-thioxo-1,2,4-triazin-5-ones (**160**) is the oxidative transformation of 3-selenoxo-1,2,4-triazin-5-ones (**172**) with potassium permanganate (342).



Lalezari (336) has shown that the basic cyclization of α-oximosemicarbazones (**173**) produces 1,2,4-triazine-3,5-diones (**161**). 6-Phenyl-1,2,4-triazine-3,5-dione (**161a**) ($R^2 = R^4 = H$, $R^6 = C_6H_5$) was isolated on treatment of compound **173A** with potassium carbonate (337).

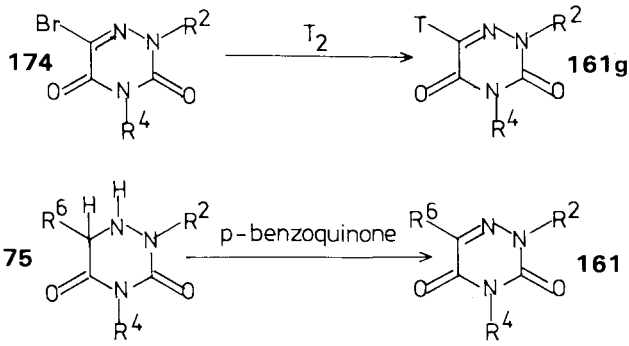


Amino-1,2,4-triazinones, (hydroxylamino)-1,2,4-triazinones, or hydrazino-1,2,4-triazinones can be hydrolyzed to 1,2,4-triazine-3,5-diones (295, 324, 336, 343–345, 409, 427) by treatment with base (324, 344), acid (295,324, 343, 345), by reaction with nitrous acid (336), or by heating them in water to 90 °C (427).

Oxidation of 1,2,4-triazin-3-ones with unsubstituted 5-positions with hydrogen peroxide in acid was used for the synthesis of 6-phenyl-1,2,4-triazine-3,5-dione (153).

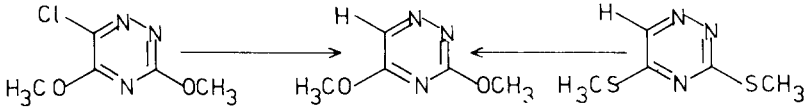
Reduction of 6-bromo-1,2,4-triazine-3,5-diones (**174**) with sodium in ammonia or by hydrogenation with palladium/charcoal leads to 1,2,4-triazine-3,5-diones (**161**), but since **174** were synthesized by bromination of **161** this reaction has no synthetic value (349). Hydrogenation of **174** with tritium was used for the synthesis of 1,2,4-triazine-3,5-dione-6-*t* (**161g**) (1080).

Oxidation of 1,6-dihydro-1,2,4-triazine-3,5-diones (**175**) has also been used for the synthesis of 1,2,4-triazine-3,5-diones (**161**) (338–341, 423); *p*-benzoquinone seems to be the best oxidant (423).



N-Substituted derivatives of 1,2,4-triazine-3,5-diones can be prepared by reaction of 1,2,4-triazine-3,5-diones with alkylating or acylating agents (see discussion of reactions below.). Derivatives of the hydroxy tautomers are mainly prepared by substitution of the chloro or methylmercapto groups, as shown for **176** (305, 389, 390, 1385, 1564).

Reduction of 6-chloro-3,5-dimethoxy-1,2,4-triazine (**174A**) is used for the synthesis of 3,5-dimethoxy-1,2,4-triazine (**170**) (678, 1565).



174A **170** **176**

2. *Compound Survey*

1,2,4-Triazine-3,5-diones reported in the literature are listed in Table II-8.

3. *Physical Properties and Theoretical Considerations*

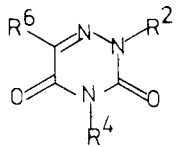
The physical properties of 1,2,4-triazine-3,5-diones (**161**), especially their sugar derivatives, have been intensively studied and a number of theoretical calculations on this system have been reported.

Theoretically the 1,2,4-triazine-3,5-dione system (**161**) can form six tautomeric structures **161a**–**161f**. To our knowledge derivatives of the tautomeric structures **161a**–**161e** are known.

Intensive infrared (215, 247, 351–357), ultraviolet (215, 251, 358–365), and NMR spectroscopic studies (359, 364, 367–376) have shown that both in

TABLE II-8. 1,2,4-TRIAZINE-3,5-DIONES

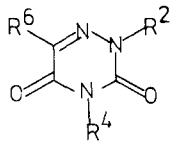
A. 1,2,4-Triazine-3,5(2H,4H)-diones



R^2	R^4	R^6	m.p. (°C)	Refs.
H	H	H	268–270	215, 216
			270–272	349, 217
			272	286, 287, 323
			275	327
			277–279	324
			278	341
			279–281	235, 236, 437
			280–281	1385, 1565, 1566
			281–283	423
			283	332
				275, 285, 343
H	H	CH_3	208–209	287
			209	286, 318, 340
			209–210	282
			210–211	1104
			210–212	215
			211–212	291
			212	443
			212–213	189, 256, 281
			214	1564
			216	336
			217	204
				259, 275

TABLE II-8. *(continued)*

A. 1,2,3-Triazine-3,5(2H,4H)-diones



R^2	R^4	R^6	m.p. (°C)	Refs.
H	H	CH_2F	127.5–128	221
			128–129.5	256
H	H	CF_3	153	346, 348
			157.5–158.5	219
			161–162	347, 473
H	H	CH_2Cl	155–157	217, 253
H	H	CH_2OH	176.5–178	258
H	H	CH_2CH_3	145–147	215
			152	227
			153	288
H	H	n-C_3H_7	132–134	215
H	H	i-C_3H_7	195	288
H	H	n-C_4H_9	135	227
H	H	i-C_4H_9	185	227
H	H	s-C_4H_9	206–207	230
H	H	t-C_4H_9	270	288
			285	207, 210
H	H	n-C_5H_{11}	131	288
H	H	n-C_7H_{15}	127–128	278, 298
H	H	n-C_9H_{19}	124–125	278, 298
H	H	n-$C_{11}H_{23}$	125–126	278, 298

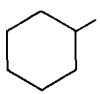
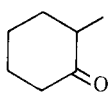
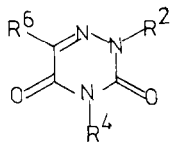
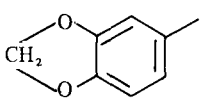
H	H	n-$C_{13}H_{27}$	125	278, 298
H	H	CH_2COOH	187–188	288
H	H	$CH_2COOC_2H_5$	182–183	288
			187–188 (dec.)	205
H	H	$(CH_2)_2COOH$	196–198	205
			197–198	313
H	H	$(CH_2)_2COOC_2H_5$	113–114	205
H	H	$(CH_2)_3COOH$	199–201	300
			204	205
H	H	$(CH_2)_3COOC_2H_5$	93–94	205
H	H	$(CH_2)_3CONH_2$	94–95	205
H	H	$(CH_2)_4COOH$	183–184	300
			187–188	205
H	H	$(CH_2)_4COOC_2H_5$	108–109	205
H	H	$(CH_2)_4CONH_2$	109–111	205
H	H	$(CH_2)_5COOH$	186–187	314
			187–188	205
H	H	$(CH_2)_5COOC_2H_5$	108–109	205
H	H	$(CH_2)_8COOH$	128–132	205
H	H	$CHF(COOC_2H_5)_2$	174–178.5	256
H	H	$CH(COOC_2H_5)(CH_2)_3COOC_2H_5$	158–159	203
H	H	$CH_3-CO-CH_2$	174–176	338, 339
H	H	 cyclohexyl	262–263	315
H	H	 2-oxocyclohexyl	239–240	338, 339

TABLE II-8. (*continued*)

A. 1,2,4-Triazine-3,5(2H,4H)-diones



R^2	R^4	R^6	m.p. (°C)	Refs.
H	H	$C_6H_5-CH_2$	208	207, 210, 259, 260, 266, 268 272, 273
H	H	4-Cl–$C_6H_4-CH_2$	202–204	248
H	H	Cl–$C_6H_4-CH_2$	234–235	321
H	H	2,4-$Cl_2-C_6H_3-CH_2$	198–199	321
H	H	4-Br–$C_6H_4-CH_2$	257–259	321
H	H	2-CH_3O–$C_6H_4-CH_2$	157–158	315
H	H	4-CH_3O–$C_6H_4-CH_2$	208–209	321
			215	237, 225
H	H	2,3$(CH_3O)_2C_6H_3-CH_2$	170–171	303
H	H	3,4$(CH_3O)_2C_6H_3-CH_2$	207–208	315
			236–237	321
H	H	$C_2H_5O-C_6H_4-CH_2$	205–206	321
H	H	2,4$(C_2H_5O)_2C_6H_3-CH_2$	210–211	321
H	H	$C_3H_7O-C_6H_4-CH_2$	196–197	321
H	H		212	247

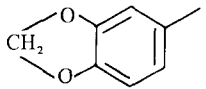
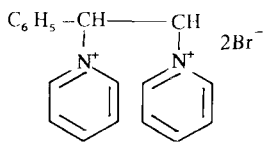
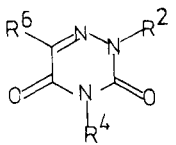
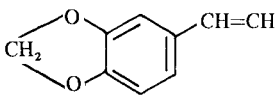
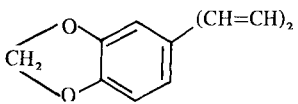
H	H	$C_6H_5-CH_2CH_2$	194	207, 210
H	H		201	247
H	H	$4\text{-}CH_3O-C_6H_4-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}$	220.5	213, 214, 270
H	H	$C_6H_5-CH_2-\underset{\displaystyle C_6H_5}{\underset{\vert}{COH}}$	236	207
H	H	$C_6H_5-\underset{\displaystyle OH}{\underset{\vert}{CH}}-\underset{\displaystyle C_6H_5}{\underset{\vert}{CH}}$	226	211
H	H	$C_6H_5-\underset{\displaystyle Br}{\underset{\vert}{CH}}-CHBr$	255	206
H	H		235	206
H	H	$C_6H_5-\underset{\displaystyle \vert}{C}=N-NH-\underset{\displaystyle S}{\underset{\Vert}{C}}-NH_2$	187.5	262, 263
H	H	$C_6H_5-CH=CH$	266	207, 210
			269–270	247
			299	312
H	H	$4\text{-}F-C_6H_4-CH=CH$	278–279	247
H	H	$4\text{-}Cl-C_6H_4-CH=CH$	268–271	248
H	H	$3\text{-}O_2N-C_6H_4-CH=CH$	232–235	316
H	H	$4\text{-}CH_3O-C_6H_4-CH=CH$	271–273	249
			272–273	247

TABLE II-8. (*continued*)

A. 1,2,4-Triazine-3,5(2H,4H)-diones



R^2	R^4	R^6	m.p. (°C)	Refs.
H	H	$2,3(CH_3O)_2C_6H_3-CH=CH$	269–270	303
H	H	$3,4(CH_3O)_2C_6H_3-CH=CH$	246–247	247
H	H	$3,4,5(CH_3O)_3C_6H_2-CH=CH$	194	247
H	H		276–277 282	247 207, 210
H	H	$C_6H_5-CH=CH-CH=CH$	269–271	312
H	H		270	247
H	H	C_6H_5	254–257 255–256 261–262 262	345 321 279, 280, 284, 288, 292, 336, 337, 342 153, 207, 209, 210, 292

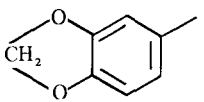
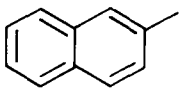
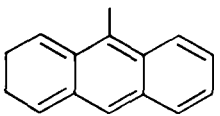
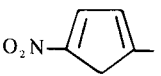
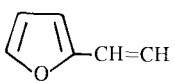
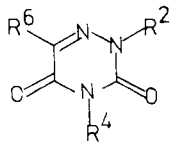
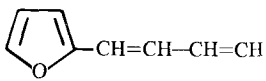
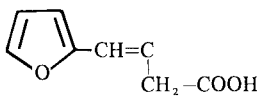
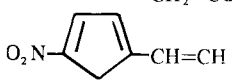
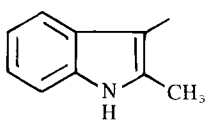
H	H	4-CH_3–C_6H_4	275	336
H	H	4-F–C_6H_4	291	336
H	H	4-Cl–C_6H_4	279	336
H	H	4-Br–C_6H_4	298	336
H	H	2-O_2N–C_6H_4	260	1294
H	H	2-H_2N–C_6H_4	350	1296
H	H	4-O_2N–C_6H_4	293	336
H	H	4-CH_3O–C_6H_4	273	207, 210, 336
H	H	3,4$(CH_3O)_2C_6H_3$	212	223
H	H	4-CH_3S–C_6H_4	273	336
H	H		304	247
H	H		289	238
H	H		338–340	316
H	H		308 309–310 318–320	245 231, 232 228
H	H		318–319 332–333	231, 233 228
H	H		256–258 285–286	312 246

TABLE II-8. (*continued*)

A. 1,2,4-Triazine-3,5(2H,4H)-diones



R^2	R^4	R^6	m.p. (°C)	Refs.
H	H		280	246
H	H		260	246
H	H		265 (dec.)	241, 243, 311
H	H		368–369 (dec.)	240
H	H		298–299 (dec.)	239
H	CH_3	H	164–165	341
			169	454, 455
			169–170	445
			170	289
			170–171	251
			171	1385
			171–172	443
				304

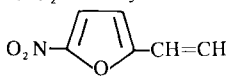
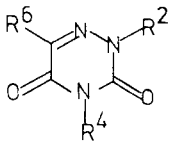
H	CH_3	CH_3	155	289, 290
			155–156	443
			157–158	429
H	CH_3	$C_6H_5-CH_2$	150	207, 208, 211
				267, 268, 271
H	CH_3	C_6H_5	204–205	279, 280
			205	170, 207, 211, 293
H	CH_3	$4\text{-}CH_3O-C_6H_4-CH_2$	144	237
H	CH_3	$4\text{-}CH_3O-C_6H_4-CH(CH_3)$	159–160	213, 214
H	CH_3	$C_6H_5-CH(HO)-CH(C_6H_5)$	184	211
H	CH_3	$C_6H_5-CH=CH$	264	206
H	CH_3	2-Furyl	240.5–241.5	212
H	CH_3	$5\text{-}O_2N$-2-furyl	239.5–240.5	212
H	CH_3		265 (dec.)	241, 311
H	CH_2CH_3	H	157	290
			159	461
H	CH_2CH_3	$C_6H_5-CH_2$	117	207, 267, 394
H	CH_2CH_3	$4\text{-}CH_3O-C_6H_4-CH_2$	140	237
H	CH_2CH_3	$4\text{-}CH_3O-C_6H_4-CH(CH_3)$	132	213, 214
H	CH_2CH_2OH	H	160	446
H	CH_2CH_2Cl	H	137–138	446
H	$n\text{-}C_8H_{17}$	$C_6H_5-CH_2$	98–100	456
H	$C_6H_5-CH_2$	H	129–130	234
H	$C_6H_5-CH_2$	$C_6H_5-CH_2$	161	207, 394
H	$C_6H_5-CH_2$	$4\text{-}CH_3O-C_6H_4-CH_2$	136	237
H	$C_6H_5-CH_2$	$4\text{-}CH_3O-C_6H_4-CH(CH_3)$	206	213, 214

TABLE II-8. (*continued*)

A. 1,2,4-Triazine-3,5(2H,4H)-diones



R^2	R^4	R^6	m.p. (°C)	Refs.
H	$(C_6H_5)_2CH$	H	183–184	234
			185–186	455
			189–190	444, 349
H	$(C_6H_5)_2CH$	CH_3	167	444
			170–171	439, 1086
			186	445
H	C_6H_5	CH_3	242.5	319
H	C_6H_5	C_6H_5–CH=CH	264	206
H	C_6H_5	C_6H_5		309, 1084
H	C_6H_5		295 (dec.)	245
H	4-CH_3–C_6H_4	CH_3	248	319
H	CF_3CO	CH_3		439
H	C_6H_5–CO	H	189–191	438
H	C_6H_5–CO	CH_3	190–191	438
H	4-CH_3–C_6H_4–SO_2	H	226–228	438
H	4-CH_3–CONH–C_6H_4–SO_2	H	248–250	438
CH_3	H	H	151–152	438
			152	277, 289, 290
			156–157	1385
			157–158	443
			159	434
			160–161	251

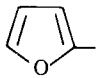
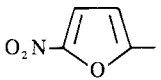
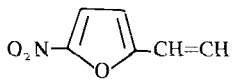
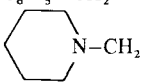
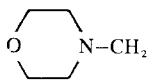
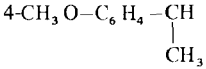
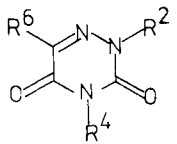
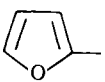
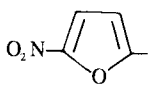
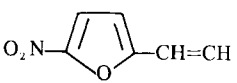
CH_3	H	CH_3	200–201	438
			200–202	289, 290
			201–203	251
CH_3	H	$C_6H_5-CH_2$	137	265, 267, 269, 274
CH_3	H	C_6H_5	178–179	280, 242
CH_3	H		234.5–236	232, 212
CH_3	H		264–265	212, 232
CH_3	H		238–240 (dec.)	241
			240–241	310
			241–242 (dec.)	244
CH_3	CH_3	H	55	341
			64–65	290, 461
			67–68	251
CH_3	CH_3	CH_3	101–103	290, 429
			157–158	251
CH_3	CH_3	$CH_3-CO-CH_2$	102–103	338, 339
CH_3	CH_3		128–130	338, 339
CH_3	CH_3	$C_6H_5-CH_2$	95	207, 211, 267
CH_3	CH_3		69	425
CH_3	CH_3		89	425
CH_3	CH_3	$4\text{-}CH_3O-C_6H_4-CH_2$	89	237
CH_3	CH_3		142.5	213, 214

TABLE II-8. (*continued*)

A. 1,2,4-Triazine-3,5(2H,4H)-diones



R^2	R^4	R^6	m.p. (°C)	Refs.
CH_3	CH_3	$C_6H_5-CH=CH$	145	206
CH_3	CH_3	C_6H_5	116–117	279
			118	170
			119	293
			125–126	280
CH_3	CH_3		157.5–159	232
CH_3	CH_3		215–215.5	232, 212
CH_3	CH_3		207–209	244
			209–210 (dec.)	241
CH_3	C_6H_5	C_6H_5		309, 1084
CH_3	$(CH_3)_2N-CH_2-CH_2$	C_6H_5		448
CH_3	C_6H_5-CO	H	101	438
CH_3	C_6H_5-CO	CH_3	144–146	438
CH_3	$4\text{-}CH_3-C_6H_4-SO_2$	H	154–156	438
CH_3	$4\text{-}CH_3CO-NH-C_6H_4-SO_2$	H	229–230	438

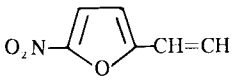
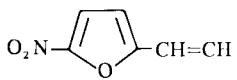
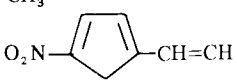
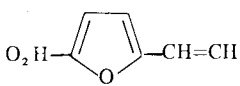
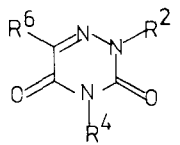
C_2H_5	H	H	87	289, 290, 461
C_2H_5	H	$C_6H_5-CH_2$	103	265, 267, 274
C_2H_5	H	5-O_2N-2-furyl	246–248	212
C_2H_5	C_2H_5	H	b.p. 106/12 mm	290, 459
C_2H_5	C_2H_5	$C_6H_5-CH_2$	Oily	394
C_2H_5	C_2H_5	4-$CH_3O-C_6H_4-CH_2$	72	237
C_2H_5	C_2H_5	4-$CH_3O-C_6H_4-CH(CH_3)$	Liquid	213, 214
CH_2Cl	H	H		443
CH_2OH	H	H	276–278[a]	443
CH_2OH	H	CH_3		443
CH_2OH	CH_3			450
CH_2OH	CH_2OH	H		443
CH_2OH	CH_2OH	CH_3		443
CH_2OH	CH_2OH	5-O_2N-2-furyl	126–127	212
CH_2OH	CH_2OH		166–167.5	451
$CH_2O-CO-CH_3$	H	H	144–146	443
$CH_2O-CO-CH_3$	H	CH_3	97–98	443
$CH_2O-CO-CH_3$	CH_3	H	86–86.5	443
$CH_2O-CO-CH_3$	CH_3	CH_3	77–79	443
$CH_2O-CO-CH_3$	CH_3		180–182	450
$CH_2O-CO-CH_3$	$CH_2O-CO-CH_3$	H	79–80	443
$CH_2O-CO-CH_3$	$CH_2O-CO-CH_3$	CH_3	116–118 resol. 128–129	443
$CH_2O-CO-CH_3$	$CH_2O-CO-CH_3$		173–175	451
$CH_2-CO-C_6H_5$	$CH_2-CO-C_6H_5$	5-O_2N-2-furyl	188–189	212

TABLE II-8. *(continued)*

A. 1,2,4-Triazine-3,5(2H,4H)-diones



R^2	R^4	R^6	m.p. (°C)	Refs.
CH_2-COOH	H	H	226–227	289
$CH_2CH_2-O-C_2H_5$	H	2-Furyl	136–137	212
$CH_2CH_2-O-C_2H_5$	H	5-O_2N-2-furyl	181-5–182.5	212
$CH_3-CH-O-CO-CH_3$	H	H		443
$CH_3-CH-O-CO-CH_3$	CH_3	H	Oily	443
$(CH_3)_2N-CH_2CH_2$	*n*-C_4H_9	C_6H_5		449
$(i\text{-}C_3H_7)_2N-CH_2CH_2$	$(i\text{-}C_3H_7)_2N-CH_2CH_2$	5-O_2N-2-furyl	98–99.5	212
CH_2CH_2CN	H	H	154–156	301, 542
CH_2CH_2CN	H	CH_3	153–155	301
CH_2CH_2CN	CH_2CH_2CN	H	107–109	301, 437
CH_2CH_2CN	CH_2CH_2CN	CH_3	84–86	301
CH_2CH_2CN	C_6H_5-CO	H	131–133	301
CH_2CH_2COOH	H	H	145–148	437
			161–163	302
$CH_2CH_2COOCH_3$	H	H	109–110	542
			109–111	302
$CH_2CH_2COOC_2H_5$	H	H	67–68	302, 542
$CH_2CH_2CONH_2$	H	H	197–199	542
			203–204	302
$CH_2CH_2CON(CH_3)_2$	H	H	184–186	302
$CH_2CH_2CONH(n-C_4H_9)$	H	H	173–175	302

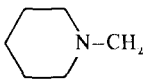
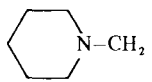
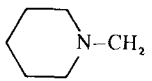
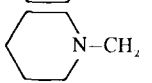
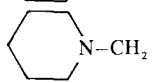
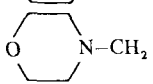
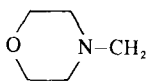
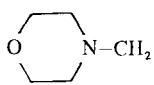
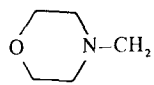
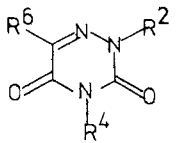
C_3H_7	H	H	106	277, 434
C_3H_7	H	2-Furyl	184.5–185	212
C_3H_7	H	5-O_2N-2-furyl	195–196.5	212
i-C_3H_7	H	2-Furyl	235–235.5	212
i-C_3H_7	H	5-O_2N-2-furyl	218.5–219	212
C_4H_9	H	H	104–106	277, 434
i-C_4H_9	H	2-Furyl	296.5–297.5	212
i-C_4H_9	H	5-O_2N-2-furyl	202–203	212
$CH_2=CH-CH_2$	H	2-Furyl	193.5–194.5	212
$CH_2=CH-CH_2$	H	5-O_2N-2-furyl	174–175	212
$CH_2=CH-CH_2$	$CH_2=CH-CH_2$	5-O_2N-2-furyl	102–103	212
C_6H_{13}	H	H	85	277, 434
	CH_3	H	114	425
		H	147	425
		C_6H_5	156	170
	H	H	149	425
	CH_3	H	179	425
		C_6H_5	160–161	170
$C_6H_5-CH_2$	H	H	183–184	234, 423, 434
$C_6H_5-CH_2$	H	$C_6H_5-CH_2$	113	265, 267, 269, 274

TABLE II-8. (*continued*)

A. 1,2,4-Triazine-3,5(2H,4H)-diones



R^2	R^4	R^6	m.p. (°C)	Refs.
$C_6H_5-CH_2$	H	4-$CH_3O-C_6H_4-CH_2$	120	237
$C_6H_5-CH_2$	$C_6H_5-CH_2$	H	101–102	234
$C_6H_5-CH_2$	$C_6H_5-CH_2$	$C_6H_5-CH_2$	108	207, 394
$C_6H_5-CH_2$	$C_6H_5-CH_2$	4-$CH_3O-C_6H_4-CH_2$	71	237
$C_6H_5-CH_2$	$C_6H_5-CH_2$	4-$CH_3O-C_6H_4-CH(CH_3)$	160.5–161.5	213, 214
2-$CH_3-C_6H_4-CH_2$	H	H	171–172	434
4-$CH_3-C_6H_4-CH_2$	H	H	204–205	434
3-$CF_3-C_6H_4-CH_2$	H	H	158–160	434
3,5-$(CF_3)_2C_6H_3-CH_2$	H	H	179–181	434
2-$F-C_6H_4-CH_2$	H	H	214–215	434
4-$F-C_6H_4-CH_2$	H	H	199–200	434
3,4-$F_2C_6H_3-CH_2$	H	H	233–234	434
4-$Cl-C_6H_4-CH_2$	H	H		434
2,4-$Cl_2C_6H_3-CH_2$	H	H	207	434
3,4-$Cl_2C_6H_3-CH_2$	H	H	177	434
3-$I-C_6H_4-CH_2$	H	H	206–208	434
2-$NC-C_6H_4-CH_2$	H	H	208–210	434
3-$NC-C_6H_4-CH_2$	H	H	179–181	434
2,4-$(O_2N)_2C_6H_3-CH_2$	H	H		434

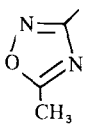
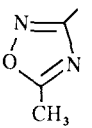
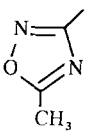
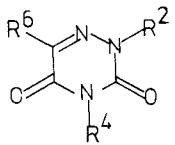
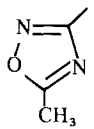
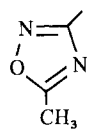
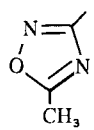
3,4-$CH_2O_2C_6H_3$–CH_2	H	H	182–183	434
4-CH_3SO_2–C_6H_4–CH_2	H	H	233–234	434
2-F–4-Cl–C_6H_3–CH_2	H	H	215–216	434
2-F–5-Cl–C_6H_3–CH_2	H	H	203–204	434
4-F–3-O_2N–C_6H_3–CH_2	H	H	198–200	434
2-Cl–4-O_2N–C_6H_3–CH_2	H	H	199–200	434
4-Cl–3-O_2N–C_6H_3–CH_2	H	H	183–185	434
2-Cl–5-CH_3O–C_6H_3–CH_2	H	H	162–163	434
4-Cl–3-CH_3O–C_6H_3–CH_2	H	H	191–193	434
$(C_6H_5)_2CH$	H	CH_3	170–171	439
$(C_6H_5)_2CH$	CF_3CO	CH_3		439
C_6H_5	H	H	213–214	329
C_6H_5	H		251–253	896
C_6H_5	H	$(C_6H_5)_2PO$	295–296	224
4-CH_3–C_6H_4	H	H	209–211	329
4-CH_3–C_6H_4	H		254–256	896
4-CH_3–C_6H_4	H	$(C_6H_5)_2PO$	254–256	224
2,3-$(CH_3)_2C_6H_3$	H	H	211–213	335
2,3-$(CH_3)_2C_6H_3$	H		249–251	335

TABLE II-8. (*continued*)

A. 1,2,4-Triazine-3,5(2H,4H)-diones



R^2	R^4	R^6	m.p. (°C)	Refs.
4-Cl–C_6H_4	H	H	232–234	329
4-Cl–C_6H_4	H		232–234	896
2,5-$Cl_2C_6H_3$	H	H	187–189	335
2,5-$Cl_2C_6H_3$	H		230–232	335
3,4-$Cl_2C_6H_3$	H	H	225–226	434
4-Br–C_6H_4	H	H	249–251	329
4-Br–C_6H_4	H		259–261	896

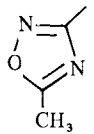
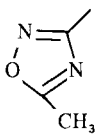
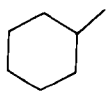
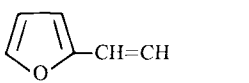
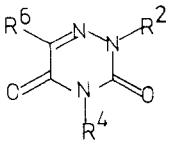
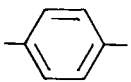
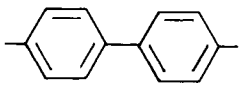
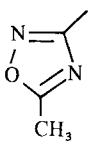
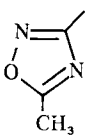
4-Br–C_6H_4	H	$(C_6H_5)_2PO$	235–237	224
4-I–C_6H_4	H	H	279–281	329
4-CH_3O–C_6H_4	H	H	233–235	329
4-CH_3O–C_6H_4	H		253–255	896
3,4,5-$(CH_3O)_3C_6H_2$	H	H	218–220	335
3,4,5-$(CH_3O)_3C_6H_2$	H		269–271	335
4-C_2H_5O–C_6H_4	H	H	221–223	329
4-O_2N–C_6H_4	H	H	234–236	332
2,4-$(O_2N)_2C_6H_3$	H	H	161–162	317 328
2,4-$(O_2N)_2C_6H_3$	H	CH_3	194–195	317
2,4-$(O_2N)_2C_6H_3$	H		210–211	317
2,4-$(O_2N)_2C_6H_3$	H	C_6H_5–CH_2	233–234	317
2,4-$(O_2N)_2C_6H_3$	H	C_6H_5	271–272	317
2,4-$(O_2N)_2C_6H_3$	H	 or $CH_2CH_2COCH_2CH_2$ 	181–183	317
4-HOOC–C_6H_4	H	H	282–284 (dec.)	331

TABLE II-8. (*continued*)

A. 1,2,4-Triazine-3,5(2H,4H)-diones



R^2	R^4	R^6	m.p. (°C)	Refs.
4-CH_3CO–NH–C_6H_4	H	H	285–289 (dec.)	332
	H	H	350	334
	H	H		333
1-Naphthyl	H	H	208–210	330
1-Naphthyl	H		251–253	330
1-Naphthyl	H	H	255–257	330
2-Naphthyl	H		269–271	330

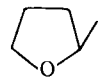
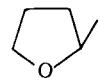
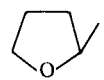
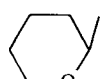
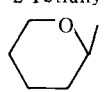
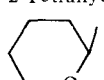
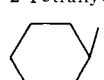
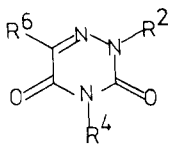
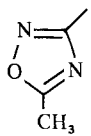
 2-Tetrahydrofuryl	H	H	121–123	471 472
 2-Tetrahydrofuryl	H	CH_3	142–143	471 2306
 2-Tetrahydrofuryl	H	Br	211–213	471
 2-Tetrahydropyranyl	H	H	160–162	471 472, 2306
 2-Tetrahydropyranyl	H	H	163–164	475
 2-Tetrahydropyranyl	H	CH_3	125–128	471
 2-Tetrahydropyranyl	H	Br	195–197	471

TABLE II-8. *(continued)*

A. 1,2,4-Triazine-3,5(2H,4H)-diones



R^2	R^4	R^6	m.p. (°C)	Refs.
 2-Pyridyl	H		293–295	888
CH_3–CO	H	H	151	445, 447, 454, 455
			154–156	438, 444
CH_3–CO	H	CH_3	115	444
CH_3–CO	H	CF_3	118	346, 436
CH_3–CO	CH_3	H	99–100	445, 454, 455
CH_3–CO	$(C_6H_5)_2CH$	H		444, 447
CH_3–CO	$(C_6H_5)_2CH$	CF_3	85	346, 436
CH_3–CO	CH_3–CO	4-CH_3O–C_6H_4–CH(CH_3)	274	226
			276–278	220
CH_3–CO	H	C_6H_5–CH_2	110	265
CH_3–CO	H	C_6H_5–CH=CH	192	206
CH_3–CO	H	4-CH_3O–C_6H_4–CH(CH_3)		214

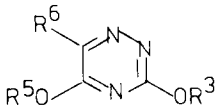
CH_3-CO	H	$C_6H_5-CH(OH)-CH(C_6H_5)$	192	211
CH_3-CO	C_6H_5-CO	H	114–115	438
CF_3-CO	H	CH_3	104–106	444, 455
CF_3-CO	$(C_6H_5)_2CH$	CH_3		444
$CH_3(CH_2)_6CO$	H	H	128–129	464
$CH_3(CH_2)_8CO$	H	H	129–131	464
$CH_3(CH_2)_{10}CO$	H	H	125–127	464
$CH_3(CH_2)_{12}CO$	H	H	130–132	464
$CH_3(CH_2)_{14}CO$	H	H	125–127	464
C_6H_5-CO	C_6H_5-CO	H	140–141	438
C_6H_5-CO	C_6H_5-CO	H	140–141	438
Cl	Cl	$C_6H_5-CH_2$	119	495, 496
Cl	Cl	$C_6H_5-CH_2CH_2$	130	495
Cl	Cl	C_6H_5	130	496
Cl	$C_6H_5-CH_2$	$C_6H_5-CH_2$	153	495, 496

B. Labelled 1,2,4-triazine-3,5(2H,4H)-diones

R^2	R^4	R^6	m.p. (°C)	Refs.
H	H	H 3-^{14}C	268–270	216
H	H	H 5,6-^{14}C	272	276, 296, 297
H	H	CH_3 6-^{14}C	208	276, 296, 297
H	H	T		1080
β-D-Ribofuranosyl	H	T		1080
2,3-Isopropylidene-β-D-ribofuranosyl	H	H 5,6-^{14}C	139–140	514
Phosphorylated β-D-ribofuranosyl	H	H 5,6-^{14}C		541

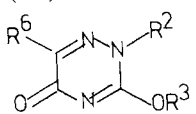
TABLE II-8. (*continued*)

C. 3,5-Dihydroxy-1,2,4-triazines

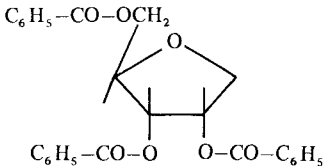
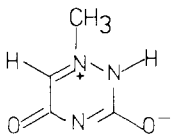


R^3	R^5	R^6	m.p. (°C)	Refs.
CH_3	CH_3	H	58–61	305
			60–63	678
			61–62	1565
			61–63	1564
CH_3	CH_3	CH_3	98–100	305
			102–103	1564
			107–108	489
$(CH_3)_3Si$	$(CH_3)_3Si$	H	b.p. 142–144/25 mm	470, 469, 475
				476, 480, 483
$(CH_3)_3Si$	$(CH_3)_3Si$	CH_3	b.p. 146–147/20 mm	470, 476, 480
$(CH_3)_3Si$	$(CH_3)_3Si$	CF_3	Oily	219, 347, 473
$(CH_3)_3Si$	$(CH_3)_3Si$	$CH_2OSi(CH_3)_3$		468
$(CH_3)_3Si$	$(CH_3)_3Si$	Br		347

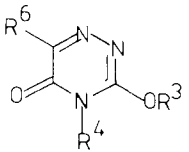
D. 3-Hydroxy-1,2,4-triazin-5(2*H*)-ones



R^2	R^3	R^6	m.p. (°C)	Refs.
H	CH_3	H	167–169	1385, 1564
H	CH_3	CH_3	182–183	1564

H		H		294
CH_3	CH_3	H	118–119	1385
CH_3	CH_3	C_6H_5	148–149	280
CH_3	C_2H_5	C_6H_5	142–143	280
			235–236	441

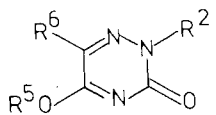
E. 3-Hydroxy-1,2,4-triazin-5(4*H*)-ones

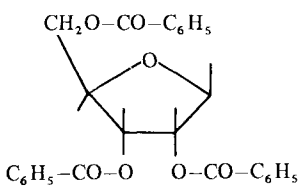


R^3	R^4	R^6	m.p. (°C)	Refs.
CH_3	CH_3	H	100–101	1385
CH_3	CH_3	*i*-C_3H_7	98	229
CH_3	CH_3	C_6H_5	101	229
			102–103	280
CH_3	CH_3	4-CH_3O–C_6H_4	103	229
CH_3	CH_3	2-Furyl	112	229

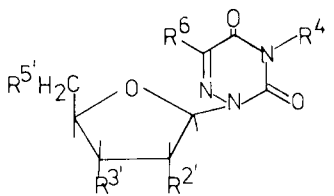
TABLE II-8. (*continued*)

F. 5-Hydroxy-1,2,4-triazin-3(2*H*)-ones



R^2	R^5	R^6	m.p. (°C)	Refs.
H	CH_3	H	165–166	1385
CH_3	CH_3	H	67–68	1385
	CH_3	H	128–130	490

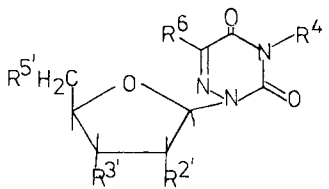
G. 2-Sugar-substituted 1,2,4-triazine-3,5-diones



$R^{2'}$	$R^{3'}$	$R^{5'}$	R^4	R^6	m.p. (°C)	Refs.
OH	OH	OH	H	H	Syrup	295
					138–139	254
					140	1086
					142–143	538
					159–160	475
					160	444, 447, 1561
					160–161	469
					161	294, 454, 455
					191–194	306, 307, 305, 343, 344, 430, 479, 480, 514, 515, 763
OH	OH	OH	H	CH_3	139–142	444, 481, 429, 455, 454, 442

TABLE II-8. (*continued*)

G. 2-Sugar-substituted 1,2,4-triazine-3,5-diones



$R^{2'}$	$R^{3'}$	$R^{5'}$	R^4	R^6	m.p. (°C)	Refs.
OH	OH	OH	H	CF_3	152–154	347
					Anomers soft. 78	346
OH	OH	OH	H	Br	214–215	347
OH	OH	OH	CH_3	H	124	445, 454
					125	455, 461
						459
OH	OH	OH	CH_2CH_2OH	H		432
OH	OH	OH	$(C_6H_5)_2CH$	CF_3		
					Anomers 47–60	346
OH	OH	H	H	H		522
OH	OH	F	H	H	161–164	435
OH	OH	F	H	CF_3	201–203	435
OH	OH	Adamantoyl-O	H	H	179–180	519, 520
OH	OH	3,5-$(CH_3)_2$-adamantoyl-O	H	H		519
OH	OH	3,5,7-$(CH_3)_3$-adamantoyl-O	H	H	122–124	519
OH	OH	$(C_6H_5)_3C$–O	H	H	95–96	512, 550
OH	OH	CH_3COO	H	H	91	514, 528
OH	OH	C_6H_5–COO	H	H	152–154	426

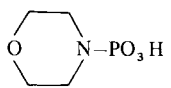
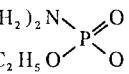
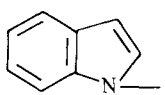
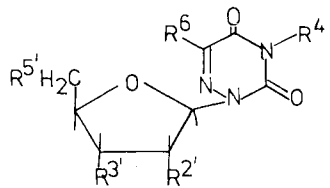
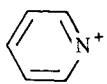
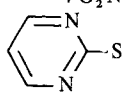
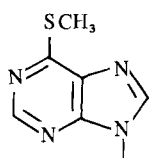
OH	OH	H_2O_3PO	H	H	Glass	538, 442
					138–139	514, 515
	Et_3N, Ba, dicyclohexylamine salt					442, 530
OH	OH	H_2O_3PO	H	CH_3		442
			Ba salt			442
OH	OH	$(CH_3)HO_3PO$	H	H		544
OH	OH	$(C_2H_5)HO_3PO$	H	H		544
OH	OH	$(C_5H_{11})HO_3PO$	H	H	99–101	544
OH	OH	$(C_6H_5)HO_3PO$	H	H	142–144	544
					Powder	442
OH	OH	$(CH_3)_2O_3PO$	H	H	Foam	544
OH	OH	$(C_5H_{11})_2O_3PO$	H	H	Oily	544
OH	OH	$(C_6H_5)_2O_3PO$	H	H	Foam	544, 442
OH	OH	$(C_6H_5)_2O_3PO$	H	CH_3		442
OH	OH		H	H		537, 556
						515
OH	OH	CH_3PO_3H	H	H	H_3N salt	525
OH	OH	H_2PO_3	H	H	Ba salt	532
OH	OH		H	H		540
OH	OH	$H_3O_6P_2O$	H	H		514
OH	OH	$H_4O_9P_3O$	H	H		510, 535, 537, 556
OH	OH	CH_3SO_2O	H	H	181–182	460
OH	OH	$4\text{-}O_2N\text{–}C_6H_4\text{–}SO_2O$	H	H	162	543
OH	OH		H	H		1085

TABLE II-8. (*continued*)

G. 2-Sugar-substituted 1,2,4-triazine-3,5-diones



$R^{2'}$	$R^{3'}$	$R^{5'}$	R^4	R^6	m.p. (°C)	Refs.
OH	OH	 $4\text{-}O_2N\text{–}C_6H_4\text{–}SO_3^-$	H	H		543
OH	OH		H	H	Foam	522
OH	OH		H	H	275	552
OH	H_2O_3PO	H	H	H		529
OH	H_2O_3PO	CH_3COO	H	H		526
OH	H_2O_2PO	H	H	H		528, 529, 527
OH	H_2O_2PO	H_2O_2PO	H	H		528
OH	$(CH_3)HO_2PO$	H	H	H $(C_2H_5)_3N$ salt		525

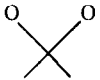
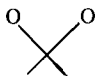
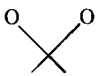
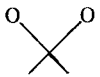
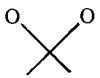
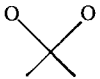
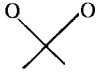
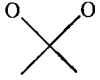
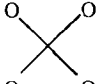
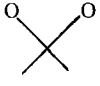
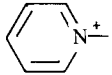
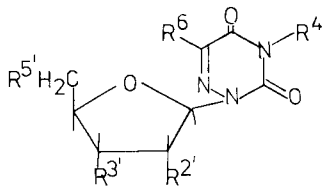
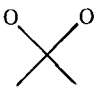
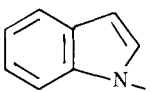
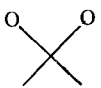
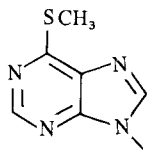
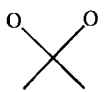
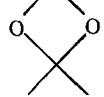
OH		H_2O_3PO	CH_3COO	H	H		526
			OH	H	H	138–139 141–142	534 515 501, 521, 533, 538, 435
			OH	CH_2CH_2OH	H		435
			I	H	H	176–181 178–181	460 553, 554
			N_3	H	H	143–147	460
			t-C_4H_9O	H	H	220 (unsharp)	460
			HCOO	H	H	149–150	557, 460
			HCOO	CH_3	H	152–154	557
			Adamantoyl-O	H	H		520
			3,5,7-$(CH_3)_3$-adamantoyl-O	H	H		520
			 4-O_2N–C_6H_4–SO_3^-	H	H	263–264	543

TABLE II-8. (*continued*)

G. 2-Sugar-substituted 1,2,4-triazine-3,5-diones



$R^{2'}$	$R^{3'}$	$R^{5'}$	R^4	R^6	m.p. (°C)	Refs.
			H	H		1085
			H	H		552
		CH_3-SO_2-O	H	H	145–147	460
		$4\text{-}CH_3-C_6H_4-SO_2-O$	H	H	156–158	533, 1085

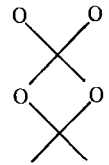
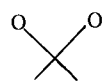
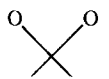
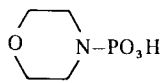
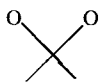
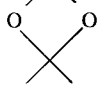
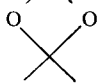
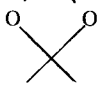
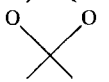
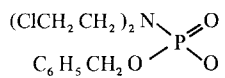
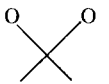
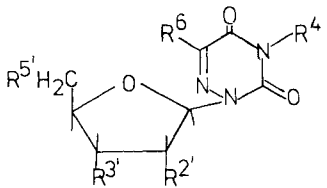
	$4\text{-}O_2N\text{–}C_6H_4\text{–}SO_2\text{–}O$	H	H	162	543
	H_2O_3PO	H	H		501, 534, 538
$(C_2H_5)_3N$ salt					530
	$(4\text{-}O_2N\text{–}C_6H_4)HO_3PO$	H	H		538
		H	H		534
	$(CH_3)_2O_3PO$	H	H	Foam	544
	$(C_5H_{11})_2O_3PO$	H	H		544
	$(C_6H_5)_2O_3PO$	H	H	Foam	544
	$(C_6H_5)HO_3PO$	H	H		528
		H	H		540
	H_2O_2PO	H	H		528

TABLE II-8. (*continued*)

G. 2-Sugar-substituted 1,2,4-triazine-3,5-diones



$R^{2'}$	$R^{3'}$	$R^{5'}$	R^4	R^6	m.p. (°C)	Refs.
$(C_2H_5)_3N$ salt						532
O O		$(C_6H_5CH_2)HO_2PO$	H	H		540
O O		$(C_6H_5O)_2PO$	H	H		528
O O		CH_3PO_3H	H	H H_3N salt		525
O O $CHOC_2H_5$		H	H	H		426, 554
O O $CHOC_2H_5$		C_6H_5COO	H	H		426
O O $CH{-}OC_2H_5$		H_2O_3PO	H	H		531

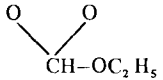
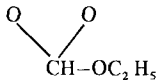
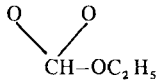
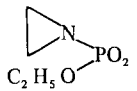
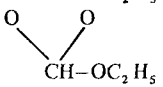
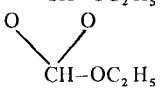
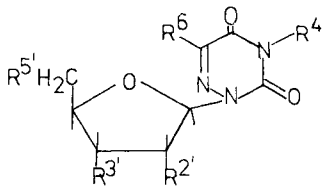
		$(ClCH_2CH_2)_2N$, PO_2, C_2H_5O	H	H		540
		$(ClCH_2CH_2)_2N$, PO_2, $C_6H_5CH_2O$	H	H		540
			H	H		540
		$(C_2H_5)HO_2PO$	H	H	Oily	540
		$(C_6H_5CH_2)HO_2PO$	H	H	Oily	540
HCOO	HCOO	HCOO	H	H		549, 557
CH_3COO	CH_3COO	CH_3COO	H	H	100–102	511
					Powder	512, 550, 763
CH_3COO	CH_3COO	F	H	H		435
CH_3COO	CH_3COO	F	H	CH_3	152–155	435
CH_3COO	CH_3COO	$(C_6H_5)_3C$	H	H		512, 550
CH_3COO	CH_3COO	HCOO	H	H		549
CH_3COO	CH_3COO	CH_3COO	H	H	102–103	475, 501, 516
					99–101	512
					97.5–99	518
						446, 493, 511, 549 557
CH_3COO	CH_3COO	CH_3COO	CH_3COO	H		464
CH_3COO	CH_3COO	H_2O_3PO	H	H		512, 548

TABLE II-8. *(continued)*

G. 2-Sugar-substituted 1,2,4-triazine-3,5-diones

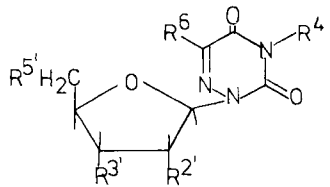


$R^{2'}$	$R^{3'}$	$R^{5'}$	R^4	R^6	m.p. (°C)	Refs.
CH_3COO	CH_3COO	$(ClCH_2CH_2)_2N$ HO_3P	H	H		540
CH_3COO	CH_3COO	$(ClCH_2CH_2)_2N$ $C_2H_5O-PO_2$	H	H		540
CH_3COO	CH_3COO	$(ClCH_2CH_2)_2N$ $C_6H_5CH_2O-PO_2$	H	H		540
CH_3COO	CH_3COO	$(C_6H_5CH_2)HO_2PO$	H	H		540
CH_3COO	CH_3COO	$(C_2H_5)HO_2PO$	H	H		540
C_2H_5COO	C_2H_5COO	H_2O_3PO	H	H		512, 548
C_6H_5COO	C_6H_5COO	C_6H_5COO	H	H	157–159	306, 307
					178	445
					183–186	295
					186–187	294
					188–191	465
					191	447
					192–194	469, 475, 476, 485

					194–195	431, 444
					240–242	431
						430, 445, 466, 493
						763
C_6H_5COO	C_6H_5COO	C_6H_5COO	H	CH_3	127–128	455
					129–130	444
					132–133	476
					133–135.5	429, 481, 485
C_6H_5COO	C_6H_5COO	C_6H_5COO	H	CH_2COCH_3	147–148	339
C_6H_5COO	C_6H_5COO	C_6H_5COO	CH_3	H	130–131	445, 454, 455
C_6H_5COO	C_6H_5COO	C_6H_5COO	$(C_6H_5)_2CH$	H	116–117	447
					118–119	444
					119	445
C_6H_5COO	C_6H_5COO	C_6H_5COO	$(C_6H_5)_2CH$	CH_3	196–197	455
					204	444
C_6H_5COO	C_6H_5COO	$(C_6H_5)_2O_3PO$	H	H	193–194	442
C_6H_5COO	C_6H_5COO	$(C_6H_5)_2O_3PO$	H	CH_3	Powder	442
C_6H_5COO	C_6H_5COO	$(C_6H_5)_2O_3PO$	$(C_6H_5)_2CH$	H	Oil	442
C_6H_5COO	C_6H_5COO	$(C_6H_5)_2O_3PO$	$(C_6H_5)_2CH$	CH_3	Oil	442
$C_6H_{11}COO$	$C_6H_{11}COO$	H_2O_3PO	H	CH_3		442
4-$CH_3-C_6H_4-COO$	4-$CH_3-C_6H_4-COO$	4-$CH_3-C_6H_4-COO$	H	H	177.5–179	483
					179	439, 457, 1086
					214–215	428
4-$CH_3-C_6H_4-COO$	4-$CH_3-C_6H_4-COO$	4-$CH_3-C_6H_4-COO$	H	CH_3	173–175	481
4-$CH_3-C_6H_4-COO$	4-$CH_3-C_6H_4-COO$	4-$CH_3-C_6H_4-COO$	4-$CH_3-C_6H_4-CO$	H	93–94	463
4-$CH_3-C_6H_4-COO$	4-$CH_3-C_6H_4-COO$	4-$CH_3-C_6H_4-COO$	$(C_6H_5)_3C$	H	136–137	439, 1086
4-$CH_3-C_6H_4-COO$	4-$CH_3-C_6H_4-COO$	4-$CH_3-C_6H_4-COO$	$(C_6H_5)_3C$	CF_3		436
				Anomers	Glass	346
4-$O_2N-C_6H_4-COO$	4-$O_2N-C_6H_4-COO$	OH	H	CF_3	209–211	347

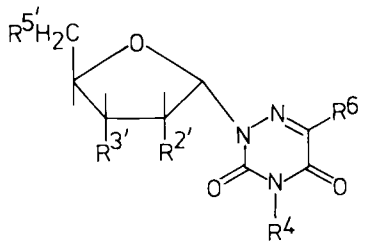
TABLE II-8. *(continued)*

G. 2-Sugar-substituted 1,2,4-triazine-3,5-diones



$R^{2'}$	$R^{3'}$	$R^{5'}$	R^4	R^6	m.p. (°C)	Refs.
4-$O_2N-C_6H_4-COO$	4-$O_2N-C_6H_4-COO$	4-$O_2N-C_6H_4-COO$	H	Br	131–132	347
OH	4-$CH_3-C_6H_4-SO_3$	OH	H	H	Semicryst.	463
OH	4-$CH_3-C_6H_4-SO_3$	CH_3-COO	H	H	165–166	463
4-$CH_3-C_6H_4-SO_3$	4-$CH_3-C_6H_4-SO_3$	CH_3-COO	H	H	110–112	463
Cl	C_6H_5-COO	C_6H_5-COO	H	H	Amorph.	431
H	OH	OH	H	H	Oily	483
					Glassy solid	440, 431
					Anomers	467
H	OH	OH	H	CF_3	152–153	219, 473
				Anomers		432
H	OH	OH	H	CH_2OH	161.5–162	468
H	OH	OH	$(C_6H_5)_2CH$	CF_3		
				Anomers	47–60	436
H	OH	H_2O_3PO	H	CH_3	142–143	2249
H	OH	H_2O_3PO	H	CF_3		219
H	C_6H_5-COO	C_6H_5-COO	H	H	175–176	431
H	4-$CH_3-C_6H_4-COO$	4-$CH_3-C_6H_4-COO$	H	H	178–179	477
					Glassy solid	440
					Anomers	467

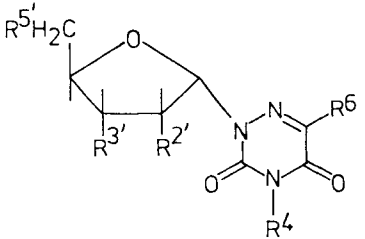
H	4-$CH_3-C_6H_4-COO$	4-$CH_3-C_6H_4-COO$	H	CH_2OH	149.5–151.5	468
H	4-$CH_3-C_6H_4-COO$	4-$CH_3-C_6H_4-COO$	H	$CH_2O-CO-CH_3$	158.5–159.5	440
H	4-$CH_3-C_6H_4-COO$	4-$CH_3-C_6H_4-COO$	$(C_6H_5)_2CH$	H	182	440
H	4-$O_2N-C_6H_4-COO$	4-$O_2N-C_6H_4-COO$	H	CF_3	206.5–207.5	219
					209–211	473
H	H_2O_3PO	OH	H	CH_3	226–227	2249
H	H_2O_3PO	H_2O_3PO	H	CH_3	201–203	2249
OH	H	H	H	H	140–141	463
OH	H	CH_3-COO	H	H	119–121	463
4-$CH_3-C_6H_4-COO$	H	4-$CH_3-C_6H_4-COO$	H	H	110	463

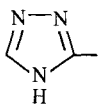
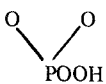
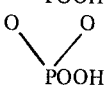
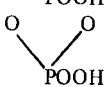


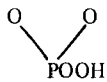
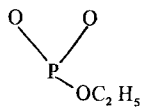
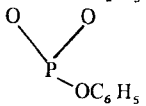
$R^{2'}$	$R^{3'}$	$R^{5'}$	R^4	R^6	m.p. (°C)	Refs.
OH	OH	OH	H	H	Syrupy	439, 1086
OH	OH	OH	H	CH_3		429
4-$CH_3-C_6H_4-COO$	4-$CH_3-C_6H_4-COO$	4-$CH_3-C_6H_4-COO$	H	H	80–100	439, 1086
4-$CH_3-C_6H_4-COO$	4-$CH_3-C_6H_4-COO$	4-$CH_3-C_6H_4-COO$	$(C_6H_5)_2CH$	H	182	439, 1086
H	OH	OH	H	H	128	440
					174	440
H	4-$CH_3-C_6H_4-COO$	4-$CH_3-C_6H_4-COO$	H	H	197–198	477
H	4-$CH_3-C_6H_4-COO$	4-$CH_3-C_6H_4-COO$	$(C_6H_5)_2CH$	H	136–137	440
H	OH	COOH	H	H	Anomers	467
H	OH	$COOCH_3$	H	H	Anomers	467

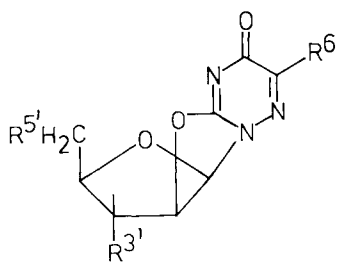
TABLE II-8. (*continued*)

G. 2-Sugar-substituted 1,2,4-triazine-3,5-diones



$R^{2'}$	$R^{3'}$	$R^{5'}$	R^4	R^6	m.p. (°C)	Refs.
H	OH	$CO-NH_2$	H	H	211–212	467
H	CH_3COO	$CO-NH_2$	H	H	216	467
H	OH	CN	H	H	165	467
H	OH		H	H Na salt·$2H_2O$	212	467
H_2O_3PO	OH	OH	H	H		529
H_2O_2PO	OH	OH	H	H		527, 528, 529
H_2O_2PO	OH	H_2O_2PO	H	H		528
		OH	H	H		524, 529
		OH	H	CH_3		524
		OH	CH_3	H		524

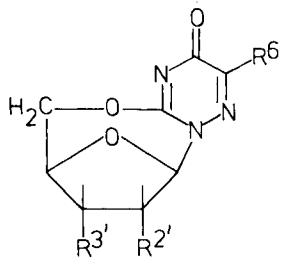
	CH_3-COO	H	H	526
	OH	H	H	527
	CH_3-COO	H	H	528

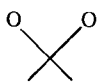
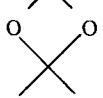


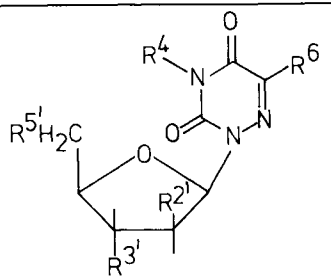
$R^{3'}$	$R^{5'}$	R^6	m.p. (°C)	Refs.
OH	OH	H	187–189	427
			194–195	428
OH	$(C_6H_5)_3C$	H	120	428
C_6H_5-COO	C_6H_5-COO	H	194–195	431
CH_3-SO_3	OH	H	185–187	458
CH_3-SO_3	$(C_6H_5)_3C$	H	196–200	458
			203–204	426

TABLE II-8. *(continued)*

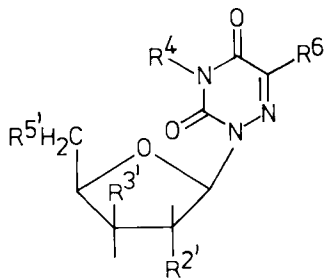
G. 2-Sugar-substituted 1,2,4-triazine-3,5-diones



$R^{2'}$	$R^{3'}$	R^6	m.p. (°C)	Refs.
		H	200–260	460 435, 533
		CH_3		435



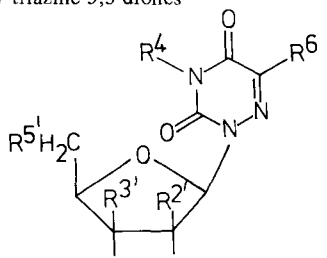
$R^{2'}$	$R^{3'}$	$R^{5'}$	R^4	R^6	m.p. (°C)	Refs.
OH	OH	OH	H	H	Syrup	427, 428
CH_3-COO	CH_3-COO	CH_3-COO	H	H	123–124	475, 476, 477, 478
$C_6H_5-CH_2O$	$C_6H_5-CH_2O$	$C_6H_5-CH_2O$	H	H	123–124	477
C_6H_5-COO	C_6H_5-COO	C_6H_5-COO	H	H	178.5–180	428
					179–181	427

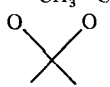


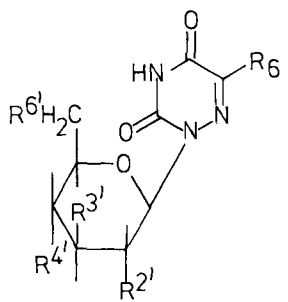
$R^{2'}$	$R^{3'}$	$R^{5'}$	R^4	R^6	m.p. (°C)	Refs.
OH	OH	OH	H	H	203–204	457
OH	I	OH	H	H	167–168	457
C_6H_5-COO	C_6H_5-COO	C_6H_5-COO	H	H	152.5–153.5	457
C_6H_5-COO	C_6H_5-COO	C_6H_5-COO	$C_6H_5-CH_2$	H	85–86	457

TABLE II-8. *(continued)*

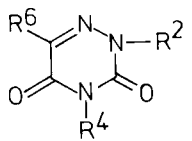
G. 2-Sugar-substituted 1,2,4-triazine-3,5-diones



$R^{2'}$	$R^{3'}$	$R^{5'}$	R^4	R^6	m.p. (°C)	Refs.
OH	OH	OH	H	H	Syrup	426
OH	OH	C_6H_5–COO	H	H	194–196	426
CH_3–COO	CH_3–COO	CH_3–COO	H	H	Foam	426
		C_6H_5–COO	H	H	185–187	426



$R^{2'}$	$R^{3'}$	$R^{4'}$	$R^{6'}$	R^6	m.p. (°C)	Refs.
OH	OH	OH	OH	H	210–212	475
CH_3COO	CH_3COO	CH_3COO	CH_3COO	H	164–165	295
					206–207	477, 478
					208–210	475
H	OH	OH	OH	H	214–215.5	470
H	OH	OH	OH	CH_3	228–230	470
H	4-O_2N–C_6H_4COO	4-O_2N–C_6H_4COO	4-O_2N–C_6H_4COO	H	241–242	
					Recryst.	
					287.5–288.5	470
H	4-O_2N–C_6H_4COO	4-O_2N–C_6H_4COO	4-O_2N–C_6H_4COO	CH_3	151–153	470



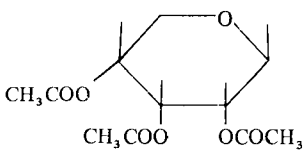
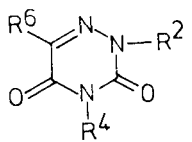
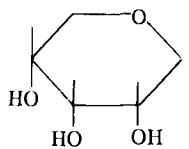
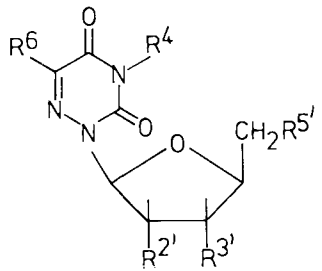
R^2	R^4	R^6	m.p. (°C)	Refs.
	H	H	172–173	475

TABLE II-8. (*continued*)

G. 2-Sugar-substituted 1,2,4-triazine-3,5-diones



R^2	R^4	R^6	m.p. (°C)	Refs.
	H	H	221–222	475
Heptaacetylcellubiosyl	H	H	241–242	474
Heptaacetylcellubiosyl	H	CH_3	150–153	474
Heptaacetylmaltosyl	H	H	130–132	474
Heptaacetylmaltosyl	H	CH_3	125–126	474, 484
Heptaacetyllactosyl	H	H		474
Heptaacetyllactosyl	H	CH_3		474
Decaacetylcellotriosyl	H	H		474
Tridecaacetylcellotetrosyl	H	H		474
β-D-glucopyranosyl	β-D-Glucopyranosyl	H	165	295
2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl	2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl	H	209	295
H	2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl	H	171–173	295



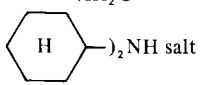
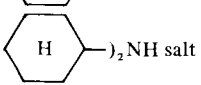
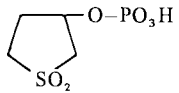
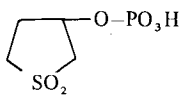
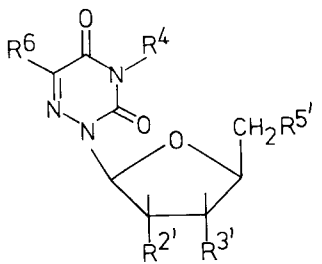
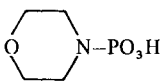
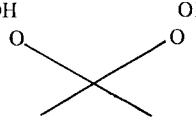
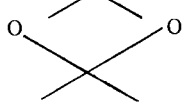
$R^{2'}$	$R^{3'}$	$R^{5'}$	R^4	R^6	m.p. (°C)	Refs.
OH	OH	OH	H	H		433
OH	OH	HCOO	H	H		557
OH	OH	$(C_6H_5)_3CO$	H	H		433
OH	OH	$H_{35}C_{17}COO$	H	H	105–106	551
OH	OH	H_2O_3PO	H	H	139–140	547, 523
$\cdot\frac{1}{2}H_2O$					139–140	547
					188–189	547
					199–200	547
OH	H_2O_3PO	OH	H	H		433, 514
OH	OH		H	H		558
OH	OH		H	H		558

TABLE II-8. *(continued)*

G. 2-Sugar-substituted 1,2,4-triazine-3,5-diones



$R^{2'}$	$R^{3'}$	$R^{5'}$	R^4	R^6	m.p. (°C)	Refs.
OH	OH	$NC-CH_2CH_2O-PO_3H$	H	H		558
OH	H_2O_2PO	OH	H	H		443
OH	OH	H_2O_3PO	CH_3	H	Syrupy	462
OH	OH		CH_3	H	Glassy	462
OH	OH	$H_3O_6P_2O$	CH_3	H		462
		OH	H	H	139–140	520
					139–141	517
					141–142	515
					142–143	547
		OH	CH_3	H	Syrupy	462
		CH_3-COO	H	H	178	514

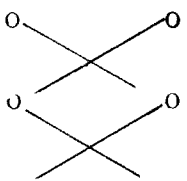
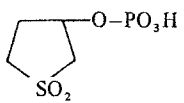
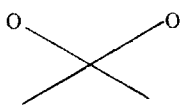
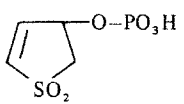
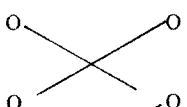
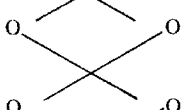
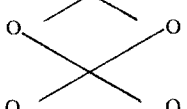
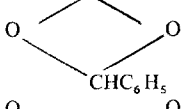
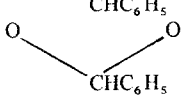
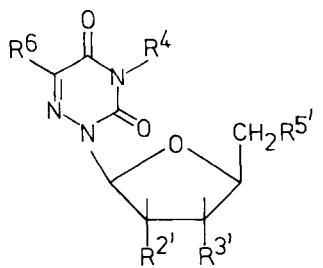
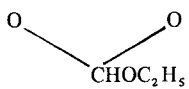
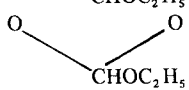
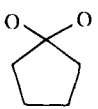
	$H_{35}C_{17}$–COO	H	H	48–49	551
	$(4\text{-}O_2N\text{–}C_6H_4)_2O_3PO$	H	H		547
		H	H		558
		H	H		558
	NC–CH_3CH_3O–PO_3H	H	H		558
	$H_3O_6P_2O$	H	H		547
	$(C_6H_5CH_2)_2HO_6P_2O$	H	H		547
	$(C_6H_5CH_2)HO_2PO$	H	H		547
	OH	H	H	156	545
	$(C_6H_5)_3CO$	H	H		545

TABLE II-8. *(continued)*

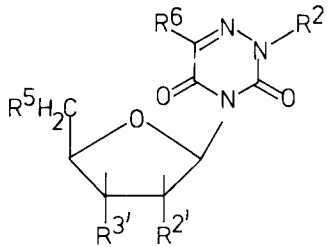
G. 2-Sugar-substituted 1,2,4-triazine-3,5-diones



$R^{2'}$	$R^{3'}$	$R^{5'}$	R^4	R^6	m.p. (°C)	Refs.
		OH	H	H		523
		H_2O_3PO	H	H		523
		OH	H	H	142–143	517
HCOO	HCOO	HCOO	H	H	100	557
CH_3COO	CH_3COO	CH_3COO	H	H	Foam	545, 557
CH_3COO	CH_3COO	HCOO	H	H		557
CH_3COO	CH_3COO	$(C_6H_5)_3CO$	H	H		545
C_6H_5COO	C_6H_5COO	OH	H	H	120–121	547
C_6H_5COO	C_6H_5COO	OH	CH_3	H	foamy	462
C_6H_5COO	C_6H_5COO	$(C_6H_5)_3CO$	H	H		547
C_6H_5COO	C_6H_5COO	C_6H_5COO	H	H		504

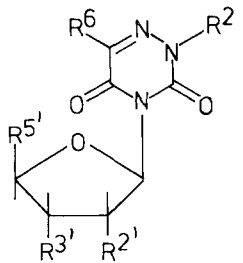
H_2O_5PO O O POOH	OH	OH	H	H	433, 514
		OH	H	H	433, 514
H_2O_2PO	OH	OH	H	H	433

H. 4-Sugar-substituted 1,2,4-triazine-3,5-diones



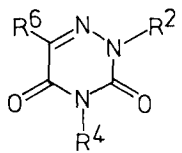
$R^{2'}$	$R^{3'}$	$R^{5'}$	R^2	R^6	m.p. (°C)	Refs.
OH	OH	OH	H	H	157–159	320
C_6H_5COO	C_6H_5COO	C_6H_5COO	H	H	188–189	465
OH	OH	OH	H	CH_3		439, 1086
4-$CH_3C_6H_4COO$	4-$CH_3C_6H_4COO$	4-$CH_3C_6H_4COO$	H	CH_3	175–176	439, 1086
4-$CH_3C_6H_4COO$	4-$CH_3C_6H_4COO$	4-$CH_3C_6H_4COO$	$(C_6H_5)_2CH$	CH_3		439, 1086

TABLE II-8. *(continued)*



$R^{2'}$	$R^{3'}$	$R^{5'}$	R^2	R^6	m.p. (°C)	Refs.
OH	OH	OH	H	CH_3	164–165	429
C_6H_5COO	C_6H_5COO	C_6H_5COO	H	CH_3		429

I. 6-Sugar-substituted 1,2,4-triazine-3,5-diones



R^2	R^4	R^6	m.p. (°C)	Refs.
H	H	$(CHOH)_3CH_2OH$ (D-ribo)	198.5–200	255
H	H	$(CHOH)_3CH_2OH$ (L-xylo)	229–231	255, 744
H	H	$(CHOH)_3CH_2OH$ (D-arabino)	266–268	255, 744
H	H	$(CHOCOCH_3)_3CH_2OCOCH_3$ (D-arabino)	Syrup	255
H	H	$(CHOH)_4CH_2OH$ (D-*allo*)	190–191	253

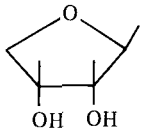
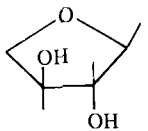
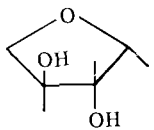
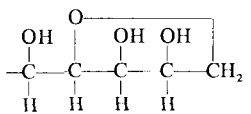
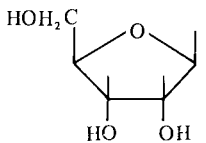
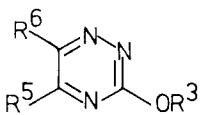
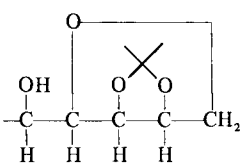
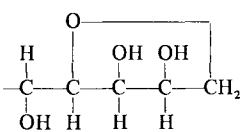
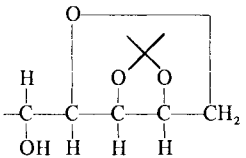
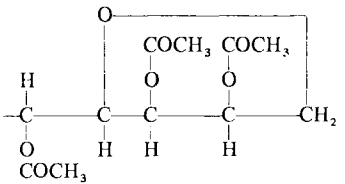
H	H	$(CHOH)_4CH_2OH$ (D-altro)	175–176.5	253, 257
H	H	$(CHOH)_4CH_2OH$ (D-gluco)	211–212.5	253
H	H	$(CHOH)_4CH_2OH$ (D-galacto)	256–257	253
H	H		169–171	255, 744
H	H		203–204.5	255, 744
H	H		150 (unsharp)	255
H	H		181.5–182.5	253
H	H		139–140	252

TABLE II-8. (*continued*)

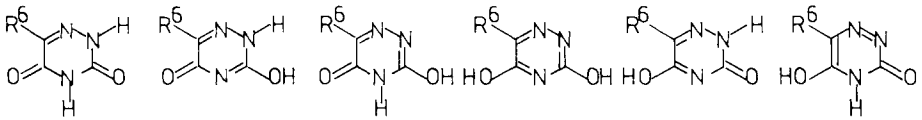
I. 6-Sugar-substituted 1,2,4-triazine-3,5-diones



R^2	R^4	R^6	m.p. (°C)	Refs.
H	H		Syrup	253
H	H		182–182.5	253, 257[a]

H	H		240–241.5	253, 254
H	H		Foam	253
CH_3	H	$(CHOH)_4CH_2OH$ (D-altro)	175–176.5	253
CH_3	H	$(CHOH)_4CH_2OH$ (D-gluco)	188–189	253

[a]Structure given in this reference is incorrect.



161a **161b** **161c** **161d** **161e** **161f**

solution and in the solid state the tautomeric form **161a** is the predominant form, in agreement with the result of theoretical calculations (390).

In the infrared spectra the N–H stretching vibrations of 1,2,4-triazine-3,5-diones can be observed only in dilute solutions; in the solid state or in concentrated solutions several very strong and diffuse bands, especially near 3200 cm^{-1}, appear. The N–H stretching vibrations for 1,2,4-triazine-3,5-dione (**161**) were found (356) at 3378 and 3423 cm^{-1}, at 3374 cm^{-1} for 2-methyl-1,2,4-triazine-3,5-dione (351), and at 3424 cm^{-1} for 4-methyl-1,2,4-triazine-3,5-dione (356). The C–H stretching vibration of **161** cannot be observed in the solid state since the region of its probable occurrence is occupied by a strong band of the associated N–H group. In solution (351) this vibration gives rise to a band at 3080 cm^{-1}.

Two very intensive bands in the double bond absorption region are observed for 1,2,4-triazine-3,5-dione (see Table II-9). The splitting of the carbonyl band into two bands has been explained by the coupling effect between the carbonyl groups (352). The systematic shifts of the carbonyl frequencies (see Table II-9), observed in *N*-alkylated 1,2,4-triazine-3,5-diones, makes possible the analytical use of the infrared spectra for distinguishing the substitution pattern.

TABLE II-9. CARBONYL FREQUENCIES IN THE INFRARED SPECTRA OF 1,2,4-TRIAZINE-3,5-DIONES

Compound	Carbonyl frequencies	
1,2,4-triazine-3,5-dione	1731	1700
2-methyl-1,2,4-triazine-3,5-dione	1723	1700
4-methyl-1,2,4-triazine-3,5-dione	1734	1687
2,4-dimethyl-1,2,4-triazine-3,5-dione	1720	1680

The infrared spectrum of 6-azauridine is not changed by addition of copper(II) ions (350). Infrared spectroscopy was used to determine hydrogen bonds in 6-azauridine and its derivatives (353, 355).

The ultraviolet spectra of 1,2,4-triazine-3,5-diones show the absorption maxima at 259 nm (pH 3) (362) or 261 nm [ethanol (362), dioxane (362), trimethyl phosphate (358)]. The absorptivity is 3.71 (362) or 5.3 (358). Methylation of the nitrogen at the 2-position is accompanied by a bathochromic

shift of the absorption maxima (273 nm) whereas methylation at the 4-position causes only a slight hypsochromic shift (258 nm) (362). The position of the absorption maxima of 2,4-dimethyl-1,2,4-triazine-3,5-dione (272 nm) is given by additive contributions of the individual methyl group effects.

The CD spectra and ORD spectra of sugar-substituted 1,2,4-triazine-3,5-diones were published by different groups (359–361, 363, 365, 366) and compared with calculated values (363). The small long-wavelength Cotton effect at 300 nm is due to a $n \rightarrow \pi$ transition (360, 361).

^{1}H and ^{13}C NMR spectra are mainly reported for sugar-substituted 1,2,4-triazine-3,5-diones and confirm the anti-structure of these molecules (359, 364, 367–370, 372–377). For the 2-(β-*D*-ribofuranosyl)-1,2,4-triazine-3,5-dione (6-azauridine) the following ^{13}C chemical shifts for the 1,2,4-triazine nucleus are reported: C_3 148.7, C_5 156.8, and C_6 136.6 ppm (376).

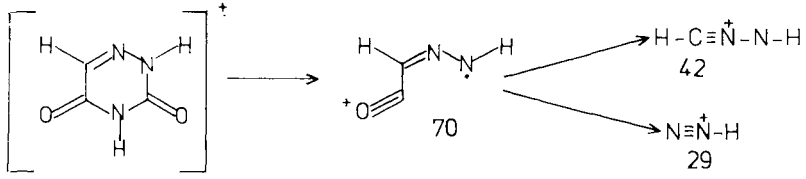
X-ray crystallographic investigations have been published by various groups (378–382, 1079). The result for 1,2,4-triazine-3,5-dione and its 6-methyl derivative is given in Table II-10 and shows that the diketo structure is the correct one (378).

TABLE II-10. STRUCTURE OF 1,2,4-TRIAZINE-3,5-DIONE AND ITS 6-METHYL DERIVATIVE

	Bond lengths (Å)	
Bond	1,2,4-Triazine-3,5-dione	6-Methyl-1,2,4-triazine-3,5-dione
N_1-N_2	1.291	1.270
N_2-C_3	1.456	1.473
C_3-N_4	1.359	1.366
N_4-C_5	1.378	1.387
C_5-C_6	1.366	1.346
C_6-N_1	1.351	1.367
C_3-O	1.224	1.240
C_5-O	1.224	1.220

Mass spectra (383–385) have been published for 1,2,4-triazine-3,5-dione (**161**), 3,5-bis(trimethylsilyloxy)-1,2,4-triazine, and 6-methyl-3,5-bis(trimethylsilyloxy)-1,2,4-triazine. The mass peaks observed for **161** are explained by the following fragmentation pattern (383).

1,2,4-Triazine-3,5-diones could be titrated with base in the presence of phenolphthalein (272, 394); their dissociation constants (393) and pK_a values were determined (215, 362, 392, 447). The pK_a values are as follows:



1,2,4-triazine-3,5-dione, 7.00 and 12.9; 2-methyl-1,2,4-triazine-3,5-dione, 6.99; and 4-methyl-1,2,4-triazine-3,5-dione, 9.25.

For the ionization of 1,2,4-triazine-3,5-dione a value of 10.18 eV was found; 9.65 eV is the calculated value (391).

1,2,4-Triazine-3,5-diones can be determined polarographically (395–399); the half-wave potential of 1,2,4-triazine-3,5-dione was found to be −1.18 V (397) at pH 7.2. The electronic structure of 1,2,4-triazine-3,5-dione was calculated by the simple MO LCAO method (389). The lowest excited singlet and triplet state were calculated (386–388), mainly by the SCF method.

Pecularities for the chromatographic determination of 1,2,4-triazine-3,5-diones are given by different groups (400–403, 724, 1548, 1558, 1559).

1,2,4-Triazine-3,5-diones form complexes with riboflavin (407). 1,2,4-Triazine-3,5-dione can be determined in the presence of 1,2,4-triazine-3,5-dione ribosides by reaction with sodium nitroprusside, giving a red color (404).

The EPR spectra of the radical formed in a single crystal of deuterated or undeuterated 6-methyl-1,2,4-triazine-3,5-dione by irridiation with γ- or X-rays was recorded by Herak and Schoffa (405). The spectrum of the deuterated compound shows 19 lines, indicating an interaction of the unpaired electron with two equivalent protons and two nonequivalent ^{14}N nuclei.

Shulman and Rahn (406) recorded the ESR spectra of metastable triplet states of 6-methyl-1,2,4-triazine-3,5-dione in ethylene glycol/water glass at 77 °K. The lowest triplet state is found to be a $\pi \rightarrow \pi^*$ state.

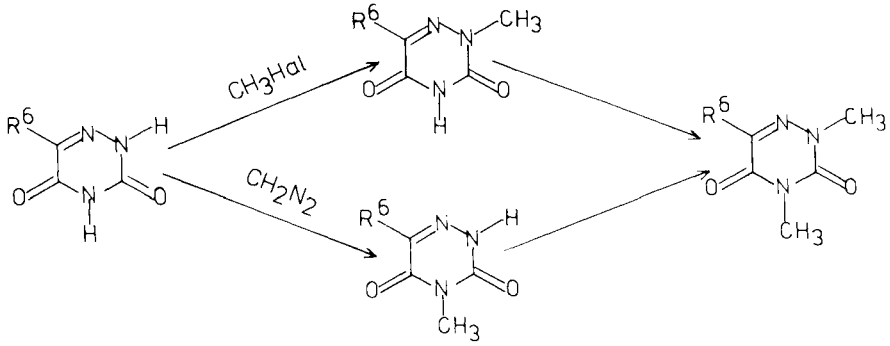
1,2,4-Triazine-3,5-diones are photochemically very unreactive and decrease the photochemical transformation of other compounds (1087).

4. *Reactions*

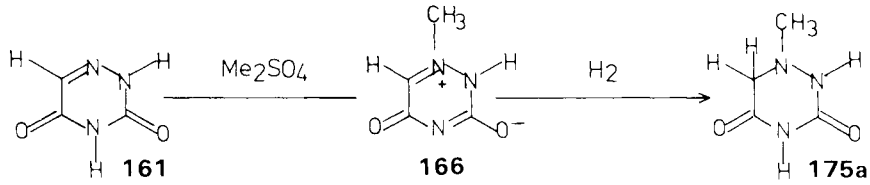
1,2,4-Triazine-3,5-diones are stable white crystalline compounds with high melting points. *N*- and *O*-alkylation or arylation generally lower the melting point. *N*-unsubstituted or *N*-2-substituted 1,2,4-triazine-3,5-diones are remarkably stable to both acid and base whereas *N*-4-substituted 1,2,4-triazine-3,5-diones can be hydrolyzed by base to semicarbazones of α-ketocarboxylic acids (207, 208, 210, 271, 290, 410, 411, 429). Fusco and Bianchetti (1137) reported the isolation of phenylacetic acid when 6-phenyl-1,2,4-triazine-3,5-dione was heated with potassium hydroxide to 330 to 360 °C. Reaction with

sodium hypobromide leads to the formation of α-monobromo- or α,α-dibromocarboxamides (207, 208, 237, 272) or the α-ketocarboxamides (394), probably via the α,α-dibromocarboxamides. 1,2,4-Triazine-3,5-diones form salts with metal ions; the mercury salts are used for the synthesis of sugar-substituted 1,2,4-triazine-3,5-diones.

Alkylation of 1,2,4-triazine-3,5-diones has been intensively studied (206, 207, 210, 211, 213, 234, 237, 264, 280, 281, 290, 301, 429, 434, 437, 441, 445, 446, 1084). Alkylation at N-2 as well as at N-4 has been reported. Studies by Gut and his collaborators (290) have shown that alkylation with methyl iodide starts at N-2, whereas alkylation with diazomethane or dimethyl sulfate gives mainly the isomeric 4-alkylated products. In all cases the dialkylated product is the 2,4-dialkyl-1,2,4-triazine-3,5-dione.



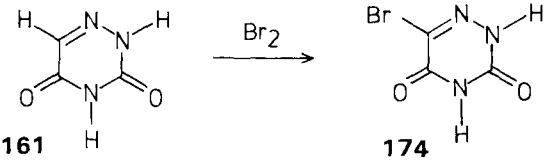
Alkylation of 1,2,4-triazine-3,5-diones (**161**) with dimethyl sulfate, without a base, at 135 to 145 °C led to the isolation of 1-methyl-5-oxo-1,2,4-triazine-3-olate (**166**) (441) the structure of which was proved by hydrogenation to 1-methyl-1,6-dihydo-1,2,4-triazine-3,5-dione (**175a**).



Reaction of 1,2,4-triazine-3,5-diones with formaldehyde, acetaldehyde, or formaldehyde and an amine led to the isolation of 2-substituted or 2,4-disubstituted 1,2,4-triazine-3,5-diones (170, 425, 443, 451, 1084).

Acylation of 1,2,4-triazine-3,5-diones starts at the nitrogen in the 2-position (436, 438, 445, 454), but acylation in the 4-position has also been reported (439). *N*-4-Sulfonyl-substituted 1,2,4-triazine-3,5-diones were obtained by reaction of 1,2,4-triazine-3,5-diones with sulfonyl chlorides (438).

6-Bromo-1,2,4-triazine-3,5-dione (**174**) is formed by reaction of 1,2,4-triazine-3,5-dione with bromine (216, 218, 251, 351, 497–500) in yields up to 72%; however decomposition is observed by reaction of bromine with the 6-methyl derivative (204). In the same way 6-chloro- or 6-iodo-1,2,4-triazine-3,5-diones can be synthesized (497). The bromine of 6-bromo-1,2,4-triazine-3,5-diones can be replaced by other nucleophiles (see halo-1,2,4-triazine-3,5-diones).

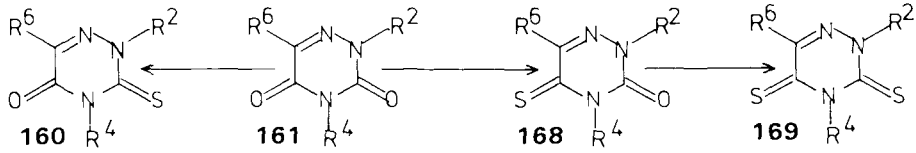


161 **174**

Cristescu and Marcus (218) observed that 1,2,4-triazine-3,5-dione cannot be nitrated.

Replacement of one or two oxo groups with chlorine by reaction with thionyl chloride (483, 486–488, 491) with thionyl chloride/dimethylformamide (492–494) or with phosphorus oxychloride/trimethylamine (341 489) is reported. *N*-Chloro-1,2,4-triazine-3,5-diones are formed by reaction of 1,2,4-triazine-3,5-diones with methyl *N,N*-dichlorocarbamidates (495, 496).

5-Thioxo-1,2,4-triazin-3-ones (**168**) (289, 327, 465, 481, 487, 488, 501, 503–505) and 1,2,4-triazine-3,5-dithiones (**169**) (251, 279, 324, 502, 503) are isolated by reaction of 1,2,4-triazine-3,5-diones with phosphorus pentasulfide. In one case the isomeric 3-thioxo-1,2,4-triazin-5-one (**160**) was obtained by this reaction (251).



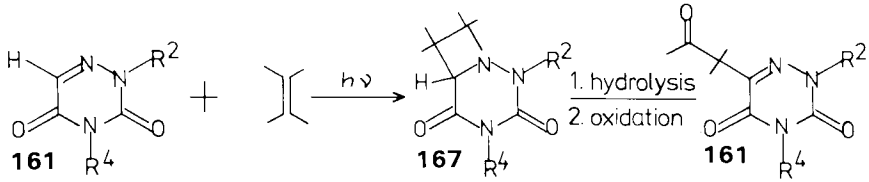
160 **161** **168** **169**

Although 1,2,4-triazine-3,5-diones are stable to water, photochemical hydration at the C=N double bond is reported (408, 412–416). Theoretical calculations have shown that it is a reaction of a triplet state (412, 415) and indicate an S_N1 mechanism for the hydration (412). Paramagnetic ions such as Cu^{2+}, Ni^{2+}, Co^{2+}, Mn^{2+}, or Cr^{3+} inhibit the photohydration (414, 415).

Contrary to the opinion of Bougault and Popovici (417) 1,2,4-triazine-3,5-diones can be reduced to 1,6-dihydro-1,2,4-triazine-3,5-diones (**175**) with hydrogen and a catalyst (290, 419–421, 423, 424), at a mercury dropping electrode (422), or electrochemically (418). Dihydro-1,2,4-triazine-3,5-diones (423) as well as ring-opened products (237, 264) are isolated by reduction with zinc and acid. Reduction with sodium amalgam forms ring-opened products (424).

Reaction of 6-phenyl-1,2,4-triazine-3,5-dione with phenylmagnesium bromide affords, depending on the reaction conditions, 5,6-diphenyl-1,2,4-triazin-3-one, 3,5,6-triphenyl-1,2,4-triazine, tetraphenyl-dihydro-1,2,4-triazine or 2,4,6-triphenyl-1,3,5-triazine, and 2,4,5,5-tetraphenylimidazole (66).

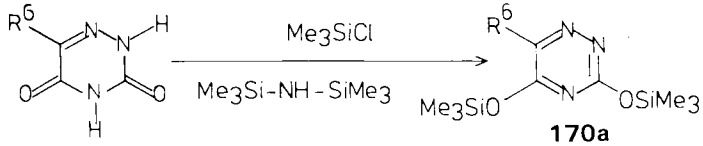
Photochemical [2 + 2] cycloaddition of olefins to the C_6N_1 double bond of 1,2,4-triazine-3,5-diones is reported by Swenton and Balchunis (338, 339) and by Hyatt and Swenton (508, 509), leading to the bicyclic compounds **167** which can be hydrolyzed and oxidized to 6-substituted 1,2,4-triazine-3,5-diones. If the 6-position is occupied 6,6-disubstituted 1,6-dihydro-1,2,4-triazine-3,5-diones are obtained (339).



161 **167** **161**

Amino-1,2,4-triazine-ones can be synthesized by reaction of 1,2,4-triazine-3,5-diones with *N,N*-dimethylchloroformimidinium chloride (492), by reaction of (trimethylsilyloxy)-1,2,4-triazinones with amines (506), by reaction of 3-alkoxy-1,2,4-triazin-5-ones with ammonia (458, 460), or by intermediate formation of chloro-1,2,4-triazinones and their reaction with amines (458, 460). In 3,5-dimethoxy-6-methyl-1,2,4-triazine only the methoxy group in the 5-position is substituted when reacted with the sodium salt of *p*-aminobenzenesulfonamide (489).

3,5-Bis[trimethylsilyloxy]-1,2,4-triazines (**170a**) are synthesized by reaction of 1,2,4-triazine-3,5-diones with trimethylsilyl chloride in the presence of hexamethyldisilazane. Compounds **170a** are used for the synthesis of sugar-substituted 1,2,4-triazine-3,5-diones (467–484). A review of the synthesis of 2-(β-D-ribofuranosyl)-1,2,4-triazine-3,5-diones by the trimethylsilyl method is given by Nishimura (479).



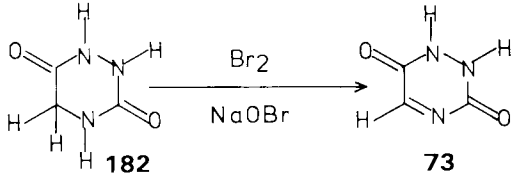
170a

In a large number of publications, especially publications dealing with sugar-substituted 1,2,4-triazines, reactions at the substituents are reported, such as removal of protecting groups, exchange of groups in the sugar moiety, or isolation and purification of sugar-substituted 1,2,4-triazine-3,5-diones. Since these reactions do not involve the 1,2,4-triazine system, they are not discussed

here, but for the sake of complete literature coverage are listed under references 452, 510–558, 1082, 1560, 2257, and 2278. All compounds described in these publications are included in Table II-8. A review of papers dealing with the preparation of 6-azanucleosides is published by Ferkas, Beranek, and Sorm (427). Compounds of the dinucleotide type, which contain a 1,2,4-triazine-3,5-dione moiety, are reported in references 409, 511, 521, 530, 531, 534, 541, 545, and 546.

F. 1,2,4-Triazine-3,6-diones (3,6-Dihydroxy-1,2,4-triazines)

At present only two publications dealing with the synthesis of 1,2,4-triazine-3,6-dione (**73**) are known (341, 559). In both cases the 1,2,4-triazine-3,6-dione was synthesized by oxidation of 4,5-dihydro-1,2,4-triazine-3,6-dione (**182**) with bromine (559) or sodium hypobromide (341). The melting points of the two



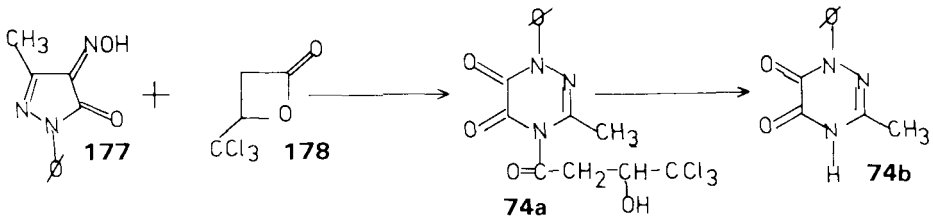
182 **73**

isolated compounds differ; Grundmann, Schroeder, and Rätz (341) published a melting point of 266 °C, but Gante (559) reports 241 to 243 °C. Gut and his collaborators (564) mentioned that the structure of the 4,5-dihydro-1,2,4-triazine-3,6-dione, used by Gante for the oxidation to 1,2,4-triazine-3,6-dione was incorrect. **73**, as reported by Gante, forms a monoacetyl derivative [m.p. 207 to 208 °C (dec.)] by reaction with acetic anhydride (559), the structure of which has not been determined.

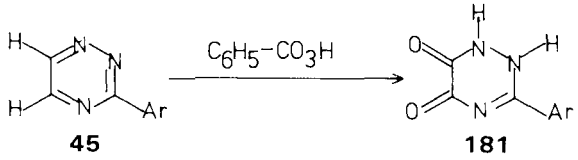
G. 1,2,4-Triazine-5,6-diones (5,6-Dihydroxy-1,2,4-triazines)

The first synthesis of a 1,2,4-triazine-5,6-dione was published in 1969 by Luknitskii and Vovsi (560). They isolated 3-methyl-1-phenyl-4-(4,4,4-trichloro-3-hydroxy-butyryl)-1,2,4-triazine-5,6-dione (**74a**) (m.p. 160–161 °C) from the reaction of 3-methyl-1-phenyl-4-isonitroso-5-pyrazolone (**177**) with the β-lactam (**178**). Reaction of **74a** with ammonia removed the 4-acyl group and led to the isolation of 3-methyl-1-phenyl-1,2,4-triazine-5,6-dione (**74b**) (m.p. 145 to 146 °C).

Neunhoeffer and Frühauf (103) in 1972 published the oxidation of 3-phenyl- and 3-(4-tolyl)-1,2,4-triazine (**45a, b**) with perbenzoic acid, leading to the



isolation of 3-phenyl- (**181a**) (m.p. 305 to 306 °C) and 3-(4-tolyl)-1,2,4-triazine-5,6-dione (**181b**) (m.p. 318 to 319 °C), respectively.



Hydrolysis of 6-amino-3-(2-pyridyl)-1,2,4-triazin-5-one was used for the synthesis of 3-(2-pyridyl)-1,2,4-triazine-5,6-dione (183).

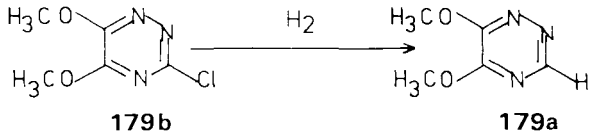
The following spectral data are reported for 1,2,4-triazine-5,6-diones:

74a: C=O stretching vibration at 1710, 1780, and 1805 cm^{-1}, ultraviolet absorption at 309 (3.96) and 255 nm (4.22).

74b: C=O stretching vibration at 1700 and 1710 cm^{-1}, ultraviolet absorption at 309 (4.12) and 255 nm (4.37).

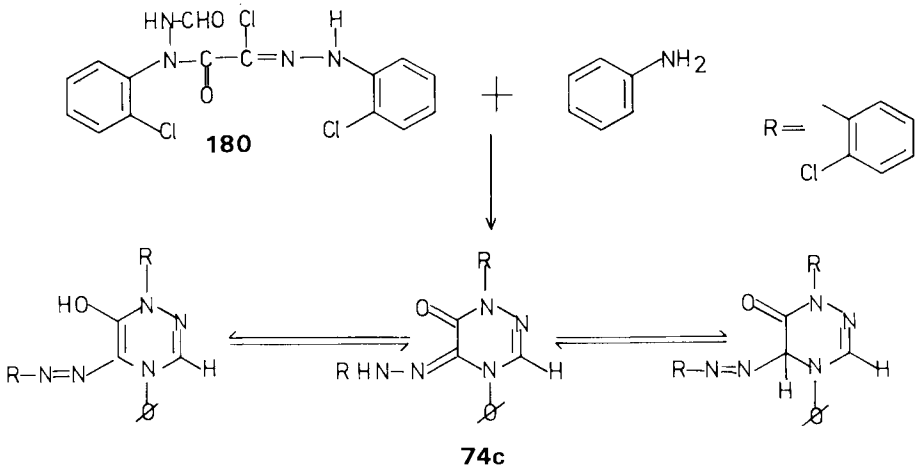
181: C=O stretching vibration at 1630 cm^{-1}, further bands at 3540, 3460, 3200, and 3080–3060 cm^{-1}, 2H singlet at -2.40τ in the PMR spectrum (DMSO-D_6).

5,6-Dimethoxy-1,2,4-triazine (**179a**) (m.p. 53 °C) was obtained by Neunhoeffer and Lehmann (678) through hydrogenation of 3-chloro-5,6-dimethoxy-1,2,4-triazine (**179b**).



Fusco and Romani (1567) cyclized compound **180** with aniline and isolated a substance (**74c**) (m.p. 216 to 217 °C) which can be treated as the 5-(2-chlorophenyl)hydrazone of 4-phenyl-1-(2-chlorophenyl)-1,2,4-triazine-5,6-dione.

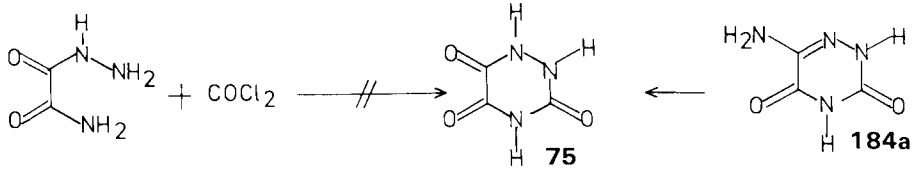
No further studies on the structure, the physical properties, or the chemistry of 1,2,4-triazine-5,6-diones have so far been reported.



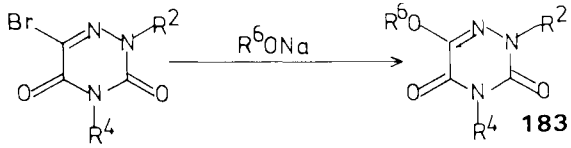
H. 1,2,4-Triazine-3,5,6-triones (3,5,6-Trihydroxy-1,2,4-triazines)

1. *Preparation*

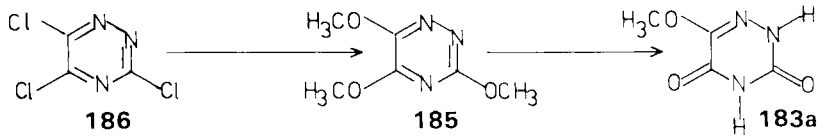
Attempts of Rätz and Schroeder (561) to prepare the 1,2,4-triazine-3,5,6-trione (**75**) by reaction of oxamic acid hydrazide with phosgene were unsuccessful. Chang isolated this compound by basic hydrolysis of 6-amino-1,2,4-triazine-3,5-dione (**184a**) (497). Lower yields of **75** could be obtained via diazotization of the amino compound in concentrated hydrochloric acid.



A number of 6-alkoxy-1,2,4-triazine-3,5-diones (**183**) were prepared by reaction of 6-bromo-1,2,4-triazine-3,5-diones with sodium alcoholates (562). No reaction took place between 6-bromo-1,2,4-triazine-3,5-dione and sodium methoxide or ethoxide. 6-Bromo-2-(2-cyanoethyl)- and 6-bromo-4-benzyl-1,2,4-triazine-3,5-dione also did not react under analogous conditions. 6-Bromo-2,4-bis(2-cyanoethyl)-1,2,4-triazine-3,5-dione reacted readily with sodium ethoxide to form 6-ethoxy-1,2,4-triazine-3,5-dione. The nucleophilic substitution of the bromine atom in 6-bromo-1,2,4-triazine-3,5-dione by action of aqueous sodium hydroxide is accompanied by ring cleavage.



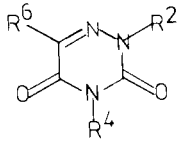
Piskala, Gut, and Sorm (563, 1565) synthesized 3,5,6-trimethoxy-1,2,4-triazine (**185**) (m.p. 124 to 125 °C) by reaction of 3,5,6-trichloro-1,2,4-triazine (**186**) with sodium methoxide; hydrolysis of **185** yields 6-methoxy-1,2,4-triazine-3,5-dione (**183a**).



2. *Compound Survey*

Compounds of this class reported in the literature are listed in Table II-11.

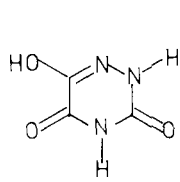
TABLE II-11. 6-HYDROXY-1,2,4-TRIAZINE-3,5(2*H*, 4*H*)-DIONES

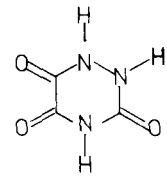


R^2	R^4	R^6	m.p. (°C)	Refs.
H	H	OH	228–230	497
H	H	OCH_3	285–286	1565, 1566
H	H	OC_2H_5	218–219	562
H	CH_3	OC_2H_5	198–200	562
CH_3	CH_3	OC_2H_5	94–95	562
CH_2CH_2CN	H	OCH_3	172–174	562
CH_2CH_2CN	H	OC_2H_5	143–145	562
CH_2CH_2CN	H	OC_4H_9	142–144	562
CH_2CH_2CN	CH_2CH_2CN	OC_2H_5	67–68	562
CH_2CH_2CN	$C_6H_5CH_2$	OC_2H_5	75–76	562
$C_6H_5CH_2$	H	OC_2H_5	166–168	562
$C_6H_5CH_2$	$C_6H_5CH_2$	OC_2H_5		562

3. *Physical Properties*

At present only a small amount of data on the structure and physical properties of 1,2,4-triazine-3,5,6-triones is available. Chang (497) prefers the 6-hydroxy-1,2,4-triazine-3,5-dione structure because of two very sharp doublets in the double bond absorption region of the infrared spectra.



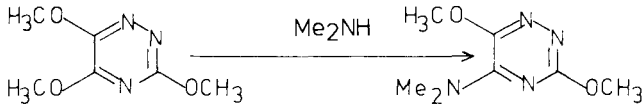


The *N*-2-substituted 6-alkoxy-1,2,4-triazine-3,5-diones display the band of a free N–H group in practically the same region (3370 cm^{-1}) as the 2-methyl-1,2,4-triazine-3,5-dione (3374 cm^{-1}) whereas *N*-4-substituted 6-alkoxy-1,2,4-triazine-3,5-diones show the N–H stretching vibration at 3430 cm^{-1} which is the same region as for 4-methyl-1,2,4-triazine-3,5-dione (3424 cm^{-1}) (562). Three C=O stretching vibrations are observed for *N*-2-substituted 6-alkoxy-1,2,4-triazine-3,5-diones at 1733 to 1736, 1710 to 1711, and 1608 to 1613 cm^{-1}.

The pK_a value for 6-hydroxy-1,2,4-triazine-3,5-dione was found to be 2.95 (497). The same compound shows an absorption maximum at 246 nm (4960) in 0.1 *N* hydrochloric acid and at 250 nm (2886) in 0.1 *N* sodium hydroxide solution (497).

4. *Reactions*

Reaction of **185** with dimethylamine affords 5-(dimethylamino)-3,6-dimethoxy-1,2,4-triazine (1566).



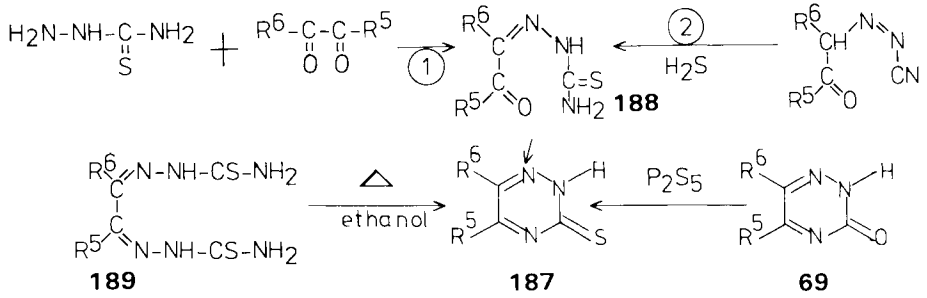
185

III. 1,2,4-TRIAZINETHIONES AND 1,2,4-TRIAZINESELENONES

A. 1,2,4-Triazine-3-thiones (3-Mercapto-1,2,4-triazines)

1. *Preparation*

1,2,4-Triazine-3-thiones (**187**) are well-known compounds. For their synthesis thiosemicarbazones (**188**) of 1,2-dicarbonyl compounds are cyclized in basic media (127–129, 131, 134, 139, 140, 147, 154, 156, 158, 565–581, 1072). The synthesis of the thiosemicarbazones (**188**) is achieved in two different ways: (1) reaction of a 1,2-dicarbonyl compound with thiosemicarbazide, and (2) reaction of α-cyano ketones with hydrogen sulfide.



In the reaction of 1,2-dicarbonyl compounds with thiosemicarbazide it is not necessary to isolate the initially formed thiosemicarbazide (**188**); direct cyclization can also be achieved by heating the two components in acetic acid (156).

1,2-Bisthiosemicarbazones (**189**) can be converted to 1,2,4-triazine-3-thiones (**187**) by heating in ethanol (571). 1,2,4-Triazine-3-thiones (**187**) were also obtained when monoximes of 1,2-dicarbonyl compounds were heated with thiosemicarbazide (292).

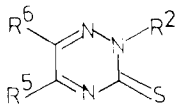
Reaction of 1,2-dicarbonyl compounds with *S*-methylthiosemicarbazide was used for the synthesis of 3-(methylmercapto)-1,2,4-triazines (14, 175).

Treatment of 1,2,4-triazine-3-ones (**69**) with phosphorus pentasulfide also yields 1,2,4-triazine-3-thiones (**187**) (65, 68, 189).

When 6-phenyl-3-thioxo-1,2,4-triazin-5-one is heated for 2 hrs with phenylmagnesium bromide in dry benzene and kept overnight at room temperature 5,6-diphenyl-1,2,4-triazine-3-thione is isolated in 40% yield (584).

TABLE II-12. 1,2,4-TRIAZINE-3-THIONES

A. 1,2,4-Triazine-3(2H)-thiones

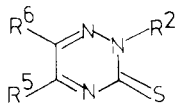


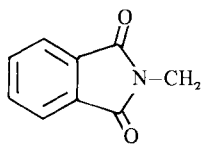
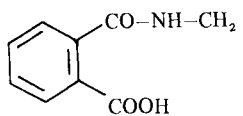
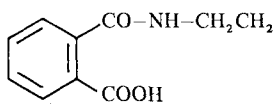
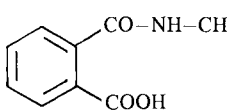
R^2	R^5	R^6	m.p. (°C)	Refs.
H	H	H	310 (dec.)	579
H	H	H	190	189
			242	292
H	CH_3	H		579
H	CH_3	CH_3	190	579
			191 (dec.)	567
			237	292
			249 (dec.)	572
H	n-C_5H_{11}	H	97	147
H	C_6H_{11}	H	225	147
H	$C_6H_5-CH_2$	H	169–170	147
H	C_6H_5	H	197–198	158
			199	717
			200	581
			200–202	151
			201–202	189
				567, 575, 577
H	C_6H_5	CH_3	169–172	717
			172	147
			194	158

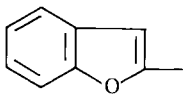
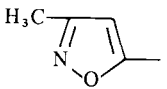
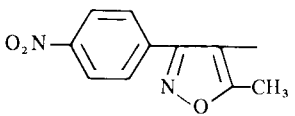
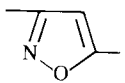
H	C_6H_5	C_2H_5	175	147
			197 (dec.)	579
H	C_6H_5	C_6H_5	200–201	569
			205	717
			209–210	572
			219–220	154
			225–228 (dec.)	156
			232	68
			233	579
			240	576, 584
			266	578
			302	140
H	4-C_6H_5–C_6H_4	H	215	147
H	2-Naphthyl	H	233–235	717
			234–235	147
H	Fluorenyl	H	290 (dec.)	128
H	Phenanthryl	H	269–270	128
H	4-O_2N–C_6H_4	H	224–225	567, 568, 1072
H	4-Cl–C_6H_4	H	208–209	158, 1072
H	4-Br–C_6H_4	H	202–203	158, 1072
H	4-HO–C_6H_4	H	243–244	147
H	4-HO–C_6H_4	4-HO–C_6H_4	270 (dec.)	576
H	2-CH_3O–C_6H_4	2-CH_3–C_6H_4	227–228	570
H	4-CH_3O–C_6H_4	4-CH_3–C_6H_4	219–220	717
			226–227	570
			255 (dec.)	576
H	3,4-$CH_2O_2C_6H_3$	3,4-$CH_2O_2C_6H_4$	225–226	570
H	4-EtS–C_6H_4	H		567, 568
H	4-H_2N–C_6H_4	H	237–238	567, 568
H	4-AcHN–C_6H_4	H	229–230	567, 568
H	4-AcHN–C_6H_4	4-AcHN–C_6H_4	315 (dec.)	576
H	4-NC–C_6H_4	H	239–240	567, 568
H	4-$C_2H_5SO_2$–C_6H_4	H	221–222	567, 568

TABLE II-12. (*continued*)

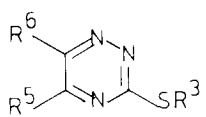
A. 1,2,4-Triazine-3(2H)-thiones



R^2	R^5	R^6	m.p. (°C)	Refs.
H	$CH_2-COOC_2H_5$	$CH_2-COOC_2H_5$	162	571
H		H	289–291	573
H		H	297–298	573
H		H	273–275	573
H		H	146	573

H	2-Furyl	H	200–201	569
			211–213	131
H	2-Thienyl	H	234	147
			238	129
H	2-Selenienyl	H	242–243 (dec.)	134
H		H		139
H		H	188–189	147
H		H	216	127
CH_3		H	188–189	147

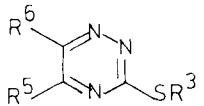
B. 3-Mercapto-1,2,4-triazines



R^3	R^5	R^6	m.p. (°C)	Refs.
CH_3	H	H	31–33	14
			b.p. 88–90/0.4	14

TABLE II-12. *(continued)*

B. 3-Mercapto-1,2,4-triazines



R^3	R^5	R^6	m.p. (°C)	Refs.
CH_3	H	CH_3	43–44	175
CH_3	H	C_6H_5	155	292
CH_3	CH_3	H	69–74	14
			74–75	175
			b.p. 60–63/0.3	14
CH_3	CH_3	CH_3	138–142	583
			b.p. 105–106/0.3	14
CH_3	CH_3	C_6H_5	51–52	175
CH_3	C_6H_5	H	94	158
			99–100.5	14
CH_3	C_6H_5	C_6H_5	119	68
			119–120	576
			121–122.5	14
CH_3	4-Cl–C_6H_4	H	163	158
CH_3	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	152	68, 157
			154	576
CH_3	4-AcHN–C_6H_4	4-AcHN–C_6H_4	347–348	576
CH_2COOH	C_6H_5	H	193	158
CH_2COOCH_3	C_6H_5	H	91	158
$CH_2COOC_2H_5$	C_6H_5	C_6H_5	95	293
$CH_2COOC_2H_5$	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	139	157
CH_2–CO–C_6H_5	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	151	157

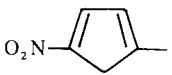
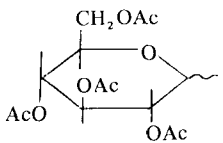
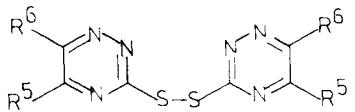
C_2H_5	H	H	210 (dec.)	579
n-C_3H_7	H	H	211	579
i-C_3H_7	H	H	197 (dec.)	579
			208	579
C_3H_5 (allyl)	H	H	197 (dec.)	579
n-C_4H_9	H	H	196 (dec.)	579
			212	579
i-C_4H_9	H	H	203 (dec.)	579
			217	579
i-C_5H_{11}	H	H	203	579
i-C_5H_{11}	CH_3	CH_3	102	579
$C_{18}H_{37}$	H	H	151	579
$C_{18}H_{37}$	CH_3	CH_3		579
$C_6H_5CH_2$	H	H	208 (dec.)	579
$C_6H_5CH_2$	CH_3	CH_3	186	579
2,4-$(O_2N)_2C_6H_3$	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	145	157
	H	H		582
$(C_4H_9)_3Sn$	C_6H_5	C_6H_5		585
	C_6H_5	C_6H_5	182	293

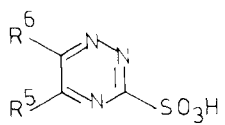
TABLE II-12. (*continued*)

C. Bis(1,2,4-triazin-3-yl) disulfides



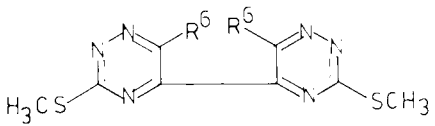
R^5	R^6	m.p. (°C)	Refs.
C_6H_5	H	183	581
		189	158
C_6H_5	C_6H_5	193–194	68
2-CH_3O–C_6H_4	2-CH_3O–C_6H_4	199	68
4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	205	68
2-Furyl	H	205–206	131

D. 1,2,4-Triazinyl-3-sulfonic acids



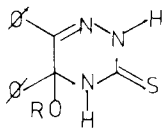
R^5	R^6	m.p. (°C)	Refs.
C_6H_5	C_6H_5	225	68
2-CH_3O–C_6H_4	2-CH_3O–C_6H_4	217	68
4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	259	68

E. 5,5′-Bi(3-mercapto-1,2,4-triazines)



R^6	m.p. (°C)	Refs.
H	165–166	175
	168.5–170	109, 110
CH_3	116.5–118	109, 110

F. Products of covalent addition of alcohols to 1,2,4-triazine-3-thiones



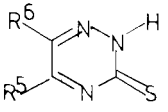
R	m.p. (°C)	Refs.
CH_3		133, 168
C_2H_5		168

2. *Compound Survey*

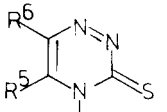
Table II-12 lists the compounds of this class reported in the literature.

3. *Properties*

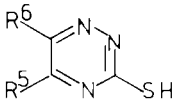
1,2,4-Triazine-3-thiones (**187**) (3-mercapto-1,2,4-triazines) are yellow to red, stable crystalline compounds with high melting points. They are soluble in most organic solvents.



187a



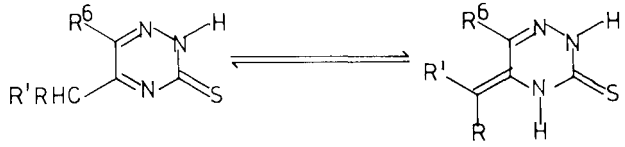
187b



187c

Three tautomeric structures can be discussed for these compounds, **187a**, **187b**, and **187c**. The infrared spectrum of 5,6-diphenyl-1,2,4-triazine-3-thione shows one sharp NH band at 3120 cm^{-1} (KBr) or 3380 cm^{-1} ($CHCl_3$) and no SH band could be observed in either medium. Therefore the tautomeric structure **187c** can be excluded (140). The comparison of the ultraviolet spectra of 5-phenyl-1,2,4-triazine-3-thione and 2-methyl-5-phenyl-1,2,4-triazine-3-thione gives the same result (158) and led to the conclusion that **187a** is the predominant tautomeric structure. The mass spectrum of 5,6-diphenyl-1,2,4-triazine-3-thione was published by Palmer, Preston, and Stevens (165).

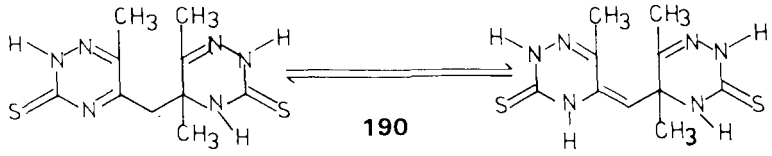
Adams and Shepherd (565) have shown that 5-alkyl-1,2,4-triazine-3-thiones display an unusual tautomerism of an α-proton to a ring nitrogen. The presence of the alkylidene groups is demonstrated by the PMR spectra in DMSO-D_6. X-ray crystallography of 6-methyl-5-ethyl-1,2,4-triazine-3-thione has confirmed the tautomeric structure (565). This tautomerism could not be observed (565) in 3-(methylmercapto)-1,2,4-triazines.

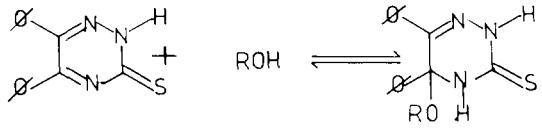


Attempts of these authors to prepare 5,6-dimethyl-1,2,4-triazine-3-thione failed; instead of the required substance they isolated the dimeric compound **190**, as was shown by PMR spectroscopy (565) and mass spectroscopy. Covalent

addition of alcohols to the 4,5 double bond of 5,6-diphenyl-1,2,4-triazine-3-thione was observed by Vinot and M'Packo (133, 168).

Polarographic studies of **187** were reported by Polonsky and his group (792).

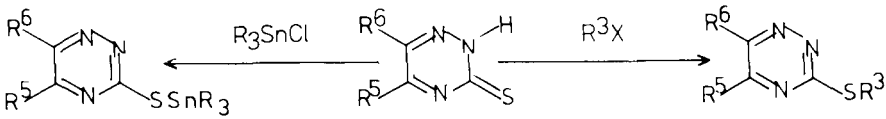




4. *Reactions*

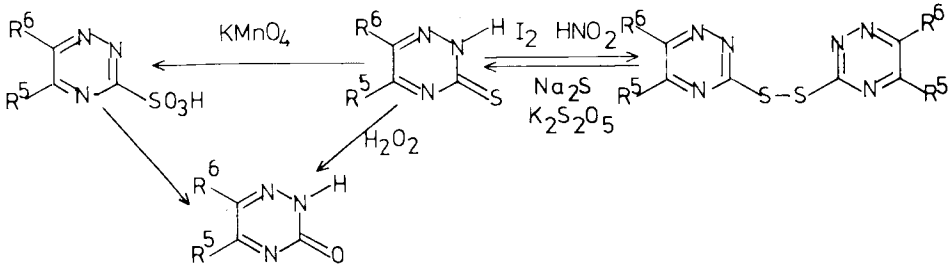
1,2,4-Triazines-3-thiones are weak acids and form red salts with alkali metal ions (147, 581). They form salts or complexes with heavy metal ions (140, 154, 576, 579, 581, 589–591). 1,2,4-Triazine-3-thiones form deep red solutions in concentrated sulfuric or hydrochloric acid; they are reprecipitated unchanged by addition of water to the acid solution (154, 581).

Alkylation of 1,2,4-triazine-3-thiones occurs exclusively at the sulfur, leading to 3-mercapto-1,2,4-triazine derivatives (68, 157, 158, 576, 579, 582–584). By reaction with trialkyistannyl chloride 3-[(trialkylstanny)mercapto]-1,2,4-triazines were obtained (585).



By oxidation of 1,2,4-triazine-3-thiones with iodine (68, 131, 158) or nitrous acid (581) disulfides were obtained which can be reduced by $K_2S_2O_5$ or Na_2S; oxidation with hydrogen peroxide (68, 156, 576) or potassium permanganate (154, 156, 571) led to the isolation of 1,2,4-triazine-3-ones (see Section II-B) (130, 157–159). The oxidation with $KMnO_4$ initially yields 1,2,4-triazine-3-sulfonic acids (68) which were isolated in a few cases.

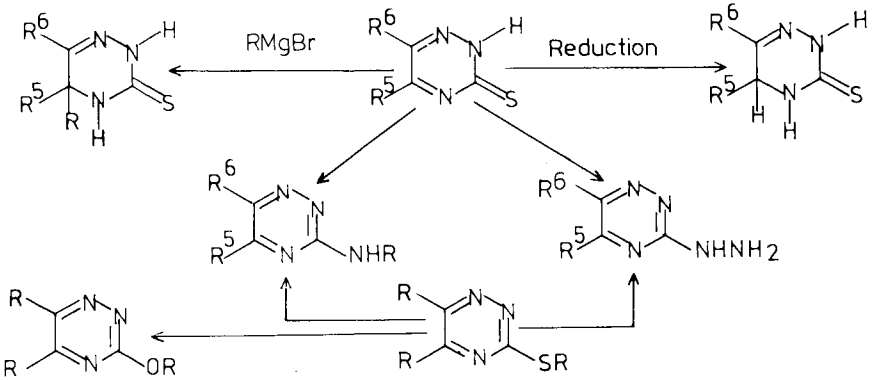
Oxidation of 1,2,4-triazine-3-thiones with 25% nitric acid destroyed the heterocyclic nucleus and diketones were obtained (156).



Reduction of 1,2,4-triazine-3-thione occurs at the 4,5 double bond, leading to 4,5-dihydro-1,2,4-triazine-3-thiones (168, 570, 584, 588).

In the same way if 1,2,4-triazine-3-thiones were reacted with Grignard reagents (584), 4,5-dihydro-1,2,4-triazine-3-thiones were isolated (133, 168, 175).

The 3-mercapto group of 1,2,4-triazine-3-thiones or 3-(alkylmercapto)-1,2,4-triazines can be exchanged with an amino group (157, 293, 576, 577) or hydrazino group (583, 586, 587, 717) by reaction with an amine or hydrazine. Replacement of the alkylmercapto group by an alkoxy group is also reported (14, 159).

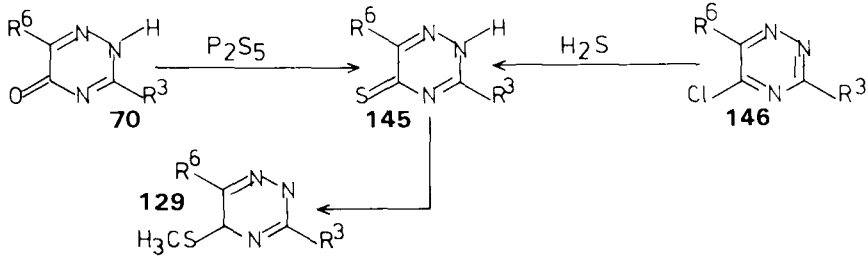


No identifiable products were obtained from the reaction of 1,2,4-triazine-3-thiones with mercury oxide or lead (II) oxide (68).

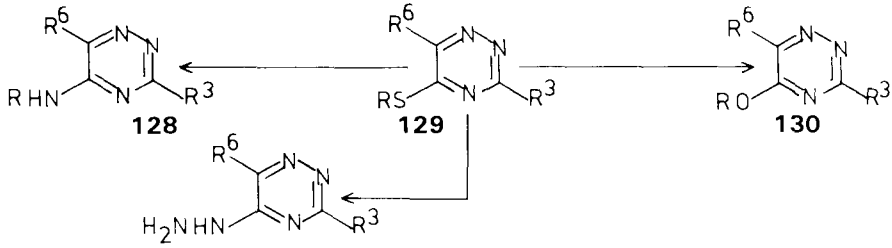
B. 1,2,4-Triazine-5-thiones (5-Mercapto-1,2,4-triazines)

1,2,4-Triazine-5-thiones (**145**) [m.p. $R^3 = H$, $R^6 = CH_3$, 180.5 °C, (dec.) (489); 186 to 187 °C (189); hydrochloride, 173 to 174 °C; ammonium salt, 177 to 178 °C (189); $R^3 = H$, $R^6 = C_2H_5$, 184 to 185 °C (489); $R^3 = H$, $R^6 = C_3H_7$, 152.5 to 153 °C (489); $R^3 = CH_3$, 228 °C (188)] were synthe-

sized by reaction of the appropriate 1,2,4-triazin-5-ones (**70**) with phosphorus pentasulfide. Fusco and Rossi (63) obtained 3,6-diphenyl-1,2,4-triazin-5-thione (**145**) ($R^3 = R^6 = C_6H_5$) as the monohydrate from the reaction of 5-chloro-3,6-diphenyl-1,2,4-triazine (**146**) with hydrogen sulfide.



Alkylation of **145** yields the 5-(methylmercapto)-1,2,4-triazines (**129**) [m.p.: $R^3 = H$, $R^6 = CH_3$, 56.5 to 57.5 °C (489); $R^3 = H$, $R_6 = C_2H_5$, 36 to 37.5 °C (489); $R^3 = H$, $R^6 = C_3H_7$, 105 to 107 °C; $R^3 = R^6 = CH_3$ (188)]. The methylmercapto group in **129** can be replaced by a methoxy, amino, or hydrazino group (188, 489).



C. 1,2,4-Triazine-6-thiones (6-Mercapto-1,2,4-triazines)

In one review of a search of *Chemical Abstracts* (59), 3-methyl-1,2,4-triazine-6-thione is mentioned. This is probably a mistake and the compound discussed is in fact the 6-methyl-1,2,4-triazine-3-thione. Therefore this reference is included in the section on 1,2,4-triazine-3-thiones.

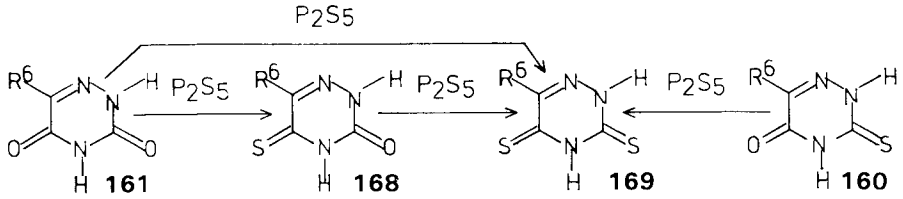
D. 1,2,4-Triazine-3,5-dithiones (3,5-Dimercapto-1,2,4-triazines)

1. *Preparation*

1,2,4-Triazine-3,5-dithiones (**169**) are mainly obtained by two methods:

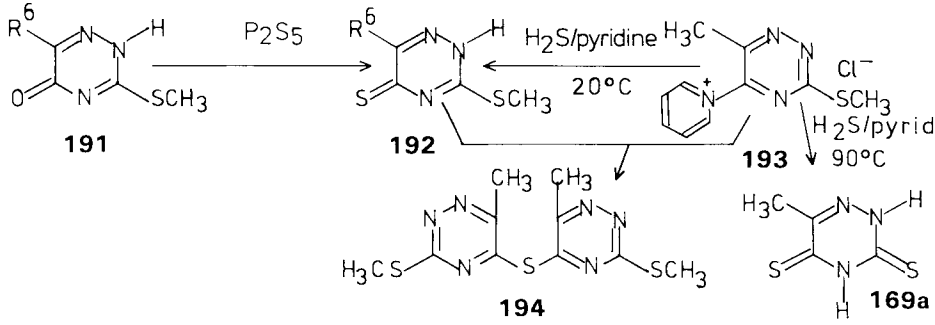
1. Reaction of 1,2,4-triazine-3,5-diones (**161**) with phosphorus pentasulfide in

tetraline (251, 324, 502), pyridine (251, 324), or xylene (289). The two oxygens are replaced stepwise, so it is possible to isolate the initially formed 5-thioxo-1,2,4-triazin-3-one (324, 327) (**168**).

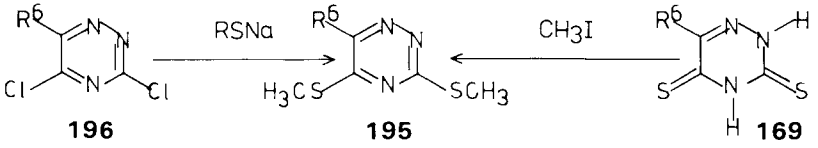


2. Reaction of 3-thioxo-1,2,4-triazin-5-ones (**160**), which are easily obtained from α-ketocarboxylic acids and thiosemicarbazide, with phosphorus pentasulfide (189, 251, 289, 304, 489, 503, 592, 593, 595, 599). For this transformation pyridine is usually used as the solvent.

Treatment of 3-(methylmercapto)-1,2,4-triazin-5-ones (**191**) with phosphorus pentasulfide was used for the synthesis of 3-(methylmercapto)-1,2,4-triazine-5-thiones (**192**) (279, 489).



Reaction of compound **193** with hydrogen sulfide in pyridine at 20 °C yields **192**, but the same reaction at 90 °C affords the 6-methyl-1,2,4-triazine-3,5-dithione (**169a**) (1096, 1103). Interaction of **192** with **193** yields the sulfide **194** (1096, 1103) (m.p. 123 to 124 °C) (1103). 3,5-Bis(methylmercapto)-1,2,4-triazines (**195**) were obtained by reaction of 3,5-dichloro-1,2,4-triazines (**196**) with sodium methylmercaptide (341). The initially formed methylmercapto-chloro-1,2,4-triazines can be isolated; the structure given for these compounds is probably the wrong isomeric form.



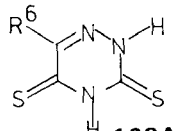
195 can also be obtained by alkylation of 3-(alkylmercapto)-1,2,4-triazine-5-thiones (**192**) or 1,2,4-triazine-3,5-dithiones (**169**) (279, 289, 594–596, 599, 1103, 1564) (see discussion of reactions).

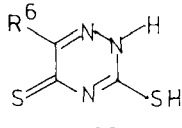
2. *Compound Survey*

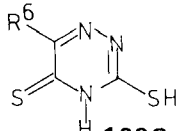
The 1,2,4-triazine-3,5-dithiones reported in the literature are listed in Table II-13.

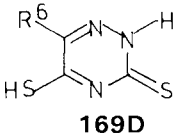
3. *Physical Properties*

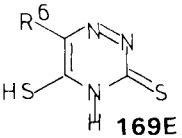
As for 1,2,4-triazine-3,5-diones six tautomeric structures are also possible for the 1,2,4-triazine-3,5-dithiones (**169A** to **169F**). Derivatives of the structures **169A**–**169E** are known; for one compound no distinction between structure **169E** and **169F** was made.

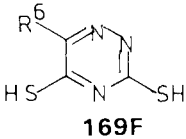

169A


169B


169C


169D


169E


169F

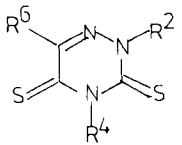
The infrared spectra of 1,2,4-triazine-3,5-dithiones show no band for the S–H stretching vibration in the 2600 to 2550 cm^{-1} region (503) but a band at 1540 cm^{-1} for an HN–C=S group and a band for a C=N vibration at 1585 cm^{-1}. This confirms that the bisthioxo tautomer **169A** is the predominant form.

Most 1,2,4-triazine-3,5-dithiones show two absorption maxima in the ultraviolet spectra around 280 and 320 nm (251, 324, 503, 601). The absorptivity is around 4.5 and 4.1. Also from the ultraviolet spectra it was concluded that the tautomeric form **169A** is the predominant form in neutral aqueous solution (601).

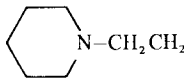
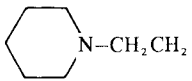
1,2,4-Triazine-3,5-dithiones are orange to deep red compounds which are typical weak acids. pK_a values were determined (289, 601) for 1,2,4-triazine-3,5-dithione (5.66), 2-methyl-1,2,4-triazine-3,5-dithione (5.76), and 4-methyl-1,2,4-triazine-3,5-dithione (7.37).

TABLE II-13. 1,2,4-TRIAZINE-3,5-DITHIONES

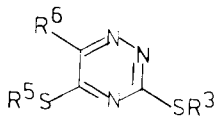
A. 1,2,4-Triazine-3,5(2H,4H)-dithiones



R^2	R^4	R^6	m.p. (°C)	Refs.
H	H	H	209–210	324
			217–218	502
			218	289
			225–226	503, 600
			230	593
				1096
H	H	CH_3	215–217	503, 593, 599, 600
			217–218	324, 1103
			217–219	289
				595
H	H	C_2H_5	185–186	503, 600
				189, 595
H	H	n-C_3H_7	160–161	503, 600
H	H	i-C_3H_7	226–228	503, 600
H	H	n-C_7H_{15}	122–123	503, 600
H	H	$C_6H_5CH_2$	181–182	503, 600
H	H	C_6H_5	234–235	279, 503, 600
			240–242	289
H	H	4-Pyridyl	275	592
H	CH_3	H	162–163	289
			164	304

H	CH_3	CH_3	128–129	251
H	CH_3	C_6H_5		279
CH_3	H	H	148	289
			156–157	304
			156–158	251
CH_3	H	CH_3	223–225	251, 304
CH_3	H	C_6H_5	194–196	304
CH_3	CH_3	H	61–62	304, 289[a]
CH_3	CH_3	CH_3	74–75	251
			75	304
CH_3	CH_3	C_6H_5	97–99	279
			100–101	304
		CH_3	92–93	594

B. 3,5-Dimercapto-1,2,4-triazines

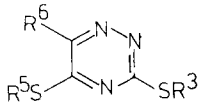


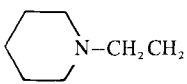
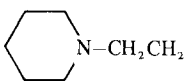
R^3	R^5	R^6	m.p. (°C)	Refs.
CH_3	CH_3	H	52 (subl.)	289
			53–54	1564
			56–57	503
			57	341

[a]The compound described in this references has another structure (304).

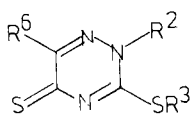
TABLE II-13. (*continued*)

B. 3,5-Dimercapto-1,2,4-triazines



R^3	R^5	R^6	m.p. (°C)	Refs.
CH_3	CH_3	CH_3	75–76	599
			76–78	1564
			78–79	1103
				489, 595
CH_3	CH_3	C_6H_5	134–136	279
			140–142	596
CH_3	C_6H_5	CH_3		1096
		CH_3	92–93	594

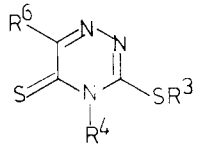
C. 3-Mercapto-1,2,4-triazine-5(2H)-thiones



R^2	R^3	R^6	m.p. (°C)	Refs.
H	CH_3	CH_3	178–179	1096, 1103
			221	489

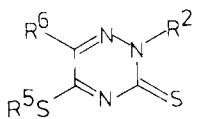
H	CH_3	C_6H_5	186–188	279
CH_3	CH_3	H	159–160	289
CH_3	CH_3	C_6H_5	157–158	279

D. 3-Mercapto-1,2,4-triazine-5(4H)-thiones



R^3	R^4	R^6	m.p. (°C)	Refs.
CH_3	CH_3	H	112	304
			115–116	279
CH_3	CH_3	C_6H_5	128–129	279

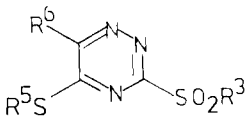
E. 5-Mercapto-1,2,4-triazine-3(2*H*)-thiones



R^2	R^5	R^6	m.p. (°C)	Refs.
H	CH_3	CH_3	174–176	594
CH_3	CH_3	C_6H_5	177–178	279

TABLE II-13. (*continued*)

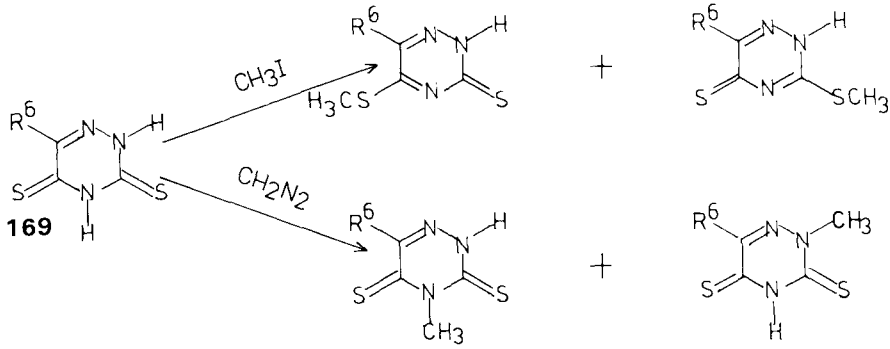
F. 5-Mercapto-3-sulfonyl-1,2,4-triazines



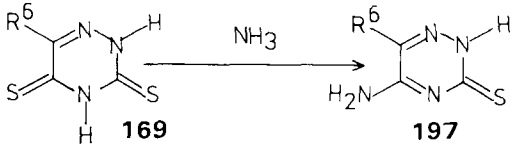
R^3	R^5	R^6	m.p. (°C)	Refs.
CH_3	CH_3	CH_3	157–158	596, 595

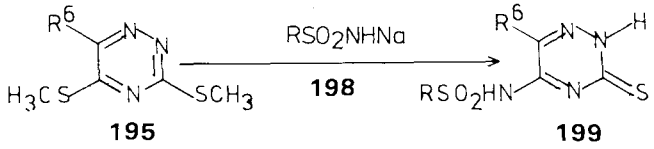
4. *Reactions*

Alkylation of 1,2,4-triazine-3,5-dithiones (**169**) and their derivatives proceeds very readily at room temperature. Alkylation with methyl iodide in aqueous alkali occurs at a sulfur atom, leading to a methylmercapto group (279, 289, 304, 595, 596, 599, 1096, 1103, 1564). Reaction of 1,2,4-triazine-3,5-dithiones (**169**) or their derivatives with diazomethane gives *N*-methylated products (289, 304).



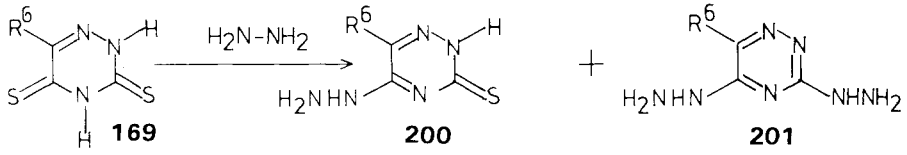
Ammonia can replace one thioxo group in **169**; the isolated products were identified as 5-amino-1,2,4-triazine-3-thiones (**197**) (251, 324, 502). Reaction of 3,5-bis(methylmercapto)-1,2,4-triazines (**195**) with sodium sulfonamides (**198**) is a method for the synthesis of 5-(sulfonylamino)-1,2,4-triazine-3-thiones (**199**) (489, 598). Benzylamine (282) and urea (598) also replace the 5-methylmercapto group in **195**.

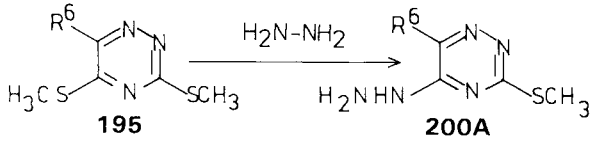




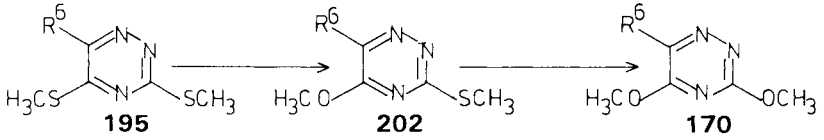
Hydrazine reacts equally well with both 1,2,4-triazine-3,5-dithiones (503, 593–595, 597, 598, 600) and 3,5-bis(methylmercapto)-1,2,4-triazines (503, 595, 599). In the first case 5-hydrazino-1,2,4-triazine-3-thiones (**200**) (595, 597, 598) were obtained as well as 3,5-dihydrazino-1,2,4-triazines (**201**) (189, 503,

593–595, 597, 598, 600); in the second case only 5-hydrazino-3-(methylmercapto)-1,2,4-triazines (**200A**) were isolated (503, 595, 599).

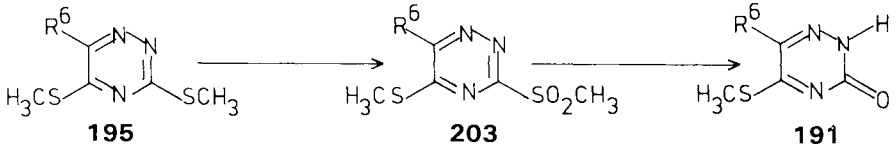




1,2,4-Triazine-3,5-dithiones also react with hydrazides (597). Sodium methoxide also replaces first the 5-methylmercapto group in **195**, leading to 5-methoxy-3-(methylmercapto)-1,2,4-triazines (**202**) which could be transformed into 3,5-dimethoxy-1,2,4-triazines (**170**) (305, 1564).



Oxidation of 3,5-bis(methylmercapto)-1,2,4-triazines (**195**) with potassium permanganate gives 5-(methylmercapto)-3-methylsulfonyl-1,2,4-triazines (**203**) which can be hydrolyzed to 5-(methylmercapto)-1,2,4-triazine-3-ones (**191**) (595, 596).



The hydrolytic formation of 1,2,4-triazine-3,5-diones (289, 304, 596) from 1,2,4-triazine-3,5-dithiones (**169**) is the reverse reaction of the synthesis of **169** and has no synthetic value. Hydrolysis of 3-(alkylmercapto)-1,2,4-triazine-5-thiones (**192**) yields 5-thioxo-1,2,4-triazin-3-ones (279) whereas hydrolysis of 5-(alkylmercapto)-1,2,4-triazine-3-thiones leads to 3-thioxo-1,2,4-triazin-5-ones (279).

E. 1,2,4-Triazine-3,6-dithiones (3,6-Dimercapto-1,2,4-triazines)

No 1,2,4-triazine-3,6-dithione could be found in the literature.

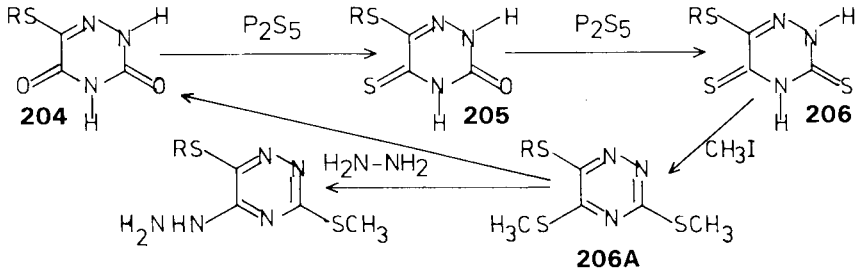
F. 1,2,4-Triazine-5,6-dithiones (5,6-Dimercapto-1,2,4-triazines)

At present no 1,2,4-triazine-5,6-dithione has been reported.

G. 1,2,4-Triazine-3,5,6-trithiones (3,5,6-Trimercapto-1,2, 4-triazines)

No detailed study of the chemistry of this class of 1,2,4-triazine derivatives has so far been reported.

Interaction of 6-mercapto-1,2,4-triazine-3,5-diones (**204**) or 6-mercapto-5-thioxo-1,2,4-triazin-3-ones (**205**) with phosphorus pentasulfide was used for the synthesis of 6-mercapto-1,2,4-triazine-3,5-dithiones (**206**) (m.p. : R = CH_3, 300 °C; R = C_2H_5; R = C_6H_5, 282 to 284 °C (dec.); R = 4-CH_3O–C_6H_4) (602, 851, 1091). The two oxo groups in **204** are replaced stepwise; the 5-oxo group is initially replaced.

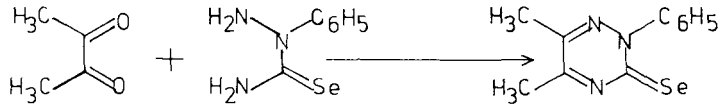


Methylation of **206** with methyl iodide in aqueous alkali affords derivatives of 6-mercapto-3,5-bis(methylmercapto)-1,2,4-triazine (**206A**) (R = CH_3, 90 to 92 °C; R = C_2H_5; R = C_6H_5 80 to 82 °C; R = 4-CH_3O–C_6H_4) (602, 851, 1090). **206A** can be hydrolyzed, leading to **204**, and reacts with hydrazine yielding 5-hydrazino-3,6-bis(methylmercapto)-1,2,4-triazines (602, 851, 603). A band around 1100 cm^{-1} is observed in the infrared spectra of **206**, indicating that the given tautomeric structure is the predominant one.

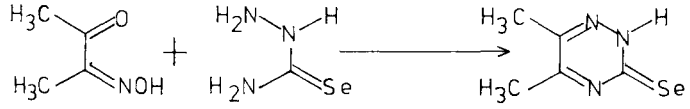
H. 1,2,4-Triazine-3-selenones

Only two 1,2,4-triazine-3-selenones (**207**) so far are reported. Bednarz obtained 5,6-dimethyl-2-phenyl-1,2,4-triazine-3-selenone (**207a**) (m.p. 149 to

150 °C) through reaction of diacetyl with 2-phenylselenosemicarbazide (1088), and Shafiee and Lalezari (342) isolated the 5,6-dimethyl-1,2,4-triazine-3-selenone (**207b**) (m.p. 203 to 204 °C) from the reaction of diacetyl monoxime with selenosemicarbazide.



207a



207b

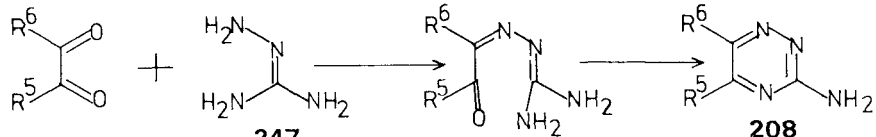
IV. AMINO-1,2,4-TRIAZINES

A. 3-Amino-1,2,4-triazines

1. *Preparation*

3-Amino-1,2,4-triazines (**208**) are well-known compounds and effective methods for their synthesis are known. A review on the synthesis and the reactions of 3-amino-1,2,4-triazines was given by Hadacek in 1960 (612).

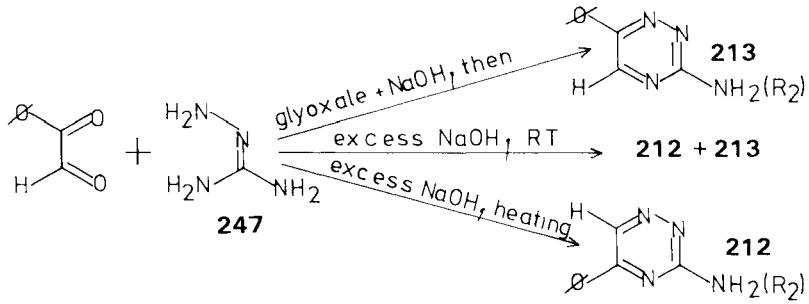
The most convenient method for the synthesis of **208** is the reaction of 1,2-dicarbonyl compounds with aminoguanidine (**247**) or its salts (129, 605–624, 636, 650, 1074, 1421).



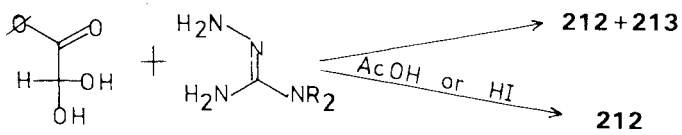
247 **211** **208**

The initially formed guanylhydrazones (**211**) can be isolated and the cyclization is achieved by heating them in 30% aqueous sodium hydroxide solution, in ethylene glycol in the presence of ammonia, or with sodium bicarbonate.

The reaction of monosubstituted glyoxals with aminoguanidine can lead to the formation of isomeric 5- or 6-substituted 3-amino-1,2,4-triazines (**212, 213**). Elvidge and co-workers (606) have shown that the results published by Ekeley and collaborators (605), who claimed the isolation of 3-amino-5-phenyl-1,2,4-triazine (**212**), 3-amino-6-phenyl-1,2,4-triazine (**213**), and the imino tautomer of **213** from phenylglyoxale and aminoguanidine under different reaction conditions, were mainly incorrect. Elvidge and co-workers have shown that phenylglyoxal and aminoguanidine, when heated in excess sodium hydroxide solution, give 3-amino-5-phenyl-1,2,4-triazine (**212**) as was claimed by Ekeley. Reaction of both components in excess sodium hydroxide solution gave a mixture of **212** and **213** and not 3-amino-6-phenyl-1,2,4-triazine (**213**), as Ekeley claimed, and the 3-amino-6-phenyl-1,2,4-triazine (**213**) is isolated when phenylglyoxal is dissolved in water and first excess sodium hydroxide then the aminoguanidine (**247**) is added.

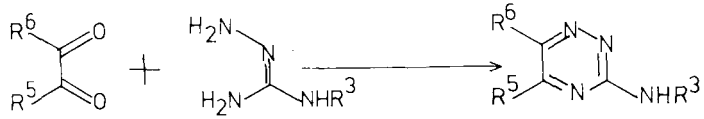


Lalezari and Shafiee (614) have shown that phenylglyoxal hydrate reacts with substituted aminoguanidines in alkaline media to yield a mixture of the isomeric 5- and 6-substituted 3-amino-1,2,4-triazines, but the reaction of both components in acetic acid or the reaction of phenylglyoxal hydrate with aminoguanidinium iodide in water gave the 3-amino-5-phenyl-1,2,4-triazines (**212**).

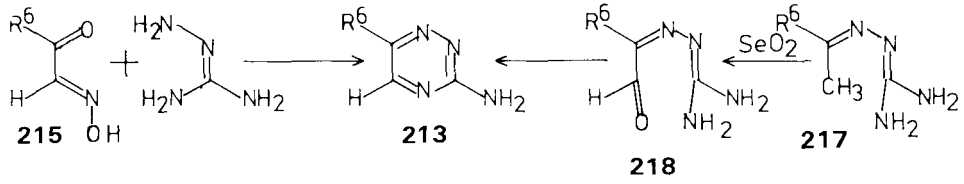


Thiele and Bihan (624) reported unsuccessful attempts to cyclize glyoxal or diacetyl with aminoguanidine.

Reaction of *N*-substituted aminoguanidines with 1,2-dicarbonyl compounds is a method for the synthesis of 3-(alkylamino)-1,2,4-triazines (611, 614, 625).

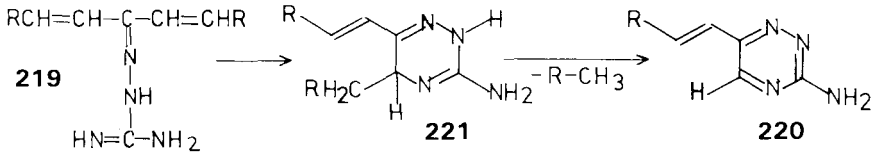


By a reaction of aminoguanidine with phenylglyoxal oxime (**215**) 3-amino-6-phenyl-1,2,4-triazine (**213**) was obtained (614).

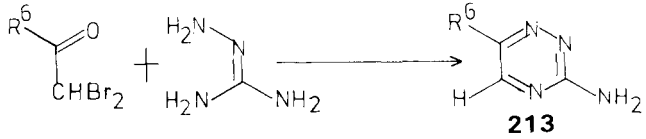


A method that is very similar to the method first described is used by Saikawa and Maeda (625–632) and by Lalezari and Shafiee (614) for the synthesis of 5-unsubstituted 3-amino-1,2,4-triazines (**213**). Guanylhydrazones of methyl ketones (**217**) were oxidized by selenium dioxide to guanylhydrazones of monosubstituted glyoxals (**218**), which cyclized to the 5-unsubstituted 3-amino-1,2,4-triazines (**213**).

Cyclization of bis(alkylidene)- or bis(arylidene)acetone guanylhydrazones (**219**) is a very frequently used method for the synthesis of 6-vinyl-substituted 3-amino-1,2,4-triazines (**220**) (633–642, 645–648). As was shown by different groups (636, 640, 646, 647), the initially formed intermediate is **221**, which is then transformed into the desired 3-amino-1,2,4-triazine (**220**).

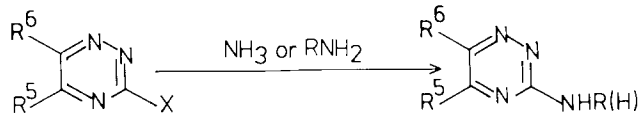


Kisa and Hadacek obtained 5-unsubstituted 3-amino-1,2,4-triazines (**213**) by a reaction of α,α-dibromo ketones with aminoguanidine in the presence of hydrochloric acid (633).

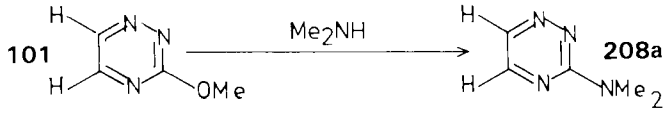


Besides these methods for the synthesis of 3-amino-1,2,4-triazines (**208**), which always start with aminoguanidine, the exchange of other groups in the

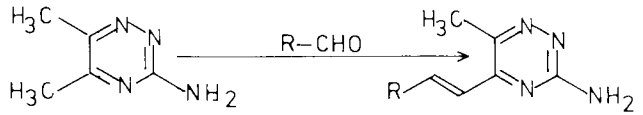
3-position of the 1,2,4-triazine nucleus, such as chloro (649), mercapto (157, 293, 576, 577, 594, 614, 1420), azido (1482, 1483), or methoxy groups (678) has been mentioned.



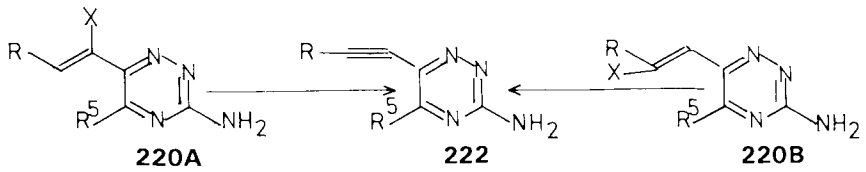
Grundmann, Schroeder, and Rätz (8) as well as Hadacek (612) reported the synthesis of 3-(dimethylamino)-1,2,4-triazine (**208a**). As was shown by Neunhoeffer and Lehmann (678) the desired product was not isolated in either case. The compound isolated by Grundmann and his co-worker was in fact the 5-(dimethylamino)-1,2,4-triazine. **208a** was obtained by reaction of 3-methoxy-1,2,4-triazine (**101**) with dimethylamine (678).



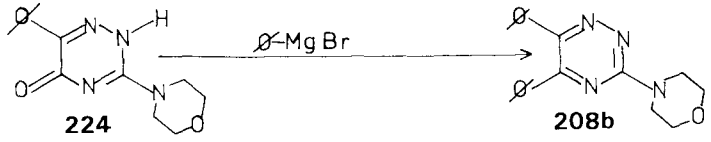
Further 3-amino-1,2,4-triazines were obtained by reaction of methyl-3-amino-1,2,4-triazines with aldehydes (620, 643, 650–652, 655). In all cases the 5-methyl group was more reactive than the 6-methyl group as is illustrated for the 3-amino-5,6-dimethyl-1,2,4-triazine:



Elimination of HX from halovinyl-substituted 3-amino-1,2,4-triazines (**220A/B**) led to the isolation of ethynyl-substituted 3-amino-1,2,4-triazines (**222**) (626, 653, 654).



Reaction of 3-morpholino-6-phenyl-1,2,4-triazin-5-one (**224a**) with phenylmagnesium bromide affords 3-morpholino-5,6-diphenyl-1,2,4-triazine (**208b**) (293).

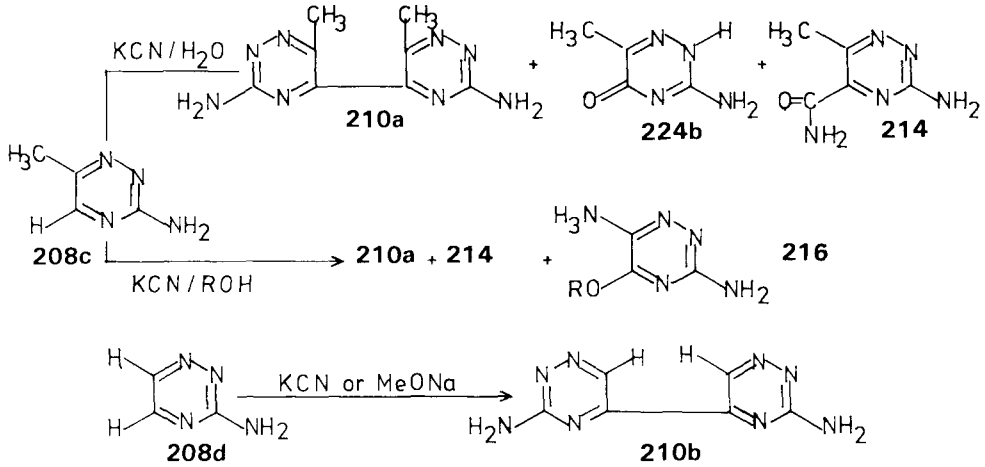


2. *Compound Survey*

Table II-14 lists the 3-amino-1,2,4-triazines reported in the literature.

In the same way reaction of 3-amino-1,2,4-triazines (**208**) with SO_2 leads to products formed by addition of sulfurous acid to the N_4C_5 bond (617, 620). The starting material is regenerated by addition of base to the addition product.

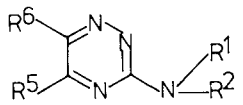
Reaction of 6-methyl-3-amino-1,2,4-triazine (**208c**) with prussic acid or of the H_2SO_3 addition product of **208c** with potassium cyanide led to the formation of three different products (620): 3,3′-diamino-6,6′-dimethyl-5,5′bi-1,2,4-triazine (**210a**), 3-amino-6-methyl-1,2,4-triazin-5-one (**224b**), and 3-amino-6-methyl-1,2,4-triazine-5-carboxamide (**214**). In the presence of alcohols 3-amino-5-alkoxy-1,2,4-triazines (**216**) are formed instead of **224b** (620, 1075). 3-Amino-1,2,4-triazine (**208d**) is transformed into 3,3′-diamino-5,-5′-bi-1,2,4-triazine (**210b**) by reaction with potassium cyanide or sodium methoxide (110).



Only three papers dealing with the alkylation of 3-amino-1,2,4-triazines are known (612, 668, 669). Hadacek (612) claimed the synthesis of 3-(dimethylamino)-1,2,4-triazine and 3-(methylamino)-5,6-dimethyl-1,2,4-triazine by

TABLE II-14. 3-AMINO-1,2,4-TRIAZINES

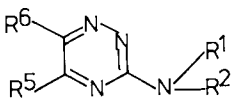
A. 3-Amino-1,2,4-triazines

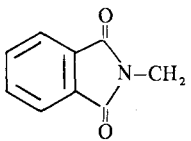
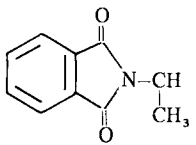
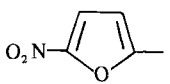
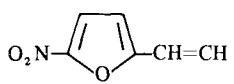


R^1	R^2	R^5	R^6	m.p. (°C)	Refs.
H	H	H	H	171.5–172.5	607, 608
				177–178	612
				177–179	151, 618
H	H	H	CH_3	182–184	617, 618
				183	151
				183–184	613
				184–185	620
H	H	H	CH_2NH_2	>300	613
H	H	H	C_6H_5	192–193	605
				193–194.5	615, 616
				194–196	625
				197	151, 606
				197–198	189
	·HCl			228–235	605
H	H	H	C_6H_5–CH=CH	170–172	625
H	H	H	C_6H_5–CH=CBr	167–169	625
H	H	H	4-O_2N–C_6H_4–CH=CH	300	625
				305 (dec.)	640, 645, 646
H	H	H	2-Furyl	162–163	131
	·HCl			266–267	131

TABLE II-14. (*continued*)

A. 3-Amino-1,2,4-triazines



R^1	R^2	R^5	R^6	m.p. (°C)	Refs.
H	H	H		250 (dec.)	613, 633
H	H	H		238	633
H	H	H		275 (dec.) 276–278 277–278	625 610 628, 631
H	H	H		266 (dec.) 268–269 (dec.) 269–270 (dec.) 270 (dec.) 270–271	636 628 641 625, 658 632

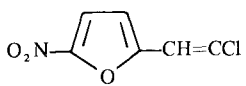
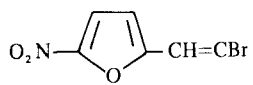
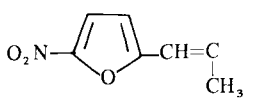
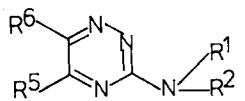
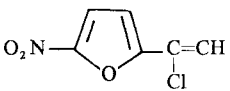
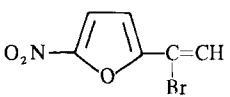
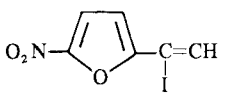
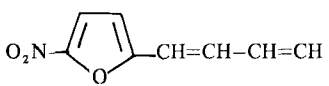
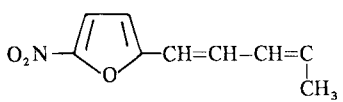
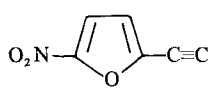
				272–273	611
				287 (dec.)	637
				269 (dec.)	648
				234–239 (dec.)	637
				235 (dec.)	632
				235–239 (dec.)	648
				239 (dec.)	641
				239 (dec.)	658
				205 (dec.)	648
				150 (dec.)	648
				163–164 (dec.)	648
				174 (dec.)	648
				300 (dec.)	648
				212 (dec.)	648
				271 (dec.)	648
				274 (dec.)	648
				132–134 (dec.)	648
				208 (dec.)	648
H	H	H		283 (dec.)	626
H	H	H		235 (dec.) 254 (dec.)	628 626, 630
H	H	H		265–266 (dec.) 268 (dec.) 269–270 (dec.) >280	640 625 640 634

TABLE II-14. (*continued*)

A. 3-Amino-1,2,4-triazines



R^1	R^2	R^5	R^6	m.p. (°C)	Refs.
H	H	H		300	626, 628 629
H	H	H		275 (dec.)	626, 629
H	H	H		243 (dec.) 221–222 (dec.)	626 653
H	H	H		>300	640
H	H	H		222–223 (dec.)	640
H	H	H		221 (dec.) 222 (dec.)	626 654

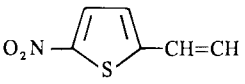
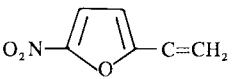
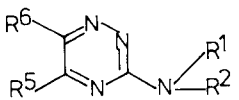
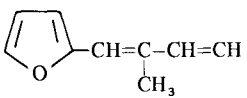
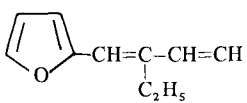
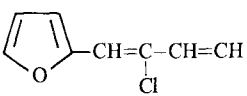
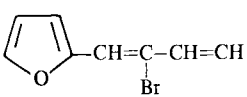
H		H	H		285 (dec.)	640
					286 (dec.)	645, 646, 648
	·HCl				262	646
	·HBr				255–256	646
H		H	CH_3	H	182–184	617, 618
					183–184	151
					185–185	620
H		H	CH_3	CH_3	208	650
					209.5–211	606
					210–211	151, 618
					210–212	612
					211–212	607, 608
H		H	CH_3			648
H		H	C_2H_5	CH_3	148–151	650
H		H	*i*-C_3H_7	CH_3	140	650
H		H	*t*-C_4H_9	H	187–189	606
H		H	*n*-C_3H_7	*n*-C_3H_7	115–117	606
H		H	*n*-C_3H_7	C_6H_5	175	133
H		H	C_6H_5	H	233–235	605, 606
					238–240	189
	·HCl				213 (dec.)	606
H		H	C_6H_5	C_6H_5	175	51, 624, 636
					176.5–177	606
H		H	C_6H_5	4-$(CH_3)_2N$–C_6H_4	202	609
H		H	4-HO–C_6H_4	4-HO–C_6H_4	>260	609
H		H	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	185	609
H		H	4-O_2N–C_6H_4–CH=CH	CH_3	241–242	650, 655

TABLE II-14. (*continued*)

A. 3-Amino-1,2,4-triazines



R^1	R^2	R^5	R^6	m.p. (°C)	Refs.
H	H	2-Furyl	H	231–232	131
	·HCl			220	131
	Picrate			218–219	131
H	H	2-Furyl	2-Furyl	228	636
				233	609
				234–235.5	606
H	H		CH_3	225	650
H	H		CH_3	214	650
H	H		CH_3	213	650
H	H		CH_3	213	650

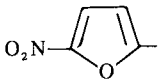
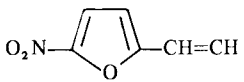
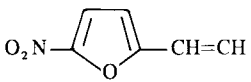
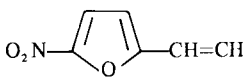
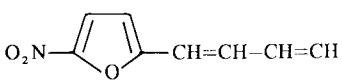
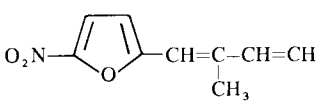
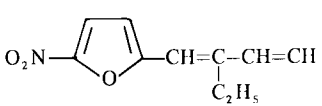
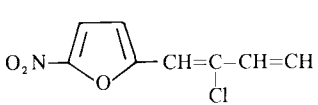
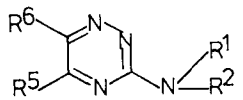
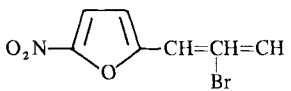
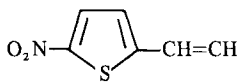
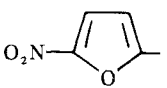
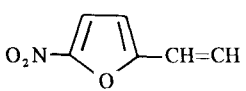
H	H			305 (dec.)	648
H	H		H	267–268 (dec.) 269 (dec.)	651 620
	$\cdot H_2SO_4$			213	651
H	H		CH_3	227.5 230 (dec.)	655 650
	$\cdot H_2SO_4$			230	655
H	H		CH_3	210	650, 655
H	H		CH_3	225 (dec.)	643
	$\cdot H_2SO_4$			228	643
H	H		CH_3	214	643
	$\cdot H_2SO_4$			206–207	643
H	H		CH_3	213	643

TABLE II-14. (*continued*)

A. 3-Amino-1,2,4-triazines



R^1	R^2	R^5	R^6	m.p. (°C)	Refs.
H	H		CH_3	213	643
H	H		CH_3	208–210	655
				220	650
	$\cdot H_2SO_4$			230	655
H	H	4-Pyridyl	H		1074
H	CH_3	CH_3	CH_3	205	612
H	CH_3	H		238	631
H	CH_3	H		234	1674
				235 (dec.)	632, 635
				235–237 (dec.)	625, 648
	$\cdot HCl$			159–160	1674
				187–188	638
	$\cdot H_2SO_4$			>300	638

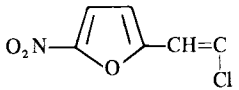
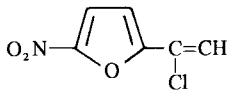
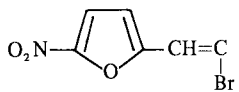
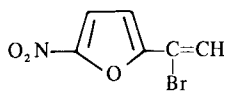
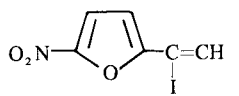
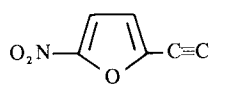
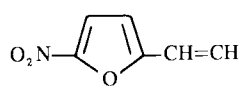
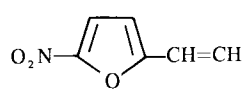
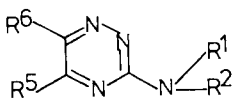
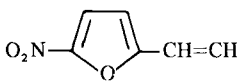
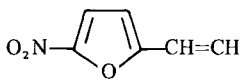
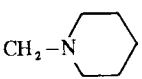
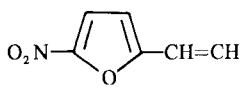
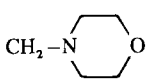
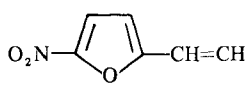
H	CH_3	H		235 (dec.)	626
H	CH_3	H		221 (dec.) 221–222 (dec.)	626 629
H	CH_3	H		210 (dec.)	626, 630
H	CH_3	H		216–217 (dec.) 217	626 628, 629
H	CH_3	H		214 (dec.)	653
H	CH_3	H		214 (dec.)	626, 654
H	C_2H_5	H	C_6H_5	133–134	614
H	C_2H_5	C_6H_5	H	133–134	614
H	C_2H_5	H		182–185 (dec.)	635
	·HCl			160 (dec.)	638
H	C_3H_7	H		194–195 (dec.)	635

TABLE II-14. *(continued)*

A. 3-Amino-1,2,4-triazines



R^1	R^2	R^5	R^6	m.p. (°C)	Refs.
H	$C_6H_5-CH_2$	H	C_6H_5	135–137	614
H	$C_6H_5-CH_2$	C_6H_5	H	153–154	614
H	$C_6H_5-CH_2$	C_6H_5	C_6H_5	190	293
H	CH_2OH	H		120 (dec.)	665, 667
H	$CH_2N(CH_3)_2$	H		136	640
	·HCl			194–195 (dec.)	640
H		H		182–196	644
	·HCl			201 (dec.)	640, 644
H		H			

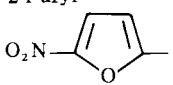
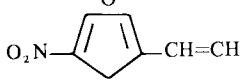
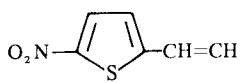
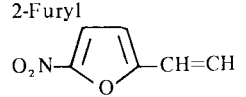
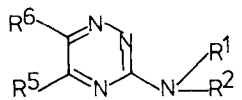
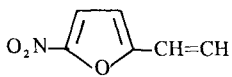
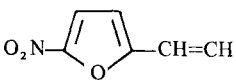
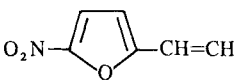
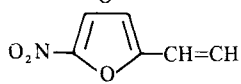
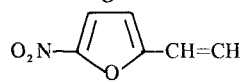
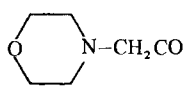
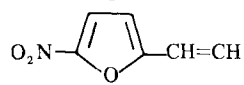
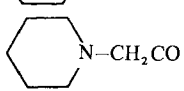
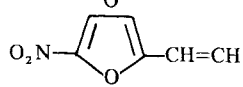
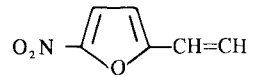
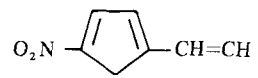
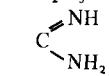
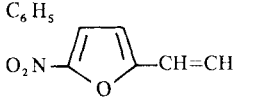
	·HCl			189 (dec.)	640
				190 (dec.)	644
	·HBr			171–173	644
H	C_6H_5	C_6H_5	C_6H_5	230	293
				230–232	649
H	C_6H_5	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	218	157
H	4-CH_3–C_6H_4	C_6H_5	C_6H_5	260	293
H	4-Cl–C_6H_4	C_6H_5	C_6H_5	240	293
H	4-Cl–C_6H_4	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	243	157
H	4-CH_3O–C_6H_4	C_6H_5	C_6H_5	232	293
H	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	200	157
H	CH_3CO	H	C_6H_5	219–221	605
				227	606
H	CH_3CO	H	4-O_2N–C_6H_4–CH=CH	288	673
H	CH_3CO	H	2-Furyl	212–213	131
H	CH_3CO	H		266–268	610
H	CH_3CO	H		278 (dec.)	641
				284	671, 673
				300	636
H	CH_3CO	H		291	673
H	CH_3CO	C_6H_5	H	182–184	605
				184	606
					672
H	CH_3CO	C_6H_5	C_6H_5	154	636
				198–201	160
H	CH_3CO	2-Furyl	H	195–195.5	131
H	CH_3CO	2-Furyl	2-Furyl	166	636
H	C_2H_5CO	H		266	671, 673

TABLE II-14. *(continued)*

A. 3-Amino-1,2,4-triazines



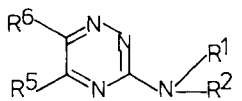
R^1	R^2	R^5	R^6	m.p. (°C)	Refs.
H	*i*-C_4H_9CO	H			671
H	$C_9H_{19}CO$	H			671
H	$C_{15}H_{31}CO$	H			671
H	$ClCH_2CO$	H			671
H	C_6H_5CO	H		243	673
H		H		145 (dec.)	657
H		H		170–172 (dec.)	657

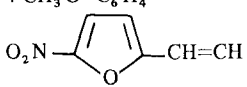
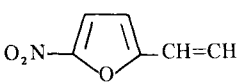
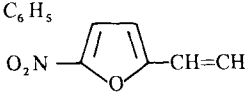
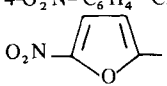
H	$C_6H_5NHCH_2CO$	H		·HCl	195 (dec.)	657
H	$3,4\text{-}Cl_2C_6H_3NHCH_2CO$	H			208 (dec.)	657
H	H_2C_5OCO	C_6H_5	H		101–102	672
H		CH_3	CH_3		288–289 (dec.)	594
	·HCOOH				225 (dec.)	594
H	SOCl	H	CH_3		340 (dec.)	613
H	$4\text{-}Cl\text{–}C_6H_4\text{–}SO_2$	H	H		148–149	621
H	$4\text{-}Cl\text{–}C_6H_4\text{–}SO_2$	CH_3	CH_3		184–186	621
H	$4\text{-}Cl\text{–}C_6H_4\text{–}SO_2$	C_6H_5	C_6H_5		240–242	621
H	$4\text{-}CH_3\text{–}C_6H_4\text{–}SO_2$	CH_3	CH_3		174–176	621
H	$4\text{-}CH_3\text{–}C_6H_4\text{–}SO_2$	C_6H_5	C_6H_5		214–216	621
H	$4\text{-}H_2N\text{–}C_6H_4\text{–}SO_2$	H	H		200–201 (dec.)	677
H	$4\text{-}H_2N\text{–}C_6H_4\text{–}SO_2$	CH_3	CH_3		229	675
H	$4\text{-}H_2N\text{–}C_6H_4\text{–}SO_2$	C_6H_5	C_6H_5		216	622, 674
H	$4\text{-}H_2N\text{–}C_6H_4\text{–}SO_2$	2-Furyl	2-Furyl		194–195	622
H	$4\text{-}CH_3CONH\text{–}C_6H_4\text{–}SO_2$	H	H		261–262 (dec.)	677
H	$4\text{-}CH_3CONH\text{–}C_6H_4\text{–}SO_2$	CH_3	CH_3		210–215	675
H	$4\text{-}CH_3CONH\text{–}C_6H_4\text{–}SO_2$	C_6H_5	C_6H_5		189	676
H	$4\text{-}C_2H_5OCONH\text{–}C_6H_4\text{–}SO_2$	CH_3	CH_3		241	675
CH_3	CH_3	H	H		27–29	678
					[a]	8, 612
CH_3	CH_3	H	C_6H_5		115–117	614
CH_3	CH_3	H			217–217.5	611, 648

[a] Structure given is incorrect.

TABLE II-14. *(continued)*

A. 3-Amino-1,2,4-triazines



R^1	R^2	R^5	R^6	m.p. (°C)	Refs.
·HCl				210–211 (dec.)	635
				210–212 (dec.)	638
·HCl·H_2O				194–195	644
CH_3	CH_3	C_6H_5	H	85–89	614
CH_3	CH_3	C_6H_5	C_6H_5	107–108	576
CH_3	CH_3	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	136–137	576
CH_3	CH_3		H	244 (dec.)	652
CH_2OH	CH_2OH	H		158–161	640
				160 (dec.)	664
CH_3CH_2	CH_3CH_2	C_6H_5	C_6H_5	109–110	1482
CH_2CH_2OH	CH_2CH_2OH	H		184 (dec.)	657
CH_3CO	CH_3CO	C_6H_5	C_6H_5	151–153	160
CH_3CO	CH_3CO	H	4-O_2N–C_6H_4–CH=CH	260	673
CH_3CO	CH_3CO	H		188.5–189	610

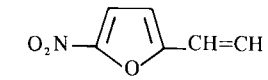
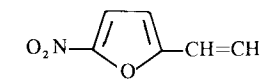
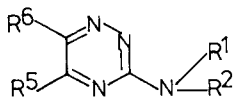
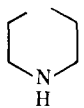
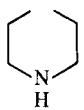
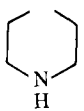
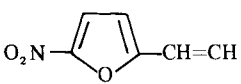
CH_3CO CH_3CO		H		265	641, 673
		H	C_6H_5	95–97	614
		C_6H_5	H	175–176	614
		C_6H_5	C_6H_5	139–140 186	1482 293
		4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	135	157
		H		204–205	644
		H	C_6H_5 ·H_2O·HCl	123–124	614
		C_6H_5	H	105–108	614
		C_6H_5	C_6H_5	143–144 144	1482 293
		4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	128	157

TABLE II-14. (*continued*)

A. 3-Amino-1,2,4-triazines



R^1 R^2	R^5	R^6		m.p. (°C)	Refs.
	C_6H_5	H	·HCl	300–305	577
	4-Cl–C_6H_4	H	·HCl ·2HCl	330 350	577 577
	4-CH_3O–C_6H_4	H	·H_2O	73	577
	C_6H_5	H	·2HCl·2H_2O	278	577
	4-CH_3O–C_6H_4	H	·2HCl	280	577
	H			265 (dec.) 268 (dec.)	665 640

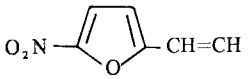
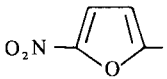
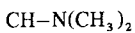
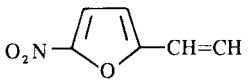
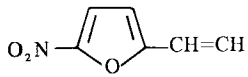
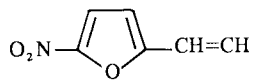
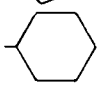
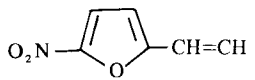
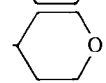
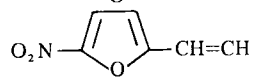
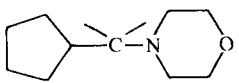
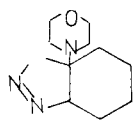
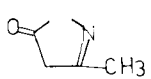
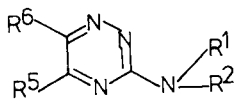
	H		223–224 (dec.)	667 659
	H		270–272 (dec.)	659, 663
	H		259–260 (dec.)	659, 662
	H		188–191 (dec.)	659, 662
	H		257–258 (dec.)	659, 660
	H		236–238 (dec.)	659, 660
	H		254–256 (dec.)	659, 660
	C_6H_5	C_6H_5	128	1483
	C_6H_5	C_6H_5	138	1483
	C_6H_5	C_6H_5		656

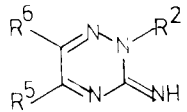
TABLE II-14. (*continued*)

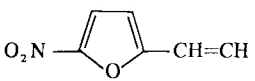
A. 3-Amino-1,2,4-triazines



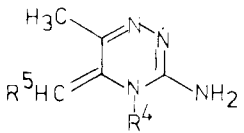
R^1	R^2	R^5	R^6	m.p. (°C)	Refs.
		C_6H_5	C_6H_5	318–320	656
		C_6H_5	C_6H_5	314–318	656
		C_6H_5	C_6H_5	308	656
		C_6H_5	C_6H_5	313–315	1482

B. 3-Imino(2H)-1,2,4-triazines



R^2	R^5	R^6	m.p. (°C)	Refs.
C_2H_5	C_6H_5	C_6H_5		669
CH_3CO	H		210 (dec.)	637

C. 4-Alkyl-5-alkylidene-3-amino-1,2,4-triazines



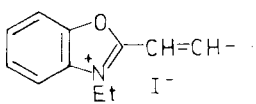
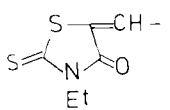
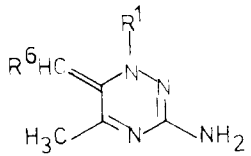
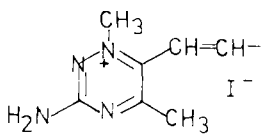
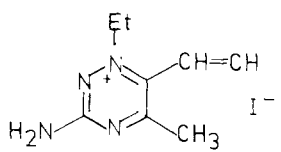
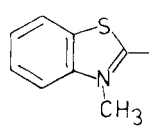
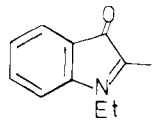
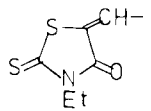
R^4	R^5	m.p. (°C)	Refs.
C_2H_5		224–225	668
C_2H_5		256–257	668

TABLE II-14. (*continued*)

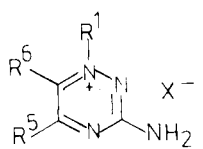
D. 1-Alkyl-6-alkylidene-3-amino-1,2,4-triazines



R^1	R^6	m.p. (°C)	Refs.
CH_3		271–273	668
C_2H_5		242–243	668
C_2H_5		315	668

C_2H_5		291–292	668
C_2H_5		300–302	668

E. 1-Alkyl-3-amino-1,2,4-triazinium salts



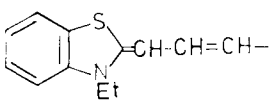
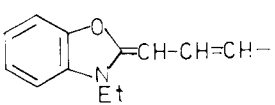
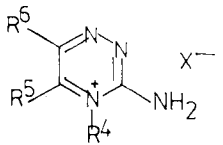
R^1	R^5	R^6	X	m.p. (°C)	Refs.
CH_3	CH_3	CH_3	CH_3SO_4		668
C_2H_5	CH_3	CH_3	$C_2H_5SO_4$		668
			I	223–225 (dec.)	668
C_2H_5	CH_3		I	244–245	688
C_2H_5	CH_3		I	246–247	668

TABLE II-14. (*continued*)

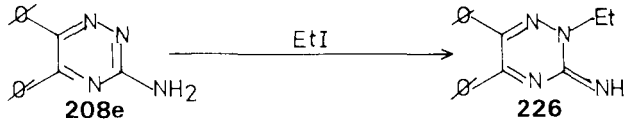
F. 4-Alkyl-3-amino-1,2,4-triazinium salts



R^4	R^5	R^6	X	m.p. (°C)	Refs.
C_2H_5	CH_3	CH_3	I	217–219	668

methylation of the NH_2 compounds with dimethyl sulfate in potassium hydroxide/ammonium hydroxide solution. Meanwhile it was shown (678) that the substance isolated by Hadacek was not the claimed 3-dimethylamino-1,2,4-triazine.

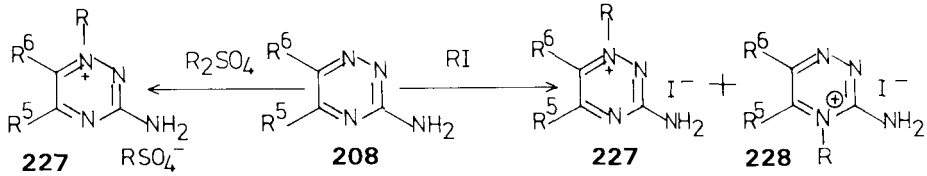
Wagner, Loewe, and Häussler (669) reported the isolation of 2-ethyl-3-imino-5,6-diphenyl-1,2,4-triazine (**226**) by reaction of 3-amino-5,6-diphenyl-1,2,4-triazine (**208e**) with ethyl iodide, but no experimental details are given.



208e **226**

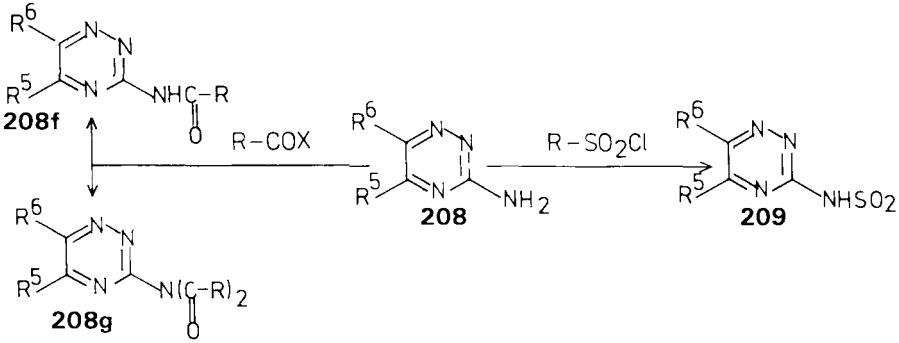
Cogrossi, Mariani, and Sgarbi (668) published the formation of 1-alkyl-3-amino-1,2,4-triazinium salt (**227**) by reaction of 3-amino-1,2,4-triazines (**208**) with dialkyl sulfates, and the isolation of a 1 : 1 mixture of **227** and 4-alkyl-3-amino-1,2,4-triazinium salts (**228**) by reaction of **208** with ethyl iodide.

These 1,2,4-triazinium salts could be converted into cyanine-like compounds by methods usually used in cyanine chemistry (668).



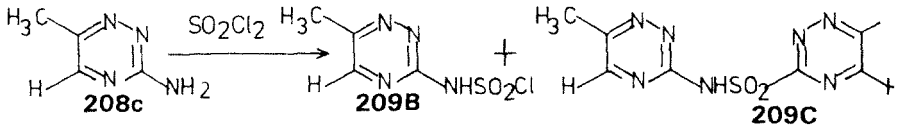
227 **208** **227** **228**

3-Acylamino- (**208f**) or 3-(diacylamino)-1,2,4-triazines (**208g**) were always isolated from the acylation of 3-amino-1,2,4-triazines (**208**) (160, 610, 636, 640, 641, 671–673). 3-Sulfamido-1,2,4-triazines (**209**) were obtained in the same way by reaction of **208** with sulfonyl chlorides (674–677).



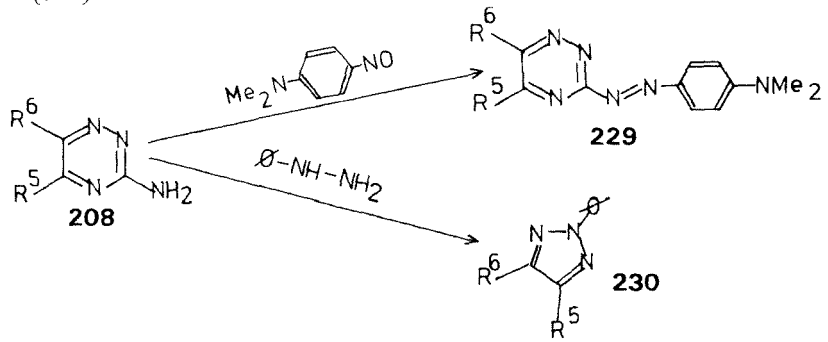
208f **208** **209** **208g**

Reaction of 6-methyl-3-amino-1,2,4-triazine (**208c**) with thionyl chloride gave two products, **209B** and **209C** (613).



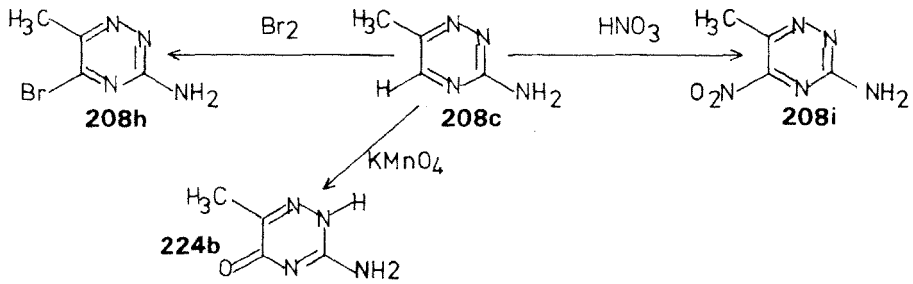
Reaction of 3-amino-1,2,4-triazines (**208**) with aldehydes (640, 664), aldehydes and amines (644), amidacetals (660, 661), or Vilsmeyer reagents (659, 662, 663) always led to substitution in the amino group.

Reaction of **208** with *p*-nitroso-*N*,*N*-dimethylaniline gave the azo compounds **229** (612).

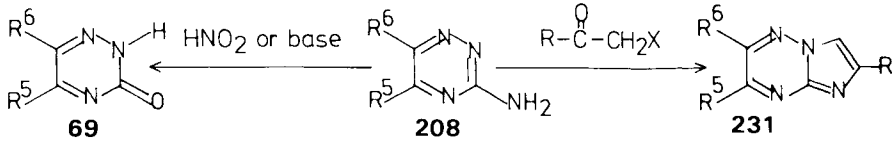


3-Amino-1,2,4-triazines (**208**) reacted with phenylhydrazine by ring contraction. The isolated products were identified as 1,2,4-triazoles (**230**) (612).

By reaction of 3-amino-6-methyl-1,2,4-triazine (**208c**) with bromine the 5-bromo compound (**208h**) was obtained, with concentrated nitrous acid the 5-nitro compound (**208i**), and with potassium permanganate 3-amino-6-methyl-1,2,4-triazin-5-one (**224**) (613).

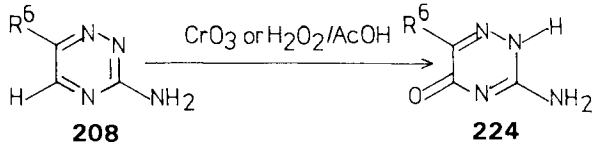


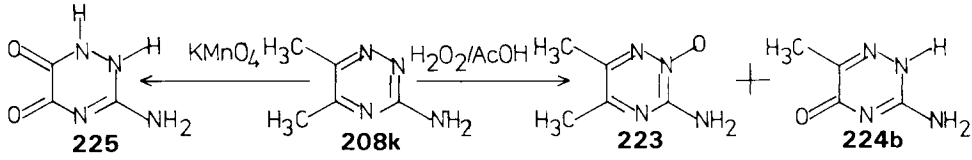
1,2,4-Triazin-3-ones (**69**) are formed by reaction of 3-amino-1,2,4-triazines (**208**) with nitrous acid or base (160, 130, 605).



The reaction of 3-amino-1,2,4-triazines (**208**) with α–halogenated ketones is an elegant and frequently used method for the synthesis of imidazo[1,2-*b*]-1,2,4-triazines (**231**) (609, 612, 615, 616, 694–700, 1420, 1422).

Different products were obtained from the oxidation of 3-amino-1,2,4-triazines (**208**). Oxidation with chromic acid produces 3-amino-1,2,4-triazin-5-ones (**224**) if the 5-position is unsubstituted (620, 641). The same products were isolated by oxidation with hydrogen peroxide in acetic acid (702). 5,6-Dimethyl-3-amino-1,2,4-triazine (**208k**) is oxidized by hydrogen peroxide in acetic acid to the 2-oxide (**223**) and to 3-amino-6-methyl-1,2,4-triazin-5-one (**224b**) (702). Further oxidations to *N*-oxides were published by Sasaki and his collaborators (160). The structure assigned by Sasaki to the *N*-oxides was corrected by Paudler and Chen (104).





Oxidation of 3-amino-5,6-dimethyl-1,2,4-triazine (**208k**) with potassium permanganate led to the isolation of 3-amino-1,2,4-triazine-5,6-dione (**225**) (701).

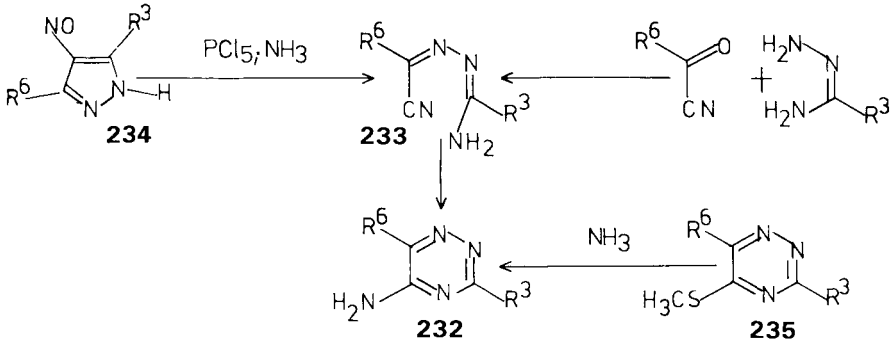
B. 5-Amino-1,2,4-triazines

1. *Preparation*

Only a few papers on the chemistry of 5-amino-1,2,4-triazines (**232**) with no other functional group have been published (63, 187, 189, 341, 489, 563, 678).

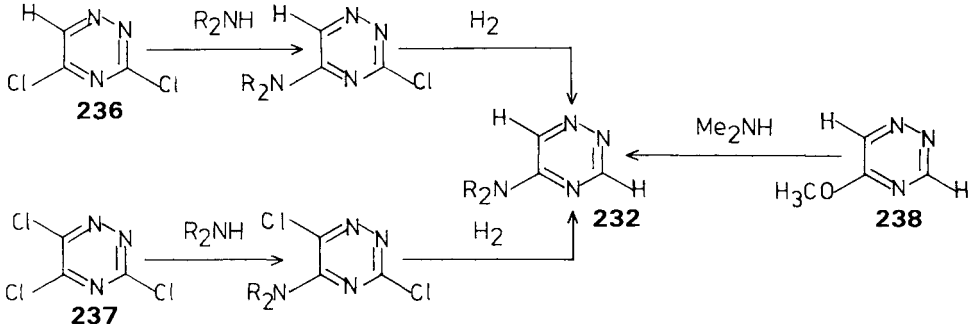
The first synthetic method was the basic cyclization of α-cyanoalkylidene-amidrazones (**233**) (63, 187), which were obtained either by reaction of

nitrosopyrazoles (**234**) with phosphorus pentachloride and ammonia (63) or amidrazones with acylcyanides (187).



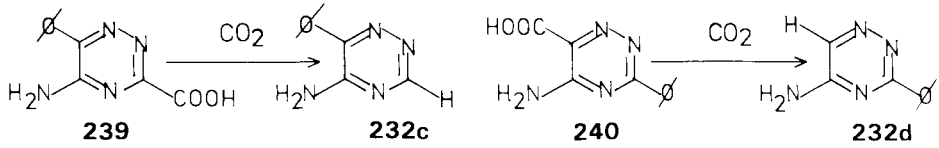
The 5-mercapto group in 5-mercapto-1,2,4-triazines (**235**) can be exchanged with ammonia, leading to 5-amino-1,2,4-triazines (**232**) (189).

Reaction of 3,5-dichloro-1,2,4-triazine (**236**) (341) or 3,5,6-trichloro-1,2,4-triazine (**237**) (563, 678) with 1 mole of dimethylamine (341, 678) or ammonia (563, 1565) leads to substitution only in the 5-position (not in the 3-position as stated in Ref. 341). Hydrogenation replaces the remaining chlorine atoms and 5-dimethylamino-1,2,4-triazine (**232a**) (341, 678) or 5-amino-1,2,4-triazine (**232b**) (563, 1565) is isolated. **232a** was also obtained by reaction of 5-methoxy-1,2,4-triazine (**238**) with dimethylamine (678).



Decarboxylation of 5-amino-6-phenyl-1,2,4-triazine-3-carboxylic acid (**239**) was used by Fusco and Rossi (63) for the synthesis of 5-amino-6-phenyl-1,2,4-triazine (**232c**); 5-amino-3-phenyl-1,2,4-triazine (**232d**) was obtained by the same group through decarboxylation of 5-amino-3-phenyl-1,2,4-triazine-6-carboxylic acid (**240**).

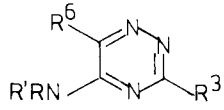
The synthesis of a 5-sulfonamido-1,2,4-triazine by treatment of a 3-(methylmercapto)-5-sulfonamido-1,2,4-triazine with Raney nickel is reported (489).



2. *Compound Survey*

The 5-amino-1,2,4-triazines reported in the literature are listed in Table II-15.

TABLE II-15. 5-AMINO-1,2,4-TRIAZINES



R^3	R	R′	R^6	m.p. (°C)	Refs.
H	H	H	H	231–232	563, 1565
H	H	H	CH_3	239–240	189
H	H	H	C_6H_5	124–125	189
				127	63
H	H	4-H_2N–C_6H_4–SO_2	CH_3	251.5 (dec.)	489
H	H	4-H_2N–C_6H_4–SO_2	C_2H_5	232–233	489
H	H	4-H_2N–C_6H_4–SO_2	n-C_3H_7	235–236	489
H	CH_3	CH_3	H	107.5	678
				108[a]	341
CH_3	H	H	CH_3	225–226	187
CH_3	H	H	C_6H_5	229–231	187
C_6H_5	H	H	H	249–250	63
C_6H_5	H	H	CH_3	202–203	187
C_6H_5	H	H	C_6H_5	219	63
				221–223	187

[a]Formulated as the 3-dimethylamino isomer.

3. *Physical Properties*

5-Amino-1,2,4-triazines are weak bases and most of them have a high melting point.

The infrared spectra of 5-amino-1,2,4-triazines exhibit bands for the stretching vibrations (3534 to 3520 cm^{-1} and 3416 to 3405 cm^{-1}) and the deformation vibration (1616 to 1606 cm^{-1}) of the amino group (187) but the stretching vibration due to an exocyclic imino group was absent. The aromatic character of these compounds is also confirmed by the presence of bands due to the ring stretching vibration of the 1,2,4-triazine ring at wave numbers very similar to those of the unsubstituted 1,2,4-triazine.

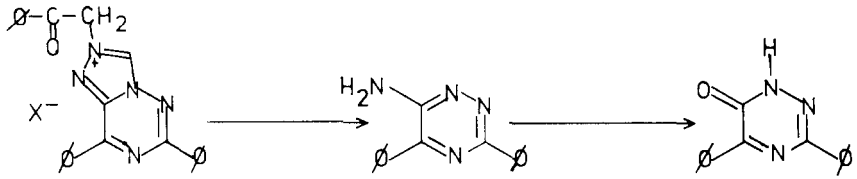
4. *Reactions*

The single reaction of 5-amino-1,2,4-triazines (**232**) published until now is the hydrolytic transformation into 1,2,4-triazine-5-ones (**241**) by acidic or basic hydrolysis (63, 187).

232 **241**

C. 6-Amino-1,2,4-triazines

The single known 6-amino-1,2,4-triazine is the 6-amino-3,5-diphenyl-1,2,4-triazine (**242**), which was obtained by Becker and his group (201) through basic hydrolysis of the quaternized 1,2,4-triazolo[3,4-*f*] 1,2,4-triazine (**243**).



243 **242** **244**

It has a melting point of 243 °C and the infrared spectrum – bands at 3470, 3450, 3310, and 1625 cm^{-1} – as well as the ultraviolet spectrum – 236 (4.25), 275 (4.55), 305 (402), and 353 nm (3.92) – confirms the amino structure.

By basic hydrolysis of **242** yields 3,5-diphenyl-1,2,4-triazin-6-one (**244**).

D. 3,5-Diamino-1,2,4-triazines

1. *Preparation*

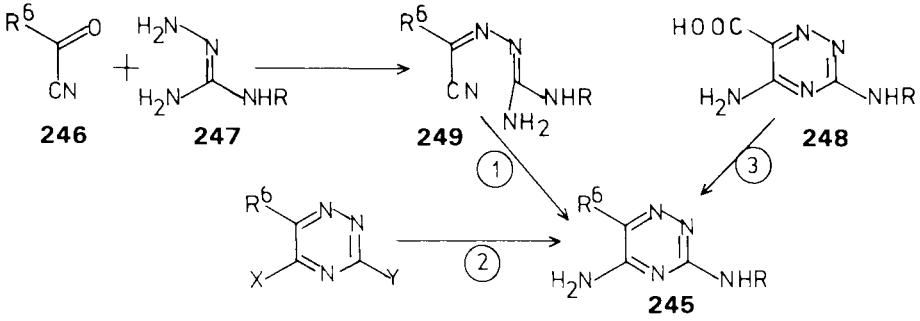
Three different principles have been used for the synthesis of 3,5-diamino-1,2,4-triazines (**245**):

1. Cyclization of acyl cyanides (**246**) with aminoguanidine (**247**) (703–707).

2. exchange of other hetero groups in the 3- and/or 5-positions with an amino group (502, 678, 708–715).

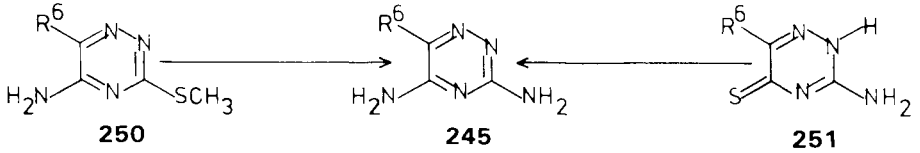
3. decarboxylation of 3,5-diamino-1,2,4-triazine-6-carboxylic acids (**248**) (716).

The reaction of acyl cyanides (**246**) with aminoguanidine (**247**) is run in acidic media; the initially formed guanylhydrazones (**249**) are cyclized in basic media.



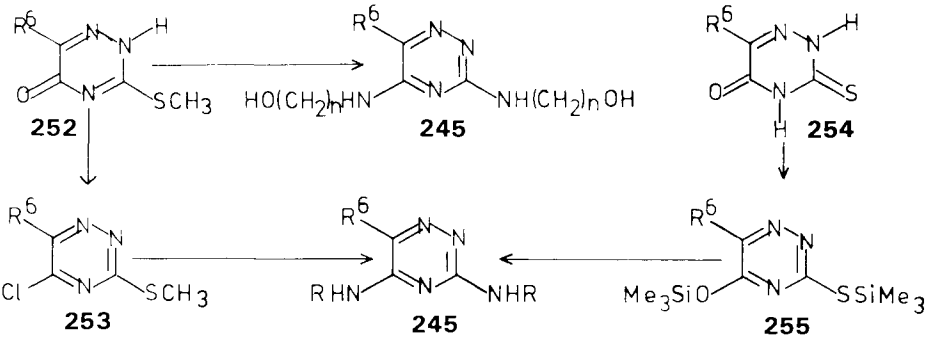
The following exchange reactions were used for the synthesis of 3,5-diamino-1,2,4-triazines (**245**):

1. reaction of 5-amino-3-(methylmercapto)-1,2,4-triazines (**250**) (562) or 3-amino-5-thioxo-1,2,4-triazines (**251**) (708) with ammonia.



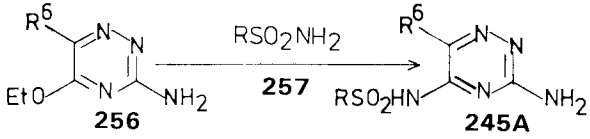
2. The direct transformation of 3-(methylmercapto)-1,2,4-triazin-5-ones (**252**) by refluxing these compounds with 2-aminoethanol or 3-amino propanol, using

the reagents as solvent, was observed by Lempert and his group (709) but in other cases **252** were first transformed into the 5-chloro-3-(methylmercapto)-1,2,4-triazines (**253**) (710–712).

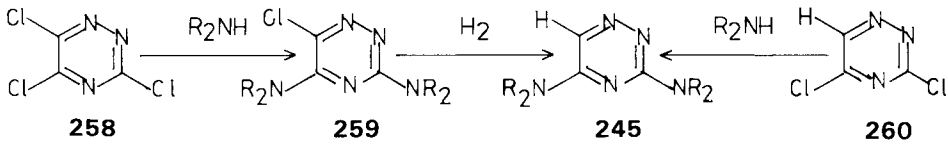


H. Vorbrüggen (713, 714) achieved the transformation of 3-thioxo-1,2,4-triazine-5-ones (**254**) into 3,5-diamino-1,2,4-triazines (**245**) by preliminary synthesis of 5-[(trimethylsilyl)oxy]-3-[(trimethylsilyl)thio]-1,2,4-triazines (**255**) and subsequent reaction of **255** with amines.

3. Saikawa and Maeda (715) obtained 3-amino-5-sulfonamido-1,2,4-triazines (**245A**) by reaction of 3-amino-5-ethoxy-1,2,4-triazines (**256**) with sulfonamides (**257**).



4. Neunhoeffer and Lehmann (678) synthesized 3,5-bis(dialkylamino)-1,2,4-triazines (**245**) by reaction of 3,5,6-trichloro-1,2,4-triazine (**258**) with dialkylamines and hydrogenation of the formed 6-chloro-3,5-bis(dialkylamino)-1,2,4-triazines (**259**). Grundmann et al. (341) were not able to obtain 3,5-bis(dialkylamino)-1,2,4-triazines by reaction of 3,5-dichloro-1,2,4-triazine (**260**) with amines, but Neunhoeffer and Lehmann (678) were able to synthesize 3,5-bis(diethylamino)-1,2,4-triazine by this reaction.



2. *Compound Survey*

Compounds of this group reported in the literature are listed in Table II-16.

3. *Physical Properties*

3,5-Diamino-1,2,4-triazines are colorless or light yellow compounds. Their ultraviolet (703, 704, 709) and and infrared spectra (709) are in agreement with the diamino structure. They are weak bases and form salts with acids.

4. *Reactions*

There have been no reports of reactions of 3,5-diamino-1,2,4-triazines.

E. 3,6-Diamino-1,2,4-triazines

No mention of a compound with this structure has yet been published.

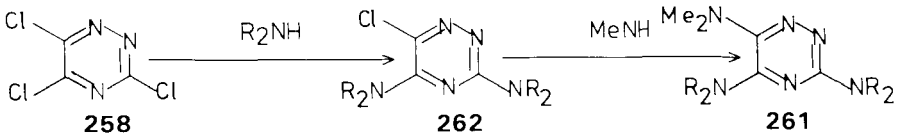
F. 5,6-Diamino-1,2,4-triazines

At present no 5,6-diamino-1,2,4-triazine is to be found in the literature.

G. 3,5,6-Triamino-1,2,4-triazines

Neunhoeffer and Lehmann (678) published reports on the only two examples of this type, the 3,5,6-tris(dimethylamino)-1,2,4-triazine (**261a**, R = CH_3, yellow oil, b.p. 100°C/0.03 torr) and the 3,5-bis(diethylamino)-6-(dimethylamino)-1,2,4-triazine (**261b**, R = C_2H_5, yellow oil, b.p. 113°C/0.07 torr).

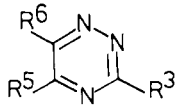
Both were obtained by reaction of 6-chloro-3,5-bis(dialkylamino)-1,2,4-triazines (**262**) with dimethylamine. **262** are synthesized by reaction of 3,5,6-trichloro-1,2,4-triazine (**258**) with 2 moles of dialkylamine.



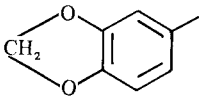
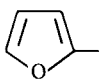
258 **262** **261**

TABLE II-16. 3,5-DIAMINO-1,2,4-TRIAZINES

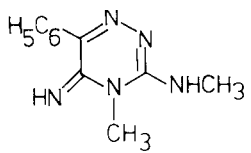
A. 3,5-Diamino-1,2,4-triazines



R^3	R^5	R^6	m.p. (°C)	Refs.
NH_2	NH_2	CH_3	234–238 (dec.)	502
			250 (dec.)	703
			254–255 (dec.)	704
$\cdot HNO_3$			228 (dec.)	703
NH_2	NH_2	C_6H_5	206	710, 712
			218–219	704
NH_2	NH_2	3,5-$(CH_3)_2C_6H_3$	232–234.5	707
NH_2	NH_2	2-F–C_6H_4	231–232	706, 707
NH_2	NH_2	3-F–C_6H_4	199–200	706, 707
NH_2	NH_2	4-F–C_6H_4	257–260	706, 707
NH_2	NH_2	2-Cl–C_6H_4	189–191	707
NH_2	NH_2	3-Cl–C_6H_4	196–197	707
NH_2	NH_2	4-Cl–C_6H_4	218–220	710, 711, 712
			218–221	707
			219–222	704
NH_2	NH_2	2,4-$Cl_2C_6H_3$	220–222	707, 710, 712
NH_2	NH_2	3,4-$Cl_2C_6H_3$	219–220	710, 711, 712
			222–224	707
NH_2	NH_2	3,4-$Cl_2C_6H_3$–$C(CH_3)_2$	251–253	707
NH_2	NH_2	3,4-$Cl_2C_6H_3CH_2CH_2$	206–208	707
NH_2	NH_2	C_6H_5–$C(CH_3)_2$	272–274	706, 707
NH_2	NH_2	4-CH_3O–C_6H_4	215–217	707
			219–219.5	704

NH_2	NH_2	3,4,5-$(CH_3O)_3C_6H_2$	295–297	704
			300–303	707
NH_2	NH_2	4-$CF_3-C_6H_4$	232–233	706, 707
NH_2	NH_2	3,5-$(CF_3)_2C_6H_3$		706
NH_2	NH_2	4-$CF_3O-C_6H_4$	210–212	707
NH_2	NH_2	 3,4(CH_2O_2)C_6H_3	236 (dec.)	708
NH_2	NH_2	 2-Furyl	229–230	704
NH_2	$C_6H_5-SO_2-NH$	CH_3	284–285 (dec.)	715
NH_2	4-$CH_3-C_6H_4-SO_2-NH$	CH_3	282–283 (dec.)	715
NH_2	4-$Cl-C_6H_4-SO_2-NH$	CH_3	288 (dec.)	715
NH_2	4-$H_2N-C_6H_4-SO_2-NH$	CH_3	292–293 (dec.)	715
$NHCH_2CH_2OH$	$NHCH_2CH_2OH$	CH_3	170–171	709
$NH(CH_2)_3OH$	$NH(CH_2)_3OH$	CH_3	126–127	709
n-C_4H_9NH	$NHCH_3$	H	114–115	716
$C_6H_5CH_2NH$	$NHCH_3$	H	158–160	716
3,4-$(CH_3O)_2C_6H_3CH_2CH_2NH$	3,4-$(CH_3O)_2C_6H_3CH_2CH_2NH$	H	136–137	713, 714
$N(CH_3)_2$	$N(CH_3)_2$	H	83	678
$N(C_2H_5)_2$	$N(C_2H_5)_2$	H	b.p. 120/0.07 torr	678

B. 3-Amino-5-imino-1,2,4-triazine



192 705

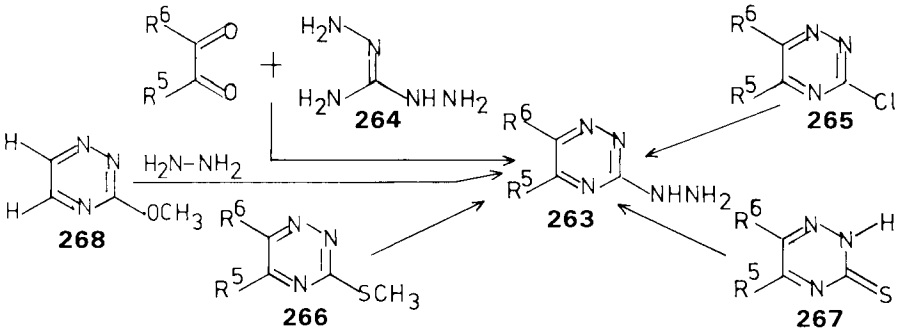
V. Hydrazino-1,2,4-triazines

A. 3-Hydrazino-1,2,4-triazines

1. *Preparation*

Two principles were used for the synthesis of 3-hydrazino-1,2,4-triazines (**263**), the reaction of 1,2-dicarbonyl compounds with diaminoguanidine (**264**) (718, 1482), and substitution of other groups in the 3-position by hydrazine (14, 51, 293, 482, 586, 587, 717).

Cyclization of benzil ($R^5 = R^6 = C_6H_5$) with diaminoguanidine (**264**) is reported by Lieber and Strojny (718) and by Stevens (1482), yielding 3-hydrazino-5,6-diphenyl-1,2,4-triazine (**263a**) ($R^6 = R^5 = C_6H_5$).



3-Chloro-1,2,4-triazines (**265**) (51,583, 586, 1482), 3-(methylmercapto)-1,2,4-triazines (**266**) (14, 293), and 1,2,4-triazine-3-thiones (**267**) (587, 717) react very easily with hydrazine, leading to the isolation of 3-hydrazino-1,2,4-triazines (**263**). Synthesis of 3-hydrazino-1,2,4-triazine (**263b**) ($R^5 = R^6 = H$) by reaction of 3-methoxy-1,2,4-triazine (**268**) with hydrazine was part of the synthesis of the unsubstituted 1,2,4-triazine, published by Paudler and Chen (14).

A review on the synthesis and the reactions of 3-hydrazino-1,2,4-triazines was given by Hadacek (720) in 1959.

2. *Compound Survey*

Table II-17 lists the 3-hydrazino-1,2,4-triazines reported in the literature.

3. *Physical Properties*

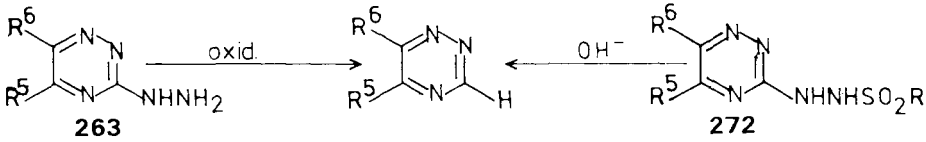
Only a small amount of data on the physical properties of 3-hydrazino-1,2,4-triazines is available. 3-Hydrazino-1,2,4-triazines (**263**) are colored compounds and weak bases. Because of the N–H stretching vibration at 3343 and 3250 cm^{-1} and the N–H deformation vibration at 1535 cm^{-1} in the infrared spectra of 3-hydrazino-5,6-diphenyl-1,2,4-triazine (583) the hydrazino structure is assigned to these compounds.

In the NMR spectrum of 3-hydrazino-1,2,4-triazine the signals for the two heterocyclic protons are observed at 1.41τ (H_6) and 1.63τ (H_5) (14).

The fragmentation pathway of 3-hydrazino-5,6-diphenyl-1,2,4-triazine is markedly different from that of 1,2,4-triazine, where loss of nitrogen from the molecular ion is an important feature. The dominant process in this case is fragmentation of the molecular ion to a highly delocalised diphenylacetylene radical ion at m/e = 178 (165).

4. *Reactions*

Oxidation of 3-hydrazino-1,2,4-triazines (**263**) with manganese dioxide (14), mercury oxide (57), or copper (II) ions forms 1,2,4-triazines with unsubstituted 3-positions. The same compounds were obtained by alkaline degradation of 3-(sulfonylhydrazino)-1,2,4-triazines (**272**) (57).



Oxidation of 3-(phenylhydrazino)-5,6-diphenyl-1,2,4-triazine (**263d**) with ferric chloride led to the isolation of a compound formulated as 5,5′,6,6′-tetraphenyl-3,3′-bi-1,2,4-triazine (**269**) (51). The phenylazo compound **270** is postulated as the intermediate.

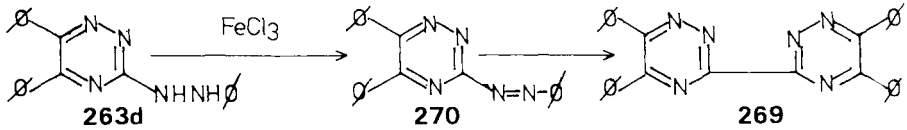
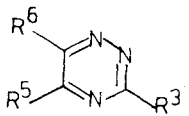
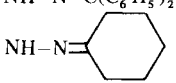
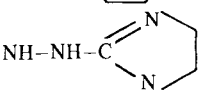


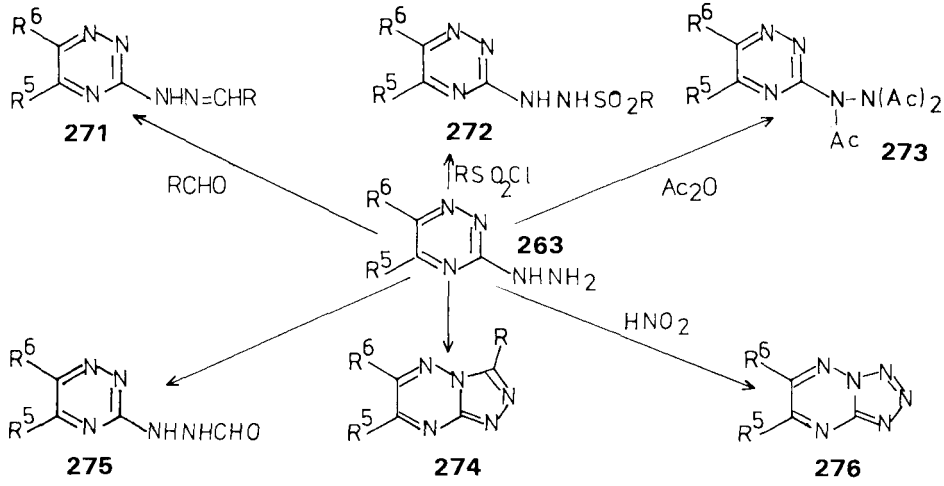
TABLE II-17. 3-HYDRAZINO-1,2,4-TRIAZINES



R^3	R^5	R^6		m.p. (°C)	Refs.
$NHNH_2$	H	H		140–142	14
$NHNH_2$	CH_3	H		163–165	14
$NHNH_2$	CH_3	CH_3		125.5–128.5	14
				145–148	583
$NHNH_2$	C_6H_{11}	H		85	717
$NHNH_2$	$C_6H_5-CH_2$	H		104–105	717
$NHNH_2$	C_6H_5	H		149–151	14
				150	717
					57, 587
$NHNH_2$	C_6H_5	CH_3		77.5	717
$NHNH_2$	C_6H_5	C_6H_5		169–170	717
				170	586
				170–172	14
				171–173	51
				172–173	1482
$NHNH_2$	4-HO–C_6H_4	H	·HCl	275	57
$NHNH_2$	4-CH_3O–C_6H_4	H		192–193	717
$NHNH_2$	4-C_6H_5–C_6H_4	H		196	717
$NHNH_2$	2-Naphthyl	H		183–185	717

$NHNH_2$	4-Cl–C_6H_4	H		176	717
NHNH–C_6H_5	C_6H_5	C_6H_5		197	293
				197–198	51
NHNH–CHO	CH_3	CH_3		198–200	583
NHNH–$SO_2C_6H_5$	C_6H_5	H		204	57
NHNH–SO_2–C_6H_5	C_6H_5	C_6H_5		170	57
NHNH–SO_2–C_6H_5	4-HO–C_6H_4	H		140	57
NH–N=CH_2	4-Cl–C_6H_4	H		207	717
NH–N=CH-*n*-C_3H_7	C_6H_5	C_6H_5		223	583
NH–N=CH–C_6H_5	C_6H_5	C_6H_5		249–251	1482
				252	586
				253	718
NH–N=CH–C_6H_4–Cl(*p*)	C_6H_5	C_6H_5		284	586
NH–N=CH–C_6H_4–Cl(*p*)	4-Cl–C_6H_4	H		273	717
NH–N=CH–C_6H_4–OCH_3(*p*)	C_6H_5	C_6H_5		268	586
NH–N=CH-2-furyl	C_6H_5	C_6H_5		235	586
NH–N=$C(CH_3)_2$	C_6H_5	C_6H_5		198	586
NH–N=$C(CH_3)_2$	4-Cl–C_6H_5	H		221	717
NH–N=$C(CH_3)C_6H_5$	C_6H_5	C_6H_5		200	586
NH–N=$C(C_6H_5)_2$	C_6H_5	C_6H_5		212	586
	C_6H_5	C_6H_5		202	586
	CH_3	CH_3	·HI	208–210	719
	C_6H_5	C_6H_5		143–144	1482

Hydrazones (**271**) are obtained by reaction of 3-hydrazino-1,2,4-triazines (**263**) with aldehydes or ketones (586, 718, 1482). 3-(Sulfonylhydrazino)-1,2,4-triazines (**272**) are obtained by reaction of **263** with sulfonyl chlorides (57), and the (triacetylhydrazino)-1,2,4-triazines (**273**) were isolated from the reaction of **263** with acetic anhydride (1482).



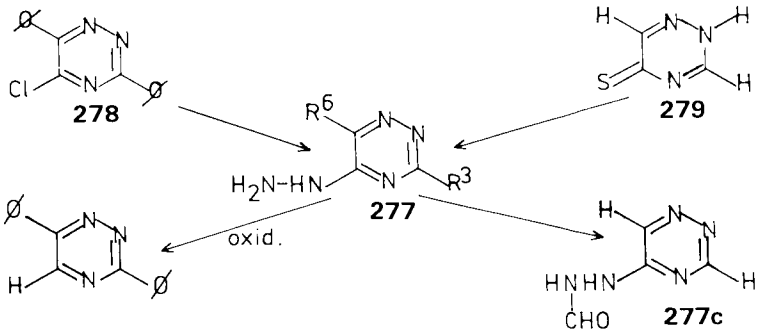
1,2,4-Triazolo[4,3-*b*] 1,2,4-triazines (**274**) can be synthesized by reaction of 3-hydrazino-1,2,4-triazines (**263**) with carboxylic acid chlorides or carbon disulfide (586, 587). Reaction of **263** with triethyl orthoformate affords 3- (formylhydrazino)-1,2,4-triazines (**275**) or 1,2,4-triazolo[4,3-*b*] 1,2,4-triazines (**274**) (832, 1482). Reaction of **263** with nitrous acid yielded tetrazolo[1,5-*b*]-1,2,4-triazines (**276**), the tautomeric 3-azido-1,2,4-triazines could not be isolated (1482, 1483).

3-Hydrazino-1,2,4-triazines (**263**) form colored complexes with metal ions (717).

B. 5-Hydrazino-1,2,4-triazines

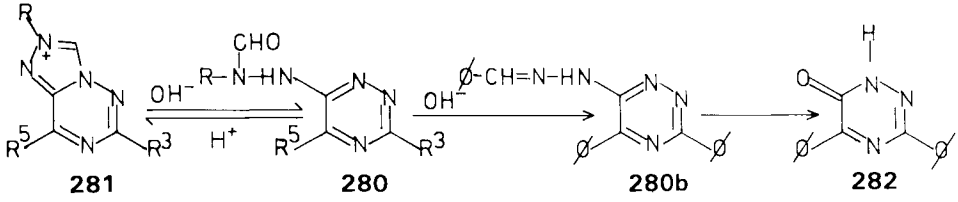
Only three 5-hydrazino-1,2,4-triazines (**277**) are known. Fusco and Rossi (63, 64) obtained 5-hydrazino-3,6-diphenyl-1,2,4-triazine (**277a**) ($R^3 = R^6 = C_6H_5$, yellow-orange, sintering at 217 to 218°C, melting above 300°C) by reaction of 5-chloro-3,6-diphenyl-1,2,4-triazine (**278**) with hydrazine while Jacquier and his collaborators (189) isolated 5-hydrazino-1,2,4-triazine (**277b**) ($R^3 = R^6 = H$, m.p. 125°C) from the reaction of 1,2,4-triazine-5-thione (**279**) with hydrazine. Reaction of the latter compound with formic acid gave 5-(formylhydrazino)-

1,2,4-triazine (**277c**) (m.p. 245°C) (595). Oxidation of **277a** yields 3,6-diphenyl-1,2,4-triazine (63, 64).



C. 6-Hydrazino-1,2,4-triazines

Three of the four known 6-hydrazino-1,2,4-triazines (**280**) were prepared by Becker and co-workers (201) through basic hydrolysis (pH = 9) of the quaternized 1,2,4-triazolo[3,4-*f*] 1,2,4-triazines (**281**). Treatment of compound **280a** ($R^3 = R^5 = C_6H_5$, $R = C_6H_5CH_2$) with base led to the formation of 6-(benzalhydrazino)-3,5-diphenyl-1,2,4-triazine (**280b**) (m.p. 243°C) (201), which could not be hydrolyzed to the 6-hydrazino-3,5-diphenyl-1,2,4-triazine but instead gave 3,5-diphenyl-1,2,4-triazin-6-one (**282**).



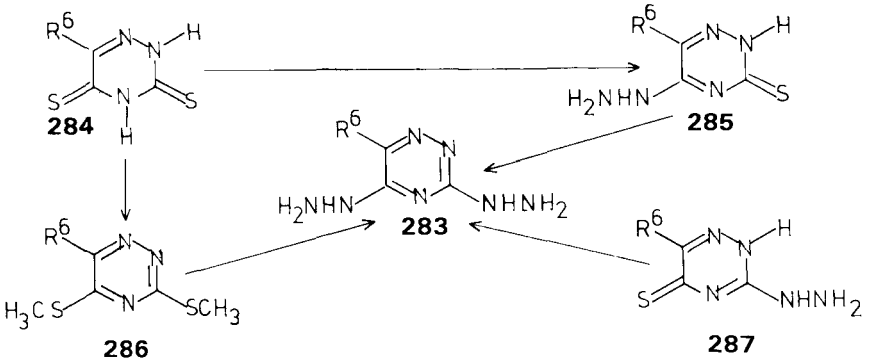
R^3	R^5	R	m.p. (°C)	
C_6H_5	C_6H_5	CH_3	148 (dec.)	UV: 241 (4.12), 264 (4.38) 320 (4.27)
C_6H_5	C_6H_5	$C_6H_5CH_2$	153 (dec.)	
3-Cl-C_6H_4	3-Cl-C_6H_4	$C_6H_5CH_2$	169 (dec.)	IR: 3220, 3200 cm^{-1} (N–H) 3080, 3030 cm^{-1} (C–H) 2942, 2875 cm^{-1} (C–H) 1682 cm^{-1} (N–CH=O) 755 cm^{-1} (C–H)

D. 3,5-Dihydrazino-1,2,4-triazines

1. *Preparation*

Most known 3,5-dihydrazino-1,2,4-triazines (**283**) are prepared by reaction of 1,2,4-triazine-3,5-dithiones (**284**) with hydrazine (189, 503, 593–595, 600, 604). The reaction must start with the replacement of the 5-thioxo group, since 5-hydrazino-1,2,4-triazine-3-thiones (**285**) can be isolated (594, 595).

D'Alo and Maserini (594) first prepared the 3,5-bis(methylmercapto)-1,2,4-triazines (**286**) and then reacted them with hydrazine whereas Jacquier and his collaborators (189) obtained 3,5-dihydrazino-1,2,4-triazines (**283**) by reaction of 3-hydrazino-1,2,4-triazine-5-thiones (**287**) with hydrazine.



2. *Compound Survey*

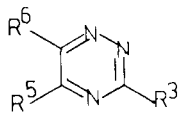
The compounds of this class reported in the literature are listed in Table II-18.

3. *Physical Properties and Reactions*

3,5-Dihydrazino-1,2,4-triazines are colored compounds, in most cases with a high melting point. They are weak bases. No further studies of the physical properties of these compounds have been published.

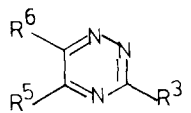
3,5-Dihydrazino-1,2,4-triazines (**283**) react with aldehydes and ketones, forming the hydrazones **288** (593, 594, 720). Reaction of **283** with formic acid gives the 3,5-bis(formylhydrazino)-1,2,4-triazines (**289**) (595) which can be cyclized to di-1,2,4-triazolo[4,3-*b*:4,3-*d*]1,2,4-triazines (**290**) (595).

TABLE II-18. 3,5-DIHYDRAZINO-1,2,4-TRIAZINES

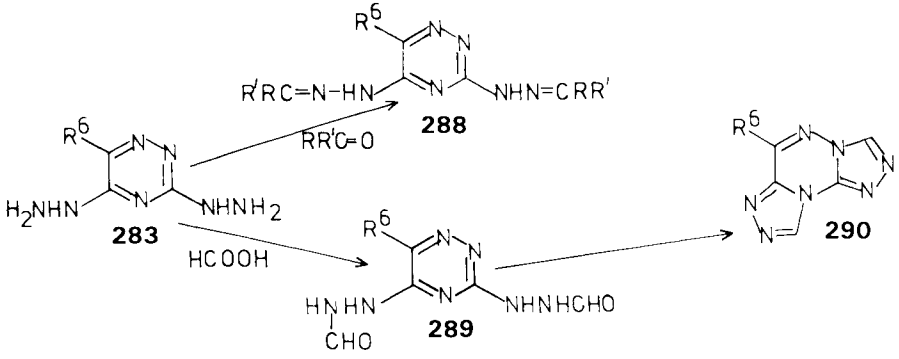


R^3	R^5	R^6		m.p. (°C)	Refs.
H_2N-NH	H_2N-NH	H		210–212 (dec.)	503
				220–221 (dec.)	593, 600
H_2N-NH	H_2N-NH	CH_3		218–219 (dec.)	593
				218–220 (dec.)	503, 595, 600
				221–222 (dec.)	189
					594, 604
H_2N-NH	H_2N-NH	C_2H_5		165 (dec.)	593, 600, 604
				165–167	503
H_2N-NH	H_2N-NH	n-C_3H_7		117–118 (dec.)	503, 600, 604
H_2N-NH	H_2N-NH	i-C_3H_7	·HCl	230 (dec.)	503, 600, 604
H_2N-NH	H_2N-NH	C_4H_9			604
H_2N-NH	H_2N-NH	n-C_7H_{15}		70–80 (dec.)	503, 600, 604
H_2N-NH	H_2N-NH	$C_6H_5CH_2$	·CH_3OH	102–103 (dec.)	503, 600
H_2N-NH	H_2N-NH	C_6H_5		175 (dec.)	600
				175–180 (dec.)	503
HN–NHCHO	HN–NHCHO	CH_3			595
HN–N=C(CH$_3$)–CH_2CH_2COOH	HN–N=C(CH$_3$)–CH_2CH_2COOH	H	·H_2O	181	593
HN–N=C(CH$_3$)–CH_2CH_2COOH	HN–N=C(CH$_3$)–CH_2CH_2COOH	CH_3	·H_2O	188	593, 720

TABLE II-18. (*continued*)



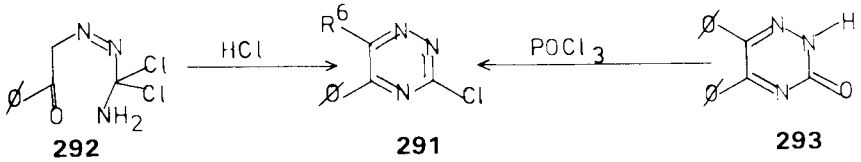
R^3	R^5	R^6		m.p. (°C)	Refs.
HN–N=C(CH$_3$)–CH$_2$ CH$_2$ COOH	HN–N=C(CH$_3$)–CH$_2$ CH$_2$ COOH	C_2H_5	·H_2O	116	593
HN–N=C(CH$_3$)–COOH	HN–N=C(CH$_3$)–COOH	H	·H_2O	300	593, 720
HN–N=C(C_6H_5)–CH$_2$ CH$_2$ COOH	HN–N=C(C_6H_6)–CH$_2$ CH$_2$ COOH	H	·H_2O	190–192	720
HN–N=CH–C_6H_4–Cl(4)	HN–N=CH–C_6H_4–Cl(4)	CH_3		329–331 (dec.)	594



VI. HALO-1,2,4-TRIAZINES

A. 3-Chloro-1,2,4-triazines

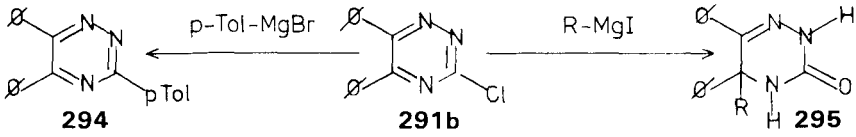
Only two 3-chloro-1,2,4-triazines (**291**) have been reported so far. Wolff and Lindenhayn (581) obtained 3-chloro-5-phenyl-1,2,4-triazine (**291a**) (R^6 = H, m.p. 122 to 123°C) through cyclization of compound **292** with hydrochloric acid. 3-Chloro-5,6-diphenyl-1,2,4-triazine (**291b**) [$R^6 = C_6H_5$, m.p. 156 to 157°C (51, 146); 157 to 157, 5°C (145)] was obtained by two different groups (51, 145, 146) by reaction of 5,6-diphenyl-1,2,4-triazin-3-one (**293**) with phosphorus oxychloride.



The chlorine in the 3-position is very reactive and can be replaced by reaction with water (581), alcohols (51, 145, 146), ammonia (51, 581) and hydrazines (51, 1482).

5,6-Diphenyl-3-p-tolyl-1,2,4-triazine (**294**) was obtained by reaction of 3-chloro-5,6-diphenyl-1,2,4-triazine (**291b**) with *p*-tolylmagnesium bromide; the same compound gave 4,5-dihydro-1,2,4-triazin-3-ones (**295**) (170) by reaction with alkylmagnesium iodides.

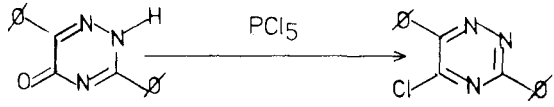
The fragmentation pathway of 3-chloro-5,6-diphenyl-1,2,4-triazine (**291b**) is markedly different from 1,2,4-triazine where loss of nitrogen from the molecular ion is an important feature. The dominant process in this case is fragmentation



of the molecular ion to a highly delocalized diphenylacetylene radical ion at m/e = 178 (165).

B. 5-Chloro-1,2,4-triazines

Fusco and Rossi obtained 5-chloro-3,6-diphenyl-1,2,4-triazine (**296**) (m.p. 132 to 134°C) by reaction of 3,6-diphenyl-1,2,4-triazin-5-one (**297**) with phosphorus pentachloride in toluene (63, 64). The chlorine can be replaced by hydrazine or hydrogen sulfide.



Metze and Meyer reported the synthesis of 6-chloro-3,5-diphenyl-1,2,4-triazine by reaction of the so-called 3,5-diphenyl-1,2,4-triazin-6-one with phosphorus pentachloride (45). But since it was shown by Becker and his group (201) that the compound used by Metze and Meyer was in fact the 3,6-diphenyl-1,2,4-triazin-5-one, the chloro compound synthesized by these authors has to be the 5-chloro-3,6-diphenyl-1,2,4-triazine. The melting point (130°C) reported by Metze and Meyer is nearly the same as Fusco and Rossi reported for their 5-chloro-3,6-diphenyl-1,2,4-triazine (132 to 134°C).

C. 6-Chloro-1,2,4-triazines

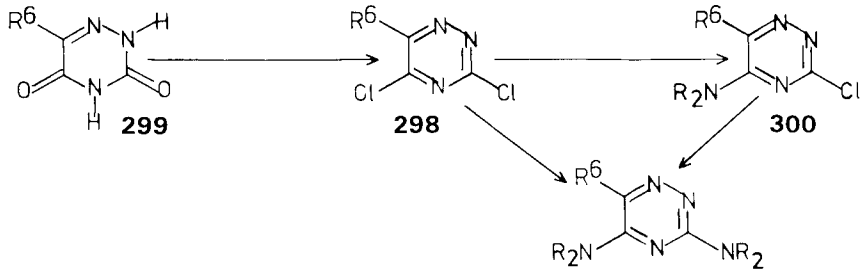
No 6-chloro-1,2,4-triazines have so far been reported (see preceding section).

D. 3,5-Dichloro-1,2,4-triazines

3,5-Dichloro-1,2,4-triazines (**298**) (m.p.: R^6 = H, 55°C; R^6 = CH_3, 41.5 to 45°C) were synthesized by reaction of 1,2,4-triazine-3,5-diones (**299**) with phosphorus oxychloride in the presence of an amine (341, 489). Both chlorines can be replaced by amino, alkoxy, and mercapto groups (341, 489, 678).

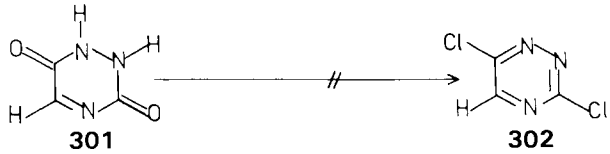
Meanwhile it was shown that the chlorine in the 5-position should be more reactive, so the correct structure of the amino-chloro-1,2,4-triazines obtained by Grundmann, Schroeder, and Rätz (341) from the reaction of **298** with ammonia or amines should be the 5-amino-3-chloro-1,2,4-triazine (**300**).

Neunhoeffer and Lehmann (678) obtained 3,5-bis(diethylamino)-1,2,4-triazine by reaction of 3,5-dichloro-1,2,4-triazine with diethylamine while Grundmann, Schroeder, and Rätz (341) were unable to synthesize the 3,5-diamino-1,2,4-triazine by this reaction.



E. 3,6-Dichloro-1,2,4-triazines and 5,6-Dichloro-1,2,4-triazines

No compounds of this structure have so far been reported. Grundmann Schroeder, and Rätz (341) were unable to transform the 1,2,4-triazine-3,6-dione (**301**) into the 3,6-dichloro-1,2,4-triazine (**302**).

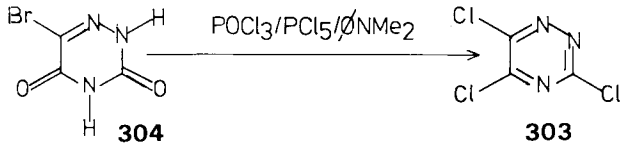


F. 3,5,6-Trichloro-1,2,4-triazine

3,5,6-Trichloro-1,2,4-triazine (**303**) is obtained by reaction of 6-bromo-1,2,4-triazine-3,5-dione (**304**) with phosphorus oxychloride (216, 497, 563, 1565). The procedure with the highest yield is reported by Loving and co-worker (721) who ran the reaction in the presence of phosphorus pentachloride and *N*,*N*-dimethylaniline. **303** is a colorless compound for which the following data are reported: b.p. 72°C/3 torr (216, 497), m.p. 57 to 58°C (563, 1565) and 60 to 62°C (721).

The ultraviolet-spectrum (hexane) shows bands at 290 (4.460), sh 301 (2.829), and 363 nm (598). The infrared spectrum has bands at 1480, 1450, 1265, 1160, 1075, 1045, 865, and 763 cm^{-1}.

The most reactive chlorine in **303** is the 5-chlorine atom, followed by the chlorine in the 3-position (563, 678). All chlorine atoms can be replaced by ammonia, amines, and methanol (563, 678, 1565, 1566).



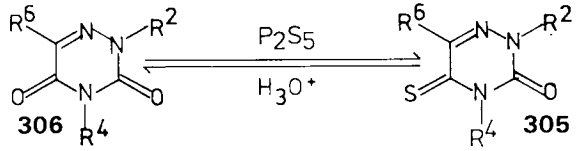
304 **303**

VII. 1,2,4-TRIAZINES WITH TWO OR THREE DIFFERENT HETERO SUBSTITUENTS

A. 5-Thioxo-1,2,4-triazin-3-ones

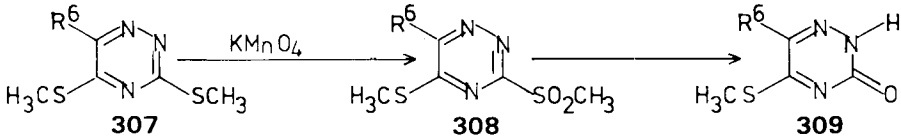
1. *Preparation*

Only a few methods have been published for the synthesis of 5-thioxo-1,2,4-triazin-3-ones (**305**). The most frequently used method is the reaction of 1,2,4-triazine-3,5-diones (**306**) with phosphorus pentasulfide (251, 289, 324, 327, 343, 368, 465, 466, 481, 487, 488, 501, 503–505, 599). In most cases pyridine is used as the solvent for this reaction.



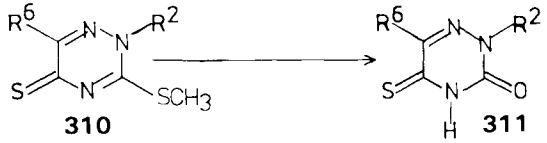
306 **305**

3,5-Bis(methylmercapto)-1,2,4-triazines (**307**) are converted by potassium permanganate to 5-(methylmercapto)-3-(methylsulfonyl)-1,2,4-triazines (**308**) which can be hydrolyzed by base to 5-(methylmercapto)-1,2,4-triazine-3-ones (**309**) (595, 596).



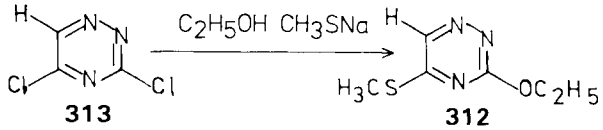
307 **308** **309**

Hydrolysis of 3- (methylmercapto)-1,2,4-triazin-5-thiones (**310**) was used by Jacquier and his group for the synthesis of 5-thioxo-1,2,4-triazine-3-ones (**311**) (279).



310 **311**

Grundmann, Schroeder, and Rätz (341) published the formation of 3-ethoxy-5-(methylmercapto)-1,2,4-triazine (**312**) by reaction of 3,5-dichloro-1,2,4-triazine (**313**) with sodium mercaptide in ethanol.



313 **312**

2. *Compound Survey*

Table II-19 lists the compounds in this group that have been reported in the literature.

3. *Physical Properties*

5-Thioxo-1,2,4-triazin-3-ones (**305**) are colored compounds (orange, yellow) and weak bases. The following dissociation constants were measured: 5-thioxo-1,2,4-triazine-3-one 6.33, 2-methyl derivative 6.25, 4-methyl derivative 8.57, and 5-(methylmercapto)-1,2,4-triazin-3-one 9.18 (601).

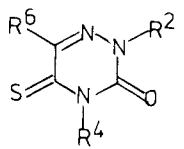
A number of ultraviolet (601) and infrared spectroscopic (351, 354–357) studies on the 5-thioxo-1,2,4-triazin-3-ones have been published. The unsubstituted 5-thioxo-1,2,4-triazine-3-one and its *N*-alkyl derivatives show two intensive bands around 245 and 330 nm and in addition a broad, low-intensity shoulder at about 450 nm; the ultraviolet spectra of 5-(methylmercapto)-1,2,4-triazin-3-ones are completely different (see Table II-20).

From these data it follows that 5-thioxo-1,2,4-triazin-3-ones and their *N*-alkyl derivatives are best formulated by the given tautomeric structure **305**.

The same result is obtained from the comparison of the infrared spectra of different 5-thioxo-1,2,4-triazin-3-ones (351), which show N–H vibrations

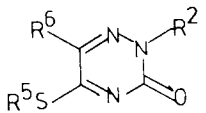
TABLE II-19. 5-THIOXO-1,2,4-TRIAZIN-3-ONES

A. 5-Thioxo-1,2,4-triazin-3(2H,4H)-ones



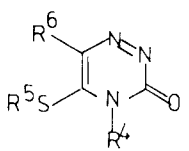
R^2	R^4	R^6	m.p. (°C)	Refs.
H	H	H	213–214	324
			215–217	599
			222	327
H	H	C_6H_5	293–295	279
H	CH_3	H	145–146	289
H	CH_3	C_6H_5	200–201	279
CH_3	H	H	141	289
			143–144	251
CH_3	H	C_6H_5	161–163	279
CH_3	CH_3	H	114–115	289
CH_3	CH_3	CH_3	128–129	251
CH_3	CH_3	C_6H_5	99–100	279

B. 5-Mercapto-1,2,4-triazin-3(2H)-ones



R^2	R^5	R^6	m.p. (°C)	Refs.
H	CH_3	H	170–171	289
			177–179	327
H	CH_3	CH_3	230–232	596, 595
H	CH_3	C_6H_5	217–219	279
			225–226	596
H	$C_6H_5CH_2$	H	201	327
CH_3	CH_3	H	102–104	289
CH_3	CH_3	C_6H_5	162–164	279

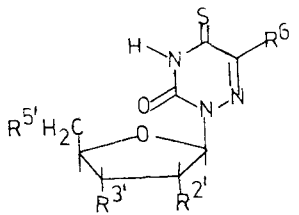
C. 5-Mercapto-1,2,4-triazin-3(4H)-ones

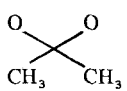
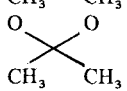


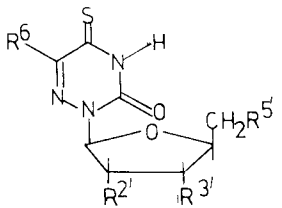
R^4	R^5	R^6	m.p. (°C)	Refs.
CH_3	CH_3	C_6H_5		279

TABLE II-19. (*continued*)

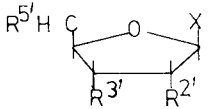
D. Sugar-substituted 5-thioxo-1,2,4-triazine-3-ones



$R^{2'}$	$R^{3'}$	$R^{5'}$	R^6	m.p. (°C)	Refs.
H	OH	OH	CH_3	Noncryst.	488
H	4-CH_3–C_6H_4COO	4-CH_3–C_6H_4COO	H	210–216	487
H	4-CH_3–C_6H_4COO	4-CH_3–C_6H_4COO	CH_3	174–175	488
H	4-CH_3–C_6H_4COO	4-CH_3–C_6H_4COO	CH_2OCOCH_3	138.5–139	468
OH	OH	OH	H	197–198	254, 501
OH	OH	O–PO_3H_2	H Ba salt		501
CH_3–COO	CH_3–COO	CH_3–COO	H	Foam	466, 501
				198–200	465
C_6H_5–COO	C_6H_5–COO	C_6H_5–COO	H		466, 504
C_6H_5–COO	C_6H_5–COO	C_6H_5–COO	CH_3	135–138	481
		OH	H	155–156	501
				188–190	254
		CH_3COO	H	143–145	501
				153–154	505



$R^{2'}$	$R^{3'}$	$R^{5'}$	R^6	m.p. (°C)	Refs.
OH	OH	OH	H	Glass	343
CH_3-COO	CH_3-COO	CH_3-COO	H		343
C_6H_5-COO	C_6H_5-COO	C_6H_5-COO	H	199.5–200.5	343



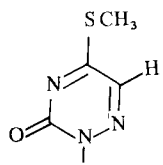
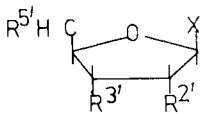
$R^{2'}$	$R^{3'}$	$R^{5'}$	X		
C_6H_5-COO	C_6H_5-COO	C_6H_5-COO		136–137	294, 295

TABLE II-19. (*continued*)



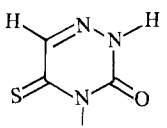
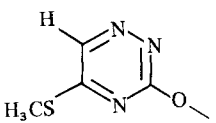
$R^{2'}$	$R^{3'}$	$R^{5'}$	X		
C_6H_5–COO	C_6H_5–COO	C_6H_5–COO		198–200	465
C_6H_5–COO	C_6H_5–COO	C_6H_5–COO		123–124	294, 295

TABLE II-20. ULTRAVIOLET SPECTRA OF 5-THIOXO-1,2,4-TRIAZIN-3-ONES

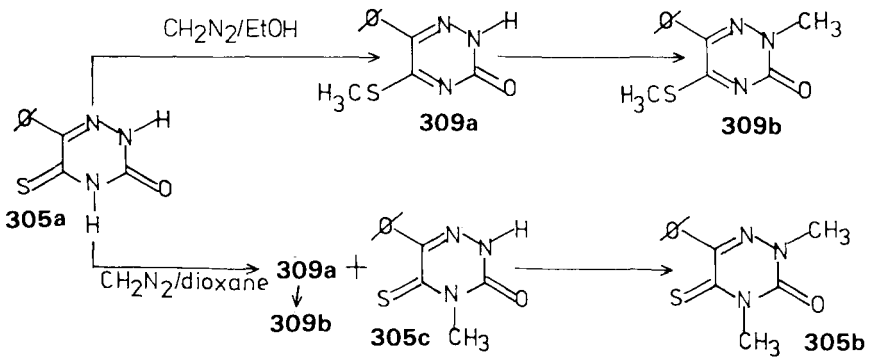
Compound	Solvent	Bands (nm) (log ϵ)		
Unsubstituted	EtOH	244 (3.69)	330 (4.10)	sh 435 (1.7)
2-Methyl	EtOH	248 (3.77)	338 (4.20)	sh 430 (1.5)
4-Methyl	EtOH	244 (3.64)	320 (4.11)	sh 450 (1.4)
2,4-Dimethyl	EtOH	248 (3.70)	332 (4.16)	sh 454 (1.5)
5-Methylmercapto	EtOH	297 (4.07)		
2-Methyl-5-methylmercapto	EtOH	sh 225 (3.65)	305 (3.99)	

around 3400 cm^{-1}, C=O-stretching vibrations between 1707 and 1739 cm^{-1}, and C=S-stretching vibrations around 1135 cm^{-1}.

Horak (724) published a method for chromatographic determination of 5-thioxo-1,2,4-triazin-3-ones.

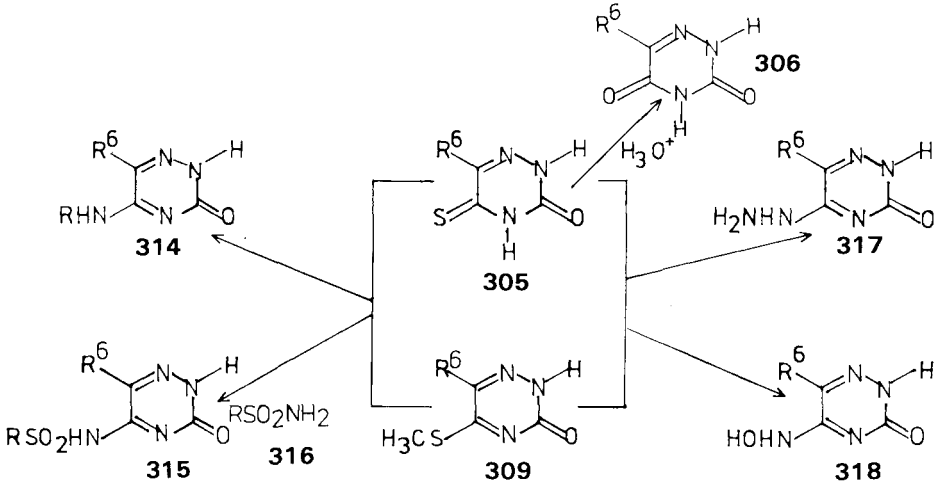
4. *Reactions*

5-Thioxo-1,2,4-triazine-3-ones (**305**) ($R^2 = R^4 = H$) can be alkylated by alkyl halides or dialkyl sulfates. Alkylation starts at the sulfur, followed by further alkylation at N–2 (297, 289, 327). Reaction of 6-phenyl-5-thioxo-1,2,4-triazin-3-one (**305a**) with diazomethane led to the 5-methylmercapto derivative **309a** in ethanol, but the 4-methyl (**305a**) (65%) and the 5-methylmercapto **309a** (35%) derivatives were isolated in dioxane (279). The dialkylated products were 2-methyl-5-(methylmercapto)-1,2,4-triazin-3-one (**309b**) in ethanol; **309b** and 2,4-dimethyl-5-thioxo-1,2,4-triazin-3-one (**305b**) were obtained in dioxane in 35 and 65% yields, respectively (279).



Reaction of the mercury salt of 5-(methylmercapto)-1,2,4-triazin-3-one with a sugar halide gave not only the *N*-2-substituted product, but also the *O*-substituted compound (295).

5-Thioxo-1,2,4-triazin-3-ones (**305**) as well as their *S*-methyl derivatives (**309**) were converted to 5-amino-1,2,4-triazin-3-ones (**314**) by treatment with ammonia (251, 295, 324, 327, 343, 465, 466, 468, 481, 487, 488, 501, 504, 505, 722, 723, 727–729) or amines (343, 466), to 5-sulfonamido-1,2,4-triazin-3-ones (**315**) by reaction with sulfonamides (**316**) (726), to 5-hydrazino-1,2,4-triazin-3-ones (**317**) by treatment with hydrazine (343, 466, 595, 596, 599), and to 5-(hydroxylamino)-1,2,4-triazin-3-ones (**318**) by reaction with hydroxylamine (343, 466).



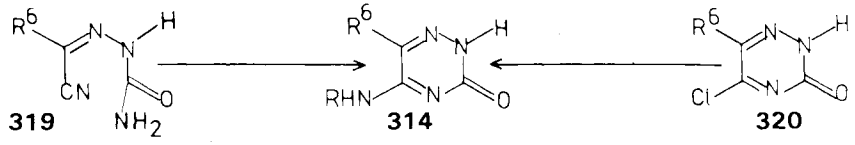
Acidic hydrolysis converts the 5-thioxo-1,2,4-triazin-3-ones (**305**) into 1,2,4-triazine-3,5-diones (**306**)(254).

B. 5-Amino-1,2,4-triazin-3-ones

1. *Preparation*

As was already stated in the preceding section 5-thioxo-1,2,4-triazin-3-ones (**305**) and their 5-methylmercapto derivatives (**309**) are converted into 5-amino-1,2,4-triazin-3-ones (**314**) by treatment with ammonia (251, 295, 324, 327, 343, 465, 466, 468, 481, 487, 488, 501, 504, 505, 722, 723, 725, 727–729) or amines (343, 466); reaction with sulfonamides forms 5-sulfonamido-1,2,4-triazin-3-ones (**315**) (726).

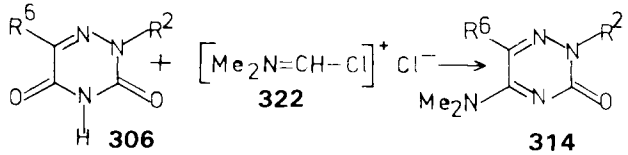
Cyclization of semicarbazones of *a*-ketonitriles (**319**) is another method for the synthesis of 5-amino-1,2,4-triazin-3-ones (**314**) (345, 730, 731).



319 **314** **320**

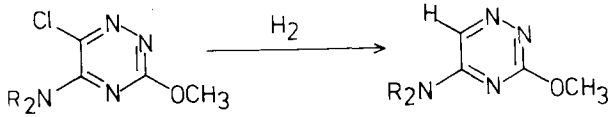
Reaction of 5-chloro-1,2,4-triazin-3-ones (**320**) with ammonia (218, 393, 481, 483, 487, 488, 490, 732) or amines (218, 486, 490, 491, 507, 733) has also been used for the synthesis of 5-amino-1,2,4-triazin-3-ones (**314**).

Zemlicka and Sorm (490) reported the synthesis of 5-amino-1,2,4-triazin-3-ones (**314**) by reaction of 1,2,4-triazine-3,5-diones (**306**) with Vilsmeyer reagent (**322**).



306 **322** **314**

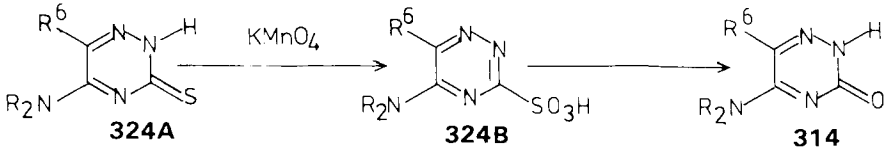
Hydrogenation of 6-chloro-3-methoxy-5-amino-1,2,4-triazines (**321a**) affords 3-methoxy-5-amino-1,2,4-triazines (**323**) [m.p.: R = H, 176 to 178°C (1565); R = CH_3, 101 to 102°C (1566)].



321 **323**

3-Methoxy-5-sulfonamido-1,2,4-triazines were obtained by reaction of 3,5-dimethoxy-1,2,4-triazine with sulfonamides or interaction of 3-(methylmercapto)-5-sulfonamido-1,2,4-triazines and sodium methoxide (489).

5-Amino-1,2,4-triazine-3-thiones (**324A**) can be converted by oxidation with potassium permanganate into 5-amino-1,2,4-triazine-3-sulfonic acids (**324B**) which are hydrolyzed with hydrochloric acid to 5-amino-1,2,4-triazin-3-ones (**314**) (324).



324A **324B** **314**

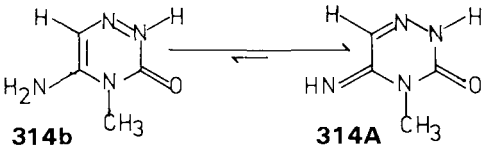
2. *Compound Survey*

Table II-21 lists the 5-amino-1,2,4-triazin-3-ones reported in the literature.

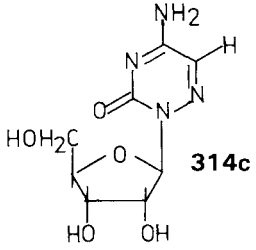
3. *Physical Properties*

5-Amino-1,2,4-triazin-3-ones (**314**) are white compounds with high melting points. Substitution at the nitrogens, especially at the amino group, lowers the melting point.

A number of infrared (350, 354, 357, 729, 737, 738), ultraviolet (729), and NMR spectroscopic (367–369, 729) studies on the structure of 5-amino-1,2,4-triazin-3-ones and their sugar-substituted derivatives have been published. These studies have shown that for 5-amino-1,2,4-triazin-3-ones and their N–2-substitituted derivatives the given 5-amino-3-oxo tautomeric structure is the predominant form in solution whereas for the 5-amino-4-methyl-1,2,4-triazin-3-one (**314b**) the 5-imino-3-oxo tautomer (**314A**) predominates.



314b **314A**



314c

The NMR spectroscopic studies (367–369) of sugar-substituted 5-amino-1,2,4-triazin-3-ones have shown that in solution the *anti*-conformation predominates.

Singh and Hodgson (736) reported the result of an X-ray crystallographic analysis of 2-(β-D-ribofuranosyl)-5-amino-1,2,4-triazine-3-one (**314c**) (6-azacytidine) and found the following data for the 1,2,4-triazine ring:

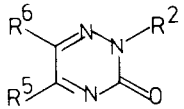
	N_1-N_2	N_2-C_3	C_3-N_4	N_4-C_5	C_5-C_6	C_6-N_1	C_3-O	C_5-N
Bond length (Å)	1.356	1.389	1.357	1.323	1.454	1.289	1.246	1.328

	$N_1N_2C_3$	$N_2C_3N_4$	$C_3N_4C_5$	$N_4C_5C_6$	$C_5C_6N_1$	$C_6N_1N_2$
Bond angle(°)	123.0	119	118.5	120.7	120	117.6

CD and ORD data on sugar-substituted 5-amino-1,2,4-triazin-3-ones are reported by different groups (360, 1089).

TABLE II-21. 5-AMINO-1,2,4-TRIAZIN-3-ONES

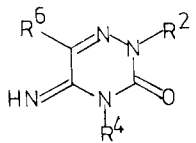
A. 5-Amino-1,2,4-triazin-3(2H)-ones



R^2	R^5	R^6	m.p. (°C)	Refs.
H	NH_2	H	320	327
			350	729
				730, 731
H	NH_2	CH_3	319–321	345
			327 (dec.)	502
H	NH_2	C_6H_5	268–271	345
H	$C_6H_5-CH_2-NH$	H	211	327
H	$(CH_3)_2N$	H	109–111	729
H	$C_6H_5-CO-NH$	CH_3	193–194.5	1089
H	$4\text{-}CH_3-C_6H_4SO_2NH$	H	149–152	726
H	$4\text{-}H_2N-C_6H_4SO_2NH$	H	200–202	726
CH_3	NH_2	H	325–326	729
			328–329	251
CH_3	$N(CH_3)_2$	H	109–111	729
CH_3	$C_6H_5SO_2NH$	CH_3	156–158.5	726
CH_3	$4\text{-}CH_3-C_6H_4SO_2NH$	H	142–144	726
CH_3	$4\text{-}CH_3-C_6H_4SO_2NH$	CH_3	133–136	726
CH_3	$4\text{-}Cl-C_6H_4SO_2NH$	H	164–166	726
CH_3	$4\text{-}H_2N-C_6H_4SO_2NH$	H	198–199.5	726
CH_3	$4\text{-}H_2N-C_6H_4SO_2NH$	CH_3	191–193	726
C_6H_5-CO	$C_6H_5-CO-NH$	CH_3	201–203	1089
$3,5\text{-}Cl_2C_6H_3$	NH_2	H	254–256	486
$3,5\text{-}Cl_2C_6H_3$	CH_3-NH	H	340–342	486
$3,5\text{-}Cl_2C_6H_3$	$(C_2H_5O)_2CH-CH_2-NH$	H	163–165	486

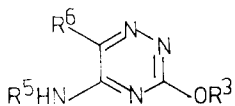
TABLE II-21. (*continued*)

B. 5-Imino-1,2,4-triazin-3(2H,4H)-ones



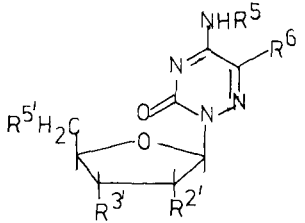
R^2	R^4	R^6	m.p. (°C)	Refs.
H	CH_3	H	230–234	729
CH_3	CH_3	H	120–122	729

C. 5-Amino-3-hydroxy-1,2,4-triazines



R^3	R^5	R^6	m.p. (°C)	Refs.
CH_3	4-H_2N–C_6H_4–SO_2	H	196–196.5	489
CH_3	4-H_2N–C_6H_4–SO_2	CH_3	172–173	489

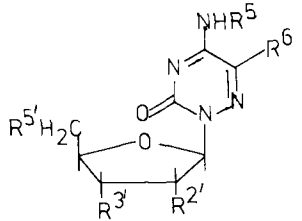
D. Sugar-substituted 5-amino-1,2,4-triazin-3-ones



$R^{2'}$	$R^{3'}$	$R^{5'}$	R^5	R^6	m.p. (°C)	Refs.
H	OH	OH	H	H	249–250	483, 487, 507, 732
						344
H	OH	OH	H	$CH_3 \cdot H_2O$	128–130	488
					129–130	507, 732
						344
H	OH	OH	H	CH_2OH	144–145.5	468
H	OH	$O-PO_3H_2$	H	H		344
H	4-$CH_3-C_6H_4-COO$	4-$CH_3-C_6H_4-COO$	H	H	209–210	487, 507, 732
H	4-$CH_3-C_6H_4-COO$	4-$CH_3-C_6H_4-COO$	H	CH_3		732
OH	OH	OH	H	H	215	504
					215–216	465
					216–217	295
					217–220	735
					220–222	505
					222–224 (dec.)	490, 493
					224	492
					231–233	428
OH	OH	OH	H	CH_3	238–239	481, 1089
OH	OH	OH	C_6H_5	H	177–178	733
OH	OH	OH	$C_6H_5CH_2$	H	129–130	733
OH	OH	OH	4-$CH_3-C_6H_4$	H	150–152	733

TABLE II-21. (*continued*)

D. Sugar-substituted 5-amino-1,2,4-triazin-3-ones



$R^{2'}$	$R^{3'}$	$R^{5'}$	R^5	R^6	m.p. (°C)	Refs.
OH	OH	OH	4-Cl–C_6H_4	H	249–251	733
OH	OH	OH	C_5H_5O	H	115	733
OH	OH	HCOO	H	H	192–193	734
OH	OH	O–PO_3H_2	H	H NH_3 salt		501
OH	OH	H_2OP–N O	H	H $(C_6H_{11})_2NH$ salt		501
OH	OH	O–$P_2O_6H_3$	H	H Ba salt		501
OH	OH	$(C_6H_5)_3C$	H	H	215–216	512
OH	O–PO_2H_2	OH	H	H Ba salt		527
HCOO	HCOO	HCOO	H	H	111–113	734
HCOO	HCOO	HCOO	CH_3CO	H		734
HCOO	HCOO	HCOO	C_2H_5CO	H		734
HCOO	HCOO	HCOO	$C_5H_{11}CO$	H		734
CH_3COO	CH_3COO	OH	H	H		512
CH_3COO	CH_3COO	CH_3COO	H	H	162–164	505
						493, 512, 722, 734
CH_3COO	CH_3COO	CH_3COO	CH_3CO	H	148–150	505
					148–149	512, 734
CH_3COO	CH_3COO	$(C_6H_5)_3C$	H	H	194–195	512

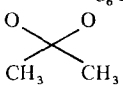
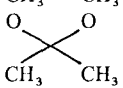
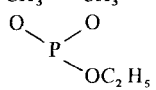
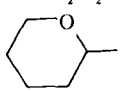
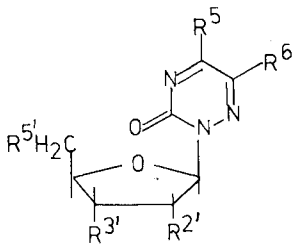
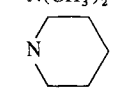
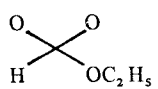
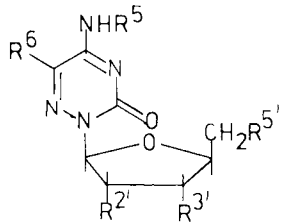
CH_3COO	CH_3COO	$(C_6H_5)_3C$	CH_3CO	H		512
CH_3COO	CH_3COO	HCOO	CH_3CO	H	146–147	734
CH_3COO	CH_3COO	HCOO	C_2H_5CO	H	152–153	734
C_2H_5COO	C_2H_5COO	HCOO	C_2H_5CO	H		734
C_2H_5COO	C_2H_5COO	C_2H_5COO	H	H		734
C_2H_5COO	C_2H_5COO	C_2H_5COO	C_2H_5CO	H		734
C_6H_5COO	C_6H_5COO	C_6H_5COO	H	H	216–218	725, 727
					218–220	505
					218	490
						492, 723, 728
C_6H_5COO	C_6H_5COO	C_6H_5COO	CH_3CO	H	202–204	505
C_6H_5COO	C_6H_5COO	C_6H_5COO	CH_3CO	CH_3	Foam	1089
C_6H_5COO	C_6H_5COO	C_6H_5COO	H	CH_3	180–183	481
C_6H_5COO	C_6H_5COO	C_6H_5COO	C_6H_5	H	204–205	733
C_6H_5COO	C_6H_5COO	C_6H_5COO	$C_6H_5CH_2$	H	122–125	733
C_6H_5COO	C_6H_5COO	C_6H_5COO	4-$CH_3C_6H_4$	H	186–187	733
C_6H_5COO	C_6H_5COO	C_6H_5COO	4-Cl–C_6H_4	H	179–181	733
C_6H_5COO	C_6H_5COO	C_6H_5COO	C_5H_5O	H	132–135	733
C_6H_5COO	C_6H_5COO	C_6H_5COO	CH_3	H	205–206	490
C_6H_5COO	C_6H_5COO	C_6H_5COO	C_6H_5CO	CH_3	129–131	1089
C_6H_5COO	C_6H_5COO	C_6H_5COO	2-Furyl	H	84–87	490
		OH	H	H	195.5–197	517
					202–203	505
		CH_3COO	H	H	173–175	505
		OH	H	H		527
$O-PO_2H_2$	OH	OH	H	H Ba salt		527
	OPO_3H_2	CH_3COO	CH_3CO	H		526

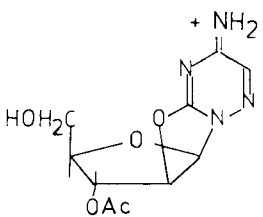
TABLE II-21. (*continued*)

D. Sugar-substituted 5-amino-1,2,4-triazin-3-ones



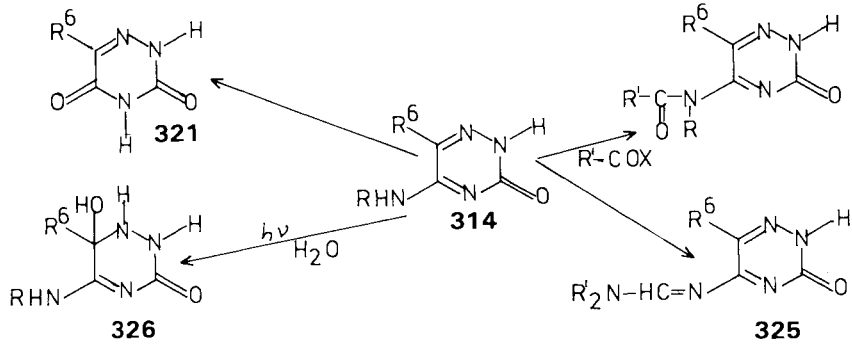
$R^{2'}$	$R^{3'}$	$R^{5'}$	R^5	R^6	m.p. (°C)	Refs.
OH	OH	OH	$N(CH_3)_2$	H	176–177	490
$O-\underset{\displaystyle OC_2H_5}{\underset{\vert}{CH}}-CH_3$	OPO_3H_2	$O-\underset{\displaystyle OC_2H_5}{\underset{\vert}{CH}}-CH_3$	$N{=}CH-N(CH_3)_2$	H		526
CH_3-COO	CH_3COO	CH_3COO	$N(CH_2CH_2OH)_2$	H	Foam	491
C_6H_5-COO	C_6H_5-COO	C_6H_5-COO	$N(CH_3)_2$	H	177–179	490, 492
C_6H_5-COO	C_6H_5-COO	C_6H_5-COO		H	159–160	490
		OH	$N{=}CH-N(CH_3)_2$	H		461



$R^{2'}$	$R^{3'}$	$R^{5'}$	R^5	R^6	m.p. (°C)	Refs.
OH	OH	OH	H	H	216–217	343
					217–219	466
OH	OH	OH	n-C_4H_9	H	Noncryst. foam	343, 466
OH	OH	HCOO	H	H	192–193	557
HCOO	HCOO	HCOO	H	H	112–114	557
HCOO	HCOO	HCOO	CH_3CO	H		557
CH_3COO	CH_3COO	HCOO	H	H	142–143	557
CH_3COO	CH_3COO	HCOO	CH_3CO	H	146–147	557
					218–219	740

4. *Reactions*

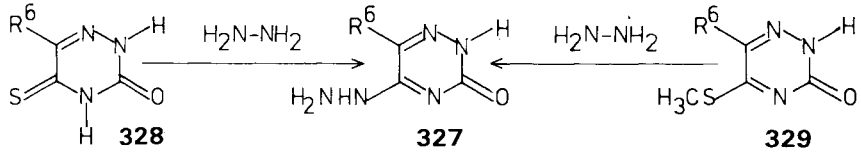
Only a few reactions of 5-amino-1,2,4-triazin-3-ones (**314**) have been reported so far. They can be acylated (512, 557, 734, 1089), hydrolysed to 1,2,4-triazine-3,5-diones (**321**) (324, 526) and converted to amidines (**325**) by treatment with formamide acetals (461, 526).



Transformation of 5-amino-1,2,4-triazin-3-ones (**314**) into 1,2,4-triazine-3,5-diones can also be achieved photochemically (408). The photochemical addition of water to the C_6N_1 double bond of **314** yielding **326** is reported by Kittler (1092).

C. 5-Hydrazino-1,2,4-triazin-3-ones

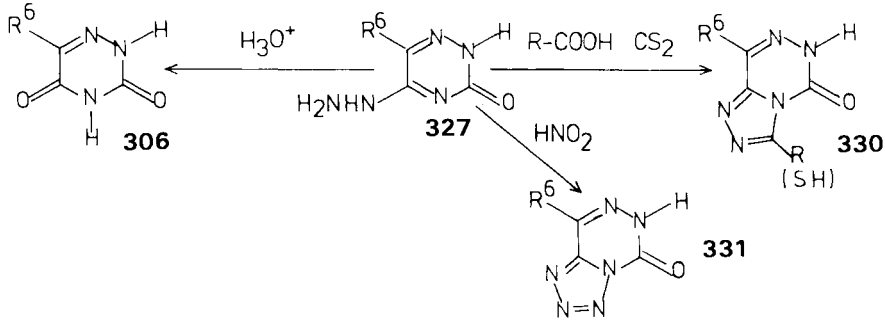
All known 5-hydrazino-1,2,4-triazin-3-ones (**327**) are prepared by reaction of 5-thioxo-1,2,4-triazin-3-ones (**328**) or their *S*-methyl derivatives (**329**) with



R^2	R^6	m.p. (°C)	Refs.
H	H	240	343, 466
		300	599
H	CH_3	290	595, 596
H	C_6H_5	290	596
β-D-Ribofuranosyl	H	glass	343, 466
Tribenzoyl-β-D-ribofuranosyl	H		343, 466

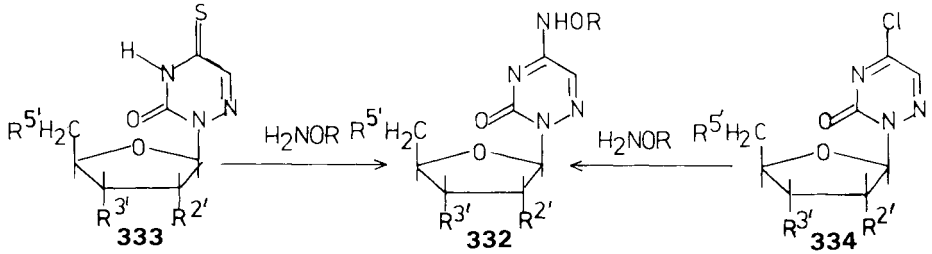
hydrazine (343, 466, 595, 596, 599). An excess of hydrazine not only transforms 2-(β-ribofuranosyl)-5-thioxo-1,2,4-triazin-3-one to the 5-hydrazino-1,2,4-triazin-3-one derivative but also removes the sugar substituent (343, 466).

Acidic hydrolysis converts the 5-hydrazino-1,2,4-triazin-3-ones (**327**) into the 1,2,4-triazine-3,5-diones (**306**) (343, 466). Reaction of 5-hydrazino-1,2,4-triazin-3-ones with nitrous acid (596), carboxylic acids (595, 596) or carbon disulfide has been used for the synthesis of the condensed heterocyclic systems **330** and **331**.



D. 5-(Hydroxylamino)-1,2,4-triazin-3-ones

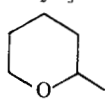
5-(Hydroxylamino)-1,2,4-triazin-3-ones (**332**) are known only as 2-(β-D-ribofuranosyl) derivatives. They are prepared by reaction of hydroxylamine with either 5-thioxo-1,2,4-triazin-3-one derivatives (**333**) (343, 466) or 5-chloro-1,2,4-triazin-3-one derivatives (**334**) (741). Acidic hydrolysis of **332** leads to 1,2,4-triazine-3,5-diones (343, 466). Known compounds are listed in Table II-22.

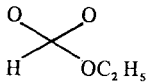
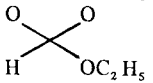
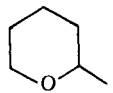
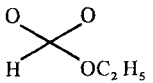
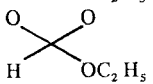
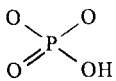


E. 5-Chloro-1,2,4-triazin-3-ones

5-Chloro-1,2,4-triazin-3-ones such as **335** (Table II-23) are prepared by treatment of 1,2,4-triazine-3,5-diones, such as **336**, with either thionyl chloride/

TABLE II-22. 5-(HYDROXYLAMINO)-1,2,4-TRIAZIN-3-ONES (**332**)

$R^{2'}$	$R^{3'}$	$R^{5'}$	R	m.p (°C)	Refs.
OH	OH	OH	H	234–235	466
				235–238	343
				247–249	741
OH	OH	OH	$CH(CH_3)(OC_2H_5)$		409
OH	OH	OH	 2-Tetrahydropyranyl		741
OH	OH	OH	$(4\text{-}CH_3OC_6H_4)_2C(H)C_6H_5$		741
OH	OH	OH	PO_3H_2		741
OH	OH	OPO_3H_2	H		741
OH	OH	OPO_3H_2	PO_3H_2		741
OH	OH	$OP_2O_6H_3$	H		741
OH	OPO_2H_2	OH	H		409
OH	OPO_3H_2	OH	H		409

CH_3COO	CH_3COO	CH_3COO	H	409, 741
CH_3COO	CH_3COO	CH_3COO	CH_3CO	741
CH_3COO	OPO_3H_2	CH_3COO	CH_3CO	409
$\overset{\displaystyle OC_2H_5}{\overset{\displaystyle |}{CH}}-CO_3$	OPO_3H_2	$\overset{\displaystyle OC_2H_5}{\overset{\displaystyle |}{CH}}-CH_3$	$\overset{\displaystyle OC_2H_5}{\overset{\displaystyle |}{CH}}-CH_3$	409
		OH	H	741
		OH	 2-Tetrahydropyranyl	741
		OH	$\overset{\displaystyle OC_2H_5}{\overset{\displaystyle |}{CH}}-CH_3$	409
		OPO_3H_2	$\overset{\displaystyle OC_2H_5}{\overset{\displaystyle |}{CH}}-CH_3$	409
OPO_2H_2	OH	OH	H	409
		OH	H	409

DMF (428, 481, 483, 487, 488, 490–494) or phosphorus oxychloride/phosphorus pentachloride (486). In most cases **335** were not isolated. The chlorine in the 5-position is very reactive and can be replaced by reaction with ammonia or amines (428, 481, 483, 486–488, 490–493, 507, 732, 733), hydrazine (739), or hydroxylamine (741). The spectrum of 2-(2′,3′,5′-tribenzoyl-β-D-ribofuranosyl)-5-chloro-1,2,4-triazin-3-one is reported by Pitha and Zemlicka (357). Replacement of a 3-methylmercapto group by halogen is reported by Restivo (793).

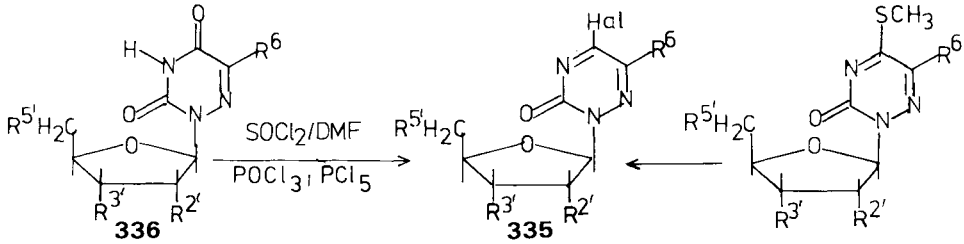


TABLE II-23. 5-CHLORO-1,2,4-TRIAZIN-3-ONES (335)

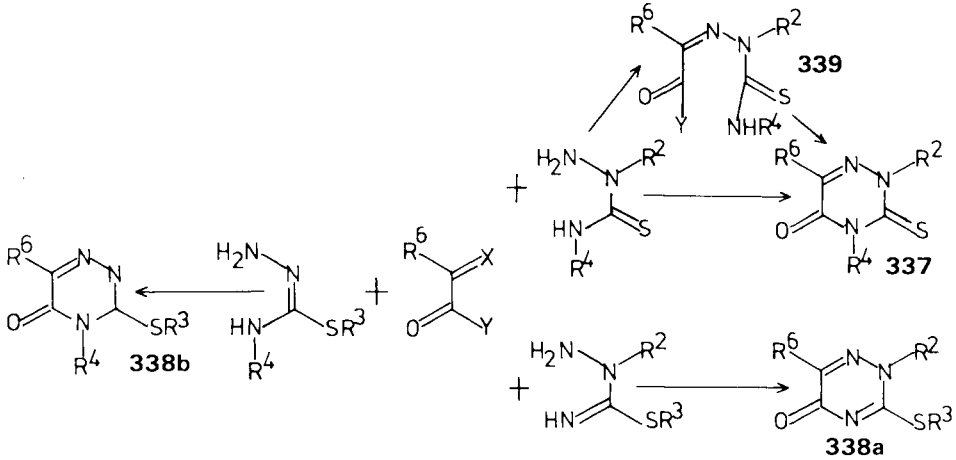
$R^{2'}$	$R^{3'}$	$R^{5'}$	Hal	R^6	m.p. (°C)	Refs.
H	4-$CH_3C_6H_4COO$	4-$CH_3C_6H_4COO$	Cl	H	167	487
			Two forms		154–159	483
					161–166.5	483
H	4-$CH_3C_6H_4COO$	4-$CH_3C_6H_4COO$	Cl	CH_3	131–134	488
OH	OH	OH	Cl	H		793
CH_3COO	CH_3COO	CH_3COO	Cl	H	Syrupy	490, 491
C_6H_5COO	C_6H_5COO	C_6H_5COO	Cl	H	149.5–151.5	490, 492, 494, 793
C_6H_5COO	C_6H_5COO	C_6H_5COO	Br	H		793

F. 3-Thioxo-1,2,4-triazin-5-ones

1. *Preparation*

3-Thioxo-1,2,4-triazine-5-ones (5-hydroxy-3-mercapto-1,2,4-triazines) (**337**) are well-known compounds; their synthesis, physical properties, and reactions have been intensively studied.

The most frequently used method for the synthesis of 3-thioxo-1,2,4-triazin-5-ones (**337**) or 3-mercapto-1,2,4-triazin-5-ones (**338**) starts with α-ketocarboxylic acids or their derivatives and thiosemicarbazide or its derivatives (189, 206, 212, 221, 225, 227, 229, 237–239, 241, 243–249, 251–259, 262, 263, 267–271, 275, 280, 281, 285–288, 290, 291, 296–300, 304, 306, 307, 311–316, 318, 319, 321, 322, 574, 575, 592, 593, 599, 600, 710, 712, 744, 746–752, 754–756, 758, 762, 764–769, 771–776, 778, 779, 782, 788, 790, 791, 794, 798–801, 803–812, 815, 900, 1094, 1095). In most cases the initially formed thiosemicarbazone (**339**) is isolated and then cyclized under basic conditions (aqueous NaOH, KOH, K_2CO_3). The reaction is achieved by heating the reaction mixture to reflux for a few minutes or, often with better yields, at room temperature with longer reaction time.



In a few cases the reaction is run in acidic media (790, 791), ethanol (206, 251, 268, 307, 311, 319, 710, 790, 791) or dimethylformamide (251). The following derivatives of α-ketocarboxylic acids were used: esters (X = O, Y = OR) (241, 251, 256–258, 287, 288, 311, 503, 592, 593, 600, 710, 712, 752, 754, 762, 799, 800, 815, 1094, 1095), amides (X = O, Y = NHR) (1562), α-oximo esters (X = NOH, Y = OR) (227, 574, 775, 779), thioketo acids (X = S, Y = OH) (812), α-imino nitriles (771, 773, 813), α-ethoxyallyl γ-butyrolactone (757), azlactones (315), rhodanine (804), thiazolidine-2,4-diones (804) and isatin (756, 758, 759, 782, 810).

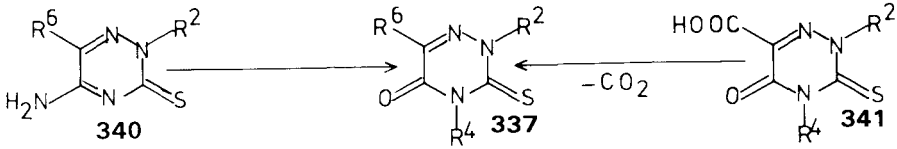
The following substituted thiosemicarbazides were used for the synthesis of substituted 3-thioxo-1,2,4-triazin-5-ones: N_2-substituted (244, 251, 269, 280, 281, 290, 304, 746, 750, 762, 782, 788), *S*-substituted (221, 237, 253, 256, 268, 307, 311, 710, 754, 776, 798) N_4-substituted (206, 212, 229, 241, 243, 245, 246, 251, 271, 280, 290, 319, 574, 749, 806), N_2N_4-disubstituted (241, 244,

251, 267, 280, 762), N_2S-disubstituted (237, 241, 267, 747, 752, 799), and N_4S-disubstituted thiosemicarbazides (241, 267, 747, 798).

To prevent the hydrolysis of the alkyl- or arylmercapto group, the reaction with *S*-substituted thiosemicarbazones should be carried out in nonaqueous solvent if stronger reaction conditions are necessary.

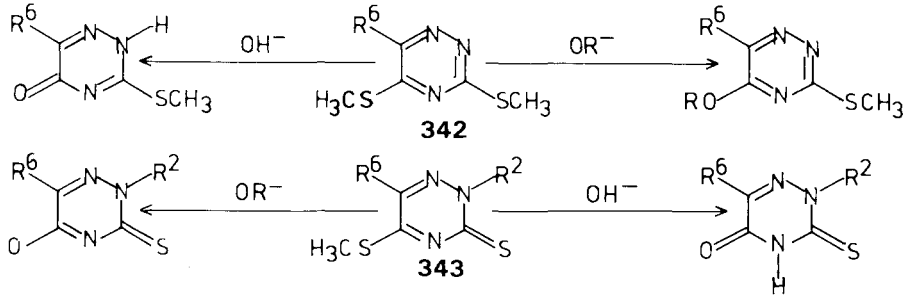
Beside this method the following reactions were used for the synthesis of 3-thioxo-1,2,4-triazine-5-ones (**337**).

5-Amino-1,2,4-triazine-3-thiones (**340**) can by hydrolyzed in both acidic and basic media to 3-thioxo-1,2,4-triazine-5-ones (**337**) (251, 324, 345, 813).

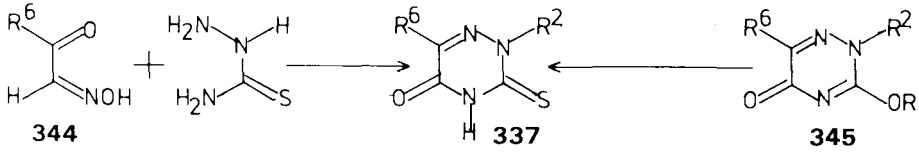


5-Oxo-3-thioxo-1,2,4-triazine-6-carboxylic acids (**341**) can be decarboxylated to 3-thioxo-1,2,4-triazine-5-ones (**337**) (287, 324).

3,5-Bis(methylmercapto)-1,2,4-triazines (**342**) or 5-(methylmercapto)-1,2,4-triazine-3-thiones (**343**) can be transformed into 3-thioxo-1,2,4-triazin-5-one derivatives by reaction with sodium hydroxide or sodium alkoxides (279, 305, 1564).

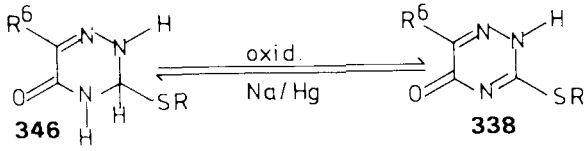


Lalezari and Golgolab (292) reported the synthesis of 3-thioxo-1,2,4-triazine-5-ones (**337**) by reaction of glyoxal aldoximes (**344**) with thiosemicarbazide in basic media.



Reaction of a 3-alkoxy-1,2,4-triazin-5-one (**345**) with hydrogen sulfide is also used for the synthesis of **337** (533).

Oxidation of 3,4-dihydro-3-(alkylmercapto)-1,2,4-triazin-5-ones (**346**) is the reverse reaction of the reduction of 3-(methylmercapto)-1,2,4-triazine-5-ones (**338**) with sodium amalgam (268, 748).



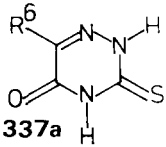
2. *Compound Survey*

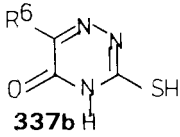
The 3-thioxo-1,2,4-triazin-5-ones reported in the literature are listed in Table II-24.

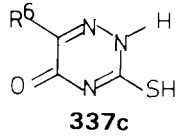
3. *Physical Properties*

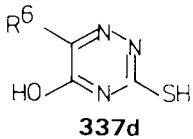
3-Thioxo-1,2,4-triazin-5-ones (**337**) (5-hydroxy-3-mercapto-1,2,4-triazines) are crystalline colorless compounds with high melting points. Substitution at the nitrogens or at the sulfur usually lowers the melting point.

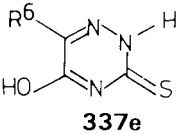
Six tautomeric structures **337a** to **337f** can be discussed for 3-thioxo-1,2,4-triazine-5-ones. Derivatives of the tautomeric forms **337a** to **337d** are known.

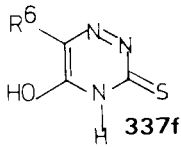

337a


337b


337c


337d


337e

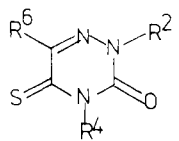

337f

Infrared (247, 280, 281, 319, 321, 351, 356, 358) and ultraviolet spectroscopic (247, 280, 281, 319, 321, 601) studies of different groups have shown that in neutral solutions the tautomeric structure **337a** predominates. In the infrared spectra of the unsubstituted 3-thioxo-1,2,4-triazin-5-one and its *N*-methyl derivatives a rather intensive band is observed for both the C=O stretching vibration and the C=S stretching vibration (351); the exact wave numbers of these vibrations and of the N–H-stretching vibrations are given in Table II-25. In the same table the ultraviolet spectra of the unsubstituted 3-thioxo-1,2,4-triazin-5-one and its *N*- and *S*-methyl derivatives are given together with the pK_a values of these compounds (289, 392, 601).

NMR values of 3-thioxo-1,2,4-triazin-5-ones are reported by Jacquier and his group (280, 281). Half-wave potentials and polarographic studies of this system were published by Polonsky and co-workers (792). 3-Thioxo-1,2,4-triazin-5-ones

TABLE II-24. 3-THIOXO-1,2,4-TRIAZIN-5-ONES

A. 3-Thioxo-1,2,4-triazin-5(2H,4H)-ones



R^2	R^4	R^6	m.p. (°C)	Refs.
H	H	H	227–228	324
			248–250 (dec.)	503, 600
			250 (dec.)	776
			250–252	275
			251	286, 287, 318
			260–262	593
				306
H	H	CH_3	201–204	345
			209	318
			210–212	593
			215–216	503
			218–219	252, 275, 287
			219–220	599
			220	259, 291, 772
			240–241	189
H	H	C_2H_5	165	227
			166–167	503, 593
			168	288
H	H	n-C_3H_7	149	227
			149–150	503
			152	298, 811

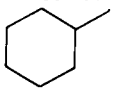
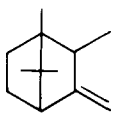
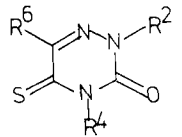
H	H	*i*-C_3H_7	215	288
			215–216	503
H	H	*n*-C_4H_9	143	227
			143–144	298, 811
H	H	*i*-C_4H_9	182	227
H	H	*t*-C_4H_9	303	288
H	H	*n*-C_5H_{11}	143	288
H	H	*n*-C_6H_{13}	135	811
H	H	*n*-C_7H_{15}	135	298
			135–136	503
H	H	*n*-C_8H_{17}	133.5–134.5	811
H	H	*n*-C_9H_{19}	134–135	298
H	H	*n*-$C_{10}H_{21}$	133–134	811
H	H	*n*-$C_{11}H_{23}$	135–136	298
H	H	*n*-$C_{12}H_{25}$	135–136	811
H	H	*n*-$C_{13}H_{27}$	135–136	298
H	H		206–208	804
			266–268	315
H	H		181–182	807
H	H	CH_2OH	235–236.5	258
H	H	CH_2OCH_3	230–233	252
H	H	$CH_2SCH_2C_6H_5$	168–170	900
H	H	CH_2CH_2OH	194–196	754, 779
H	H	$CH_2CH_2CH_2OH$	166	755
H	H	$CH_2CH_2NH_2$	255–256	773
			256	774
	·HCl		243–245	774

TABLE II-24. (*continued*)

A. 3-Thioxo-1,2,4-triazin-5(2H,4H)-ones



R^2	R^4	R^6	m.p. (°C)	Refs.
H	H	CH_2COOH	181	288
H	H	$CH_2COOC_2H_5$	185	288
			186–188	1094, 1095
		(methylene)	278–279	800
H	H	$CH_3-CH-COOC_2H_5$	150–153	815
H	H	$CHFCOOC_2H_5$	153.5–155	256
H	H	CH_2CH_2COOH	212–213	313
H	H	$CH_2CH_2COOCH_3$	178–180	313
H	H	$(CH_2)_3COOH$	186–188	301
H	H	$(CH_2)_4COOH$	193–194	301
H	H	$(CH_2)_5COOH$	169–170	314
H	H	$C_6H_5CH_2$	188–190	503
			194	266, 322
			194–195	315, 321, 804
H	H	$4\text{-}CH_3C_6H_4CH_2$	182–183	321
H	H	$4\text{-}(n\text{-}C_3H_7)C_6H_4CH_2$	186–187	321
H	H	$4\text{-}Cl\text{-}C_6H_4CH_2$	226–227	321
H	H	$4\text{-}Br\text{-}C_6H_4CH_2$	230–232	321
H	H	$2,4\text{-}Cl_2C_6H_3CH_2$	203–204	321
H	H	$4\text{-}HO\text{-}C_6H_4CH_2$	221–222	321
H	H	$2\text{-}CH_3OC_6H_4CH_2$	157–158	315
H	H	$4\text{-}CH_3OC_6H_4CH_2$	170–171	321
			176–177	804
			177	225, 812

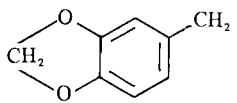
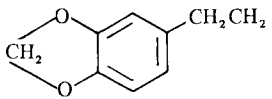
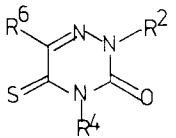
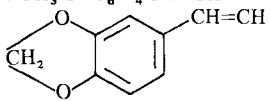
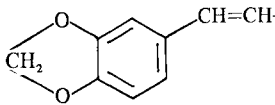
H	H	2,3-$(CH_3O)_2C_6H_3CH_2$	177	303
H	H	3,4-$(CH_3O)_2C_6H_3CH_2$	204–205	321
			207–208	315, 804
H	H	4-$CH_3OC_6H_4CH(CH_3)$	165.5	270
			171	748
H	H	4-$C_2H_5OC_6H_4CH_2$	198–199	321
H	H	3,4-$(C_2H_5O)_2C_6H_3CH_2$	156–157	321
H	H		225–226	247
H	H	$C_6H_5COCH_2$	240 (dec.)	790, 791, 806
H	H	$C_6H_5CH_2CH_2$	210	322
H	H		188	247
H	H	$C_6H_5COOCH_2$	167–168	754
H	H	$C_6H_5CHBrCHBr$		206
H	H	$C_6H_5C(=N-NH-CSNH_2)-CH_2$	250	262, 263
			252	791
			255	806
H	H	2-HOOC–$C_6H_5CONHCH_2CH_2$	280–282	773
H	H	$C_6H_5-CH=CH-2Br^-$ (N-pyridinium)		206
H	H	$C_6H_5CH=CH$	264	247
			266	206
				312
H	H	4-F–$C_6H_4CH=CH$	263–264	247

TABLE II-24. (*continued*)

A. 3-Thioxo-1,2,4-triazin-5(2H,4H)-ones



R^2	R^4	R^6	m.p. (°C)	Refs.
H	H	4-Cl–C_6H_4CH=CH	286–288	248
H	H	4-CH_3O–C_6H_4CH=CH	273	247
			286–288	249
H	H		270	805
			272.5–273.5	247/743
H	H	2,3-$(CH_3O)_2C_6H_3$CH=CH	266–268	303
H	H	3,4-$(CH_3O)_2C_6H_3$CH=CH	257–258	247
H	H	3,4,5-$(CH_3O)_2C_6H_2$CH=CH	242–243	247
H	H	4-O_2N–C_6H_4CH=CH	222–224	316
H	H	C_6H_5CH=CH–CH=CH	265–267	312
H	H	4-CH_3O–C_6H_4CH=CH–CH=CH	263–264	247
H	H		248	247
H	H	C_6H_5	170	321
			209	717
H	H		255–256	288
			256	322
			257–258	710, 712
			258–259	189, 280, 503
			265	292/575

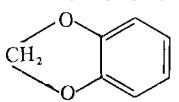
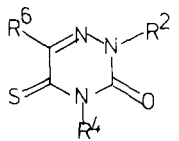
H	H	4-$CH_3C_6H_4$	258	292
H	H	1-Naphthyl	228–229	574
H	H	2-Naphthyl	274	234
H	H		325–327 (dec.)	316
H	H	4-F–C_6H_4	249	292
H	H	4-Cl–C_6H_4	273	292
			284	710, 712
			288–290	574
			290 (dec.)	768
H	H	2,4-$Cl_2C_6H_3$	219–220	710, 712
H	H	3,4-$Cl_2C_6H_3$	227–230	710, 712
H	H	4-Br–C_6H_4	278–280	574
			280 (dec.)	768
			285	295
H	H	2-HO–C_6H_4	266	808, 1562
H	H	4-HO–C_6H_4	266 (dec.)	810
			282–283	574
			286 (dec.)	768
H	H	4-CH_3O–C_6H_4	272	292
			278–280	574
			280 (dec.)	768
H	H	4-$HOCH_2CH_2OC_6H_4$	266–268	574
			268 (dec.)	768
H	H	3-CH_3O-4-CH_3–C_6H_3	273 (dec.)	768
H	H	2,4-$(HO)_2C_6H_3$	310 (dec.)	768
			312	574
H	H	3,4-$(HO)_2C_6H_3$	310–320	574
H	H	3-CH_3O-4-HO–C_6H_3	274–276	574
			277 (dec.)	768
H	H	3,4-$(CH_3O)_2C_6H_3$	276	574
H	H		270 (dec.) 277	803 247

TABLE II-24. *(continued)*

A. 3-Thioxo-1,2,4-triazin-5(2H,4H)-ones

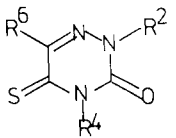


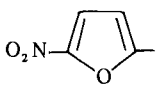
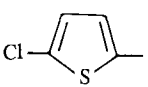
R^2	R^4	R^6	m.p. (°C)	Refs.
H	H	3-HOOC-4-HO–C_6H_3	292	574
H	H	2-HS–C_6H_4	250 (dec.)	809
H	H	4-CH_3S–C_6H_4	238–240	574, 765
			240	768
H	H	4-C_2H_5S–C_6H_4	265 (dec.)	768
			266–268	574
H	H	4-CH_3SO_2–C_6H_4	307–308	574
			308 (dec.)	768
H	H	4-$C_2H_5SO_2$–C_6H_4	302–304	574
			304 (dec.)	768
H	H	2-H_2N–C_6H_4	>300	758
			>330	759, 810
H	H	2-CH_3NH–C_6H_4	270–280 (dec.)	758
			275–280	759
H	H	2-HCONH–C_6H_4	290–291 (dec.)	758
H	H	2-HCO–$N(CH_3)$–C_6H_4	290–291 (dec.)	759
H	H	2-CH_3CONH–C_6H_4	299–300 (dec.)	758
			301–303 (dec.)	759
H	H	2-$CH_3CON(CH_3)$–C_6H_4	256–257 (dec.)	758, 759
H	H	3,5-Br_2-2-H_2N–C_6H_2	>360	759
H	H	5-O_2N-2-H_2N–C_6H_3	337–340 (dec.)	759
H	H	3-H_2N–C_6H_4	227–229	574
H	H	3-CH_3CONH–C_6H_4	245–247	574
H	H	3-C_6H_5CONH–C_6H_4	289–292	574

H	H	3-$C_2H_5OCONH-C_6H_4$	247–249	574
H	H	3-$CH_3SO_2NH-C_6H_4$	259–261	574
H	H	3-$C_6H_5-CH=N-C_6H_4$	206–208	574
H	H	4-$H_2N-C_6H_4$	302–303	758
			306 (dec.)	574, 768
				766
H	H	4-$CH_3CONH-C_6H_4$	350 (dec.)	766, 764
				768
			350–352 (dec.)	574, 758
				575
H	H	4-$(CH_3)_2C=CHCONH-C_6H_4$	264–266	274
			266	768
H	H	4-$C_6H_5CH=N-C_6H_4$	250–255	574
H	H	4-$CH_3OCONH-C_6H_4$	298–300	574
H	H	4-$C_2H_5OCONH-C_6H_4$	320–330	574
			330	768
H	H	4-$CH_3NHCSNH-C_6H_4$	230–235	574
			235	768
H	H	4-$C_2H_5NHCONH-C_6H_4$	334 (dec.)	574, 768
H	H	4-$CH_3SO_2NH-C_6H_4$	300 (dec.)	768
H	H	4-$C_6H_5CONH-C_6H_4$	311–312	574
			312 (dec.)	768
H	H	4-(4-$CH_3C_6H_4CONH)C_6H_4$	317	768
H	H	4-(4-$CH_3OC_6H_4CONH)C_6H_4$	315–317	574
H	H	4-[3,4-$(CH_3)_2C_6H_3COHN]C_6H_4$	310–315	574
H	H	3-$O_2N-C_6H_4$	226–227	574
H	H	4-$O_2N-C_6H_4$	253–254	758
			258–259	574
			259 (dec.)	768
H	H	2-$HOOC-C_6H_4$	263	574
H	H	4-$HOOC-C_6H_4$	240	574
H	H	2-Pyridyl	324	574
				575, 777

TABLE II-24. (*continued*)

A. 3-Thioxo-1,2,4-triazin-5(2H,4H)-ones



R^2	R^4	R^6	m.p. (°C)	Refs.
H	H	3-Pyridyl	336	574
				575, 777
H	H	4-Pyridyl	264–266	574
			304	592
			308 (dec.)	775
			313	292
				575, 777
H	H	2-Furyl	246–247	788
			320	212
			328–330 (dec.)	245
H	H	 5-O_2N-2-furyl	210–212	788
			249–250	212
H	H	2-Thienyl	279	292
			282–284	574
			283	767, 769
				575
H	H		266–268	574

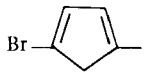
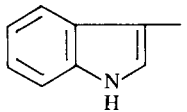
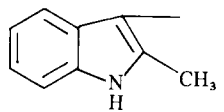
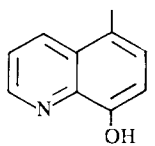
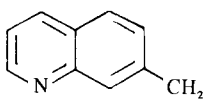
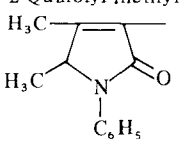
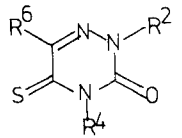
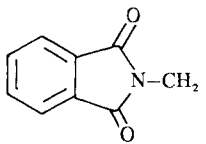
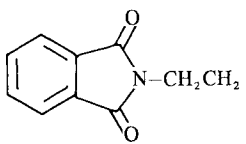
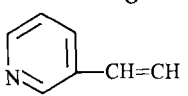
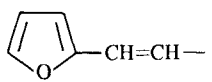
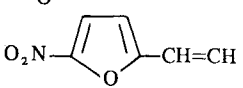
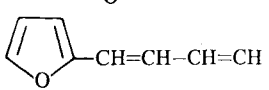
H	H	 5-Br–2-thienyl	278	574
H	H	 3-Indolyl	320–322	794
H	H	 2–CH_3–3-indolyl	252–254 (dec.)	241
H	H	 8–HO–5-quinolyl	300	574
H	H	 2-Quinolyl methyl	288–290	574
H	H		288–289	801

TABLE II-24. (*continued*)

A. 3-Thioxo-1,2,4-triazin-5(2H,4H)-ones



R^2	R^4	R^6	m.p. (°C)	Refs.
H	H		286	771
H	H		280–282	773
H	H		342–345	299
H	H		267–269	246, 312
H	H		>300	241, 243
H	H		250	246

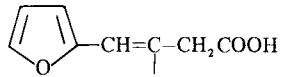
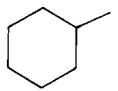
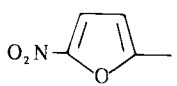
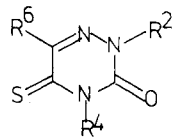
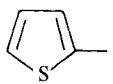
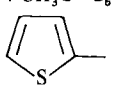
H	H		260–261	246
H	CH_3	H	158–160	289
H	CH_3	CH_3	186	229, 806
			188–190	251
			189–190	281
H	CH_3	i-C_3H_7	193	229, 806
H	CH_3	CH_2CH_2COOH	200	229, 806
H	CH_3	$CH_2CH_2COOCH_3$	147	229, 806
H	CH_3	 Cyclohexyl	189	229, 806
H	CH_3	C_6H_5	219	229, 806
			221–222	280
			223–224	574
H	CH_3	$C_6H_5CH_2$	175.5	271, 749
			182	229, 806
H	CH_3	$C_6H_5-CH=CH$	~240	206
H	CH_3	3-CH_3–C_6H_4	195	229, 806
H	CH_3	4-Cl–C_6H_4	224	229, 806
H	CH_3	4-Cl–C_6H_4–CH_2	229	229, 806
H	CH_3	3-CH_3O–C_6H_4	164	229, 806
H	CH_3	4-CH_3S–C_6H_4	181–182	574
H	CH_3	2-Furyl	247	229, 806
			261–262.5	212
H	CH_3	5-O_2N-2-furyl	210–211	212
H	CH_3		207–208	243
			209–210 (dec.)	241

TABLE II-24. (*continued*)

A. 3-Thioxo-1,2,4-triazin-5(2H,4H)-ones



R^2	R^4	R^6	m.p. (°C)	Refs.
H	C_2H_5	$C_6H_5CH_2$	175	271
			176	749
H	C_2H_5	C_6H_5	207–208	574
			208	229, 806
H	C_2H_5	 2-Thienyl	252–253	574
H	*i*-C_3H_7	C_6H_5	175	229, 806
H	CH_2=$CHCH_2$	C_6H_5	186–187	574
			187	229, 806
H	CH_2=$CHCH_2$	4-CH_3O–C_6H_4	180–181	574
H	CH_2=$CHCH_2$	4-CH_3S–C_6H_4	215–216	574
H	CH_2=$CHCH_2$	 2-Thienyl	223–224	574
H	2,4-$(O_2N)_2C_6H_3NHN$=$CHCH_2$	CH_3	196	780
H	*i*-C_4H_9	CH_3	176	229, 806
H	*i*-C_4H_9	C_6H_5	173	229, 806
H	C_6H_5	C_6H_5	275	229, 806
			285–286	319
H	C_6H_5	C_6H_5–CH=CH	272	206

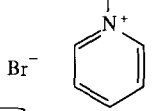
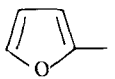
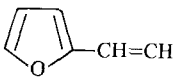
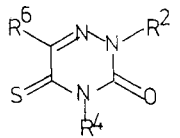
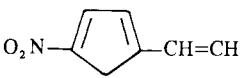
H	C_6H_5	C_6H_5–CHBrCHBr		215 (dec.)	206
H	C_6H_5	C_6H_5–CHBr–CH	(or isomer)	295 (dec.)	206
					
H	C_6H_5			295 (dec.)	245
		2-Furyl			
H	C_6H_5			264–265	246
H	2-$CH_3C_6H_4$	C_6H_5		235–236	319
H	3-$CH_3C_6H_4$	CH_3		230–231	319
H	3-$CH_3C_6H_4$	C_6H_5		263–264	319
H	4-$CH_3C_6H_4$	CH_3		208	319
H	4-$CH_3C_6H_4$	C_6H_5		307–308	319
H	2-$CH_3OC_6H_4$	CH_3		226	319
H	4-$CH_3OC_6H_4$	CH_3		184–185	319
H	4-$CH_3OC_6H_4$	C_6H_5		290	319
H	2-$C_2H_5OC_6H_4$	CH_3		156	319
H	3-Cl–C_6H_4	C_6H_5		250–251	319
H	4-Cl–C_6H_4	CH_3		224–225	319
H	4-Cl–C_6H_4	C_6H_5		318–320	319
CH_3	H	H		216–218	290
				222–223	251
					289, 304
CH_3	H	CH_3		163–164	304
				163–165	251
				164–165	281
CH_3	H	$C_6H_5CH_2$		152.5	269
				153.5	750

TABLE II-24. (*continued*)

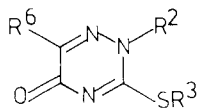
A. 3-Thioxo-1,2,4-triazin-5(2H,4H)-ones



R^2	R^4	R^6	m.p. (°C)	Refs.
CH_3	H	C_6H_5	192–193	279
			195–196	280
			196–197	279
			199	304
CH_3	H	2-Br–C_6H_4	235.5	782
CH_3	H	2-H_2N–C_6H_4	>300	782
CH_3	H	2-CH_3NH–C_6H_4	211	782
CH_3	H	2-O_2N–C_6H_4	247.5	782
CH_3	H	2-Furyl	246–247	212
CH_3	H	5-O_2N-2-furyl	210–212	212
CH_3	H	5-O_2N-2-furylvinyl	232	244
CH_2OCH_3	H	H	166–169	1093
$C_6H_5CH_2$	H	H	275(dec.)	1093
			232–233	241
$C_6H_5CH_2$	H	$C_6H_5CH_2$	123	269, 750
$C_6H_5CH_2$	H	2-Thienyl	250–251	574
CH_3	CH_3	H	115–116	289
CH_3	CH_3	CH_3	63–64	304
			64–65	251, 281
CH_3	CH_3	$C_6H_5CH_2$	83	267

CH_3	CH_3	C_6H_5	125–126	280
			134–135	293, 304
CH_3	CH_3		218–221	244
			222–223 (dec.)	241
CH_2CH_2CN	CH_2CH_2CN	CH_3	97–98	780
C_6H_5	CH_3	C_6H_5	150	762
C_6H_5	C_6H_5	C_6H_5–CH=CH	202	206

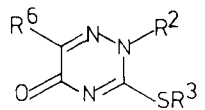
B. 3-Mercapto-1,2,4-triazin-5(2H)-ones

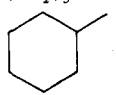


R^2	R^3	R^6	m.p. (°C)	Refs.
H	CH_3	H	213–215	503, 600
			214–216	289
			218–220	275
			220–222	776
			221–222	306
			222–223	307
				256
H	CH_3	CH_3	219–222	345
			222–224	289, 599
			222–223	275, 324
			223–225	503
			224–225	281
			225–227	1104
			226–227	291, 772

TABLE II-24. (*continued*)

B. 3-Mercapto-1,2,4-triazin-5(2H)-ones



R^2	R^3	R^6	m.p. (°C)	Refs.
H	CH_3	$HOCH_2$	154.5–156	258
H	CH_3	FCH_2	185–187 (dec.)	221
				256
H	CH_3	$CH_2SCH_2C_6H_5$	155–156	900
H	CH_3	$CH_2COOC_2H_5$	260 (dec.)	800
H	CH_3	$CH_3-CH-COOC_2H_5$	167–170	815
H	CH_3	$CHFCOOC_2H_5$		256
H	CH_3	CH_2CH_2OH	184–185	754
H	CH_3	CH_2CH_2COOH	231–233	313
H	CH_3	$CH_2CH_2CH_2OH$	175–176	754
H	CH_3	$(CH_2)_3COOH$	175–176	301
H	CH_3	$(CH_2)_4COOH$	173–175	301
H	CH_3	$(CH_2)_5COOH$	182–183	314
H	CH_3	 Cyclohexyl	199–201	317
H	CH_3	C_6H_5	235–236	710, 712
			236–237	321
			239–240	279, 280
			240–242	574
			248–252	583

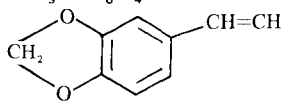
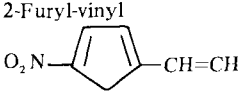
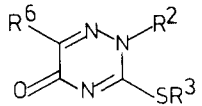
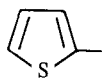
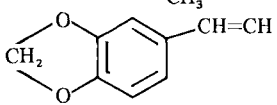
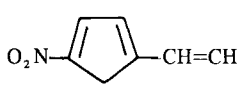
H	CH_3	4-Cl–C_6H_4	280–282	710, 712
H	CH_3	2,4-Cl_2–C_6H_3	250–253	710, 712
H	CH_3	3,4-Cl_2–C_6H_3	272–280	710, 712
H	CH_3	4-O_2N–C_6H_4	320	574
H	CH_3	2-H_2N–C_6H_4	305–307	758, 759
H	CH_3	2-HCONH–C_6H_4	250–255	758
H	CH_3	2-CH_3CONH–C_6H_4	263	758
H	CH_3	4-H_2N–C_6H_4	230 (dec.)	758
H	CH_3	$C_6H_5CH_2$	200–201	321
			202	268
H	CH_3	4-$CH_3C_6H_4CH_2$	218–219	321
H	CH_3	2,4-Cl_2–$C_6H_3CH_2$	232–233	321
H	CH_3	4-Br–$C_6H_4CH_2$	264–265	321
H	CH_3	4-CH_3O–$C_6H_4CH_2$	211	237, 812
H	CH_3	3,4-$(CH_3O)_2C_6H_3CH_2$	183–184	321
H	CH_3	C_6H_5–C(=N–NH–CS–NH_2)–CH_2		262, 263
H	CH_3	4-CH_3O–C_6H_4–CH(–CH_3)	216.5	270, 748
H	CH_3	C_6H_5–CH=CH	146–147	743
H	CH_3	4-Cl–C_6H_4–CH=CH	265–267	248
H	CH_3	4-CH_3O–C_6H_4–CH=CH	250–252	249
H	CH_3		248–250	743
H	CH_3	3,4,5-$(CH_3O)_3C_6H_2$–CH=CH	209–210	743
H	CH_3	3-O_2N–C_6H_4–CH=CH	248–250	316
H	CH_3	2-Furyl	260–261.5	212
H	CH_3	5-O_2N-2-furyl	311–312	212
H	CH_3	2-Furyl-vinyl	273 (dec.)	214, 798
H	CH_3		273 (dec.)	241, 798

TABLE II-24. (*continued*)

A. 3-Mercapto-1,2,4-triazin-5(2H)-ones



R^2	R^3	R^6	m.p. (°C)	Refs.
H	CH_3		258	574
H	C_2H_5	H	130–132	289
			132–133	275
				476
H	C_2H_5	CH_3	162–164	275
			163–164	668
H	C_2H_5	$CH_2CH_2CH_2OH$	133–134	754
H	C_2H_5	$C_6H_5CH_2$	200–201	268
H	C_2H_5	$4\text{-}CH_3O\text{-}C_6H_4CH_2$	187	237, 812
H	C_2H_5		126	270, 748
H	C_2H_5		231–232	743
H	C_2H_5		268–269 (dec.)	798
H	$CH_2CH{=}CH_2$	CH_3	186	291, 772

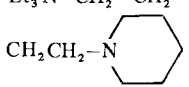
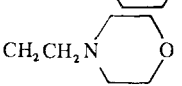
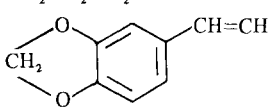
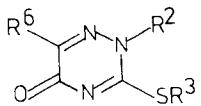
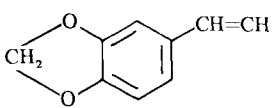
H		$CH_2COOC_2H_5$	H	128–129	288/289
H		CH_2COOH	CH_3	182	288
H		$CH_2COOC_2H_5$	CH_3	165–166	289
				173–174	753
H		CH_2CONH_2	CH_3	202–204	755/753
H		$CH_2CONHC_6H_5$	CH_3	215	742
H		$CH_2CONHC_6H_5$	C_6H_5	205	742
H		CH_2COOH	t-C_4H_9	182–183	288
H		CH_2COOH	$C_6H_5CH_2$		260
H		$CH_2COOC_2H_5$	$C_6H_5CH_2$		260
H		CH_2COOH	C_6H_5	160–162	260
				185–187	288
H		$CH_2COOC_2H_5$	C_6H_5		260
H		$CH_2COOC_2H_5$	4-CH_3O–C_6H_4	160	157
H		$CH_2COC_6H_5$	4-CH_3O–C_6H_4	212	157
H		$CH_2CH_2N(C_2H_5)_2$	CH_3	130–132	594
	Oxalate			191–193 (dec.)	594
H		$Et_3\overset{+}{N}-CH_2-CH_2$ I^-	CH_3		594
H			CH_3	147–149	594
H			CH_3	148–150	594
H		CH_2CH_2COOH	CH_3	186	753
H		$CH_2CH_2COOC_2H_5$	CH_3	108–109	753
H		CH_2CH_2COOH	$CH_2CH_2CH_2OH$	197–198	754
H		CH_2CH_2COO-n-C_4H_9		163–164	743
H		$CH_2CH_2CH_2N(C_2H_5)_2$	CH_3	168–170	594

TABLE II-24. (*continued*)

A. 3-Mercapto-1,2,4-triazin-5(2H)-ones



R^2	R^3	R^6	m.p. (°C)	Refs.
Oxalate			209–211	594
H	$(CH_2)_4COOH$		227–228	743
H	$(CH_2)_4COOC_2H_5$		167–168	743
H	$(CH_2)_4COO\text{-}n\text{-}C_4H_9$			802
H	$(CH_2)_5COOH$		223–224	743/802
H	$(CH_2)_5COOC_2H_5$		169–170	743/802
H	$C_6H_5CH_2$	H	175	275/306

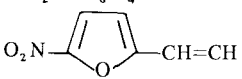
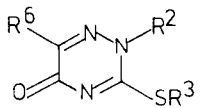
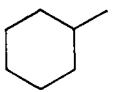
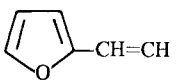
H	$C_6H_5CH_2$	CH_3	185–186	275
H	$C_6H_5CH_2$	CH_2CH_2OH	154–155	754
H	$C_6H_5CH_2$	$CH_2CH_2CH_2OH$	140–141	754
H	$C_6H_5CH_2$	$C_6H_5CH_2$	166–167	268
			167	751
H	$C_6H_5CH_2$	$4\text{-}CH_3O\text{–}C_6H_4CH_2$	184	237, 812
H	$C_6H_5CH_2$	$4\text{-}CH_3O\text{–}C_6H_4\text{–}CH(CH_3)$	165.5	270, 748
H	$2,4\text{-}(O_2N)_2C_6H_3$	$4\text{-}CH_3O\text{–}C_6H_4$	285	157
CH_3	CH_3	H	156–159	289, 290
				192
CH_3	CH_3	CH_3	105–107	289
			106–107	281
CH_3	CH_3	$C_6H_5CH_2$	116.5	267, 747, 751
				752
CH_3	CH_3	C_6H_5	150–151	280
				279
CH_3	CH_3	$2\text{-}H_2N\text{–}C_6H_4$	215	283
CH_3	CH_3		254–256 (dec.)	796, 797, 241, 799
CH_3	$CH_2COOC_2H_5$	CH_3	87–88	289
C_2H_5	C_2H_5	H	114–115	289
C_2H_5	C_2H_5	$C_6H_5CH_2$	Oil	267, 751
CH_2COOH	CH_3	CH_3	112–113	709
$CH_2COOC_2H_5$	CH_3	H	97–98	289
CH_2CONH_2	CH_3	CH_3	228–230	709
CH_2CH_2CN	CH_3	H	130–131	301, 302
CH_2CH_2CN	CH_3	CH_3	123–125	301
$C_6H_5CH_2$	CH_3	$CH_3\text{–}CH(COOC_2H_5)$	82–84	815
$C_6H_5CH_2$	$C_6H_5CH_2$	$C_6H_5CH_2$	106	267, 751
$C_6H_5CH_2$	$C_6H_5CH_2$	$4\text{-}CH_3OC_6H_4CH_2$	Oil	237, 812

TABLE II-24. *(continued)*

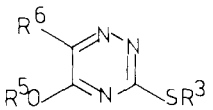
A. 3-Mercapto-1,2,4-triazin-5(2H)-ones



R^2	R^3	R^6	m.p. (°C)	Refs.
2,4-$(O_2N)_2C_6H_3$	CH_3	H	192–193	317
2,4-$(O_2N)_2C_6H_3$	CH_3	CH_3	188–189	317
2,4-$(O_2N)_2C_6H_3$	CH_3		146–147	317
2,4-$(O_2N)_2C_6H_3$	CH_3	C_6H_5	177–178	317
2,4-$(O_2N)_2C_6H_3$	CH_3	$C_6H_5CH_2$	184–185	317
2,4-$(O_2N)_2C_6H_3$	CH_3		194–195	317
CH_3CO	CH_3	CH_3	110–111	753
CH_3CO	CH_3	2-$CH_3CONH-C_6H_4$	172–173	758
C_2H_5	CH_3	C_6H_5	71	229
C_2H_5	C_2H_5	$C_6H_5-CH_2$	Oil	267
i-C_3H_7	CH_3	C_6H_5	121	229
$CH_2=CH-CH_2$	CH_3	2-Furyl	133	229
$CH_2=CH-CH_2$	C_6H_5	CH_3	128	229
$CH_2=CH-CH_2$	C_6H_5	C_6H_5	153	229
$ClCH=CCl-CH_2$	CH_3	C_6H_5	109	229
4-$O_2N-C_6H_4-CH_2$	CH_3	C_6H_5	150	229
4-$O_2N-C_6H_4-CH_2$	C_6H_5	CH_3	178	229

4-$O_2N-C_6H_4-CH_2$	C_6H_5	C_6H_5	169	229
4-$Cl-C_6H_4-CH_2$	CH_3	C_6H_5	135	229
4-$Cl-C_6H_4-CH_2$	C_6H_5	CH_3	169	229
4-$Cl-C_6H_4-CH_2$	C_6H_5	C_6H_5	185	229

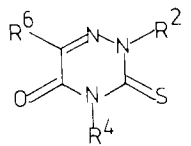
C. 5-Hydroxy-3-mercapto-1,2,4-triazines

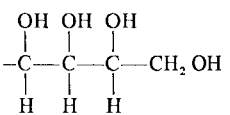
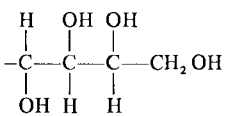
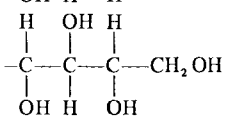
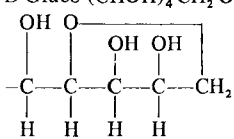


R^3	R^5	R^6	m.p. (°C)	Refs.
CH_3	CH_3	H	66–67	192
			66–68	305, 1564
CH_3	CH_3	CH_3	79–80	281
			82–83	305, 1564
CH_3	CH_3	C_6H_5	75–76	280
CH_3	C_2H_5	CH_3		282, 1096
CH_3	C_6H_5	CH_3	61–62	1096, 1103
CH_3	2-$CH_3-C_6H_4$	CH_3	102–103	1096, 1103
CH_3	3-$CH_3-C_6H_4$	CH_3		1096
CH_3	2-$O_2N-C_6H_4$	CH_3	121–122	1096, 1103
CH_3	3-$O_2N-C_6H_4$	CH_3	116–117	1096, 1103
CH_3	4-$O_2N-C_6H_4$	CH_3	149–150	1096, 1103
CH_3	3-Methylmercapto-6-methyl-1,2,4-triazin-5-yl	CH_3	154–155	1096, 1103, 1104
$(CH_3)_3Si$	$(CH_3)_3Si$	H	b.p. 120/0.1torr	1094, 1095 320, 713, 763, 787
$(CH_3)_3Si$	$(CH_3)_3Si$	CH_3	b.p. 160/0.02 torr	1094, 1095
$(CH_3)_3Si$	$(CH_3)_3Si$	$CH_2COOC_2H_5$	b.p. 140/0.01 torr	1094, 1095

TABLE II-24. (*continued*)

D. Sugar-substituted 3-thioxo-1,2,4-triazin-5-ones



R^2	R^4	R^6	m.p. (°C)	Refs.
H	H		200–201	255
H	H		270 (dec.)	255, 744
H	H		202–203	255, 744
H	H	D-Allo $(CHOH)_4 CH_2OH$	182–183.5	253
H	H	D-Altro $(CHOH)_4 CH_2OH$	209–210.5	253, 257
H	H	D-Galacto $(CHOH)_4 CH_2OH$	261–262	253
H	H	D-Gluco $(CHOH)_4 CH_2OH$	257–260	253
H	H		119.5–121	253

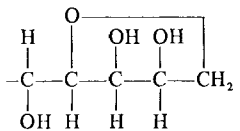
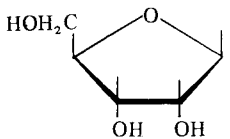
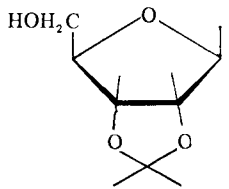
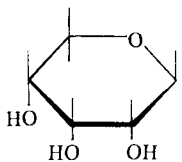
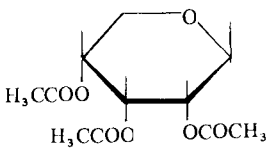
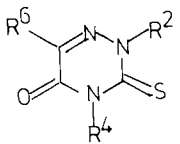
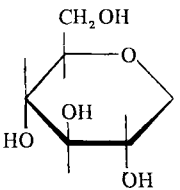
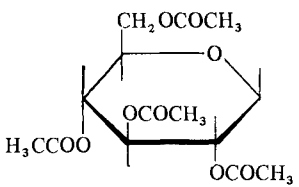
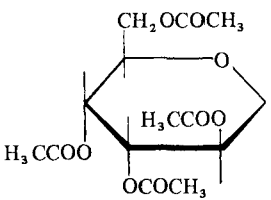
H	H		233–235	253
H	H		197–198	252
H	H		188–190	252
	H	H	239–241	475, 1094 1095
	H	H	Foam	475, 1094 1095

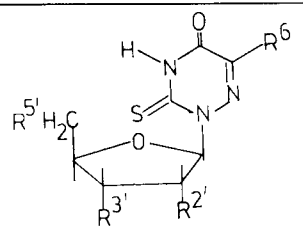
TABLE II-24. *(continued)*

D. Sugar-substituted 3-thioxo-1,2,4-triazin-5-ones



R^2	R^4	R^6	m.p. (°C)	Refs.
	H	H	Glass 246–250	475 1094
	H	H	225 225–226	1094 475
	H	H	225	476

Heptaacetylcellobiosyl	H	H			474
Heptaacetylmaltosyl	H	H		181–182	474
Heptaacetyllactosyl	H	H			474



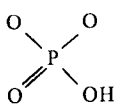
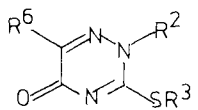
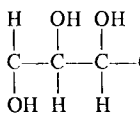
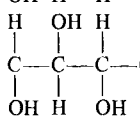
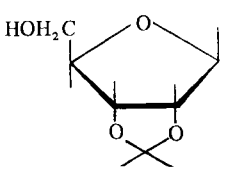
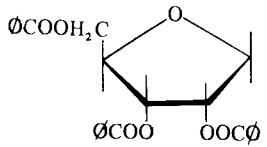
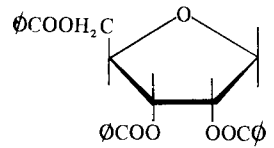
$R^{2'}$	$R^{3'}$	$R^{5'}$	R^6	m.p. (°C)	Refs.
OH	OH	OH	H	197.5	1094, 1095
				197–198	787
				199–201	320
				201–203	475
OH	OH	OH	CH_3	218–220	1094, 1095
OH	OH	OH	CH_2COOCH_3	127–129	1094, 1095
CH_3COO	CH_3COO	CH_3COO	H	76–78	1094, 1095
				101–103	476
				101–104	475
CH_3COO	CH_3COO	CH_3COO	CH_3	156–157	476
C_6H_5COO	C_6H_5COO	C_6H_5COO	H	173	787, 1094, 1095
				173–174	320/485
C_6H_5COO	C_6H_5COO	C_6H_5COO	CH_3	151–154	1094
				156–157	1095
C_6H_5COO	C_6H_5COO	C_6H_5COO	$CH_2COOC_2H_5$	oil	1094, 1095
		OH	H		524

TABLE II-24. (*continued*)

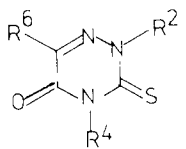
E. Sugar-substituted 3-mercapto-1,2,4-triazin-5-ones



R^2	R^3	R^6	m.p. (°C)	Refs.
H	CH_3		220–221	255, 744
H	CH_3		185–186	255, 744
H	CH_3	D-Allo $(CHOH)_4CH_2OH$	159–161	253
H	CH_3	D-Altro $(CHOH)_4CH_2OH$	172.5–173	253
			172.5–174	257
H	CH_3	D-Gluco $(CHOH)_4CH_2OH$	191–192	253
H	CH_3		Syrup	252

	CH_3	H	306
	$C_6H_5CH_2$	H	306

F. Labelled 3-thioxo-1,2,4-triazin-5-ones



R^2	R^4	R^6	Label	m.p. (°C)	Refs.
H	H	H	5,6-^{14}C		296, 297
H	H	H	3-^{35}S		785
H	H	CH_3	5-^{14}C	216	296, 297
			3-^{35}S		784
			1,2-^{15}N	217	778
			1,2-^{15}N, 3-^{35}S	219–220	778

TABLE II-25. INFRARED AND ULTRAVIOLET SPECTRA AND pK_a VALUES OF 3-TIOXO-1,2,4-TRIAZIN-5-ONES

Compound	pK_a	IR spectra			UV spectra	λ_{max} (log ϵ) (ethanol)	
		ν(N–H)	ν(C=O)	ν(C=S)			
3-Thioxo-1,2,4-triazin-5-one	5.98	3404 3385	1723	1191	224 (4.10)	265 (4.35)	sh 298 (3.59)
2-Methyl-3-thioxo-1,2,4-triazin-5-one	6.24	3363	1720	1129	220 (4.27)	267 (4.40)	sh 312 (3.56)
4-Methyl-3-thioxo-1,2,4-triazin-5-one	8.12	3406	1711	1140	218 (4.00)	270 (4.27)	sh 310 (3.55)
2,4-Dimethyl-3-thioxo-1,2,4-triazin-5-one			1730	1124	225 (4.12)	264 (4.38)	sh 310 (3.55)
3-(Methylmercapto)-1,2,4-triazin-5-one	5.94	3401			234 (4.27)		sh 300 (3.0)

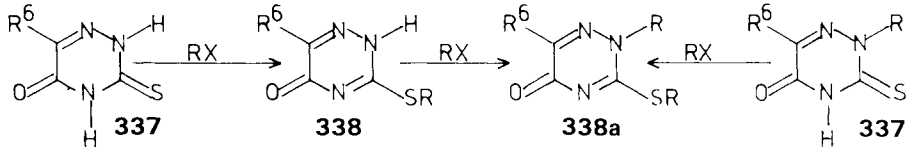
are weak acids and can be titrated in the presence of phenolphthalein (748, 750, 751). Oxidative determination of 3-thioxo-1,2,4-triazin-5-ones is reported by two groups (272, 786); paper chromatographic determination is published by Horak (724).

The values for force constants were correlated with values of π-electron densities of nitrogen atoms by Pitha and Vasickova (356).

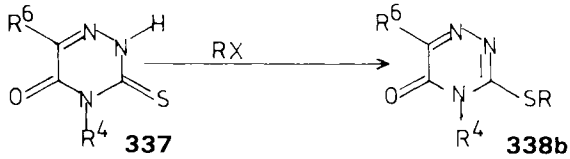
3-Methylmercapto-6-methyl-1,2,4-triazin-5-one forms a complex with ethanolamine and 3-aminopropanol (709).

4. *Reactions*

The alkylation of 3-thioxo-1,2,4-triazine-5-ones (**337**) is the most intensively studied reaction of these compounds. Alkylation with alkyl halides or dialkyl sulfates occurs predominantly at the sulfur, leading to 3-(alkylmercapto)-1,2,4-triazin-5-ones (**338**); subsequent alkylation transforms **338** into 2-alkyl-3-(alkylmercapto)-1,2,4-triazin-5-ones (**338a**) (157, 212, 241, 249, 257, 258, 260–264, 267, 268, 270, 275, 279–281, 288, 289, 293, 299, 300, 302, 313, 314, 316, 317, 321, 324, 503, 594, 599, 668, 710, 712, 742, 748, 749, 751–754, 758, 759, 763, 772, 796, 800, 802, 806, 815, 900).



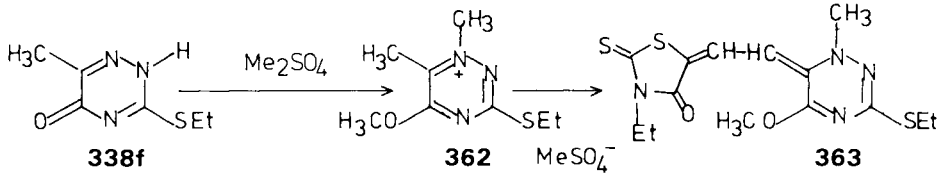
2-Alkyl-3-thioxo-1,2,4-triazin-5-ones (**337**) are converted to 2-alkyl-3-(alkylmercapto)-1,2,4-triazin-5-ones (**338a**) by treatment with alkyl halides; 4-alkyl-1,2,4-triazin-5-ones (**337**) give 4-alkyl-3-(alkylmercapto)-1,2,4-triazin-5-ones (**338b**) by reaction with alkyl halides (267, 281, 290).



Different results were observed when using diazomethane as the alkylating agent (92, 280, 281, 283, 293, 304, 307). Using dioxane as the solvent for this reaction the nitrogen in the 4-position is alkylated first followed by the sulfur, whereas in ethanol the order of alkylation is reversed (281). Reaction of the unsubstituted 3-thioxo-1,2,4-triazin-5-one with diazomethane in dioxane gave a

70:30 mixture of the 4-alkyl and 3-alkylmercapto derivatives. The 3-thioxo-2-methyl-1,2,4-triazin-5-one is transformed into the 2,4-dimethyl (52%) and the 2-methyl-3-methylmercapto derivative (48%). The 4-methyl-3-thioxo-1,2,4-triazine-5-one gives nearly 100% of the 4-methyl-3-methylmercapto derivative whereas the 3-(methylmercapto)-1,2,4-triazin-5-one is converted into a mixture of 5-methoxy-3-(methylmercapto)-1,2,4-triazine (48%), 2-methyl-3-(methylmercapto)-1,2,4-triazine-5-one (30%), and 4-methyl-3-(methylmercapto)-1,2,4-triazin-5-one (22%) (281).

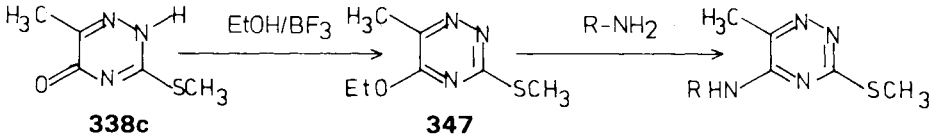
Alkylation of 3-(ethylmercapto)-6-methyl-1,2,4-triazin-5-one (**338f**) with dimethyl sulfate yields 3-(ethylmercapto)-5-methoxy-1,6-dimethyl-1,2,4-triazinium methylsulfate (**362**), which can be converted into the compound **363** (m.p. 217 to 219°C).



338f **362** **363**

Reaction of 3-thioxo-1,2,4-triazin-5-one with olefins leads to N_2- and N_4-substitution (301, 302, 780). 3-Thioxo-1,2,4-triazine-5-ones can be acylated with carboxylic anhydrides (206, 753); the 3-mercapto derivative is acylated at the nitrogen in the 2-position (753).

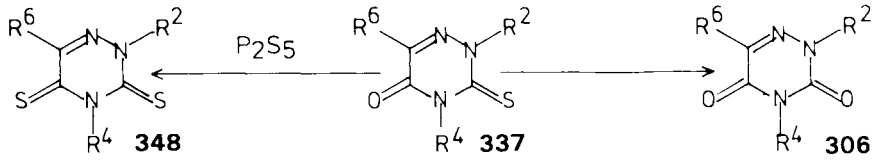
6-Methyl-3-(methylmercapto)-1,2,4-triazin-5-one (**338c**) is converted into 5-ethoxy-6-methyl-3-(methylmercapto)-1,2,4-triazine (**347**) by reaction with ethanol in the presence of acids or boron trifluoride (282). The ethoxy group is more easily substituted by amines than the methylmercapto group (282). The same observation is reported for 5-aryloxy-3-(methylmercapto)-1,2,4-triazines (1096, 1103, 1104).



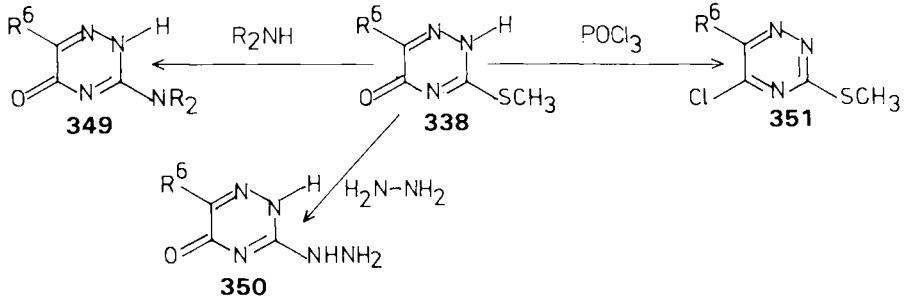
338c **347**

3-Thioxo-1,2,4-triazin-5-ones (**337**) can be transformed into 1,2,4-triazine-3,5-diones (**306**) by various methods; this reaction has already been discussed in Section II-E. The conversion of **337** into 1,2,4-triazine-3,5-dithiones (**348**) by reaction with phosphorus pentasulfide was discussed in Section III-D.

The reaction of 3-(methylmercapto)-1,2,4-triazin-5-ones (**338**) with ammonia or amines was used for the synthesis of 3-amino-1,2,4-triazin-5-ones (**349**) (51, 157, 212, 229, 282, 293, 594, 612, 701, 709, 742, 754, 776, 793, 795) and the

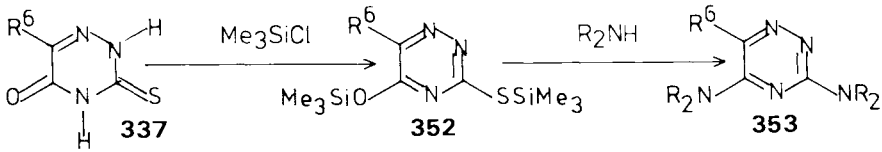


reaction with hydrazine for the synthesis of 3-hydrazino-1,2,4-triazin-5-ones (**350**) (51, 63, 189, 583, 586, 587, 595, 600, 717, 760, 761, 770, 783, 814).



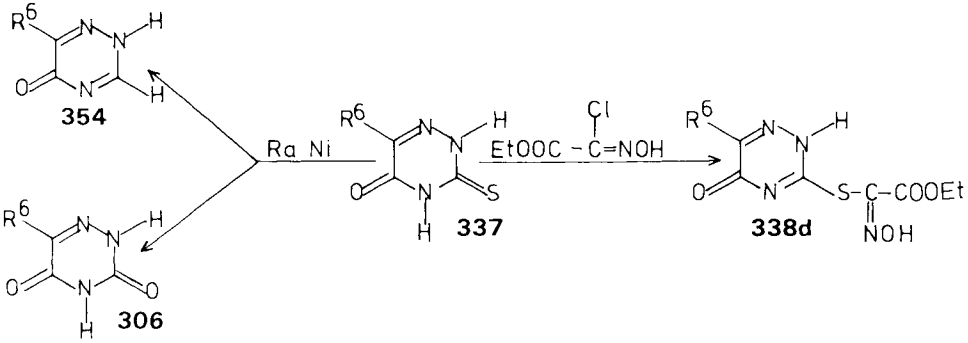
Reaction of 3-(methylmercapto)-1,2,4-triazin-5-ones (**338**) with phosphorus oxychloride converts these compounds into 5-chloro-3-(methylmercapto)-1,2,4-triazines (**351**) which were reacted with amines without isolation, leading to 3,5-diamino-1,2,4-triazines (710, 712).

Reaction of 3-thioxo-1,2,4-triazine-5-ones (**337**) with trimethylsilyl chloride in the presence of hexamethyldisilazane gives 3-[(trimethylsilyl)mercapto]-5-[(trimethylsilyl)oxy]-1,2,4-triazines (**352**), which have been used for the synthesis of 2-substituted **337** (1093), 3,5-diamino-1,2,4-triazines (**353**) (713) or sugar-substituted 3-thioxo-1,2,4-triazine-5-ones (320, 474–476, 763, 787, 1094, 1095).

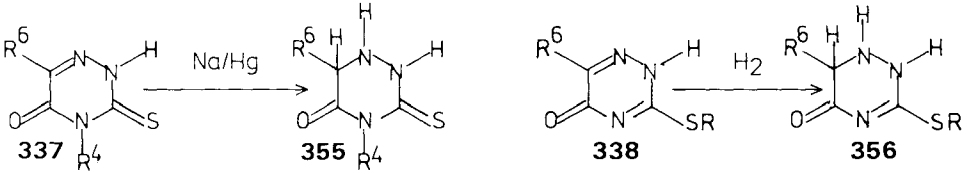


3-Thioxo-1,2,4-triazin-5-ones (**337**) can be converted into 1,2,4-triazin-5-ones (**354**) (189, 190, 193) or into 1,2,4-triazine-3,5-diones (**306**) (745) by treatment with Raney nickel. Dornow and Voigt (284) reported the conversion of **337** into **338d** by reaction with hydroximic acid chlorides.

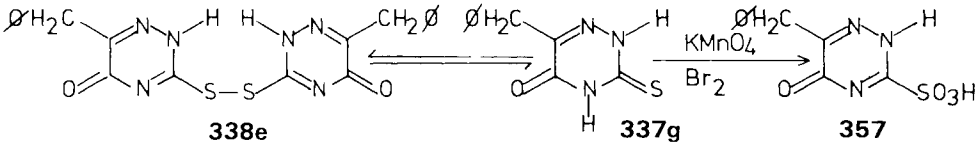
2-Substituted 3-thioxo-1,2,4-triazin-5-ones are not reduced by sodium amalgam, but 3-(alkylmercapto)-1,2,4-triazin-5-ones (**338**) are reduced to the 3,4-dihydro compounds (**346**) (see page 433) and the 4-substituted 3-thioxo-1,2,4-triazin-5-ones (**337**) to the 1,6-dihydro compounds (**355**) (237, 264, 268, 270, 271, 746, 748).



The hydrogenation of 3-(alkylmercapto)-1,2,4-triazin-5-ones (**338**) leads to 1,6-dihydro derivatives (**356**) (751), whereas hydrogenation of 4-alkyl-3-thioxo-1,2,4-triazin-5-ones gives open-ring products (749).

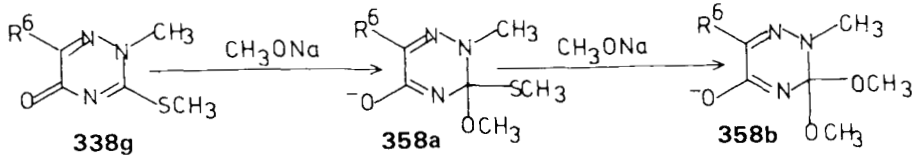


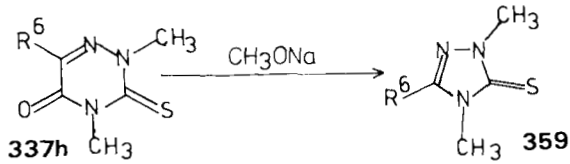
Mild oxidation converts 6-benzyl-3-thioxo-1,2,4-triazine-5-one (**337g**) into the disulfide (**338e**) (m.p. 172.5°C, 173°C), which can be reduced to the starting compound by reaction with ammonium sulfide or sodium hydrogen sulfite (264, 266, 273). With stronger oxidation reagents (Br_2 or potassium permanganate) 6-benzyl-5-oxo-1,2,4-triazine-3-sulfonic acid (**357**) can be obtained (189, 225).

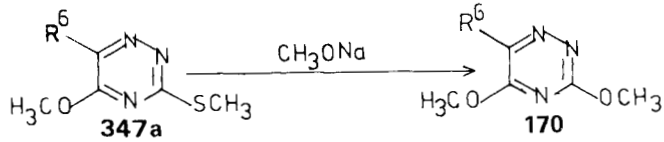


2-Methyl-3-(methylmercapto)-1,2,4-triazin-5-ones (**338g**) react with sodium methoxide to give compounds **358a** and **358b**; 2,4-dimethyl-3-thioxo-1,2,4-triazin-5-ones (**337h**) are converted into triazoline thiones (**359**) by reaction with sodium methoxide (280). Interaction of 5-methoxy-3-(methylmercapto)-1,2,4-triazines (**347a**) with sodium methoxide was used for the synthesis of 3,5-dimethoxy-1,2,4-triazines (**170**) (305, 1564).

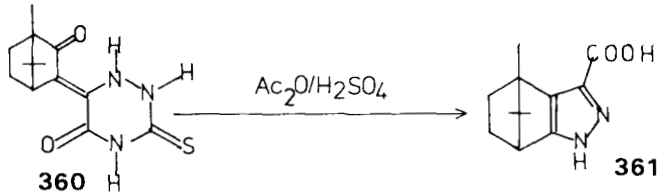
Ring opening of 3-thioxo-1,2,4-triazin-5-one derivatives is observed when they are reacted with mercury oxide (319) or sodium hypobromide (790, 791) or reduced by the Clemensen reaction (790, 791).



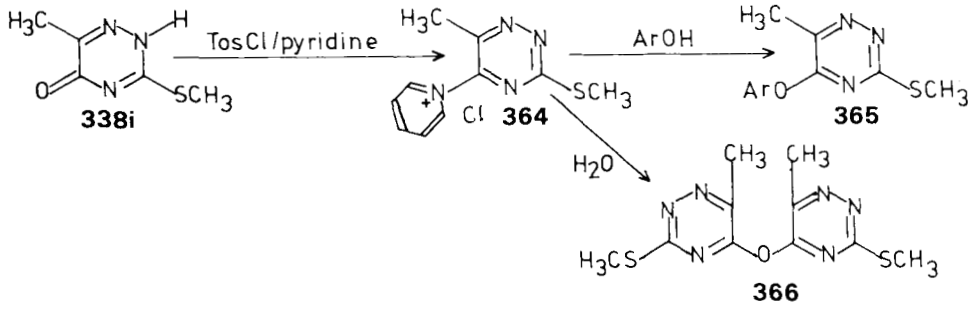




Acetic anhydride and sulfuric acid convert compound **360** into compound **361** (807).



Reaction of 6-methyl-3-(methylmercapto)-1,2,4-triazin-5-one (**338i**) with tosyl chloride and pyridine yields the pyridinium compound **364** (m.p. 138 to **140** °C, dec.) (1096, 1104), which reacts with phenols to give 5-(aryloxy)-3-(methylmercapto)-1,2,4-triazines (**365**) (1096, 1103), with water to afford compound **366** (m.p. 154 to 155 °C) (1103, 1104) and with other nucleophiles (1096).

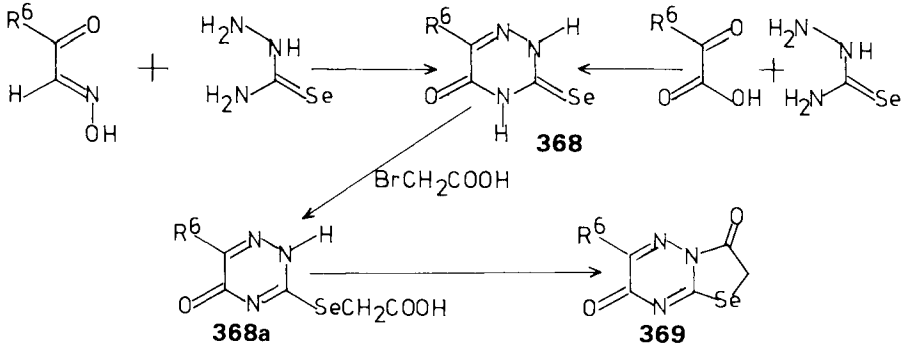


Condensed 1,2,4-triazine systems were synthesized by reaction of various 3-thioxo-1,2,4-triazine-5-ones with dihaloalkanes (755, 756, 781, 789), acrolein (780), or chloroacetic acid and acetic anhydride (742, 753). Further syntheses of condensed systems are reported in references 283 and 754–756. All these reactions are discussed in the section 'condensed 1,2,4-triazines'.

G. 3-Selenoxo-1,2,4-triazine-5-ones

Reaction of selenosemicarbazide with phenylglyoxaldoximes in boiling aqueous sodium carbonate solution affords 6-aryl-3-selenoxo-1,2,4-triazine-5-ones (**368**) in yields up to 90% (342). **368** can also be obtained by reaction of selenosemicarbazide with α-ketocarboxylic acids or α-ketocarboxylates (342).

Reaction of **368** with bromoacetic acid in the presence of sodium ethoxide leads to alkylation at the selenium, and 3-(carboxymethylseleno)-1,2,4-triazin-5-ones (**368a**) ($R^6 = CH_3$, m.p. 145 to 150°C; $R^6 = C_6H_5$, m.p. 160 to 162°C) were obtained, which can be cyclized with acetic anhydride to **369** (342).



368 **368a** **369**

R^6	m.p. (°C)	Refs.
H	200–204	342
CH_3	208–209	342
C_6H_5	235–236	342
4-F–C_6H_4	220–222	342
4-Br–C_6H_4	235–237	342
4-CH_3S–C_6H_4	185–190	342

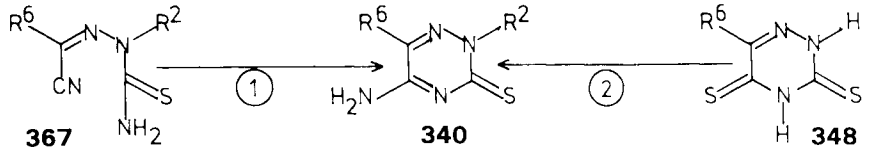
H. 5-Amino-1,2,4-triazine-3-thiones

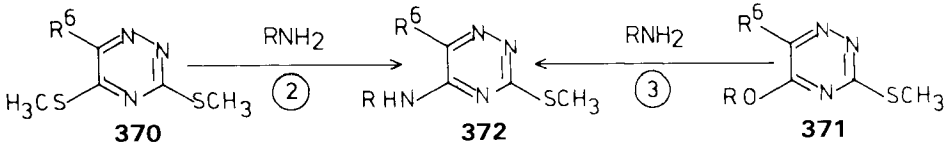
Three different methods are used for the synthesis of 5-amino-1,2,4-triazine-3-thiones (**340**) and (**372**) (251, 282, 324, 345, 502, 598, 813);

1. Cyclization of thiosemicarbazones of α-ketonitriles (**367**) (345, 813) which can be synthesized by reaction of thiosemicarbazide with α-ketonitriles (345) or with α-iminonitriles (813),

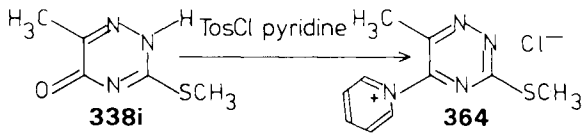
2. Reaction of 1,2,4-triazine-3,5-dithiones (**348**) with ammonia (251, 324, 502) or of 3,5-bis(methylmercapto)-1,2,4-triazines (**370**) with sulfonamides (498, 598).

3. Substitution of the alkoxy or aroxy group in 5-alkoxy- or 5-aroxy-3-(methylmercapto)-1,2,4-triazines (**371**) by amines (282, 1096, 1103, 1104).





Reaction of 6-methyl-3-(methylmercapto)-1,2,4-triazin-5-one (**338i**) with tosyl chloride and pyridine yields the pyridinium salt **364** (m.p. 138 to 140°C, dec.), the reactions of which have already been mentioned in Section VII-F (1096, 1104).

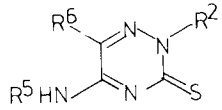


5-Amino-1,2,4-triazine-3-thiones (**340**) (Table II-26) are yellow compounds with high melting points. Until now no studies on the structure of these compounds have been reported, but our knowledge of the structure of other hetero-substituted 1,2,4-triazines leads us to assume that the tautomeric structure used in this discussion is the predominant form.

5-Amino-1,2,4-triazine-3-thiones (**340**) can be alkylated at the sulfur by reaction with dialkyl sulfates (324, 502); they can be oxidized to 5-amino-1,2,4-triazine-3-sulfonic acids (**373**) (324, 502), which can be hydrolyzed to 5-amino-1,2,4-triazin-3-ones (**374**). Hydrolysis of 5-amino-1,2,4-triazine-3-thiones (**340**) leads to the formation of 3-thioxo-1,2,4-triazin-5-ones (**375**) (251, 324, 345,

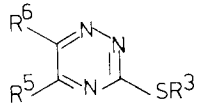
TABLE II-26. 5-AMINO-1,2,4-TRIAZINE-3-THIONES

A. 5-Amino-1,2,4-triazine-3(2H)-thiones



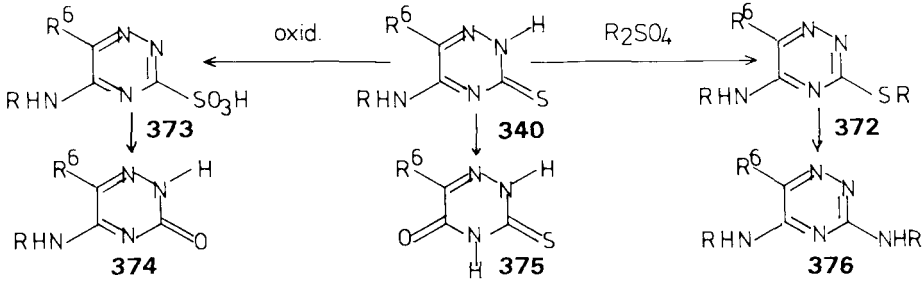
R^2	R^5	R^6	m.p. (°C)	Refs.
H	H	CH_3	310	324, 345, 502
H	H	C_6H_5	270	813
CH_3	H	CH_3	258–259	251

B. 5-Amino-3-mercapto-1,2,4-triazines



R^3	R^5	R^6	m.p. (°C)	Refs.
CH_3	NH_2	CH_3	164–165	324, 502
			173–174	345, 1097
CH_3	n-C_3H_7–NH	CH_3	113	282
	·HCl		193–194	282
CH_3	i-C_3H_7–NH	CH_3	159–160	1103
CH_3	n-C_4H_9–NH	CH_3	114	282, 1097
	·HCl		174–175	282
CH_3	i-C_4H_9–NH	CH_3	118–119	1103
CH_3	C_6H_5–NH	CH_3	160–161	1096, 1103
	·4-O_2N–C_6H_4–OH		136–137	1103
CH_3	4-CH_3–C_6H_4–NH	CH_3	174–175	1096, 1103
	·4-O_2N–C_6H_4–OH		155–156	1103
CH_3	4-Cl–C_6H_4–NH	CH_3	200–201	1103
CH_3	C_6H_5–CH_2–NH	CH_3	147	282
CH_3	C_6H_5–SO_2–NH	CH_3	196–198	598
CH_3	4-CH_3–C_6H_4–SO_2–NH	CH_3	194–196	598
CH_3	4-Cl–C_6H_4–SO_2–NH	CH_3	185–187	598
CH_3	4-H_2N–C_6H_4–SO_2–NH	H	206–207 (dec.)	498
CH_3	4-H_2N–C_6H_4–SO_2–NH	CH_3	207–208	498
CH_3	4-H_2N–C_6H_4–SO_2–NH	C_2H_5	198–199	498
CH_3	$(C_2H_5)_2N$	CH_3	124–126	1100, 1103
CH_3	Piperidyl	CH_3	55–56	1103
CH_3	1-Oxo-2-isoquindyl	CH_3		1096
CH_3	6-CH_3-3-CH_3S-5-oxo-1,2,4-triazin-4-yl	CH_3		1096
C_2H_5	CH_3–N–$CONHCH_3$	H		920

813). Reaction of 5-amino-3-(methylmercapto)-1,2,4-triazines (**372**) with amines is used for the synthesis of 3,5-diamino-1,2,4-triazines (**376**) (502).



I. 5-Hydrazino-1,2,4-triazine-3-thiones

All known 5-hydrazino-1,2,4-triazine-3-thiones (**377**, **378**) (Table II-27) are prepared by reaction of either 1,2,4-triazine-3,5-dithiones (**348**) or 3,5-bis-(methylmercapto)-1,2,4-triazines (**370**) with hydrazines (594, 595, 597, 599).

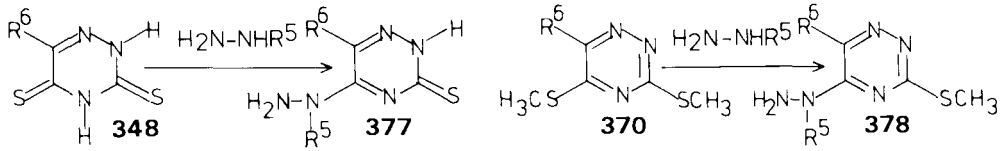
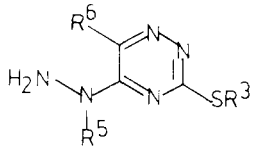
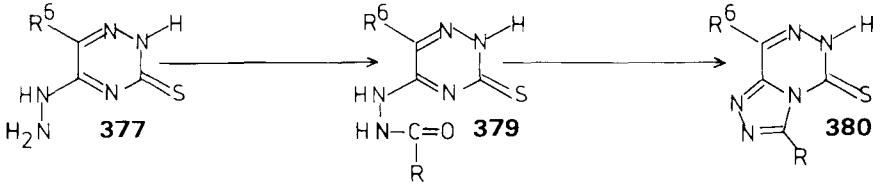


TABLE II-27. 5-HYDRAZINO-1,2,4-TRIAZINE-3-THIONES AND 5-HYDRAZINO-3-(METHYLMERCAPTO)-1,2,4-TRIAZINES



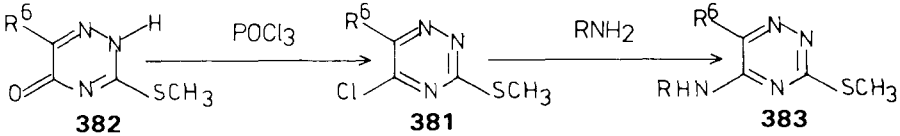
R^3	R^5	R^6	m.p. (°C)	Refs.
H	H	CH_3	300	599
			350 (subl.)	594/595
H	CH_3CO	H	238–240	597
H	CH_3CO	CH_3	227–229	597
H	C_6H_5CO	H	257–259	597
H	C_6H_5CO	CH_3	265–267	597
CH_3	H	CH_3	168–170 (dec.)	599/595
CH_3	HCO	CH_3		595

5-Hydrazino-1,2,4-triazine-3-thiones (**377**, **378**) can be acylated at the hydrazino group and the 5-(acylhydrazino)-1,2,4-triazine-3-thiones (**379**) can be cyclized to 1,2,4-triazolo[4,3-*d*] 1,2,4-triazines (**380**) (595, 597, 599), as is shown for **377**.

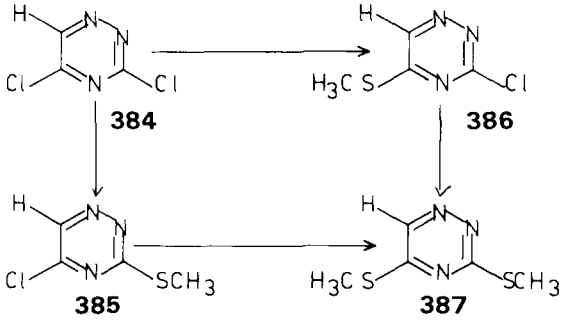


J. 5-Chloro-1,2,4-triazine-3-thiones

Only three papers dealing with 5-chloro-1,2,4-triazine-3-thiones have been published. In two cases (710, 712) the 5-chloro-1,2,4-triazine-3-thiones (**381**) were prepared by reaction of 3-(methylmercapto)-1,2,4-triazin-5-ones (**382**) with phosphorus oxychloride, but were transformed, without isolation, into 5-amino-3-(methylmercapto)-1,2,4-triazines (**383**) by reaction with amines.



Grundmann, Rätz, and Schroeder (341) reported the transformation of 3,5-dichloro-1,2,4-triazine (**384**) into 5-chloro-3-(methylmercapto)-1,2,4-triazine (**385**) by reaction with sodium mercaptide, but since it has meanwhile been shown that the chlorine in the 5-position is more reactive than that in the 3-position, the isolated compound is probably the 3-chloro-5-(methylmercapto)-1,2,4-triazine (**386**). Further reaction of the isolated chloro-(methyl-

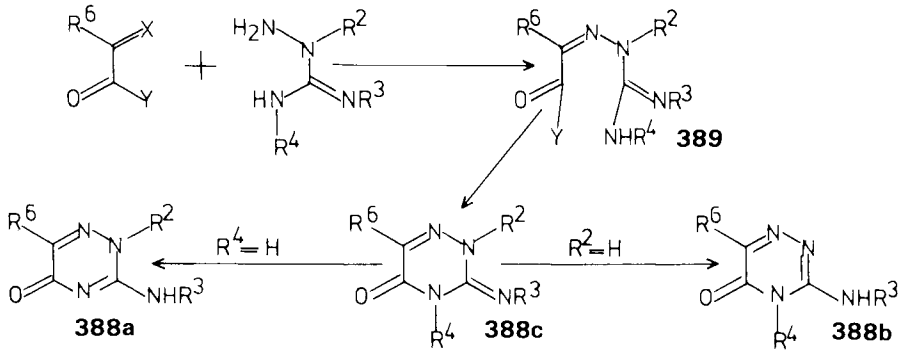


mercapto)-1,2,4-triazine with sodium mercaptide gave the 3,5-bis(methylmercapto)-1,2,4-triazine (**387**) (341).

K. 3-Amino-1,2,4-triazin-5-ones

1. *Preparation*

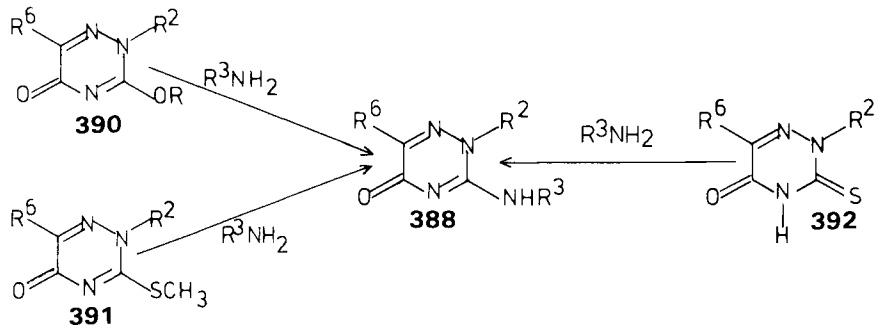
3-Amino-1,2,4-triazin-5-ones (**388**) are well-known compounds and a number of methods for their synthesis have been published. The most frequently used method starts with a α-ketocarboxylic acids or their derivatives and aminoguanidine or its derivatives (189, 212, 229, 241, 622, 641, 666, 708, 800, 815–824). The initially formed guanylhydrazone (**389**) can be isolated but direct cyclization is also reported.



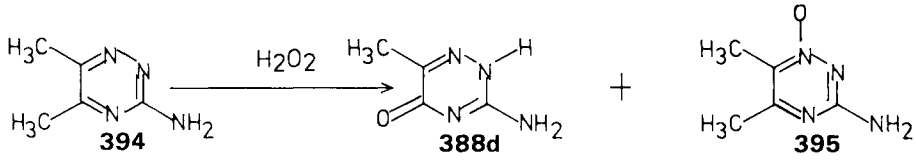
The following derivatives of α-ketocarboxylic acids were used: esters (241, 641, 666, 800, 815, 820, 822), thiol esters (821), chloral (819), and azlactones (823). The following derivatives of aminoguanidine were used: N_2-substituted (241, 821, 822), N_3-substituted (819, 820), N_2, N_3-disubstituted (816), and N_3, N_3-disubstituted (229) aminoguanidines.

The reaction of 3-alkoxy-1,2,4-triazin-5-ones (**390**) (458, 460), 3-(methylmercapto)-1,2,4-triazin-5-ones (**391**) or 3-thioxo-1,2,4-triazin-5-ones (**392**) with ammonia or amines is very often used for the synthesis of 3-amino-1,2,4-triazin-5-ones (**388**) (229, 282, 293, 594, 612, 701, 719, 742, 754, 776, 795, 816). In one case the hydrolysis of a 3,5-diamino-1,2,4-triazine, leading to **388** is reported (1103).

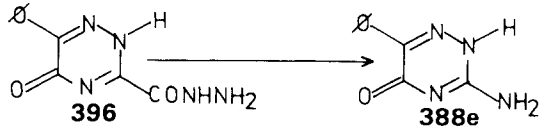
Takai and Saikawa (641) obtained 3-amino-1,2,4-triazin-5-ones (**388**) through oxidation of 3-amino-1,2,4-triazines with an unsubstituted 5-position (**393**) with chromic acid; Sasaki and Minamoto used hydrogen peroxide as the oxidizing agent (702).



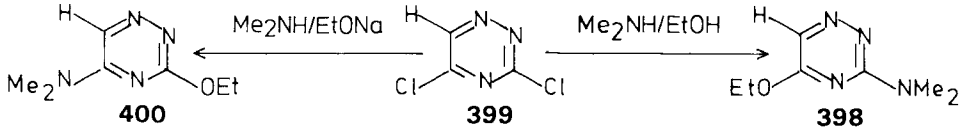
Oxidation of 3-amino-5,6-dimethyl-1,2,4-triazine (**394**) with hydrogen peroxide led to the isolation of 3-amino-6-methyl-1,2,4-triazin-5-one (**388d**) besides the 3-amino-5,6-dimethyl-1,2,4-triazine-1-oxide (**395**) (702).



Fusco and Rossi (63) converted 5-oxo-6-phenyl-1,2,4-triazine-3-carboxhydrazide (**396**) into 3-amino-6-phenyl-1,2,4-triazin-5-one (**388e**) by means of a Curtius degradation.

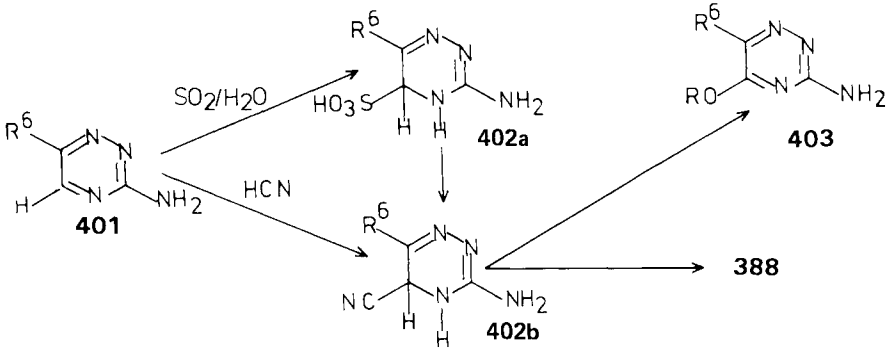


Grundmann, Schroeder, and Rätz (341) reported the synthesis of 5-ethoxy-3-(dimethylamino)-1,2,4-triazine (**398**) by reaction of 3,5-dichloro-1,2,4-triazine (**399**) with dimethylamine and sodium ethoxide, but the correct



structure of the isolated product is probably the isomeric 3-ethoxy-5-(dimethylamino)-1,2,4-triazine (**400**).

3-Amino-1,2,4-triazines (**401**) add SO_2 or HCN readily to the N_4C_5 double bond, forming the addition products **402**. **402a** yields **402b** on reaction with potassium cyanide. **402b** affords 5-alkoxy-3-amino-1,2,4-triazines (**403**) by reaction with alcohols and yields **388** by reaction with water (620, 1075).

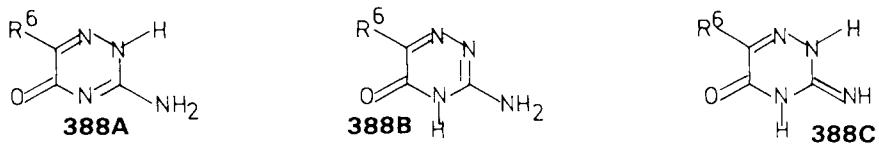


2. *Compound Survey*

The known 3-amino-1,2,4-triazin-5-ones are listed in Table II-28.

3. *Physical Properties*

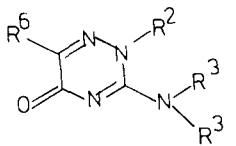
3-Amino-1,2,4-triazin-5-ones (**388**) are stable compounds with very high melting points, in most cases over 200°C. The interpretation of the infrared spectra of these compounds led to two different results for the predominant tautomeric structure. Owing to an erroneous interpretation of the infrared spectra of **388** in potassium bromide, Ueda and Furukawa stated that the oxo–imino form **388C** should be the predominant tautomeric structure of 3-amino-1,2,4-triazin-5-ones (824).



Sasaki and Minamoto (702) as well as Gut and his co-workers (830) have shown by infrared and ultraviolet spectroscopic studies that 3-amino-1,2,4-triazin-5-ones capable of existing in the amino form are in this form. The

TABLE II-28. 3-AMINO-1,2,4-TRIAZIN-5-ONES

A. 3-Amino-1,2,4-triazin-5(2H)-ones



R^2	R^3	R^3	R^6	m.p. (°C)	Refs.
H	H	H	H	>300	816
H	H	H	CH_3	>300	189, 702, 816, 824
				>340	612
				350 (dec.)	594
·HCl				208–209	189
H	H	H	C_2H_5	316	824
H	H	H	n-C_3H_7	305	824
H	H	H	n-C_4H_9	310–311	824
H	H	H	n-C_5H_{11}	291–292	824
H	H	H	n-C_7H_{15}	289–290	824
H	H	H	n-C_9H_{19}	274–275	824
H	H	H	CH_2CH_2OH	268–269	709, 754
H	H	H	$EtOOC-CH(C_3H_7)$	263–265	815
H	H	H	$C_3H_7-CO-NH-CH_2$	>300	815
H	H	H	$C_3H_7-CO-NH-CH(CH_3)$	316 (dec.)	815
H	H	H	i-$C_4H_9-CO-NH-CH(CH_3)$	271	815
				281	1442
H	H	H	sec-$C_4H_9-CO-NH-CH(CH_3)$	268–270	1442

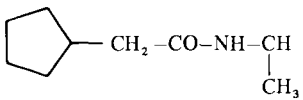
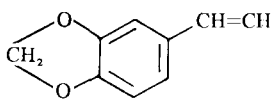
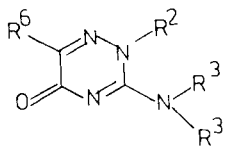
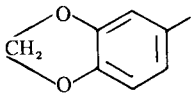
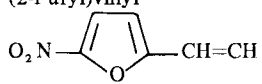
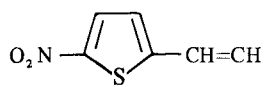
H		H	H	$Me_2CH-CH_2-CH_2-CO-NH-CH(CH_3)$	280–283	1442
H		H	H	$C_2H_5(CH_3)CH-CH_2-CO-NH-CH(CH_3)$	298–300	1442
H		H	H		313–315	1442
H		H	H	$C_6H_{11}-CH_2-CO-NH-CH(CH_3)$	200–202	1442
H		H	H	$HOCH_2CH_2CH_2$	267–268	709, 754
	·HCl				183–184	754
H		H	H	$EtOOC-CH_2$	260–262	800
H		H	H	$EtOOC-CH(CH_3)$	265.5–275.5	815
H		H	H	$EtOOC-CH(C_3H_7)$	263–265	815
H		H	H	$C_6H_5CH_2$	301–304	823
H		H	H	$4\text{-}O_2N-C_6H_4-CH=CH$		817
H		H	H		>350	743
H		H	H	C_6H_5	300	189, 818
					329	63
H		H	H	$4\text{-}CF_3-C_6H_4$	341–350	707
H		H	H	$2\text{-}CH_3O-C_6H_4$	299–302	823
H		H	H	$4\text{-}CH_3O-C_6H_4$	300–303	823
H		H	H	$2,3\text{-}(CH_3O)_2C_6H_3$	271–273	823
H		H	H	$3,4\text{-}(CH_3O)_2C_6H_3$	278–281	823

TABLE II-28. (continued)



R^2	R^3	R^3	R^6		m.p.(°C)	Refs.
H	H	H			>300	708
					320–325	823
H	H	H	5-O_2N-2-furyl		350	212
H	H	H	(2-Furyl)vinyl		>300	818
H	H	H			>300	641, 666
					>310	812/648
	·H_2SO_4				274 (dec.)	812
H	H	H				817
H	CH_3	H	H		321	816
H	CH_3	H	CH_3		313–314	816
					319–321	816
H	n-C_4H_9	H	H		244–245	776
H	n-C_4H_9	H	CH_3		289–290	1103
H	$ClCH_2CH_2$	H	CH_3	·HCl	172–174	709
H	$HOCH_2CH_2$	H	CH_3		256	709
H	$HOCH_2CH_2CH_2$	H	CH_3		247–248 (dec.)	709

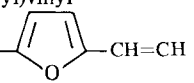
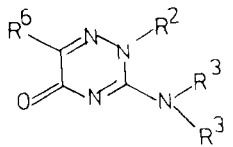
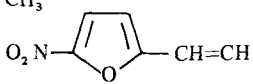
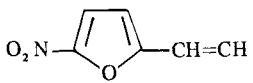
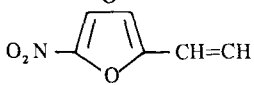
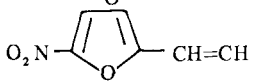
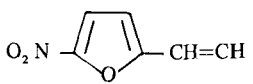
H	$C_6H_5CH_2$	H	H	238–239	776
H	$C_6H_5CH_2$	H	CH_3	278–280	282
H	$C_6H_5CH_2$	H	C_6H_5	320	293
H	C_6H_5	H	H	280–283	816
H	C_6H_5	H	CH_3	316	742
				315–319	816
H	C_6H_5	H	C_6H_5	321	742
				325	293
H	C_6H_5	H	4-CH_3O–C_6H_4	321	157
H	4-$CH_3C_6H_4$	H	C_6H_5	334	293
H	4-Cl–C_6H_4	H	C_6H_5	252	293
H	4-Cl–C_6H_4	H	4-CH_3O–C_6H_4	330	157
H	4-Br–C_6H_4	H	CH_3	345	742
H	4-CH_3O–C_6H_4	H	C_6H_5	260	293
H	4-CH_3O–C_6H_4	H	4-CH_3O–C_6H_4	324	157
H	2-Furyl	H	H	261–262	793
H	CH_3CO	H	H	>300	702
H	CH_3CO	H	CH_3	>300	702
H	CH_3CO	H	C_6H_5	282 (dec.)	818
H	CH_3CO	H	2-Furyl	303–308	212
H	CH_3CO	H	5-O_2N-2-furyl	334–334.5	212
H	CH_3CO	H	(2-Furyl)vinyl	289	818
H	CH_3CO	H		289 (dec.)	641, 666 817
H	C_6H_5–SO_2	H	CH_3	191–194	795
				194–195	819
H	4-$CH_3C_6H_4$–SO_2	H	H	202–204	795, 819
H	4-$CH_3C_6H_4$–SO_2	H	CH_3	228–230	795
				232–234	819
H	4-$CH_3C_6H_4$–SO_2	H	C_6H_5	242.5–244,5	795, 819
H	4-Cl–C_6H_4–SO_2	H	CH_3	233–225	795, 819
H	4-H_2N–C_6H_4–SO_2	H	CH_3	249	622, 795

TABLE II-28. (continued)



R^2	R^3	R^3	R^6	m.p.(°C)	Refs.
CH_3	H	H	CH_3	296–298	816
CH_3	H	H		>300	241, 821, 822
C_2H_5	H	H		272–273 (dec.)	241, 821, 822
C_3H_7	H	H		233–235 (dec.)	241, 825
n-C_4H_9	H	H		225 (dec.)	241, 825
n-$C_{16}H_{33}$	H	H		214–215 (dec.)	825
$C_6H_5-CH_2$	H	H	H_2N-CH_2	195.5–197.5	815
$C_6H_5-CH_2$	H	H	$H_2N-CH(CH_3)$	244–246	815
$C_6H_5-CH_2$	H	H	$H_2N-CH(C_3H_7)$	216–218	815
$C_6H_5-CH_2$	H	H	$C_3H_7-CO-NH-CH_2$	195–198	815
$C_6H_5-CH_2$	H	H	$EtOOC-CH_2$	188	815

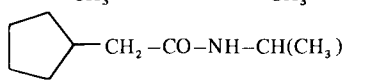
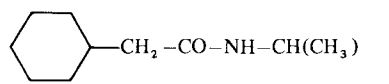
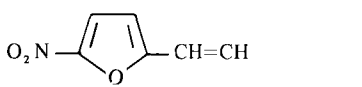
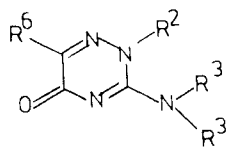
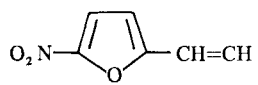
$C_6H_5-CH_2$	H	H	$H_2N-CO-CH_2$	272–274	815
$C_6H_5-CH_2$	H	H	$H_2N-NH-CO-CH_2$	249–251	815
$C_6H_5-CH_2$	H	H	$CH_3CO-NH-CH(CH_3)$	216–219	815
$C_6H_5-CH_2$	H	H	$C_3H_7-CO-NH-CH(CH_3)$	193–194	815
$C_6H_5-CH_2$	H	H	$i\text{-}C_3H_7-CO-NH-CH(CH_3)$	226–228	1442
$C_6H_5-CH_2$	H	H	$C_4H_9-CO-NH-CH(CH_3)$	191	815
$C_6H_5-CH_2$	H	H	$i\text{-}C_4H_9-CO-NH-CH(CH_3)$	149.5	1442
				213.6	815
$C_6H_5-CH_2$	H	H	$Me_2CHCH_2CH_2-CO-NH-CH(CH_3)$	188–190	1442
$C_6H_5-CH_2$					
$C_6H_5-CH_2$	H	H	$C_2H_5-CH(CH_3)-CO-NH-CH(CH_3)$	233–235	1442
$C_6H_5-CH_2$	H	H	$C_2H_5-CH(CH_3)-CH_2-CO-NH-CH(CH_3)$	212–215	1442
$C_6H_5-CH_2$	H	H		195–196.5	1442
$C_6H_5-CH_2$	H	H		200–202	1442
$C_6H_5-CH_2$	H	H	$EtOOC-CH(CH_3)$	151–152	815
$C_6H_5-CH_2$	H	H	$H_2N-NH-CO-CH(CH_3)$	246	815
$C_6H_5-CH_2$	H	H	$EtOOC-CH(C_3H_7)$	128–129	815
$C_6H_5-CH_2$	H	H	$H_2N-NH-CO-CH(C_3H_7)$	235–239	815
$C_6H_5-CH_2$	CH_3	H	$EtOOC-CH(CH_3)$	133–135	815
CH_3	CH_3CO	H		193–195 (dec.)	826, 241

TABLE II-28. (continued)



R^2	R^3	R^3	R^6	m.p.(°C)	Refs.
CH_3	4-Cl–C_6H_4–SO_2	H	CH_3	128–133	795
CH_3	4-$CH_3C_6H_4SO_2$	H	H	156	795, 820
CH_3	4-$CH_3C_6H_4SO_2$	H	CH_3	143–144	795
				146–148	820
CH_3	4-$H_2NC_6H_4SO_2$	H	CH_3	177.5–178.5	795, 820
C_2H_5	CH_3CO	H		188–191 (dec.)	826, 241
CH_2CONH–C_4H_9	H	C_4H_9	CH_2CH_2OH	190–191	709
CH_2CONH–C_4H_9	H	C_4H_9	CH_3	188–189	709
H	CH_3	CH_3	H	280–283	816
				298–299 (dec.)	776
H	CH_3	CH_3	CH_3	218–220	701
				253–255	816
H	CH_3	C_6H_5	H	244–245	776
H	C_2H_5	C_2H_5	CH_3	212–214	701
H	$CH_2CH_2CH_2CH_2CH_2$		H	257–258	776/793
H	$CH_2CH_2CH_2CH_2CH_2$		C_6H_5	329	293
H	$CH_2CH_2CH_2CH_2CH_2$		4-CH_3O–C_6H_4	272	157
H	$CH_2CH_2CH_2CH_2CH_2$		2-Furyl	349–350	212

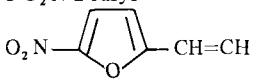
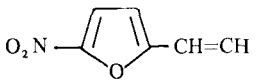
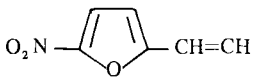
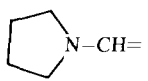
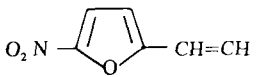
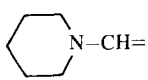
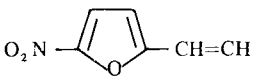
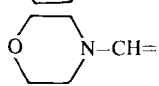
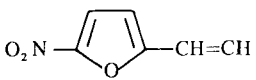
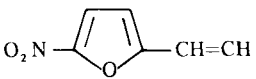
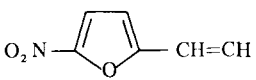
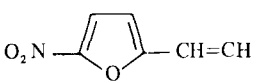
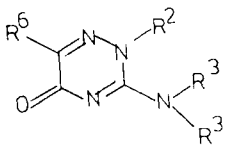
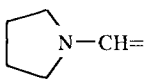
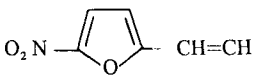
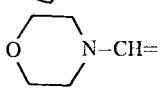
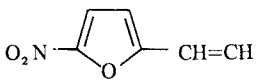
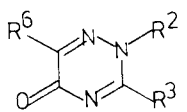
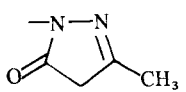
H	$CH_2CH_2CH_2CH_2CH_2$	5-O_2N-2-furyl	340	212
H	$CH_2CH_2OCH_2CH_2$	H	341–342 (dec.)	776/793
H	$CH_2CH_2OCH_2CH_2$	C_6H_5	319	293
H	$CH_2CH_2OCH_2CH_2$	4-CH_3O–C_6H_4	321	157
H	$CH_2CH_2OCH_2CH_2$	2-Furyl	325	212
H	$CH_2CH_2OCH_2CH_2$	5-O_2N-2-furyl	330	212
CH_3	CH_3NH–CH=		330	827
CH_3	$(CH_3)_2$N–CH=		248–249	828
CH_3	$(C_2H_5)_2$N–CH=		204–206	828
CH_3			239–241 (dec.)	829
CH_3			252–253 (dec.)	829
CH_3			283–284 (dec.)	829
C_2H_5	CH_3NH–CH=		286 (dec.)	827
C_2H_5	$(CH_3)_2$N–CH=		235–236 (dec.)	828
C_2H_5	$(C_2H_5)_2$N–CH=		188–189	828

TABLE II-28. (continued)



R^2	R^3	R^3	R^6	m.p.(°C)	Refs.
C_2H_5				238–240 (dec.)	829
C_2H_5				249–250 (dec.)	829



R^2	R^3	R^6	m.p. (°C)	Refs.
H		CH_3	285	831

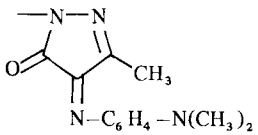
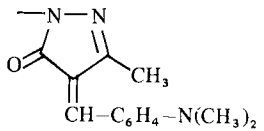
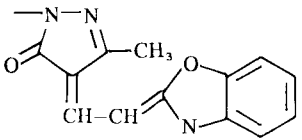
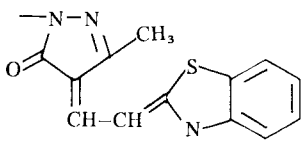
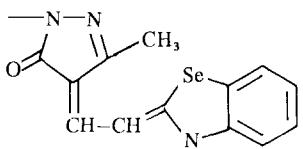
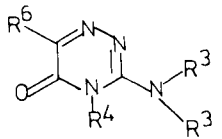
H		CH_3	210	831
H		CH_3	263–264	831
H		CH_3	324–326	831
H		CH_3	325–326	831
H		CH_3	321–324	831

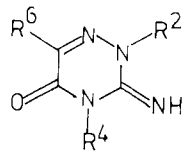
TABLE II-28. (continued)

B. 3-Amino-1,2,4-triazin-5(4H)-ones



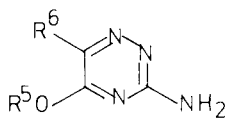
R^3	R^3	R^4	R^6	m.p. (°C)	Refs.
H	H	CH_3	H	235–238	816
H	H	CH_3	CH_3	251–254	816
H	H	CH_3	$C_3H_7CO-NH-CH(CH_3)$	230–231	815
H	H	CH_3	C_6H_5	270	229
H	CH_3	CH_3	H	246–252	816
H	CH_3	CH_3	CH_3	250–251	816
H	CH_3	CH_3	i-C_3H_7	217	229
H	CH_3	CH_3	C_6H_5	249	229
CH_3	CH_3	CH_3	C_6H_5	198	229
C_4H_9	C_4H_9	CH_3	C_6H_5	145	229
		CH_3	C_2H_5	132	229
		CH_3	C_6H_5	130	229

C. 3-Imino-1,2,4-triazin-5-ones



R^2	R^4	R^6	m.p. (°C)	Refs.
CH_3	CH_3	CH_3	101–103	819
$C_6H_5-CH_2$	CH_3	$C_3H_7-CO-NH-CH(CH_3)$	202–203	815

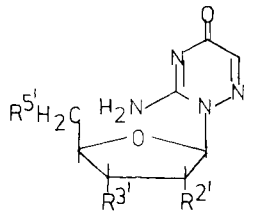
D. 3-Amino-5-hydroxy-1,2,4-triazines

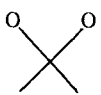
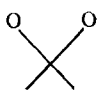
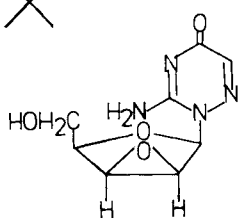


R^5	R^6	m.p. (°C)	Refs.
CH_3	CH_3	272–273 (dec.)	1075
C_2H_5	CH_3	157–159	1075
C_3H_7	CH_3	126–127	1075

TABLE II-28. (continued)

E. Sugar-substituted 3-amino-1,2,4-triazin-5(2H)-ones

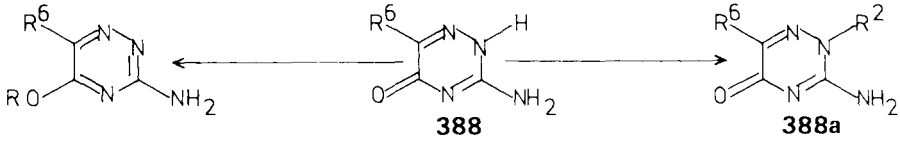


$R^{2'}$	$R^{3'}$	$R^{5'}$	m.p. (°C)	Refs.
OH	OH	OH	243–245	793
			260–261	460
C_6H_5COO	C_6H_5COO	C_6H_5COO		793
		OH	267–269	460
		2-Tetrahydro-pyranyl	225–227	460
			182	458

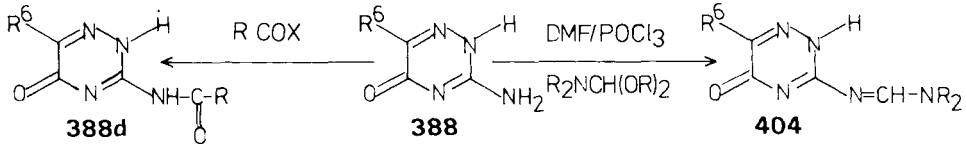
tautomeric structure **388A** predominates over the form **388B** and the constant for the tautomeric equilibrium between these two forms is in the order of 10^2. Gut and his group (830) have determined the pK_a values of a number of 3-amino-1,2,4-triazin-5-ones (1.55 for the unsubstituted, 2.19 for the 6-methyl, 1.90 for the 2,6-dimethyl, and 4.52 for the 4,6-dimethyl derivative) and have calculated the π-electron densities and bond orders by simple HMO calculations. Ultraviolet spectra were measured in ethanol and at different pH values (830).

4. *Reactions*

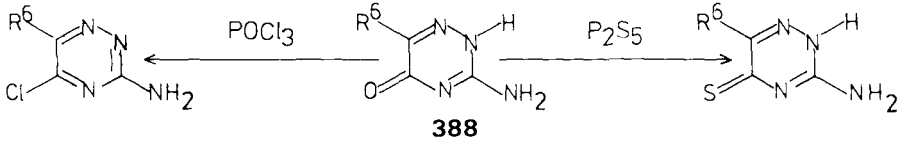
3-Amino-1,2,4-triazin-5-ones (**388**) are converted into 2-alkyl-3-amino-1,2,4-triazin-5-ones (**338a**) by alkylation agents (241, 815, 825); the alkylation of the oxygen with dimethyl sulfate is reported (612).



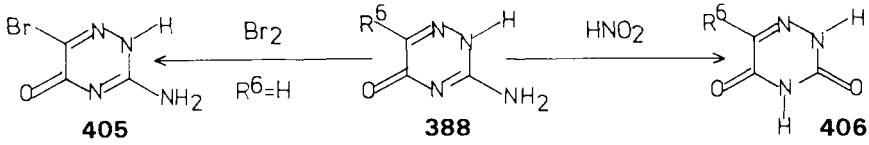
3-(Acylamino)-1,2,4-triazin-5-ones (**388d**) are prepared by reaction of **388** with acylating agents (241, 641, 666, 702, 818, 826). Reaction of **388** with amide acetals or dimethylformamide/phosphorus oxychloride leads to the formation of amidine type compounds (**404**) (827–829).



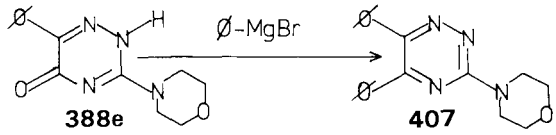
When 3-amino-1,2,4-triazin-5-ones (**388**) are treated with phosphorus oxychloride or phosphorus pentasulfide the oxygen in position 5 is replaced by chlorine (701) or sulfur (189, 708).



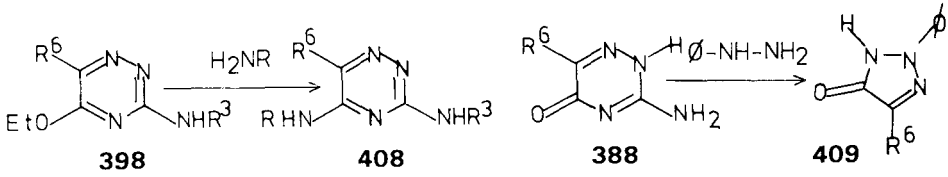
3-Amino-1,2,4-triazin-5-ones (**388**) with an unsubstituted 6-position are transformed into 3-amino-6-bromo-1,2,4-triazin-5-ones (**405**) by reaction with bromine (776); reaction of **388** with nitrous acid gives 1,2,4-triazine-3,5-diones (**406**) (336).



Reaction of 3-morpholino-6-phenyl-1,2,4-triazin-5-one (**388e**) with phenylmagnesium bromide was used for the synthesis of 3-morpholino-5,6-diphenyl-1,2,4-triazine (**407**) (293).



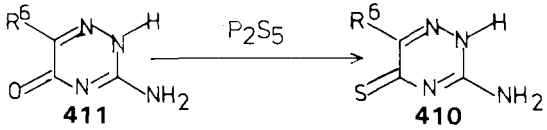
The ethoxy group in 3-amino-5-ethoxy-1,2,4-triazines (**398**) can be replaced by an amino group (715) leading to 3,5-diamino-1,2,4-triazines (**408**). Hadacek reported the condensation of the 3-amino group in **388** with 4-nitroso-*N*,*N*-dimethylaniline (612) and the formation of 4-methyl-2-phenyl-1,2,3-triazol-5-one (**409**) by reaction of **388** with phenylhydrazine (612).

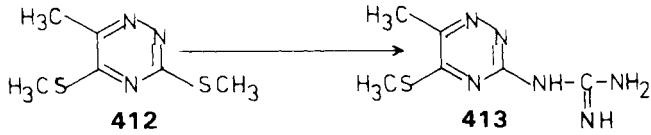


The synthesis of condensed 1,2,4-triazines from 3-amino-1,2,4-triazin-5-ones (**388**) is reported in Refs. 612, 709, and 815.

L. 3-Amino-1,2,4-triazin-5-thiones

Two 3-amino-1,2,4-triazine-5-thiones (**410**) (m.p. $R^6 = C_6H_5$, 275 to 279°C (189); R^6 = 3,4-$CH_2O_2C_6H_3$, 260°C) (708) were prepared by reaction of 3-amino-1,2,4-triazin-5-ones (**411**) with phosphorus pentasulfide in pyridine (189, 708). Reaction of 6-methyl-3,5-bis(methylmercapto)-1,2,4-triazine (**412**) with guanidine was used for the synthesis of 3-guanyl-6-methyl-5-(methylmercapto)-1,2,4-triazine (**413**) (m.p. 264 to 265°C) (594).



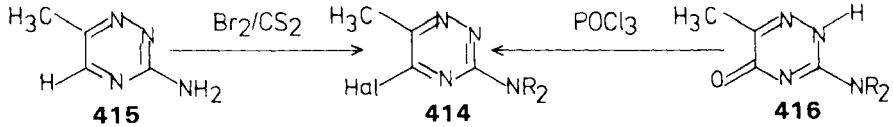


412 413

The three known 3-amino-1,2,4-triazine-5-thiones are compounds with melting points over 250°C. The single reported reaction is the transformation into 3,5-diamino-1,2,4-triazines by reaction with ammonia (708).

M. 3-Amino-5-halo-1,2,4-triazines

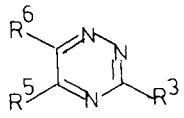
Three 3-amino-5-halo-1,2,4-triazines (**414**) are definitely known (613, 701) (Table II-29). They are synthesized either by reaction of 3-amino-6-methyl-1,2,4-triazine (**415**) with bromine in carbon disulfide (613) or by reaction of 3-(dialkylamino)-6-methyl-1,2,4-triazin-5-ones (**416**) with phosphorus oxychloride (701).



415 414 416

Three other 3-amino-5-chloro-1,2,4-triazines are reported by Grundmann, Schroeder, and Rätz (341) but the compounds isolated by reaction of

TABLE II-29. 3-AMINO-5-HALO-1,2,4-TRIAZINES



R^3	R^5	R^6	m.p. (°C)	Refs.
NH_2	Br	CH_3	165	613
$N(CH_3)_2$	Cl	CH_3	212	701
$N(C_2H_5)_2$	Cl	CH_3	221–223	701
NH_2	Cl	H	250 (dec.)[a]	341
$N(CH_3)_2$	Cl	H	119[a]	341
	Cl	H	95[a]	341

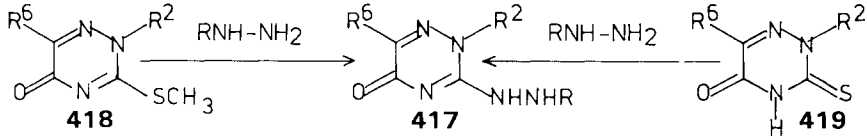
[a]Structure given in the publication is probably incorrect.

3,5-dichloro-1,2,4-triazine with amines are probably 5-amino-3-chloro-1,2,4-triazines instead.

N. 3-Hydrazino-1,2,4-triazin-5-ones

1. *Preparation*

All known 3-hydrazino-1,2,4-triazin-5-ones (**417**) are synthesised by reaction of 3-(methylmercapto)-1,2,4-triazin-5-ones (**418**) or 3-thioxo-1,2,4-triazine-5-ones (**419**) with hydrazines or hydrazides (63, 189, 293, 583, 586, 587, 595, 600, 717, 743, 760, 761, 770, 783, 814).



2. *Compound Survey*

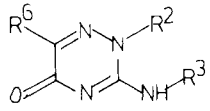
The 3-hydrazino-1,2,4-triazin-5-ones reported in the literature are listed in Table II-30.

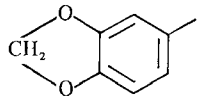
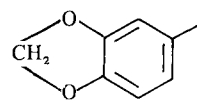
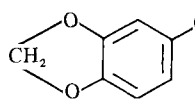
3. *Physical Properties*

The 3-hydrazino-1,2,4-triazin-5-ones (**417**) are stable compounds with high melting points. The infrared spectra show two bands in the region of N–H stretching vibration, a broad band between 3238 and 3266 cm^{-1}, and a sharp band at 3328 to 3345 cm^{-1}. The broadening of the band between 3238 and 3266 cm^{-1} is explained by superposition of the band of ring-bonded NH with the ν_s(N–H) absorption band of the NH_2 group (583). The intensive absorption band at 1637 to 1640 cm^{-1} indicates the oxo structure for the 3-hydrazino-1,2,4-triazin-5-ones. The wave number of the C=O stretching vibration in the infrared spectra indicates that the given tautomeric structure predominates (583).

pK_a Values of 3-hydrazino-1,2,4-triazin-5-ones were measured by Kalfus (392). The same author calculated the energy of proton transition and the acidity function of these compounds (392).

TABLE II-30. 3-HYDRAZINO-1,2,4-TRIAZIN-5-ONES

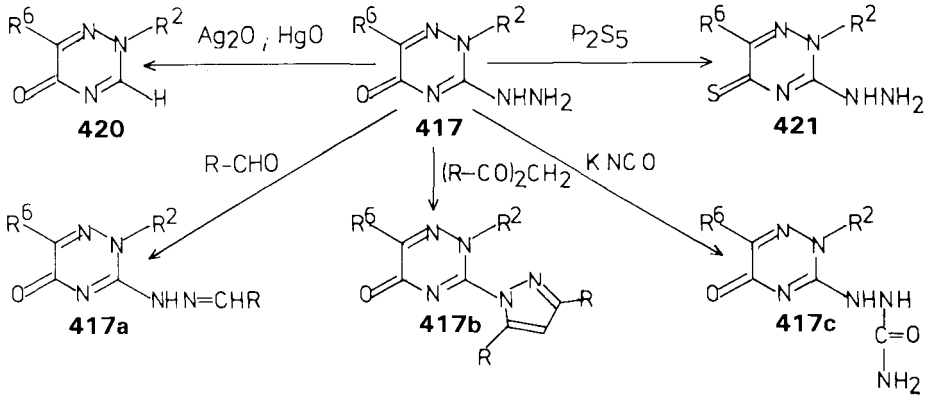


R^2	R^3	R^6	m.p. (°C)	Refs.
H	NH_2	H	248–250 (dec.)	600
H	NH_2	CH_3	237–238	770, 783
			238	814
			240	586
			240–242	599
				189, 587, 595
H	NH_2	C_6H_5	220–222	717
			235	760
	·HCl		292–293	63
H	NH_2	$C_6H_5CH_2$	246–250	583
H	NH_2		>350	743
H	$NH-C_6H_5$	C_6H_5	260	293
H	NH–CHO	H	205–206	814
H	NH–CHO	CH_3	266	814/834
H	NH–CHO	C_6H_5	231	814
H	$NH-COCH_3$	CH_3	235–236	783
			240–242	814/834
H	$NH-CONH_2$	CH_3	227	783
H	$NH-COC_6H_5$	CH_3	265–266	814
H	NH–CSSH	CH_3		835
H	$NH-CSSCH_3$	CH_3	208–210	835
H	$N=CHCH_3$	CH_3	296–297	814
H	$N=C(CH_3)C_2H_5$	CH_3	221.5–222.5	770
H	$N=CHC_6H_5$	CH_3	302	814
			303	783
H	$N=CHC_6H_5$		290–291	743
H	$N=CHC_6H_4Cl(4)$	CH_3	331	586
H	$N=CHC_6H_4$-(4)OCH_3	CH_3	305	586
H	$N=CHC_6H_4$-(4)OCH_3		292–295	743
CH_3	NH_2	H	248–249	192
CH_3	NH_2	CH_3	245	761/814
CH_3	$N=CH_2$	CH_3	237–238	814
CH_3	$N=CHCH_3$	CH_3		814
CH_3	$N=CHC_6H_5$	CH_3	243	761

4. *Reactions*

1,2,4-Triazin-5-ones (**420**) are obtained by oxidation of 3-hydrazino-1,2,4-triazin-5-ones (**417**) with silver oxide or mercuric oxide (63, 192). Hydrazones (**417a**) are formed by reaction of **417** with aldehydes (586, 814, 831). Reaction of **417** with phosphorus pentasulfide is used for the synthesis of 3-hydrazino-1,2,4-triazine-5-thiones (**421**) (189).

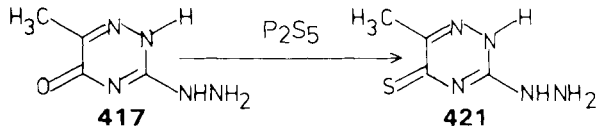
Reaction of 3-hydrazino-1,2,4-triazin-5-ones (**417**) with 1,3-dicarbonyl compounds converts the hydrazino group into a pyrazolyl group (**417b**) (831, 833). Acylation of the hydrazino group was reported in one case (834); addition of carbon disulfide to the hydrazino group was published by Dornow and his group (586) and in a French patent (835). Reaction with potassium cyanate gives the semicarbazone (**417c**) (586). The hydrazino group can be oxidized to a diazonium group, which couples with 1-naphthol (783).



In a large number of cases 3-hydrazino-1,2,4-triazin-5-ones (**417**) were used as starting compounds for the synthesis of condensed 1,2,4-triazines. The following were used as the second component: carboxylic acids and their derivatives (583, 595, 760, 761, 770, 814, 832, 834), carbon disulfide (586, 814, 835), urea (586), 1,2-bifunctional compounds (760, 761, 770, 835), nitric acid (760, 761, 770), and potassium cyanate (586).

O. 3-Hydrazino-1,2,4-triazine-5-thiones

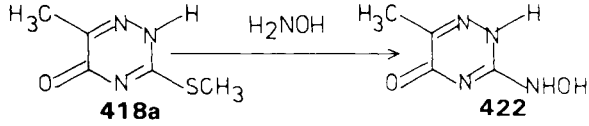
The single known 3-hydrazino-1,2,4-triazine-5-thione, the 3-hydrazino-6-methyl-1,2,4-triazine-5-thione (**421**) (m.p. 250°C) was obtained by Jacquier and his group through reaction of 3-hydrazino-6-methyl-1,2,4-triazin-5-one (**417**) with phosphorus pentasulfide (189).



417 **421**

P. 3-(Hydroxylamino)-1,2,4-triazin-5-ones

The 3-(hydroxylamino)-6-methyl-1,2,4-triazin-5-one (**422**) (dec. 210-330°C) was synthesized through reaction of 6-methyl-3-(methylmercapto)-1,2,4-triazin-5-one (**418a**) with hydroxylamine (1078).



418a **422**

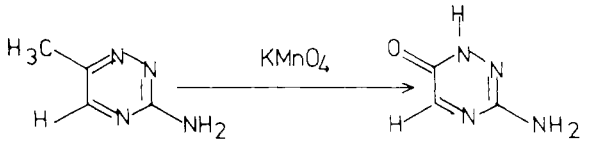
Q. 5-Amino-3-chloro-1,2,4-triazines

Hydrogenation of 5-(dimethylamino)-3,6-dichloro-1,2,4-triazine (**423**) in ether under atmospheric pressure and at room temperature in the presence of *N*-ethylpiperidine over 10% palladium on active charcoal as catalyst for 10 hr affords 3-chloro-5-(dimethylamino)-1,2,4-triazine (**425**) in 16% yield [m.p. 117 to 118°C (dec.)] (1566).

423 **425**

R. 3-Amino-1,2,4-triazin-6-ones

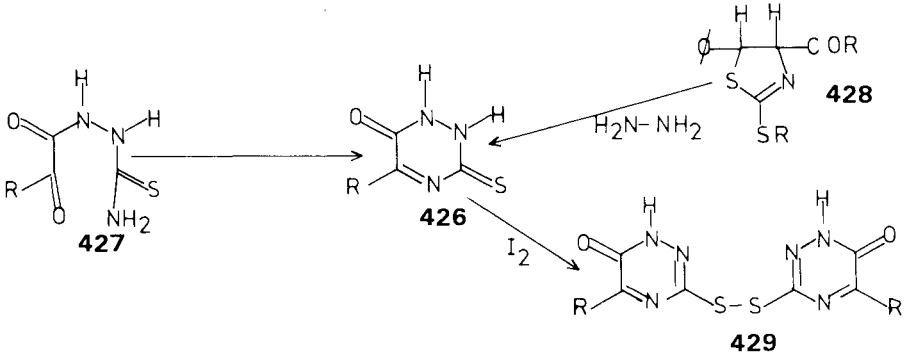
Hadacek and Kisa published the synthesis of 3-amino-1,2,4-triazin-6-one (**424**) (m.p. 184°C) by oxidation of 3-amino-6-methyl-1,2,4-triazine (**208c**) with potassium permanganate (613). **424** is the single known compound of this structure.



208c **424**

S. 3-Thioxo-1,2,4-triazin-6-ones

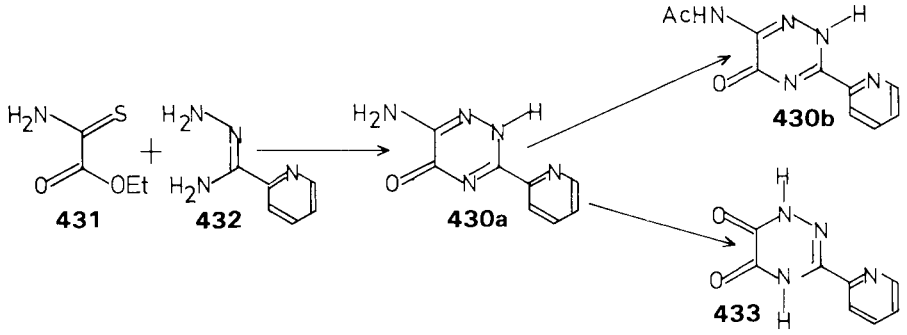
3-Thioxo-1,2,4-triazin-6-ones (**426**) [a: R = 2–HO–C_6H_4, 243°C (808); b: R = C_6H_5–CH_2, 244 to 246°C (837), 251°C (836)] are prepared either by basic cyclization of 1-(α-ketoacyl)thiosemicarbazides (**427**) (808) or by reaction of rhodanines (**428**) with hydrazine (836, 837).



No detailed study of the predominant tautomeric structure has been reported so far; three different tautomeric forms are given in the three publications. 3-Thioxo-1,2,4-triazin-6-one (**426a**) can be oxidized with iodine to the disulfide (**429**) (m.p. 229°C) (808). Methylation of 5-benzyl-3-thioxo-1,2,4-triazin-6-one (**426b**) or its tautomers [m.p. 244 to 246°C (837), 251°C (836)] with methyl iodide and base gave two different products [m.p. 163 to 164°C (837), 227 (dec.) (836)] the structure of which was not clearly identified.

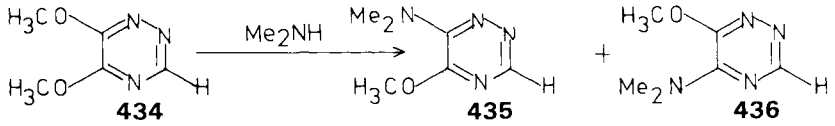
T. 6-Amino-1,2,4-triazin-5-ones

At present only three 6-amino-1,2,4-triazin-5-ones (**430**) are known. The 6-amino-3-pyridyl-1,2,4-triazin-5-one (**430a**) was obtained from the reaction of



ethyl oxalthioamidate (**431**) with 2-pyridylamidrazone (**432**) (183). It can be acetylated to the 6-acetylamino derivative (**430b**) and hydrolyzed in aqueous acid to the 3-(2-pyridyl)-1,2,4-triazine-5,6-dione (**433**) (183).

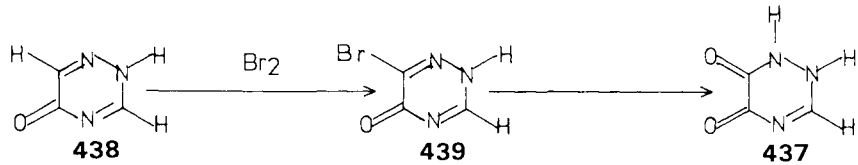
Neunhoeffer and Lehmann (678) converted the 5,6-dimethoxy-1,2,4-triazine (**434**) into a mixture of 6-(dimethylamino)-5-methoxy-1,2,4-triazine (**435**) (m.p. 101 to 102°C) and 5-(dimethylamino)-6-methoxy-1,2,4-triazine (**436**) by reaction with dimethylamine.



434 **435** **436**

U. 6-Bromo-1,2,4-triazin-5-ones

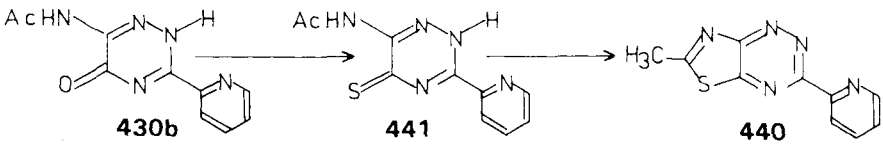
Brown and Jonas (192) synthesized the 1,2,4-triazine-5,6-dione (**437**) by reaction of 1,2,4-triazin-5-one (**438**) with bromine. The initially formed intermediate of this reaction should be the 6-bromo-1,2,4-triazin-5-one (**439**) which is then hydrolyzed to the isolated compound.



438 **439** **437**

V. 6-Amino-1,2,4-triazine-5-thiones

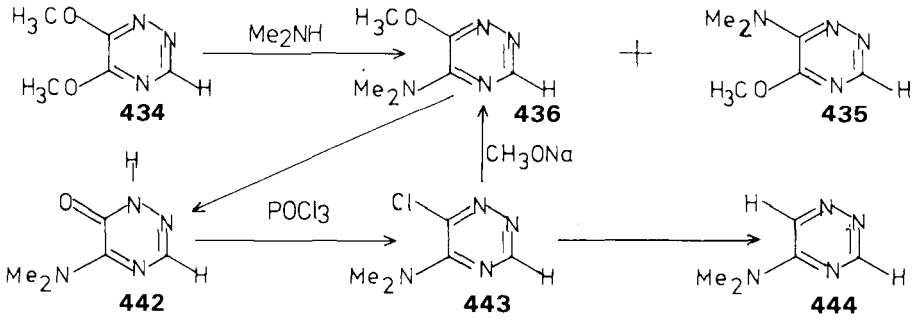
Reaction of 6-(acetylamino)-3-(2-pyridyl)-1,2,4-triazin-5-one (**430b**) with phosphorus pentasulfide was used for the synthesis of 1,3-thiazolo-[5,4–*e*] 1,2,4-triazine (**440**) (183). The 6-(acetylamino)-3-(2-pyridyl)-1,2,4-triazine-5-thione (**441**) can be formulated as an intermediate of this reaction.



430b **441** **440**

W. 5-Amino-1,2,4-triazin-6-ones

The two known compounds of this class were prepared by Neunhoeffer and Lehmann (678). The 5-(dimethylamino)-6-methoxy-1,2,4-triazine (**436**) (m.p. 46 to 50°C) is one product of the reaction of 5,6-dimethoxy-1,2,4-triazine (**434**) with dimethylamine. During an attempt to substitute the second methoxy group with a dimethylamino group by reaction of **436** with dimethylamine at high temperatures 5-(dimethylamino)-1,2,4-triazin-6-one (**442**) (m.p. 188°C) was obtained, which reacts with phosphorus oxychloride to form 6-chloro-5-(dimethylamino)-1,2,4-triazine (**443**) (678), which forms **436** with sodium methoxide.



X. 5-Amino-6-chloro-1,2,4-triazines

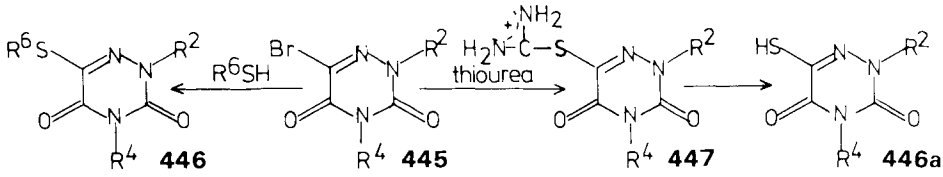
As was stated in the preceding chapter the 6-chloro-5-(dimethylamino)-1,2,4-triazine (**443**) is obtained by reaction of 5-(dimethylamino)-1,2,4-triazin-6-one (**442**) with phosphorus oxychloride (678). Reaction of **442** with sodium methoxide gives 5-(dimethylamino)-6-methoxy-1,2,4-triazine (**436**), whereas 5-(dimethylamino)-1,2,4-triazine (**444**) is obtained by catalytic reduction (678).

Y. 6-Mercapto-1,2,4-triazine-3,5-diones

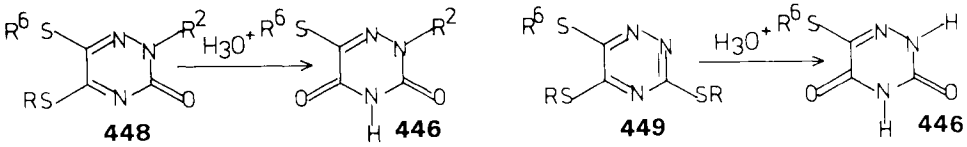
1. *Preparation*

In most cases 6-bromo-1,2,4-triazine-3,5-diones (**445**) are the starting materials for the synthesis of 6-mercapto-1,2,4-triazine-3,5-diones (**446**) (218, 349, 498, 838–842). **445** are either directly converted into **446** by reaction with mercaptans (218, 349, 838, 839) or the isothiuronium salts **447**, which were

obtained by reaction of **445** with thiourea, are hydrolyzed to the *S*-unsubstituted 6-mercapto-1,2,4-triazine-3,5-diones (**446a**) (218, 349, 498, 840–842).



Besides these methods the formation of **446** by acidic hydrolysis of 5,6-dimercapto-1,2,4-triazin-3-ones (**448**) (602, 843) or tris(methylmercapto)-1,2,4-triazines (**449**) (602) is reported.



2. *Compound Survey*

Table II-31 lists the known 6-mercapto-1,2,4-triazine-3,5-diones.

3. *Physical Properties*

6-Mercapto-1,2,4-triazine-3,5-diones (**446**) are yellow or orange crystalline compounds with melting points greater than 200°C; alkylation or acylation lowers the melting point. They are weak acids. Like all 1,2,4-triazines with hetero substituents they can form different tautomeric structures, but so far no detailed study on the predominant tautomeric form has been reported.

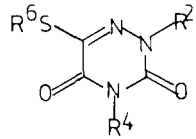
4. *Reactions*

S-Unsubstituted 6-mercapto-1,2,4-triazine-3,5-diones (**446a**) are alkylated by alkyl halides in basic media first at the sulfur, then at the nitrogen in position 4 (218, 839, 844–846). In the same way acylation also starts at the sulfur (846, 847).

Reaction of 6-mercapto-1,2,4-triazine-3,5-diones (**446**) with phosphorus pentasulfide in pyridine, containing 0.1 to 0.3% of water, converts them into

TABLE II-31. 6-MERCAPTO-1,2,4-TRIAZINE-3,5-DIONES

A. 6-Mercapto-1,2,4-triazine-3,5(2H,4H)-diones



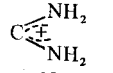
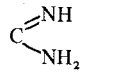
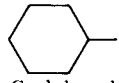
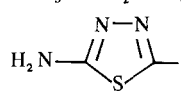
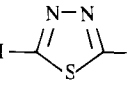
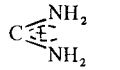
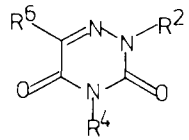
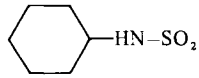
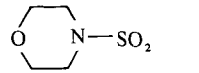
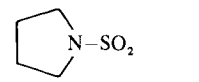
R^2	R^4	R^6	m.p. (°C)	Refs.
H	H	H	278–279	218
			327 (dec.)	840
				498, 842
H	H	Na	327–329	349
$\cdot 2H_2O$			313–314	841
				846, 850
H	Na	Na	315–317 (dec.)	847
			327–329	218
H	H	CH_3	269–270	855
			270	845
H	H	C_2H_5	254–255	845, 855/843
H	H	$CH_2=CH-CH_2$	201–203	218, 839
H	H	n-C_4H_9	214–215	845, 855/843
H	H	n-C_6H_{13}	208–210	845, 855/843
H	H	$HOOC-CH_2$	230–232	845, 855
H	H		234–236	218/840
H	H			498, 842
H	H	 Cyclohexyl	272–274	845, 855
H	H	$C_6H_5-CH_2$	213–214	845, 855
			224–226	349, 850/844
H	H	4-$CH_3O-C_6H_4-CH_2$	237–239	843
H	H	C_6H_5-CO	224–226	847
H	H	C_6H_5	186–188	218, 839
H	H	4-Cl-C_6H_4	278–279	218, 839
H	H	2-$H_2N-C_6H_4$	>300	838
H	H	4-CH_3-2-$H_2N-C_6H_3$	>300	838
H	H	5-CH_3-2-$H_2N-C_6H_3$	>300	838
H	H	4-Cl-2-$H_2N-C_6H_3$	>300	838
H	H	6-Cl-2-$H_2N-C_6H_3$	>300	838
H	H	5-HO-2-$H_2N-C_6H_3$	>300	838
H	H	3-CH_3O-2-$H_2N-C_6H_3$	>300	838
H	H		260–262	218, 839

TABLE II-31 (continued)

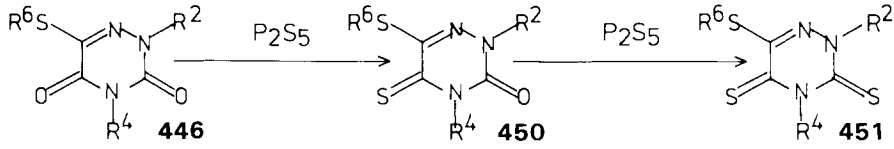
H	H	CH_3CONH– 	290–291	218, 839
H	$C_6H_5CH_2$	$C_6H_5CH_2$		846
H	$(C_6H_5)_2CH$	$C_6H_5CH_2$	220–221	349
H	C_6H_5CO	$C_6H_5CH_2$		846
H	C_6H_5CO	C_6H_5CO	112–114	847/846
CH_3	H	Na	335–337 (dec.)	847
			336–337 (dec.)	349
CH_3	H	 Br^-	245–247 (dec.)	349
CH_3	H	$C_6H_5CH_2$	173–175	349, 850
CH_3	$(C_6H_5)_2CH$	$C_6H_5CH_2$	163–164	349
CH_3	C_6H_5–CO	C_6H_5–CO	139–141	847
$HOOC-CH_2$	H	2-$H_2N-C_6H_4$	>300	838
CH_3CO	H	CH_3CO	146–148	847
C_6H_5CO	C_6H_5CO	C_6H_5CO		847
$Hg_{1/2}$	C_6H_5CO	C_6H_5CO	230 (dec.)	847

B. 6-Sulfoxyl- and 6-sulfonyl-1,2,4-triazine-3,5(2H,4H)-diones

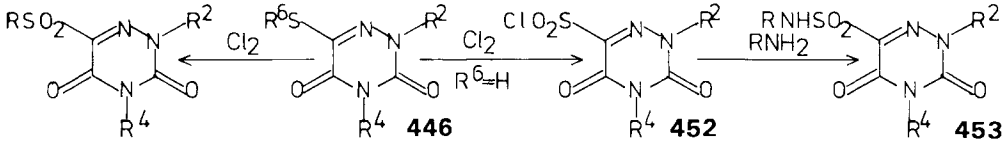


R^2	R^4	R^6	m.p. (°C)	Refs.
H	H	2-$H_2N-C_6H_4-SO-$		838
H	H	CH_3-SO_2	238–239	845, 852
H	H	$C_2H_5-SO_2$	228–229	845, 852
H	H	n-$C_4H_9-SO_2$	193–194	845, 852
H	H	n-$C_{16}H_{13}-SO_2$	207–208	845, 852
H	H	$C_6H_5-SO_2$	261–262 (dec.)	845, 852
H	H	SO_2Cl	207–208 (dec.)	853
			208–209 (dec.)	845, 852
H	H	$(CH_3)_2N-SO_2$	280–281 (dec.)	853
			290 (dec.)	845, 852
H	H	n-$C_4H_9-NH-SO_2$	255–256	853
H	H		244–245	853
H	H		292–293 (dec.)	853
H	H		272–273 (dec.)	853

6-mercapto-5-thioxo-1,2,4-triazin-3-ones (**450**) (602, 843, 848–851); increasing the amount of phosphorus pentasulfide fourfold leads to the formation of 1,2,4-triazine-3,5,6-trithiones (**451**) (602, 1091).

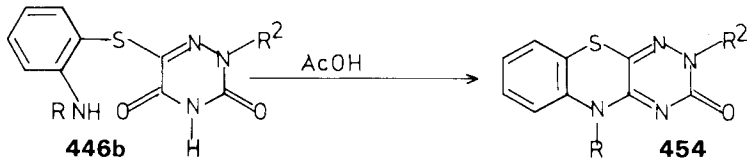


The 6-mercapto group in **446** is transformed into a sulfonyl group by reaction with chlorine (845, 852, 853). Starting with the unsubstituted mercapto group or with the sodium salt, the sulfonyl chloride (**452**) is isolated which reacts with amines to give sulfonamides (**453**) (845, 852, 853). Oxidation of **446** with sodium periodate affords sulfoxides (838).



Mercury salts of S,N_4-disubstituted 6-mercapto-1,2,4-triazine-3,5-diones are reported by Cristescu and Lazarescu (847, 854).

6-[(2-Aminophenyl)mercapto]-1,2,4-triazine-3,5-diones (**446b**) can be cyclized in acetic acid, yielding benzo[*b*]1,2,4-triazino[5,6-*e*]1,4-thiazines (**454**) (1554, 1556).



Z. 6-Amino-1,2,4-triazine-3,5-diones

Most 6-amino-1,2,4-triazine-3,5-diones (**455**) (Table II-32) were prepared by reaction of 6-bromo-1,2,4-triazine-3,5-diones (**456**) with ammonia or amines (218, 473, 497, 500, 839, 856). Curtius degradation of 6-(azidocarbonyl)-1,2,4-triazine-3,5-diones (**457**) also affords 6-amino-1,2,4-triazine-3,5-diones (**455**) (905).

6-Amino-5-cyano-3-ethoxy-1,2,4-triazine (**458**) was easily hydrolyzed, affording 6-amino-3-ethoxy-1,2,4-triazin-5-one (**459**) (m.p. 230°C) (1099).

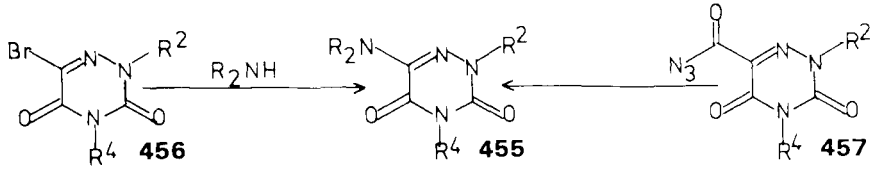
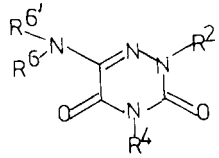
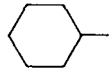
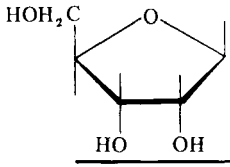


TABLE II-32. 6-AMINO-1,2,4-TRIAZINE-3,5-DIONES



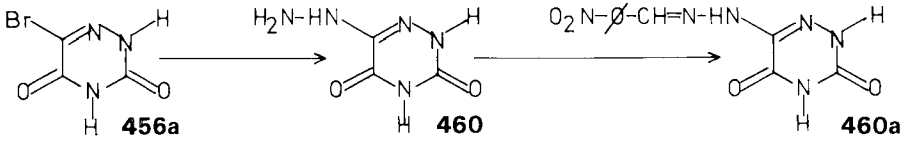
R^2	R^4	R^6	$R^{6'}$	m.p. (°C)	Refs.
H	H	H	H	310–315	497
				>320	856
H	H	H	CH_3	>320	856
H	H	H	C_2H_5	242	856
H	H	H	n-C_3H_7	185	856
H	H	H	i-C_3H_7	171	856
H	H	H	$HOOC-CH_2$	265–267	500
H	H	H	$CH_3OOC-CH_2$	176–179	500
H	H	H	$HOOC-CH(CH_3)$	272–276	500
H	H	H	$HOOC-CH$ $H_3C-CH-CH_3$	268–271	500
H	H	H	$C_6H_5CH_2OCONHCH_2CO$	229–231	500
H	H	H	 ·HBr	236	856
H	H	H	$C_6H_5CH_2$ ·HBr	224	856
H	H	CH_3	CH_3	201	856
				202–204	218, 839
H	H		$CH_2CH_2OCH_2CH_2$	263	856,
				263–265	218, 839
H	H		$CH_2CH_2CH_2CH_2$	255	856
H	H		$CH_2CH_2CH_2CH_2CH_2$	220	856
C_6H_5	H	H	$OOC-CH_3$	185–187	905
C_6H_5	H	H	OOC-n-C_4H_9	142–144	905
	H	CH_3	CH_3		473

458 459

6-Amino-1,2,4-triazine-3,5-diones (**455**) are stable, colorless, crystalline compounds which can be hydrolyzed to 1,2,4-triazine-3,5,6-triones. No study of the predominant tautomeric structure of these compounds has been reported so far.

A . 6-Hydrazino-1,2,4-triazine-3,5-diones

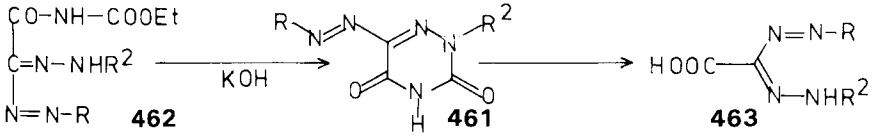
6-Bromo-1,2,4-triazine-3,5-dione (**456a**) is converted into the 6-hydrazino-1,2,4-triazine-3,5-dione (**460**) (m.p. 248 to 250°C) by reaction with hydrazine (218, 839). **460** forms a hydrazone with 4-nitrobenzaldehyde (**460a**) (m.p. 332 to 333°C) (218).



456a 460 460a

B′. 6-(Arylazo)-1,2,4-triazine-3,5-diones

Whiteley and Yapp (857) synthesized three 6-(arylazo)-1,2,4-triazine-3,5-diones (**461**) by cyclization of compounds **462** with potassium hydroxide.



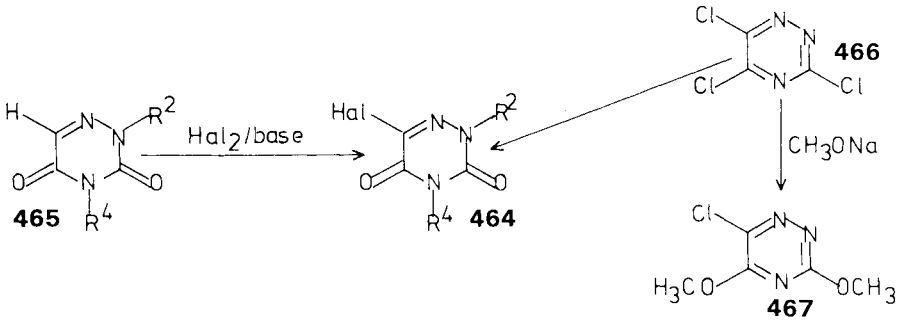
462 461 463

All 6-(arylazo)-1,2,4-triazine-3,5-diones [R = C_6H_5, m.p. 256°C (dec.); 4–CH_3–C_6H_4, m.p. 246°C; 2–O_2N–C_6H_4, m.p. 224°C (dec.)] can be hydrolyzed to the formazans **463** (857).

C'. 6-Halo-1,2,4-triazine-3,5-diones

1. *Preparation*

6-Chloro- (**464a**) (497), 6-bromo- (**464b**) (216, 218, 251, 349, 351, 497–500), and 6-iodo-1,2,4-triazine-3,5-diones (**464c**) (497) are synthesized by reaction of 1,2,4-triazine-3,5-diones (**465**) with the appropriate halogen in the presence of a base.



The 6-fluoro-2,4-dimethyl-1,2,4-triazine-3,5-dione was obtained by nucleophilic substitution of the 6-bromine by fluorine (499).

Hydrolysis of 3,5,6-trichloro-1,2,4-triazine (**466**) leads to 6-chloro-1,2,4-triazine-3,5-dione (**464a**) ($R^2 = R^4 = H$) (497). The same substance is obtained by hydrolysis of the compounds, synthesized through reaction of **466** with ammonia, amines, or methoxide (563, 1565, 1566).

A reaction of 3,5,6-trichloro-1,2,4-triazine (**466**) with sodium methoxide was used for the synthesis of 6-chloro-3,5-dimethoxy-1,2,4-triazine (**467**) (563, 678, 1565).

2. *Compound Survey*

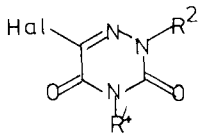
Table II-33 lists the 6-halo-1,2,4-triazine-3,5-diones reported in the literature.

3. *Physical Properties*

6-Halo-1,2,4-triazine-3,5-diones (**464**) are almost colorless compounds with high melting points. They are weak acids; the pK_a value of 6-bromo-1,2,4-triazine-3,5-dione (6.00) was determined by Jonas and Gut (393). No detailed study of the predominant tautomer has so far been reported.

TABLE II-33. 6-HALO-1,2,4-TRIAZINE-3,5-DIONES

A. 6-Halo-1,2,4-triazine-3,5(2H,4H)-diones



R^2	R^4	Hal	m.p. (°C)	Refs.
CH_3	CH_3	F	130–131	499
H	H	Cl	225–227	216, 497, 563
			232–233	1565, 1566
H	H	I	218–220	497
H	H	Br	232–234	216, 218, 349, 497, 498
H	CH_3	Br	190–191	499
H	$C_6H_5CH_2$	Br		859
H	$(C_6H_5)_2CH$	Br	194–195	349
CH_3	H	Br	207–208	251
			208–209	349
CH_3	CH_3	Br	100–102	351
			101.5–102.5	562
			105–106, recryst. 138	499
CH_3	$(C_6H_5)_2CH$	Br	148–149	349
CH_3CO	H	Br	148–150	349
CH_3CO	CH_3	Br	111.5–113	499
CF_3CO	CH_3	Br	136–138, recryst. 183	499
CH_2CH_2CN	H	Br	212–214	859

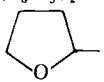
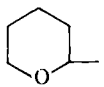
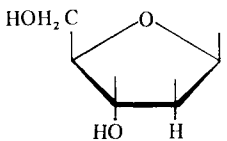
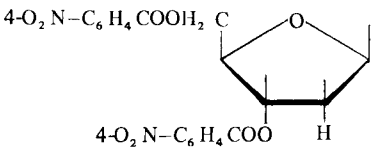
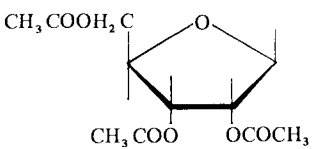
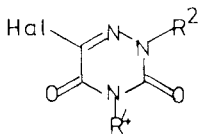
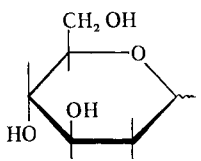
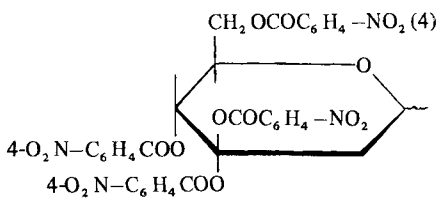
CH_2CH_2CN	CH_2CH_2CN	Br	143–145	859
CH_2CH_2CN	CH_3	Br	113–115	562
CH_2CH_2CN	$C_6H_5CH_2$	Br	104–106	859
$C_6H_5CH_2$	$C_6H_5CH_2$	Br	131–132	859
$(C_6H_5)_2CH$	$(C_6H_5)_2CH$	Br	183–185	499
 2-Tetrahydrofuryl	H	Br		472, 2306
 2-Tetrahydropyranyl	H	Br		472, 2306
	H	Br	214–215	347, 473
	H	Br	131–132	347, 473
	H	Br	123–124	476

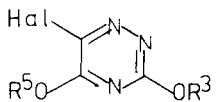
TABLE II-33. (continued)

A. 6-Halo-1,2,4-triazine-3,5(2H,4H)-diones



R^2	R^4	Hal	m.p.(°C)	Refs.
	H	Br	239–241	858
	H	Br	263–265	858

B. 6-Halo-3,5-dihydroxy-1,2,4-triazines



R^3	R^5	Hal	m.p. (°C)	Refs.
CH_3	CH_3	Cl	61–62	563, 678
$(CH_3)_3Si$	$(CH_3)_3Si$	Br	44 p.b. 98–99/0.2	858

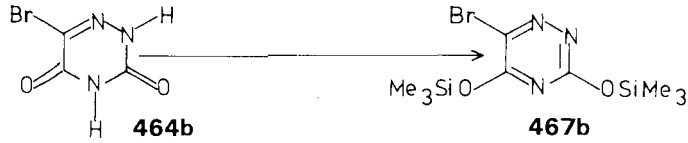
4. *Reactions*

The halogen (bromine) in the 6-position of 6-halo-1,2,4-triazine-3,5-diones (**464**) is very reactive and can be substituted by other nucleophiles, such as fluorine (499), a cyano group (251), ammonia or amines (218, 473, 497, 500, 839, 856), hydrazine (218, 839), mercaptans (218, 349, 838, 839), thiourea (218, 349, 498, 838–842), or alkoxides (562).

6-Halo-1,2,4-triazine-3,5-diones (**464**) can be alkylated (349, 562, 859) or acylated (349) at both nitrogens.

Reaction of 6-bromo-1,2,4-triazine-3,5-dione (**464b**) is used for the synthesis of 3,5,6-trichloro-1,2,4-triazine (**466**) by reaction with phosphorus oxychloride (216, 497, 563, 721).

6-Bromo-3,5-bis(trimethylsilyloxy)-1,2,4-triazine (**467b**) is obtained from the reaction of **464b** with trimethylsilyl chloride and is used for the synthesis of N_2-sugar-substituted 6-bromo-1,2,4-triazine-3,5-diones (347, 473, 476, 858).



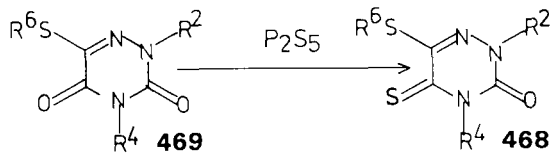
464b **467b**

1,2,4-Triazine-3,5-diones are obtained by reduction of 6-bromo-1,2,4-triazine-3,5-diones with sodium/ammonia (349) or butyllithium (216).

D′. 6-Mercapto-5-thioxo-1,2,4-triazin-3-ones

1. *Preparation*

All known 6-mercapto-5-thioxo-1,2,4-triazin-3-ones (**468**) are prepared by thionation of 6-mercapto-1,2,4-triazine-3,5-diones (**469**) with phosphorus pentasulfide in pyridine (602, 843, 848–851). Best yields were obtained in the presence of 0.1 to 0.3% water and a molar ratio **469** : P_2S_5 of 2 : 1 (602, 843).



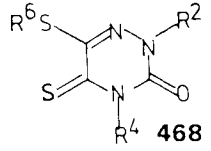
469 **468**

2. *Compound Survey*

The compounds of this class reported in the literature are listed in Table II-34.

TABLE II-34. 6-MERCAPTO-5-THIOXO-1,2,4-TRIAZIN-3-ONES

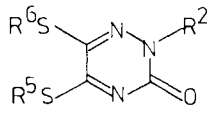
A. 6-Mercapto-5-thioxo-1,2,4-triazin-3-(2H,4H)-ones



468

R^2	R^4	R^6	m.p. (°C)	Refs.
H	H	CH_3	306 (dec.)	602, 848
H	H	C_2H_5	226–228 (dec.)	843, 848
H	H	*n*-C_4H_9	244–246 (dec.)	843
H	H	*n*-C_6H_{13}	246–248 (dec.)	843, 848
H	H	$C_6H_5CH_2$	272–273	849, 850
H	H	4-CH_3O–$C_6H_4CH_2$	227–229 (dec.)	843
H	H	C_6H_5	237–238 (dec.)	848, 851

B. 5,6-Dimercapto-1,2,4-triazin-3-ones



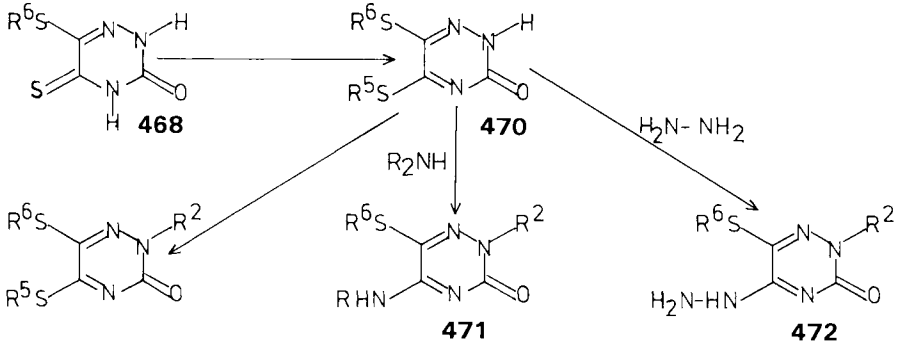
R^2	R^5	R^6	m.p. (°C)	Refs.
H	CH_3	CH_3	227–228	602, 864
H	CH_3	C_2H_5	178–180	843, 864
H	CH_3	*n*-C_4H_9	110–111	843, 864
H	CH_3	*n*-C_6H_{13}	181–182 (dec.)	843
H	CH_3	$C_6H_5CH_2$	184–186	850, 861
H	CH_3	C_6H_5	204–206	851, 864
H	*n*-C_4H_9	$C_6H_5CH_2$	128–130	850, 861
H	$C_6H_5CH_2$	$C_6H_5CH_2$	159–161	850, 861
CH_3	CH_3	$C_6H_5CH_2$	95–97	850, 863

3. *Physical Properties*

6-Mercapto-5-thioxo-1,2,4-triazin-3-ones (**468**) are orange, crystalline compounds with high melting points. 5,6-Dimercapto-1,2,4-triazin-3-ones (**470**) are pale yellow or colorless compounds with lower melting points. The infrared spectra of compounds **468** show an intensive absorption band at 1650 to 1750 cm^{-1} (C=O) and a second band near 1140 cm^{-1} (C=S), indicating that the predominant tautomer is the structure used in this discussion (602, 843).

4. *Reactions*

Alkylation of 6-mercapto-5-thioxo-1,2,4-triazin-3-ones (**468**) starts at the sulfur, leading to 5,6-dimercapto-1,2,4-triazin-3-ones (**470**), followed by alkylation at the nitrogen in position 2 (602, 843, 851, 861, 863, 864). 5-Amino-6-mercapto-1,2,4-triazin-3-ones (**471**) are obtained by reaction of **470** with ammonia or amines and 5-hydrazino-6-mercapto-1,2,4-triazin-3-ones (**472**) by the analogous reaction of **470** with hydrazine (602, 843, 860).



The oxygen in **468** is replaced by sulfur by reaction with phosphorus pentasulfide (602, 1091); acid hydrolysis yields 6-mercapto-1,2,4-triazine-3,5-diones (602). Mercury salts of 5,6-bis(alkylmercapto)-1,2,4-triazin-3-ones are described by Cristescu and Badea (862).

E′. 3-Thioxo-1,2,4-triazine-5,6-diones

The chemistry of 3-thioxo-1,2,4-triazine-5,6-diones (**473**) was studied by Pesson and Antoine (865–868). **473** are synthesized by reaction of diethyl oxalate with substituted thiosemicarbazides or by cyclization of (*N,N*-dialkyloxamoyl)thiosemicarbazides (**474**) in the presence of sodium alkoxides.

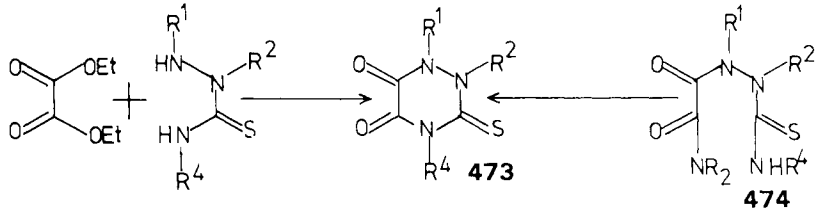
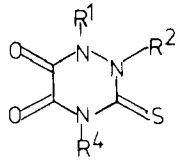


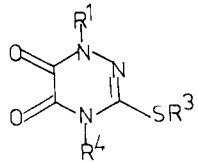
TABLE II-35. 3-THIOXO-1,2,4-TRIAZINE-5,6-DIONES

A. 3(4H)-Thioxo-1,2,4-triazine-5,6(1H,2H)-diones



R^1	R^2	R^4	m.p. (°C)	Refs.
H	H	CH_3	220 (dec.)	866–868
$\cdot H_2O$			215–220 (dec.)	866
H	H	C_6H_5	203–204	866
H	CH_3	CH_3	218–219 (dec.)	865, 867
CH_3	H	CH_3	268 (dec.)	865, 868

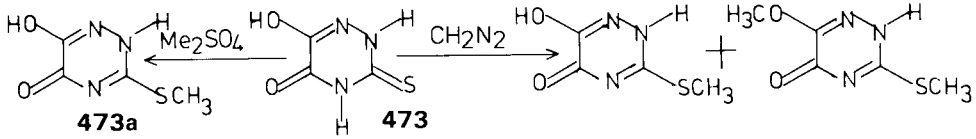
B. 3-Mercapto-1,2,4-triazine-5,6(1H,4H)-diones



R^1	R^3	R^4	m.p. (°C)	Refs.
H	CH_3	CH_3	249–250 (dec.)	866, 868
CH_3	CH_3	CH_3	205–206	865, 866, 868
			206–208	865
6-methoxy-2,4-dimethyl-3-thioxo-1,2,4-triazin-5-one			180	865, 867
6-methoxy-3-(methylmercapto)-4-methyl-1,2,4-triazin-5-one			171	865

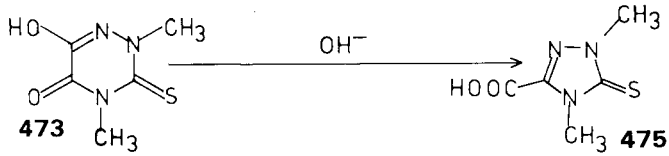
3-Thioxo-1,2,4-triazine-5,6-diones (**473**) are colorless compounds with high melting points. They are soluble in bases and are reprecipitated by addition of acids. Concentrated bases or acids destroy the triazine system.

By comparison of the ultraviolat spectra of *S*- and *N*-methylated derivatives of 3-thioxo-1,2,4-triazine-5,6-dione the given tautomeric structure seems to be the predominant form in alcoholic solution (865).



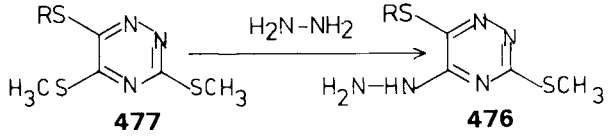
Alkylation of 3-thioxo-1,2,4-triazine-5,6-diones (**473**) with dimethyl sulfate starts at the sulfur (865, 866, 868), whereas diazomethane alkylates the sulfur and the oxygen in position 6 (865, 867).

Treatment of 3-thioxo-1,2,4-triazine-5,6-diones (**473**) with acids or bases leads to the formation of 1,2,4-triazoles (**475**) (865–868) as is illustrated for the 2,4-dimethyl-3-thioxo-1,2,4-triazine-5,6-dione.



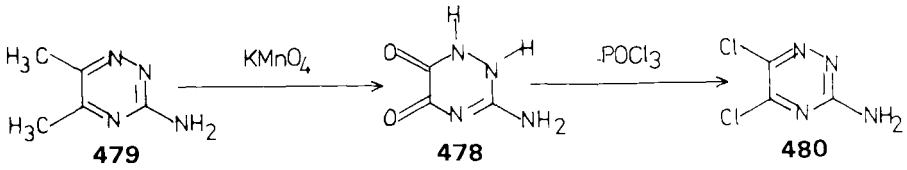
F′. 5-Hydrazino-3,6-dimercapto-1,2,4-triazines

The two known 5-hydrazino-3,6-dimercapto-1,2,4-triazines (**476**) [R = CH_3 m.p. 169 to 170°C (dec.), R = C_6H_5 m.p. 149 to 151°C (dec.)] were synthesized by reaction of 3,5,6-trimercapto-1,2,4-triazines (**477**) with hydrazine (602, 603, 851).



G′. 3-Amino-1,2,4-triazine-5,6-diones

Hadacek and Kisa obtained 3-amino-1,2,4-triazine-5,6-dione (**478**) (m.p. 330°C) through oxidation of 3-amino-5,6-dimethyl-1,2,4-triazine (**479**) with potassium permanganate in the presence of a base (701).

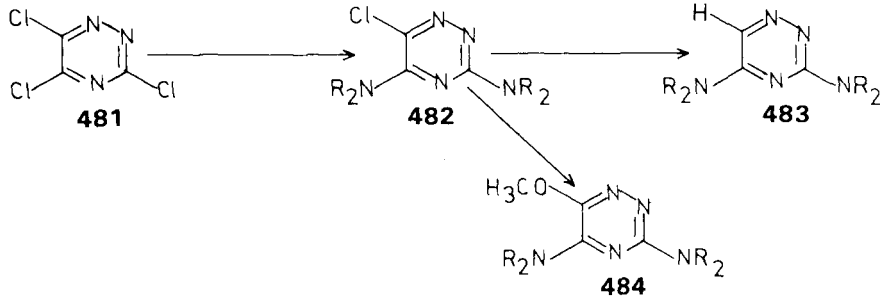


H'. 3-Amino-5,6-dichloro-1,2,4-triazines

Reaction of 3-amino-1,2,4-triazine-5,6-dione (**478**) with phosphorus oxychloride was used by Hadacek and Kisa for the synthesis of 3-amino-5,6-dichloro-1,2,4-triazine (**480**) (m.p. 186 to 188°C) (701).

I'. 3,5-Diamino-6-chloro-1,2,4-triazines

Reaction of 3,5,6-trichloro-1,2,4-triazine (**481**) with dimethylamine or diethylamine led to the isolation of 6-chloro-3,5-bis(dimethylamino)-1,2,4-triazine (**482a**) (m.p. 36 to 38°C, b.p. 118°C/0.02 torr; picrate; 174 to 175°C) or 6-chloro-3,5-bis(diethylamino)-1,2,4-triazine (**482b**) (b.p. 129°C/0,07 torr) (678, 1566).



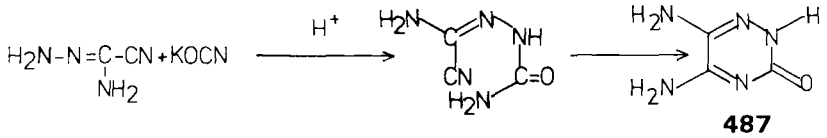
Both can be reduced to 3,5-bis(dialkylamino)-1,2,4-triazines (**483**) and react with sodium methoxide or amines by replacement of the chlorine in the 6-position (678).

J'. 3,5-Diamino-6-hydroxy-1,2,4-triazines

Two 3,5-bis(dialkylamino)-6-methoxy-1,2,4-triazines (**484a**) [R = CH_3, m.p. 93 to 94°C (1566); 96 to 97°C (678)] and **484b** [R = C_2H_5, b.p. 119°C/0.04 torr (678)], were obtained by reaction of 6-chloro-3,5-bis(dialkylamino)-1,2,4-triazines (**482**) with sodium methoxide (678, 1566).

K′. 5,6-Diamino-1,2,4-triazin-3-ones

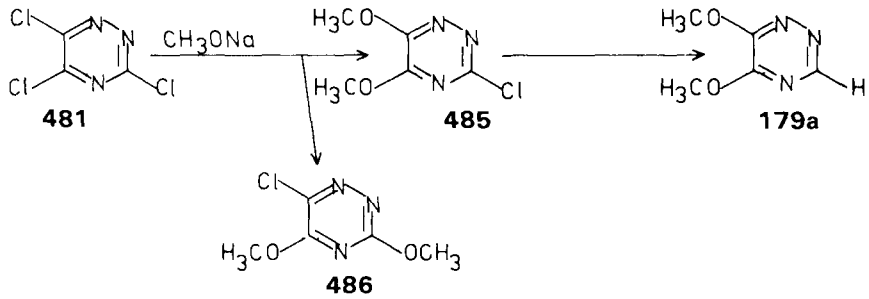
Matsuda and Morin (873) reported the synthesis of 5,6-diamino-1,2,4-triazin-3-one (**487**) through reaction of 1-cyanoformamidrazone with potassium cyanate in acidic media. The structure of **487** was not fully established.



487

L′ 3-Chloro-5,6-dihydroxy-1,2,4-triazines

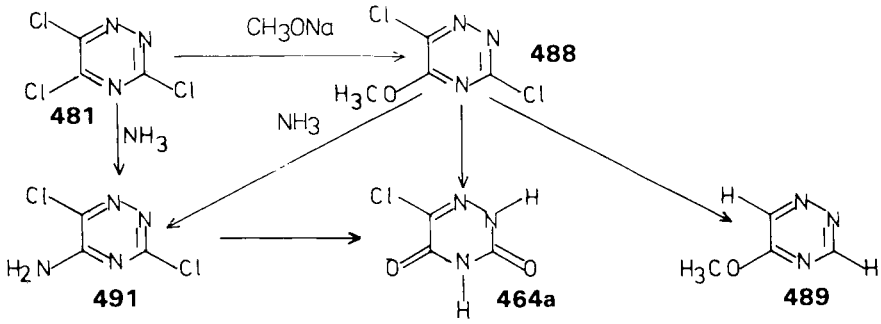
3,5,6-Trichloro-1,2,4-triazine (**481**) is converted into a mixture of 3-chloro-5,6-dimethoxy-1,2,4-triazine (**485**) (m.p. 92 to 93°C) and 6-chloro-3,5-dimethoxy-1,2,4-triazine (**486**) by reaction with 2 moles of sodium methoxide (563, 678, 1565). **485** can be reduced to 5,6-dimethoxy-1,2,4-triazine (**179a**) (678).



481 **485** **179a** **486**

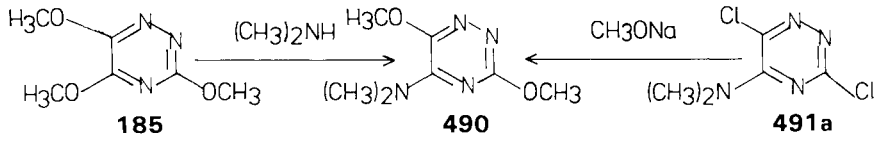
M′. 3,6-Dichloro-5-hydroxy-1,2,4-triazines

3,6-Dichloro-5-methoxy-1,2,4-triazine (**488**) (m.p. 62 to 63°C) is synthesized through reaction of 3,5,6-trichloro-1,2,4-triazine (**481**) with 1 mole of sodium methoxide (563, 678, 1565). It can be reduced to 5-methoxy-1,2,4-triazine (**489**) (678) and hydrolyzed to 6-chloro-1,2,4-triazine-3,5-dione (**464a**) (563), and it reacts with ammonia forming 3,6-dichloro-5-amino-1,2,4-triazine (**491**) (563).



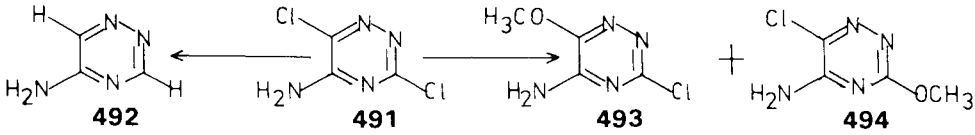
N′. 5-Amino-3,6-dihydroxy-1,2,4-triazines

5-(Dimethylamino)-3,6-dimethoxy-1,2,4-triazine (**490**) was prepared by reaction of dimethylamine with 3,5,6-trimethoxy-1,2,4-triazine (**185**) or by reaction of 3,6-dichloro-5-(dimethylamino)-1,2,4-triazine (**491a**) with sodium methoxide. It has a melting point of 76°C (1566).



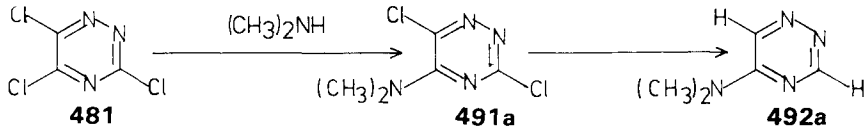
O′. 5-Amino-3,6-dichloro-1,2,4-triazines

5-Amino-3,6-dichloro-1,2,4-triazine (**491**) (m.p. 203 to 205°C, dec.) is obtained by reaction of ammonia with either 3,5,6-trichloro-1,2,4-triazine (**481**) or 3,6-dichloro-5-methoxy-1,2,4-triazine (**488**) (563, 1565). It can be reduced to 5-amino-1,2,4-triazine (**492**) and hydrolyzed to 6-chloro-1,2,4-triazine-3,5-dione (**464a**) and it reacts with sodium methoxide to yield a mixture of 5-amino-3-chloro-6-methoxy-1,2,4-triazine (**493**) and 5-amino-6-chloro-3-methoxy-1,2,4-triazine (**494**) (563).



Reaction of **481** with dimethylamine gives 3,6-dichloro-5-(dimethylamino)-

1,2,4-triazine (**491a**) [m.p. 74 to 75°C (1566); 75 to 76°C (678)], which can be reduced to 5-(dimethylamino)-1,2,4-triazine (**492a**) (678).



P'. 5-Amino-6-mercapto-1,2,4-triazin-3-ones

All known 5-amino-6-mercapto-1,2,4-triazin-3-ones (**495**) (Table II-36) were synthesized by reaction of 5,6-dimercapto-1,2,4-triazin-3-ones (**496**) with ammonia (602, 843, 850, 860).

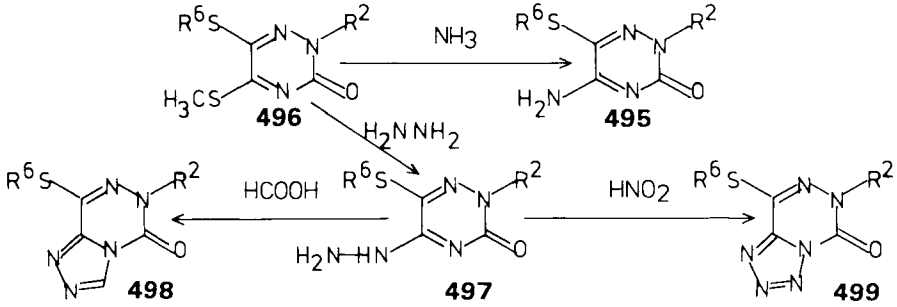
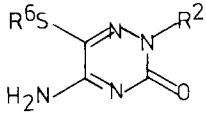


TABLE II-36. 5-AMINO-6-MERCAPTO-1,2,4-TRIAZIN-3-ONES



R^2	R^6	m.p. (°C)	Refs.
H	CH_3	299–301 (dec.)	602
H	C_2H_5	256–258 (dec.)	843
H	n-C_4H_9	235–237 (dec.)	843
H	n-C_6H_{13}	262–263 (dec.)	843
H	$C_6H_5CH_2$	250–252 (dec.)	850, 860
CH_3	$C_6H_5CH_2$	175–177	850, 860

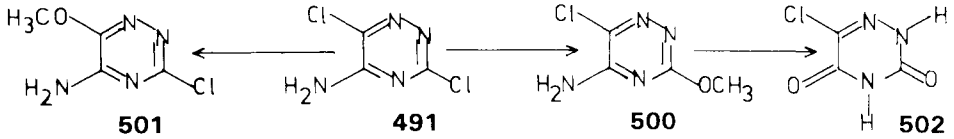
The infrared spectra of these compounds show an intensive band at 1650 to 1708 cm^{-1}, indicating that the given oxo tautomer is the predominant tautomeric form (602, 843).

Q′. 5-Hydrazino-6-mercapto-1,2,4-triazin-3-ones

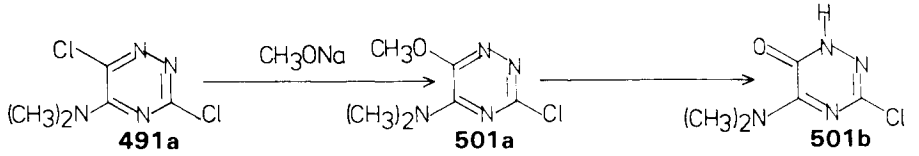
5-Hydrazino-6-mercapto-1,2,4-triazin-3-ones (**497**) are obtained by reaction of 5,6-dimercapto-1,2,4-triazin-3-ones (**496**) with hydrazine (602, 851) (R = CH_3 or C_6H_5, m.p. > 300°C). Condensed 1,2,4-triazines (**498**, **499**) were obtained by reaction of **496** with formic acid or nitrous acid (602, 851, 1555).

R′. 5-Amino-6-chloro-3-hydroxy-1,2,4-triazines and 5-Amino-3-chloro-6-hydroxy-1,2,4-triazines

Reaction of 5-amino-3,6-dichloro-1,2,4-triazine (**491**) with 1 mole of sodium methoxide gives a mixture of 5-amino-6-chloro-3-methoxy-1,2,4-triazine (**500**) [m.p. 166 to 167°C (563); 169 to 170°C (1565)] and 5-amino-3-chloro-6-methoxy-1,2,4-triazine (**501**) [m.p. 156 to 157°C (563)]. **500** can be hydrolyzed to 6-chloro-1,2,4-triazine-3,5-dione (**502**) (563).



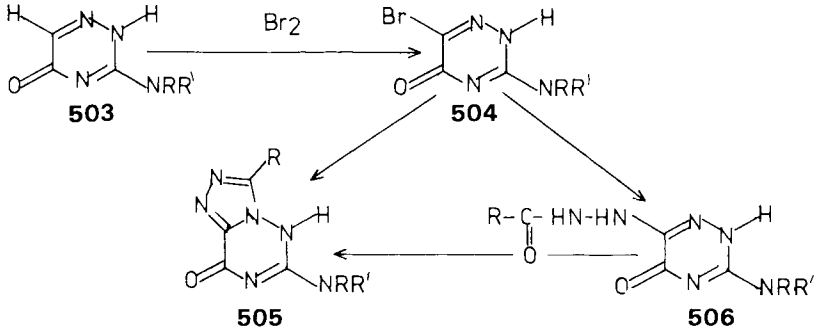
3-Chloro-5-(dimethylamino)-6-methoxy-1,2,4-triazine (**501a**) (m.p. 143°C) was prepared by reaction of 3,6-dichloro-5-(dimethylamino)-1,2,4-triazine (**491a**) with 1 mole of sodium methoxide (1566). It can be hydrolyzed to 3-chloro-5-(dimethylamino)-1,2,4-triazin-6-one (**501b**) (m.p. 223 to 224°C) (1566).



S′. 3-Amino-6-bromo-1,2,4-triazin-5-ones

Reaction of 3-amino-1,2,4-triazin-5-ones (**503**) with an unsubstituted 6-position with bromine is used for the synthesis of 3-amino-6-bromo-1,2,4-tri-

azin-5-ones (**504**) (776), which react with hydrazides, forming 2-amino-1,2,4-triazolo[3,4-*f*] 1,2,4-triazin-4-ones (**505**) (776).



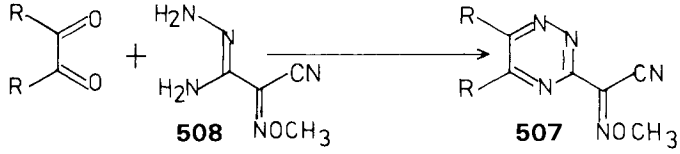
NRR′	m.p. (°C)	Refs.
$(CH_3)_2N$	271–272	776
4-Br–C_6H_4–$N(CH_3)$	278–280	776
	255–256	776
	280–281	776

T′. 3-Amino-6-hydrazino-1,2,4-triazin-5-ones

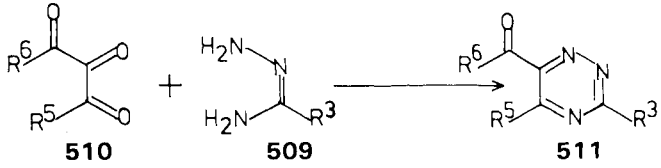
Reaction of 3-amino-6-bromo-1,2,4-triazin-5-ones (**504**) with hydrazides is used for the synthesis of 1,2,4-triazolo[4,3-*f*] 1,2,4-triazin-ones (**505**) (776). The intermediate formation of 3-amino-6-hydrazino-1,2,4-triazin-5-ones (**506**) can be assumed (see preceding section).

VIII. 1,2,4-TRIAZINES WITH CARBONYL SUBSTITUENTS

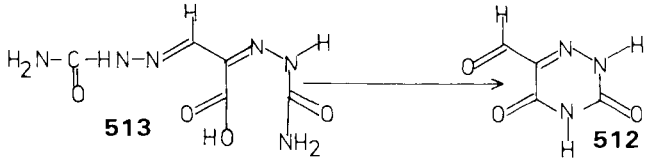
So far only five papers dealing with 1,2,4-triazines with carbonyl substituents have been published (869–872, 1464). Blanchard (869) obtained the 1,2,4-triazines **507** (R = CH_3, 140 to 143°C; R = C_6H_5, 165 to 167°C) by reaction of the amidrazone **508** with 1,2-dicarbonyl compounds.



Reaction of amidrazones (**509**) with 1,2,3-tricarbonyl compounds (**510**) was used for the synthesis of 1,2,4-triazin-6-yl ketones (**511**) (870, 872).



3,5-Dioxo-1,2,4-triazine-6-carbaldehyde (**512**) was synthesized by cyclization and saponification of the di-semicarbazone **513** (871).



Mackie and Tennant (1464) reported the formation of two 6-benzoyl-1,2,4-triazines (**511A**) ($R^5 = CH_3$, C_6H_5) when the 1,2,3-triazolo[5,1-*c*]1,2,4-triazines (**526**) were heated in glacial acetic acid.

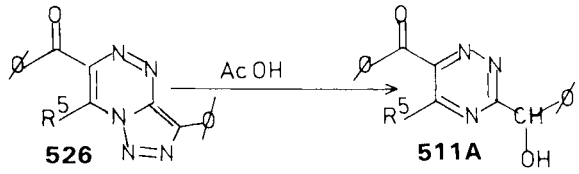


TABLE II-37. 1,2,4-TRIAZIN-6-YL KETONES (511)

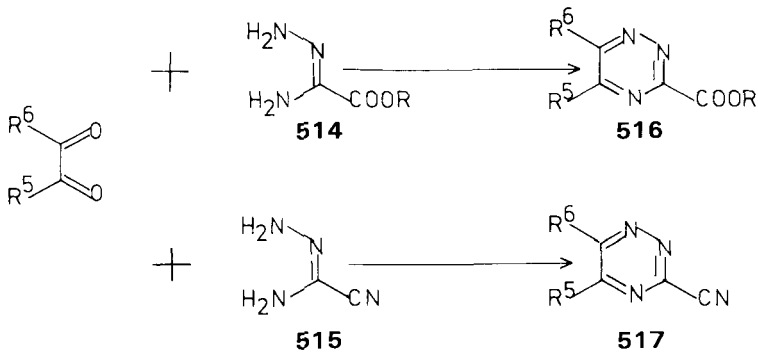
R^3	R^5	R^6	m.p. (°C)	Refs.
4-CH_3–C_6H_4	C_6H_5	C_6H_5	155–156	872
2-Pyridyl	C_6H_5	C_6H_5	186–187	872
4-Pyridyl	C_6H_5	C_6H_5	214–215	872
6-CH_3-2-pyridyl	C_6H_5	C_6H_5	172–173	872
4-CH_3-2-pyridyl	C_6H_5	C_6H_5	158–159	870
4-C_6H_5-2-pyridyl	C_6H_5	C_6H_5	156	870
6-(2-pyridyl)-2-pyridyl	C_6H_5	C_6H_5	194	870
2-(1,10-phenanthrolyl)	C_6H_5	C_6H_5	182	870
2-Thiazolyl	C_6H_5	C_6H_5	201–202	870
	C_6H_5	C_6H_5	280–282	872

IX. 1,2,4-TRIAZINE CARBOXYLIC ACIDS

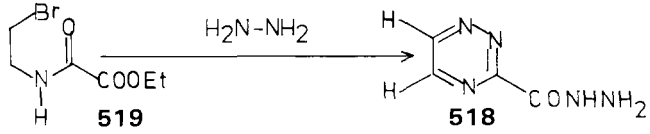
A. 1,2,4-Triazine-3-carboxylic Acid and Derivatives

1. *Preparation*

Reaction of 1,2-dicarbonyl compounds with either oxalamidrazonates (**514**) (11, 12, 62, 94, 119, 876–878) or cyanoformamidrazone (**515**) (873, 874) is used for the synthesis of 1,2,4-triazine-3-carboxylates (**516**) or 3-cyano-1,2,4-triazines (**517**).



The hydrazide **518** was obtained by reaction of compound **519** with hydrazine (10).



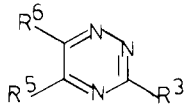
2. *Compound Survey*

The known compounds of this class are listed in Table II-38.

3. *Physical Properties*

1,2,4-Triazine-3-carboxylic acids and their derivatives are yellow crystalline compounds with low melting points. They are soluble in most organic solvents. The ultraviolet spectra of the unsubstituted ethyl 1,2,4-triazine-3-carboxy-

TABLE II-38. 1,2,4-TRIAZINE-3-CARBOXYLIC ACID AND DERIVATIVES

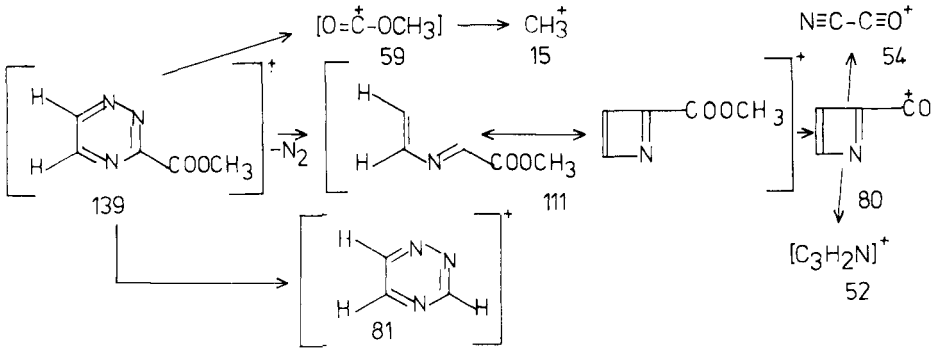


R^3	R^5	R^6	m.p. (°C) b.p. (°C/torr)	Refs.
COOH	H	H		11
COOD	H	H		11
COOK	H	H	250–280 (dec.)	11, 12
$COOCH_3$	H	H	91.5–92.5	94
$COOC_2H_5$	H	H	72–73	876
			72.5–73.8	11, 12
COO-*t*-C_4H_9	H	H	52.5–53.5	94
$CONHNH_2$	H	H		10
$COOCH_3$	H	C_6H_5	163–165	878
			164–165	877
$COOCH_3$	C_6H_5	H	140–141	878
			141–142	877
$COOCH_3$	CH_3	CH_3	81–82	876
$COOC_2H_5$	CH_3	CH_3	122–125/0.12	876
			135–136/0.18	62
$CONH_2$	CH_3	CH_3	169–170	62
$CONHNH_2$	CH_3	CH_3	156–157	62
CN	CH_3	CH_3	41–43	873, 874
$COOCH_3$	C_6H_5	C_6H_5	122–123	876
			Oil	119
COOH	C_6H_5	C_6H_5	156–157 (dec.)	62
$COOC_2H_5$	C_6H_5	C_6H_5	99–100	119, 62
			100–101	876
CN	C_6H_5	C_6H_5	154–155	873, 874
$COOC_2H_5$	4-O_2N–C_6H_4	4-O_2N–C_6H_4	174–177	876
$COOC_2H_5$	4-Cl–C_6H_4	4-Cl–C_6H_4	138–139	62

late (**516a**) and the methyl 5,6-dimethyl-1,2,4-triazine-3-carboxylate show two absorbtion bands, one in the region of 365 to 380 nm, with an absorptivity around 500, and a second in the 255 nm region with an absorptivity around 4000 (876).

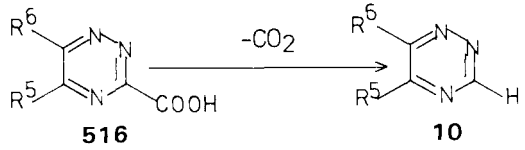
In the NMR spectra of **516a** the signals for the two protons were observed at 0.42 and 1.00τ (876) or 0.48 and 1.07τ (11).

The mass spectra of methyl, ethyl, and tert-butyl 1,2,4-triazine-3-carboxylates are reported by Paudler and Herbener (94). The following fragmentation pattern is given for methyl 1,2,4-triazine-3-carboxylate.

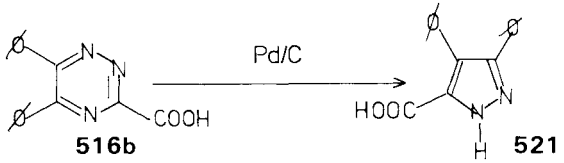


4. *Reactions*

1,2,4-Triazine-3-carboxylic acids (**516**) can be decarboxylated to give 3-unsubstituted 1,2,4-triazines (**10**) (11, 12, 62). This reaction was used for the synthesis of the unsubstituted 1,2,4-triazine (11, 12,).

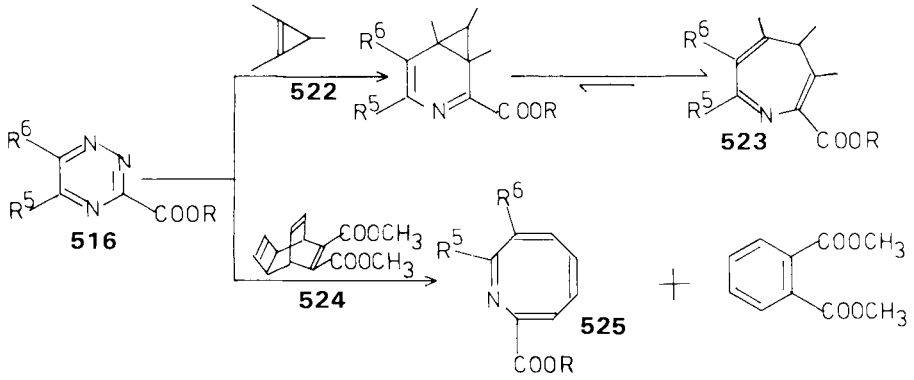


Hydrogenation of 5,6-diphenyl-1,2,4-triazine-3-carboxylic acid (**516b**) at palladium/C gives 3,4-diphenylpyrazole-5-carboxylic acid (**521**) (875). The same reaction is observed with the ethyl ester (875).



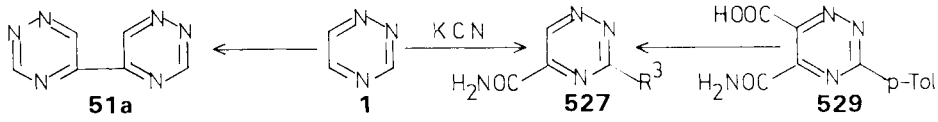
1,2,4-Triazine-3-carboxylates are widely used in cycloaddition reactions (115–119) since they are electron-deficient dienes and easily react with electron-rich dienophiles or dienophiles with strained double bonds. The following were used as dienophiles: enamines (115), vinyl esters (115), vinyl ethers (115), norbornene (115, 118), norbornadiene (115, 119), ynamines (116), cyclopropenes (115, 117), and tricyclo[4.2.2.$O^{2,5}$]deca-3,4,9-triene-7,8-dicarboxylates (118, 119). Reaction of 1,2,4-triazine-3-carboxylates (**516**) with cyclopropenes (**522**) is an easy method for the synthesis of azepines (**523**) (115,

117), whereas the reaction with **524** was used for the synthesis of azocines (**525**) (118, 119).



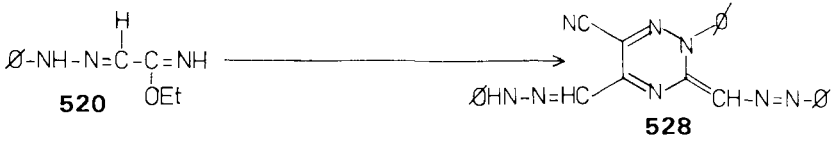
B. 1,2,4-Triazine-5-carboxylic Acids

Krass and Paudler (109) isolated 1,2,4-triazine-5-carboxamide (**527a**) (R^3 = H) (m.p. 133 to 135°C) in addition to 5,5'-bi-1,2,4-triazine (**51a**) from the reaction of 1,2,4-triazine (**1**) with potassium cyanide. 3-(4-Tolyl)-1,2,4-triazine-5-carboxamide (**527b**) (R^3 = 4-CH_3–C_6H_5) (m.p. 244 to 246°C) was obtained by decarboxylation of the 6-carboxylic acid (**529**) (78).



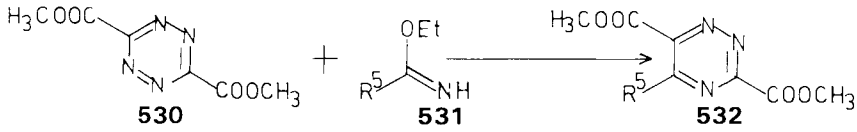
C. 1,2,4-Triazine-6-carboxylic Acids

Heating compound **520** for 1 h at 125 to 133°C affords purple-red crystals, which were formulated as **528** (2305) (m.p. 285–286°C).



D. 1,2,4-Triazine-3,6-dicarboxylic Acids

The only two compounds (**532**) of this class were synthesized by Roffey and Verge (879, 880) through cycloaddition reaction of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**530**) with imidates (**531**) (**532**: R = CH_3, m.p. 82 to 83°C; R = C_6H_5, 110 to 113°C).

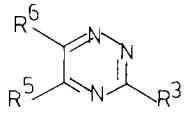


530 **531** **532**

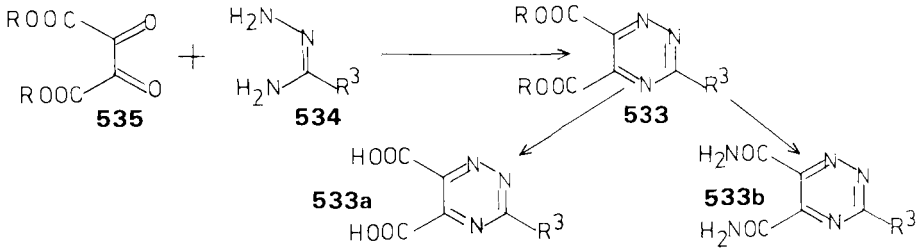
E. 1,2,4-Triazine-5,6-dicarboxylic Acids

1,2,4-Triazine-5,6-dicarboxylates (**533**) were obtained by reaction of amidrazones (**534**) with diketosuccinates (**535**) (15, 78). Through saponification or reaction with ammonia the isolated esters were converted to the free acids (**533a**) or the carboxamides (**533b**) (78). See Table II-39.

TABLE II-39. 1,2,4-TRIAZINE-5,6-DICARBOXYLIC ACIDS AND DERIVATIVES

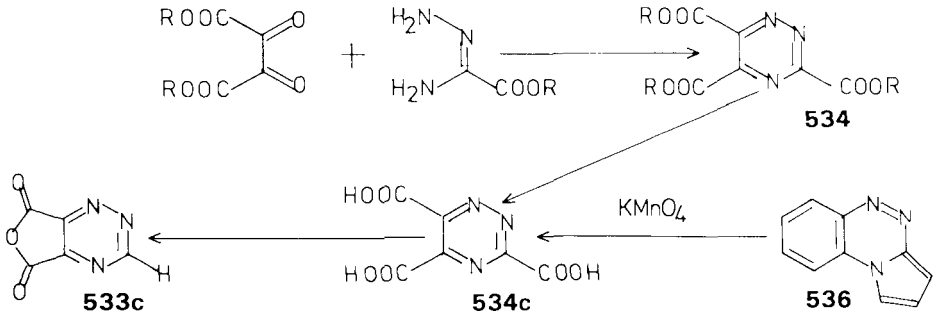


R^3	R^5	R^6	m.p. (°C)	Refs.
H	CO–O–CO			9
H	$COOC_2H_5$	$COOC_2H_5$	165/5 torr	9
CH_3	$COOC_2H_5$	$COOC_2H_5$	56–58	15, 78
CH_3	$CONH_2$	$CONH_2$	232–234	78
C_6H_5	$COOC_2H_5$	$COOC_2H_5$	105–106	15, 78
C_6H_5	$CONH_2$	$CONH_2$	225–227	78
4-$CH_3C_6H_4$	$COOC_2H_5$	$COOC_2H_5$	89–90	15, 78
4-$CH_3C_6H_4$	$CONH_2$	$COOC_2H_5$	193–195	78
4-$CH_3C_6H_4$	$CONH_2$	$CONH_2$	246–248	78
4-$CH_3C_6H_4$	CO–NH–CO		296–300	78
4-$CH_3C_6H_4$	COOH	COOH	150–152	78



F. 1,2,4-Triazine-3,5,6-tricarboxylic Acid

Trimethyl (**534a**) (m.p. 90 to 91°C) (876, 878) and triethyl (**534b**) (b.p. 168 to 169°C/1 torr; 173°C/3 torr) (9) 1,2,4-triazine-3,5,6-tricarboxylate are synthesized by reaction of oxalamidrazonates with diketosuccinates.



Saponification of the triethyl ester was used for the synthesis of 1,2,4-triazine-3,5,6-tricarboxylic acid (**534c**) which was transformed into the anhydride (**533c**) during an attempted synthesis of the unsubstituted 1,2,4-triazine through decarboxylation of **534c** (9). The trimethyl ester (**534a**) has two absorption bands in the ultraviolet spectrum at 391 (412) and 254 nm (4.590) (876).

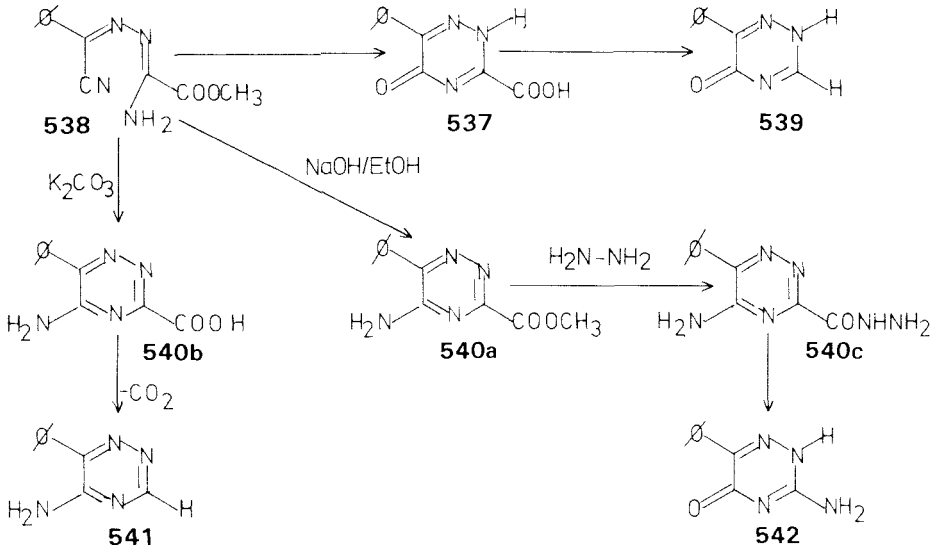
Gross and Gloede (1396) isolated **534c** when they oxidized pyrrolo[2,1-*c*] 1,2,4-triazine (**536**) with potassium permanganate. **534c** was transformed into **533c**.

X. 1,2,4-Triazine Carboxylic Acids with Additional Hetero Substituents

A. 5-Oxo-1,2,4-triazine-3-carboxylic Acids

Fusco and Rossi (63) obtained 5-oxo-6-phenyl-1,2,4-triazine-3-carboxylic acid (**537**) (m.p. 265°C) through basic ($NaOH/H_2O$) cyclization of

compound **538**. **537** can be decarboxylated yielding 6-phenyl-1,2,4-triazin-5-one (**539**).

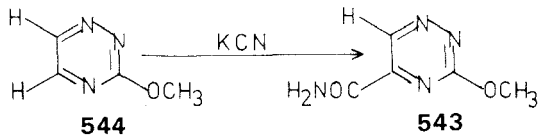


b. 5-Amino-1,2,4-triazine-3-carboxylic Acids

Cyclization of compound **538** with sodium hydroxide in ethanol yields methyl 5-amino-6-phenyl-1,2,4-triazine-3-carboxylate (**540a**) (m.p. 229°C) while cyclization with potassium carbonate yields the free acid (**540b**) (m.p. 178°C, dec.) which can be decarboxylated to **541** (63). By reaction of the ester **540a** with hydrazine the hydrazide **540c** (m.p. 261 to 262°C) is obtained which can be transformed into 3-amino-6-phenyl-1,2,4-triazin-5-one (**542**) by reaction with nitrous acid (63).

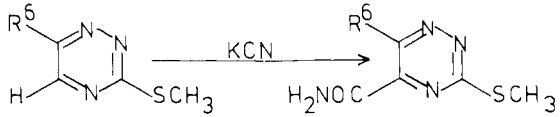
C. 3-Oxo-1,2,4-triazine-5-carboxyclic Acids

The single known member of this class, the 3-methoxy-1,2,4-triazine-5-carboxamide (**543**) (m.p. 173.5 to 175°C) was synthesized by Krass and Paudler through reaction of 3-methoxy-1,2,4-triazine (**544**) with potassium cyanide (109).



D. 3-Thioxo-1,2,4-triazine-5-carboxylic Acids

Two members of this group are known, the 3-(methylmercapto)-1,2,4-triazine-5-carboxamide (**545a**) (R^6 = H, m.p. 180 to 181°C) and the 6-methyl-3-(methylmercapto)-1,2,4-triazine-5-carboxamide (R^6 = CH_3, m.p. 124 to 126°C) which were both obtained by reaction of the 1,2,4-triazines **546a** and **546b** with potassium cyanide (109).



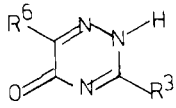
546 **545**

E. 5-Oxo-1,2,4-triazine-6-carboxylic Acids

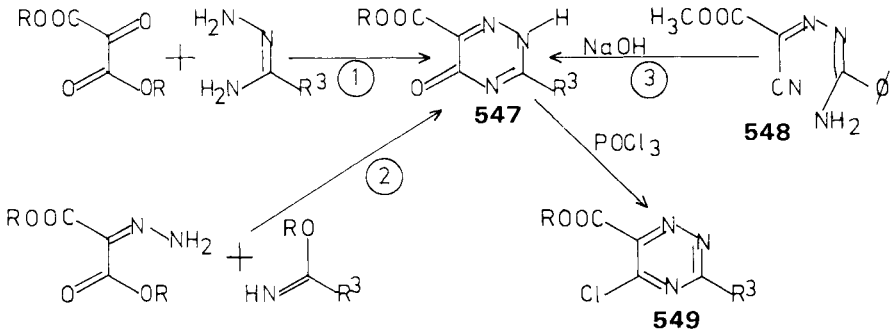
Three methods were used for the synthesis of 5-oxo-1,2,4-triazine-6-carboxylic acids (**547**):

1. Reaction of amidrazones with diethyl mesoxalate (881, 882).
2. reaction of imidates with the hydrazone of diethyl mesoxalate (882).
3. cyclization of compound **548** with sodium hydroxide (63).

TABLE II-40. 5-OXO-1,2,4-TRIAZINE-5,6-CARBOXYLIC ACIDS AND DERIVATIVES



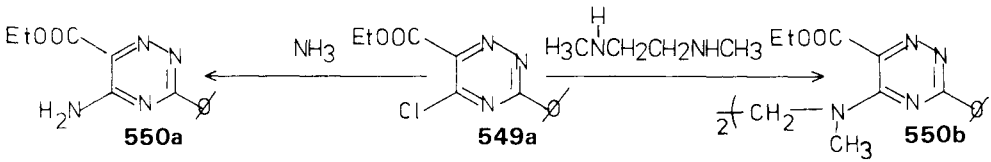
R^3	R^6	m.p. (°C)	Refs.
CH_3	$COOC_2H_5$	160–161	882
CH_3	$CONH_2$	270	882
C_2H_5	$COOC_2H_5$	202–204	882
C_2H_5	$CONH_2$	266 (dec.)	882
C_6H_5	COOH	179–180	63
C_6H_5	$COOC_2H_5$	197–199	881
		202–203	882
C_6H_5	$CONH_2$	301	882
4-CH_3–C_6H_4	$COOC_2H_5$	222–223	882
4-CH_3–C_6H_4	$CONH_2$	319–320	882
4-Cl–C_6H_4	$COOC_2H_5$	244	882
4-Cl–C_6H_4	$CONH_2$	322–323	882
2-Pyridyl	$COOC_2H_5$	142–143	882
2-Pyridyl	$CONH_2$	294–295	882



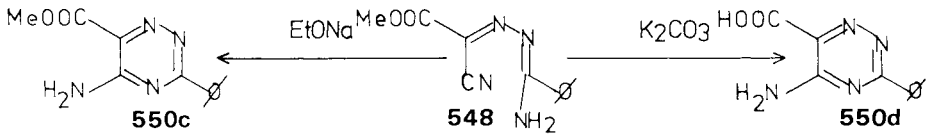
By reaction with phosphorus oxychloride these compounds can be transformed into derivatives of 5-chloro-1,2,4-triazine-6-carboxylic acids (**549**) (881, 882).

F. 5-Amino-1,2,4-triazine-6-carboxylic Acids

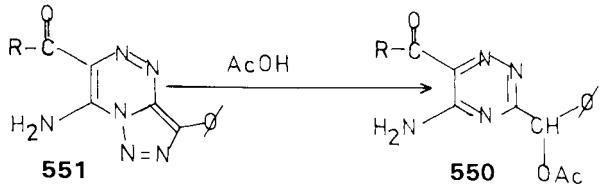
Reaction of ethyl 5-chloro-3-phenyl-1,2,4-triazine-6-carboxylate (**549a**) with ammonia was used for the synthesis of ethyl 5-amino-3-phenyl-1,2,4-triazine-6-carboxylate (**550a**) (m.p. 190 to 193°C) (881). Reaction of the chloro compound **549a** with *N,N'*-dimethylethylenediamine gave the substrate **550b** (m.p. 222°C) which contains two 1,2,4-triazine rings (881).



Fusco and Rossi obtained methyl 5-amino-3-phenyl-1,2,4-triazine-6-carboxylate (**550c**) (m.p. 232°C) by cyclization of compound **548** with sodium ethoxide while the free acid (**550d**) (m.p. 184°C) was isolated when **548** was cyclized in the presence of potassium carbonate (63).



Mackie and Tennant (1464) obtained **550e** (R = OEt) and **550f** (R = NH_2) when they heated **551a** (R = OEt) and **551b** (R = NH_2) in glacial acetic acid.



G. 5-Chloro-1,2,4-triazine-6-carboxylic Acids

All known 5-chloro-1,2,4-triazine-6-carboxylic acid derivatives (**549**) (Table II-41) were synthesized by reaction of 5-oxo-1,2,4-triazine-6-carboxylic acid derivatives (**547**) with phosphorus oxychloride (881, 882).

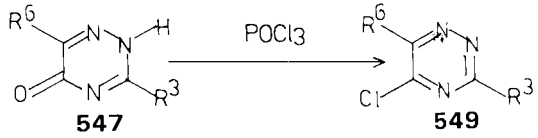
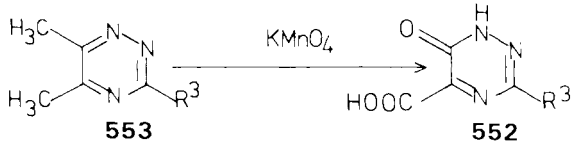


TABLE II-41. 5-CHLORO-1,2,4-TRIAZINE-6-CARBOXYLIC ACID DERIVATIVES

R^3	R^6	m.p. (°C)	Refs.
C_6H_5	$COOC_2H_5$	73–75	881
C_6H_5	$CONH_2$	184–185	882
4-CH_3–C_6H_4	$CONH_2$	201–202	882
4-Cl–C_6H_4	$CONH_2$	152–153	882
2-Pyridyl	$CONH_2$	151–153	882

H. 6-Oxo-1,2,4-triazine-5-carboxylic Acids

Metze and co-workers reported the synthesis of two examples of this class (**552**) [$R^3 = C_6H_5$, m.p. 238°C; $R^3 = (C_6H_5)_2COH$] through oxidation of the 5,6-dimethyl-1,2,4-triazines **553a** and **553b** with potassium permanganate (44, 45).



I. 6-Amino-1,2,4-triazine-5-carboxylic Acids

1. *Preparation*

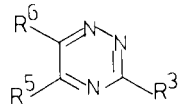
Most known 6-amino-1,2,4-triazine-5-carboxylic acids (**554**) and their derivatives were synthesized by degradation of pyrimido[5,4-*e*] 1,2,4-triazines (**555**) with a hetero substituent (NH_2, O) in position 5 (883–887, 1350).

555 **554**

2. *Compound Survey*

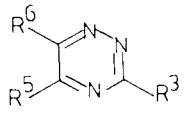
Table II-42 lists the compounds of this group that are known.

TABLE II-42. 6-AMINO-1,2,4-TRIAZINE-5-CARBOXYLIC ACIDS AND DERIVATIVES



R^3	R^5	R^6	m.p. (°C)	Refs.
H	COOH	NH_2	250 (dec.)	886
H	$COOCH_3$	NH_2	186–187	1350
H	$COOC_2H_5$	NH_2	119	1350
H	$CONH_2$	NH_2	253	1350
			253–254	886/887
H	$CONHN(CH_3)_2$	NH_2	150–152	884
H	$CONHOCH_3$	NH_2	203–206	884
H		NH_2	165	884
H	CONHCN	NH_2	Indef.	885
H		NH_2	179	886
H		NH_2	245 (dec.)	886

TABLE II-42. (continued)



R^3	R^5	R^6	m.p.(°C)	Refs.
H	$CO-NH-C(=NH)-NH_2$	NH_2	>264	885
H	$CONH_2$	NH–CHO	210	886
H	$CONH_2$	$NHCH_3$	132–134	883
H	$CONHOCH_3$	$N{=}CH-NHOCH_3$	168–170	884
H	$CONHCH_3$	$N(CH_3)CONHCH_3$	250–251	883
H	$CONHCH_3$	$N(CH_3)CONHC_2H_5$	213–215	883
H	$CONHCH_3$	$N(CH_3)CONH$-*i*-C_3H_7	213–215	883
H	$CONHCH_3$	$N(CH_3)CONH$-*n*-C_4H_9	183–185	883
H	$CONHCH_3$	$N(CH_3)CONH-CH_2C_6H_5$	238–239	883
H	$CONHCH_3$	$N(CH_3)CONHNH_2$	213–215	883
H	$CONHCH_3$	$N(CH_3)CONHN(CH_3)_2$	234–235	883
CH_3	$CONHCH_3$	$N(CH_3)CONHCH_3$	239–241	883
·HNO_3			161–162	883
CH_3	$CONHCH_3$	$N(CH_3)CONHC_2H_5$	216–217	883
·HNO_3			158–160	883
CH_3	$CONHCH_3$	$N(CH_3)CONH$-*i*-C_3H_7	152–154	883
·HNO_3			148	883
CH_3	$CONHCH_3$	$N(CH_3)CONH$-*n*-C_4H_9	166–168	883
·HNO_3			146	883
CH_3	$CONHCH_3$	$N(CH_3)CONH-CH_2C_6H_5$	110	883
·HNO_3			154–155	883
CH_3	$CONHCH_3$	$N(CH_3)CONHNH_2$	207	883
CH_2Cl	$COOCH_3$	NH_2		1350
CH_2Br	$COOCH_3$	NH_2		1350
CH_2N_3	$COOC_2H_5$	NH_2	134–135	1350
CH_2OCH_3	$COOCH_3$	NH_2	144–145	1350
CH_2OCH_3	$CONH_2$	NH_2	206–207	1350
$CHBrCOOC_2H_5$	$COOC_2H_5$	NH_2	115	1350

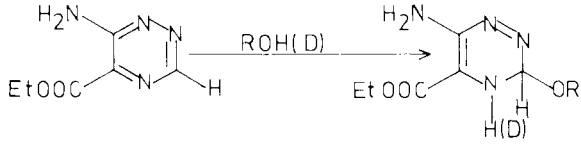
3. *Physical Properties*

6-Amino-1,2,4-triazine-5-carboxylic acids and their derivatives are stable crystalline yellow or colorless compounds. Many of them show two absorption bands in the ultraviolet spectra, one around 245 nm with an absorptivity around 10^4 and a second around 350 nm with an absorptivity around 4.000 (885, 886).

The proton in position 3 of the 1,2,4-triazine nucleus gives a signal around 1.00τ in the PMR spectra (884–886). In one publication a signal around 2.30τ is reported for this proton (883). Mass spectra of a number of compounds of this class were published by Clark and Smith (884).

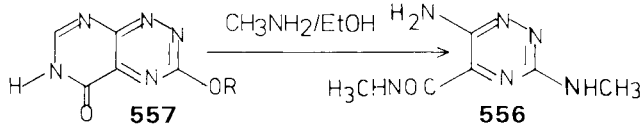
4. *Reactions*

Only a few reactions of 6-amino-1,2,4-triazine-5-carboxylic acids and their derivatives have been reported, most reactions were used to build up the pyrimido[5,4-*e*] 1,2,4-triazine system (883, 886, 887). Covalent addition of water or ethanol to the C_3N_4 double bond of ethyl 6-amino-1,2,4-triazine-5-carboxylate is reported by Temple, Kussner, and Montgomery (1350). The ethanol addition product has a melting point of 191°C.



J. 3,6-Diamino-1,2,4-triazine-5-carboxylic Acids

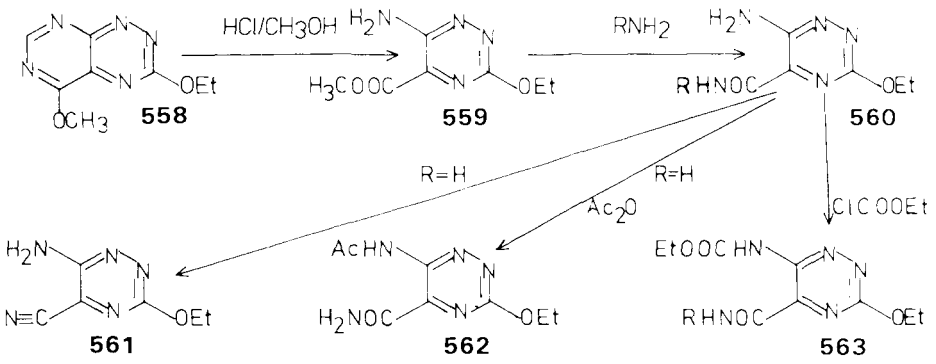
6-Amino-*N*-methyl-3-(methylamino)-1,2,4-triazine-5-carboxamide (**556**) (m.p. 205 to 206°C) was obtained on treatment of 3-methoxy- or 3-ethoxy-pyrimido[5,4-*e*] 1,2,4-triazin-5-one (**557**) with methylamine in ethanol (1099).



557 **556**

K. 6-Amino-3-hydroxy-1,2,4-triazine-5-carboxylic Acids

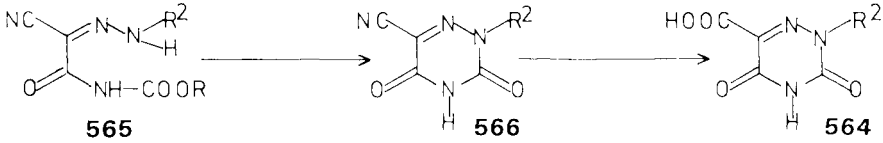
Treatment of 3-ethoxy-5-methoxypyrimido[5,4-*e*] 1,2,4-triazine (**558**) with hydrochloric acid in methanol afforded methyl 6-amino-3-ethoxy-1,2,4-triazine-5-carboxylate (**559**) (m.p. 173 to 174°C), which was transformed into the amides **560** (R = H, 182 to 183°C; R = CH_3, 199 to 200°C). Starting from **560** (R = H) the nitrile **651** (m.p. 139°C), the acetamido compound **562** (m.p. 166 to 167°C) and the carbamates **563** (R = H, 162°C; R = CH_3, 159°C) were synthesized (1099).



L. 3,5-Dioxo-1,2,4-triazine-6-carboxylic Acids

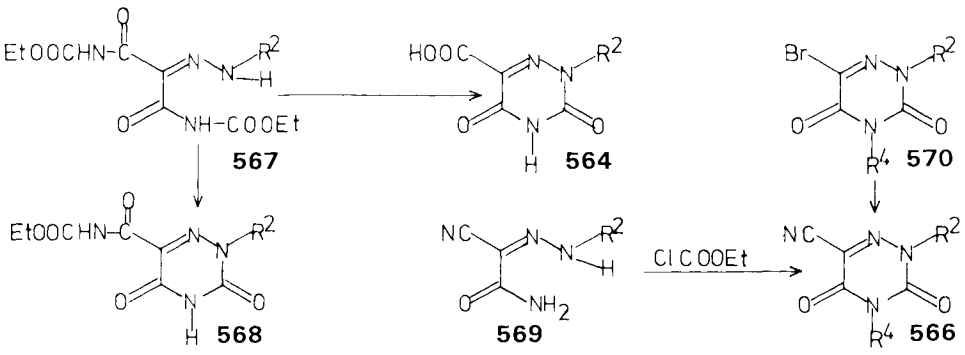
1. *Preparation*

A number of methods for the synthesis of 3,5-dioxo-1,2,4-triazine-6-carboxylic acids and their derivatives (**564**) are known. The most frequently used method is the basic or thermal cyclization of compounds **565** which yields 6-cyano-1,2,4-triazine-3,5-diones (**566**) (330–335, 888–897). The cyano compounds can be transformed into the carboxylic acids by saponification (329–335, 411, 888).

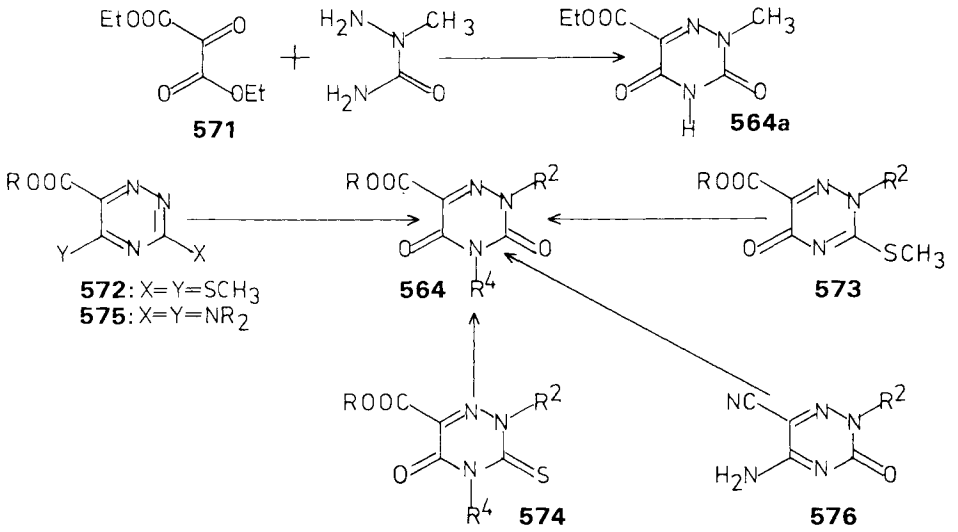


Basic cyclization of the hydrazono maleic diamides (**567**) leads directly to the 1,2,4-triazine-3,5-dione-6-carboxylic acids (**564**) and thermal cyclization forms the amides (**568**) (857, 898, 1081). The 6-cyano derivatives (**566**) were obtained by reaction of compounds **569** with ethyl chloroformate (411, 890). The cyano derivatives can also be synthesized by nucleophilic replacement of the bromine in position 6 of **570** by a cyano group (251).

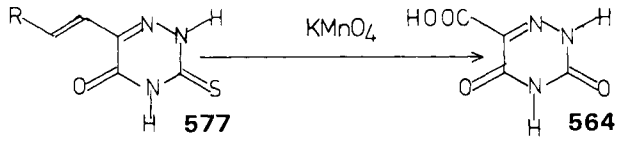
The synthesis of **564a** ($R^2 = CH_3$) by reaction of diethyl mesoxalate (**571**) with 2-methylsemicarbazide is reported by Cheng and Zee-Cheng (251). 1,2,4-triazine-6-carboxylic acids with hetero substituents in positions 3 and/or 5, for example, 3,5-bis(methylmercapto)-1,2,4-triazine-6-carboxylic acids (**572**) (899), 3-(methylmercapto)-5-oxo-1,2,4-triazine-6-carboxylic acids (**573**) (323), 5-oxo-3-thioxo-1,2,4-triazine-6-carboxylic acids (**574**) (251, 324, 327, 586, 900–902), 3,5-diamino-1,2,4-triazine-6-carboxylic acids (**575**) (716), and 5-amino-6-cyano-



1,2,4-triazin-5-ones (**576**) (903) can be converted to 3,5-dioxo-1,2,4-triazine-6-carboxylic acids (**564**).

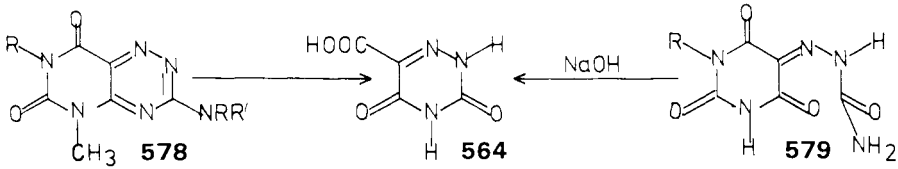


Oxidation of the 3-thioxo-6-vinyl-1,2,4-triazin-5-ones (**577**) with potassium permanganate led not only to the replacement of the sulfur by oxygen but also to an oxidative degradation of the vinyl group (312).



Formation of 1,2,4-triazine-3,5-dione-6-carboxylic acids (**564**) by cleavage of the pyrimido[5,4-*e*] 1,2,4-triazines (**578**) or by treatment of the alloxane

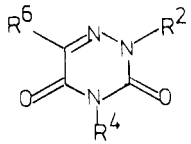
semicarbazone (**579**) with sodium hydroxide is reported by Heinisch and his group (716, 920).



2. *Compound Survey*

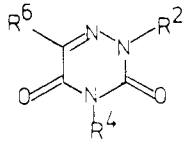
Known compounds of this group are listed in Table II-43.

TABLE II-43. 3,5-DIOXO-1,2,4-TRIAZINE-6-CARBOXYLIC ACIDS AND DERIVATIVES



R^2	R^4	R^6	m.p. (°C)	Refs.
CH_3	H	CN	191–193	251
C_6H_5	H	CN	243–245	891
			244–245	890
2-CH_3–C_6H_4	H	CN	240–242	897
3-CH_3–C_6H_4	H	CN	176–178	897
4-CH_3–C_6H_4	H	CN	229–231	891
			230–231	898
2,3-$(CH_3)_2C_6H_3$	H	CN	246–248	897
1-Naphthyl	H	CH	263–265	330, 890
2-Naphthyl	H	CN	270–272	330, 890
3-F–C_6H_4	H	CN	213–214	897
4-F–C_6H_4	H	CN	223–225	897
2-Cl–C_6H_4	H	CN	321–323	897
3-Cl–C_6H_4	H	CN	206–208	897
4-Cl–C_6H_4	H	CN	211–213	895
			213–214	890
2,5-$Cl_2C_6H_3$	H	CN	242–244	894
2-Br–C_6H_4	H	CN	234–236	897
3-Br–C_6H_4	H	CN	192–194	897
4-Br–C_6H_4	H	CN	245–247	890, 891
2-I–C_6H_4	H	CN	233–235	897
3-I–C_6H_4	H	CN	202–204	897

TABLE II-43. (continued)



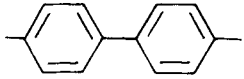
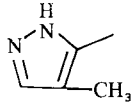
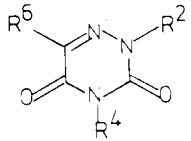
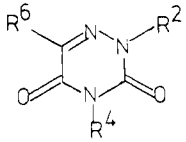
R^2	R^4	R^6	m.p.(°C)	Refs.
4-I–C_6H_4	H	CN	265–267	890, 895
3-O_2N–C_6H_4	H	CN	268–271	894
4-O_2N–C_6H_4	H	CN	234–236	332
2-CH_3O–C_6H_4	H	CN	237–239	897
3-CH_3O–C_6H_4	H	CN	212–213	897
4-CH_3O–C_6H_4	H	CN	234–236	895
			235–236	890
3,4,5-$(CH_3O)_3C_6H_2$	H	CN	236–238	335
4-C_2H_5O–C_6H_4	H	CN	197–199	895
			199–200	890
4-CH_3–CO–C_6H_4	H	CN	224–226	331
4-OHC–C_6H_4	H	CN	232–233	889
4-HON=CH–C_6H_4	H	CN	200–202	897
4-H_2N–CS–NHN=CH–C_6H_4	H	CN	267–270 (dec.)	889
4-$NCCH_2CONHN$=CH–C_6H_4	H	CN	278–282 (dec.)	897
2-HOOC–C_6H_4	H	CN	250–252	892
2-CH_3OOC–C_6H_4	H	CN	162–163	892
2-H_2NCO–C_6H_4	H	CN	250–260 (dec.)	892
			360–365	892
2-NC–C_6H_4	H	CN	224–226	892
3-HOOC–C_6H_4	H	CN	294–296	897
4-HOOC–C_6H_4	H	CN	282–284 (dec.)	331
4-H_5C_2OOC–C_6H_4	H	CN	231–233	331
4-$(C_2H_5)_2NCH_2CH_2OOC$–C_6H_4	H	CN	220–222	897
4-H_2N–SO_2–C_6H_4	H	CN	279–281	331
4-CH_3–CO–NH–C_6H_4	H	CN	295–298 (dec.)	332
	H	CN	>360	333
3-Pyridyl	H	CN	298–300	888
	H	CN	298–300	893
C_6H_5	CH_3	CN	153–155	411
4-CH_3–C_6H_4	CH_3	CN	139–141	411
4-Cl–C_6H_4	CH_3	CN	160–162	411
4-CH_3O–C_6H_4	CH_3	CN	137–139	411
4-H_5C_2O–C_6H_4	CH_3	CN	116–118	411

TABLE II-43. (continued)



R^2	R^4	R^6	m.p.(°C)	Refs.
H	H	COOH	238 (dec.)	586
			238–239	312, 324, 899, 900
			241	920, 323, 327
			245–246 (dec.)	920/716
CH_3	H	COOH	267–268	251
C_6H_5	H	COOH	202–204	891
			224–226	329, 898, 903
$\cdot H_2O$			203–205	329
4-CH_3–C_6H_4	H	COOH	209–211	329, 891, 898
$\cdot H_2O$			209–211	329
2,3-$(CH_3)_2C_6H_3$	H	COOH	267–268	335
1-Naphthyl	H	COOH	262–264 (dec.)	330
2-Naphthyl	H	COOH	240–242 (dec.)	330
4-Cl–C_6H_4	H	COOH	199–201	329, 898
$\cdot H_2O$			199–201	329
2,5-$Cl_2C_6H_3$	H	COOH	232–234	335
4-Br–C_6H_4	H	COOH	216–218	898, 329
			217–219	891
$\cdot H_2O$			216–218	329
4-I–C_6H_4	H	COOH	232–234	329, 898
$\cdot H_2O$			232–234	329
4-O_2N–C_6H_4	H	COOH	245–247 (dec.)	332
4-CH_3O–C_6H_4	H	COOH	215–217	329, 898
$\cdot H_2O$			215–217	329
4-H_5C_2O–C_6H_4	H	COOH	208–210	329, 898
$\cdot H_2O$			208–210	329
3,4,5-$(CH_3O)_3C_6H_2$	H	COOH	207–209	335
4-CH_3–CO–C_6H_4	H	COOH	216–218 (dec.)	331
2-CH_3OOC–C_6H_4	H	COOH	253–255 (dec.)	892
4-HOOC–C_6H_4	H	COOH	285–287 (dec.)	331
4-H_2N–C_6H_4	H	COOH	283–290 (dec.)	332
$\cdot$HCl			283–286 (dec.)	332
4-(4-Cl–C_6H_4–S)-3,5-$(CH_3)_2C_6H_2$	H	COOH		1081
4-H_5C_2OOC–NHCO–C(CN)=N–NH–C_6H_4	H	COOH	208–212 (dec.)	334
			280–283	334

TABLE II-43. (continued)



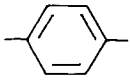
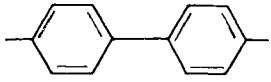
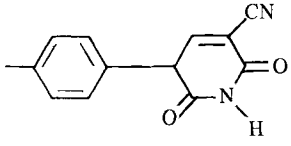
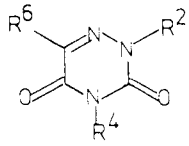
R^2	R^4	R^6	m.p.(°C)	Refs.
4-$H_2N-SO_2-C_6H_4$	H	COOH	261–263 (dec.)	331
3-Pyridyl	H	COOH	271–273 (dec.)	888, 898
·HCl			271–273 (dec.)	888
H	CH_3	COOH	253–254	251
CH_3	CH_3	COOH	221–222	251
C_6H_5	CH_3	COOH	214–215	411
H	H	$COOCH_3$	193	902
C_6H_5	H	$COOCH_3$	227–229	906
3-$CH_3OOC-C_6H_4$	H	$COOCH_3$	193–195	892
H	H	$COOC_2H_5$	181–182	900
			181–183	899
			182	902
CH_3	H	$COOC_2H_5$	130–132	251
C_6H_5	H	$COOC_2H_5$	190–191	906
H	H	COO-*i*-C_3H_7	242	902
H	H	COCl	255	902
CH_3	H	COCl	203–205	251.
C_6H_5	H	COCl	172–174	906
C_6H_5	H	CON_3	105–107	905
H	H	$CONH_2$	300	900
			310	901
NH_3 salt				904
	H	COOH	>310 (dec.)	334
	H	COOH	>360	333
	H	COOH	305–307 (dec.)	334
CH_3	H	$CONH_2$	279–281	251
C_6H_5	H	$CONH_2$	279–281	891
			282–284	906
4-$CH_3-C_6H_4$	H	$CONH_2$	291–293	891

TABLE II-43. (continued)



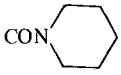
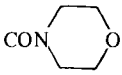
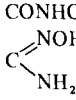
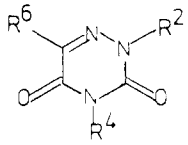
R^2	R^4	R^6	m.p.(°C)	Refs.
4-Br–C_6H_4	H	$CONH_2$	293–295	891
2-NC–C_6H_4	H	$CONH_2$	279–281	892
2-H_3COOC–C_6H_4	H	$CONH_2$	137–139	892
2-H_2N–CO–C_6H_4	H	$CONH_2$	270–280 (dec.)	892
			320–325	892
CH_3	H	$CONHCH_3$	171–172	251
C_6H_5	H	$CONHCH_3$	292–293	906
C_6H_5	H	$CON(CH_3)_2$	247–248	906
C_6H_5	H	$CONHC_2H_5$	245–246	906
C_6H_5	H	$CON(C_2H_5)_2$	240	906
H	H	CONH-*n*-C_3H_7	234–236	900
			234–235	901
H	H	$CONHCH_2C_6H_5$	267–268	900, 901
C_6H_5	H		275	906
C_6H_5	H		247–248	906
H	H	$CONHCH_2CH_2N(C_2H_5)_2$	212–213	251
C_6H_5	H	$CONHCOOC_2H_5$	209–211	898
4-CH_3–C_6H_4	H	$CONHCOOC_2H_5$	216–218	898
			218 (dec.)	857
4-Cl–C_6H_4	H	$CONHCOOC_2H_5$	226–228	898
4-Br–C_6H_4	H	$CONHCOOC_2H_5$	218–220	898
4-I–C_6H_4	H	$CONHCOOC_2H_5$	222–225	898
4-O_2N–C_6H_4	H	$CONHCOOC_2H_5$	205	857
4-CH_3O–C_6H_4	H	$CONHCOOC_2H_5$	204–206	898
4-C_2H_5O–C_6H_4	H	$CONHCOOC_2H_5$	203–205	898
4-(4-Cl–C_6H_4–S)-3,5-$(CH_3)_2C_6H_2$	H	$CONHCOOC_2H_5$		1081
3-Pyridyl	H	$CONHCOOC_2H_5$	237–239	898
H	H	$CONHCH_2COOC_2H_5$	275–276 (dec.)	900. 901
H	H	$CONHNH_2$	302–304 (dec.)	899, 900, 901
H_2N–NH_2 salt				904
C_6H_5	H	$CONHNH_2$	260–262 (dec.)	906
C_6H_5	H	CONHOH	210–211 (dec.)	906
C_6H_5	H		259–261 (dec.)	896

TABLE II-43. (continued)



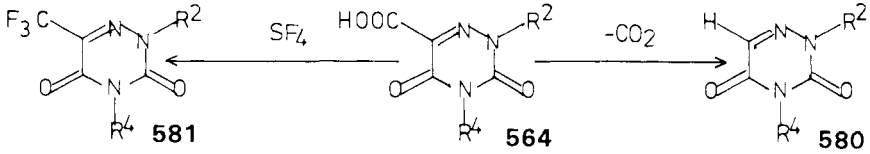
R^2	R^4	R^6	m.p.(°C)	Refs.
4-CH_3–C_6H_4	H		260–262 (dec.)	896
2,3-$(CH_3)_2C_6H_3$	H		258–260	335
1-Naphthyl	H		284–286 (dec.)	330
2-Naphthyl	H		289–291 (dec.)	330
4-Cl–C_6H_4	H		264–267 (dec.)	896
2,5-$Cl_2C_6H_3$	H		272–273	335
4-Br–C_6H_4	H		273–276 (dec.)	896
4-CH_3O–C_6H_4	H		250–252 (dec.)	896
3,4,5-$(CH_3O)_3C_6H_2$	H		256–258	335
3-Pyridyl	H		265–267 (dec.)	888
C_6H_5	H	$CSNH_2$	245–247	895
4-CH_3–C_6H_4	H	$CSNH_2$	251–253	895
4-Cl–C_6H_4	H	$CSNH_2$	254–256	895
4-Br–C_6H_4	H	$CSNH_2$	261–263	895
4-I–C_6H_4	H	$CSNH_2$	256–258	895
4-CH_3O–C_6H_4	H	$CSNH_2$	229–231	895
4-C_2H_5O–C_6H_4	H	$CSNH_2$	242–244	895
4-CH_3–CO–C_6H_4	H	$CSNH_2$	250–252 (dec.)	331
4-H_2N–CS–NHN=CH–C_6H_4	H	$CSNH_2$	265–267 (dec.)	889
4-HOOC–C_6H_4	H	$CSNH_2$	295–298 (dec.)	331
4-H_5C_2OOC–C_6H_4	H	$CSNH_2$	251–253 (dec.)	331
4-H_2N–SO_2–C_6H_4	H	$CSNH_2$	263–265 (dec.)	331
3-Pyridyl	H	$CSNH_2$	245–247 (dec.)	888

3. *Physical Properties*

3,5-Dioxo-1,2,4-triazine-6-carboxylic acids and their derivatives are colorless or yellow compounds with high melting points. The pK_a values of ethyl 3,5-dioxo-1,2,4-triazine-6-carboxylate (6.34) was reported by Jonas and Gut (393). Stransky and Gruz (907) describe the titrimetric determination of 2-aryl-3,5-dioxo-1,2,4-triazine-6-carboxylic acids.

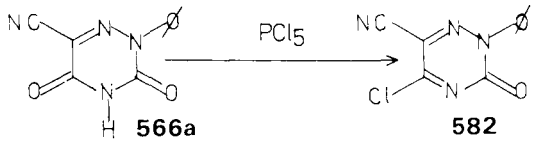
4. *Reactions*

Only a few reactions of 3,5-dioxo-1,2,4-triazine-6-carboxylic acids and their derivatives have been published. Decarboxylation of the acids (**564**) is used for the synthesis of 1,2,4-triazine-3,5-diones (**580**) (251, (323, 324, 327, 329–335).



Reaction of the free acids (**564**) with sulfur tetrafluoride is a method for the synthesis of 6-trifluoromethyl-1,2,4-triazine-3,5-diones (**581**) (346–348).

Reaction of 6-cyano-2-phenyl-1,2,4-triazine-3,5-dione (**566a**) with phosphorus pentachloride leads to 5-chloro-6-cyano-2-phenyl-1,2,4-triazin-3-one (**582**) as reported by Slouka and Švecova (903).

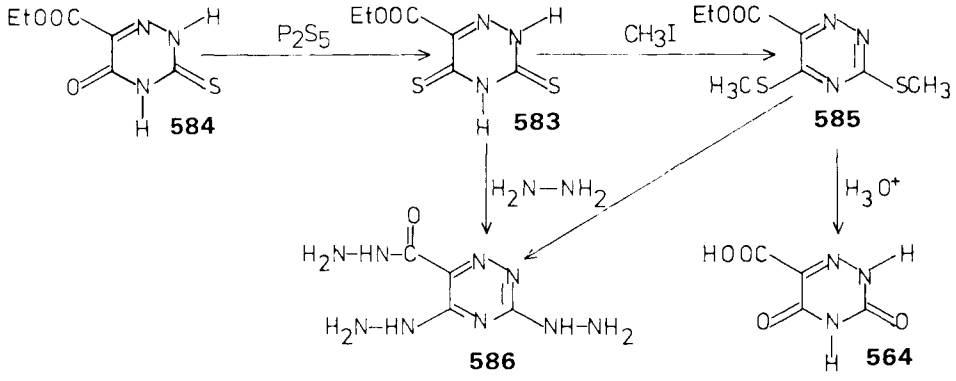


The synthesis of condensed 1,2,4-triazine derivatives, starting with 3,5-dioxo-triazine-6-carboxylic acid derivatives was reported by Slouka and Bekárek (892).

M. 3,5-Dithioxo-1,2,4-triazine-6-carboxylic Acids

Ethyl 3,5-dithioxo-1,2,4-triazine-6-carboxylate (**583**) (m.p. 178–180°C) was synthesized by Cristescu (899, 908) by reaction of ethyl 5-oxo-3-thioxo-1,2,4-triazine-6-carboxylate (**584**) with phosphorus pentasulfide. Reaction of **583** with methyl iodide/sodium hydroxide gives ethyl 3,5-bis(methylmercapto)-1,2,4-triazine-6-carboxylate (**585**) (m.p. 78 to 80°C). Both compounds react with hydrazine leading to 3,5-dihydrazino-1,2,4-triazine-6-carboxhydrazide (**586**)

(899, 908). **585** can be hydrolyzed to 1,2,4-triazine-3,5-dione-6-carboxylic acid (**564**) (899).



N. 3,5-Dihydrazino-1,2,4-triazine-6-carboxylic Acids

3,5-Dihydrazino-1,2,4-triazine-6-carboxhydrazide (**586**) (m.p. > 300°C) is obtained by reaction of hydrazine with either ethyl 3,5-dithioxo-1,2,4-triazine-6-carboxylate (**583**) or ethyl 3,5-bis(methylmercapto)-1,2,4-triazine-6-carboxylate (**584**) (899, 908).

O. 3,5-Diamino-1,2,4-triazine-6-carboxylic Acids

Four methods have been used for the synthesis of 3,5-diamino-1,2,4-triazine-6-carboxylic acid derivatives (**587**) (Table II-44); (1) reaction of dibromomalodinitrile (**588**) with aminoguanidine carbonate (912, 913); (2) reaction of ethyl 5-amino-3-ethoxy-1,2,4-triazine-6-carboxylate (**589**) with ammonia (911); (3) cleavage of pyrimido[4,5-e] 1,2,4-triazine derivatives (**590**) with amines (716, 909, 910, 920); and (4) reaction of ethyl 5-chloro-3-thioxo-1,2,4-triazine-6-carboxylate (**591**) with ammonia (914).

3,5-Diamino-1,2,4-triazine-6-carboxylic acids and their derivatives are colorless or pale yellow compounds. From the infrared spectra of the free acids it follows that these compounds have a zwitterionic structure with the ammonium group in position 5 (716). The half-wave potential (–950 mV) of 3-(benzylamino)-5-(methylamino)-1,2,4-triazine-6-carboxylic acid was determined by Heinisch (716).

3,5-Diamino-1,2,4-triazines (**592**) are formed by decarboxylation of 3,5-diamino-1,2,4-triazine-6-carboxylic acids (**587**) (R^6 = COOH) in vacuum in the

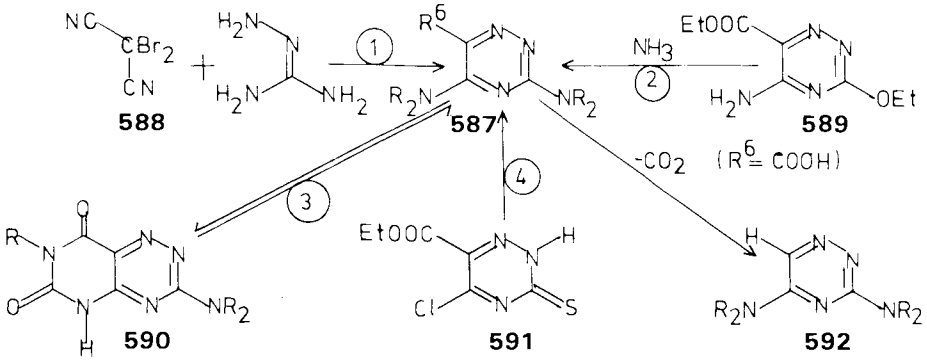
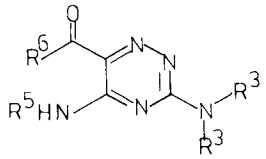


TABLE II-44. 3,5-DIAMINO-1,2,4-TRIAZINE-6-CARBOXYLIC ACIDS AND DERIVATIVES



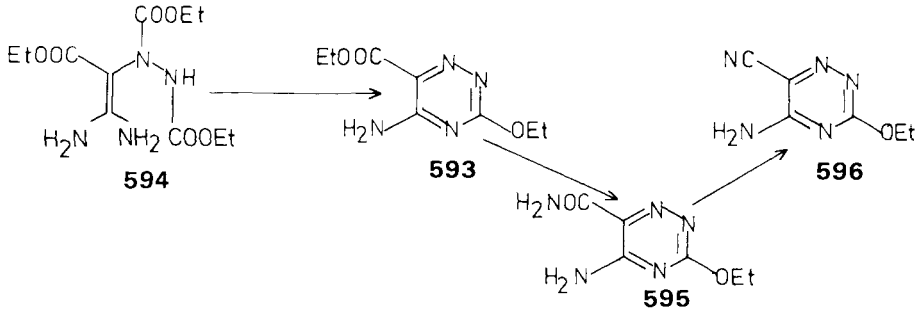
R^3	R^3	R^5	R^6	m.p. (°C)	Refs.
H	H	H	NH_2	320 350	909 911–913, 914
H	H	CH_3	OH	353–355 (dec.)	716
H	*n*-C_4H_9	CH_3	OH	209–210 (dec.)	716
H	*n*-C_4H_9	CH_3	$NHCH_3$	140–142	910
H	$C_6H_5CH_2$	CH_3	OH	213–215 (dec.)	716
H	$C_6H_5CH_2$	$C_6H_5CH_5$	$NHCH_2C_6H_5$	164–165	920
$CH_2CH_2CH_2CH_2CH_2$		CH_3	OH	242–243 (dec.)	716
$CH_2CH_2OCH_2CH_2$		CH_3	$NHCH_3$	179–180	716

presence of phosphorus pentoxide (716). Hydrolysis of **587** leads to 3,5-dioxo-1,2,4-triazine-6-carboxylic acids (716). 3,5-Diamino-1,2,4-triazine-6-carboxamides (**587**) ($R^6 = CONH_2$) can be cyclized to pyrimido[4,5-*e*]1,2,4-triazines (**590**) (912, 913).

P. 5-Amino-3-oxo-1,2,4-triazine-6-carboxylic Acids

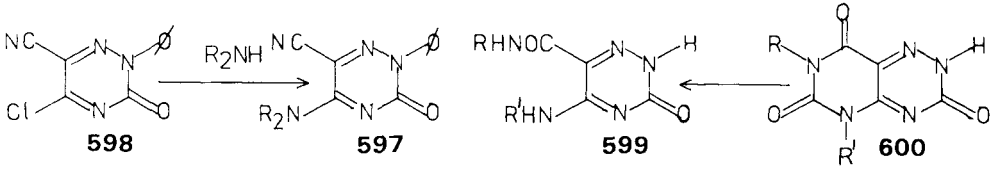
Ethyl 5-amino-3-ethoxy-1,2,4-triazine-6-carboxylate (**593**) (m.p. 127 to 128°C) was obtained by Taylor and Martin (911) through cyclization of

α-[1,2-(dicarbethoxy)hydrazino]carbethoxyacetamidine (**594**). **593** was transformed into the amide (**595**) (m.p. 228 to 229°C) (911, 1099) and the nitrile (**597**) [m.p. 225°C (dec.)] (910).



594 **593** **596** **595**

Slouka and Švecová (903) prepared 5-amino-6-cyano-2-phenyl-1,2,4-triazin-3-ones (**597**) (R = H, 200°C; R = C_2H_5, m.p. 133 to 134°C; $R_2 = (CH_2)_5$, m.p. 214 to 215°C) by reaction of 5-chloro-6-cyano-2-phenyl-1,2,4-triazin-3-ones (**598**) with ammonia or amines. Heinisch synthesized 5-amino-3-oxo-1,2,4-triazin-6-carboxamides (**599**) (R = ϕCH_2, R′ = CH_3 m.p. 229 to 231°C; R = CH_3, R′ = ϕCH_2, m.p. 256 to 257°C; R = R′ = ϕCH_2, m.p. 250 to 241°C) by cleavage of pyrimido[4,5-*e*] 1,2,4-triazines (**600**) (910).

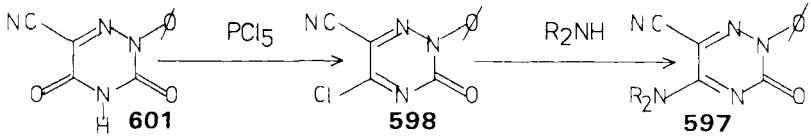


598 **597** **599** **600**

5-Amino-3-oxo-1,2,4-triazine-6-carboxylic acid derivatives are colorless compounds, which can be hydrolyzed to 3,5-dioxo-1,2,4-triazine-6-carboxylic acids (903, 910) and which were used for the synthesis of pyrimido[4,5-*e*] 1,2,4-triazines (911).

Q. 5-Chloro-3-oxo-1,2,4-triazine-6-carboxylic Acids

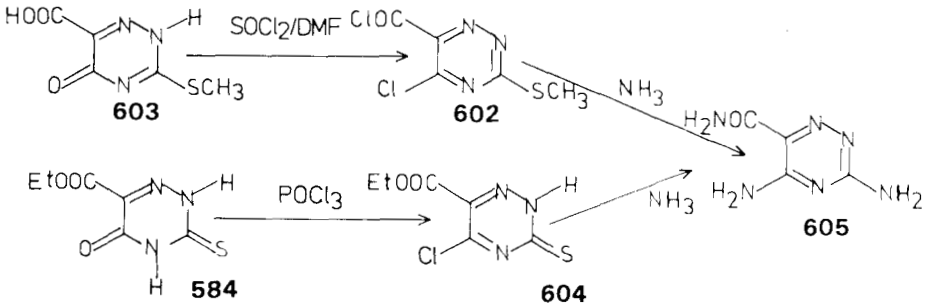
5-Chloro-6-cyano-2-phenyl-1,2,4-triazin-3-one (**598**) (m.p. 170 to 171°C) was obtained by reaction of 6-cyano-2-phenyl-1,2,4-triazine-3,5-dione (**601**) with phosphorus pentachloride (903); it reacts with amines to yield 5-amino-6-cyano-2-phenyl-1,2,4-triazin-3-ones (**597**).



601 **598** **597**

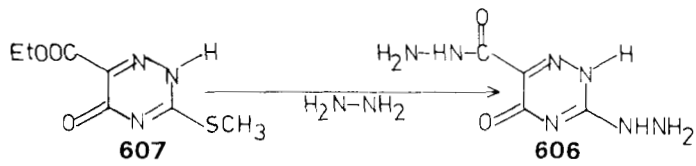
R. 5-Chloro-3-thioxo-1,2,4-triazine-6-carboxylic Acids

5-Chloro-3-(methylmercapto)-1,2,4-triazine-6-carbonyl chloride (**602**) was obtained by reaction of 3-(methylmercapto)-5-oxo-1,2,4-triazine-6-carboxylic acid (**603**) with thionyl chloride and dimethylformamide (909) and ethyl 5-chloro-3-thioxo-1,2,4-triazine-6-carboxylate (**604**) was synthesized by reaction of ethyl 5-oxo-3-thioxo-1,2,4-triazine-6-carboxylate (**584**) with phosphorus oxychloride (914). Both compounds formed 3,5-diamino-1,2,4-triazine-6-carboxamide (**605**) by reaction with ammonia.



S. 3-Hydrazino-5-oxo-1,2,4-triazin-6-carboxylic Acids

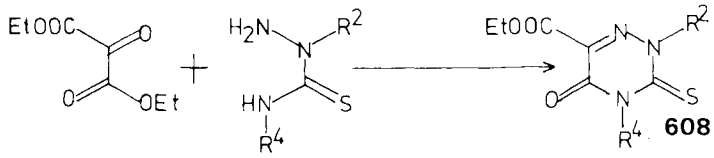
The single known example of this class of 1,2,4-triazine derivatives, the 3-hydrazino-5-oxo-1,2,4-triazine-6-carboxhydrazide (**606**) (>300°C), is synthesized by reaction of ethyl 3-(methylmercapto)-5-oxo-1,2,4-triazine-6-carboxylate (**607**) with hydrazine (503, 589, 899, 904).



T. 5-Oxo-3-thioxo-1,2,4-triazine-6-carboxylic Acids

1. *Preparation*

Reaction of diethyl mesoxalate with thiosemicarbazides is the reaction of choice for the synthesis of ethyl 5-oxo-3-thioxo-1,2,4-triazine-6-carboxylates (**608**) (251, 323, 324, 503, 900, 902, 915).



608

Besides this method the cleavage of pyrimido[4,5-*e*]1,2,4-triazine derivatives (920) and cyclization of alloxan thiosemicarbazide was used for the synthesis of 5-oxo-3-thioxo-1,2,4-triazine-6-carboxylic acid derivatives (920).

2. *Compound Survey*

Table II-45 lists the compounds of this class reported in the literature.

3. *Physical Properties*

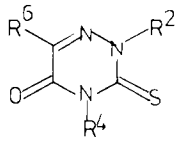
5-Oxo-3-thioxo-1,2,4-triazine-6-carboxylic acids and their derivatives are colorless or yellow compounds. Comparison of the ultraviolet spectra of the unsubstituted 5-oxo-3-thioxo-1,2,4-triazine-6-carboxylic acid and their esters with the ultraviolet spectra of N_2-, N_4-, and/or *S*-methylated derivatives has shown that the given tautomeric structure is the predominant form of these compounds (902). Most 5-oxo-3-thioxo-1,2,4-triazine-6-carboxylic acid derivatives have two absorption bands in the ultraviolet spectra at pH 1, one near 270 nm and the other near 325 nm (251, 324, 902). The spectra have different shapes at pH 7 and pH 11. NMR spectra of 5-oxo-3-thioxo-1,2,4-triazine-6-carboxylic acid derivatives are reported by Daunis and Follet (902).

4. *Reactions*

Reaction of ethyl 3-(methylmercapto)-5-oxo-1,2,4-triazine-6-carboxylate (**607**) (X = OEt) with hydrazine was used for the synthesis of 3-hydrazino-5-oxo-1,2,4-triazine-6-carboxhydrazide (**606**) (503, 586, 899, 904). Treatment of 5-oxo-3-thioxo-1,2,4-triazine-6-carboxylic acid derivatives (**608**) with phosphorus pentasulfide gives 3,5-dithioxo-1,2,4-triazine-6-carboxylic acid derivatives (**609**) (899, 908). **608** can be converted into 3,5-dioxo-1,2,4-triazine-6-carboxylic acids (**610**) by various methods (251, 323, 324, 327, 586, 900). When 3-(methylmercapto)-5-oxo-1,2,4-triazine-6-carboxylic acid (**607**) (X = OH) is treated with thionyl chloride, 5-chloro-3-(methylmercapto)-1,2,4-triazine-6-carbonyl chloride (**611**) is obtained (909). Decarboxylation of 5-oxo-3-thioxo-1,2,4-triazine-6-carboxylic acid is reported by Falco and his group (324).

TABLE II-45. 5-OXO-3-THIOXO-1,2,4-TRIAZINE-6-CARBOXYLIC ACID DERIVATIVES

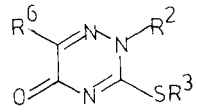
A. 5-Oxo-3-thioxo-1,2,4-triazine-6(2H,4H)-carboxylic acids and derivatives



R^2	R^4	R^6	m.p. (°C)	Refs.
H	H	COOH	222–224	324, 900
			223–225	503
			244–245 (dec.)	920
			247 (dec.)	323
			248	902
H	H	$COOCH_3$	195	902
H	H	$COOC_2H_5$	206–207	323, 586, 915
			207–209	503, 900
			209	902
H	H	COO-*i*-C_3H_7	105	902
H	H	COO-*t*-C_4H_9		902
H	H	$CONH_2$	>350	915/904
H	H	$CONHCH_3$	333–335	915
H	H	$CONHCH_2C_6H_5$	274–275	915
H	H	COCl		902
H	CH_3	COOH	244	902
H	CH_3	$COOCH_3$	195	902
H	CH_3	$COOC_2H_5$	199	902
			201–203	251
			240	229
H	CH_3	COO-*i*-C_3H_7	222	902
CH_3	H	COOH	248	902
			351–353	251
CH_3	H	$COOCH_3$	168	902
CH_3	H	$COOC_2H_5$	145	902
			150–151	251
CH_3	H	COO-*i*-C_3H_7	160	902
CH_3	H	$CONH_2$	291–293	251
CH_3	H	$CONHCH_2CH_2N(C_2H_5)_2$	230–232	251
CH_3	CH_3	COOH	185	902
			185–187	251
CH_3	CH_3	$COOCH_3$	106	902
CH_3	CH_3	$COOC_2H_5$	88	902
			88–89	251
CH_3	CH_3	COO-*i*-C_3H_7	108	902

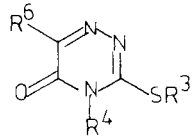
TABLE II-45 (continued)

B. 3-Mercapto-5(2H)-oxo-1,2,4-triazine-6-carboxylic acids and derivatives



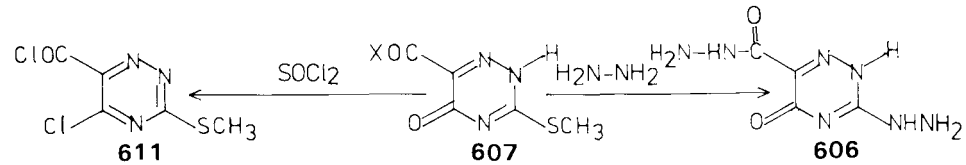
R^2	R^3	R^6	m.p. (°C)	Refs.
H	CH_3	COOH	176/212–214	323
			213–215	503
			215	902
H	CH_3	$COOCH_3$	195	902
H	CH_3	$COOC_2H_5$	139	902
			139–140	899, 900, 901
			142–143	586
H	CH_3	COO-*i*-C_3H_7	110	902
H	CH_3	$CONH_2$		904
H	CH_3	COCl		909
H	C_2H_5	COOH	152	920
H	$CH_2C_6H_5$	$COOC_2H_5$	135–136	900, 901
CH_3	CH_3	$COOCH_3$	185	902
CH_3	CH_3	$COOC_2H_5$	120	902
			159	229
CH_3	CH_3	COO-*i*-C_3H_7	105	902

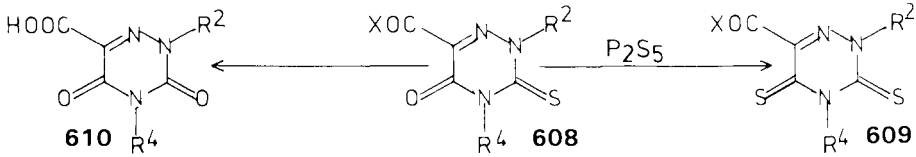
C. 3-Mercapto-5(4H)-oxo-1,2,4-triazine-6-carboxylic acids and derivatives



R^3	R^4	R^6	m.p. (°C)	Refs.
CH_3	CH_3	COOH	244	902
CH_3	CH_3	$COOCH_3$	140	902
CH_3	CH_3	$COOC_2H_5$	102	902
CH_3	CH_3	COO-*i*-C_3H_7	82	902

Daunis and Follet (902) studied the methylation of methyl 5-oxo-3-thioxo-1,2,4-triazine-6-carboxylates and reported the following results: methyl iodide yields the 3-methylmercapto derivative exclusively, if methylation at the sulfur is possible. In methyl 3-(methylmercapto)-5-oxo-1,2,4-triazine-6-carboxylate

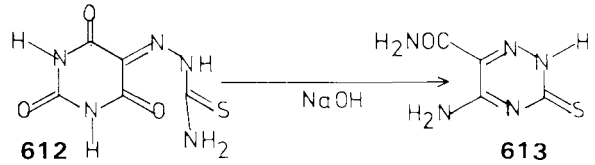


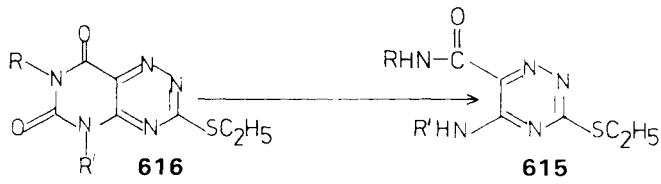


only methylation at N–2 is observed with methyl iodide. Methylation at all possible positions is observed if diazomethane is used as the methylating agent. The ratio of the different methylated products depends on the solvent used (dioxane, ethanol).

U. 5-Amino-3-thioxo-1,2,4-triazine-6-carboxylic Acids

Only four compounds of this class of 1,2,4-triazine derivatives are known. Treatment of alloxan thiosemicarbazone (**612**) with sodium hydroxide gave 5-amino-3-thioxo-1,2,4-triazine-6-carboxamide (**613**) (m.p. 208 to 210°C) (920). 5-Amino-3-(methylmercapto)-1,2,4-triazine-6-carboxamide (**614**) (m.p. 242°C) was obtained by reaction of 5-chloro-3-(methylmercapto)-1,2,4-triazine-6-carbonyl chloride (**611**) with ammonia (909), and *N*-benzyl-3-(ethylmercapto)-5-(ethylamino)-1,2,4-triazine-6-carboxamide (**615a**) (m.p. 124 to 125°C) and 3-(ethylmercapto)-5-(benzylamino)-*N*-methyl-1,2,4-triazine-6-carboxamide (**615b**) (m.p. 134 to 135°C) were synthesized by cleavage of pyrimido[4,5-*e*] 1,2,4-triazines (**616**) (910, 920).





616 615

V. 3-Amino-5-nitro-1,2,4-triazine-6-carboxylic Acids

3-Amino-5-nitro-1,2,4-triazine-6-carboxylic acid (**617**) [m.p. 240°C (dec.)] was prepared by Hadacek and Kisa through nitration of 3-amino-1,2,4-triazine-6-carboxylic acid (**618**) (613).

618 617

XI. 1,2,4-TRIAZINE *N*-OXIDES

A. 1,2,4-Triazine 1-Oxides and 1,2,4-Triazine 2-Oxides

1. *Preparation*

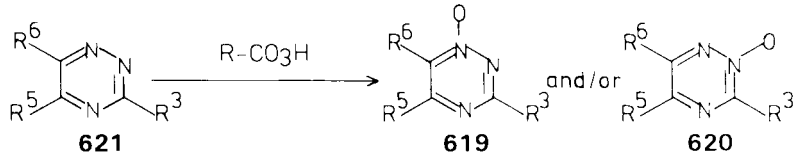
1,2,4-Triazine 1-oxides (**619**) and 1,2,4-triazine 2-oxides (**620**) are synthesized by oxidation of 1,2,4-triazines (**621**) with peracids (104–106, 159, 161, 649, 672, 702, 916).

Euler and his group in 1959 prepared the first 1,2,4-triazine *N*-oxide (m.p. 204°C) by oxidation of 3,5,6-triphenyl-1,2,4-triazine with peracetic acid, but made no decision as to the site of the oxidation (106). Five years later Atkinson and co-workers repeated the oxidation of 3,5,6-triphenyl-1,2,4-triazine and isolated two compounds, the 3,5,6-triphenyl-1,2,4-triazine 1-oxide (**619a**) (m.p. 207°C) and the 3,5,6-triphenyl-1,2,4-triazine 2-oxide (**620a**) (m.p. 194°C) (105). The structure of the two compounds were assigned by determination of the dipole moments (105).

Between 1964 and 1969 Sasaki and Minamoto et al. studied the oxidation of 3-amino-, 3-methoxy-, or 3-phenoxy-1,2,4-triazines and 1,2,4-triazine-3-ones with peracids (160, 161, 649, 672, 702, 916, 917). For the differentiation between 1-oxides and 2-oxides they used chemical reactions and mass spectrometry.

Paudler and Chen (104, 169) oxidized 3-unsubstituted and 3-methoxy-1,2,4-triazines with peracids and used NMR spectroscopy and mass spectrometry for the structure determination. From their studies they came to the following conclusions: 3-unsubstituted and 3-methoxy-1,2,4-triazines are oxidized at N-1, whereas 3-amino-1,2,4-triazines afford the N-2 oxides as major products; thus most structural assignments made by Sasaki and Minamoto should be considered incorrect.

Most 1,2,4-triazines with an unsubstituted 5-position are oxidized by peracids to 1,2,4-triazin-5-ones, not to 1,2,4-triazine *N*-oxides.



621 **619** **620**

2. *Compound Survey*

The 1- and 2-oxides reported in the literature are listed in Table II-46.

3. *Physical Properties*

1,2,4-Triazine 1-oxides (**619**) and 1,2,4-triazine-2-oxides (**620**) are stable crystalline compounds which are colorless or yellow. The NMR spectra of 1,2,4-triazine 1-oxides has been reported for ^{1}H and ^{13}C (104, 159). The parent 1-oxide shows three signals at 1.00, 1.45, and 1.95τ, which were attributed to H-3, H-5, and H-6 (104). Four ^{13}C signals were observed for 3-methoxy-1,2,4-triazine 1-oxide at 167.3, 156.4, 125.6, and 55.7 ppm, which were attributed to C-3, C-5, C-6, and CH_3 group (159).

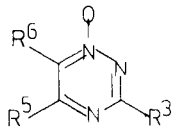
3-Amino-5,6-diphenyl-1,2,4-triazine 1-oxides usually show three maxima in the ultraviolet spectra in the 225, 260 and 365 nm region with absorptivities around 4.30, 4.45, and 3.80 (161). Mass spectra of 1,2,4-triazine *N*-oxides are reported by Paudler and Chen (169) and by Sasaki and his group (649). Dipole moments of 1,2,4-triazine *N*-oxides were measured by Atkinson and his group (105) and by Sasaki and Minamoto (702).

4. *Reactions*

Only a few reactions of 1,2,4-triazine 1-oxides or 1,2,4-triazine 2-oxides have so far been reported. They can be reduced to 1,2,4-triazines (106, 159, 1071) or

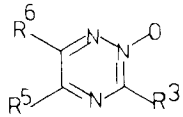
TABLE II-46. 1,2,4-TRIAZINE *N*-OXIDES[a]

A. 1,2,4-Triazine 1-oxides



R^3	R^5	R^6	m.p. (°C)	Refs.
H	H	H	61.5–64	104
H	CH_3	H	65–67	104
H	CH_3	CH_3	84–85.5	104
H	C_6H_5	H	137.5–139.5	104
H	C_6H_5	C_6H_5	170–172	104
C_6H_5	C_6H_5	C_6H_5	204	106
			207	105
CH_3O	H	H	70.5–72	104, 159
CH_3O	CH_3	H	120–121.5	104
CH_3O	CH_3	CH_3	56–57.2	104
CH_3O	C_6H_5	H	127–128.5	104
CH_3O	C_6H_5	C_6H_5	156–158	104
			157.5–158.5	161
Me_3SiO	H	H		1071
C_6H_5O	C_6H_5	C_6H_5	208–210	161
NH_2	C_6H_5	H	228.5–230.5	104
			230–231	161
NH_2	C_6H_5	C_6H_5	240–241	161
ND_2	CH_3	CH_3		169
ND_2	C_6H_5	C_6H_5		169
$NHCH_3$	C_6H_5	C_6H_5	240–241	161
$NH-CO-CH_3$	C_6H_5	C_6H_5	272–273	161
$NHCH_2CH_2OH$	C_6H_5	C_6H_5	196–197	161
NHC_6H_5	C_6H_5	C_6H_5	225–227	161
$NHNH_2$	H	H	194 (dec.)	104
$NHNH_2$	CH_3	CH_3		104
$NHNH_2$	C_6H_5	C_6H_5		104

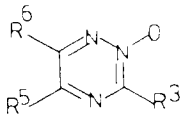
B. 1,2,4-Triazine 2-oxides[a]



R^3	R^5	R^6	m.p.(°C)	Refs.
C_6H_5	C_6H_5	C_6H_5	194	105
NH_2	CH_3	CH_3	197.5–198.5	702, 916

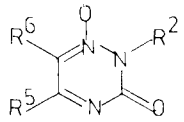
TABLE II-46. (continued)

B. 1,2,4-Triazine 2-oxides[a]



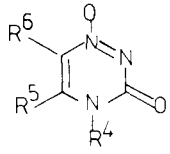
R^3	R^5	R^6	m.p.(°C)	Refs.
NH_2	C_6H_5	H	217–219	672, 916
NH_2	C_6H_5	C_6H_5	189–190	160, 916
NH–CO–CH_3	C_6H_5	H	192–194	672
NH–CO–CH_3	C_6H_5	C_6H_5	160–162	160
NH–$COOC_2H_5$	C_6H_5	H	151–154	672
NH–C_6H_5	C_6H_5	C_6H_5	224–226	649

C. 1,2,4-Triazin-3(2H)-one 1-oxides



R^2	R^5	R^6		m.p.(°C)	Refs.
H	C_6H_5	C_6H_5	$\cdot H_2O$	232–234	160, 916
CH_3	C_6H_5	C_6H_5	$\cdot H_2O$	160–170	160, 916
CH_3CO	C_6H_5	C_6H_5	$\cdot H_2O$	149–151	160

D. 1,2,4-Triazin-3(4H)-one 1-Oxides



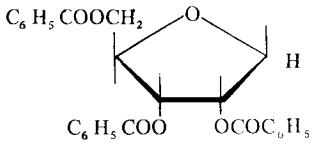
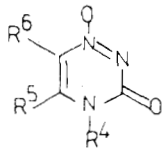
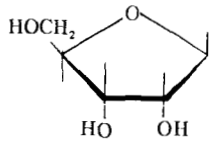
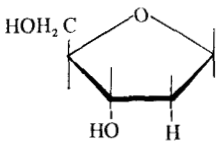
R^4	R^5	R^6	m.p.(°C)	Refs.
H	H	H	234 (dec.)	159
	H	H	236–238	159

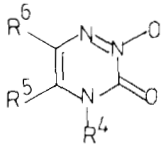
TABLE II-46. (continued)

D. 1,2,4-Triazin-3(4H)-one 1-Oxides



R^3	R^5	R^6	m.p.(°C)	Refs.
	H	H	174–176	159, 1071
	H	H		1071

E. 1,2,4-Triazin-3(4H)-one 2-Oxides



R^4	R^5	R^6	m.p.(°C)	Refs.
H	C_6H_5	C_6H_5	222–224	161
CH_3	C_6H_5	C_6H_5	>300	161

[a]Structures given by Sasaki et al. were corrected according to the studies of Paudler and Chen.

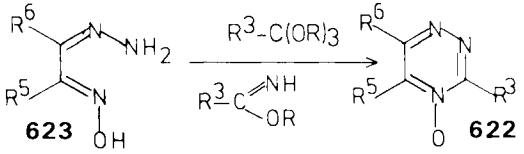
to dihydro-1,2,4-triazines (159, 161). Five-membered ring systems were obtained by drastically heating 1,2,4-triazine *N*-oxides with bases or acids (161, 672, 917). N_4-Sugar substituted 1,2,4-triazine-3-one 1-oxides were synthesized by Szekeres and his group (159, 1071).

B. 1,2,4-Triazine 4-Oxides

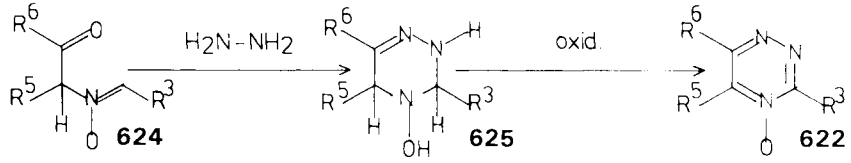
1. *Preparation*

At present only 4 papers dealing with 1,2,4-triazine-4-oxides (**622**) are known. Scott and Reilly (918) reported in 1952 that Walsh was able to synthesize 3-amino-5,6-diphenyl-1,2,4-triazine 4-oxide by cyclization of benzil guanylhydrazone oxime but no experimental details were given and no publication by Walsh followed this report.

A large number of 1,2,4-triazine 4-oxides (**622**) were synthesized by Neunhoeffer and his group (59, 60). The best method is the cyclization of α-oximohydrazones (**623**) with orthocarboxylates or imidates (59, 60), but the synthesis of **622** was also achieved by reaction of hydrazide oximes with 1,2-dicarbonyl compounds (59) and of amidrazones with α-oximo ketones (59), and by cyclization of 2-(2-ethoxymethylenehydrazono) ketones with hydroxylamine (59).



A Russian group (61) reported the synthesis of **622** by reaction of the nitrones (**624**) with hydrazine and oxidation of the initially formed tetrahydro-4-hydroxy-1,2,4-triazines (**625**).



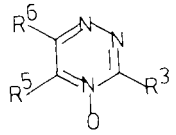
2. *Compound Survey*

Table II-47 lists the 4-oxides reported in the literature.

3. *Physical Properties*

1,2,4-Triazine 4-oxides (**622**) are stable, cyrstalline colorless or pale yellow compounds. The infrared spectra of **622** show a band for the N-O stretching

TABLE II-47. 1,2,4-TRIAZINE 4-OXIDES

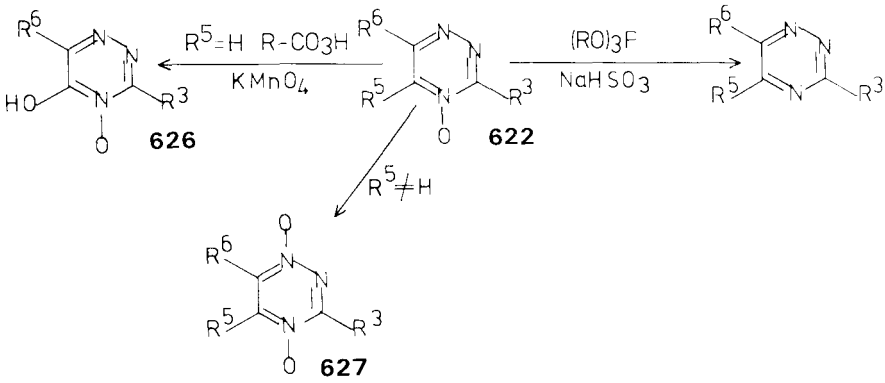


R^3	R^5	R^6	m.p.(°C)	Refs.
H	H	CH_3	60	60, 919
H	H	C_6H_5	141	60
			143	59, 919
H	H	4-CH_3O–C_6H_4	229–230	59, 919
H	H	4-O_2N–C_6H_4	250–252	919
H	CH_3	CH_3	75	59, 60, 919
H	CH_3	C_6H_5	140	59, 60, 919
H	C_6H_5	C_6H_5	198	59, 60, 919
CH_3	H	CH_3	129	919
CH_3	H	C_6H_5	184	59, 60, 919
CH_3	CH_3	C_6H_5	122–124	61
			135–137	59, 919
CH_3	C_6H_5	C_6H_5	155	919
C_2H_5	H	C_6H_5	125	919
C_2H_5	CH_3	C_6H_5	118–119	919
C_6H_5	H	CH_3	127	919
C_6H_5	H	C_6H_5	168–169	61
			171	59, 60, 919
C_6H_5	CH_3	CH_3	106	60
			108	59, 919
C_6H_5	CH_3	C_6H_5	131–133	61
			145	59, 919
C_6H_5	C_6H_5	C_6H_5		60
4-CH_3O–C_6H_4	H	C_6H_5	224–225	919
4-O_2N–C_6H_4	H	C_6H_5	276–282	919

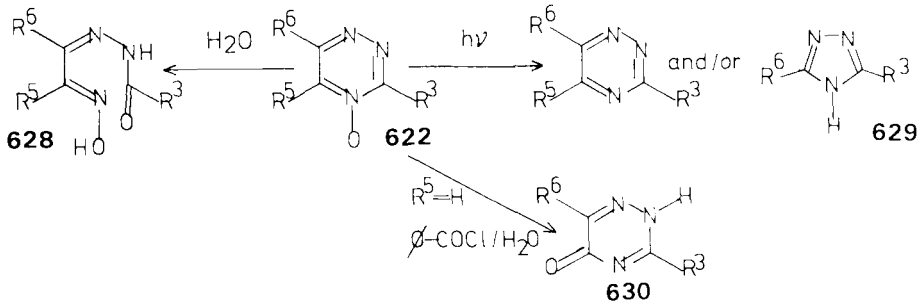
vibration in the 1280 cm^{-1} region. In the PMR spectra of **622** the signals are shifted to higher fields in comparison with the PMR spectra of 1,2,4-triazines. 6-Methyl-1,2,4-triazine 4-oxide shows two signals in the PMR spectra at 0.72 and 1.78τ which were attributed to H-3 and H-5. Since both signals are doublets the protons in the 3- and 5-position couple contrary to these protons in the 1,2,4-triazines. The mass spectra of 1,2,4-triazine 4-oxides show an intensive mass-peak but a very weak peak for M^+ -16. In the ultraviolet spectra of **622**, one band in the 270 nm region and an inflection in the 300 nm region are observed.

4. *Reactions*

The most intensively studied reaction of **622** is the reduction to 1,2,4-triazines (59–61, 919), which can be achieved by reaction with trivalent phosphorus compounds (59, 60, 919) or with sodium hydrogen sulfite (61). Oxidation of 1,2,4-triazine 4-oxides with peracids leads to 1,2,4-triazin-5-one 4-oxides (**626**) if the 5-position is unsubstituted, whereas 1,2,4-triazine 1,4-dioxides (**627**) were isolated if the 5-position in **622** is substituted (919). Potassium permanganate oxidizes only 1,2,4-triazine 4-oxides with an unsubstituted 5-position, leading to **626** (919).



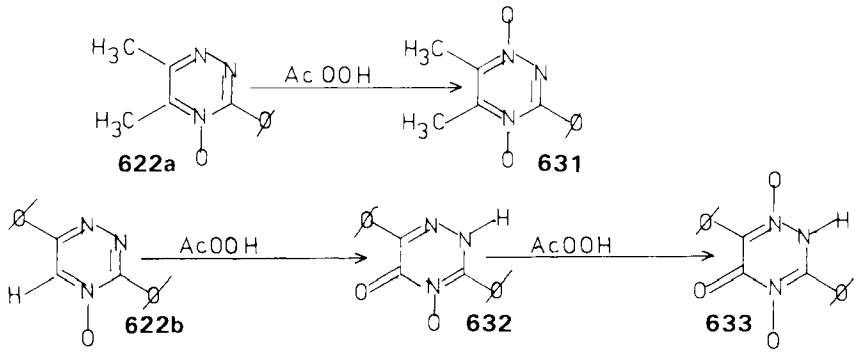
1,2,4-Triazine 4-oxides (**622**) can be hydrolyzed by both acid and base; in both cases acylhydrazono oximes (**628**) are obtained (919). Irradiation of **622** with ultraviolet light leads to the formation of 1,2,4-triazines and to 1,2,4-triazoles (**629**) if the 5-position is unoccupied (919).



Reaction of **622** with benzoyl chloride in the presence of water gives 1,2,4-triazine-5-ones (**630**) (919).

C. 1,2,4-Triazine 1,4-Dioxides

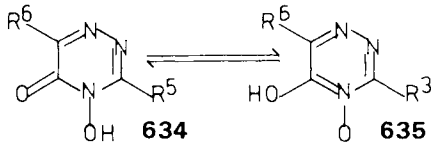
Oxidation of 3-phenyl-5,6-dimethyl-1,2,4-triazine 4-oxide (**622a**) with peracetic acid was used for the synthesis of 5,6-dimethyl-3-phenyl-1,2,4-triazine 1,4-dioxide (**631**) (m.p. 137°C). 3,6-Diphenyl-1,2,4-triazine 4-oxide (**622b**) is first oxidized by peracetic acid to 3,6-diphenyl-1,2,4-triazin-5-one 4-oxide (**632**) which can be further oxidized to 3,6-diphenyl-1,2,4-triazin-5-one 1,4-dioxide (**633**) (m.p. 265°C) (919). The structure of both compounds was proved by reduction with trivalent phosphorus compounds and by NMR spectroscopy.

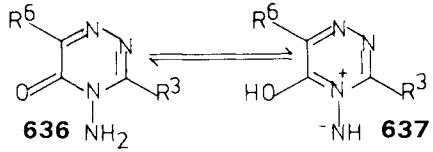


XII. 1,2,4-TRIAZINES WITH A HETERO SUBSTITUENT IN THE 4-POSITION

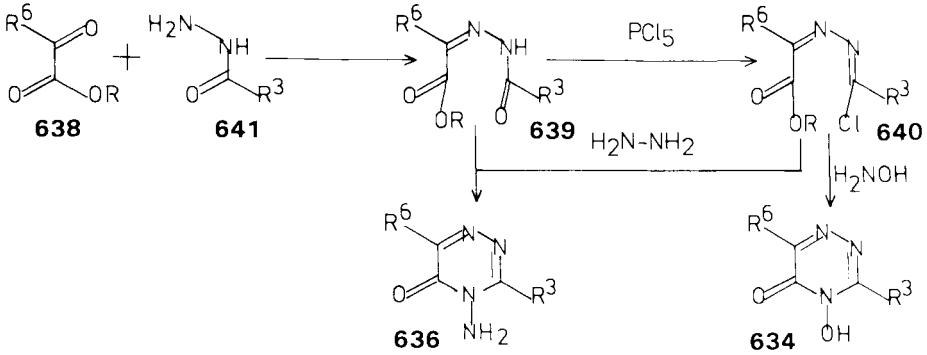
A. 4-Hydroxy-1,2,4-triazin-5-ones (5-Hydroxy-1,2,4-triazine 4-Oxides)

The definite structure of the compounds belonging to this group is still unknown; they can be treated as derivatives of the 1,2,4-triazin-5(4*H*)-ones (**634**) or, because of the possible tautomeric structure **635**, as 1,2,4-triazine 4-oxides. The same problem occurs with the 4-amino-1,2,4-triazin-5-ones, which can be treated either as *N*-amino derivatives of 1,2,4-triazin-5(4*H*)-ones (**636**) or, because of the tautomeric structure **637**, as nitrogen analogues of *N*-oxides. For this reason we discuss the 1,2,4-triazines with a hetero substituent in the 4-position separately.





The three known 4-hydroxy-1,2,4-triazin-5-ones (**634**) ($R^3 = C_2H_5$, $R^6 = t\text{-}C_4H_9$, m.p. 132°C; $R^3 = C_2H_5$, $R^6 = C_6H_5$, m.p. 171 to 171.5°C; $R^3 = t\text{-}C_4H_9$, $R^6 = t\text{-}C_4H_9$, m.p. 160 to 162°C) were synthesized as illustrated: reaction of glyoxalates (**638**) with hydrazides (**641**) gives the acylhydrazones **639**, which were treated with phosphorus pentachloride and the formed chloro compounds (**640**) are cyclized by reaction with hydroxylamine (185).



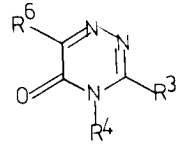
B. 4-Amino-1,2,4-triazin-5-ones

All known derivatives of 4-amino-1,2,4-triazin-5-one (**636**) (Table II-48) or of the tautomeric structure **637** are described in four German patents (185, 921–923) They are synthesized by reaction of α-ketocarboxylates (**638**) with hydrazides (**641**) and cyclization of the formed acylhydrazones (**639**) directly with hydrazine (922, 923) or after reaction with phosphorus pentachloride (185, 922). The amino group in **636** reacts with aldehydes, ketones, and amide acetals (921).

C. 4-Amino-1,2,4-triazine-3,5-diones

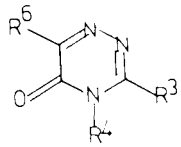
At present only four derivatives of the 4-amino-1,2,4-triazine-3,5-dione system (**642**) have been reported (924, 925, 1078), the 6-methyl- (**642a**) [$R = CH_3$, m.p. 156 to 157°C (1078); 159°C (925)] and the 6-phenyl-4-amino-1,2,4-triazine-3,5-dione (**642b**) [$R = C_6H_5$, m.p. 196°C (1078)] and the 6-isopropyl- (924) and the 6-phenyl-3-methoxy-4-amino-1,2,4-triazine-5-one (m.p. 167°C) (925). The diones **642** can be synthesized by reaction of carbohydrazide (**643**) with α-ketocarboxylic acids (**638**, R = H) or α-ketocarboxylates (**638**), by hydrolysis of 4-amino-3-hydrazino-1,2,4-triazin-5-ones (**644**), and by reaction of 1,3,4-oxadiazolo[2,3-*c*] 1,2,4-triazin-7-ones (**645**) with hydrazine (see page 567).

TABLE II-48. 4-AMINO-1,2,4-TRIAZIN-5-ONES



R^3	R^4	R^6	m.p. (°C)	Refs.
H	NH_2	t-C_4H_9	113–114	185, 923
CH_3	NH_2	t-C_4H_9	158–159	185, 923
CH_3	NH_2	C_6H_5	167–169	185, 922
CH_3	NH_2	3-CH_3–C_6H_4	107	922
CH_3	NH_2	4-CH_3–C_6H_4	199	185, 922
CH_3	NH_2	3-CF_3–C_6H_4	169	922
CH_3	NH_2	3-t-C_4H_9–C_6H_4	140	922
CH_3	NH_2	4-CH_3O–C_6H_4	206	185, 922
CH_3	NH_2	3,4-$(CH_3O)_2C_6H_3$	220	922
CH_3	NH_2	3-Cl–C_6H_4	138–139	922
CH_3	NH_2	4-Cl–C_6H_4	97	185, 922
CH_3	NH_2	4-O_2N–C_6H_4	233	922
CH_3	N=$C(CH_3)_2$	C_6H_5	99	921
CH_3	N=$CHN(CH_3)_2$	C_6H_5	110	921
CH_3	N=CH– 	C_6H_5	117	921
CH_3	N=CHC_6H_5	C_6H_5	179	921
CH_3	N=CH–C_6H_4–CH_3 (*p*)	C_6H_5	150–152	921
CH_3	N=CH–C_6H_4–Cl(*p*)	C_6H_5	195	921
CH_3	N=CH–C_6H_4–NO_2(*p*)	C_6H_5	183–185	921
C_2H_5	NH_2	t-C_4H_9	154	185. 923
C_2H_5	NH_2	C_6H_5	164	185, 921
C_2H_5	NH_2	4-CH_3–C_6H_4	148	185
C_2H_5	NH_2	4-CH_3O–C_6H_4	164–166	185
C_2H_5	NH_2	3,4-$(CH_3O)_2C_6H_3$	167–169	185
C_2H_5	NH_2	4-Cl–C_6H_4	156	185
C_2H_5	NH–CHO	4-Cl–C_6H_4	101	921
C_2H_5	NH–CHO	4-O_2N–C_6H_4	219	921
C_2H_5	N=CH–OC_2H_5	t-C_4H_9	86	921
C_2H_5	N=$CHN(CH_3)_2$	C_6H_5	123	921
C_2H_5	N=$CHN(CH_3)_2$	C_6H_5	123	921
C_2H_5	N=$C(CH_3)_2$	t-C_4H_9	62–63	921
C_2H_5	N=$C(CH_3)_2$	C_6H_5	146	921
C_2H_5	N=$C(CH_3)_2$	4-CH_3–C_6H_4	152	921
C_2H_5	N=$C(CH_3)_2$	3-CF_3–C_6H_4	136	921
C_2H_5	N=$C(CH_3)_2$	3-Cl–C_6H_4	96	921
C_2H_5	N=$C(CH_3)_2$	4-O_2N–C_6H_4	162	921

TABLE II-48. (continued)



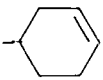
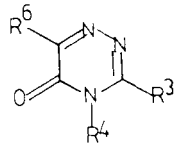
R^3	R^4	R^6	m.p.(°C)	Refs.
C_2H_5	N=CH– 	C_6H_5	124–126	921
C_2H_5	$N{=}CHC_6H_5$	t-C_4H_9	103–105	921
C_2H_5	$N{=}CHC_6H_5$	C_6H_5	115–117	921
C_2H_5	$N{=}CHC_6H_5$	4-CH_3–C_6H_4	143	921
C_2H_5	$N{=}CHC_6H_5$	3-CF_3–C_6H_4	128	921
C_2H_5	$N{=}CHC_6H_5$	3-Cl–C_6H_4	124	921
C_2H_5	$N{=}CHC_6H_5$	4-O_2N–C_6H_4	192	921
C_2H_5	$N{=}CHC_6H_4$–CH_3 (p)	C_6H_5	122	921
C_2H_5	N= 	t-C_4H_9	58–60	921
C_2H_5	N=CH– 	t-C_4H_9	112–114	921
n-C_3H_7	NH_2	i-C_3H_7	95.5	185
n-C_3H_7	NH_2	t-C_4H_9	105–106	185
n-C_3H_7	NH_2	C_6H_5	104–106	185
n-C_3H_7	NH_2	4-Cl–C_6H_4	120.5	185
n-C_3H_7	$N{=}C(CH_3)_2$	C_6H_5	102	921
i-C_3H_7	NH_2	t-C_4H_9	140–141	185, 923
i-C_3H_7	NH_2	C_6H_5	121–122	923
			126–127	185
i-C_3H_7	NH_2	4-CH_3–C_6H_4	131–132	185
i-C_3H_7	NH_2	4-Cl–C_6H_4	145–147	185
i-C_3H_7	$N{=}C(CH_3)_2$	t-C_4H_9	89	921
i-C_3H_7	$N{=}C(CH_3)_2$	C_6H_5	96–99	921
i-C_3H_7	$N{=}C(CH_3)_2$	4-CH_3–C_6H_4	109	921
i-C_3H_7	$N{=}CHC_6H_5$	4-CH_3–C_6H_4	118	921
n-C_4H_9	NH_2	t-C_4H_9	94–96	185
n-C_4H_9	NH_2	C_6H_5	138–139	185
n-C_4H_9	NH_2	4-Cl–C_6H_4	152–153	185
n-C_4H_9	$N{=}C(CH_3)_2$	C_6H_5	91	921
sec-C_4H_9	NH_2	C_6H_5	92	185
i-C_4H_9	NH_2	t-C_4H_9	140–142	185
t-C_4H_9	NH_2	t-C_4H_9	165.5	185
t-C_4H_9	NH_2	C_6H_5	138	185

TABLE II-48. (continued)



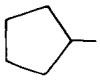
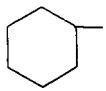
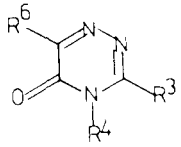
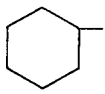
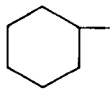
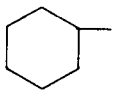
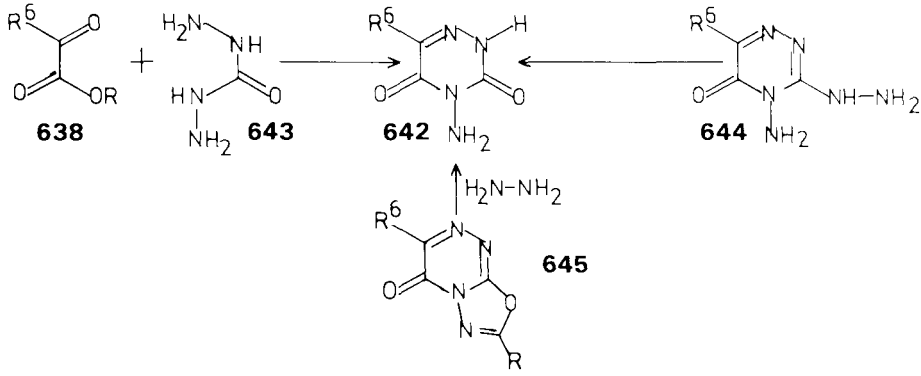
R^3	R^4	R^6	m.p.(°C)	Refs.
t-C_4H_9	NH_2	4-Cl–C_6H_4	179–181	185
CH_2CN	NH_2	t-C_4H_9	156–157	185
$CH_2OC_2H_5$	NH_2	t-C_4H_9	64–67	185
n-C_5H_{11}	$N{=}C(CH_3)_2$	C_6H_5	82–89	921
n-C_5H_{11}	N=CH– 	C_6H_5	62	921
n-C_5H_{11}	$N{=}CHC_6H_5$	C_6H_5	106–108	921
$(CH_2)_2CH(CH_3)_2$	$N{=}C(CH_3)_2$	C_6H_5	83.5	921
$(CH_2)_2CH(CH_3)_2$	$N{=}CHC_6H_5$	C_6H_5	80.5	921
n-C_6H_{13}	$N{=}C(CH_3)_2$	C_6H_5	78–79	921
n-C_6H_{13}	$N{=}CHC_6H_5$	C_6H_5	91–92	921
n-$C_{13}H_{27}$	$N{=}C(CH_3)_2$	C_6H_5	77	921
 Cyclopropyl	NH_2	t-C_4H_9	109–110	185
 Cyclopropyl	NH_2	C_6H_5	121	185
 Cyclopropyl	NH_2	4-Cl–C_6H_4	161.5	185
 Cyclopropyl	$N{=}C(CH_3)_2$	C_6H_5	146.5	921
 Cyclopentyl	NH_2	t-C_4H_9	196.5	185
 Cyclohexyl	NH_2	t-C_4H_9	175–180	185

TABLE II-48. (continued)



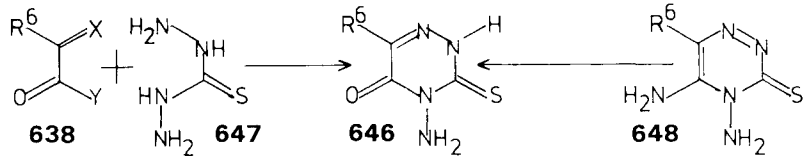
R^3	R^4	R^6	m.p.(°C)	Refs.
 Cyclohexyl	NH_2	C_6H_5	182	185
 Cyclohexyl	NH_2	4-Cl–C_6H_4	180–181	185
 Cyclohexyl	$N{=}C(CH_3)_2$	C_6H_5	131–134	921
C_6H_5	NH_2	t-C_4H_9	126–127	185
C_6H_5	$N{=}C(CH_3)_2$	C_6H_5	137–140	921



D. 4-Amino-3-thioxo-1,2,4-triazin-5-ones

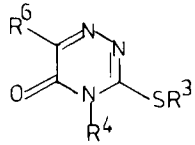
The 4-amino-3-thioxo-1,2,4-triazin-5-ones (**646**) (Table II-49) are intensively studied compounds since they show biological activities and one of them is used

as a herbicide. They are synthesized by reaction of thiocarbohydrazide (**647**) with α-ketocarboxylic acids (**638a**, X = O, Y = OH) (938), their esters (**638b**, X = O, Y = OR) (925, 928, 935), α-oximino carboxylates (**638c**, X = NOH, Y = OR) (935), or α-ketoamides (**638d**, X = O, Y = NH_2) (926) which can be synthesized from acyl chlorides and isonitriles. The hydrolysis of 4,5-diamino-1,2,4-triazine-3-thiones (**648**) to **646** is reported in one paper (927).



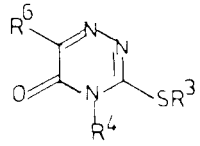
No studies on the structure of 4-amino-3-thioxo-1,2,4-triazine-5-ones have been reported so far. The determination of 4-amino-3-methylmercapto-6-*tert*-butyl-1,2,4-triazin-5-one (BAY 94337) was published by two groups (929, 939).

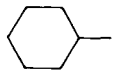
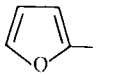
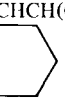
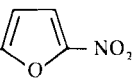
TABLE II-49. 4-AMINO-3-THIOXO-1,2,4-TRIAZIN-5-ONES



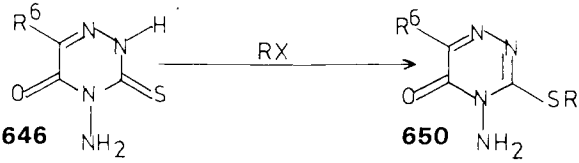
R^3	R^4	R^6	m.p. (°C)	Refs.
H	NH_2	H	211–215	928
H	NH_2	CH_3	180	938
			187	935
H	NH_2	t-C_4H_9	215–217	926
H	NH_2	CH_2CH_2OH	156–157	935
H	NH_2	$CH_2CH_2CH_2OH$	142	935
H	NH_2	C_6H_5	231 (dec.)	938
H	$NHCOC_6H_5$	CH_3	225	933
H	$N(COCH_3)_2$	CH_3	162	938
H	$N{=}CHC_6H_5$	CH_3	204–206	938
H	$N{=}CHC_6H_4{-}NO_2$(p)	CH_3	185–186	935
CH_3	NH_2	CH_3	165	938/924
CH_3	NH_2	C_2H_5	120	925/924
CH_3	NH_2	n-C_3H_7		924
CH_3	NH_2	i-C_3H_7	123	925/924
CH_3	NH_2	i-C_4H_9	66	925/924
CH_3	NH_2	t-C_4H_9	126–127	926/924
				927
CH_3	NH_2	i-C_5H_{11}	Oil	925/924

TABLE II-49. (continued)

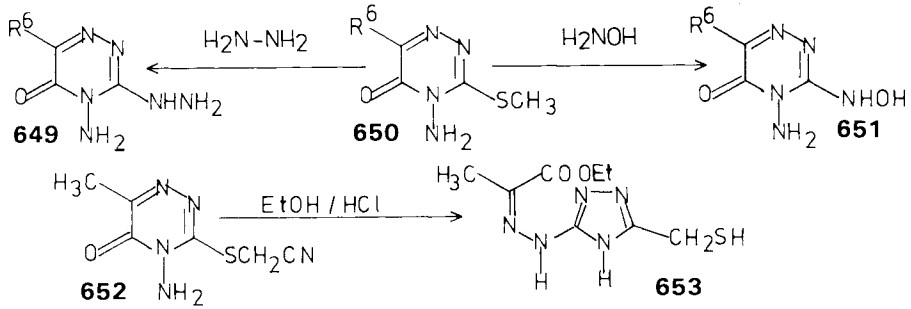


R^3	R^4	R^6	m.p.(°C)	Refs.
CH_3	NH_2	n-C_6H_{13}	63	925/924
CH_3	NH_2		154	925/924
CH_3	NH_2	$C_6H_5CH_2$	205	925
CH_3	NH_2	C_6H_5	186	938/924
CH_3	NH_2		225	925
CH_3	NH_2	2-Tetra-hydropyranyl		924
CH_3	$NHCH_2CH{=}CH_2$	C_6H_5	159	925
CH_3	$NHCH(OH)CCl_3$	C_6H_5	147	925
CH_3	$NHCOCH_3$	C_6H_5	213	925
CH_3	$N(COCH_3)_2$	C_6H_5	122	925
CH_3	$N{=}C(CH_3)_2$	C_6H_5	152	925
CH_3	$N{=}CHCH(CH_3)_2$	C_6H_5	136	925
CH_3		C_6H_5	140	925
CH_3	$N{=}CHC_6H_5$	C_6H_5	180	925
CH_3	$N{=}C(CH_3)C_6H_5$	C_6H_5	154	925
CH_3	$N{=}CHC_6H_4{-}NO_2$ (p)	CH_3	215–216	935
CH_3		C_6H_5	172	925
CH_3		C_6H_5	207	925
CH_3		C_6H_5	205	925
C_2H_5	NH_2	C_6H_5	157	925
$CH_2CH{=}CH_2$	NH_2	C_6H_5	137	925
CH_2CN	NH_2	CH_3	193	935
CH_2CN	NH_2	CH_2CH_2CN	166	935
$CH_2COOC_2H_5$	NH_2	CH_3	153	935
$C_6H_5CH_2$	NH_2	CH_3		928

4-Amino-3-thioxo-1,2,4-triazine-5-ones (**646**) can be alkylated at the sulfur yielding 4-amino-3-(alkylmercapto)-1,2,4-triazin-5-ones (**650**) (927).



Photochemical deamination is observed for 4-amino-3-(methylmercapto)-1,2,4-triazine-5-one (930) and its 6-phenyl derivative (**650**) (931). Reaction of **650** with hydrazine was used for the synthesis of 4-amino-3-hydrazino-1,2,4-triazin-5-ones (**649**) (760, 938); reaction with hydroxylamine affords 4-amino-3-(hydroxylamino)-1,2,4-triazin-5-ones (**651**) (1078). 4-Amino-3-[(cyanomethyl)-mercapto]-6-methyl-1,2,4-triazin-5-one (**652**) is converted into the 1,2,4-triazole (**653**) by treatment with ethanolic hydrogen chloride (934, 935). The synthesis of condensed 1,2,4-triazines from 4-amino-3-thioxo-1,2,4-triazine-5-ones was published by various groups (760, 933–935, 1078).



E. 3,4-Diamino-1,2,4-triazin-5-ones

3,4-Diamino-1,2,4-triazin-5-ones (**654**) (Table II-50) were obtained either by reaction of α-ketocarboxylic acids (**638**) with diaminoguanidine (**655**) or by treatment of 4-amino-3-thioxo-1,2,4-triazin-5-ones (**646**) with amines (925, 937, 938, 1100).

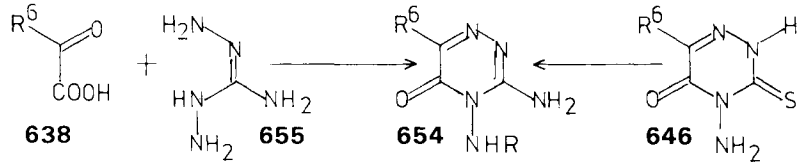
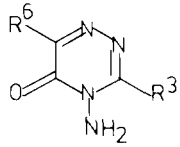
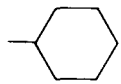
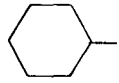
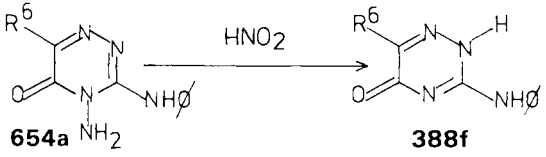


TABLE II-50. 3,4-DIAMINO-1,2,4-TRIAZIN-5-ONES



R^3	R^6	m.p. (°C)	Refs.
NH_2	CH_3	245	938, 1100
NH_2	C_6H_5	259–260 (dec.)	938
$NHCH_3$	CH_3	180	925, 937
$NHCH_3$	*i*-C_3H_7	142	924, 937
$NHCH_3$	*t*-C_4H_9	234	937
$NHCH_3$	 Cyclohexyl	141	937
$NHCH_3$	C_6H_5	212	925, 937
$NHCH_3$	4-Cl–C_6H_4	159	925
NHC_2H_5	*i*-C_3H_7	158	937
NHC_2H_5	*t*-C_4H_9	178	937
NHC_2H_5	C_6H_5	158	925
NH-*n*-C_3H_7	C_6H_5	176	925
$NHCH_2CH{=}CH_2$	C_6H_5	165	925
NH-*n*-C_4H_9	CH_3	88.5	938
NH-*n*-C_4H_9	*i*-C_3H_7	125	937
NH-*n*-C_4H_9	C_6H_5	182	938
NH-*n*-C_4H_9	 Cyclohexyl	173	937
NH-*n*-$C_{12}H_{25}$	*i*-C_3H_7	104	937
$NHCH_2C_6H_5$	CH_3	167	938
$NHCH_2C_6H_5$	*i*-C_3H_7	144	937
$NHCH_2C_6H_5$	C_6H_5	167	938
NHC_6H_5	CH_3	235–236	938
NHC_6H_5	*i*-C_3H_7	162	937
NHC_6H_5	C_6H_5	215.5	938
	C_6H_5	163	925
	C_6H_5	163	938

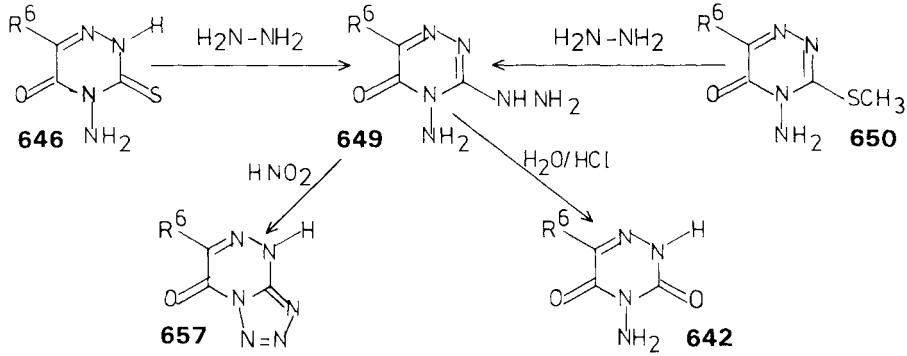
Reaction of 3,4-diamino-6-methyl-1,2,4-triazin-5-one with acetic anhydride yields a triacetyl derivative (1100). 4-Amino-3-anilino-6-phenyl-1,2,4-triazin-5-one (**654a**) is converted into 3-anilino-6-phenyl-1,2,4-triazin-5-one (**388f**) by reaction with nitrous acid (760). Starting from 3,4-diamino-1,2,4-triazin-5-ones (**654**) a number of condensed 1,2,4-triazines can be synthesized (932, 934, 938, 1078).



654a **388f**

F. 4-Amino-3-hydrazino-1,2,4-triazin-5-ones

The 6-methyl- (**649a**) ($R^6 = CH_3$, m.p. 283 to 285°C) (760, 938) and the 6-phenyl-4-amino-3-hydrazino-1,2,4-triazin-5-one (**649b**) ($R^6 = C_6H_5$, m.p. 273°C) (760) were prepared by reaction of 4-amino-3-thioxo-1,2,4-triazin-5-ones (**646**) or 4-amino-3-(methylmercapto)-1,2,4-triazin-5-ones (**650**) with hydrazine. They were used for the synthesis of tetrazolo[5,1-*c*]1,2,4-triazin-7-ones (**657**) (760). Hydrolysis of **649** in the presence of hydrochloric acid yields 4-amino-1,2,4-triazine-3,5-diones (**642**) (1078); reaction of **649** with acetic anhydride affords a triacetyl derivative (1078).



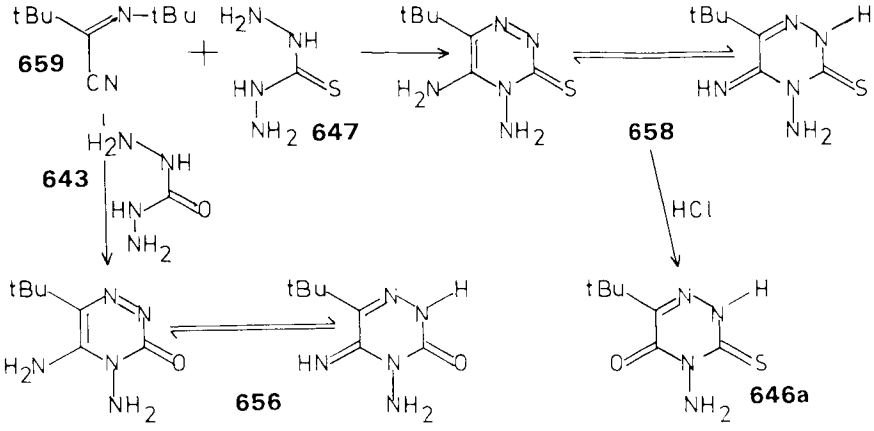
646 **649** **650** **657** **642**

G. 4,5-Diamino-1,2,4-triazin-3-ones

Interaction of the α-iminonitrile (**659**) with carbohydrazide (**643**) affords 4,5-diamino-6-(*tert*-butyl)-1,2,4-triazin-3-one (**656**) (m.p. 182 to 184°C) or its imino tautomer (929).

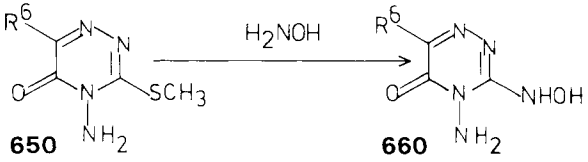
H. 4,5-Diamino-1,2,4-triazine-3-thiones

4,5-Diamino-6-(*tert*-butyl)-1,2,4-triazine-3-thione (**658**) (m.p. 181°C) or its imino tautomer was synthesized by reaction of the α-iminonitrile (**659**) with thiocarbohydrazide (**647**) (927). Hydrolysis of **658** with hydrochloric acid affords **646a** (927), whereas 1,2,4-triazolo[1,5-*d*] 1,2,4-triazines are obtained by reaction with carboxylic acid derivatives (936).



I. 4-Amino-3-(hydroxylamino)-1,2,4-triazin-5-ones

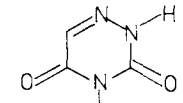
The 6-methyl (m.p. 230°C) a 1 6-phenyl derivatives (m.p. 252°C) of 4-amino-3-(hydroxylamino)-1,2,4-triazin-5-one (**660**) were synthesized by reaction of 4-amino-3-(methylmercapto)-1,2,4-triazin-5-ones (**650**) with hydroxylamine (1078). A number of condensed 1,2,4-triazine systems were prepared from **660** (1078).



J. 4-Mercapto-1,2,4-triazine-3,5-diones

The single known member of this class of 1,2,4-triazine derivatives, the 4-[(trichloromethyl)mercapto]-1,2,4-triazine-3,5-dione (**661**) is reported by

Matolcsy and his group (2308, 2309), who prepared it and tested it for its biochemical properties.



661

Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

III

Uncondensed Reduced 1,2,4-Triazines

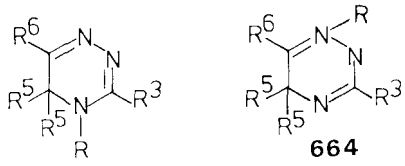
I DIHYDRO-1,2,4-TRIAZINES

A. Alkyl-, Aryl-, and Heterocyclic-Substituted Dihydro-1,2,4-triazines

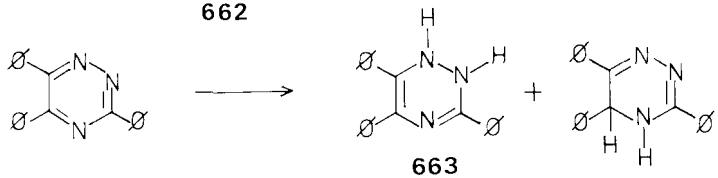
1. *Preparation*

Dihydro-1,2,4-triazines are well-known compounds and effective methods for their synthesis have been published. Surprisingly no thorough study of the structure of dihydro-1,2,4-triazines has at present been reported. Atkinson and Cossey (52) observed a maximum at 1453 cm^{-1} in the infrared spectrum of dihydro-3,6-diphenyl-1,2,4-triazine which is attributed to the deformation frequency of a 5–CH_2 group. This observation together with maxima at 3424 and 3448 cm^{-1} for the 5-methyl analogue confirms the 2,5- (**664**) or 4,5-dihydro structure (**662**). Shvaika and Fomenko (944) observed a peak for the 5–CH_2 group in the PMR spectra of dihydro-1,2,4-triazines. Pinson and his group (108) were able to isolate two dihydro-3,5,6-triphenyl-1,2,4-triazines, which they formulated on the basis of PMR spectroscopic studies as 1,2-dihydro (**663**) (m.p. 264.5°C) and 4,5-dihydro-3,5,6-triphenyl-1,2,4-triazine (**662a**). Under the synthetic conditions the two compounds do not interconvert. In the following discussion we usually use the 4,5-dihydro-1,2,4-triazine structure, but this does not imply that this structure is well established.

Dihydro-1,2,4-triazines (**662**) can be synthesized from α-amino ketones (**665a**), which are acylated at the amino group, followed by reaction with hydrazines, which may lead directly to dihydro-1,2,4-triazines (**662**) (52, 56, 58, 940) or to α-(acylamino)hydrazones (**665b**) (941, 942). Treatment of the hydrazones (**665b**) with hydrochloric acid transforms them into the dihydro-1,2,4-triazines (**662**). The α-(acylamino) ketones (**667**) can be converted into the

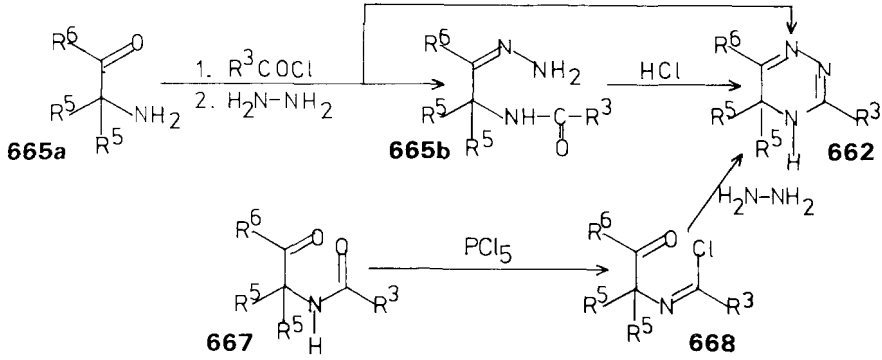


662 664



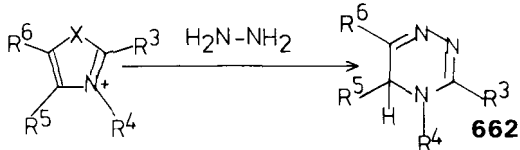
663 662a

imid chlorides (**668**) by reaction with phosphorus pentachloride and can then be cyclized by reaction with hydrazine (643).



665a 665b 662 667 668

Another method for the synthesis of dihydro-1,2,4-triazines (**662**) is the reaction of 1,3-oxazolium salts (**669**) or 1,3-thiazolium salts (**670**) with hydrazine (944–946).

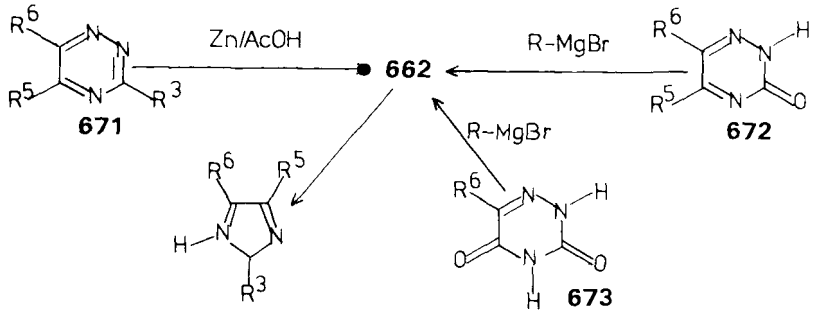


662

669: X=O
670: X=S

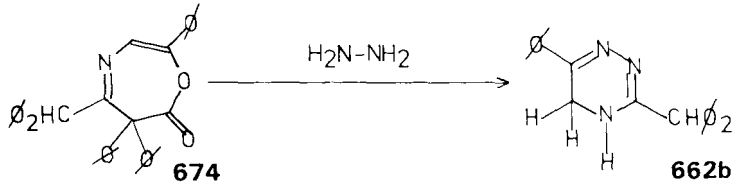
1,2,4-Triazines (**671**) can be reduced to dihydro-1,2,4-triazines (**662**) (51, 73, 107, 108, 122) either with zinc and acetic acid or electrochemically. The first reduction product is the dihydro-1,2,4-triazine which is transformed into imidazoles by further reduction (50, 51, 107, 122). Dihydro-1,2,4-triazines (**662**) can also be isolated from the reaction of 1,2,4-triazin-3-ones (**672**)

or 1,2,4-triazine-3,5-diones (**673**) with Grignard reagents (66); the preferred structure of the isolated products is the 2,3-dihydro structure [3,3,5,6-$(C_6H_5)_4$, m.p. 198°C; 5,6-$(C_6H_5)_2$-3,3-$(4-CH_3O-C_6H_4)_2$, m.p. 205°C].



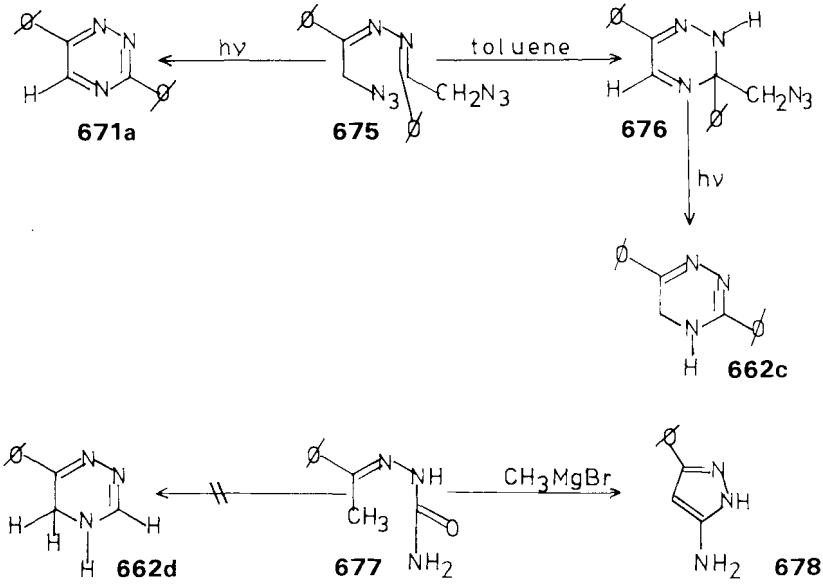
Busch and Küspert (987) obtained dihydro-1,2,4-triazines by treatment of 4-amino-2,3,4,5-tetrahydro-1,2,4-triazines (**666**) with hydrochloric acid. The isolated compounds were formulated as 2,3-dihydro-1,2,4-triazines.

3-(Diphenylmethyl)-6-phenyldihydro-1,2,4-triazine (**662b**) was isolated by Haddadin and Hassner (947) from the reaction of the 1,4-oxazepin-7-one (**674**) with hydrazine.



1,6-Diazido-2,5-diphenyl-3,4-diazahexadi-2,4-ene (**675**) is converted into 3-(azidomethyl)-3,6-diphenyl-2,3-dihydro-1,2,4-triazine (**676**) in boiling toluene (73). Irradiation of **675** leads to the formation of 3,6-diphenyl-1,2,4-triazine (**671a**), and irridiation of **676** affords **662c**.

Searles and Kash (950) demonstrated that the 6-phenyldihydro-1,2,4-triazine (**662d**) isolated by Diquard (951) from the reaction of acetophenone semicarbazone (**677**) with methylmagnesium bromide was, in fact, the 3-amino-5-phenylpyrazole (**678**).



2. *Compound Survey*

Table III-1 lists the known compounds of this group.

3. *Physical Properties*

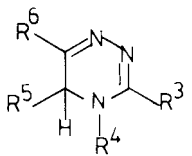
Dihydro-1,2,4-triazines are colorless or pale yellow compounds. The reported infrared (52, 108, 944), ultraviolet (52), and PMR spectroscopic data (108, 944) do not allow any general statement of the spectroscopic properties of dihydro-1,2,4-triazines. Hangay and Lukats (949) reported that dihydro-1,2,4-triazine palmoates and ethionamides are stable to irradiation.

4. *Reactions*

Only a few reactions of dihydro-1,2,4-triazines have been reported so far. They can be oxidized to 1,2,4-triazines (52, 56–58), they disproportionate to 1,2,4-triazines and imidazoles (107), and they form a diacetyl derivative by reaction with acetic anhydride (107).

TABLE III-1. DIHYDRO-1,2,4-TRIAZINES WITH ALKYL, ARYL, AND HETEROCYCLIC SUBSTITUENTS

A. 4,5-Dihydro-1,2,4-triazines



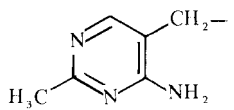
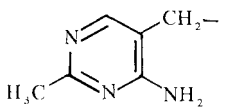
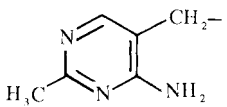
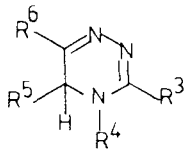
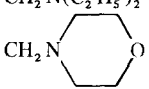
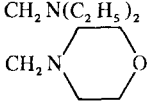
R^3	R^4	R^5	R^6		m.p. (°C)	Refs.
H	H	CH_3	CH_3		b.p.120–121/14 torr	107
H		CH_3	CH_3		216	942
H		CH_3	CH_2CH_2OH		196–197	942
H		CH_3	$CH_2CH_2OCOC_6H_5$	·2HCl	201–202 (dec.)	940
CH_3	H	H	C_6H_5		134	58
CH_3	H	CH_3	CH_3		108	107
					115	56
CH_3	H	CH_3	C_6H_5		124	56
CH_3	H	C_6H_5	CH_3		123–125	107
CH_3	H	C_6H_5	C_6H_5		239	107
	Diacetyl deriv.				215–216	107

TABLE III-1. (continued)

A. 4,5-Dihydro-1,2,4-triazines



R^3	R^4	R^5	R^6		m.p.(°C)	Refs.
CH_3	H	CH_2OH	C_6H_5		192	58
CH_2Cl	H	H	C_6H_5		140–145	940
·HCl					235 (dec.)	940
CH_2Cl	H	CH_2Cl	C_6H_5	·HCl	178 (dec.)	948
					189	948
$CH_2NHCH_2CH{=}CH_2$	H	H	C_6H_5	·2HCl	210 (dec.)	940
$CH_2NHCH_2CH_2OH$	H	H	C_6H_5	·2HCl	190–192 (dec.)	940
$CH_2NHCH_2C_6H_5$	H	H	C_6H_5	·2HCl	238–240	940
$CH_2N(CH_3)_2$	H	H	C_6H_5	·2HCl	232–235	940
$CH_2N(C_2H_5)_2$	H	H	C_6H_5	·2HCl	235 (dec.)	940
	H	H	C_6H_5	·2HCl	231–235	940
CH_2Cl	H	CH_2OH	C_6H_5		185 (dec.)	940
$CH_2NHCH_2CH{=}CH_2$	H	CH_2OH	C_6H_5	·2HCl	212–215 (dec.)	940
$CH_2NHCH_2CH_2OH$	H	CH_2OH	C_6H_5		202 (dec.)	940
$CH_2NHCH_2C_6H_5$	H	CH_2OH	C_6H_5	·2HCl	215 (dec.)	940
$CH_2N(CH_3)_2$	H	CH_2OH	C_6H_5	·2HCl	203 (dec.)	940
$CH_2N(C_2H_5)_2$	H	CH_2OH	C_6H_5		84–85	940
	H	CH_2OH	C_6H_5		210	940

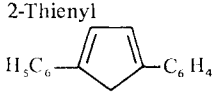
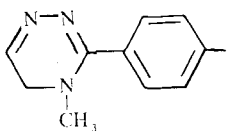
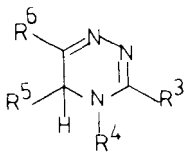
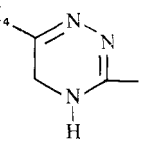
$CH_2N(CH_2CH_2OH)_2$	H	H	C_6H_5	·2HCl	182–185	948
$CH_2N(CH_2CH_2OH)_2$	H	CH_2OH	C_6H_5	·2HCl	255	948
$CH_2N(CH_2CH_2Cl)_2$	H	H	C_6H_5	·HCl	179–180	948
$CH_2N(CH_2CH_2Cl)_2$	H	CH_2OH	C_6H_5	·HCl	149 (dec.)	948
C_6H_5	H	H	C_6H_5		196	58
					195–198	52
C_6H_5	H	CH_3	CH_3		106	107
C_6H_5	H	CH_3	C_6H_5		194–195	52
C_6H_5	H	C_6H_5	CH_3		170	107
C_6H_5	H	C_6H_5	C_6H_5		237–240	122
					239	107
					249.5	108
4-CH_3O–C_6H_4	H	CH_3	C_6H_5		196–198	52
C_6H_5 ·$HClO_4$	CH_3	H	C_6H_5		130	945
					228–230	944
C_6H_5	C_6H_5	H	C_6H_5		176–178	944
C_6H_5	C_6H_5	H	4-Br–C_6H_4		220–223	944
C_6H_5	4-CH_3–C_6H_4	H	4-Br–C_6H_4		166–169	944
C_6H_5	C_6H_5	C_6H_5	C_6H_5		183	943
C_6H_5	4-CH_3O–C_6H_4	C_6H_5	C_6H_5		175	943
4-C_6H_5–C_6H_4 ·$HClO_4$	CH_3	H	C_6H_5		194–195	944
					278–280	944
4-Cl–C_6H_4	C_6H_5	C_6H_5	C_6H_5		213	943
4-CH_3O–C_6H_4	C_6H_5	C_6H_5	C_6H_5		172	943
4-O_2N–C_6H_4	C_6H_5	C_6H_5	C_6H_5		172–173	943
2-Furyl	C_6H_5	H	4-Br–C_6H_4		199–200	944
2-Thienyl	C_6H_5	H	C_6H_5		176–179	944
	C_2H_5	H	C_6H_5		177	945
	CH_3	H	C_6H_5		150	945

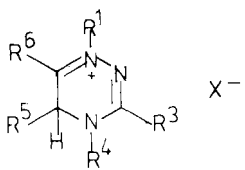
TABLE III-1. (continued)

A. 4,5-Dihydro-1,2,4-triazines



R^3	R^4	R^5	R^6	m.p.(°C)	Refs.
4-Cl–C_6H_4 	H	H	4-Cl–C_6H_4	216	978

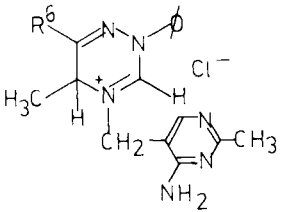
B. 1-Alkyl-4,5-dihydro-1,2,4-triazinium salts



R^1	R^3	R^4	R^5	R^6	X	m.p. (°C)	Refs.
CH_3	C_6H_5	CH_3	H	C_6H_5	ClO_4	222–224	944
	Tosylate					152–154	944
CH_3	C_6H_5	C_6H_5	H	4-Br–C_6H_4	ClO_4	236–237	944
CH_3	C_6H_5	4-CH_3–C_6H_4	H	4-Br–C_6H_4	ClO_4	126–127	944

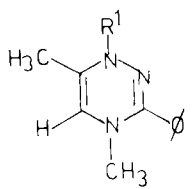
CH_3	4-C_6H_5–C_6H_4	CH_3	H	C_6H_5	ClO_4	211–213	944
CH_3	2-Thienyl	C_6H_5	H	C_6H_5	ClO_4	206–207	944
C_2H_5	4-C_6H_5–C_6H_4	CH_3	H	C_6H_5	ClO_4	283	944
	Tosylate					236–237	944

C. 2,5-Dihydro-1,2,4-triazinium salts



R^6		m.p. (°C)	Refs.
CH_3	·HCl	265–266 (dec.)	942
CH_2CH_2OH	·HCl	271 (dec.)	942

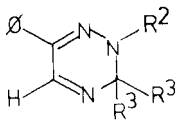
D. 1,4-Dihydro-1,2,4-triazines



R^1		m.p. (°C)	Refs.
H		120	945
CH_3	picrate	130	945

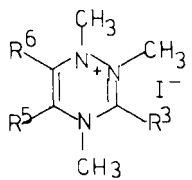
TABLE III-1. (continued)

E. 2,3-Dihydro-1,2,4-triazines



R^2	R^3	R^3		m.p. (°C)	Refs.
H	CH_2N_3	C_6H_5			73
C_6H_5	H	H		94	987
			·HCl	152	987
C_6H_5	C_6H_5	H		164	987

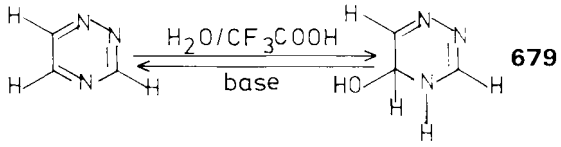
F. 1,4-Dihydro-1,2,4-triazinium salts



R^3	R^5	R^6	m.p. (°C)	Refs.
C_6H_5	C_6H_5	C_6H_5	235–237	107

B. 5-Hydroxy-4,5-dihydro-1,2,4-triazines

Addition of water to a solution of 1,2,4-triazine in trifluoroacetic acid rapidly generates a new species the amount of which is directly proportional to the amount of water added to the acid solution (14). From the PMR spectra of this species it follows that compound **679** is formed by covalent hydration of the N_4-C_5 bond. Addition of base to a solution of this compound quantitatively regenerates the 1,2,4-triazine. Attempts to isolate the hydrated species have so far failed.

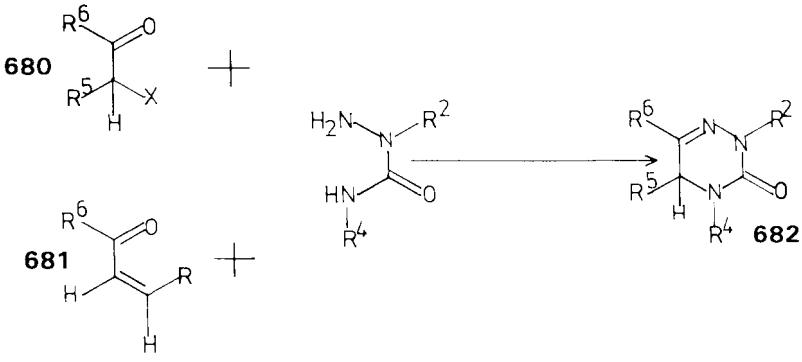


C. Dihydro-1,2,4-triazin-3-ones

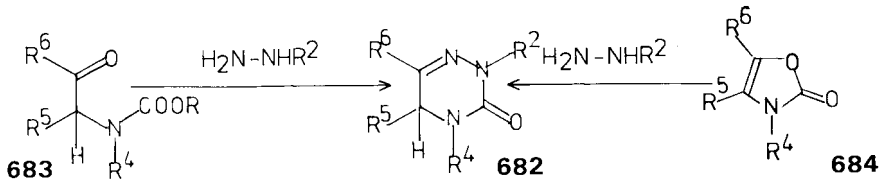
1. *Preparation*

Dihydro-1,2,4-triazin-3-ones are well-known compounds and various methods for their synthesis have been published. All synthetic methods can be classified according to two principles, synthesis by a cyclization reaction or transformation of a 1,2,4-triazine system into the dihydro derivative.

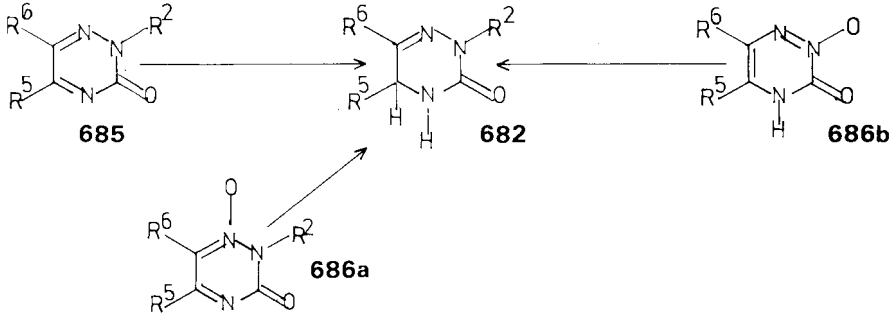
Whereas the reaction of semicarbazides with 1,2-dicarbonyl compounds is used for the synthesis of 1,2,4-triazin-3-ones, reaction of semicarbazides with α-hydroxy ketones (**680a**, X = OH) (952–955), α-methoxy ketones (**680b**, X = OCH_3) (956), α-chloro ketones (**680c**, X = Cl) (957), α-bromo ketones (**680d**, X = Br) (958, 959), α-amino ketones (**680e**, X = NH_2) (960, 1043), or α,β-unsaturated ketones (**681**) (961–965) affords dihydro-1,2,4-triazine-3-ones (**682**).



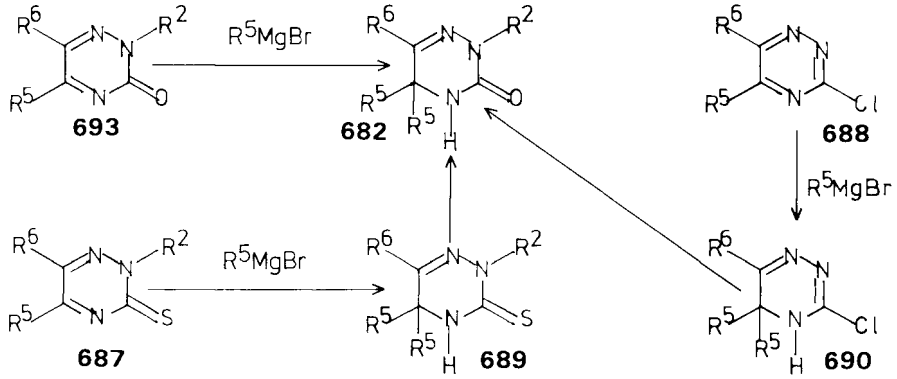
Reaction of α-ethoxycarbonylamino ketones (**683**) (966–968) or 1,3-oxazolin-2-ones (**684**) (969, 970) with hydrazine is another method used for the synthesis of dihydro-1,2,4-triazin-3-ones (**682**).



1,2,4-Triazin-3-ones (**685**) (108, 133, 136, 138, 155, 157, 159, 168, 171, 174, 176) and 1,2,4-triazin-3-one *N*-oxides (**686**) (159, 161, 917) can be reduced to dihydro-1,2,4-triazin-3-ones (**682**). The following were used as reducing agents: Raney nickel (172–174), zinc and acetic acid (136, 138, 161, 172), hydrogen and a catalyst (133, 159, 168, 171–174), lithium aluminum hydride (157, 159, 176, 917), sodium borohydride (157), *p*-toluenemercaptan (157) or electrochemical reduction (108, 155).

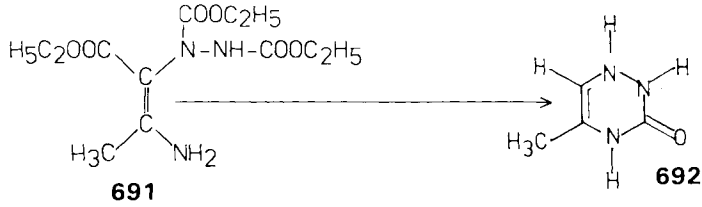


1,2,4-Triazin-3-ones (**693**) can be converted into dihydro-1,2,4-triazin-3-ones (**682**) by reaction with Grignard reagents (65, 66, 157, 168, 175, 176).



Dihydro-1,2,4-triazin-3-ones (**682**) were also isolated by the reaction of 1,2,4-triazine-3-thiones (**687**) or 3-chloro-1,2,4-triazines (**688**) (170, 175, 584) with Grignard reagents by the hydrolytic transformation of the initially formed dihydro-1,2,4-triazine-3-thiones (**689**) or 3-chlorodihydro-1,2,4-triazines (**690**).

Treatment of compound **691** with sodium hydroxide led to the isolation of a substance that is formulated as 5-methyl-1,4-dihydro-1,2,4-triazin-3-one (**692**) (911).

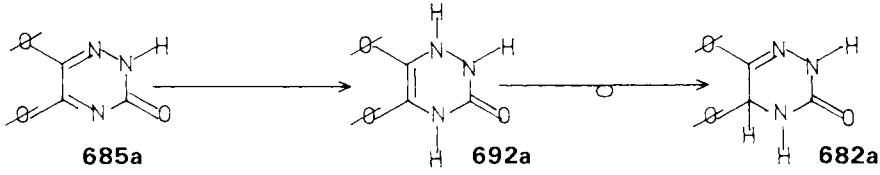


2. *Compound Survey*

Known 4,5-dihydro-1,2,4-triazin-3-ones are listed in Table III-2.

3. *Physical Properties*

4,5-Dihydro-1,2,4-triazin-3-ones are white crystalline compounds which are stable to both acids and bases. Ultraviolet, infrared, and PMR spectroscopic studies (108, 133, 159, 161, 164, 173–175, 917) have confirmed the 4,5-dihydro-1,2,4-triazin-3-one structure. Pinson, M'Packo, and Vinot (108) demonstrated that the first product of the polarographic reduction of 5,6-diphenyl-1,2,4-triazin-3-one (**685a**) is the 1,4-dihydro derivative (**692a**) which rearranges very easily to the 4,5-dihydro compound (**682a**). They were able to isolate both isomeric compounds.

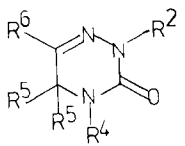


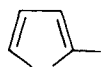
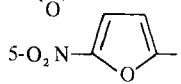
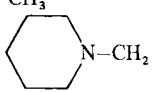
4. *Reactions*

The only published reactions of dihydro-1,2,4-triazin-3-ones (**682**) are the reduction to tetrahydro-1,2,4-triazin-3-ones (**694**) (108, 171–174) and the acylation (138, 171, 173, 174).

TABLE III-2. 4,5-DIHYDRO-1,2,4-TRIAZIN-3-ONES

A. 4,5-Dihydro-1,2,4-triazin-3(2H)-ones



R^2	R^4	R^5	R^5	R^6	m.p. (°C)	Refs.
H	H	H	H	H	135–136	159
H	H	H	H	CH_3	200–202	957
H	H	H	H	$CH_2CH_2CH{=}N{-}NHCONH_2$	222	956
H	H	H	H	C_6H_5	228	987, 988
H	H	H	H	$C_6H_5CH{=}CH$	227–228	952, 953
H	H	H	H		168.5–169.5	966, 967
H	H	H	H		244–245.5 (dec.)	212, 967
H	H	H	CH_3	$4\text{-}CH_3O{-}C_6H_4$	224	133
H	H	H		$C_6H_5CH_2CH(C_6H_5)$	136–137	960
H	H	H	C_2H_5	CH_2Br	115–117 (dec.)	958[a]
H	H	H	H	CH_3CH_2CHBr		
H	H	H	C_2H_5	$H_2NCONHNHCH_2$	229–230 (dec.)	958
H	H	H	C_2H_5	C_6H_5	216	133
H	H	H	$n\text{-}C_3H_7$	C_6H_5	196	133

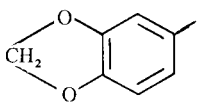
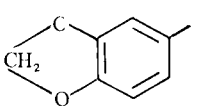
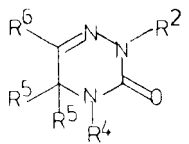
d	H	H	i-C_3H_7	CH_3	129	961, 963, 965[a]
					131	962[a]
					b.p. 212–215	965
H	H	H	C_6H_5	CH_3		168
H	H	H	C_6H_5	C_2H_5	210	133/168
H	H	H	C_6H_5	n-C_3H_7	166	133/168
H	H	H	C_6H_5	C_6H_5	275	171
					275–276	136, 138
					276	108, 172, 173, 176, 155
					278–280	161/168
H	H	H	4-CH_3O–C_6H_4	C_2H_5	174	133/168
H	H	H	4-CH_3O–C_6H_4	n-C_3H_7	147	133/168
H	H	H	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	210	157
					212–213	136, 138 168
H	H	H			285	136, 138
H	H	H	4-i-C_3H_7–C_6H_4	4-i-C_3H_7–C_6H_4	255–256	136, 138
H	H	CH_3	CH_3	C_6H_5	243	66
H	H	CH_3	C_6H_5	H	191–192	65
H	H	CH_3	C_6H_5	CH_3	246–247	65
H	H	CH_3	C_6H_5	C_2H_5	250	133/168
H	H	CH_3	C_6H_5	C_6H_5	266–267	65
					268	170, 176 584
H	H	CH_3	4-CH_3O–C_6H_4	C_2H_5	238	133/168
H	H	CH_3	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4		168
H	H	C_2H_5	C_6H_5	C_2H_5	240	133/168

TABLE III-2. (continued)

A. 4,5-Dihydro-1,2,4-triazin-3(2H)-ones



R^2	R^4	R^5	R^5	R^6	m.p.(°C)	Refs.
H	H	C_2H_5	C_6H_5	C_6H_5	278	170
					278–279	176, 584
H	H	C_2H_5	4-CH_3O–C_6H_4	C_2H_5	230	133/168
H	H	*n*-C_3H_7	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	270	157
H	H	*i*-C_3H_7	C_6H_5	H	167–168	65
H	H	*n*-C_4H_9	C_6H_5	C_6H_5	267	170, 176
						584
H	H	*n*-C_4H_9	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	253	157
H	H	$CH_2CH_2CH_2CH_2$		H	216–218	955
H	H	$CH_2CH_2CH_2CH_2CH_2$		H	221–223	954
H	H	$C_6H_5CH_2$	C_6H_5–CH_2	C_6H_5	282	66
H	H	$C_6H_5CH_2$	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	137	157
H	H	C_6H_5	C_6H_5	H	224–225	65
H	H	C_6H_5	C_6H_5	CH_3	211–212	65
H	CH_3	H	C_6H_5	C_6H_5	239–240	161
H	CH_3CO	H	C_6H_5	C_6H_5	148–149	171, 174
H	C_6H_5	H	H	C_6H_5	181	1043
H	4-CH_3–C_6H_4	H	H	C_6H_5	208	1043

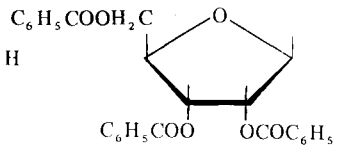
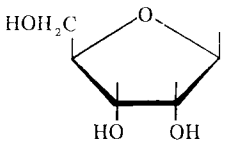
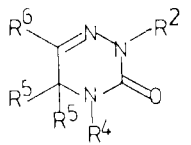
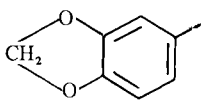
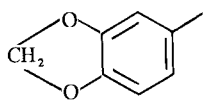
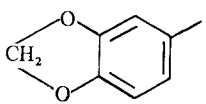
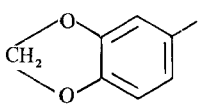
		H	H	H		Oil	159
		H	H	H		Oil	159
CH_3	H	H	C_6H_5	C_6H_5		195	108, 176
						199	172, 138
							917
CH_3	H	CH_3	C_6H_5	H		110–111	65
CH_3	H	CH_3	C_6H_5	C_6H_5		178	176
						178–179	65
CH_3	H	C_2H_5	C_6H_5	C_6H_5		172	172
CH_3	H	$C_6H_5CH_2$	C_6H_5	C_6H_5		180	176
CH_3	H	C_6H_5	C_6H_5	H		114–115	65
C_2H_5	H	H	C_6H_5	C_6H_5			176
C_2H_5	H	CH_3	C_6H_5	C_6H_5		175	176
C_2H_5	H	C_2H_5	C_6H_5	C_6H_5		150	176
CH_2CH_2N (pyrrolidine)	H	H	C_6H_5	C_6H_5			
					·HBr	207–210	172
C_6H_5	H	CH_3	C_6H_5	C_6H_5		152	176
C_6H_5	H	C_2H_5	C_6H_5	C_6H_5		160	176
CH_3CO	H	H	C_6H_5	C_6H_5		207–209	171–174
CH_3CO	CH_3CO	H	C_6H_5	C_6H_5		138	138
						140–141	173
						141	172
						142–143	171, 174

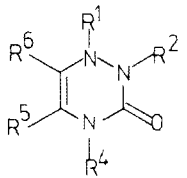
TABLE III-2. (continued)

A. 4,5-Dihydro-1,2,4-triazin-3(2H)-ones



R^2	R^4	R^5	R^5	R^6	m.p.(°C)	Refs.
CH_3CO	CH_3CO	H	4-*i*-C_3H_7–C_6H_4	4-*i*-C_3H_7–C_6H_4	123	138
CH_3CO	CH_3CO	H	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	132	138
CH_3CO	CH_3CO	H			163	138
C_6H_5CO	C_6H_5CO	H	C_6H_5	C_6H_5	188–189	138
C_6H_5CO	C_6H_5CO	H	4-*i*-C_3H_7–C_6H_4	4-*i*-C_3H_7–C_6H_4	188	138
C_6H_5CO	C_6H_5CO	H	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	194–195	138
C_6H_5CO	C_6H_5CO	H			212–213	138

B. 1,4-Dihydro-1,2,4-triazin-3(2H)-ones



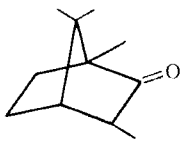
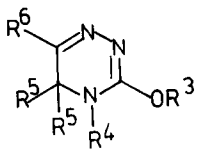
R^1	R^2	R^4	R^5	R^6	m.p. (°C)	Refs.
H	H	H	H	H	314–315	968
H	H	H	H	C_6H_5		969
H	H	H	CH_3	H	222–224	911
H	H	H	C_6H_5	C_6H_5	150	108
H	H	H	CH_3		223–224	964[a]
H	H	CH_3	H	C_6H_5		969
H	H	4-C_6H_5–C_6H_4	H	C_6H_5		969
H	H	4-O_2N–C_6H_4	H	C_6H_5		969
H	CH_3	H	C_6H_5	C_6H_5	153	108

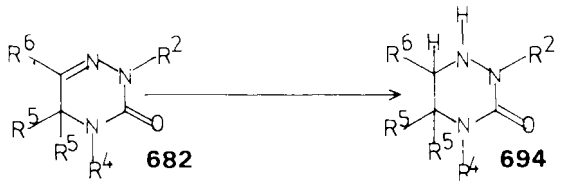
TABLE III-2. (continued)

C. 3-Hydroxy-4,5-dihydro-1,2,4-triazines



R^3	R^4	R^5	R^5	R^6	m.p. (°C)	Refs.
CH_3	H	H	CH_3	H	65–66	175
CH_3	H	H	C_6H_5	H	85–87	175
CH_3	H	H	C_6H_5	C_6H_5	160–161	171, 174
CH_3	H	CH_3	CH_3	H	40–41	175
CH_3	H	CH_3	CH_3	CH_3	62–63	175
CH_3	H	CH_3	C_6H_5	H	95–96	175
CH_3	H	CH_3	C_6H_5	CH_3	43–44	175
CH_3	H	CH_3	C_6H_5	C_6H_5	68–69	175
CH_3	H	C_6H_5	C_6H_5	H	110–112	175
CH_3	CH_3CO	H	C_6H_5	C_6H_5	123–124	171, 174
CH_2CH_2N	H	H	C_6H_5	C_6H_5	117–118	171

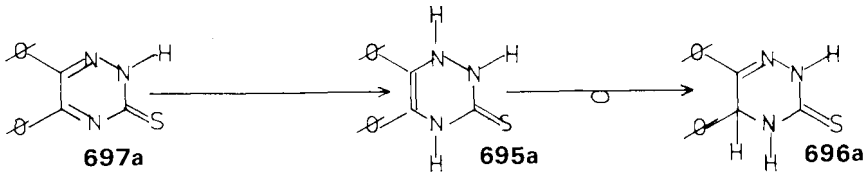
a) In original paper not formulated as dihydro-1,2,4-triazin-3(2H)one.



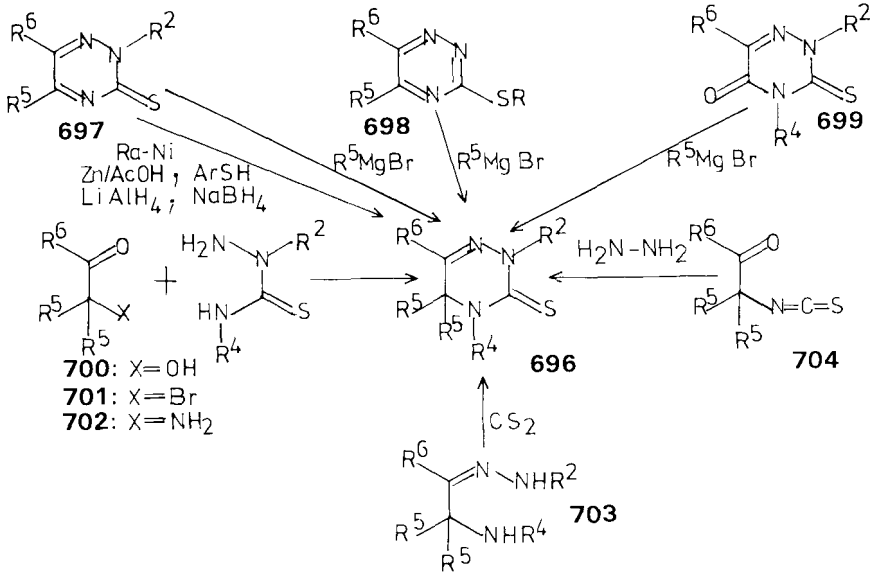
D. Dihydro-1,2,4-triazine-3-thiones

1. *Preparation*

In the literature the dihydro-1,2,4-triazine-3-thiones are formulated either as 1,4-dihydro- (**695**) or 4,5-dihydro compounds (**696**). Since it was shown for the dihydro-1,2,4-triazin-3-ones that the 4,5-dihydro structure is the most likely one and since Pinson and his group (108) have shown that the 5,6-diphenyl-1,4-dihydro-1,2,4-triazine-3-thione (**695a**) (m.p. 210°C), which is formed by polarographic reduction of 5,6-diphenyl-1,2,4-triazine-3-thione (**697a**), rearranges to the 4,5-dihydro derivative (**696a**), we use the 4,5-dihydro structure (**696**) for all dihydro-1,2,4-triazine-3-thiones and note those compounds in Table III-3 which were formulated in the literature as 1,4-dihydro-1,2,4-triazine-3-thiones (514, 927).



The well-known dihydro-1,2,4-triazine-3-thiones (**696**) can be prepared by various methods; reaction of Grignard compounds with 1,2,4-triazine-3-thiones (**697**) (133, 168), mercapto-1,2,4-triazines (**698**) (175, 584), or 3-thioxo-1,2,4-triazine-5-ones (**699**) (584); reduction of 1,2,4-triazine-3-thiones (**697**) with Raney nickel (108, 168), zinc/acetic acid (588), *p*-toluene mercaptan (157, 584), lithium aluminum hydride (157), or sodium borohydride (157), or electrochemically (108); reaction of α-hydroxy ketones (**700**) (570), α-bromo ketones (**701**) (994), α-amino ketones (**702**) (971) with thiosemicarbazides; cyclization of α-aminohydrazones (**703**) with carbon disulfide (990); or reaction of α-acylisothiocyanates (**704**) with hydrazine (158, 972, 990).



2. *Compound Survey*

The dihydro-1,2,4-triazine-3-thiones reported in the literature are listed in Table III-3.

3. *Physical Properties*

4,5-Dihydro-1,2,4-triazine-3-thiones are stable colorless compounds and the 5,6-diphenyl-1,4-dihydro-1,2,4-triazine-3-thione is yellow. The few published spectroscopic data (108, 133, 175) show that the 4,5-dihydro structure should be the more stable and predominant form.

4. *Reactions*

The only reported reaction of dihydro-1,2,4-triazine-3-thiones is their reduction to tetrahydro-1,2,4-triazine-3-thiones (108).

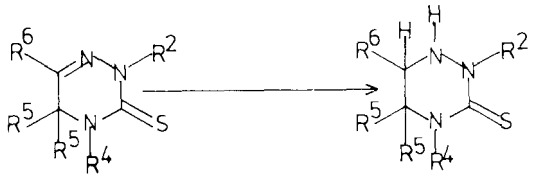
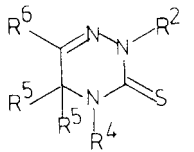


TABLE III-3. DIHYDRO-1,2,4-TRIAZINE-3-THIONES

A. 4,5-Dihydro-1,2,4-triazin-3(2H)-ones



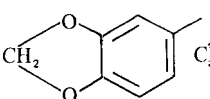
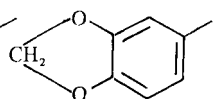
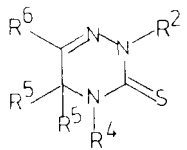
R^2	R^4	R^5	R^5	R^6		m.p. (°C)	Refs.
H	H	H	H	H		200–202	158
H	H	H	*i*-C_3H_7	H	·H_2O	180–190	971
H	H	H	*i*-C_4H_9	H		90–91	971
H	H	H	$C_6H_5CH_2$	H	·H_2O	208–210	971
H	H	H	C_6H_5	C_6H_5		222	108
						222–223	570
						223	584
							168, 972
H	H	H	2-CH_3O–C_6H_4	2-CH_3O–C_6H_4		252	570/972
H	H	H	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4		160	570
						166	157/972
H	H	H				222	570
H	H	CH_3	CH_3	H		Oil	994
Picrate						228–229	994
H	H	CH_3	C_6H_5	C_6H_5		217	584
						219	133
							168
H	H	C_2H_5	C_6H_5	C_6H_5		230	584
						231	133/168

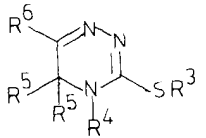
TABLE III-3. (continued)

A. 4,5-Dihydro-1,2,4-triazin-3(2H)-ones



R^2	R^4	R^5	R^5	R^6	m.p.(°C)	Refs.
H	H	n-C_4H_9	C_6H_5	C_6H_5	205	584
H	H	i-C_4H_9	C_6H_5	C_6H_5		168
H	H	n-C_5H_{11}	C_6H_5	C_6H_5	185	584
H	H	$C_6H_5CH_2$	C_6H_5	C_6H_5	208	584
H	H	C_6H_5	C_6H_5	C_6H_5	288 (dec.)	584
C_6H_5	H	H	CH_3	CH_3	202[a]	972
					210–220[a]	990
C_6H_5	H	H	CH_3	C_6H_5	230[a]	990
C_6H_5	H	H	$CH_2CH_2CH_2CH_2$		220[a]	990
4-Cl–C_6H_4	H	H	CH_3	CH_3	218–219[a]	990, 972
4-O_2N–C_6H_4	H	H	CH_3	CH_3	251[a]	990, 972
3-HOOC–C_6H_4	H	H	CH_3	CH_3	260 (dec.)[a]	990
4-HOOC–C_6H_4	H	H	CH_3	CH_3	256–257[a]	990
2-Cl-4-HO_3S–C_6H_3	H	H	CH_3	CH_3	260[a]	990
4-NaO_3S–C_6H_4	H	H	CH_3	CH_3	260[a]	990
2,5-$(NaO_3S)_2C_6H_3$	H	H	CH_3	CH_3	260[a]	990

B. 3-Mercapto-4,5-dihydro-1,2,4-triazines



R^3	R^4	R^5	R^5	R^6	m.p. (°C)	Refs.
CH_3	H	H	CH_3	H	75–76	175
CH_3	H	H	CH_3	CH_3	Oil	175
CH_3	H	H	C_6H_5	H	95–96	175
CH_3	H	H	C_6H_5	CH_3	Oil	175
CH_3	H	H	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	165	175
CH_3	H	CH_3	CH_3	H	92–93	175
CH_3	H	CH_3	CH_3	CH_3	85–86	175
CH_3	H	CH_3	CH_3	C_6H_5	92–93	175
CH_3	H	CH_3	C_6H_5	H	50–51	175
CH_3	H	CH_3	C_6H_5	CH_3	68–69	175
CH_3	H	CH_3	C_6H_5	C_6H_5	120	584
					121–122	175
CH_3	H	C_6H_5	C_6H_5	H	102–103	175

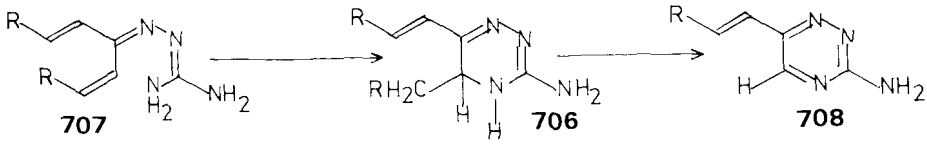
[a]Formulated in the original paper as 1,4-dihydro derivatives.

E. 3-Aminodihydro-1,2,4-triazines

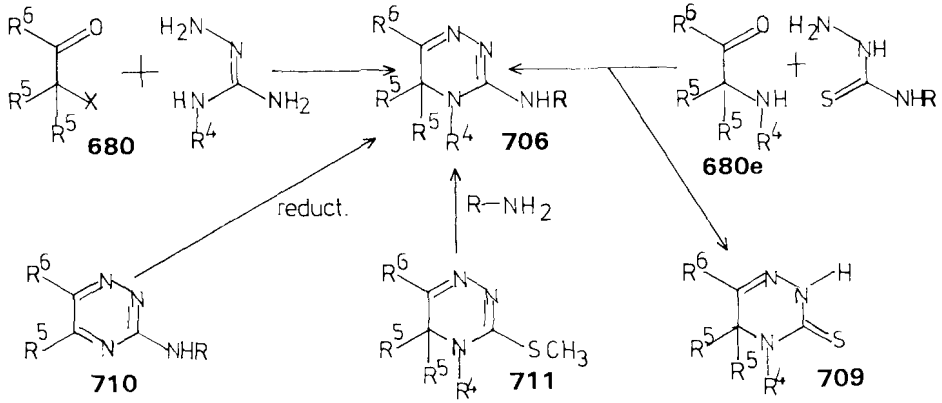
1. *Preparation*

With one exception (978) all 3-amino-dihydro-1,2,4-triazines are formulated as the 4,5-dihydro derivatives (**706**) if they can exist in this structure. Therefore in this discussion we always use the 4,5-dihydro structure for these compounds.

3-Amino-4,5-dihydro-1,2,4-triazines (**706**) were formed as the first reaction product from 1,4-pentadien-3-one guanylhydrazones (**707**) by heating in butanol or dimethylformamide (636, 640, 641, 647, 973, 974). **706** can be transformed into 3-amino-1,2,4-triazines (**708**) by treatment with base.

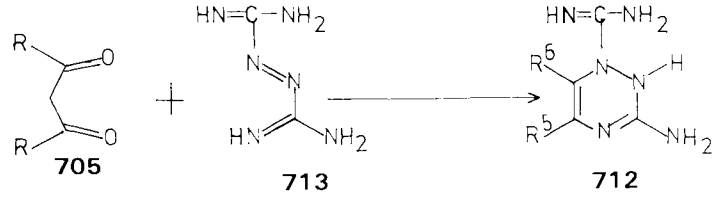


Reaction of aminoguanidine with α-chloro- (**680c**, X = Cl) (977) or α-bromo ketones (**680d**, X = Br) (978, 994) is another method for the synthesis of **706**. *Reaction of α-amino ketones* (**680e**) *with thiosemicarbazide* gave a mixture of 3-amino-4,5-dihydro-1,2,4-triazines (**706**) and 4,5-dihydro-1,2,4-triazine-3-thiones (**709**) (971). The synthesis of **706** through reduction of 3-amino-1,2,4-triazines (**710**) is reported by Mansour and his co-worker (157). The same authors reported the synthesis of **706** by substitution of the 3-methylmercapto group in 3-(methylmercapto)-4,5-dihydro-1,2,4-triazines (**711**) by aniline (157).



The formation of 1-guanyl-substituted 3-amino-1,2-dihydro-1,2,4-triazines (**712**) [R^5 = H, R^6 = HCO, · HNO_3 · H_2O, m.p. 149 to 150°C (dec); R^5 = CH_3, R_6 = CH_3CO, · HNO_3, m.p. 225 to 227°C (dec.)] was observed by

Kreutzberger and Schücker (975, 976) in the reaction of 1,3-dicarbonyl compounds **705** with azodicarboxamidine (**713**).



2. *Compound Survey*

Table III-4 lists the 3-amino-4,5-dihydro-1,2,4-triazines reported in the literature.

3. *Physical Properties and Reactions*

3-Amino-4,5-dihydro-1,2,4-triazines are stable, crystalline colorless or yellow compounds. The two 3-amino-1,2-dihydro-1,2,4-triazines are crystalline colorless compounds. Most 3-amino-4,5-dihydro-1,2,4-triazines show three absorption maxima in the ultraviolet spectra in the following absorption regions, 230 to 235, 305 to 317, and 370 to 380 nm (636, 973). The infrared spectra of a few derivatives were published by two groups (636, 973). 3-Amino-4,5-dihydro-1,2,4-trazines can be oxidized to 3-amino-1,2,4-triazines (636, 640, 641, 646, 658) and can be acylated (636, 973).

F. 6-Amino-1,2-dihydro-1,2,4-triazines

A compound formulated as 6-amino-3-benzyl-1,2-dihydro-1,2,4-triazine (**715**) was obtained by Jacquier and his group (1102) through reaction of ethyl *N*-(cyanomethyl)phenylacetimidate (**716**) with hydrazine.

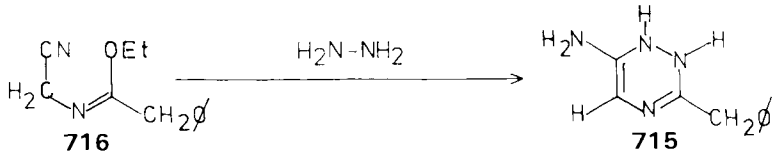
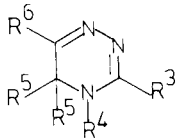
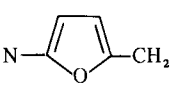
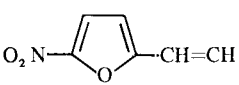
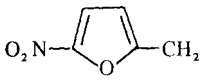
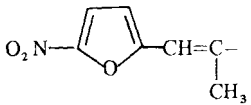
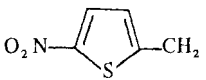
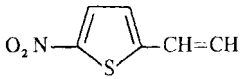
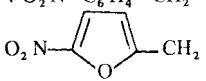
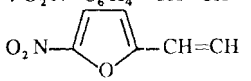


TABLE III-4. 3-AMINO-4,5-DIHYDRO-1,2,4-TRIAZINES

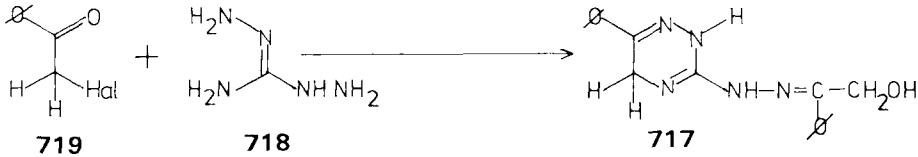


R^3		R^4	R^5	R^5	R^6		m.p. (°C)	Refs.
NH_2		H	H	H	CH_3		244 (dec.)	978
	Picrate						280 (dec.)	978
	·HCl						243–245 (dec.)	977
NH_2		H	H	H	i-C_3H_7	·HCl	265–267 (dec.)	977
NH_2		H	H	CH_3	H	·HCl·$4H_2O$	135–137	971
NH_2		H	H	CH_3	CH_3		231–233	994
NH_2		H	H	i-C_3H_7	H	·HCl	143–145	971
NH_2		H	H	i-C_4H_9	H	·HCl	185–187	971
NH_2		H	H	4-O_2N–C_6H_4–CH_2	4-O_2N–C_6H_4–CH=CH		170–173	973
	·HCl						144	647
NH_2		H	H			α-Form	175–178 (dec.)	974
							178–180 (dec.)	973

					β-Form	112–114 (dec.)	974
						114–115 (dec.)	973
	·HCl					244–246 (dec.)	974, 636
						245 (dec.)	973, 974
						247 (dec.)	973
	$\cdot H_2SO_4$					239 (dec.)	974
	$\cdot H_2Cr_2O_7$					190 (dec.)	973
NH_2	H	H			·HCl·H_2O	118–120 (dec.)	973
	$\cdot H_2Cr_2O_7$					85–90	973
NH_2	H	H				195–200 (dec.)	647, 973
$NHCH_3$	H	H	H	CH_3	·HCl	238–240 (dec.)	977
NHC_6H_5	H	H	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4		190	157
$NHCOCH_3$	CH_3CO	H	4-O_2N–C_6H_4–CH_2	4-O_2N–C_6H_4–CH=CH		202–205	973
$NHCOCH_3$	CH_3CO	H				209–210	973
						215	636

G. 3-Hydrazino-2,5-dihydro-1,2,4-triazines

Beyer and his group (978) obtained the 3-hydrazino-2,5-dihydro-1,2,4-triazine derivative (**717**) (m.p. 174 to 175°C) by reaction of diaminoguanidine (**718**) with phenacyl halides (**719**). No spectroscopic details were given to confirm the 2,5-dihydro structure.

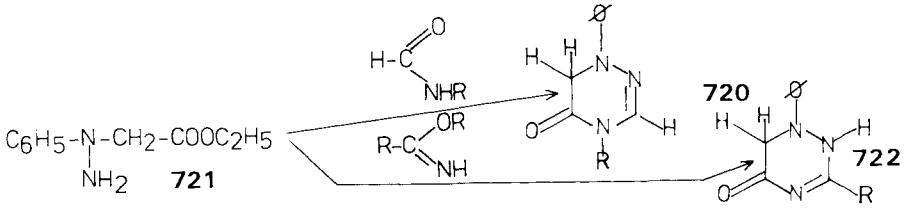


719 **718** **717**

H. Dihydro-1,2,4-triazin-5-ones

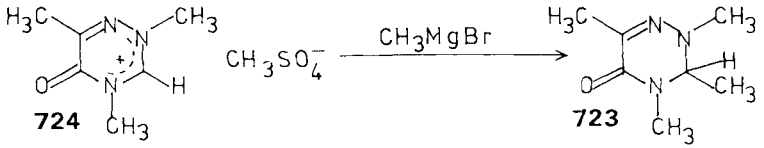
1. *Preparation*

The synthesis of dihydro-1,2,4-triazin-5-ones is reported in four papers (191, 979, 980, 1077). Harries (979) obtained 1,6-dihydro-1,2,4-triazin-5(4*H*)-ones (**720**) by reaction of ethyl (1-phenylhydrazino)acetate (**721**) with formamides whereas Ried and Czack (980) preferred the 1,6-dihydro-1,2,4-triazine-5(2*H*)-one structure (**722**) for the compounds isolated from the reaction of **721** with imidates.



721 **720** **722**

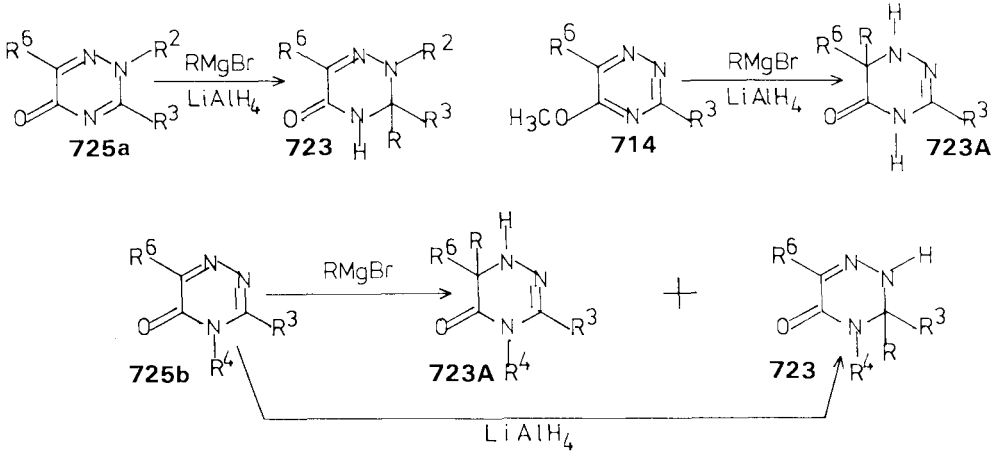
Daunis observed the formation of 2,3,4,6-tetramethyl-3,4-dihydro-1,2,4-triazin-5-one (**723**) (oil) by reaction of compound **724** with methylmagnesium bromide (191).



724 **723**

Daunis and Jacquier (1077) studied the reaction of 1,2,4-triazin-5(2*H*)-ones (**725a**), 1,2,4-triazin-5(4*H*)-ones (**725b**), and 5-methoxy-1,2,4-

triazines (**714**) with Grignard reagents as well as their reduction with lithium aluminum hydride and isolated 3,4-dihydro- (**723**) and/or 1,6-dihydro-1,2,4-triazin-5-ones (**723A**).



2. *Compound Survey*

Table III-5 lists the dihydro-1,2,4-triazin-5-ones reported in the literature.

5-Methoxy-3,6-dimethyl-2,3-dihydro-1,2,4-triazine is an oil (1077).

Oxidation of dihydro-1,2,4-triazin-5-ones with bromine affords 1,2,4-triazin-5-ones (1077).

I. Dihydro-1,2,4-triazin-6-ones

Three methods have been reported for the synthesis of dihydro-1,2,4-triazin-6-ones (981–984). Widman (981) obtained 1,4-diphenyl-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (**726a**) ($R^3 = R^5 = H$, $R^1 = R^4 = \emptyset$) by reaction of 1-(*N*-phenylglycyl)phenylhydrazine (**727**) with formic acid. Kjaer (982) synthesized 4,5-dihydro-1,2,4-triazin-6-ones (**726**) by cyclization of α-(ethoxybenzylidenamino)carboxylates (**728**) with hydrazine.

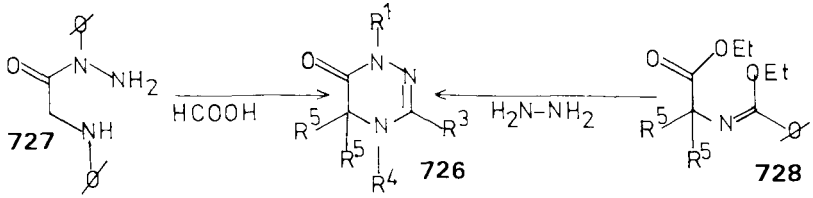
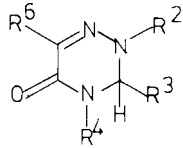


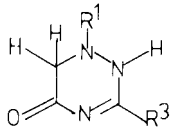
TABLE III-5. DIHYDRO-1,2,4-TRIAZIN-5-ONES

A. 3,4-Dihydro-1,2,4-triazin-5(2H)-ones



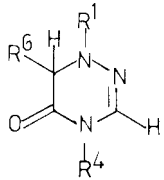
R^2	R^3	R^4	R^6	m.p. (°C)	Refs.
H	H	CH_3	CH_3	Oil	1077
H	CH_3	CH_3	CH_3	Oil	1077
H	C_6H_5	CH_3	CH_3	194–195	1077
CH_3	H	H	CH_3	109–110	1077
CH_3	H	CH_3	CH_3	Oil	1077
CH_3	CH_3	H	CH_3	107–108	1077
CH_3	CH_3	CH_3	CH_3	Oil	191
CH_3	C_6H_5	H	CH_3	125–126	1077

B. 1,6-Dihydro-1,2,4-triazin-5(2H)-ones



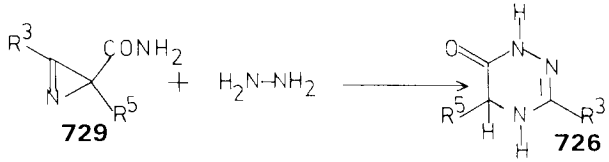
R^1	R^3	m.p. (°C)	Refs.
C_6H_5	CH_3	181–183	980
C_6H_5	C_6H_5	240–241	980
C_6H_5	$C_6H_5-CH_2$	192	980

C. 1,6-Dihydro-1,2,4-triazin-5(4H)-ones



R^1	R^4	R^6	m.p. (°C)	Refs.
H	H	CH_3	109–110	1077
H	CH_3	CH_3	87–88	1077
C_6H_5	H	H	204–205 (dec.)	979
C_6H_5	CH_3	H	179–180	979
C_6H_5	C_6H_5	H	204–205	979

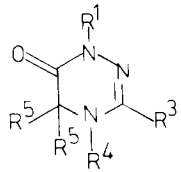
Nishiwaki and Saito (983, 984) used the reaction of azirine-3-carboxamides (**729**) with a second substituent in the 3-position with hydrazine for the synthesis of **726**. They have shown by ultraviolet, infrared, PMR and mass spectral data that the given, 4,5-dihydro structure is the preferred one; therefore we give the 4,5-dihydro structure for all dihydro-1,2,4-triazin-6-ones in Table III-6.



729 **726**

Ohta has shown (985) that the synthesis of dihydro-1,2,4-triazin-6-ones from *N*-(acylamino)carboxylic acids and phenylhydrazine, claimed by Sen (986) is incorrect.

TABLE III-6. 4,5-DIHYDRO-1,2,4-TRIAZIN-6(1*H*)-ONES

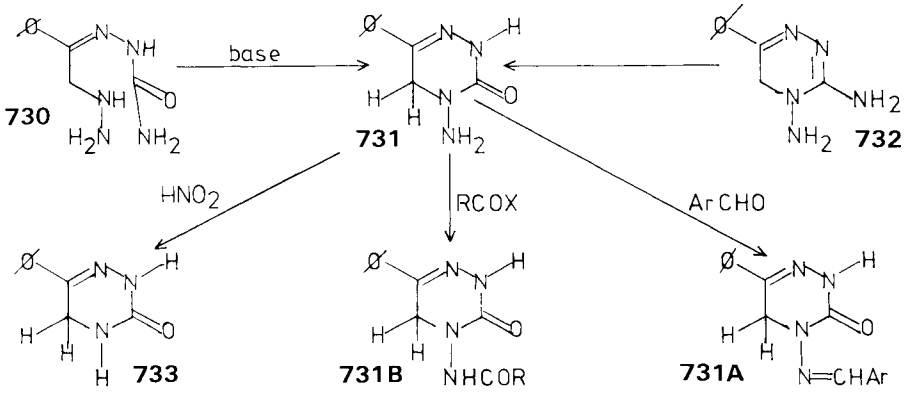


R^1	R^3	R^4	R^5	R^5	m.p. (°C)	Refs.
H	C_6H_5–CH_2	H	H	H	184–186	982
H	C_6H_5–CH_2	H	H	CH_3	189–190	982
H	C_6H_5–CH_2	H	H	$CH_2CONHNH_2$	197–198	982
H	C_6H_5–CH_2	H	H	CH_2CONH–N=CHC_6H_5	200 (dec.)	982
H	C_6H_5–CH_2	H	H	$C_6H_5CH_2$	171	982
H	C_6H_5	H	H	C_6H_5	203–204	983, 984
H	4-Cl–C_6H_4	H	H	C_6H_5	231–232	983, 984
H	4-CH_3–C_6H_4	H	H	C_6H_5	246–248	983
C_6H_5	H	C_6H_5	H	H	173–174	981
C_6H_5	C_6H_5	H	H	C_6H_5	228–229	983

J. 4-Aminodihydro-1,2,4-triazin-3-ones

Phenacylhydrazine semicarbazone (**730**) was converted into 4-amino-6-phenyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (**731**) by treatment with base (987).

The same compound was isolated through hydrolysis of 3,4-diamino-6-phenyl-4,5-dihydro-1,2,4-triazine (**732**) (988, 989). Reaction with benzaldehyde (987) or *p*-nitrobenzaldehyde (988) gives the benzylidene compounds (**731A**). The amino-group can be acylated (988) and is removed by reaction with nitrous acid (987), yielding **731B** and **733**, respectively.



Reaction of phenacylhydrazine phenylhydrazone (**734**) with phosgene affords the 4-(benzylidenamino)-2,6-diphenyl-4,5-dihydro-1,2,4-triazin-3-one (**731a**) (987).

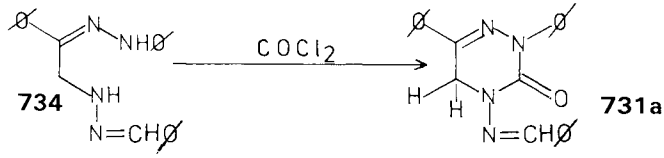
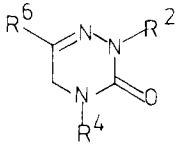


TABLE III-7. 4-AMINO-4,5-DIHYDRO-1,2,4-TRIAZIN-3(2*H*)-ONES

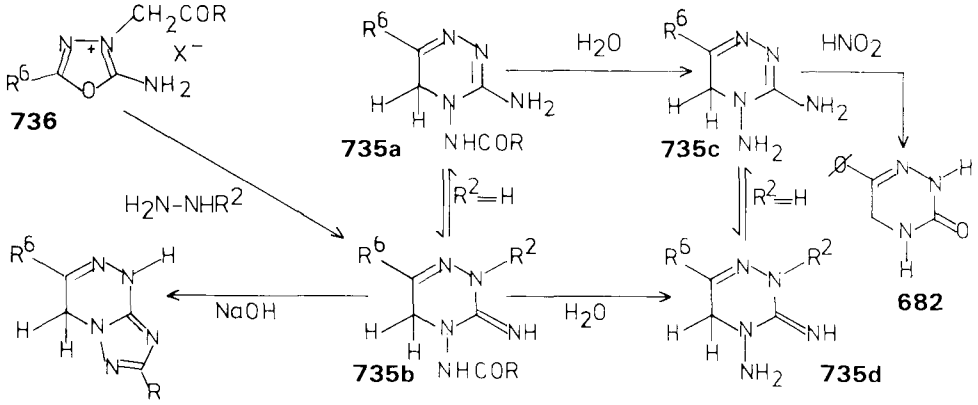


R^2	R^4	R^6	m.p. (°C)	Refs.
H	NH_2	C_6H_5	200	987, 988
	·HCl		180	987
H	$NHCOCH_3$	C_6H_5	204–206	988, 989
H	$N{=}CHC_6H_5$	C_6H_5	203	987
H	$N{=}CHC_6H_4{-}NO_2$(p)	C_6H_5	242	988
C_6H_5	$N{=}CHC_6H_5$	C_6H_5	199	987

K. 3,4-Diamino-4,5-dihydro-1,2,4-triazines

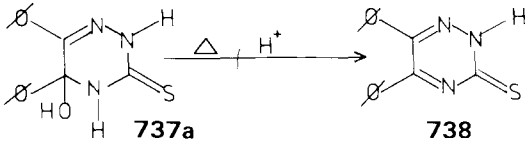
3-Amino-4-(acylamino)-4,5-dihydro-1,2,4-triazines (**735a**) or their 3-imino tautomers (**735b**) were prepared by reaction of 2-amino-3-phenacyloxadiazolium bromides (**736**) with hydrazine or alkylhydrazines (988, 989). Depending on the reaction conditions, the acyl group, the 3-amino group, or both groups can be hydrolyzed. The 4-amino group reacts with *p*-nitrobenzaldehyde and acetyl chloride. Reaction of **735c** (R^2 = H, R^6 = Ø) with nitrous acid gave 6-phenyl-4,5-dihydro-1,2,4-triazin-3-one (**682**) (988, 989). Treatment of **735** with base was used for the synthesis of 1,2,4-triazolo[5,1-*c*]1,2,4-triazines (988).

Until now no information has been given as to which of the two tautomeric structures **735a/c** and **735b/d** is the predominant one.



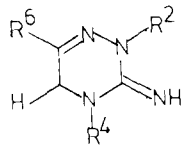
L. 5-Hydroxy-4,5-dihydro-1,2,4-triazin-3-ones and 5-Hydroxy-4,5-dihydro-1,2,4-triazine-3-thiones

Tomtschin and his group (580) have shown that the benzil thiosemicarbazone is in fact the 5-hydroxy-5,6-diphenyl-4,5-dihydro-1,2,4-triazine-3-thione (**737a**), which forms the 5,6-diphenyl-1,2,4-triazine-3-thione (**738**) by heating or treatment with acids. The Russian authors observed the formation of a 5-hydroxy-4,5-dihydro-1,2,4-triazine-3-thione (**737**) from no other thiosemicarbazone.



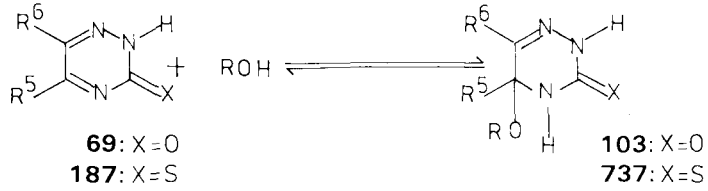
Covalent addition of alcohols to the N_4C_5-bond of 1,2,4-triazin-3-ones (**69**) and 1,2,4-triazine-3-thiones (**187**), leading to **103** and **737**, respectively, is

TABLE III-8. 4-AMINO-3-IMINO-4,5-DIHYDRO-1,2,4-TRIAZINES



R^2	R^4	R^6		m.p. (°C)	Refs.
H	NH_2	C_6H_5		194 (dec.)	988, 989
·HCl				224–225 (dec.)	988, 989
H	NH_2	4-CH_3–C_6H_4		205–206 (dec.)	988
·HCl				231–232 (dec.)	988, 989
H	NH_2	4-CH_3O–C_6H_4		204–205 (dec.)	988
·HCl				223–224 (dec.)	988, 989
H	NHCHO	C_6H_5		221–223 (dec.)	988
H	$NHCOCH_3$	C_6H_5		140 (dec.)	989
·HCl				241–242 (dec.)	988, 989
H	$NHCOCH_3$	4-CH_3–C_6H_4	·HCl	232–233 (dec.)	988, 989
H	$NHCOCH_3$	4-CH_3O–C_6H_4	·HCl	224–225 (dec.)	988, 989
H	$NHCOC_2H_5$	C_6H_5	·HCl	235–236 (dec.)	988, 989
H	$NHCOC_2H_5$	4-CH_3–C_6H_4	·HCl	248–250 (dec.)	988
H	$NHCOCH_2C_6H_5$	C_6H_5	·HCl	220–221 (dec.)	988, 989
H	$NHCOC_6H_5$	C_6H_5	·HCl	254–255 (dec.)	988, 989
H	N=CHC_6H_4–NO_2(*p*)	C_6H_5	·HCl	239–240 (dec.)	988
CH_3	$NHCOCH_3$	C_6H_5	·HCl	254–256 (dec.)	988, 989
CH_3	$NHCOCH_3$	4-CH_3–C_6H_4	·HCl	284–286 (dec.)	988
CH_3	$NHCOCH_3$	4-Cl–C_6H_4	·HCl	274–275 (dec.)	988
CH_3	$NHCOC_2H_5$	C_6H_5	·HCl	277–278 (dec.)	988
CH_3	$NHCOCH_2C_6H_5$	C_6H_5	·HCl	274–276 (dec.)	988
CH_3	$NHCOC_6H_5$	C_6H_5	·HCl	280–281 (dec.)	988
CH_3	$NHCOC_6H_5$	4-CH_3O–C_6H_4	·HCl	275–277 (dec.)	988
$C_6H_5CH_2$	$NHCOCH_3$	C_6H_5	·HCl	238–240 (dec.)	988

reported by various groups (51, 130, 133, 168). The compounds formed are listed in Tables II-5, part F, and II-12, part F.

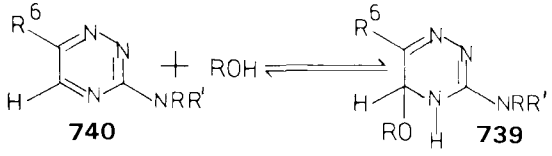


69: X=O
187: X=S

103: X=O
737: X=S

M. 3-Amino-5-hydroxy-4,5-dihydro-1,2,4-triazines

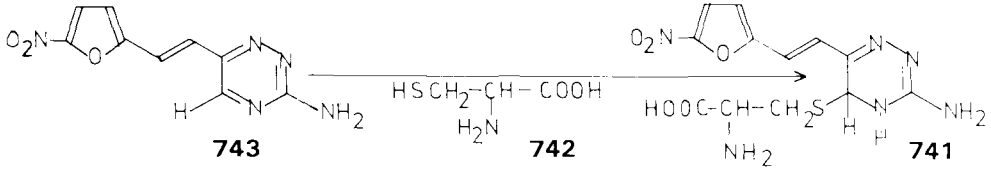
3-Amino-5-hydroxy-4,5-dihydro-1,2,4-triazines (**739**) (Table III-9) are the reaction products of covalent addition of water or alcohols to the N_4C_5 bond of 3-amino-1,2,4-triazines (**740**) (640–642, 693). The addition is catalyzed by acids.



740 **739**

N. 3-Amino-5-mercapto-4,5-dihydro-1,2,4-triazines

Only one compound of this class has so far been reported, the covalent addition product (**741**) (m.p. 300°C) of cystein (**742**) to the N_4C_5 double bond of 3-amino-6-[(5-nitrofuryl)vinyl]-1,2,4-triazine (**743**) (692).

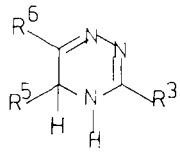


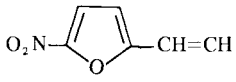
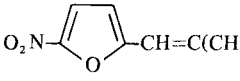
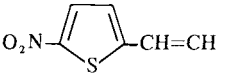
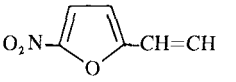
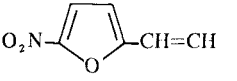
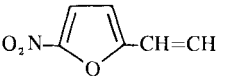
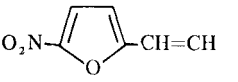
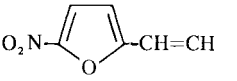
743 **742** **741**

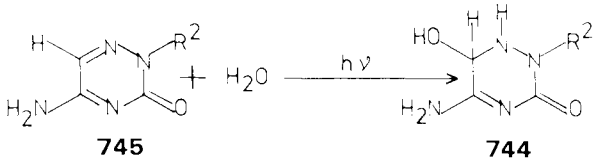
O. 5-Amino-6-hydroxy-1,6-dihydro-1,2,4-triazin-3-ones

Kittler (1092) obtained 5-amino-6-hydroxy-1,6-dihydro-1,2,4-triazin-3-ones (**744**) through photochemical addition of water to 5-amino-1,2,4-triazin-3-ones (**745**).

TABLE III-9. 3-AMINO-5-HYDROXY-4,5-DIHYDRO-1,2,4-TRIAZINES



R^3	R^5	R^6		m.p. (°C)	Refs.
NH_2	OH			269 (dec.)	642
	$\cdot HOCH_2CH_2OCH_3$			269	642
	$\cdot HCl$			235–239	642
	$\cdot HCl \cdot H_2O$			239 (dec.)	641
	$\cdot HBr$			205	642
	$\cdot HBr \cdot H_2O$			200 (dec.)	641
	$\cdot H_2SO_4$			177–178	642
	$\cdot HNO_3$			163–164	642
	$\cdot H_3PO_4$			174	642
	Acetate			>300	642
	Oxalate			212	642
	Malonate			271	642
	Maleate			274	642
	Cyclohexylsulfamate			132–134	642
	Saccharinate			208	642
NH_2	OH		$\cdot HCl$	244	640
NH_2	OH		$\cdot HCl$	256	640
NH_2	OCH_3		$\cdot HCl$	241 (dec.)	693
	$\cdot HBr$			168 (dec.)	641, 693
	$\cdot HNO_3$			156 (dec.)	693
	Oxalate			153 (dec.)	693
NH_2	OC_2H_5		$\cdot HCl$	245 (dec.)	693
	$\cdot HBr$			171 (dec.)	641
				175 (dec.)	693
NH_2	O–*i*-C_3H_7		$\cdot HBr$	225 (dec.)	693
NH_2	$OCH_2CH{=}CH_2$		$\cdot HBr$	179 (dec.)	693
NH_2	O–*n*-C_4H_9		$\cdot HBr$	191 (dec.)	693

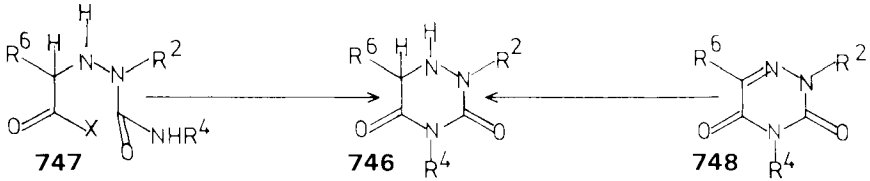


745 744

P. 1,6-Dihydro-1,2,4-triazine-3,5-diones

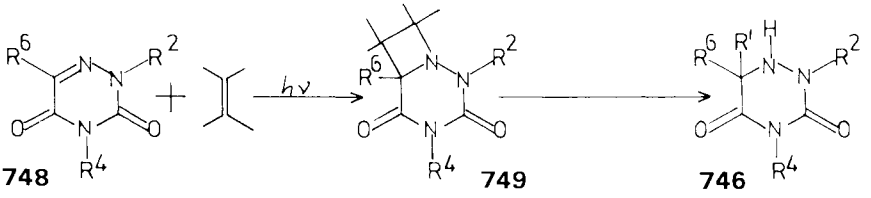
1. *Preparation*

Although while 1,2,4-triazine-3,5-diones were obtained from semicarbazones of α-ketocarboxylic acid derivatives 1,6-dihydro-1,2,4-triazine-3,5-diones (**746**) can be prepared by cyclization of α-semicarbazido carboxylic acid derivatives (**747**) (204, 215, 340, 341, 441, 991–993, 995, 996).



747 746 748

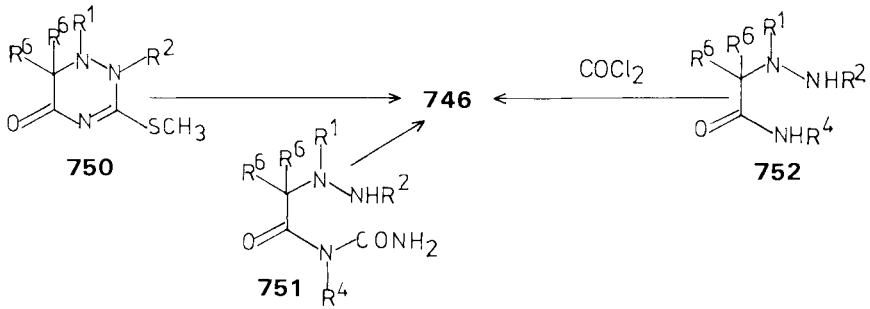
Reduction of 1,2,4-triazine-3,5-diones (**748**) has also been used for the synthesis of 1,6-dihydro-1,2,4-triazine-3,5-diones (**746**) (290, 419–422, 441). Another method for the synthesis of **746** from **748** was reported by Swenton and his group (338, 339, 508, 509). Photochemical addition of olefins to the C_6N_1 bond in **748** affords the bicyclic compounds **749** which can be transformed into **746** by hydrolytic ring opening.



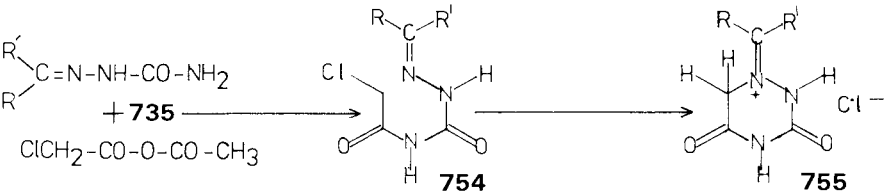
748 749 746

Reactions that were reported only once for the synthesis of **746** are the hydrolysis of 3-(methylmercapto)-1,6-dihydro-1,2,4-triazin-5-ones (**750**) (994), cyclization of a α-hydrazinoureide (**751**) (999), and reaction of α-hydrazinocarboxamides (**752**) with phosgene (998).

Treatment of semicarbazones of aliphatic aldehydes or ketones (**753**) with the mixed anhydride of acetic acid and chloroacetic acid gives the intermediates **754** which cyclize to the 1,2,4-triazinium salts **755** (1000) (H, CH_3, m.p. 128 to



130°C; CH_3, CH_3, 142 to 144°C; CH_3, C_2H_5, 149 to 150°C; $-(CH_2)_5-$, 131 to 133°C).



2. *Compound Survey*

Table III-10 lists the known 1,6-dihydro-1,2,4-triazine-3,5-diones,

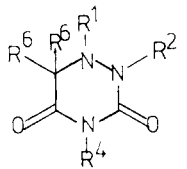
3. *Physical Properties*

1,6-Dihydro-1,2,4-triazine-3,5-diones seem to be colorless crystalline compounds. p*K* Values are reported for the unsubstituted (10.3), the 2-methyl (10.6), and the 4-methyl (>11) derivatives (290, 393). Infrared spectra of 1,6-dihydro-1,2,4-triazine-3,5-diones were published in three papers (339, 352, 564). The unsubstituted compound in chloroform shows two bands in the N–H region (3439, 3394 cm^{-1}) and two bands in the C = O region (1740, 1722 cm^{-1}) (564). Some PMR data have also been reported (339, 441). The 2-methyl-1,6-dihydro-1,2,4-triazine-3,5-dione shows the following signals in DMSO-D_6; −0.36τ (H_4), 0.90τ (H_2), 6.52τ (CH_2), and 7.45τ (CH_3) (441).

4. *Reactions*

Only a few reactions of 1,6-dihydro-1,2,4-triazine-3,5-diones (**746**) have so far been reported (338–341, 419, 423, 564, 991, 994, 1001). Oxidation of **746**

TABLE III-10. 1,6-DIHYDRO-1,2,4-TRIAZINE-3,5-DIONES



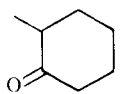
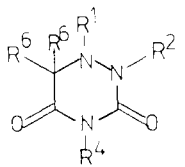
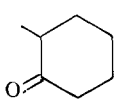
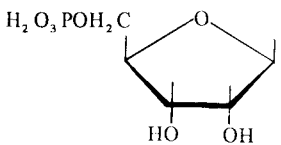
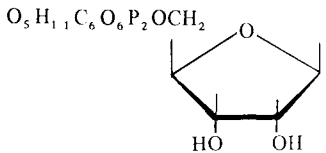
R^1	R^2	R^4	R^6	R^6	m.p. (°C)	Refs.
H	H	H	H	H	210	240
					220–222	290
					225	992, 341
H	H	H	H	CH_3	214	340, 991
					214–215	290
H	H	H	H	CH_2COCH_3	191–193	338, 339
H	H	H	H		224–226	338, 339
H	H	H	CH_3	CH_3	228	995
					228–230	996
					230	991
					234–235	994
H	H	H	CH_3	C_2H_5	156	995
					218–220	996
H	H	H	CH_3	i-C_3H_7	195–196	215
H	H	H	CH_3	n-C_5H_{11}	126–128	215
H	H	H	CH_3	n-C_7H_{15}	117–119	215
H	H	H	CH_3	$C_6H_5CH_2$	204–206	215

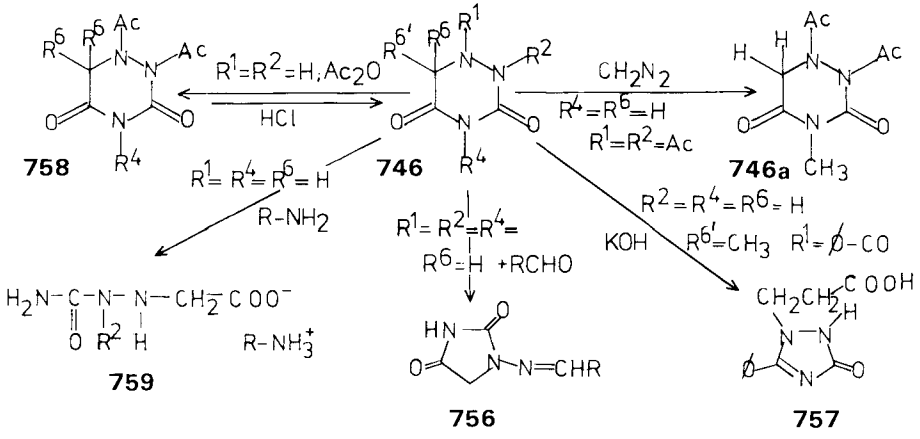
TABLE III-10. (continued)



R^1	R^2	R^4	R^6	R^6	m.p.(°C)	Refs.
H	H	H	C_2H_5	C_2H_5	215–217	996
H	H	H	C_2H_5	i-C_3H_7	196–199	996
H	H	H	CH_2COCH_3	CH_2COCH_3	204–206	339
H	H	CH_3	H	H	159–161	290
H	H	CH_3	H	CH_3	168–169	290
H	H	C_2H_5	H	H	90–91	290
H	CH_3	H	H	H	188–189	290
H	CH_3	CH_3	H	H	97–99	290
H	CH_3	CH_3	H	CH_2CHO		508
H	CH_3	CH_3	H	$CH_2CH{=}N{-}NH{-}C_6H_3(NO_2)_2$	159–162	508, 509
H	CH_3	CH_3	H	CH_2COCH_3	90–92	338, 339
H	CH_3	CH_3	H	$\begin{matrix}CH_3\\CH_2\end{matrix}\!\!>\!C{=}N{-}NH{-}C_6H_3(NO_2)_2$	157–158	509
H	CH_3	CH_3	H		112–114	338, 339

H	CH_3	CH_3	CH_3	$CH_2CH{=}N{-}NH{-}C_6H_3(NO_2)_2$	211–212	509
H	CH_3	CH_3	CH_2COCH_3	CH_2COCH_3	96–98	339
H	C_2H_5	H	H	H	138–140	290
H	C_2H_5	C_2H_5	H	H	b.p. 149/11 torr	290
H	$C_6H_5{-}CH_2$	H	H	H	175–176	423
H	CH_3CO	H	H	H	140–143	419
H		H	H	H		421
H		H	H	H		421
CH_3	H	H	H	H	189–190	441
CH_2COOCH_3	H	H	H	H	183.5	992
$CH_2COOC_2H_5$	H	H	H	H	138.5	992
C_6H_5	H	H	H	H	225	993
					229	999
C_6H_5	H	C_2H_5	H	H	135–136	993
C_6H_5	H	C_6H_5	H	H	257–258	998
CH_3CO	CH_3	CH_3	H	H	b.p. 150/0.5	419
CH_3CO	CH_3	CH_3CO	H	H	236–237	419
CH_3CO	CH_3CO	H	H	H	185–188	419
CH_3CO	CH_3CO	CH_3	H	H	146–148	419
C_6H_5CO	H	H	H	CH_3	210	991
$N{=}N{-}C_6H_4{-}NO_2(m)$	H	H	CH_3	CH_3	130	204

was used for the synthesis of 1,2,4-triazine-3,5-diones (338–341, 423); *p*-benzoquinone seems to be the best oxidant (423). Acetylation of **746** with acetic anhydride leads to 1,2-diacetyl derivatives (**758**); monoacetyl derivatives were obtained only if the 1- or 2-position were substituted (419). The acetyl derivatives are quite easily hydrolyzed by dilute hydrochloric acid but they are stable to short heating with water or ethanol (419). **746** can be methylated with diazomethane (419). Open-ring products (**759**) were obtained by reaction of **746** with amines (1001). Reaction of **746** with aldehydes affords 1-alkylidenaminohydantoins (**756**) (564). 1-Benzoyl-6-methyl-1,6-dihydro-1,2,4-triazine-3,5-dione (**746**) is transformed into the 1,2,4-triazolinone derivative (**757**) by treatment with potassium hydroxide solution (991).

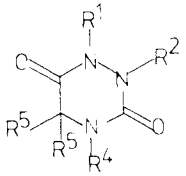


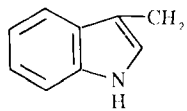
Q. 4,5-Dihydro-1,2,4-triazine-3,6-diones

For the synthesis of 4,5-dihydro-1,2,4-triazine-3,6-diones (**760**) (Table III-11) the cyclization of the following compounds with hydrazines is used: α-[(alkoxycarbonyl)amino]carboxylates (**761**) (X = 0) (1002–1004, 1006), α-[(alkoxycarbonyl)amino]thiocarboxylates (**761**) (X = S) (1005), and α-{[(phenylthio)carbonyl]amino}carboxylates (**762**) (1008). Cyclization of the following compounds also affords 4,5-dihydro-1,2,4-triazine-3,6-diones (**760**): α-(4-semicarbazido)thiocarboxylates (**763**) (X = S) (1005), α-(4-semicarbazido)carboxylates (**763**) (X = 0) (1006), α-(4-semicarbazido)carboxhydrazides (**764**) (1006), *N*-[(phenylthio)carbonyl]glycinecarbobenzhydrazide (**765**) (1008), and α-({[benzyl(or phenyl)thio]carbonyl}amino)carboxhydrazides (**766**) (1009, 1010).

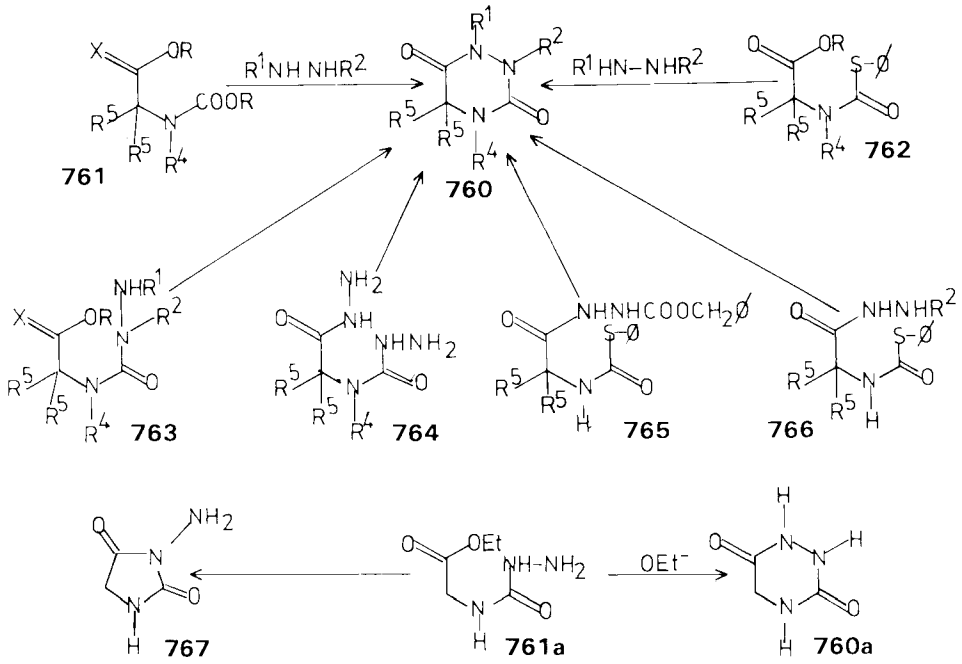
Gante and Lautsch reported the synthesis of the unsubstituted 4,5-dihydro-1,2,4-triazine-3,6-dione (**760a**) through cyclization of ethyl (4-semicarbazido)-acetate (**761a**) with sodium ethoxide (1007). Gut and his co-workers (564)

TABLE III-11. 4,5-DIHYDRO-1,2,4-TRIAZINE-3,6-DIONES



R^1	R^2	R^4	R^5	R^5	m.p. (°C)	Refs.
H	H	H	H	H	195–196	1007, 1008
H	H	H	H	CH_3	135–136	1004
H	H	H	H	CH_2CH_2OH	129–131	1006
H	H	H	H	CH_2CH_2SH	92	1005
H	H	H	H	*i*-C_3H_7	150–153	1004
H	H	H	H	$C_6H_5CH_2$	205–206	1004
H	H	H	H	4-HO–$C_6H_4CH_2$	215–216	1004
H	H	H	H		220–223	1004
H	H	H	CH_3	*n*-C_3H_7	178–180	1003
H	H	H	C_2H_5	C_2H_5	183	1002, 1003
H	H	H	C_2H_5	*i*-C_5H_{11}	165	1002, 1003
					b.p.178–180/0.4	1002, 1003
H	H	H	C_2H_5	C_6H_5	153–154	1002, 1003
H	C_6H_5	H	H	H	165–166.5	1009
H	C_6H_5	H	H	$CH_2CH_2SCH_3$	122–123.5	1009
H	$C_6H_5CH_2OCO$	H	H	H	168–169	1008
C_6H_5	H	H	H	CH_2CH_2OH	176–178	1008
C_6H_5	H	H	H	CH_2CH_2SH	135–137	1005
C_6H_5	C_6H_5	H	H	H	224–227	1010
C_6H_5	C_6H_5	H	H	CH_3	176–179	1010
C_6H_5	C_6H_5	H	H	*i*-C_3H_7	174	1010
C_6H_5	C_6H_5	H	H	CH_2CH_2SH	197–201	1005
C_6H_5	C_6H_5	H	H	*i*-C_4H_9	132	1010
C_6H_5	C_6H_5	H	H	$CH_2COOC_2H_5$	214	1010
CH_3CO	C_6H_5	CH_3CO	H	H	157–158	1009

mentioned that the isolated compounds should in fact be 1-amino-hydantoin (**676**), but the melting point reported by Gante and Lautsch (195 to 196°C) is the same as Lindemann and his group reported for the unsubstituted 4,5-dihydro-1,2,4-triazine-3,6-dione (195 to 196°C) (1008).

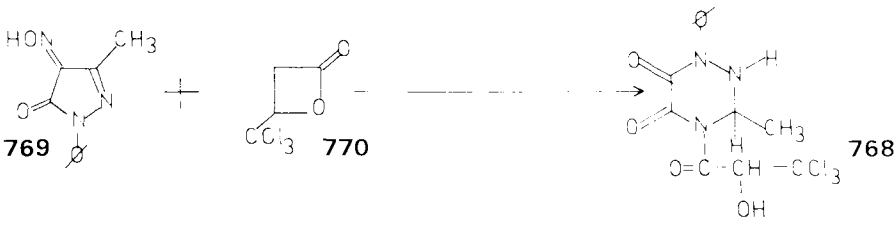


So far only a small amount of infrared (1005, 1010), ultraviolet (1004, 1011), and NMR spectroscopic data (1005, 1006) of 4,5-dihydro-1,2,4-triazine-3,6-diones (**760**) has been reported. No systematic study of the spectroscopic properties of these compounds has at present been published. Korte and his group (1005) observed two bands in the C = O region (1770 to 1760 and 1710 to 1700 cm^{-1}) of the infrared spectra of **760.**

Oxidation of **760** to 1,2,4-triazine-3,6-diones is reported by Grundmann and co-workers (341); *N*-acetyl derivatives are formed by reaction of **760** with acetic anhydride (1009) and hydrolysis leads to α-aminocarboxylic acids, hydrazine, and carbon dioxide (1004). Gante (559) isolated 1-(benzylidenamino)-hydantoins from the reaction of **760** with benzaldehydes, but the structure of the starting material was doubtful (564).

R. 3,4-Dihydro-1,2,4-triazine-5,6-diones

In a Russian patent the synthesis of 4-(4,4,4-trichloro-3-hydroxybutyryl)-3-methyl-1-phenyl-3,4-dihydro-1,2,4-triazine-5,6-dione (**768**) through reaction of 3-methyl-1-phenyl-4-isonitroso-5-pyrazolone (**769**) with β-(trichloromethyl)-β-propiolactone (**770**) is reported (1015). No further publication on this class of compounds was found.

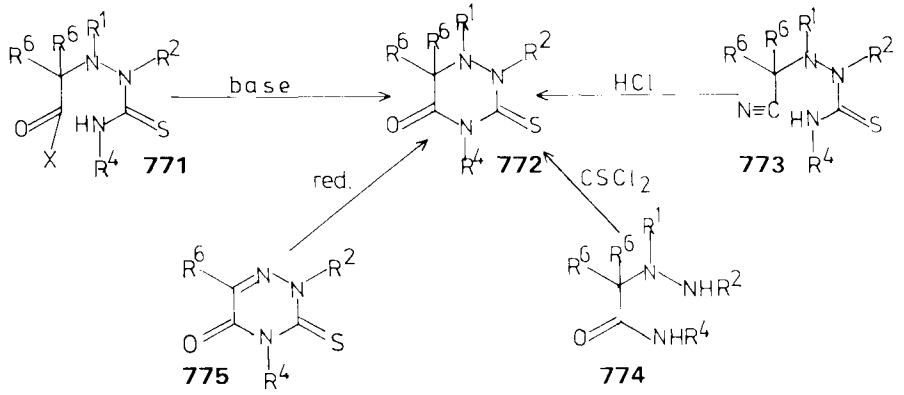


769 770 768

S. 1,6-Dihydro-3-thioxo-1,2,4-triazine-5-ones

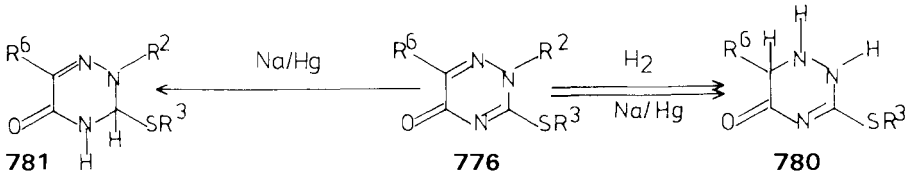
1. *Preparation*

α-(1-Thiosemicarbazido)carboxylates (**771a**) (X = OR) can be cyclized in the presence of base to 1,6-dihydro-3-thioxo-1,2,4-triazine-5-ones (**772**) (993, 995, 997, 1012). α-(1-Semicarbazido)nitriles (**773**) were converted into **772** by treatment with aqueous hydrochloric acid (996, 1013, 1014). Hadacek and Slotova (1016) used the reaction of α-hydrazinocarboxamides (**774**) with thiophosgene for the synthesis of **772**.



Reduction of 3-thioxo-1,2,4-triazine-5-ones (**775**) is reported by Girard (237) and Cattelain (264, 268, 270, 271, 746, 748, 751). Cattelain found during his studies, that 2-alkyl-3-thioxo-1,2,4-triazine-5-ones were not reduced by sodium amalgam, while 4-alkyl-3-thioxo-1,2,4-triazine-5-ones afforded the 1,6-dihydro compounds (**772**) (264, 271, 746). 3-(Alkylmercapto)-1,2,4-triazin-5-ones (**776**) are reduced by sodium amalgam (264, 268, 270 746, 748) at the C_3N_4 double bond yielding **781**, while hydrogenation converts the 3-(alkylmercapto)-1,2,4-triazin-5-ones into the 1,6-dihydro derivatives (**780**) (751).

Girard (237) formulated the reduction products of 3-(alkylmercapto)-1,2,4-triazin-5-ones with sodium amalgam as the 1,6-dihydro derivatives.



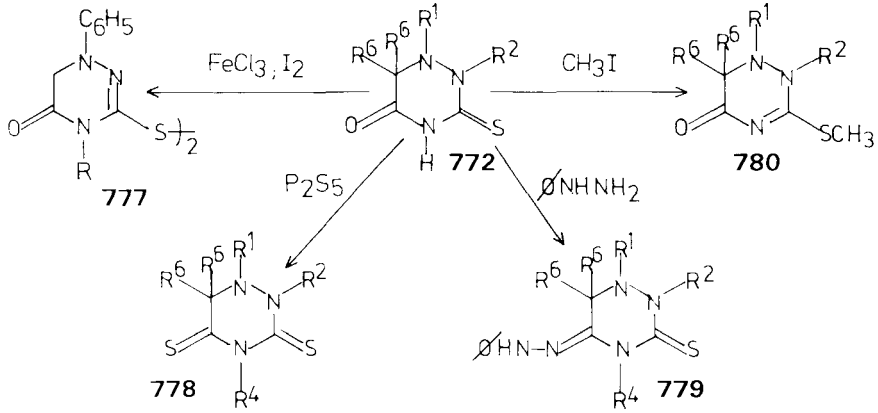
781 776 780

2. *Compound Survey*

Table III-12 lists the known compounds of this class.

3. *Physical Properties and Reactions*

1,6-Dihydro-3-thioxo-1,2,4-triazin-5-ones (**772**) are crystalline compounds with weak acidic character. Tisler (1012) reported some ultraviolet and infrared spectroscopic data and concluded from these measurements that the given tautomeric structure is the predominant one. Polarographic studies of these compounds are published by Polonsky and his group (792). Alkylation of **772** with methyl iodide in the presence of a base affords the 3-methylmercapto compounds **780** (994, 997). Oxidation of **772** with ferric chloride or iodine leads to the formation of the disulfides **777** (H, m.p. 159 °C; C_2H_5, m.p. 123 °C; C_6H_5, m.p. 190°C) (997). Treatment of **772** with phosphorus pentasulfide converted them into 1,6-dihydro-1,2,4-triazine-3,5-dithiones (**778**) (1013). Reaction of 6,6-dimethyl-1,6-dihydro-3-thioxo-1,2,4-triazin-5-ones with nitrous

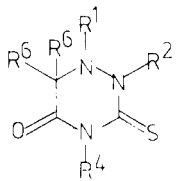


777 772 780

778 779

TABLE III-12. 3-MERCAPTO- AND 3-THIOXO-1,6-DIHYDRO-1,2,4-TRIAZIN-5-ONES

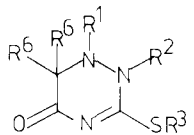
A. 1,6-Dihydro-3-thioxo-1,2,4-triazin-5-ones



R^1	R^2	R^4	R^6	R^6	m.p. (°C)	Refs.
H	H	H	CH_3	CH_3	245	995
					248–249	1013, 1014
					256–257	994
H	H	H	CH_3	C_2H_5	176–177	996, 1014
					184	995
H	H	H	C_2H_5	C_2H_5	187–188	1014
H	H	H	$CH_2CH_2CH_2CH_2$		226–228 (dec.)	1014
H	H	H	$CH_2CH_2CH_2CH_2CH_2$		223–224 (dec.)	1014
					224	995
					226–227	994
H	H	CH_3	H	$C_6H_5CH_2$	140–143	271
H	H	C_2H_5	H	$C_6H_5CH_2$	127–128	271
H	C_6H_5	C_6H_5	H	H	127	1016
H	C_6H_5	4-$CH_3COC_6H_4$	H	H	172–173	1016
H	C_6H_5	4-O_2N-C_6H_4	H	H	156	1016
C_6H_5	H	H	H	H	172–173	997
C_6H_5	H	C_2H_5	H	H	145	997
C_6H_5	H	C_6H_5	H	H	201 (dec.)	993
C_6H_5	H	3-CH_3–C_6H_4	H	H	173	1012
C_6H_5	H	4-CH_3–C_6H_4	H	H	196	1012
C_6H_5	H	2,3-$(CH_3)_2C_6H_3$	H	H	180	1012
C_6H_5	H	3-Cl–C_6H_4	H	H	200–201	1012

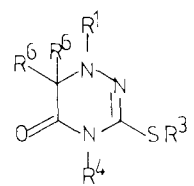
TABLE III-12 (continued)

B. 3-Mercapto-1,2,4-triazin-5(2H)-ones



R^1	R^2	R^3	R^6	R^6	m.p. (°C)	Refs.
H	H	CH_3	CH_3	CH_3	166–167	994
H	H	CH_3	$CH_2CH_2CH_2CH_2CH_2$		134	994
H	H	$C_6H_5-CH_2$	H	$C_6H_5-CH_2$	125	751
H	H	$C_6H_5-CH_2$	H	$4\text{-}CH_3O-C_6H_4-CH(CH_3)$	72	237
C_6H_5	H	CH_3	H	H	196–197	997

C. 3-Mercapto-1,2,4-triazin-5(4H)-ones



R^1	R^3	R^4	R^6	R^6	m.p. (°C)	Refs.
H	$C_6H_5-CH_2$	$C_6H_5-CH_2$	$C_6H_5-CH_2$	H	Oil	751

acid gave a *N*-nitroso compound (m.p. 141 to 142 °C), the structure of which is not fully established (994). Reaction of 1,6-dihydro-3-thioxo-1,2,4-triazin-5-ones (**772**) with phenylhydrazine yielded the 5-(phenylhydrazones) (**779**) (1016).

T. 3-Mercapto-3,4-dihydro-1,2,4-triazin-5-ones

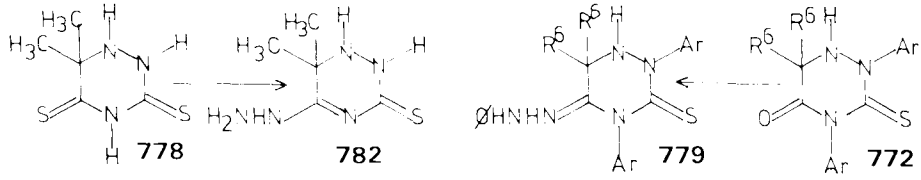
3-(Alkylmercapto)-1,2,4-triazin-5-ones (**776**) are reduced at the C_3-N_4 bond when treated with sodium amalgam yielding **781** (264, 268, 270, 746, 748), as found by Cattelain. Girard (237) prefered the 1,6-dihydro structure for the reduction products.

766 **781**

R^3	R^6	m.p. (°C)	Refs.
CH_3	4-CH_3O-C_6H_4-$CH(CH_3)$	174	270, 748
C_2H_5	$C_6H_5CH_2$	108.5	268
C_2H_5	4-CH_3O-C_6H_4-$CH(CH_3)$		270
$C_6H_5CH_2$	$C_6H_5CH_2$	123–124	268
$C_6H_5CH_2$	4-CH_3O-C_6H_4-$CH(CH_3)$	135	270, 748

U. 5-Hydrazino-1,6-dihydro-1,2,4-triazine-3-thiones

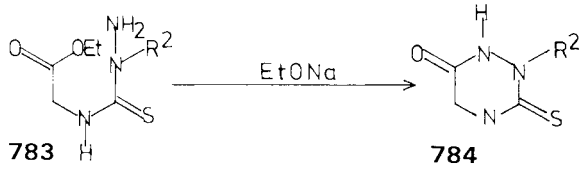
Jacquier and co-workers (994) obtained 5-hydrazino-6,6-dimethyl-1,6-dihydro-1,2,4-triazine-3-thione (**782**) (m.p. 268 to 269 °C) from the reaction of 6,6-dimethyl-1,6-dihydro-1,2,4-triazine-3,5-dithione (**778**) with hydrazine. 2,4-Diaryl-5-(phenylhydrazono)-1,6-dihydro-1,2,4-triazine-3-thiones (**779**) were the products, isolated from the reaction of 2,4-diaryl-1,6-dihydro-3-thioxo-1,2,4-triazin-5-ones (**772**) with phenylhydrazine (1016).



778 **782** **779** **772**

V. 4,5-Dihydro-3-thioxo-1,2,4-triazin-6-ones

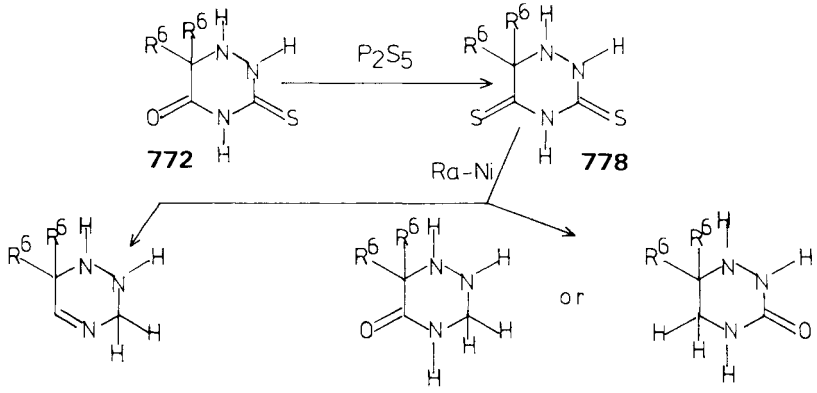
Gante and Lautsch (1007) reported the conversion of ethyl α-(4-thiosemicarbazido)acetates (**783**) into 4,5-dihydro-3-thioxo-1,2,4-triazin-6-ones (**784**) [R^2 = H, m.p. 172 to 173 °C (dec.); $R^2 = C_6H_5$, m.p. 220 °C (dec.)] by treatment with sodium ethoxide. The work of Gut et al. (564) sheds some doubt as to the structure of the isolated compounds.



783 **784**

W. 1,6-Dihydro-1,2,4-triazine-3,5-dithiones

Treatment of 1,6-dihydro-3-thioxo-1,2,4-triazin-5-ones (**772**) with phosphorus pentasulfide was used for the synthesis of 1,6-dihydro-1,2,4-triazine-3,5-dithiones (**778**) (1013). Desulfuration of **778** with Raney nickel led, depending on the reaction conditions, to either tetrahydro-1,2,4-triazines or tetrahydro-1,2,4-triazinones (994). The structure of the isolated compounds was not fully established.

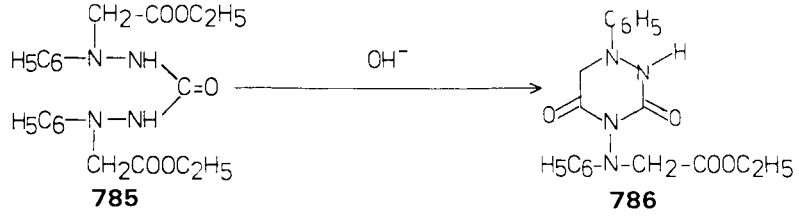


772 **778**

R^6	R^6	m.p. (°C)	Refs.
CH_3	CH_3	220–222	1013
CH_3	C_2H_5	204–205	1013
C_2H_5	C_2H_5	205–206	1013
$CH_2CH_2CH_2CH_2$		196–197	1013
$CH_2CH_2CH_2CH_2CH_2$		227–228	1013

X. 4-Amino-1,6-dihydro-1,2,4-triazine-3,5-diones

Treatment of the carbohydrazide **785** with base yielded a compound (m.p. 176 °C) which Busch formulated as the 4-amino-1,6-dihydro-1,2,4-triazine-3,5-dione derivative (**786**) (993).

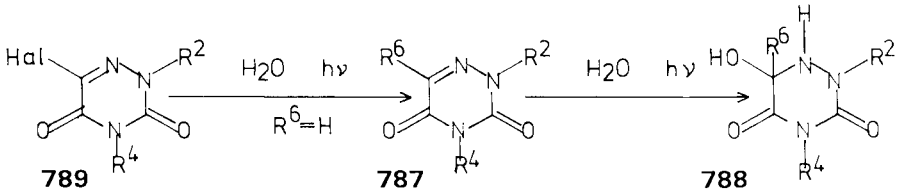


785 **786**

Y. 6-Hydroxy-1,6-dihydro-1,2,4-triazine-3,5-diones

Photochemical addition of water to the C_6-N_1 double bond of 1,2,4-triazine-3,5-diones (**787**) affords 6-hydroxy-1,6-dihydro-1,2,4-triazine-3,5-diones (**788**) (408, 412–416). Theoretical calculations have shown that the hydration is a reaction of a triplet state (412, 415) and indicates an S_N mechanism for the reaction (412). Paramagnetic ions such as Cu^{2+}, Ni^{2+}, Co^{2+}, Mn^{2+}, or Cr^{3+} inhibit the photohydration of 1,2,4-triazine-3,5-diones (414, 415).

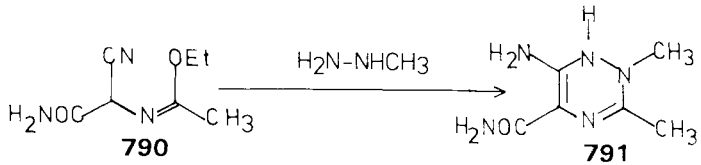
6-Halo-1,2,4-triazine-3,5-diones (**789**) under the reaction conditions of the photochemical hydration are first dehalogenated and the formed 1,2,4-triazine-3,5-dione then adds water, leading to **788** (413).



789 **787** **788**

Z. 6-Amino-1,2-dihydro-1,2,4-triazine-5-carboxylic Acids

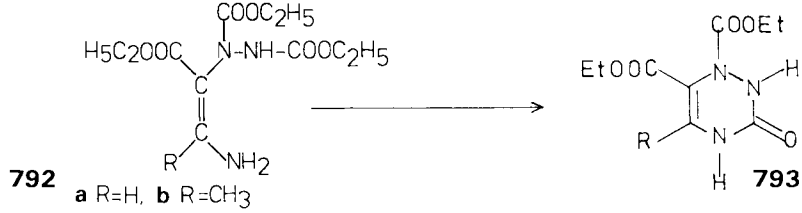
Reaction of compound **790** with methylhydrazine led to the isolation of a substance, which can be formulated as 6-amino-2,3-dimethyl-1,2,-dihydro-1,2,4-triazine-5-carboxamide (**791**) [m.p. 254 °C (dec.)] (1067).



790 **791**

A′. 1,4-Dihydro-3-oxo-1,2,4-triazine-1,6-dicarboxylic Acids

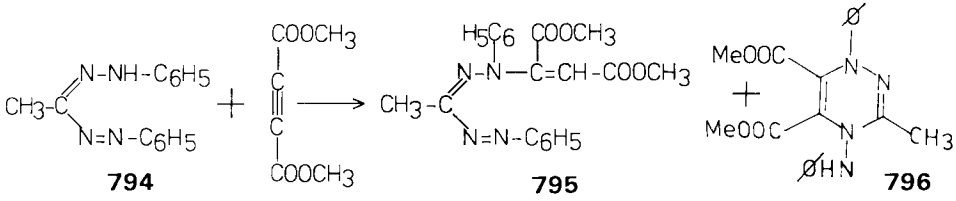
Treatment of the compounds **792a** and **792b** with thallium ethoxide affords diethyl 1,4-dihydro-3-oxo-1,2,4-triazine-1,6-dicarboxylate (**793a**) (m.p. 172 to 173 °C) or its 5-methyl derivative **793b** (m.p. 166 °C) (911).



792 **a** R=H, **b** R=CH3 **793**

B′. 4-Amino-1,4-dihydro-1,2,4-triazine-5,6-dicarboxylic Acids

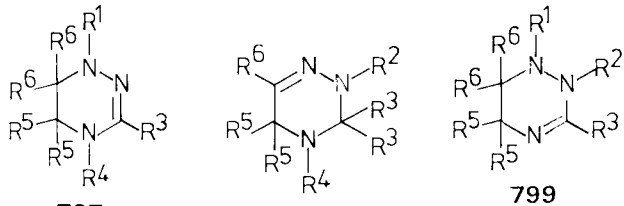
The formazane **794** reacts with dimethyl acetylenedicarboxylate to yield the addition product **795** and the dimethyl 4-anilino-3-methyl-1-phenyl-1,4-dihydro-1,2,4-triazine-5,6-dicarboxylate (**796**) (m.p. 155 °C) (1017).



794 **795** **796**

II. TETRAHYDRO-1,2,4-TRIAZINES

Tetrahydro-1,2,4-triazines are well-known compounds and various methods for their synthesis have been published. Most known tetrahydro-1,2,4-triazines are formulated either as 1,4,5,6-tetrahydro-1,2,4-triazines (**797**) or as 2,3,4,5-tetrahydro-1,2,4-triazines (**798**). Only in two publications (1019, 1020) are the isolated compounds formulated as 1,2,5,6-tetrahydro-1,2,4-triazines (**799**).



797 **798** **799**

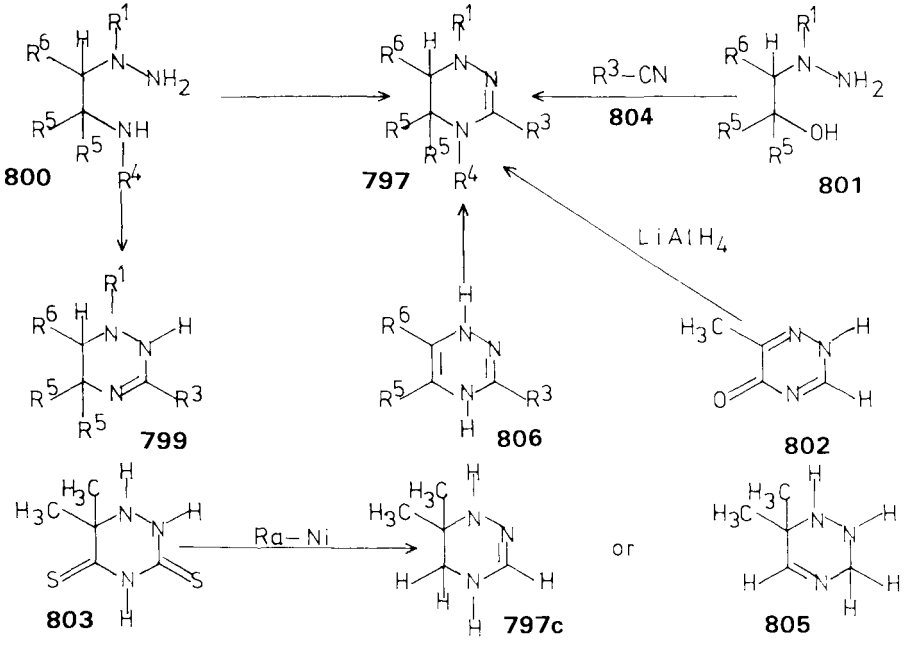
Until now only a few papers have been presented containing spectroscopic data which confirm the given structure. In this discussion we always use the structure given in the original publication, but we cannot exclude the possibility that some of these structures may have to be corrected in the future.

A. 1,4,5,6-Tetrahydro-1,2,4-triazines

For the synthesis of 1,4,5,6-tetrahydro-1,2,4-triazines (**797**) the cyclization of (2-aminoethyl)hydrazines (**800**) with nitriles (1018, 1021, 1031), imidates (1018, 1021–1028, 1032), thioimidates (1021, 1031), or ortho-carboxylates (1028–1030) or the reaction of 2-hydrazinoethanols (**801**) with nitriles (**804**) (1032–1034) is used. The cyclization products of the reaction of (2-aminoethyl)hydrazines with carboxylic acids (1020) or 1,3,5-triazine (1019) are formulated as 1,2,5,6-tetrahydro-1,2,4-triazines (**799**). Electrochemical reduction of 3,5,6-triphenyl-1,4-dihydro-1,2,4-triazine (**806**) affords *cis*-3,5,6-triphenyl-1,4,5,6-tetrahydro-1,2,4-triazine (**797a**) (108).

Desulfuration of 6,6-dimethyl-1,6-dihydro-1,2,4-triazine-3,5-dithione (**803**) with Raney nickel afforded a compound (m.p. 163 to 164 °C) that is formulated as either 6,6-dimethyl-1,4,5,6-tetrahydro-1,2,4-triazine (**797c**) or the 1,2,3,6-tetrahydro isomer (**805**) (994).

Reduction of 6-methyl-1,2,4-triazin-5-one (**802**) with lithium aluminum hydride yields 6-methyl-1,4,5,6-tetrahydro-1,2,4-triazine (**797b**) (1077).



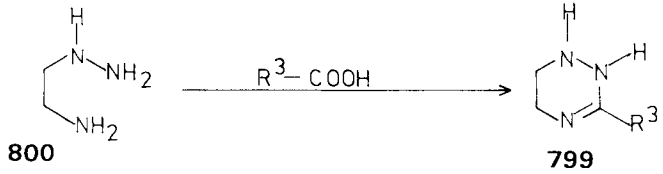
2. *Compound Survey*

Compounds of this class reported in the literature are listed in Table III-13.

So far only a small amount of spectroscopic data on the 1,4,5,6-tetrahydro-1,2,4-triazines has been reported (108, 1033). Trepanier and his group (1049, 1050) used 1,4,5,6-tetrahydro-1,2,4-triazines for the synthesis of condensed 1,2,4-triazines.

B. 1,2,5,6-Tetrahydro-1,2,4-triazines

The compounds isolated from the reaction of 2-aminoethylhydrazine (**800**) with carboxylic acids (1020) or 1,3,5-triazine (1019) were formulated as 1,2,5,6-tetrahydro-1,2,4-triazines (**799**) (R^3 = H, b.p. 146 to 147 °C/15torr; $R^3 = CH_3$, 110 to 113 °C/1.0 torr; $R^3 = C_2H_5$, 97 to 102 °C/O.5 to 0.8 torr; $R^3 = n\text{-}C_3H_7$, 124 °C/1.5 torr). Derivatives with unknown structure were prepared by Grundman and Rätz (1019).

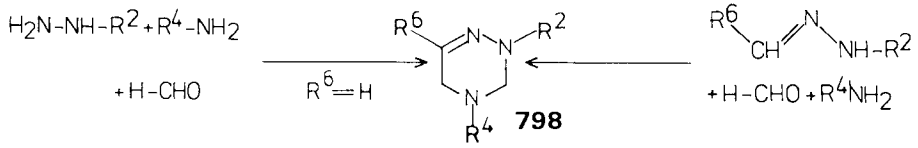


800 **799**

C. 2,3,4,5-Tetrahydro-1,2,4-triazines

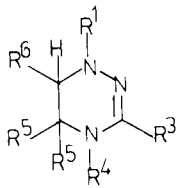
1. *Preparation*

Reaction of hydrazines or hydrazones with formaldehyde and primary amines was used for the synthesis of 2,3,4,5-tetrahydro-1,2,4-triazines (**798**) (1036, 1037, 1039, 1041). A method very similar to the initially described reaction is the cyclization of α-aminohydrazones (**807**) with aldehydes (1042–1044). By similar methods 6-nitro- (1035, 1045) and 6-acyl-2,3,4,5-tetrahydro-1,2,4-triazines (1038, 1040, 1047) can be prepared. Reaction of 6-acyl-2,3,4,5-tetrahydro-1,2,4-triazines (**798a**) with Grignard reagents affords 6-(hydroxyalkyl)-



798

TABLE III-13. 1,4,5,6-TETRAHYDRO-1,2,4-TRIAZINES



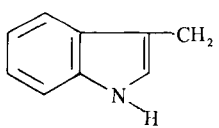
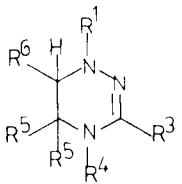
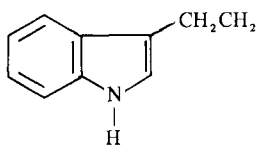
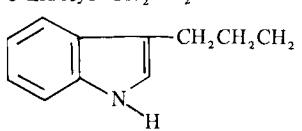
R^1	R^3	R^4	R^5	R^6	R^6	m.p. (°C)	Refs.
H	H	H	H	H	H	b.p98–100/0.3	1028
	Picrate					136–138	1028
H	H	H	H	H	CH_3	b.p153–155/20	1027
H	CH_3	H	H	H	H	b.p82–85/0.12	1028
H	C_2H_5	H	H	H	H	b.p99–101/0.3	1028
H	C_6H_5	H	H	H	H	87–88	1018
H	C_6H_5	H	H	H	CH_3	62–70	1018
H	C_6H_5–CH_2	H	H	H	H		1018
H	2,6-$Cl_2C_6H_3CH_2$	H	H	H	H	159–160	1028, 1032
H	3,4-$(CH_3O)_2C_6H_3CH_2$	H	H	H	H	77–79	1032
H	 3-Indolyl-CH_2	H	H	H	H	197–198	1023
H	3,4-$Cl_2C_6H_3OCH_2$	H	H	H	H	223–224 (dec.)	1028, 1032
	·HCl					223–224	1032
H	3-Cl–4-H_2N–$C_6H_3OCH_2$	H	H	H	H		102
	·2HCl					236–237	1024

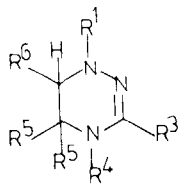
TABLE III-13. (continued)

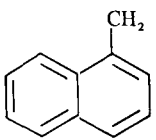
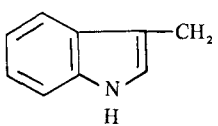


R^1	R^3	R^4	R^5	R^6	R^6	m.p.(°C)	Refs.
H	3-Cl–4-CH_3CONH–$C_6H_3OCH_2$	H	H	H	H	197–199	1024 102
H	$(C_6H_5)_2CH$	H	H	H	H	159–160	1021, 1031
H	(4-Cl–C_6H_4)(C_6H_5)CH	H	H	H	H	176–178	1021, 1031
H	$C_6H_5CH_2CH_2$	H	H	H	H	114–115	1021, 1025
H	$(C_6H_5)_2CHCH_2$	H	H	H	H	104–105	1021, 1031
H	$C_6H_5CH_2$–$CH(CH_3)$ ·HCl	H	H	H	H	160–161 160–161	1021 1025
H	$C_6H_5CH_2$–$CH(C_6H_5)$	H	H	H	H	107–108	1021, 1025
H	 3-Indolyl–CH_2CH_2	H	H	H	H	80–81	1023
H	 3-Indolyl–$CH_2CH_2CH_2$	H	H	H	H		1023

H	C_6H_5	H	H	C_6H_5	C_6H_5		108
H	C_6H_5	H	CH_3	C_6H_5	H		1032, 1034
H	4-CH_3–C_6H_4	H	H	C_6H_5	CH_3	142–143	1033
H	4-F_3C–C_6H_4	H	CH_3	C_6H_5	CH_3		1032, 1034
H	4-Cl–C_6H_4	H	H	H	H	136–137	1028, 1032
H	4-Cl–C_6H_4	C_2H_5	H	H	H	62.4–64	1032
H	3,4,5-$(CH_3O)_3C_6H_2$	H	H	H	H	132	1032
H	1-Naphthyl	H	H	H	H	249–250 (dec.)	1021
	·HBr					249–250 (dec.)	1025
H	2-Furyl	H	H	H	H		1018
H	2-Furyl	H	H	H	CH_3	108–112	1018
CH_3	CH_3	H	H	H	H	b.p.73–75/0.5	1028, 1030
CH_3	CH_3	H	H	CH_3	H	b.p.74–76/0.7	1022, 1028, 1030
CH_3	CH_3	H	CH_3	CH_3	H	126–127	1033, 1034
	·CH_3I					216–217	1051
CH_3	CH_3	H	H	C_6H_5	H	84–85	1032, 1033
	·CH_3I					239–240	1051
CH_3	C_2H_5	H	H	H	H	b.p.80–83/0.7	1028, 1032
						b.p.99–101/0.3	1030
CH_3	C_2H_5	H	CH_3	CH_3	H		1032
CH_3	C_3H_7	H	H	CH_3	H		1032
CH_3	CH_2=CH	H	CH_3	CH_3	H		1034
CH_3	CH_2=CH	H	H	C_6H_5	H	b.p.145/0.15	1033
						b.p.146/1.5	1034
CH_3	$(C_2H_5)_2NCH_2$	H	H	C_6H_5	H	b.p.143/0.24	1032
CH_3	$(CH_3)_2NCH_2CH_2$	H	H	H	H	b.p.113–115/1.7	1028
CH_3	$(CH_3)_2NCH_2CH_2$	H	CH_3	CH_3	H		1034
CH_3	$(CH_3)_2NCH_2CH_2$	H	H	C_6H_5	H	b.p.143/0.24	1034
CH_3	C_6H_5–CH_2	H	H	CH_3	H	89–90	1031
CH_3	3,4-$(CH_3)_2C_6H_3$–CH_2	H	H	H	H	129–132	1032
CH_3	2,3,6-$(C_6H_5)_3C_6H_2$–CH_2	H	H	H	H	167–168	1028
CH_3	2,3,6-$(C_6H_5)_3C_6H_2$–CH_2	H	H	CH_3	H	161–163	1028
CH_3	4-Cl–C_6H_4	C_2H_5	H	H	H	63–64	1022, 1028

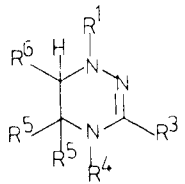
TABLE III-13. (continued)



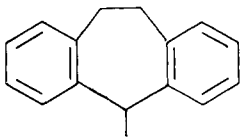
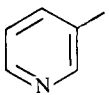
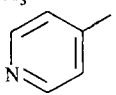
R^1	R^3	R^4	R^5	R^6	R^6	m.p.(°C)	Refs.
CH_3	2,6-$Cl_2C_6H_3-CH_2$	H	H	H	H	128–130	1028, 1032
CH_3	2,6-$Cl_2C_6H_3-CH_2$	H	H	CH_3	H	158–159	1022, 1028, 1032
CH_3	2,3,6-$Cl_3C_6H_2-CH_2$	H	H	H	H	167–168	1032
CH_3	2,3,6-$Cl_3C_6H_2-CH_2$	H	H	CH_3	H	161–163	1032
CH_3	3,4-$(CH_3O)_2C_6H_3-CH_2$ ·HCl	H	H	H	H	165–168	1032
CH_3	3,4-$(CH_3O)_2C_6H_3-CH_2$	CH_3	H	H	H	152–153	1032
CH_3	 1-Naphthyl-CH_2	H	H	H	H	99.5–100.5	1025
CH_3	 3-Indolyl-CH_2	H	H	H	H	75–77	1023

CH_3	3,4-$Cl_2C_6H_3$–OCH_2	H	H	H	H	83–85	1028, 1032
CH_3	3,4-$Cl_2C_6H_3$–OCH_2	H	H	CH_3	H	181–183 (dec.)	1028
	·HCl					181–183 (dec.)	1032
CH_3	3-Cl–4-H_2N–C_6H_3–OCH_2	H	H	H	H		
	·2HCl					217–218 (dec.)	1024, 1026, 1027
CH_3	3-Cl–4-CH_3CONH–C_6H_3–OCH_2	H	H	H	H	144–146	1024, 1026, 1027
CH_3	$(C_6H_5)_2CH$	H	H	H	H	121–122	1021, 1031
CH_3	$(C_6H_5)_2CH$	H	H	H	CH_2CH_2OH	179–181	1031
CH_3	$(C_6H_5)_2CH$	H	H	CH_3	H	89–91	1021
						121–125	1031
CH_3	$(C_6H_5)_2CH$	H	CH_3	CH_3	H	138–139	1021, 1031
CH_3	$(C_6H_5)_2CH$	CH_2CH_2OH	H	H	H	179–181	1021
CH_3	(4-Cl–C_6H_4)(C_6H_5)CH	H	H	H	H	140–141	1021, 1031
CH_3	(4-Cl–C_6H_4)(C_6H_5)CH	H	H	CH_3	H	123–125	1021
CH_3	$C_6H_5CH_2CH_2$	H	H	H	H	145–146	1021
	·HCl					145–145.5	1025
CH_3	4-Cl–$C_6H_4CH_2CH_2$	H	H	H	H	133–134	1028
CH_3	C_6H_5	H	H	H	H	88–89	1022, 1028, 1032
CH_3	C_6H_5	H	H	CH_3	H	135–137	1028, 1032
CH_3	C_6H_5	H	CH_3	CH_3	H	95–96	1032–1034
CH_3	C_6H_5	H	H	C_6H_5	H	133–134	1032–1034
CH_3	C_6H_5	H	H	C_6H_5	CH_3	146–147	1032–1034
CH_3	C_6H_5	C_2H_5	H	H	H	b.p. 118–119/0.2	1028, 1032
CH_3	2-CH_3–C_6H_4	H	H	C_6H_5	CH_3	227–229	1032–1034
	·HCl					227–229	1032
CH_3	3-CH_3–C_6H_4	H	H	C_6H_5	CH_3	147–148	1032–1034
	·CH_3I					195–196	1051
CH_3	4-CH_3–C_6H_4	H	H	C_6H_5	H	103–105	1033
CH_3	4-CH_3–C_6H_4	H	H	C_6H_5	CH_3	142–143	1032, 1034
	·CH_3I					205–206	1051
CH_3	4-FH_2C–C_6H_4	H	H	C_6H_5	H	80–83	1032
CH_3	4-CF_3–C_6H_4	H	H	C_6H_5	H	80–83	1033, 1034
CH_3	4-CF_3–C_6H_4	H	H	C_6H_5	CH_3	119–120	1032–1034

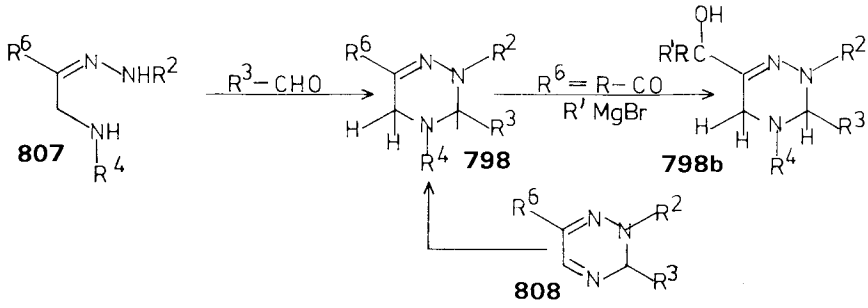
TABLE III-13. (continued)



R^1	R^3	R^4	R^5	R^6	R^6	m.p.(°C)	Refs.
CH_3	2-F–C_6H_4	H	H	C_6H_5	CH_3	118–121	1032–1034
CH_3	2-Cl–C_6H_4	H	H	H	CH_3		
	·HCl					256–257	1032
CH_3	2-Cl–C_6H_4	H	H	CH_3	H		
	·HBr					183–185	1032
CH_3	2-Cl–C_6H_4	H	CH_3	CH_3	H	183–185	1033
CH_3	2-Cl–C_6H_4	H	H	C_6H_5	H	92–93	1032, 1033, 1034
CH_3	2-Cl–C_6H_4	H	H	C_6H_5	CH_3	256–257	1032, 1033, 1034
CH_3	4-Cl–C_6H_4	H	H	H	H	133–134	1032
CH_3	4-Cl–C_6H_4	H	H	C_6H_5	H	107–108	1032, 1033, 1034
CH_3	4-Cl–C_6H_4	H	H	C_6H_5	CH_3	132–133	1032, 1034
						134–135	1033
CH_3	4-Cl–C_6H_4	C_2H_5	H	H	H	63–64	1032
CH_3	4-O_2N–C_6H_4	H	H	C_6H_5	CH_3	110–111	1032, 1033, 1034
CH_3	4-CH_3O–C_6H_4	H	H	C_6H_5	H	103–105	1032, 1034
CH_3	4-CH_3O–C_6H_4	H	H	C_6H_5	CH_3	134–135	1032, 1033
CH_3	3,4,5-$(CH_3O)_3C_6H_2$	H	H	H	H	115.9–116.5	1022
						132–133	1028
						148–149	1032

CH_3	3,4,5-$(CH_3O)_3C_6H_2$	H	H	CH_3	H	148–149	1028
CH_3	2-H_2N–C_6H_4	H	H	H	H	139–141	1050
CH_3	2-H_2N–CO–NH–C_6H_4	H	H	H	H	181–182	1050
CH_3	1-Naphthyl	H	H	H	H	100–101	1021
CH_3		H	H	H	H	145–147	1021
CH_3	 3-Pyridyl	H	H	C_6H_5	CH_3	146–147	1032, 1033, 1034
	$\cdot CH_3I$					230–231	1051
CH_3	 4-Pyridyl	H	H	H	H	117–118	1032
CH_3	 4-Pyridyl	C_2H_5	H	H	H	b.p.118/0.12	1022, 1032

2,3,4,5-tetrahydro-1,2,4-triazines (**798b**) (1046). Busch and Küspert (987) obtained **798**, by reduction of 2,3-dihydro-1,2,4-triazines (**808**) with zinc/acetic acid or by reduction of 4-nitroso-2,3,4,5-tetrahydro-1,2,4-triazines (**798**, R^4 = NO).

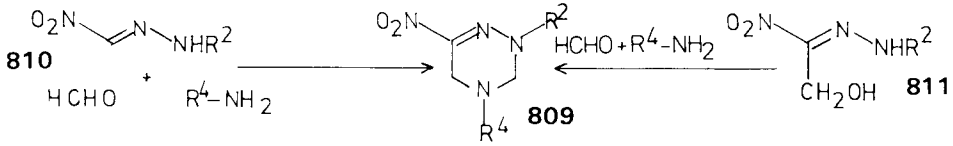


2. *Compound Survey*

Known 2,3,4,5-tetrahydro-1,2,4-triazines are listed in Table III-14. 2,3,4,5-Tetrahydro-1,2,4-triazines are mostly colorless compounds the physical properties and reactions of which have not yet been studied.

D. 6-Nitro-2,3,4,5-tetrahydro-1,2,4-triazines

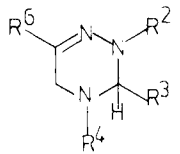
Dytshenko and his group obtained 6-nitro-2,3,4,5-tetrahydro-1,2,4-triazines (**809**) through reaction of nitroformaldehyde hydrazones (**810**) with formaldehyde and primary amines (1035) and Hahn and Zawadzka (1045) used the reaction of α-nitro-β-hydroxy hydrazones (**811**) with primary amines and formaldehyde for the synthesis of **809**. Compounds of this class reported in the literature are listed in Table III-15.



E. 6-Hydroxy-1,2,5,6-tetrahydro-1,2,4-triazines

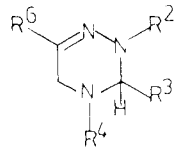
Reaction of the oxazolium salts (**812**) with methylhydrazine led to the formation of the two derivatives (**813a**) (R = C_6H_5, m.p. 104 to 105 °C)

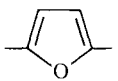
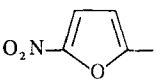
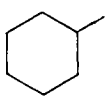
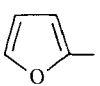
TABLE III-14. 2,3,4,5-TETRAHYDRO-1,2,4-TRIAZINES



R^2	R^3	R^4	R^6	m.p. (°C)	Refs.
CH_3	H	CH_3	H	b.p.50–57/12	1036
C_6H_5	H	H	C_6H_5	160	987
·HCl				190	987
C_6H_5	H	CH_3	4-O_2N–C_6H_4	119–120	1044
				151–152	1041
C_6H_5	H	CH_3	C_6H_5–C(OH)–CH_3		1046
C_6H_5	H	CH_3	$(C_6H_5)_2$C(OH)–H		1046
C_6H_5	H	CH_3	C_6H_5–CH_2–C(OH)–C_6H_5		1046
C_6H_5	H	C_2H_5	4-O_2N–C_6H_4	123–124.5	1041
C_6H_5	H	*i*-C_3H_7	4-O_2N–C_6H_4	122.5–124	1044
				127.5–128.5	1041
C_6H_5	H	CH_2=CH–CH_2	4-O_2N–C_6H_4	102–103.5	1044
C_6H_5	H	C_4H_9	4-O_2N–C_6H_4	110–111.5	1044
				115–116	1041
C_6H_5	H	C_4H_9	 2-furyl	b.p.80–90/11–13	1037

TABLE III-14. (continued)



R^2	R^3	R^4	R^6	m.p.(°C)	Refs.
C_6H_5	H	C_4Hg	 2-furyl		1037
C_6H_5	H	t-C_4H_9		155	1037
C_6H_5	H	$HOOC-CH_2$	$4\text{-}O_2N-C_6H_4$	138–140	1039
C_6H_5	H	 Cyclopropyl	$4\text{-}O_2N-C_6H_4$	106–107	1041
C_6H_5 ·HCl	H	 Cyclohexyl	$4\text{-}O_2N-C_6H_4$	169.5–170.5 172–173 178.5–179	1041 1044 1041
C_6H_5	H	$C_6H_5-CH_2$	$4\text{-}O_2N-C_6H_5$	102–102.5 104–106	1041 1044
C_6H_5	H	$C_6H_5-CH_2$		45–50/3–4	1037

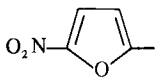
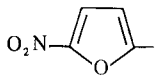
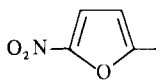
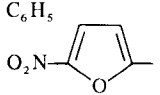
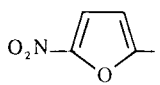
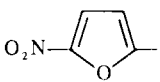
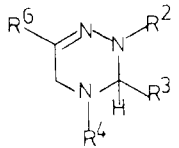
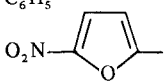
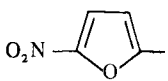
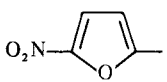
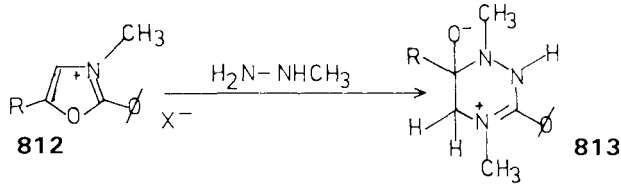
C_6H_5	H	$C_6H_5-CH_2$		138	1037
C_6H_5	H	C_6H_5	4-$O_2N-C_6H_4$	120–123 176–177	1044 1041
C_6H_5	H	C_6H_5	$C_6H_5-CH_2-\underset{\underset{OH}{|}}{C}-C_6H_5$		1046
C_6H_5	H	C_6H_5		177	1037
C_6H_5	H	4-$O_2N-C_6H_4$		135	1037
C_6H_5	C_6H_5	H	C_6H_5	164	987
C_6H_5	C_6H_5	4-$CH_3-C_6H_4$	C_6H_5	76–77 78 126	1043 1043 1043
C_6H_5	2-$HO-C_6H_4$	4-$CH_3-C_6H_4$	C_6H_5	161	1043
C_6H_5	4-$(CH_3)_2N-C_6H_4$	4-$CH_3O-C_6H_4$	C_6H_5	158	1042
4-$CH_3-C_6H_4$	H	C_4H_9		93–95	1037
4-$CH_3-C_6H_4$	H	*sec*-C_4H_9	 2-Furyl	114	1037
4-$CH_3-C_6H_4$	H	$C_6H_5-CH_2$	 2-furyl	158	1037

TABLE III-14. (continued)



R^2	R^3	R^4	R^6	m.p.(°C)	Refs.
2-CH_3–C_6H_4	H	4-CH_3O–C_6H_4	C_6H_5	143–144	1042
2-CH_3–C_6H_4	CH_3	4-CH_3O–C_6H_4	C_6H_5	127–128	1042
2-CH_3–C_6H_4	C_6H_5	4-CH_3O–C_6H_4	C_6H_5	170	1042
2-CH_3–C_6H_4	4-Cl–C_6H_4	4-CH_3O–C_6H_4	C_6H_5	139–140	1042
2-CH_3–C_6H_4	4-CH_3O–C_6H_4	4-CH_3O–C_6H_4	C_6H_5	166	1042
4-O_2N–C_6H_4	H	C_4H_9	 2-furyl	179	1037
4-O_2N–C_6H_4	H	C_6H_5–CH_2	 2-furyl	211–215	1037
4-HOOC–C_6H_4	H	C_6H_5–CH_2	 2-furyl	180	1037

and (**813b**) (R = 4-C_6H_5-C_6H_4, m.p. 128 °C) of 6-hydroxy-1,2,5,6-tetrahydro-1,2,4-triazine (944).



812 **813**

F. Tetrahydro-1,2,4-triazin-3-ones

Reduction of 1,2,4-triazin-3-ones (**814**) or 4,5-dihydro-1,2,4-triazin-3-ones (**815**) either catalytically or electrochemically is used for the synthesis of tetrahydro-1,2,4-triazin-3-ones (**816**) (108, 171–174). Reaction of (chlorocarbonyl)(2-chloroethyl)amines (**817**) with alkyl hydrazines affords **816** (1056), whereas reaction of **817** with 1,1-dimethyl-hydrazine gave the 1,1-dimethyl-4-(2-chloroethyl)tetrahydro-1,2,4-triazine-3-on-1-ium salt (**818**) (m.p. 209 to 210 °C, dec.) (1055). The formation of **816** through hydrolysis of tetrahydro-1,2,4-triazine-3-thiones (**819**) was observed in one case (1057).

3-Methoxy-1,4,5,6-tetrahydro-1,2,4-triazines (**820**) were synthesized through reduction of 3-methoxy-1,2,4-triazines (**821**) or 3-methoxy-4,5-dihydro-1,2,4-triazines (**822**) (171, 174), **820** can be hydrolyzed to tetrahydro-1,2,4-triazin-3-ones (**816**).

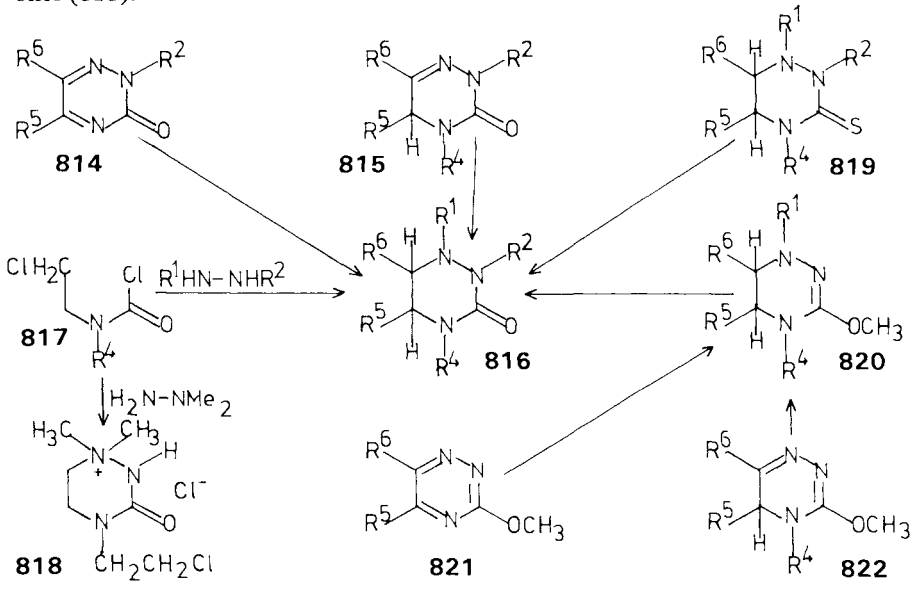


TABLE III-15. 6-NITRO-2,3,4,5-TETRAHYDRO-1,2,4-TRIAZINES (809)

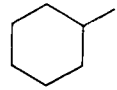
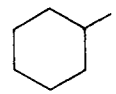
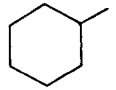
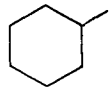
R^2	R^4	m.p. (°C)	Refs.
C_6H_5	CH_3	85.5–86	1045
C_6H_5	C_2H_5	74–75	1045
C_6H_5	i-C_3H_7	122.5–124	1045
C_6H_5	CH_2=CH–CH_2	89–90	1045
C_6H_5	HOOC–CH_2	191–192	1045
C_6H_5	 Cyclohexyl	99.5–101	1045
C_6H_5	C_6H_5–CH_2	78–79.5	1045
C_6H_5	C_6H_5	104–106	1035
		109–110.5	1045
C_6H_5	4-Cl–C_6H_4	147–149	1035
C_6H_5	4-Br–C_6H_4	164–166	1035
2,3-$(CH_3)_2C_6H_3$	4-Cl–C_6H_4	98–100	1035
4-Cl–C_6H_4	CH_3	104.5–105	1045
4-Cl–C_6H_4	i-C_3H_7	92–93.5	1045
4-Cl–C_6H_4	CH_2=CH–CH_2	62–63.5	1045
4-Cl–C_6H_4	C_4H_9	80.5–82	1045
4-Cl–C_6H_4	$HOCH_2CH_2$	115–116	1045
4-Cl–C_6H_4	 Cyclohexyl	116–117.5	1045
4-Cl–C_6H_4	C_6H_5–CH_2	123–124.5	1045
		125–126	1035
4-Cl–C_6H_4	C_6H_5	129.5–131	1045
4-Cl–C_6H_4	4-Cl–C_6H_4	135–137	1035
4-Cl–C_6H_4	4-Br–C_6H_4	148–150	1035
4-Br–C_6H_4	C_6H_5–CH_2	120–121	1035
4-Br–C_6H_4	4-CH_3–C_6H_4	148–151	1035
4-Br–C_6H_4	4-Br–C_6H_4	130–132	1035
4-O_2N–C_6H_4	CH_3	180–180.5 (dec.)	1045
4-O_2N–C_6H_4	C_2H_5	141–142	1045
4-O_2N–C_6H_4	CH_2=CH–CH_2	102.5–103.5	1045
4-O_2N–C_6H_4	 Cyclohexyl	133–134	1045
4-O_2N–C_6H_4	C_6H_5–CH_2	150–151	1035
		158–159	1045
4-O_2N–C_6H_4	C_6H_5	194–194.5 (dec.)	1045
4-O_2N–C_6H_4	4-Cl–C_6H_4	184–185	1035
4-O_2N–C_6H_4	4-Br–C_6H_4	190–192	1035

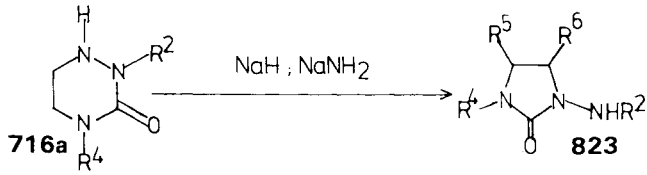
TABLE III-15. (continued)

R^2	R^4	m.p.(°C)	Refs.
4-H_5C_2O–C_6H_4	CH_3	107.5–108	1045
4-H_5C_2O–C_6H_4	C_2H_5	73.4–74	1045
4-H_5C_2O–C_6H_4	CH_2=CH–CH_2	72–73	1045
4-H_5C_2O–C_6H_4	 Cyclohexyl	87–87.5	1045
4-H_5C_2O–C_6H_4	C_6H_5–CH_2	117.5–119	1045
4-H_5C_2O–C_6H_4	C_6H_5	146–146.5	1045

Jacquier and his group (994) converted 6,6-dimethyl-1,6-dihydro-1,2,4-triazine-3,5-dithione into a tetrahydro-1,2,4-triazinone (m.p. 233 to 234 °C) by treatment with Raney nickel in ethanol–water. No decision could be made between the 3-oxo and 5-oxo structures.

Tetrahydro-1,2,4-triazin-3-ones (Table III-16) are colorless crystalline compounds. In the infrared spectra a band for the C=O stretching vibration is observed in the 1630 to 1690 cm^{-1} region (108, 1056, 1057). In the PMR spectra of the 2-methyl derivative two triplets are observed for the two CH_2-groups at $\tau = 6.55$ and 7.00 while the *N*-methyl group shows a signal at $\tau = 7.35$ (1057). The PMR spectra of *cis*- and *trans*-5,6-diphenyl-tetrahydro-1,2,4-triazin-3-one was reported by Pinson and his group (108).

2-Alkylated tetrahydro-1,2,4-triazin-3-ones (**716a**) are rearranged by sodium hydride and sodium amide into 1-(alkylamino)imidazolidin-2-ones (**823**) (1056).



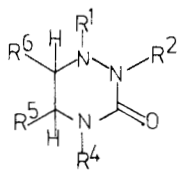
G. Tetrahydro-1,2,4-triazine-3-thiones

Most known tetrahydro-1,2,4-triazine-3-thiones (**824**) were prepared by the reaction of (2-aminoethyl)hydrazines (**800**) with carbon disulfide (1057–1061).

Pinson and his group (108) isolated the *cis*-5,6-diphenyltetrahydro-1,2,4-triazine-3-thione (**824b**, $R^1 = R^4 = H$, $R^5 = R^6 = \emptyset$) from the electrochemical

TABLE III-16. TETRAHYDRO-1,2,4-TRIAZIN-3-ONES

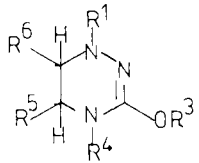
A. 1,4,5,6-Tetrahydro-1,2,4-triazin-3(2H)-ones

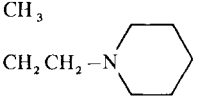


R^1	R^2	R^4	R^5	R^6	m.p. (°C)	Refs.
H	H	H	C_6H_5	C_6H_5		
				trans	220	108
				cis	240	108
					293 (dec.)	171, 172, 173, 174
H	CH_3	C_6H_5	H	H	114–116	1056
H	$(CH_3)_2N-CH_2CH_2$	C_6H_5	H	H	89–91	1056
H	$(CH_3)_2N-(CH_2)_3$	C_6H_5	H	H	95–97	1056
H	$C_6H_5-CH_2$	C_6H_5	H	H	149–151	1056
H	C_6H_5	C_6H_5	H	H	176–178	1056
H	CH_3CO	CH_3CO	C_6H_5	C_6H_5	218–219	172, 173

CH_3	H	H	H	H	154–155	1057
CH_3CO	CH_3CO	CH_3CO	C_6H_5	C_6H_5	203–204	171, 172, 173
C_6H_5	H	C_6H_5	H	H	210–212	1056
CH_3CO	C_6H_5	C_6H_5	H	H	120–121	1056
$4\text{-}CH_3\text{–}C_6H_4\text{–}SO_2$	C_6H_5	C_6H_5	H	H	152–154	1056

B. 3-Hydroxy-1,4,5,6-tetrahydro-1,2,4-triazines



R^1	R^3	R^4	R^5	R^6	m.p. (°C)	Refs.
H	CH_3	H	C_6H_5	C_6H_5	179–180	174
					181–182	171
H	CH_3	CH_3CO	C_6H_5	C_6H_5	172–172.5	171, 174
H		H	C_6H_5	C_6H_5	148–150/160	171
CH_3CO	CH_3	H	C_6H_5	C_6H_5	208	171, 174

reduction of 5,6-diphenyl-4,5-dihydro-1,2,4-triazine-3-thione (**825**, $R^5 = R^6 = \emptyset$).

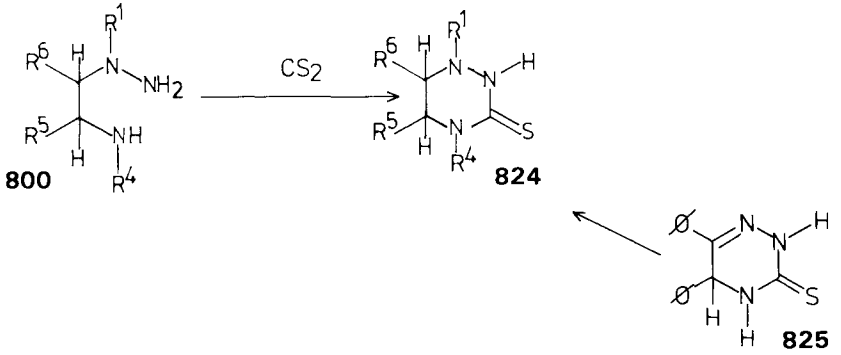
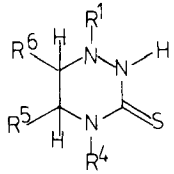


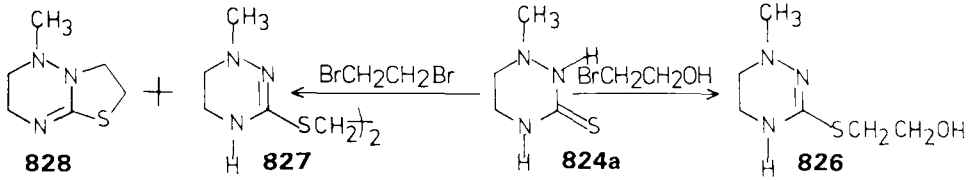
TABLE III-17. TETRAHYDRO-1,2,4-TRIAZINE-3-THIONES



R^1	R^4	R^5	R^6		m.p. (°C)	Refs.
H	H	H	H		163–164	1057
					176	1059
					178–180 (dec.)	1060
H	H	C_6H_5	C_6H_5	*cis*	215	108
CH_3	H	H	H		188–191	1058, 1061
					191	1059
CH_3	CH_2CH_2OH	H	H		109–110.5	1057, 1061
CH_3	$CH_2CH(OC_2H_5)_2$	H	H		99.5–101.5	1057
CH_3	$CH_2CH(C_6H_5)OH$	H	H		155–156	1057

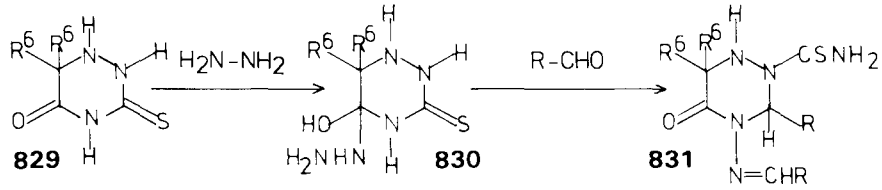
Tetrahydro-1,2,4-triazine-3-thiones (**824**) (Table III-17) are white or yellow compounds. Infrared and PMR spectroscopic data have been reported for most known **824** (1057, 1060, 1061). Alkylation of 1-methyl-tetrahydro-1,2,4-triazine-3-thione (**824a**) with 2-bromoethanol affords the 3-[(hydroxyethyl)-mercapto]-1-methyltetrahydro-1,2,4-triazine (**826**, oil) (1057) whereas reaction with 1,2-dibromoethane gave two compounds, the 3,3′-(ethylenedithio)-bis(1,4,5,6-tetrahydro-1-methyl-1,2,4-triazine) (**827**) (m.p. 131 to 132.5 °C)

and the 2,3,6,7-tetrahydro-5-methyl-5*H*-thiazolo[3,2-*b*] 1,2,4-triazine (**828**) (1061). Reaction of **824**, with 1,2-bifunctional compounds has been widely used for the synthesis of condensed 1,2,4-triazine systems (1057, 1058, 1061–1063).



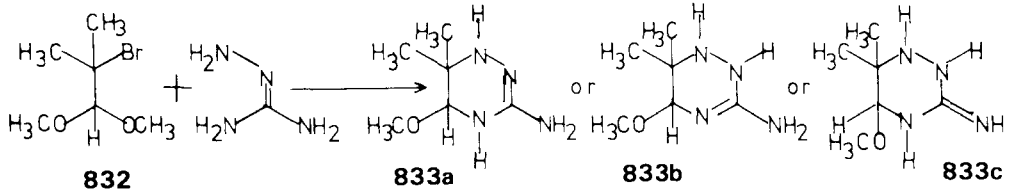
H. 5-Hydrazino-5-hydroxy-1,4,5,6-tetrahydro-1,2,4-triazine-3-thiones

Treatment of 3-thioxo-1,6-dihydro-1,2,4-triazin-5-ones (**829**) with hydrazine leads to an addition of hydrazine to the C=O-double bond of **829** and **830** (994) (CH_3, CH_3, 221 to 222 °C; $(CH_2)_5$, 198 to 199 °C) were isolated. Reaction of these compounds with benzaldehyde or isobutyraldehyde yields substances which may be formulated as the 1,2,4-triazine derivatives **831**.



I. 3-Amino-5-methoxytetrahydro-1,2,4-triazines

The product isolated from the reaction of 2-bromoisobutyraldehyde dimethylacetal (**832**) and aminoguanidine has one of the three given tautomeric structures **833a** to **833c** (994).



J. 5,6-Dihydroxy-1,4,5,6-tetrahydro-1,2,4-triazin-3-ones

Whereas reaction of 1,2-dicarbonyl compounds with semicarbazide is used for the synthesis of 1,2,4-triazin-3-ones, reaction of the sodium bisulfite addition products of aliphatic 1,2-dicarbonyl compounds with semicarbazide yields 5,6-dihydroxy-1,4,5,6-tetrahydro-1,2,4-triazin-3-ones (**834**) (Table III-18), (150, 151) which can be treated as the addition products of 2 moles of water to 1,2,4-triazin-3-ones. Reaction of these compounds with phosphorus trichloride affords 5,6-dichloro-1,4,5,6-tetrahydro-1,2,4-triazin-3-ones (**835**) (150).

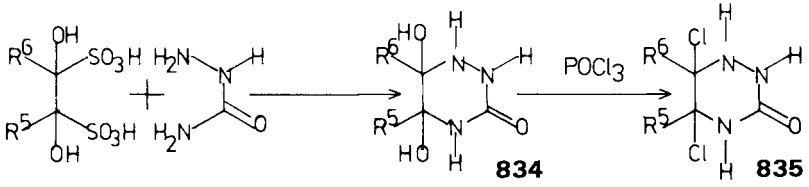


TABLE III-18. 5,6-DIHYDROXY-1,4,5,6-TETRAHYDRO-1,2,4-TRIAZIN-3-ONES (834)

R^5	R^6	Decomposition temp. (°C)	Refs.
H	H	265–270	150
H	CH_3 [a]	250–255	150, 151
CH_3	CH_3 [a]	240–245	150
CH_3	C_2H_5 [a]	230–235	150
CH_3	C_3H_7 [a]	240–245	150
CH_3	C_4H_9 [a]	230–235	150
CH_3	C_5H_{11} [a]	100–105	150

[a] And/or isomer.

K. 5,6-Dichloro-1,4,5,6-tetrahydro-1,2,4-triazin-3-ones

5,6-Dihydroxy-1,4,5,6-tetrahydro-1,2,4-triazin-3-ones (**834**) are converted into 5,6-dichloro-1,4,5,6-tetrahydro-1,2,4-triazin-3-ones (**835**) (Table III-19) by treatment with phosphorus trichloride (150).

L. 2,3,4,5-Tetrahydro-1,2,4-triazin-6-yl Ketones

Reaction of the monohydrazones of glyoxales (**836**) with formaldehyde and primary amines has been used for the synthesis of 2,3,4,5-tetra-

TABLE III-19. 5,6-DICHLORO-1,4,5,6-TETRAHYDRO-1,2,4-TRIAZIN-3-ONES (835)

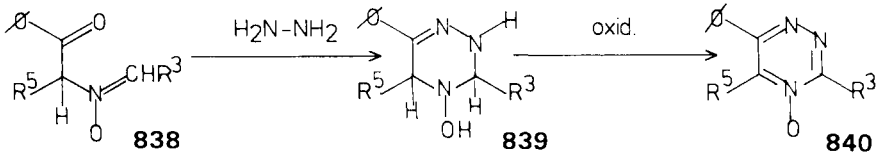
R^5	R^6	Decomposition temp. (°C)	Refs.
H	H	265–270	150
H	CH_3[a]	260–270	150
CH_3	CH_3	250–260	150
CH_3	C_2H_5[a]	240–245	150
CH_3	C_3H_7[a]	230–235	150

[a]And/or isomer.

hydro-1,2,4-triazin-6-yl ketones (**837**) (Table III-20) (1038–1040, 1544–1547). The carbonyl group of these substances reacts with Grignard reagents (1046); the methyl group in 6-acetyl derivatives can be condensed with aldehydes (1047).

M. 4-Hydroxy-2,3,4,5-tetrahydro-1,2,4-triazines

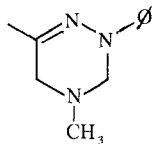
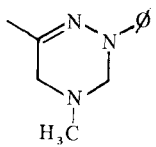
Reaction of the nitrones (**838**) with hydrazine yields the three 4-hydroxy-2,3,4,5-tetrahydro-1,2,4-triazines (**839**) ($R^3 = \emptyset$, R^5 = H, m.p. 172 to 174 °C; $R^3 = R^5 = CH_3$, 154 to 155 °C; $R^3 = \emptyset$, $R^5 = CH_3$, 181 to 183 °C), which can be oxidized to 1,2,4-triazine 4-oxides (**840**) (61).



N. 4-Amino-2,3,4,5-tetrahydro-1,2,4-triazines

Two methods are reported for the synthesis of 4-amino-2,3,4,5-tetrahydro-1,2,4-triazines (**841**), the reaction of β-hydrazonohydrazines (**842**) with carbonyl compounds (987, 1052, 1053), and the oxidative dimerization of formaldehyde phenylhydrazone (**843**) (1054).

TABLE III-20. 2,3,4,5-TETRAHYDRO-1,2,4-TRIAZIN-6-YL KETONES (837)

R^2	R^4	R^6	m.p. (°C)	Refs.
C_6H_5	CH_3	CH_3	88–90	1038, 1040, 1547
$\cdot CH_3I$			208–210	1038
$\cdot C_2H_5I$			189	1038
C_6H_5	CH_3	C_6H_5	101–103	1038, 1040
C_6H_5	CH_3	$C_6H_5-CH=CH$	151–151.5	1047
C_6H_5	CH_3	$4\text{-}O_2N-C_6H_4$	151–152	1041
C_6H_5	CH_3	$4\text{-}O_2N-C_6H_4-CH=CH$	183–184	1047
C_6H_5	CH_3	2-Furyl–CH=CH	118–119	1047
C_6H_5	CH_3		145.5–147	1544
$\cdot CH_3I$			89–90	1544
C_6H_5	C_2H_5	CH_3	52–53	1038, 1040
C_6H_5	C_2H_5	$4\text{-}O_2N-C_6H_4$	123–124.5	1041
C_6H_5	C_2H_5		189–191	1544
C_6H_5	C_3H_7	CH_3	79–80.5	1038, 1040
C_6H_5	$i\text{-}C_3H_7$	CH_3	64–65	1038, 1040
C_6H_5	$i\text{-}C_3H_7$	$4\text{-}O_2N-C_6H_4$	127.5–128.5	1041
C_6H_5	$CH_2=CH-CH_2$	CH_3	43–44	1038, 1040
C_6H_5	$CH_2=CH-CH_2$	$4\text{-}O_2N-C_6H_4$	106–107	1041

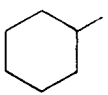
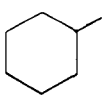
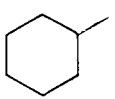
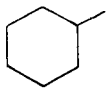
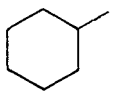
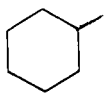
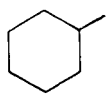
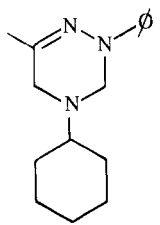
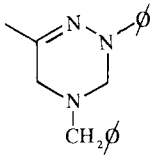
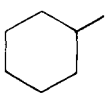
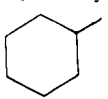
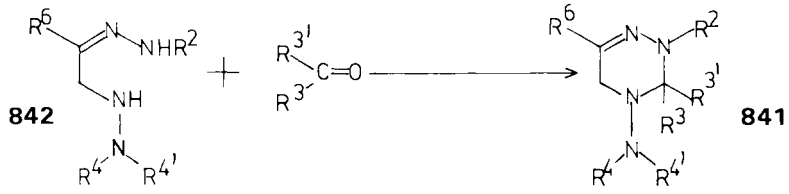
C_6H_5	C_4H_9	CH_3	·HCl	150–152	1038, 1040
C_6H_5	C_4H_9	$4\text{-}O_2N\text{–}C_6H_4$		115–116	1041
C_6H_5	$HOCH_2CH_2$	CH_3		92.5–93.5	1038
C_6H_5	$HOOC\text{–}CH_2$	CH_3		155–157	1039, 1546
C_6H_5	$HOOC\text{–}CH_2$	C_6H_5		146–148	1039, 1546
C_6H_5	$HOOC\text{–}CH_2$	$4\text{-}O_2N\text{–}C_6H_4$		138–140	1546
C_6H_5	$HOOC\text{–}CH(CH_3)$	CH_3		150–152	1039, 1546
C_6H_5	$HOOC\text{–}CH(CH_3)$	C_6H_5		165–167	1039, 1546
C_6H_5	$HOOC\text{–}CH(CH_3)$	$4\text{-}O_2N\text{–}C_6H_4$		144–146	1546
C_6H_5	$HOOC\text{–}CH(C_4H_9)$	CH_3		160–161	1039
C_6H_5	$HOOC\text{–}CH(CH_2CHMe_2)$	CH_3		169–170	1546
C_6H_5	$HOOC\text{–}CH(CH_2CHMe_2)$	C_6H_5		171–172	1546
C_6H_5	$HOOC\text{–}CH(CH_2\emptyset)$	CH_3		160–161	1546
C_6H_5	$HOOC\text{–}CH(CH_2\emptyset)$	C_6H_5		173–174	1546
C_6H_5	$HOOC\text{–}CH(CH_2COOH)$	CH_3		178–179	1546
C_6H_5	$HOOC\text{–}CH(CH_2COOEt)$	CH_3		88–89	1546
C_6H_5	$HOOC\text{–}CH(CH_2CH_2COOH)$	CH_3		150–151	1546
C_6H_5	 Cyclohexyl	CH_3		70–71	1040, 1547
C_6H_5	 Cyclohexyl	C_6H_5		101.5–102.5	1038
C_6H_5	 Cyclohexyl	$C_6H_5\text{–}CH{=}CH$		114–115	1047

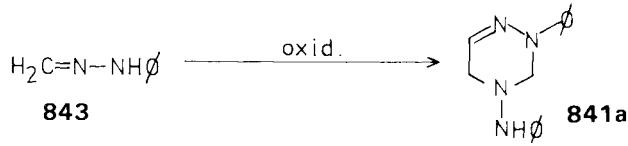
TABLE III-20. (continued)

R^2	R^4	R^6	m.p.(°C)	Refs.
C_6H_5	 Cyclohexyl	4-O_2N–C_6H_5	169.5–170.5	1041
·HCl			178.5–179	1041
C_6H_5	 Cyclohexyl	4-O_2N–C_6H_4–CH=CH	178.5–179.5	1047
C_6H_5	 Cyclohexyl	2-Furyl–CH=CH	99–100	1047
C_6H_5	 Cyclohexyl		112–113	1544
C_6H_5	C_6H_5–CH_2	CH_3	73–74	1040, 1547
C_6H_5	C_6H_5–CH_2	C_6H_5	95–96	1038
C_6H_5	C_6H_5–CH_2	C_6H_5–CH=CH	123–124	1047
C_6H_5	C_6H_5–CH_2	4-O_2N–C_6H_4	102–102.5	1041

C_6H_5	$C_6H_5-CH_2$	4-$O_2N-C_6H_4-CH=CH$	169–170	1047
C_6H_5	$C_6H_5-CH_2$	2-Furyl–CH=CH	105–106	1047
C_6H_5	$C_6H_5-CH_2$		138.5–139.5	1544
C_6H_5	C_6H_5	CH_3	119–121	1038, 1040
C_6H_5	C_6H_5	C_6H_5	126–128	1038, 1040
C_6H_5	C_6H_5	4-$O_2N-C_6H_4$	176–177	1041
C_6H_5	2-Naphthyl	CH_3	160–161	1038
4-Cl–C_6H_4	CH_3	2-Pyridyl	146–148	1545
4-Cl–C_6H_4	$C_6H_5-CH_2$	C_6H_5	140–141	1040, 1547
4-$O_2N-C_6H_4$	CH_3	CH_3	150–152	1038
4-$O_2N-C_6H_4$	CH_3	C_6H_5	149–151	1038
4-$O_2N-C_6H_4$	*i*-C_3H_7	CH_3	121–122	1038
4-$O_2N-C_6H_4$	HOOC–CH_2	CH_3	161–162	1546
4-$O_2N-C_6H_4$	HOOC–$CH(CH_3)$	CH_3	185–186	1546
2,4-$(O_2N)_2C_6H_3$	 Cyclohexyl	C_6H_5	158–160	1040, 1547
4-$CH_3O-C_6H_4$	 Cyclohexyl	C_6H_5	99–100.5	1040, 1547
3-HOOC–C_6H_4	CH_3	C_6H_5	231–233	1038, 1040
4-HOOC–C_6H_4	CH_3	C_6H_5	239–241	1038, 1040



842 841



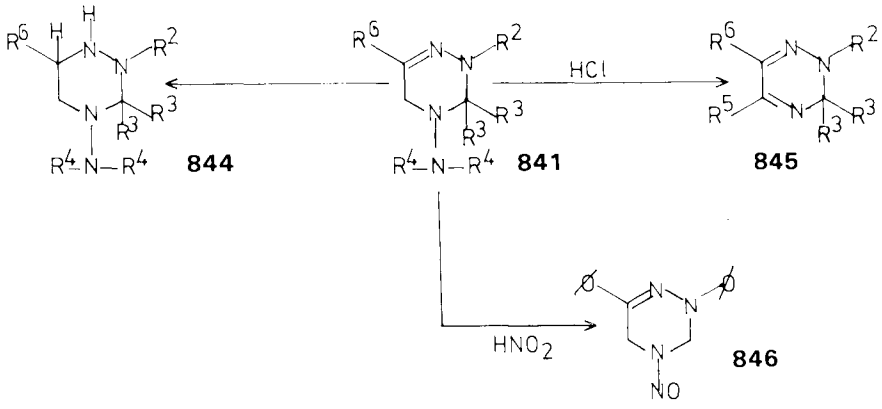
843 841a

4-Amino-2,3,4,5-tetrahydro-1,2,4-triazines (Table III-21) are usually colorless compounds which are soluble in most organic solvents, they can be recrystallized from alcohols. PMR data have been reported for only one compound (1053). Reduction of **841** either with lithium aluminum hydride or catalytically yields 4-amino-hexahydro-1,2,4-triazines (**844**) (1048, 1053). Treatment of **841** with HCl converts these compounds into 2,3-dihydro-1,2,4-triazines (**845**) (987).

TABLE III-21. 4-AMINO-2,3,4,5-TETRAHYDRO-1,2,4-TRIAZINES (841)

R^2	R^3	$R^{3'}$	R^4	$R^{4'}$	R^6	m.p. (°C)	Refs.
C_6H_5	H	H	H	H	C_6H_5	130	987
C_6H_5	H	H	H	C_6H_5	H	112	1048
						113–113.5	1054
C_6H_5	H	H	4-Cl–C_6H_4–CH=		4-Br–C_6H_4	180 (dec.)	1052
C_6H_5	H	CH_3	H	C_6H_5	H	116–117	1053
C_6H_5	H	CH_3	C_6H_5–CH=		C_6H_5	126	987
C_6H_5	H	CH_3	4-Cl–C_6H_4–CH=		4-Br–C_6H_4	166	1052
C_6H_5	H	C_6H_5	H	C_6H_5	H	142–143	1053
C_6H_5	H	C_6H_5	C_6H_5–CH=		C_6H_5	159–160	987
C_6H_5	H	C_6H_5	4-Cl–C_6H_4–CH=		4-Br–C_6H_4	163–164	1052
C_6H_5	H	2-O_2N–C_6H_4	H	C_6H_5	H	118–119	1053
C_6H_5	H	2-HO–C_6H_4	H	C_6H_5	H	150–152	1053
C_6H_5	H	C_6H_5–CH=CH	H	C_6H_5	H	143–145	1053
C_6H_5	CH_3	CH_3	H	C_6H_5	H	143–144	1053
C_6H_5	CH_3	CH_3	C_6H_5–CH=		C_6H_5	176	987
C_6H_5	CH_3	C_2H_5	H	C_6H_5	H	135–136	1053
C_6H_5	CH_3	$CH_2COOC_2H_5$	H	C_6H_5	H	119–120	1053
C_6H_5	CH_3	C_6H_5	C_6H_5–CH=		C_6H_5	153–154	987
C_6H_5		$-(CH_2)_5-$	H	C_6H_5	H	162–165	1053
$CONH_2$	H	C_6H_5	C_6H_5–CH=		C_6H_5	205–206	987

Reaction of 4-amino-2,6-diphenyl-2,3,4,5-tetrahydro-1,2,4-triazine (**841b**) (R^3 = R^4 = H, R^2 = R^6 = Ø) with nitrous acid led to the isolation of 4-nitroso-2,6-diphenyl-2,3,4,5-tetrahydro-1,2,4-triazine (**846**) (m.p. 109 to 110 °C) (987).



III. HEXAHYDRO-1,2,4-TRIAZINES

A. Alkyl- and Aryl-Substituted Hexahydro-1,2,4-triazines

Hexahydro-1,2,4-triazines (**847**) (Table III-22) are obtained through reaction of 1-[2-(methylamino)ethyl]-1-methylhydrazine (**848**) with carbonyl compounds (1064, 1065). Treatment of 2-[(dimethylamino)methyl]-1-methyl-1-(2-chloroethyl)hydrazine (**849**) with base converts it into 1,4,4-trimethylhexahydro-1,2,4-triazinium chloride (**850**) (1066, 1563), which can be transformed into a crystalline dipicrate (m.p. 153 to 156 °C).

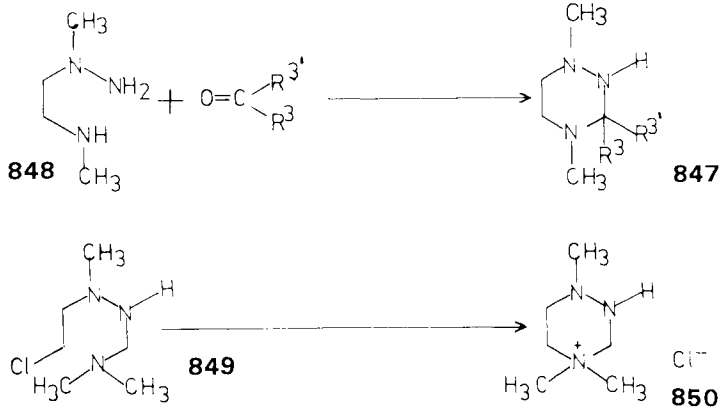
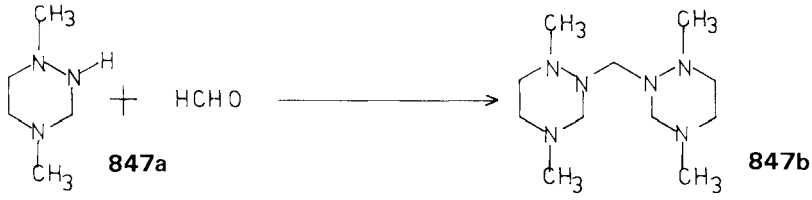


TABLE III-22. HEXAHYDRO-1,2,4-TRIAZINES

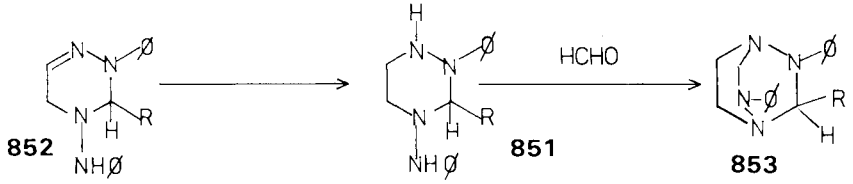
R^3	$R^{3'}$	b.p. (°C/torr)	Refs.
H	H	66/40	1064
H	CH_3	76/40	1064
H	C_2H_5	66/20	1064
H	*i*-C_3H_7	75/20	1064
H	*i*-C_4H_9	94/20	1064
CH_3	CH_3	49/20	1064
CH_3	C_2H_5	91/40	1064
H	C_6H_5	114–115/1.5	1065

Reaction of the 1,4-dimethyl-hexahydro-1,2,4-triazine (**847a**) with formaldehyde yields the bis(1,4-dimethylhexahydro-1,2,4-triazin-2-yl)methane (**847b**) (160 °C/5 torr) (1064).



B. 4-Aminohexahydro-1,2,4-triazines

Two 4-amino-hexahydro-1,2,4-triazines (**851**) (R = H, oily; R = CH_3, m.p. 131 to 132 °C) were synthesized through reduction of 4-amino-2,3,4,5-tetrahydro-1,2,4-triazines (**852**) (1048, 1053). 4-Anilino-2-phenylhexahydro-1,2,4-triazine (**851a**) (R^3 = H) is converted into the bicyclic compound **853**, when treated with formaldehyde (1048).



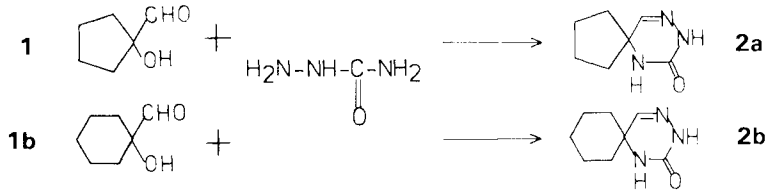
Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

IV

Condensed 1,2,4-Triazine Systems

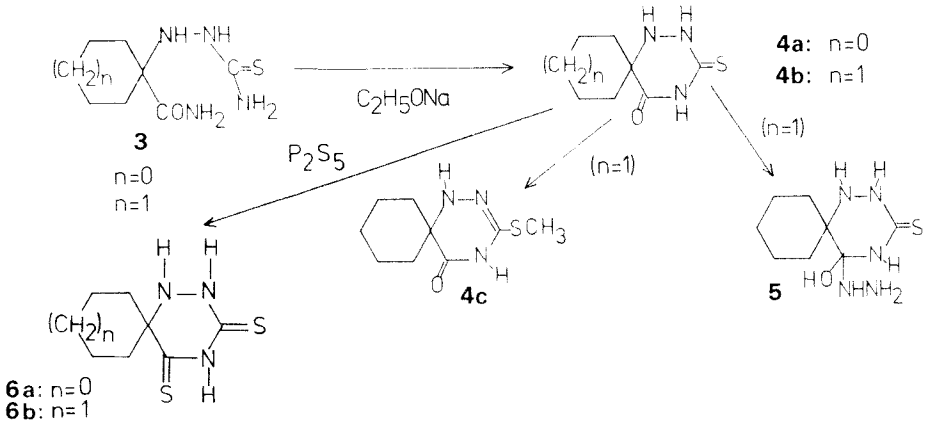
I. 1,2,4-TRIAZINE RINGS AS PARTS OF SPIRO RING SYSTEMS

Two compounds in which the 1,2,4-triazine ring has one carbon atom in common with an alicyclic ring and shares no other, have been reported by Venus-Danilova (954, 955). Reaction of 1-hydroxycyclopentanecarboxaldehyde (**1a**) or 1-hydroxycyclohexanecarboxaldehyde (**1b**) with semicarbazide yielded, respectively, 6,8,9-triazaspiro[4.5]dec-9-en-7-one (**2a**) (m.p. 216 to 218 °C) and 1,3,4-triazaspiro[5.5]hendec-4-ene-2-one (**2b**) (m.p. 221 to 223 °C). Both compounds are soluble in warm acidic or basic solution and are reprecipitated unchanged upon neutralization; they were mentioned in Section I-C of Chapter III.



Cyclization of 1-(1-thiosemicarbazido)cycloalkanecarboxamides (**3**) with sodium ethoxide yields 8-thioxo-6,7,9-triazaspiro[4.5]decan-10-one (**4a**) [m.p. 226 to 228 °C (dec.)] (1014) and 3-thioxo-1,2,4-triazaspiro[5.5]hendecan-5-one (**4b**) [m.p. 223 to o 224 °C (1014), 224 °C (995), 226 to 227 °C (994)], respectively. **4b** is methylated to give 3-(methylmercapto)-1,2,4-triazaspiro-[5.5]hendec-2-en-5-one (**4c**) [m.p. 134 °C (994)] and adds hydrazine to afford 5-hydrazino-5-hydroxy-1,2,4-triazaspiro[5.5]hendecane-3-thione (**5**) [m.p. 198 to 199 °C (994)]. Treatment of **4a** and **4b** with phosphorus pentasulfide was used for the synthesis of the two dithiones **6a** (m.p. 196–197 °C) and **6b** (m.p.

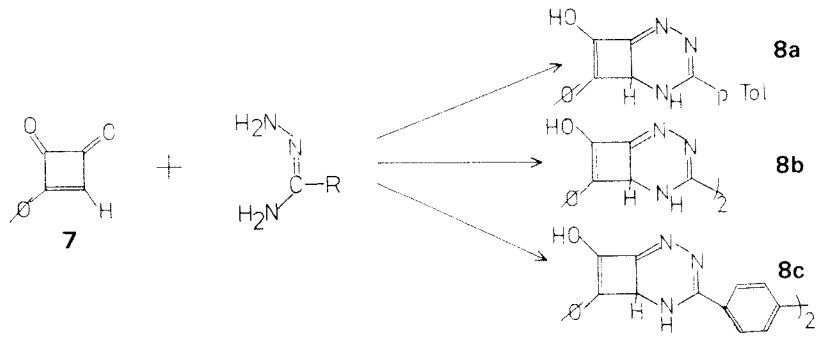
227–228 °C) (1013). Compounds **4a** to **4c**, **5**, **6a** and **6b** have been mentioned in previous chapters.



II. 1,2,4-TRIAZINE RINGS CONDENSED WITH ALICYCLIC RING SYSTEMS

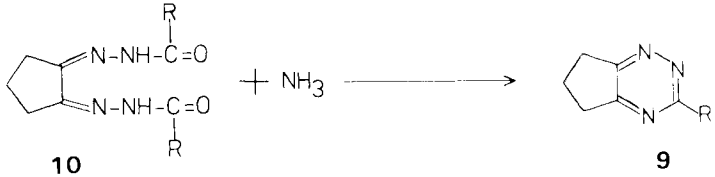
A. Condensed with Cyclobutane

Ried and Schomann (1105) studied the reaction of 1-phenylcyclobutene-3,4-dione (**7**) with amidrazones and observed the formation of the three 1-hydroxy-2-phenyl-2a,3-dihydrocyclobuta[e] 1,2,4-triazines (**8a** to **8c**): [**8a**, m.p. 159 to 160 °C, ·HCl 175 to 177 °C (dec.); **8b**, 225 to 227 °C (dec.); **8c**, 260 to 261 °C (dec.)]. They were not able to oxidize the isolated compounds, but methylation of **8a** (m.p. 190 to 192 °C) and acetylation of **8a** (m.p. 177 to 178 °C) is reported. The structure of the derivatives of **8a** is not fully established.



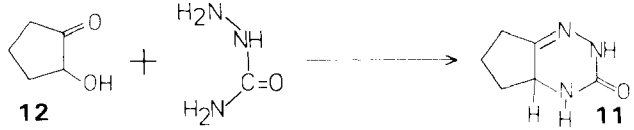
B Condensed with Cyclopentane

Metze and Schreiber (1106) observed the formation of cyclopenta[*e*] 1,2,4-triazines (**9**) (R = H, b.p. 109 to 111 °C/12 torr; R = CH_3, b.p. 118 to 120 °C, m.p. 46 to 47 °C; R = C_6H_5, m.p. 100 °C) when the bis-(acylhydrazones) of cyclopentane-1,2-dione (**10**) were heated with ammonia in methanol. The yellow compounds isolated were unstable and darkened when stored in the air.



10 **9**

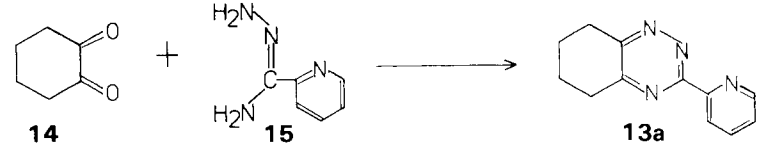
Venus–Danilova (1107) isolated 4,5-dihydrocyclopenta[*e*] 1,2,4-triazin-3-one (**11**) upon heating 2-hydroxycyclopentanone (**12**) with semicarbazide. The light yellow powder has a melting point of 194 °C (dec.) and is soluble in warm acids and bases.



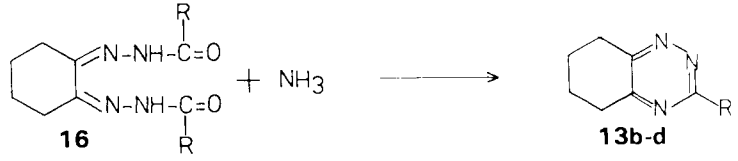
12 **11**

C. Condensed with Cyclohexane

Case (24) synthesized 3-(2-pyridyl)cyclohexa[*e*] 1,2,4-triazine (**13a**) (m.p. 119 to 120 °C) from the reaction of cyclohexane-1,2-dione (**14**) with picolinamide hydrazone (**15**); Metze and Schreiber (1106) converted the bisacyl-hydrazones of **14** (**16**) into **13b** to **13d** by treatment with ammonia in methanol [**13b**, R = H, m.p. 14 °C, b.p. 125 °C/14 torr, ·HCl m.p. 207 °C (dec.); **13c**, R = CH_3, m.p. 77 °C, ·HCl m.p. 202 °C (dec.); **13d**, R = C_6H_5, m.p. 93 °C, ·HCl m.p. 213 °C, (dec.)].

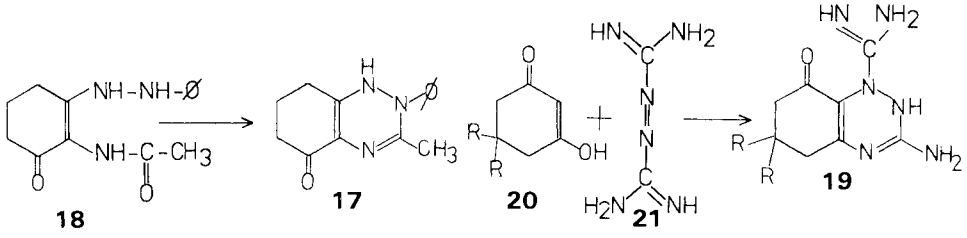


14 **15** **13a**



16 **13b-d**

Teuber and his group (1108) obtained 3-methyl-5-oxo-2-phenyl-1,2-dihydrocyclohexa[*e*] 1,2,4-triazine (**17**) (m.p. 248 °C) through cyclization of compound **18**, and Kreutzberger and Schücker (1109) synthesized 3-amino-1-guanyl-1,2-dihydrocyclohexa[*e*] 1,2,4-triazin-8-ones (**19**) [R = H, $\cdot HNO_3 \cdot H_2O$, m.p. 134 to 135 °C (dec.); R = CH_3, $\cdot HNO_3 \cdot H_2O$, m.p. 158 to 159 °C (dec.)] by the reaction of cyclohexane-1,3-diones (**20**) with azodicarboxylic acid diamidine (**21**).



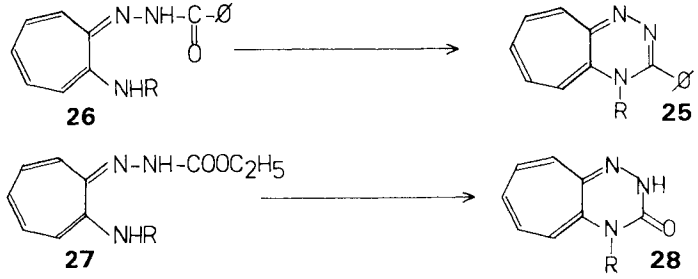
18 **17** **20** **21** **19**

D. Condensed with Cycloheptane

The condensation of cycloheptane-1,2-dione (**22**) with formamidrazone (**23**) was used for the synthesis of cyclohepta[*e*] 1,2,4-triazine (**24**) (b.p. 64 °C/0.1 torr) (1110).

22 **23** **24**

A number of cyclohepta[*e*] 1,2,4-triazine derivatives (**25**) were synthesized by Sato and Soma (1111, 1112) by cyclization of 1-amino-2-(benzoylhydrazono)cycloheptatrienes (**26**). Cyclization of 1-amino-2-[(ethoxycarbonyl)hydrazono] cycloheptatrienes (**27**) yielded cyclohepta[*e*] 1,2,4-triazin-3-ones (**28**) [R = H, m.p. 231 °C (dec.); R = CH_3, m.p. 199 °C; R = 4-CH_3O-C_6H_4, m.p. 225 °C]. The hydroxy tautomer of **28** could not be detected by infrared spectroscopy.



26 **25** **27** **28**

Reaction of 5-nitrosotropolones (**29**) with aminoguanidine was used for the synthesis of 3-amino-7-nitrosocyclohepta[*e*] 1,2,4-triazines (**30**) (1559). Known compounds of this class are listed in Table IV-1.

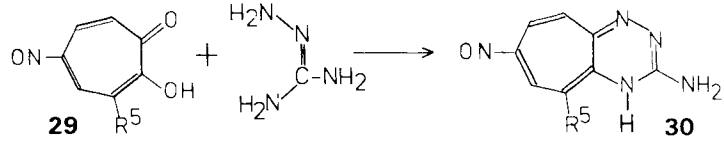
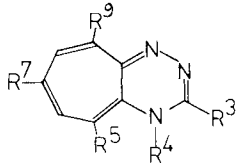


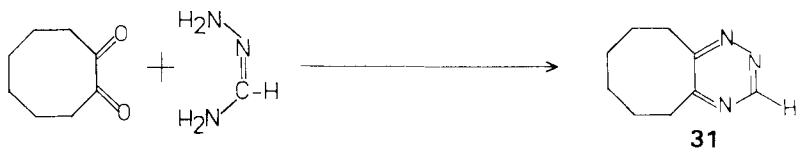
TABLE IV-1. CYCLOHEPTA[*e*] 1,2,4-TRIAZINES



R^3	R^4	R^5	R^7	R^9	m.p. (°C)	Refs.
C_6H_5	H	H	H	H	101	1111
C_6H_5	CH_3	H	H	H	173	1111, 1112
C_6H_5	CH_3	H	Cl	H	181	1111
C_6H_5	CH_3	H	H	CH_3	167	1111
C_6H_5	C_6H_5	H	H	H	217	1111
C_6H_5	C_6H_5	H	Cl	H	185	1111
C_6H_5	4-CH_3–C_6H_4	H	H	H	196	1111
C_6H_5	4-CH_3O–C_6H_4	H	H	H	163	1111
NH_2	H	H	NO	H	300	1559
NH_2	H	CH_3	NO	H	300	1559
NH_2	H	C_6H_5O	NO	H	217 (dec.)	1559
NH_2	H	HCONH	NO	H	300	1559
$NHCOCH_3$	H	H	NO	H	215	1559
$NHCOC_6H_5$	H	H	NO	H	205	1559

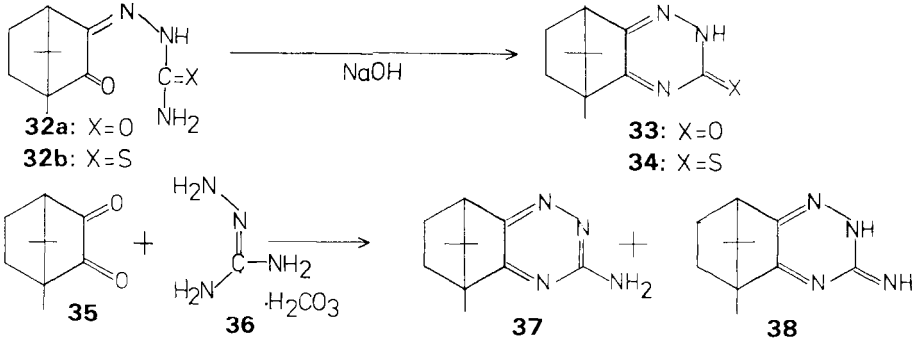
E. Condensed with Cyclooctane

The reaction of cyclooctane-1,2-dione with formamidrazone affords cyclooctano[*e*] 1,2,4-triazine (**31**) (b.p. 75 °C/0.1 torr) in high yields (1110).



F. Condensed with the Norcamphane System

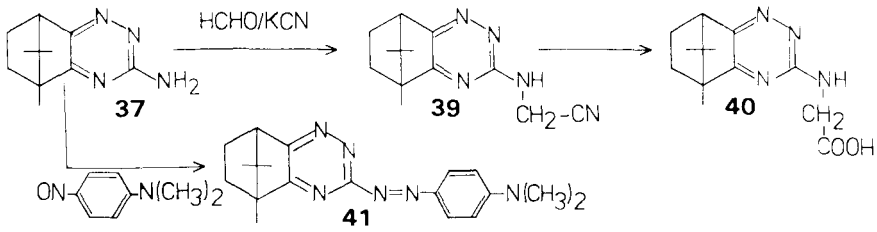
Cyclization of camphorquinone semicarbazone (**32a**) or thiosemicarbazone (**32b**) in sodium hydroxide solution afforded, respectively, 9,9-dimethyl-5,6,7,8-tetrahydro-5,8-methano-1,2,4-benzotriazin-3-one (**33**) (m.p. 166 to 167 °C) or -3-thione (**34**) (m.p. 207 °C) (1113, 1114). Hadacek and Kisa isolated two compounds from the reaction of camphorquinone (**35**) with aminoguanidine carbonate (**36**). These were formulated as 3-amino-9,9-dimethyl-5,6,7,8-tetrahydro-5,8-methano-1,2,4-benzotriazine (**37**) (m.p. 265 °C) and its imino tautomer (**38**) (m.p. 235 °C) (670). Compound **38**, which shows three maxima in the ultraviolet spectrum (225, 275, and 318 nm), is slowly transformed into compound **37**, which shows only two maxima (223 and 318 nm).



Compounds **33** and **34** can be acetylated (X = O, m.p. 168 to 169 °C) and benzoylated (X = O, 193 to 194 °C) (1113, 1114). The structure of the isolated compounds was not determined. It can be assumed, because of the 2-acylation of uncondensed 1,2,4-triazine-3-ones or -3-thiones, that the 2-acylated products were obtained. Compound **34** can be converted into **33** by treatment with silver oxide in ammonia (1114).

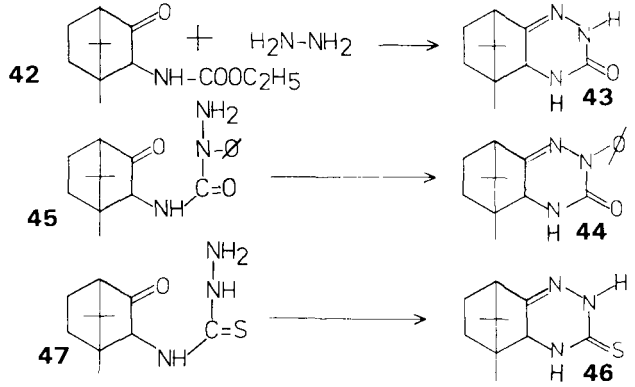
Reaction of the amino compound (**37**) with formaldehyde and potassium cyanide affords the cyanomethylamino derivative (**39**) (m.p. 186 °C) which can be hydrolyzed to the acid (**40**) (670). The azo compound (**41**) was isolated from the reaction of **37** with p-nitrosodimethylaniline (670). Compound **37** reacts with nitrous acid. The structure of the isolated nitroso compound is unknown (670).

Rupe and Buxtorf (968) treated 3-camphorylurethane (**42**) with hydrazine and obtained the dihydro derivative (**43**) of **33** (m.p. 314 to 315 °C). **43** forms a monoacetyl derivative (m.p. 183 °C) by treatment with acetic anhydride. The dihydro derivative (**46**) of **34** (m.p. 239 °C) is reported by McRae and Stevens (1116), who cyclized 4-(3-camphoryl)thiosemicarbazide (**47**) with dilute



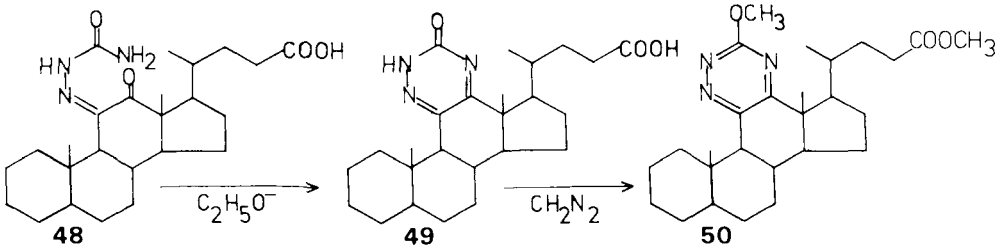
hydrochloric acid. The silver salt of **46** reacts with methyl iodide to form the *S*-methyl derivative (m.p. 107 °C) (116).

The 2-phenyl derivative **44** (m.p. 235 °C) was synthesized by Forster and Jackson (1115) through cyclization of 4-(3-camphoryl)-2-phenylsemicarbazide (**45**).



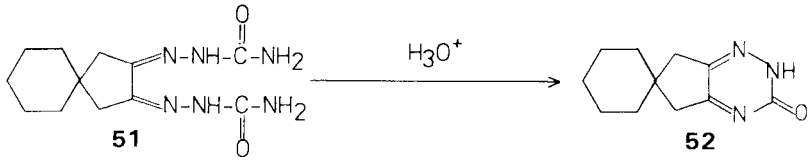
G. Condensed with the Cyclopentaphenanthrene System

Bergström and Haslewood (1117) prepared the monosemicarbazone of 11,12-dioxocholanic acid (**48**). This, subjected to the conditions of the Wolff–Kishner reaction, gave a 1,2,4-triazine, the structure of which is probably **49** (m.p. 292 to 293 °C). Methylation of **49** with diazomethane yielded **50** (m.p. 142 to 143 °C).



H. Condensed with the Spiro[4.5]decane System

Kon (1118) prepared the bis-(semicarbazone) of 2,3-dioxospiro[4.5] decane (**51**) and transformed it into the 1,2,4-triazin-3-one (**52**) [m.p. 295 °C (dec.)] by treatment with mineral acids. **52** is soluble in sodium hydroxide solution and dissolves in concentrated sulfuric acid, giving a deep orange color.



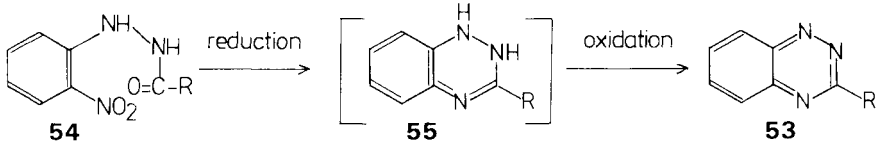
III. CONDENSED WITH THE BENZENE RING

A. 1,2,4-Benzotriazines

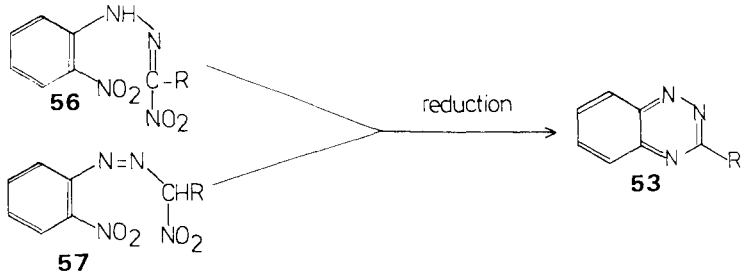
1. *Alkyl-, Aryl-, and Heterocyclic-Substituted 1,2,4-Benzotriazines*

a. PREPARATION. For many years this ring system was called α-phentriazine, following a proposal by Widman (1146) in 1888. In the following discussion we call all compounds of this structure 1,2,4-benzotriazines. A review on 1,2,4-benzotriazines is published by Armarego (2315).

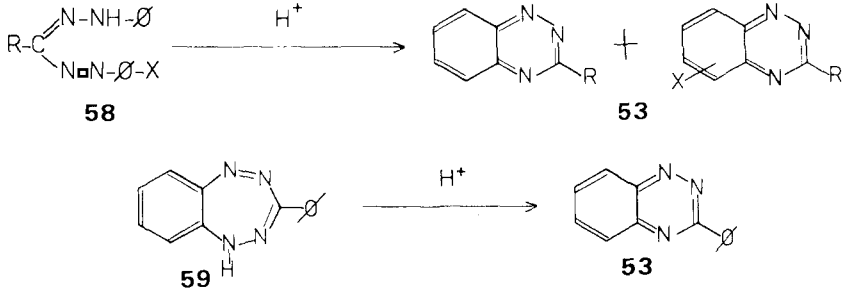
Bischler (1147) in 1889 reported the first synthesis of the parent compound (**53a**), by reduction of the *o*-nitrophenylhydrazide of formic acid (**54a**) with sodium amalgam in alcoholic acetic acid. The initially formed dihydro-1,2,4-benzotriazine (**55a**) was not isolated but oxidized with potassium ferricyanide. The reduction of the *o*-nitrophenylhydrazides of carboxylic acids (**54**) was used for the synthesis of substituted 1,2,4-benzotriazines (**53**) (1119, 1147, 1148).



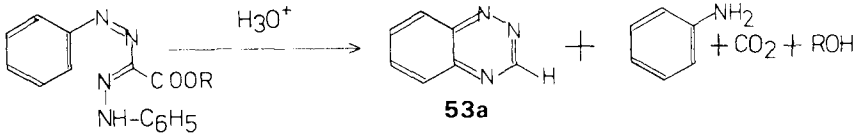
A method that is very similar to the first described synthesis, was first used by Jerchel and Elder (1145) in 1955 for the synthesis of the unsubstituted 1,2,4-benzotriazine and later by Fusco and his group (1137, 1139) and by Kwee and Lund (1138) for the synthesis of substituted 1,2,4-benzotriazines. By this method 1,2,4-benzotriazines (**53**) were obtained through reduction of nitroaldehyde *o*-nitrophenylhydrazones (**56**) or of the tautomeric azo compounds (**57**).



At present the most frequently used method for the synthesis of 1,2,4-benzotriazines (**53**) is the conversion of formazanes (**58**) into **53** by treatment with sulfuric acid in acetic acid (1119–1132). Using mixed formazanes as starting material two different 1,2,4-benzotriazines can be synthesized. Intensive studies by Jerchel and Woticky (1125) showed that, in most cases, both 1,2,4-benzotriazines were formed but that one was predominant. This result corrects earlier statements on this reaction, in which it was stated that only one of the 1,2,4-benzotriazines could be isolated. Cyclic formazanes, such as **59**, can also be used for the synthesis of **53** (1145).

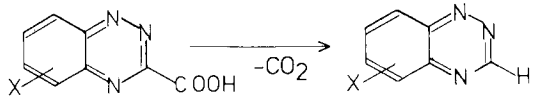


When the formazanes (**58a** and **58b**) were used in this reaction the unsubstituted 1,2,4-benzotriazine (**53a**) was obtained [Bamberger and Wheelwright (1121, 1122)]. From this result it follows that, under the reaction conditions used, not only cyclization with elimination of aniline occurs, but also saponification and decarboxylation.



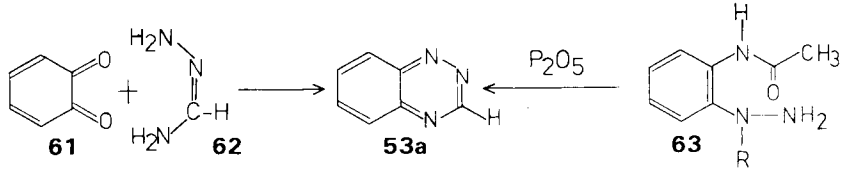
58a. R = H, **58b**: R = CH_3

Decarboxylation of 1,2,4-benzotriazine-3-carboxylic acids (**60**) was used by Fusco and Rossi (1133, 1134) for the synthesis of **53**.



60 **53**

The synthesis of the unsubstituted 1,2,4-benzotriazine (**53a**) by the reaction of *o*-quinone (**61**) with formamidrazone (**62**) is reported by Neunhoeffer and Hennig (13), but the yield is very low (4%). Hempel (1135) has reported an interesting synthesis of the unsubstituted 1,2,4-benzotriazine (**53a**). 1-(*o*-Acetamidophenyl)-1-methylhydrazine (**63a**) or its ethyl analogue (**63b**) are converted into **53a** on standing with phosphorus pentoxide at room temperature.

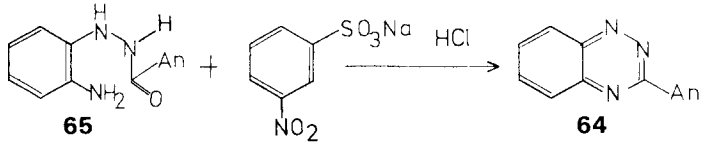


61 **62** **53a** **63**

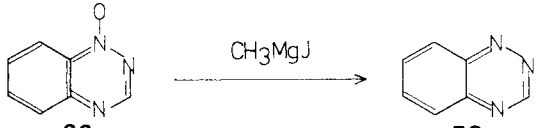
a: R = CH_3

b: R = C_2H_5

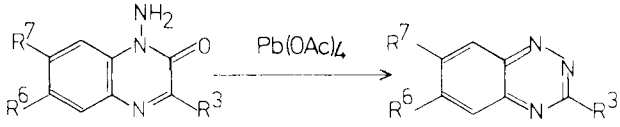
Glover and his co-worker (1136) obtained 3-(4-anisyl)-1,2,4-benzotriazine (**64**), in addition to other products, when they treated the *o*-aminophenylhydrazide (**65**) with concentrated hydrochloric acid in the presence of sodium *m*-nitrobenzenesulfonate. Reduction of 1,2,4-benzotriazine 1-oxide (**66**) with methylmagnesium iodide is reported by Igeta and his group (1142). The catalytic reduction of 1,2,4-benzotriazine 1-oxides is published by Tennant (1144). Rees and his co-worker (1143) reported the conversion of 1-aminoquinoxalinones (**67**) into **53** by treatment with lead tetraacetate.



65 **64**

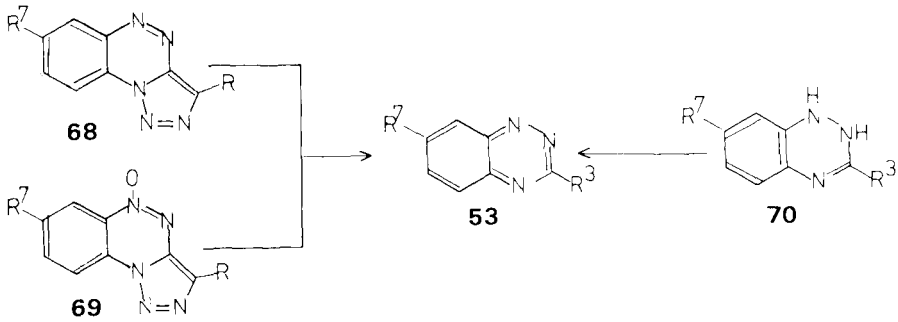


66 **53a**

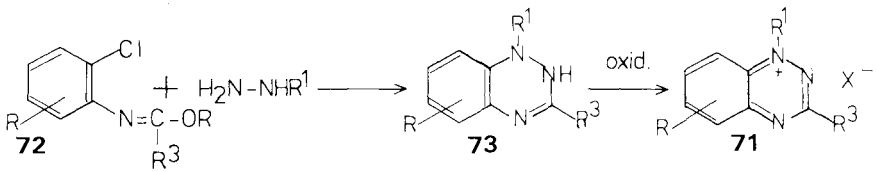


67 **53**

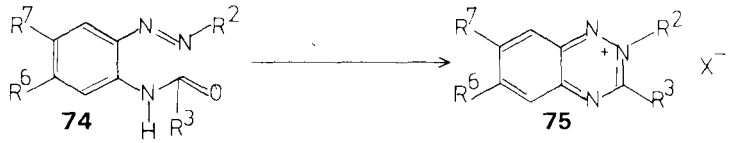
Tennant (1131, 1144) obtained 1,2,4-benzotriazines (**53**) when he heated 1,2,3-triazolo[5,1-*c*]1,2,4-benzotriazines (**68**) or their 5-oxides (**69**) in glacial acetic acid. In some cases sodium dithionite was added. He also obtained **53** through oxidation of dihydro-1,2,4-benzotriazines (**70**).



1-Alkyl- or 1-aryl-1,2,4-benzotriazinium salts (**71**) were obtained by Pallos and Benko (1141), starting from *o*-chlorophenyl imidates (**72**) and substituted hydrazines, with subsequent oxidation of the initially formed dihydro compounds (**73**).



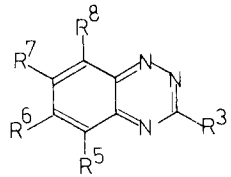
2-Alkyl- or 2-aryl-1,2,4-benzotriazinium salts (**75**) are reported by Leverenz and Schuendehuette (1140) who cyclized *o*-acylamidophenylazo compounds (**74**).



b. COMPOUND SURVEY. Compounds of this class that have been reported in the literature are listed in Table IV-3.

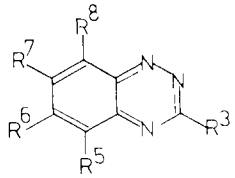
c. PHYSICAL PROPERTIES. The 1,2,4-benzotriazines discussed in this section are yellow, orange, or orange-red crystalline, stable compounds. Most of them are soluble in the majority of organic solvents. Unsubstituted 1,2,4-benzotriazine and its 3-methyl analogue can be distilled at normal pressure without

TABLE IV-2. ALKYL-, ARYL-, AND HETEROCYCLIC-SUBSTITUTED 1,2,4-BENZOTRIAZINES



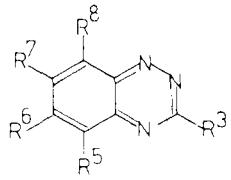
R^3	R^5	R^6	R^7	R^8	m.p. (°C)	Refs.
H	H	H	H	H	65–66	13, 1135, 1147
					71–72	1138
					74	1134
					74–75	1121, 1122, 1145
					76–77	1119
						1142, 1143
					b.p. 235–240	1147
					238–240	1135
H	H	H	H	OCH_3	149–150	1119
H	H	CH_3	H	H	68	1134
H	H	Cl	H	H	104	1134
H	H	Br	H	H		1148
H	H	OCH_3	H	H	154	1134
H	H	CH_3CO	H	H	138–139	1133
H	H	NH_2	H	H	297–298	1133
					298–299	1119
Picrate					227–228	1133
CH_3	H	H	H	H	88–89	1147
					89–90	1138
					90	1139
					97–98	1119
						1143
CH_3	H	H	H	OCH_3	124–125	1119
CH_3	H	CH_3	H	H	58–59	1139
CH_3	H	Cl	H	H	86	1139
CH_3	H	Br	H	H	115	1148
CH_3	H	OCH_3	H	H	148–149	1139
CH_3	H	NH_2	H	H	265–266	1119
C_2H_5	H	H	H	H	140–142	1137
						1138
t-C_4H_9	H	NO_2	H	H	91–92	1126
n-C_5H_{11}	H	H	H	H	b.p. 131–135/76	1139
n-C_7H_{15}	H	H	H	H	b.p. 160/0.8	1139
$C_6H_5-CH_2$	H	H	H	H	76–77	1137
					87	1131, 1144

TABLE IV-2. (continued)



R^3	R^5	R^6	R^7	R^5	m.p.(°C)	Refs.
$C_6H_5-CH_2$	H	H	CH_3	H	81	1131, 1144
C_6H_5-CHCl	H	H	CH_3	H	109	1144
C_6H_5-CHOH	H	H	H	H	130	1144
C_6H_5-CHOH	H	H	CH_3	H	145	1144
C_6H_5-CH $\vert$ $OCOCH_3$		H	CH_3	H	99	1144
C_6H_5	H	H	H	H	122–123	1138, 1139
					123	1124, 1128, 1145
					123–124	1125
					126–127	1119
						1143
C_6H_5	H	H	H	NO_2	204–205	1125
C_6H_5	H	H	H	OH	178–179	1129
					184–185	1125
C_6H_5	H	H	H	OCH_3	155–156	1119
C_6H_5	H	H	H	COOH	230–231	1125
C_6H_5	H	H	CH_3	H		1143
C_6H_5	H	H	Cl	H	164–165	1139
C_6H_5	H	CH_3	H	H	95–96	1125, 1128
						1143
C_6H_5	H	C_6H_5	H	H	135–136	1125
C_6H_5	H	Cl	H	H	134–135	1129, 1139
					135–136	1125
C_6H_5	H	NO_2	H	H	187–189	1129
					189–190	1125
C_6H_5	H	OCH_3	H	H	191	1139
					194–195	1125
					197–198	1119
C_6H_5	H	NH_2	H	H	251–252	1129
C_6H_5	H	COOH	H	H	240–242	1125
$4\text{-}O_2N-C_6H_4$	H	H	H	H	241–243	1129
$4\text{-}O_2N-C_6H_4$	H	OCH_3	H	H	228–229	1129
$4\text{-}Cl-C_6H_4$	H	H	H	H	151–152	1129
$4\text{-}Cl-C_6H_4$	H	H	H	Cl	259–260	1129
$4\text{-}Cl-C_6H_4$	H	H	H	OH	248–249	1129
$2\text{-}HO-C_6H_4$	H	H	H	H	167	1123

TABLE IV-2. (continued)



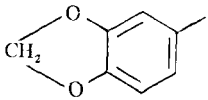
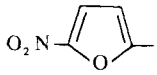
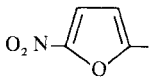
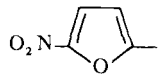
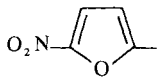
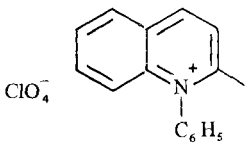
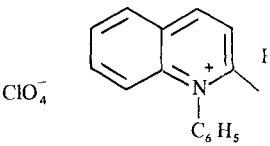
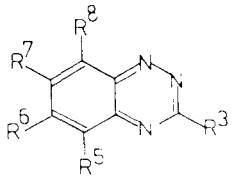
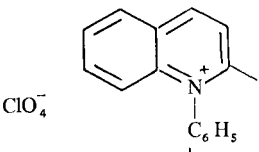
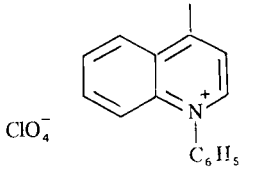
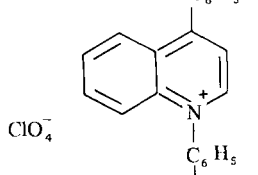
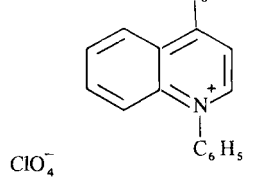
R^3	R^5	R^6	R^7	R^8	m.p.(°C)	Refs.
4-CH_3O–C_6H_4	H	H	H	H	139–140	1129 1139
4-CH_3O–C_6H_4	H	Cl	H	H	147–148	1129
4-CH_3O–C_6H_4	H	NO_2	H	H	314–315	1129
	H	H	H	H	154	1123
4-H_2N–C_6H_4	H	H	H	H	186–188	1129
4-H_2N–C_6H_4	H	OCH_3	H	H	190–192	1129
2,4-$(H_2N)_2C_6H_3$	H	H	H	H		1127
2,4-$(H_2N)_2C_6H_3$	H	Br	H	H	180	1127
	H	H	H	H	249–250	1120
	H	CH_3	H	H	241–242	1120
	H	NO_2	H	H	233–234	1120
	H	Cl	H	H	258–259	1120
	H	H	H	CH_3	212–213	1130
	H	H	H	Cl	220–221	1130

TABLE IV-2. (continued)



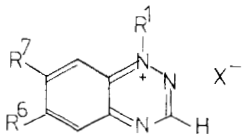
R^3	R^5	R^6	R^7	R^5	m.p.(°C)	Refs.
 ClO_4^-	H	H	H	OCH_3	239–230	1130
 ClO_4^-	H	H	H	CH_3	215–217	1130
 ClO_4^-	H	H	H	OCH_3	242–244	1130
 ClO_4^-	H	OCH_3	H	H	279–280	1130

decomposition. It is necessary to distill the higher homologues under reduced pressure. Carbon-14-labeled 1,2,4-benzotriazines were synthesized by Jerchel and Woticky (1125).

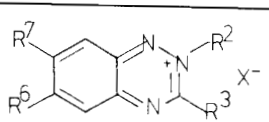
Until now only a small amount of spectroscopic data on 1,2,4-benzotriazines has been reported in the literature (85, 86, 1119, 1120, 1131, 1144, 1149–1153). Amarego and his group (1149) and Arata and co-workers (1120) published some bands of the infrared spectra of 1,2,4-benzotriazines.

The electronic spectra of 1,2,4-benzotriazines were measured by different groups in various solvents (1119, 1131, 1144, 1151–1153). Calculations of the electronic spectra were reported by the following methods: the Hückel

TABLE IV-3. 1,2,4-BENZOTRIAZINIUM SALTS



R^1	R^6	R^7	X	m.p. (°C)	Refs.
H	H	H	Cl	64–66	1141
H	H	CH_3	Br	201–203	1141
H	H	NO_2	Cl	161–162	1141
H	CF_3	H	Cl	272–274	1141
CH_3	H	H	Cl	258–260	1141
CH_3CO	H	H	Cl	131–132	1141
CH_3CO	H	CH_3	Br	154–156	1141
CH_3CO	H	NO_2	Cl	146–148	1141
C_6H_5	H	H	Cl	70–72	1141
C_6H_5	H	CH_3	Br	165–170	1141
C_6H_5	CF_3	H	Cl	98–100	1141
$2\text{-}O_2N\text{–}C_6H_4$	H	H	Cl	172	1141
$2\text{-}O_2N\text{–}C_6H_4$	H	NO_2	Cl	190–192	1141
$C_6H_5\text{–}CO$	H	H	Cl	145–150	1141
$C_6H_5\text{–}CO$	H	NO_2	Cl	139–141	1141



R^2	R^3	R^6	R^7	X	Refs.
$4\text{-}CH_3O\text{–}C_6H_4$	H	NEt_2	H	ClO_4	1140
$4\text{-}CH_3O\text{–}C_6H_4$	H	OCH_3	CH_3	Cl	1140

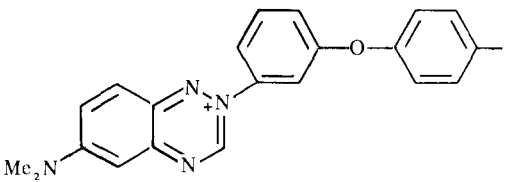
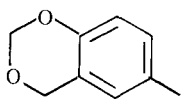
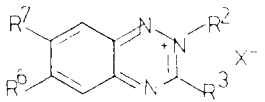
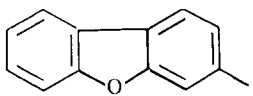
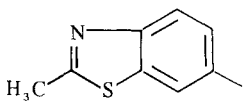
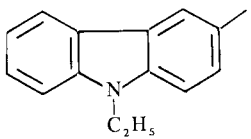
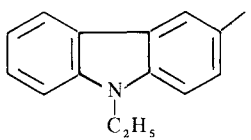
4-EtO–C_6H_4	EtO	C_6H_5–N–CH_3	H	BF_4	1140
4-C_6H_5–CH_2O–C_6H_4	NH_2	Et–N–CH_2CH_2OH	H	$ZnCl_3$	1140
4-C_6H_5–O–C_6H_4	H	NEt_2	H	Cl	1140
4-Et_2N–C_6H_4	H	NEt_2	H	ClO_4	1140
4-Et_2N–C_6H_4	H	OCH_3	OCH_3	ClO_4	1140
4-($C_6H_5(CH_3)N$)–C_6H_4	H	NEt_2	H	$ZnCl_3$	1140
2-EtO-1-naphthyl	H	NEt_2	H	Cl	1140
6-MeO-2-naphthyl	H	EtNH	CH_3	BF_4	1140
	H	NMe_2	H	2 $ZnCl_3$	1140
3,4-$(MeO)_2C_6H_3$	H	NEt_2	H	ClO_4	1140
2,4-$(MeO)_2C_6H_3$	CH_3	NEt_2	H	ClO_4	1140
3-Me-4-MeO–C_6H_3	C_6H_5	NEt_2	H	Cl	1140
2-MeO-4-(AcNEt)–C_6H_3	H	NH–CH_2–C_6H_5	H	Cl	1140
3-NO_2-4-EtO–C_6H_3	H	NH–Et	$COOC_2H_5$	Cl	1140
3-$Me_3\overset{+}{N}$-4-MeO–C_6H_3	H	NH–C_6H_5	H	Cl, Ø–SO_3	1140
3-EtCO-NH-4-MeO–C_6H_3	H	NH–CH_2CH_2CN	H	$ZnCl_3$	1140
2,5-$(MeO)_2$-4-Cl–C_6H_2	H	Et–N–$CH_2C_6H_5$	H	$ZnCl_3$	1140
2,5-$(MeO)_2$-4-AcNH–C_6H_2	H	Et–N–C_6H_{11}	H	Cl	1140
2,5-$(MeO)_2$-4-(4-MeO–C_6H_4–N=N)–C_6H_2	H	(n-C_3H_7)$_2$N	H	Cl	1140
2,5-$(MeO)_2$-4-(C_6H_5COHN)–C_6H_2	H	$N(CH_2CH_2OH)_2$	CH_3O	Cl	1140
	H	(n-C_4H_9)$_2$N	H	Cl	1140

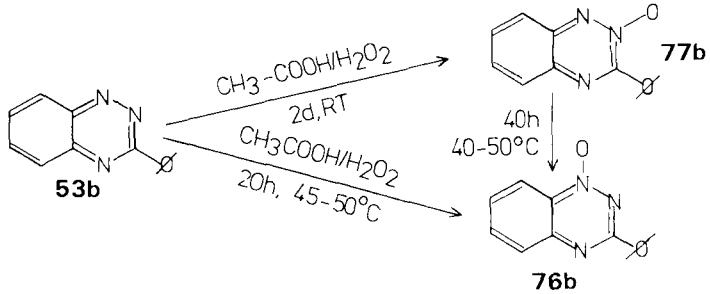
TABLE IV-3. (coninued)



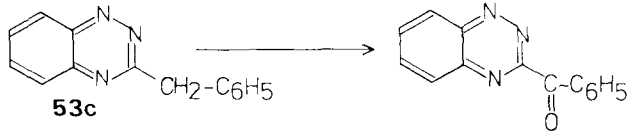
R^2	R^3	R^6	R^7	X	Refs.
	H	NEt_2	CH_3O	Cl	1140
	H	NMe_2	H	Cl	1140
	H	$NHCH_2CH_2CN$	Cl	ClO_4	1140
	H	NMe_2	H	$ZnCl_3$	1140
3-Cl–4-MeO–C_6H_3	H	$EtN–CH_2CH_2CH_2–$		ClO_4	1140
4-(4-CH_3–C_6H_4–O)–C_6H_4	H	$MeN–\underset{\displaystyle CH_3}{\underset{\vert}{CH}}–C(CH_3)_2–$		$ZnCl_3$	1140

method (1150), the semiempirical method of Pariser–Parr–Pople (85), the simplified version of the P-treatment given by Heilbronner and others (86), the standard LCAO method (1152), and the Pariser–Parr method (1150, 1152).

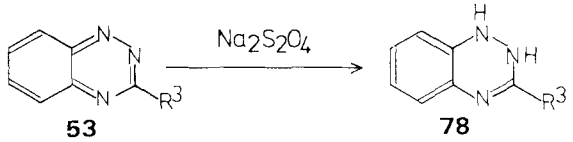
d. REACTIONS. The oxidation of 1,2,4-benzotriazines (**53**) with peracetic acid leads to the formation of 1,2,4-benzotriazine 1-oxides (**76**) (1129, 1142). The oxidation of the 3-phenyl-1,2,4-benzotriazine (**53b**) with peracetic acid gave two isomeric compounds, depending on the reaction conditions, which were formulated as the 1-oxide (**76b**) and the 2-oxide (**77b**). Heating of the 2-oxide (**77b**) for 40 h at 45 to 50 °C in acetic acid yielded the 1-oxide (1129).



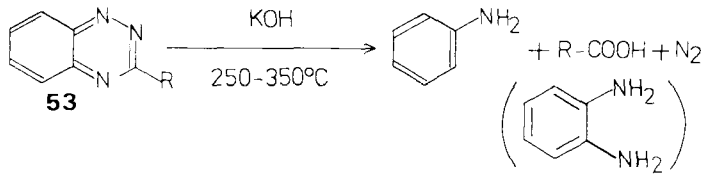
The oxidation of the benzyl group in 3-benzyl-1,2,4-benzotriazine (**53c**) to the benzoyl group is reported by Tennant (1131).



Reduction of **53** with sodium dithionite affords the 1,2-dihydro-1,2,4-benzotriazines (**78**) (1131, 1144).



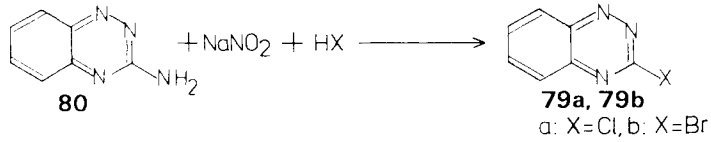
Aniline, carboxylic acids, and nitrogen were obtained when the 1,2,4-benzotriazines (**53**) were heated, with potassium hydroxide, to 250 to 350 °C. The



3-methyl- and 3-ethyl analogues afforded *o*-phenylenediamine in addition to aniline under the same reaction conditions (1137).

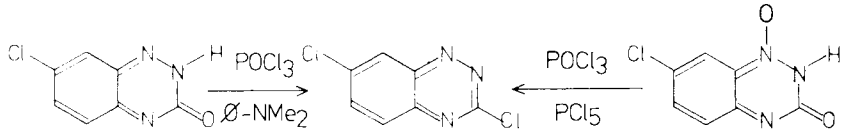
2. *3-Halo-1,2,4-benzotriazines*

Until now the preparation of only three 3-halo-1,2,4-benzotriazines (**79**) has been reported. Arndt and Rosenau (1154) converted 3-amino-1,2,4-benzotriazine (**80**) to 3-chloro-1,2,4-benzotriazine (**79a**) (m.p. 100 to 101 °C) and 3-bromo-1,2,4-benzotriazine (**79b**) (m.p. 122 °C) by treatment with sodium nitrite and hydrochloric acid or hydrobromic acid. Reduction of 3-chloro-1,2,4-benzotriazine 1-oxide (**81**) with zinc dust and ammonium chloride also yields **79a** (m.p. 96 to 98 °C) (1171).



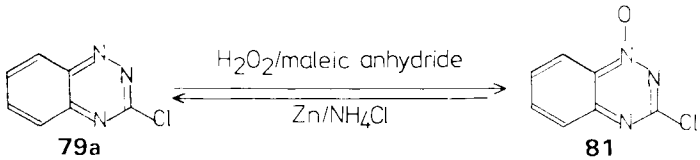
80 **79a, 79b**
a: X=Cl, b: X=Br

3,7-Dichloro-1,2,4-benzotriazine (**79c**) was obtained from the reaction of (1) 7-chloro-1,2,4-benzotriazin-3-one (**82**) with phosphoryl chloride in the presence of *N,N*-dimethylaniline (1155), or (2) 7-chloro-1,2,4-benzotriazine-3-one 1-oxide (**83**) with phosphoryl chloride and phosphorus pentachloride (1155).



82 **79c** **83**

The 3-halo-1,2,4-benzotriazines (**79**) are yellow, crystalline compounds which are soluble in most organic solvents. The halogen in the 3-position is very reactive and can be replaced by other nucleophiles (1156–1160, 1171). Oxidation of **79a** with hydrogen peroxide and maleic anhydride yields **81** (1156).



79a **81**

3. *1,2,4-Benzotriazin-3-ones*

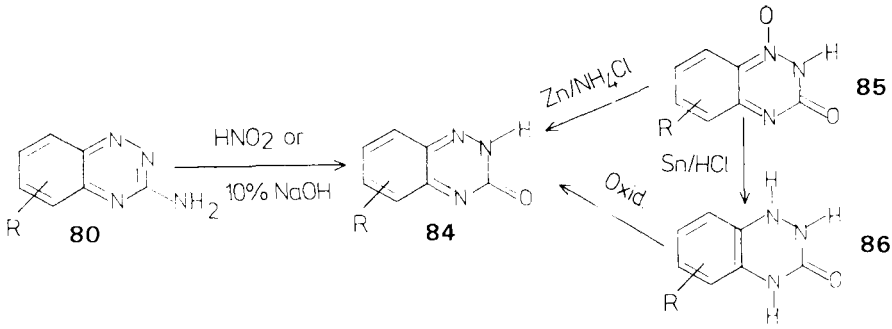
The chemistry of the 1,2,4-benzotriazin-3-ones (**84**) has been far less intensively studied than the chemistry of the uncondensed 1,2,4-triazin-3-ones. Only a few derivatives of this class (**84**) are known. The following methods are available for the synthesis of **84**:

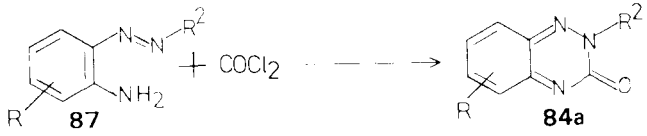
1. reaction of 3-amino-1,2,4-benzotriazines (**80**) with nitrous acid (1154, 1161, 1162) or 10% sodium hydroxide solution (1163).

2. reduction of the 1,2,4-benzotriazin-3-one 1-oxides (**85**) with zinc and ammonium chloride (1160) or tin and hydrochloric acid (1154) to give the 1,4-dihydro-1,2,4-benzotriazin-3-ones (**86**) which are then oxidized to the desired products (**84**).

3. reaction of *o*-aminophenylazo compounds (**87**) with phosgene (1164) to give 2-substituted 1,2,4-benzotriazin-3-ones (**84a**).

3-Ethoxy-1,2,4-benzotriazine (**88b**) (m.p. 74 to 76 °C) was prepared by the reaction of 3-chloro-1,2,4-benzotriazine (**79a**) with sodium ethoxide (1156).

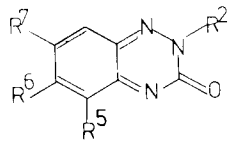




The 1,2,4-benzotriazin-3-ones (**84**) (Table IV-4) are yellow, crystalline compounds with high melting points. Alkylation or arylation at the nitrogen or

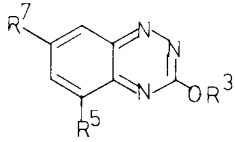
TABLE IV-4. 1,2,4-BENZOTRIAZIN-3-ONES

A. 1,2,4-Benzotriazin-3(2H)-ones



R^2	R^5	R^6	R^7	m.p. (°C)	Refs.
H	H	H	H	207–210	1163
				209–210	1154
H	H	H	CH_3	187	1166
H	H	H	Cl	210	1166
				220–222	1161
				228–229	1162
H	H	H	OCH_3	184	1166
H	H	OCH_3	H		1166
H	CH_3	H	H	186	1166
H	CH_3	H	CH_3	219	1166
CH_3	H	H	H	157–158 (dec.)	1165
C_6H_5	H	NHCN	H	258 (dec.)	1184
C_6H_5	H	$NHCONH_2$	H	300	1184
4-CH_3–C_6H_4 ·HCl	H	H	CH_3	168	1164
				154	1164

B. 3-Hydroxy-1,2,4-benzotriazines



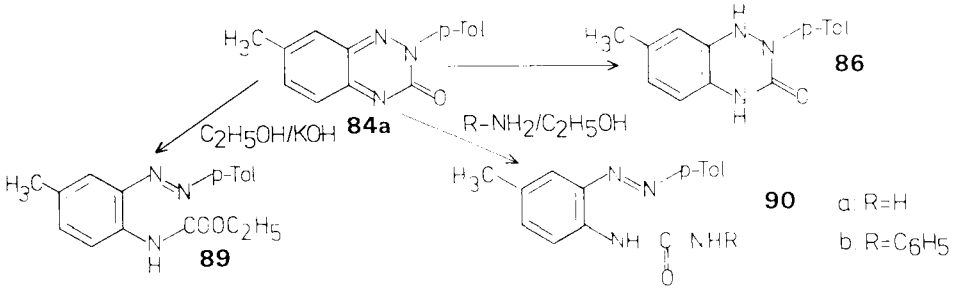
R^3	R^5	R^7	m.p. (°C)	Refs.
CH_3	H	H	106	1165
C_2H_5	H	H	74–76	1156
$(EtO)_2P{=}O$	H	Cl	105	1166
$(EtO)_2P{=}O$	H	OCH_3	70	1166
$(EtO)_2P{=}O$	CH_3	CH_3	68	1166
$(EtO)_2P{=}S$	H	CH_3	52	1166
$(EtO)_2P{=}S$	H	Cl	53	1166
$(EtO)_2P{=}S$	H	OCH_3	57	1166
$(EtO)_2P{=}S$	CH_3	H	45	1166
$(EtO)_2P{=}S$	CH_3	CH_3	68	1166
$(i\text{-}PrO)_2P{=}O$	H	OCH_3	69	1166
$(i\text{-}PrO)_2P{=}O$	CH_3	H	55	1166
$(i\text{-}PrO)_2P{=}O$	CH_3	CH_3	75	1166
$(i\text{-}PrO)_2P{=}S$	H	CH_3	106	1166
$(i\text{-}PrO)_2P{=}S$	H	Cl	72	1166
$(i\text{-}PrO)_2P{=}S$	H	OCH_3	73	1166
$(i\text{-}PrO)_2P{=}S$	CH_3	H	64	1166
$(i\text{-}PrO)_2P{=}S$	CH_3	CH_3	89	1166

oxygen lowers the melting point. 3-Ethoxy-1,2,4-benzotriazine (**88b**) is a colorless, crystalline compound.

As weak acids, **84** are soluble in bases and are reprecipitated by addition of acids. At room temperature they are stable to both acids and bases but at higher temperatures the heterocyclic ring is destroyed (1164).

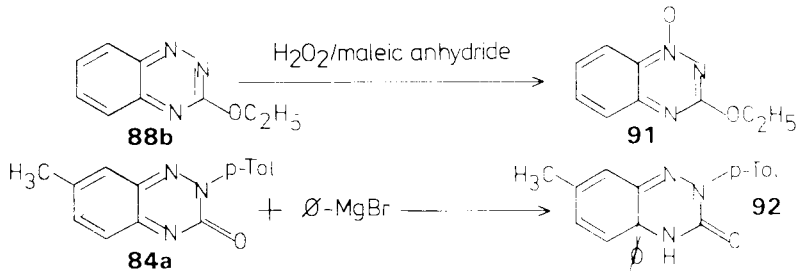
The reaction of 7-methyl-2-(4-tolyl)-1,2,4-benzotriazin-3-one (**84a**) with ethanol in the presence of potassium hydroxide yields the urethane (**89**) and the reaction with ammonia or aniline in ethanol affords the ureas **90a** and **90b** (1164).

The 1,2,4-benzotriazin-3-ones (**84**) can be reduced to the 1,4-dihydro-1,2,4-benzotriazin-3-ones (**86**) (1164, 1165, 1184).

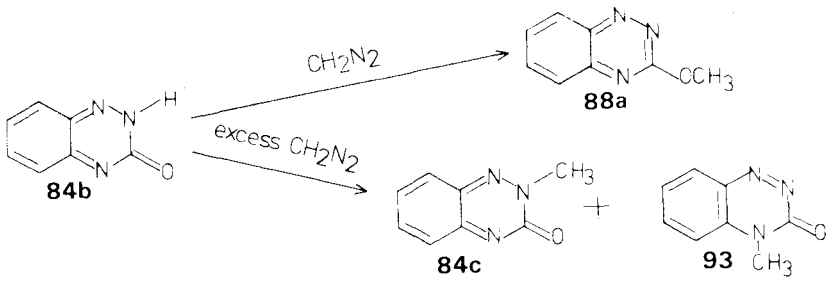


3-Ethoxy-1,2,4-benzotriazine (**88b**) is converted into 3-ethoxy-1,2,4-benzotriazine 1-oxide (**91**) by a reaction with hydrogen peroxide and maleic anhydride (1156).

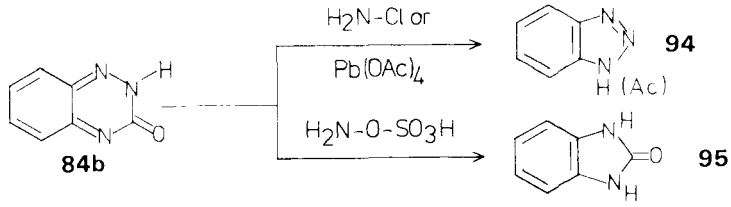
Treatment of 7-methyl-2-(4-tolyl)-1,2,4-benzotriazin-3-one (**84a**) with phenylmagnesium bromide leads to the formation of 7-methyl-4a-phenyl-2-(4-tolyl)-4,4a-dihydro-1,2,4-benzotriazin-3-one (**92**) (176).



The reaction of the 1,2,4-benzotriazin-3-ones (**84**) with phosphoryl chloride and *N*,*N*-dimethylaniline converts them to the 3-chloro-1,2,4-benzotriazines (**79**) (1155). Slow addition of an ethereal diazomethane solution to 1,2,4-benzotriazin-3-one (**84b**) yields only 3-methoxy-1,2,4-benzotriazine (**88a**) (m.p. 106 °C), whereas addition of **84** to an excess of diazomethane yielded the 2-methyl- and the 4-methyl-1,2,4-benzotriazin-3-one (**93**) (m.p. 202 °C) (1165).



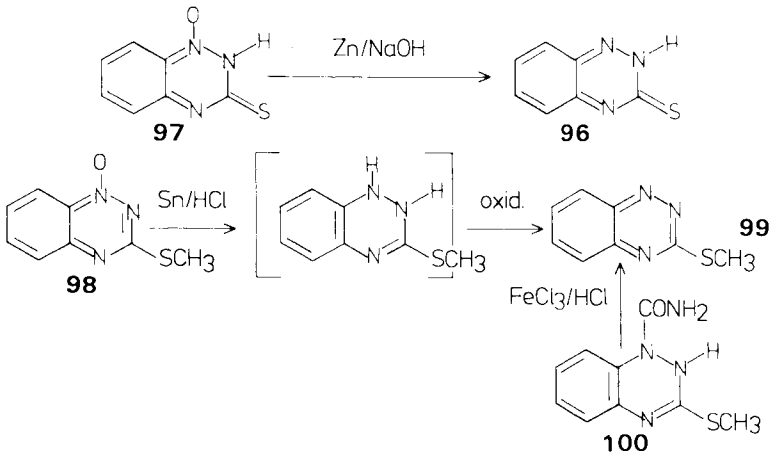
Ring contraction of 1,2,4-benzotriazin-3-one (**84b**) is observed on treatment with hydroxylamine-*O*-sulfonic acid, *O*-(2,4-dinitrophenyl)-hydroxylamine, chloramine, or lead tetraacetate (177–179). Benzotriazoles (**94**) were formed on treatment with ethereal chloramine at room temperature or lead tetraacetate in boiling benzene, and the benzimidazolin-2-one (**95**) were isolated on treatment with hydroxylamine derivatives.



O-Phosphorylation of the 1,2,4-benzotriazin-3-ones (**84**) is reported in two patents (1166, 1167).

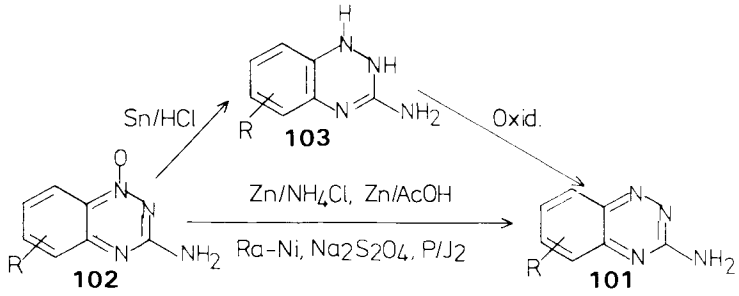
4. *1,2,4-Benzotriazine-3-thiones*

Only two compounds of this type are reported in the literature. Arndt and Rosenau (1154) prepared the 1,2,4-benzotriazine-3-thione (**96**) (m.p. 208 to 209 °C) through reduction of 1,2,4-benzotriazine-3-thione 1-oxide (**97**) with zinc dust in sodium hydroxide solution. Reduction of 3-(methylmercapto)-1,2,4-benzotriazine 1-oxide (**98**) with tin in hydrochloric acid yielded a dihydro compound which was oxidized to 3-(methylmercapto)-1,2,4-benzotriazine (**99**) (m.p. 104 °C) (1154). **99** was also prepared by Arndt and Eistert (1168) through the oxidation of 3-(methylmercapto)-1,2-dihydro-1,2,4-benzotriazine-1-carboxamide (**100**) with ferric chloride in hydrochloric acid. Both compounds are yellow; **96** is soluble in bases, whereas **99** is soluble in glacial acetic acid, concentrated hydrochloric acid, ether, benzene, and ethanol, but nearly insoluble in water.

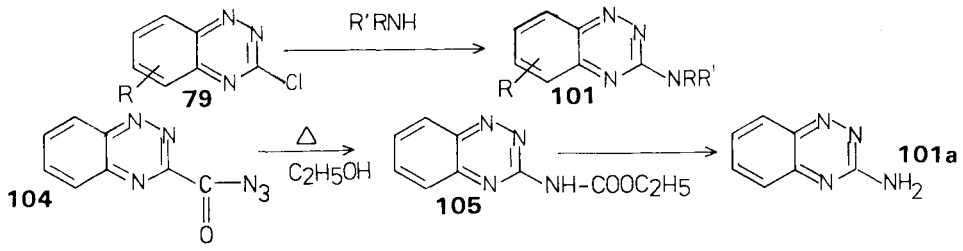


5. *3-Amino-1,2,4-benzotriazines*

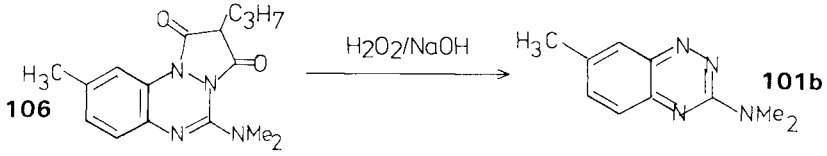
a. PREPARATION. The 3-amino-1,2,4-benzotriazines (**101**) are the best studied class of 1,2,4-benzotriazine derivatives. In most cases the synthesis starts from the easily preparable 3-amino-1,2,4-benzotriazine 1-oxides (**102**), which are then reduced (1154, 1157, 1162, 1163, 1169, 1171, 1172, 1176, 1183). Reduction of **102** with tin and hydrochloric acid (1154, 1169, 1171, 1176) produced dihydro derivatives (**103**) which were then oxidized to **101**, whereas reduction of **102** with zinc/ammonium chloride (1171), zinc/acetic acid (1163), sodium dithionite (1172), Raney nickel (1157, 1162, 1183), and phosphorus/iodine (1157, 1162, 1183) yields **101** directly.



3-Chloro-1,2,4-benzotriazines (**79**) can be converted to **101** by treatment with amines (1157, 1160, 1171). Curtius degradation of 3-azidocarbonyl-1,2,4-benzotriazine (**104**) affords 3-[(ethoxycarbonyl)amino]-1,2,4-benzotriazine (**105**) which can be hydrolyzed to **101a** (1134).

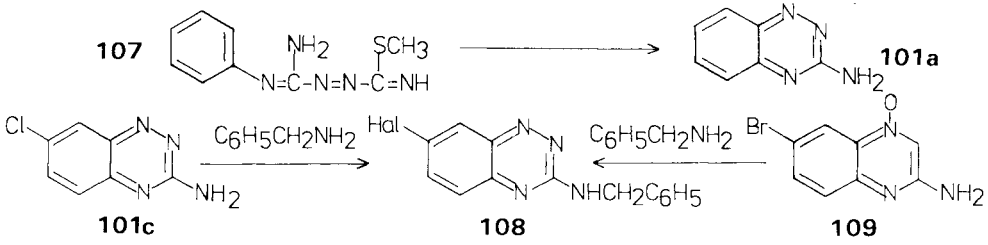


Mixich obtained a 3-amino-1,2,4-benzotriazine (**101b**) from the degradation of azopropazone (**106**) with hydrogen peroxide in the presence of sodium hydroxide (1173, 1174).



Arndt and Eistert (1168) isolated 3-amino-1,2,4-benzotriazine (**101a**) when they heated the azo compound **107** to 200 °C without a solvent.

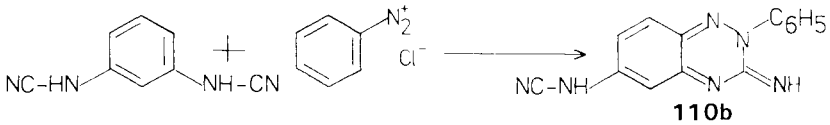
The 3-(benzylamino)-7-halogeno-1,2,4-benzotriazines (**108**) were obtained from 3-amino-7-chloro-1,2,4-benzotriazine (**101c**) or 3-amino-7-bromo-1,2,4-benzotriazine 1-oxide (**109**) and benzylamine (1177).



Busch and Bergmann synthesized 2-(4-tolyl)-3-arylimino-1,2,4-benzotriazines (**110**) [R = 2—CH_3—C_6H_4, m.p. 167 °C; R = 4—CH_3—C_6H_4, m.p. 147 °C; R = 3—O_2N—C_6H_4, m.p. 185 to 190 °C (dec.)] and 2-phenyl-3-(phenylimino)-7-methyl-1,2,4-benzotriazine (**110a**) (m.p. 127.5 °C) and their hydrochlorides starting from the thioureylphenylazo compounds **111** (1164, 1170).

Pierron reported the formation of 6-cyanamido-3-imino-2-phenyl-1,2,4-benzotriazine (**110b**) (m.p. 209 °C, recryst. 290 °C, ·HCl 230 °C) when he

carried out the reaction of benzenediazonium chloride with an alkaline solution of *m*-bis(cyanamido)benzene (1184).



110b

b. COMPOUND SURVEY. Table IV-5 lists the known 3-amino-1,2,4-benzotriazines.

c. PHYSICAL PROPERTIES. The 3-amino-1,2,4-benzotriazines (**101**) are yellow to red, stable, crystalline compounds with high melting points. Substitution in the amino group generally lowers the melting point. They are weak bases and form salts with mineral acids. Until now only a small amount of PMR spectroscopic data has been reported, by Mason and Tennant (1172).

d. REACTIONS. The replacement of the 3-amino group in **101** by a halogen (1154) or a hydroxy group (1154, 1161–1163) has already been discussed. The reaction of 3-amino-1,2,4-benzotriazines (**101**) with sulfonyl chlorides was used for the synthesis of the 3-(sulfonamido)-1,2,4-benzotriazines (**112**) (1162, 1178).

Nitration of 3-amino-1,2,4-benzotriazines is reported by Robbins and Schofield (1129) but the site of the substitution has not been established.

3-Amino-1,2,4-benzotriazines (**101**) can be oxidized to mono- and dioxides (1076, 1129, 1154, 1163, 1172) but there has been a long controversy over the site of the oxidation. In 1970 Mason and Tennant demonstrated that the oxidation of **101** at room temperature leads almost exclusively to 2-oxide (**113**) whereas prolonged oxidation at 50 °C yields the 1,4-dioxides (**114**).

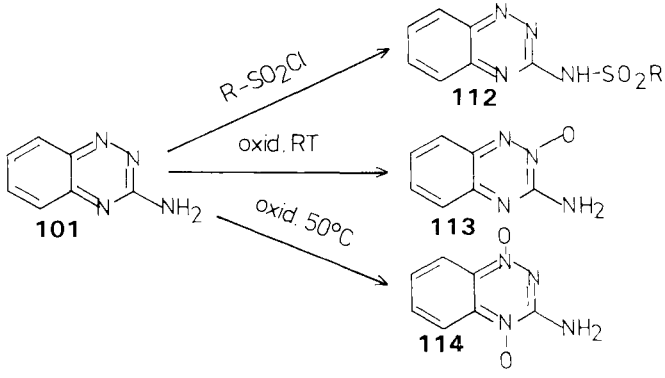
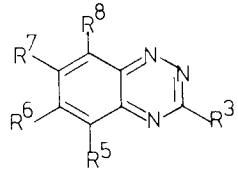


TABLE IV-5. 3-AMINO-1,2,4-BENZOTRIAZINES



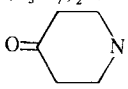
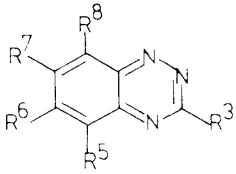
R^3	R^5	R^6	R^7	R^8	m.p. (°C)	Refs.
NH_2	H	H	H	H	205–208	1162
					207	1134, 1168, 1169, 1172
					211–211.5	1163
NH_2	H	H	CH_3	H	217–218	1162, 1183
					218	1172
NH_2	H	H	OCH_3	H	221–222	1162, 1183
					222	1172
NH_2	H	H	Cl	H	254–255	1162, 1183
					255	1172
NH_2	H	H	Br	H	253	1162
NH_2	H	Cl	H	H	250–251	1162, 1183
NH_2	H	CH_3	CH_3	H	286	1172
NH_2	CH_3	H	H	H	207–208	1162, 1183
$NH-C_4H_9$	H	H	Cl	H	151–152	1157
$(CH_3)_2NCH_2CH_2NH$	H	H	H	H	98–100	1171
$(C_2H_5)_2NCH_2CH_2CHNH$ (CH$_3$ branch)	H	H	Cl	H	b.p. 70/0.003	1157
$C_6H_5-CH_2NH$	H	H	Cl	H	175	1157, 1177
$C_6H_5-CH_2NH$	H	H	Br	H	173–174	1177
C_6H_5-NH	H	H	H	H	197	1154
$H_2C_5OOC-NH$	H	H	H	H	132	1134
$4\text{-}O_2N-C_6H_4-SO_2-NH$	H	H	H	H	250–252	1162
					252–253	1178
$4\text{-}O_2N-C_6H_4-SO_2-NH$	H	H	Cl	H	240	1162, 1178
$4\text{-}H_2N-C_6H_4-SO_2-NH$	H	H	H	H	216–217	1162
					216–218	1178
$4\text{-}H_2N-C_6H_4-SO_2-NH$	H	H	Cl	H	219–220	1162, 1178
$(CH_3)_2N$	H	H	CH_3	H	61–62	1174
$(CH_3)_2N$	H	H	CF_3	H		1176
$(CH_3)_2N$	H	H	F	H		1176
$(CH_3)_2N$	H	OH	CH_3	H	Very high	1173
$(C_6H_5)CH_3N$	H	H	CF_3	H		1176
$(C_6H_5)CH_3N$	H	H	Cl	H	145–146	1157
$(C_3H_7)_2N$	H	H	Cl	H	66	1157
	H	H	H	H	237–239.5	1171

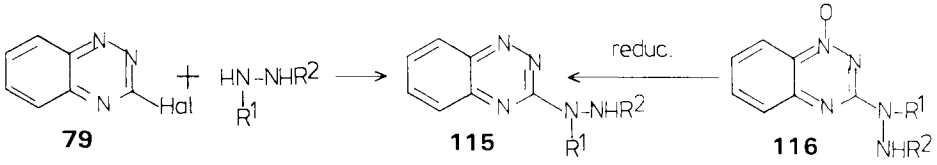
TABLE IV-5. (continued)



R^3	R^5	R^6	R^7	R^8	m.p.(°C)	Refs.
1-Imidazolyl	H	H	H	H	103	1160
1-Imidazolyl	H	H	CH_3	H	168–170	1160
					174–175	1160
1-Imidazolyl	H	H	CF_3	H		1160
1-Imidazolyl	H	H	Cl	H	168.5	1160
2-Methyl-1-imidazolyl	H	H	CH_3	H	190	1160
2-Ethyl-1-imidazolyl	H	H	CH_3	H	141–142	1160
2-Propyl-1-imidazolyl	H	H	CH_3	H	104.5–105.5	1160
2-Isopropyl-1-imidazolyl	H	H	CH_3	H	119.5–120	1160
2-Phenyl-1-imidazolyl	H	H	CH_3	H	164–166	1160
2-Ethyl-4-methyl-1-imidazolyl	H	H	CH_3	H	109–110	1160

6. *3-Hydrazino-1,2,4-benzotriazines*

The 3-hydrazino-1,2,4-benzotriazines (**115**) were prepared either by nucleophilic substitution of 3-halo-1,2,4-benzotriazines (**79**) with hydrazines (1158, 1159, 1171) or by reduction of 3-hydrazino-1,2,4-benzotriazine 1-oxides (**116**) with stannous chloride in hydrochloric acid (1129).



79 **115** **116**

R^1	R^2	m.p. (°C)	Refs.
H	H	168–170	1129
		173–175	1159, 1171
H	$CSNH_2 \cdot HCl$	214 (dec.)	1158
H	COC_6H_5	242–244	1156
CH_3	H	85–90	1159, 1171
C_3H_7	H		1159

The 3-hydrazino-1,2,4-benzotriazines (**115**) are yellow, crystalline compounds, which can be benzoylated with benzoyl chloride (1156) and give condensed 1,2,4-benzotriazines by reaction with formic acid or carbon disulfide (1156). Reaction of **115** with nitrous acid yields a compound that exists in solution predominantly as 3-azido-1,2,4-benzotriazine but in the crystalline state as tetrazolo[5,1-*c*] 1,2,4-benzotriazine (1267) (see Section XIII-D in Chapter VI). 3-Amino-1,2,4-benzotriazine 1-oxide was isolated in 5% yield from the reaction of 3-hydrazino-1,2,4-benzotriazine with percarbonic acids (1156).

7. *1,2,4-Benzotriazin-3-yl Ketones*

Most 1,2,4-benzotriazin-3-yl ketones (**117**) were synthesized by the formazane method through acidic cyclization of the acylformazanes **118** (1132, 1185–1188). Tennant (1131, 1144) oxidized 3-benzyl-1,2,4-benzotriazines (**119**) with chromium trioxide and obtained 3-benzoyl-1,2,4-benzotriazines (**117a**) in good yields. Tennant also isolated the 3-benzoyl-1,2,4-benzotriazines (**117a**) when he refluxed the 3-phenyl-1,2,3-triazolo[5,1-*c*]-1,2,4-benzo-

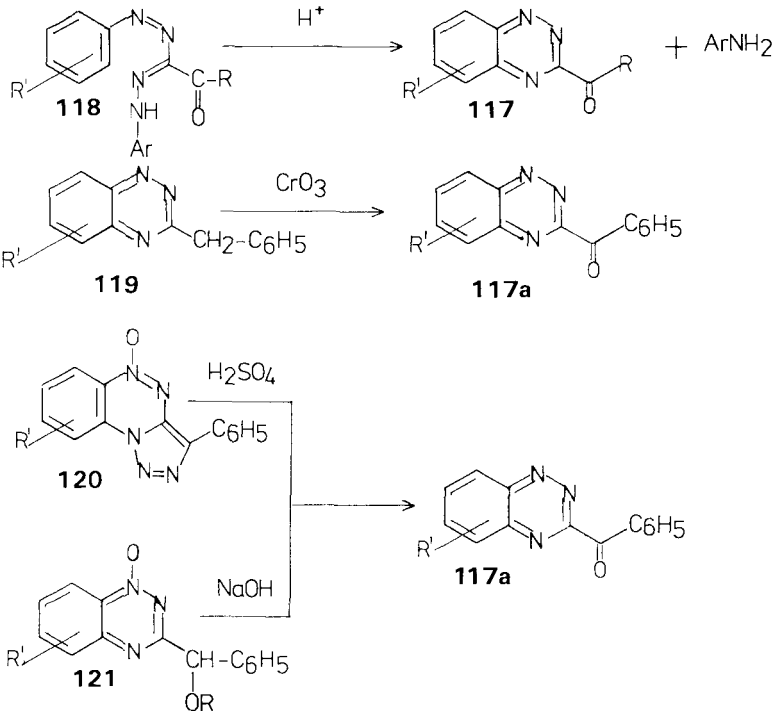
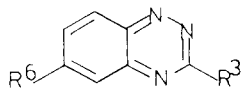


TABLE IV-6. 1,2,4-BENZOTRIAZIN-3-YL KETONES



R^3	R^6	m.p. (°C)	Refs.
CH_3-CO	H	121–122.5	1132, 1187
$CH_3-C(=N-NH-C_6H_5)$	H	202	1132, 1187
$CH_3-C(=N-NH-C_6H_4-OCH_3(p))$	H	151	1189
C_6H_5-CO	H	114 115	1131, 1185, 1188 1144
$C_6H_5-C(=NOH)$	H	256	1131
$C_6H_5-C(=N-NH_2)$	H	252	1131
$C_6H_5-C(=N-NHC_6H_5)$	H	185	1185, 1188
C_6H_5-CO	CH_3	165 168	1131 1144
$C_6H_5-C(=NOH)$	CH_3	235	1131
$C_6H_5-C(=N-NH_2)$	CH_3	181	1131
$HOOC-CO$	SO_3H		1186

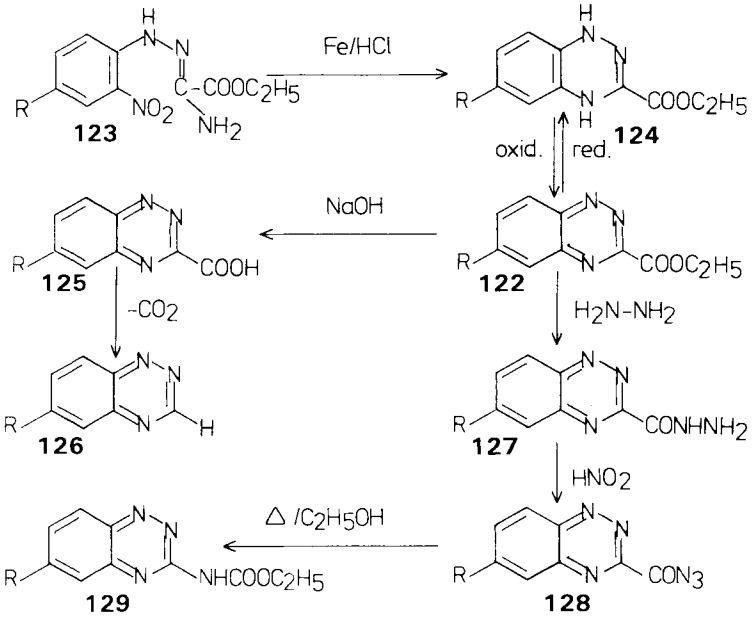
triazine 5-oxides (**120**) with 20% aqueous sulfuric acid in glacial acetic acid for 2 h or by warming the 3-(α-hydroxybenzyl)-1,2,4-benzotriazine 1-oxides (**121**) with 2*N* aqueous sodium hydroxide in ethanol at 100 °C for 10 min (1144).

The 1,2,4-benzotriazin-3-yl ketones (**117**) (Table IV-6) are yellow or orange-yellow crystalline compounds. They are soluble in concentrated mineral acids and reprecipitate on addition of water. They are soluble in most organic solvents. The carbonyl band of the benzoyl ketones (**117a**) is found in the infrared spectra at 1,680 cm^{-1} (1131). The following ultraviolet spectrum is reported for **117a** (R = H): λ_{max} = 209, 250, and 335 nm (infl.) (log ϵ: 4.24, 4.63, 3.57) (1131). Oxidation of the hydrazones of the 1,2,4-benzotriazin-3-yl ketones is used for the synthesis of triazolo-1,2,4-benzotriazines (1131, 1189).

8. *1,2,4-Benzotriazine-3-carboxylic Acids*

1,2,4-Benzotriazine-3-carboxylates (**122**) were prepared by Fusco and Rossi (1133, 1134) by reduction of the ethyl *N*-(*o*-nitrophenyl)-

oxalamidrazonates (**123**) with iron and hydrochloric acid and subsequent oxidation of the formed 1,4-dihydro-1,2,4-benzotriazine-3-carboxylates (**124**). Saponification of **122** yields the free acids (**125**), which can be decarboxylated to 1,2,4-benzotriazines (**126**). Reaction of **122** with hydrazine yields the hydrazides **127**, which can be transformed to the azides **128**. Curtius degradation of **128** in ethanol affords the urethanes **129**. Hydrogenation of **122** to **124** is also reported. Known compounds of this class are listed in Table IV-7.



9. *1,2,4-Benzotriazine 1-Oxides*

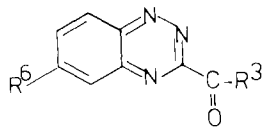
a. PREPARATION. The 1,2,4-benzotriazine 1-oxides (**130**) were synthesized by three different methods.

1. Oxidation of 1,2,4-benzotriazines (**131**) with hydrogen peroxide in acetic acid (1129, 1142).

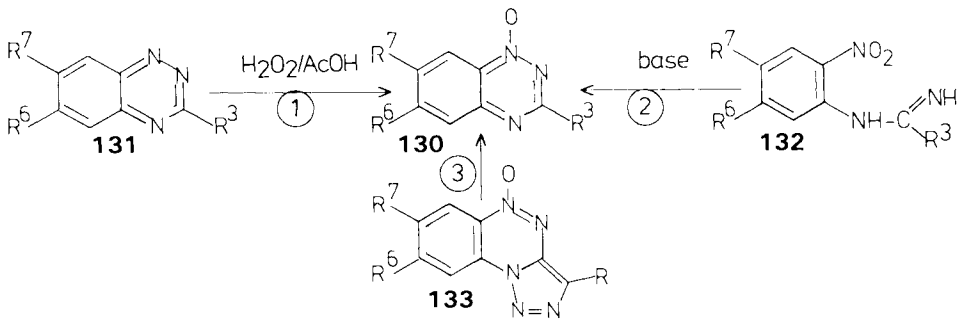
2. Cyclization of *o*-nitrophenylamidines (**132**) with sodium hydroxide or sodium ethoxide (1192, 1195),

3. Ring opening of 1,2,3-triazolo[5,1-*c*] 1,2,4-benzotriazine 5-oxides (**133**) (1144).

TABLE IV-7. 1,2,4-BENZOTRIAZINE-3-CARBOXYLIC ACIDS



R^3	R^6	m.p. (°C)	Refs.
OH	H	dec.	1134
OH	CH_3	dec.	1134
OH	Cl	dec.	1134
OH	OCH_3	dec.	1134
OH	CH_3CO		1133
OH	COOH	280	1133
OH	NH_2	204	1133
OC_2H_5	H	93	1134
OC_2H_5	CH_3	107	1134
OC_2H_5	Cl	93	1134
OC_2H_5	NO_2	141	1133
OC_2H_5	OCH_3	158	1134
OC_2H_5	CH_3CO	149–149.5	1133
OC_2H_5	CH_3CONH	242	1133
$NHNH_2$	H	207	1134
$NHNH_2$	CH_3	176	1134
$NHNH_2$	Cl	178	1134
$NHNH_2$	OCH_3	228	1134
N_3	H	127	1134



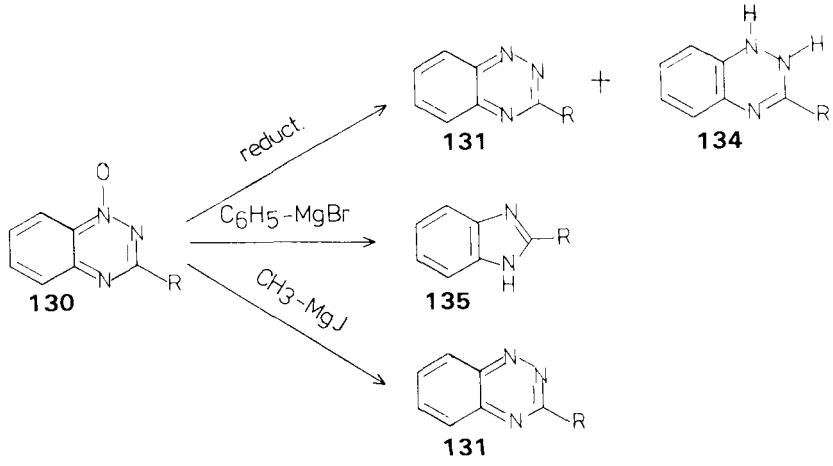
b. COMPOUND SURVEY. Table IV-8 lists the compounds of this group that have been reported in the literature.

TABLE IV-8. 1,2,4-BENZOTRIAZINE 1-OXIDES (**130**)

R^3	R^6	R^7	R^8	m.p. (°C)	Refs.
H	H	H		138–140	1129
H	H	H	OCH_3	208–210 (dec.)	1129
CH_3	H	H		92–93	1142
C_6H_5–CH=CH	H	H		58–59	1192
C_6H_5–CHOH	H	H		109	1144
C_6H_5–CHOH	H	CH_3		134	1144
C_6H_5–CH(OCOCH$_3$)	H	H		112	1144
C_6H_5–CH(OCOCH$_3$)	H	CH_3		120	1144
C_6H_5–CHCl	H	H		140	1144
C_6H_5–CHCl	H	CH_3		138	1144
C_6H_5–CHBr	H	H		155	1144
C_6H_5–CHBr	H	CH_3		132	1144
C_6H_5	H	H		132	1192
				132–133	1129
C_6H_5	H	CH_3		172	1192
C_6H_5	H	Cl		201–202	1192
C_6H_5	H	OCH_3		175.5–176	1192
C_6H_5	Cl	H		148–150	1129
4-Cl–C_6H_4	H	H		211–214	1192
				215–216	1129
4-O_2N–C_6H_4	H	H		232	1192
				247–248	1129
4-O_2N–C_6H_4	H	OCH_3		199.5–200.5	1129
4-CH_3O–C_6H_4	H	H		139–140	1129
				172–173	1192
4-CH_3O–C_6H_4	H	Cl		210–211	1182
4-CH_3O–C_6H_4	Cl	H		187–188	1129
4-H_2N–C_6H_4	H	H		235–237	1129
4-H_2N–C_6H_4	OCH_3	H		245–246	1129
 4-Thiazolyl	H	NH–CO–C_6H_5			1195
 4-Thiazolyl	H	NH–CO–C_6H_4–$F_{(p)}$			1195
 4-Thiazolyl	H	NH–CO–OCH$(CH_3)_2$			1195

c. PHYSICAL PROPERTIES. The 1,2,4-benzotriazine 1-oxides (**130**) are stable, crystalline, colored (cream, yellow, orange) compounds. As far as has been reported, the ultraviolet spectra shows three absortion maxima in the following regions (absorptivities given in parenthesis); 205 to 210 (4.30), 240 to 250 (4.45), and 350 to 360 (3.50) (1144). The following PMR spectrum has been published for 3-methyl-1,2,4-benzotriazine 1-oxide: $\tau = 7.30$ (CH_3), 2.46 (H-7), 2.20 (H-6), 2.17 (H-5), and 1.67 (H-8) (1142).

d. REACTIONS. Reduction of the 1,2,4-benzotriazine 1-oxides (**130**) yields the 1,2,4-benzotriazines (**131**), the 1,2-dihydro-1,2,4-benzotriazines (**134**) (1144) or the benzimidazoles (**135**) (1195). Reaction of **130** with phenylmagnesium bromide affords the benzimidazoles (**135**), whereas the 1,2,4-benzotriazines (**131**) were isolated if methylmagnesium iodide was used (1142).



10. *3-Halo-1,2,4-benzotriazine 1-Oxides*

3-Halo-1,2,4-benzotriazine 1-oxides (**136**) were synthesized either by oxidation of 3-halo-1,2,4-benzotriazines (**137**) with percarbonic acids (1156) or by the reaction of 1,2,4-benzotriazin-3-one 1-oxides (**138**) with phosphoryl chloride or phosphoryl bromide (1129, 1155, 1171, 1177, 1181, 1207). The conversion of 3-amino-1,2,4-benzotriazine 1-oxides (**139**) to 3-chloro-1,2,4-benzotriazine 1-oxides (**136a**) by the Sandmeyer reaction is reported by Mueller (1159).

3-Halo-1,2,4-benzotriazine 1-oxides (**136**) (Table IV-9) are crystalline compounds and seem to be colorless. The mass spectra of 3-chloro-1,2,4-benzotriazine-7-carboxanilide 1-oxide is recorded by Bild and Hesse (1196).

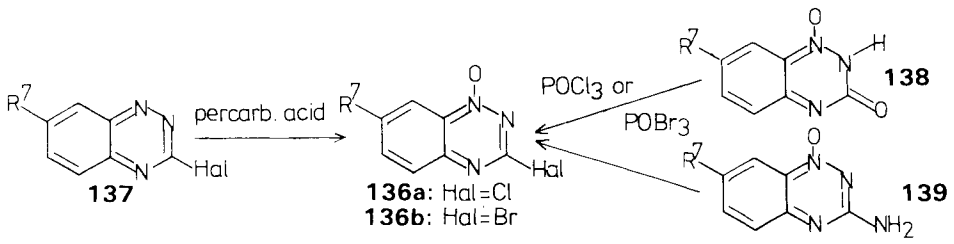
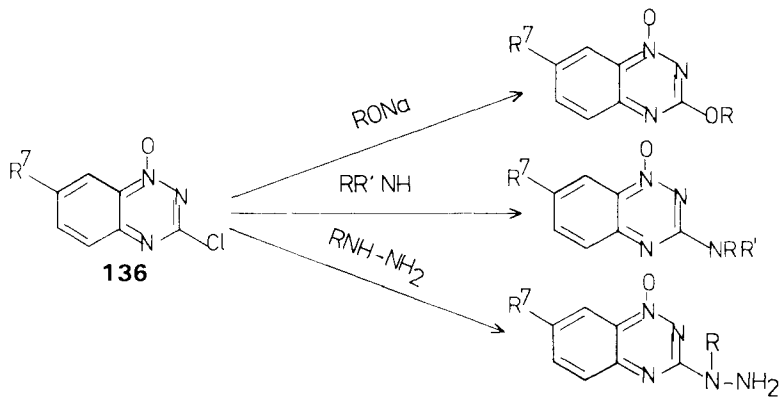


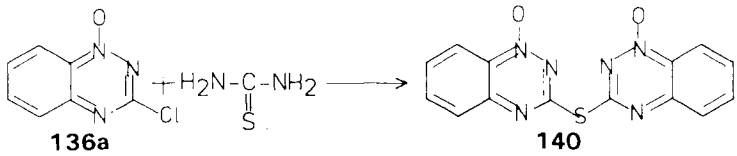
TABLE IV-9. 3-HALO-1,2,4-BENZOTRIAZINE 1-OXIDES (136)

Hal	R^7	m.p. (°C)	Refs.
Cl	H	117–118	1129
		117–119	1171
		118–119	1159
Cl	Cl	140	1155
		153–154	1181
		155	1177
		157–158.5	1171
Cl	OCH_3	188.5–190.5	1171
Cl	COOH	206 (dec.)	1207
Cl	COCl	189–190	1207
Cl	$COOC_2H_5$	97–98	1207
Cl	$CONHC_6H_5$	274–275 (dec.)	1207
Br	H	154–158	1171

The halogen in the 3-position of **136** is very reactive and can be replaced by reaction with sodium alkoxides (1171, 1177, 1207), amines (1129, 1171, 1177, 1182, 1193, 1194, 1207), or hydrazines (1129, 1156, 1159, 1171, 1193). Reaction of 3-chloro-1,2,4-benzotriazine-7-carboxylic acid chloride 1-oxide with amines to yield the corresponding carboxamides, which were used for the synthesis of dyes, is reported in two patents (1199, 2280).



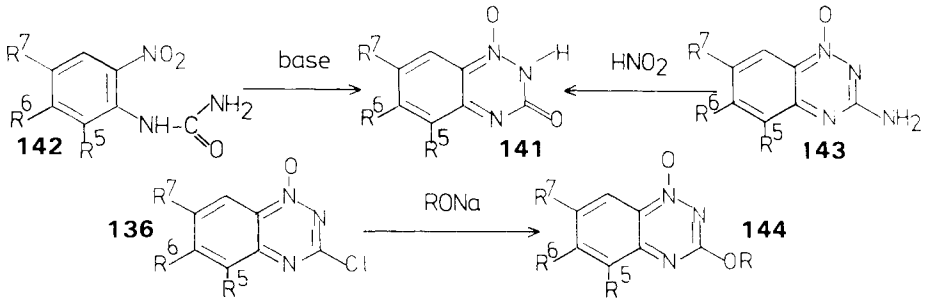
Reaction of 3-chloro-1,2,4-benzotriazine 1-oxide with thiourea yielded the bis(1-oxo-1,2,4-benzotriazin-3-yl)sulfide (**140**) (1171).



136a **140**

11. *1,2,4-Benzotriazin-3-one 1-Oxides*

a. PREPARATION. The 1,2,4-benzotriazin-3-one 1-oxides (**141**) were obtained through basic cyclization of *o*-nitrophenylureas (**142**) (1169, 1177, 1180) or by the reaction of the 3-amino-1,2,4-benzotriazine 1-oxides (**143**) with nitrous acid (1163, 1169, 1171, 1180). The reaction of the 3-chloro-1,2,4-benzotriazine 1-oxides (**136**) with sodium alkoxides has been used for the synthesis of 3-alkoxy-1,2,4-benzotriazine 1-oxides (**144**) (1171, 1177, 1196, 1207).



142 **141** **143**

136 **144**

b. COMPOUND SURVEY. The compounds reported in the literature are listed in Table IV-10.

c. PHYSICAL PROPERTIES. The 1,2,4-benzotriazin-3-one 1-oxides (**141**) are stable, crystalline, compounds which seem to be yellow and which are soluble in bases and hot water or ethanol, but insoluble in acids. The 3-alkoxy-1,2,4-benzotriazine 1-oxides (**144**) are stable, crystalline, compounds, one of which is reported to be yellow-white.

d. REACTIONS. Methylation of 1,2,4-benzotriazin-3-one 1-oxide (**141a**) with methyl iodide gave a product which was identified as 4-methyl-1,2,4-benzotriazin-3-one 1-oxide (**145**) (m.p. 237 to 241 °C) (1171). Reaction of **141** with phosphoryl chloride or phosphoryl bromide in the presence of an amine affords

TABLE IV-10. 1-OXIDES OF 1,2,4-BENZOTRIAZIN-3-ONE AND 3-HYDROXY-1,2,4-BENZOTRIAZINES

A. 1,2,4-Benzotriazin-3-one 1-oxides (**141**)

R^2	R^5	R^6	R^7	m.p. (°C)	Refs.
H	H	H	H	214	1200
				219	1169
				244–246	1171
H	H	H	CH_3	202	1200
H	H	H	Cl	204–205	1180
				226	1200
				230–231	1177, 1180
				232–234	1162
				259–262	1171
H	H	H	CH_3O	219 (dec.)	1200
				244–246	1171
H	H	H	COOH	250–251 (dec.)	1207
H	H	H	COCl	210 (dec.)	1207
H	H	H	$COOC_2H_2$	228 (dec.)	1207
H	H	CH_3O	H	215–218	1200
H	CH_3	H	H	230 (dec.)	1200
H	CH_3	H	CH_3	231 (dec.)	1200

B. 3-Hydroxy-1,2,4-benzotriazine 1-oxides (**144**)

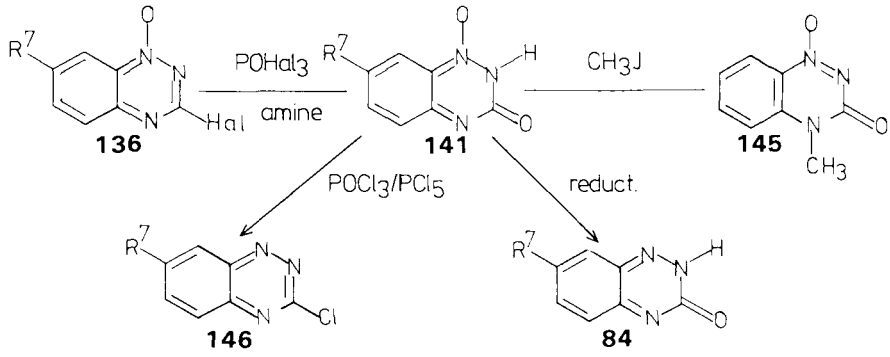
R^3	R^5	R^7	m.p. (°C)	Refs.
CH_3	H	Cl	157	1177
C_2H_5	H	H	111–113	1171, 1156
C_2H_5	H	COOH	240–241	1207
C_2H_5	H	$COOC_2H_5$	195–196	1209
n-C_4H_9	H	H	53–54	1171
$(EtO)_2P{=}O$	H	H	61	1200
$(EtO)_2P{=}O$	H	CH_3	88–90	1200
$(EtO)_2P{=}O$	H	CH_3O	82	1200
$(EtO)_2P{=}O$	CH_3	H	75	1200
$(EtO)_2P{=}O$	CH_3	CH_3	98	1200
$(EtO)_2P{=}S$	H	H	64	1200
$(EtO)_2P{=}S$	H	CH_3	170	1200
$(EtO)_2P{=}S$	H	CH_3O	78	1200
$(EtO)_2P{=}S$	CH_3	H	66	1200
$(EtO)_2P{=}S$	CH_3	CH_3	124	1200
$(i\text{-}PrO)_2P{=}O$	H	H	48	1200
$(i\text{-}PrO)_2P{=}O$	H	CH_3O	65	1200
$(i\text{-}PrO)_2P{=}O$	CH_3	H	96	1200
$(i\text{-}PrO)_2P{=}O$	CH_3	CH_3	125	1200
$(i\text{-}PrO)_2P{=}S$	H	CH_3O	82	1200
$(i\text{-}PrO)_2P{=}S$	CH_3	H	95	1200

TABLE IV-10. (continued)

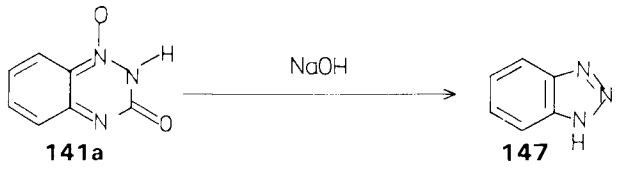
B. 3-Hydroxy-1,2,4-benzotriazine 1-oxides (144)

R^2	R^5	R^7	m.p.(°C)	Refs.
$(i\text{-PrO})_2P{=}S$	CH_3	CH_3	125	1200
Me(EtO)P=S	H	H	93	1200
Me(EtO)P=S	H	CH_3	95	1200
Me(EtO)P=S	H	CH_3O	99	1200
Me(EtO)P=S	CH_3	H		1200
Me(EtO)P=S	CH_3	CH_3	103	1200
Et(EtO)P=S	H	H	86	1200
Et(EtO)P=S	H	CH_3	92	1200
Et(EtO)P=S	H	CH_3O	79	1200
Et(EtO)P=S	CH_3	H	97	1200
Et(EtO)P=S	CH_3	CH_3	115	1200
C_6H_5(EtO)P=S	H	H	73	1200
C_6H_5(EtO)P=S	H	CH_3	110–113	1200
C_6H_5(EtO)P=S	H	CH_3O	120	1200
C_6H_5(EtO)P=S	CH_3	H	72	1200
C_6H_5(EtO)P=S	CH_3	CH_3	120	1200

the 3-chloro- or 3-bromo-1,2,4-triazine 1-oxides (**136**), whereas reaction with phosphoryl chloride and phosphorus pentachloride yields 3-chloro-1,2,4-benzotriazines (**146**) (1129, 1155, 1171, 1177, 1181, 1207). Reduction of **141** has been used for the synthesis of the 1,2,4-benzotriazin-3-ones (**84**) (1161, 1183).



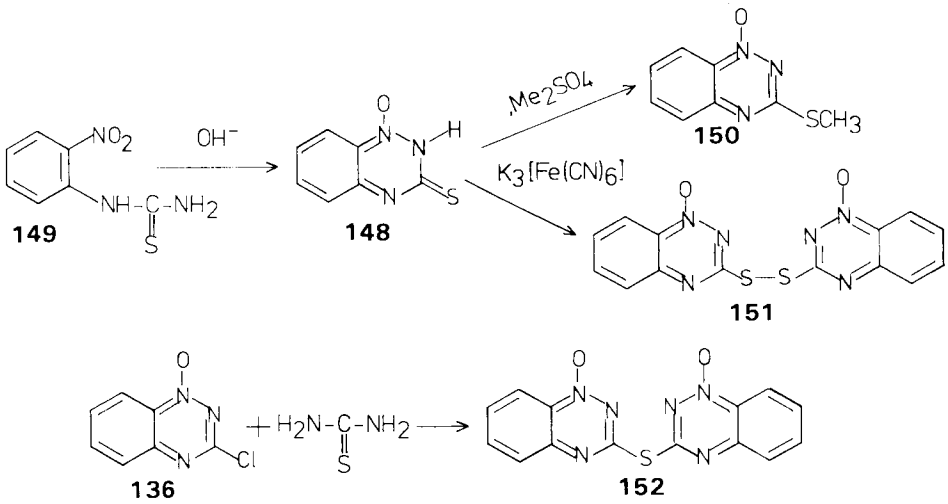
When **141a** was treated with sodium hydroxide, benzotriazole (**147**) was isolated (1163). The formation of *O*-(1-oxo-1,2,4-benzotriazin-3-yl)phosphates is reported in a German patent (1200).



141a 147

12. *1,2,4-Benzotriazine-3-thione 1-Oxides*

1,2,4-Benzotriazine-3-thione 1-oxide (**148**) (m.p. 184 °C) was prepared by Arndt and Rosenau (1154) through basic cyclization of *o*-(nitrophenyl)-thiourea (**149**). Methylation of **148** with dimethyl sulfate yielded 3-(methyl-mercapto)-1,2,4-benzotriazine 1-oxide (**150**) (m.p. 123 °C) and oxidation with potassium ferricyanide yielded the disulfide (**151**) (m.p. 205 °C) (1154). Jiu and Mueller (1171) observed the formation of bis(1-oxo-1,2,4-benzotriazin-3-yl)-sulfide (**152**) (m.p. 267 to 271 °C), when 3-chloro-1,2,4-benzotriazine 1-oxide (**136**) was treated with thiourea.



149 148 150 151

136 152

13. *3-Amino-1,2,4-benzotriazine 1-Oxides*

a. PREPARATION. Three methods have been reported for the synthesis of the 3-amino-1,2,4-benzotriazine 1-oxides (**153**).

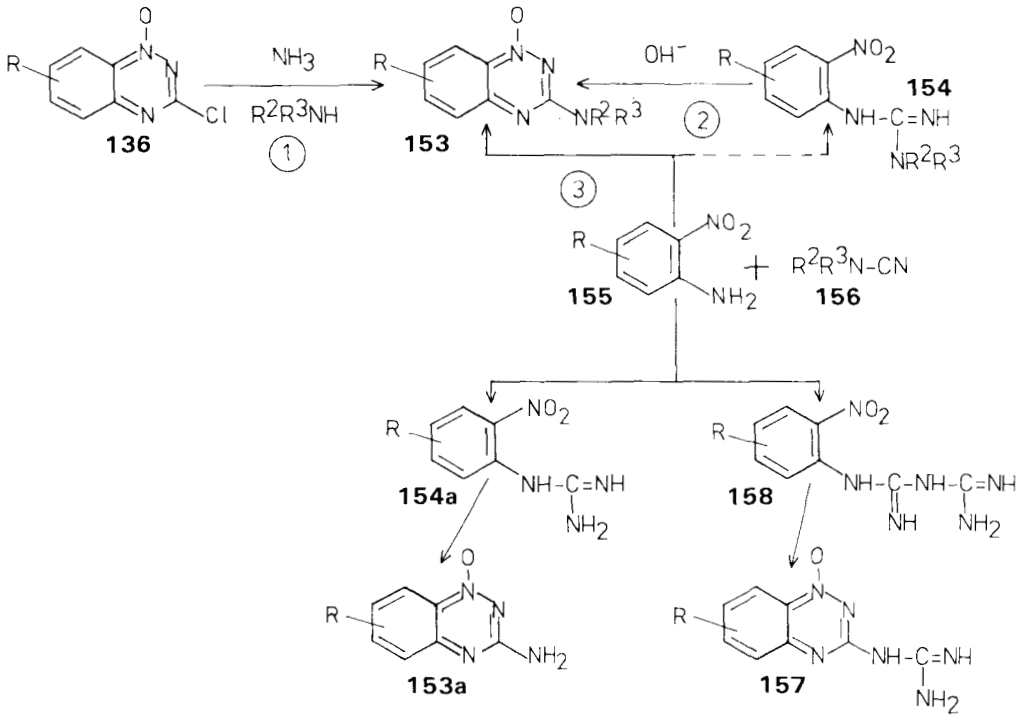
1. Nucleophilic substitution of the chlorine in the 3-chloro-1,2,4-benzotriazine 1-oxides (**136**) by ammonia or amines (1129, 1171, 1177, 1182, 1193, 1194, 1196, 1197, 1207).

2. Base-catalyzed cyclization of *o*-nitrophenylguanidines (**154**) (1154, 1169, 1172, 1190, 1191, 1228).

3. The reaction of *o*-nitroanilines (**155**) with cyanamides (**156**) (1129, 1162, 1172, 1173, 1179, 1190).

The first product of the latter reaction should be **154**.

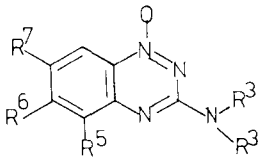
Carbon (1163) reports that the reaction of *o*-nitroaniline with cyanamide yield not only 3-amino-1,2,4-benzotriazine 1-oxide (**153a**) but also 3-guanidino-1,2,4-benzotriazine 1-oxide (**157**), which was overlooked in previous synthesis. **157** is probably formed by base catalysed ring closure of *o*-nitrophenylbiguanide (**158**).



b. COMPOUND SURVEY. Table IV-11 lists the compounds of this group that have been reported in the literature.

c. PHYSICAL PROPERTIES. The 3-amino-1,2,4-benzotriazine 1-oxides (**153**) are stable, crystalline compounds of yellow color and high melting points. Substitution in the amino group generally lowers the melting point. **153** are weak bases and form salts with mineral acids. Surprisingly, despite the fact that

TABLE IV-11. 3-AMINO-1,2,4-BENZOTRIAZINE 1-OXIDES



R^3	R^3	R^5	R^6	R^7	m.p. (°C)	Refs.
H	H	H	H	H	267–268	1162
					269	1169
					269–270	1129
					270–271	1190
					275	1172
H	H	H	H	CH_3	265–270	1183
					271	1162, 1172
					275	1229
H	H	H	H	C_6H_5	303–305	1171
H	H	H	H	Cl	>300	1171
					302–305	1162
					312	1172
H	H	H	H	Br	294–295	1162
H	H	H	H	I	296–297	1162
H	H	H	H	NO_2	289–290 (dec.)	1191, 1228
H	H		(H, H, NO_2)		287–289 (dec.)	1129
H	H	H	H	OCH_3	258–259	1183, 1162
					271	1172
					278–281	1171
H	H	H	H	OC_2H_5	276–278	1171
H	H	H	H	CH_3CO	272–273 (dec.)	1129

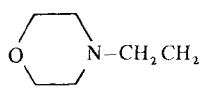
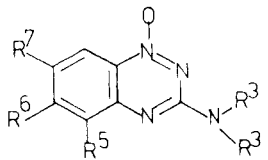
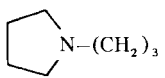
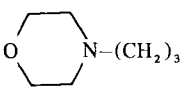
H	H	H	Cl	H_2N-SO_2	>300	1191
H	H	H	CH_3	CH_3	288 (dec.)	1172
H	H	H	Cl	H	293–295	1162
H	H	H	Cl	$(C_2H_5)_2N-SO_2$	284–285	1191
H	H	CH_3	H	H	258–260	1183
					260	1162
H	H	CH_3	H	CH_3	251–253	1171
H	H	Cl	H	H	258–260	1162
H	H	Cl	H	Cl	287	1162
H	H	OC_2H_5	H	H	245.5–247.5	1129
H	CH_3	H	H	Cl	236	1177
H	$CH_2=CH-CH_2$	H	H	H	159–160	1182
H	n-C_4H_9	H	H	Cl	170	1177, 1182
H	n-$C_6H_{13}CH(CH_3)$	H	H	H	89–90	1177, 1182
H	n-$C_{12}H_{25}$	H	H	Cl	140	1177, 1182
H	$C_6H_5-CH_2$	H	H	Cl	186	1177, 1182
H	$C_6H_5-CH_2CH_2$	H	H	H	193–195	1171, 1193
H	$C_6H_5-CH_2CH_2$	H	H	Cl	195–196	1177, 1182
H	3,4-$(CH_3O)_2C_6H_3(CH_2)_2$	H	H	Cl	183–184	1177, 1182
H	$HOCH_2CH_2$	H	H	H	114–116	1171, 1193
H	$HOCH_2CH_2$	H	H	Cl	186	1177, 1182
H	$(C_2H_5)_2NCH_2CH_2SCH_2CH_2$	H	H	Cl	104–105	1177, 1182
H	$(CH_3)_2NCH_2CH_2$	H	H	H	157–161	1171
H	$(CH_3)_2NCH_2CH_2$	H	H	Cl	128.5–131	1171
H	$(C_2H_5)_2NCH_2CH_2$	H	H	H	77.5–80	1171
H		H	H	H	170.5–173	1171, 1194
H	$(C_2H_5)_2N(CH_2)_3$	H	H	Cl	79	1177
H	$(C_4H_9)_2N(CH_2)_3$	H	H	H	77–78.5	1171

TABLE IV-11 (continued)



R^3	R^3	R^5	R^6	R^7	m.p. (°C)	Refs.
H		H	H	H		1194
H		H	H	H	143–144.5	1171, 1194
H	$(CH_3)_2C(OH)-CH_2$	H	H	H	159–160	1171
H	$CH_3-CH(OH)-CH_2CH_2$	H	H	H	159–160	1193
H	$CH_3-CH_2-CH(CH_2OH)$	H	H	H	138	1177
H	$(HOH_2C)_2-C(CH_3)$	H	H	H	127–128	1171, 1193
H	Hydroxy-2-butyl	H	H	Cl	138	1182
H	$(C_2H_5)_2N(CH_2)_3CH(CH_3)$	H	H	H	88–89	1182

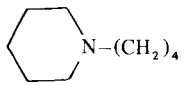
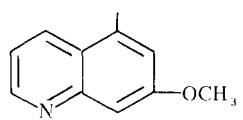
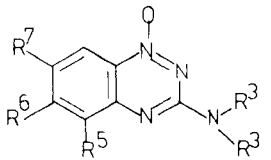
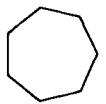
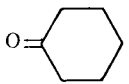
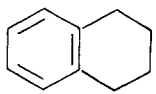
H		H	H	H		1194
H	$(C_2H_5)_2N(CH_2)_3CH(CH_3)$	H	H	Cl	b.p. 130/3	1177
H	$HOOC-CH(NH_2)-(CH_2)_4$	H	H	Cl	248	1177, 1182
H	C_6H_5	H	H	H	197	1154
H	C_6H_5	H	H	$CONHC_6H_5$	276–277 (dec.)	1207
H	4-$CH_3O-C_6H_4$	H	H	Cl	210–211	1183
					211	1177
H	4-$HOOC-C_6H_4$	H	H	Cl	300	1177, 1182
H	4-$HOOC-(CH_2)_3C_6H_4$	H	H	Cl	250–251	1177, 1182
H	4-$CH_3CONH-C_6H_4$	H	H	Cl	285–286	1182
H	4-(4-$H_2N-C_6H_4-SO_2$)-C_6H_4	H	H	Cl	293	1177, 1182
H	CH_3CO	H	H	H	190–191.5	1228
					191–192	1129
H	CH_3CO	H	H	Cl	250	1162
					256	1183
H	$HOOCCH_2CH_2CO$	H	H	Cl	250–254	1162, 1183
H	C_6H_5-CO	H	H	H	206–209	1129
H	3-$O_2N-C_6H_4$	H	H	H	233–237	1129
H	$H_2N-C(=NH)-NH$	H	H	H	269–270	1163
	·HCl				>300	1163
H	$H_2N-C(=NH)-NH$	H	H	Cl	282	1177, 1182
H		H	H	Cl	254	1182

TABLE IV-11 (continued)



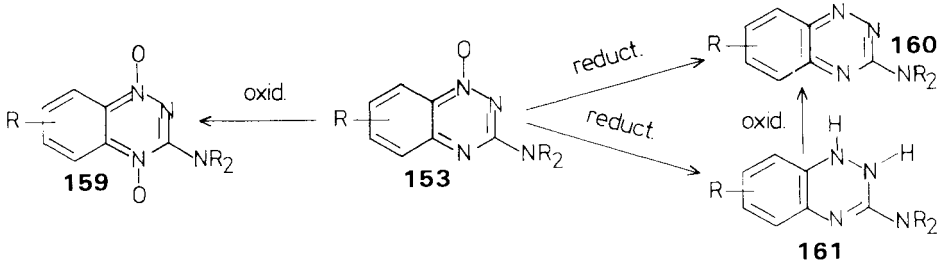
R^3	R^3	R^5	R^6	R^7	m.p. (°C)	Refs.
H	 2-Furyl	H	H	H	172–178	1171, 1193
H	 2-Thienyl	H	H	Cl	142–143	1182
H	Pyridoxylamino	H	H	Cl	213–214	1177, 1182
CH_3	CH_3	H	H	H	161–161.5	1190
CH_3	CH_3	H	$C_6H_5-CH_2O$	CH_3	180	1173
CH_3	$HOOC-\underset{\displaystyle NH_2}{\underset{\vert}{CH}}-(CH_2)_3$	H	H	H	135–137	1193
CH_3	C_6H_5	H	H	H	158.5–160	1171
n-C_3H_7	n-C_3H_7	H	H	Cl	105–106	1177, 1182
		H	H	H	108–110	1171, 1193

	H	H	Cl	142	1177, 1182
	H	H	H	121–122.5	1171, 1193
	H	H	H	254–257	1171, 1193
	H	H	H	174–176	1171, 1193
	H	H	Cl	175	1177, 1182
	H	H	H	125–126	1193, 1171

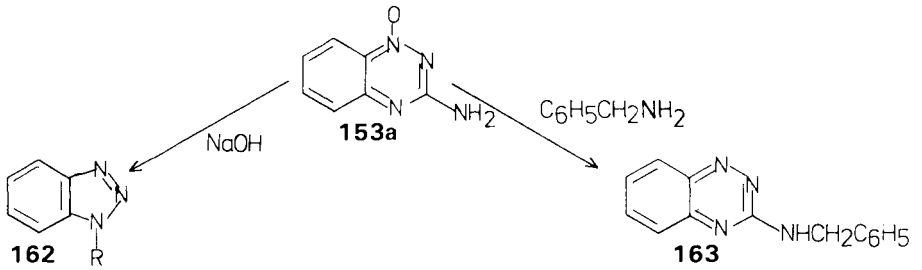
153 are well-known compounds hardly any spectroscopic data have so far been reported. The PMR spectra of a few 3-amino-1,2,4-benzotriazine 1-oxides were published by Mason and Tennant (1172). The four protons of the unsubstituted compound give signals at $\tau = 2.21$ (H-5), 1.86 (H-6), 2.21 (H-7), and 1.55 (H-8). A few details of the mass spectrum of 3-anilino-1,2,4-benzotriazine 7-carboxanilide 1-oxide were published by Bild and Hesse (1196).

d. REACTIONS. The 3-amino-1,2,4-benzotriazine 1-oxides (**153**) can be acylated, leading to the formation of 3-(acylamino)-1,2,4-benzotriazine 1-oxides (1129, 1162, 1183). The amino group in **153** can be replaced by chlorine (1159) or by a hydroxy group (1169, 1171, 1180).

Oxidation of **153** yields the 3-amino-1,2,4-benzotriazine 1,4-dioxides (**159**) (1129, 1172). Reduction of **153** with sodium dithionite, zinc and ammonium chloride, or phosphorus and iodine yields the 3-amino-1,2,4-benzotriazines (**160**) (1157, 1161, 1162, 1171, 1172, 1183); reduction with stronger reducing agents, such as tin and hydrochloric acid, affords 3-amino-1,2-dihydro-1,2,4-benzotriazines (**161**) (1154, 1169, 1171, 1173, 1176, 1197, 1198), which can be oxidized to **160**.



3-Amino-1,2,4-benzotriazine 1-oxide (**153a**) is converted to benzotriazole (**162a**) and 1-acetylbenzotriazole (**162b**) by treatment with sodium hydroxide (1163). 3-(Benzylamino)-1,2,4-benzotriazine (**163**) was isolated from the reaction of 3-amino-1,2,4-benzotriazine 1-oxide (**153a**) with benzylamine (1177).



14. *3-Hydrazino-1,2,4-benzotriazine 1-Oxides*

All known 3-hydrazino-1,2,4-benzotriazine 1-oxides (**164**) (Table IV-12) were prepared by the reaction of 3-chloro-1,2,4-benzotriazine 1-oxides (**136**) with hydrazines (1129, 1156, 1159, 1171, 1193).

They are stable, crystalline, yellow compounds with high melting points. They can be acylated (1129, 1156) and reduced to the 3-hydrazino-1,2,4-benzotriazines (**165**) by treatment with stannous chloride in hydrochloric acid (1129). Oxidation of the unsubstituted 3-hydrazino-1,2,4-benzotriazine 1-oxide (**164a**) with copper sulfate was used for the synthesis of the unsubstituted 1,2,4-benzotriazine 1-oxide (**166**) (1129). Sasaki and Murata (1156) used **164** for the synthesis of heterocyclic condensed 1,2,4-benzotriazines.

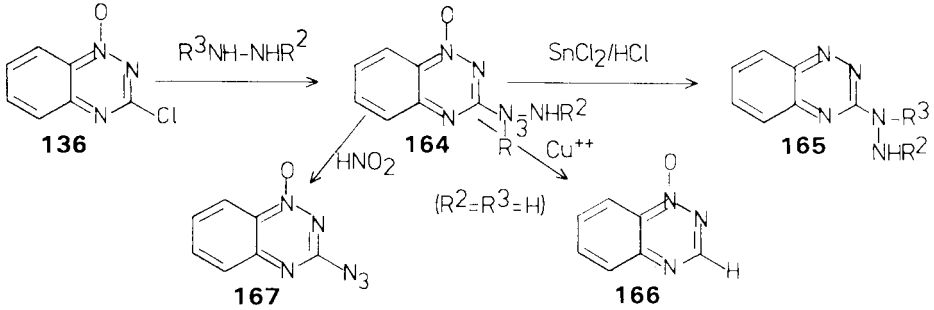
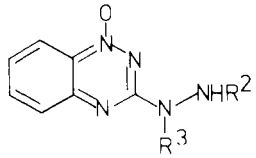


TABLE IV-12. 3-HYDRAZINO-1,2,4-BENZOTRIAZINE 1-OXIDES



R^3	R^2	m.p. (°C)	Refs.
H	H	201–203	1129
		207–209.5	1159
		207.5–213.5	1171
H	CHO	235–237	1156
H	CH_3–CO	253.5–255	1156
H	C_6H_5–CO	273–275	1156
H	H_2N–CS	253–255 (dec.)	1171, 1193
H	4-CH_3–C_6H_4–SO_2	223–225 (dec.)	1129
CH_3	H	134–135	1171
		138–139	1159
C_2H_5	H		1159

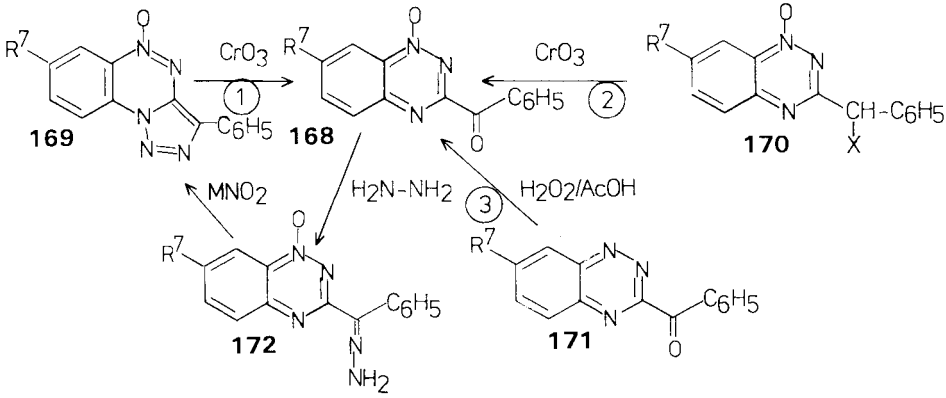
The reaction of **164a** with nitrous acid affords 3-azido-1,2,4-benzotriazine 1-oxide (**167**) (m.p. 119–121 °C) (1156).

15. *3-Acyl-substituted 1,2,4-Benzotriazine 1-Oxides*

Tennant (1144) obtained two 3-benzoyl-1,2,4-benzotriazine 1-oxides (**168**) [R^7 = H, m.p. 152 °C, λ_{max} (log ϵ) = 207 (4.36), 247 (4.44), 345 nm (3.66); R^7 = CH_3, m.p. 174 °C, λ_{max} (log ϵ) = 215 (4.28), 257 (4.43), 357 nm (3.63)] by the following methods.

1. Oxidation of 1,2,3-triazolo[5,1-*c*] 1,2,4-benzotriazine 5-oxides (**169**).
2. Oxidation of the α-substituted 3-benzyl-1,2,4-benzotriazine 1-oxides (**170**) (X = OH, OAc, Cl, Br) with chromium trioxide in 70% acetic acid.
3. Oxidation of the 3-benzoyl-1,2,4-benzotriazines (**171**) with hydrogen peroxide in glacial acetic acid.

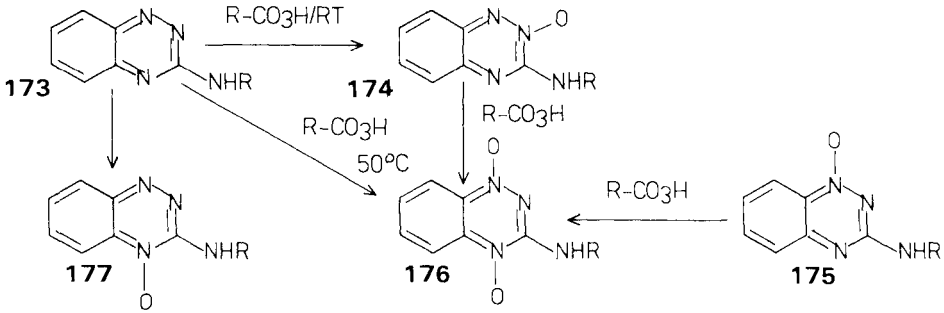
Both oxides (**168**) were pale yellow and crystalline. They form orange-colored hydrazones (**172**) [R^7 = H, m.p. 218 °C; R^7 = CH_3, 202 °C (dec.)], which afford **169**, by oxidation with manganese dioxide.



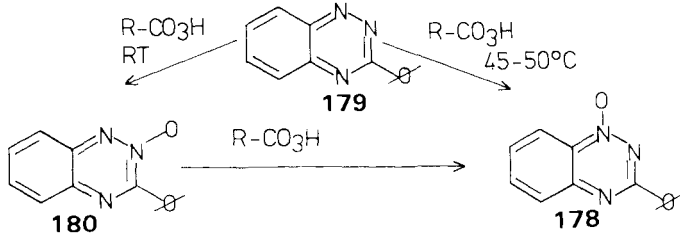
16. *1,2,4-Benzotriazine 2-Oxides*

a. PREPARATION. Arndt and Rosenau (1154) in 1917 published the oxidation of 3-amino-1,2,4-benzotriazines (**173**) with hydrogen peroxide in acetic acid and formulated the isolated compounds as 3-amino-1,2,4-benzotriazine 2-oxides (**174**). Robbins and Schofield (1129) in 1957 observed that the *N*-oxides obtained by Arndt and Rosenau could be further oxidized yielding the

same dioxides (**176**) that the 3-amino-1,2,4-benzotriazine 1-oxides (**175**) yielded on oxidation. Since the dioxides (**176**) were formulated as 1,4-dioxides the 4-oxide **177** structure was suggested for the oxidation products of **173**. Mason and Tennant (1172) determined the structure of 3-amino-1,2,4-benzotriazine monoxides and dioxides by PMR spectroscopy and were able to show that oxidation of **173** at room temperature leads almost exclusively to the 3-amino-1,2,4-benzotriazine 2-oxides (**174**), whereas prolonged oxidation of **173** at 50 °C yields the 1,4-dioxides (**176**). Because of this result, in this discussion we formulate all oxidation products of 3-amino-1,2,4-benzotriazines (**173**) as the 2-oxides (**174**). Oxidation of 3-amino-1,2,4-benzotriazines is also reported in a Swiss patent (1076).

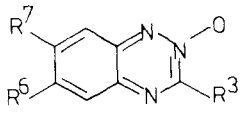


The results of Mason and Tennant suggest a rearrangement of 3-amino-1,2,4-benzotriazine 2-oxides (**174**) during further oxidation to the 1,4-dioxides (**176**). A similar rearrangement was probably observed by Robbins and Schofield (1129), who isolated the 3-phenyl-1,2,4-benzotriazine 1-oxide (**178**) when 3-phenyl-1,2,4-benzotriazine (**179**) was oxidized with peracetic acid at 45 to 50 °C, while oxidation of **179** with peracetic acid at room temperature gave an isomeric monoxide (**180**) which rearranged to **178** on heating with peracetic acid. **180** is formulated as 3-phenyl-1,2,4-benzotriazine 2-oxide.



b. COMPOUND SURVEY. The 1,2,4-benzotriazine 2-oxides reported in the literature are listed in Table IV-13.

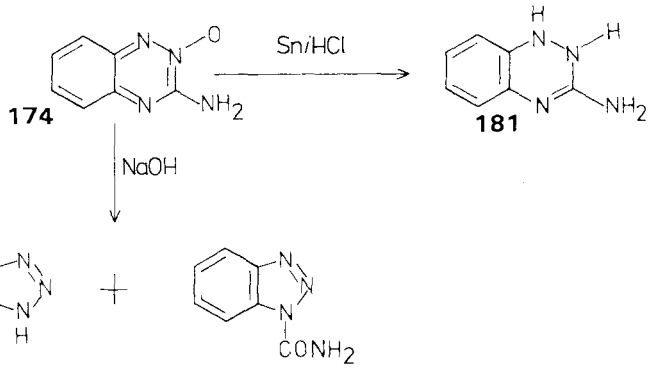
TABLE IV-13. 1,2,4-BENZOTRIAZINE 2-OXIDES



R^3	R^6	R^7	m.p. (°C)	Refs.
C_6H_5	H	H	105–107	1129
NH_2	H	H	187	1154
			200	1172
NH_2	H	Cl	223	1172
			213–215	1129
NH_2	H	OCH_3	196	1172
			182–183	1129
NH_2	H	CH_3	203	1172
NH_2	CH_3	CH_3	238	1172
NHC_6H_5	H	H	163	1154

c. PHYSICAL PROPERTIES AND REACTIONS. 1,2,4-Benzotriazine 2-oxides are stable, crystalline, yellow compounds.

The 3-amino derivative (**174**) can be reduced to 3-amino-1,2-dihydro-1,2,4-benzotriazine (**181**) on treatment with tin and hydrochloric acid (1154) and was converted to benzotriazole and benzotriazole-1-carboxamide on treatment with sodium hydroxide (1163).

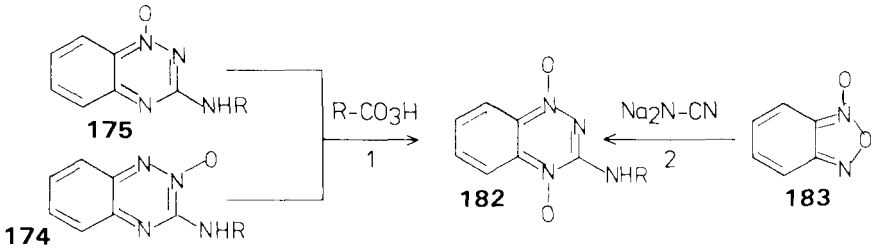


17. *3-Amino-1,2,4-benzotriazine 1,4-Dioxides*

Two methods are reported for the synthesis of the 3-amino-1,2,4-benzotriazine 1,4-dioxides (**182**):

1. Oxidation of the 3-amino-1,2,4-benzotriazine monoxides (**175**, **174**) with percarbonic acids (1129, 1172, 1201).

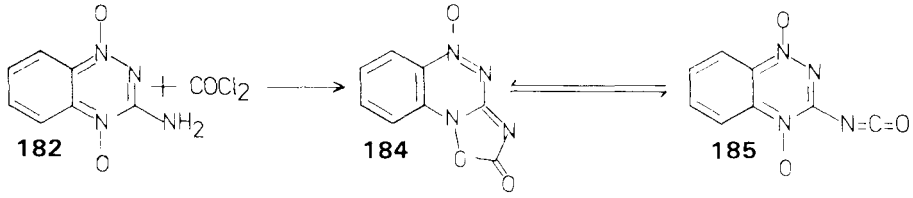
2. Reaction of benzofuroxanes (**183**) with disodium cyanamide (1175, 1202, 1203).



The 3-amino-1,2,4-benzotriazine 1,4-dioxides (**182**) are stable, crystalline, orange to red compounds which can be reduced to the 3-amino-1,2,4-benzotriazine 1-oxides (**175**) by reduction with sodium dithionite (1172). The titrimetric determination of **182** with perchloric acid in acetic anhydride is reported by Wimer (1204). The PMR spectra of **182** have been published by Mason and Tennant (1172); the unsubstituted compound shows the following signals: τ = 1.91 (H-5), 1.71 (H-6), 2.16 (H-7), and 1.56 (H-8).

The amino group of **182** can be alkylated and acylated and reacts with isocyanates (1129, 1172, 1175, 1201, 1205, 1206). Reaction of **182** with phosgene affords the tricyclic compound (**184**) which reacts with nucleophiles as expected for the isocyanate (**185**) (1175, 1202).

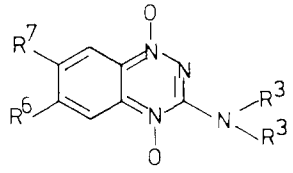
Table IV-14 lists the known compounds of this group.



18. *Dihydro-1,2,4-benzotriazines*

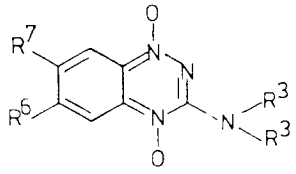
a. PREPARATION. Dihydro-1,2,4-benzotriazines are well-known compounds and a number of methods for their synthesis are reported. In this section we discuss all compounds with a dihydro-1,2,4-benzotriazine structure independent of the group in the 3-position. In most cases the dihydro-1,2,4-benzotriazines are formulated as the 1,2-dihydro derivatives (**186**) owing to their easy oxidation to the 1,2,4-benzotriazines; for this reason we use this structure

TABLE IV-14. 3-AMINO-1,2,4-BENZOTRIAZINE 1,4-DIOXIDES



R^3	R^3	R^6	R^7	m.p. (°C)	Refs.
H	H	H	H	220 (dec.)	1202, 1203, 1205
H	H		H, CH_3 [a]	145 (dec.)	1203
H	H		H, Cl [a]	280 (dec.)	1203
H	H		H, CH_3O [a]	220 (dec.)	1203
H	H		H, C_2H_5O [a]	202 (dec.)	1203
H	CH_3	H	H	210 (dec.)	1205, 1206
				211–213 (dec.)	1201
H	CH_2CH_2OH	H	H	190–193	1201
H	CH_3CO	H	H	200 (dec.)	1205, 1206
H	C_2H_5CO	H	H	168 (dec.)	1205, 1206
H	$C_{17}H_{35}CO$	H	H	148 (dec.)	1205, 1206
H	CH_3COCH_2CO	H	H	169 (dec.)	1205, 1206
H	C_6H_5CO	H	H	178 (dec.)	1205, 1206
H	3,5-$(O_2N)_2C_6H_3$	H	H	203–205	1201
H	H_2N–CO	H	H	191–193	1201
				216 (dec.)	1202
H	H_2N–CO	H	CH_3O	218–220	1201
H	CH_3NH–CO	H	H	198 (dec.)	1205, 1206
				211–213	1201
				213–215	1202
H	$(CH_3)_2N$–CO	H	H	150–151 (dec.)	1202
				138–140	1201
H	C_2H_5–NH–CO	H	H	196–197 (dec.)	1202
				199–201	1201
H	$(C_2H_5)_2N$–CO	H	H	120–123	1201
H	*t*-C_4H_9NH–CO	H	H	169–171	1201
H	$C_7H_{15}NH$–CO	H	H	188–189	1201
H	$C_{12}H_{25}NH$–CO	H	H	178–180	1201
H	$C_6H_5CH_2NH$–CO	H	H	184–186	1201
H	$C_6H_5CH_2NH$–CO	H	CH_3	192–194	1201
H	2,4-$Cl_2C_6H_3$–CH_2NH–CO	H	H	204–208	1201
H	2,4-$Cl_2C_6H_3$–CH_2NH–CO	H	CH_3	210–215	1201
H	4-Cl–C_6H_4–CH_2CH_2NH–CO	H	H	202–204	1201
H	4-Cl–C_6H_4–CH_2CH_2NH–CO	H	CH_3	212–214	1201
H	2,6-$Cl_2C_6H_3$–CH_2CH_2NHCO	H	CH_3	210–213	1201
H	$C_6H_5(CH_2)_3NH$–CO	H	H	168–171	1201
H	2,4-$Cl_2C_6H_3(CH_2)_3NH$–CO	H	CH_3	200–202	1201
H	3,4-$Cl_2C_6H_3(CH_2)_3NH$–CO	H	CH_3	193–195	1201

TABLE IV-14. (continued)



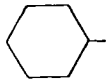
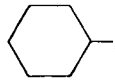
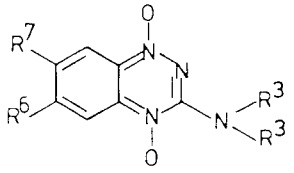
R^3	R^3	R^6	R^7	m.p.(°C)	Refs.
H	$C_6H_5(CH_2)_4NH-CO$	H	H	174–178	1201
H	$C_6H_5(CH_2)_4NH-CO$	H	CH_3	199–202	1201
H	C_6H_5NH-CO	H	H	192–198	1201
H	4-HOOC–CH_2–C_6H_4NH–CO	H	CH_3O	175	1201
H	 Cyclopropyl-	H	CH_3O	204–205	1201
H	 Cyclohexyl-	H	H	203–206 (dec.)	1202, 1205, 1206
H	 Cyclohexyl-	H	CH_3O	208–211	1201
H	3-Pyridyl-NH–CO	H	H	181–183	1201
H	$HOCH_2CH_2NH-CO$	H	H	186–188 (dec.) 191–192 (dec.)	1201 1202
H	$HOCH_2CH_2NH-CO$	H	CH_3	184–186	1201
H	$(CH_3)_2NCH_2CH_2NH-CO$	H	H	144–145	1201
H	$HOOC-(CH_2)_5NH-CO$	H	H	192–194	1201
H		H	H	156–158 180–183	1201 1202
H		H	H	173–174 (dec.)	1202
H		H	CH_3O	167–169 (dec.) 172–174	1202 1201
H		H	CH_3	196–198	1201
H		H	H	178–179	1201

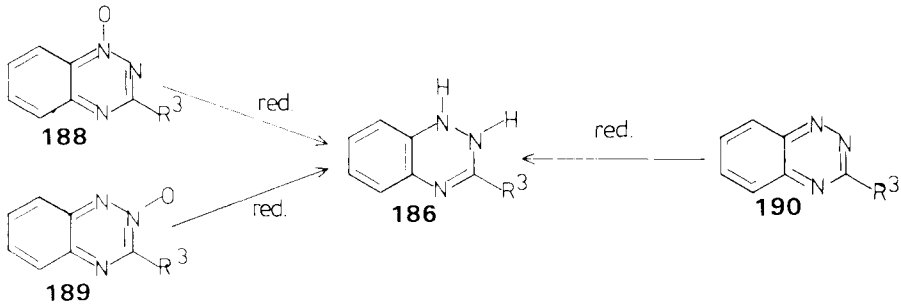
TABLE IV-14. (continued)



R^3	R^3	R^6	R^7	m.p.(°C)	Refs.
H	H_2C_5>N–CO, H_5C_6	H	H	188–189	1201
H	H_5C_2>N–CO, $HOCH_2–H_2C$–CH_2OH	H	H	152–154	1201
	$(CH_3)_2N–CH=$	H	CH_3	196–198	1201
	$(CH_3)_2N–C=$ (CH_3)	H	CH_3	168–170	1201
H	i-$C_4H_9O–CO$	H	CH_3	150–153	1201
H	$C_6H_5CH_2O–CO$	H	H	146	1201

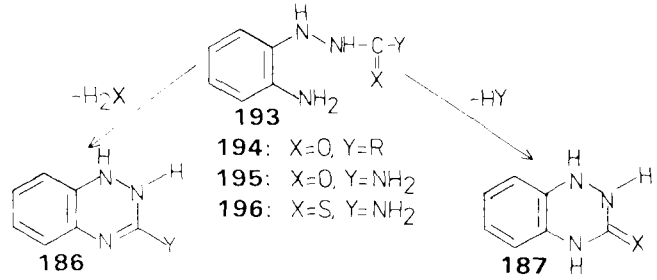
[a] Mixture of isomers.

in this chapter as far as possible. Besides **186** 1,4-dihydro-1,2,4-benzotriazines (**187**) have also been reported, and we use this structure if it is the more likely or the only possible structure.

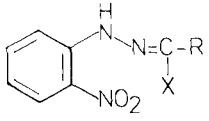


The dihydro-1,2,4-benzotriazines (**186**, **187**) were very often obtained through the reduction of the 1,2,4-benzotriazine 1-oxides (**188**) or 2-oxides (**189**) (1144, 1154, 1171, 1173, 1174, 1176, 1183, 1197, 1198, 1207), 1,2,4-benzotriazines (**190**) (1133, 1144), 1,2,4-benzotriazin-3-ones (**191**) (1165, 1184), or 3-imino-1,2,4-benzotriazines (**192**) (1164). Owing to the easy oxidation of **186** or **187** they are not very often isolated, but only mentioned as intermediates in the transformation of **188** or **189** to **190**. In this section we discuss only those publications that describe the isolation of **186** or **187**.

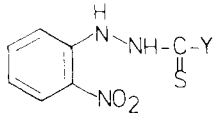
Besides these reduction methods a number of cyclization reactions have been reported for the synthesis of **186** and **187**. The principle of most cyclization reactions is the conversion of a compound of the general structure **193** to **186** or **187**. The following systems, having the structure **193**, were used: *o*-aminophenylhydrazides (**194**) (1147), *o*-aminophenylsemicarbazides (**195**) (1208), or *o*-aminophenylthiosemicarbazides (**196**) (1209).



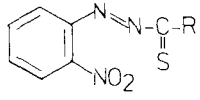
In many cases the compounds of the general structure **193** were not isolated but were the intermediates in the synthesis of **186** and **187**, when *o*-nitrophenyl compounds such as *o*-nitrophenylamidrazones (**197**) (1133, 1134), *o*-nitrophenylhydrazone of α-nitrobenzaldehyde (**198**) (1138), *o*-nitrophenylthiosemicarbazide (**199**) (1211), methyl ω-nitrophenyldithiocarbazinate (**200**) (1213), *o*-nitrophenylazo compounds (**201**) (1210), and azo compounds of the general structure **202** (1132, 1211, 1212) were used as the starting material.



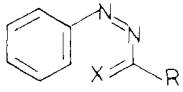
197: X=NH2
198: X=NO2



199: Y=NH2
200: Y=SCH3



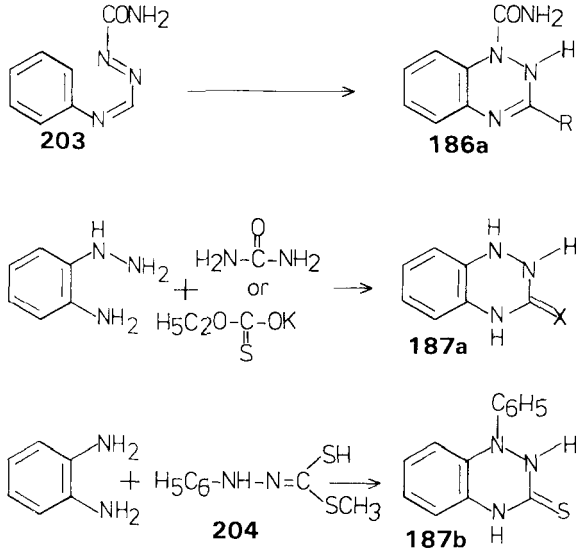
201



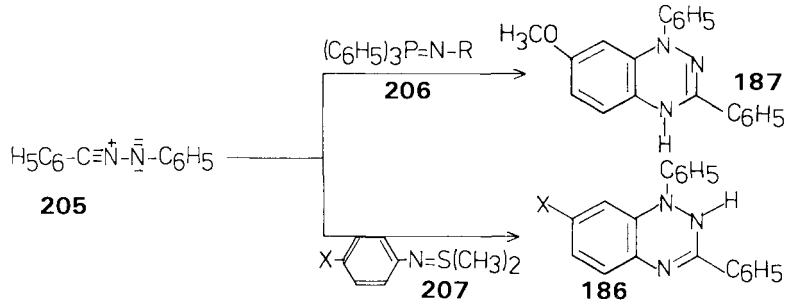
X=N-NHR
X=NR

202

Additional published methods for the synthesis of **186** or **187** are – cyclization of compound **203** (1168), reaction of *o*-aminophenylhydrazine with urea or xanthogenates (1214), or reaction of *o*-phenylenediamine with methyl ω-phenyldithiocarbazinate (**204**) (1215).

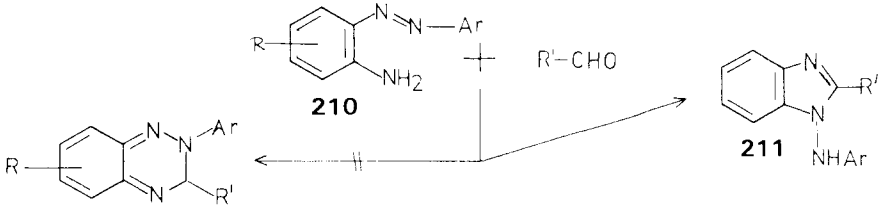


Mixich (1174) isolated some 1,2-dihydro-1,2,4-benzotriazines (**186**) as degradation products from azapropazon. Huisgen and Wulff (1216) postulated the formation of a dihydro-1,2,4-benzotriazine (**187**) in the reaction of nitrilimines (**205**) with phosphinimines (**206**), and Rees and his co-workers observed the formation of **186** in the reaction of **205** with sulfinimines (**207**) (1218).

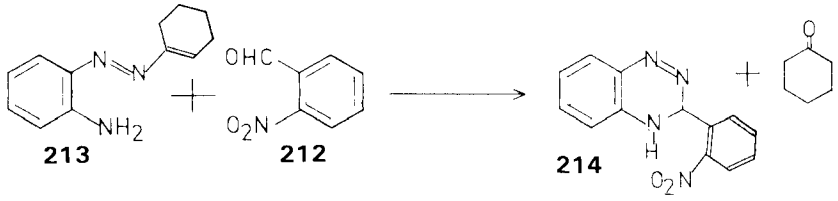


A large number of compounds, formulated as dihydro-1,2,4-benzotriazines, were synthesized through the reaction of substituted *o*-aminoazobenzenes (**210**) with aldehydes (1170, 1219–1223). Because Fischer (1224, 1225) has shown

that the isolated compounds were in fact 1-aminobenzimidazoles (**211**), these publications are not discussed here.



Sparatore (1223) in 1955 reported the reaction of *o*-nitrobenzaldehyde (**212**) with *o*-aminobenzeneazo-1-cyclohexene (**213**) and isolated, in addition to cyclohexanone, a crystalline red compound of m.p. 155 to 157 °C which he formulated as 3-(*o*-nitrophenyl)-3,4-dihydro-1,2,4-benzotriazine (**214**), but, owing to the work of Fischer, there should be some doubt of the structure.



b. COMPOUND SURVEY. Table IV-15 lists the compounds of this class reported in the literature.

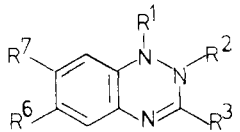
c. PHYSICAL PROPERTIES. The dihydro-1,2,4-benzotriazines are crystalline compounds which are, depending on the substituents, colorless to yellow or purple (3-benzoyl derivatives). Most are soluble in acids and reprecipitate on adding bases. They are generally soluble in most organic solvents.

So far only a small amount of spectroscopic data has been reported. For the 1,3-diphenyl-1,2-dihydro-1,2,4-benzotriazine the following spectrum is published: λ_{max} = 216 sh (20.274), 248 (21.976), 302 (8.171), 336 sh (5.577), and 420 nm sh (1.073) (1212). The 1-acetyl-3-benzyl-1,2-dihydro-1,2,4-benzotriazine shows the following absorption bands: λ_{max} (log ϵ) = 210 (4.27), 234 (4.41), 258 infl (3.97), and 313 nm (3.73) (1131).

d. REACTIONS. The dihydro-1,2,4-benzotriazines are very easily oxidized, even in air, to the 1,2,4-benzotriazines (1133, 1134, 1138, 1154, 1164, 1168, 1171, 1176, 1147). The 1-aryl-dihydro-1,2,4-benzotriazines (**208**) are easily converted to stable 1,2,4-benzotriazinyl radicals (**209**) (1211, 1212, 1216, 1218).

TABLE IV-15. DIHYDRO-1,2,4-BENZOTRIAZINES

A. 1,2-Dihydro-1,2,4-benzotriazines

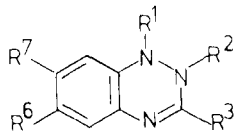


R^1	R^2	R^3	R^6	R^7		m.p. (°C)	Refs.
H	H	H	H	H			1147
H	H	H	H	CH_3	·HBr		1141
H	H	H	H	NO_2	·HCl		1141
H	H	H	CF_3	H	·HCl		1141
H	H	CH_3–CHOH	H	H		183	1132[a]
H	H	C_6H_5–CH_2	H	H		119	1131, 1144
H	H	C_6H_5–CH_2	H	CH_3		117	1131, 1144
H	H	C_6H_5–CHOH	H	H		142	1144
H	H	C_6H_5–CHOH	H	CH_3		120	1144
H	H	C_6H_5	H	H		150	1210
H	H	OC_3H_7	H	H	·HCl	110–111	1198
H	H	SCH_3	H	H		199–200	1213[b]
							1154
H	H	S⟩$_2$	H	H		208–210	1214[b]
H	H	NH_2	H	H			1154
						85	1213[c]
					·HCl	248–249	1213[c]
H	H	NH_2	H	Cl	·HCl	231–233	1198
H	H	CH_3NH	H	Cl		190–192	1198
H	H	C_2H_5NH	H	Cl	·HCl	193–195	1198
H	H	C_3H_7NH	H	Cl	·HCl	171–173	1198
H	H	i-C_4H_9NH	H	Cl	·HCl	177–179	1198

H	H	$C_6H_5CH_2NH$	H	Cl	·HCl	180	1198
H	H	C_6H_5NH	H	H			1154
							1214[c]
H	H	$(CH_3)_2N$	H	H	·HCl		1198
H	H	$(CH_3)_2N$	H	Cl	·HCl	215–220	1198
H	H	$(CH_3)_2N$	$C_6H_5CH_2O$	CH_3			1173
H	H		H	Cl	·HCl	203–207	1198
H	H	C_6H_5–CO	H	H		153 (dec.)	1144
H	H	C_6H_5–CO	H	CH_3		124 (dec.)	1144
H	H	$COOC_2H_5$	H	H			1133[b]
						155	1134[b]
H	H	$COOC_2H_5$	Cl	H		206	1134[b]
H	H	$COOC_2H_5$	CH_3CO	H			1133[b]
H	H	$COOC_2H_5$	CH_3CONH	H		224	1133[b]
H	4-CH_3–C_6H_4	C_6H_5–NH	H	CH_3		141	1164[c]
H	4-CH_3–C_6H_4	4-CH_3–C_6H_4–NH	H	CH_3		166–168	1164[c]
H	n-C_4H_9–CO	$(CH_3)_2N$	H	CH_3		154–156 (dec.)	1174
H	C_3H_7–CH(OH)–CO	$(CH_3)_2N$	H	CH_3		174–176	1174
H	C_3H_7–CH(COOH)–CO	$(CH_3)_2N$	H	CH_3		161–162 (dec.)	1174
H	C_3H_7–C(OH)(COOH)–CO	$(CH_3)_2N$	H	CH_3		126–127	1174
CH_3	H	H	H	H	·HCl		1141
C_6H_5	H	H	H	H	·HCl		1141
C_6H_5	H	H	H	CH_3	·HBr		1141
C_6H_5	H	H	CF_3	H	·HCl		1141
C_6H_5	H	C_6H_5	H	H		105–107 (dec.)	1211, 1212[b]
					·HBr	230–235 (dec.)	1211, 1212[b]

TABLE IV-15. (continued)

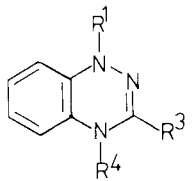
A. 1,2-Dihydro-1,2,4-benzotriazines



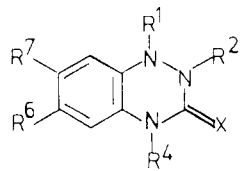
R^1	R^2	R^3	R^6	R^7		m.p.(°C)	Refs.
C_6H_5	H	C_6H_5	H	Br	·HBr	229–232 (dec.)	1211[b]
C_6H_5	H	C_6H_5	H	OCH_3			1216[b]
C_6H_5	H	S⟩–	H	H		300	1215[b]
4-CH_3–C_6H_4	H	C_6H_5	CH_3	H	·HBr		1212[b]
2-O_2N–C_6H_4	H	H	H	H	·HCl		1141
2-O_2N–C_6H_4	H	H	H	NO_2	·HCl		1141
CH_3CO	H	H	H	H	·HCl		1141
CH_3CO	H	H	H	CH_3	·HBr		1141
CH_3CO	H	H	H	NO_2	·HCl		1141
CH_3CO	H	CH_2=CH	H	H		88–89	1132[a]
CH_3CO	H	C_6H_5–CH_2	H	H		158	1131
CH_3CO	H	C_6H_5–CH_2	H	CH_3		158	1131
CH_3CO	H	C_6H_5–CH(O–CO–CH_3)	H	H		215	1131, 1144
CH_3CO	H	OC_3H_7	H	CH_3		184	1131, 1144
CH_3CO	H	$(CH_3)_2N$	H	H	·HCl	144–145	1198
CH_3CO	H	C_6H_5–CO	H	Cl		181–183	1198
CH_3CO	H	C_6H_5–CO	H	H		145	1144
CH_3CO	H	$(CH_3)_2N$	H	CH_3	·HCl	146	1144
CH_3CO	HCO	$(CH_3)_2N$	H	Cl	·HCl	179–183	1198
CH_3CO	CH_3CO	H	H	Cl		152	1198

C_6H_5-CO	H	H	H	H	·HCl		1141
C_6H_5-CO	H	H	H	CH_3	·HBr		1141
C_6H_5-CO	H	H	H	NO_2	·HCl		1141
$COOC_2H_5$	$COOC_2H_5$	$(CH_3)_2N$	H	CH_3	·HCl	105	1198
$CONH_2$	H	SCH_3	H	Cl	·HCl	208–210	1168

B. 1,4-Dihydro-1,2,4-benzotriazines

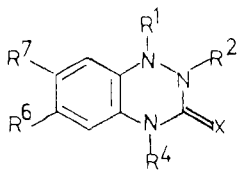


R^1	R^3	R^4	m.p. (°C)	Refs.
H	S-)-$_2$	C_6H_5	175–176	1209
H	S-)-$_2$	4-$CH_3-C_6H_4$	97–98	1209



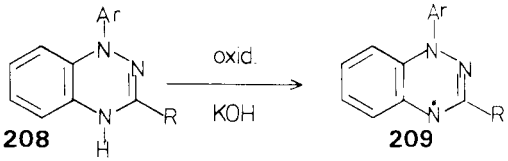
R^1	R^2	X	R^4	R^6	R^7		m.p. (°C)	Refs.
H	H	O	H	H	H	·$2H_2O$	310–312	1214
H	H	O	H	H	CH_3		256–258	1207, 1208 1174

TABLE IV-15. (continued)



R^1	R^2	X	R^4	R^6	R^7	m.p. (°C)	Refs.
H	H	O	CH_3	H	H	146–147 (dec.)	1165
H	H	O	C_6H_5	H	H	170–171	1213
H	CH_3	O	H	H	H	147–152 (dec.)	1165
H	C_6H_5	O	H	NHCN	H	210 (dec.)	1184
H	4-CH_3–C_6H_4	O	H	H	CH_3	146	1164
H	C_4H_9–CO	O	H	H	CH_3	176–178	1174
H	C_3H_7–CH(COOH)–CO	O	H	H	CH_3	193–194 (dec.)	1174
CH_3CO	CH_3CO	O	CH_3CO	H	H		1217
CH_3CO	4-CH_3–C_6H_4	O	H	H	CH_3	190	1164
H	H	S	H	H	H	298–300	1214
							1154
H	H	S	C_6H_5	H	H	151	1209
H	H	S	4-CH_3–C_6H_4	H	H	182	1209
C_6H_5	H	S	H	H	H	292–293	1215
Acetyl deriv.						203–204	1215
C_6H_5CO	H	S	H	H	H	174	1214

[a]Structure doubtful.
[b]Formulated as 1,4-dihydro derivative.
[c]Imino structure given.

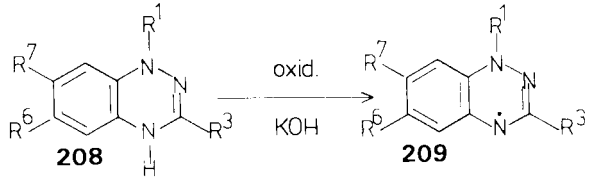


208 209

Dihydro-1,2,4-benzotriazines can be acylated (1131, 1164, 1198) and were used as starting materials for the synthesis of tricyclic compounds (1173, 1174, 1198).

19. *1,2,4-Benzotriazinyl Radicals*

1-Aryl-dihydro-1,2,4-benzotriazines (**208**) are readily oxidized, even by oxygen, in alkaline media to the stable 1,2,4-benzotriazinyl radicals (**209**) (1211, 1212, 1216, 1218). These radicals are stable, deeply colored crystals, the stability of which appears to be at least comparable to that of the stable free radical 2,2-diphenyl-1-picrylhydrazyl. 1,3-Diphenyl-1,2,4-benzotriazinyl radical shows the following absorptions in the ultraviolet/visible spectrum: 260 sh (33.020), 268 (36.130), 320 (7.150), 370 (5.490), 420 sh (2.630), 490 (1.330), and 570 nm sh (540) (1212). Because of the paramagnetic character of the radicals no PMR spectra could be observed.



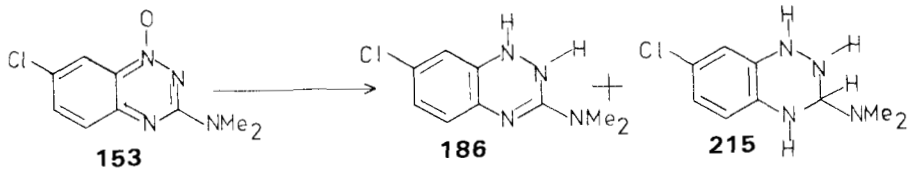
208 209

R^1	R^3	R^6	R^7	m.p. (°C)	Refs.
C_6H_5	C_6H_5	H	H	113–115	1211, 1212 1218
C_6H_5	C_6H_5	H	Cl		1218
C_6H_5	C_6H_5	H	Br	236–239	1211
C_6H_5	C_6H_5	H	OCH_3	142–144	1216
4-CH_3–C_6H_4	C_6H_5	CH_3	H	123–125	1211, 1212

20. *1,2,3,4-Tetrahydro-1,2,4-benzotriazines*

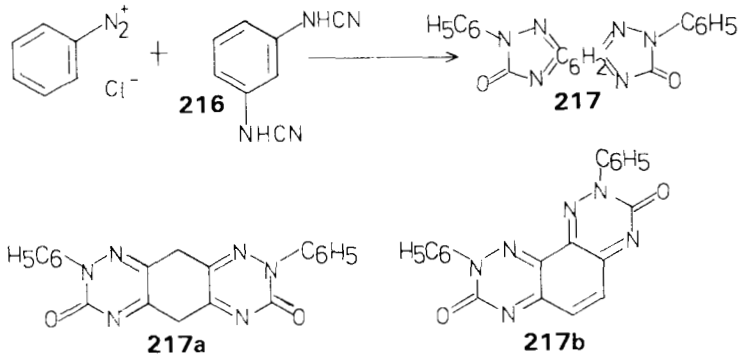
So far only one 1,2,3,4-tetrahydro-1,2,4-benzotriazine, the 7-chloro-3-(dimethylamino)-1,2,3,4-tetrahydro-1,2,4-benzotriazine hydrochloride (**215**) (m.p. 203 to 205 °C) has been reported (1198). **215** is the by-product in the

synthesis of 7-chloro-3-(dimethylamino)-1,2-dihydro-1,2,4-benzotriazine (**186**) through reduction of 7-chloro-3-(dimethylamino)-1,2,4-benzotriazine 1-oxide (**153**) with tin and hydrochloric acid.



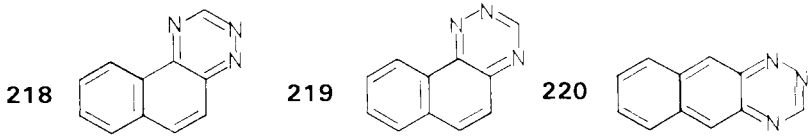
B. Two 1,2,4-Triazine Rings Condensed with One Benzene Ring

Pierron (1184) reacted benzenediazonium chloride with an alkaline solution of *m*-bis(cyanamido)benzene (**216**) and obtained a complex mixture from which he isolated several products, including a yellow compound of m.p. 310 °C which he formulated as **217**. The structure is not fully established since only the nitrogen content was determined. The following two structures, **217a** and **217b**, can be discussed for the substance. **217a** would be a derivative of the benzo[1,2-*e*:5,4-*e'*]bis-1,2,4-triazine system, and **217b** would be a derivative of the benzo[1,2-*e*:4,3-*e'*]bis-1,2,4-triazine system.



IV. CONDENSED WITH THE NAPHTHALENE SYSTEM

At present derivatives of only two of the three possible naphtho-1,2,4-triazines (**218** to **220**), the naphtho[1,2-*e*]1,2,4-triazine (**218**) and the naphtho[2,1-*e*]1,2,4-triazine (**219**), are known.



A. Naphtho[1,2-*e*]1,2,4-triazines

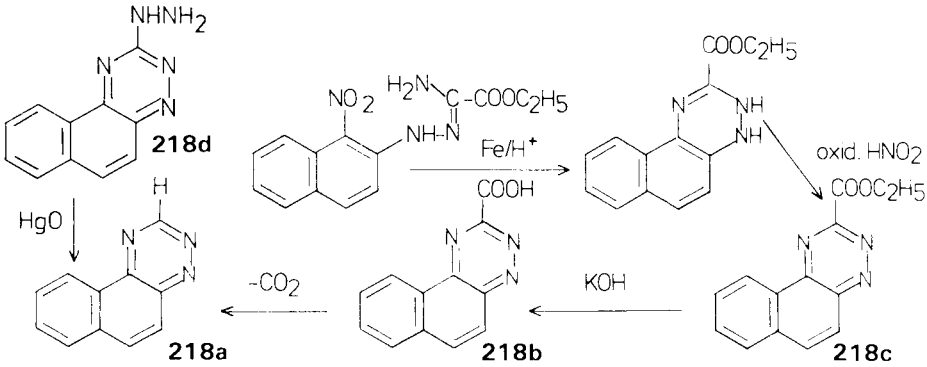
1. *Preparation*

Since the number of known naphtho[1,2-*e*]1,2,4-triazines (**218**) is still very low, we discuss all derivatives of **218** together.

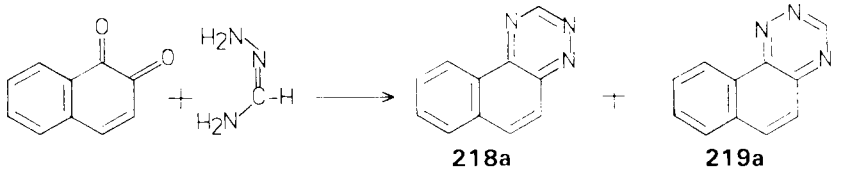
Unsubstituted naphtho[1,2-*e*]1,2,4-triazine (**218a**) was synthesized by Fusco and Bianchetti by two methods.

1. Decarboxylation of naphtho[1,2-*e*]1,2,4-triazine-2-carboxylic acid (**218b**), which was obtained by the following reaction sequence (1229).

2. Oxidation of 2-hydrazinonaphtho[1,2-*e*]1,2,4-triazine (**218d**) with mercuric oxide (1233).

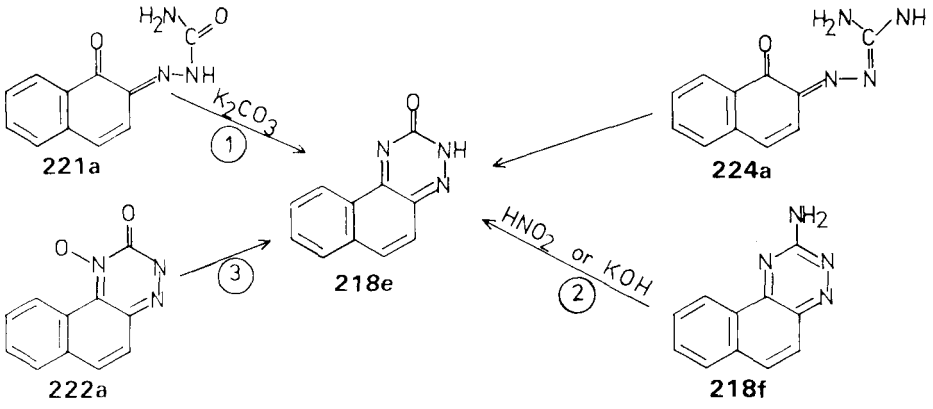


Neunhoeffer and Hennig (13) isolated **218a** and **219a** in very low yields from the reaction of 1,2-naphthoquinone with formamidrazone.



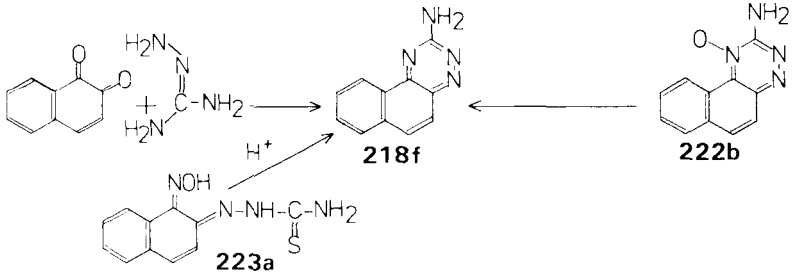
Scott and Lalor (1232) obtained naphtho[1,2-*e*]1,2,4-triazin-2-one (**218e**) by the following methods.

1. Cyclization of the β-semicarbazone of 1,2-naphthoquinone (**221a**) in the presence of potassium carbonate.
2. Reaction of 2-aminonaphtho[1,2-*e*]1,2,4-triazine (**218f**) with nitrous acid, this reaction is also reported by Fusco and Bianchetti (1233).
3. Reduction of naphtho[1,2-*e*]1,2,4-triazin-2-one 1-oxide (**222a**).

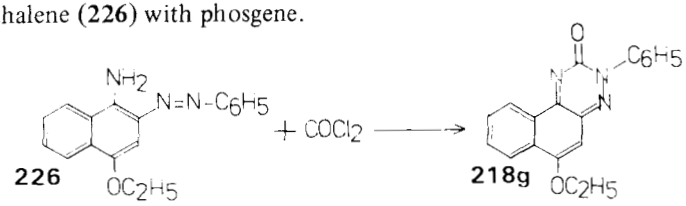


218e had already been isolated by Thiele and Barlow (1230) who had intended to cyclize the β-guanylhydrazone of 1,2-naphthoquinone (**224a**) to give **218f** but instead isolated another compound of formula $C_{11}H_7N_3O$. The initially formed **218f** was probably converted to **218e** under the basic reaction conditions. This was pointed out by De (1227), who had transformed **218f** to **218e** by treatment with potassium hydroxide.

2-Aminonaphtho[1,2-*e*]1,2,4-triazine (**218f**) was obtained through reduction of 2-aminonaphtho[1,2-*e*]1,2,4-triazine 1-oxide (**222b**) (623, 1231, 1233, 1550) and by heating the β-thiosemicarbazone of 1,2-naphthoquinone 1-oxime (**223a**) with aqueous acid (1231, 1550). De (1227) refluxed a solution of 1,2-naphthoquinone and aminoguanidine hydrochloride in acetic acid for 4 h, but the compound isolated had another melting point than that reported for **218f**.

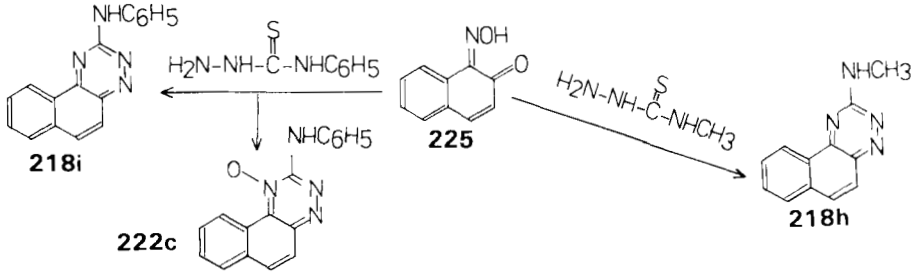


Busch and Bergmann (1170) prepared 6-ethoxy-3-phenylnaphtho-[1,2-*e*] 1,2,4-triazin-2-one (**218g**) by the reaction of 1-amino-4-ethoxy-2-(phenylazo)naphthalene (**226**) with phosgene.

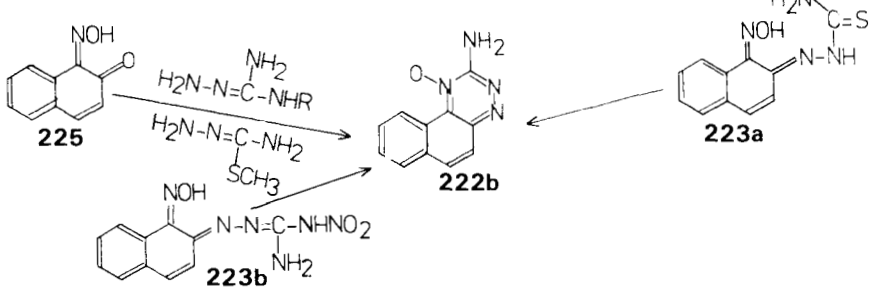


226 **218g**

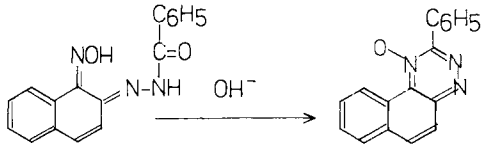
Refluxing a solution of 1,2-napthoquinone 1-oxime (**225**) and 4-methylthiosemicarbazide afforded 2-(methylamino)naphtho[1,2-*e*] 1,2,4-triazine (**218h**); interaction of **225** and 4-phenylthiosemicarbazide yielded, depending on the reaction conditions, 2-*anilinonaphtho*[1,2-*e*] 1,2,4-*triazine* (**218i**) or the corresponding 1-oxide (**222c**) (1550).



2-Aminonaphtho[1,2-*e*] 1,2,4-triazine 1-oxide (**222b**) was obtained by interaction of 1,2-naphthoquinone 1-oxime (**225**) and aminoguanidine, 4-methyl-, 4-phenyl-, 4-(*p*-tolyl)-aminoguanidine, or *S*-methylisothiosemicarbazide, or by cyclization of the thiosemicarbazone of 1,2-naphthoquinone 1-oxime (**223a**) in the presence of a base (623, 1231, 1233, 1550). The 4-nitroguanylhydrazone of 1,2-naphthoquinone 1-oxime (**223b**) is transformed into **222b** in acidic or neutral solution, whereas in basic solution a mixture of **222a** and **222b** was isolated (1550). Scott and Reilly mentioned that Thiele and Dralle (623) had already isolated **222b**, when they reacted 1-nitroso-2-naphthol (tautomer of **225**) with aminoguanidine.

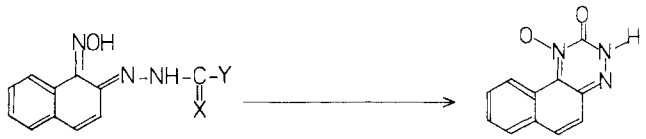


2-Phenylnaphtho[1,2-*e*]1,2,4-triazine 1-oxide (**222d**) was prepared through cyclization of the 2-benzoylhydrazone (**223c**) of 1,2-naphthoquinone 1-oxime in basic solution (1550).



223c **222d**

Cyclization of the β-semicarbazone (**223d**), the β-thiosemicarbazone (**223e**), the β-(4-phenylthiosemicarbazone) (**223f**), or the β-(2-ethoxycarbonylhydrazone) (**223g**) of 1,2-naphthoquinone 1-oxime was used for the synthesis of naphtho[1,2-*e*]1,2,4-triazin-2-one 1-oxide (**222a**) (1550).

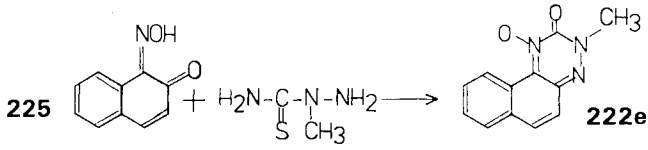


223d-g **222a**

d: X=O, Y=NH_2 **e**: X=S, Y=NH_2

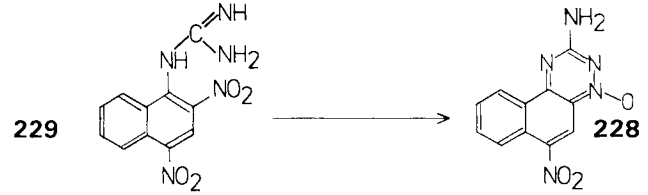
f: X=S, Y=NHC_6H_5 **g**: X=O, Y=OC_2H_5

Interaction of **225** and 2-methylsemicarbazide yields 2-methylnaphtho[1,2-*e*]1,2,4-triazin-2-one 1-oxide (**222e**) (1550).



225 **222e**

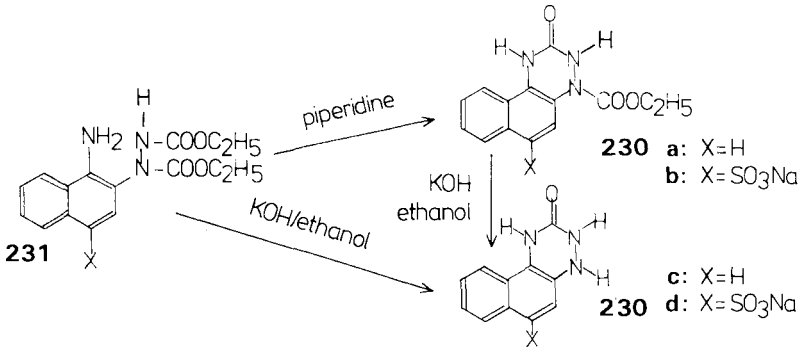
6-Nitro-2-aminonaphtho[1,2-*e*]1,2,4-triazine 4-oxide (**228**) is reported by Horner and Henry (1228), who converted 2,4-dinitro-1-guanylnaphthalene (**229**) into **228** by treatment with sodium hydroxide.



229 **228**

Fusco and Bianchetti (1137) observed the formation of naphtho[1,2-*d*]1,2,3-triazole (**227**) when **222b** was treated with potassium hydroxide.

Diels (1226) has prepared several derivatives of dihydronaphtho[1,2-*e*] 1,2,4-triazin-2-one (**230**) through the cyclization of 1-amino-2-(1,2-bis(ethoxycarbonyl)hydrazino)naphthalene (**231a**) and its 4-sulfonate (**231b**) and subsequent conversion of the synthesized dihydronaphtho[1,2-*e*] 1,2,4-triazine-4-carboxylates (**230a, b**) to dihydronaphtho[1,2-*e*] 1,2,4-triazin-2-one (**230c**) and its 6-sulfonic acid derivative (**230d**). It is also possible to obtain **230c, d** directly from **231a, b**.



2. *Compound Survey*

Known compounds of this class are listed in Table IV-16.

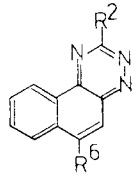
B. Naphtho[2,1-*e*]1,2,4-triazines

1. *Preparation*

Unsubstituted naphtho[2,1-*e*] 1,2,4-triazine (**219a**) was synthesized by Fusco and Bianchetti (1229) in the same way as unsubstituted naphtho[1,2-*e*] 1,2,4-triazine (**218a**). The reaction sequence for the synthesis of **219a** is given in the next reaction scheme. Neunhoeffer and Hennig (13) obtained **219a** in low yield as well as **218a** from the reaction of 1,2-naphthoquinone with formamidrazone. Acidic cyclization of the formazane **232** was used by Fichter and Schiess (1124) for the synthesis of 3-phenylnaphtho[2,1-*e*] 1,2,4-triazine (**219d**).

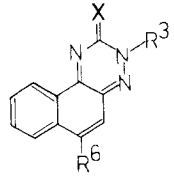
TABLE IV-16. NAPHTHO[1,2-*e*]1,2,4-TRIAZINES, N-OXIDES AND DIHYDRO DERIVATIVES

A. Naphtho[1,2-*e*]1,2,4-triazines



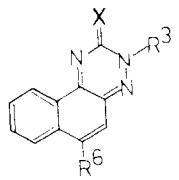
R^2	R^6		m.p. (°C)	Refs.
H	H		140–141	13, 1229, 1233
C_6H_5	H	1-Oxide	164–165	1550
COOH	H		204–206	1229
$COOC_2H_5$	H		158–160	1229
Cl	H		170–171	1233
NH_2	H		198–199	1550
			200–201	1233
			201	623
			240	1227 (incorrect)
Tribromo deriv.				1227
1-Oxide			241	1231, 1550
			242–243	1233
NH_2	NO_2	4-Oxide	291–292 (dec.)	1228
$NHCH_3$	H		223–224	1550
NHC_6H_5	H		268–270	1550
1-Oxide			222–223	1550
$NHCOCH_3$	H		208	1227
$NHNH_2$	H		217–218	1233

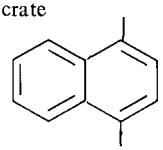
B. Naphtho[1,2-*e*]1,2,4-triazin-2-ones, -2-thiones and -2-imines



X	R^3	R^6	m.p. (°C)	Refs.
O	H	H	272–273	1232, 1550
				1227, 1230, 1233
1-Oxide			217	1232, 1550
1-Oxide·H_2O			167 (dec.)	1232, 1550
O	C_6H_5	C_2H_5O	236	1270
S	H	H	178–180	1550
N–C_6H_5	C_6H_5	Br	189	1270
·HCl			180	1270

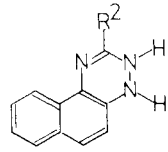
TABLE IV-16. (continued)



X	R^3	R^6	m.p.(°C)	Refs
N–C_6H_5	C_6H_5	OC_2H_5	230	1270
	·1½HCl		237	1270
	Picrate		195	1270
N–C_6H_5		H	275	1270

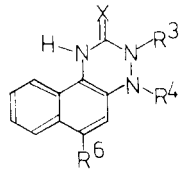
4-Ethyoxy-
1-naphthyl

C. Dihydronaphtho[1,2-*e*]1,2,4-triazines

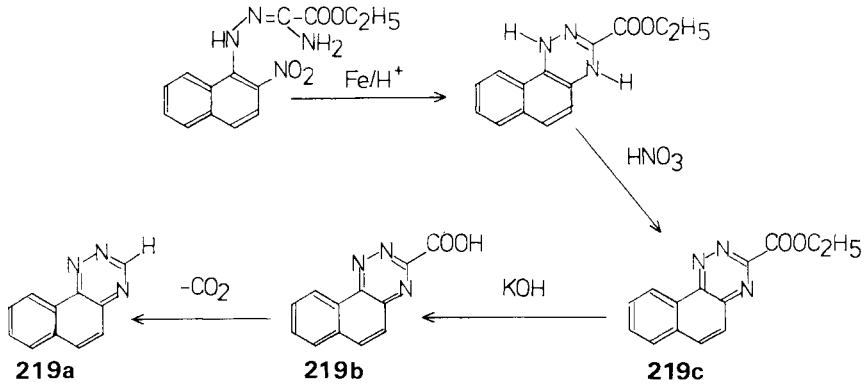


R^2	m.p. (°C)	Refs.
$COOC_2H_5$	176	1229

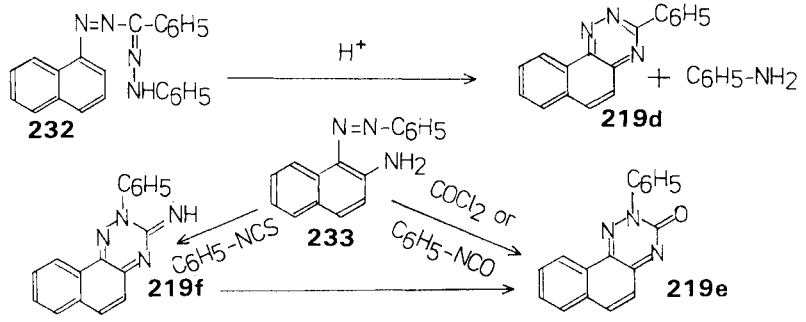
D. Dihydronaphtho[1,2-*e*]1,2,4-triazin-2-ones and -2-imines



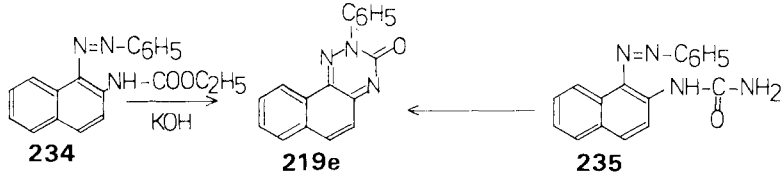
X	R^3	R^4	R^6	m.p. (°C)	Refs.
O	H	H	H	299	1226
O	H	H	SO_3H	330	1226
O	H	$COOC_2H_5$	H	272–273	1226
O	H	$COOC_2H_5$	SO_3H	135 (dec.)	1226
N–C_6H_5	C_6H_5	H	OC_2H_5	207	1170



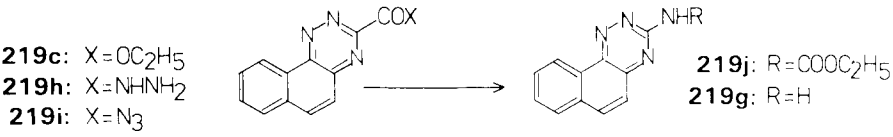
Reaction of 1-phenylazo-2-naphthylamine (**233**) with phenylisocyanate (1220) or phosgene (176, 1164) yields 2-phenylnaphtho[2,1-*e*]1,2,4-triazin-3-one (**219e**), and reaction of **233** with phenylisothiocyanate (1170) affords 2-phenyl-3-iminonaphtho[2,1-*e*]1,2,4-triazine (**219f**).



219e was also obtained by the action of cold alcoholic potassium hydroxide on ethyl 1-(phenylazo)-2-naphthylcarbamate (**234**) (1164), by hydrolysis of **219f** (1184), and by cyclization of 1-phenylazonaphthylurea (**235**) (1184).



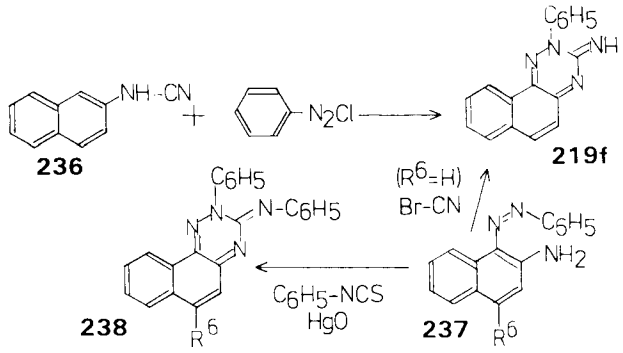
3-Aminonaphtho[2,1-*e*]1,2,4-triazine (**219g**) was prepared by Fusco and Bianchetti (1233), starting from ethyl naphtho[2,1-*e*]triazine-3-carboxylate (**219c**) passing the hydrazide **219h**, the azide **219i**, and the urethane **219j**.



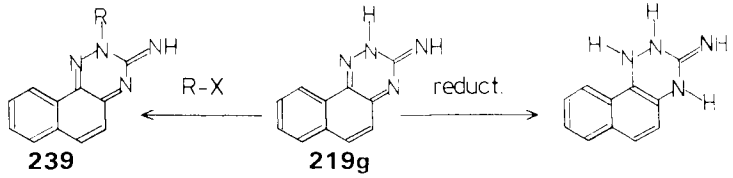
Pierron (1184) isolated 3-imino-2-phenylnaphtho[2,1-*e*] 1,2,4-triazine (**219f**) via two pathways.

1. Treatment of 2-cyanamidonaphthalene (**236**) with benzenediazonium chloride.
2. Reaction of 1-(phenylazo)-2-naphthylamine (**237**) with bromocyanogen.

Busch and Bergmann (1170) obtained several 2-phenyl-3-(phenylimino)-naphtho[2,1-*e*] 1,2,4-triazines (**238**) by heating 2-amino-1-phenylazonaphthalenes (**237**) with phenylisothiocyanate and mercuric oxide.

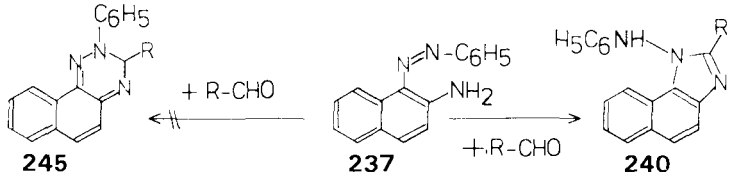


Alkylation of the 3-aminonaphtho[2,1-*e*] 1,2,4-triazines (**219g**) or their imino tautomers is reported by two groups (669, 1234), leading to the 2-alkyl-3-imino-naphtho[2,1-*e*] 1,2,4-triazines (**239**). Most reported 3-iminonaphtho[2,1-*e*]-1,2,4-triazines are easily reduced by stannous chloride (1184) or hydrogen sulfide (1170).



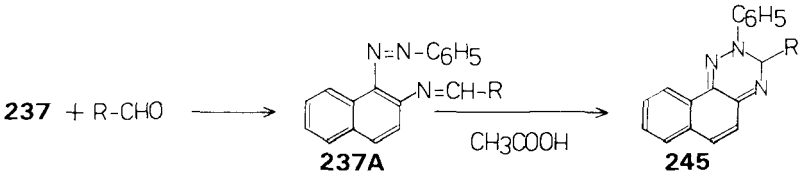
A large number of compounds claimed to be dihydronaphtho[2,1-*e*] 1,2,4-triazines (**245**), were prepared from 1-(phenylazo)-2-naphthylamine (**237**) and aldehydes (1219, 1220, 1239, 1240–1249). Fischer, in 1922, and 1924, showed that the isolated products were, in fact, naphthimidazoles (**240**) (1224, 1225). Despite this result, compounds formulated as naphtho[2,1-*e*] 1,2,4-triazines were

prepared by this method until 1941. All compounds isolated by this method have not been included in the tables here.

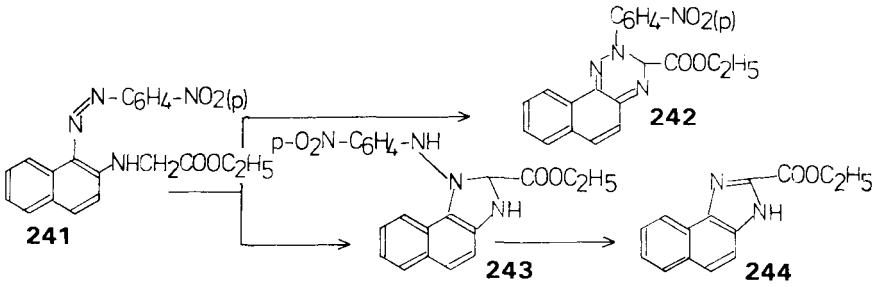


In 1973 Oleinikova and Pozharskii (1255) reported the unexpected formation of dihydronaphtho[2,1-*e*]1,2,4-triazines (**245**) when the Schiff bases **237A**, formed from **237** and aldehydes, were heated in glacial acetic acid.

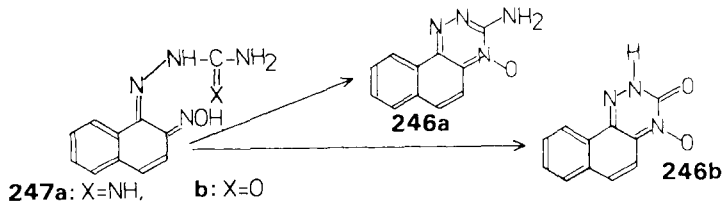
Anderau (1250) used compounds of structure **245** for the synthesis of azo dyes but the method of preparing such compounds was not disclosed.



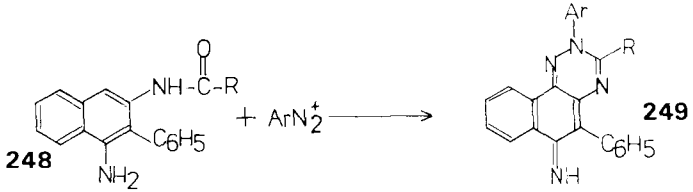
Fierz and Sallmann (1235) heated ethyl [1-[(*p*-nitrophenyl)azo]-2-naphthyl] aminoacetate (**241**) in acetic acid and formulated the isolated product as ethyl 2-(*p*-nitrophenyl)-2,3-dihydronaphtho[2,1-*e*]1,2,4-triazine-3-carboxylate (**242**). However, this structure is questionable and the naphthoimidazoline structure (**243**) has to be discussed due to the formation of the naphthoimidazole derivative (**244**) and *p*-nitroaniline on treatment with hydrochloric acid, first in ether, then in water.



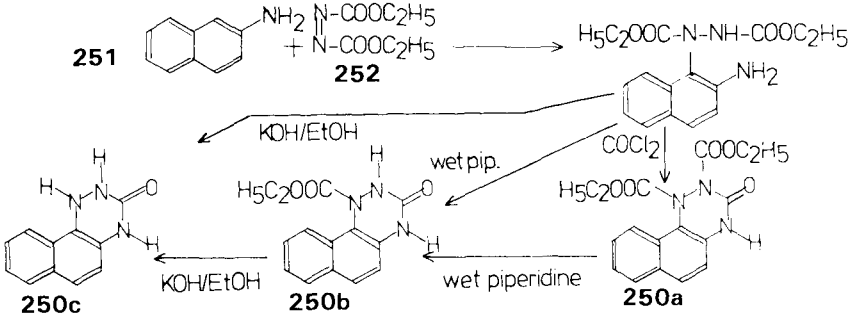
Scott and Lalor (1232, 1550) prepared 3-aminonaphtho[2,1-*e*]1,2,4-triazine 4-oxide (**246a**) and naphtho[2,1-*e*]1,2,4-triazin-3-one 4-oxide (**246b**) by boiling the α-guanylhydrazone (**247a**) or the α-semicarbazone (**247b**) of 1,2-naphthoquinone 2-oxime in water.



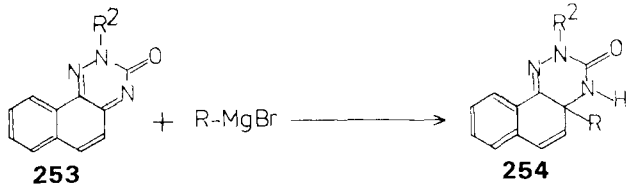
The reaction of 1-amino-2-phenyl-3-(acylamido)naphthalenes (**248**) with aryldiazonium salts is reported in two patents (1237, 1238) to lead to the naphtho[2,1-*e*] 1,2,4-triazine system (**249**).



Diels (1236) synthesized the three 1,4-dihydronaphtho[2,1-*e*] 1,2,4-triazin-3-ones (**250a** to **250c**), starting from 2-aminonaphthalene (**251**) and diethyl azodicarboxylate (**252**).



Mustafa and his group (176) published the reaction of the naphtho[2,1-*e*]-1,2,4-triazin-3-ones (**253**) with Grignard reagents. The isolated compounds are formulated as 4, 4a-dihydronaphtho[2,1-*e*] 1,2,4-triazin-3-ones (**254**).



In the infrared spectrum the amide band of 2-phenylnaphtho[2,1-*e*]1,2,4-triazin-3-one is observed at 1695 cm^{-1}, while the band at 1610 cm^{-1} is attributed to the C=N bond (164).

2. *Compound Survey*

Tables IV-17 to IV-20 list the naphtho[2,1-*e*]1,2,4-triazines reported in the literature.

V. CONDENSED WITH THE ANTHRACENE SYSTEM

A. Anthra[2,1-*e*]1,2,4-triazines

Mosby and Berry (1321) obtained two 1,4-dihydro-7*H*,12*H*-anthra[2,1-*e*]-1,2,4-triazine-7,12-diones (**255A**) [R = C_6H_5, m.p. 260 to 265°C; (dec.); R = 2-aminoanthraquinonyl, 360°C] through treatment of the 1-(2-acylhydrazino)-2-nitroanthraquinones (**256**) with sodium sulfide in pyridine. Oxidation of **255A** with peracetic acid in acetic acid affords the two 7*H*,12*H*-anthra[2,1-*e*]1,2,4-triazine-7,12-diones (**255B**) [R = C_6H_5, m.p. 255 to 257°C (dec.)].

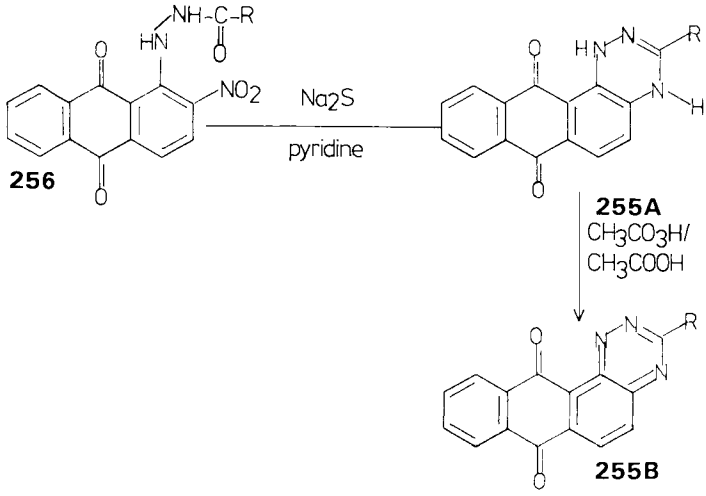
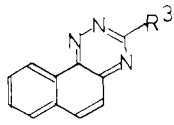
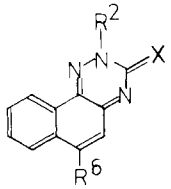


TABLE IV-17. NAPHTHO[2,1-*e*]1,2,4-TRIAZINES



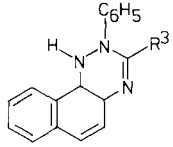
R^3		m.p. (°C)	Refs.
H		124–125	13, 1229
C_6H_5		145	1124
COOH		176–177	1229
$COOC_2H_5$		150–151	1229
$CONHNH_2$		234–235	1233
CON_3		150–155	1233
NH_2		292–294	1233
$NHCOOC_2H_5$		180–181	1233
NH_2	4-Oxide	279–281	1232

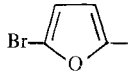
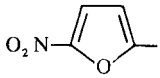
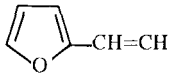
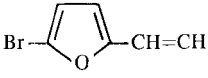
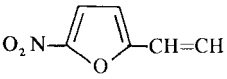


R^2	X	R^6		m.p. (°C)	Refs.
CH_3	NH	H	·HCl	>200 (dec.)	1234
C_2H_5	NH	H	·HCl	>100 (dec.)	1234, 669
C_3H_7	NH	H	·HCl	>200 (dec.)	1234
C_6H_5	O	H		252	1220
				255	176, 1164, 1184
C_6H_5	NH	H		~160	1184
·HCl				230	1184
C_6H_5	$N-C_6H_5$	H		166	1170
·HCl				248	1170
C_6H_5	$N-C_6H_5$	C_2H_5O		230	1170
·1.5HCl				237	1170
C_6H_5	$N-C_6H_5$	Br		189	1170
·HCl				180	1170
$3\text{-}CH_3-C_6H_4$	O	H		225	176
$4\text{-}CH_3-C_6H_4$	O	H		246	176
$4\text{-}Cl-C_6H_4$	O	H		198	176
$4\text{-}Br-C_6H_4$	O	H		292	176
$4\text{-}CH_3O-C_6H_4$	O	H		242	176
C_2H_5O	$N-C_6H_5$	OC_2H_5		215	1170

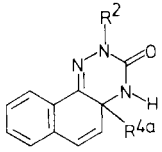
TABLE IV-18. DIHYDRONAPHTHO[2,1-*e*]1,2,4-TRIAZINES

A. 1,2-Dihydronaphtho[2,1-*e*]1,2,4-triazines.



R^3	m.p. (°C)	Refs.
CH_3	231–232	1255
	221–222	1255
	215–216	1255
	227–228	1255
	226–228	1255
	180–182	1255
	241–243	1255

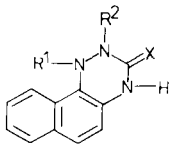
B. 2,4a-Dihydronaphtho[2,1-*e*]1,2,4-triazin-3(4H)ones



R^2	R^{4a}	m.p. (°C)	Refs.
C_6H_5	C_2H_5		176
C_6H_5	C_6H_5	245–247	176
4-CH_3–C_6H_4	C_6H_5	286	176
4-Cl–C_6H_4	C_6H_5	291–292	176
4-Br–C_6H_4	C_6H_5	159	176
4-CH_3O–C_6H_4	C_6H_5	215	176

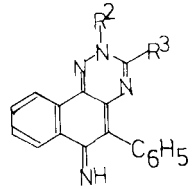
TABLE IV-18 (continued)

C. 1,2-Dihydronaphtho[2,1-*e*]1,2,4-triazin-3(4H)ones and -imines



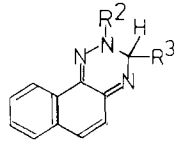
R^1	R^2	X	m.p. (°C)	Refs.
H	H	O	315–320	1236
H	C_6H_5	N–C_6H_5	207	1170
$COOC_2H_5$	H	O	265 (dec.)	1236
$COOC_2H_5$	$COOC_2H_5$	O	180–181	1236
·CH_3COOH			127–128	1236

TABLE IV-19. NAPHTHO[2,1-*e*]1,2,4-TRIAZINES WITH STRUCTURE **249**



R^2	R^3	m.p. (°C)	Refs.
C_6H_5	CH_3	228–229	1237
		228–230	1238
C_6H_5	C_2H_5	165–167	1237, 1238
C_6H_5	*t*-C_4H_9	193–195	1237, 1238
C_6H_5	C_6H_5	220–221	1237
		219–220	1238
4-CH_3–C_6H_4	CH_3	195–196	1237, 1238
4-CH_3O–C_6H_4	CH_3	168–169	1237, 1238
4-F–C_6H_4	CH_3	170	1238
·HCl	Sinters	280	1237
		310–318	1238
2,4-$Cl_2C_6H_3$	CH_3	213–214	1237
2,4-$Br_2C_6H_3$	CH_3	220	1238
		221	1237

TABLE IV-20. 2,3-DIHYDRONAPHTHO[2,1-*e*] 1,2,4-TRIAZINES



R^2	R^3	m.p. (°C)	Refs.
$4\text{-}O_2N\text{–}C_6H_5$	$COOC_2H_5$	210	1235[a]
·HCl		186	1235

[a]Structure questionable.

VI. CONDENSED WITH THE PHENANTHRENE SYSTEM

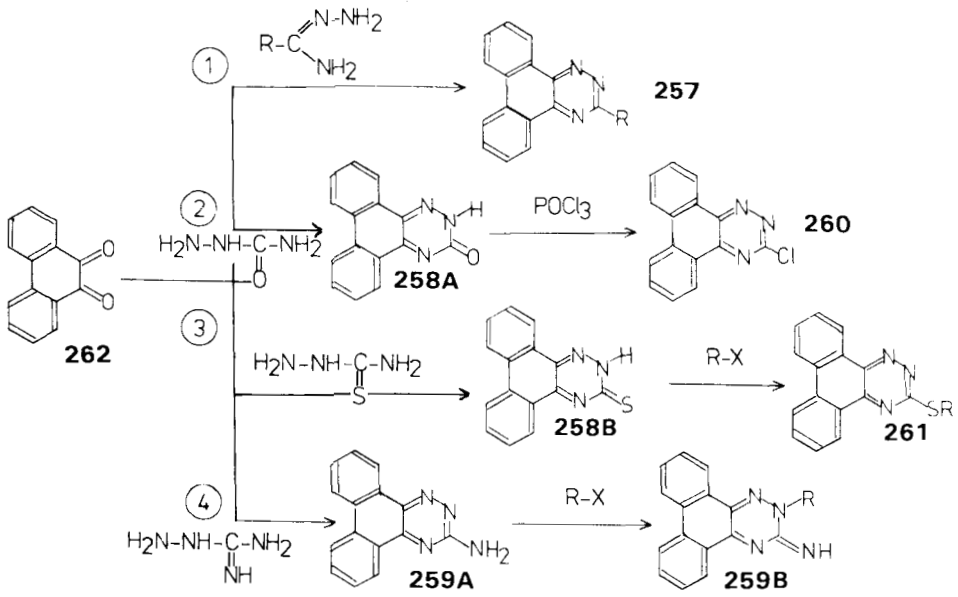
A. Phenanthro[9,10-*e*]1,2,4-triazines

1. *Preparation*

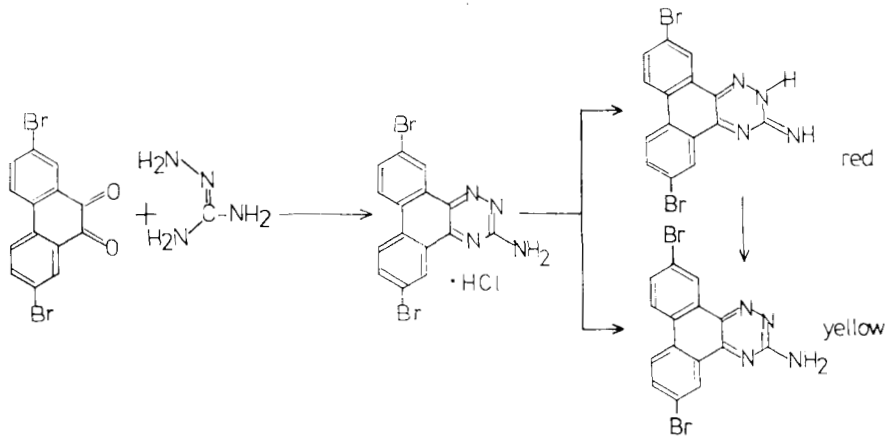
Most known phenanthro[9,10-*e*] 1,2,4-triazines (**257** to **261**) are synthesized by the reaction of 9,10-phenanthrenequinone (**262**) with the following compounds:

1. With amidrazones (35, 62), giving 3-substituted phenanthro[9,10-*e*] 1,2,4-triazines (**257**).
2. With semicarbazide (51, 1251–1253) to give phenanthro[9, 10-*e*] 1,2,4-triazin-3-ones (**258A**).
3. With thiosemicarbazide (579, 1251) yielding phenanthro[9,10-*e*] 1,2,4-triazine-3-thiones (**258B**).
4. With aminoguanidine (609, 624, 1227, 1252) resulting in 3-amino-phenanthro[9,10-*e*] 1,2,4-triazines (**259A**).

Alkylation of **258B** yields 3-(alkylmercapto)phenanthro[9,10-*e*] 1,2,4-triazines (**261**) (579), whereas alkylation of **259A** has been reported to afford 2-alkyl-3-iminophenanthro[9,10-*e*] 1,2,4-triazines (**259B**) (669, 1234). Treatment of **258A** with phosphoryl chloride has been used for the synthesis of 3-chlorophenanthro[9,10-*e*] 1,2,4-triazine (**260**) (51).



Schmidt, Schairer, and Glatz (1253) obtained **258A** from the reaction of phenanthraquinone monoxime and semicarbazide. Schmidt and Bückert (1252) isolated the hydrochloride of the expected reaction product in quantitative yield when they heated 2,7-dibromophenanthraquinone with aminoguanidine hydrochloride and a slight excess of hydrochloric acid in ethanol for 7 hr. This product, treated with ammonia to give the free base, was found to contain two substances. One was a stable yellow material, and the other was a labile red



substance, which was transformed to the yellow form in boiling ethanol or when heated at 200°C. The stable form was formulated as the amino tautomer while the red substance was thought to be the imino tautomer. Both forms give the same salts and derivatives.

If unsymmetrically substituted phenanthraquinones are used, only one product is usually isolated, but it is still not possible to say which of the two possible isomers is obtained.

2. *Compound Survey*

Table IV-21 lists the phenanthro[9,10-*e*]1,2,4-triazines reported in the literature.

3. *Physical Properties and Reactions*

Most isolated phenanthro[9,10-*e*]1,2,4-triazines are yellow compounds which are sparingly soluble in the usual organic solvents.

Phenanthro[9,10-*d*]1,2,3-triazole (**263**) was isolated when **258A** was treated with chloramine (178); phenanthro[9,10-*d*]imidazolinone (**264**) was obtained from the reaction of **258A** with hydroxylamine-*O*-sulfonic acid or *O*-2,4-dinitrophenylhydroxylamine (177, 178). Fusco and Bianchetti (1137) treated **259A** with potassium hydroxide and isolated a compound which was thought to be tetrabenzo[*a*, *c*, *h*, *i*]phenazine (**265**).

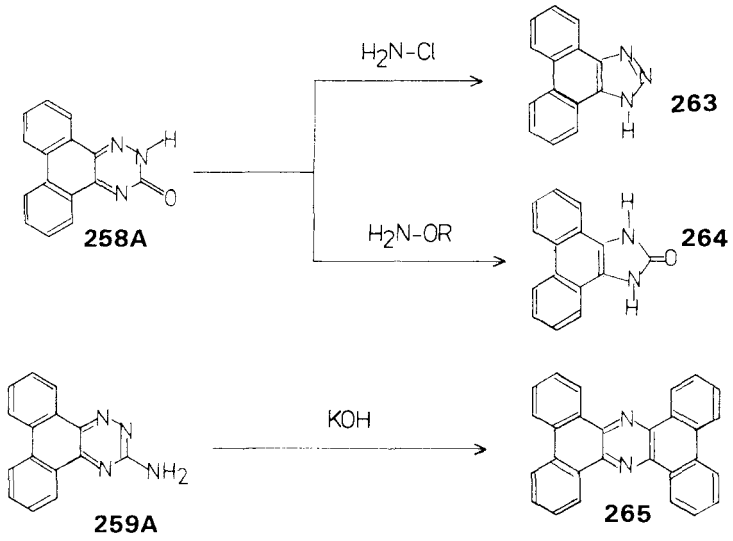
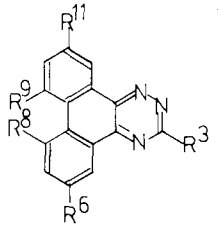
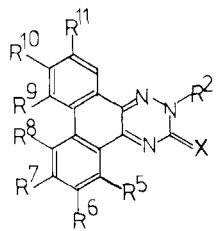


TABLE IV-21. PHENANTHRO[9,10-*e*]1,2,4-TRIAZINES



R^3	R^6	R^{11}	R^8	R^9	m.p. (°C)	Refs.
$COOC_2H_5$	H	H	H	H	179–181	62
$CH_2NHCOOCH_2C_6H_5$	H	H	H	H	158–159	35
NH_2	H	H	H	H	262	624
NH_2	H, Br		H	H	235	1227
NH_2	Br	Br	H	H	288	1227
					333	1252
·HCl					238	1252
·$HClO_4$					258 (dec.)	1252
Picrate					293	1252
NH_2	H	H	Br	Br	305	1227
NH_2	H	H	NO_2, H		215	1227
NH_2	H	H	NO_2	NO_2	265	1227
NH_2	NO_2, H		H	H	280	1227
NH_2	NO_2	NO_2	H	H	310	1227
$NHCOCH_3$	H, Br		H	H	278	1227
$NHCOCH_3$	Br	Br	H	H	309	1252
$NHCOCH_3$	H	H	Br	Br	310	1227
$NHCOCH_3$	H	H	NO_2, H		270	1227
$NHCOCH_3$	H	H	NO_2	NO_2	275	1227
$NHCOCH_3$	H, NO_2		H	H	298	1227
$NHCOCH_3$	NO_2	NO_2	H	H	310	1227
$NHCOC_6H_5$	Br	Br	H	H	240 (dec.)	1252
Cl	H	H	H	H	238–240	51

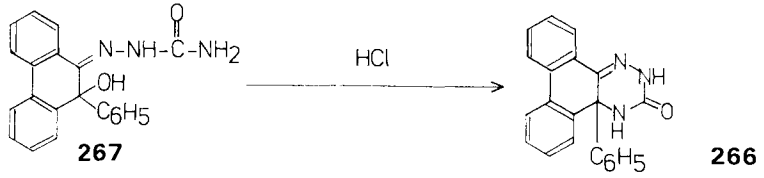
TABLE IV-21 (continued)



R^2	X	R^5	R^6	R^{11}	R^7	R^{10}	R^8	R^9	m.p. (°C)	Refs.
H	=O	H	H	H	H	H	H	H	285 (dec.)	1253
									287	1251
									288 (dec.)	51
H	=O	H	H	H	H	H	H, NO_2		286	1251
H	=O	H	H	H	H, NO_2		H	H	273–274 (dec.)	1253
H	=O	H	H, NO_2		H	H	H	H	285 (dec.)	1253
H	=O	H	H	H	H, Br		H	H	304	1253
H	=O	H	Br	Br	H	H	H	H	295	1251, 1252
H	=O	H	H, Cl		H	H	H	H	288	1253

H	=S	H	H	CH_3	*i*-C_3H_7	H	H	H		284 (dec.)	579
										318	579
H	=S	H	H	H	H	H	H	H		198	1251
										216 (dec.)	579
										233	579 (when heated quickly)
H	=S	H	H	H	H	H	H, NO_2			230	1251
H	=S	H	H, NO_2		H	H	H	H		300	1251
H	=S	H	NO_2	NO_2	H	H	H	H		220	1251
H	=NH	H	Br	Br	H	H	H	H		(333)	1252
CH_3	=NH	H	H	H	H	H	H	H		142–144 (dec.)	1234
CH_3	=NH	CH_3	H	*i*-C_3H_7	H	H	H	H		186 (dec.)	1234
C_2H_5	=NH	H	H	H	H	H	H	H		75 (dec.)	1234
										183 (dec.)	669
C_2H_5	=NH	CH_3	H	*i*-C_3H_7	H	H	H	H		140	1234
$HOCH_2CH_2$	=NH	H	H	H	H	H	H	H		175 (dec.)	1234
$HOCH_2CH_2$	=NH	CH_3	H	*i*-C_3H_7	H	H	H	H		184 (dec.)	1234
C_3H_7	=NH	H	H	H	H	H	H	H		136 (dec.)	1234
C_3H_7	=NH	CH_3	H	*i*-C_3H_7	H	H	H	H		120 (dec.)	1234
i-C_3H_7	=NH	H	H	H	H	H	H	H	·HI	250 (dec.)	1234
C_4H_9	=NH	H	H	H	H	H	H	H		115	1234
C_4H_9	=NH	CH_3	H	*i*-C_3H_7	H	H	H	H		108 (dec.)	1234

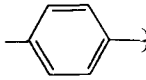
At present only one dihydro-phenanthro[9,10-*e*] 1,2,4-triazine derivative is known. Awad and his group (1255a) obtained 4a-phenyl-4,4a-dihydro-phenanthro[9,10-*e*] 1,2,4-triazin-3-one (**266**) (m.p. 304°C) when compound **267** was heated with alcoholic hydrochloric acid.

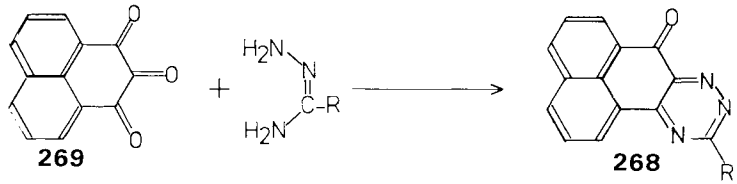


267 **266**

VII. CONDENSED WITH THE PHENALENE SYSTEM

A. Phenaleno[1,2-*e*]1,2,4-triazines

Ried and Schomann (872) reported the synthesis of three phenaleno[1,2-*e*]-1,2,4-triazin-3-ones (**268**) (R = 4-tolyl, m.p. 220 to 221°C; R = 6-methyl-2-pyridyl, 235 to 236°C; R =  , 360°C) through the reaction of the triketone (**269**) with amidrazones. In the infrared spectra of the isolated yellow compounds the absorption band for the C=O group is found at 1666 to 1670 cm^{-1}.



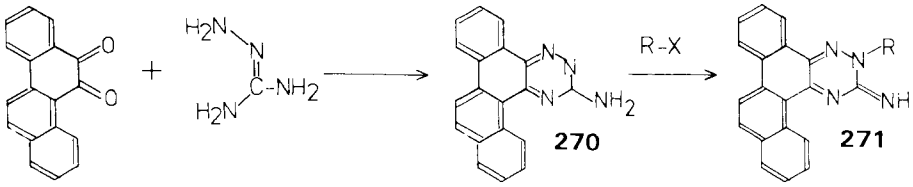
269 **268**

VIII. CONDENSED WITH THE CHRYSENE SYSTEM

A. Chryseno[5,6-*e*]1,2,4-triazines

At present only 3-aminochryseno[5,6-*c*] 1,2,4-triazine (**270**) (m.p. >260°C) and a few 2-alkyl-3-iminochryseno[5,6-*e*] 1,2,4-triazines (**271**) [R = CH_3; R = C_2H_5, m.p. 129°C (dec.); R = $HOCH_2CH_2$, 174 to 175°C (dec.)] are known (609, 1234). **270** was prepared from chrysenequinone (**272**) and aminoguanidine nitrate (609). Alkylation of **270** is reported to yield **271** (1234).

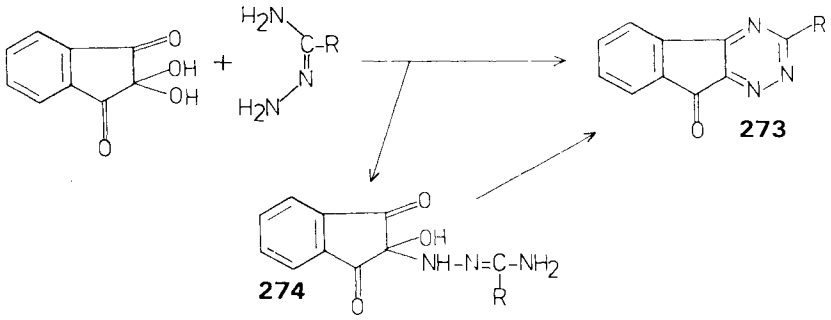
Wagner, Loewe, and Häussler (669) published the ethylation of **270** but the formula given for the isolated product is not a 2-ethyl-3-iminochryseno[5,6-*e*]-1,2,4-triazine but a 2-ethyl-3-iminobenzo[*c*]phenanthro[5,6-*c*]1,2,4-triazine.

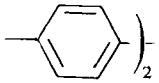
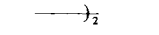


IX. CONDENSED WITH THE INDENE SYSTEM

A. Indeno[1,2-*e*]1,2,4-triazines

The reaction of ninhydrin with amidrazones yields either the indeno-[1,2-*e*] 1,2,4-triazin-9-ones (**273**) or the hydrazines (**274**), which can be cyclized to **273** in the presence of acids or by heating over 110°C (872).



R	m.p. (°C)	Refs.
4-CH_3–C_6H_4	219–220	872
2-Naphthyl	214–215	872
2-Pyridyl	242–243	872
4-Pyridyl	231–232	872
6-Methyl-2-pyridyl	223–224	872
	373–374	872
	340 (dec.)	872

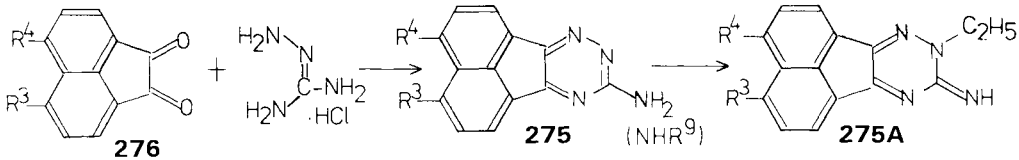
The isolated compounds are yellow, orange, or brown and show the C=O absorption in the infrared spectra between 1710 and 1730 cm^{-1}. Jeney and Zsolnai (1256) claimed to have tested 2-aminoindeno[1,2-*e*]1,2,4-triazin-9-one hydrochloride as a tuberculostata, but no details on the synthesis and the properties of the compound were reported.

X. CONDENSED WITH THE ACENAPHTHENE SYSTEM

A. Acenaphtho[1,2-*e*]1,2,4-triazines

So far only a few compounds have been prepared which contain the acenaphtho[1,2-*e*]1,2,4-triazine system (669, 1227, 1254). According to De (1227) and De and Dutta (1254), the reaction of acenaphthoquinones (**276**) with aminoguanidine hydrochloride proceeds smoothly in acetic acid solution, yielding 9-aminoacenaphtho[1,2-*e*]1,2,4-triazines (**275**). With unsymmetrically substituted acenaphthoquinones two compounds are possible; however, only one isomer appears to be isolated. The structure of the isolated isomer has not been established.

The compounds that have been isolated so far are yellow and insoluble in both water and organic solvents. Alkylation of **275a** ($R^3 = R^4 = H$) with ethyl iodide is reported by Wagner and his group (669), leading to 8-ethyl-9-imino-acenaphtho[1,2-*e*]1,2,4-triazine (**275A**). Acetylation affords the acetamido derivative (1227).



R^3	R^4	R^9	m.p. (°C)	Refs.
H	H	H	305	1227
H	H	CH_3CO	268	1227
H, NO_2		H	290	1254
NO_2	NO_2	H	300	1254

Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

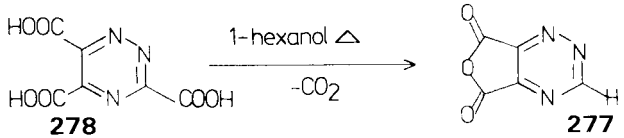
V

1,2,4-Triazine Rings Condensed with Heterocycles through Carbon Atoms

I. CONDENSED WITH THE FURAN RING

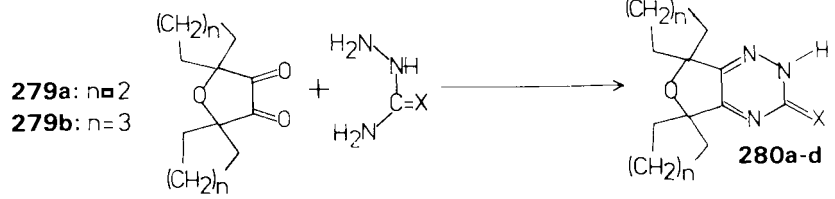
A. Furano[3,4-*e*]1,2,4-triazines

At present only a few compounds are known which can be treated as derivatives of furano[3,4-*e*] 1,2,4-triazine. Rätz and Schroeder (9) obtained the anhydride (**277**) of 1,2,4-triazine-5,6-dicarboxylic acid when they heated 1,2,4-triazine-3,5,6-tricarboxylic acid (**278**) in 1-hexanol. An alternative name for **277** is furano[3,4-*e*] 1,2,4-triazine-5,7-dione.

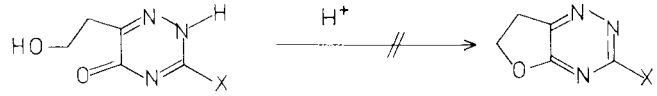


278 **277**

Yur'ev and co-workers (1257) condensed the two spiro compounds (**279a** and **279b**) with semicarbazide and thiosemicarbazide and cyclized the isolated semicarbazones and thiosemicarbazones in alkaline media yielding the four furano[3,4-*e*] 1,2,4-triazine derivatives (**280a** to **d**) (**a**: $n = 2$, X = O, m.p. 194.5 to 195°C; **b**: $n = 2$, X = S, 194 to 195°C; **c**: $n = 3$, X = O, 214°C; **d**: $n = 3$, X = S, 210.5 to 211.5°C).



Doleschall and his group (754) were not able to isolate furano[2,3-*e*] 1,2,4-triazine derivatives, such as **281**, through acidic cyclization of 6-(hydroxyethyl)-1,2,4-triazin-5-one derivatives (**282**).

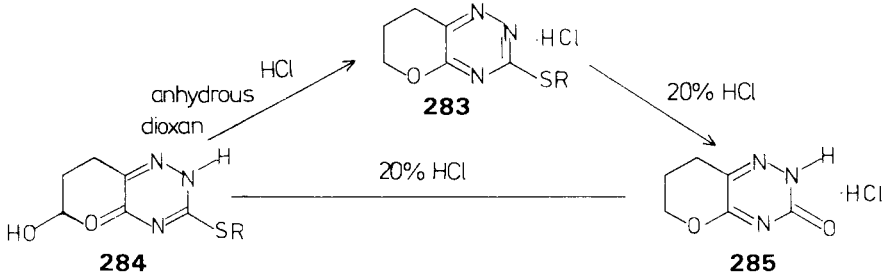


282 **281**

II. CONDENSED WITH THE PYRAN RING

A. Pyrano[2,3-*e*] 1,2,4-triazines

Doleschall and his group (754) isolated 3-mercapto-7,8-dihydro-6*H*-pyrano-[2,3-*e*] 1,2,4-triazine hydrochlorides (**283**) (R = CH_3, m.p. 155 to 156°C; R = C_2H_5, 124 to 125°C; R = C_6H_5-CH_2, 150 to 151°C), when they treated 3-mercapto-6-(3-hydroxypropyl)-1,2,4-triazin-5-ones (**284**) with hydrochloric acid in anhydrous dioxan. Treatment of **283** or **284** with 20% hydrochloric acid afforded 7,8-dihydro-6*H*-pyrano[2,3-*e*] 1,2,4-triazin-3-one hydrochloride (**285**·HCl) (m.p. 230 to 232°C) which could be converted to the free base (**285**) [m.p. 248 to 257°C (dec.)] by reaction with diazomethane in ether. All attempts to prepare 3-amino-substituted pyrano[2,3-*e*] 1,2,4-triazines were unsuccessful.

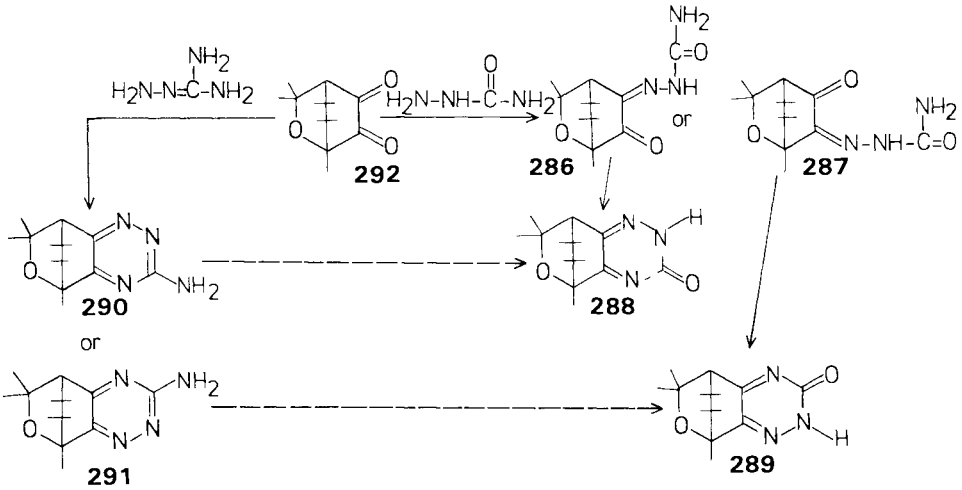


284 **283** **285**

B. Pyrano[3,4-*e*] 1,2,4-triazines and Pyrano[4,3-*e*] 1,2,4-triazines

Cusmano (1258) has reported that dioxocineole reacts with semicarbazide in aqueous alcohol solution to give a monosemicarbazone (**286** or **287**), which was converted to 5,7,7-trimethyl-5,8-ethano-5,8-dihydro-7*H*-pyrano[3,4-*e*]-1,2,4-triazin-3-one (**288**) or 6,6,8-trimethyl-5,8-dihydro-6*H*-pyrano[4,3-*e*] 1,2,4-triazin-3-one (**289**) by treatment with sodium ethoxide in ethanol or by

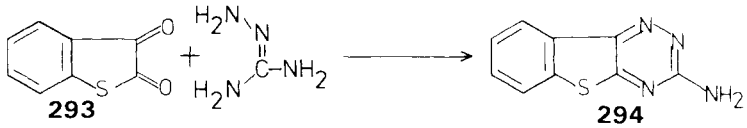
dissolving it in 15% potassium hydroxide solution and then acidifying the basic solution. One of the two 3-amino derivatives (**290** or **291**) was prepared from an alcoholic solution of dioxocineole (**292**) and aminoguanidine in 1:1 molar ratio, with excess sodium acetate as catalyst. The colorless crystals (m.p. 225°C) afforded **288** or **289** by reaction with sodium nitrite in sulfuric acid. **288** or **289** in chloroform add two atoms of bromine, forming a precipitate that slowly loses bromine and reverts to the parent compound. All compounds of this class are colorless, crystalline substances.



III. CONDENSED WITH THE THIONAPHTHENE SYSTEM

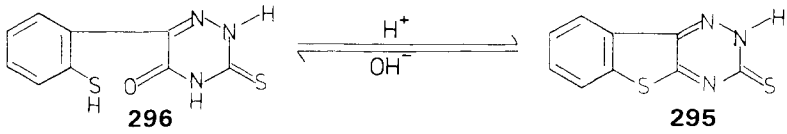
A. Thionaphtheno[2,3-*e*]1,2,4-triazines

The first compound of this class was prepared by Rossi and Trave (619), through the reaction of 2,3-dioxo-2,3-dihydrothionaphthene (**293**) with aminoguanidine, and is formulated as 3-aminothionaphtheno[2,3-*e*] 1,2,4-triazine (**294**) (m.p. 250°C).



Tomtschin and Ioffe (1271) obtained thionaphtheno[2,3-*e*] 1,2,4-triazine-3-thione (**295**) (m.p. 255°C) by boiling 6-(2-mercaptophenyl)-3-thioxo-1,2,4-

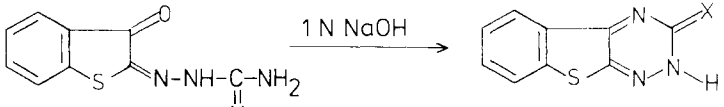
triazin-5-one (**296**) in concentrated hydrochloric acid. Treatment of **295** with base reconverts it to **296**.



296 **295**

B. Thionaphtheno[3,2-*e*]1,2,4-triazines

Two derivatives of thionaphtheno[3,2-*e*] 1,2,4-triazine, the thionaphtheno-[3,2-*e*] 1,2,4-triazin-3-one (**297**) (m.p. 280°C) and the 3-thione (**298**) (m.p. 263°C) were prepared by Tomtschin and his group (1259) by heating the α-isomer of the 2,3-dioxo-2,3-dihydrothionaphthene 2-semicarbazone (**299**) or the 2-thiosemicarbazone (**300**) in 1*N* sodium hydroxide for 4 hr (**299**) or 25 min (**300**).



299: X = O
300 X = S

297: X = O
298: X = S

IV. CONDENSED WITH THE PYRAZOLE RING

A. Pyrazolo[3,4-*e*]1,2,4-triazines

Lister and his group (1260) report the cyclization of 4-thiosemicarbazono-pyrazol-5-ones (**301**) in aqueous potassium carbonate under reflux conditions, leading to pyrazolo[3,4-*e*] 1,2,4-triazine-3-thiols (**302**) or their tautomers, which were readily methylated with alkaline dimethyl sulfate. The resulting methyl-mercapto derivatives (**303**) readily react with primary or secondary amines to give the 3-amino analogues (**304**). **303** did not react with ammonia. Heating **302** in 2-ethoxyethanol in air yields the disulfide (**305**).

It was not possible to cyclize the semicarbazone and the guanylhydrazone of pyrazole-4,5-dione to the 3-hydroxy or 3-amino derivative of pyrazolo[3,4-*e*]-1,2,4-triazine.

Slouka and Peč (1261) synthesized 2-aryl-6-phenyl-3,4,6,7-tetrahydro-2*H*-pyrazolo[3,4-*e*] 1,2,4-triazine-3,7-diones (**306**) or their 5*H*-tautomers (**307**)

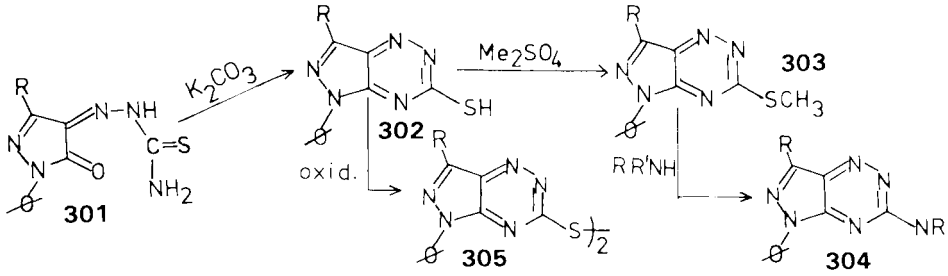
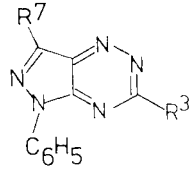
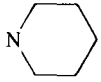
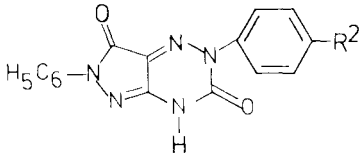


TABLE V-1. PYRAZOLO[3,4-*e*]1,2,4-TRIAZINES



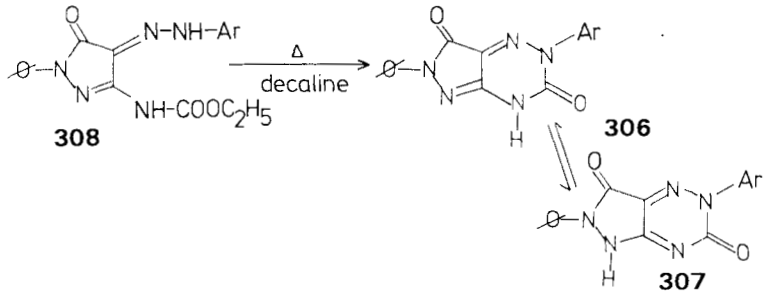
R^3	R^7	m.p. (°C)	Refs.
SH	CH_3	208–210	1260
SH	C_2H_5	219–220	1260
S→$_2$	CH_3	211–213	1260
S→$_2$	C_2H_5	174–176	1260
S–CH_3	CH_3	120–122	1260
S–CH_3	C_2H_5	100–101	1260
NH–CH_2–C_6H_5	CH_3	208–209	1260
	CH_3	170	1260



R^2	m.p. (°C)	Refs.
H	282–283	1261
F	298–300	1261
Cl	301–302	1261
Br	308–309	1261
I	327–328	1261

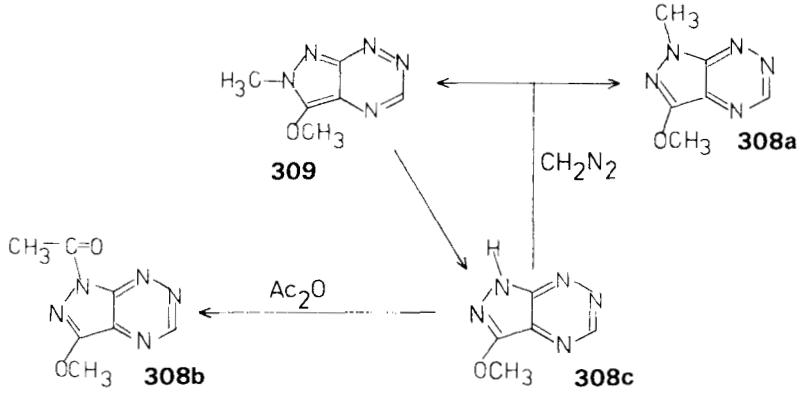
through cyclization of 3-[(ethoxycarbonyl)amino]-4-(arylhydrazono)-1-phenyl-pyrazol-5-ones (**308**) in decalin under reflux conditions. The isolated compounds are crystalline, red-violet substances.

Known compounds of this class are listed in Table V-I.



B. Pyrazolo[4,3-*e*]1,2,4-triazines

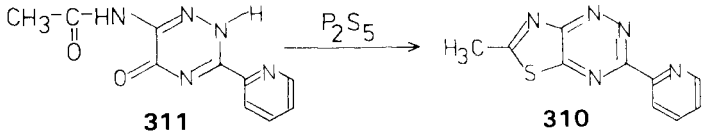
Lindner and Schaden (1263) have shown by X-ray analysis that the red pigment pseudoiodinine of *Pseudomonas fluorescens* var. *pseudoiodinium* is a derivative of the pyrazolo[4,3-*e*] 1,2,4-triazine system. Pseudoiodinine is readily demethylated to the yellow pigment normethylpseudoiodinine (**308c**) (m.p. 196°C), the structure of which was shown by X-ray analysis to be 3-methoxy-1*H*-pyrazolo[4,3-*e*] 1,2,4-triazine. Methylation of **308c** with diazomethane affords two compounds, one of which is pseudoiodinine, formulated as 2-methyl-3-methoxypyrazolo[4,3-*e*] 1,2,4-triazine (**309**) (m.p. 112°C); the other is the isomeric 1-methyl-3-methoxypyrazolo[4,3-*e*] 1,2,4-triazine (**308a**) (m.p. 149°C). Acetylation of **308c** with acetic anhydride yields 1-acetyl-3-methoxy-pyrazolo[4,3-*e*] 1,2,4-triazine (**308b**) (m.p. 147°C).



V. CONDENSED WITH THE THIAZOLE RING

A. Thiazolo[5,4-*e*]1,2,4-triazines

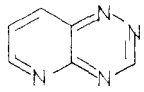
Treatment of 6-(acetylamino)-3-(-2-pyridyl)-1,2,4-triazin-5-one (**311**) with phosphorus pentasulfide was used for the synthesis of 2-methyl-6-(-2-pyridyl)-thiazolo[5,4-*e*]1,2,4-triazine (**310**) (183).



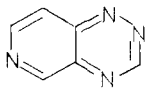
311 **310**

VI. CONDENSED WITH THE PYRIDINE RING

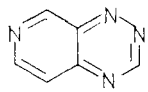
Derivatives of all four possible pyrido-1,2,4-triazines (**312** to **315**) are known. Calculations on these systems were reported by Wait and Wesley (1150).



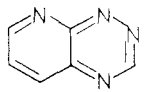
Pyrido[2,3-e]
1,2,4-triazine
312



Pyrido[3,4-e]
1,2,4-triazine
313



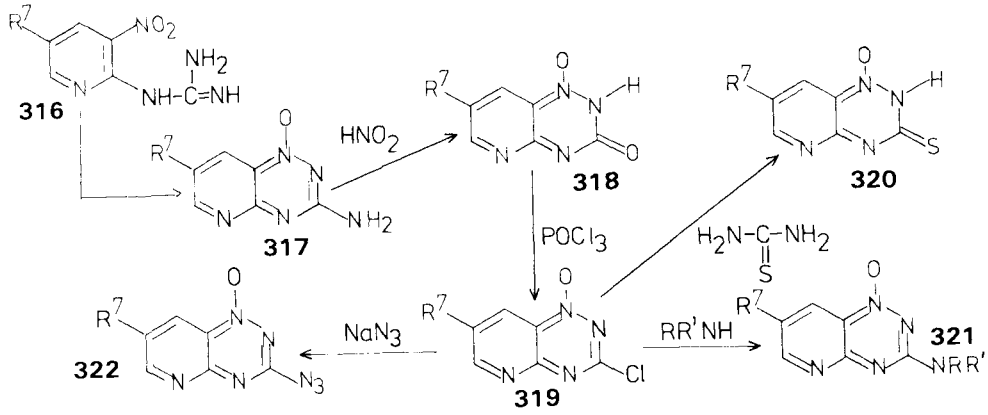
Pyrido[4,3-e]
1,2,4-triazine
314



Pyrido[3,2-e]
1,2,4-triazine
315

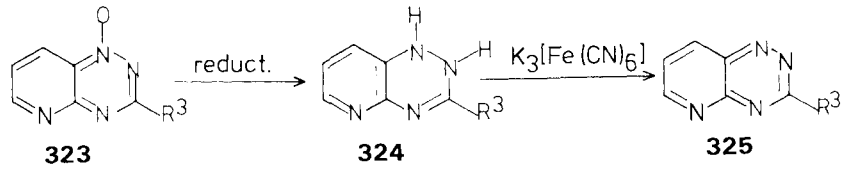
A. Pyrido[2,3-*e*]1,2,4-triazines

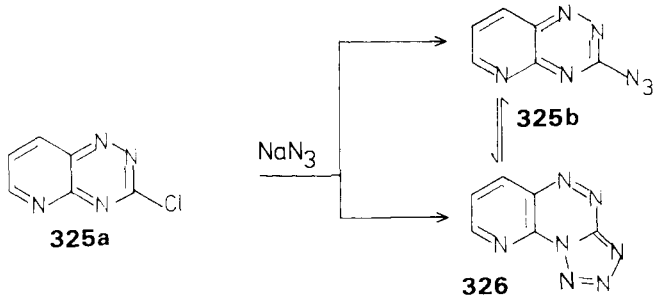
The 2-guanido-3-nitropyridines (**316**), when heated with aqueous potassium carbonate on a steam bath, afford 3-aminopyrido[2,3-*e*]1,2,4-triazine 1-oxides (**317**) (1264–1266). **317** are converted to pyrido[2,3-*e*]1,2,4-triazin-3-one 1-oxides (**318**) on treatment with nitrous acid (1264–1266). These yield the 3-chloropyrido[2,3-*e*]1,2,4-triazine 1-oxides (**319**) on treatment with phosphoryl chloride (1264, 1265). **319** can be converted to the 3-thioxo compounds (**320**) by reaction with thiourea (1264, 1265) or to the 3-amino derivatives (**321**) through reaction with amines (1264, 1265). Reaction of **319** with sodium azide affords the 3-azido derivatives (**322**) which have the azido structure in both the solid phase and in solution (1267).



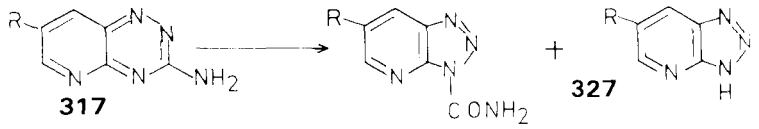
Reduction of pyrido[2,3-*e*]1,2,4-triazine 1-oxides (**323**) affords the 1,2-dihydropyrido[2,3-*e*]1,2,4-triazines (**324**) (R = Cl, m.p. 151 to 153°C, dec.) which are oxidized by potassium ferricyanide to the pyrido[2,3-*e*]1,2,4-triazines (**325**) (1264, 1267).

Reaction of 3-chloropyrido[2,3-*e*]1,2,4-triazine (**325a**) with sodium azide yields a mixture of 3-azidopyrido[2,3-*e*]1,2,4-triazine (**325b**) and the pyrido-[2,3-*e*]tetrazolo[5,1-*c*]1,2,4-triazine (**326**) (1267). Both compounds are interconvertible.



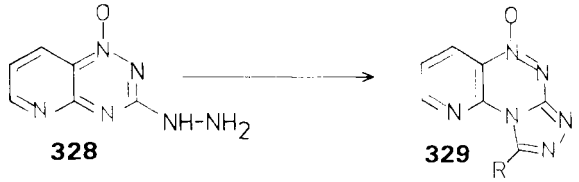


The 3-aminopyrido[2,3-*e*]1,2,4-triazine 1-oxides (**317**) are unstable in basic solutions and are transformed to pyrido[*b*]triazoles (**327**) (1264).



317 327

3-Hydrazinopyrido[2,3-*e*]1,2,4-triazine 1-oxide (**328**) was used for the synthesis of the pyrido[2,3-*e*]triazolo[3,4-*c*]1,2,4-triazine 1-oxides (**329**) (1267). **328** was prepared by interaction of **319** and hydrazine.

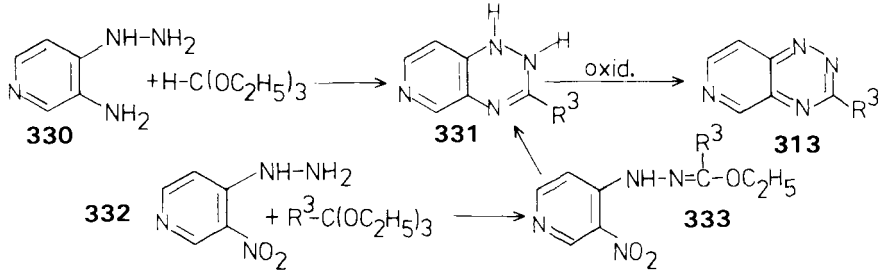


328 329

Table V-2 lists the pyrido[2,3-*e*]1,2,4-triazines and their 1-oxides reported in the literature.

B. Pyrido[3,4-*e*]1,2,4-triazines

Lewis and Shephard (1272) obtained the unsubstituted pyrido[3,4-*e*]1,2,4-triazine (**313**) [R^3 = H, m.p. 90 to 91°C (dec.) (1272); 91°C (dec.) (1268)] when they reacted 3-amino-4-hydrazinopyridine (**330**) with triethyl orthoformate and oxidized the isolated 1,2-dihydropyrido[3,4-*e*]1,2,4-triazine dihydrochloride (**331**, R^3 = H) with potassium ferricyanide in the presence of ammonium hydroxide. The same compound was isolated when 4-hydrazino-3-nitropyridine (**332**) was converted to the 4-[2-(ethoxymethylene)hydrazino]-3-nitropyridine (**333**), by reaction with triethyl orthoformate, followed by catalytic reduction of the nitro group and oxidation of the formed **331** (1268). By the latter method also 3-substituted pyrido[3,4-*e*]1,2,4-triazines [R^3 = CH_3, m.p. 112 to 113°C (1268); 114 to 115°C (1272); R^3 = C_6H_5, 127 to 127.5°C (1268)] were prepared.

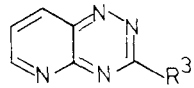


330 331 313

332 333

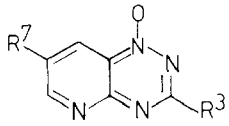
TABLE V-2. PYRIDO[2,3-*e*]1,2,4-TRIAZINES AND THEIR 1-OXIDES

A. Pyrido[2,3-*e*]1,2,4-triazines



R^3	m.p. (°C)	Refs.
Cl	126–127	1267
NH_2	242–244	1264
N_3	61–62	1267
$N{=}P(C_6H_5)_3$	180–182	1267

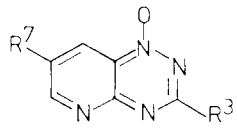
B. Pyrido[2,3-*e*]1,2,4-triazine 1-oxides

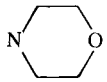
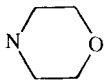


R^3	R^7	m.p. (°C)	Refs.
OCH_3	H	149	1265
		149–149.5	1264
OC_4H_9	H	99–100	1265
		99.5–100.5	1264
SH	H	197–198 (dec.)	1264, 1265
OH	H	233–235 (dec.)	1264
		235–237	1266
OH	CH_3	230–231 (dec.)	1264, 1266
Cl	H	139–140	1265
		139.5–140.5	1264
Cl	CH_3	182.5–183	1264
N_3	H	114–115	1267
NH_2	H	254–255 (dec.)	1264
		256–257	1266
NH_2	CH_3	267–268	1266
		268–269 (dec.)	1264
NH_2	Cl	>260	1264, 1266
$NH{-}C_4H_9$	H	174–175	1265
		174.5–175	1264
$NH{-}CH_2CH_2Cl$	H	174.5–175	1264
$NH{-}(CH_2)_3N(CH_3)_2$	H	250–251 (dec.)	1264, 1265
$NH{-}C_6H_{11}$	H	190.5–191	1264
$NH{-}C_6H_{11}$	CH_3	219.5–220	1264
$N(C_2H_5)_2$	H	124.5–125	1264
$N(C_2H_5)_2$	CH_3	102–103	1265
$N(C_2H_5)(C_6H_5)$	H	174–175	1265
$N(C_6H_{11})_2$	H	190–191	1265

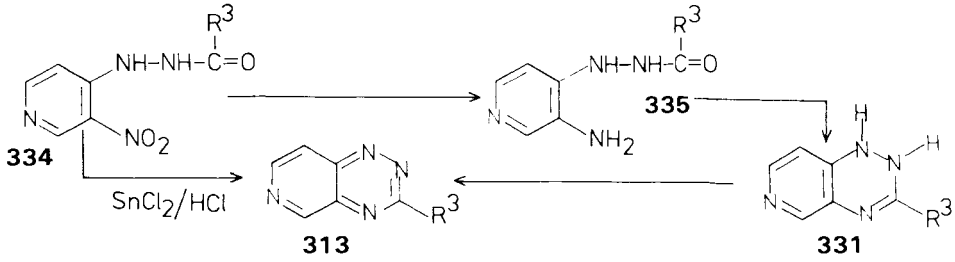
TABLE V-2. (continued)

B. Pyrido[2,3-*e*]1,2,4-triazine 1-oxides



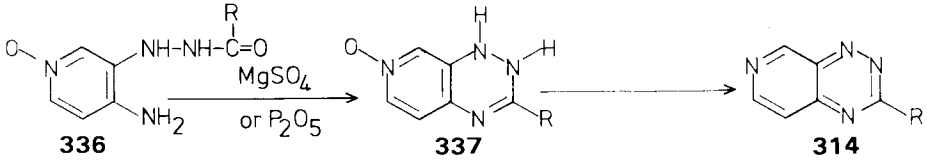
R^3	R^7	m.p.(°C)	Refs.
$N(C_6H_{11})_2$	CH_3	219–220	1265
	H	169–170	1265
		169–169.5	1264
	CH_3	242–243	1264, 1265
	H	116.5–117.5	1264
	CH_3	137–138	1265
		137.5–138.5	1264
$NHNH_2$	H	252–253 (dec.)	1264, 1265
$NHNH_2$	CH_3	245–246	1264, 1265

As starting material for the synthesis of 3-substituted pyrido[3,4-*e*]1,2,4-triazines (**313**) also the 4-(2-acylhydrazino)-3-nitropyridines (**334**) were used, which were reduced either with stannous chloride, yielding **313** directly (1270), or catalytically to 3-amino-4-(2-acylhydrazino)pyridines (**335**) (1268, 1269, 1272, 1354), which cyclize to the 1,2-dihydropyrido[3,4-*e*]1,2,4-triazines (**331**) [R^3 = H,·2HCl, m.p. 230°C (dec.) (1272); $R^3 = CH_3$, ·HCl, 220 to 221°C (1268); 297°C (1272); $R^3 = C_6H_5$, ·HCl, 253 to 254°C (1268)]. Oxidation of **331** affords the 3-pyrido[3,4-*e*]1,2,4-triazines (**313**).



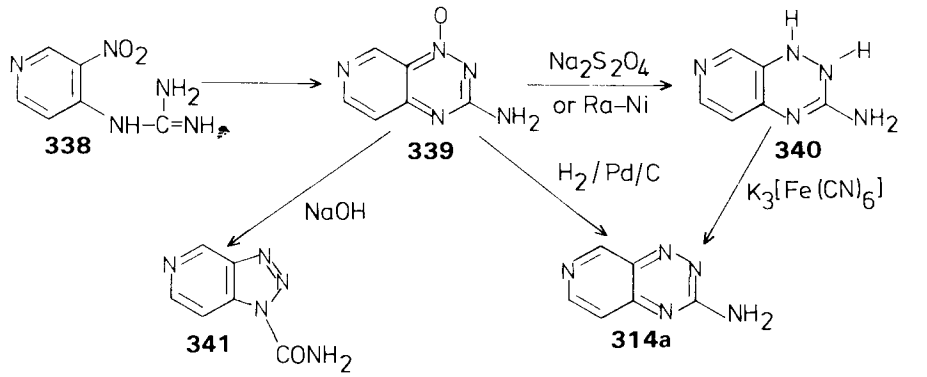
C. Pyrido[4,3-*e*]1,2,4-triazines

Treatment of 3-(2-acylhydrazino)-4-aminopyridine 1-oxides (**336**) with magnesium sulfate or phosphorus pentoxide affords the 3-substituted pyrido-[4,3-*e*] 1,2,4-triazines (**314**) (R = H, m.p. 143°C; R = CH_3, 145°C) (1275). The first step of this reaction is probably the formation of the 1,2-dihydropyrido-[4,3-*e*] 1,2,4-triazine 7-oxides (**337**) which yield **314** by an intramolecular redox reaction.



336 **337** **314**

3-Aminopyrido[4,3-*e*] 1,2,4-triazine (**314a**) is prepared by the following reaction sequence (1272–1274): cyclization of 4-guanyl-3-nitropyridine (**338**) in the presence of base yields 3-aminopyrido[4,3-*e*] 1,2,4-triazine 1-oxide (**339**) [m.p. 292 to 293°C (dec.); 303 to 304°C (1274)]. Reduction of **339** with sodium dithionite or Raney nickel affords 1,2-dihydro-3-aminopyrido[4,3-*e*]-1,2,4-triazine (**340**) (m.p. 250 to 251°C) which is oxidized to **314a** with potassium ferricyanide (1272, 1274). **314a** [277 to 279°C (1272); 284 to 285°C (1274)] can be prepared directly from **339** by catalytic reduction (1274).



338 **339** **340** **341** **314a**

339 is converted to pyrido[3,4-*d*] 1,2,3-triazole-1-carboxamide (**341**) by treatment with sodium hydroxide (1272).

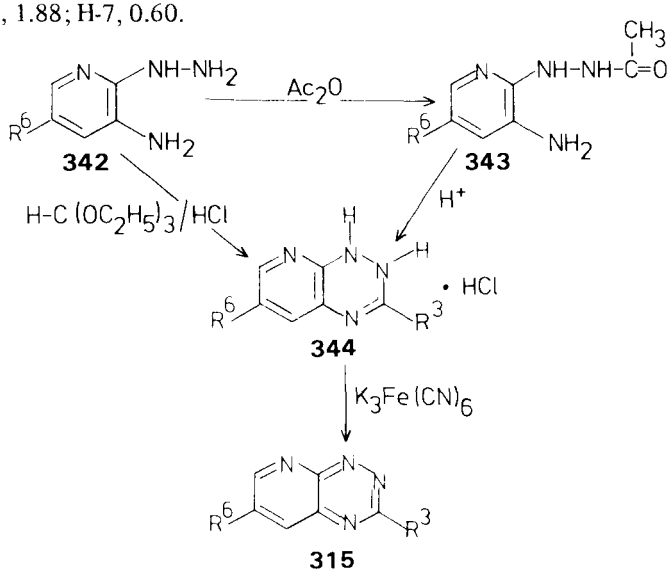
D. Pyrido[3,2-*e*]1,2,4-triazines

All the known pyrido[3,2-*e*] 1,2,4-triazines (**315**) have been prepared by Lewis and Shepherd (1276, 1277). The synthetic procedure is given in the next

reaction sequence. 3-Amino-2-hydrazinopyridines (**342**) are either (1) acetylated with acetic anhydride, yielding 3-amino-2-(2-acetylhydrazino)pyridines (**343**), or (2) cyclized with triethyl orthoformate to 1,2-dihydropyrido[3,2-*e*] 1,2,4-triazine hydrochlorides (**344**).

343 were transformed to **344** by treatment with ethanolic hydrochloric acid. Oxidation of **334** with potassium ferricyanide affords the orange or red pyrido[3,2-*e*] 1,2,4-triazines (**315**).

The electronic absorption spectra of **315** show five absorption maxima in the following regions and with the given absorptivities: 210 (28.000), 262 to 283 (3.330 to 4.750), 305 to 320 (5.320 to 8.840), 315 to 332 (4.750 to 9.384), and 470 to 495 nm (175 to 280). The following proton chemical shifts were observed for the unsubstituted pyrido[3,2-*e*] 1,2,4-triazine: H-3, τ = 0.11; H-5, 1.43; H-6, 1.88; H-7, 0.60.



Starting from 3-amino-2-(1-methylhydrazino)pyridine (**345**), two 1-methyl-1,2-dihydropyrido[3,2-*e*] 1,2,4-triazine hydrochlorides (**346**) were prepared by the reaction with triethyl orthoformate or with acetic anhydride (1276).

Attempts to convert **346** to 1-methylpyrido[3,2-*e*] 1,2,4-triazinium chlorides (**347**) using oxygen with ferric chloride or platinum resulted only in the recovery of the starting material.

Table V-3 and V-4 list pyrido[3,2-*e*] 1,2,4-triazines known.

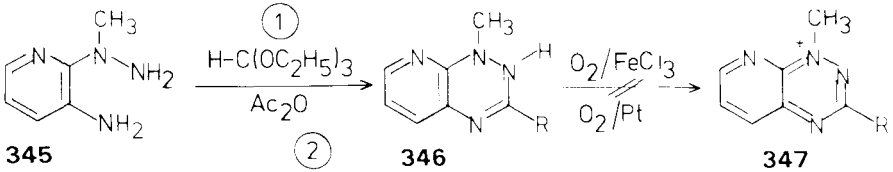
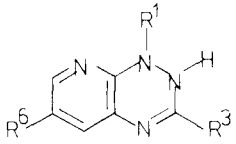
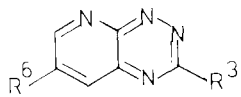


TABLE V-3. 1,2-DIHYDROPYRIDO[3,2-*e*]1,2,4-TRIAZINES



R^1	R^3	R^6	m.p. (°C)	Refs.
H	H	H	182–184	1276, 1277
H	H	Cl	218	1276, 1277
H	H	$COOCH_3$	192–193	1276, 1277
H	CH_3	H	220	1276, 1277
H	CH_3	Cl	240	1276, 1277
H	CH_3	$COOCH_3$	237–239	1276, 1277
CH_3	H	H	245	1276
CH_3	CH_3	H	270	1276

TABLE V-4. PYRIDO[3,2-*e*]1,2,4-TRIAZINES



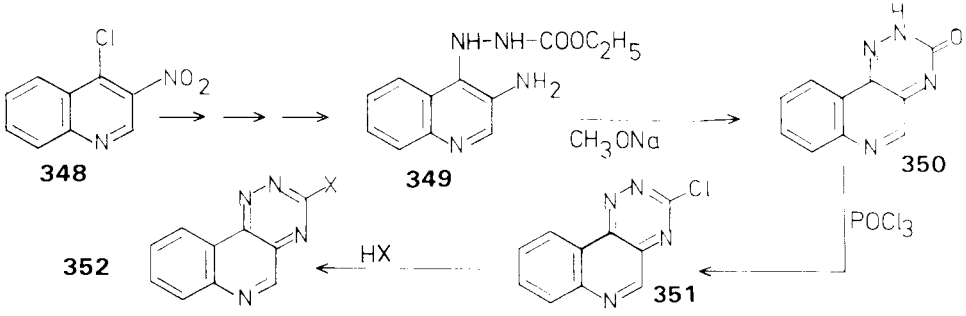
R^3	R^6	m.p. (°C)	Refs.
H	H	151–152	1276, 1277
H	Cl	125–126	1276, 1277
H	$COOCH_3$	131–132	1276, 1277
H	COOH	235 (dec.)	1276, 1277
CH_3	H	171–172	1276, 1277
CH_3	Cl	129–130	1276, 1277
CH_3	$COOCH_3$	217–218	1276, 1277
CH_3	COOH	215 (dec.)	1276, 1277

VII. CONDENSED WITH THE QUINOLINE SYSTEM

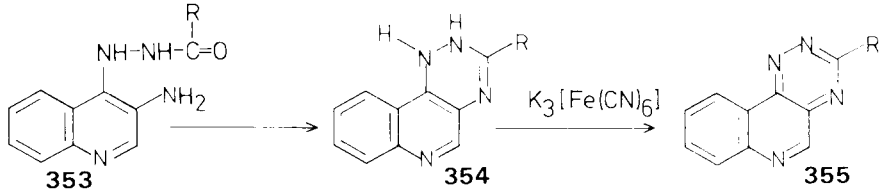
A. 1,2,4-Triazino[5,6-*c*]quinolines

Starting from 4-chloro-3-nitroquinoline (**348**), 3-amino-4-[2-(ethoxycarbonyl)hydrazino]quinoline (**349**) was prepared, which cyclizes to 1,2,4-triazino[5,6-*c*]quinolin-3-one (**350**) in the presence of sodium methoxide and

air (1278, 1279). Reaction of **350** with phosphoryl chloride yields the 3-chloro derivative (**351**), which was used for the synthesis of 3-amino- or 3-methoxy-1,2,4-triazino[5,6-*e*]quinolines (**352**).



Cyclization of 3-amino-4-(2-acylhydrazino)quinolines (**353**) affords 3-substituted 1,2-dihydro-1,2,4-triazino[5,6-*c*]quinolines (**354**), which can be oxidized by potassium ferricyanide, leading to 3-substituted 1,2,4-triazino-[5,6-*c*]quinolines (**355**) (1280, 1281).



Reaction of 4-hydrazino-3-nitroquinoline (**356**) with triethyl orthoformate affords 4-[2-(ethoxymethylene)hydrazino]-3-nitroquinoline (**357**). This was reduced with palladium catalyst in ethanol, yielding **354a**, which was then oxidized with potassium ferricyanide to the unsubstituted 1,2,4-triazino[5,6-*c*]-quinoline (**355a**) (1281).

Table V-5 lists the compounds of this class reported in the literature.

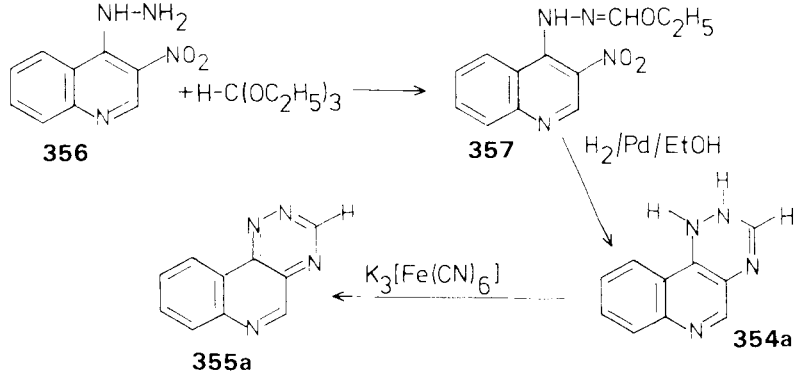
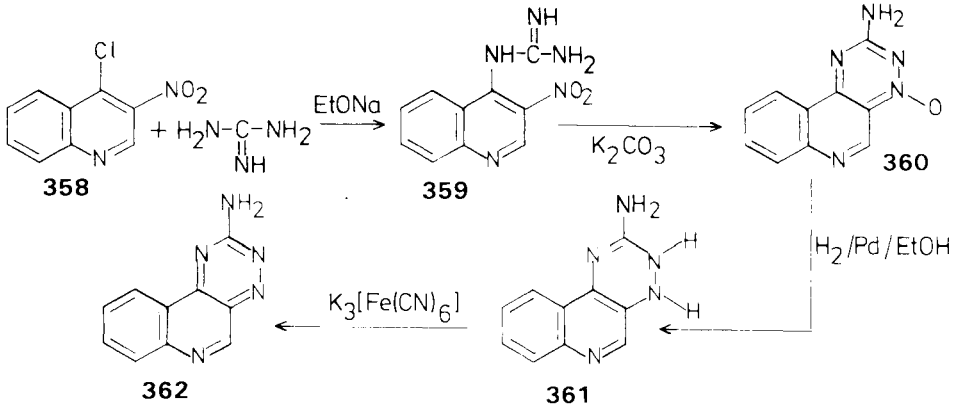


TABLE V-5. 1,2,4-TRIAZINO[5,6-*c*]QUINOLINES (**355**) AND 1,2-DIHYDRO-1,2,4-TRIAZINO[5,6-*c*]QUINOLINES (**354**)

355			**354**			
R	m.p. (°C)	Refs.	R		m.p. (°C)	Refs.
H	162–164	1280, 1281	H	·HCl	285–287	1280, 1281
CH_3	137–138	1280, 1281	CH_3	·HCl	301–303	1280, 1281
C_2H_5	106–108	1280, 1281	C_6H_5	·HCl	297–298	1280, 1281
C_6H_5	203–204	1280, 1281		·HBr	309–311	1280
4-Br–C_6H_4	245–247	1280	4-HO–C_6H_4	·HCl	312–313	1280
4-HO–C_6H_4	246	1280	4-H_2N–C_6H_4	·HCl	308–310	1280
3,4,5-$(CH_3O)_3C_6H_2$	182–183	1280	C_6H_5–CH_2	·HCl	296–298	1280
4-H_2N–C_6H_4	268–270	1280	4-Pyridyl	·HCl	308–310	1280
C_6H_5–CH_2	150–152	1280				
3,4-$(CH_3O)_2C_6H_3$	150–151	1280				
4-Pyridyl	213–214	1280				
OH (taut.)	288–300 (dec.)	1278				
Na salt		1278				
OCH_3	163–167	1278				
Cl	174–175	1278				
NH_2	300 (dec.)	1278				
$HOCH_2CH_2NH$	216–220	1278				
$(CH_2{=}CH{-}CH_2)_2N$	68–70	1278				

B. 1,2,4-Triazino[6,5-*c*]quinolines

The reaction of 4-chloro-3-nitroquinoline (**358**) with guanidine in the presence of sodium ethoxide yields 4-guanidino-3-nitroquinoline (**359**), which was converted to 2-amino-1,2,4-triazino[6,5-*c*]quinoline 4-oxide (**360**) (m.p. 302 to 304°C) on treatment with aqueous potassium carbonate. Catalytic reduction of **360** with palladium catalyst in ethanol affords 2-amino-3,4-dihydro-1,2,4-triazino[6,5-*c*]quinoline (**361**) (·HCl, m.p. 262 to 264°C), which is then oxidized to 2-amino-1,2,4-triazino[6,5-*c*]quinoline (**362**) (m.p. 290 to 291°C), with potassium ferricyanide (1282).



358 **359** **360** **361** **362**

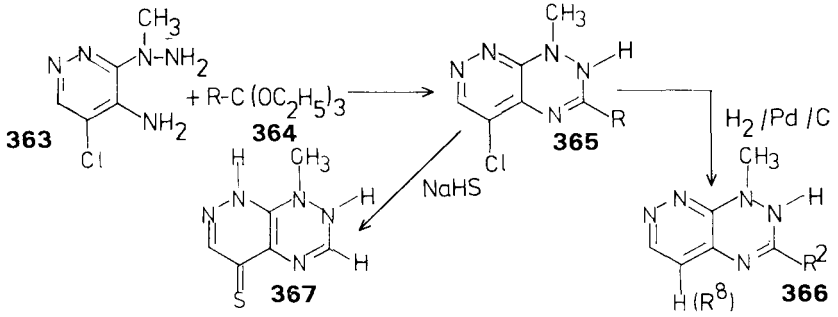
VIII. CONDENSED WITH THE PYRIDAZINE RING

Calculations on the various pyridazino-1,2,4-triazines were reported by Wait and Wesley (1150).

A. Pyridazino[4,3-*e*]1,2,4-triazines

The reaction of 4-amino-5-chloro-3-(1-methylhydrazino)pyridazine (**363**) with triethyl orthocarboxylates (**364**) was used for the synthesis of the 8-chloro-4-methyl-3,4-dihydropyridazino[4,3-*e*] 1,2,4-triazines (**365a** to **365c**) (1283). The chlorosubstituted pyridazinotriazines **365a** to **365c** could be catalytically dechlorinated with hydrogen to give the hydrochlorides of **366a** to **366c**. It was possible to replace the chlorine in **365a** with a sulfur atom by reaction with sodium hydrosulfide hydrate, to give 4-methyl-3,4-dihydropyridazino[4,3-*e*]-1,2,4-triazine-8-thione (**367**) (m.p. 259 to 260°C) (1283). The isolated com-

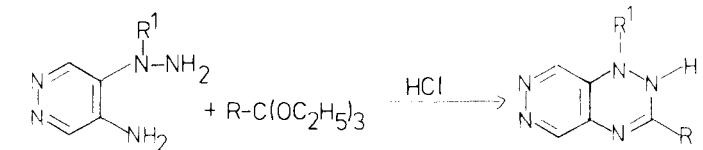
pounds are yellow to red crystalline substances. The following signals were observed in the PMR spectrum of **365a** (R = H): $\tau = 0.94$ (H-7), 2.00 (H-2), 3.60 (N-H), and 7.10 (CH_3). The electronic spectrum of **365a** shows two absorption maxima at 231 (20.380) and 341 to 345 nm (4.771).



R^2	R^8		m.p. (°C)	R^2	R^8		m.p. (°C)
H	H	·HCl	249–251	CH_3	Cl		183–185
H	Cl		231–232			·HCl	255
		·HCl	245	C_2H_5	H	·HCl	285–286
CH_3	H	·HCl	295	C_2H_5	Cl		185–187
						·HCl	232–233

B. Pyridazino[5,4-*e*]1,2,4-triazines

Four compounds of this series are known at present (1283). They were prepared by the reaction of 4-amino-5-hydrazinopyridazine (**368**) with triethyl orthocarboxylates to give 3-substituted 1,2-dihydropyridazino-[5,4-*e*] 1,2,4-triazine hydrochlorides (**369**) (R = H, m.p. 192 to 194°C; R = CH_3, 220 to 225°C; R = C_2H_5, 218 to 221°C) or through cyclization of 4-amino-5-(1-methylhydrazino)pyridazine (**370**) with triethyl orthoformate, yielding the hydrochloride of 1-methyl-1,2-dihydropyridazino[5,4-*e*] 1,2,4-triazine (**371**) (m.p. 300°C) in low yield.



368 R^1 = H
370 R^1 = CH_3
369 R^1 = H
371 R^1 = CH_3

All compounds are purple and show two absorption maxima in the electronic spectra, between 231 and 236 nm and 310 and 340 nm. In the PMR spectrum of the unsubstituted compound the following signals were observed: τ = 2.70–2.78 (H-5, H-8) and 3.86 (H-3).

IX. CONDENSED WITH THE 4,7-PHENANTHROLINE SYSTEM

A. 4,7-Phenanthrolino[5,6-*e*] 1,2,4-triazines

Most known 4,7-phenanthrolino[5,6-*e*] 1,2,4-triazines (**372**, **373**), which have also been named 1,2,4-triazino[5,6-*f*]4,7-phenanthrolines, have been synthesized by the reaction of 4,7-phenanthrolino-5,6-quinone (**374**) with amidrazones (23, 26–29), with semicarbazide (1284), or with thiosemicarbazide (1284, 1285). The thio derivative (**373b**) can be methylated with dimethyl sulfate and sodium hydroxide to give the methylmercapto compound (**375**), which was used for the synthesis of amino- and hydrazino-4,7-phenanthrolino[5,6-*e*] 1,2,4-triazines (**376**) (1285).

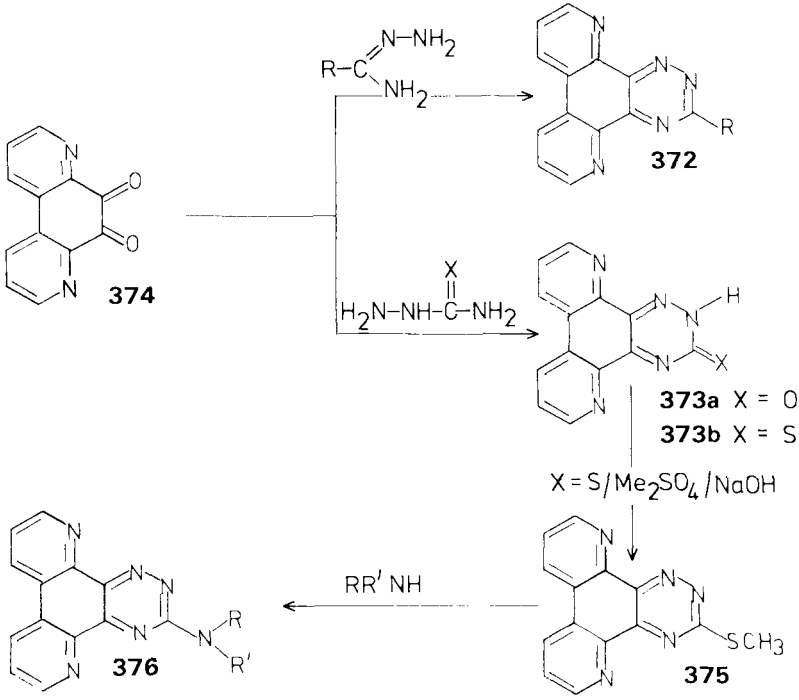
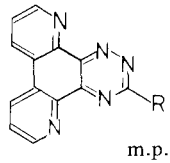
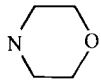
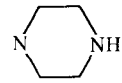
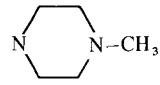
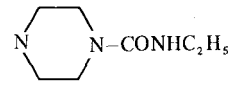
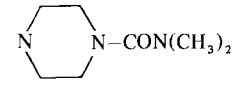
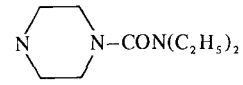


Table V-6 lists the compounds of this class reported in the literature.

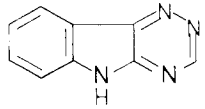
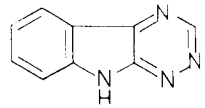
TABLE V-6. 4,7-PHENANTHROLINO[5,6-*e*]1,2,4-TRIAZINES



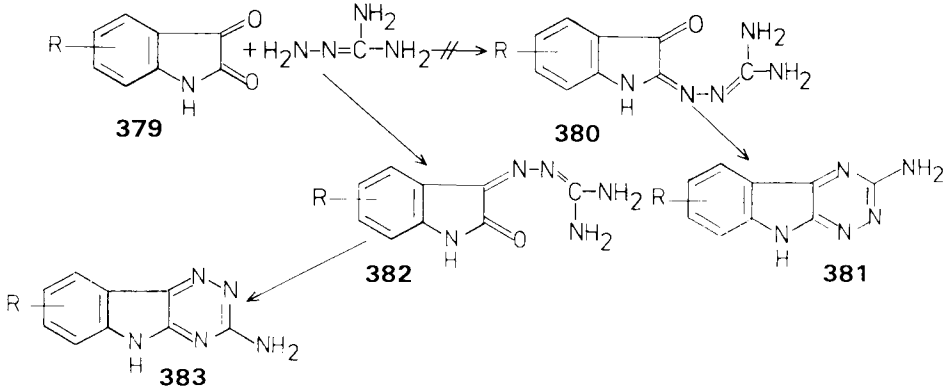
R	m.p. (°C)	Refs.
2-Pyridyl	325	28
4-Methyl-2-pyridyl	321–322	28
4-Phenyl-2-pyridyl	358–359	28
6-(2-Pyridyl)-2-pyridyl	372	27
3-Pyridazyl	380	26
4-Pyrimidyl	380	23
3-Pyrazyl	361–362	26
3-Isoquinolyl	350–351	29
2-Thiazolyl	348–349	28
OH (tautomer)	303–305	1284
SH (tautomer)	266–267 (dec.)	1284, 1285
SCH_3	283–284	1285
NH_2	360	1285
$HOCH_2CH_2NH$	300	1285
$(C_2H_5)_2NCH_2CH_2NH$	120–125	1285
	292–294	1285
	341	1285
	292–294	1285
	285–287	1285
	298–300 (dec.)	1285
	301 (dec.)	1285
	239 (dec.)	1285
$NHNH_2$	238–239	1285

X. CONDENSED WITH THE INDOLE SYSTEM

Two classes of 1,2,4-triazinoindoles, in which the 1,2,4-triazine ring is condensed through carbon atoms with the five-membered ring of the indole system are possible. Compounds of both classes, that is, of the 1,2,4-triazino-[5,6-*b*]indoles (**377**) and the 1,2,4-triazino[6,5-*b*]indoles, (**378**) are known.

377   **378**

In the older literature a number of 1,2,4-triazino[6,5-*b*]indoles (**378**) were reported by De (1227), De and Dutta (1254), and Rajagopalan (1286 1287), who obtained these compounds through the reaction of isatines (**379**) with aminoguanidine. These authors believed that the first step of the reaction is the formation of the α-guanylhydrazones (**380**), which were further cyclized to the 3-amino-1,2,4-triazino[6,5-*b*]indoles (**381**). King and Wright (1288) have shown that the first reaction products are not the α-guanylhydrazones (**380**) but the *syn*-β-guanylhydrazones (**382**), which can be cyclized to the 3-amino-1,2,4-triazino[5,6-*b*]indoles (**383**). Owing to the work of King and Wright the compounds isolated by De and Dutta are now known to be derivatives of the 1,2,4-triazino[5,6-*b*]indole system (**377**), whereas the compounds reported by Rajagopalan should be isatin β-guanylhydrazones.

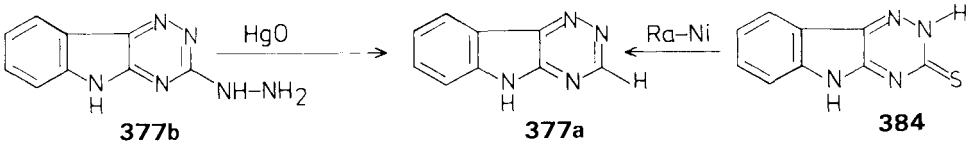


A. 1,2,4-Triazino[5,6-*b*]indoles

1. *1,2,4-Triazino[5,6-b]indole*

Unsubstituted 1,2,4-triazino[5,6-*b*]indole (**377a**) was synthesized either through the oxidation of the 3-hydrazino-1,2,4-triazino[5,6-*b*]indole (**377b**)

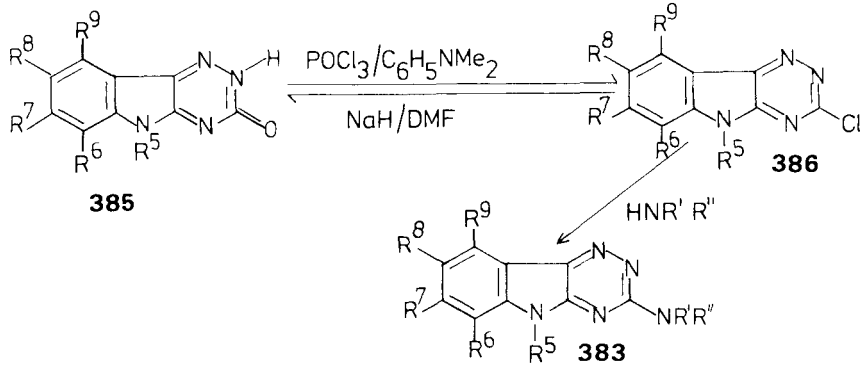
with yellow mercuric oxide or by treatment of 1,2,4-triazino[5,6-*b*]indole-3-thione (**384**) with Raney nickel (1289, 1314). **377a** is a light brown microcrystalline powder of m.p. 255 to 258°C (1289) or 264 to 266°C (1314).



377b **377a** **384**

2. *3-Chloro-1,2,4-triazino[5,6-b]indoles*

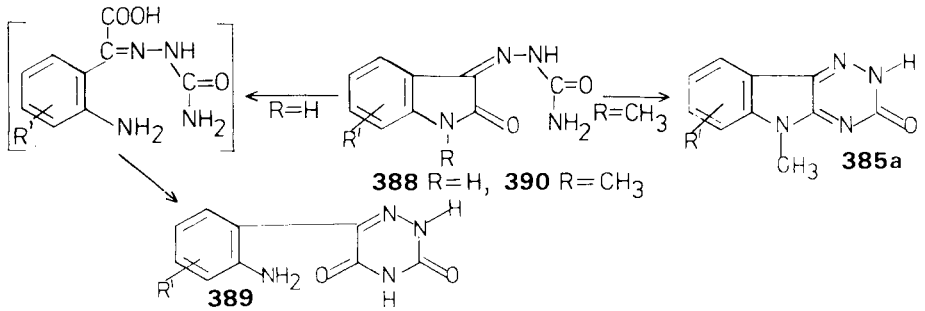
At present only few 3-chloro-1,2,4-triazino[5,6-*b*]indoles (**386**) are known. They are prepared by the reaction of the 1,2,4-triazino[5,6-*b*]indol-3-ones (**385**) with phosphoryl chloride in the presence of *N*,*N*-dimethylaniline (1290–1292, 1303). The reaction of **386** with amines was used for the synthesis of the 3-amino-1,2,4-triazino[5,6-*b*]indoles (**383**) (1290, 1291, 1303). Treatment of **386a** with sodium hydride in dimethylformamide led to the isolation of **385a** (R^5, R^6, R^7, R^8, R^9 = H) (1293).



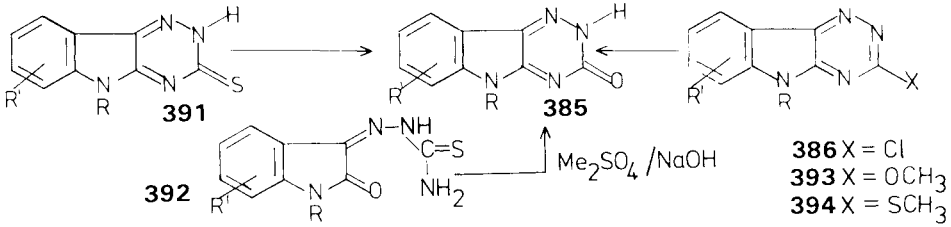
385 **386** **383**

3. *1,2,4-Triazino[5,6-b]indol-3-ones*

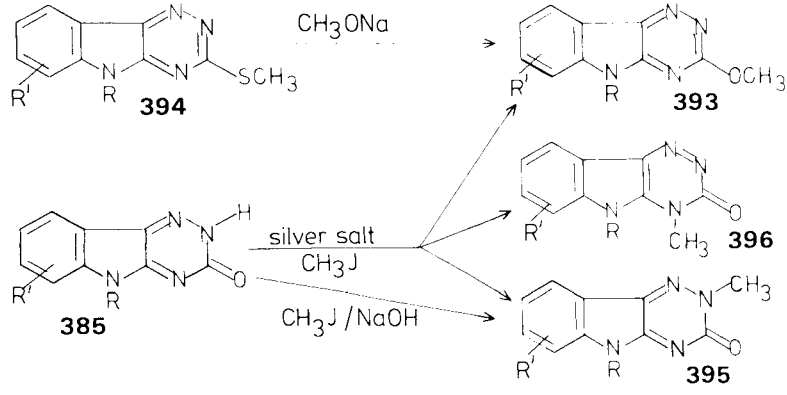
The 5-methyl-1,2,4-triazino[5,6-*b*]indol-3-ones (**385a**) can be obtained by basic cyclization of the *syn*-β-semicarbazones of *N*-methylisatins (**390**) (1294–1296), while 6-(2-aminophenyl)-1,2,4-triazine-3,5-diones (**389**) were isolated when the *syn*-β-semicarbazones of isatins (**388**) were treated with a base (1294, 1299). **389** can be converted to **385**, when they were treated with hydrochloric acid or phosphorus pentoxide (1271, 1299).



1,2,4-Triazino[5,6-*b*]indole-3-thiones (**391**) can be converted to **385** by treatment with sodium hydroxide (1290), hydrogen peroxide (1289, 1303), chloroacetic acid (1289), or potassium permanganate (1300). **385** were also obtained when isatin-β-thiosemicarbazones (**392**) were treated with dimethyl sulfate and sodium hydroxide (1297) or by reaction of the 3-chloro- (**386**), 3-methoxy- (**393**), or 3-(methylmercapto)-1,2,4-triazino[5,6-*b*]indoles (**394**) with sodium hydride in dimethylformamide (1293).

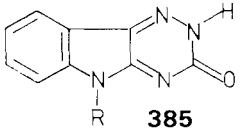


Treatment of **394** with sodium methoxide affords **393** (1293). Methylation of **385** with methyl iodide in alkaline solution yields 2-methyl-1,2,4-triazino[5,6-*b*]indol-3-ones (**395**) whereas methylation of the silver salts of **385** with methyl iodide in benzene yields **393**, **395**, and 4-methyl-1,2,4-triazino-[5,6-*b*]indol-3-ones (**396**) (1298).

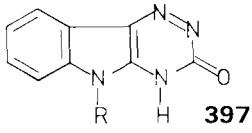


Treatment of **385** with phosphoryl chloride in the presence of *N,N*-dimethylaniline was used for the synthesis of 3-chloro-1,2,4-triazino[5,6-*b*]-indoles (**386**) (1290–1292, 1303).

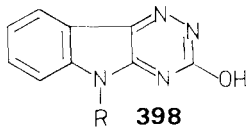
1,2,4-Triazino[5,6-*b*]indol-3-ones (**385**) are yellow, crystalline compounds, which are mostly stable to alkali (1299). By comparison of the electronic spectra of **385**, its 2-methyl (**395**) and 4-methyl derivatives (**396**), and 3-methoxy-1,2,4-triazino[5,6-*b*]indole (**393**), it was shown that of the three possible tautomeric forms (**385**, **397**, and **398**) the predominant tautomeric structure is the 2*H*-tautomer (**385**) (1298).



385



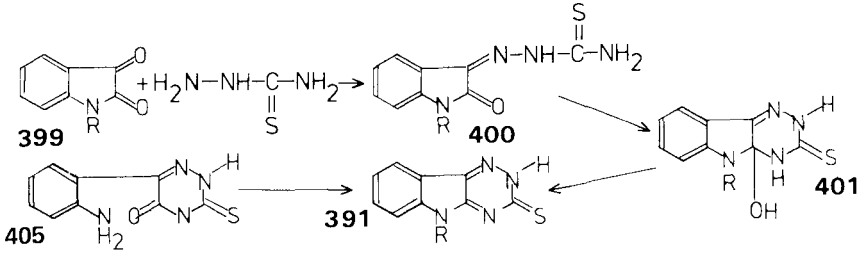
397



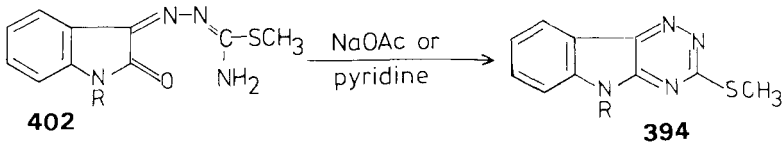
398

4. *1,2,4-Triazino[5,6-b]indole-3-thiones*

The 1,2,4-triazino[5,6-*b*]indole-3-thiones (**391**) were synthesized either from isatins (**399**) and thiosemicarbazide (1289, 1290, 1303) or by basic cyclization of the β-thiosemicarbazones of isatins (**400**) (574, 758, 782, 1289, 1295, 1299, 1301–1304, 1557). The first step of the reaction is the formation of a 4,4a-dihydro-4-hydroxy-1,2,4-triazino[5,6-*b*]indole-3-thione (**401**) which can be isolated in few cases (758).

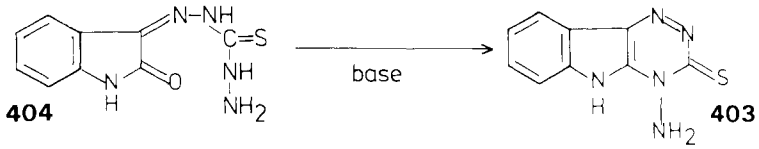


Contrary to earlier statements (1301), the *S*-methyl thiosemicarbazones (**402**) of isatin can also be cyclized if the reaction is run in the presence of sodium acetate or pyridine (758). Formation of **391** was also observed when 6-(2-amino-phenyl)-3-thioxo-1,2,4-triazin-5-ones (**405**) were treated with acid or heated in DMF (758).

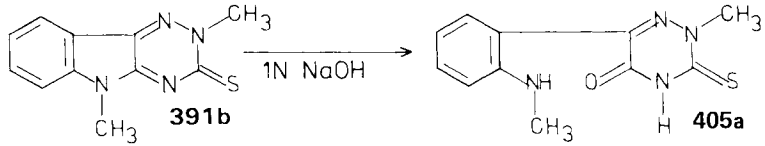


402 **394**

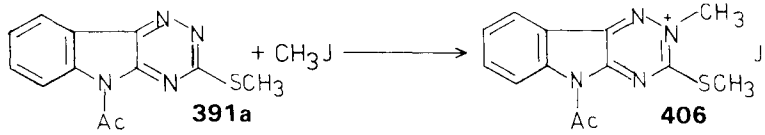
4-Amino-1,2,4-triazino[5,6-*e*]indole-3-thione (**403**) was prepared by Tomtschin and Ioffe (1305) through cyclization of the β-thiocarbohydrazone of isatin (**404**) in the presence of a base.



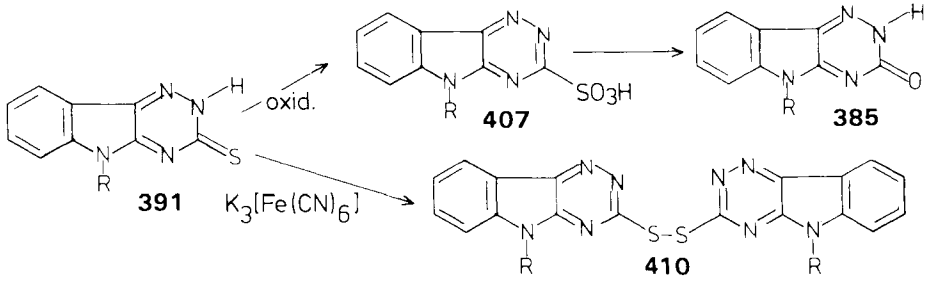
1,2,4-Triazino[5,6-*b*]indole-3-thiones (**391**) are yellow or orange crystalline compounds. Most of them are stable to bases, but the 2,5-dimethyl-1,2,4-triazino[5,6-*b*]indole-3-thione (**391b**) is readily hydrolyzed by 1*N* sodium hydroxide to 2-methyl-6-[2-(methylamino)phenyl]-3-thioxo-1,2,4-triazin-5-one (**405a**) (1299). Tomtschin and his group (1301) have shown by UV spectroscopy that the 2*H* tautomer is the predominant tautomeric structure in neutral solution.

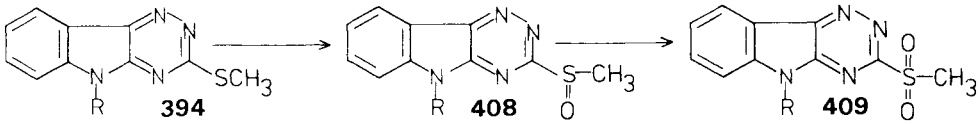


Alkylation of **391** always yields 3-(alkylmercapto)-1,2,4-triazino[5,6-*b*]-indoles (**394**) (758, 1289, 1290, 1300, 1303, 1304, 1306). Alkylation of 5-acetyl-3-(methylmercapto)-1,2,4-triazino[5,6-*b*]indole (**391a**) with methyl iodide affords 5-acetyl-2-methyl-3-(methylmercapto)-1,2,4-triazino[5,6-*b*]-indolium iodide (**406**) (dec. above 190°C) (283).



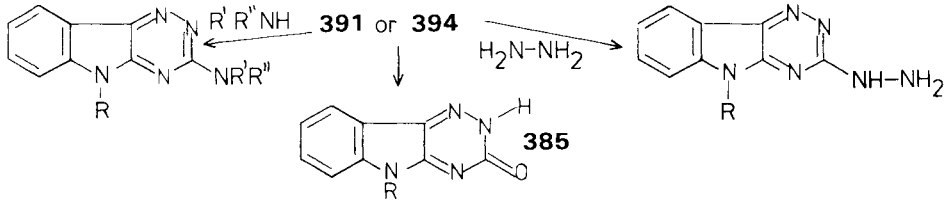
Oxidation of **391** yields the 3-sulfonic acids (**407**) which can be hydrolyzed to **385** (1300), whereas the sulfoxides (**408**) (1289) or the sulfones (**409**) (1289,



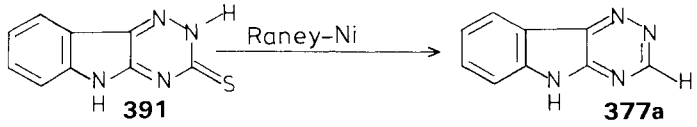


1300, 1303) were isolated when **394** were oxidized. Oxidation of **391** with potassium ferricyanide affords the disulfides (**410**) (1302).

The thioxo or the methylmercapto group is replaced when **391** or **394** were treated with amines (1289, 1291, 1303), hydrazines (1289, 1307), sodium methoxide (1293), sodium hydride in dimethylformamide (1293), sodium hydroxide (1290), hydrogen peroxide (1289, 1303), chloroacetic acid (1289), or potassium permanganate (1300). The last five reactions all yield **385**.



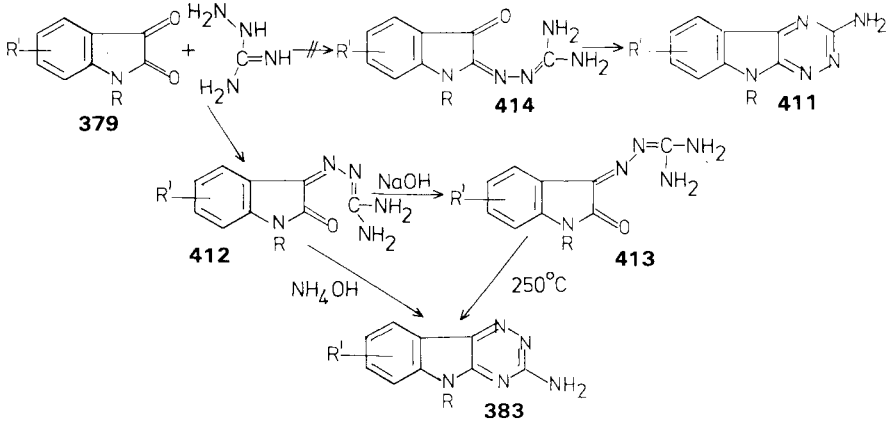
Desulfuration of **391** with Raney nickel was used for the synthesis of the unsubstituted 1,2,4-triazino[5,6-*b*]indole (**377a**) (1289).



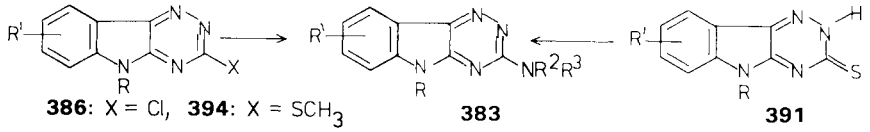
5. *3-Amino-1,2,4-triazino[5,6-b]indoles*

The first 3-amino-1,2,4-triazino[5,6-*b*]indoles (**383**) were probably synthesized by De (1227) and De and Dutta (1254), starting from isatins (**379**) and aminoguanidine. These authors formulated the isolated products as 2-amino-1,2,4-triazino[6,5-*b*]indoles (**411**), since they assumed that the α-guanylhydrazones (**414**) were initially formed. King and Wright (1288) have pointed out that carbonyl reagents react with the β-oxo group in isatins rather than with the α-oxo group, so the compounds isolated by De and Dutta should be 3-amino-1,2,4-triazino[5,6-*b*]indoles (**383**). King and Wright (1288) also repeated the work of Rajagopalan (1286, 1287), who also claimed to have isolated **411** from the reaction of isatins with aminoguanidine and obtained, not 1,2,4-triazinoindoles, but rather isatin β-*syn*-guanylhydrazones (**412**). Digestion of **412** with sodium hydroxide solution converted it to the *anti* form (**413**).

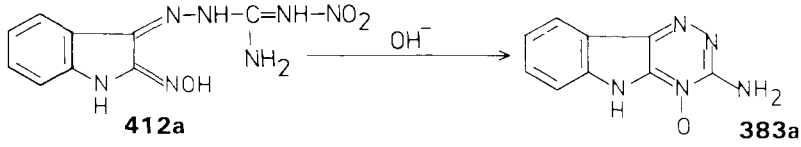
Cyclization of **412** was achieved by heating its hydrochloride with excess ammonium hydroxide solution, and **413** was cyclized by heating it at 250°C under very low pressure. The reaction of isatins (**379**) with aminoguanidine was also used by three other groups for the synthesis of **383** (619, 1308, 1557).



3-Amino-1,2,4-triazino[5,6-*b*]indoles (**383**) can also be obtained by reaction of 3-chloro- (**386**) or 3-(methylmercapto)-1,2,4-triazino[5,6-*b*]indoles (**394**) or 1,2,4-triazino[5,6-*b*]indole-3-thiones (**391**) with amines (1289–1292, 1303) or by alteration of substituents in **383** (1312, 1313).



Lalor and Scott (1550) reported that isatin 2-oxime 3-(nitroguanyl)hydrazone (**412a**) is readily converted with dilute base into 3-amino-1,2,4-triazino-[5,6-*b*]indole 4-oxide (**383a**).



Most 3-amino-1,2,4-triazino[5,6-*b*]indoles (**383**) are yellow crystalline compounds of high melting points. **383** form hydrates (1310, 1311) and salts with mineral acids. Infrared spectroscopy and X-ray diffraction were used for

the identification of two polymorphic forms and a hydrate of 3-[(3-hydroxy-3-methylbutyl)amino]-5-methyl-1,2,4-triazino[5,6-*b*]indole (1311).

The transformation of 3-amino-1,2,4-triazino[5,6-*b*]indoles into tetracyclic compounds is reported in a Dutch patent (1309).

6. *3-Hydrazino-1,2,4-triazino[5,6-b]indoles*

The 3-hydrazino-1,2,4-triazino[5,6-*b*]indoles (**415**) were synthesized by the reaction of 3-(methylmercapto)-1,2,4-triazino[5,6-*b*]indoles (**394**) or 1,2,4-triazino[5,6-*b*]indole-3-thiones (**391**) with hydrazine (1289, 1307, 1314).

They are yellow, crystalline compounds with high melting points. The electronic spectra of **415** are reported by Tomtschin and his group (1314).

Oxidation of **415** with yellow mercuric oxide was used for the synthesis of 1,2,4-triazino[5,6-*b*]indoles (**377**) without a substituent in the 3-position (1289, 1314). The conversion of 3-hydrazino-1,2,4-triazino[5,6-*b*]indoles to tetracyclic compounds is published by two groups (1309, 1314).

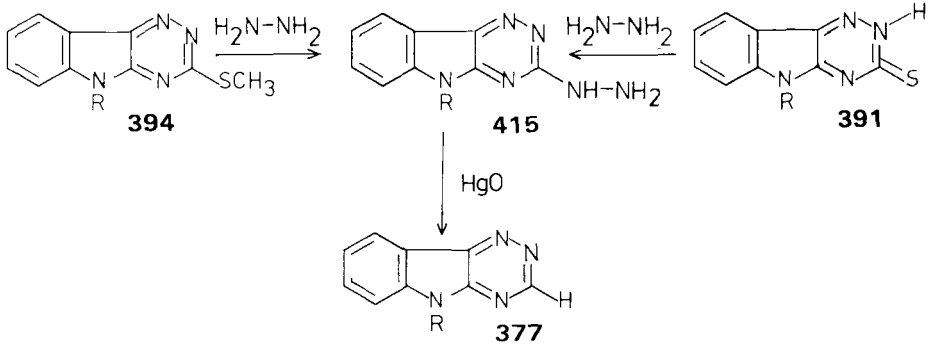
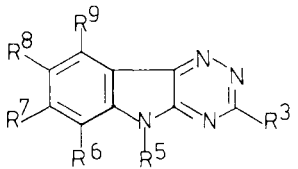


Table V-7 lists the 1,2,4-triazino[5,6-*b*]indoles reported in the literature.

B. 1,2,4-Triazino[6,5-*b*]indoles

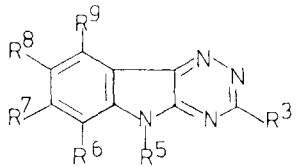
All known 1,2,4-triazino[6,5-*b*]indoles have been synthesized by two Russian groups (1315–1319). 1,2,4-Triazino[6,5-*b*]indol-3-ones (**416**) were obtained by basic cyclization of isatin α-semicarbazones (**417**) (1315, 1316), while cyclization of the α-thiosemicarbazones (**418**) was used for the synthesis of 1,2,4-triazino[6,5-*b*]indole-3-thiones (**419**) (1315, 1316, 1318). Methylation of **419a** (R = H) yields 3-(methylmercapto)-1,2,4-triazino[6,5-*b*]indoles (**420**) (1316, 1318), which were also prepared through cyclization of the *S*-methylthio-

TABLE V-7. 1,2,4-TRIAZINO[5,6-*b*]INDOLES



R^3	R^5	R^6	R^7	R^8	R^9	m.p. (°C)	Refs.
H	H	H	H	H	H	255–258	1289
						264–266	1314
H	CH_3	H	H	H	H	183	1314
Cl	CH_3	H	H	H	H	218–219	1291
						219.5–220.5	1290, 1292
Cl	CH_3	H	H	NO_2	H	241–243	1290
Cl	CH_3	H	H	Br	Cl	285–286	1303
Cl	CH_3	H	CH_3	Br	CH_3		1303
Cl	CH_3	H	Cl	H	Cl	252–255	1303
Cl	CH_3	H	Cl	Br	H	267–269	1303
Cl	CH_3	H	OCH_3	H	H	239–241	1303
Cl	CH_3	H	OCH_3	NO_2	H	233–235	1303
Cl	CH_3	H	OCH_3	Br	H		1303
Cl	CH_3	H	$O-CH_2-O$		H	263–266	1303
Cl	CH_3	Br	CH_3	Br	CH_3	256–272	1303
OCH_3	CH_3	H	H	H	H	135	1298
						149–151	1293
SCH_3	H	H	H	H	H	305	1301
						308–309	758
						314	1289
SCH_3	H	H	H	CH_3	H	326–326.5 (dec.)	1290

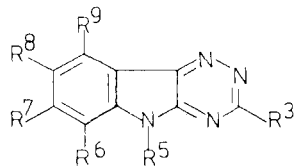
TABLE V-7. (continued)

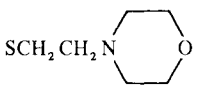
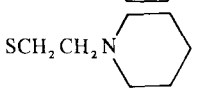
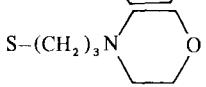


R^3	R^5	R^6	R^7	R^8	R^9	m.p.(°C)	Refs.
SCH_3	CH_3	H	H	H	H	177	758
						180	1301
						185	1304
$\cdot CH_3I$						203–204	1289
SCH_3	CH_3	H	H	H	CH_3	310–314 (dec.)	1303
SCH_3	CH_3	H	H	H	Cl		1303
SCH_3	CH_3	H	H	CH_3	H	195–196	1290
SCH_3	CH_3	H	H	CH_3	CH_3	259–260	1303
SCH_3	CH_3	H	H	C_4H_9	H	138–139	1290
SCH_3	CH_3	H	H	NO_2	H	251	1290
SCH_3	CH_3	H	H	NO_2	CH_3	261–263	1303
SCH_3	CH_3	H	H	NO_2	Cl	243–256	1303
SCH_3	CH_3	H	H	NO_2	NH_2		1303
SCH_3	CH_3	H	H	F	H	214–215	1290
SCH_3	CH_3	H	H	Cl	H	237	1289
SCH_3	CH_3	H	H	Br	H	250–252	1289
SCH_3	CH_3	H	H	OH	Br		1303
SCH_3	CH_3	H	H	OCH_3	H	164–167	1290
SCH_3	CH_3	H	H	OCH_3	Br		1303
SCH_3	CH_3	H	H	NH_2	Cl	276–278	1303
SCH_3	CH_3	H	CH_3	H	H	216–218	1303

SCH_3	CH_3	H	CH_3	H	CH_3	250–252	1303
SCH_3	CH_3	H	CH_3	CH_3	H	227–230 (dec.)	1303
SCH_3	CH_3	H	CH_3	NO_2	H	263–265	1303
SCH_3	CH_3	H	CH_3	NO_2	CH_3	260–262	1303
SCH_3	CH_3	H	CH_3	CHO	H		1303
SCH_3	CH_3	H	CH_3	CH_3CO	H		1303
SCH_3	CH_3	H	CH_3	NO_2	H		1303
SCH_3	CH_3	H	CF_3	H	H		1303
SCH_3	CH_3	H	CF_3	NO_2	H		1303
SCH_3	CH_3	H	CF_3	NH_2	H		1303
SCH_3	CH_3	H	Cl	H	H	222–224	1303
SCH_3	CH_3	H	Cl	NO_2	H	254–256	1303
SCH_3	CH_3	H	Cl	OCH_3	H	259–260	1303
SCH_3	CH_3	H	Cl	NH_2	H	290–292	1303
SCH_3	CH_3	H	Cl	NHCHO	H		1303
SCH_3	CH_3	H	Cl	$NHCOCH_3$	H		1303
SCH_3	CH_3	H	Br	H	H		1303
SCH_3	CH_3	H	Br	NO_2	H		1303
SCH_3	CH_3	H	Br	OH	H		1303
SCH_3	CH_3	H	Br	OCH_3	H		1303
SCH_3	CH_3	H	NO_2	H	H		1303
SCH_3	CH_3	H	NO_2	NO_2	H		1303
SCH_3	CH_3	H	OCH_3	Br	H		1303
SCH_3	CH_3	H	OCH_3	$CONH_2$	H		1303
SCH_3	CH_3	H	COOH	H	H		1303
SCH_3	CH_3	H	COOH	NO_2	H		1303
SCH_3	CH_3	H	COOH	NH_2	H		1303
SCH_3	CH_3	H	CN	NO_2	H		1303
SCH_3	C_3H_7	H	H	H	H	129–130	1289, 1304, 1306
SCH_3	C_3H_7	H	H	Cl	H	187	1289
SCH_3	CH_3CO	H	H	H	H	163	758

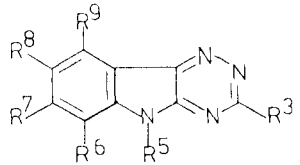
TABLE V-7. (continued)



R^3	R^5	R^6	R^7	R^8	R^9	m.p.(°C)	Refs.
SC_2H_5	H	H	H	H	H	303	1289
						303–304	1304
SC_2H_5	CH_3	H	H	H	H	154	1289
$SCH_2CH{=}CH_2$	CH_3	H	H	H	H	141	1289
						141–143	1304
$SCH_2C_6H_5$	CH_3	H	H	H	H	174	758
$SCH_2CH_2N(CH_3)_2$	CH_3	H	H	H	H	128	1289
						128–130	1304
$SCH_2CH_2N(C_2H_5)_2$	CH_3	H	H	H	H	101	1289
						101–103	1304
	CH_3	H	H	H	H	145–146	1304
						146–147	1289, 1306
	CH_3	H	H	H	H	144	1304
	CH_3	H	H	H	H	101–102	1304

S–CH=CH–N⟨O⟩	CH_3	H	H	H	H		1557
$S–CH_2CO–CH_3$	CH_3	H	H	H	H		1557
SCH_2COOH	CH_3	H	H	H	H	239	1300
SCH_2CH_2COOH	H	H	H	H	H	>350	1300
$4\text{-}O_2N–C_6H_4S$	CH_3	H	H	H	H	206–207	1289
$2,4\text{-}(O_2N)_2C_6H_3S$	CH_3	H	H	H	H	209	1289
						209–211	1304
$S\text{-})_2$	H	H	H	H	H	>350	1302
$S\text{-})_2$	CH_3	H	H	H	H	278	1302
SO_2CH_3	H	H	H	H	H	256	1300
SO_2CH_3	CH_3	H	H	H	H	224	1289
SO_2CH_3	CH_3	H	H	Cl	H	231	1289
SO_2CH_3	CH_3	H	H	NO_2	H	236	1289
SO_2CH_3	CH_3	H	OCH_3	Br	H		1303
$SO_2C_2H_5$	CH_3	H	H	H	H	175	1289
$SO_2CH_2CH_2N$⟨O⟩	CH_3	H	H	H	H	180	1289
SO_3H	H	H	H	H	H	>350	1300
NH_2	H	H	H	H	H	296	1227
						350–354 (dec.)	1288
						>360	1304
·HCl						324 (eff.)	1288
$\cdot HNO_3$						228	1288
NH_2	H	H	H	Cl	H	184	1254
NH_2	H	H	H	Br	H	>295	1254
NH_2	H	H	H	NO_2	H	>350	1304
NH_2	H	H	H	OCH_3	H	330	1304
NH_2	H	H	H	NO_2	H	>300	1254
NH_2	H	Br	H	Br	H	>295	1254
NH_2	H	NO_2	H	Br	H	268 (dec.)	1254

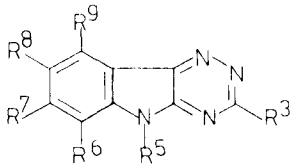
TABLE V-7. (continued)



R^3	R^5	R^6	R^7	R^8	R^9	m.p.(°C)	Refs.
NH_2	CH_3	H	H	H	H	314	1288
						335	1304
·HNO_3						210 (dec.)	1288
NH_2	CH_3	H	H	NO_2	H	>300	1304
NH_2	H	H	SO_3H	H	H	>310	1288
Na salt						>300	1288
NH_2	H	H	SO_2Cl	H	H		1288
NH_2	H	H	SO_2NH_2	H	H	>320	1288
$NHCH_3$	CH_3	H	H	H	H	250	1289
NHC_2H_5	CH_3	H	H	H	H	213	1289
						214	1304
·HCl						262	1289
·$C_{12}H_{25}I$						156	1289
NHC_3H_7	CH_3	H	H	H	H	189	1289
NH–*i*-C_3H_7	CH_3	H	H	H	H	198	1289
NHC_4H_9	CH_3	H	H	H	H	165	1289
NHC_5H_{11}	CH_3	H	H	H	H	168	1289
NH–*i*-C_5H_{11}	CH_3	H	H	H	H	187	1289
						187–189	1304
NHC_6H_{13}	CH_3	H	H	H	H	162	1289
NHC_7H_{15}	CH_3	H	H	H	H	136	1289

NHC_8H_{17}	CH_3	H	H	H	H	131	1289
$NHC_{10}H_{21}$	CH_3	H	H	H	H	125	1289
$\cdot CH_3I$						253	1289
$NHC_{12}H_{25}$	CH_3	H	H	H	H	119–121	1304
$NHC_{16}H_{33}$	CH_3	H	H	H	H	112	1289
$NHC_{18}H_{37}$	CH_3	H	H	H	H	99	1289,
						104–105	1304
$NHCH_2C_6H_5$	CH_3	H	H	H	H	224	1289
$\cdot HCl$						213	1289
$NHCH_2CH_2C_6H_5$	CH_3	H	H	H	H	186	1289
$\cdot HCl$						220	1289
$NHCH_2CH_2OH$	H	H	H	H	H	270–271	1289, 1304
$NHCH_2CH_2OH$	CH_3	H	H	H	H	235–235.5	1289
						235–236	1304
$NHCH_2CH_2OH$	CH_3	H	H	Cl	H	262–263	1289
$NHCH_2CH_2CH_2OH$	H	H	H	H	H	248–249	1289, 1304
$NHCH_2CH_2CH_2OH$	CH_3	H	H	H	H	164–165	1289, 1292
							1304
$NHCH_2CH_2CH_2OH$	CH_3	H	H	Cl	H	203–204	1289, 1304
$NHCH_2CH_2CH_2OH$	CH_3	H	H	NO_2	CH_3		1303
$NHCH_2CH_2CH_2OH$	CH_3	H	H	OH	Br		1303
$NHCH_2CH_2CH_2OH$	CH_3	H	H	NH_2	CH_3		1303
$NHCH_2CH_2CH_2OH$	CH_3	H	CH_3	NO_2	H		1303
$NHCH_2CH_2CH_2OH$	CH_3	H	CH_3	NO_2	CH_3		1303
$NHCH_2CH_2CH_2OH$	CH_3	H	CH_3	NH_2	H		1303
$\cdot HCl$							1303
$NHCH_2CH_2CH_2OH$	CH_3	H	CH_3	NH_2	CH_3		1303
$NHCH_2CH_2CH_2OH$	CH_3	H	CH_3	NO_2	H		1303
$NHCH_2CH_2CH_2OH$	CH_3	H	OCH_3	NH_2	H		1303
$\cdot 2H_2SO_4$							1303
$NHCH_2CH_2CH_2OH$	C_2H_5	H	Cl	H	H	151–152	1304
$NHCH_2CH_2CH_2OH$	C_3H_7	H	H	H	H	142–143	1304
$NHCH_2CH_2CH_2OH$	$C_6H_5CH_2$	H	H	H	H	186–187	1304

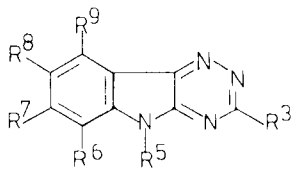
TABLE V-7. (continued)



R^3	R^5	R^6	R^7	R^8	R^9	m.p.(°C)	Refs.
$NHCH_2CH_2CH_2OH$	$C_6H_5CH_2CH_2$	H	H	H	H	154–155	1292, 1304
$NHCH_2CH_2CH_2OCH_3$	CH_3	H	H	H	H	140.5–141.5	1312
						141	1304
$NHCH_2CH_2CH_2OCOCH_3$	CH_3	H	H	H	H	185.5–186.5	1312
						186	1304
$NHCH_2CH_3CH_2OCOC_2H_5$	CH_3	H	H	H	H	158–160	1304, 1312
$NHCH_2CHOHCH_2OH$	CH_3	H	Cl	NH_2	H		1303
$NHCH_2CHOHCH_2OH$	CH_3	H	CH_3	NO_2	H		1303
$NHCH_2CHOHCH_2OH$	CH_3	H	CH_3	NO_2	CH_3		1303
$NHCH_2CHOHCH_2OH$	CH_3	H	CH_3	NH_2	H		1303
$NHCH_2CHOHCH_2OH$	CH_3	H	CH_3	NH_2	CH_3		1303
$NH(CH_2)_3OCO(CH_2)_2COOH$	CH_3	H	H	H	H	186–187	1304
$NH(CH_2)_3SCH_3$	CH_3	H	H	H	H	150–151	1304
$NH(CH_2)_3NH_2$	CH_3	H	H	H	H	155–156	1304
$NH(CH_2)_3NHCOCH_3$	CH_3	H	H	H	H	192–193	1304
$NH(CH_2)_4OH$	CH_3	H	H	H	H	146–147	1304
$NH(CH_2)_5OH$	CH_3	H	H	H	H	158–158.5	1289
·HCl						191–192	1289
$NH(CH_2)_6OH$	CH_3	H	H	H	H	124–125	1289, 1292, 1304
$NH(CH_2)_6OH$	CH_3	H	Cl	NH_2	H		1303

$NH(CH_2)_6OH$	CH_3	H	OCH_3	NO_2	H		1303
$NH(CH_2)_6OH$	CH_3	H	OCH_3	NH_2	H		1303
$NH(CH_2)_{12}OH$	CH_3	H	H	H	H	119–120	1289
$NHCH_2CH_2CHOHCH_3$	CH_3	H	H	H	H	168–168.5	1290
						169	1304/1557
$NHCH_2CH_2CHOHCH_3$	CH_3	H	H	OH	Br		1303
$NHCH_2CH_2$-2-pyridyl	CH_3	H	H	H	H		1557
$NHCH_2C(CH_3)_2CH_2OH$	CH_3	H	H	H	H	226–227	1291, 1292
						228	1304
						228–228.5	1290
$NHCH_2CH_2C(CH_3)_2OH$	H	H	OCH_3	NO_2	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	H	H	H	190–191.5	1291, 1292
						192–193	1290
						194	1304/1557
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	H	H	Cl		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	H	H	NH_2		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	H	CH_3	H	206.5–207	1290
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	H	CH_3	CH_3	219–221	1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	H	CH_3	Cl		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	H	CH_3	NH_2		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	H	C_4H_9	H	125–127	1290
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	H	Cl	H	222–223	1290
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	H	Cl	NH_2		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	H	Br	Cl	255–257	1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	H	NO_2	CH_3	260–262	1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	H	NO_2	NH_2		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	H	OH	CH_3		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	H	OH	CF_3		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	H	OH	F		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	H	OH	Cl		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	H	OH	Br		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	H	OH	COOH		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	H	OH	$COOCH_3$		1303

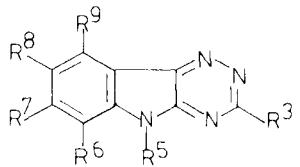
TABLE V-7. (continued)



R^3	R^5	R^6	R^7	R^8	R^9	m.p.(°C)	Refs.
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	H	OCH_3	H	184–184.5	1290
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	H	NH_2	CH_3	227–229	1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	H	NH_2	CF_3		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	H	NH_2	C_2H_5		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	H	NH_2	i-C_3H_7		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	H	NH_2	F		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	H	NH_2	Cl	249–251	1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	H	NH_2	NH_2		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	CH_3	H	CH_3	203–205	1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	CH_3	CH_3	H	202–204	1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	CH_3	NO_2	H	245–246	1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	CH_3	NO_2	CH_3	251–252	1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	CH_3	Br	CH_3		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	CH_3	OH	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	CH_3	CN	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	CH_3	CHO	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	CH_3	CH_3CO	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	CH_3	NH_2	H	207–209	1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	CH_3	NH_2	CH_3	207–209	1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	CH_3	CH_3SO_2	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	CF_3	NH_2	H		1303

$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	C_2H_5	NH_2	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	i-C_3H_7	NH_2	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	F	OH	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	Cl	H	Cl	222–224	1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	Cl	Br	H	232–234	1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	Cl	OH	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	Cl	OH	Cl		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	Cl	OCH_3	H	252–253	1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	Cl	SH	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	Cl	SCH_3	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	Cl	NH_2	H	214–216.5	1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	Cl	NHCHO	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	Cl	$NHCOCH_3$	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	Br	OH	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	NO_2	Br	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	NO_2	NH_2	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	NO_2	$NHCH_3$	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	NO_2	NHC_2H_5	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	NO_2	$N(CH_3)_2$	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	NO_2	$N(C_2H_5)_2$	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	NO_2	$NHCOCH_3$	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	OH	OH	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	OH	Br	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	OCH_3	Cl	CH_3		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	OCH_3	Br	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	OCH_3	Br	OCH_3		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	OCH_3	NO_2	H	242–244	1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	OCH_3	NO_2	OCH_3	201–202.5	1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	OCH_3	OCH_3	H	201–202.5	1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	OCH_3	NH_2	H	226–228	1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	OCH_3	NH_2	OCH_3		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	OCH_3	$CONH_2$	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	OCH_3	$C(NH)NH_2$	H		1303

TABLE V-7. (continued)



R^3	R^5	R^6	R^7	R^8	R^9	m.p.(°C)	Refs.
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	$-O-CH_2-O$		H	225–227	1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	CN	NO_2	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	CN	NH_2	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	COOH	OH	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	COOH	NH_2	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	$COOCH_3$	OH	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	$COOCH_3$	NH_2	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	NH_2	Br	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	H	NH_2	NH_2	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	Br	H	Br	Br		1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	Br	CH_3	Br	CH_3	229–231	1303
$NHCH_2CH_2C(CH_3)_2OH$	CH_3	OH	Cl	OH	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	C_2H_5	H	Cl	OCH_3	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	C_3H_7	H	Cl	OCH_3	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	$C_6H_5CH_2$	H	Cl	NH_2	H		1303
$NHCH_2CH_2C(CH_3)_2OH$	$C_6H_5CH_2CH_2$	H	Cl	NH_2	H		1303
$NHCH_2CH_2C(CH_3)_2CH_2OH$	CH_3	H	H	CF_3	H	210–211	1290
$NHCH_2CH_2C(CH_3)_2CH_2OH$	CH_3	H	H	NO_2	H	259–261 (dec.)	1290
$NHCH_2CH_2C(CH_3)_2CH_2OH$	CH_3	H	H	F	H	223–224	1290
$NHCH_2CH_2C(CH_3)_2CH_2OH$	CH_3	H	H	Br	H	195–196	1290

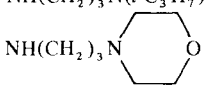
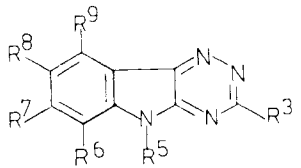
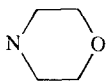
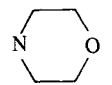
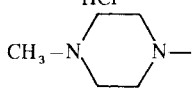
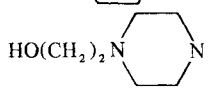
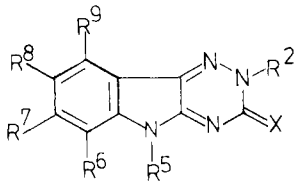
$NHCH_2CH_2C(CH_3)_2CH_2OH$	CH_3	H	H	OH	H	218–220	1290
$NHCH_2CH_2C(CH_3)_2CH_2OH$	CH_3	H	H	OC_4H_9	H	140–142	1290
$NHCH_2CH_2C(CH_3)_2CH_2OH$	CH_3	H	H	NH_2	H		1290
$NHCH_2\underset{\displaystyle OH}{\underset{\vert}{C}}HCH_2OH$	CH_3	H	H	H	H	194–195	1290, 1304
$NH\underset{\displaystyle CH_2OH}{\underset{\vert}{C}}HCH_2CH_3$	CH_3	H	H	H	H	176	1304
						176–176.5	1290
$NHCH_2\underset{\displaystyle C_6H_5}{\underset{\vert}{\overset{\displaystyle CH_3}{\overset{\vert}{C}}}}CH_2OH$	CH_3	H	H	H	H	186.5–188	1290
						187–188	1304
$NHCH_2CH_2COOH$	CH_3	H	H	H	H	247–250 (dec.)	1313
$NHCH_2CH_2COOCH_3$	CH_3	H	H	H	H	189–190	1313
$NHCH_2CH_2$-2-pyridyl	CH_3	H	H	H	H	214	1304
$NH(CH_2)_2NH(CH_2)_2OH$	CH_3	H	H	H	H	174–175	1304
$NH(CH_2)_2N(C_2H_5)_2$	CH_3	H	H	H	H	148	1289
$NH(CH_2)_3N(CH_3)_2$	CH_3	H	H	H	H	154	1304/1557
$NH(CH_2)_3N(C_2H_5)_2$	CH_3	H	H	H	H	128	1289
$NH(CH_2)_3N(i\text{-}C_3H_7)_2$	CH_3	H	H	H	H	132	1289
	CH_3	H	H	H	H	183–184	1304
4-HO–C_6H_4–NH	CH_3	H	H	H	H	184–185	1304
$NHCOCH_3$	H	H	H	H	H	200	1227
$NHCOCH_3$	CH_3CO	H	H	H	H	283	1288
$N(CH_3)_2$	H	H	H	H	H	342–343	1289
·HCl						256	1289
$N(CH_3)_2$	CH_3	H	H	H	H	170	1289
						170–173	1304
$N(CH_3)_2$	CH_3	H	H	Cl	H	217–218	1289
$N(CH_3)(CH_2)_3OH$	CH_3	H	Cl	NH_2	H		1303

TABLE V-7. (continued)

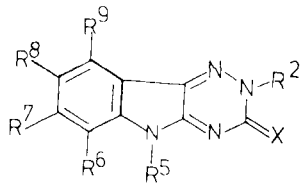


R^3	R^5	R^6	R^7	R^8	R^9	m.p.(°C)	Refs.
	CH_3	H	H	H	H	180	1289
·HCl						222	1289
	CH_3	H	H	H	H	169–170	1289, 1304 1557
·HCl						234	1289
	CH_3	H	H	H	H	174–175	1304
	CH_3	H	H	H	H	156–157	1304
$NCH_2CH_2CH_2OCOCH_3$ $COCH_3$	CH_3	H	H	H	H	83.5–85.5	1312
$NHNH_2$	H	H	H	H	H	270–272	1314
$NHNH_2$	CH_3	H	H	H	H	212–214	1304
						221–223	1289
$NHNHCSNH_2$	H	H	H	H	H	>320	1314



R^2	X	R^5	R^6	R^7	R^8	R^9	m.p. (°C)	Refs.
H	O	H	H	H	H	H	>320	1299
							>360	1300, 1271
H	O	H	H	H	H	CH_3	370	1295
H	O	CH_3	H	H	H	H	340	1294, 1300
								1296
							345	1289, 1290
	Na salt							1298
	Ag salt							1289
H	O	H	H	H	Br	Cl	>325	1303
H	O	CH_3	H	CH_3	Br	CH_3	304–310	1303
H	O	CH_3	H	Cl	H	Cl	343–347 (dec.)	1303
H	O	CH_3	H	Cl	Br	H	>335	1303
H	O	CH_3	H	OCH_3	H	H	316–318	1303
H	O	CH_3	H	OCH_3	Br	H		1303
H	O	CH_3	H	$O-CH_2-O$		H	329–338	1303
H	O	CH_3	Br	CH_3	Br	CH_3	300–305	1303
CH_3	O	H	H	H	H	H	327	1295, 1298,
								1300
CH_3	O	CH_3	H	H	H	H	255	1298, 1299,
								1300
							269–270	1297

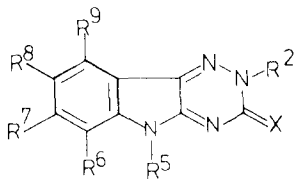
TABLE V-7. (continued)



R^2	X	R^5	R^6	R^7	R^8	R^9	m.p. (°C)	Refs.
H	S	H	H	H	H	H	>300	1304
							>350	1271, 1302
							>360	758, 1289
							>380	574
H	S	H	H	H	H	CH_3	370	1295
H	S	H	H	H	H	Cl	>335	1303
H	S	H	H	H	CH_3	H	350	1290
H	S	H	H	H	NO_2	H	>350	1289
H	S	H	H	H	OCH_3	H	331	1289
H	S	H	H	Cl	H	H	>335	1303
H	S	H	H	Cl	OCH_3	H	300–305 (dec.)	1303
H	S	H	H	OCH_3	H	H	309	1289, 1303
H	S	CH_3	H	H	H	H	275	1302
							279–281	1289, 1304
							291–292 (dec.)	758/1557
H	S	CH_3	H	H	H	CH_3	310–314 (dec.)	1303
							322	1295
H	S	CH_3	H	H	CH_3	H	299–301	1290
H	S	CH_3	H	H	CH_3	CH_3	316–318 (dec.)	1303
H	S	CH_3	H	H	CF_3	H	274	1290
H	S	CH_3	H	H	C_4H_9	H	242–244 (dec.)	1290

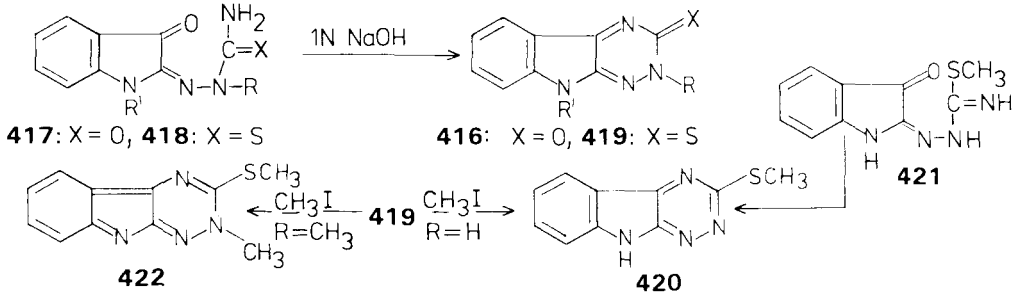
H	S	CH_3	H	H	NO_2	H	283	1289
							283–284	1304
H	S	CH_3	H	H	F	H	308–310 (dec.)	1290
H	S	CH_3	H	H	Cl	H	297	1304
							315–316	1289
H	S	CH_3	H	H	Br	H	289–291	1290
							>350	1289
H	S	CH_3	H	H	Br	Cl	320–325	1303
H	S	CH_3	H	H	OH	H	312–314	1290
H	S	CH_3	H	H	OCH_3	H	310–314	1290
H	S	CH_3	H	H	OCH_3	Br		1303
H	S	CH_3	H	H	OC_4H_9	H	251.5–253.5	1290
H	S	CH_3	H	CH_3	H	H	305–307	1303
H	S	CH_3	H	CH_3	H	CH_3		1303
H	S	CH_3	H	CH_3	CH_3	H	321–322	1303
H	S	CH_3	H	CH_3	Br	CH_3	>320	1303
H	S	CH_3	H	CF_3	H	H		1303
H	S	CH_3	H	Cl	H	Cl	296–300	1303
H	S	CH_3	H	Cl	Br	H	291–293	1303
H	S	CH_3	H	Cl	SH	H		1303
H	S	CH_3	H	Cl	SCH_3	H		1303
H	S	CH_3	H	Br	H	H		1303
H	S	CH_3	H	Br	OCH_3	H		1303
H	S	CH_3	H	OH	OH	H		1303
H	S	CH_3	H	OCH_3	H	H	282–284	1303
H	S	CH_3	H	OCH_3	Cl	OCH_3		1303
H	S	CH_3	H	OCH_3	Br	H		1303
H	S	CH_3	H	OCH_3	OCH_3	H	279–280	1303
H	S	CH_3	H	OCH_3	CN	H		1303
H	S	CH_3	H	OCH_3	$CONH_2$	H		1303
H	S	CH_3	H	$-O-CH_2-O-$		H		1303
H	S	CH_3	Br	CH_3	Br	CH_3	270–275	1303
H	S	C_2H_5	H	H	H	H	294	1289, 1304

TABLE V-7. (continued)



R^2	X	R^5	R^6	R^7	R^8	R^9		m.p. (°C)	Refs.
H	S	C_3H_7	H	H	H	H		278	1289, 1304
H	S	C_3H_7	H	H	Cl	H		270–275	1289, 1304
H	S	$C_6H_5CH_2$	H	H	H	H		269–271	1304
H	S	$C_6H_5CH_2CH_2$	H	H	H	H		245–246	1304
CH_3	S	H	H	H	H	H		>350	1301
CH_3	S	CH_3	H	H	H	H		259	1271
								260	1301
CH_3CO	S	CH_3	H	H	H	H		191–192	758
CH_3	NH	H	H	H	H	H			1308
CH_3	NH	CH_3	H	H	H	H	$\cdot CH_3I$	302	1308
CH_3	$N-NH_2$	H	H	H	H	H		198	1314

semicarbazone **421** (1316). Methylation of **419b** (R = CH_3) led to the isolation of **422** (1316).



Cyclization of the unsubstituted α-thiocarbohydrazone (**423**) affords 4-amino-1,2,4-triazino[6,5-*e*]indole-3-thione (**424**) (m.p. 200°C), which is converted to **419a** when heated in the presence of a base (1317). Oxidation of **419a** with iodine yields the disulfide **425** (1217). When **416a** (R = H) was treated with phosphoryl chloride 3-chloro-1,2,4-triazino[6,5-*b*]indole (**426**) was obtained (1319), which has been used for the synthesis of 3-amino- (**427**) and 3-hydrazino-1,2,4-triazino[6,5-*e*]indoles (**428**) (1319). When **419a** is treated with hydrazines, the sulfur is replaced by a hydrazino group (1308, 1318). Acetylation of **419a** with acetic anhydride yields the 2,9-diacetyl derivative

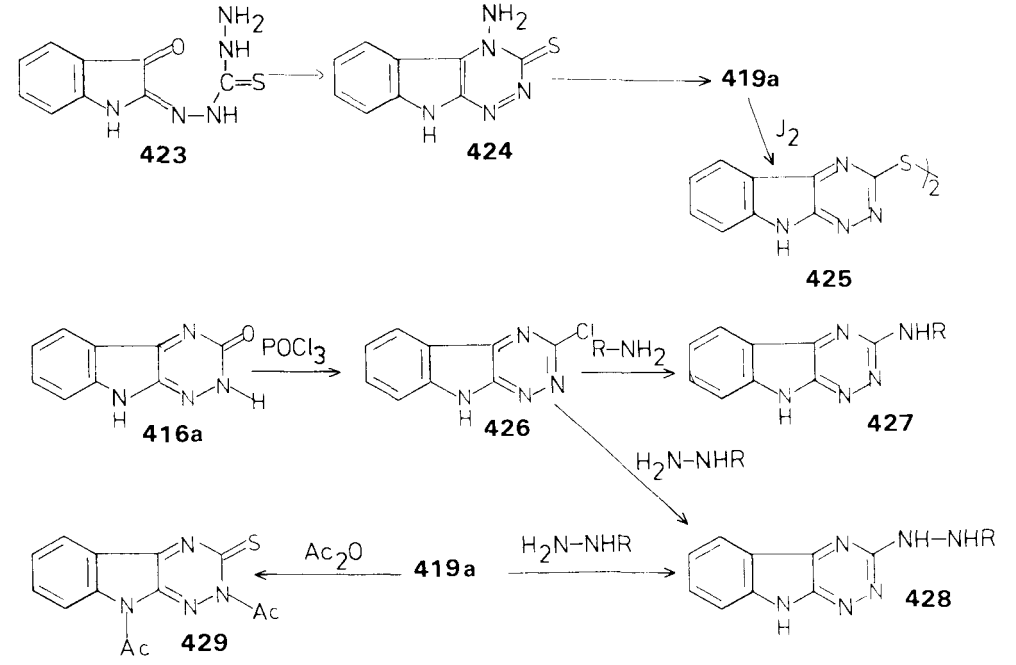
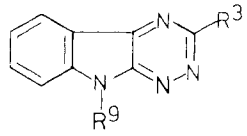
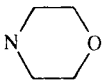
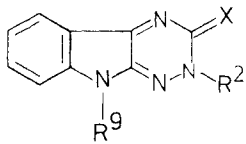


TABLE V-8. 1,2,4-TRIAZINO[6,5-*b*]INDOLES



R^3	R^9	m.p. (°C)	Refs.
Cl	H	294–296	1319
S–)$_2$	H	288	1317
SCH_3	H	207	1316
		213–214	1318
SCH_3	CH_3	193.5	1316
$HOCH_2CH_2NH$	H	234–235	1319
C_6H_5–NH	H	272–273	1319
3-CH_3O–C_6H_4–NH	H	260–261	1319
	H	210–211	1319
	H	290–292	1319
$NHNH_2$	H	244	1308
		253–254	1318, 1319
C_6H_5–NHNH	H	256–257	1319
C_6H_5–CH=N–NH	H	>330	1318
·HCl		>330	1318
4-O_2N–C_6H_4–CH=N–NH		>330	1318
C_6H_5–NHCSNHNH	H	>330	1318
4-Br–C_6H_4–NHCSNHNH	H	>330	1318
3-O_2N–C_6H_4–NHCSNHNH	H	>330	1318



R^2	X	R^9	m.p. (°C)	Refs.
H	O	H	320	1315, 1319
H	S	H	330	1315, 1317, 1318
H	S	CH_3	311	1316
CH_3	O	H	321	1316
CH_3	S	H	283.5	1316
CH_3	S	CH_3	245.5	1316
CH_3CO	S	CH_3CO	290–292	1318

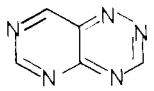
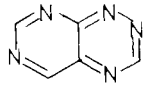
429 (1318). The hydrazino group in **428** reacts with aldehydes and isothiocyanates (1318).

By comparison of the electronic spectra of **419** and **420** it was shown that the predominant tautomeric form is the given thione structure **419** (1316). The electronic spectra of **428** is also reported (1308). All 1,2,4-triazino[6,5-*b*]indoles are colored crystalline compounds of high melting points.

Table V-8 lists the 1,2,4-triazino[6,5-*b*]indoles reported in the literature.

XI. CONDENSED WITH THE PYRIMIDINE RING

Two-ring systems of this type are possible, the pyrimido[4,5-*e*]1,2,4-triazines (**430**) and the pyrimido[5,4-*e*]1,2,4-triazines (**431**). Derivatives of both classes are well known and the chemistry of these compounds has been intensively studied, since a number of naturally occuring antibiotics are derivatives of **431** and biochemical activities were observed for derivatives of both **430** and **431**.

430   **431**

In many cases, the pyrimidine ring of the known derivatives of **430** and **431** is not fully aromatic but has hetero substituents in the 6- and/or 8-positions which are bound to the pyrimidine ring by a double bond.

A review on the synthesis, reactions, and biochemical activities of pyrimido-1,2,4-triazines (**430**, **431**) is published by Yoneda (1330). Calculations on these systems were reported by Wait and Wesley (1150).

A. Pyrimido[4,5-*e*]1,2,4-triazines

1. *3-H, 3-Aryl-, and 3-Heteroaryl-substituted Pyrimido[4,5-e]1,2,4-triazines*

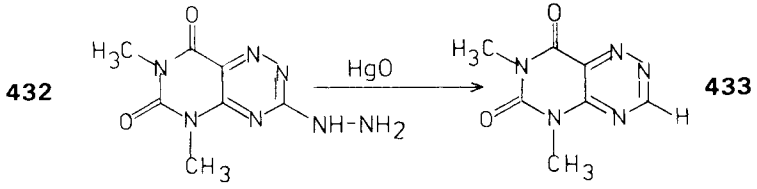
a. PREPARATION. Three principles were used for the synthesis of pyrimido-[4,5-*e*]1,2,4-triazines with a proton, an aryl, or a heteroaryl substituent in the 3-position (881, 882, 1322–1325):

1. Starting with 1,2,4-triazine derivatives and synthesis of the pyrimidine ring (881, 882).

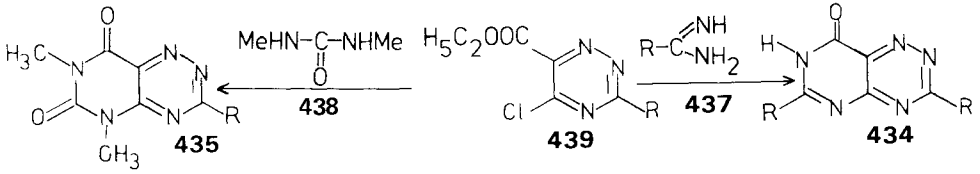
2. Starting with pyrimidine derivatives and construction of the 1,2,4-triazine ring (1323–1325).

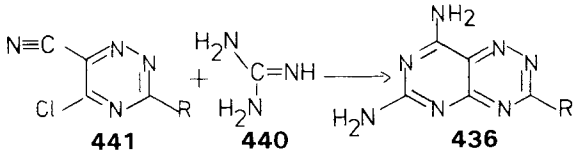
3. Transformation of other pyrimido[4,5-*e*] 1,2,4-triazines into the desired derivatives.

Oxidation of 3-hydrazino-5,7-dimethylpyrimido[4,5-*e*] 1,2,4-triazine-6,8-dione (**432**) with mercuric oxide was used for the synthesis of 5,7-dimethylpyrimido[4,5-*e*] 1,2,4-triazine-6,8-dione (**433**) (1322).

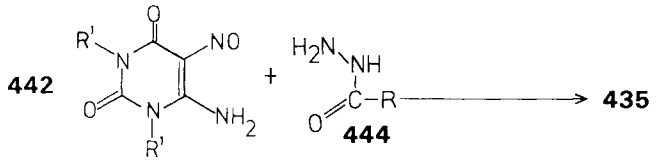


When the synthesis of **434** to **436** is begun from 1,2,4-triazine derivatives, (1) amidines (**437**) or ureas (**438**) are reacted with 3-substituted 5-chloro-1,2,4-triazine-6-carboxylates (**439**) (881), or (2) guanidine (**440**) is reacted with 3-substituted 5-chloro-1,2,4-triazine-6-carbonitril (**441**) (882).

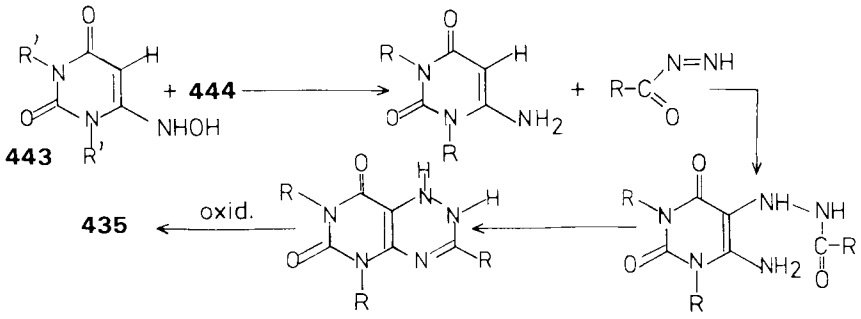




Either 5-nitroso-6-amino- (**442**) or 6-(hydroxylamino)-pyrimidine-2,4-diones (**443**) were used as pyrimidine precursors for the synthesis of **435**, by means of a reaction with hydrazides (**444**) (1323–1325).



The following mechanism is suggested for the reaction of **443** with **444** (1323).

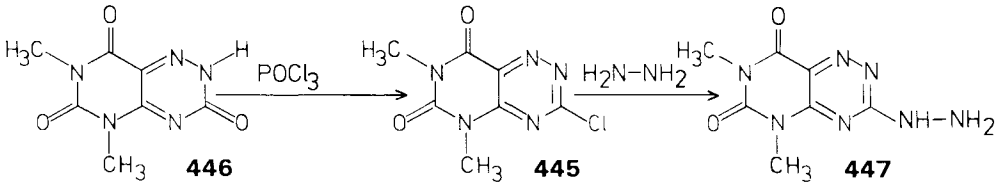


b. COMPOUND SURVEY. Known compounds of this group are listed in Table V-9.

c. PHYSICAL PROPERTIES. The isolated compounds are yellow, crystalline substances with high melting points. A few spectroscopic data (ultraviolet, infrared, PMR) were reported by Korte and his group (881), while Yoneda and co-workers (325) studied the mass spectrometric fragmentation of these compounds.

2. *3-Chloropyrimido[4,5-e]1,2,4-triazines*

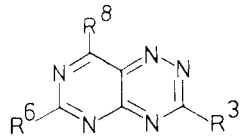
So far only 3-chloro-5,7-dimethylpyrimido[4,5-*e*]1,2,4-triazine-6,8-dione (**445**) (m.p. 250.5°C (1322), 251 to 253°C (920)) has been synthesized, through the reaction of 5,7-dimethylpyrimido[4,5-*e*]1,2,4-triazine-3,6,8-trione (**446**) with phosphoryl chloride (920, 1322). When **445** is treated with hydrazine the chlorine is replaced by a hydrazino group.



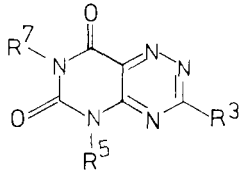
3. *Pyrimido[4,5-e]1,2,4-triazin-3-ones*

The same principles as discussed in Section XI-A-1 were used for the synthesis of the known derivatives of pyrimido[4,5-*e*]1,2,4-triazin-3-ones:

TABLE V-9. PYRIMIDO[4,5-*e*]1,2,4-TRIAZINES



R^3	R^6	R^8	m.p. (°C)	Refs.
C_6H_5	CH_3	OH	304–306 (tautomer)	881
C_6H_5	C_6H_5	OH	346–347 (tautomer)	881
C_6H_5	NH_2	NH_2	>300	882
4-CH_3–C_6H_4	NH_2	NH_2	>300	882
4-Cl–C_6H_4	NH_2	NH_2	>300	882
2-Pyridyl	NH_2	NH_2	>300	882



R^3	R^5	R^7	m.p. (°C)	Refs.
H	H	H	199–200	1325
H	CH_3	CH_3	212.4	1322
C_6H_5	H	H		1325
C_6H_5	CH_3	CH_3	137–139	1323
			241	881, 1324
2-HO–C_6H_4	CH_3	CH_3	292	1323
4-H_2N–C_6H_4	CH_3	CH_3	>300	1323
2-Furyl	CH_3	CH_3	275–276	1323, 1325
2-Thienyl	CH_3	CH_3	249–250	1323, 1325
3-Pyridyl	CH_3	CH_3	245	1323, 1325
4-Pyridyl	CH_3	CH_3	292–294	1323, 1325

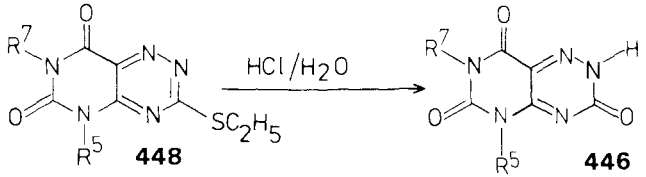
1. Transformation of pyrimido[4,5-*e*]1,2,4-triazines, with various substituents in the 3-position, into pyrimido[4,5-*e*]1,2,4-triazin-3-ones (716, 910, 920).

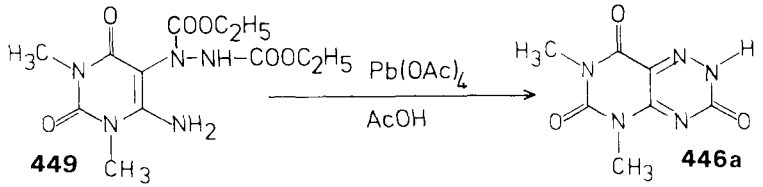
2. Using derivatives of 1,2,4-triazin-3-one (911) or pyrimidine (1322) as starting materials

Acid hydrolysis of 3-(ethylmercapto)pyrimido[4,5-*e*]1,2,4-triazine-5,7-diones (**448**) is used by Heinisch and his group (716, 910, 920) for the synthesis of the pyrimido[4,5-*e*]1,2,4-triazine-3,6,8-triones (**446**).

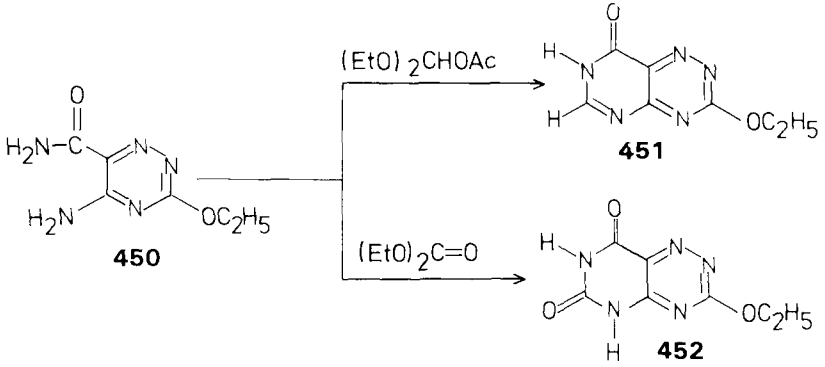
Treatment of the pyrimidine derivative (**449**) with lead tetraacetate in glacial

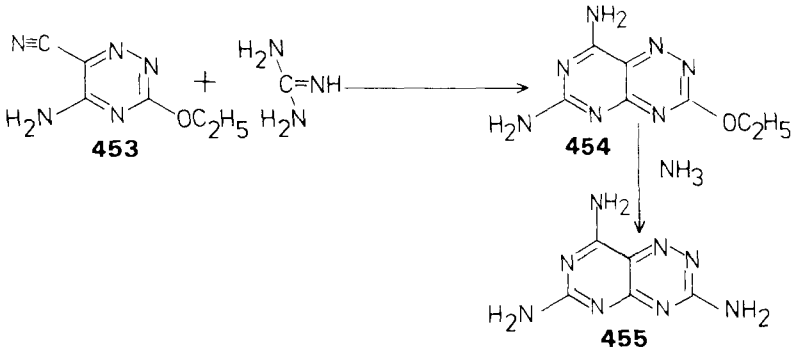
acetic acid at 50 to 55°C for 1 hr gave 5,7-dimethylpyrimido[4,5-*e*] 1,2,4-triazine-3,6,8-trione (**446a**) on cooling (1322).





The reaction of 5-amino-3-ethoxy-1,2,4-triazine-6-carboxamide (**450**) with diethoxymethyl acetate or diethyl carbonate is reported, by Taylor and Martin (911), to yield 3-ethoxypyrimido[4,5-*e*] 1,2,4-triazin-8-one (**451**) (m.p. 204 to 205°C) or the 6,8-dione (**452**) (m.p. 247 to 248°C).

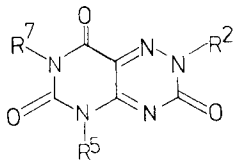




Condensation of 5-amino-6-cyano-3-ethoxy-1,2,4-triazine (**453**) with guanidine affords 6,8-diamino-3-ethoxypyrimido[4,5-*e*] 1,2,4-triazine (**454**) (m.p. 300°C), which is converted to the 3,6,8-triamino compound **455** on treatment with ethanolic ammonia (911).

Table V-10 lists the triones reported in the literature.

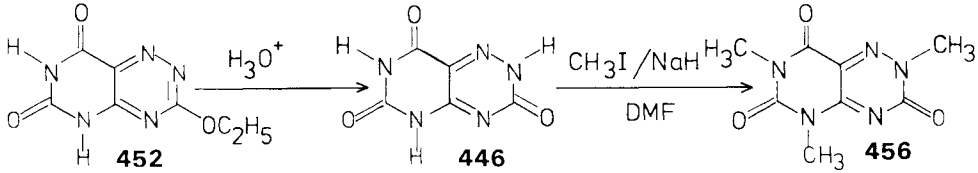
TABLE V-10. PYRIMIDO[4,5-*e*] 1,2,4-TRIAZINE-3,6,8-TRIONES



R^2	R^5	R^7	m.p. (°C)	Refs.
H	H	H	300	911
			360	920
H	H	CH_3	315–317 (dec.)	920
H	CH_3	H	343–345	716
			344–346 (dec.)	910
H	CH_3	CH_3	281.7 (dec.)	1322
			284–285 (dec.)	920
H	CH_3	C_6H_5–CH_2	232–234	910
H	C_6H_5–CH_2	CH_3	272–273	910
CH_3	CH_3	CH_3	184–185	911

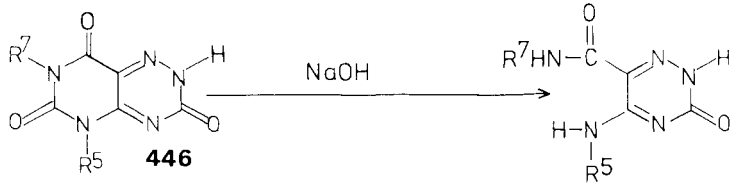
The isolated derivatives of pyrimido[4,5-*e*] 1,2,4-triazin-3-one are colorless, crystalline compounds. Their half-wave potentials were measured to be in the range from -580 to -630 mV (716). The first p*K* value is found at 5.6 to 5.88 (N_2–H), the second at 8.4 (N_5–H), and the third at 9.5 (N_7–H) (716, 910).

Hydrolysis of 3-ethoxypyrimido[4,5-*e*] 1,2,4-triazine-6,8-dione (**452**) affords **446** ($R^5 = R^7 = H$) which is methylated with methyl iodide and sodium hydride in DMF yielding 2,5,7-trimethylpyrimido[4,5-*e*] 1,2,4-triazine-3,6,8-trione (**456**) (911).



When pyrimido[4,5-*e*] 1,2,4-triazine-3,6,8-trione (**446**) ($R^5 = R^7 = CH_3$) was treated with phosphoryl chloride, the 3-chloro derivative (**445**) was isolated

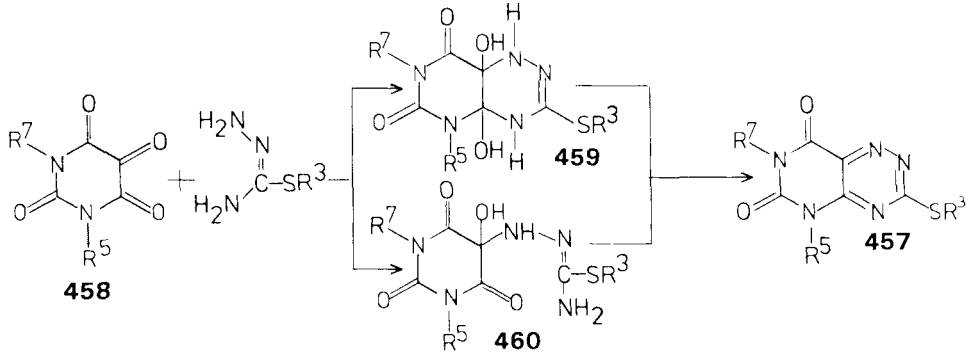
(920, 1322). If **446** are treated with sodium hydroxide solution, opening of the pyrimidine ring is observed (716, 910, 920).



446

4. *Pyrimido[4,5-e]1,2,4-triazine-3-thiones*

The 3-(alkylmercapto)pyrimido[4,5-*e*] 1,2,4-triazine-6,8-diones (**457**) were prepared by the reaction of *S*-alkylisothiosemicarbazides with alloxans (**458**) (920). In some cases an addition product of the two reagents is isolated, the structure of which is formulated as **459** or **460**. All attempts to cyclize alloxan thiosemicarbazone were unsuccessful. In all cases monocyclic 1,2,4-triazines were obtained (920).

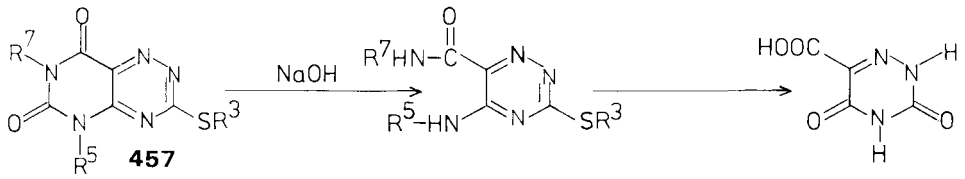


458 **459** **460** **457**

The isolated **457** were colorless to yellow, crystalline compounds, which have three absorption maxima in the electronic spectra. The following spectrum is reported for **457a** ($R^3 = C_2H_5$, $R^5 = R^7 = H$): 231, 269, and 380 nm (22.900, 12.800, 17.200) (920). Two p*K*a values were measured for **457**: 6.63 to 6.83 for N_5–H and 8.45 for N_7–H.

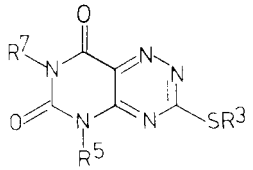
Treatment of **457** with hydrochloric acid affords pyrimido[4,5-*e*] 1,2,4-triazine-3,6,8-triones (**446**), and reaction with amines yields 3-amino derivatives (716, 910, 920). N–H Groups in the pyrimidine ring can be alkylated (910). Treatment of **457** with sodium hydroxide solution leads to monocyclic 1,2,4-triazines through ring opening of the pyrimidine ring (910, 920).

Table V-11 lists the compounds of type **457** that have been reported in the literature.



457

TABLE V-11. 3-(ALKYLMERCAPTO)PYRIMIDO[4,5-*e*]1,2,4-TRIAZINE-6,8-DIONES



R^3	R^5	R^7	m.p. (°C)	Refs.
CH_3	H	H	340–342 (dec.)	920
CH_3	CH_3	CH_3	215	920
C_2H_5	H	H	296–297	920
C_2H_5	H	CH_3	247–248	920
C_2H_5	H	C_6H_5–CH_2	244–246	910
C_2H_5	CH_3	H	215	920
			215–216	910
C_2H_5	CH_3	CH_3	146–147	920
C_2H_5	CH_3	C_6H_5–CH_2	165–167	910
C_2H_5	C_6H_5–CH_2	CH_3	167–168	910
C_2H_5	C_6H_5–CH_2	C_6H_5–CH_2		910

5. *3-Aminopyrimido[4,5-e]1,2,4-triazines*

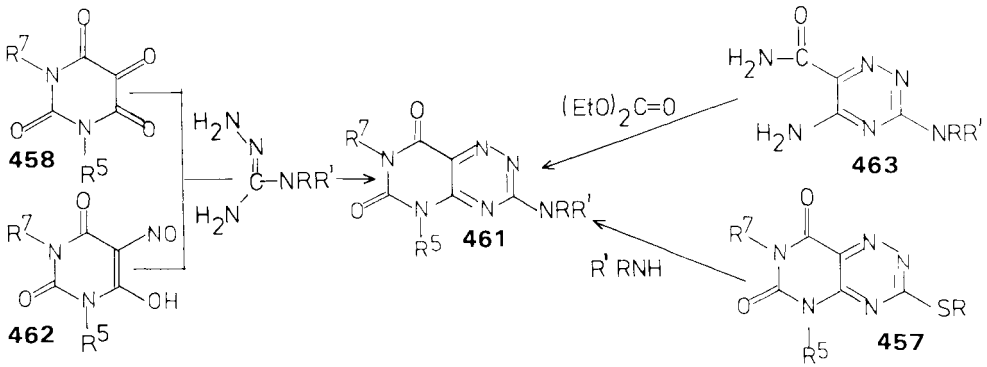
The 3-aminopyrimido[4,5-*e*]1,2,4-triazine-6,8-diones (**461**) were prepared by the following methods:

1. Reaction of alloxans (**458**) (910, 912, 913, 1327) or 6-hydroxy-5-nitroso-pyrimidine-2,4-diones (**462**) (1328) with aminoguanidines.

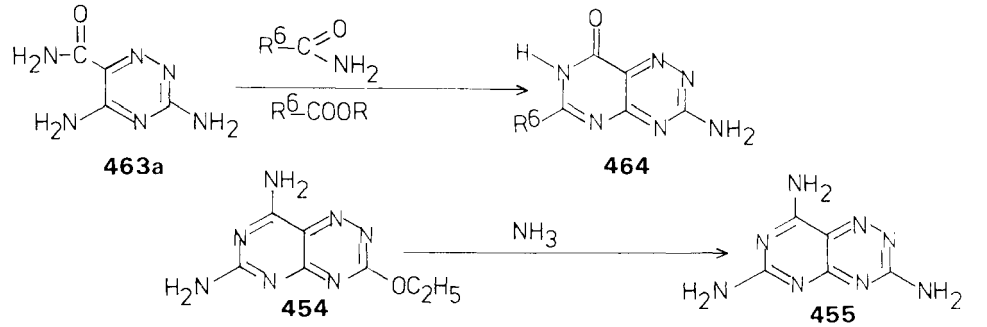
2. Cyclization of 3,5-diamino-1,2,4-triazine-6-carboxamides (**463**) with diethyl carbonate (912, 913).

3. Nucleophilic substitution of the 3-alkylmercapto group in pyrimido[4,5-*e*]-1,2,4-triazine-6,8-diones (**457**) by amines (716, 910, 920).

Reaction of **463a** with amides or carboxylates yields 3-aminopyrimido[4,5-*e*]-1,2,4-triazin-8-ones (**464**) (912, 913) (m.p.: $R^6 = H$, $R^6 = CH_3 > 350°C$).



Ethanolic ammonia converts 6,8-diamino-3-ethoxypyrimido[4,5-*e*]-1,2,4-triazine (**454**) to 3,6,8-triaminopyrimido[4,5-*e*] 1,2,4-triazine (**455**) (911) (m.p. > 300°C).



The 3-aminopyrimido[4,5-*e*] 1,2,4-triazine-6,8-diones (**461**) (Table V-12) are mainly colorless compounds with high melting points. The electronic spectra of a number of compounds have been reported (911, 912, 920, 1327, 1328). The electronic spectrum of 3-aminopyrimido[4,5-*e*] 1,2,4-triazine-6,8-dione shows three absorption maxima (912, 1327, 1328) and the following absorptivities were reported (912): 215 (32.600), 244 (13.600), and 329 (8.300). The pK_a value of the same compound is reported to be 7.08 (1328).

The N–H groups in the pyrimidine ring of **461** can be alkylated (910, 1326). Treatment of **461** with aqueous sodium hydroxide gives monocyclic 1,2,4-triazines (716).

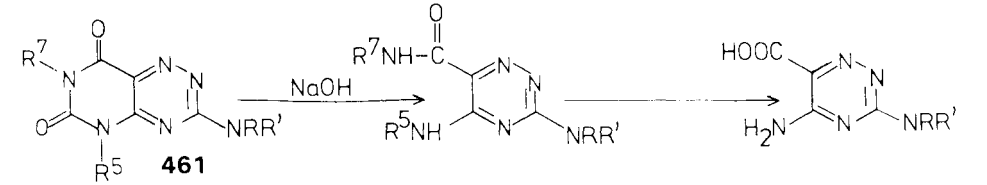
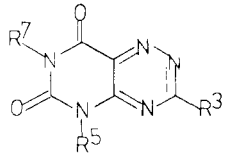
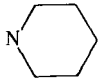
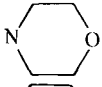
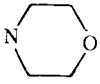


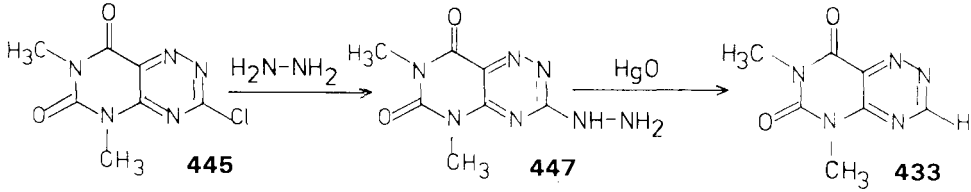
TABLE V-12. 3-AMINOPYRIMIDO[4,5-*e*]1,2,4-TRIAZINE-6,8-DIONES



R^3	R^5	R^7	m.p. (°C)	Refs.
NH_2	H	H	>300	1328
			>350	910, 912, 1327
			>360	913, 920
NH_2	H	CH_3	>400	910
NH_2	CH_3	H	>400	910
NH_2	CH_3	CH_3	363–365 (dec.)	910
CH_3NH	H	H	>300	1328
			>350	920
CH_3NH	CH_3	CH_3	290–291	1328
C_2H_5NH	H	H	>300	1328
			>350	910
C_2H_5NH	CH_3	CH_3	267–267.5	1328
n-C_3H_7NH	H	H	311–313	920
n-C_3H_7NH	CH_3	CH_3	214–215	910
n-C_4H_9NH	H	H	290–292	920
n-C_4H_9NH	H	CH_3	324–326	910
n-C_4H_9NH	CH_3	H	283–285	1326
			284–285	910
·½H_2O			209–211 (dec.)	716
n-C_4H_9NH	CH_3	CH_3	197–199	910
n-C_4H_9NH	CH_3	$C_6H_5CH_2$	225–227	910
$C_6H_5CH_2NH$	H	H	317–319	920
			319–321	910
$C_6H_5CH_2NH$	H	CH_3	322–323	910
$C_6H_5CH_2NH$	CH_3	H	286–288	910, 1326
C_6H_5NH	H	H ·CH_3COOH	>350	920
·Pyridine			357–359	920
	H	H	314–315	920
	CH_3	H	242–243	716
	H	H	264–265	716
	CH_3	H	>350	716

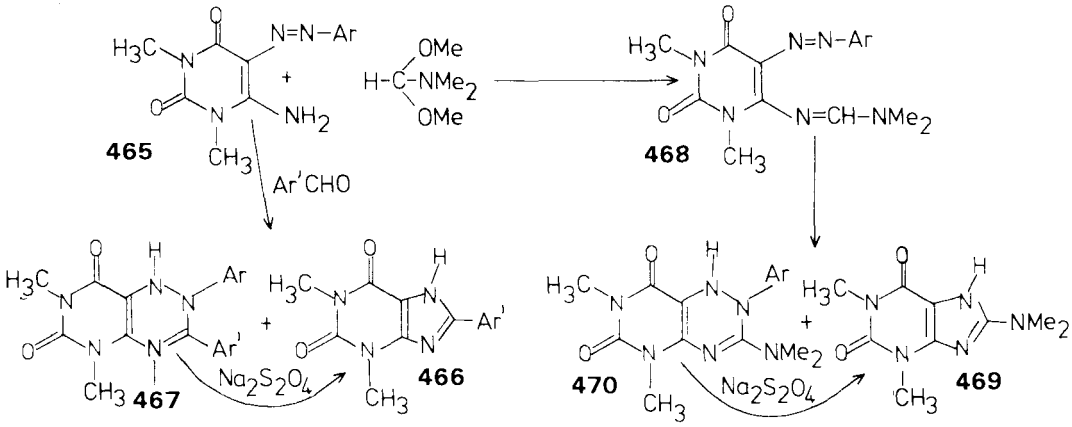
6. *3-Hydrazinopyrimido[4,5-e]1,2,4-triazines*

3-Chloro-5,7-dimethylpyrimido[4,5-*e*]1,2,4-triazine-6,8-dione (**445**) is converted to 3-hydrazino-5,7-dimethylpyrimido[4,5-*e*]1,2,4-triazine-6,8-dione (**447**) (m.p. 247.2°C) by reaction with hydrazine (1322). Oxidation of **447** with mercuric oxide was used for the synthesis of 5,7-dimethylpyrimido-[4,5-*e*]1,2,4-triazine-6,8-dione (**433**) (1322).



7. *1,2-Dihydropyrimido[4,5-e]1,2,4-triazines*

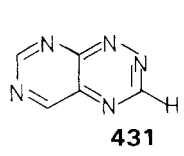
Heating of 4-amino-1,3-dimethyl-5-arylazouracils (**465**) with arylaldehydes at 220°C for 3 hr, followed by cooling, caused the imidazo[4,5-*e*]pyrimidine derivatives (**466**) to separate. The dihydropyrimido[4,5-*e*]1,2,4-triazine-6,8-diones (**467**) (Ar = Ar′ = C_6H_5, m.p. 248°C; Ar = C_6H_5, Ar′ = 4-Cl-C_6H_5, 250°C) were isolated from the filtrate (1329). Treatment of **465** with dimethylformamide dimethylacetal gave **468** which were transformed to **469** and 3-dimethylamino-1,2-dihydropyrimido[4,5-*e*]1,2,4-triazine-6,8-diones (**470**) (Ar = C_6H_5, m.p. 251°C; Ar = CH_3-C_6H_4, 197°C), when heated at 210 to 220°C for 15 min with exclusion of moisture (1329). Treatment of **467** or **470** with sodium dithionite led to the isolation of **466** or **469**.



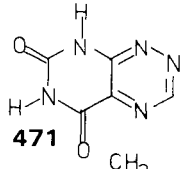
B. Pyrimido[5,4-*e*] 1,2,4-triazines

1. *Introduction*

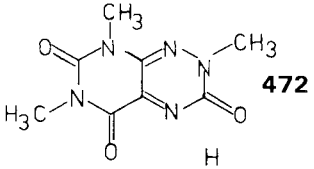
The chemistry of the pyrimido[5,4-*e*] 1,2,4-triazines (**431**) has been intensively studied, since the *N*-methyl derivatives of pyrimido[5,4-*e*] 1,2,4-triazine-5,7-dione (**471**) are the natural occurring antibiotics fervenulin (planomycin) (**471a**), toxoflavin (xanthothricin) (**471b**), and reumycin (**471c**), and the antibiotic MSD-92 (**472**) is 2,6,8-trimethylpyrimido[5,4-*e*] 1,2,4-triazine-3,5,7-trione. A review of the literature on pyrimido[5,4-*e*] 1,2,4-triazines until 1969 is given by Yoneda (1330).



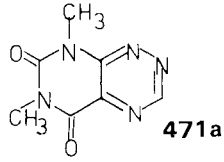
431



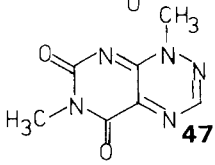
471



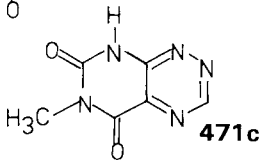
472



471a



471b



471c

The name toxoflavin was given to a highly toxic substance, which was found by Mertens and van Veen (1331) to have caused numerous mass fatal food poisonings in the province of Banjumas in central Java. It occurs periodically in "bongkret" – a popular and otherwise harmless native coconut product prepared by the action of certain fungi. The presence of toxoflavin has been shown to be due to contamination of the bacterium *Pseudomonas cocovenenans*. After various efforts to elucidate the structure of toxoflavin (1332) it was identified as 1,6-dimethylpyrimido[5,4-*e*] 1,2,4-triazine-5,7-dione (**471b**) (1333), which was found to be identical with xanthothricin (1334). Fervenulin is produced by *Streptomyces fervens* and its structure was found to be 6,8-dimethylpyrimido-[5,4-*e*] 1,2,4-triazine-5,7-dione (**471a**) (1335) which is identical with planomycin. Reumycin was isolated from a bacterial strain *Actomyces* (1336) and was identified as 6-methylpyrimido[5,4-*e*] 1,2,4-triazine-5,7-dione (**471c**). MDS-92 was isolated from an unidentified actinomycete and found to be 2,6,8-trimethylpyrimido[5,4-*e*] 1,2,4-triazine-3,5,7-trione (**472**) (1337).

2. *3-H-, 3-Alkyl-, 3-Aryl-, and 3-Heteroaryl-substituted Pyrimido-[5,4-e]1,2,4-triazines*

a. PREPARATION. Three general principles have been used for the

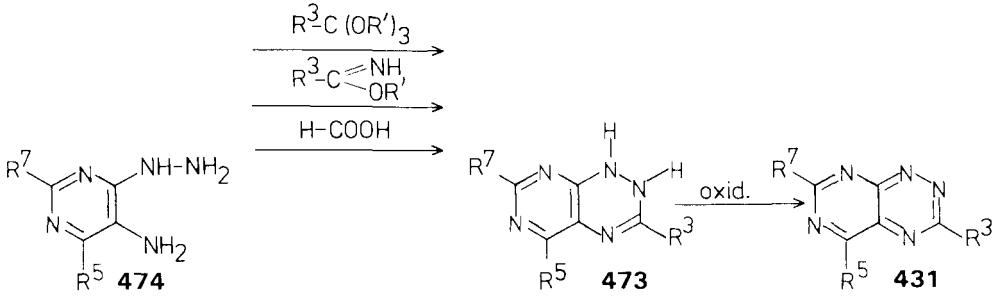
synthesis of pyrimido[5,4-*e*] 1,2,4-triazines:

1. Using pyrimidine precursors and construction of the 1,2,4-triazine ring.
2. Starting from 1,2,4-triazine derivatives and synthesis of the pyrimidine ring.
3. Rearrangement of pyrimido[5,4-*e*] 1,2,4-triazine-5,7(1*H*,6*H*)-diones to pyrimido[5,4-*e*] 1,2,4-triazine-5,7(6*H*,8*H*)-diones (1359, 1369–1371).

Most synthetic methods for pyrimido[5,4-*e*] 1,2,4-triazines which start with pyrimidine precursors can be generalized as follows:

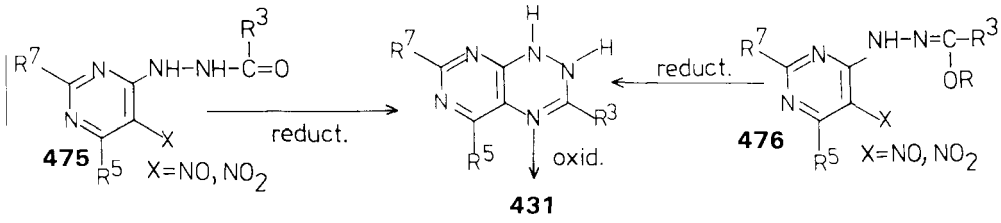
A 5-amino-4-hydrazinipyrimidine derivative is synthesized, which is then cyclized by a reaction with a carboxylic acid derivative, leading to 1,2-dihydropyrimido[5,4-*e*] 1,2,4-triazines (**473**), which are easily oxidized to pyrimido[5,4-*e*] 1,2,4-triazines by air (885, 1339, 1341, 1342, 1344, 1347, 1351, 1352, 1355), silver oxide (909, 1338, 1340, 1350, 1357, 1361), manganese dioxide (1352), mercuric oxide (1368), azodicarboxylate (1348), or chlorobenzotriazole (1355, 1356).

5-Amino-4-hydrazinopyrimidines (**474**) were cyclized (1) with orthocarboxylates at room temperature in the presence of a catalytic amount of hydrochloric acid (885–887, 1338, 1339, 1348, 1350, 1352, 1355, 1356, 1365, 1366, 1383), (2) with imidates (1349, 1351, 1352), (3) with formic acid (1380, 1384).



474 **473** **431**

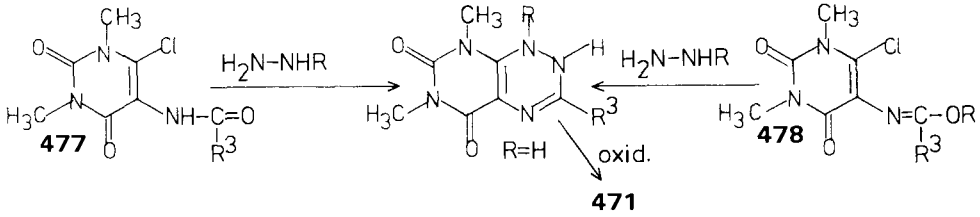
In addition to the 5-amino-4-hydrazinopyrimidines (**474**), 5-nitroso- or 5-nitro-4-(2-acylhydrazino)pyrimidines (**475**) (883, 1338, 1340–1344, 1354, 1355, 1367) or 5-nitroso or 5-nitro-4-(2-alkoxymethylenhydrazono)pyrimidines (**476**) (909, 1338, 1357, 1361, 1362, 1368) were used for the



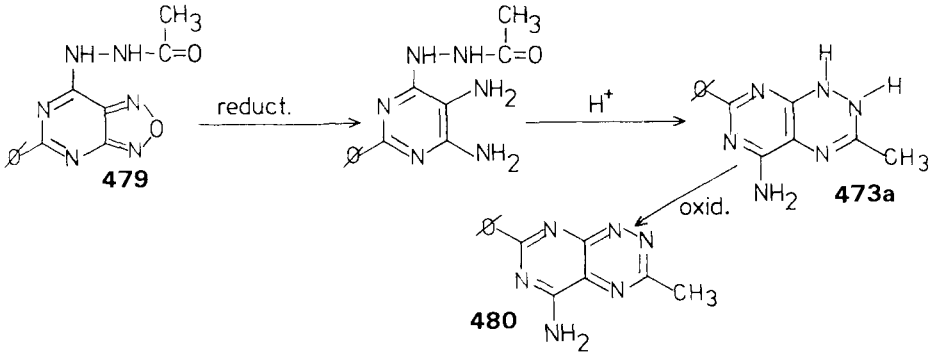
475 **476** **431**

synthesis of pyrimido[5,4-*e*] 1,2,4-triazines. In most cases the cyclization is achieved together with the reduction of the nitroso or nitro group.

The reaction of 5-(acylamino)-4-chloropyrimidines (**477**) (1343, 1382, 1385) or 5-(alkoxymethylenamino)-4-chloropyrimidines (**478**) (886, 1347, 1383) with hydrazines has also been used for the synthesis of pyrimido[5,4-*e*] 1,2,4-triazines.



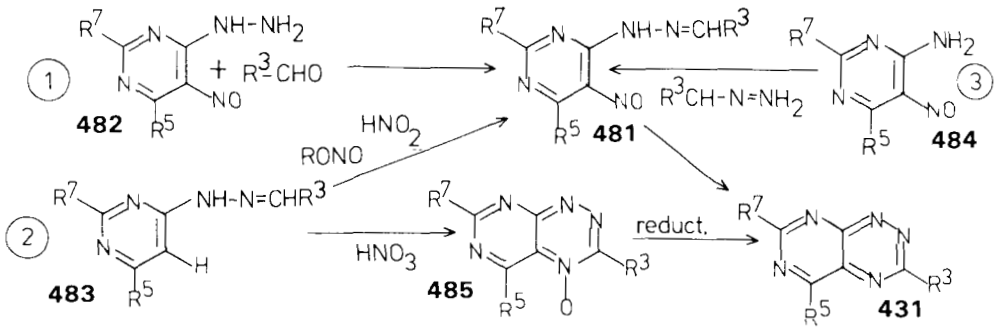
Catalytic reduction of 5-phenyl-7-(acetylhydrazino)furazano[3,4-*d*] pyrimidine (**479**), followed by acid-catalyzed cyclization and final oxidation of the 1,2-dihydropyrimido[5,4-*e*] 1,2,4-triazine (**473a**) with isoamyl nitrite, gave 5-amino-3-methyl-7-phenylpyrimido[5,4-*e*] 1,2,4-triazine (**480**) in 53% overall yield (1353).



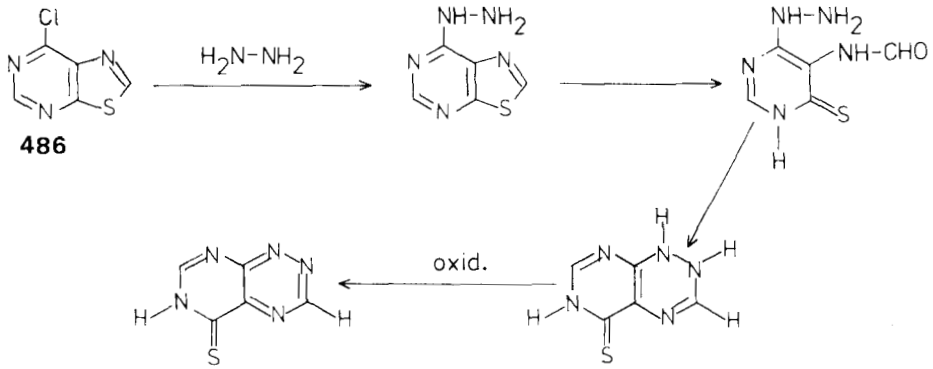
Direct synthesis of pyrimido[5,4-*e*] 1,2,4-triazines (**431**) without intermediate formation of 1,2-dihydropyrimido[5,4-*e*] 1,2,4-triazines was achieved through cyclization of 5-nitroso-4-(2-alkylidenehydrazino)pyrimidines (**481**). **481** can be obtained by the following methods:

1. Reaction of 4-hydrazino-5-nitrosopyrimidines (**482**) with aldehydes (1341).
2. Treatment of 4-(2-alkylidenehydrazino)pyrimidines (**483**) with nitrous acid or its derivatives (1345, 1346, 1359, 1381).
3. Reaction of 4-amino-5-nitrosopyrimidines (**484**) with aldehyde hydrazones (1258, 1364).

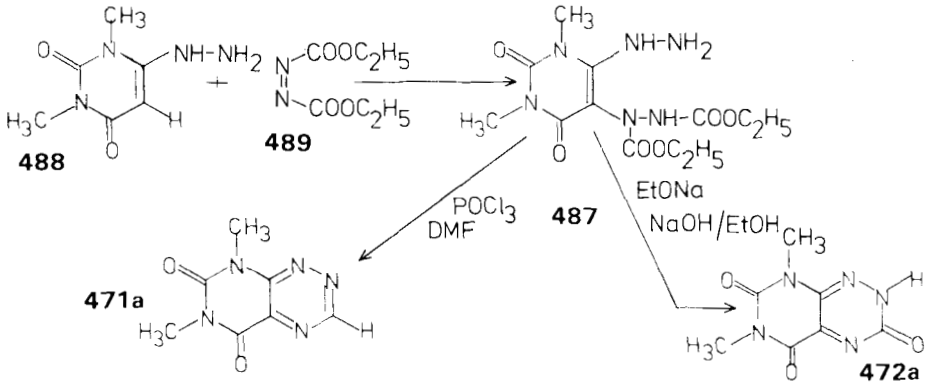
Reaction of **483** with nitric acid instead of nitrous acid yields pyrimido[5,4-*e*] 1,2,4-triazine 4-oxides (**485**) which can be reduced to pyrimido[5,4-*e*] 1,2,4-triazines (**431**) (1360).



A pyrimido[5,4-*e*]1,2,4-triazine was also isolated from the reaction of 7-chlorothiazolo[5,4-*e*]pyrimidine (**486**) with hydrazine (885, 1348). This reaction is best explained by the following mechanism:

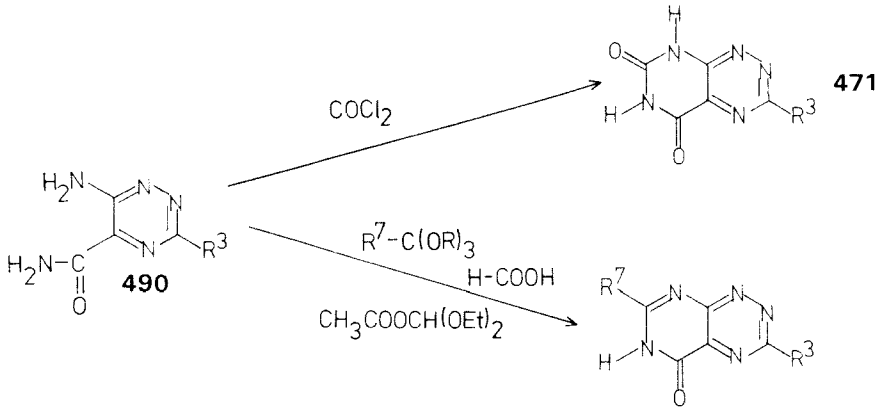


A special reaction is reported by Taylor and Sowinsky (1322, 1378) who isolated the 4,5-dihydrazinopyrimidine-2,6-dione (**487**) from the reaction of a 4-hydrazinopyrimidine-2,6-dione (**488**) with azodicarboxylate (**489**). Treatment of **487** with phosphoryl chloride in DMF gave the pyrimido[5,4-*e*]1,2,4-

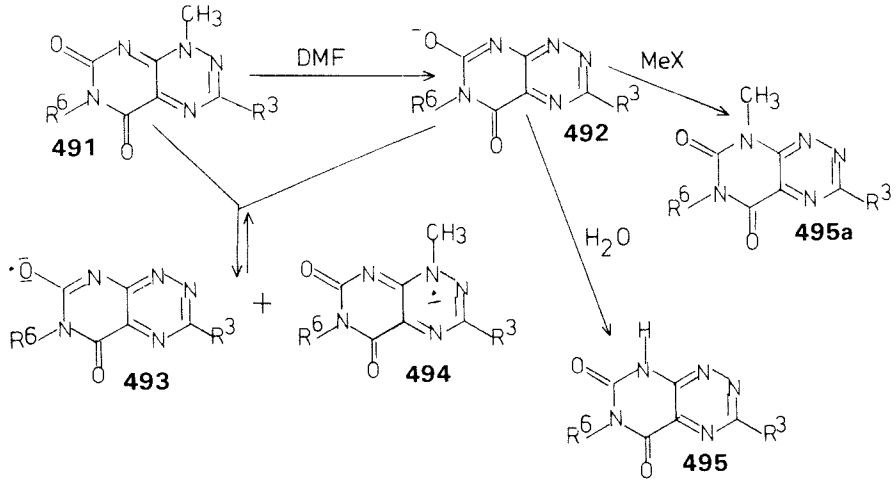


triazine-5,7-dione (**471a**), while treatment of **487** with sodium ethoxide or sodium hydroxide in ethanol gave the pyrimido[5,4-*e*] 1,2,4-triazine-3,5,7-trione (**472a**).

Only a few preparations of pyrimido[5,4-*e*] 1,2,4-triazines which start from 1,2,4-triazine derivatives have been reported (886, 887, 1099). In all cases 6-amino-1,2,4-triazine-5-carboxamide (**490**) was used as the starting material and was cyclized with phosgene/pyridine in dioxane (886, 887), orthocarboxylates (1099), formic acid/acetic anhydride in DMF in the presence of potassium carbonate (886), or diethoxymethyl acetate (886).



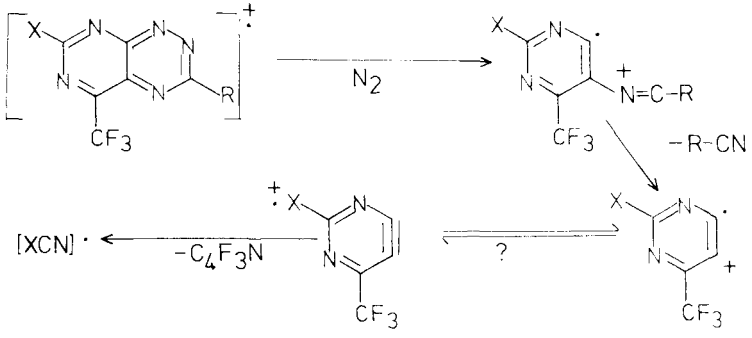
Yoneda and his co-worker (1359, 1369–1371) observed the demethylation of toxoflavin derivatives (**491**) on treatment with dimethylformamide. The formation of deeply colored radicals during this reaction was shown by ESR



spectroscopy. Therefore the following mechanism was suggested as the most reasonable: demethylation of **491** affords the anion **492** which forms the radicals **493** and **494** by reaction with **491**. Addition of water led to the isolation of **495** whereas the same reaction in the presence of methylating agents, using longer reaction times, gave the methylated products (**495a**).

b. COMPOUND SURVEY. Compounds of this class reported in the literature are listed in Table V-13.

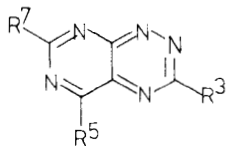
c. PHYSICAL PROPERTIES. Pyrimido[5,4-*e*]1,2,4-triazines are crystalline, colored (yellow, orange, red) compounds. Depending on their substituents, their melting points vary between below 100°C and > 360°C. In the same way their solubility in organic solvents is highly variable. Ultraviolet (885, 1338–1340, 1343, 1346–1348, 1350–1352, 1355–1357), infrared (885, 1341, 1343, 1347, 1348, 1352), and PMR spectroscopic data (885, 887, 1338–1341, 1347, 1348, 1352, 1353, 1355, 1356) of most pyrimido[5,4-*e*]1,2,4-triazines are reported. The following spectra were published for 3-methyl-pyrimido[5,4-*e*]-1,2,4-triazine (1338). Ultraviolet spectra (cyclohexane): λ_{max} (log ϵ) = 530 (2.01), 360 (2.54), 325 (3.66), 320 (3.71), 313 (3.77), 308 (3.70), 301 (3.60), and 211 nm (4.24). PMR spectra ($CDCl_3$): τ = 0.06 (H-7), 0.25 (H-5), and 6.68 (CH_3). The mass spectra of 7-substituted 5-trifluoromethylpyrimido[5,4-*e*]-1,2,4-triazines were published by Clark (1375). The fragmentation of these compounds is dominated by consecutive losses of nitrogen and prussic acid from the 1,2,4-triazine ring. The following fragmentation pattern is given:



pK_a values of pyrimido[5,4-*e*]1,2,4-triazines were reported by three groups (1339, 1346, 1355). The following values were given (water, 20°C) for 5-trifluoromethyl-7-chlorpyrimido[5,4-*e*]1,2,4-triazine = 5.99 ± 0.06 (1355) and fervenuline −1.0 ± 0.1 (1346).

The polarographic determination of fervenuline is reported by Kramarczyk and Berg (1372). The redox potential of fervenuline was determined to be −370 mV by Blankenhorn and Pfleiderer (1346). The PMR spectral differences

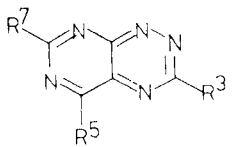
TABLE V-13. PYRIMIDO[5,4-*e*]1,2,4-TRIAZINES

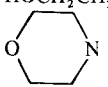


R^3	R^5	R^7	m.p. (°C)	Refs.
H	H	H		1338
H	H	OCH_3	110 (dec.)	1362
H	CH_3	CH_3	104 (dec.)	1362
H	CF_3	Cl	157	1355
H	CF_3	$NHCH_3$	194	1355
H	CF_3	$N(CH_3)_2$	90	1355
H	CF_3		127	1355
H	OCH_3	H	99–100	1350
			100	1338, 1362
H	OCH_3	CH_3	110	1338, 1357
H	OCH_3	OCH_3	155	1339
			155–156	1377
H	OC_2H_5	H	95–96	1362
H	OC_2H_5	OCH_3	145–146	1377
H	OC_2H_5	OC_2H_5	140–141	1377
H	O–*n*-C_3H_7	O–*n*-C_3H_7	87–88	1377
H	O–*i*-C_3H_7	O–*i*-C_3H_7	118–120	1377
H	SCH_3	H	137–139	1348
H	SCH_3	OCH_3	185–189	1377
H	$SCH_2C_6H_5$	H	113	1348

H	$SCH_2C_6H_5$	NH_2	226 (dec.)	885
H	NH_2	H	>264	886
H	NH_2	CH_3	240 (dec.)	1366
H	NH_2	CF_3	157–159.5	1366
H	NH_2	C_2H_5	195–196 (dec.)	1366
H	NH_2	C_6H_{13}	171–172 (dec.)	1366
H	NH_2	C_6H_5	278–279	1366
H	NH_2	OH (taut.)	>300	1339
H	NH_2	OCH_3	>210 (dec.)	1339
H	NH_2	NH_2	>264	885
			>300	1339
H	CH_3NH	CH_3	271 (dec.)	1336
H	CH_3NH	CF_3	180–182	1336
H	CH_3NH	C_6H_5	204–206	1366
H	CH_3NH	*neo*-C_5H_{11}	162–163	1366
H	$(CH_3)_2N$	H	180–181	1340
H	$(CH_3)_2N$	CH_3	179–180	1340
			190–191	1366
H	$(CH_3)_2N$	CF_3	126–127.5	1366
H	$(CH_3)_2N$	*neo*-C_5H_{11}	187–188.5	1366
H	$(CH_3)_2N$	C_6H_5–CH_2	158–160	1366
H	$(CH_3)_2N$	C_6H_5	243.5–245.5	1366
H	$(CH_3)_2N$	OCH_3	214–216	1339
H	C_2H_5NH	H	172	886
H	C_2H_5NH	CH_3	192.5–194.5	1366
H	$(C_2H_5)_2N$	H	127	886
H	$(C_2H_5)_2N$	CH_3	123	1366
H	*n*-C_3H_7NH	H	143–145	1340
H	*i*-C_3H_7NH	CH_3	119–121	1366
H	*n*-C_4H_9NH	CH_3	116.5–118	1366
H	*n*-C_4H_9NH	*n*-C_4H_9NH	133–134	1339
H	$(C_6H_5)_2CH$–NH	H	155	1348
H	CH_2=CH–CH_2–NH	CH_3	132–133.5	1366

TABLE V-13. (continued)

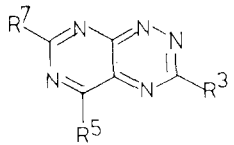


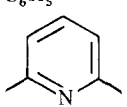
R^3	R^5	R^7	m.p.(°C)	Refs.
H	$HC{\equiv}C{-}CH_2{-}NH$	CH_3	185–186	1366
H		CH_3	151–152	1366
H	$HOCH_2CH_2{-}NH$	C_2H_5	153–154	1366
H		CH_3	207–209	1366
H	$CH_3{-}CO{-}NH$	CH_3	185–186 (dec.)	1366
H	$C_2H_5{-}CO{-}NH$	CH_3	156	1366
H	$i\text{-}C_3H_7{-}CO{-}NH$	CH_3	157.5–159	1366
H	$4\text{-}Cl{-}C_6H_4{-}CO{-}NH$	CH_3	203 (dec.)	1366
H	$H_2N{-}NH$	H	>264	886
H	HONH	H	>264	1348
H	HONH	CH_3	265–270	1366
H	$NH{-}C(NH)NH_2$	H	>264	1348
H	$COOC_2H_5$	Cl	87	1356
H	$COOC_2H_5$	$N(CH_3)_2$	124	1356
H	$COOC_2H_5$		102	1356
CH_3	H	H	81–82	1338
CH_3	H	CH_3	107–109	1338

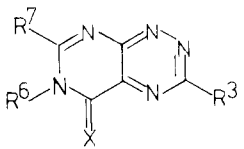
CH_3	H	OCH_3	148–150	1362
CH_3	CH_3	CH_3	91 (dec.)	1338
CH_3	CH_3	OCH_3	99–100	1362
CH_3	CF_3	NH_2	205 (dec.)	1355
CH_3	CF_3	$N(CH_3)_2$	116	1355
CH_3	OCH_3	H	168–169	1377
			169	1338, 1357
CH_3	OCH_3	CH_3	189	1338, 1357
CH_3	OCH_3	OCH_3	160	1377
CH_3	OC_2H_5	H	118–119	1377
CH_3	OC_2H_5	CH_3	148–150	1377
CH_3	OC_2H_5	OC_2H_5	140–141	1377
CH_3	O–*n*-C_3H_7	H	45–46	1377
CH_3	O–*i*-C_3H_7	H	117–119	1377
CH_3	SCH_3	H	190–191	1362
CH_3	$SCH_2C_6H_5$	H	125–126	1352
CH_3	NH_2	H	270	1362
			277–280 (dec.)	1347
CH_3	NH_2	CH_3	245–246 (dec.)	1366
CH_3	NH_2	C_6H_5	237	1353
			243–244	2366
CH_3	$NHCH_3$	H	256 (dec.)	1340
CH_3	$NHCH_3$	$NHCH_3$	238–239	1339[a]
CH_3	$N(CH_3)_2$	H	218	1340
CH_3	$N(CH_3)_2$	CH_3	222–223	1340
CH_3	$N(CH_3)_2$	OCH_3	244–245	1340
CH_3	NH–*n*-C_3H_7	H	181–182	1340
CH_3	NH–*n*-C_3H_7	CH_3	114–116	1340
CH_3	NH–*n*-C_4H_9	NH–*n*-C_4H_9	109–110	1339
C_2H_5	NH_2	H	223–225 (dec.)	1347
C_2H_5	NH–$CH_2C_6H_5$	H	152–153 (dec.)	886
			153–154 (dec.)	1347

[a]Structure not fully established.

TABLE V-13. (continued)

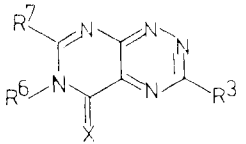


R^3	R^5	R^7	m.p.(°C)	Refs.
C_2H_5	$NHNH_2$	H	>200	1347
CH_2Cl	OCH_3	H	79–81	1350
CH_2N_3	NH_2	H	177 (dec.)	1350
CH_2OCH_3	OCH_3	H	91	1350
CH_2OCH_3	NH_2	H	178–180	1350
$CH_2COOC_2H_5$	NH_2	H	175	1350
CH_2CONH_2	NH_2	H	>264	1350
$CHBr-COOC_2H_5$	NH_2	H	~187 (dec.)	1350
$CH_2NH-C_6H_4-COOC_2H_5$(p)	$SCH_2C_6H_5$	NH_2	>264	1349, 1352
$CH_2NH-C_6H_4-COOC_2H_5$(p)	NH_2	NH_2	>264	1349, 1352
$CH_2NH-C_6H_4CONH-CH(CH_2CH_2COOC_2H_5)COOC_2H_5$	NH_2	NH_2	Indef.	1352
$CH_2NH-C_6H_4CONH-CH(CH_2CH_2COOC_2H_5)COOC_2H_5$	$SCH_2C_6H_5$	NH_2	151	1351, 1352
C_6H_5	NH_2	CH_3	269	1366
C_6H_5	NH_2	C_2H_5	239–240	1366
C_6H_5	NH_2	C_6H_5	>300	1352
C_6H_5	CH_3NH	CH_3	224–225	1366
C_6H_5	$(CH_3)_2N$	CH_3	226–227	1366
	OCH_3	OCH_3	>350	1346

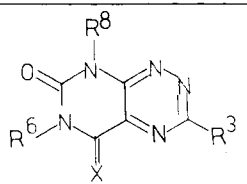


R^3	X	R^6	R^7	m.p. (°C)	Refs.
H	O	H	H	245–250 (dec.)	1362
				256	886
H	O	H	OCH_3	185	1377, 1339
H	O	H	OC_2H_5	186	1377
H	O	H	NH_2	>264	885
				>320	1339
H	O	H	$N(CH_3)_2$	299–300	1339
H	O	H	NH–*n*-C_4H_9	213–214	1339
CH_3	O	H	H	199–200 (sol.)	
				213–215	1347
				210–212	1362
CH_3	O	H	$NHCH_3$	>270	1339
CH_3	O	H	NH–*n*-C_4H_9	210–211	1339
C_2H_5	O	H	H	185–188 (dec.)	1347
CH_2OCH_3	O	H	H	~175 (dec.)	1350
CH_2NH–C_6H_4–$COOC_2H_5$(p)	O	H	NH_2		1349
				·HCl >264	1352
CH_2HN–C_6H_4–CONH–CH(–CH_2CH_2COOH)–COOH	O	H	NH_2	·1½H_2O >260	1351, 1352
CH_2NH–C_6H_4CONH–CH(–$CH_2CH_2COOC_2H_5$)–$COOC_2H_5$	O	H	NH_2		1351
H	S	H	H	>260	1348
H	S	H	NH_2		885

TABLE V-13. (continued)



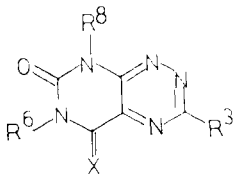
R^3	X	R^6	R^7		m.p.(°C)	Refs.
CH_3	S	H	H			1352
CH_2OCH_3	S	H	H	$\cdot\frac{1}{2}H_2O$	160–161	1350
$CH_2NH-C_6H_4-COOC_2H_5(p)$	S	H	NH_2			1349
					~264	1352
$CH_2NH-C_6H_4CONH-CH(CH_2CH_2COOC_2H_5)-COOC_2H_5$	S	H	NH_2	$\cdot H_2O$	255 (dec.)	1352
$\cdot$HCl					164 (dec.)	1352

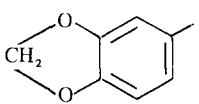
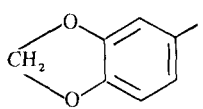


R^3	X	R^6	R^8	m.p. (°C)	Refs.
H	O	H	H	>264	886, 887
				338–340	1339
				~340 (dec.)	1377
H	O	CH_3	H	210 (dec.)	1370
				239–240 (dec.)	1342
					1336

H	O	CH_3	CH_3	175	1358, 1369
				175.7	1322
				176	1367
				177	886, 887
				178	1345, 1346
				178–179	1341, 1344, 1335, 1343
CH_3	O	H	H	281–282	1363
CH_3	O	CH_3	H	247 (dec.)	1370
CH_3	O	CH_3	CH_3	127	1344, 1345, 1346
CCl_3	O	CH_3	CH_3	194	1345, 1346
i-C_3H_7	O	CH_3	CH_3	157/173–174	1345/1345, 1346
$C_6H_5CH_2$	O	CH_3	CH_3	196	1345, 1346
C_6H_5–CH=CH	O	CH_3	H	>300	1370
C_6H_5–CH=CH	O	C_6H_5–CH_2	H	>300	1359
C_6H_5	O	CH_3	H	>300	1370
C_6H_5	O	CH_3	CH_3	270	1358, 1369
				276	1370
				277	1345, 1346
C_6H_5	O	CH_3	C_2H_5	223	1370
				228	1369
C_6H_5	O	CH_3	*n*-C_3H_7	214	1370
C_6H_5	O	CH_3	*i*-C_3H_7	226	1370
C_6H_5	O	CH_3	CH_2–CH=CH_2	213	1370
C_6H_5	O	CH_3	CH_2CH_2OH	215	1370
C_6H_5	O	$C_6H_5CH_2$	H	>300	1359
C_6H_5	S	CH_3	CH_3	269	1376
2-CH_3–C_6H_4	O	CH_3	CH_3	210	1345, 1346
4-Cl C_6H_4	O	CH_3	H	>300	1370
4-Cl–C_6H_4	O	CH_3	CH_3	235	1346
				286	1346
				275	1358
				280	1369
4-Cl C_6H_4	O	CH_3	C_2H_5	255	1369

TABLE V-13. (continued)



R^3	X	R^6	R^8	m.p.(°C)	Refs.
4-Cl–C_6H_4	O	C_6H_5–CH_2	H	>300	1359
4-Cl–C_6H_4	S	CH_3	CH_3	273	1376
3,4-$Cl_2C_6H_3$	O	CH_3	H	>300	1370
3,4-$Cl_2C_6H_3$	O	CH_3	CH_3	165	1360
3,4-$Cl_2C_6H_3$	O	C_6H_5–CH_2	H	>300	1359
4-Br–C_6H_4	O	CH_3	CH_3	303	1358
4-O_2N–C_6H_4	O	CH_3	CH_3	323	1358
				325	1345, 1346
				337	1346
2-HO–C_6H_4	O	CH_3	CH_3	282	1358
4-CH_3O–C_6H_4	O	CH_3	CH_3	268	1369
3,4-$(CH_3O)_2C_6H_3$	O	CH_3	CH_3	>300	1370
3,4-$(CH_3O)_2C_6H_3$	O	CH_3	CH_3	305	1358, 1369
	O	CH_3	CH_3	203	1358
				274	1369
	O	CH_3	C_2H_5	238	1369

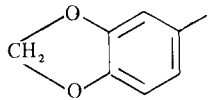
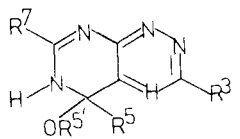
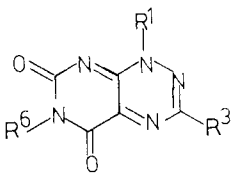
	S	CH_3	CH_3	290	1376
4-$(CH_3)_2N-C_6H_4$	O	CH_3	CH_3	>300	1369
				340 (dec.)	1345, 1346
4-$(CH_3)_2N-C_6H_4$	O	CH_3	C_2H_5	258	1369
2-Pyridyl	O	CH_3	H	>300	1370
2-Pyridyl	O	CH_3	CH_3	280	1345, 1346
				285	1358
2-Pyridyl	S	CH_3	CH_3	252	1376
3-Pyridyl	O	CH_3	H	>300	1370
3-Pyridyl	O	CH_3	CH_3	178	1359
				213	1358, 1369
				218	1345, 1346
				285 (dec.)	1346
3-Pyridyl	O	$C_6H_5CH_2$	H	>300	1359
3-Pyridyl	S	CH_3	CH_3	210	1376
4-Pyridyl	O	CH_3	H	>300	1370
4-Pyridyl	O	CH_3	CH_3	262	1358, 1369
				270	1345, 1346
				280 (dec.)	1346
4-Pyridyl	S	CH_3	CH_3	250	1376
4-Pyridyl	O	$C_6H_5CH_2$	H	>300	1359
2-Thienyl	O	CH_3	H	>300	1370
2-Thienyl	O	CH_3	CH_3	272	1358
3-Indolyl	O	CH_3	CH_3	>360	1345, 1346

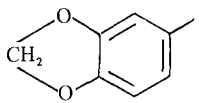
TABLE V-13. (continued)



R^3	R^5	$R^{5'}$	R^7	m.p. (°C)	Refs.
H	CF_3	H	Cl	107–110	1355
H	H	CH_3	H	150 (dec.)	1338
H	H	CH_3	CH_3	>300	1338
CH_3	H	CH_3	H	213–214	1338
				214	1357
CH_3	H	CH_3	CH_3	>330	1338
CH_3	H	C_2H_5	H	114	1357

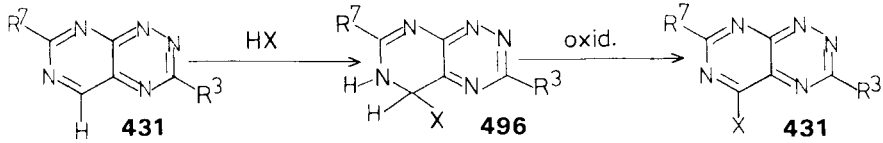


R^1	R^3	R^6	m.p. (°C)	Refs.
CH_3	H	CH_3	170 (dec.)	1333
			172	1369, 1381
			172–173 (dec.)	1343, 1382
			178–179	1335

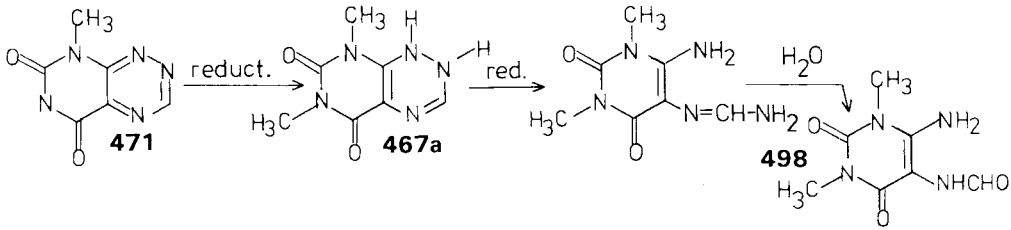
CH_3	CH_3	CH_3	180–181	1381
			181–182 (dec.)	1343
CH_3	C_6H_5	CH_3	197	1369, 1381
CH_3	C_6H_5	$C_6H_5-CH_2$	223	1359
CH_3	$C_6H_5-CH=CH$	CH_3	210–213	1381
CH_3	$C_6H_5-CH=CH$	$C_6H_5-CH_2$	126	1359
CH_3	4-Cl–C_6H_4	CH_3	207	1369
CH_3	4-Cl–C_6H_4	$C_6H_5-CH_2$	175	1359
CH_3	3,4-$Cl_2C_6H_3$	$C_6H_5-CH_2$	195	1359
CH_3	3,4-$(CH_3O)_2C_6H_3$	CH_3	229	1369, 1381
CH_3	4-CH_3O–C_6H_4	CH_3	244	1369
CH_3		CH_3	265	1369
CH_3	4-$(CH_3)_2N$–C_6H_4	CH_3	>300	1369
CH_3	2-Pyridyl	CH_3	210	1381
CH_3	3-Pyridyl	CH_3	205 (dec.)	1369, 1381
CH_3	3-Pyridyl	$C_6H_5-CH_2$	137	1359
CH_3	4-Pyridyl	CH_3	209 (dec.)	1369, 1381
CH_3	4-Pyridyl	$C_6H_5-CH_2$	121	1359
CH_3	2-Thienyl	CH_3	233	1381

produced by addition of adenosine to reumycin (**471c**) and toxoflavin (**471b**) are published by a Russian group (1373). The authors conclude from their results that the compounds **471b** and **471c** were able to form self-condensed or stacked systems. Calculations on the pyrimido[5,4-*e*] 1,2,4-triazine system were reported by Wait and Wesley (1150).

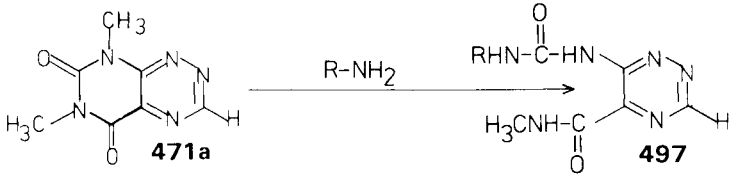
d. REACTIONS. A very interesting reaction of high synthetic value is the introduction of alkoxy or amino substituents into the 5-positions of pyrimido[5,4-*e*] 1,2,4-triazines (**431**) through the reaction of **431** with alcohols or amines (1338–1340, 1350, 1355–1357). The mechanism of this reaction was shown to proceed via a covalent addition of the alcohol or the amine to the 5,6-double bond of **431** and subsequent oxidation of the formed 5,6-dihydro compound **496**. Brown and Sugimoto (1340) have reported that even 5-alkyl substituents can be replaced by this reaction.



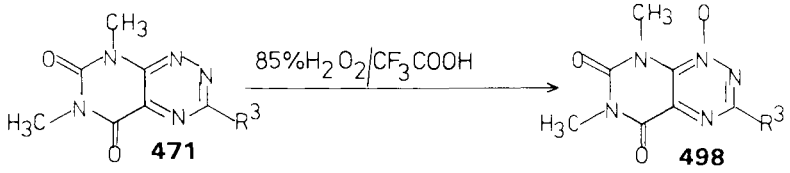
Reduction of **471** affords 1,2-dihydro-pyrimido[5,4-*e*] 1,2,4-triazines (**467a**) (1346). Reduction with Raney nickel at elevated temperatures yields pyrimidine derivatives (**498**) (1346). The formation of **498** probably proceeds via **497** and subsequent opening of the 1,2,4-triazine ring. A reaction of this type has been reported by several groups (886, 1341, 1348).



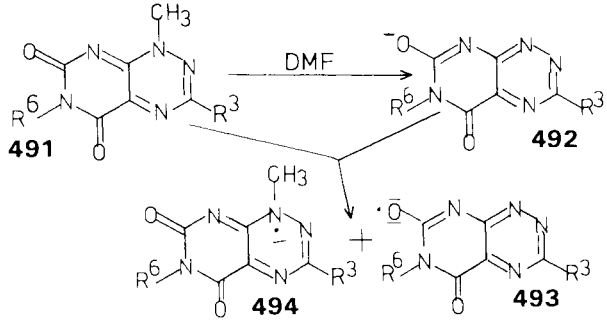
Ring cleavage in the pyrimidine ring of pyrimido[5,4-*e*] 1,2,4-triazines occurs with the same ease in basic media (886, 887, 1350, 1376), in acidic media (1099, 1350), with bromine in methanol (1350), or with amines, hydrazines, or hydroxylamines (883, 884), leading to 1,2,4-triazine derivatives, as is illustrated for the reaction of fervenuline (**471a**) with amines.



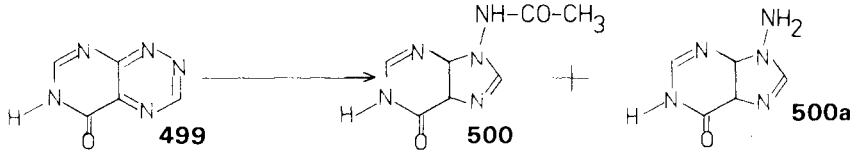
Pyrimido[5,4-*e*]1,2,4-triazines (**471**) can be oxidized only with difficulty (1346). Pyrimido[5,4-*e*]1,2,4-triazine 1-oxides (**498**) were isolated from the oxidation reaction with hydrogen peroxide and trifluoroacetic acid.



Treatment of toxoflavines (**491**) with dimethylformamide led, via the anion **492** to the formation of deeply colored radicals (**493**, **494**) which were detected by their ESR spectra (1359, 1369–1371).

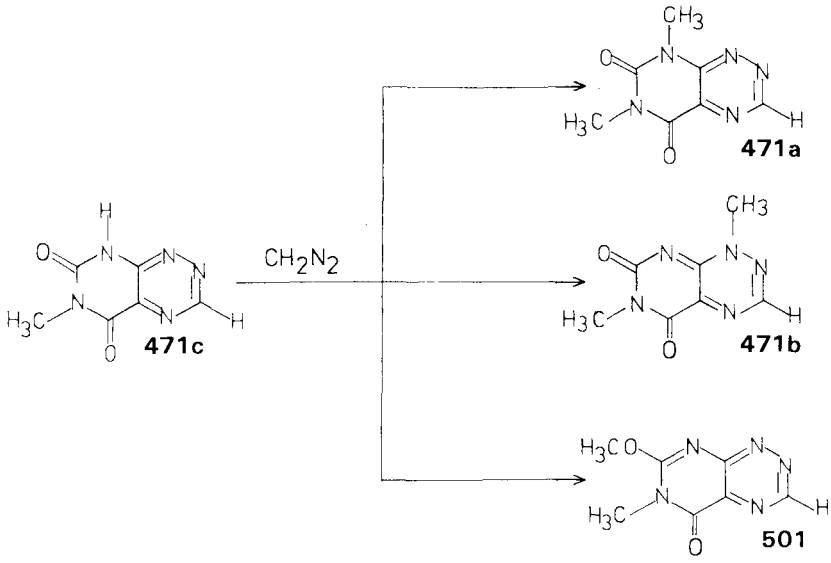


Treatment of pyrimido[5,4-*e*]1,2,4-triazin-5-one (**499**) with sodium dithionite in acetic acid gave a mixture of 9-acetamidohypoxanthine (**500**) and a small amount of 9-aminohypoxanthine (**500a**) (886).



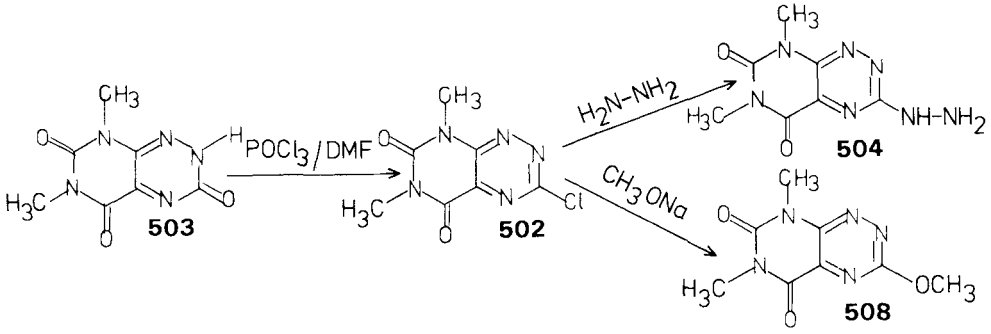
Nucleophilic substitution of different substituents occurs with equal ease in the pyrimidine ring or in the 1,2,4-triazine ring. This is reported by different groups (885, 887, 909, 1339, 1340, 1347–1352, 1355, 1356, 1361, 1368, 1377).

Methylation of N-H groups in pyrimido[5,4-*e*]1,2,4-triazine-5,7-diones is reported by Montgomery and his group (887). Treatment of reumycin (**471c**) with diazomethane afforded fervenuline (**471a**), toxoflavin (**471b**), and 7-methoxy-6-methylpyrimido[5,4-*e*]1,2,4-triazin-5-one (**501**) (1336).



3. *3-Chloropyrimido[5,4-e]1,2,4-triazines*

At present only the 3-chloro-6,8-dimethylpyrimido[5,4-*e*] 1,2,4-triazine-5,7-dione (**502**) (m.p. 147°C) is known (1322). **502** was prepared from 6,8-dimethylpyrimido[5,4-*e*] 1,2,4-triazine-3,5,7-trione (**503**) by a reaction with phosphoryl chloride in the presence of dimethylformamide. It reacts with hydrazine or sodium methoxide, yielding 3-hydrazino- (**504**) or 3-methoxy-6,8-dimethylpyrimido[5,4-*e*] 1,2,4-triazine-5,7-dione (**508**) (1322, 1378).



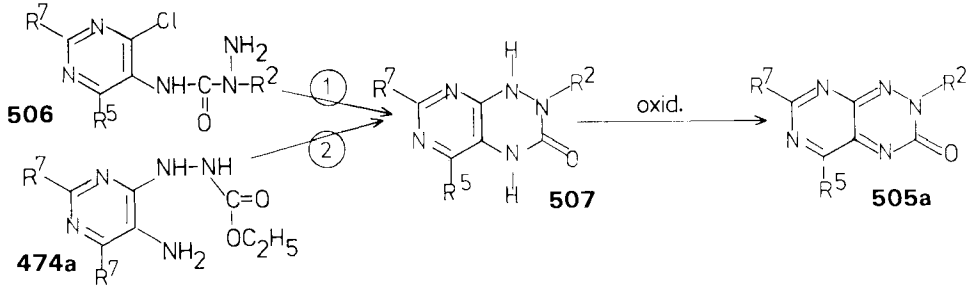
4. *Pyrimido[5,4-e]1,2,4-triazin-3-ones*

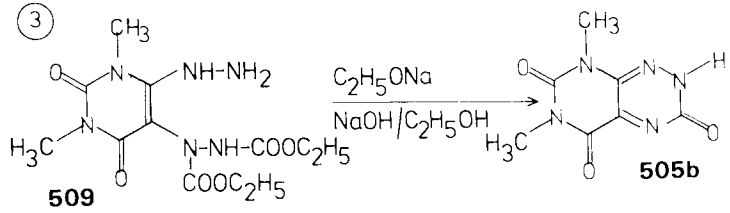
a. PREPARATION. 2,6,8-Trimethylpyrimido[5,4-*e*] 1,2,4-triazine-3,5,7-trione (**472**) is the antibacterial substance MSD-92, which was isolated from an unidentified actinomycete (1337). For the synthesis of pyrimido[5,4-*e*] 1,2,4-triazin-3-ones (**505a**, **b**) three methods are reported:

1. Cyclization of 4-chloro-5-(4-semicarbazido)pyrimidines (**506**) (1378) and oxidation of the initially formed dihydro compounds (**507**).

2. Cyclization of 5-amino-4-[2-(ethoxycarbonyl)hydrazino] pyrimidines (**474a**) and oxidation of the initially formed **507** (1354).

3. Treatment of the 4,5-dihydrazinopyrimidine (**509**) with sodium ethoxide or sodium hydroxide in ethanol (1322, 1378).



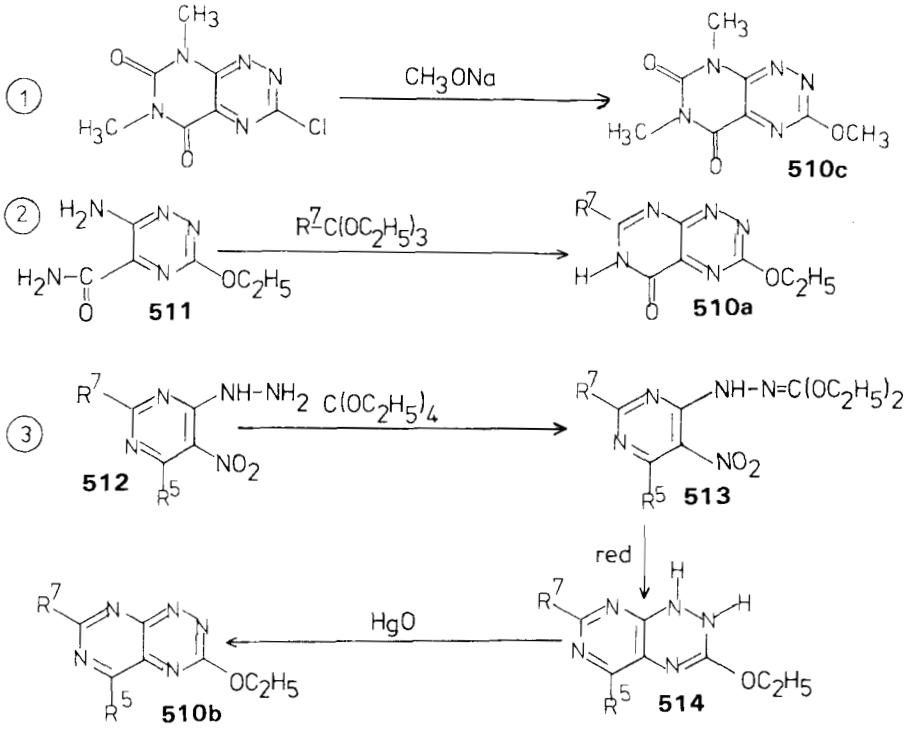


3-Alkoxypyrimido[5,4-*e*] 1,2,4-triazines (**510**) are prepared by one of the following methods.

1. Reaction of the 3-chloro derivative (**502**) with sodium methoxide (1378).

2. Cyclization of 3-ethoxy-6-amino-1,2,4-triazine-5-carboxamide (**511**) with orthocarboxylates (1099).

3. Reaction of 4-hydrazino-5-nitropyrimidines (**512**) with tetraethyl orthocarbonate, cyclization of the formed 4-[2-(diethoxymethylene)hydrazino]-5-nitropyrimidines (**513**), to give 3-alkoxy-1,2-dihydropyrimido[5,4-*e*] 1,2,4-triazines (**514**), which are then oxidized with mercuric oxide (1368).

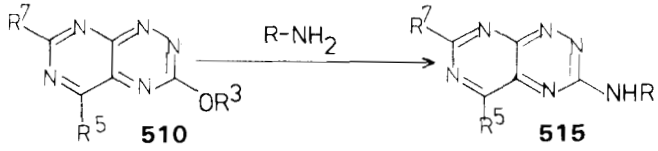


The reaction of 6,8-dimethylpyrimido[5,4-*e*] 1,2,4-triazine-3,5,7-trione (**503**) with phosphoryl chloride was used for the synthesis of 3-chloro-6,8-dimethyl-pyrimido[5,4-*e*] 1,2,4-triazine-5,7-dione (**502**) (1322). Methylation of **503** with diazomethane affords three compounds: the 2-methyl derivative, the 4-methyl derivative (m.p. 218 to 220°C, dec.), and the 3-methoxy derivative (1378).

b. COMPOUND SURVEY. Known pyrimido[5,4-*e*] 1,2,4-triazin-3-ones are listed in Table V-14.

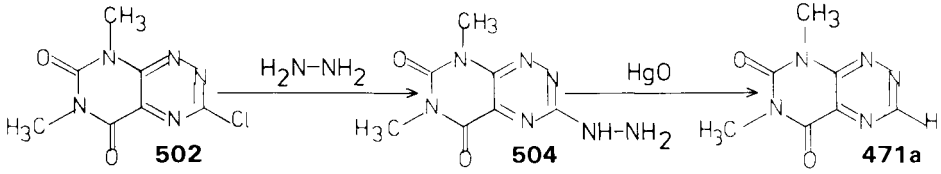
5. *3-Aminopyrimido[5,4-e]1,2,4-triazines*

The 3-amino-pyrimido[5,4-*e*] 1,2,4-triazines (**515**) were prepared by reaction of the 3-alkoxy-pyrimido[5,4-*e*] 1,2,4-triazines (**510**) with ammonia or amines (1099, 1368). Known 3-amino compounds are listed in Table V-14.



6. *3-Hydrazinopyrimido[5,4-e]1,2,4-triazines*

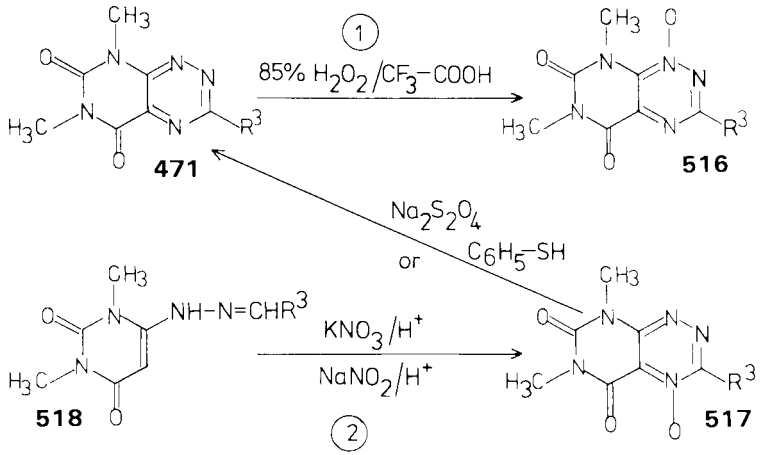
The reaction of 3-chloro-6,8-dimethylpyrimido[5,4-*e*]1,2,4-triazine-5,7-dione (**502**) with hydrazine gave 3-hydrazino-6,8-dimethyl-pyrimido[5,4-*e*]-1,2,4-triazine-5,7-dione (**504**) (m.p. 221.2°C), which was oxidized with mercuric oxide to 6,8-dimethylpyrimido[5,4-*e*]1,2,4-triazine-5,7-dione (**471a**) (ferveniuline) (1322).



7. *Pyrimido[5,4-e]1,2,4-triazine N-oxides*

Blankenhorn and Pfleiderer (1346) reported the oxidation of pyrimido[5,4-*e*]-1,2,4-triazine-5,7-diones (**471**) with 85% hydrogen peroxide in trifluoroacetic acid, yielding the corresponding 1-oxides (**516**) (reaction 1).

Yoneda and his group published the synthesis of 4-oxide analogues (**517**) of **471** through the reaction of 1,3-dimethyl-4-(2-alkylidenehydrazino)pyrimidine-2,6-diones (**518**) with potassium nitrate in acetic acid in the presence of sulfuric acid (1360) or sodium nitrite in acetic acid (1381) (reaction 2).

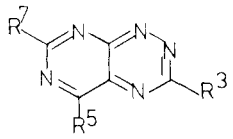


517 can be reduced to **471** at room temperature with sodium dithionite (1360) or benzenethiol (1381).

The *N*-oxides reported in the literature are listed in Table V-15.

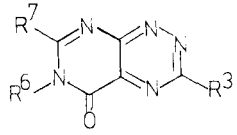
TABLE V-14. PYRIMIDO[5,4-*e*]1,2,4-TRIAZIN-3-ONES, 3-AMINO- AND 3-HYDRAZINOPYRIMIDO[5,4-*e*]1,2,4-TRIAZINES

A. Pyrimido[5,4-*e*]1,2,4-triazin-3-ones and 3-Aminopyrimido[5,4-*e*]-1,2,4-triazines



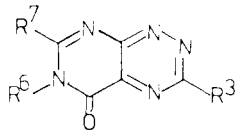
R^3	R^5	R^7	m.p. (°C)	Refs.
OCH_3	OCH_3	H	152–153	1368
OCH_3	OCH_3	OCH_3	181 (dec.)	1368
OC_2H_5	OCH_3	H	139–140	1368
OC_2H_5	OCH_3	CH_3	169–171	1368
OC_2H_5	OCH_3	OCH_3	157	1368
OC_2H_5	OCH_3	O-*n*-C_3H_7	122–123	1368
OC_2H_5	OC_2H_5	H	90–91	1368
OC_2H_5	OC_2H_5	OC_2H_5	145–146	1368
OC_2H_5	NH_2	H	>242 (dec.)	1368
OC_2H_5	NH_2	O-*n*-C_3H_7	209–210 (dec.)	1368
OC_2H_5	$NHCH_3$	H	>247 (dec.)	1368
OC_2H_5	$NHCH_3$	CH_3	215 (dec.)	1368
OC_2H_5	$NHCH_3$	O-*n*-C_3H_7	160–161 (dec.)	1368
NH_2	OCH_3	CH_3	>220 (dec.)	1368
NH_2	NH_2	H	>340	1368
NH_2	NH_2	CH_3	>315	1368
NH_2	NH_2	OCH_3	>275	1368
NH_2	NH_2	OC_2H_5	>260	1368
NH_2	NH_2	O-*n*-C_3H_7	>270	1368
$NHCH_3$	OCH_3	CH_3	194	1368
$NHCH_3$	$NHCH_3$	H	267–268	1368
$NHCH_3$	$NHCH_3$	CH_3	>245 (dec.)	1368
$NHCH_3$	$NHCH_3$	O-*n*-C_3H_7	200–201	1368
$NHCH_3$	$NHCH_3$	$NHCH_3$	>257 (dec.)	1368
OH	H	H (tautomer)		1354

B. Pyrimido[5,4-*e*]1,2,4-triazin-3,5-diones and 3-Aminopyrimido[5,4-*e*]1,2,4-triazin-5-ones



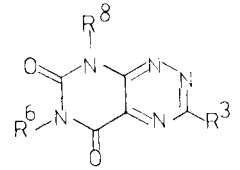
R^3	R^6	R^7	m.p. (°C)	Refs.
OCH_3	H	H	>150 (dec.)	1099
OC_2H_5	H	H	198 (dec.)	1099
OC_2H_5	H	C_2H_5O	191 (dec.)	1099
OC_2H_5	H	C_3H_7O	170–171	1099

TABLE V-14. (continued)



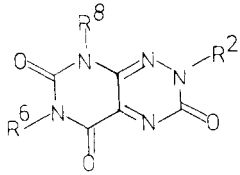
R^3	R^5	R^7	m.p.(°C)	Refs.
OC_2H_5	CH_3	H	211–212 (dec.)	1099
NH_2	H	H	>340	1099
NH_2	H	CH_3	>320	1099
NH_2	H	NH_2	>340	1099
NH_2	CH_3	H	>340	1099
CH_3NH	H	H	>320	1099
CH_3NH	H	CH_3NH	>340	1099
OH	H	H (tautomer)	290	1099

C. Pyrimido[5,4-*e*]1,2,4-triazine-3,5,7-triones
3-Amino- and 3-Hydrazinopyrimido[5,4-*e*]1,2,4-triazine-5,7-diones



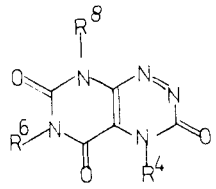
R^3	R^6	R^8	m.p. (°C)	Refs.
OCH_3	CH_3	CH_3	144–145	1378
OC_2H_5	H	H	263 (dec.)	1368
OC_2H_5	CH_3	H	217	1099
NH_2	H	H	340	1099
NH_2	CH_3	H	330	1099
$NHNH_2$	CH_3	CH_3	221.2	1322

D. Pyrimido[5,4-*e*]1,2,4-triazine-3,5,7-triones



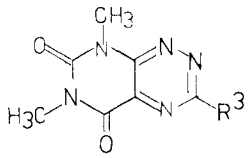
R^2	R^6	R^8	m.p. (°C)	Refs.
H	H	H	330 (dec.)	1368
H	CH_3	CH_3	251.4	1322
CH_3	CH_3	CH_3	181–182 (dec.)	1378
			183–185 (dec.)	1337

TABLE V-14. (continued)

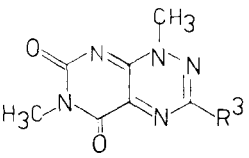


R^4	R^6	R^8	m.p. (°C)	Refs.
CH_3	CH_3	CH_3	218–220 (dec.)	1378

TABLE V-15. PYRIMIDO[5,4-*e*]1,2,4-TRIAZINE *N*-OXIDES



R^3		m.p. (°C)	Refs.
H	1-Oxide	166–168	1346
CH_3	1-Oxide	196–198	1346
2-Pyridyl	1-Oxide	233	1346
C_6H_5	4-Oxide	233	1360
3,4-$Cl_2C_6H_3$	4-Oxide	165	1360
3-Pyridyl	4-Oxide	178	1360



R^3		m.p. (°C)	Refs.
H	4-Oxide	215 (dec.)	1381
4-Cl–C_6H_4	4-Oxide	207	1381
3,4-$Cl_2C_6H_3$	4-Oxide	222	1381

8. *Dihydropyrimido[5,4-e]1,2,4-triazines*

Dihydropyrimido[5,4-*e*] 1,2,4-triazines (**473**) are the first reaction products of most synthetic methods for the pyrimido[5,4-*e*] 1,2,4-triazines, starting from pyrimidine derivatives. Since the dihydro compounds are easily oxidized, in many cases they were not isolated but formulated as the intermediates in the synthesis of pyrimido[5,4-*e*] 1,2,4-triazines. In this chapter we discuss only those papers in which the dihydro compounds were isolated; all other publications were mentioned in Section XI-B-2.

a. PREPARATION. For the synthesis of 1,2-dihydropyrimido[5,4-*e*]-1,2,4-triazines (**473**) the same reaction procedures were used as for the synthesis of pyrimido[5,4-*e*] 1,2,4-triazines.

1. Reaction of 5-amino-4-hydrazinopyrimidines (**474**) with orthocarboxylates (885, 1338, 1339, 1348, 1350, 1356, 1383).

2. Cyclization of the 5-amino-4-(2-acylhydrazino)pyrimidines (**519**), which were obtained through reduction of 5-nitroso- or 5-nitro-4-(2-acylhydrazino)-pyrimidines (**475**) (1338, 1340, 1352, 1354, 1355).

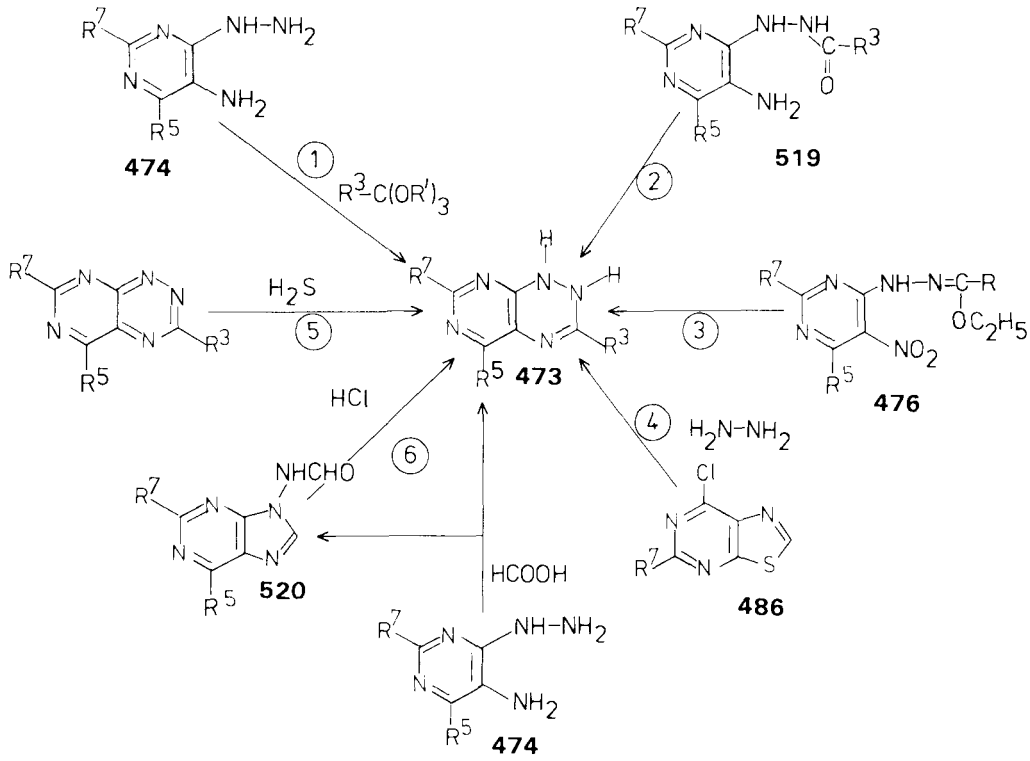
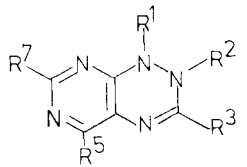


TABLE V-16. DIHYDROPYRIMIDO[5,4-*e*]1,2,4-TRIAZINES

A. 1,2-Dihydropyrimido[5,4-*e*]1,2,4-triazines

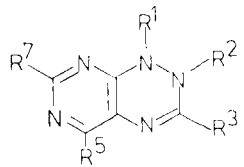


R^1	R^2	R^3	R^5	R^7		m.p. (°C)	Refs.
H	H	H	H	H		>350	1338, 1357
Picrate						197	1338, 1357
H	H	H	H	CH_3		>350	1338, 1357
Picrate						198–199	1338
						199	1357
H	H	H	H	Cl		>250 (dec.)	1339
H	H	H	CH_3	H		190	1338
·HCl						295 (dec.)	1340
						308–309	1384
·½H_2O						153–154.5	1384
·HCOOH						185–187	1384
H	H	H	CH_3	CH_3	·HCOOH	210–211	1338
H	H	H	CH_3	Cl		>300	1339
H	H	H	CF_3	Cl		212 (dec.)	1355
H	H	H	SH	H (taut.)		>264	1348
H	H	H	SH	NH_2 (taut.)		>264	885
H	H	H	SCH_3	H		208–209	1348
H	H	H	SCH_2CN	H		228 (dec.)	1348[a]
H	H	H	$SCH_2C_6H_5$	H		160	1348

H		H	H	$COOC_2H_5$	Cl		278	1356
H		H	H	Cl	H	·HCl	Indef.	1383
H		H	H	Cl	CH_3	·HCl		1366
H		H	H	Cl	CF_3	·HCl	184 (dec.)	1366
H		H	H	Cl	C_2H_5	·HCl		1366
H		H	H	Cl	*neo*-C_5H_{11}			1366
H		H	H	Cl	C_6H_{13}			1366
H		H	H	Cl	$C_6H_5CH_2$	·HCl	175–185 (dec.)	1366
H		H	H	Cl	C_6H_5		182–184 (dec.)	1366
H		H	CH_3	H	H		350	1338, 1357
	Picrate						205	1338, 1357
	·2HCl						300	1340
H		H	CH_3	H	CH_3		330	1338
							350	1357
	Picrate						195	1357
H		H	CH_3	H	Cl		230 (dec.)	1339
H		H	CH_3	CH_3	H	·2HCl	252–253 (dec.)	1338
H		H	CH_3	CH_3	CH_3		189–190	1338
H		H	CH_3	CF_3	Cl		214	1355
H		H	CH_3	CF_3	OCH_3		196–198	1355
H		H	CH_3	CF_3	OC_2H_5		180–182	1355
H		H	CH_3	CF_3	SH (taut.)		230 (dec.)	1355
H		H	CH_3	*n*-C_3H_7	H	·HCl	222–224	1340
H		H	CH_3	Cl	H			1352
H		H	CH_3	Cl	CH_3	·HCl		1366
H		H	CH_3	Cl	C_6H_5		184–185	1366
H		H	CH_3	OCH_3	H		172	1338
	Picrate						168–170	1338
H		H	CH_3	SH	H (taut.)		264	1352
H		H	CH_3	$C_6H_5CH_2S$	H		145–146	1352
H		H	CH_2Cl	Cl	H		180–181 (dec.)	1350
H		H	CH_2OCH_3	Cl	H		148–150	1350
	·HCl						147–149	1350

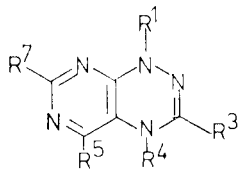
[a] Structure questionable.

TABLE V-16. (continued)



R^1	R^2	R^3	R^5	R^7		m.p.(°C)	Refs.
H	H	CH_2OCH_3	SH	H (taut.)		253–254 (dec.)	1350
H	H	CH_2OCH_3	$C_6H_5CH_2S$	H		134–135	1350
H	H	$CH_2COOC_2H_5$	Cl	H		177	1350
H	H	C_6H_5	H	H	·HCl	234–235	1354
	·HCl·½H_2O					250–251	1354
H	H	C_6H_5	CH_3	H		265	1354
H	H	C_6H_5	CH_3	C_6H_5NH		230	1354
H	H	C_6H_5	Cl	CH_3	·HCl		1366
H	H	C_6H_5	Cl	C_2H_5		172–173	1366
CH_3	H	H	H	H		202 (dec.)	1380
CH_3	H	H	Cl	H	·HCl	191–195	1383
CH_3	H	H	$SCH_2C_6H_5$	H		131 (dec.)	885
CH_3	H	CH_3	Cl	H	·HCl	180–182 (dec.)	1383
$C_6H_5CH_2$	H	H	H	H			1380
$C_6H_5CH_2$	H	H	Cl	H		182–183 (dec.)	1380
CH_3	CH_3	H	Cl	H	·HCl	Indef.	1383

B. 1,4-Dihydropyrimido[5,4-*e*]1,2,4-triazines



R^1	R^3	R^4	R^5	R^7		m.p. (°C)	Refs.
H	H	CH_3	Cl	H	·HCl	199–200	1383
CH_3	H	CH_3	Cl	H	·HCl	Indef.	1383

3. Cyclization of 5-nitro-4-[2-(ethoxyalkylidene)hydrazino] pyrimidines (**476**) through reduction of the nitro group (1338, 1357, 1362, 1368).

4. Reaction of the thiazolo[5,4-*d*] pyrimidines (**486**) with hydrazine (885, 1348).

5. Reduction of the pyrimido[5,4-*e*] 1,2,4-triazines with hydrogen sulfide (1348, 1352).

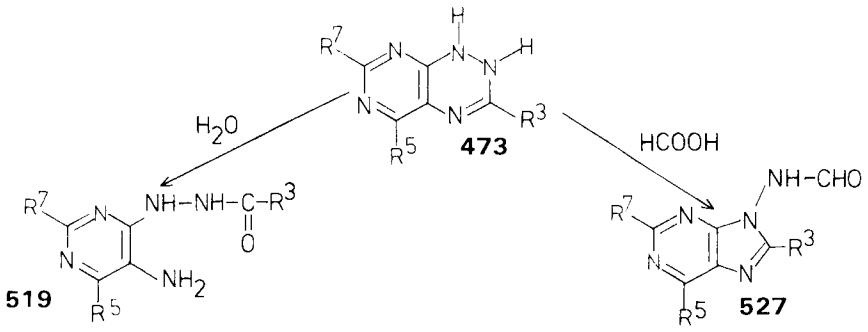
6. Cyclization of 5-amino-4-hydrazinopyrimidines (**474**) with formic acid (1348, 1380, 1384).

In the latter reaction 9-aminopurines (**520**) were also formed which could be transformed to **473** by treatment with hydrochloric acid (1384).

b. COMPOUND SURVEY. The dihydro compounds reported in the literature are listed in Table V-16.

c. PHYSICAL PROPERTIES. 1,2-Dihydropyrimido[5,4-*e*] 1,2,4-triazines (**473**) are colorless to yellow, crystalline compounds, which are easily oxidized to pyrimido[5,4-*e*] 1,2,4-triazines (885, 886, 1338–1340, 1348, 1350, 1354–1357, 1362, 1368). Ultraviolet (885, 1338, 1339, 1348, 1350, 1352), infrared (885, 1348, 1352), and PMR spectroscopic data (885, 1338, 1339, 1348, 1352, 1355, 1356) for these compounds were published by different groups. For the unsubstituted **473** the following data were reported (1338). Ultraviolet (EtOH): λ_{max} (log ϵ) = 334 (3.72), 272 (3.31), 238 (3.68), and 216 nm (4.31). NMR (DMSO-D_6): τ = 1.20 and 1.92 (H-1, H-2), 2.25 (H-7), 3.08 (H-5), and 3.61 (H-3). The mass spectra of 7-substituted 1,2-dihydro-5-trifluoromethylpyrimido[5,4-*e*] 1,2,4-triazines were published by Clark (1374). He found that loss of HF initiated the major breakdown pathway, unless a large 7-substituent was present, which then fragmented preferentially.

d. REACTIONS. In 1,2-dihydropyrimido[5,4-*e*] 1,2,4-triazines (**473**) the 1,2,4-triazine ring is readily opened to yield the pyrimidine derivatives (**519**) (885, 886, 1348, 1384). Treatment of **473** with formic acid affords purine derivatives (**527**) (1339, 1384).



9. *Dihydropyrimido[5,4-e]1,2,4-triazin-3-ones*

At present only a few dihydropyrimido[5,4-*e*]1,2,4-triazin-3-ones (**522**) are known (1354, 1378, 1379). They were prepared by one of the following methods.

1. Cyclization of 5-amino-4-[2-(methoxycarbonyl)hydrazino]pyrimidines (**523**) with sodium hydroxide (1354).

2. Cyclization of 5-[(ethoxycarbonyl)amino]-4-hydrazinopyrimidines (**524**) by heating in ethanol with sodium ethoxide (1378).

3. Pyrolysis of 4-chloro-5-(4-semicarbazido)pyrimidines (**525**) at 135 to 140°C/0.01 torr (1378).

4. Reaction of 5-amino-4-hydrazinopyrimidines (**524a**) with phosgene and rearrangement of the formed 9-amino-8-purinols (**527a**) by refluxing them in ethanolic hydrochloric acid (1379).

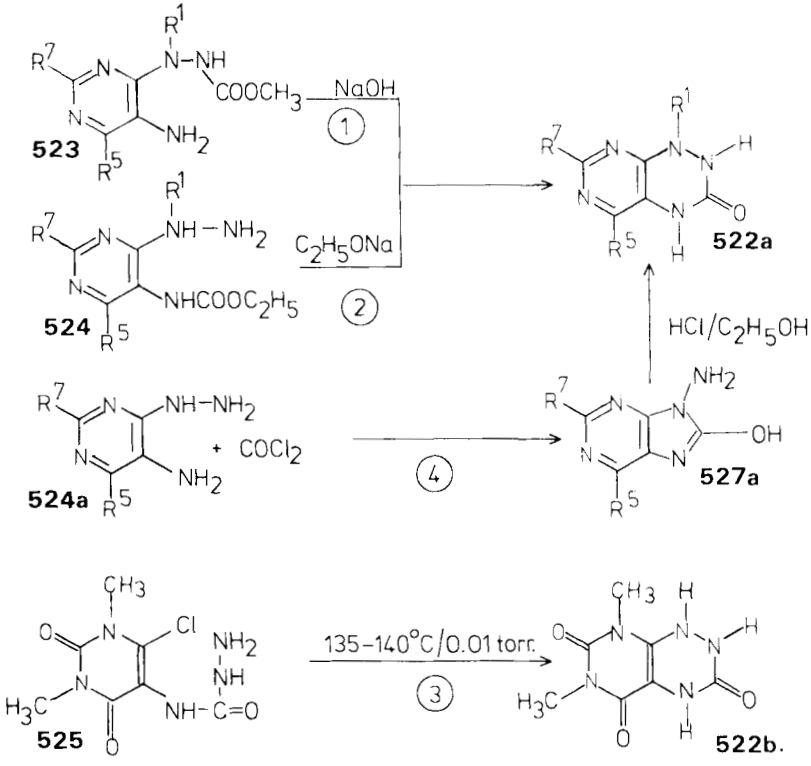
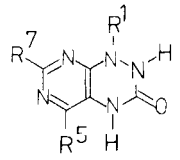


Table V-17 lists the known compounds of this class.

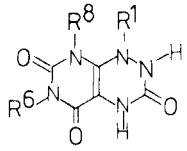
TABLE V-17. DIHYDROPYRIMIDO[5,4-*e*]1,2,4-TRIAZIN-3-ONES AND 3,5,7-TRIONES

A. 1,4-Dihydropyrimido[5,4-*e*]1,2,4-triazin-3-ones



R^1	R^5	R^7	m.p. (°C)	Refs.
H	H	H	>280	1354
H	CH_3	H	>280	1354
H	CH_3	OH (taut.)	>280	1354
H	CH_3	C_6H_5NH	>280	1354
H	Cl	H	>320 (dec.)	1379
CH_3	Cl	H	>295 (dec.)	1379

B. 1,4-Dihydropyrimido[5,4-*e*]1,2,4-triazine-3,5,7-triones



R^1	R^6	R^8	m.p. (°C)	Refs.
H	CH_3	CH_3	250–251	1378
CH_3	CH_3	CH_3	241–242 (dec.)	1378

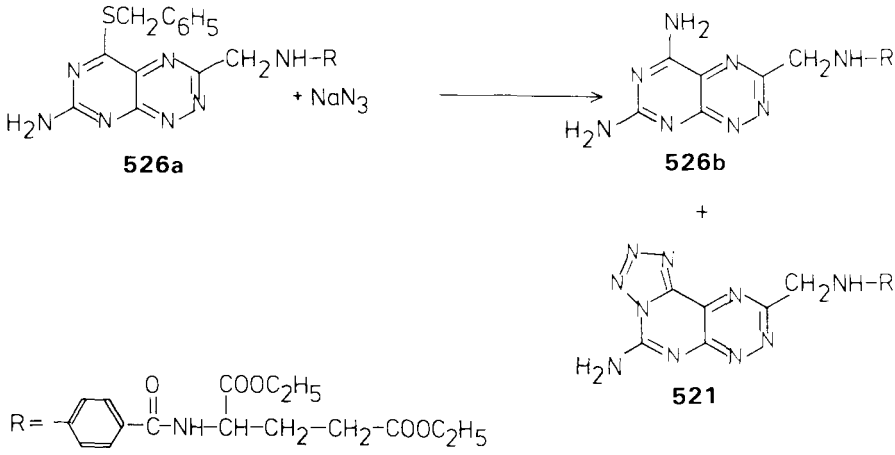
XII. CONDENSED WITH THE PYRAZINE RING

Calculations on the various pyrazino-1,2,4-triazines were reported by Wait and Wesley (1150).

XIII. CONDENSED WITH THE TETRAZOLO [1,5-*c*] PYRIMIDINE SYSTEM

A. Tetrazolo[1′,5′:1,6]pyrimido[5,4-*e*]1,2,4-triazines

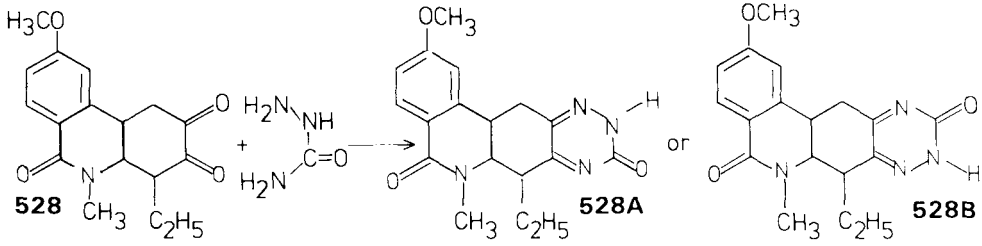
Treatment of the 7-amino-5-(benzylmercapto)pyrimido[5,4-*e*]1,2,4-triazine derivative (**526a**) with sodium azide in dimethyl sulfoxide afforded the 5,7-diamino derivative (**526b**) and diethyl *N*-(*p*-{[(5-aminotetrazolo[1′,5′:1,6]-pyrimido[5,4-*e*]1,2,4-triazin-8-yl)methyl]amino}benzoyl)-1-glutamate hydrate (**521**) (m.p. indefinite) (1352).



XIV. CONDENSED WITH THE PHENANTHRIDINE SYSTEM

A. 1,2,4-Triazino[6,5-*b*]phenanthridines

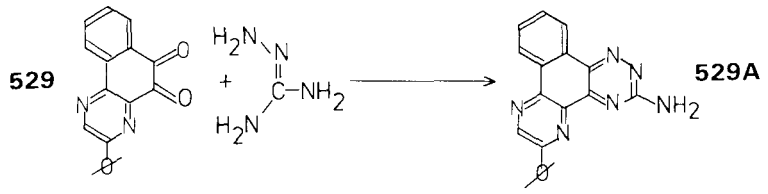
Kondo and Ishiwata (1320) obtained the ketone (**528**) through oxidation of the alkaloid lycoramin, which was then reacted with semicarbazide. Of the two possible isomeric compounds **528A** and **528B** they preferred structure **528A** [m.p. 238°C (dec.)].



XV. CONDENSED WITH THE BENZO[*f*] QUINOXALINE SYSTEM

A. Benzo[*f*]1,2,4-triazino[6,5-*h*]quinoxalines

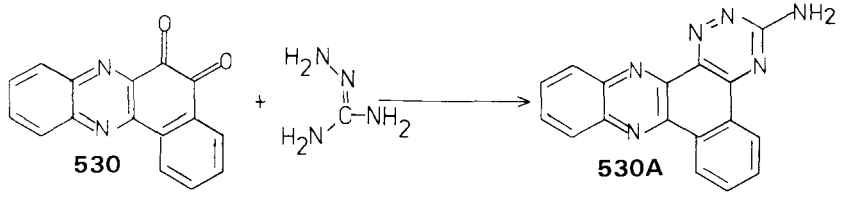
Rossi and Trave (619) reported the reaction of the quinone (**529**) with aminoguanidine and formulated the isolated compound as 3-amino-6-phenylbenzo[*f*]1,2,4-triazino[6,5-*h*]quinoxaline (**529A**) (m.p. 290°C).



XVI. CONDENSED WITH THE BENZO[*a*]PHENAZINE SYSTEM

A. Benzo[*a*]1,2,4-triazino[5,6-*c*]phenazines

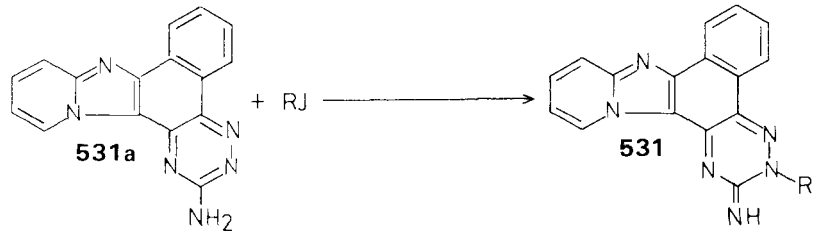
Rossi and Trave reacted the quinone (**530**) with aminoguanidine and formulated the isolated compound as **530A** (m.p. 324 to 325°C) (619).



XVII. CONDENSED WITH THE NAPHTH[1′2′:4,5]IMIDAZO-[1,2-*a*]PYRIDINE SYSTEM

A. Benzo[*h*]pyrido[2′,1′:2,3]imidazo[4,5-*f*]1,2,4-benzotriazines

A number of 2-alkyl-3-iminonaphth[1′2′;4,5]imidazo[1,2-*a*]pyrido[5,6-*e*]-1,2,4-triazines or 3-alkyl-2-iminobenzo[*h*]pyrido[2′,1′:2,3]imidazo[4,5-*f*]-1,2,4-benzotriazines (**531**) were synthesized through alkylation of the 3-amino compound (**531a**) (669, 1234) [R = CH_3, m.p. > 250°C (dec.); R = C_2H_5, 210°C; R = C_3H_7, 198°C (dec.); R = C_4H_9, 192°C (dec.); R = CH_2CH_2OH, ·HCl, 280°C (dec.)].

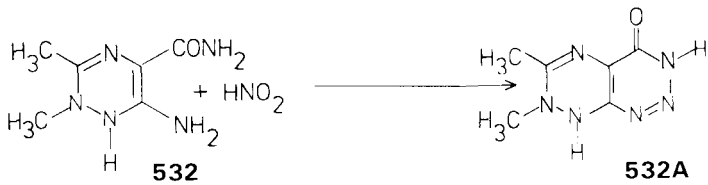


XVIII. CONDENSED WITH THE 1,2,3-TRIAZINE RING

Calculations on the various 1,2,3-triazino-1,2,4-triazines were reported by Wait and Wesley (1150).

A. 1,2,4-Triazino[6,5-*d*]1,2,3-triazines

Treatment of 6-amino-2,3-dimethyl-1,2-dihydro-1,2,4-triazine-5-carboxamide (**532**) with nitrous acid yields a compound which is formulated as 7,8-dihydro-6,7-dimethyl-1,2,4-triazino[6,5-*d*] 1,2,3-triazine-4-one (**532A**) [m.p. 194°C (dec.)] (1067).



532 **532A**

XIX. CONDENSED WITH THE 1,2,4-TRIAZINE RING

Calculations on 1,2,4-triazino-1,2,4-triazines were reported by Wait and Wesley (1150).

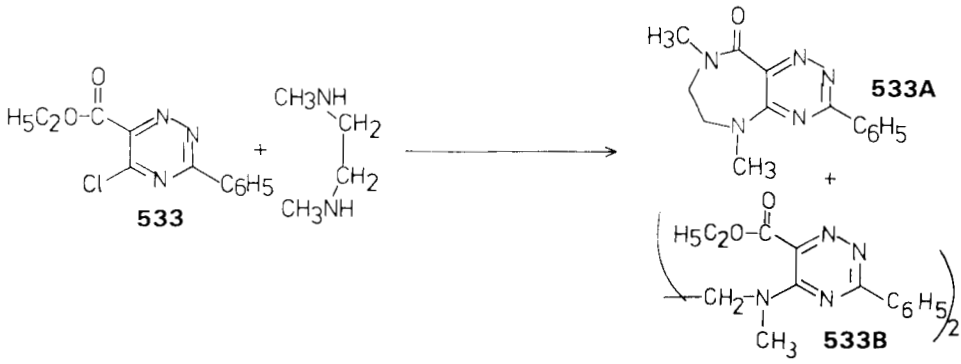
XX. CONDENSED WITH THE 1,2,3,4-TETRAZINE RING

Calculations on the 1,2,4-triazino[5,6-*e*] 1,2,3,4-tetrazine were reported by Wait and Wesley (1150).

XXI. CONDENSED WITH THE 1,4-DIAZEPINE RING

A. 1,2,4-Triazino[5,6-*e*]1,4-diazepines

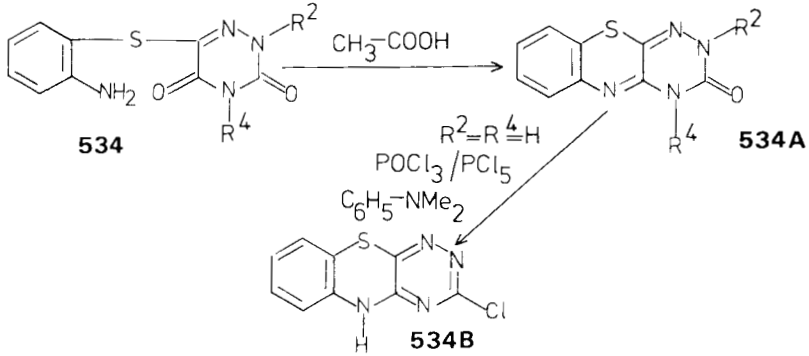
Treatment of ethyl 5-chloro-3-phenyl-1,2,4-triazine-6-carboxylate (**533**) with 1,2-bis(methylamino)ethane affords 5,8-dimethyl-3-penyl-5,6,7,8-tetrahydro-9*H*-1,2,4-triazino[5,6-*e*] 1,4-diazepin-9-one (**533A**) (m.p. 268°C) and compound **533B** (881).



XXII. CONDENSED WITH THE BENZO[*b*]1,4-THIAZINE SYSTEM

A. Benzo[*b*]1,2,4-triazino[5,6-*e*]1,4-thiazines

Refluxing 6-[(2-aminophenyl)mercapto]-1,2,4-triazine-3,5-diones (**534**) in acetic acid yields 4*H*-benzo[*b*]1,2,4-triazino[5,6-*e*]1,4-thiazin-3-ones (**534A**) ($R^2 = R^4 = H$; $R^2 = H$, $R^4 = C_6H_5CH_2$; $R^2 = C_6H_5CH_2$, $R^4 = H$; $R^2 = C_6H_5CH_2$, $R^4 = CH_3$; $R^2 = R^4 = C_6H_5CH_2$) (1554, 1556). Treatment of **534A** ($R^2 = R^4 = H$) with phosphoryl chloride and phosphorus pentachloride in the presence of *N*,*N*-dimethylaniline yields 3-chloro-5*H*-benzo[*b*]1,2,4-triazino[5,6-*e*]1,4-thiazine (**534B**) (1553).



Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

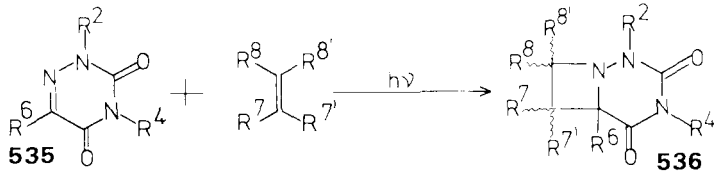
VI

1,2,4-Triazine Rings Condensed with Heterocycles through a Carbon and a Nitrogen Atom

I. CONDENSED WITH THE AZETIDINE RING

A. 1,2,4-Triazabicyclo[4.2.0]octanes

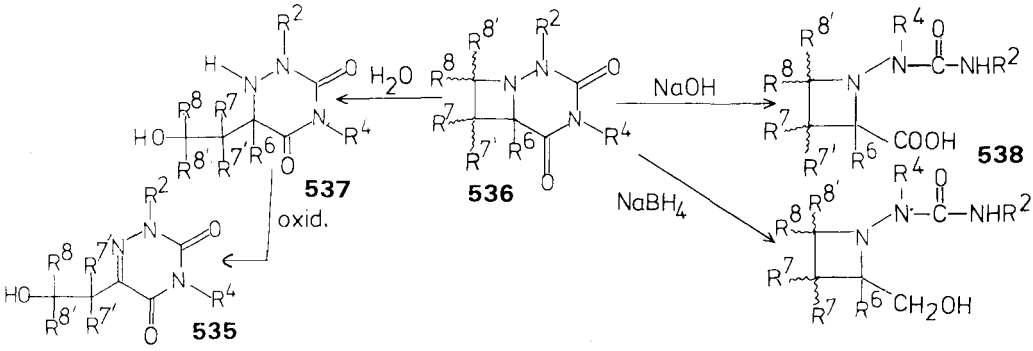
Swenton and co-workers (338, 339, 508, 509) have shown that acetone sensitized irradiation of 1,2,4-triazine-3,5-diones (**535**) in the presence of olefins, such as ethylene, tetramethylethylene, isobutene, vinyl ether, and vinyl acetates, produces good yields of the corresponding azetidines (**536**). In the case of the oxygen-substituted olefins, epimeric 8-substituted 1,2,4-triazabicyclo[4.2.0]-octane-3,5-diones (**536**) were formed with greater than 95% regioselectivity. Compound **536a** ($R^2 = R^4 = R^8 = CH_3$, $R^6 = R^7 = R^{7'} = H$, $R^{8'} = OAc$), isolated from 2,4-dimethyl-1,2,4-triazine-3,5-dione (**535a**) ($R^6 = H$, $R^2 = R^4 = CH_3$) and isopropenyl acetate, showed a PMR spectrum consistent only with the given orientation.



535 **536**

The cycloaddition products (**536**) (Table VI-1) can be isolated by careful chromatography, but not all prepared **536** have been isolated. Hydrolysis of **536** affords dihydro-1,2,4-triazine-3,5-diones (**537**) which ($R^2 = H$) can be oxidized to 1,2,4-triazine-3,5-diones (**535**). Treatment of **536** with sodium hydroxide or

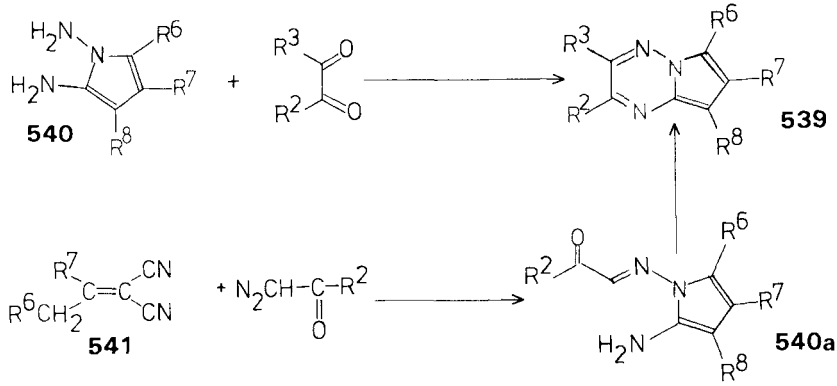
sodium borohydride opens the 1,2,4-triazine ring and gives monocyclic azetidines (**538**) (509).



II. CONDENSED WITH THE PYRROLE RING

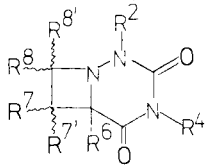
A Pyrrolo[1,2-*b*]1,2,4-triazines

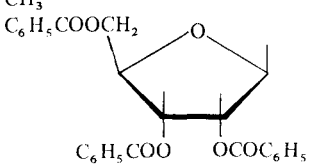
Two methods are reported for the synthesis of pyrrolo[1,2-*b*]1,2,4-triazines (**539**) (1386–1388) (RRI 11880): cyclocondensation of 1,2-diaminopyrroles (**540**) with 1,2-dicarbonyl compounds (1386, 1387) and addition of diazoketones or diazoacetate to alkylidenemalodinitriles (**541**) and cyclization of the formed 2-amino-1-(alkylideneamino)pyrroles (**540a**) (1386).



The isolated **539** (Table VI-2) are crystalline, stable, colored (orange, red) compounds with high melting points. The electronic spectrum of the 8-cyano-6-7-tetramethylene-2-phenylpyrrolo[1,2-*b*]1,2,4-triazine shows the following absorption maxima and absorptivities (1388): λ_{max} (log ϵ) = 499 (3.35), 463 sh

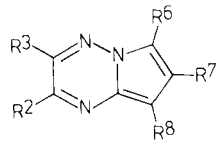
TABLE VI-1. 1,2,4-TRIAZABICYCLO[4.2.0]OCTANES



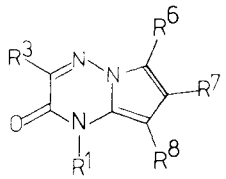
R^2	R^4	R^6	R^7	$R^{7'}$	R^8	$R^{8'}$	m.p. (°C)	Refs.
H	H	H	H	H	CH_3	$OCOCH_3$		338, 339
H	H	H	H	$-(CH_2)_4-$		$OCOCH_3$		338, 339
H	H	CH_3COCH_2	H	H	CH_3	$OCOCH_3$		339
CH_3	CH_3	H	H	H	H	H	b.p. 73–75/0.15	509
CH_3	CH_3	H	H	H	H	OC_2H_5	58–61 (*)	508, 509
							Oil	509
CH_3	CH_3	H	H	H	H	$OCOCH_3$	78.5–80 (*)	509
							82–83	509
CH_3	CH_3	H	H	H	CH_3	CH_3	b.p. 65/0.01	509
CH_3	CH_3	H	H	$-(CH_2)_4-$		H	47–50	509
CH_3	CH_3	H	H	$-(CH_2)_6-$		H	b.p. 110/0.01	509
CH_3	CH_3	H	H	H	CH_3	$OCOCH_3$	99–102	338, 339, 509
CH_3	CH_3	H	H	$-(CH_2)_4-$		$OCOCH_3$		338, 339
CH_3	CH_3	H	CH_3	CH_3	CH_3	CH_3	61–63	509
CH_3	CH_3	CH_3	H	H	H	$OCOCH_3$	104–105.5 (*)	509
							oil	509
CH_3	CH_3	CH_3COCH_2	H	H	CH_3	$OCOCH_3$		339
CH_3	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3	74–75	509
	H	H	H	H	CH_3	$OCOCH_3$		339

*Epimers which structure could not be established.

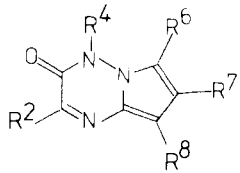
TABLE VI-2. PYRROLO[1,2-*b*]1,2,4-TRIAZINES



R^2	R^3	R^6	R^7	R^8	m.p. (°C)	Refs.
H	H	NH_2	CN	CN	288–290	1386, 1387
CH_3	CH_3	NH_2	CN	CN	276–278 (dec.)	1386, 1387
CH_3	CH_3	$N{=}CH{-}C_6H_5$	CN	CN	263–265	1386, 1387
CH_3	CH_3	$N(CH_3)_2$	CN	CN	242–243	1386
C_6H_5	H	$-(CH_2)_4-$		CN	211	1388
C_6H_5	C_6H_5	NH_2	CN	CN	300	1386, 1387
C_6H_5	C_6H_5	$N{=}CH{-}C_6H_5$	CN	CN	276–277	1386, 1387
4-$O_2N{-}C_6H_4$	H	H	C_6H_5	CN	296	1388
4-$O_2N{-}C_6H_4$	H	$-(CH_2)_4-$		CN	268	1388



R^1	R^3	R^6	R^7	R^8	m.p. (°C)	Refs.
H	H	$-(CH_2)_4-$		CN	293–295	1388
CH_3	H	$-(CH_2)_4-$		CN	218–220	1388

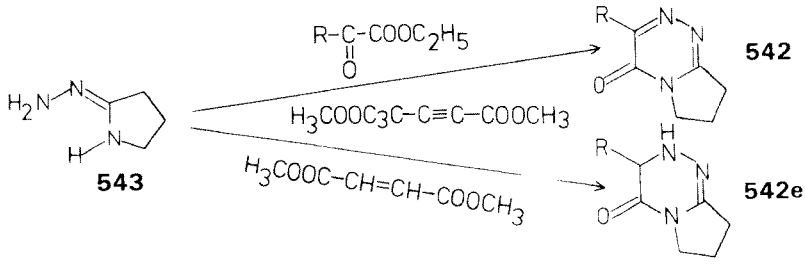


R^2	R^4	R^6	R^7	R^8	m.p. (°C)	Refs.
CH_3	H	NH_2	CN	CN	>300	1386, 1387
$COOC_2H_5$	H	NH_2	CN	CN	>300	1386, 1387

(3.81), 441 (3.86), 337 sh (3.62), 292 (4.46), and 250 sh nm (4.03). The amino group in the 6-position reacts with aldehydes and can be methylated (1386, 1387).

B. Pyrrolo[2,1-*c*]1,2,4-triazines

The five known tetrahydropyrrolo[2,1-*c*]1,2,4-triazines (**542**) were prepared by the reaction of the cyclic amidrazone (**543**) with ethyl pyruvate, ethyl phenylglyoxalate, diethyl oxalate, dimethyl acetylenedicarboxylate, or dimethyl maleate (181, 1390).



The following melting points are reported: R = CH_3 (**542a**), 133°C; R = C_6H_5, 158°C; R = OH (tautomer), 181°C; R = CH_2COOCH_3, 138–141°C; **542e**, 88°C.

542a shows the following signals in the PMR spectrum ($CDCl_3$): τ = 5.88 (H-6), 7.92 (H-7), 6.90 (H-8), and 7.60 (CH_3). The electronic spectrum of **542a** shows two maxima at 268 and 219 nm; the absorptivities are log ϵ = 3.76 and 3.79.

C. Pyrrolo[1,2-*d*]1,2,4-triazines

Three methods have been used for the synthesis of the known pyrrolo[1,2-*d*]1,2,4-triazines (**544–546**) (1391–1393).

1. Base-catalyzed cyclodehydration of pyrrole-2-carbaldehyde acylhydrazones (**547a**) (1393) to give the pyrrolo[1,2-*d*]1,2,4-triazines (**544**).

2. Reaction of 1-(ethoxycarbonyl)pyrrole-2-carbaldehyde (**547b**) with hydrazines and cyclization of the formed hydrazones (**548**) yields pyrrolo[1,2-*d*]1,2,4-triazin-4-ones (**545**) (1391).

3. Pyrrolo[1,2-*d*]1,2,4-triazin-1-ones (**546**) were prepared through rearrangement of pyrrolyl-2-oxadiazoles (**549**) (1392) with potassium hydroxide in ethanol.

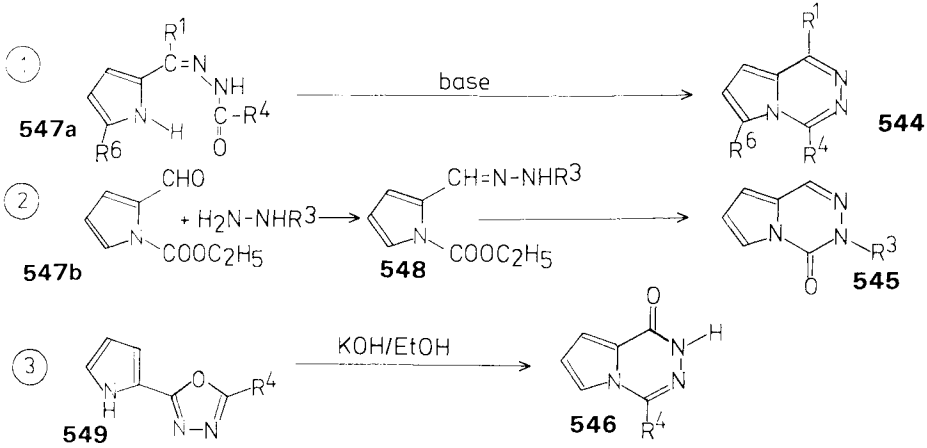


Table VI-3 lists compounds of this group reported in the literature.

The following PMR spectrum and electronic spectrum were reported for the unsubstituted pyrrolo[1,2-*d*] 1,2,4-triazine (**544a**) (1393). PMR (DMSO-d_6): $\tau = 0.55$ (H-4), 0.85 (H-1), 2.19 (H-6), and 2.90–3.20 (H-7, H-8); λ_{max} (ϵ) = 322 (2.900), 278 (5.550), 268 (6.550), 262 (6.300), 232 sh (31.500), and 223 nm (37.100).

Bromination of **546** yields 6-bromopyrrolo[1,2-*d*] 1,2,4-triazin-1-ones (**550a**), nitration yields 6,8-dinitropyrrolo[1,2-*d*] 1,2,4-triazin-1-ones (**550b**), and treatment of **546** with phosphorus pentasulfide affords the pyrrolo[1,2-*d*] 1,2,4-triazine-1-thiones (**552**) (1392).

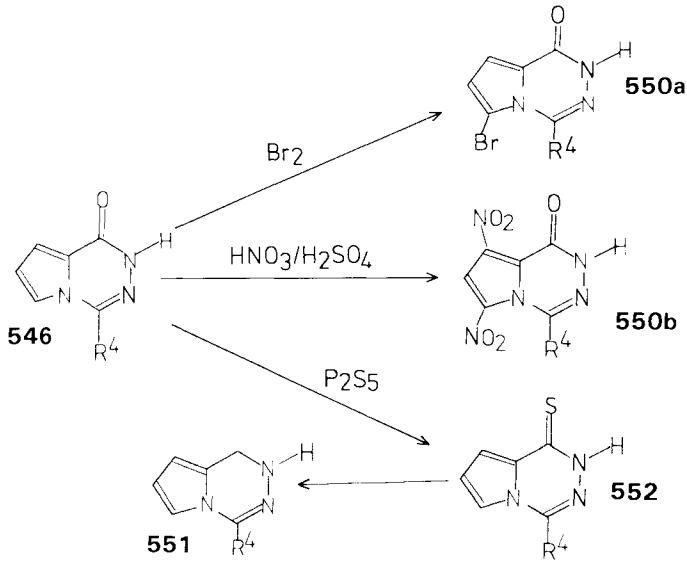


TABLE VI-3. PYRROLO[1,2-*d*]1,2,4-TRIAZINES

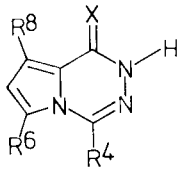
A. Pyrrolo[1,2-*d*] 1,2,4-triazines (**544**)

R^1	R^4	R^6	m.p. (°C)	Refs.
H	H	H	113–114	1393
H	H	CH_3		1393
H	H	Br	103–104	1393
H	CH_3	H		1393
CH_3	H	H		1390

B. Pyrrolo[1,2-*d*] 1,2,4-triazin-4-ones (**545**)

R^3	m.p. (°C)	Refs.
H	157	1391
CH_3	47	1391
C_6H_5	88	1391
CH_2CH_2OH	84	1391
$COOC_2H_5$		1391

C. Pyrrolo[1,2-*d*] 1,2,4-triazin-1-ones (**546**) and -1-thiones (**552**)



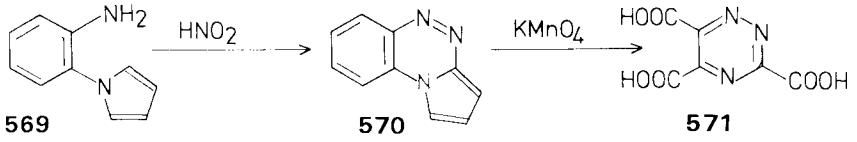
X	R^4	R^6	R^8	m.p. (°C)	Refs.
O	H	H	H	265	1392
O	H	Br	H	212	1392
O	H	NO_2	NO_2	>265	1392
O	CH_3	H	H	232	1392
O	OH	H	H (tautomer)	268	1392
O	OH	Br	H (tautomer)	265	1392
S	H	H	H	228	1392
S	CH_3	H	H	215	1392

Reduction of **552** (R^4 = H) with hydrogen in the presence of 10% palladium/carbon affords the 1,2-dihydro-pyrrolo[1,2-*d*] 1,2,4-triazine (**551**) (m.p. 64°C) (1392).

D. Pyrrolo[2,1-*c*]1,2,4-benzotriazine

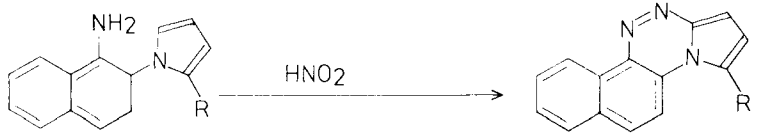
Gross and Gloede (1396) obtained pyrrolo[2,1-*c*] 1,2,4-benzotriazine (**570**) (m.p. 243 to 244°C) when 1-(2-aminophenyl)pyrrole (**569**) was diazotized.

Oxidative degradation of **570** with potassium permanganate yields 1,2,4-triazine-3,5,6-tricarboxylic acid (**571**).



E. Naphtho[2,1-*e*]pyrrolo[2,1-*c*]1,2,4-triazines

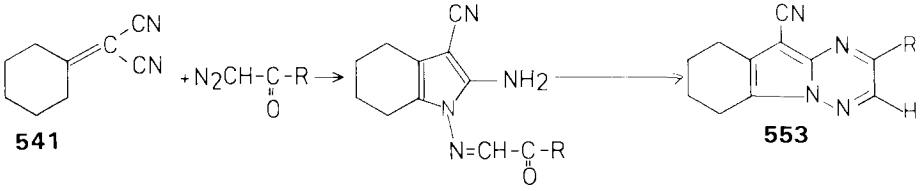
The known naphtho[2,1-*e*]pyrrolo[2,1-*c*] 1,2,4-triazines (**572**) were prepared by treating 1-amino-2-(1-pyrrolyl)naphthalenes (**573**) with aqueous nitrous acid (1402, 1403) (R = H, m.p. 241°C; R = CN, 265 to 266°C; R = CHO, 217 to 220°C; R = CHNOH, 240 to 243°C; R = $CONH_2$, 350°C).



III. CONDENSED WITH THE INDOLE SYSTEM

A. 1,2,4-Triazino[4,5-*a*]indoles

Three tetrahydro-1,2,4-triazino[2,3-*a*]indoles (**553**) were prepared by Gewald and co-workers (1388) through the reaction of alkylidenemalodinitriles (**541**) with diazo compounds. The melting points of these compounds are included in Table VI-2.

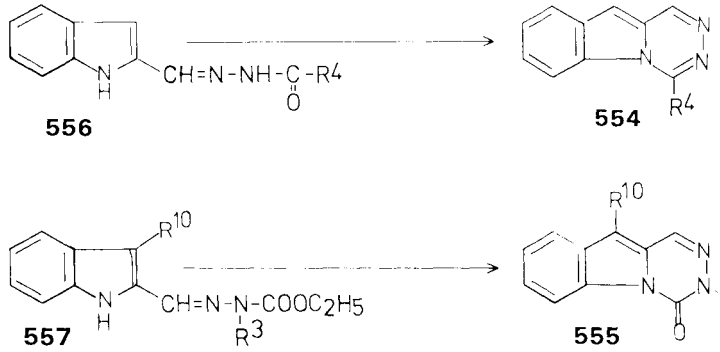


B. 1,2,4-Triazino[4,5-*a*]indoles

Robba and his group (1394, 1395) obtained 1,2,4-triazino[4,5-*a*]-indoles (**554**) and 1,2,4-triazino[4,5-*a*]indol-4-ones (**555**) through cyclization

of the acylhydrazones (**556**) or (ethoxycarbonyl)hydrazones (**557**) of indole-2-carbaldehyde. For the synthesis of 1,2,4-triazino[4,5-*a*]indol-1-ones (**558**) and 1,2,4-triazino[4,5-*a*]indole-1,4-diones (**559**) the rearrangement of 2-(1,3,4-oxadiazol-2-yl)indoles (**560**, **561**) and cyclization of acylhydrazides (**562**) or (ethoxycarbonyl)hydrazides (**563**) of indole-2-carboxylic acid were used.

Table VI-4 lists the known 1,2,4-triazino[4,5-*a*]indoles.



Treatment of 1,2,4-triazino[4,5-*a*]indol-1-ones (**558**) with phosphoryl chloride gives 1-chloro-1,2,4-triazino[4,5-*a*]indoles (**564**); 1,2,4-triazino[4,5-*a*]-indole-1-thiones (**565**) were obtained when **558** were treated with phosphorus pentasulfide. Both **564** and **565** can be converted to 1-alkoxy- (**566**) or 1-hydrazino-1,2,4-triazino[4,5-*a*]indoles (**567**).

Treatment of **565** with Raney nickel gives **554** and reduction with hydrogen in the presence of palladium/charcoal affords 1,2-dihydro-1,2,4-triazino[4,5-*a*]-indole (**568**) (m.p. 198°C). Bromination of 1,2,4-triazino[4,5-*a*]indoles always gives the 10-bromo derivatives.

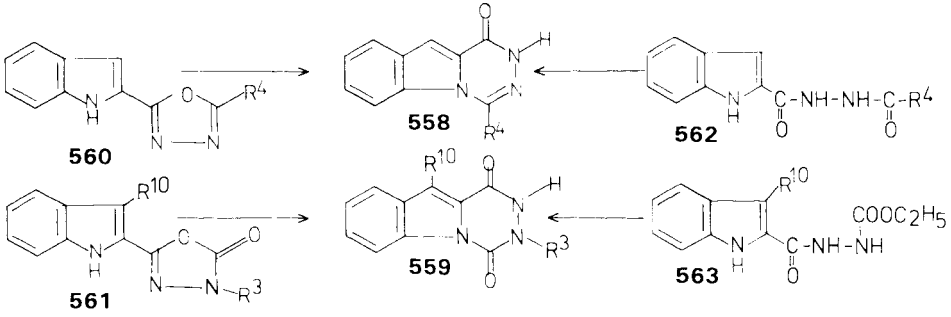
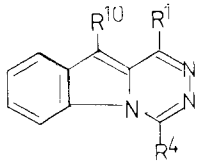


TABLE VI-4. 1,2,4-TRIAZINO[4,5-*a*]INDOLES AND OXO AND THIOXO DERIVATIVES

A. 1,2,4-Triazino[4,5-*a*]indoles

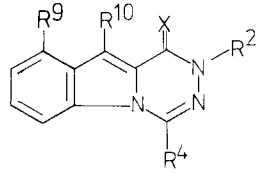


R^1	R^4	R^{10}	m.p. (°C)	Refs.
H	H	H	152	1395
Cl	H	Br	267	1395
Cl	CH_3	H	175	1395
OCH_3	CH_3	H	183	1395
OC_2H_5	H	H	238	1395
$NHNH_2$	H	H	264	1395
$NHNH_2$	CH_3	H	222	1395

B. 1,2,4-Triazino[4,5-*a*]indol-4-ones (**555**)

R^3	R^{10}	m.p. (°C)	Refs.
H	H	219	1395
H	Br	235	1395
CH_3	H	120	1395

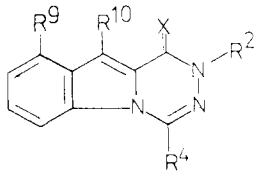
C. 1,2,4-Triazino[4,5-*a*]indol-1-ones and 1-thiones



X	R^2	R^4	R^9	R^{10}	m.p. (°C)	Refs.
O	H	H	H	H	275	1394
O	H	H	H	Br	305	1395
O	H	H	Cl	H	274	1395
O	H	CH_3	H	H	320	1394
O	H	$CH_2OC_3H_7$	H	H	184	1395
O	CH_3	H	H	H	190	1395
O	CH_3	CH_3	H	H	182	1395
O	CH_2COOH	H	H	H	320	1395
O	$C_6H_5CH_2$	H	H	H	194	1395

TABLE VI-4. (continued)

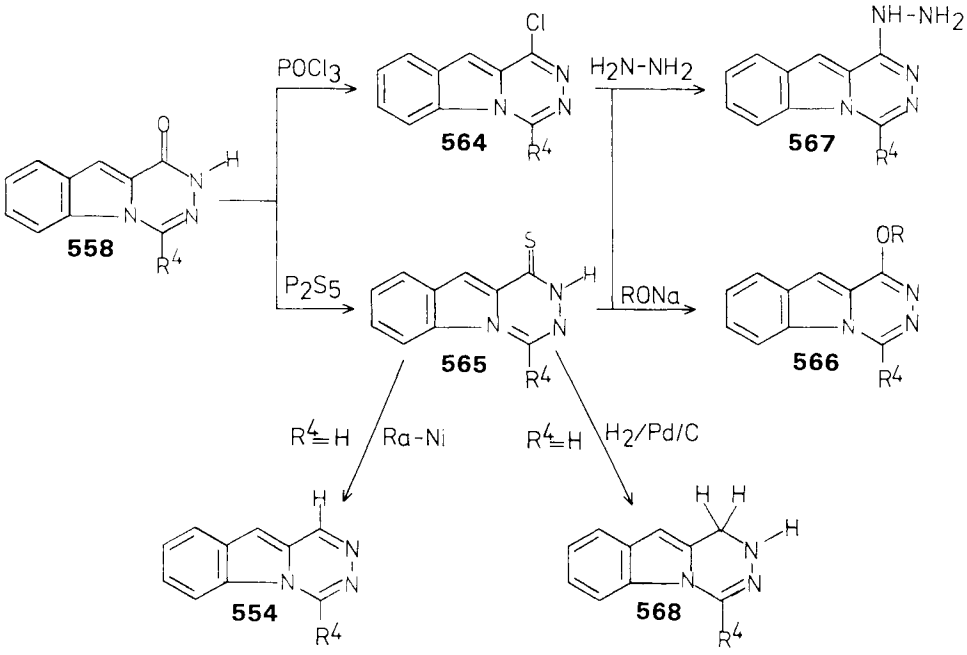
C. 1,2,4-Triazino[4,5-*a*]indol-1-ones and 1-thiones



X	R^2	R^4	R^9	R^{10}	m.p.(°C)	Refs.
S	H	H	H	H	260	1395
S	H	CH_3	H	H	320	1395

D. 1,2,4-Triazino[4,5-*a*]indole-1,4-diones (559)

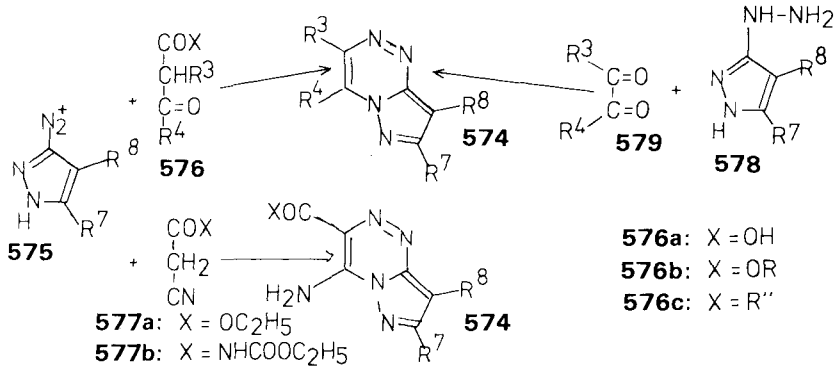
R^3	R^{10}	m.p. (°C)	Refs.
H	H	238	1395
		360	1394
H	Br	350	1395
CH_3	H	312	1395



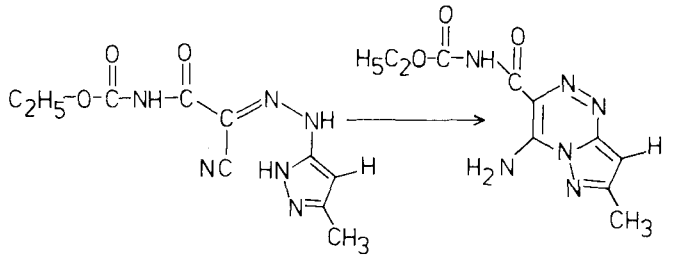
IV. CONDENSED WITH THE PYRAZOLE RING

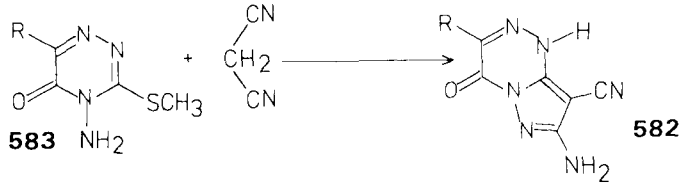
A. Pyrazolo[5,1-*c*]1,2,4-triazines

The pyrazolo[5,1-*c*]1,2,4-triazines (**574**) were synthesized from both pyrazole and 1,2,4-triazine precursors. **574** have been prepared from pyrazole derivatives, by interaction of diazotized 3-aminopyrazole (**575**) and a β-keto acid (**576a**), and similarly from a β-keto ester (**576b**), a β-diketone (**576c**), cyanoacetate (**577a**) (1397), or ethyl cyano acetylcarbamidate (**577b**) (893), and by condensation of 3-hydrazinopyrazole (**578**) and a α-diketone (**579**) (1397).



Slouka and his group (893) obtained **580** when they heated the pyrazole derivative **581** in ethanol. Dornow and Pietsch (1078) reported the synthesis of



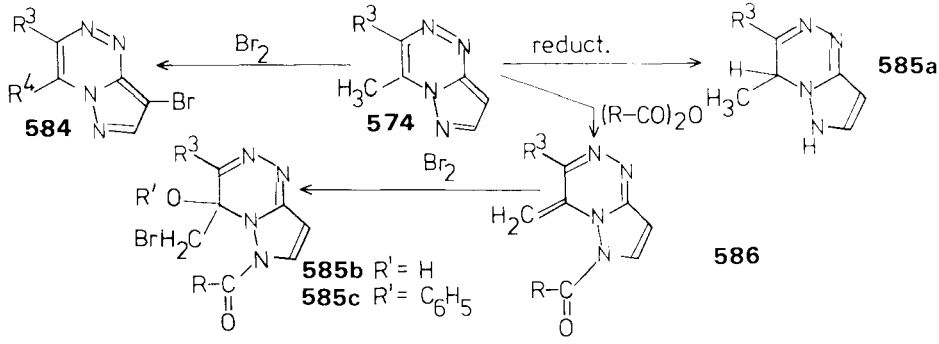


582 from interaction of 4-amino-3-(methylmercapto)-1,2,4-triazin-5-ones (**583**) with malodinitrile.

Table VI-5 lists the compounds of this group reported in the literature.

Pyrazolo[5,1-*c*] 1,2,4-triazines are mostly yellow, crystalline compounds. The following electronic spectrum is reported for the 4-methylpyrazolo[5,1-*c*] 1,2,4-triazine: λ_{max} (log ϵ): 350 (3.41), 295 infl. (3.15), 287 (3.28), and 226 nm (4.50) (1397). The mass spectra of pyrazolo[5,1-*c*] 1,2,4-triazines were studied by Stevens and his group (165).

Reduction of pyrazolo[5,1-*c*] 1,2,4-triazines (**574**) gives 4,6-dihydropyrazolo[5,1-*c*] 1,2,4-triazines (**585a**) (1397). Acylation of 4-methyl derivatives of **574** affords 6-acyl-4-methylene-4,6-dihydropyrazolo[5,1-*c*] 1,2,4-triazines (**586**) (1397). Bromination of **574** yields the 8-bromo derivative (**584**), whereas 6-acyl-4-methylene-4,6-dihydropyrazolo[5,1-*c*] 1,2,4-triazines (**586**) give a 4-bromohydrin (**585b**) or its ether (**585c**), depending on the reaction conditions (1404).

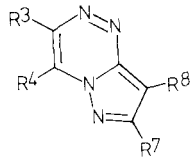


Treatment of pyrazolo[5,1-*c*] 1,2,4-triazines with carbonyl reagents led to a degradation of the 1,2,4-triazine ring (1389). The synthesis of a pyrazolo[5,1-*c*]-pyrimido[4,5-*e*] 1,2,4-triazine from a pyrazolo[5,1-*c*] 1,2,4-triazine is reported by Slouka and his group (893).

B. Pyrazolo[1,5-*d*] 1,2,4-triazines

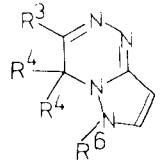
Pyrazolo[1,5-*d*] 1,2,4-triazines (**587**), also called pyrazolo[2,3-*d*] 1,2,4-triazines (RRI 1158), were prepared by cyclization of pyrazole-3-carboxylic acid hydrazides (**588**) with triethyl orthoformate (1398–1400) or acetic anhydride (1401). Reaction of **588** ($R^2 = CH_3$) and carbon disulfide in alcoholic potassium hydroxide yielded potassium dithiocarbazate (**589**) which can be transformed to the methyl derivatives (**590**) (1398). Heating and acidification of both compounds (**589** and **590**) afforded 2-methyl-7-mercaptopyrazolo[1,5-*d*]-1,2,4-triazin-4-one (**591a**).

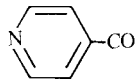
TABLE VI-5. PYRAZOLO[5,1-*c*] 1,2,4-TRIAZINES AND 4,6-DIHYDRO DERIVATIVES

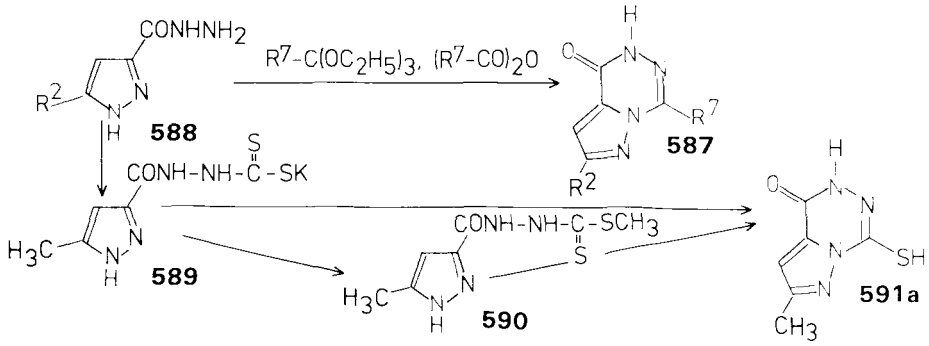


R^3	R^4	R^7	R^8	m.p. (°C)	Refs.
H	CH_3	H	H	102–103	1397
H	OH	H	H	344–345 (taut.)	1397
H	$OCOC_6H_5$	H	H	234–236	1397
H	NH_2	H	H	295 (dec.)	1397
H	$N(COCH_3)_2$	H	H	148–149	1397
CH_3	CH_3	H	H	105–106	1397, 1404
CH_3	CH_3	H	Br	135–136	1404
CH_3	CH_3	H	$COOC_2H_5$	130–131	1397
CH_3	OH	H	H	290 (taut.)	1397
CH_3	OH	NH_2	CN	280–340 (dec.) (taut.)	1078
C_6H_5	C_6H_5	H	H	193–194	1397
C_6H_5	OH	NH_2	CN	300–360 (dec.) (taut.)	1078
C_6H_5	OH	NH_2	$CONH_2$	293–294 (dec.) (taut.)	1078
CH_3CO	CH_3	H	H	94–95	1397
COOH	CH_3	H	H	174–175	1397
COOH	C_6H_5	H	H	280–290 (efferv.)	1397
COOH	NH_2	H	H	285–290 (efferv.)	1397
$COOC_2H_5$	CH_3	H	H	92–93	1397
$COOC_2H_5$	C_6H_5	H	H	120–121	1397
$COOC_2H_5$	NH_2	H	H	154–155	1397
$COOC_2H_5$	$N(COCH_3)_2$	H	H	135–136	1397
$COOC_2H_5$	$N(CH_2CH_2Cl)_2$	H	H	133–134	1397
$COOC_2H_5$	$N(CH_2CH_2OH)_2$	H	H	184–185	1397
$CONHNH_2$	NH_2	H	H	276–277	1389
$CONHN{=}CHC_6H_5$	NH_2	H	H	300 (dec.)	1389
CONHNHCHO	NH_2	H	H	300–301 (dec.)	1389
$CONHCOOC_2H_5$	NH_2	CH_3	H	208–210	893

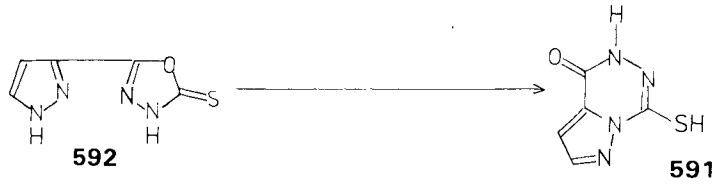
TABLE VI-5. (continued)



R^3	R^4	R^4	R^6	m.p. (°C)	Refs.
CH_3		$=CH_2$	CH_3CO	97–98	1397
CH_3		$=CH_2$	$ClCH_2CO$	155–156	1397
CH_3		$=CH_2$	FCH_2CO	156–157	1397
CH_3		$=CH_2$	JCH_2CO	112–113	1397
CH_3		$=CH_2$	Cl_2CHCO	114–115	1397
CH_3		$=CH_2$	C_6H_5CO	109–110	1397
CH_3		$=CH_2$	$C_6H_5SO_2$	163–164	1397
CH_3		$=CH_2$	$4\text{-}O_2N\text{-}C_6H_4SO_2$	238–240	1397
CH_3		$=CH_2$	$4\text{-}CH_3CONH\text{-}C_6H_4SO_2$	214–216	1397
CH_3		$=CH_2$	Phthalimidoacetyl	222–223	1397
CH_3		$=CH_2$		149–150	1397
CH_3	H	CH_3	H	111–113	1397
CH_3	H	CH_3	CH_3CO	89–90	1397
CH_3	OH	CH_2Br	CH_3CO	143–144 (dec.) (benzene)	1404
				153–154 (dec.) ($CHCl_3$)	1404
CH_3	OH	CH_2Br	$ClCH_2CO$	154–155	1404
CH_3	OC_2H_5	CH_2Br	CH_3CO	96–97	1404
CH_3	OC_2H_5	CH_2Br	$ClCH_2CO$	149–150	1404
CH_3	OH	CH_2–N 	CH_3CO	141–142	1404



Ainsworth (1399) observed the thermal isomerization of 2-(3-pyrazolyl)-1,3,4-oxadiazoline-5-thione (**592**) to 7-mercaptopyrazolo [1,5-*d*]1,2,4-triazin-4-one (**591b**).



Compounds of this group reported in the literature are listed in Table VI-6.

Pyrazolo[1,5-*d*] 1,2,4-triazines are crystalline, stable compounds. Pyrazolo-[1,5-*d*] 1,2,4-triazin-4-ones or 4-thiones are soluble in bases and are reprecipitated by acid. The pK_a value of 7-mercaptopyrrolo[1,5-*d*] 1,2,4-triazine was found to be 4.1 (1399); the following electronic spectrum is reported for the same compound: λ_{max} (log ϵ): 297 (4.09), 262 (4.11), and 234 nm (3.81) (1399). Pyrazolo[1,5-*d*] 1,2,4-triazin-4-one has only one absorption maximum at 262 nm (log ϵ = 4.11) (1399). The PMR spectrum of 2-methyl-pyrazolo[1,5-*d*] 1,2,4-triazin-4-one is reported by Ajello and Arnone (1398): τ = −2.40 (N–H), 1.08 (H-7), 2.98 (H-3), and 7.56 (CH_3).

Pyrazolo[1,5-*d*] 1,2,4-triazin-4-ones (**587**) can be converted to the 4-thiones (**593**) and the 4-chloro derivatives (**594**) by treatment with phosphorus pentasulfide and phosphoryl chloride, respectively (1401). Reaction of the chloro derivatives (**594**) with sodium methoxide gives the 4-methoxy derivatives (**595**) (1401).

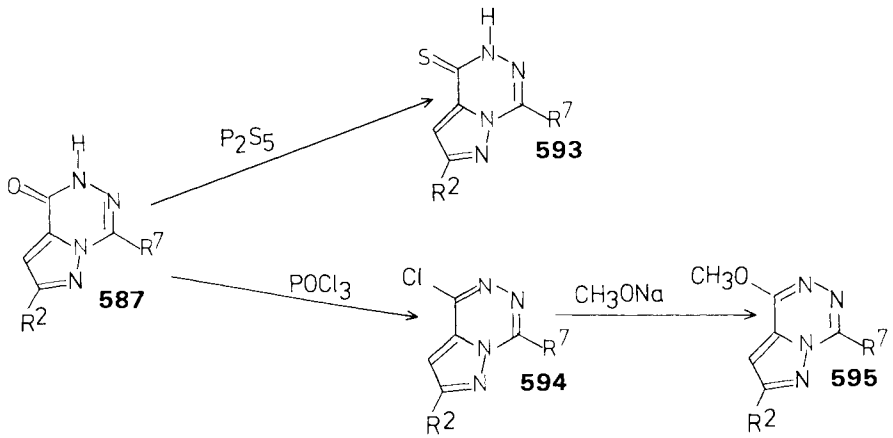
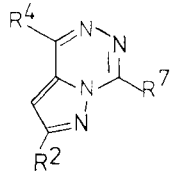


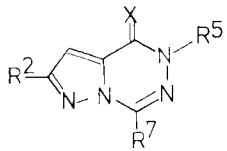
TABLE VI-6. PYRAZOLO[1,5-*d*]1,2,4-TRIAZINES AND OXO AND THIOXO DERIVATIVES

A. Pyrazolo[1,5-*d*]1,2,4-triazines



R^2	R^4	R^7		m.p. (°C)	Refs.
CH_3	Cl	CH_3		132–133	1401
CH_3	OCH_3	CH_3		164–166	1401
			6-MeJ	145–147 (dec.)	1401
CH_3	SCH_3	CH_3		151–153	1401
			6-MeJ	233 (dec.)	1401
			6-EtJ	220 (dec.)	1401
CH_3	SC_2H_5	CH_3		67–69	1401
			6-EtJ	220 (dec.)	1401
CH_3	$SCH_2C_6H_5$	CH_3		56–58	1401
			6-MeJ	196–198 (dec.)	1401
C_6H_5	SCH_3	CH_3		148–150	1401

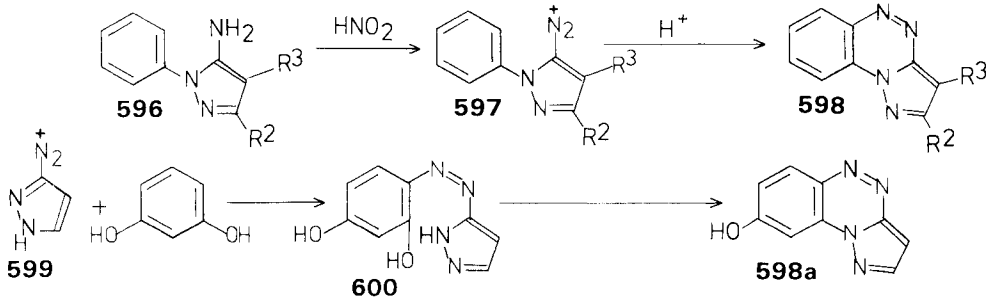
B. Pyrazolo[1,5-*d*]1,2,4-triazin-4-ones and 4-thiones



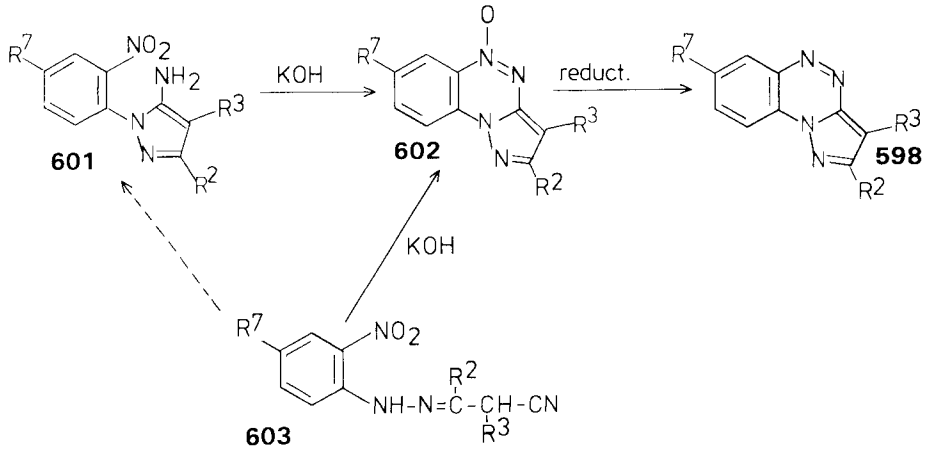
R^2	X	R^5	R^7	m.p. (°C)	Refs.
H	O	H	H	265	1400
				265–267	1399
H	O	H	SH	201–202	1399
CH_3	O	H	H	282	1398
CH_3	O	H	CH_3	226–228	1401
CH_3	O	H	SH	188	1398
CH_3	O	CH_3	SCH_3	97	1398
CH_3	O	$CH_2CH_2N(C_2H_5)_2$	H	56	1398
	·HCl			222	1398
CH_3	O	CH_3CO	H	169	1398
CH_3	O	CH_3CO	SH	196	1398
C_6H_5	O	H	CH_3	254–256	1401
C_6H_5	S	H	CH_3	228–230	1401
CH_3	S	H	CH_3	224–226	1401

C. Pyrazolo[5,1-*c*]1,2,4-benzotriazines

Diazotization of the 1-phenyl-5-aminopyrazoles (**596**) yields the diazonium salts (**597**) which are converted to the pyrazolo[5,1-*c*] 1,2,4-benzotriazines (**598**) when heated in dilute mineral acid (1405–1407). The reaction of diazotized 3-aminopyrazole (**599**) and resorcinol affords a coupling product (**600**), which is readily cyclized to **598a** (1389) (RRI 2726).

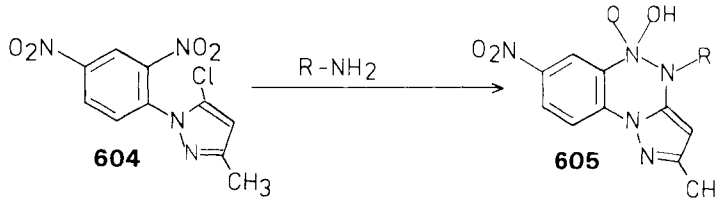


Treatment of 1-(2-nitrophenyl)-5-aminopyrazoles (**601**) with potassium hydroxide has been used for the synthesis of pyrazolo[5,1-*c*] 1,2,4-benzotriazine 5-oxides (**602**) (1407). **602** were also obtained by Sprio and Plescia (1408) when the 2-nitrophenylhydrazones of the β-ketonitriles (**603**) were treated with potassium hydroxide. In this reaction **601** are probably the intermediates. Reduction of the *N*-oxides (**602**) with sodium dithionite (1408) or by catalytic hydrogenation (1407) gives **598**.



Rojahn and Fegeler (1409) reported the reaction of 1-(2,4-dinitrophenyl)-5-chloro-3-methylpyrazole (**604**) with amines. The products isolated were

formulated as **605** [R = H, m.p. 204°C; R = C_6H_5, 190°C; R = 4–CH_3 –C_6H_4, 166°C; R = C_6H_5–NH, 216°C (dec.); R = HCO, 286°C].



Known pyrazolo[5,1-*c*]1,2,4-benzotriazines and 5-oxides are listed in Table VI-7.

Pyrazolo[5,1-*c*]1,2,4-benzotriazines are stable, colored (yellow, brown, orange-red) crystalline compounds. They are weak bases, are soluble in concentrated mineral acids, giving a blood-red solution, and reprecipitate on addition of water (1406). They are insoluble in bases and do not react with acetic anhydride. The following electronic spectrum is published for the 8-hydroxy derivative: λ_{max} (log ϵ) = 376 (3.96), 326 infl. (3.71), 290 infl. (3.50), 282 (3.55), 268 infl. (3.98), 251 (4.28), and 227 nm (4.49) (1389). The mass spectra of two pyrazolo[5,1-*c*]1,2,4-benzotriazines were recorded by Palmer, Preston, and Stevens (165).

D. Naphtho[1′,2′-*e*]pyrazolo[5,1-*c*]1,2,4-triazines

Only one compound of this structure has been reported so far (1410). Reimlinger and van Overstraten interacted diazotized 3-aminopyrazole (**606**) and

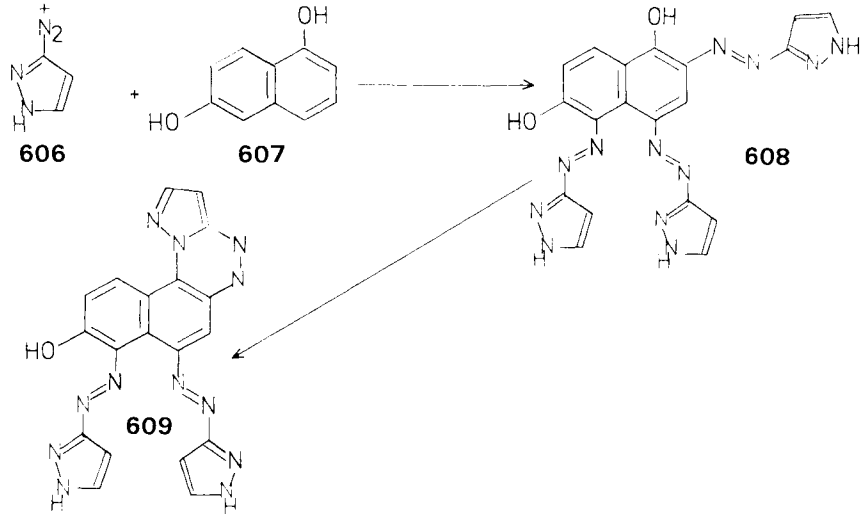
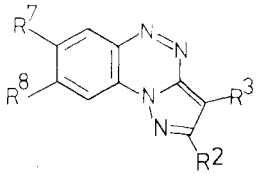
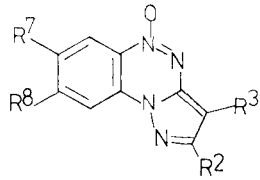


TABLE VI-7. PYRAZOLO[5,1-*c*] 1,2,4-BENZOTRIAZINES AND 5-OXIDES



R^2	R^3	R^7	R^8	m.p. (°C)	Refs.
H	H	H	OH	305–306	1389
H	H	H	$OCOCH_3$	153–154	1389
H	C_6H_5	H	H	166–167	1407
H	4-CH_3O–C_6H_4	H	H	152–153	1407
CH_3	H	H	H		1408
CH_3	CH_3	H	H	145	1406, 1408
				b.p. 208–215/15	1406
				b.p. 225–226/30	1406
CH_3	C_2H_5	H	H	106	1406
				b.p. 210/14	1406
CH_3	C_6H_5–CH_2	H	H	128–130	1406
	Ag salt			169–170	1406
C_6H_5	H	H	H		1408

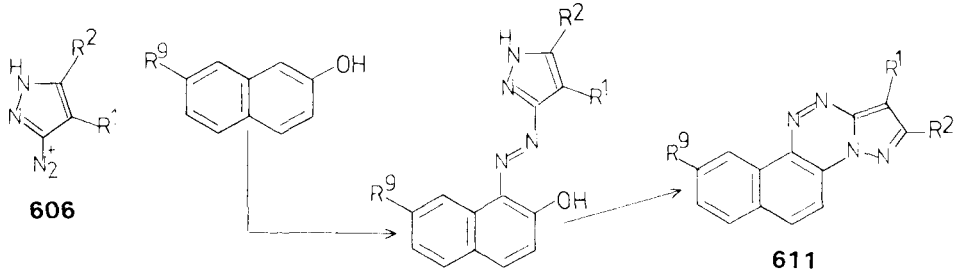


R^2	R^3	R^7	R^8	m.p. (°C)	Refs.
H	C_6H_5	H	H	213–214	1407
H	C_6H_5	NO_2	H	262–263	1407
H	4-Cl–C_6H_4	H	H	236–237	1407
H	4-Cl–C_6H_4	NO_2	H	286–287	1407
H	4-CH_3O–C_6H_4	H	H	218–219	1407
H	4-CH_3O–C_6H_4	NO_2	H	257–258	1407
CH_3	H	H	H		1408
CH_3	CH_3	H	H		1408
C_6H_5	H	H	H		1408

1,6-dihydroxynaphthalene (**607**). Depending on the reaction conditions they obtained a mono-, a di-, and a triazo compound (**608**). **608** cyclized readily even at room temperature, yielding the 7,8-bis(3-pyrazolylazo)-9-hydroxynaphtho-[1′,2′-*e*]pyrazolo[5,1-*c*] 1,2,4-triazine (**609**) (dec. 230°C).

E. Naphtho[2′,1′-*e*]pyrazolo[5,1-*c*]1,2,4-triazines

Coupling of diazotized 3-aminopyrazoles (**606**) with 2-naphthols yields the azo compounds **610** which cyclize readily, even below 0°C, (1262, 1410–1412), giving naphtho[2′,1′-*e*]pyrazolo[5,1-*c*]1,2,4-triazines (**611**) (RRI 10770).



606 **610** **611**

R^1	R^2	R^9	m.p. (°C)	Refs.
H	H	H	192–194	1410, 1411
			193–194	1262
H	H	OH	345–347	1410
C_6H_5	H	H	212.5–213.5	1410
$COOC_2H_5$	H	H		1412
NO_2	H	H		1412
NO_2	CH_3	H		1412

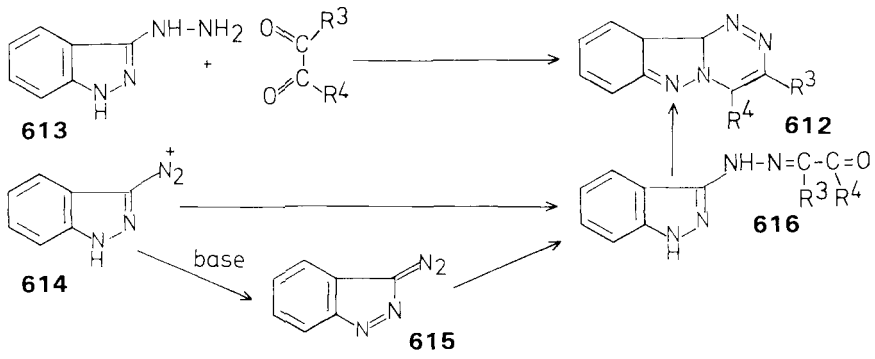
V. CONDENSED WITH THE INDAZOLE SYSTEM

A. 1,2,4-Triazino[4,3-*b*]indazoles

1,2,4-Triazino[4,3-*b*]indazoles (**612**) can be prepared by interaction of 3-hydrazinoindazole (**613**) and 1,2-dicarbonyl compounds (1413) and also from the product (**616**) of a Japp–Klingemann reaction on an indazole-3-diazonium salt (**614**) or 3-diazo-3*H*-indazole (**615**) (1413–1415).

Table VI-8 lists the known 1,2,4-triazino[4,3-*b*]indazoles, along with some 4,6-dihydro derivatives.

1,2,4-Triazino[4,3-*b*]indazoles (**612**) are stable, colored (yellow, golden, red), crystalline compounds. The electronic spectrum of the unsubstituted **612** is reported by Stevens and co-workers (1413): λ_{max} (log ϵ): 409 (3.44), 351 (3.78), 339 (3.73), 282 infl. (4.22), 272 (4.42), and 228 nm (4.31). PMR spectral data and mass spectra of **612** have been published by Tisler and his



group (1414) and by Reichardt and co-workers (1415). The detailed structure of 3-acetyl-4-methyl-1,2,4-triazino[4,3-*b*]indazole was elucidated by X-ray diffraction (1415).

Prolonged boiling with 10*N* sodium hydroxide caused partial decomposition of the 3,4-dimethyl derivative to 3-aminoindazole, but not of the 3,4-diphenyl compound (1413). The 1,2,4-triazine ring was readily degraded by ketonic reagents and by vigorous reduction. Reduction in the presence of Adams catalyst or with amalgamated zinc and aqueous acetic acid furnished the 4,6-dihydro derivatives **617** (1413). Reduction of ethyl 4-methyl-1,2,4-triazino[4,3-*b*]-indazole-3-carboxylate (**612d**) over palladinized carbon at room temperature gives a hexahydro derivative, the structure of which is either **618** or **619**

The 4-methyl groups in **612** are reactive and give the 4-styryl derivatives (**620**) on treatment with benzaldehyde (1413). 3,4-Dimethyl-1,2,4-triazino-

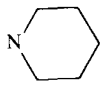
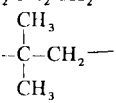
TABLE VI-8. 1,2,4-TRIAZINO[4,3-*b*]INDAZOLES AND 4,6-DIHYDRO COMPOUNDS

A. 1,2,4-Triazino[4,3-*b*]indazoles (**612**)

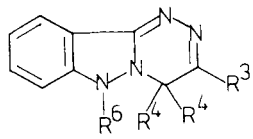
R^3	R^4	m.p. (°C)	Refs.
H	H	137–138	1413
H	CH_3	236–238	1413
H	$CH{=}CH{-}C_6H_5$	194–196	1413
H	OH	315 (taut.)	1414
CH_3	H	188–189	1413
CH_3	CH_3	182–183.5	1413
Picrate		209–211	1413
Sulfate		233–234	1413
Methiodide		222–224	1413
CH_3	CH_2Br	162–165 (dec.)	1413
CH_3	$CH{=}CH{-}C_6H_5$	216–218	1413
CH_3	CH_3CO	221–223	1413

TABLE VI-8. (continued)

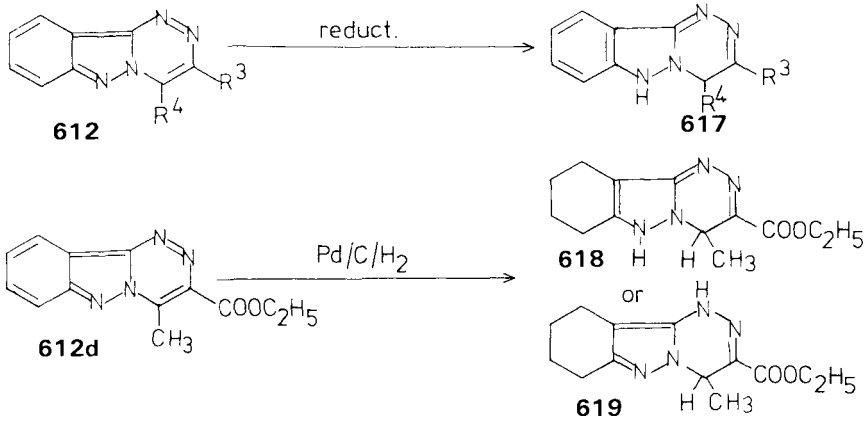
A. 1,2,4-Trizino[4,3-*b*]indazoles

R^3	R^4	m.p.(°C)	Refs.
CH_3	Cl	177–178.5	1413
CH_3	OH	348–350 (taut.)	1413
Acetyl der.		221–223	1413
CH_3		167–168	1413
—$(CH_2)_4$—		167–168	1413
Acetyl der.		136–137	1413
C_6H_5	C_6H_5	272–274	1413
CHO	H	234–235	1415
CH_3CO	H	217–218 (dec.)	1415
CH_3CO	CH_3	177.5–178	1415
		178	1414
CH_3CO	C_6H_5	198.5–199	1414
—CO–CH_2 CH_2 CH_2—		215–216	1414
		235	1414
$COOC_2H_5$	CH_3	149–150	1413
		150	1414
$COOC_2H_5$	$CH_2COOC_2H_5$	114–115	1414
$COOC_2H_5$	C_6H_5	148	1414
$COOC_2H_5$	OH	165 (taut.)	1414
$COOC_2H_5$	NH_2	260–262	1413
$CONHNH_2$	CH_3	291–293	1413
CONHOH	CH_3	220–221	1413

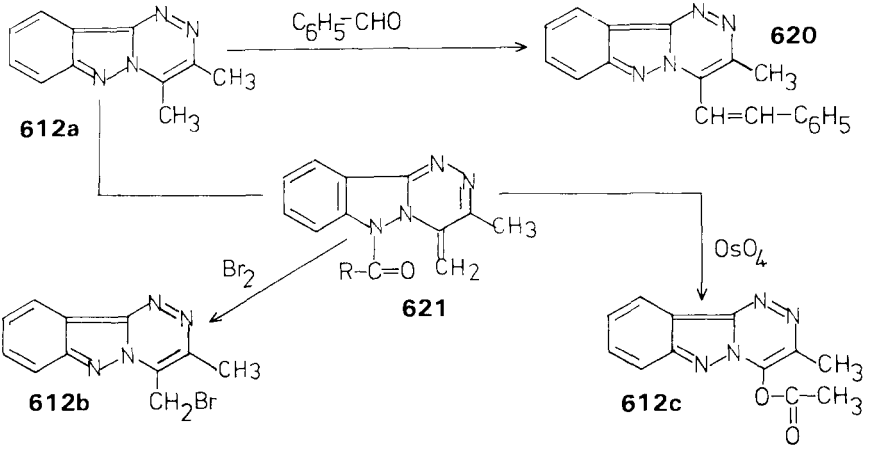
B. 4,6-Dihydro-1,2,4-triazino[4,3-*b*]indazoles



R^3	R^4	R^4	R^6	m.p. (°C)	Refs.
CH_3	H	CH_3	H	231–233	1413
CH_3	H	CH_3	CH_3CO	129–130.5	1413
CH_3	$=CH_2$		CH_3CO	156–157	1413
CH_3	$=CH_2$		C_6H_5CO	192.5–194	1413
C_6H_5	H	C_6H_5	H	266–268	1413
C_6H_5	H	C_6H_5	CH_3CO	168–169	1413



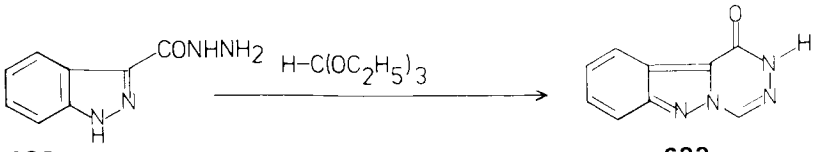
[4,3-*b*]indazole (**612a**) afforded 6-acyl-3-methyl-4-methylene-1,2,4-triazino-[4,3-*b*]indazoles (**621**) when refluxed with acetic anhydride or benzoyl chloride in the presence of pyridine (1413). Bromination of the 6-acetylderivative (**621a**) gave 3-methyl-4-(bromomethyl)-1,2,4-triazino[4,3-*b*]indazole (**612b**), whereas osmium tetroxide – periodate oxidation afforded 3-methyl-4-acetoxy-1,2,4-triazino[4,3-*b*]indazole (**612c**) (1413). Hydroxyl groups in **612**, or their tautomeric structures, can be converted to chloro groups by reaction with phosphoryl chloride (1413).



B. 1,2,4-Triazino[4,5-*b*]indazoles

So far only one example of this class, the 1,2,4-triazino[4,5-*b*]indazol-1-one (**622**) or its tautomer (m.p. 240 to 242°C) is known. **622** was prepared by

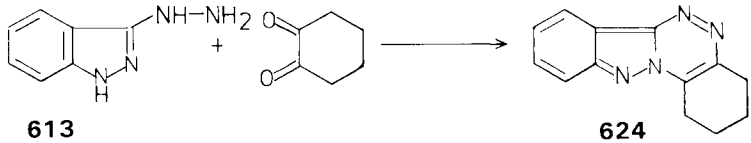
Stevens and co-workers (1413) through cyclization of indazole-carboxylic acid hydrazide (**623**) with triethyl orthoformate.



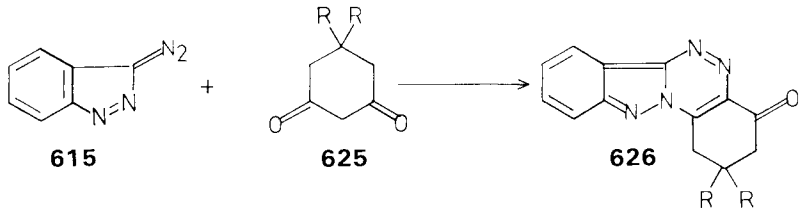
623 **622**

C Indazolo[3,2-*c*]1,2,4-benzotriazines

At present only three 1,2,3,4-tetrahydroindazolo[3,2-*c*]1,2,4-benzotriazines (**624**) are known (1413, 1414). Stevens and co-workers (1413) obtained the unsubstituted **624** from the reaction of 3-hydrazinoindazole (**613**) and cyclohexane-1,2-dione, and Tisler and his group (1414) prepared **626a** and **626b** by interaction of 3-diazo-3*H*-indazole (**615**) and cyclohexane-1,3-dione (**625a**) or dimedone (**625b**). The melting points of these compounds are included in Table VI-8.



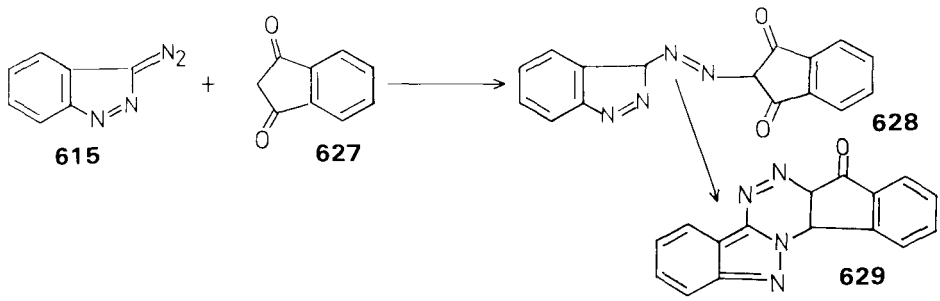
613 **624**



615 **625** **626**

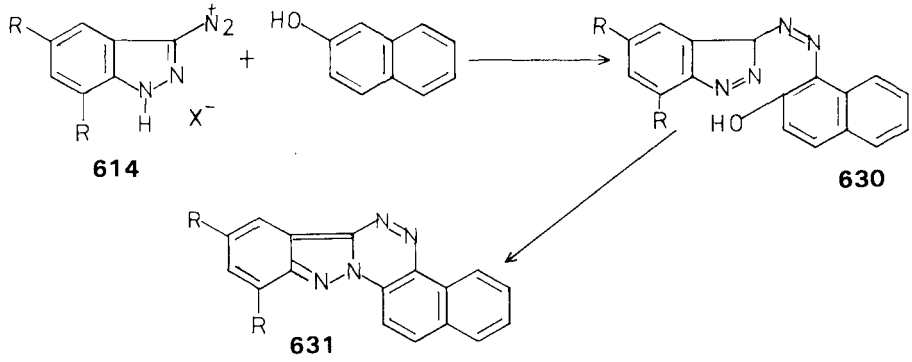
D. Indeno[1′,2′: 5,6]1,2,4-triazino[4,3-*b*]indazol

The reaction of 3-diazo-3*H*-indazole (**615**) and indane-1,3-dione (**627**) yields product **628**, which was heated in a tube at 240°C for about 30 min, affording 7*H*-indeno[1′,2′:5,6]1,2,4-triazino[4,3-*b*] indazol-7-one (8*H*-indazolo[3,2-*c*]indeno[1,2-*e*] 1,2,4-triazin-8-one) (**629**) (m.p. > 300°C) (1414).



E. Indazolo[3,2-*c*]naphtho[2,1-*e*]1,2,4-triazines

Reaction of the indazolium salts (**614**) with 2-naphthol affords the azo compounds **630**, which cyclize to indazolo[3,2-*c*]naphtho[2,1-*e*]1,2,4-triazines (**631**) (RRI 5808) (R = H, m.p. 249°C; R = CH_3, 267°C), when heated in pentanol or glacial acetic acid (1416–1418). The 7-methyl-7,8,9,10-tetrahydro derivative (m.p. 152 to 154°C) was prepared (1419) by the same method. **631** are soluble in concentrated sulfuric acid or hydrochloric acid; they reprecipitate from the deeply colored solution on addition of water.



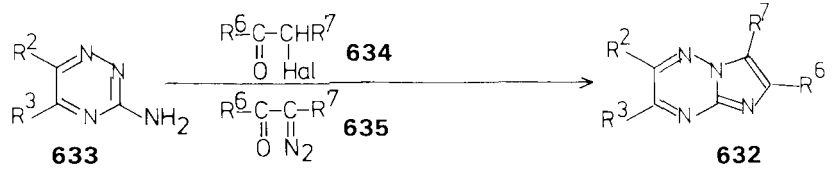
VI. CONDENSED WITH THE IMIDAZOLE RING

A. Imidazo[1,2-*b*]1,2,4-triazines

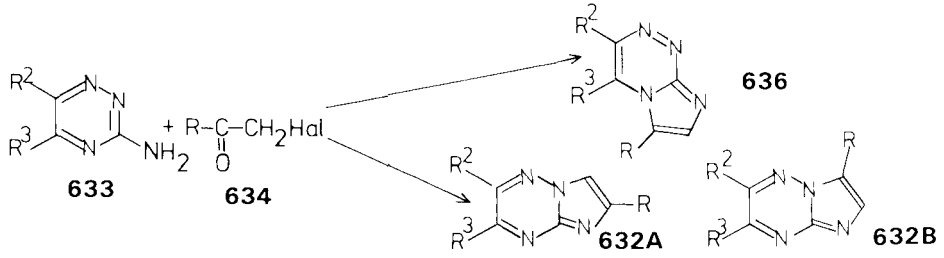
1. *Preparation*

The generally used method for the synthesis of imidazo[1,2-*b*]1,2,4-triazines (**632**) (RRI 1163) is the reaction of 3-amino-1,2,4-triazines (**633**) with

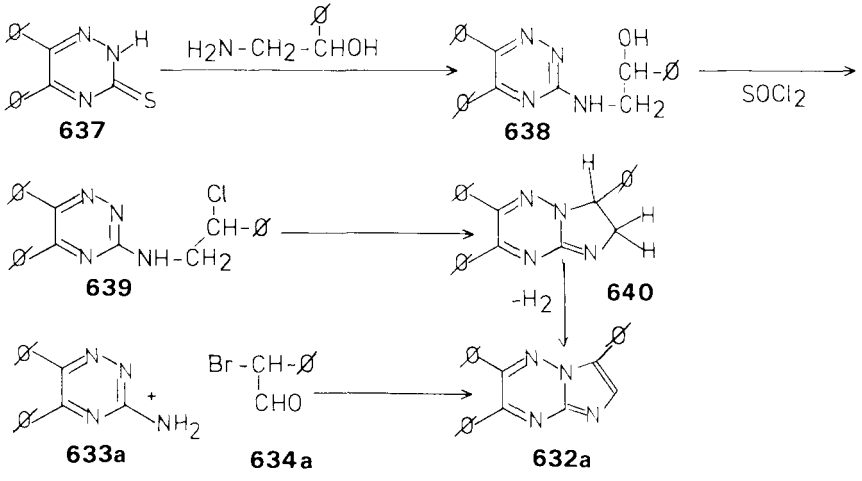
α-halo ketones (**634**) (609, 612, 615, 616, 670, 694–700, 1420–1423). Instead of the α-halo ketones (**634**) α-diazo ketones (**635**) can be used (612).



In connection with this reaction two questions arose: (1) are the isolated compounds imidazo[1,2-*b*]1,2,4-triazines (**632**) or imidazo[2,1-*c*]1,2,4-triazines (**636**); and (2) if **632** were formed, does the keto group or the halomethyl group react with the amino group in **633** to yield **632A** or **632B**, respectively?

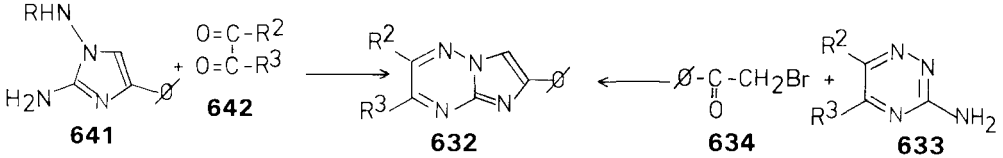


Fusci and Rossi (1420) had already proved that the keto group in **634** reacts with the amino group of **633** by showing that the substance, obtained from the condensation of 3-amino-5,6-diphenyl-1,2,4-triazine (**633a**) with α-bromophenylacetaldehyde (**634a**) is the same compound (**632a**) they isolated from the following reaction sequence: condensation of 5,6-diphenyl-1,2,4-triazine-3-



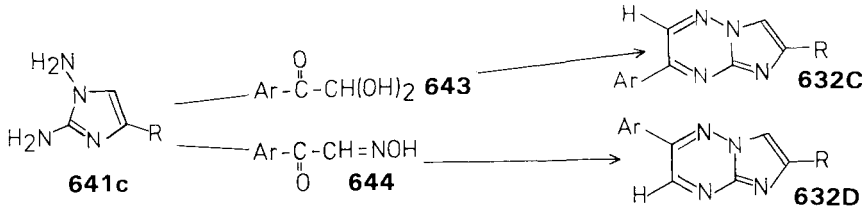
thione (**637**) with 2-phenyl-2-ethanolamine and treatment of the product (**638**) with thionyl chloride yielded **639**. Boiling pyridine converted **639** into **640** which spontaneously dehydrogenated to **632a**. A similar reaction sequence is reported by Lempert and co-workers (709) for the synthesis of 2-methyl-6,7-dihydroimidazo[1,2-*b*]1,2,4-triazin-3(5*H*)-one (m.p. 262°C).

The unambiguous proof of the imidazo[1,2-*b*]1,2,4-triazine structure (**632**) was given by Lempert and co-workers (709), who compared the ultraviolet spectra of imidazo[1,2-*b*]1,2,4-triazin-3-ones and monocyclic1,2,4-triazin-5-ones, and finally by Beyer and his group (1423), who obtained imidazo[1,2-*b*]-1,2,4-triazines (**632**) identical with those from the reaction of **633** and **634**, through the condensation of 1-(acylamino)-2-amino-4-phenylimidazole (**641a**) or 1,2-diamino-4-phenylimidazole (**641b**) with 1,2-dicarbonyl compounds (**642**) (1425).



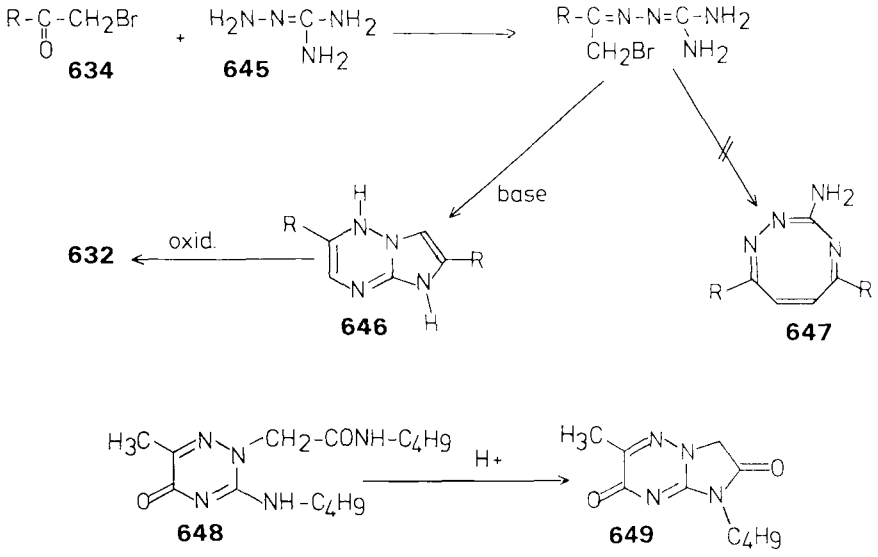
a: R = R - CO
b: R = H

Lalezari and Levi (1424) have shown that the reaction of 1,2-diaminoimidazole (**641c**) with phenylglyoxal hydrates (**643**) affords mainly 3-substituted imidazo[1,2-*b*]1,2,4-triazines (**632C**); the reaction of **642** and phenylglyoxaldoximes (**644**) yields the 2-isomers (**632D**).



Loev and Goodman (1421) proved that the reaction of aminoguanidine (**645**) and α-halo ketones (**634**), reported by Beyer and his group (1425–1427), is a method for the synthesis of 1,5-dihydroimidazo[1,2-*b*]1,2,4-triazines (**646**), which can easily be oxidized to **632**. The claimed synthesis of 1,2,4-triazocines (**647**) is incorrect.

Conversion of compound **648** by acid was used by Lampert and his group (709) for the synthesis of 5-(*n*-butyl)-2-methylimidazo[1,2-*b*]1,2,4-triazine-3,6-dione (**649**) (m.p. 126°C).



2. *Compound Survey*

Table VI-9 lists the compounds of this class reported in the literature.

3. *Physical Properties*

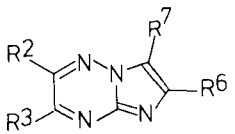
Imidazo[1,2-*b*]1,2,4-triazines (**632**) are stable, yellow, crystalline compounds. So far only a small amount of spectroscopic data has been reported. The PMR spectrum of the unsubstituted **632** shows four doublets at τ = 1.48 (H-3), 1.52 (H-2), 1.95 (H-7), and 1.97 (H-6) and the two coupling constants $J_{2,3}$ = 1.8 Hz and $J_{6,7}$ = 1.7 Hz. (698). Since most of the imidazo[1,2-*b*]1,2,4-triazines show fluorescence, a number of them were claimed as fluorescent pigments (695).

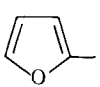
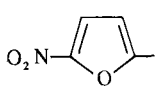
4. *Reactions*

Imidazo[1,2-*b*]1,2,4-triazines (**632**) can be reduced with sodium borohydride, yielding 1,5-dihydroimidazo[1,2-*b*]1,2,4-triazines (**646**) (615, 616, 1421) or 1,2,3,4-tetrahydroimidazo[1,2-*b*]1,2,4-triazines (**650**) (1428). Reaction of the unsubstituted **632** with phenyllithium gives the 3-phenyl

TABLE VI-9. IMIDAZO[1,2-*b*]1,2,4-TRIAZINES AND 1,5-DIHYDRO COMPOUNDS

A. Imidazo[1,2-*b*]1,2,4-triazines

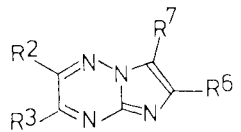


R^2	R^3	R^6	R^7	m.p. (°C)	Refs.
H	H	H	H		698
H	H	CH_2NH_2	H	125	612
H	H	C_6H_5	H	171–172	1423
H	CH_3	C_6H_5	H (or isomer)	177	697
H	C_6H_5	H	H	173	698/1428
H	C_6H_5	C_6H_5	H	196	694, 695, 1420
				200	609, 696
				200–201	1424
					1421/1428
H	C_6H_5	C_6H_5	C_6H_5	227	694, 695, 1420
H	C_6H_5	4-Cl–C_6H_4	H	252–253	**1424/1428**
H	C_6H_5	4-Br–C_6H_4	H	243–245	1424
H	C_6H_5	4-O_2N–C_6H_4	H	258	694, 695, 1420
H	C_6H_5	2-Naphthyl	H	222–225	1424
H		 5-O_2N–2-furyl	H	>300	699

CH_3	CH_3	C_6H_5	H	213	697
				218–219.5	700
				218–220	1423
				219–220	1424/1422
CH_3	CH_3	C_6H_5	C_6H_5	205–206	697/1422
CH_3	CH_3	4-Cl–C_6H_4	H	250–252	1424
CH_3	CH_3	4-Br–C_6H_4	H	267–270	1424
CH_3	CH_3	3,4,5-$(CH_3O)_3C_6H_2$	H	228–230	612
CH_3	CH_3	2-Naphthyl	H	256–259	1424
		C_6H_5	H	236	670
C_6H_5	H	C_6H_5	H	220–222	1423
				224–227	616
				228–230	1424/1421, 1425
C_6H_5	H	4-CH_3–C_6H_4	H		615
C_6H_5	H	4-Cl–C_6H_4	H	305–306	1424/615
C_6H_5	H	2-Cl–C_6H_4	H		615
C_6H_5	H	4-Br–C_6H_4	H	307–308	1424/615
C_6H_5	H	3-CH_3O–C_6H_4	H		615
C_6H_5	H	2-Naphthyl	H	258–259	1424
C_6H_5	C_6H_5	H	C_6H_5	248–249	1420
C_6H_5	C_6H_5	C_6H_5	H	177–178	609, 696
				186	694, 695, 1420
				186–187	1423
C_6H_5	C_6H_5	C_6H_5	C_6H_5	238–239	619, 694, 695, 1420
C_6H_5	C_6H_5	4-O_2N–C_6H_4	H	228–229	694, 695, 1420
C_6H_5	C_6H_5	4-$ClCH_2CO$–C_6H_4	H	162–163	1420
C_6H_5	C_6H_5	1-Naphthyl	C_6H_5	234	619
C_6H_5	C_6H_5	2-Naphthyl	C_6H_5	264	619

TABLE VI-9. (continued)

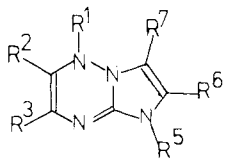
A. Imidazo[1,2-*b*] 1,2,4-triazines



R^2	R^3	R^6	R^7	m.p. (°C)	Refs.
C_6H_5	Br	C_6H_5	H		1421
·HBr					1421
2-CH_3–C_6H_4	H	C_6H_5	H		615
2-CH_3–C_6H_4	H	2-CH_3–C_6H_4	H		615
3-CF_3–C_6H_4	H	C_6H_5	H		615
4-F–C_6H_4	H	4-F–C_6H_4	H		615
4-Cl–C_6H_4	H	C_6H_5	H		615
4-Br–C_6H_4	H	C_6H_5	H		615
4-HO–C_6H_4	4-HO–C_6H_4	H	H	260	696
4-HO–C_6H_4	4-HO–C_6H_4	C_6H_5	H	260	696
4-CH_3O–C_6H_4	H	C_6H_5	H		615
3-CH_3O–C_6H_4	H	3-CH_3O–C_6H_4	H		615
CH_3O–C_6H_4	CH_3O–C_6H_4	H	H	185	696
CH_3O–C_6H_4	CH_3O–C_6H_4	C_6H_5	H	206	609, 696
$(CH_3)_2N$–C_6H_4	C_6H_5	H	H	202	696
$(CH_3)_2N$–C_6H_4	C_6H_5	C_6H_5	H	126–134	609, 696
C_6H_5–CH=CH	CH_3	C_6H_5	H	239–240	697, 1429
4-$(CH_3)_2N$–C_6H_5–CH=CH	CH_3	C_6H_5	H	242–243	697, 1429
2-Furyl	2-Furyl	H	H	233	615, 696
2-Furyl	2-Furyl	C_6H_5	H	199	609, 695, 696

CH_3	OH	C_6H_5	H (taut.)	289–290	1424
CH_3	OH	4-Cl–C_6H_4	H (taut.)	311–313	1424
CH_3	OH	4-Br–C_6H_4	H (taut.)	312–316	1424
CH_3	OH	2-Naphthyl	H (taut.)	312–315	1424
CH_3	OH	3,4,5-$(CH_3O)_3C_6H_2$	H (taut.)	227 (dec.)	612
C_6H_5	OH	C_6H_5	H (taut.)	310–312	1424
C_6H_5	OH	4-Cl–C_6H_4	H (taut.)	310–315	1424
C_6H_5	OH	4-Br–C_6H_4	H (taut.)	321–330	1424
C_6H_5	OH	2-Naphthyl	H (taut.)	317–322	1424

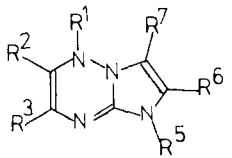
B. 1,5-Dihydroimidazo[1,2-*b*]1,2,4-triazines



R^1	R^2	R^3	R^5	R^6	R^7	m.p. (°C)	Refs.
H	C_6H_5	H	H	C_6H_5	H	204–208	616/1425
						207 (dec.)	1426[a]
						208 (dec.)	1427[a]
	·HCl					227	1427[a]
	·HBr					216	1427[a]
	acetyl deriv.					198	1427[a]
	benzoyl deriv.					192	1427[a]
H	C_6H_5	H	H	4-CH_3–C_6H_4	H		615
H	C_6H_5	H	H	2-Cl–C_6H_4	H		615
H	C_6H_5	H	H	4-Cl–C_6H_4	H		615
H	C_6H_5	H	H	4-Br–C_6H_4	H		615
H	C_6H_5	H	H	3-CH_3O–C_6H_4	H		615

TABLE VI-9. (continued)

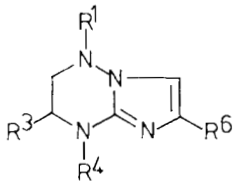
B. 1,5-Dihydroimidazo[1,2-*b*]1,2,4-triazines



R^1	R^2	R^3	R^5	R^6	R^7	m.p. (°C)	Refs.
H	2-CH_3–C_6H_4	H	H	C_6H_5	H		615
H	4-CF_3–C_6H_4	H	H	C_6H_5	H		615
H	4-F–C_6H_4	H	H	4-F–C_6H_4	H		615
H	4-Cl–C_6H_4	H	H	C_6H_5	H		615
H	4-Cl–C_6H_4	H	H	4-Cl–C_6H_4	H	233 (dec.)	1427[a]
H	2-CH_3–C_6H_4	H	H	2-CH_3–C_6H_4	H		615
H	4-Br–C_6H_4	H	H	C_6H_5	H		615
H	4-Br–C_6H_4	H	H	4-Br–C_6H_4	H	240 (dec.)	1427[a]
H	3-O_2N–C_6H_4	H	H	3-O_2N–C_6H_4	H	236 (dec.)	1427[a]
H	3-H_5C_2O–C_6H_4	H	H	3-H_5C_2O–C_6H_4	H		615
H	4-CH_3O–C_6H_4	H	H	C_6H_5	H		615
CH_3	C_6H_5	H	CH_3	C_6H_5	H		1421
CH_3	C_6H_5	H	CH_3	C_6H_5	H		615, 616
CH_3CO	C_6H_5	H	CH_3CO	C_6H_5	H	204–208	1421
NO	C_6H_5	H	H	C_6H_5	H	162	1421

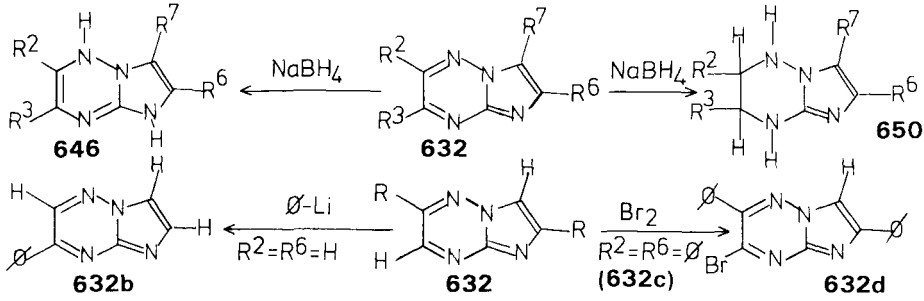
[a]Incorrect structure published.

C. 1,2,3,4-Tetrahydroimidazo[1,2-*b*]1,2,4-triazines **(1428)**

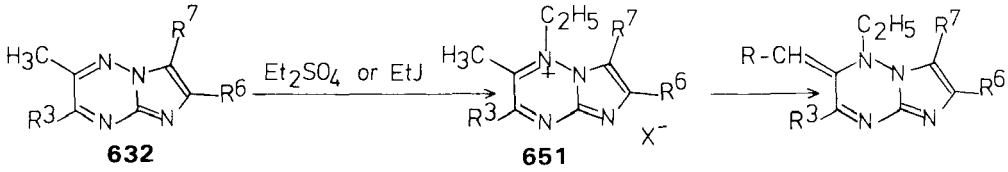


R^1	R^3	R^4	R^6
H	C_6H_5	H	C_6H_5
H	C_6H_5	H	3-Cl–C_6H_4
H	C_6H_5	CH_3	C_6H_5
H	C_6H_5	C_2H_5	C_6H_5
H	C_6H_5	C_3H_7	C_6H_5
H	C_6H_5	CH_3CO	C_6H_5
H	C_6H_5	CH_3CH_2CO	C_6H_5
CH_3	C_6H_5	H	C_6H_5
CH_3	C_6H_5	CH_3	C_6H_5
C_2H_5	C_6H_5	H	C_6H_5
C_2H_5	C_6H_5	C_2H_5	C_6H_5
C_3H_7	C_6H_5	H	C_6H_5
C_3H_7	C_6H_5	C_3H_7	C_6H_5
CH_3CO	C_6H_5	H	C_6H_5
CH_3CO	C_6H_5	CH_3CO	C_6H_5
CH_3CH_2CO	C_6H_5	H	C_6H_5
CH_3CH_2CO	C_6H_5	CH_3CH_2CO	C_6H_5

derivative (**632b**) (698). Bromination of 2,6-diphenylimidazo[1,2-*b*]1,2,4-triazine (**632c**) afforded the 3-bromo derivative (**632d**) (1421).

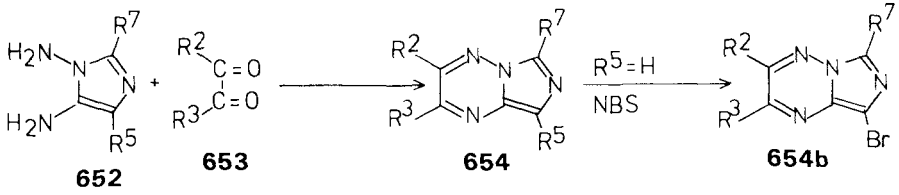


Imidazo[1,2-*b*]1,2,4-triazines (**632**) can be alkylated at N-1, the isolated salts (**651**) having been used for the synthesis of cyanines (697, 1429).



B. Imidazo[1,5-*b*]1,2,4-triazines

The reaction of 1,5-diaminoimidazoles (**652**) with 1,2-dicarbonyl compounds (**653**) has been used by Jacquier and his group (1102) for the preparation of the imidazo[1,5-*b*]1,2,4-triazines (**654**) (Table VI-10). Bromination of 2,3-dimethyl-7-phenylimidazo[1,5-*b*]1,2,4-triazine (**654a**) with *N*-bromosuccinimide affords the 5-bromo derivative (**654b**).



C. Imidazo[2,1-*c*]1,2,4-triazines

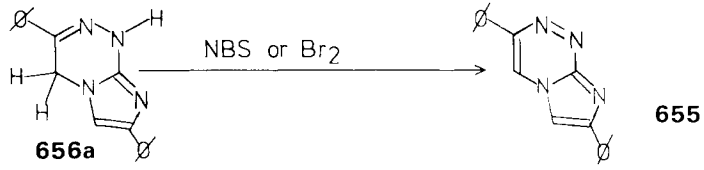
So far only one fully unsaturated imidazo[2,1-*c*]1,2,4-triazine, the 3,7-diphenylimidazo[2,1-*c*]1,2,4-triazine (**655**) [m.p. 344 to 345°C (dec.)] is known

TABLE VI-10. IMIDAZO[1,5-*b*]1,2,4-TRIAZINES (1102)

654

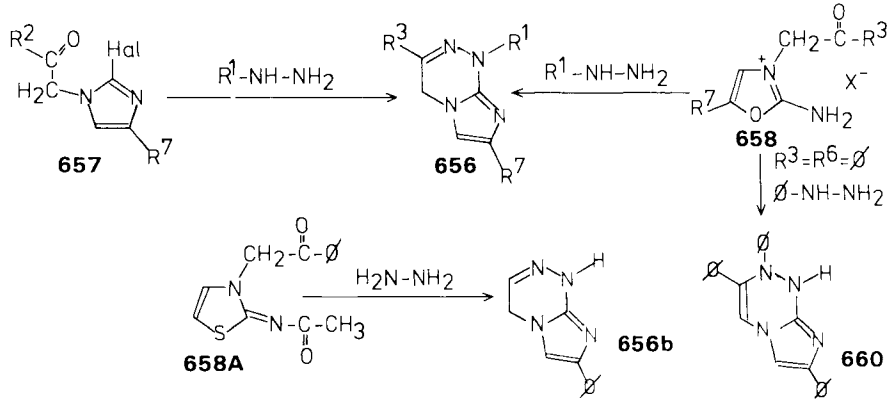
R^2	R^3	R^5	R^7	m.p. (°C)
H	H	$CONH_2$	C_6H_5	183
CH_3	CH_3	H	C_6H_5	125
·HCl				165
CH_3	CH_3	H	$C_6H_5-CH_2$	87
CH_3	CH_3	Br	C_6H_5	160
CH_3	CH_3	$CONH_2$	C_6H_5	270

(1437). It was prepared by Hetzheim and Pusch (1437) through oxidation of the 1,4-dihydro derivative (**656a**) with *N*-bromosuccinimide or bromine.



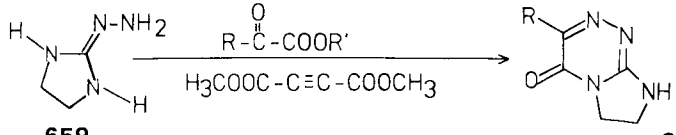
656a **655**

1,4-Dihydroimidazo[2,1-*c*]1,2,4-triazines (**656**) were obtained by the reaction of either 1-phenacyl-2-haloimidazoles (**657**) (1430, 1431) or 2-amino-3-phenacyloxazolium bromides (**658**) with hydrazines (1432, 1437). Reaction of **658** and phenylhydrazine yields 2,3,7-triphenyl-1,2-dihydroimidazo[2,1-*c*]-1,2,4-triazine (**660**) (m.p. 184 to 185°C) (1437). Dunwell and Evans (1524) prepared 7-phenyl-1,4-dihydroimidazo[2,1-*c*]1,2,4-triazine (**656b**) through the reaction of 2-acetylimino-3-phenacyl-4-thiazoline (**658A**) with hydrazine.



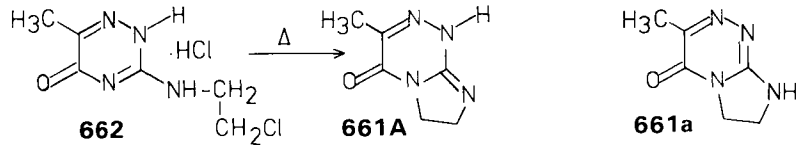
657 **656** **658** **658A** **656b** **660**

The reaction of the cyclic amidrazones (**659**) with α-ketocarboxylates yields the 6,7-dihydroimidazo[2,1-*c*] 1,2,4-triazin-4(8*H*)-ones (**661**) (1435, 1436), which were also obtained from **659** and dimethyl acetylenedicarboxylate (1434).



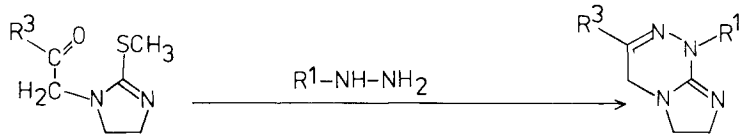
659 **661**

Lempert and co-workers (709) observed the formation of a dihydroimidazo-[2,1-*c*] 1,2,4-triazinone, when they heated the hydrochloride of 3-[(2-chloro-ethyl)amino] -6-methyl-1,2,4-triazin-5-one (**662**). The isolated compound is formulated as the tautomer **661A**, but its melting point is identical with the tautomer **661a**, reported by Brugger and Korte (1436). The 1-methyl derivative of **661A** is reported by Le Count and Taylor (1435) (m.p. 142°C).



662 **661A** **661a**

The synthesis of 1,4,6,7-tetrahydroimidazo[2,1-*c*] 1,2,4-triazines (**663**) is reported in a United States patent (1433). 1-(Phenacyl)-2-(methylmercapto)-imidazolines (**664**) were converted to **663** by interaction with hydrazines.



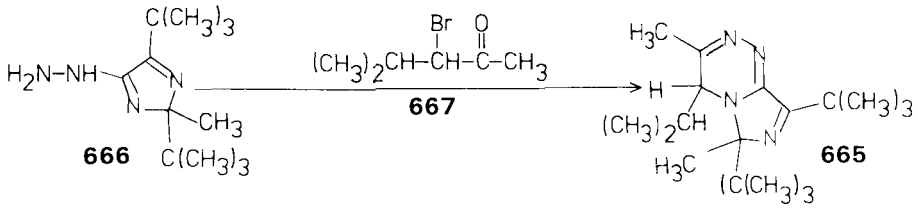
664 **663**

Table VI-11 lists the known dihydro- and tetrahydroimidazo[2,1-*c*] 1,2,4-triazines.

D. Imidazo[5,1-*c*]1,2,4-triazines

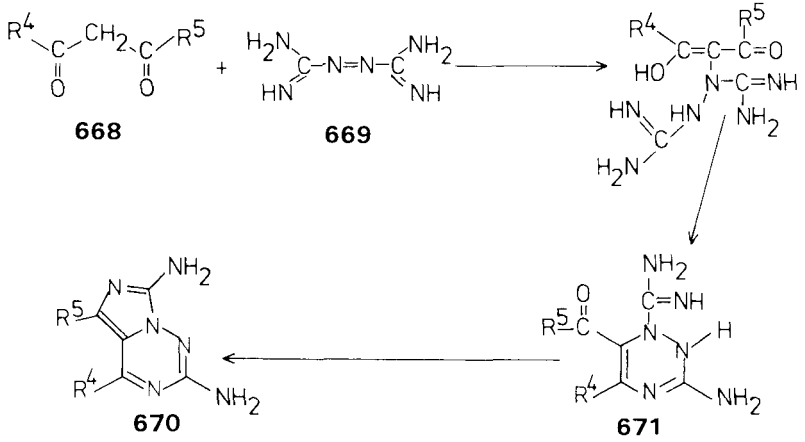
Asinger and co-workers (1438) obtained the single representative of this class, the 3,6-dimethyl-4-isopropyl-6,8-di-tert-butyl-4,6-dihydroimidazo[5,1-*c*] 1,2,4-triazine (**665**) (b.p. 110 to 120°C/0.3 torr) from the reaction of 4-hydrazino-2-

methyl-2,5-di-*tert*-butylimidazole (**666**) and 3-bromo-4-methyl-2-pentanone (**667**).



E. Imidazo[5,1-*f*]1,2,4-triazines

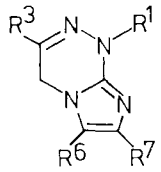
Interaction of β-dicarbonyl compounds (**668**) with azodicarboxamidine (**669**) is used by Kreutzberger and his group (975, 976, 1439–1441) for the synthesis of 2,7-diaminoimidazo[5,1-*f*]1,2,4-triazines (**670**). The primary reaction step consists of an addition of the active methylene group in **668** to the N=N double bond in **669**, followed by cyclization to 3-amino-1-guanyl-6-acyl-1,2-dihydro-1,2,4-triazines (**671**), which can be isolated in certain cases (975, 976). The final step is the conversion of **671** to **670**.



Treatment of 3-amino-6-[1-(acylamino)alkyl]-1,2,4-triazin-5-ones (**672**) or their 2-benzyl derivatives with phosphoryl chloride or polyphosphoric acid yields 2-aminoimidazo[5,1-*f*]1,2,4-triazin-4-ones (**673**) (815, 1442). Reduction of **673** with lithium aluminum hydride affords 2-amino-3,4-dihydroimidazo-[4,3-*f*]1,2,4-triazines (**674**), which can be dehydrogenated to the appropriate 2-aminoimidazo[5,1-*f*]1,2,4-triazines **675**.

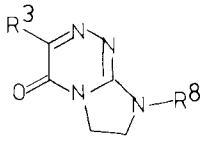
TABLE VI-11. DIHYDRO- AND TETRAHYDROIMIDAZO[2,1-*c*]1,2,4-TRIAZINES

A. 1,4-Dihydroimidazo[2,1-*c*]1,2,4-triazines



R^3	R^1	R^7	R^6	m.p. (°C)	Refs.
C_6H_5	H	C_6H_5	H	295–297 (dec.)	1437/1432
·HCl				264–265 (dec.)	1437
C_6H_5	CH_3CO	C_6H_5	H	195	1437
C_6H_5	C_2H_5CO	C_6H_5	H	218–219	1437
C_6H_5	C_6H_5CO	C_6H_5	H	219–220	1437
C_6H_5	C_6H_5NHCO	C_6H_5	H	289–291 (dec.)	1437
C_6H_5	CH_3	C_6H_5	H	160	1437/1432
C_6H_5	H	C_6H_5	C_6H_5		1430
C_6H_5	C_6H_5	C_6H_5	H		1432
C_6H_5	C_6H_5	C_6H_5	C_6H_5		1430
4-Br–C_6H_4	H	C_6H_5	C_6H_5		1430
4-Br–C_6H_4	C_6H_5	C_6H_5	C_6H_5		1430

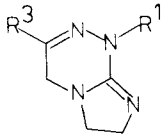
B. 6,7-Dihydroimidazo[2,1-*c*]1,2,4-triazin-4(8*H*)-ones



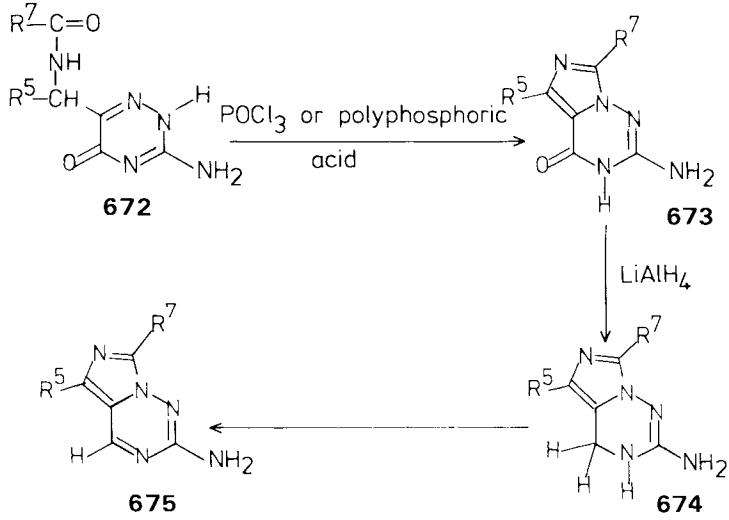
R^3	R^8	m.p. (°C)	Refs.
CH_3	H	291–292	709, 1435, 1436
·HCl		272–273	709
CH_3	CH_3	102–103	1435
CH_3	C_6H_5	225–227	1435
CH_2COOCH_3	H	202	1434, 1435
CH_2COOCH_3	CH_3	98–99	1434, 1435
C_6H_5	H	210	1435, 1436
·H_2O		188–190	1436
C_6H_5	CH_3	184–185	1435

TABLE VI-11. (continued)

C. 1,4,6,7-Tetrahydroimidazo[2,1-*c*]1,2,4-triazines



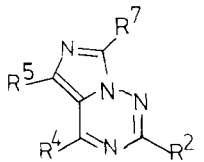
R^3	R^1	m.p. (°C)	Refs.
C_6H_5	H	228–230	1433
·HCl		287	1433
4-F–C_6H_4	H	253–256	1433
4-F–C_6H_4	CH_3	269–271	1433
4-Cl–C_6H_4	H	264–265	1433
·HCl		222–223	1433
4-Cl–C_6H_4	CH_3	295–297	1433
·HBr		282–284	1433
2,4-$Cl_2C_6H_3$	H	194–197	1433
2,4-$Cl_2C_6H_3$	CH_3	103–105	1433
4-CH_3O–C_6H_4	H	258–260	1433
·HCl		255–258	1433



Compounds of this class reported in the literature are listed in Table VI-12.

TABLE VI-12. IMIDAZO[5,1-*f*]1,2,4-TRIAZINES AND DERIVATIVES

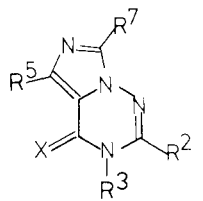
A. Imidazo [5,1-*f*] 1,2,4-triazines



R^2	R^4	R^5	R^7		m.p. (°C)	Refs.
NH_2	H	H	NH_2		283–285 (dec.)	975
NH_2	H	CH_3	C_3H_7	·HCl	146	1442
NH_2	H	CH_3	*i*-C_4H_9		84–86	1442
Hydrogen maleate					178–180	1442
NH_2	H	CH_3	*sec*-C_4H_9		275–290	1442
NH_2	CH_3	CH_3	C_3H_7			
Hydrogen maleate					155–156	1442
NH_2	CH_3	CH_3	NH_2		270–274 (dec.)	1442
·HNO_3					225–227	976
·HCl·½H_2O					275–285 (dec.)	1439
·HCl·2H_2O					275–285 (dec.)	1439
NH_2	C_2H_5	C_2H_5	NH_2		228–231	1441
NH_2	C_3H_7	C_3H_7	NH_2		174–175	1441
NH_2	*i*-C_3H_7	*i*-C_3H_7	NH_2		197–200	1441
NH_2	4-CH_3O–C_6H_4	CH_3	C_3H_7	·HCl	224–226	1442
NH_2	CH_3S	CH_3	C_3H_7		139–140	1442
·HCl					207–208	1442
C_3H_7–NH	H	CH_3	C_3H_7	·HCl	201–206	1442
i-C_4H_9–NH	H	CH_3	C_3H_7		87–88	1442
·HCl					201–213	1442

$C_6H_5CH_2$–NH	H	CH_3	C_3H_7		
Hydrogen maleate				141–142	1442
$C_6H_5CH_2CH_2$–NH	H	CH_3	C_3H_7	124–128	1442
3,4-$(CH_3O)_2C_6H_3$–NH	H	CH_3	C_3H_7	158–160	1442
Hydrogen maleate				118–121	1442
CH_3CO–NH	CH_3	CH_3	CH_3CO–NH	226–228	1440/1439
C_6H_5CO–NH	CH_3	CH_3	C_6H_5CO–NH	201–202	1440

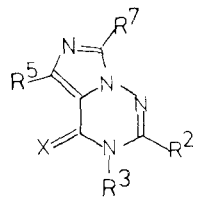
B. Imidazo[5,1-*f*] 1,2,4-triazin-4-ones

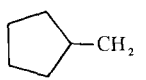
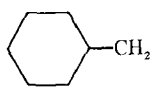


R^2	X	R^3	R^5	R^7		m.p. (°C)	Refs.
NH_2	O	H	H	C_3H_7	·HCl	231–232	815
NH_2	O	H	CH_3	CH_3		380–384 (dec.)	815
NH_2	O	H	CH_3	C_3H_7		259–261	815
·HCl						285–289	815
NH_2	O	H	CH_3	*i*-C_3H_7		310–314	1442
NH_2	O	H	CH_3	C_4H_9		214–215	815
NH_2	O	H	CH_3	*i*-C_4H_9		251	1442
						251–252 (dec.)	815
NH_2	O	H	CH_3	2-Pentyl		262–268	1442
NH_2	O	H	CH_3	$(CH_3)_2CHCH_2CH_2$		251–255	1442
NH_2	O	H	CH_3	$(CH_3)_3C$–CH_2	·HCl	261–263	815
NH_2	O	H	CH_3	$CH_3CH_2\underset{\displaystyle CH_3}{\underset{\vert}{C}}H$–$CH_2$		220–232	1442

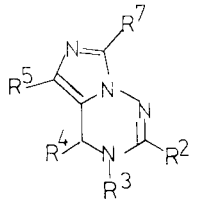
TABLE VI-12. (continued)

B. Imidazo[5,1-*f*]1,2,4-triazin-4-ones



R^2	X	R^3	R^5	R^7		m.p. (°C)	Refs.
NH_2	O	H	CH_3			299–302	815
NH_2	O	H	CH_3			159–160	1442
NH_2	O	H	CH_3			278–283	1442
NH_2	O	H	CH_3	$C_6H_5CH_2CH_2$	·HCl	271–274	815
NH_2	O	H	CH_3	$C_6H_5CH_2$		270.5–271.5	815
NH_2	O	H	CH_3	C_6H_5	·HCl	315–317 (dec.)	815
NH_2	O	H	C_3H_7	CH_3	·HCl	270–274 (dec.)	815
NH_2	O	CH_3	CH_3	C_3H_7	·HCl	202–203	815
CH_3CONH	O	H	CH_3	C_3H_7		221–223	815
·HCl						267–269	815
C_3H_7CONH	O	H	CH_3	C_3H_7	·HCl	237–239	815
NH_2	S	H	CH_3	C_3H_7	·HCl	290–292	1442

C. 3,4-Dihydroimidazo[5,1-*f*]1,2,4-triazines



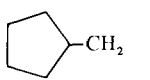
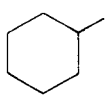
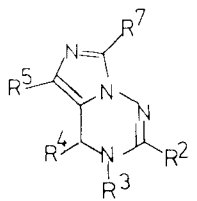
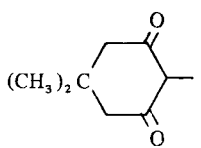
R^2	R^3	R^4	R^5	R^7	m.p. (°C)	Refs.
NH_2	H	H	H	$Me_2CHCH_2CH_2$	167–172	1442
NH_2	H	H	CH_3	n-C_3H_7	242–246	1442
·HCl					263 (dec.)	1442
·Barbituric acid					256–258	1442
·Barbituric acid·HCl					200–205	1442
NH_2	H	H	CH_3	i-C_3H_7	284–286	1442
·HCl					210–212	1442
NH_2	H	H	CH_3	i-C_4H_9	258–263	1442
·HCl					225–228	1442
NH_2	H	H	CH_3	$CH_3CH_2CH(CH_3)CH_2$	207–213	1442
·HCl					203–205.5	1442
NH_2	H	H	CH_3		194–198	1442
·HCl					255–257	1442
NH_2	H	H	CH_3		228–230	1442
Hydrogen maleate					130–133	1442

TABLE VI-12. (continued)

C. 3,4-Dihydroimidazo[5,1-*f*]1,2,4-triazines



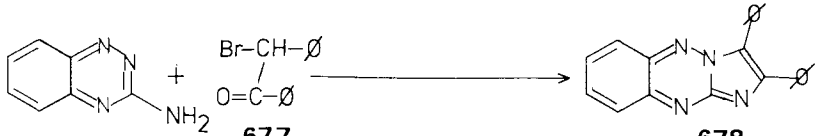
R^2	R^3	R^4	R^5	R^7		m.p. (°C)	Refs.
NH_2	H	H	CH_3	C_6H_5		262–264	1442
·HCl						328–331	1442
NH_2	H	CH_3	CH_3	C_3H_7		268–271	1442
·HCl						252–254	1442
NH_2	H	CH_3	CH_3	*i*-C_4H_9		265–169	1442
·HCl						142–143	1442
NH_2	H	C_2H_5	CH_3	C_3H_7	·HCl	170–172	1442
NH_2	H	CH_2=CH–CH_2	CH_3	C_3H_7			
Hydrogen maleate						229–231	1442
NH_2	H	C_6H_5	CH_3	C_3H_7	·HCl	179–181	1442
NH_2	H	4-CH_3O–C_6H_4	CH_3	C_3H_7	·HCl	178–181	1442
NH_2	H	4-CH_3O–C_6H_4–C(=O)–CH_2	CH_3	C_3H_7	·HCl	122	1442
NH_2	H		CH_3	C_3H_7		243	1442

NH_2	H	HO_3S	CH_3	C_3H_7		232–234	1442
CH_3–NH	H	H	CH_3	*i*-C_4H_9	·HCl	290–293 (dec.)	1442
C_2H_5–NH	H	H	CH_3	C_3H_7			
Hydrogen maleate						129–130.5	1442
C_3H_7–NH	H	H	CH_3	C_3H_7	·HCl	264–272	1442
i-C_5H_{11}–NH	H	H	CH_3	C_3H_7		157–167	1442
·HCl						271–276	1442
$C_6H_5CH_2$–NH	H	H	CH_3	C_3H_7	·HCl	235–240 1	1442
3,4-$(CH_3O)_2C_6H_3CH_2$ –NH	H	H	CH_3	C_3H_7		120–123	1442
$C_6H_5CH_2CH_2$–NH	H	H	CH_3	C_3H_7	·HCl	199–200	1442
Et_2N	H	H	CH_3	C_3H_7	·HCl	83–84	1442
HCO–NH	H	H	CH_3	C_3H_7		188.5–190.5	1442
Hydrogen maleate						159–161	1442
HCO–NH	H	H	CH_3	*i*-C_4H_9		209–211	1442
·HCl						257–258	1442
CH_3CO–NH	H	H	CH_3	C_3H_7	·HCl	302	1442
CH_3CO–NH	H	H	CH_3	*i*-C_3H_7		319–321	1442
CH_3CO–NH	H	H	CH_3	*i*-C_4H_9		269–271	1442
CH_3CO–NH	H	CH_3	CH_3	C_3H_7	·HCl	272–274	1442
CH_3CO–NH	H	C_6H_5–CH_2	CH_3	C_3H_7	·HCl	240–241	1442
C_2H_5CO–NH	H	OH	CH_3	C_3H_7	·HCl	252–257[a]	1442
C_3H_7CO–NH	H	H	CH_3	C_3H_7	·HCl	161–162	1442
i-C_3H_7CO–NH	H	OH	CH_3	C_3H_7	·HCl	248–255[a]	1442
i-C_4H_9CO–NH	H	H	CH_3	C_3H_7	·HCl	233–235	1442
$C_6H_5CH_2CO$–NH	H	OH	CH_3	C_3H_7	·CH_3SO_3H	214–219	1442
C_6H_5CO–NH	H	H	CH_3	C_3H_7	Hydrogen maleate	183–185	1442
C_6H_5CO–NH	H	OH	CH_3	C_3H_7	·CH_3SO_3H	198–200.5[a]	1442
4-Cl–C_6H_4CO–NH	H	H	CH_3	*i*-C_4H_9		236–239	1442
·HCl						240–247	1442
3,4-$(CH_3O)_2C_6H_3CH_2$ –NH	H	OH	CH_3	C_3H_7	·CH_3SO_3H	211–213.5[a]	1442
CH_3CO–N–C_2H_5	H	H	CH_3	C_3H_7	·HCl	190–192	1442

[a]Tautomeric structure.

F. Imidazo[1,2-*b*]1,2,4-benzotriazines

Interaction of 3-amino-1,2,4-benzotriazine (**676**) and desyl bromide (**677**) yields 2,3-diphenylimidazo[1,2-*b*] 1,2,4-benzotriazine (**678**) (m.p. 205°C) (619) (RRI 8408).

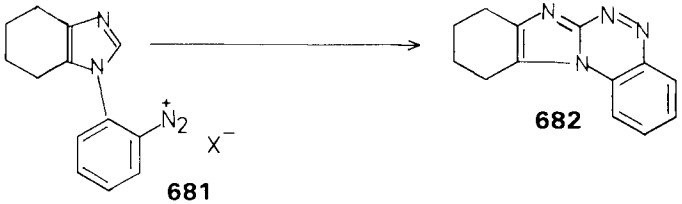


676 **677** **678**

G. Imidazo[2,1-*c*]1,2,4-benzotriazines

2-(1-Imidazolyl)phenyldiazonium ion (**679**), formed by the diazotization of *N*-(2-aminophenyl)imidazole (**680**), undergo intramolecular azo coupling at pH 5 to 6 at position 5 of the imidazole ring (see next section). If position 5 is occupied, azo coupling may take place at position 2 of the imidazole ring, though with greater difficulty. Thus the diazonium salt **681** gives the 4,5-tetramethyleneimidazo[2,1-*c*] 1,2,4-benzotriazine (**682**) (m.p. 226 to 229°C) (1443, 1444). Ultraviolet spectra and results of LCAO MO calculation are given in Ref. 1444.

The possible formation of a tetrahydroimidazo[2,1-*c*] 1,2,4-benzotriazine is discussed in a paper of Doleschall and his group (1445).

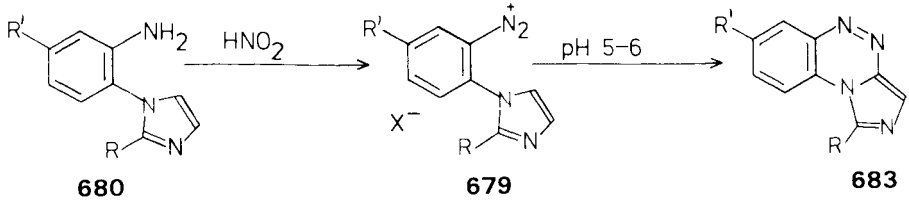


681 **682**

H. Imidazo[5,1-*c*]1,2,4-benzotriazines

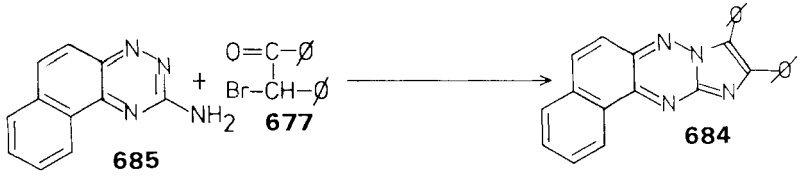
2-(1-Imidazolyl)phenyldiazonium salts (**679**) undergo intramolecular azo coupling at pH 5 to 6 at position 5 of the imidazole ring, affording derivatives of imidazo[5,1-*c*] 1,2,4-benzotriazines (**683**) (1443, 1444). **683** are yellow compounds of rather low basicity; the pK_a value of the unsubstituted compound was found to be 1.84. The melting points of **683** are as follows: R = R′ = H, 210 to 211°C; R = H, R′ = CH_3, 211 to 212°C; R = H, R′ = Br, 242 to 243°C;

R = H, R′ = NO_2, 194 to 195°C; R = H, R′ = CH_3O, 251 to 252°C; and R = CH_3, R′ = H, 229 to 230°C. Ultraviolet spectra and results of LCAO MO calculations are given in Ref. 1444.



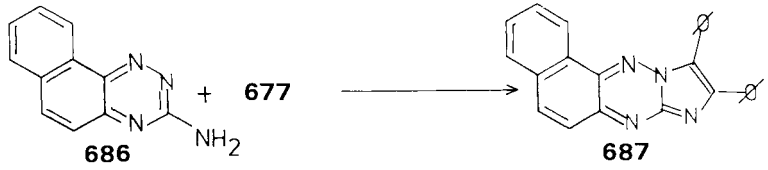
I. Imidazo[1,2-*b*]naphtho[1,2-*e*]1,2,4-triazines

Rossi and Trave (619) obtained 9,10-diphenylimidazo[1,2-*b*]naphtho[1,2-*e*]-1,2,4-triazine (**684**) (m.p. 257°C) (RRI 8873) through the reaction of 2-aminonaphtho[1,2-*e*] 1,2,4-triazine (**685**) with desyl bromide (**677**).



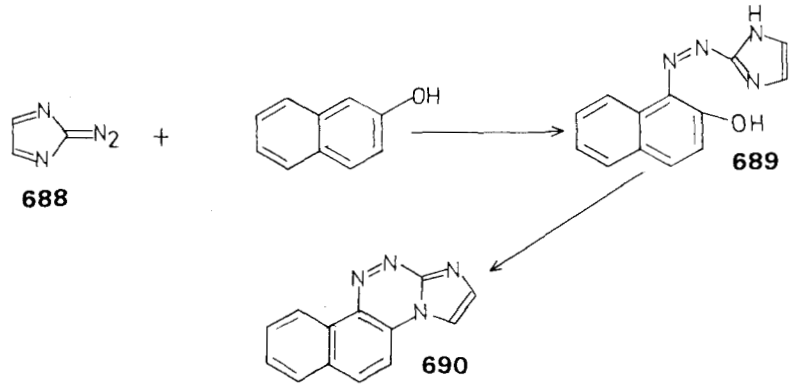
J. Imidazo[1,2-*b*]naphtho[2,1-*e*]1,2,4-triazines

Interaction of 3-aminonaphtho[2,1-*e*] 1,2,4-triazine (**686**) and desylbromide (**677**) yields 9,10-diphenylimidazo[1,2-*b*] naphtho[2,1-*e*] 1,2,4-triazine (**687**) (m.p. 251 to 252°C) (RRI 8872) (619).



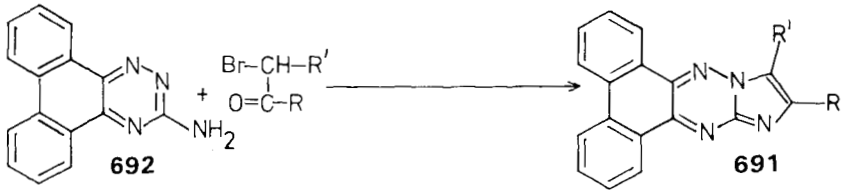
K. Imidazo[2,1-*c*]naphtho[2,1-*e*]1,2,4-triazines

Coupling of 2-diazoimidazole (**688**) with 2-naphthol yields the azo compound (**689**), which cyclizes to imidazo[2,1-*c*] naphtho[2,1-*e*] 1,2,4-triazine (**690**) (m.p. 270 to 271°C) when heated in ethanol (1262).



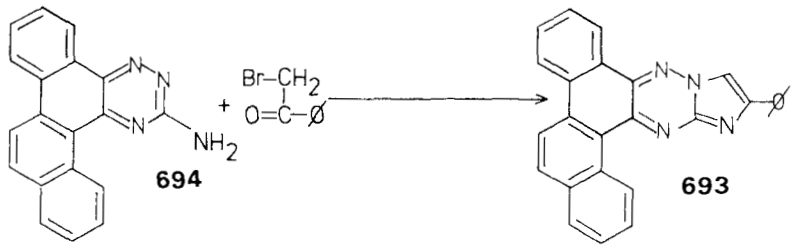
L. Imidazo[1,2-*b*]phenanthro[9,10-*e*]1,2,4-triazines

A number of substituted imidazo[1,2-*b*]phenanthro[9,10-*e*]1,2,4-triazines (**691**) (RRI 9247) were prepared by Rossi and Trave (619), who reacted the 3-aminophenanthro[9,10-*e*]1,2,4-triazine (**692**) with α-bromoketones. The 6-phenyl derivative is reported in two patents (609, 696). The following melting points are given: R = R′ = H, 236 to 240°C; R = R′ = C_6H_5, 316°C; R - 4-O_2N–C_6H_4, R′ = H, 325°C and R = 2-naphthyl, R′ = C_6H_5, 265°C.



M. Chryseno[5,6-*e*]imidazo[1,2-*b*]1,2,4-triazines

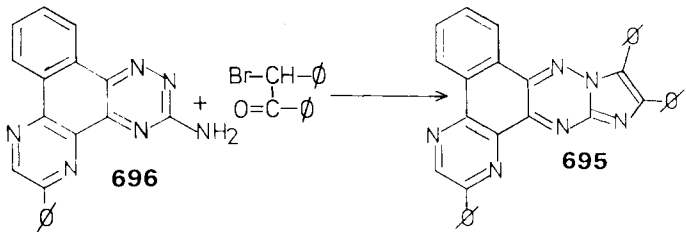
Two representatives of the chryseno[5,6-*e*]imidazo[1,2-*b*]1,2,4-triazine system (**693**) (RRI 14048) are reported in the literature, the unsubstituted



compound (m.p. 245 to 250°C) (609, 696) and the 14-phenyl derivative (m.p. 260°C) (609). The latter is prepared by interaction of the amino-1,2,4-triazine **694** and phenacyl bromide.

N. Benz[*f*]imidazo[1′,2′:2,3]1,2,4-triazino[6,5-*h*]quinoxalines

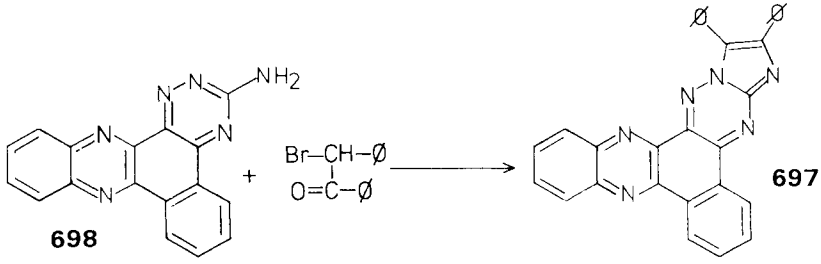
The 2,11,12-triphenyl derivative of benz[*f*]imidazo[1′,2′:2,3]1,2,4-triazino-[6,5-*h*]quinoxaline (**695**) (RRI 9246) (m.p. 354°C) is reported by Rossi and Trave (619), who reacted the amino-1,2,4-triazine **696** with desyl bromide.



696 **695**

O. Benz[*a*]imidazo[1′,2′:2,3]1,2,4-triazino[5,6-*c*]phenazines

Rossi and Trave (619) prepared the 1,2-diphenyl derivative of benz[*a*]imidazo[1′,2′:2,3]1,2,4-triazino[5,6-*c*]phenazine (**697**) (RRI 9474) (m.p. 297°C) through the interaction of the amino-1,2,4-triazine (**698**) and desyl bromide.



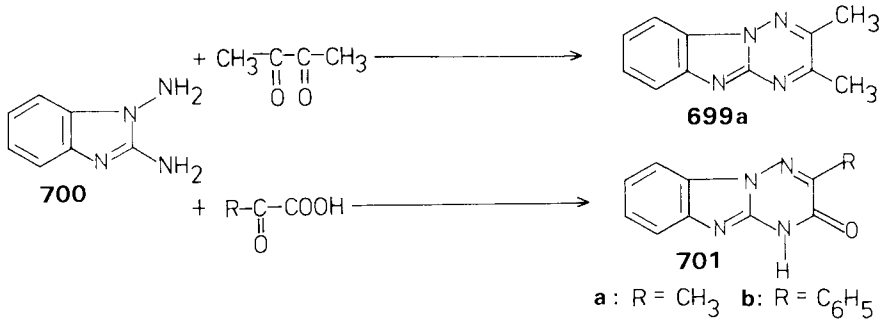
698 **697**

VII. CONDENSED WITH THE BENZIMIDAZOLE SYSTEM

A. 1,2,4-Triazino[2,3-*a*]benzimidazoles

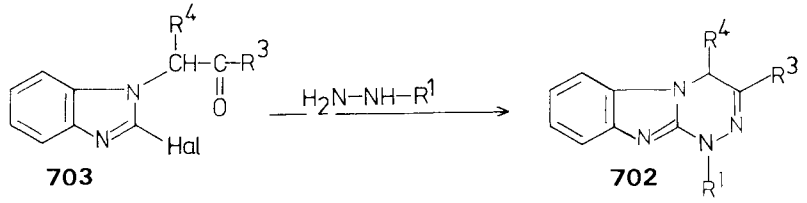
So far only three derivatives of the 1,2,4-triazino[2,3-*a*]benzimidazole system are known (1446). 1,2-Diaminobenzimidazole (**700**) reacted with

2,3-butanedione to form 2,3-dimethyl-1,2,4-triazino[2,3-*a*]benzimidazole (**699a**) (m.p. 236 to 239°C). Reaction with pyruvic acid and benzoyl formic acid gave 2-methyl- (**701a**) (m.p. 350 to 355°C) and 2-phenyl-1,2,4-triazino[2,3-*a*]-benzimidazol-3-one (**701b**) (m.p. 355 to 358°C), respectively. **699a** is a yellow solid whereas the oxo derivatives (**701**) are colorless crystals.

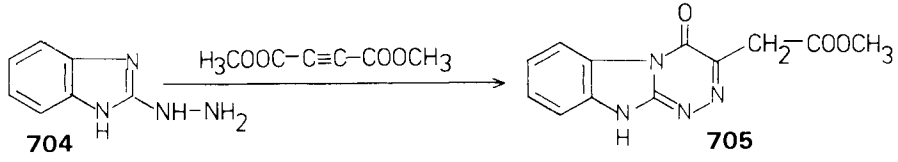


B. 1,2,4-Triazino[4,3-*a*] benzimidazoles

1,4-Dihydro-1,2,4-triazino[4,3-*a*]benzimidazoles (**702**) were prepared by condensation of 1-(acylalkyl)-2-halobenzimidazoles (**703**) with hydrazines in an organic solvent (1447).



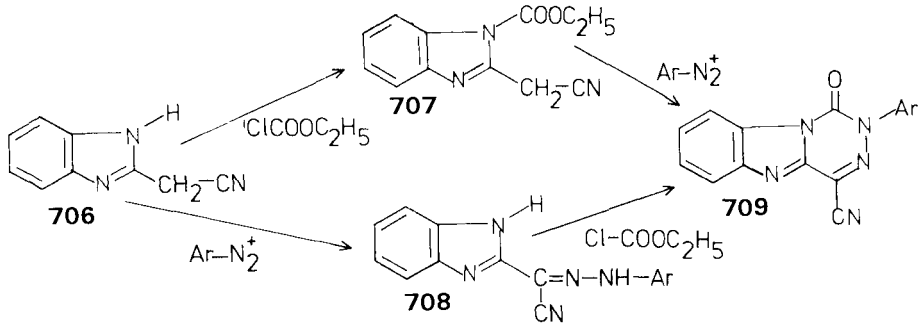
Interaction of 2-hydrazinobenzimidazole (**704**) and dimethyl acetylenedicarboxylate afforded methyl 1,2,4-triazino[4,3-*a*]benzimidazol-3-yl acetate (**705**) [m.p. 289°C; (1434)].



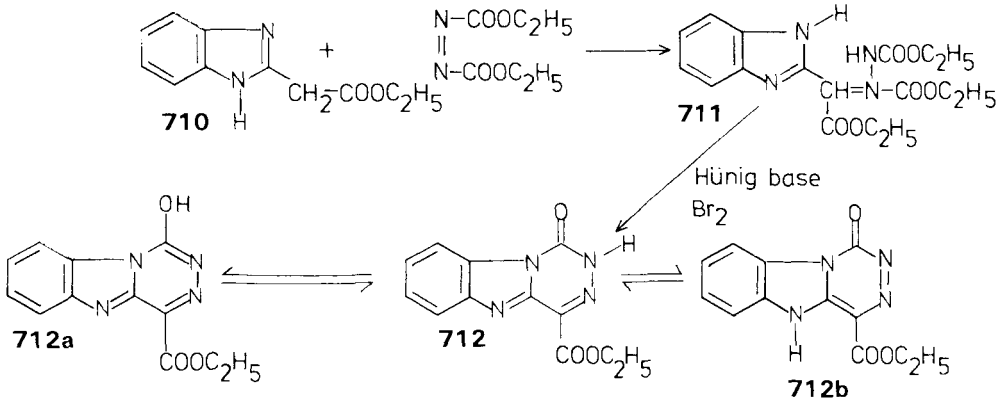
C. 1,2,4-Triazino[4,5-*a*]benzimidazoles

1. *Preparation*

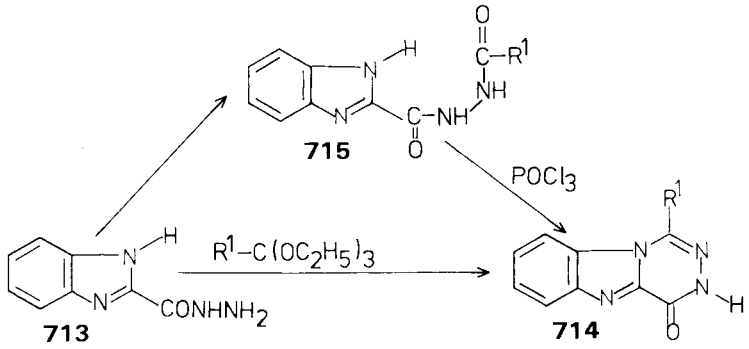
At present mainly the oxo derivatives of the 1,2,4-triazino[4,5-*a*]benzimidazole system are known. They were prepared by three groups, by three different methods. Slouka and co-workers (411, 1448–1450) started from benzimidazol-2-ylacetonitrile (**706**), which was either reacted with ethyl chloroformate to yield 1-(ethoxycarbonyl)-2-(cyanomethyl)benzimidazole (**707**) or with aryldiazonium salts affording the coupled products (**708**). Reaction of **707** with aryldiazonium salts or **708** with ethyl chloroformate gave 2-aryl-1-oxo-1,2,4-triazino[4,5-*a*]benzimidazol-4-carbonitriles (**709**).



Finch and Gemenden (1451, 1452) reacted ethyl 2-benzimidazol-2-ylacetate (**710**) with diethyl azodicarboxylate and obtained the addition product **711**, which was cyclized with bromine in the presence of Hünig base yielding ethyl 1-oxo-1,2,4-triazino[4,5-*a*]benzimidazole-4-carboxylate (**712**).



Pankina and Shchukina (1453–1457) used benzimidazole-2-carboxhydrazide (**713**) as the starting material for their synthesis. **713** could be cyclized by reaction with triethyl orthocarboxylates, yielding 1,2,4-triazino[4,5-*a*]benzimidazol-4-ones (**714**), or were acylated to give the acylhydrazides (**715**) which were converted to **714** on treatment with phosphoryl chloride.

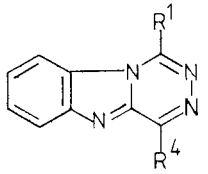


2. *Compound Survey*

Table VI-13 lists the compounds of this group that have been reported in the literature.

TABLE VI-13. 1,2,4-TRIAZINO[4,5-*a*]BENZIMIDAZOLES AND OXO DERIVATIVES

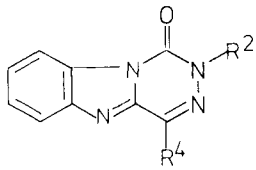
A. 1,2,4-Triazino[4,5-*a*] benzimidazoles



R^1	R^4	m.p. (°C)	Refs.
H	H		1453
H	C_6H_5		1453
H	OCH_3	210	1455
		212–214	1454
OH	$COOC_2H_5$	243–244	1451, 1452
OC_2H_5	$COOC_2H_5$	154–155	1451, 1452
$OCOCH_3$	$COOC_2H_5$	149–151	1451, 1452
$OCOCH_2Cl$	$COOC_2H_5$	188–190	1451

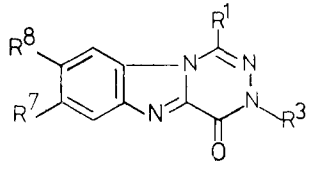
TABLE VI-13. (continued)

B. 1,2,4-Triazino[4,5-*a*]benzimidazol-1-ones



R^2	R^4	m.p. (°C)	Refs.
H	$COOC_2H_5$	240–242	1451, 1452
H	CO–N⟨ ⟩	266–268	1451
C_2H_5	$COOC_2H_5$	161–162	1451, 1452
C_6H_5	CN	170–171	1450
		200–201	1449
4-CH_3–C_6H_4	CN	221–222	1449, 1450
4-F–C_6H_4	CN	198	1448
4-Cl–C_6H_4	CN	251–253	1448
4-Br–C_6H_4	CN	265–267	1449
4-I–C_6H_4	CN	252–254	1448
4-CH_3O–C_6H_4	CN	220–221	1449
4-C_2H_5O–C_6H_4	CN	198–199	1449
4-CH_3CONH–C_6H_4	CN	291–293	1448
4-H_5C_2OOC–C_6H_4	CN	212–214	1448

C. 1,2,4-Triazino[4,5-*a*]benzimidazol-4-ones



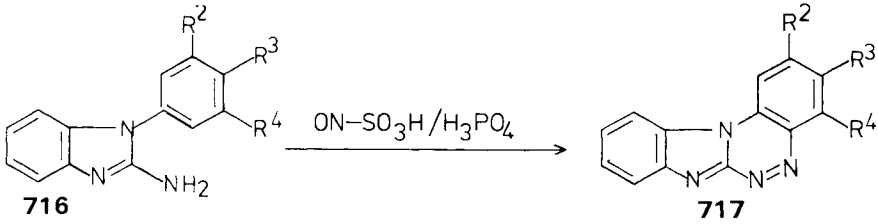
R^1	R^3	R^7	R^8	m.p. (°C)	Refs.
H	H	H	H	336	1454, 1455
					1453
H	H	NO_2	H		1457
H	H	H	NO_2		1457
H	CH_3	H	H	308–310	1455
H	C_2H_5	H	H	232	1455
H	CH_2OH	H	H	351–352 (dec.)	1456
H	CH_2O–$COCH_3$	H	H	244–246 (dec.)	1456
H	$C_6H_5CH_2$	H	H	289–290 (dec.)	1456
H	CH_2CH_2CN	H	H	277–278 (dec.)	1456
CH_3	H	H	H	345	1455
CH_3	CH_3	H	H	241–243	1455

3. *Physical Properties and Reactions*

The isolated 1,2,4-triazino[4,5-*a*]benzimidazole derivatives are colorless or yellow, crystalline compounds. In the ultraviolet spectra of ethyl 1-ethoxy-1,2,4-triazino[4,5-*a*]benzimidazole-4-carboxylate three maxima were observed: $\lambda_{max}(\epsilon)$: 320 (5.920), 250 (30.550), and 227 nm (16.120) (1451). Enolization of ethyl 1-oxo-1,2,4-triazino[4,5-*a*]benzimidazole-4-carboxylate (**712**) was observed by Finch and Gemenden (1451, 1452). In an aprotic solvent, such as acetonitrile, **712** is completely enolized, as is demonstrated by the infrared spectra, which shows a signal for one carbonyl group. The enolized compound (**712a**) was isolated by recrystallization from DMF, and recrystallization from ethanol yielded the amide isomer (**712**). **712** can be alkylated and acetylated (1451, 1452). When **712** is treated with aqueous pyridine or with amines (411, 1451) the 1,2,4-triazine ring is opened.

D. Benzimidazo[2,1-*c*]1,2,4-benzotriazines

Diazotization of 2-amino-1-arylbenzimidazoles (**716**) with nitrosylsulfonic acid and phosphoric acid was used by Simonov and his group for the synthesis of benzimidazo[2,1-*c*]1,2,4-benzotriazines (**717**) (1458). The initially formed diazonium salts were not isolated. The following melting points are reported: $R^2 = R^3 = R^4 = H$, 312 to 313°C; $R^2 = R^4 = H$, $R^3 = CH_3$, 289 to 290°C; $R^2 = R^4 = H$, $R^3 = CH_3O$, 255 to 256°C; $R^2 = R^3 = H$, $R^4 = CH_3$ or $R^3 = R^4 = H$, $R^2 = CH_3$, 288 to 289°C and 308 to 309°C.



716 **717**

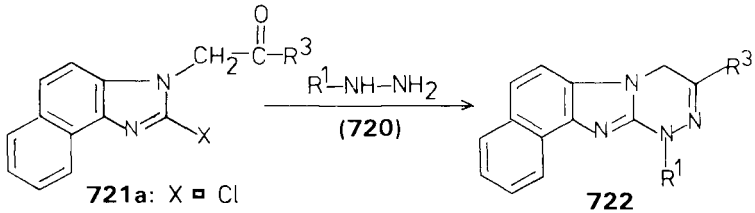
The tetrahydro derivative **719** (m.p. 226 to 229°C) was obtained through cyclization of the (tetrahydro-1-benzimidazolyl)phenyldiazonium salt (**718**) (1443, 1444).

718 **719**

VIII. CONDENSED WITH THE NAPHTH[1,2-*d*]IMIDAZOLE SYSTEM

A. Naphth[1,2-*d*]imidazo[3,2-*c*]1,2,4-triazines

The reaction of 2-chloro- (**721a**) (1459) or 2-(methylmercapto)-1-(acylmethyl)naphth[1,2-*d*]imidazoles (**721b**) (1460) with hydrazines (**720**) has been used for the synthesis of the 1,4-dihydronaphth[1,2-*d*]imidazo[3,2-*c*]1,2,4-triazines (**722**). The following compounds are reported: $R^1 = H$, $R^3 = CH_3$, 301 to 303°C; $R^1 = H$, $R^3 = t\text{-}C_4H_9$; $R^1 = H$, $R^3 = C_6H_5$, 310 to 312°C; $R^1 = H$, $R^3 = 4\text{-Br-}C_6H_4$, 320 to 322°C; $R^1 = R^3 = C_6H_5$, 246 to 247°C; and $R^1 = C_6H_5$, $R^3 = 4\text{-Br-}C_6H_4$, 243 to 244°C.



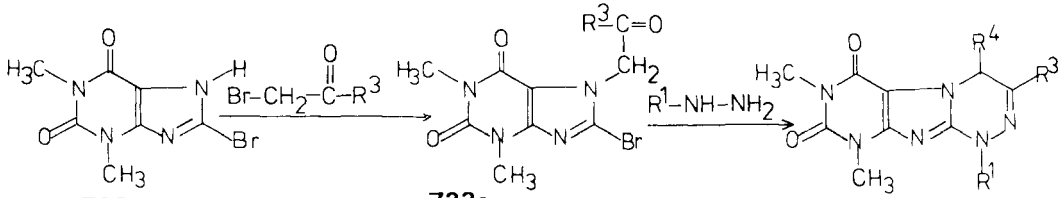
721a: X = Cl
721b: X = SCH_3

722

IX. CONDENSED WITH THE IMIDAZO[4,5-*d*]PYRIMIDINE SYSTEM (PURINE SYSTEM)

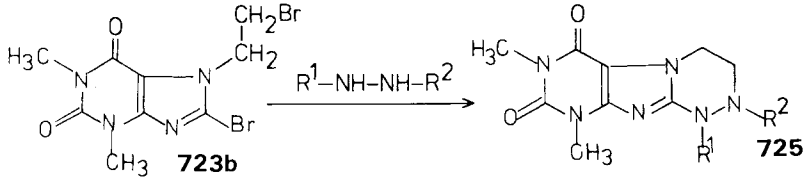
A. Pyrimido[4′,5′:4,5]imidazo[2,1-*c*]1,2,4-triazines (1,2,4-Triazino[3,4-*f*]-purines)

8-Bromotheophylline (**723**) was reacted with α-bromoketones to give 7-acylmethyl-8-bromotheophyllines (**723a**) which were cyclized with hydrazines to yield 1,4-dihydro-7,9-dimethyl-1,2,4-triazino[3,4-*f*]purine-6,8-diones (**724**) (1540, 1542, 1552). **724** can be acylated at N-1 and reacts with acrylonitrile to give 1-(2-cyanoethyl) derivatives (1542, 1552).



723 **723a** **724**

Reaction of 8-bromo-7-(2-bromoethyl)theophylline (**723b**) with hydrazines yields the tetrahydro derivatives (**725**) ($R^1 = R^2 = H$, m.p. 290°C; R^1, $R^2 = H$, C_6H_5CO, 318 to 325°C; $R^1 = R^2 = CH_3CO$, 220°C; R^1, $R^2 = H$, $OC-CH_2CH_2COOH$, 257 to 261°C) (1551).

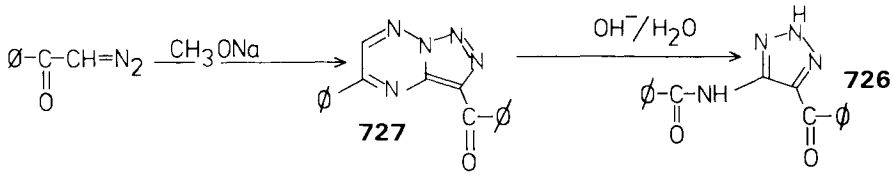


R^1	R^3	R^4	m.p. (°C)	Refs.
H	CH_3	H	310	1542
H	C_6H_5	H	320	1542/1540
H	C_6H_5	C_6H_5	305–306	1552
H	4-O_2N–C_6H_4	H		1540
CH_3	CH_3	H	278	1542
CH_2CH_2CN	CH_3	H	210–211	1542
CH_3CO	CH_3	H	310	1542
CH_3CO	C_6H_5	H	275	1542
CH_3CO	C_6H_5	C_6H_5	278	1552
C_6H_5	4-Br–C_6H_4	H		1540

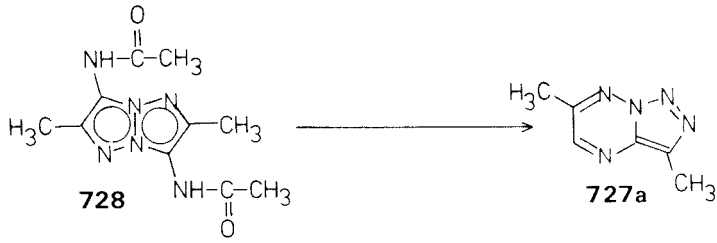
X. CONDENSED WITH THE 1,2,3-TRIAZOLE RING

A. 1,2,3-Triazolo[1,5-*b*]1,2,4-triazines

At present three publications are known in which the formation of a compound with the 1,2,3-triazolo[1,5-*b*]1,2,4-triazine structure is discussed (1461–1463) (RRI 9917). Yates and Farnum (1461, 1462) treated α-diazoacetophenone with a concentrated solution of sodium methoxide and obtained, in addition to other compounds, a substance with the formula $C_{17}H_{11}N_5O$ (m.p. 203 to 204°C). Owing to the formation of 4-benzoyl-5-benzoylamino-1,2,4-triazole (**726**) on hydrolysis with base the 3-benzoyl-5-phenyl-1,2,3-triazolo[1,5-*b*]-1,2,4-triazine structure (**727**) was considered to be the most probable for the isolated compound.



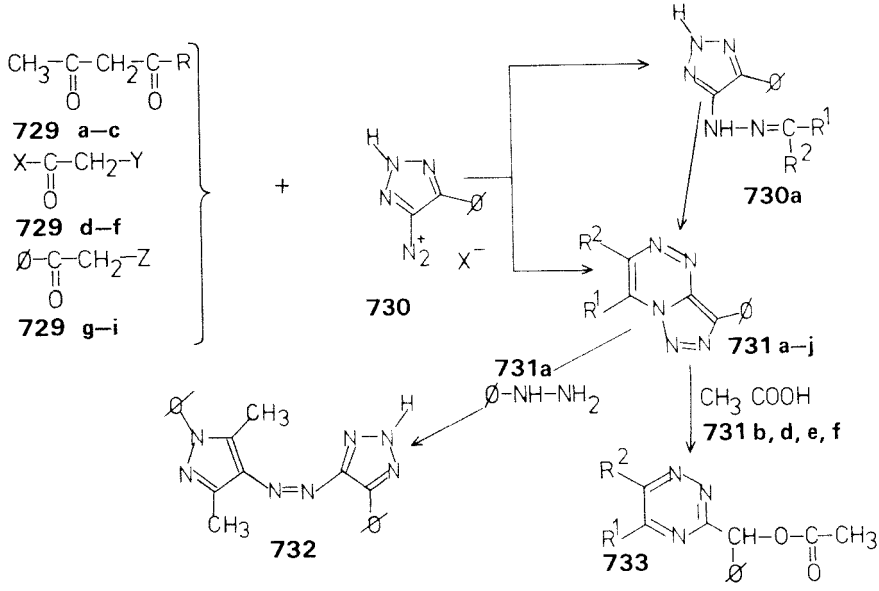
Pfleger, Garthe, and Rauer (1463) obtained a substance with the formula $C_6H_7N_5$ (m.p. 161 to 162°C) when they tried to hydrolyze 3,7-diacetamido-2,6-dimethyl-1,5-dehydro-1,2,3-triazolo[2,1-*a*]1,2,3-triazole (**728**) with 2*N* hydrochloric acid. They suggest structure **727a** for the isolated compound, which is the 3,6-dimethyl-1,2,3-triazolo[1,5-*b*]1,2,4-triazine.



728 **727a**

B. 1,2,3-Triazolo[5,1-*c*]1,2,4-triazines

1,3-Dicarbonyl compounds (**729a** to **729c**) (**a**: R = CH_3, **b**: R = C_6H_5, **c**: R = OC_2H_5) coupled with the diazonium salt (**730**) in aqueous ethanol at room temperature in the presence of sodium acetate to give 6-acyl-7-alkyl-3-phenyl-

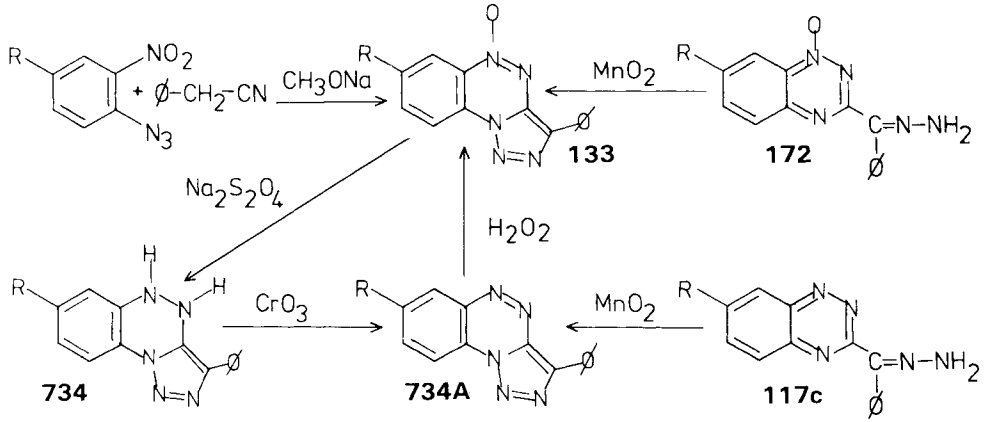


a	b	c	d	e	f	g	h	i	j
CH_3	CH_3	CH_3	NH_2	NH_2	NH_2	C_6H_5	C_6H_5	OH	OH
CH_3CO	C_6H_5CO	$COOC_2H_5$	$COOC_2H_5$	$CONH_2$	C_6H_5CO	C_6H_5CO	$COOC_2H_5$	$COOC_2H_5$	C_6H_5CO

1,2,3-triazolo[5,1-*c*] 1,2,4-triazines (**731a** to **731c**) (1464). Coupling of **730** with diethyl malonate (**729d**) ($X = OC_2H_5$, $Y = COOC_2H_5$), ethyl cyanoacetate (**731e**) ($X = OC_2H_5$, $Y = CN$) or cyanoacetamide (**731f**) ($X = NH_2$, $Y = CN$) gave mixtures of the 1,2,3-triazolo[5,1-*c*] 1,2,4-triazines (**731d**, **e**, **i**) and the hydrazones (**730a**), whereas the hydrazones (**730a**) were the sole products of the coupling reaction of **730** with benzoylacetonitrile (**729g**) ($Z = CN$), ethyl benzoylacetate (**729h**) ($Z = COOC_2H_5$), or dibenzoylmethane (**729i**) ($Z = C_6H_5CO$). On heating in aqueous ethanolic sodium acetate the hydrazones (**730a**) afforded the corresponding **731d** to **731j**. **731a** reacted with phenylhydrazine to give the azo compounds (**732**). The 3-(α-acetoxybenzyl)-1,2,4-triazines (**733**) were isolated by heating the compounds **731b**, **d**, **e**, and **g** under reflux in glacial acetic acid (1464).

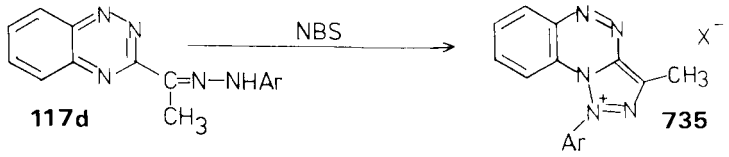
C. 1,2,3-Triazolo[5,1-*c*]1,2,4-benzotriazines

Condensation of 2-nitrophenyl azides with phenylacetonitrile in the presence of sodium methoxide yields 1,2,3-triazolo[5,1-*c*] 1,2,4-benzotriazine 5-oxides (**133**) (1131, 1465) [R = H, m.p. 220 to 222°C (dec.) (1465), 223°C (dec.) (1131); $R = CH_3$, 232°C (dec.) (1131)], which can be reduced to 4,5-dihydro-1,2,3-triazolo[5,1-*c*] 1,2,4-benzotriazines (**734**) (1131) [R = H, 197°C (dec.); $R = CH_3$, 191°C (dec.)]. Oxidation of **734** affords 1,2,3-triazolo[5,1-*c*] 1,2,4-benzotriazines (**734A**) (R = H, 207°C; $R = CH_3$, 211°C), which were also obtained by oxidation of the hydrazones of 3-benzoyl-1,2,4-benzotriazines (**117c**) with activated manganese dioxide (1131). **133** were isolated when the *N*-oxides of **117c** (**172**) were oxidized with manganese dioxide (1144) or when **734A** were treated with hydrogen peroxide in glacial acetic acid (1131).

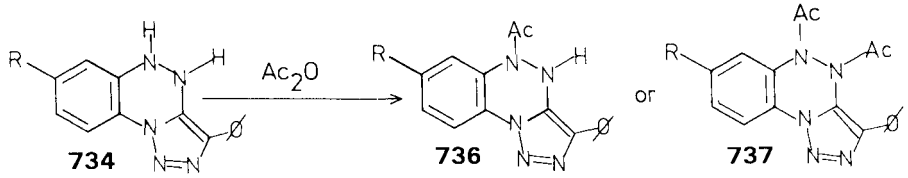


Oxidation of the arylhydrazones of 3-acetyl-1,2,4-benzotriazine (**117d**) with

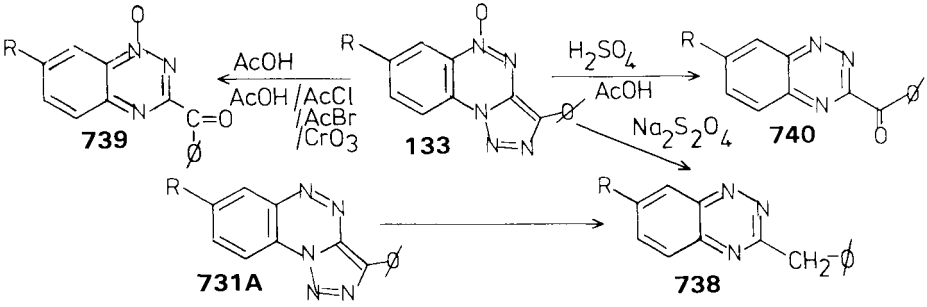
N-bromosuccinimide afforded the 1-aryl-1,2,3-triazolo[5,1-*c*]1,2,4-benzotriazinium salts (**735**) (1189) (Ar = C_6H_5, X = Br, m.p. 183°C, X = BF_4, 212°C, X = ClO_4, 217°C; Ar = 4-CH_3O-C_6H_4, X = Br, 165°C, X = BF_4, 211°C, X = ClO_4, 215°C).



The dihydro compounds (**734**) can be acetylated, yielding monoacetyl derivatives (**736**) [R = H, m.p. 192°C (dec.); R = CH_3, 195°C (dec.)] and diacetyl derivatives (**737**) (R = H, m.p. 182°C; R = CH_3, 197°C) (1131).



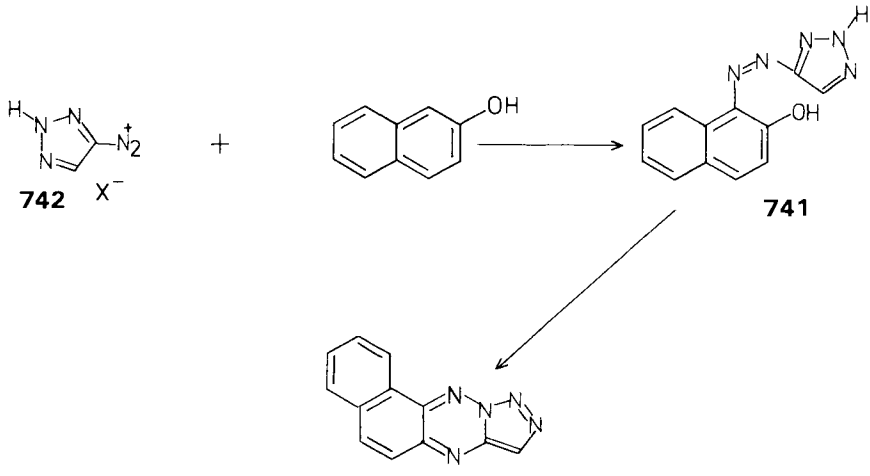
Reduction of the *N*-oxides (**133**) with sodium dithionite in acetic acid gives 3-benzyl-1,2,4-benzotriazines (**738**) (1131, 1144). Treatment of **133** with acetic acid alone or with acetic acid containing acetyl chloride, acetyl bromide, or chromium trioxide converted them into the 3-benzoyl-1,2,4-benzotriazine 1-oxides (**739**) (1144); warming **133** in aqueous sulfuric acid or acetic acid yields the 3-benzoyl-1,2,4-benzotriazines (**740**) (1144). 1,2,3-Triazolo[5,1-*c*]1,2,4-benzotriazines (**731A**) undergo acid-catalyzed conversion into 3-benzyl-1,2,4-benzotriazines (**738**) (1144).



D. Naphtho[2,1-*e*]1,2,3-triazolo[1,5-*b*]1,2,4-triazines

The coupling product (**741**) of the 1,2,3-triazolediazonium salt (**742**) and 2-naphthol were refluxed in methanol for 2 days, yielding naphtho[2,1-*e*]1,2,3-

triazolo[1,5-*b*]1,2,4-triazine (**743**) [m.p. 198 to 200°C (dec.)] which is the single known representative of this class (1262).



XI. CONDENSED WITH THE 1,2,4-TRIAZOLE RING

A. 1,2,4-Triazolo[4,3-*b*]1,2,4-triazines

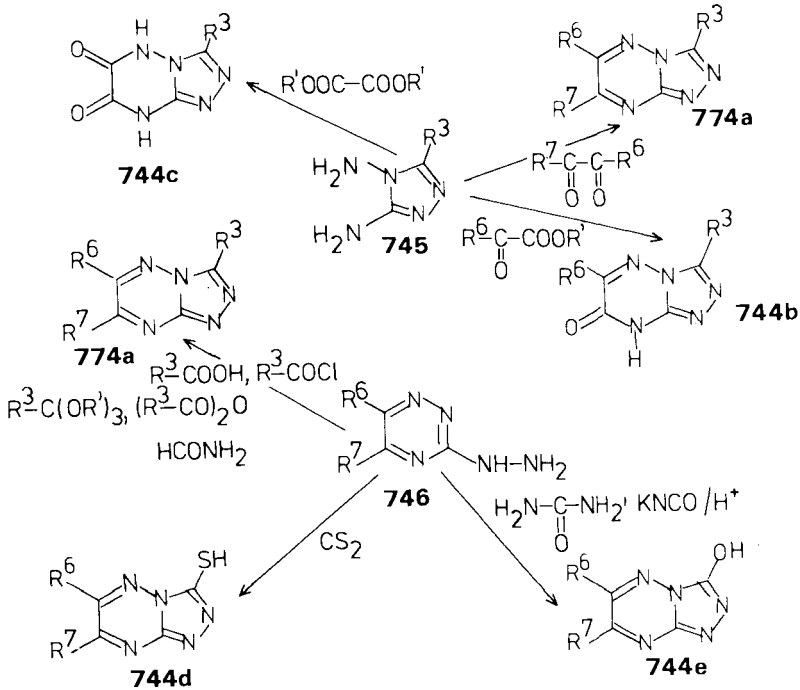
1. *Preparation*

1,2,4-Triazolo[4,3-*b*]1,2,4-triazines (**744**) (RRI 1076) are well-known compounds. Two methods have been reported for their synthesis:

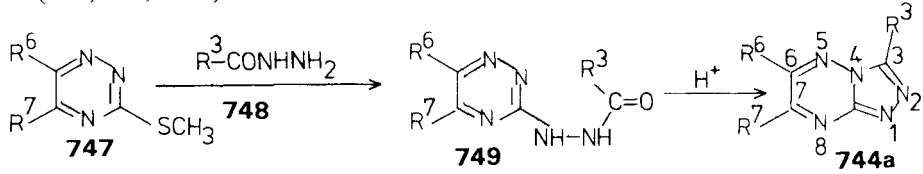
1. Starting from 3,4-diamino-1,2,4-triazoles (**745**) and synthesizing the 1,2,4-triazine ring by the reaction of **745** with 1,2-dicarbonyl compounds (587, 814, 1467–1470), ketocarboxylates (834, 1466, 1470, 1473), ketoacids (586, 814), or oxalates (1471, 1472).

2. Using 3-hydrazino-1,2,4-triazines (**746**) as the starting material and constructing the 1,2,4-triazole ring through condensation of **746** with carboxylic acids (586, 587, 595, 760, 814, 834, 1466, 1472), orthocarboxylates (392, 583, 814), acyl chlorides (587, 770), acetic anhydride (770, 814, 832), carbon disulfide (586, 1466), formamide (770), cyanuric acid (586), and urea (586).

A method that is quite similar to the synthesis of **744** from **746** and carboxylic acids or their derivatives is the reaction of 3-(methylmercapto)-1,2,4-



triazines (**747**) and acylhydrazines (**748**) and subsequent cyclization of the formed 3-(acylhydrazino)-1,2,4-triazines (**749**) by heating in carboxylic acids (814, 834, 1466).



2. *Compound Survey*

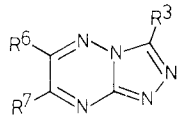
Known compounds of this class are listed in Table VI-14.

3. *Physical Properties and Reactions*

The 1,2,4-triazolo[4,3-*b*]1,2,4-triazines (**744**) are stable crystalline compounds which are mostly colored (yellow, orange, red) only a few were reported

TABLE VI-14. 1,2,4-TRIAZOLO[4,3-*b*]1,2,4-TRIAZINES

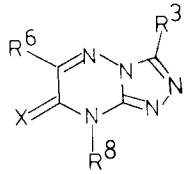
A. 1,2,4-Triazolo[4,3-*b*]1,2,4-triazines



R^3	R^7	R^6	m.p. (°C)	Refs.
H	SCH_3	CH_3	170–171	595
H	$NHNH_2$	H	245 (dec.)	1474
H	$NHNH_2$	CH_3	245–247	595, 1474
			246–248 (dec.)	832
H	4-Cl–C_6H_4CH=N–NH	CH_3	305–306 (dec.)	832
H	NHNHCHO	CH_3	242–243	595
H	$CH_3CONHNH$	CH_3	247–249	1474
H	$C_6H_5CONHNH$	H	283–284	1474
H	$C_6H_5CONHNH$	CH_3	268–269	832
			272–273	1474
H	4-Cl–$C_6H_4CONHNH$	CH_3	285 (dec.)	832
H	4-CH_3O–$C_6H_4CONHNH$	CH_3	260 (dec.)	832
CH_3	C_6H_5	H	127	587
CH_3	CH_3COO	CH_3	183	770
CH_3	NH_2NH	CH_3	310 (dec.)	832
$(CH_3)_2C=CH$	C_6H_5	H	253	587
CH_2OH	C_6H_5	H	230–232	587
$CH_2OC_2H_5$	C_6H_5	H	171–172 (dec.)	587
COOH	C_6H_5	H	229–230	587
C_6H_5	CH_3	CH_3	203	1469
C_6H_5	C_6H_5	C_6H_5	250	587, 1469
4-CH_3O–C_6H_4	CH_3	CH_3	215	1468
4-CH_3O–C_6H_4	C_6H_5	C_6H_5	247	1468
OH	C_6H_5	C_6H_5	278–280 (dec.)	586
SH	C_6H_5	C_6H_5	305.4–306.6	1470
			298–300 (dec.)	586
SCH_3	C_6H_5	C_6H_5	197 (dec.)	586
			201–203	1470
			201–202	1467
SCH_2COOH	C_6H_5	C_6H_5	236	586
SCH_2COOCH_3	C_6H_5	C_6H_5	162	586
NH_2	CH_3	CH_3	299–300	1470
NH_2	C_6H_5	C_6H_5	263–264	1470
NH_2	4-Cl–C_6H_4	4-Cl–C_6H_4	228–230	1470

TABLE VI-14. (continued)

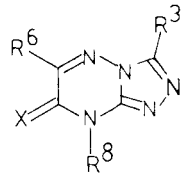
B. 1,2,4-Triazolo[4,3-*b*]1,2,4-triazin-5-ones and 5-thiones



R^3	R^8	X	R^6	m.p. (°C)	Refs.
H	H	O	H	268–274 (dec.)	1474
				271–272	814, 834, 1466
H	H	O	CH_3	266	587, 760
				274–275	834, 1470
				275–280	814
				276	770
				279–282	392, 583
H	H	O	C_6H_5	265	760
				270–272	814
				274–277 (dec.)	834, 1466
H	H	S	H	230–240 (dec.)	1474
H	H	S	CH_3	230–240 (dec.)	1474
				248–250	595
				256–258 (dec.)	832
H	NH_2	O	CH_3	168	760
H	NH_2	O	C_6H_5	217 (dec.)	760
H	HCONH	O	CH_3	251–252 (dec.)	760
H	HCONH	O	C_6H_5	212 (dec.)	760
CH_3	H	O	H	275–280	814, 834
CH_3	H	O	CH_3	240–242	814
				245–245.5	583
				245–246	392
				246–248	832
				247–248	1466
				248	834
·HCl				256–259 (dec.)	832
CH_3	H	O	C_6H_5	310–313 (dec.)	834, 1466
CH_3	H	S	CH_3	292–293 (dec.)	832
CH_3	CH_3CO	O	CH_3	187–189	832
C_2H_5	H	O	H	226	834
C_2H_5	H	O	CH_3	186	834, 1466
C_2H_5	H	O	C_6H_5	226	1466
C_6H_5	H	O	CH_3	267–268	814
				270	770
SH	H	O	CH_3	302–305 (dec.)	586
				310–315	834, 1466
SH	H	O	C_6H_5	293–294	834, 1466
SCH_3	H	O	H	280–290 (dec.)	834, 1466

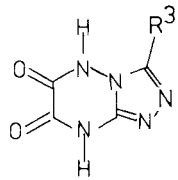
TABLE VI-14. (continued)

B. 1,2,4-Triazolo[4,3-*b*]1,2,4-triazin-5-ones and 5-thiones



R^3	R^8	X	R^6	m.p. (°C)	Refs.
SCH_3	H	O	CH_3	235–237	586
				260–262	834, 1466
SCH_3	H	O	C_6H_5	249–254	834, 1466
SCH_2COOH	H	O	CH_3	235	586
$SCH_2C_6H_5$	H	O	H	230	834, 1466
$SCH_2C_6H_5$	H	O	CH_3	204	834, 1466
NH_2	H	O	CH_3 (or isomer)	317–318	1470

C. 1,2,4-Triazolo[4,3-*b*]1,2,4-triazine-5,6-diones



R^3	m.p. (°C)	Refs.
CH_3	310	1472
	315 (dec.)	1471
C_2H_5	292 (dec.)	1471
$\cdot H_2O$	290–291	1472
C_4H_9	285.5	1471
i-C_4H_9	310–315	1472
C_5H_{11}	276	1471
C_7H_{15}	272	1471
C_9H_{19}	267	1471
$C_6H_5CH_2$	298–300	1472
$C_6H_5CH_2CH_2$	308	1471

to be colorless. Ultraviolet and PMR spectra have been published mainly for the 1,2,4-triazolo[4,3-*b*]1,2,4-triazin-5-ones and 5-thiones (595, 814, 1473, 1474). For the unsubstituted **744b** the following spectroscopic data are reported (814). Ultraviolet λ_{max} (ϵ) = 295 (7.620) and 235 nm (11.730). PMR spectrum: two signals at τ = 0.93 and 2.10. Kalfus (392) has measured the pK_a values for the

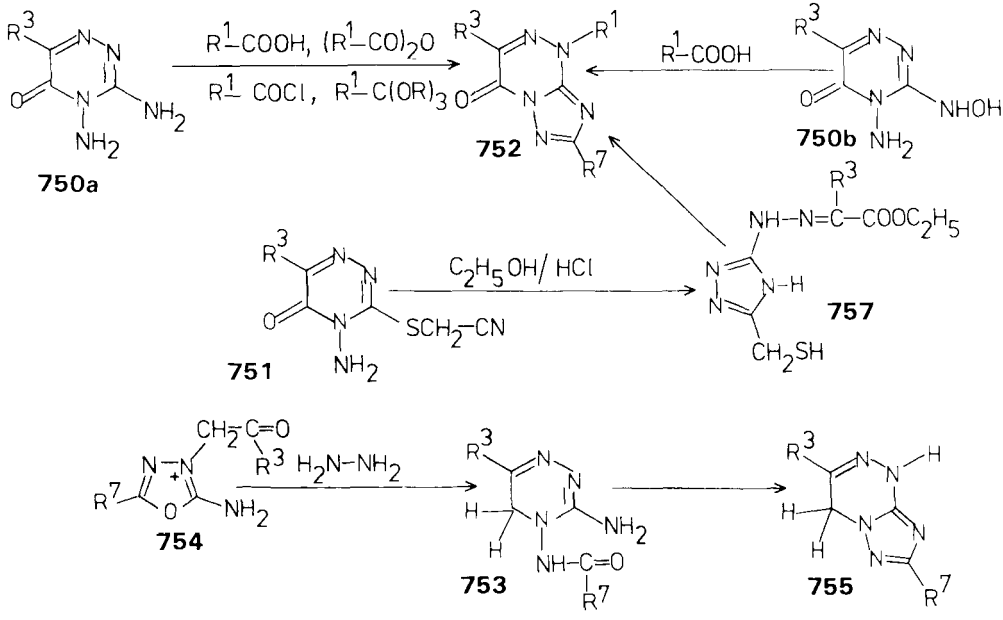
6-methyl- and the 1,6-dimethyl-1,2,4-triazolo[4,3-*b*] 1,2,4-triazin-5-one and reports the following values: water, 5.40 and 5.85 (dimethyl); methanol, 8.74 and 9.34 (dimethyl).

Exchange of hetero substituents in the 1, 5, and 6 positions of the 1,2,4-triazolo[4,3-*b*] 1,2,4-triazine system is reported by different groups (595, 814, 832, 1474). Construction of tricyclic systems, starting from **744**, has been published by three groups (832, 1474, 1475).

B. 1,2,4-Triazolo[5,1-*c*] 1,2,4-triazines

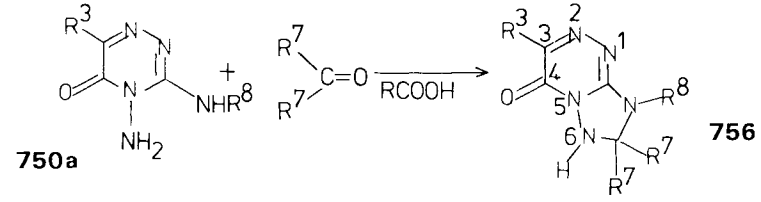
1. *Preparation*

The reaction of the 3,4-diamino-1,2,4-triazin-5-ones (**750a**) or 4-amino-3-(hydroxylamino)-1,2,4-triazin-5-ones (**750b**) (1078) with formic acid (814, 938, 1078), acetic anhydride (814, 938, 1078), orthocarboxylates (934), or benzoyl chloride (814) was used for the synthesis of the 1,2,4-triazolo[5,1-*c*] 1,2,4-triazin-4-ones (**752**). A similar method is reported by Hetzheim and Singelmann (988), who cyclized the 3-amino-4-(acylamino)-4,5-dihydro-1,2,4-triazines (**753**), which were obtained by the reaction of oxadiazolium salts (**754**) and hydrazine, affording 1,4-dihydro-1,2,4-triazolo[5,1-*c*] 1,2,4-triazines (**755**).

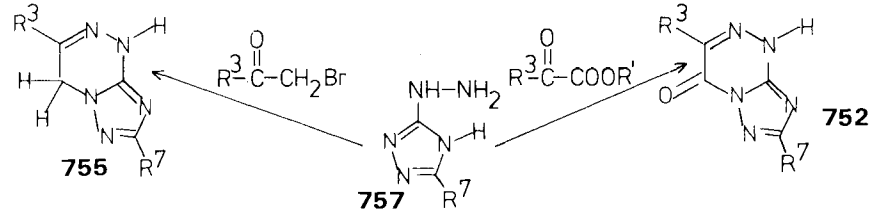


Lempert and Zauer (934) isolated **752** when they heated 4-amino-3-[(cyanomethyl)thio]-1,2,4-triazin-5-ones (**751**) with ethanolic hydrochloric acid and thermally cyclized the formed 1,2,4-triazole derivatives (**757**).

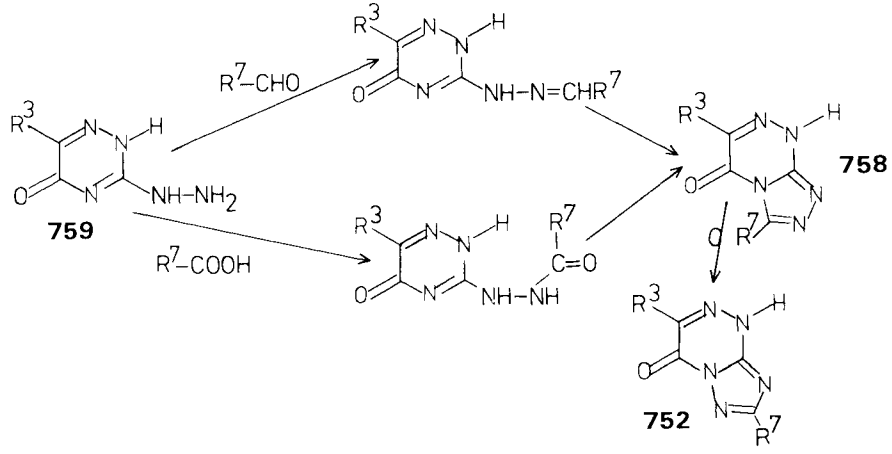
3,4-Diamino-1,2,4-triazin-5-ones (**750a**) reacted with aldehydes or ketones in the presence of a carboxylic acid, unexpectedly yielding the 7,8-dihydro-1,2,4-triazolo[5,1-*c*] 1,2,4-triazin-4-ones (**756**) (937).



Interaction of 3-hydrazino-1,2,4-triazoles (**757**) and α-ketocarboxylic acids (1078), α-ketocarboxylates (934), or α-bromo ketones (1476) is another method for the synthesis of **752** or **755**.



Jacquier and his group (595, 814) have shown that 1,2,4-triazolo[3,4-*c*]-1,2,4-triazin-5-ones (**758**) may readily be thermally isomerized to the corresponding **752** in the presence of a carboxylic acid. By means of this



isomerization **752** were prepared from 3-hydrazino-1,2,4-triazin-5-ones (**759**) and aldehydes or carboxylic acids (814).

2. *Compound Survey*

Table VI-15 lists the compounds of this group reported in the literature.

3. *Physical Properties and Reactions*

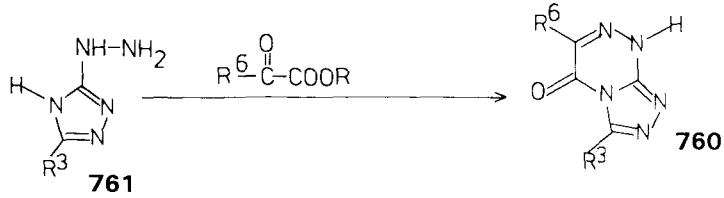
So far only a small amount of spectroscopic data of 1,2,4-triazolo[5,1-*c*]-1,2,4-triazines has been reported (814, 934). The unsubstituted 1,2,4-triazolo-[5,1-*c*] 1,2,4-triazin-4-one has two absorption bands in the ultraviolet region, at 296 (6.375) and 240 nm (3.840), and two signals in the PMR spectrum, at $\tau = 1.60$ (H-2) and 2.15 (H-6).

Ring opening of 1,2,4-triazolo[5,1-*c*] 1,2,4-triazin-4-ones (**752**) by hydrazine is reported by Dornow and Pietsch (1078). 4-Hydrazino-3-methyl-1,2,4-triazolo[5,1-*c*] 1,2,4-triazine (m.p. 258 to 259°C) is obtained from the corresponding 4-thione and hydrazine and was formylated to give 4-(formylhydrazino)-3-methyl-1,2,4-triazolo[5,1-*c*] 1,2,4-triazine (m.p. 133 to 134°C) (595).

C. 1,2,4-Triazolo[3,4-*c*] 1,2,4-triazines

1. *Preparation*

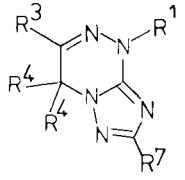
The 1,2,4-triazolo[3,4-*c*] 1,2,4-triazin-5-ones (**760**) were prepared by the condensation of 3-hydrazino-1,2,4-triazoles (**761**) with α-ketocarboxylates or α-ketocarboxylic acids (835).



The reaction of the 3-hydrazino-1,2,4-triazin-5-ones (**762**) with condensation agents leads, depending on the reaction conditions, either to 1,2,4-triazolo-[3,4-*c*] 1,2,4-triazin-5-ones (**760**) or to 1,2,4-triazolo[4,3-*b*] 1,2,4-triazin-7-

TABLE VI-15. 1,2,4-TRIAZOLO[5,1-*c*]1,2,4-TRIAZINES

A. 1,2,4-Triazolo[5,1-*c*]1,2,4-triazin-4(1H)-ones and 1,4-Dihydro-1,2,4-triazolo[5,1-*c*]1,2,4-triazines



(or tautomers)

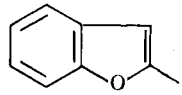
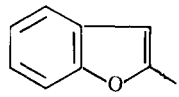
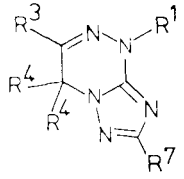
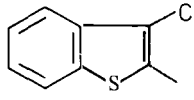
R^7	R^1	R^3	R^4	R^4	m.p. (°C)	Refs.
H	H	H	=O		240	814
H	H	CH_3	=O		250–251	938
					254–256	1078
					255–256	814
					261–262	934
H	H	C_6H_5	=O		236–237	1078
					246–247	814
H	CH_3	CH_3	=O		117–118	934
					128–129	814
H	C_2H_5	CH_3	=O		103	934
CH_3	H	H	=O		216–217	814
CH_3	H	CH_3	=O		250–253	938
					262	814
					262–263	934
CH_3	H	C_6H_5	H	H	255–257	988
CH_3	H	C_6H_5	=O		247–248	938
CH_3	CH_3	CH_3	=O		155–156	814
CH_3	CH_3	C_6H_5	H	H	143	988
CH_2SH	H	CH_3	=O		191	934
$CH_2-S-)_2$	H	CH_3	=O		282–283	934
C_6H_5	H	CH_3	=O		296–297	814
OH	CH_3	C_6H_5	H	H	283–286	1476
OH	CH_3	4-$O_2N-C_6H_4$	H	H	307	1476
OH	CH_3	4-Br–C_6H_4	H	H	304	1476
OH	CH_3		H	H	306	1476
OH	C_2H_5	C_6H_5	H	H	269	1476
OH	C_2H_5	4-$O_2N-C_6H_4$	H	H	302	1476
OH	C_2H_5	4-Br–C_6H_4	H	H	296–299	1476
OH	C_2H_5		H	H	290–292	1476

TABLE VI-15. (continued)

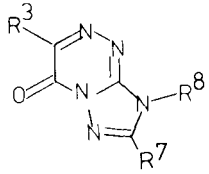
A. 1,2,4-Triazolo[5,1-*c*]1,2,4-triazin-4(1H)ones and 1,4-Dihydro-1,2,4-triazolo[5,1-*c*]1,2,4-triazines



(or tautomers)

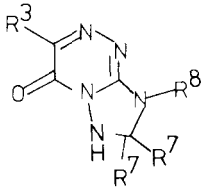
R^7	R^1	R^3	R^4	R^4	m.p. (°C)	Refs.
OH	C_2H_5		H	H	266	1476
SH	NH_2	CH_3	=O		227–228 (dec.)	1078
SH	NH_2	C_6H_5	=O		207–208 (dec.)	1078

B. 1,2,4-Triazolo[5,1-*c*]1,2,4-triazin-4(8H)-ones



R^7	R^8	R^3	m.p. (°C)	Refs.
H	*n*-C_4H_9	C_6H_5	166	938
CH_3	*n*-C_4H_9	C_6H_5	173–174	1078
H	$C_6H_5CH_2$	CH_3	192	938
H	$C_6H_5CH_2$	C_6H_5	191–193	938
H	C_6H_5	C_6H_5	212	938

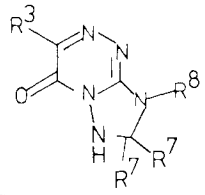
C. 7,8-Dihydro-1,2,4-triazolo[5,1-*c*]1,2,4-triazin-4(6H)-ones



R^7	R^7	R^8	R^3	m.p. (°C)	Refs.
H	CCl_3	CH_3	*i*-C_3H_7	126 (dec.)	937
H	*i*-C_3H_7	CH_3	*t*-C_4H_9	153 (dec.)	937

TABLE VI-15. (continued)

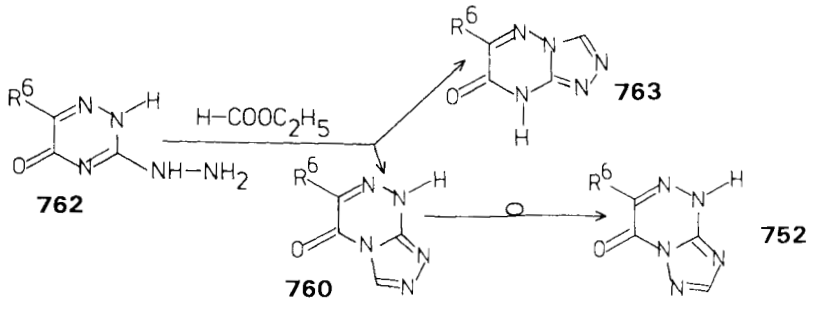
C. 7,8-Dihydro-1,2,4-triazolo[5,1-*c*]1,2,4-triazin-14(6H)-ones



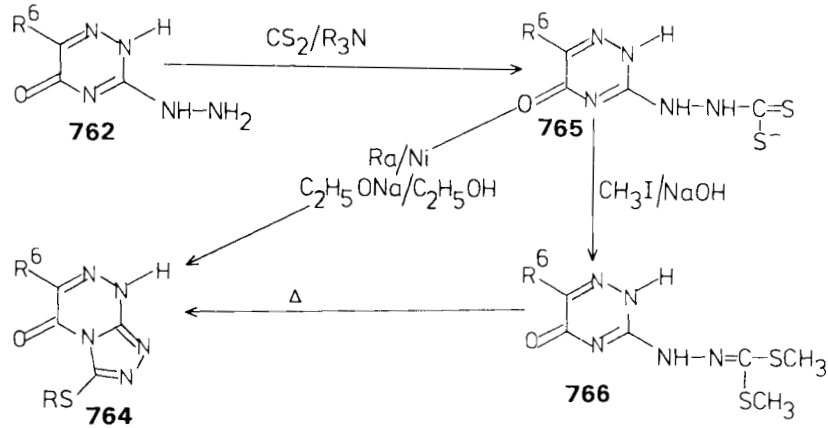
R^7	R^7	R^8	R^3	m.p. (°C)	Refs.
H	*i*-C_4H_9	CH_3	*t*-C_4H_9	116	937
H		CH_3	*t*-C_4H_9	144	937
CH_3	CH_3	CH_3	CH_3	131	937
CH_3	CH_3	CH_3	*i*-C_3H_7	165	937
CH_3	CH_3	CH_3	*t*-C_4H_9	165–168 (dec.)	937
CH_3	CH_3	CH_3		91	937
CH_3	CH_3	CH_3	C_6H_5	179	937
CH_3	CH_3	C_2H_5	*i*-C_3H_7	110	937
CH_3	CH_3	*n*-C_4H_9	*i*-C_3H_7	187	937
CH_3	CH_3	C_6H_5	*i*-C_3H_7	167	937
CH_3	C_2H_5	CH_3	*t*-C_4H_9	131 (dec.)	937
CH_3	*i*-C_3H_7	CH_3	*t*-C_4H_9	142 (dec.)	937
$-(CH_2)_4-$		CH_3	*t*-C_4H_9	132	937
$-(CH_2)_5-$		CH_3	*i*-C_3H_7	173	937
$-(CH_2)_5-$		CH_3	*t*-C_4H_9	146	937
$-(CH_2)_5-$		CH_3		85	937
$-(CH_2)_5-$		C_2H_5	*t*-C_4H_9	180	937
$-(CH_2)_5-$		*n*-C_4H_9		176	937
$-(CH_2)_5-$		*n*-$C_{12}H_{25}$	*i*-C_3H_7	50	937
$-(CH_2)_5-$		$C_6H_5CH_2$	*i*-C_3H_7	150	937
$-(CH_2)_5-$		C_6H_5	*i*-C_3H_7	169	937
$-(CH_2)_5-$		CH_3	CH_3	168	937
$-(CH_2)_5-$		CH_3	C_6H_5	204	937

ones (**763**) (814). **760** were not isolated in all cases since they can rearrange, yielding the isomeric 1,2,4-triazolo[5,1-*c*] 1,2,4-triazin-4-ones (**752**).

If 2,6-dimethyl-3-hydrazino-1,2,4-triazin-5-one (**762a**) is reacted with formaldehyde (761), 6,8-dimethyl-1,2,4-triazolo[3,4-*c*] 1,2,4-triazin-5-one (**760a**) is the only reaction product.



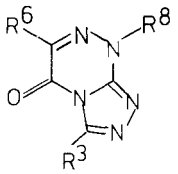
The 3-mercapto-1,2,4-triazolo[3,4-*c*] 1,2,4-triazin-5-ones (**764**) can be obtained by reaction of the 3-hydrazino-1,2,4-triazin-5-ones (**762**) with carbon disulfide in the presence of a tertiary amine to give **765**. This is followed by either (a) alkylation of **765**, followed by heating of the formed **766** above the melting point or by refluxing it in acetic acid, or (b) treating **765** with Raney nickel or with sodium ethoxide in ethanol (835).



2. *Compound Survey*

Table VI-16 lists the known 1,2,4-triazolo[3,4-*c*] 1,2,4-triazines.

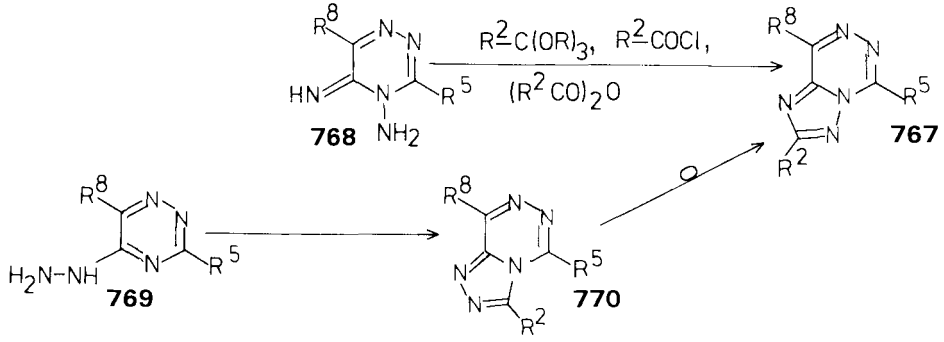
TABLE VI-16. 1,2,4-TRIAZOLO[3,4-*c*]1,2,4-TRIAZINES



R^3	R^8	R^6	m.p. (°C)	Refs.
H	H	H	255–257	835/814
H	H	CH_3	248	814
			262–264	835
H	CH_3	CH_3	118	814
			131	761
H	H	C_6H_5	243–245	835
CH_3	H	H	215–216	835
CH_3	H	CH_3	263–264	835
CH_3	CH_3	CH_3	116–119	814
C_6H_5	H	CH_3		814
SH	H	CH_3	250–270	835
SCH_3	H	H	233–236	835
SCH_3	H	C_6H_5	325–326	835
SCH_3	H	CH_3	259–260	835

D. 1,2,4-Triazolo[1,5-*d*]1,2,4-triazines

Two methods were reported for the synthesis of 1,2,4-triazolo[1,5-*d*]1,2,4-triazines (**767**), cyclization of 4-amino-5-imino-1,2,4-triazines (**768**) with ortho-carboxylates, acyl chlorides, or carbonic acid anhydrides (936) or, starting from 5-hydrazino-1,2,4-triazines (**769**), cyclization to 1,2,4-triazolo[4,3-*d*]1,2,4-triazines (**770**) and rearrangement of **770** to **767** (595).

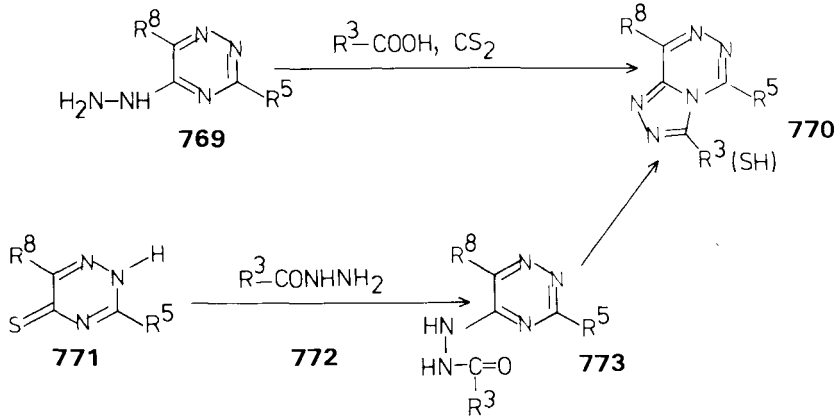


767

R^2	R^8	R^5	m.p. (°C)	Refs.
H	CH_3	OH (taut.)	182–183	595
H	CH_3	SH (taut.)	265–266	595
H	t-C_4H_9	SH (taut.)	287	936
H	t-C_4H_9	SCH_3	109–110	936
CH_3	t-C_4H_9	SH (taut.)	193–194	936
CH_3	t-C_4H_9	SCH_3	100–101	936
CF_3	t-C_4H_9	SH (taut.)	176–177	936
C_3H_7	t-C_4H_9	SH (taut.)	104–105	936
C_6H_5	t-C_4H_9	SH (taut.)	261–262	936
C_6H_5	t-C_4H_9	SCH_3	182–183	936

E. 1,2,4-Triazolo[4,3-*d*]1,2,4-triazines

Cyclization of 5-hydrazino-1,2,4-triazines (**769**) with carbonic acids or carbon disulfide is used for the synthesis of 1,2,4-triazolo[4,3-*d*] 1,2,4-triazines (**770**) (595–597, 851, 994, 1555). **770** can also be obtained if 1,2,4-triazine-5-thiones (**771**) are reacted with acylhydrazides (**772**) and the formed 5-(acylhydrazino)-1,2,4-triazines (**773**) are cyclized by treatment with acetic acid or polyphosphoric acid (597). As mentioned in the preceding section, 1,2,4-triazolo[4,3-*d*] 1,2,4-triazines (**770**) may be readily isomerized to the corresponding 1,2,4-triazolo[5,1-*d*] 1,2,4-triazines (**767**) (595). This rearrangement may be the reason for the surprising differences in ultraviolet spectra Sasaki and his group observed for different 1,2,4-triazolo[4,3-*d*] 1,2,4-triazines (597).



Interaction of 1,4,5,6-tetrahydro-1,2,4-triazine **774** and formic acid affords the 7,8-dihydro-1,2,4-triazolo[4,3-*d*] 1,2,4-triazine **775** (m.p. 250 to 253°C) (994).

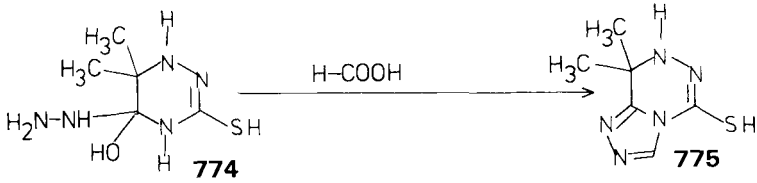
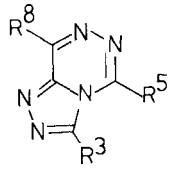


Table VI-17 lists the known compounds of this group.

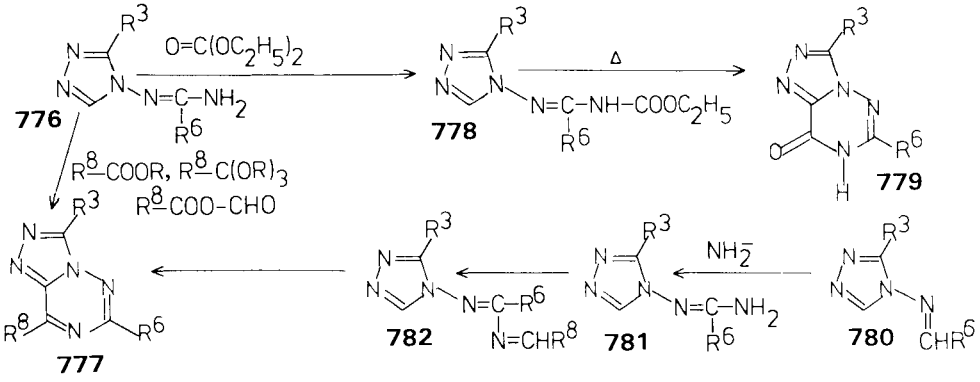
TABLE VI-17. 1,2,4-TRIAZOLO[4,3-*d*]1,2,4-TRIAZINES



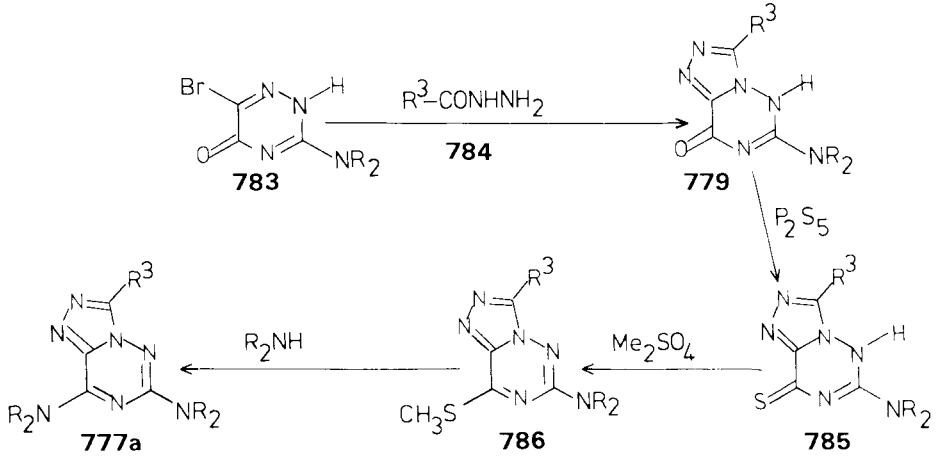
R^3	R^8	R^5	m.p. (°C)	Refs.
H	CH_3	OH (taut.)	186–188	596
			195–196	595
H	CH_3	SH (taut.)	290–291	595
			300	597
H	CH_3	SCH_3	193–194	595
H	CH_3	$NHNH_2$	120–122	595
H	C_6H_5	OH (taut.)	271–272	596
H	$SCH_2C_6H_5$	OH (taut.)	183–185 (dec.)	581
H	SC_6H_5	OH (taut.)	221–223	581
CH_3	H	SH (taut.)	223–224	597
CH_3	H	NH_2	280 (subl.)	597
CH_3	CH_3	OH (taut.)	226–228	596
			228–230	597
CH_3	CH_3	SH (taut.)	246–248	597
CH_3	CH_3	SCH_3	131–132	597
CH_3	CH_3	NH_2	280 (subl.)	597
CH_3	C_6H_5	OH (taut.)	260 (subl.)	596
C_6H_5	H	SH (taut.)	290–292	597
C_6H_5	CH_3	H	235–237	597
C_6H_5	CH_3	SH (taut.)	265–267	597
C_6H_5	CH_3	SCH_3	159–160	597
C_6H_5	CH_3	$NHNH_2$	179–180	597
SH	CH_3	OH (taut.)	246–248	596
SH	C_6H_5	OH (taut.)	271–272	596

F. 1,2,4-Triazolo[3,4-*f*]1,2,4-triazines

1,2,4-Triazolo[3,4-*f*]1,2,4-triazines were prepared starting from 1,2,4-triazole derivatives as well as from 1,2,4-triazine derivatives. Condensation of 1,2,4-triazol-4-yl-amidines (**776**) with orthocarboxylates (201), carboxylates (201), or the mixed anhydride of formic and propionic acids (1477) yields 1,2,4-triazolo-[3,4-*f*]1,2,4-triazines (**777**), whereas **776** are converted to **778** on reaction with diethyl carbonate in the presence of an alkoxide (201). **778** can be transformed into 1,2,4-triazolo[3,4-*f*]1,2,4-triazin-8-ones (**779**) by heating in 2-methoxy-ethanol or phenol (201). Treatment of 4-(arylidenamino)-1,2,4-triazoles (**780**) with sodium amide also affords **777**; the intermediates **781** and **782** were postulated (201) for this reaction.

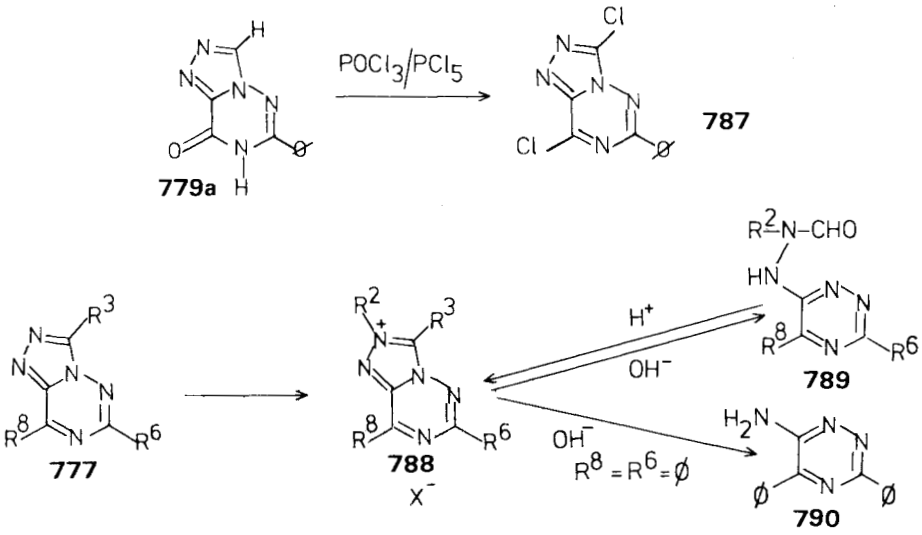


Interaction of 3-amino-6-bromo-1,2,4-triazin-5-ones (**783**) and acylhydrazines (**784**) affords 1,2,4-triazolo[3,4-*f*]1,2,4-triazin-8-ones (**779**) (776), which are converted to the 8-thiones (**785**) by treatment with phosphorus pentasulfide



in pyridine (776). **785** are methylated with dimethyl sulfate, yielding the 8-(methylmercapto)-1,2,4-triazolo[3,4-*f*] 1,2,4-triazines (**786**) in which the methylmercapto group is replaced, by treatment with ammonia or amines (776).

Treatment of 6-phenyl-1,2,4-triazolo[3,4-*f*] 1,2,4-triazin-8-one (**779a**) with phosphoryl chloride and phosphorus pentachloride affords 3,8-dichloro-6-phenyl-1,2,4-triazolo[3,4-*f*] 1,2,4-triazine (**787**) (201). 1,2,4-Triazolo[3,4-*f*]-1,2,4-triazines (**777**) can be readily alkylated at N-2, yielding the quarternary salts (**788**), which were then hydrolyzed by aqueous bases giving 6-[(2-alkyl-2-formyl)hydrazino]-1,2,4-triazines (**789**), or 6-amino-3,5-diphenyl-1,2,4-triazine (**790**) (201). **789** cyclized to **788** when treated with hydrochloric acid.



Interaction of **788** and nitric acid or sulfur and pyridine yields 2-benzyl-6,8-diphenyl-1,2,4-triazolo[3,4-*f*] 1,2,4-triazin-3-one (**791**) (m.p. 228°C) and 2-methyl- (**792a**) (m.p. 304°C) or 2-benzyl-6,8-diphenyl-1,2,4-triazolo[3,4-*f*] 1,2,4-triazine-3-thione (**792b**), respectively (201).

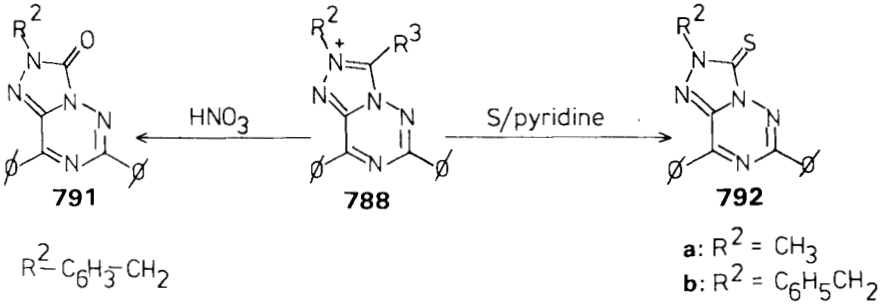
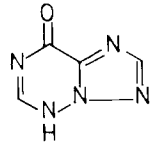


Table VI-18 lists the 1,2,4-triazolo[3,4-*f*]1,2,4-triazines and their oxo and thioxo derivatives reported in the literature.

G. 1,2,4-Triazolo[5,1-*f*]1,2,4-triazines

The use of 1,2,4-triazolo[5,1-*f*]1,2,4-triazin-8(5H)one as a photographic stabilizer in silver halide emulsions is claimed in a German patent (2298).



H. 1,2,4-Triazolo[3,4-*c*]1,2,4-benzotriazines

Only one paper dealing with the synthesis of 1,2,4-triazolo[3,4-*c*]1,2,4-benzotriazines has so far been published (1156). Cyclization of 3-hydrazino-1,2,4-benzotriazine (**793**) with formic acid or carbon disulfide yields 1,2,4-tri-

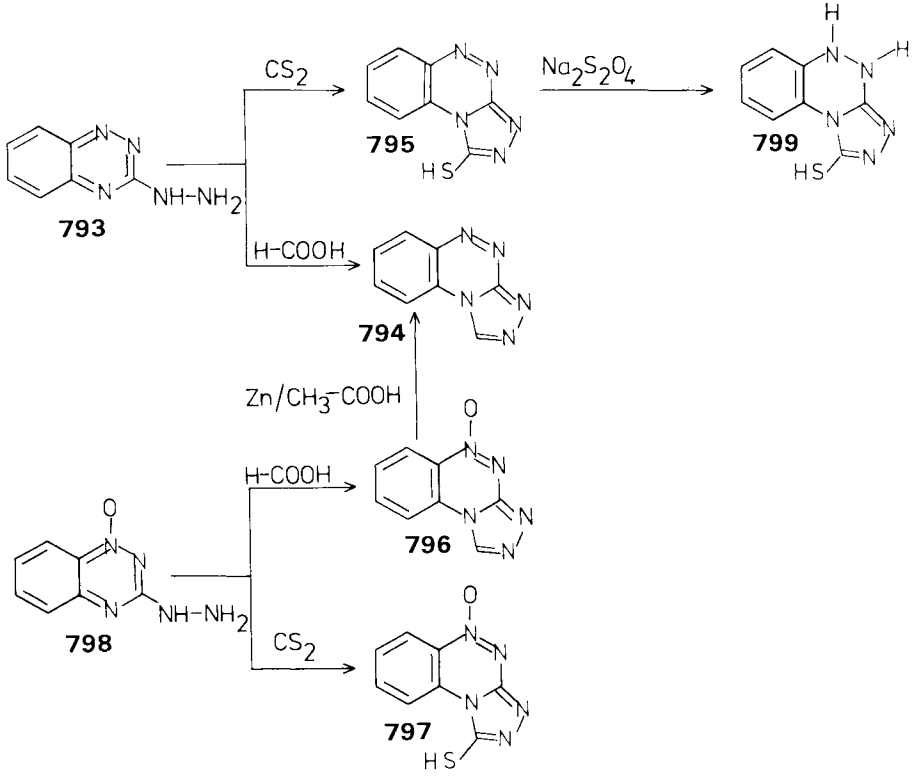
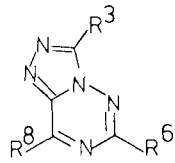


TABLE VI-18. 1,2,4-TRIAZOLO[3,4-*f*]1,2,4-TRIAZINES AND 8-OXO AND 8-THIOXO DERIVATIVES

A. 1,2,4-Triazolo[3,4-*f*]1,2,4-triazines



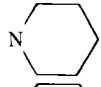
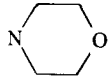
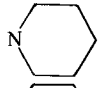
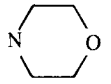
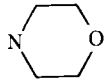
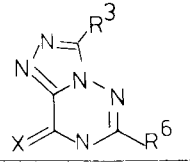
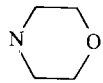
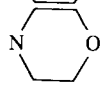
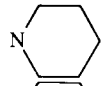
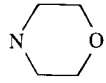
R^3	R^8	R^6	m.p. (°C)	Refs.
H	H	H	>360	201
H	H	CH_3	>360	201
H	H	*i*-C_3H_7	>360	201
H	H	$C_6H_5CH_2$	>360	201
H	H	C_6H_5	>360	201
			368–371	1477
H	H	4-$CH_3C_6H_4$	>360	201
H	H	4-Cl–C_6H_4	>360	201
H	H	1-Naphthyl	>360	201
H	H	1-Pyridyl	>360	201
H	C_6H_5	C_6H_5	186	201
H	3-Cl–C_6H_4	3-Cl–C_6H_4	193	201
H	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	243	201
H	SCH_3	$N(CH_3)_2$	220–221	776
H	SCH_3		125–126	776
H	SCH_3		181–182	776
H	NH_2	$N(CH_3)_2$	345–347	776
H	$N(CH_2CH_2OH)_2$		145–146	776
H	$N(CH_2CH_2OH)_2$		177–178	776
H	$C_6H_5CH_2NH$	$N(CH_3)_2$	261–263	776
H		$N(CH_3)_2$	148–149	776
H			129–130	776
Cl	Cl	C_6H_5	233	201

TABLE VI-18. (continued)

B. 1,2,4-Triazolo[3,4-*f*] 1,2,4-triazin-8-ones and 8-thiones



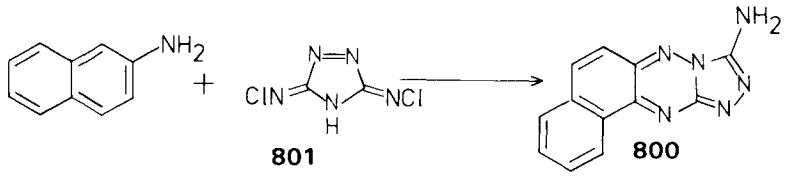
R^3	X	R^6	m.p. (°C)	Refs.
H	O	$C_6H_5CH_2$	268	201
H	O	2-Cl–$C_6H_4CH_2$	316	201
H	O	4-Cl–$C_6H_4CH_2$	308	201
H	O	2,4,6-$(CH_3)_3C_6H_2CH_2$	296	201
H	O	C_6H_5	314	201
H	O	4-$CH_3C_6H_4$	332	201
H	O	4-Cl–C_6H_4	325	201
H	O	4-CH_3O–C_6H_4	329	201
H	O	1-Naphthyl	314	201
H	O	$N(CH_3)_2$	365 (dec.)	776
H	S	$N(CH_3)_2$	305–306 (dec.)	776
H	O	4-Br–C_6H_4–N–CH_3	248–250	776
H	O		306–307	776
H	S		301–302	776
H	O		258–260	776
H	S		319–320	776
CH_3	O	$N(CH_3)_2$	317–318 (dec.)	776
CH_3	O		332–333	776
CH_3	O		360	776

azolo[3,4-*c*] 1,2,4-benzotriazine (**794**) (m.p. 265 to 267°C) and 1,2,4-triazolo[3,4-*c*] 1,2,4-benzotriazine-1-thione (**795**) [m.p. 270 to 280°C (dec.)], respectively. By the same methods, the two 5-oxides **796** (m.p. 298 to 300°C) and **797** (270 to 280°C) were prepared from 3-hydrazino-1,2,4-benzotriazine 1-oxide (**798**). Reduction of **796** with zinc and acetic acid affords **794**, and

4,5-dihydro-1,2,4-triazolo[3,4-*c*]1,2,4-benzotriazine-1-thione (**799**) [m.p. 283°C (dec.)] was obtained through reduction of **795** with sodium dithionite.

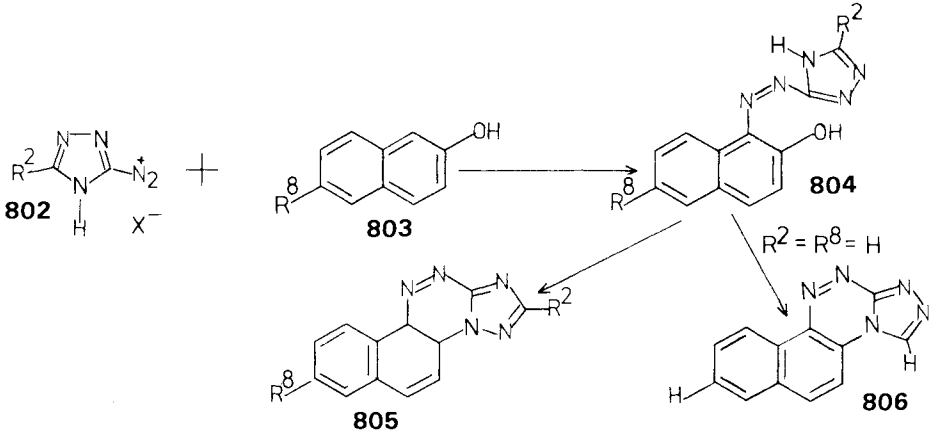
I. Naphtho[1,2-*e*]1,2,4-triazolo[4,3-*b*]1,2,4-triazines

Stolle and Dietrich (1478) obtained a compound **800** (m.p. 285°C), which they formulated as 9-amino-naphtho[1,2-*e*]1,2,4-triazolo[4,3-*b*]1,2,4-triazine (**800**) (RRI 4365), when they reacted 2-amininonaphthalene and the chloro compound (**801**).



J. Naphtho[2,1-*e*]1,2,4-triazolo[5,1-*c*]1,2,4-triazines

1,2,4-Triazole-3-diazonium salts (**802**) couple with 2-naphthols (**803**), giving the azo compounds **804**, which can be cyclized to naphtho[2,1-*e*]1,2,4-triazolo[5,1-*c*]1,2,4-triazines (**805**) (1262, 1479) (RRI 4366). Vilarrasa and Granados (1262) observed that, depending on the reaction conditions, in addition to **805** naphtho[2,1-*e*]1,2,4-triazolo[3,4-*c*]1,2,4-triazine (**806**) can also be formed. The unsubstituted **805** has a melting point of 272–274°C; PMR and infrared spectrum are given by Vilarrasa and Granados (1262).

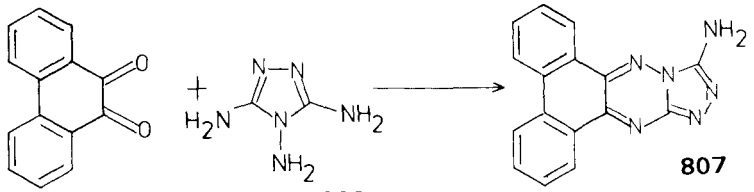


K. Naphtho[2,1-*e*]1,2,4-triazolo[3,4-*c*]1,2,4-triazines

The unsubstituted compound of this class (**806**) (m.p. 310 to 312°C) is prepared by Vilarrasa and Granados (1262), who also report its infrared and PMR spectra. For the method of preparation see the preceding chapter.

L. 1,2,4-Triazolo[4,3-*b*]phenanthro[9,10-*e*]1,2,4-triazines

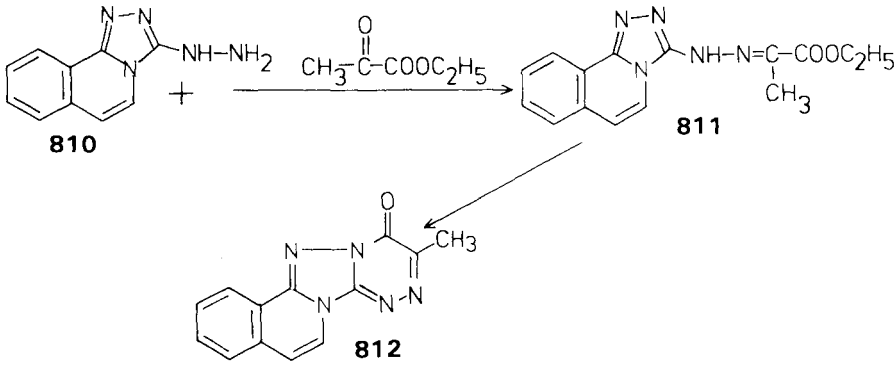
The single known derivative of this class, the 11-amino-1,2,4-triazolo[4,3-*b*]phenanthro[9,10-*e*]1,2,4-triazine (**807**) [m.p. 334 to 336°C (dec.)] (RRI 5786) was prepared by Taylor and his co-worker through condensation of 9,10-phenanthrenequinone (**808**) and guanazine (**809**) (1470).



XII. CONDENSED WITH THE 1,2,4-TRIAZOLO[3,4-*a*]-ISOQUINOLINE SYSTEM

A. 1,2,4-Triazino[4′,3′:1,5]1,2,4-triazolo[3,4-*a*]isoquinolines

Interaction of 3-hydrazino-1,2,4-triazolo[3,4-*a*]isoquinoline (**810**) and ethyl pyruvate yields the condensation product (**811**) which was cyclized in



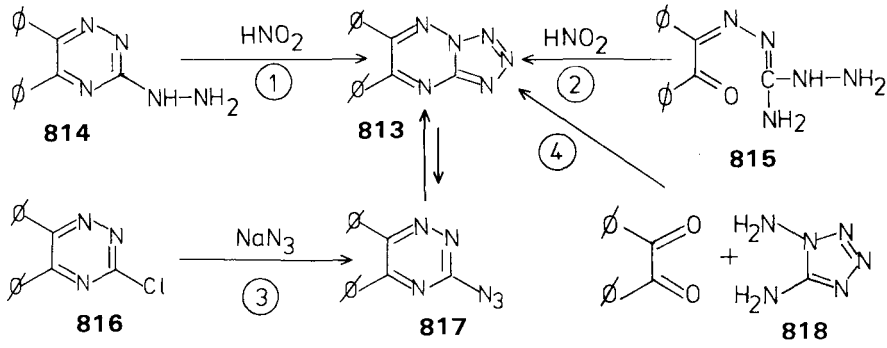
boiling xylene to give 10-methyl-1,2,4-triazino[4′,3′: 1,5]1,2,4-triazolo[3,4-*a*]-isoquinolin-11-one (**812**) (m.p. 325 to 328°C) (1480, 1481).

XIII. CONDENSED WITH THE TETRAZOLE RING

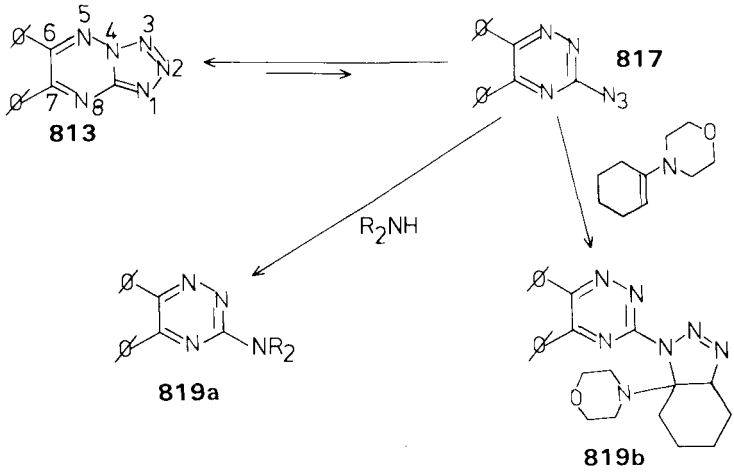
A. Tetrazolo[1,5-*b*]1,2,4-triazines

6,7-Diphenyltetrazolo[1,5-*b*]1,2,4-triazine (**813**) [m.p. 197 to 198°C (1482), 198°C (1483), 201 to 202°C (1484)] was prepared by the following methods.

1. Diazotization of 3-hydrazino-5,6-diphenyl-1,2,4-triazine (**814**) with nitrous acid (1482–1484).
2. Reaction of the aminoguanylhydrazone of benzil (**815**) with nitrous acid (1482).
3. Treatment of 3-chloro-5,6-diphenyl-1,2,4-triazine (**816**) with sodium azide (1482). This yields the valence tautomer 3-azido-5,6-diphenyl-1,2,4-triazine which is immediately converted into **813**.
4. Condensation of 1,5-diaminotetrazole (**818**) with benzil (1482).

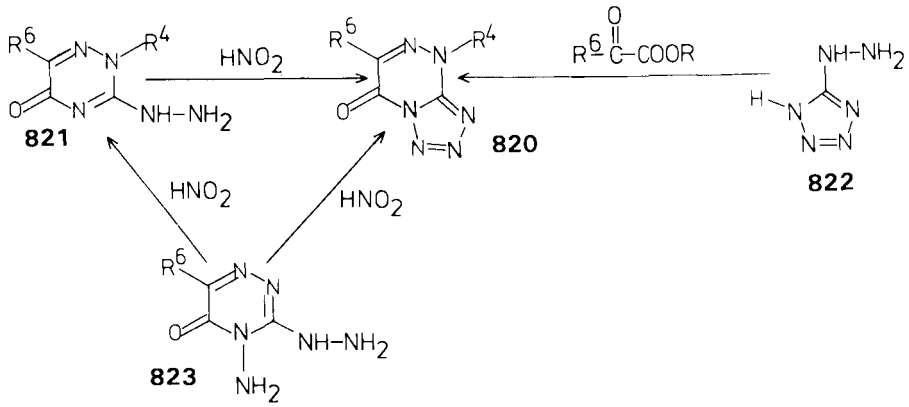


As was shown by infrared spectroscopy, in the solid state only compound **813** can be observed. The valence tautomer 3-azido-5,6-diphenyl-1,2,4-triazine (**817**) can be observed in very low amounts in tetrahydrofuran, dimethyl sulfoxide, or trifluoroacetic acid (1482–1484). The azido tautomer **817** was detected by a reaction with amines, to yield 3-amino-5,6-diphenyl-1,2,4-triazines (**819a**) (1482), or by a cycloaddition reaction with 1-morpholinocyclohexene, affording **819b** (1483).



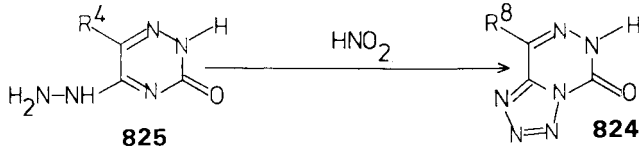
B. Tetrazolo[5,1-*c*]1,2,4-triazines

Tetrazolo[5,1-*c*]1,2,4-triazin-7-ones (**820**) were isolated when 3-hydrazino-1,2,4-triazin-5-ones (**821**) are treated with nitrous acid (761, 770). The structure was proved by condensation of 5-hydrazinotetrazole (**822**) and α-ketocarboxylates (760, 761). Reaction of 4-amino-3-hydrazino-1,2,4-triazin-5-ones (**823**) with nitrous acid also yields **820**, which is best explained by preliminary deamination of **823**, giving **821**, which were then converted to **820** (760) [R^4 = H, R^6 = CH_3, m.p. 217°C (761), 222°C (770), 223°C (760); R^4 = H, R^6 = C_6H_5, 226 to 227°C (dec.); R^4 = R^6 = CH_3, 102°C (761)] (RRI 9906).



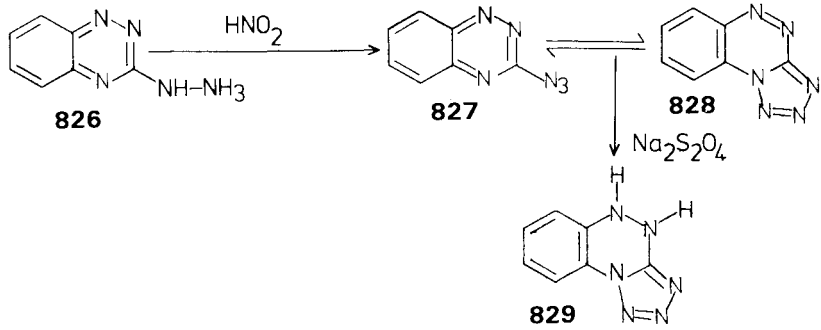
C. Tetrazolo[1,5-*d*]1,2,4-triazines

Four tetrazolo[1,5-*d*]1,2,4-triazin-5-ones (**824**) [$R^8 = CH_3$, m.p. 143 to 145°C (596); $R^8 = C_6H_5$, 218 to 219°C (596); $R^8 = CH_3S$, 162 to 164°C (602); $R^8 = C_6H_5S$, 169 to 171°C (851)] were prepared through reaction of 5-hydrazino-1,2,4-triazin-3-ones (**825**) with nitrous acid (596, 602, 851).



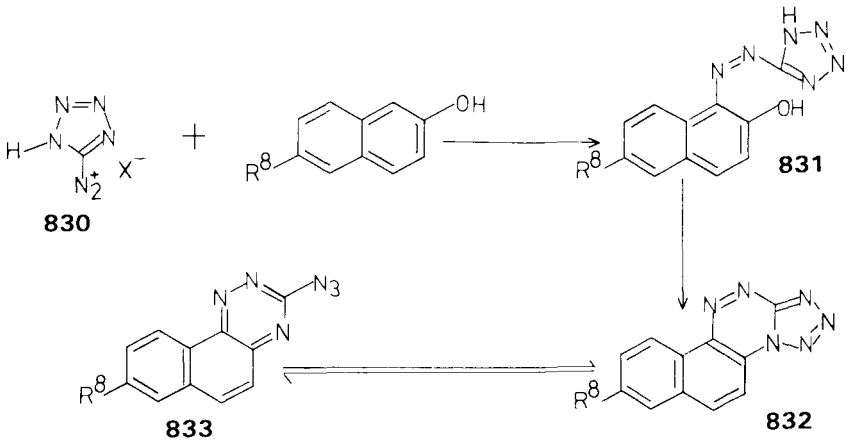
D. Tetrazolo[5,1-*c*]1,2,4-benzotriazines

Diazotization of 3-hydrazino-1,2,4-benzotriazine (**826**) gives a compound which is the open 3-azido-1,2,4-benzotriazine (**827**) in solution whereas the crystalline substance is tetrazolo[5,1-*c*]1,2,4-benzotriazine (**828**) (m.p. 115 to 117°C) (1267). Sodium dithionite reduction of **828** yields 4,5-dihydrotetrazolo[5,1-*c*]1,2,4-benzotriazine (**829**) [m.p. 194°C (dec.)], which exists as the cyclic tetrazole tautomer (1267) both in solution and in the solid state.



E. Naphtho[2,1-*e*]tetrazolo[5,1-*c*]1,2,4-triazines

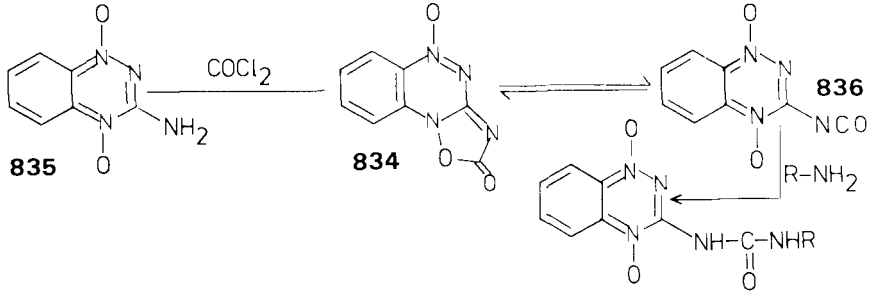
Diazotized 5-aminotetrazole (**830**) couples with 2-naphthols to give the azo compounds (**831**) which can be cyclized yielding the naphtho[2,1-*e*]-tetrazolo[5,1-*c*]1,2,4-triazines (**832**) (1262, 1479) [R^8 = H, m.p. 190 to 191°C (1262)]. Vilarrasa and Granados have shown that the unsubstituted **832** shows azide–tetrazole equilibrium. In the solid state only **832** is present, while in chloroform the azide structure (**833**) predominates (1262)(RRI 4353).



XIV. CONDENSED WITH THE 1,2,4-OXADIAZOLE RING

A. 1,2,4-Oxadiazolo[3,2-*c*]1,2,4-benzotriazines

Seng and Ley (1175) prepared 1,2,4-oxadiazolo[3,2-*c*]1,2,4-benzotriazin-2-one 5-oxide (**834**) [m.p. 262°C (dec.)] through the reaction of 3-amino-1,2,4-benzotriazine 1,4-dioxide (**835**) with phosgene. **834** reacted with nucleophiles, such as amines, as the tautomeric isocyanate form (**836**).

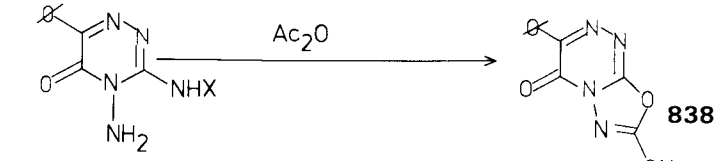


XV. CONDENSED WITH THE 1,3,4-OXADIAZOLE RING

A. 1,3,4-Oxadiazolo[2,3-*c*]1,2,4-triazines

Heating 4-amino-3-anilino-6-phenyl-1,2,4-triazin-5-one (**837a**) or 4-amino-3-(hydroxylamino)-6-phenyl-1,2,4-triazin-5-one (**837b**) with acetic anhydride

affords 7-methyl-3-phenyl-1,3,4-oxadiazolo[2,3-*c*]1,2,4-triazin-4-one (**838**) (m.p. 217 to 218°C) (1078).

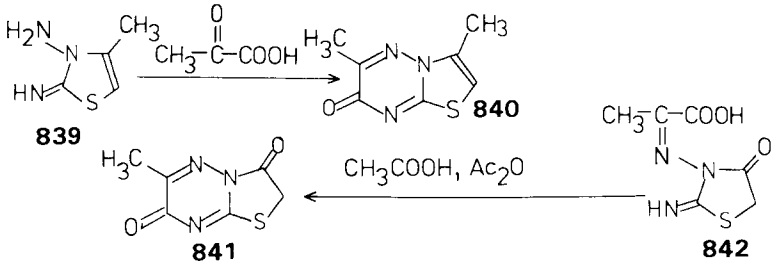


837a: X = Ø
837b: X = OH

XVI. CONDENSED WITH THE THIAZOLE RING

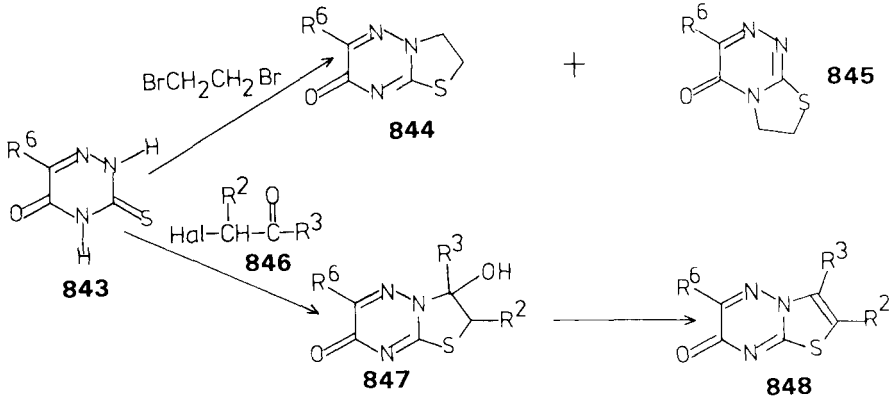
A. Thiazolo[3,2-*b*]1,2,4-triazines

Condensation of 3-amino-4-methyl-thiazole-2-imine (**839**) with pyruvic acid yields 3,6-dimethylthiazolo[3,2-*b*]1,2,4-triazin-7-one (**840**) (1473). Similarly 6-methylthiazolo[3,2-*b*]1,2,4-triazine-3,7-dione (**841**) was obtained through cyclization of the pyruvic acid hydrazone (**842**) in the presence of acetic acid and acetic anhydride (755) (RRI 9932).

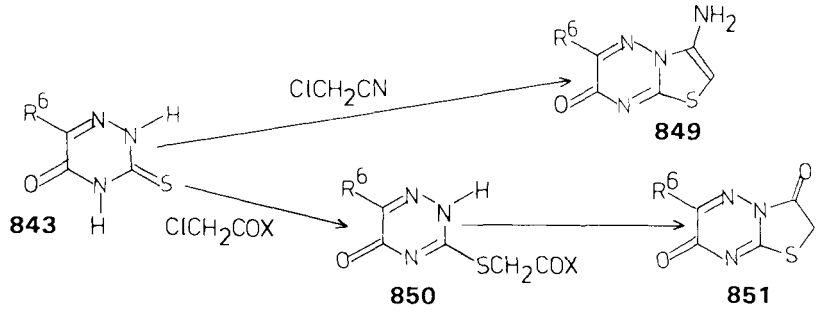


In a large number of examples of the synthesis of thiazolo[3,2-*b*]1,2,4-triazine derivatives, 3-thioxo-1,2,4-triazin-5-ones (**843**) were reacted with 1,2-bifunctional compounds. Reaction of **843** with 1,2-dibromoethane yields a mixture of 2,3-dihydro-6-methylthiazolo[3,2-*b*]1,2,4-triazin-7-one (**844**) and 6,7-dihydro-3-methylthiazolo[2,3-*c*]triazin-4-one (**845**) (789, 781). Interaction of **843** with α-halo ketones (**846**) affords 3-hydroxy-2,3-dihydrothiazolo[3,2-*b*]-1,2,4-triazin-7-ones (**847**) which can be dehydrated to give thiazolo[3,2-*b*]-1,2,4-triazin-7-ones (**848**) (755).

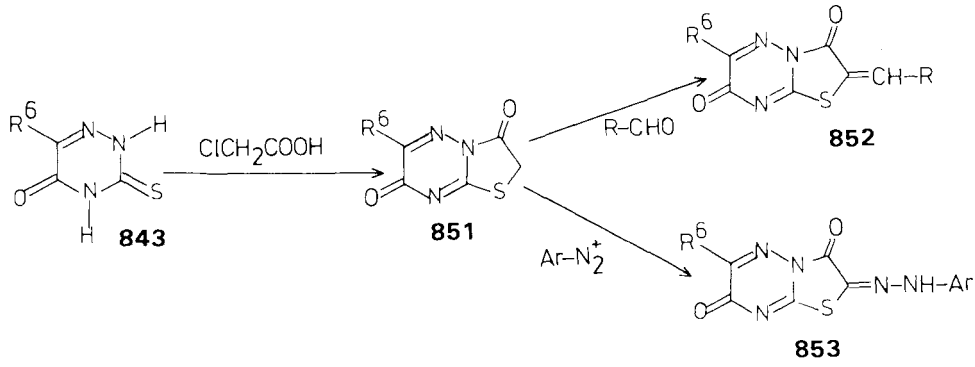
3-Aminothiazolo[3,2-*b*]1,2,4-triazin-7-ones (**849**) were obtained from **843** and chloroacetonitrile (755, 781). Reaction of **843** with haloacetic acid,



chloroacetates, chloroacetic acid anhydride, or chloroacetamide gives the intermediates **850** which can be cyclized to yield thiazolo[3,2-*b*] 1,2,4-triazine-3,7-diones (**851**) (342, 742, 755, 781).



Treatment of **843** with chloroacetic acid in the presence of aldehydes affords 2-alkylidenethiazolo[3,2-*b*] 1,2,4-triazine-3,7-diones (**852**) (742). The first step of the reaction is the formation of **851** which then condense with aldehydes to



give **852**. An analogous reaction of **851**, with aryldiazonium salts, affords the 2-arylhydrazones of thiazolo[3,2-*b*] 1,2,4-triazine-2,3,7-triones (**853**) (742).

In a Russian patent (1485) the formation of 4,5(7,8)-dihydrothiazolo-[3,2-*b*] 1,2,4-triazines was claimed when 4,5-dihydro-1,2,4-triazine-3-thiones were treated with α-halo ketones in alcohol or acetic acid, but this result seems very unlikely to us, as one would expect the formation of thiazolo[3,2-*b*]-1,2,4-triazines or 3-hydroxy-2,3-dihydro-7H-thiazolo[3,2-*b*] 1,2,4-triazines from this reaction.

5-Methyl-tetrahydrothiazolo[3,2-*b*] 1,2,4-triazine (**854**) was isolated from the interaction of 1-methyl-1,4,5,6-tetrahydro-1,2,4-triazine-3-thione (**855**) and 1,2-dibromoethane or 2-bromoethyl 4-toluenesulfonate (1057, 1061) (b.p. for **854**: 142°C/1.2 torr, 140 to 144°C/2 torr; hydrobromide, m.p. 204 to 205°C; methiodide, m.p. 153 to 154.5°C).

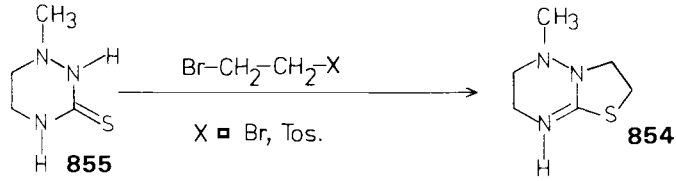


Table VI-19 lists the thiazolo[3,2-*b*] 1,2,4-triazines reported in the literature.

B. Thiazolo[2,3-*c*] 1,2,4-triazines

Interaction of pyruvic acid thiosemicarbazone (**856**) and bromoacetone yielded the 4-methyl-2-thiazolylhydrazone of pyruvic acid (**857**) which was cyclized to give 3,6-dimethylthiazolo[2,3-*c*] 1,2,4-triazin-4-one (**858**) (m.p. 146°C) on treatment with acetic anhydride (781, 1486). The isomeric 3,7-dimethylthiazolo[2,3-*c*] 1,2,4-triazin-4-one (**859**) (m.p. 169°C) was isolated by Doleschall and Lempert (1486) when the hydrazone (**860**) was heated in morpholine. Heating of the chloroacetylhydrazone (**861**) was used for the synthesis of thiazolo[2,3-*c*] 1,2,4-triazine-3,6-dione (**862**) (m.p. 185 to 186°C) (1487).

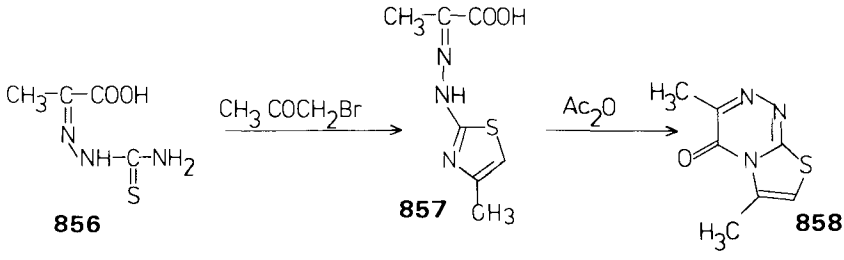
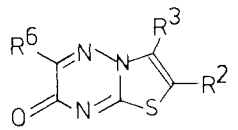


TABLE VI-19. THIAZOLO[3,2-*b*]1,2,4-TRIAZINES

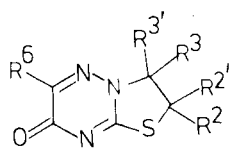
A. Thiazolo[3,2-*b*]1,2,4-triazin-7-ones



R^2	R^3	R^6	m.p. (°C)	Refs.
H	CH_3	H	194–195	755
H	CH_3	CH_3	227	755, 1473
H	CH_3	CH_2CH_2OH	268–270	755
H	CH_3	CH_2COOH	276 (dec.)	755
H	CH_3	$CH_2CH_2CH_2OH$	193–194	755
H	CH_3	$CH_2CH_2CH_2Cl$	152	755
H	CH_3	CH_2CH_2COOH	243–244 (dec.)	755
H	CH_3	$CH_2CH_2CH_2$-N(CH$_2$CH$_2$)$_2$O	208–209	755
H	CH_2Cl	CH_3		781
H	NH_2	CH_3	183–184 (dec.)	755, 781
H	NH_2	CH_2CH_2OH	150 (dec.)	755
H	NH_2	$CH_2CH_2CH_2OH$	146–147 (dec.)	755
H	$NHCOCH_3$	CH_3	212–213	755
$CH_2=CH$	CH_3	CH_3	179–180	755
CH_2CH_2OH	CH_3	CH_3	182–184 (dec.)	755
CH_2CH_2Cl	CH_3	CH_3	179–180 (dec.)	755
$-(CH_2)_4-$		CH_3	159–160	755

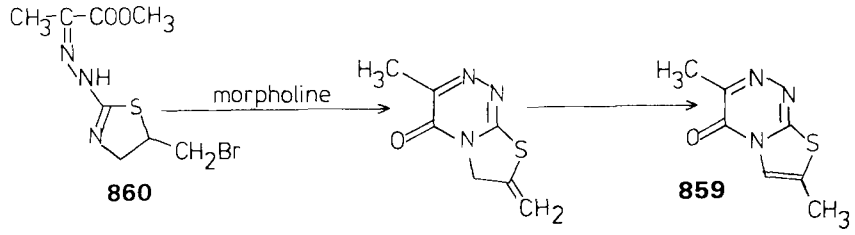
TABLE VI-19. (continued)

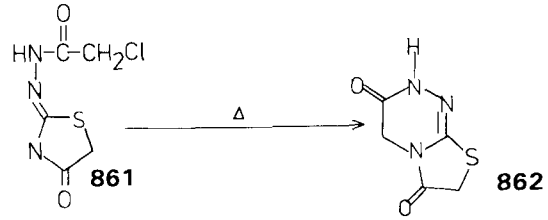
B. 2,3-Dihydrothiazolo[3,2-*b*]1,2,4-triazin-7-ones, Thiazolo[3,2-*c*]1,2,4-triazine-3,7-diones and 2,3,7-triones



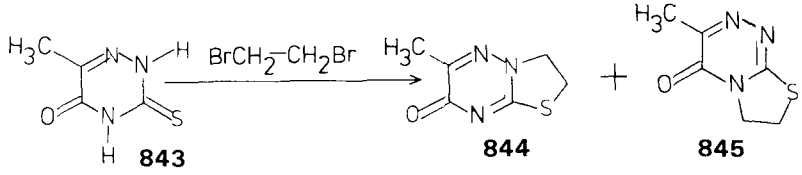
R^2	$R^{2'}$	R^3	$R^{3'}$	R^6	m.p. (°C)	Refs.
H	H	H	H	CH_3	181–182	789, 781
H	H	H	OH	CH_3	209–210	755
H	H	CH_3	OH	H	170–171	755
H	H	CH_3	OH	CH_3	180–181	755
H	H	CH_2Cl	OH	CH_3	188–189 (dec.)	755, 781
H	H	CH_3	OH	CH_2CH_2OH	175–176	755
H	H	$COOC_2H_5$	OH	CH_3	172–173	755
H	H	$CH_2COOC_2H_5$	OH	CH_3	128–129	755
H	$-(CH_2)_3-$		OH	CH_3	235–238 (dec.)	755
H	$-(CH_2)_4-$		OH	CH_3	176–177	755
H	$CH_2CH_2OCOCH_3$	CH_3	OH	CH_3	147–149	755

H	H	=O	CH_3	175	753
	$C_6H_5-CH=$	=O	CH_3	261	742
	4-Cl-$C_6H_4-CH=$	=O	CH_3	321	742
	4-$O_2N-C_6H_4-CH=$	=O	CH_3	325	742
	4-$CH_3O-C_6H_4-CH=$	=O	CH_3	286	742
	$C_6H_5-CH=$	=O	C_6H_5	265	742
	$C_6H_5-CH=$	=O	$C_6H_5-CH=CH$	277	742
	$C_6H_5-CH=$	=O	4-$CH_3O-C_6H_4-CH=CH$	284	742
	4-Cl-$C_6H_4-CH=$	=O	C_6H_5	333	742
	4-Cl-$C_6H_4-CH=$	=O	$C_6H_5-CH=CH$	334	742
	4-Cl-$C_6H_4-CH=$	=O	4-$CH_3O-C_6H_4-CH=CH$	340	742
	4-$O_2N-C_6H_4-CH=$	=O	C_6H_5	338	742
	4-$O_2N-C_6H_4-CH=$	=O	$C_6H_5-CH=CH$	341	742
	4-$O_2N-C_6H_4-CH=$	=O	4-$CH_3O-C_6H_4-CH=CH$	334	742
	4-$CH_3O-C_6H_4-CH=$	=O	C_6H_5	272	742
	4-$CH_3O-C_6H_4-CH=$	=O	$C_6H_5-CH=CH$	297	742
	4-$CH_3O-C_6H_4-CH=$	=O	4-$CH_3O-C_6H_4-CH=CH$	305	742
	$C_6H_5-NH-N=$	=O	CH_3	287	742
	$C_6H_5-NH-N=$	=O	C_6H_5	278	742
	4-Cl-$C_6H_4-NH-N=$	=O	CH_3	297	742
	4-Br-$C_6H_4-NH-N=$	=O	CH_3	308	742
	4-Br-$C_6H_4-NH-N=$	=O	C_6H_5	310	742

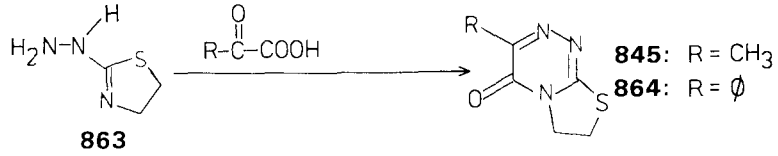




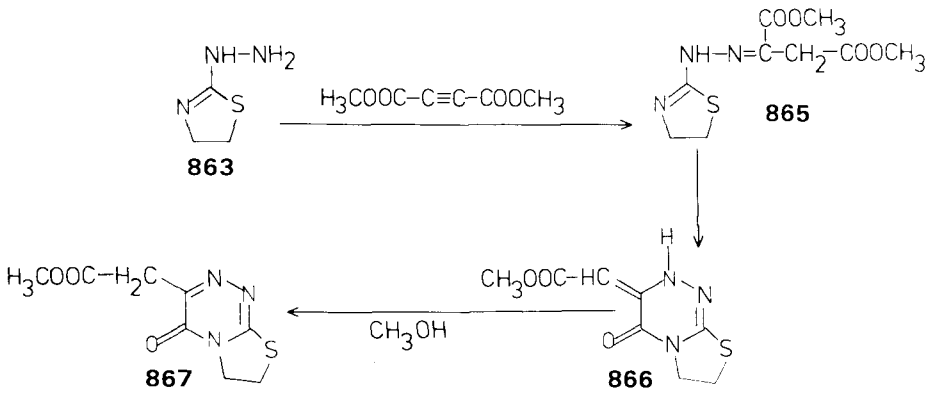
Reaction of 3-thioxo-6-methyl-1,2,4-triazin-5-one (**843**) with 1,2-dibromoethane yielded a mixture of 2,3-dihydro-6-methylthiazolo[3,2-*b*] 1,2,4-triazin-7-one (**844**) and 6,7-dihydro-3-methylthiazolo[2,3-*c*] 1,2,4-triazin-4-one (**845**) (m.p. 171 to 172°C), which was separated by chromatography (789, 781).



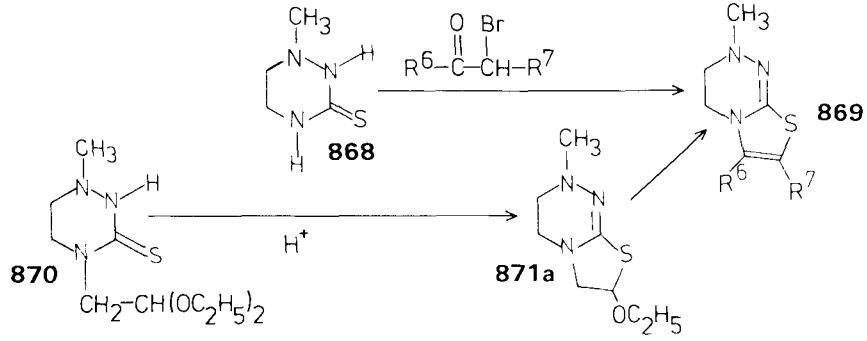
Condensation of 2-hydrazinothiazoline (**863**) with α-ketocarboxylic acids was used for the synthesis of 3-methyl- (**845**) (m.p. 171 to 172°C) and 3-phenyl-6,7-dihydrothiazolo[2,3-*c*] 1,2,4-triazin-4-one (**864**) (m.p. 134 to 135°C) (1435).



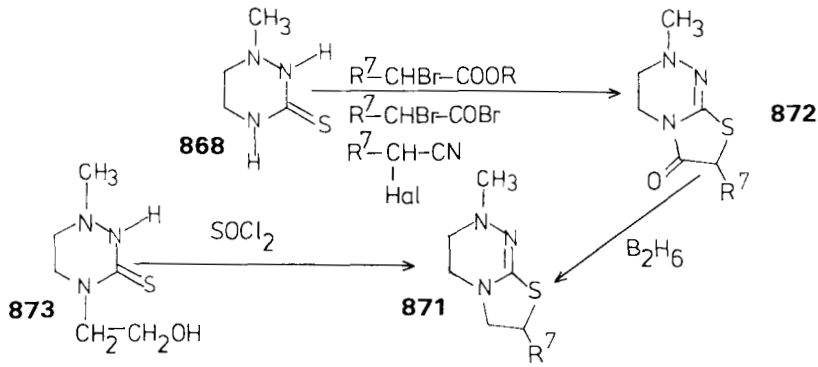
Addition of dimethyl acetylenedicarboxylate to **863** afforded the hydrazone (**865**) which can be cyclized to the 6,7-dihydrothiazolo[2,3-*c*] 1,2,4-triazin-4-one (**866**) (m.p. 153 to 156°C) with an exocyclic double bond. When refluxed in methanol, **866** tautomerizes to give methyl 2-(6,7-dihydro-4-oxothiazolo[2,3-*c*] 1,2,4-triazinyl-3)-acetate (**867**) (m.p. 121 to 123°C) (1324, 1488).



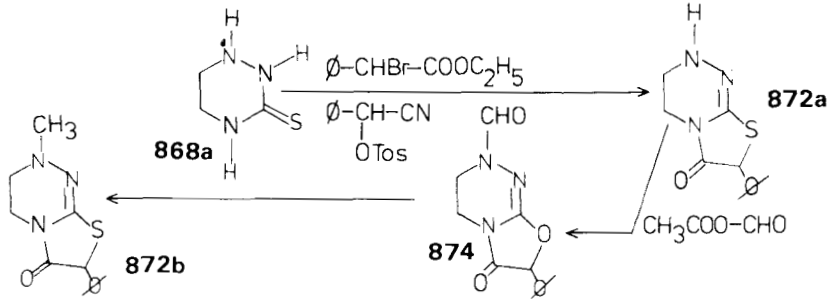
Reaction of 1-methyl-1,4,5,6-tetrahydro-1,2,4-triazine-3-thione (**868**) and α-bromocarbonyl compounds affords 3,4-dihydrothiazolo[2,3-*c*] 1,2,4-triazines (**869**) ($R^6 = R^7 = H$, b.p. 128 to 129°C/0.2 torr; $R^7 = H$, $R^6 = C_6H_5$, m.p. 221 to 223°C; $R^6 = R^7 = C_6H_5$, m.p. 244 to 245°C) (1057, 1063). To prove the structure of the condensation products 4-(2,2-diethoxyethyl)-1,4,5,6-tetrahydro-1-methyl-1,2,4-triazine-3-thione (**870**) was prepared and cyclized by treatment with sulfuric acid to give 7-ethoxy-2-methyl-3,4,6,7-tetrahydrothiazolo[2,3-*c*]-1,2,4-triazine (**871a**) (oil) and finally **869** ($R^6 = R^7 = H$) (1057).



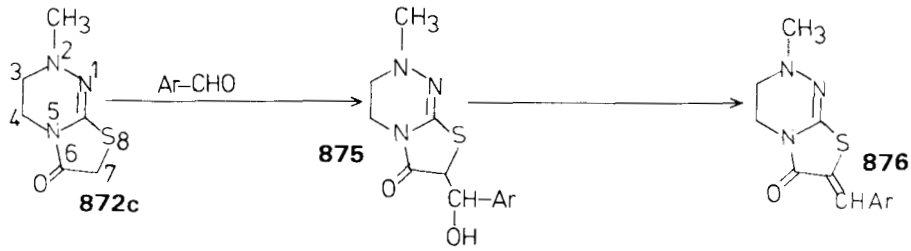
3,4-Dihydrothiazolo[2,3-*c*] 1,2,4-triazin-6-ones (**872**) ($R^7 = H$, m.p. 109 to 112°C; $R^7 = C_6H_5$, 94 to 96°C) were obtained from the reaction of **868** and α-halonitriles, α-bromocarboxylates, or α-bromoacyl bromides (1057, 1058, 1061). Reduction of **872** with diborane yields 3,4,6,7-tetrahydrothiazolo[2,3-*c*]-1,2,4-triazines (**871**) ($R^7 = H$, m.p. 50.5 to 51.5°C, b.p. 152°C/0.4 torr; hydrobromide, m.p. 141 to 142°C; methiodide, 230.5 to 232°C; $R^7 = C_6H_5$, 80 to 83°C) (1057, 1061). **871** can also be obtained through cyclization of 4-(2-hydroxyethyl)-1,4,5,6-tetrahydro-1,2,4-triazine-3-thione (**873**) with thionyl chloride (1057, 1061).



The reaction of 1,4,5,6-tetrahydro-1,2,4-triazine-3-thione (**868a**) and ethyl α-bromophenylacetate or α-tosyloxyphenylacetonitrile affords 7-phenyl-3,4-dihydrothiazolo[2,3-*c*]1,2,4-triazin-6-one (**872a**) (m.p. 160 to 162°C), which was formylated to give 2-formyl-7-phenyl-3,4-dihydrothiazolo[2,3-*c*]1,2,4-triazin-6-one (**874**) (m.p. 151 to 151.5°C). Reduction of **874** with diborane yields **872b** ($R^7 = C_6H_5$) (1057).



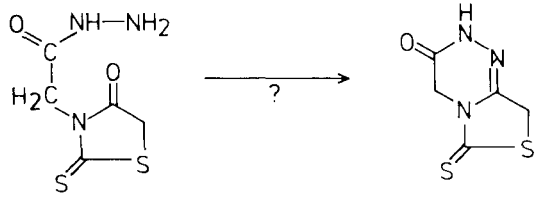
3,4-Dihydro-2-methyl-thiazolo[2,3-*c*]1,2,4-triazine-6-one (**872c**) can be condensed with aromatic aldehydes in the presence of a base, such as piperidine, to yield the α-hydroxybenzyl derivatives (**875**) (Ar = 3,4-$Cl_2C_6H_3$, m.p. 163.5 to 164.5°C; Ar = 3,4,5-$(CH_3O)_3C_6H_2$, 195 to 196.5°C) or the condensation products (**876**) (Ar = 3,4-$Cl_2C_6H_3$, m.p. 191 to 192°C; 3,4,5-$(CH_3O)_3C_6H_2$,



185 to 188°C; 3-indolyl, 285 to 286°C; 2-pyridyl, 170 to 171°C; 3-pyridyl, 133 to 134.5°C; 4-pyridyl, 171.5 to 172.5°C) (1062).

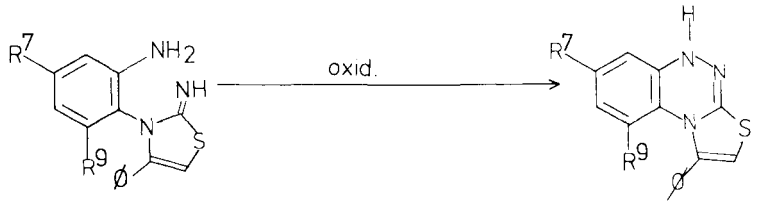
C. Thiazolo[4,3-*c*]1,2,4-triazines

The antiplasmodic activity and the toxicity of 6H-2,8-dihydro-6-thioxothiazolo[4,3-*c*]1,2,4-triazin-3(4H)-one is tested by Zapadnyuk (2316). This compound was probably prepared by cyclization of rhodanine acetic acid hydrazide.



D. Thiazolo[2,3-*c*]1,2,4-benzotriazines

The synthesis of 5*H*-thiazolo[2,3-*c*]1,2,4-benzotriazines (**877**) was achieved by the oxidative cyclization of 3-(2-aminophenyl)-2-imino-4-phenyl-Δ^4-thiazolines (**878**) (1489) ($R^7 = R^9 = H$; $R^7 = H$, $R^9 = CH_3$; $R^7 = CH_3$, $R^9 = H$; $R^7 = OCH_3$, $R^9 = H$).



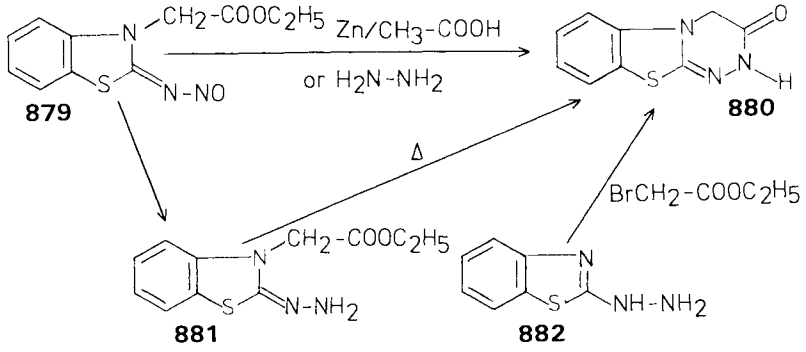
878 **877**

XVII. CONDENSED WITH THE BENZOTHIAZOLE SYSTEM

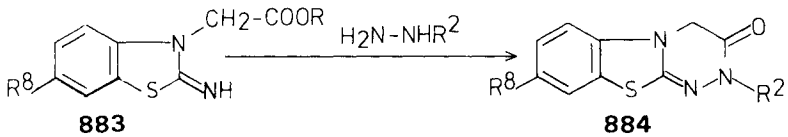
A. 1,2,4-Triazino[3,4-*b*]benzothiazoles

Reduction of the *N*-nitroso compound (**879**) with zinc and acetic acid yields 3,4-dihydro-1,2,4-triazino[3,4-*b*]benzothiazol-3-one (**880**) (1490). Hydrogenation of **879** using palladium charcoal catalyst gave a mixture which was shown

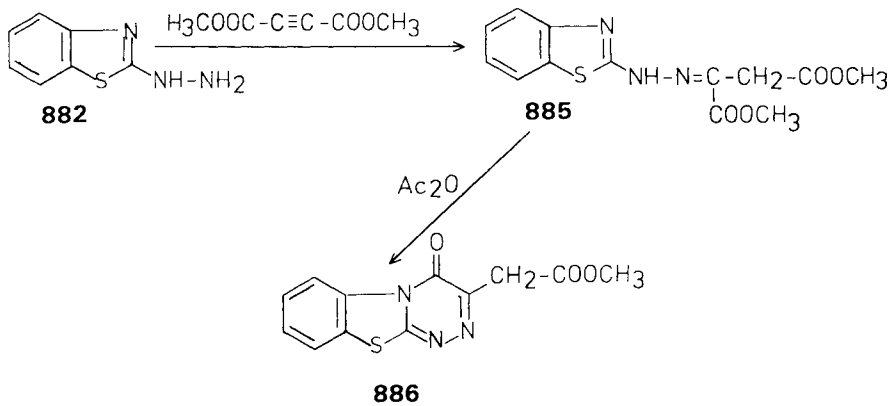
by its infrared spectra to be the hydrazone ester (**881**), contaminated with a small amount of **880**. The hydrazone **881** readily underwent ring closure to **880** on heating in benzene, ethanol, or dilute hydrochloric acid (1491). An alternative synthesis of **880** from **879** was effected by treatment with hydrazine (1491). The structure of **880** was confirmed by its synthesis from 2-hydrazinobenzothiazole (**882**) and ethyl bromoacetate (1491).



Treatment of 3-[(hydroxycarbonyl)methyl]-2-iminobenzothiazoline (**833a**) or its ethyl ester (**883b**) with alkyl hydrazines was used for the synthesis of 2-alkyl-1,2,4-triazino[3,4-*b*]benzothiazol-3-ones (**884**) (1491). The infrared spectra of **884** have no peaks in the region of 2.7 to 3.1 μ, indicating



a: R = H, **b**: R = C_2H_5

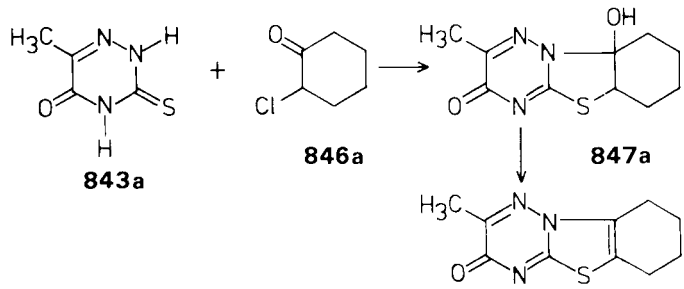


that there is no OH group present [$R^2 = R^8 = H$, m.p. 260 to 261°C; $R^2 = CH_3$, $R^8 = H$, 181 to 189°C (dec.); $R^2 = CH_2CH_2OH$, $R^8 = H$, 165°C; $R^2 = CH_2CF_3$, $R^8 = H$, 182 to 184°C; $R^2 = C_6H_5CH_2$, $R^8 = H$, 191 to 197°C; $R^2 = CH_2CF_3$, $R^8 = C_2H_5O$, 196 to 198°C].

Reaction of **882** with dimethyl acetylenedicarboxylate gave the hydrazone (**885**), which cyclizes to yield methyl 2-(4-oxo-1,2,4-triazino[3,4-*b*]-benzothiazol-3-yl)acetate (**886**) (m.p. 223°C) (1434) when heated in acetic anhydride.

B. 1,2,4-Triazino[3,2-*b*]benzothiazoles

Reaction of 6-methyl-3-thioxo-1,2,4-triazin-5-one (**843a**) with 2-chlorocyclohexanone (**846a**) affords 5a,6,7,8,9,9a-hexahydro-9a-hydroxy-2-methyl-3H-1,2,4-triazino[3,2-*b*]benzothiazol-3-one (**847a**) (m.p. 176 to 177°C) which is dehydrated to 6,7,8,9-tetrahydro-2-methyl-3H-1,2,4-triazino[3,2-*b*]benzothiazol-3-one (**848a**) (m.p. 159 to 160°C) (955). Both compounds were mentioned in Sections VI-XVI-A and are included in Tables VI-19 and VI-20.



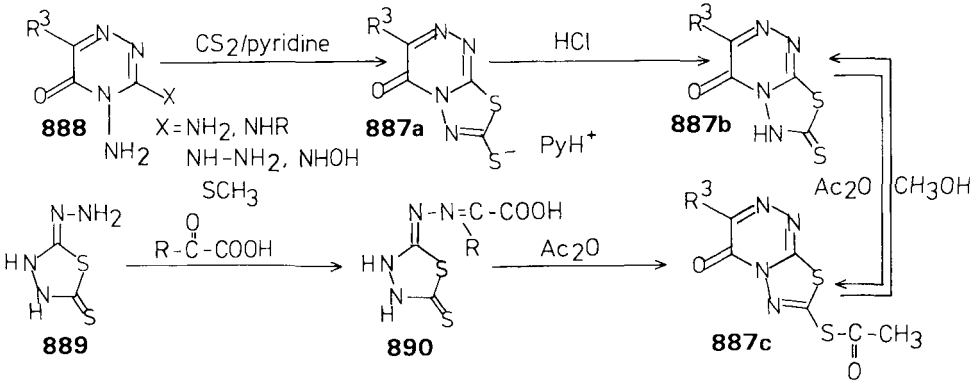
843a **846a** **847a** **848a**

XVIII. CONDENSED WITH THE 1,3,4-THIADIAZOLE RING

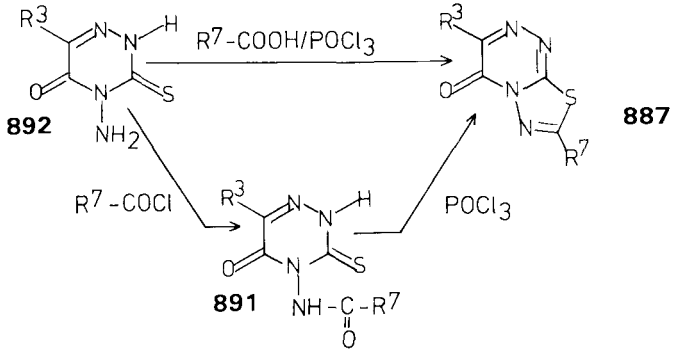
A. 1,3,4-Thiadiazolo[2,3-*c*]1,2,4-triazines

All known 1,3,4-thiadiazolo[2,3-*c*]1,2,4-triazines are derivatives of 1,3,4-thiadiazolo[2,3-*c*]1,2,4-triazin-4-one (**887**). Reaction of 3-amino-, 3-hydrazino-, 3-(hydroxylamino)-, or 3-(methylmercapto)-4-amino-1,2,4-triazin-5-ones (**888**) with carbon disulfide in the presence of pyridine yields the pyridinium salts of the 7-mercapto-1,3,4-thiadiazolo[2,3-*c*]1,2,4-triazin-4-ones (**887a**) which can be

transformed into the free acids (**887b**) by addition of hydrochloric acid (932, 1078). The structure of **887b** was confirmed by reaction of the thiadiazole (**889**) with α-ketocarboxylic acids, followed by cyclization of the synthetized hydrazones (**890**) with acetic anhydride to give the 7-acetylmercapto compounds (**887c**), which can be transformed into **887b** by addition of methanol (932). The reverse of the latter reaction has also been reported.



Lalezari and his group (933) prepared 1,3,4-thiadiazolo[2,3-*c*] 1,2,4-triazin-4-ones (**887**) through the interaction of 4-amino-3-thioxo-1,2,4-triazin-5-ones (**892**) and carbonic acids in the presence of phosphoryl chloride. The same compounds (**887**) were obtained when **892** were reacted with acyl chlorides and the formed amides (**891**) treated with phosphoryl chloride. Both reactions were only successful in cases of aromatic or conjugated acids and acyl chlorides.



7-Amino-1,3,4-thiadiazolo[2,3-*c*] 1,2,4-triazin-4-ones (**887d**) were prepared through reaction of **892** with bromocyanogene (935).

Compounds **887b** are unstable in both acidic and basic media. They are soluble in sodium carbonate and the formed sodium salts (**887d**) can be alkylated (932) or oxidized with iodine to the disulfides (**887e**). Aqueous sodium hydro-

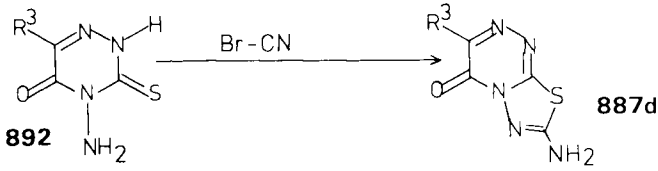
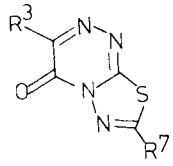


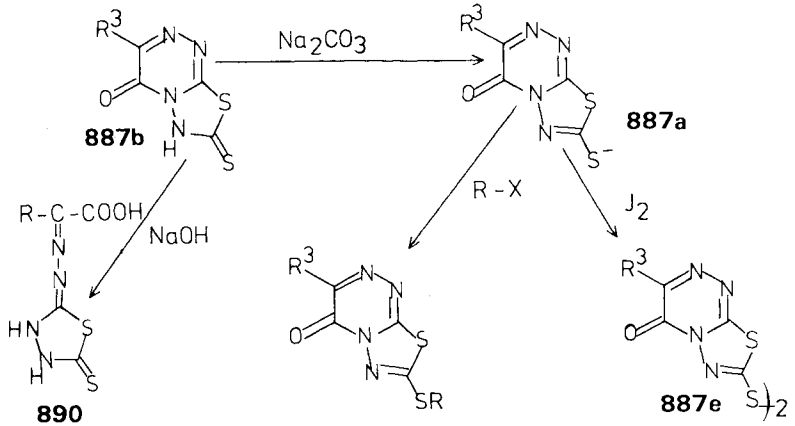
TABLE VI-20. 1,3,4-THIADIAZOLO[2,3-*c*]1,2,4-TRIAZIN-4-ONES



R^3	R^7	m.p. (°C)	Refs.
CH_3	$CH_3CH{=}CH$	220	933
CH_3	$C_6H_5CH{=}CH$	275	933
CH_3	C_6H_5	265	933
CH_3	4-CH_3–C_6H_4	215	933
CH_3	4-F–C_6H_4	266	933
CH_3	4-Cl–C_6H_4	230	933
CH_3	4-O_2N–C_6H_4	270	933
CH_3	4-CH_3O–C_6H_4	227	933
CH_3	SH (taut.)	240–241 (dec.)	932
Na salt		265 (dec.)	932
Pyridinium salt		216 (dec.)	932
CH_3	SCH_3	195–196	932
CH_3	SCH_2COOH	207	932
CH_3	$SCH_2C_6H_5$	171	932
CH_3	S-2	200 (dec.)	932
CH_3	NH_2	294–296	935
·$HClO_4$		274–275 (dec.)	935
CH_2CH_2OH	NH_2	245–247	935
C_6H_5	$CH_3CH{=}CH$	225	933
C_6H_5	$C_6H_5CH{=}CH$	293	933
C_6H_5	C_6H_5	238	933
C_6H_5	4-CH_3–C_6H_4	246	933
C_6H_5	4-F–C_6H_4	335	933
C_6H_5	4-Cl–C_6H_4	257	933
C_6H_5	4-O_2N–C_6H_4	322	933
C_6H_5	4-CH_3O–C_6H_4	217	933
C_6H_5	SH (taut.)	245 (dec.)	932
Na salt		192 (dec.)	932
Pyridinium salt		230	932, 1078
C_6H_5	SCH_3	165	932
C_6H_5	SCH_2COOH	220	932
C_6H_5	$SCH_2C_6H_5$	180	932
C_6H_5	$SCOCH_3$	215 (dec.)	932

xide solution opens the 1,2,4-triazinone ring leading to the 1,3,4-thiadiazole derivatives (**890**).

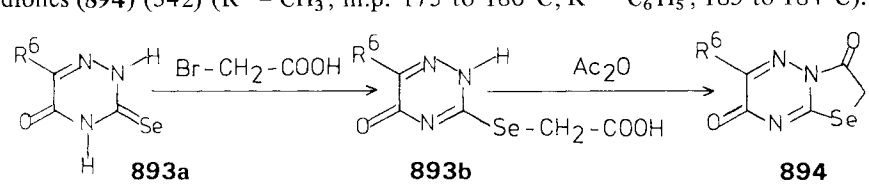
Table VI-20 lists the 1,3,4-thiadiazolo[2,3-*c*]1,2,4-triazin-4-ones that have been reported in the literature.



XIX. CONDENSED WITH THE SELENAZOL RING

A. Selenazolo[3,2-*b*]1,2,4-triazines

3-Selenoxo-1,2,4-triazin-5-ones (**893a**) were condensed with bromoacetic acid to give 3-{[(hydroxycarbonyl)methyl]seleno}-1,2,4-triazin-5-ones (**893b**) which could be cyclized with acetic anhydride to selenazolo[3,2-*b*]1,2,4-triazine-3,7-diones (**894**) (342) ($R^6 = CH_3$, m.p. 175 to 180°C; $R^6 = C_6H_5$, 183 to 184°C).

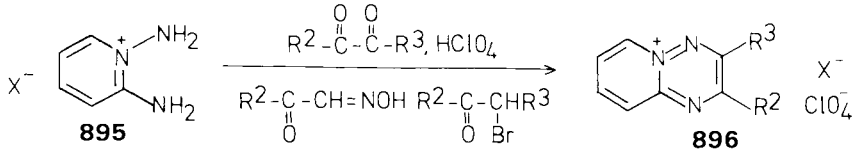


XX. CONDENSED WITH THE PYRIDINE RING

A. Pyrido[1,2-*b*]1,2,4-triazines

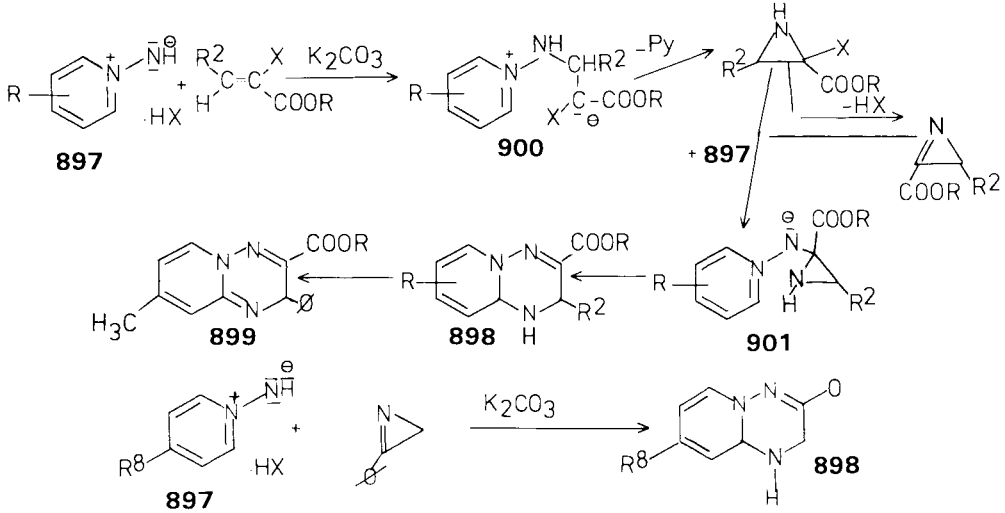
Condensation of 1,2-diaminopyridinium salts (**895**) and 1,2-dicarbonyl compounds, α-bromo ketones, or isonitrosoacetophenone in an organic solvent

in the presence of a mineral acid was used by Kost and his group for the synthesis of pyrido[1,2-*b*]1,2,4-triazinium salts (**896**) (1492–1494).



895 **896**

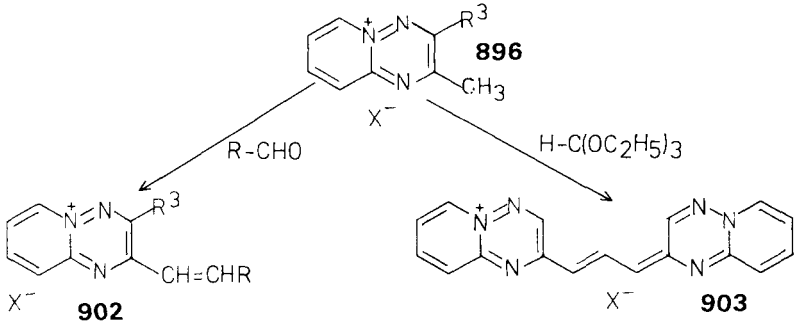
1-Aminopyridinium salts (**897**) react with α-chlorocinnamates and methyl α-bromocrotonate, in the presence of alkali at room temperature, to afford the corresponding 1,9a-dihydro-2*H*-pyrido[1,2-*b*]1,2,4-triazine derivatives (**898**). Structural elucidation of these compounds was accomplished by physical and spectral means and by conversion to the dehydrogenated 2*H*-pyrido[1,2-*b*]-1,2,4-triazines (**899**) (1495) [R = CH_3, m.p. 108 to 110°C, picrate 178–181°C (dec.), R = C_2H_5, picrate 189 to 192°C (dec.)]. For the synthesis of **898** the following mechanism was suggested: reaction of the pyridine-*N*-imine and the α-haloacrylate gives **900**, which eliminates the pyridine and forms a halo-aziridine. This may react directly with a second pyridine-*N*-imine (**897**) or may react after elimination of hydrogen halide. The intermediate, **901**, is formed, which is transformed to the isolated **898**. This mechanism is confirmed by the same authors by isolation of the 1,9a-dihydro-2*H*-pyrido[1,2-*b*]1,2,4-triazines (**898**) from the reaction of 1-aminopyridinium salts (**897**) and 2-phenylazirine (1496).



897 **900** **897** **899** **898** **901** **897** **898**

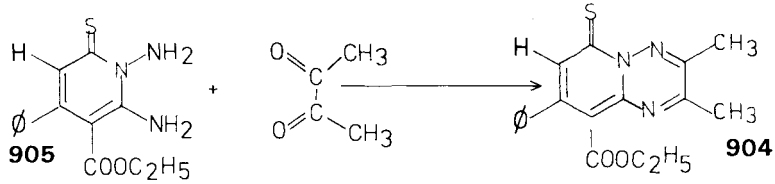
Methyl groups in the 2-position of pyrido[1,2-*b*]1,2,4-triazinium salts (**896**) are very reactive and can be condensed with aldehydes or orthocarboxylates to

afford the 2-vinylpyrido[1,2-*b*]1,2,4-triazinium salts (**902**) or the cyanines **903** (1493).



Gewald and co-workers (1497) obtained 2,3-dimethyl-8-phenyl-9-(ethoxycarbonyl)pyrido[1,2-*b*]1,2,4-triazine-6-thione (**904**) (m.p. 195 to 197°C) when they condensed 1,2-diamino-4-phenyl-3-(ethoxycarbonyl)pyridine-6-thione (**905**) and diacetyl.

Known compounds of this class are listed in Table VI-21.



B. Pyrido[2,1-*c*]1,2,4-triazines

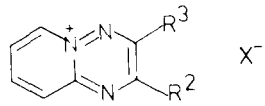
Condensation of 2-hydrazinopyridine (**906**) and pyruvic acid or ethyl pyruvate was used by Reimlinger and his group (1481) for the synthesis of 3-methylpyrido[2,1-*c*]1,2,4-triazin-4-one (**907a**) (m.p. 184 to 186°C). Analogously 3-methyl- (**908a**) (m.p. 95°C) and 3-phenyl-6,7,8,9-tetrahydropyrido[2,1-*c*]1,2,4-triazin-4-one (**908b**) (m.p. 160°C) were prepared by Korte and his group (181) from 2-hydrazino-3,4,5,6-tetrahydropyridine (**909**) and α-ketocarboxylates.

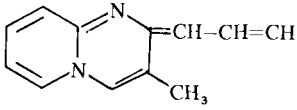
Interaction of **906** or **909** and dimethyl acetylenedicarboxylate affords methyl 4-oxopyrido[2,1-*c*]1,2,4-triazin-3-ylacetate (**907b**) (m.p. 171 to 173°C) (1434) and methyl 4-oxo-6,7,8,9-tetrahydropyrido[2,1-*c*]1,2,4-triazin-3-ylacetate (**908c**) (m.p. 71 to 74°C) (1390), respectively.

3-Cyano-1-phenacyl-pyridinium salts (**910**) and hydrazine afford 1,9a-dihydro-4*H*-pyrido[2,1-*c*]1,2,4-triazines (**911**) [R = H, m.p. 154 to 155°C

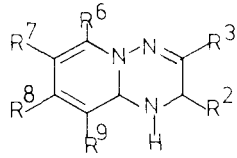
TABLE VI-21. PYRIDO[1,2-*b*]1,2,4-TRIAZINES

A. Pyrido[1,2-*b*]1,2,4-triazinium Salts

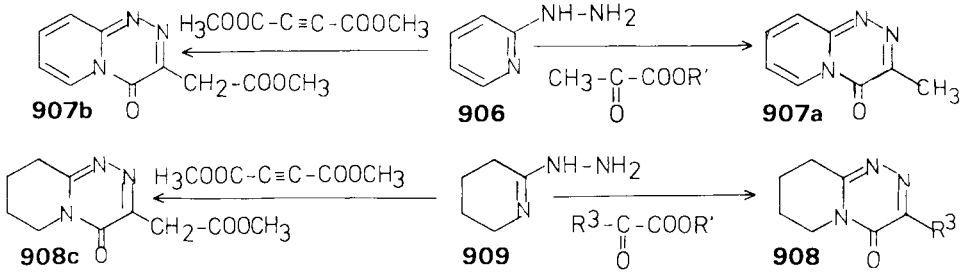


R^2	R^3	X	m.p. (°C)	Refs.
H	H	ClO_4	225–226	1493
CH_3	H	ClO_4	198–199	1493
CH_3	CH_3	ClO_4	243–244	1492, 1493
		$HSO_4 \cdot J_2$	178	1493
		J_3	181–182	1493
C_6H_5	H	ClO_4	302–304	1492, 1493
C_6H_5	C_6H_5	ClO_4	249–250	1492
			259–260	1493
C_6H_5–CH=CH	H	ClO_4	237–238	1493
C_6H_5–CH=CH	CH_3	ClO_4	226–227	1493
4-*i*-C_3H_7–C_6H_4–CH=CH	CH_3	ClO_4	220–221	1493
4-HO–C_6H_4–CH=CH	H	ClO_4	273–274	1493
4-HO–C_6H_4–CH=CH	CH_3	ClO_4	266	1493
2-CH_3O–C_6H_4–CH=CH	CH_3	ClO_4	219	1493
	CH_3	ClO_4	223–224	1493

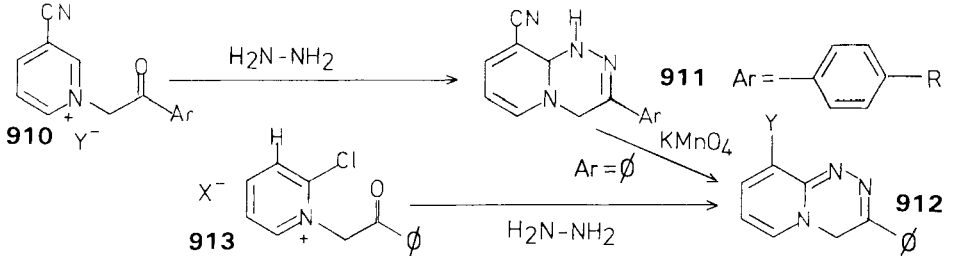
B. 1,9a-Dihydro-2H-pyrido[1,2-*b*]1,2,4-triazines



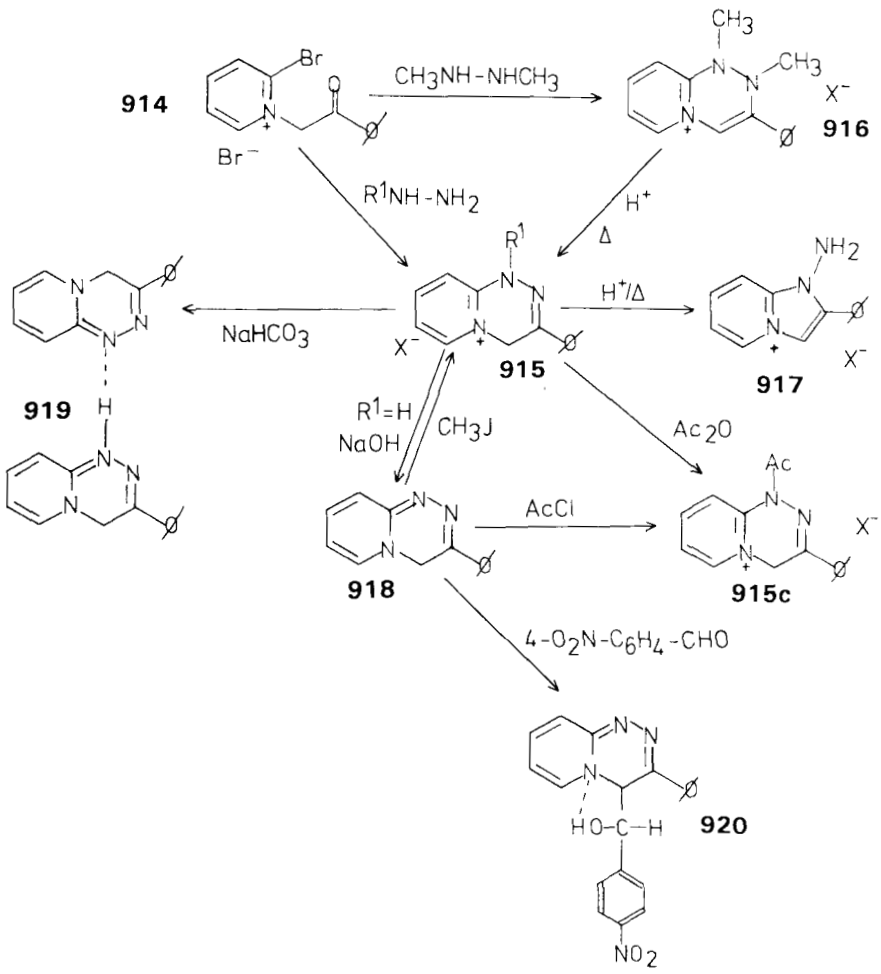
R^2	R^3	R^6	R^7	R^8	R^9	m.p. (°C)	Refs.
H	C_6H_5	H	H	H	H	95–97	1496
H	C_6H_5	H	H	CH_3	H	112–115	1496
CH_3	$COOCH_3$	H	H	CH_3	H	74–76	1495
C_6H_5	$COOCH_3$	H	H	CH_3	H	143–145	1495
C_6H_5	$COOC_2H_5$	H	H	H	H	125–127	1495
C_6H_5	$COOC_2H_5$	H	H	H	CH_3	136–139	1495
C_6H_5	$COOC_2H_5$	H	H	CH_3	H	112–115	1495
C_6H_5	$COOC_2H_5$	H	CH_3	H	CH_3	106–109	1495
C_6H_5	$COOC_2H_5$	CH_3	H	H	H	91–93	1495



(dec.); R = Br, 168 to 169°C (dec.); R = NO_2, 112°C (dec.); R = OCH_3, m.p. 158 to 159°C], which can be oxidized by potassium permanganate to give 4*H*-pyrido[2,1-*c*]1,2,4-triazines (**912**) [Y = CN, m.p. 235 to 236°C, (dec.)] (1499, 1500). 2-Chlorophenacylpyridinium salt (**913**) and hydrazine yielded 3-phenyl-4*H*-pyrido[2,1-*c*]1,2,4-triazine (**912**) (Y = H, m.p. 159 to 160°C) (1500).



The reaction of 2-bromo-1-phenacylpyridinium bromide (**914**) with hydrazine or methylhydrazine leads to the 3-phenyl-1,4-dihydropyrido[2,1-*c*]1,2,4-triazinium ion (**915a**) (X = Br·1/2 H_2O, m.p. 212 to 215°C; X = Br·H_2O, 125 to 126°C; X = ClO_4, 199 to 200°C) or its 1-methyl analogue (**915b**) (X = ClO_4, m.p. 188°C) (1498), whereas with 1,2-dimethylhydrazine the product was 1,2-dimethyl-3-phenyl-1,2-dihydropyrido[2,1-*c*]1,2,4-triazinium ion (**916**) (X = ClO_4, m.p. 210 to 211°C). In boiling acid **916** loses the methyl group at position 2, affording **915b**, whereas **915a** in boiling acid undergoes ring contraction to 1-amino-2-phenylimidazo[1,2-*a*]pyridinium ion (**917**) (1498). When **915a** was treated with sodium bicarbonate a compound [m.p. 197 to 199°C (dec.)] was isolated having the composition of 1 mole of the salt **915a** and 1 mole of the free base **918**. Its structure is formulated as **919**. The free base **918** (m.p. 222 to 223°C) was obtained when sodium hydroxide was added to **915a**. The base **918** underwent methylation and acetylation with ease, presumably at position 1, leading to **915b** and **915c** (X = Br, m.p. 206 to 208°C; X = ClO_4, 228 to 230°C). **918** reacts with 4-nitrobenzaldehyde at position 4. From the evidence of the PMR spectrum, structure **920** (m.p. 184 to 185°C) is suggested for the reaction product (1498).

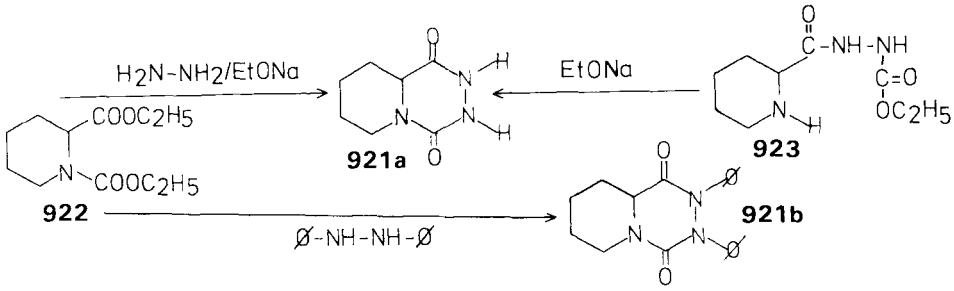


Potts and Burton (1501) have proved that the synthesis of pyrido[2,1-*c*]-1,2,4-triazines, claimed by Kaufmann and his group (1502), is incorrect. 2-Hydrazinopyridine and oxalic acid yield 1,2,4-triazolo[4,3-*a*]pyridine-3-carboxylic acid instead of 3-hydroxypyrido[2,1-*c*]1,2,4-triazin-4-one.

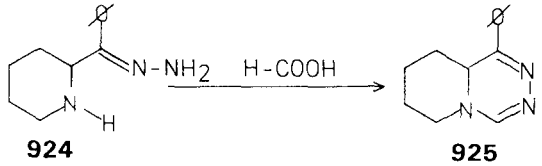
C Pyrido[1,2-*d*]1,2,4-triazines

At present no fully unsaturated pyrido[1,2-*d*]1,2,4-triazine derivative is known. Winterfeld and Nair (1503) prepared 6,7,8,9-tetrahydro-9a*H*-pyrido-[1,2-*d*]1,2,4-triazine-1,4-dione (**921a**) (m.p. 176°C) by heating diethyl piperi-

dine-1,2-dicarboxylate (**922**) with anhydrous hydrazine in the presence of sodium ethoxide or by cyclization of the ethoxycarbonylhydrazide (**923**) in the presence of sodium ethoxide. Interaction of **922** and hydrazobenzene afforded 2,3-diphenyl-6,7,8,9-tetrahydro-9a*H*-pyrido[1,2-*d*]1,2,4-triazine-1,4-dione (**921b**) [m.p. 245°C (dec.)].



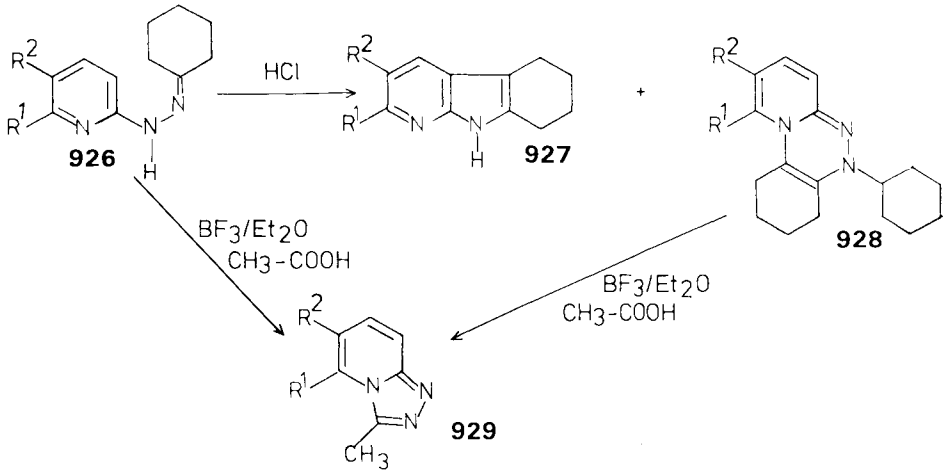
Dissolving 2-piperidylphenyl ketone hydrazone (**924**) in formic acid and refluxing it for 3 hr gave 1-phenyl-6,7,8,9-tetrahydro-9a*H*-pyrido[1,2-*d*]-1,2,4-triazine (**925**) (m.p. 129 to 133°C) (1504, 1505).



D. Pyrido[2,1-*c*]1,2,4-benzotriazines

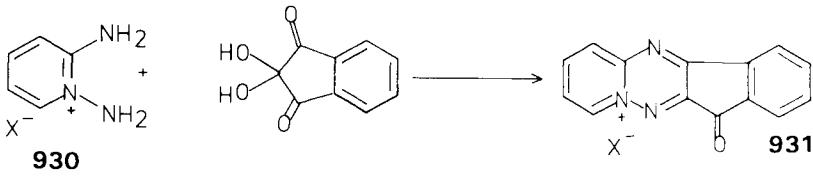
Treatment of cyclohexanone 2-pyridylhydrazones (**926**) with hydrochloric acid affords tetrahydro-α-carbolines (**927**) and 6-cyclohexyl-7,8,9,10-tetrahydro-6*H*-pyrido[2,1-*c*]1,2,4-benzotriazines (**928**) (1506–1509) [m.p.: R^2 = R^1 = H, 77 to 78°C (1506, 1507), ·HCl, 192 to 193°C (dec.) (1507); R^2 = H, R^1 = CH_3, 107 to 108°C (1506, 1507); R^2 = H, R^1 = Br, 129 to 130°C (1509); R^2 = CH_3, R^1 = H, 98 to 99°C (1506, 1508); R^2 = Cl, R^1 = H, 112.5 to 113.5°C (1506, 1508)]. Addition of cyclohexanone to the reaction mixture increases the yield of **928** up to 87% (1506). **928** is converted to 3-methyl-1,2,4-triazolo[4,3-*a*]pyridine (**929**) when heated with boron trifluoride etherate in acetic acid for 6 hr at 180°C in a sealed tube (1507). **929** is also obtained when **926** is treated under the same conditions (1507).

Treatment of **926** with zinc chloride, cuprous chloride, polyphosphoric acid, sulfosalicylic acid, or 4-toluenesulfonic acid gives only **927** (1507–1509).



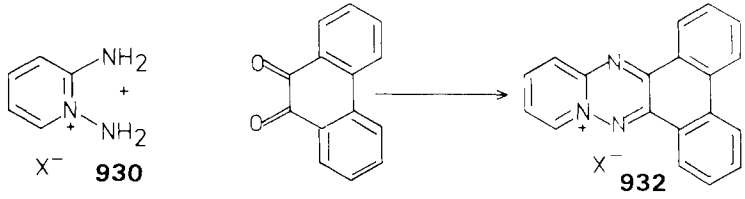
E. Pyrido[1,2-*b*]indano[1,2-*e*]1,2,4-triazines

Condensation of the 1,2-diaminopyridinium salt (**930**) with ninhydrin yields the pyrido[1,2-*b*]indano[1,2-*e*]1,2,4-triazinium salt (**931**) (X = ClO_4, m.p. 295 to 296°C) (1493).



F. Pyrido[1,2-*b*]phenanthro[9,10-*e*]1,2,4-triazines

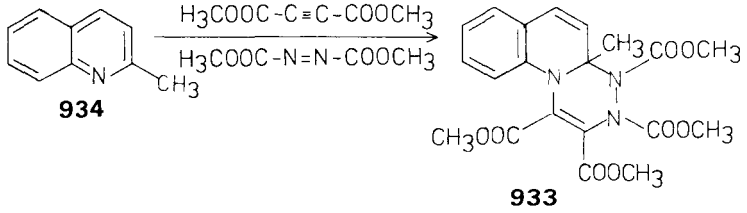
Condensation of the 1,2-diaminopyridinium salt (**930**) with 9,10-phenanthrenequinone was used for the synthesis of the pyrido[1,2-*b*]phenanthro[9,10-*e*]1,2,4-triazinium salt (**932**) [m.p. X = ClO_4, 350°C (1492), 354°C (1493)].



XXI. CONDENSED WITH THE QUINOLINE SYSTEM

A. 1,2,4-Triazino[4,3-*a*]quinolines

Huisgen and co-workers (1510) observed the formation of tetramethyl 4a-methyl-4,4a-dihydro-3*H*-1,2,4-triazino[4,3-*a*]quinolinetetracarboxylate (**933**) when they reacted quinaldine (**934**) with dimethyl azodicarboxylate and dimethyl acetylenedicarboxylate in ether [**933**, m.p. 183.5 to 184.5°C (dec.)].

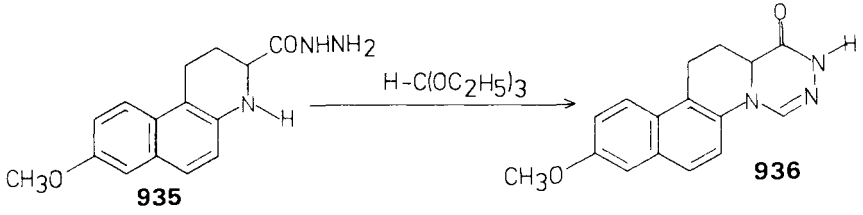


934 **933**

XXII. CONDENSED WITH THE BENZO[*f*]QUINOLINE SYSTEM

A. Benzo[*f*]1,2,4-triazino[4,5-*a*]quinolines

Cyclization of 1,2,3,4-tetrahydro-8-methoxybenzo[*f*]quinoline-3-carbohydrazide (**935**) with triethyl orthoformate was used by Jones for the synthesis of 13,13a-dihydro-9-methoxy-2*H*-benzo[*f*]1,2,4-triazino[4,5-*a*]quinolin-1(12H)-one (**936**) [m.p. 255 to 256°C (dec.)] (1511).



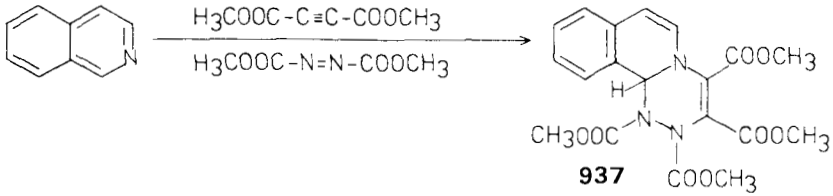
935 **936**

XXIII. CONDENSED WITH THE ISOQUINOLINE SYSTEM

A. 1,2,4-Triazino[3,4-*a*]isoquinolines

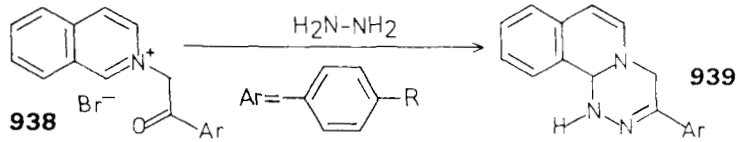
Tetramethyl 1,11b-dihydro-2*H*-1,2,4-triazino[3,4-*a*]isoquinoline 1,2,3,4-tetracarboxylate (**937**) [m.p. 187 to 188°C (dec.)] is isolated when isoquinoline is

reacted with dimethyl azodicarboxylate and dimethyl acetylenedicarboxylate in ether at 0°C (1510).



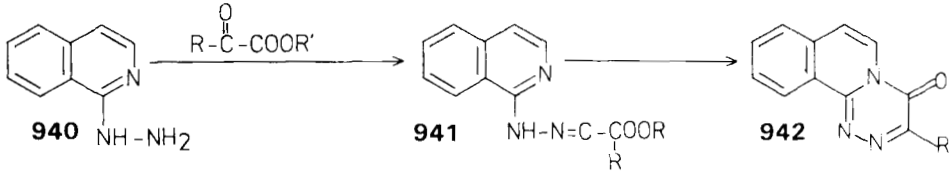
937

When 2-phenacylisoquinolinium bromides (**938**) were reacted with aproximately 2 equivalents of hydrazine the unstable 3-aryl-1,11b-dihydro-4*H*-1,2,4-triazino[3,4-*a*]isoquinolines (**939**) [R = H, m.p. 151 to 154°C (dec.); R = NO_2, 90°C (dec.) (1500)] were obtained (1500, 1512).



938 **939**

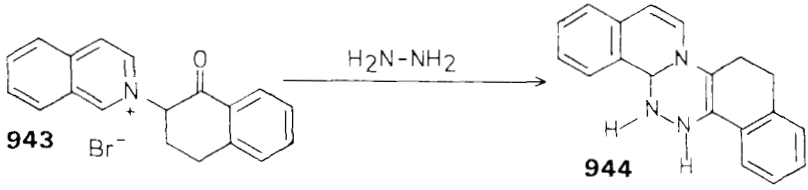
The reaction of 1-hydrazinoisoquinoline (**940**) and ethyl pyruvate or phenylglyoxylic acid yielded the hydrazones (**941**) which were then cyclized by heating in xylene or butanol, to give 3-methyl- (m.p. 227 to 229°C) and 3-phenyl-4-oxo-4*H*-1,2,4-triazino[3,4-*a*]isoquinoline (**942**) (m.p. 217 to 219°C) (1481).



940 **941** **942**

B. Naphtho[2,1-*e*]1,2,4-triazino[3,4-*a*]isoquinolines

Interaction of *N*-α-tetralonylisoquinolinium bromide (**943**) and hydrazine yields 1,2,10,11-tetrahydro-2aH-naphtho[2,1-*e*]1,2,4-triazino[3,4-*a*]isoquinoline (**944**) (1499).

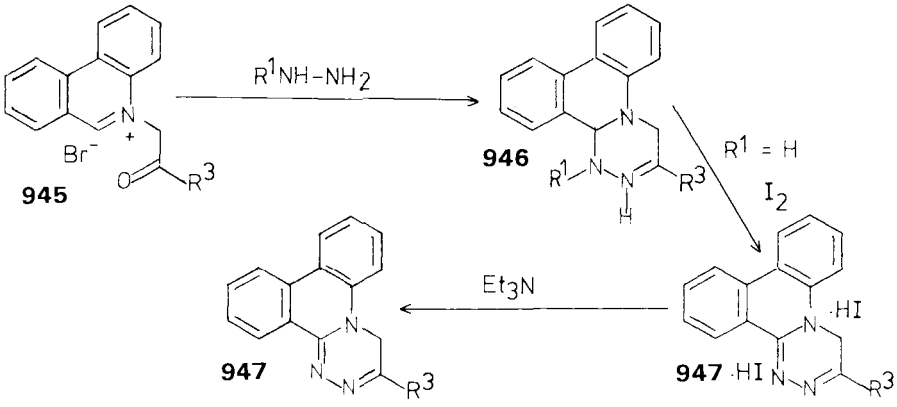


943 **944**

XXIV. CONDENSED WITH THE PHENANTHRIDINE SYSTEM

A. 1,2,4-Triazino[4,3-*f*]phenanthridines

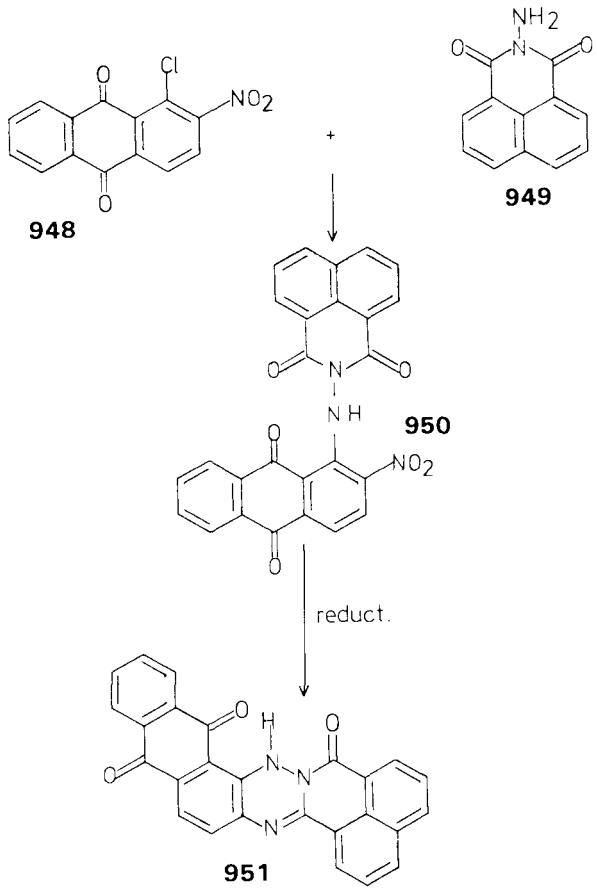
5-Phenacyl- (**945a**) and 5-acetonylphenanthridinium bromide (**945b**) react with hydrazine and methylhydrazine to give the cyclization products 1,13b-dihydro-4*H*-1,2,4-triazino[4,3-*f*]phenanthridines (**946**) (m.p.: $R^1 = H$, $R^3 = CH_3$, 159 to 160°C; $R^1 = H$, $R^3 = C_6H_5$, 185 to 186°C; $R^1 = R^3 = CH_3$, 156 to 157°C; $R^1 = CH_3$, $R^3 = C_6H_5$, 155 to 156°C) (1512). **946** ($R^1 = H$) were readily oxidized in acidic media, or by iodine, to give the 4*H*-1,2,4-triazino-[4,3-*f*]phenanthridine hydroiodides (**947**·HI) (m.p.: $R^3 = CH_3$, 297 to 298°C; $R^3 = C_6H_5$, 270 to 271°C) which were transformed into the free bases **947** (m.p.: $R^3 = CH_3$, 155 to 156°C; $R^3 = C_6H_5$, 160 to 161°C) by addition of triethylamine (1512).



XXV. CONDENSED WITH THE BENZO[4,5]ISOQUINOLINE SYSTEM

A. Anthra[2,1-*e*]benz[4,5]isoquinolo[2,1-*b*]1,2,4-triazines

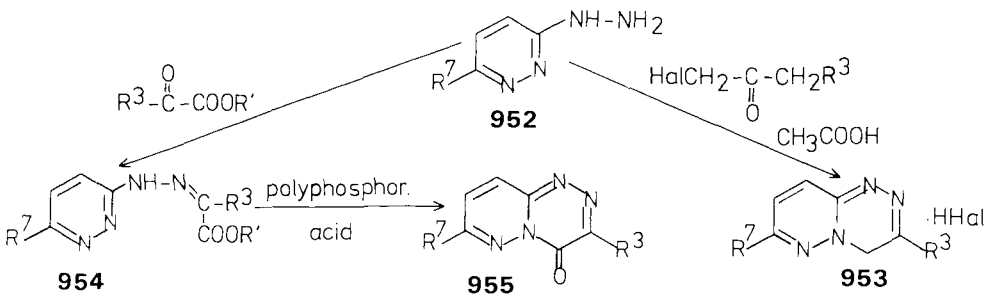
When 1-chloro-2-nitroanthraquinone (**948**) was reacted with *N*-aminonaphthalimide (**949**), *N*-(2-nitro-1-anthraquinonylamino)-naphthalimide (**950**) was formed. Reduction of the nitro group with sodium sulfide was accompanied by closure of the 1,2,4-triazine ring to yield the deep blue 5*H*,15*H*,17*H*,18*H*-anthra[2,1-*e*]benz[4,5]isoquinolo[2,1-*b*]1,2,4-triazine-5,15,18-trione (**951**) (m.p. > 360°C) (1321)(RRI 11448).



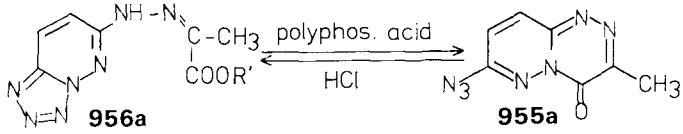
XXVI. CONDENSED WITH THE PYRIDAZINE RING

A. Pyridazino[6,1-*c*]1,2,4-triazines

Reaction of 3-hydrazinopyridazines (**952**) with α-bromo or α-chloro ketones in acetic acid yields 4*H*-pyridazino[6,1-*c*] 1,2,4-triazine hydrochlorides or hydrobromides (**953**) (1513, 1514). **952** and α-ketocarboxylates form the hydrazones (**954**) which are cyclized to give pyridazino[6,1-*c*] 1,2,4-triazin-4-ones (**955**) on heating with polyphosphoric acid at 140°C for 1 hr (1515–1517).



When the tetrazolo[1,5-*b*]pyridazinyl 6-hydrazones **956a** and **956b** were heated with polyphosphoric acid the 1,2,4-triazine ring was formed concurrently with the opening of the tetrazole ring, leading to 7-azido-3-methylpyridazino[6,1-*c*]1,2,4-triazin-4-one (**955a**) (1516) and 7-azido-3-phenyl-4*H*-pyridazino[6,1-*c*]1,2,4-triazine (**957**) (1514). Treatment of **955a** with hydrochloric acid affords the starting material **956a**.



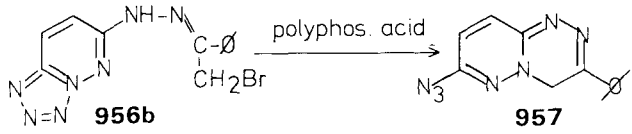


Table VI-22 lists the pyridazino[6,1-*c*]1,2,4-triazines known.

B. Pyridazino[6,1-*d*]1,2,4-triazines

5,8-Dibenzoyl-2-*p*-tolyl-8*H*-pyridazino[6,1-*d*]1,2,4-triazine (**958**) was obtained from 3-*p*-tolylpyridazinium phenacylide (**959**) and benzoyldiazomethane (**960**) via an unstable intermediate that dehydrated spontaneously. **958** exists as a keto–enol mixture (1518).

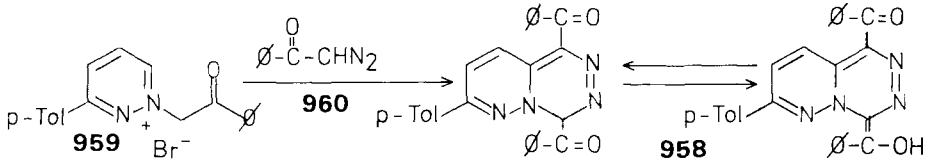
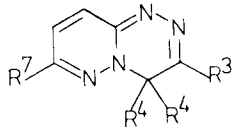


TABLE VI-22. PYRIDAZINO[6,1-*c*]1,2,4-TRIAZINES



R^3	R^4	R^4	R^7		m.p. (°C)	Refs.
H	H	H	H		218	1513
H	H	H	Cl	·HBr	>300	1513
CH_3	H	H	H	·HCl	250–252	1513
CH_3	H	H	Cl	·HCl	205–207	1513
CH_3	=O		Cl		150–153 (dec.)	1515
CH_3	=O		N_3		147–148	1516
CH_3	=O		OH		285–287	1517
C_6H_5	H	H	H	·HBr	263–265	1513
C_6H_5	H	H	CH_3	·HBr	270	1513
C_6H_5	H	H	Cl	·HBr	>320	1513
C_6H_5	H	H	OC_6H_5	·HBr	258	1513
C_6H_5	H	H	N_3		237–239	1514
C_6H_5	H	H	$NHNH_2$		230–231[a]	1513
					239–241	1514
				·HBr	215–220[a]	1513
C_6H_5	H	H	COOH		263	1513
C_6H_5	H	H	$CONH_2$	·HBr	283–284	1513
3-O_2N–C_6H_4	H	H	Cl	·HCl	>300	1513
4-O_2N–C_6H_4	H	H	H	·HCl	256–258	1513
4-O_2N–C_6H_4	H	H	CH_3		230–232	1513
4-O_2N–C_6H_4	H	H	Cl	·HBr	>320	1513

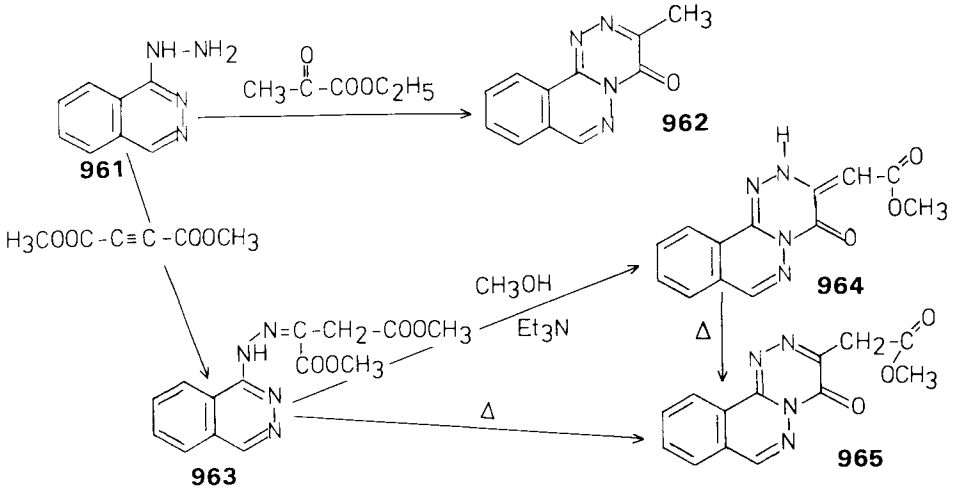
[a]Incorrect structure given (1514).

XXVII. CONDENSED WITH THE PHTHALAZINE SYSTEM

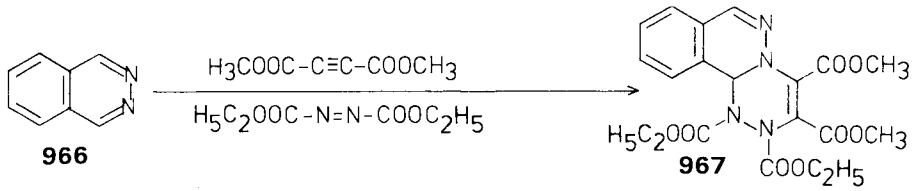
A. 1,2,4-Triazino[3,4-*a*]phthalazines

Condensation of 1-hydrazinophthalazine (**961**) with ethyl pyruvate affords a compound which is formulated as 3-methyl-4*H*-1,2,4-triazino[3,4-*a*]phthalazin-4-one (**962**) (m.p. 250 to 252°C) (1519). Interaction of **961** and dimethyl acetylenedicarboxylate gives the hydrazone (**963**) which yields the exocyclic tautomer (**964**) (m.p. 217 to 218°C) when cyclized under basic conditions (methanol/triethylamine) and the endocyclic tautomer methyl 2-(4-oxo-4*H*-

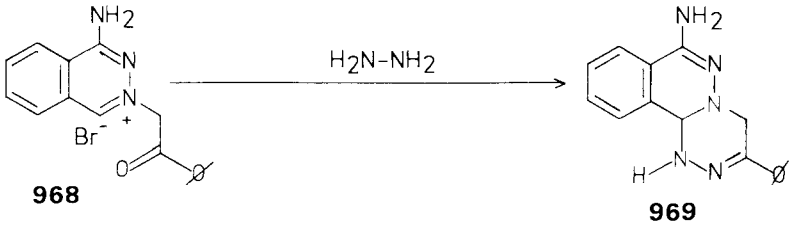
1,2,4-triazino[3,4-*a*]phthalazin-3-yl)acetate (**965**) (m.p. 217 to 218°C) by thermal cyclization (1434, 1488).



Reaction of phthalazine (**966**) with diethyl azodicarboxylate and dimethyl acetylenedicarboxylate gives 1,2-diethyl-3,4-dimethyl-1,11b-dihydro-2*H*-1,2,4-triazino[3,4-*a*]phthalazine-1,2,3,4-tetracarboxylate (**967**) [m.p. 130 to 131°C (dec.)] (1520).



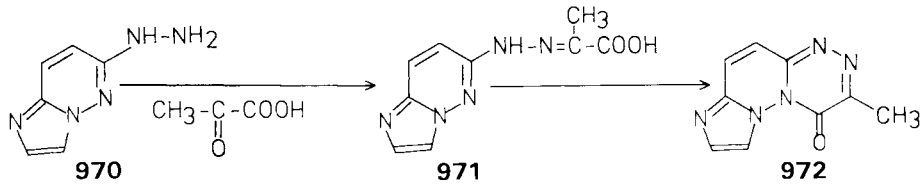
1-Amino-phenacylphthalazinium bromide (**968**) cyclized with hydrazine to give 7-amino-3-phenyl-1,11b-dihydro-4*H*-1,2,4-triazino[3,4-*a*]phthalazine (**969**) (1521).



XXVIII. CONDENSED WITH THE IMIDAZO[1,2-*b*]-PYRIDAZINE SYSTEM

A. Imidazo[1′,2′:2,3]pyridazino[6,1-*c*]1,2,4-triazines

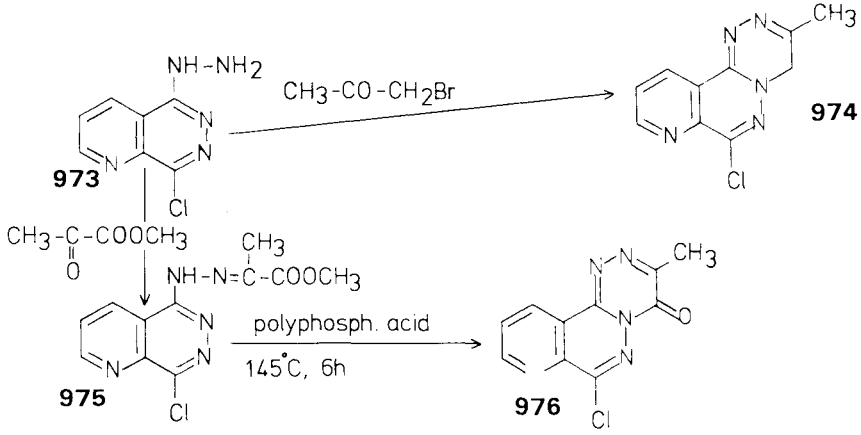
The hydrazone (**971**) was obtained from 6-hydrazinoimidazo[1,2-*b*]pyridazine (**970**) and pyruvic acid. Heating **971** with polyphosphoric acid at 150 to 160°C for 1.5 hr yields 2-methylimidazo[1′,2′:2,3]pyridazino[6,1-*c*]1,2,4-triazin-1-one (**972**) (m.p. 160 to 162°) (1515).



XXIX. CONDENSED WITH THE PYRIDO[2,3-*d*]-PYRIDAZINE SYSTEM

A. Pyrido[2′,3′:4,5]pyridazino[6,1-*c*]1,2,4-triazines

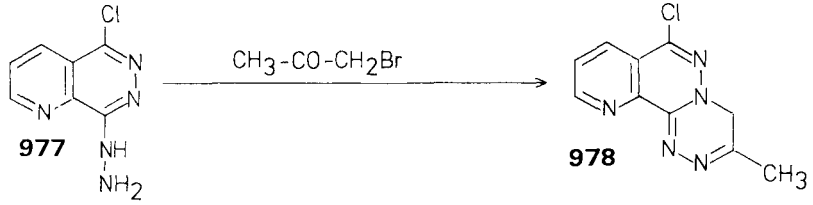
Interaction of 8-chloro-5-hydrazinopyrido[2,3-*d*]pyridazine (**973**) and bromoacetone affords 7-chloro-3-methyl-4*H*-pyrido[2′,3′:4,5]pyridazino[6,1-*c*]-1,2,4-triazine hydrobromide (**974**) [m.p. 200 to 203°C (dec); perchlorate 184 to 186°C (dec.)] (1517). Reaction of **973** and methyl pyruvate yielded the



hydrazone (**975**) which was cyclized with polyphosphoric acid at 145°C for 6 hr to give 7-chloro-3-methyl-4*H*-pyrido[2′,3′:4,5]pyridazino[6,1-*c*]1,2,4-triazin-4-one (**976**) (m.p. 305 to 308°C) (1517).

B. Pyrido[3′,2′:4,5]pyridazino[6,1-*c*]1,2,4-triazines

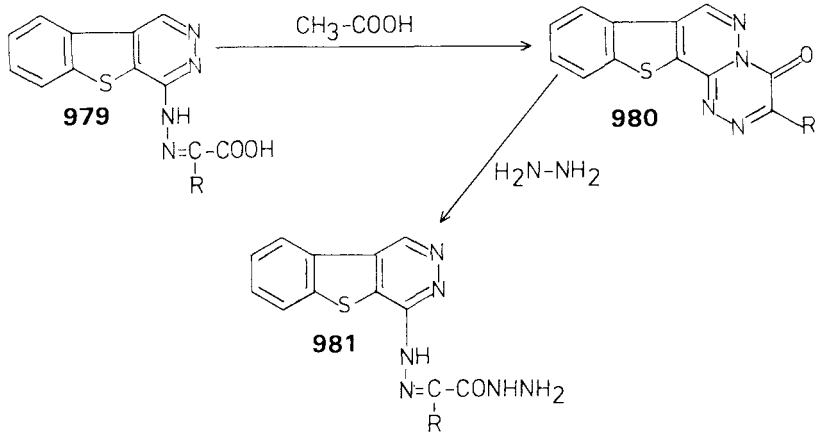
Stirring a mixture of 5-chloro-8-hydrazinopyrido[2,3-*d*]pyridazine (**977**) and bromoacetone in ethanol at room temperature for 1 hr yields 7-chloro-3-methyl-4*H*-pyrido[3′,2′:4,5]pyridazino[6,1-*c*]1,2,4-triazine hydrobromide (**978**) [m.p. 210 to 213°C (dec.), perchlorate 195 to 198°C (dec.)] (1517).



XXX. CONDENSED WITH THE [1]BENZOTHIENO[2,3-*d*]PYRIDAZINE SYSTEM

A. [1]Benzothieno[2′,3′:4,5]pyridazino[3,2-*c*]1,2,4-triazines

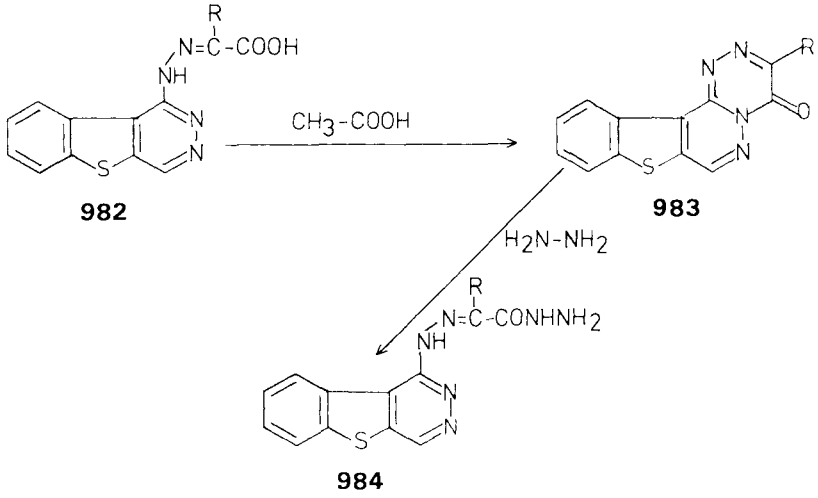
The hydrazones (**979**) cyclized to 3-methyl- (m.p. 328°C) and 3-phenyl-4-oxo-4*H*-[1]benzothieno[2′,3′:4,5]pyridazino[3,2-*c*]1,2,4-triazine (**980**) (m.p.



375°C) on refluxing in acetic acid (1522). Hydrazine opens the 1,2,4-triazine ring of **980**, leading to the hydrazones of α-ketocarboxhydrazides (**981**).

B. [1]Benzothieno[3',2':4,5]pyridazino[3,2-*c*]1,2,4-triazines

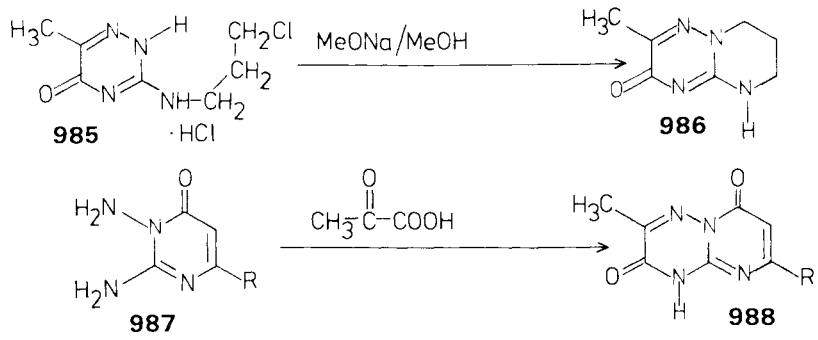
Refluxing the hydrazones (**982**) in acetic acid affords 3-methyl- (m.p. > 330°C) and 3-phenyl-4-oxo-4*H*-[1]benzothieno[3',2':4,5]pyridazino-[3,2-*c*] 1,2,4-triazine (**983**) (m.p. 295°C), respectively (1522). The 1,2,4-triazine ring in **983** is opened by reaction with hydrazine, leading to the hydrazides (**984**).



XXXI. CONDENSED WITH THE PYRIMIDINE RING

A. Pyrimido[1,2-*b*]1,2,4-triazines

Refluxing a solution of 3-[(3-chloropropyl)amino]-6-methyl-1,2,4-triazin-5-one hydrochloride (**985**) in methanol for 6 hr in the presence of sodium methoxide afforded 5,6,7,8-tetrahydro-2-methyl-3*H*-pyrimido[1,2-*b*]1,2,4-triazin-3-one (**986**) (m.p. 295 to 296°C) as colorless needles (709). Tsuji and Ueda (1523) prepared pyrimido[1,2-*b*]1,2,4-triazine-2,6-diones (**988**) (R = H, m.p. 282°C; R = CH_3, 300°C) through the reaction of 2,3-diaminopyrimidin-4-ones (**987**) and pyruvic acid.



B. Pyrimido[2,1-*c*]1,2,4-triazines

Reaction of the cyclic amidrazones (**989**) with α-ketocarboxylates (**990**) has been used for the synthesis of 6,7,8,9-tetrahydropyrimido[2,1-*c*]1,2,4-triazin-4-ones (**991**) (1435, 1436) [$R^3 = CH_3$, R^9 = H, m.p. 277°C (1436), 280°C (1435); $R^3 = R^9 = CH_3$, 133°C (1435); $R^3 = C_6H_5$, R^9 = H, 267°C (1435), 271°C (1435)].

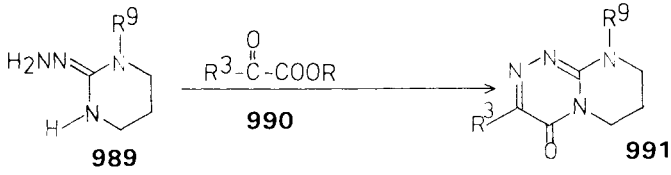
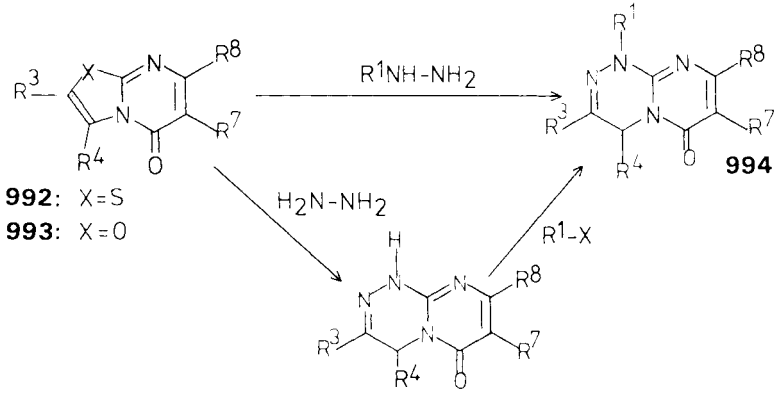


TABLE VI-23. PYRIMIDO[2,1-*c*]1,2,4-TRIAZIN-6-ONES (1524, 1525)

994					
R^1	R^3	R^4	R^7	R^8	m.p. (°C)
H	H	H	H	CH_3	290
H	H	H	$COOC_2H_5$	H	262
H	H	H	$CONHNH_2$	H	>330
H	H	CH_3	H	CH_3	240
H	CH_3	H	$COOC_2H_5$	H	249–250
H	C_6H_5	H	$COOC_2H_5$	H	285
CH_3	H	H	$COOC_2H_5$	H	173
CH_3	CH_3	H	$COOC_2H_5$	H	158
CH_3	CH_3	H	$CONHNHCH_3$	H	196
sec-C_4H_9	H	H	CH_3	H	77
$C_6H_5CH_2$	H	H	$COOC_2H_5$	H	148
4-O_2N-$C_6H_4CH_2$	H	H	$COOC_2H_5$	H	162

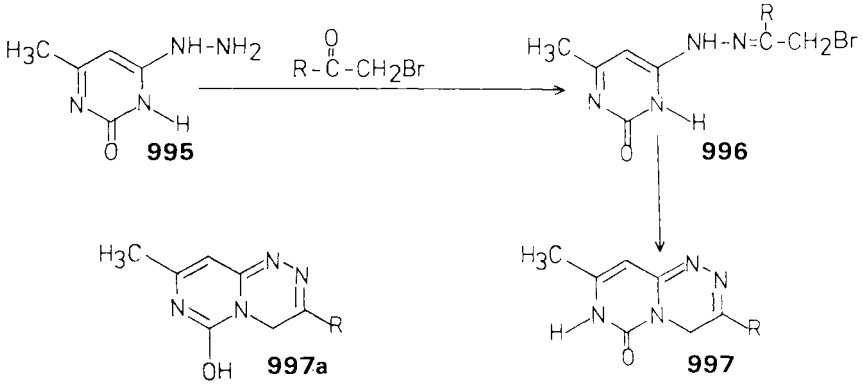
The reaction of hydrazines with various thiazolo[3,2-*a*]pyrimidin-5-ones (**992**) and an oxazolo[3,2-*a*]pyrimidin-5-one (**993**) to give 1,4-dihydropyrimido-[2,1-*c*] 1,2,4-triazin-6-ones (**994**) has been studied by Dunwell and Evans (1524, 1525, 1541). The position of alkylation in **994a** was determined to be position 1.

Compounds of this group reported in the literature are listed in Table VI-23.



C. Pyrimido[6,1-*c*]1,2,4-triazines

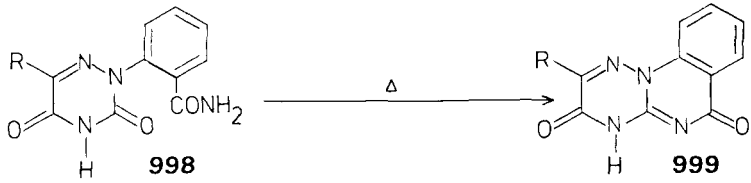
Treatment of 4-hydrazino-6-methylpyrimidin-2-one (**995**) with α-bromo ketones afforded the hydrazones **996**, which were cyclized to give 4*H*-pyrimido[6,1-*c*] 1,2,4-triazin-6-ones (**997**) or their tautomers (**997a**) (R = H, CH_3 C_6H_5) (1526).



XXXII. CONDENSED WITH THE QUINAZOLINE SYSTEM

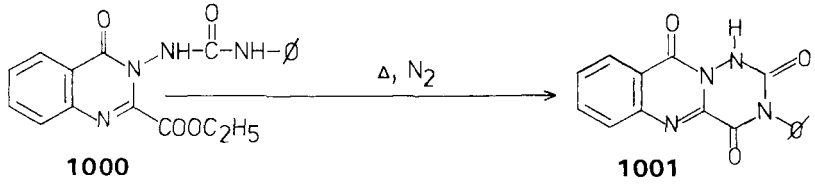
A. 1,2,4-Triazino[2,3-*a*]quinazolines

2-(2-Carbamoylphenyl)-3,5-dioxo-1,2,4-triazine-6-carboxylic acid derivatives (**998**) can be cyclized thermally to yield derivatives of the 3,6-dioxo-1,2,4-triazino[2,3-*a*]quinazoline-2-carboxylic acid (**999**) (892) (R = COOH, m.p. 255 to 257°C (dec.); R = $CONH_2$, 335 to 337°C (dec.); R = CN, 367 to 370°C; R = $C(NH_2)NOH$, 302 to 305°C (dec.); R = 5-methyl-1,2,4-oxdiazolyl-3, 338 to 341°C). **999** are stable to boiling hydrochloric acid.



B. 1,2,4-Triazino[6,1-*b*]quinazolines

2-(Ethoxycarbonyl)-3-(*N*-phenylureido)-4-quinazolone (**1000**) was cyclized by fusion under nitrogen at 245°C to give 3-phenyl-1*H*-1,2,4-triazino[6,1-*b*]-quinazoline-2,4,10-trione (**1001**) (1527). The 3-butyl derivative is also known.

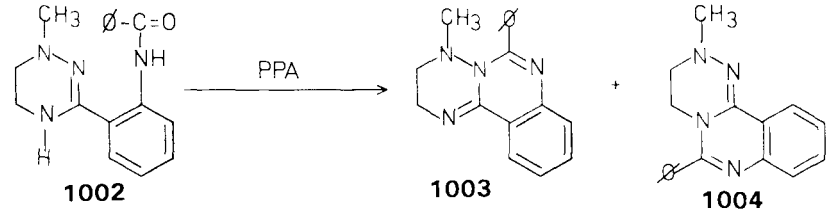


1000 **1001**

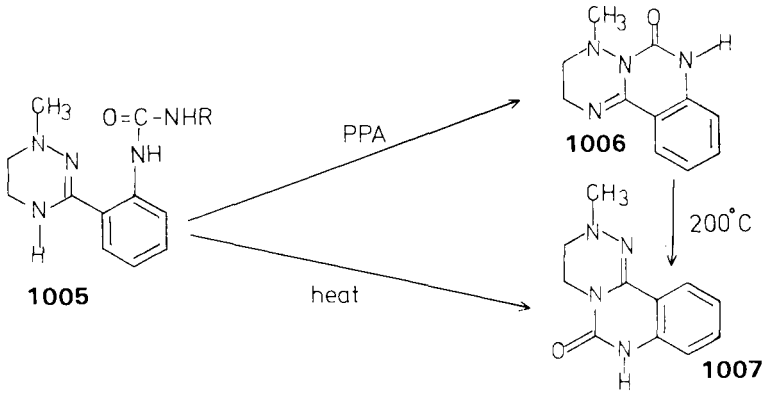
C. 1,2,4-Triazino[2,3-*c*]quinazolines

Polyphosphoric acid-catalyzed cyclodehydration of 3-[2-(benzoylamino)-phenyl]-1-methyl-1,4,5,6-tetrahydro-1,2,4-triazine (**1002**) yielded a mixture of 3,4-dihydro-4-methyl-6-phenyl-2*H*-1,2,4-triazino[2,3-*c*]quinazoline (**1003**) (m.p. 206 to 207°C) and 3,4-dihydro-2-methyl-6-phenyl-2*H*-1,2,4-triazino[4,3-*c*]-

quinazoline (**1004**) (1049). When the ureas (**1005**) (R = H or C_6H_5) were heated in polyphosphoric acid at 100°C they afforded 2,3,4,7-tetrahydro-4-methyl-6*H*-1,2,4-triazino[2,3-*c*]quinazolin-6-one (**1006**) (m.p. 196 to 197°C) whereas the isomeric 2,3,4,7-tetrahydro-2-methyl-6*H*-1,2,4-triazino[4,3-*c*]quinazoline-6-one (**1007**) was isolated when **1005** was heated neat at 200°C (1050). **1007** is the thermodynamically stable isomer as evidenced by the fact that heating **1006** at 200°C in ethylene glycol isomerized it to **1007**.



1002 **1003** **1004**



1005 **1006** **1007**

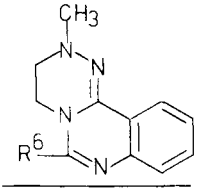
D. 1,2,4-Triazino[4,3-*c*]quinazolines

Reaction of 3-(2-aminophenyl)-1-methyl-1,4,5,6-tetrahydro-1,2,4-triazine (**1008**) with orthocarboxylates yields 3,4-dihydro-2-methyl-2*H*-1,2,4-triazino-[4,3-*c*]quinazolines (**1004**). The same compounds (**1004**) were obtained by interaction of **1008** and acyl chlorides to give the amides (**1002**) which were cyclodehydrated at 170 to 180°C to yield **1004** (1049). Heating of **1002** with polyphosphoric acid yields a mixture of **1004** and **1003**.

Aldehydes and ketones reacted with **1008** to give 3,4,6,7-tetrahydro-2-methyl-2*H*-1,2,4-triazino[4,3-*c*]quinazolines (**1009**). **1009**, obtained from **1008** and aldehydes, can be dehydrogenated with sulfur to yield **1004** (1049). The

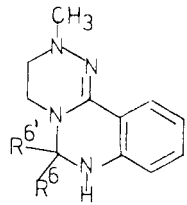
TABLE VI-24. 1,2,4-TRIAZINO[4,3-*c*]QUINAZOLINES (1049)

A. 3,4-Dihydro-2H-1,2,4-triazino[4,3-*c*]quinazolines



R^6	m.p. (°C)
H	55–56
C_6H_5	142–143
4-CH_3–C_6H_4	134–135
2-F–C_6H_4	132–133
4-F–C_6H_4	157–158
3,4-$Cl_2C_6H_3$	184–185
3-Br–C_6H_4	186–187
4-Br–C_6H_4	183–184
3,4,5-$(CH_3O)_3C_6H_2$	186–187
4-NC–C_6H_4	189–190

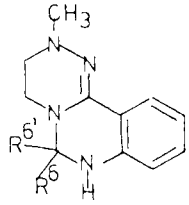
B. 3,4,6,7-Tetrahydro-2H-1,2,4-triazino[4,3-*c*]quinazolines



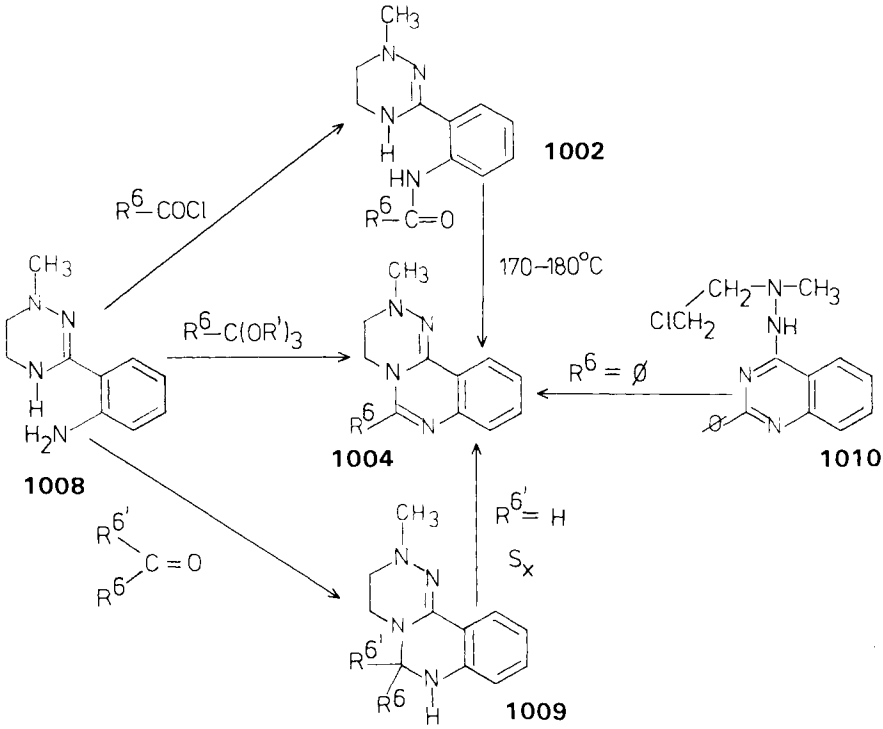
R^6	$R^{6'}$	m.p. (°C)
H	$(CH_3)_2CH$	128–130
H	$CH_3(CH_2)_4$	101–102
H	$CH_3(CH_2)_5$	90–91
H	C_6H_5	204–205
H	4-$(CH_3)_2CH$–C_6H_4	190–191
H	4-F–C_6H_4	224–226
H	3,4-$Cl_2C_6H_3$	189–190
H	4-O_2N–C_6H_4	227–228
H	3,4-$(O_2N)_2C_6H_3$	213–214 (dec.)
H	2-HO–C_6H_4	156–158
H	4-HO–C_6H_4	223–224
H	3,4-$(CH_3O)_2C_6H_3$	172–178
H	3,4,5-$(CH_3O)_3C_6H_2$	189–191
H	4-$(C_2H_5)_2N$–CH_2CH_2O–C_6H_4	151.5–153
H	4-$(CH_3)_2N$–C_6H_4	208–210

TABLE VI-24. (continued)

B. 3,4,6,7-Tetrahydro-2H-1,2,4-triazino[4,3-*c*]quinazolines



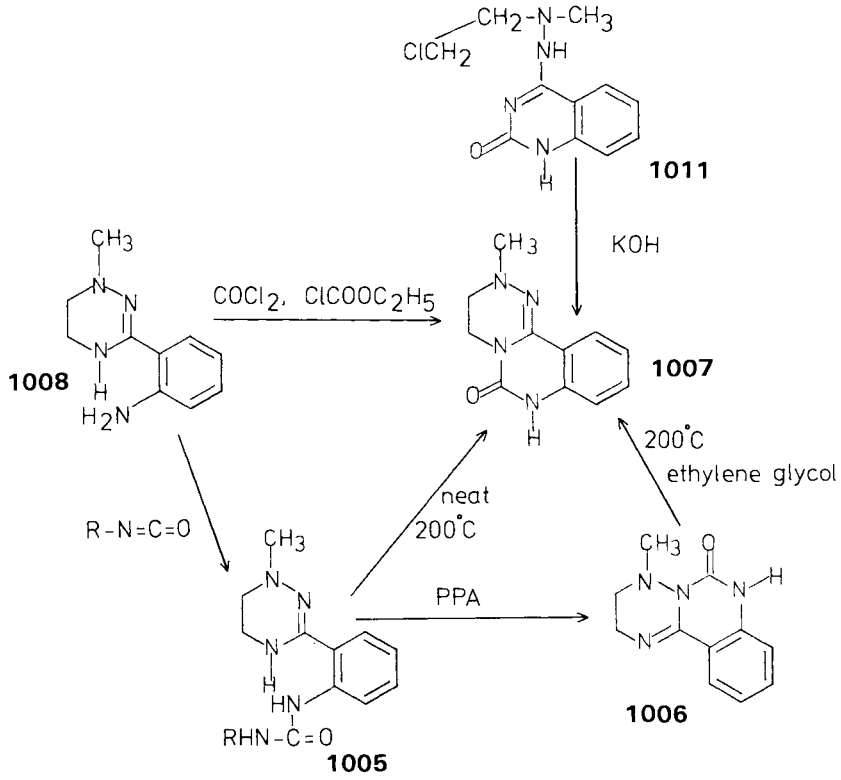
R^6	$R^{6'}$	m.p. (°C)
H	3-CH_3CO–NH–C_6H_4	123–124.5
H	2-Pyridyl	143–145
H	3-Pyridyl	155–156
H	4-Pyridyl	188–189.5
CH_3	C_6H_5	206–208
CH_3	2-Naphthyl	193–194
CH_3	4-F–C_6H_4	198.5–200
CH_3	4-HO–C_6H_4	238–240



structure of **1004** was proved by an unequivocal synthesis of the 6-phenyl derivative (**1004a**) through cyclization of 4-[2-(2-chloroethyl)-2-methylhydrazino]-2-phenylquinazoline hydrochloride (**1010**) with sodium hydroxide (1049).

Condensation of **1008** with phosgene or ethyl chloroformate yielded 2,3,4,7-tetrahydro-2-methyl-1,2,4-triazino[4,3-*c*]quinazolin-6-one (**1007**) (m.p. 201 to 202°C), which was also obtained when **1008** was reacted with isocyanates and the formed ureas (**1005**) were heated at 200°C (1049, 1050). Heating **1005** in polyphosphoric acid afforded **1006** which isomerized to **1007** when heated in ethylene glycol at 200°C. The structure of **1007** was proved by synthesizing it through cyclization of 4-[2-(2-chloroethyl)-2-methylhydrazino]quinazolin-2-one (**1011**) with potassium hydroxide (1049, 1050).

Table VI-24 lists the known 1,2,4-triazino[4,3-*c*]quinazolines.

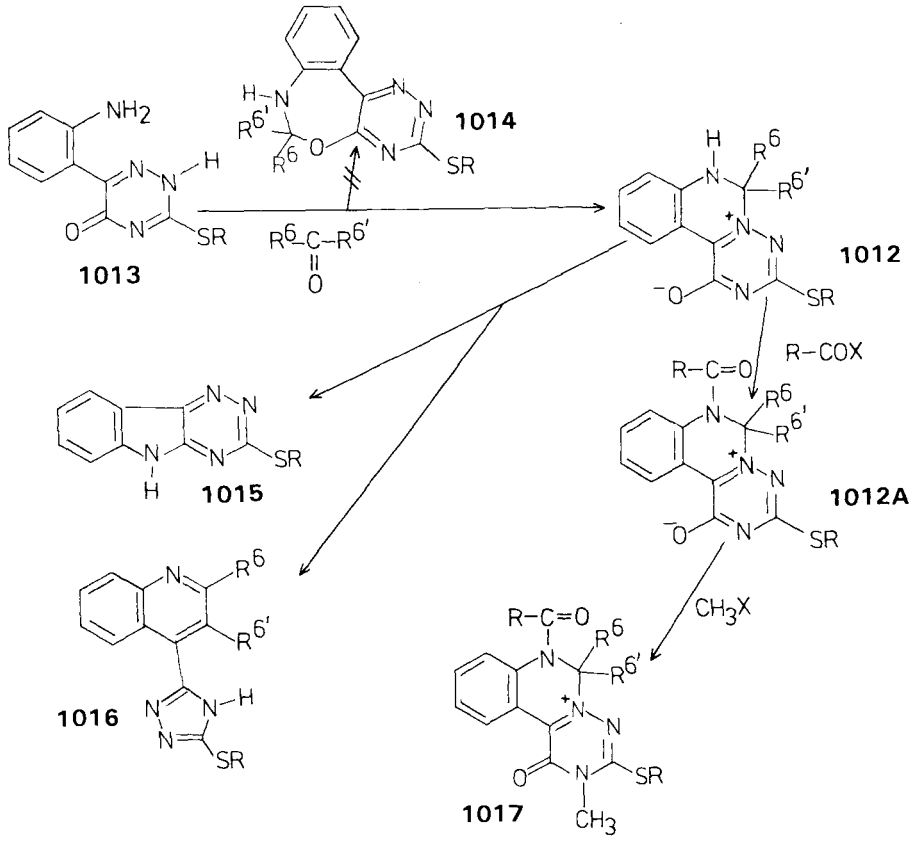


E. 1,2,4-Triazino[1,6-*c*]quinazolines

3-(Alkylmercapto)-6,7-dihydro-1,2,4-triazino[1,6-*c*]quinazolin-5-ium-1-olates (**1012**) were prepared by Doleschall and Lempert (283, 756, 757) by condensa-

tion of 3-(alkylmercapto)-6-(2-aminophenyl)-1,2,4-triazin-5-ones (**1013**) with oxo compounds or the corresponding Schiff bases. The structure of **1012** was determined by X-ray crystallographic analysis. Because of this result the initially assumed structure (**1014**) for the condensation product is known to be incorrect.

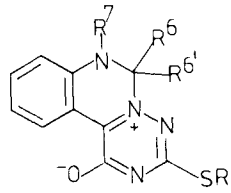
1012 can be acylated at the nitrogen in position 7, affording **1012A**; alkylation of **1012A** proceeds at the nitrogen in position 2, leading to **1017** (282). **1012** were transformed by thermolysis and/or acidic treatment into 3-(alkylmercapto)-1,2,4-triazino[5,6-*b*]indoles (**1015**) and/or 4-(5-alkylmercapto -1,2,4-triazol-3-yl)-quinolines (**1016**) (756).

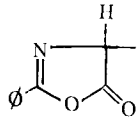


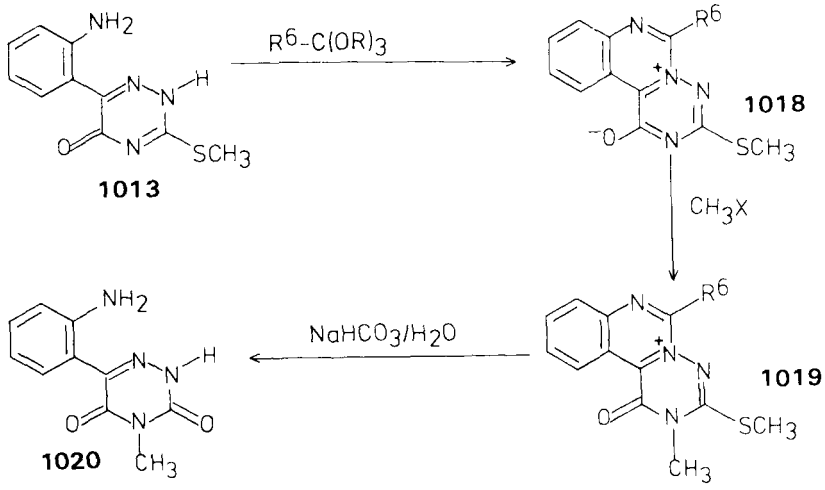
Interaction of **1013** and orthocarboxylates was used for the synthesis of 3-(alkylmercapto)-1,2,4-triazino[1,6-*c*]quinazolin-5-ium-1-olates (**1018**) (R^6 = H, m.p. 211 to 212°C; $R^6 = CH_3$, 243 to 244°C) (757) which were methylated to yield **1019**. Hydrolysis of **1019** with sodium bicarbonate affords 6-(2-aminophenyl)-4-methyl-1,2,4-triazine-3,5-dione (**1020**) (757).

Table VI-25 lists the known compound of this class.

TABLE VI-25. 6,7-DIHYDRO-1,2,4-TRIAZINO[1,6-*c*]QUINAZOLIN-5-IUM-1-OLATES



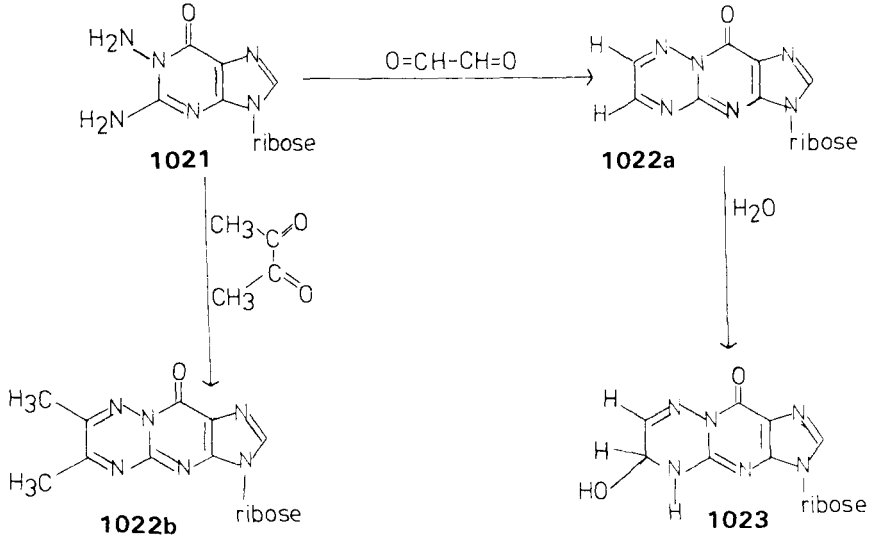
R^6	$R^{6'}$	R	R^7	m.p. (°C)	Refs.
H	H	CH_3	H	238–239 (dec.)	757
H	H	CH_3	CH_3CO	201	757
H	CH_3	CH_3	H	237–238 (dec.)	757
H	CH_3	CH_3	CH_3CO	234	757
H	CH_3	*n*-C_4H_9	H	187–188 (dec.)	757
H	CH_2COOCH_3	CH_3	H	189–192 (dec.)	756
				198–199 (dec.)	757
H	$C_6H_5CO-NH-CH_2$	CH_3	H	256–257 (dec.)	757
H	C_6H_5	CH_3	H	252–253 (dec.)	757
H	4-Cl–C_6H_4	CH_3	H	241–242 (dec.)	757
H	4-Cl–C_6H_4	CH_3	CH_3CO	230–231	757
H	4-O_2N–C_6H_4	CH_3	H	235–236 (dec.)	757
H		CH_3	H	259–260 (dec.)	757
H	OC_2H_5	CH_3	H	213–215	757
CH_3	CH_3	CH_3	H	223–224 (dec.)	757
CH_3	CH_3	CH_3	HCO	232–233 (dec.)	757
CH_3	CH_3	CH_3	CH_3CO	195–196	757
CH_3	CH_3	*n*-C_8H_{17}	H	174–175	757
CH_3	CH_3	$C_6H_5-CH_2$	H	201–205 (dec.)	756
CH_3	C_2H_5	CH_3	H	186–187 (dec.)	757
CH_3	$C_6H_5CH_2$	CH_3	H	176–177 (dec.)	756
CH_3	CH_3COOCH_2	CH_3	H	169–170 (dec.)	757
CH_3	COOH	CH_3	H	182–183 (dec.)	757
CH_3	$COOCH_3$	CH_3	H	209–210 (dec.)	757
CH_3	$CH_2COOC_2H_5$	CH_3	H	159 (dec.)	757
CH_3	$CH_2COOC_2H_5$	$C_6H_5CH_2$	H	124 (dec.)	756
CH_3	$(CH_2)_2-COOH$	CH_3	H	194–195 (dec.)	757
CH_3	$(CH_2)_2-COOC_2H_5$	CH_3	H	165–166 (dec.)	757
CH_2OH	CH_2OH	CH_3	H	217–218 (dec.)	757
CH_3COOCH_2	CH_3COOCH_2	CH_3	H	215–216 (dec.)	757
$-(CH_2)_4-$		CH_3	H	205–206 (dec.)	757
$-(CH_2)_4-$		CH_2CH_2OH	H	140 (dec.)	756
$-(CH_2)_4-$		CH_2COOH	H	175–176 (dec.)	757
$-(CH_2)_5-$		CH_3	H	207–208 (dec.)	757
$-CH(CH_3)-(CH_2)_4-$		CH_3	H	190–192 (dec.)	757



XXXIII. CONDENSED WITH THE IMIDAZO[4,5-*d*]PYRIMIDINE SYSTEM (PURINE SYSTEM)

A. Imidazo[4′,5′:4,5]pyrimido[1,2-*b*]1,2,4-triazines (1,2,4-Triazino[2,3-*a*]purines)

Condensation of 1-aminoguanosine (**1021**) with butane-2,3-dione yielded 6,7-dimethyl-10-oxo-3-(β-ribofuranosyl)-1,2,4-triazino[2,3-*a*]purine (**1022b**) (m.p. 169 to 171°C). Interaction of **1021** and glyoxal gave a compound, the

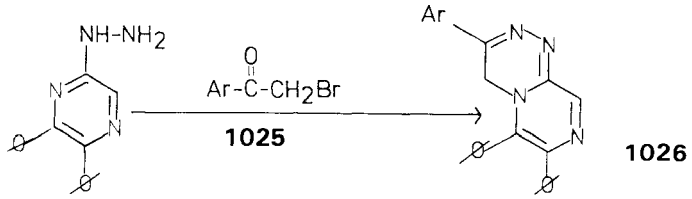


ultraviolet spectrum of which was grossly different from those of **1022b**, and the elemental analysis revealed the presence of water. From these data and the PMR spectrum the isolated product is formulated as the covalent hydrate **1023** (m.p. 180°C) (1528).

XXXIV. CONDENSED WITH THE PYRAZINE RING

A. Pyrazino[2,1-*c*]1,2,4-triazines

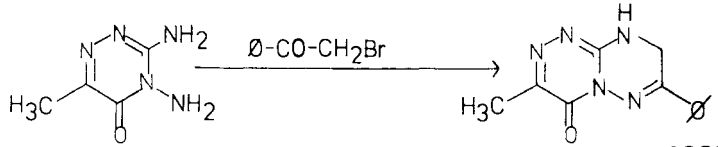
The reaction of 5-hydrazino-2,3-diphenylpyrazine (**1024**) with phenacyl-bromides (**1025**) was used for the synthesis of 4*H*-pyrazino[2,1-*c*] 1,2,4-triazines (**1026**) (1526).



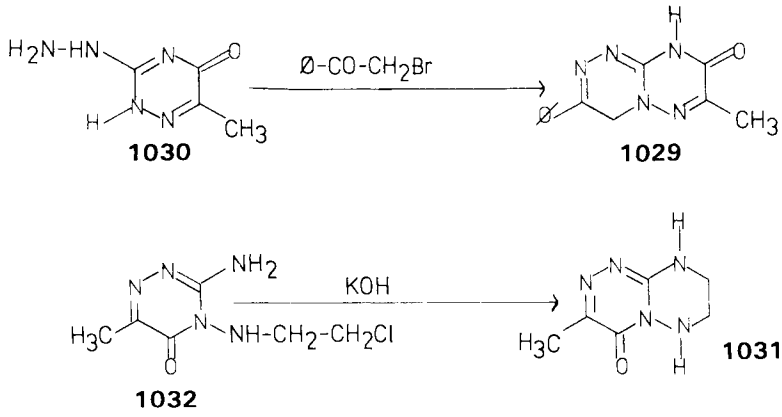
XXXV. CONDENSED WITH THE 1,2,4-TRIAZINE RING

A. 1,2,4-Triazino[4,3-*b*]1,2,4-triazines

The reaction of 3,4-diamino-6-methyl-1,2,4-triazin-5-one (**1027**) with phenacyl bromide yielded 3-methyl-7-phenyl-8,9-dihydro-4*H*-1,2,4-triazino[4,3-*b*]-1,2,4-triazin-4-one (**1028**) (m.p. 290 to 292°C) (938). The isomeric 7-methyl-3-phenyl-8,9-dihydro-4*H*-1,2,4-triazino[4,3-*b*] 1,2,4-triazine-8-one (**1029**) [m.p. 303°C (dec.)] was prepared from 3-hydrazino-6-methyl-1,2,4-triazin-5-one (**1030**) and phenacyl bromide (761). Lempert and his group (709) obtained 6,7,8,9-tetrahydro-3-methyl-4*H*-1,2,4-triazino[4,3-*b*] 1,2,4-triazin-4-one (**1031**)

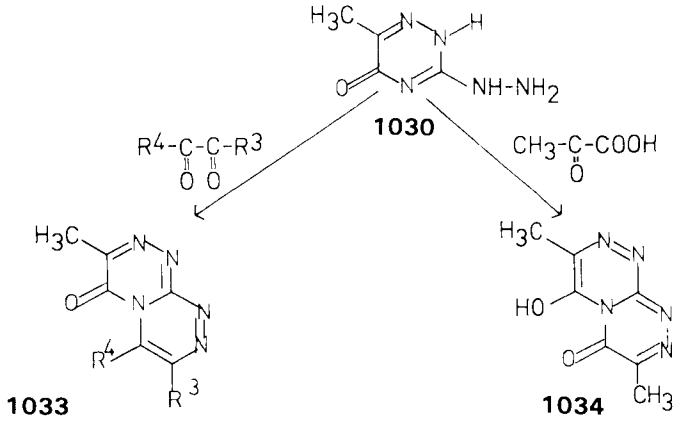


(m.p. 299 to 300°C) when they treated 3-amino-4-[(2-chloroethyl)amino]-6-methyl-1,2,4-triazin-5-one (**1032**) with potassium hydroxide.



B. 1,2,4-Triazino[3,4-*c*]1,2,4-triazines

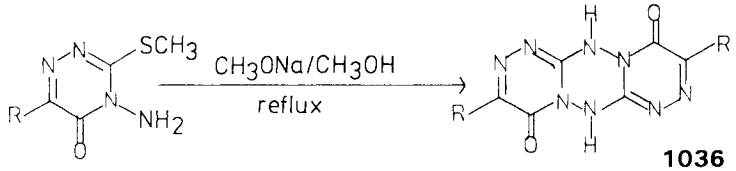
Hadacek (770) condensed 3-hydrazino-6-methyl-1,2,4-triazin-5-one (**1030**) with butane-2,3-dione, pentane-2,3-dione, and pyruvic acid. The isolated compounds were formulated as 3,4,7-trimethyl-1,2,4-triazino[3,4-*c*]1,2,4-triazin-6-one (**1033a**) (m.p. 215 to 216°C), 3,7-dimethyl-4-ethyl- (**1033b**), or 4,7-dimethyl-3-ethyl-1,2,4-triazino[3,4-*c*]1,2,4-triazin-6-one (**1033c**) (m.p. 173°C) and 3,7-dimethyl-6-hydroxy-1,2,4-triazino[3,4-*c*]1,2,4-triazin-4-one (**1034**) or one of its tautomers (RRI 10028).



XXXVI. CONDENSED WITH THE 1,2,4,5-TETRAZINE RING

A. Bis-1,2,4-triazino[4,3-*b*:4′,3′-*e*]1,2,4,5-tetrazines

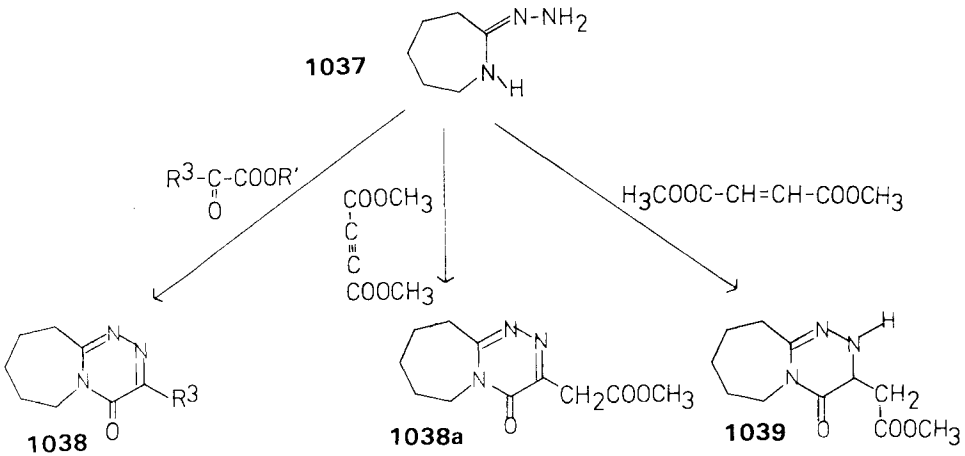
Heating 4-amino-3-(methylmercapto)-1,2,4-triazin-5-ones (**1035**) under reflux in methanol in the presence of sodium methoxide afforded 4,10-dioxo-4,6,10,12-tetrahydrobis-1,2,4-triazino[4,3-*b*:4′,3′-*e*]1,2,4,5-tetrazines (**1036**) (R = CH_3, charred from 350°C; R = C_6H_5, charred from 350°C) (1078).



XXXVII. CONDENSED WITH THE AZEPINE RING

A. 1,2,4-Triazino[4,3-*a*]azepines

The starting material for the synthesis of all known derivatives of the 1,2,4-triazino[4,3-*a*]azepine system is the cyclic amidrazone **1037** (181, 1390,

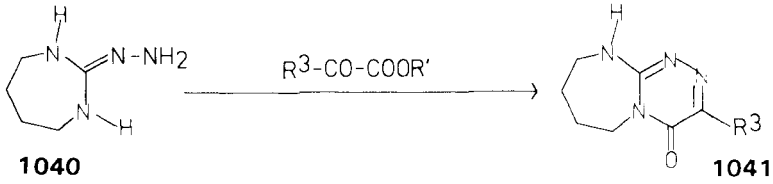


1435, 1481, 1529). Interaction of **1037** with α-oxocarboxylates yields 7,8,9,10-tetrahydro-6*H*-1,2,4-triazino[4,3-*a*]azepin-4-ones (**1038**) [R^3 = H, 98 to 100°C (1529); $R^3 = CH_3$, 80°C (1481), 80 to 81°C (1435), hydrochloride 204°C, subl.(181); $R^3 = C_6H_5$, 137°C (181)]; reaction of **1037** with dimethyl acetylenedicarboxylate or dimethyl maleate afforded 3-[(methoxycarbonyl)methyl]-7,8,9,10-tetrahydro-6*H*-1,2,4-triazino[4,3-*a*]azepin-4-one (**1038a**) (m.p. 127 to 130°C) and 3-[(methoxycarbonyl)methyl]-2,3,7,8,9,10-hexahydro-6*H*-1,2,4-triazino[4,3-*a*]azepin-4-one (**1039**) (m.p. 113°C) (1390), respectively.

XXXVIII. CONDENSED WITH THE 1,3-DIAZEPINE RING

A. 1,2,4-Triazino[4,3-*a*]1,3-diazepines

Condensation of the cyclic aminoguanidine (**1040**) with α-oxocarboxylates was used for the synthesis of 7,8,9,10-tetrahydro-6*H*-1,2,4-triazino[4,3-*a*]1,3-diazepin-4-ones (**1041**) [$R^3 = CH_3$, 218°C (1436), 228°C (1435); $R^3 = C_6H_5$, 224°C (1435, 1436)].



1040 **1041**

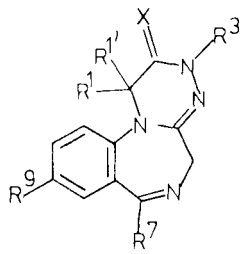
XXXIX. CONDENSED WITH THE BENZO[*f*]1,4-DIAZEPINE SYSTEM

A. 1,2,4-Triazino[4,3-*a*]1,4-benzodiazepines

The reaction of the benzodiazepinethiones (**1042**) with hydrazines yields 3,5-dihydro-1,2,4-triazino[4,3-*a*]1,4-benzodiazepin-2-ones (**1043**) which can be oxidized with 3-chloroperbenzoic acid to give the 6-oxides (**1044**) or transformed into the 3,5-dihydro-1,2,4-triazino[4,3-*a*]1,4-benzodiazepine-2-thiones (**1045**) on treatment with phosphorus pentasulfide (1530).

Table VI-26 lists the known 1,2,4-triazino[4,3-*a*]1,4-benzodiazepines and their 6-oxides.

TABLE VI-26. 1,2,4-TRIAZINO[4,3-*a*]1,4-BENZODIAZEPINES and their 6-OXIDES



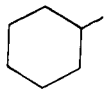
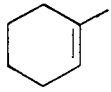
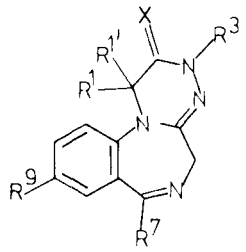
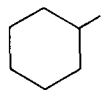
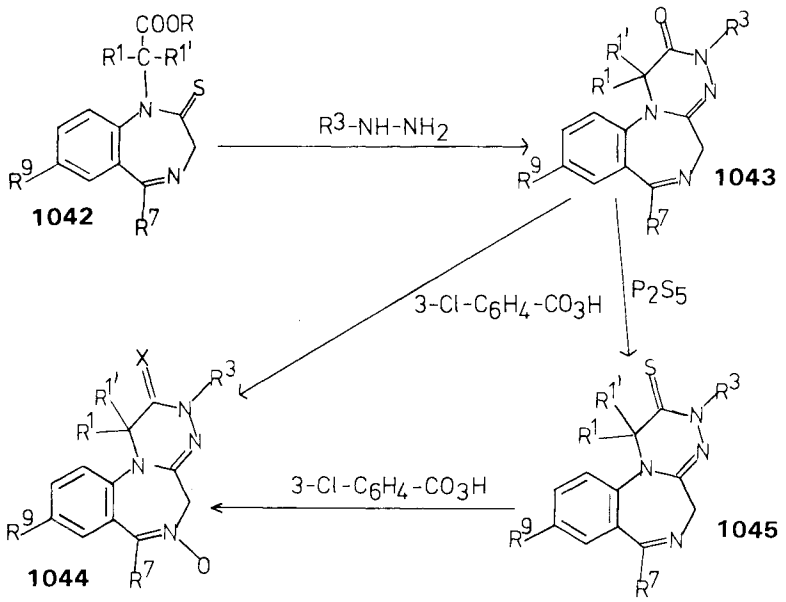
R^1	R^1	X	R^3	R^7	R^9	m.p. (°C)
H	H	O	H	C_6H_5	F	
H	H	O	H	C_6H_5	Cl	267–270
	6-Oxide					
H	H	O	H	C_6H_5	Br	
H	H	O	H	C_6H_5	CF_3	
H	H	O	H	C_6H_5	NO_2	
H	H	O	H	C_6H_5	CN	
H	H	O	H	C_6H_5	CH_3S	
H	H	O	H	2-F–C_6H_4	F	
H	H	O	H	2-F–C_6H_4	Cl	
H	H	O	H	2-F–C_6H_4	Br	
H	H	O	H	2-F–C_6H_4	CF_3	
H	H	O	H	2-F–C_6H_4	NO_2	
H	H	O	H	2-F–C_6H_4	CN	
H	H	O	H	2-F–C_6H_4	CH_3S	
H	H	O	H	2-Cl–C_6H_4	H	195–196.5
	6-Oxide					
H	H	O	H	2-Cl–C_6H_4	F	
H	H	O	H	2-Cl–C_6H_4	Cl	232–233
	6-Oxide					
H	H	O	H	2-Cl–C_6H_4	Br	
H	H	O	H	2-Cl–C_6H_4	CF_3	
H	H	O	H	2-Cl–C_6H_4	NO_2	
H	H	O	H	2-Cl–C_6H_4	CN	
H	H	O	H	2-Cl–C_6H_4	CH_3S	
H	H	O	H		CF_3	
H	H	O	H		CN	

TABLE VI-26. (continued)



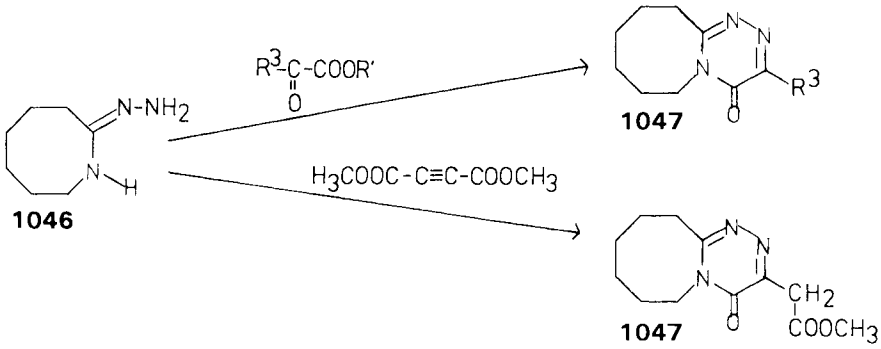
R^1	R^1	X	R^3	R^7	R^9	m.p. (°C)
H	H	O	H	2-Furyl	Br	
H	H	O	H	2-Pyrrolyl	F	
H	H	O	H	2-Thienyl	NO_2	
H	H	O	H	2-Pyrimidinyl	Cl	
H	H 6-Oxide	O	CH_3	C_6H_5	Cl	175–176
H	H 6-Oxide	O	CH_3	2-Cl–C_6H_4	H	Oil
H	H 6-Oxide	O	CH_3	2-Cl–C_6H_4	CH_3	170–171
H	H	O	C_3H_7	C_6H_5	CF_3	
H	CH_3	O	C_2H_5	2,6-$F_2C_6H_3$	Cl	
H	C_3H_7	O	C_2H_5	2-Pyridyl	Br	
H	*i*-C_3H_7	O	C_3H_7		Cl	
H	CH_3	O	*i*-C_3H_7	C_6H_5	Cl	
H	C_2H_5	O	CH_3	2-Cl–C_6H_4	Cl	
H	H 6-Oxide	S	H	C_6H_5	Cl	
H	H 6-Oxide	S	H	2-Cl–C_6H_4	H	
H	H 6-Oxide	S	H	2-Cl–C_6H_4	Cl	
H	H 6-Oxide	S	CH_3	C_6H_5	Cl	
H	H 6-Oxide	S	CH_3	2-Cl–C_6H_4	H	
H	H 6-Oxide	S	CH_3	2-Cl–C_6H_4	Cl	



XL. CONDENSED WITH THE AZOCINE RING

A. 1,2,4-Triazino[4,3-*a*]azocines

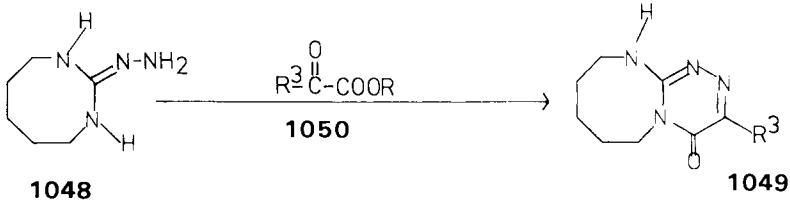
Interaction of the cyclic amidrazone (**1046**) with α-ketocarboxylates or dimethyl acetylenedicarboxylate gives the three 6,7,8,9,10,11-hexahydro-4*H*-1,2,4-triazino[4,3-*a*]azocin-4-ones (**1047**) [$R^3 = CH_3$, m.p. 102 to 103°C; $R^3 = C_6H_5$, 115°C (181); $R^3 = CH_2COOCH_3$, 134 to 137°C (1390)].



XLI. CONDENSED WITH THE 1,3-DIAZOCINE RING

A. 1,2,4-Triazino[4,3-*a*]1,3-diazocines

Condensation of the cyclic aminoguanidine **1048** with α-ketocarboxylates (**1050**) was used for the synthesis of the two known 6,7,8,9,10,11-hexahydro-4*H*-1,2,4-triazino[4,3-*a*]diazocin-4-ones (**1049**) ($R^3 = CH_3$, m.p. 203°C; $R^3 = C_6H_5$, 207°C) (1436).

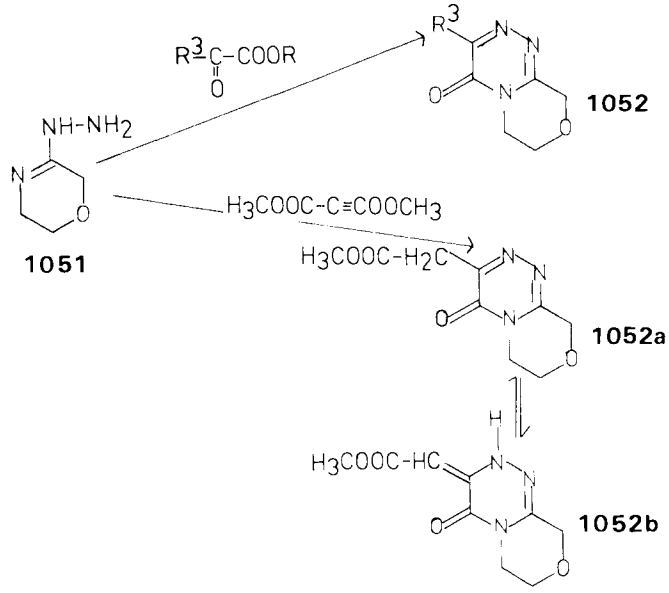


1048 **1049**

XLII. CONDENSED WITH THE 1,4-OXAZINE RING

A. 1,4-Oxazino[3,4-*c*]1,2,4-triazines

Interaction of 3-hydrazino-5,6-dihydro-2*H*-1,4-oxazine (**1051**) and α-keto-carboxylates or dimethyl acetylenedicarboxylate yields 6,7-dihydro-1,4-



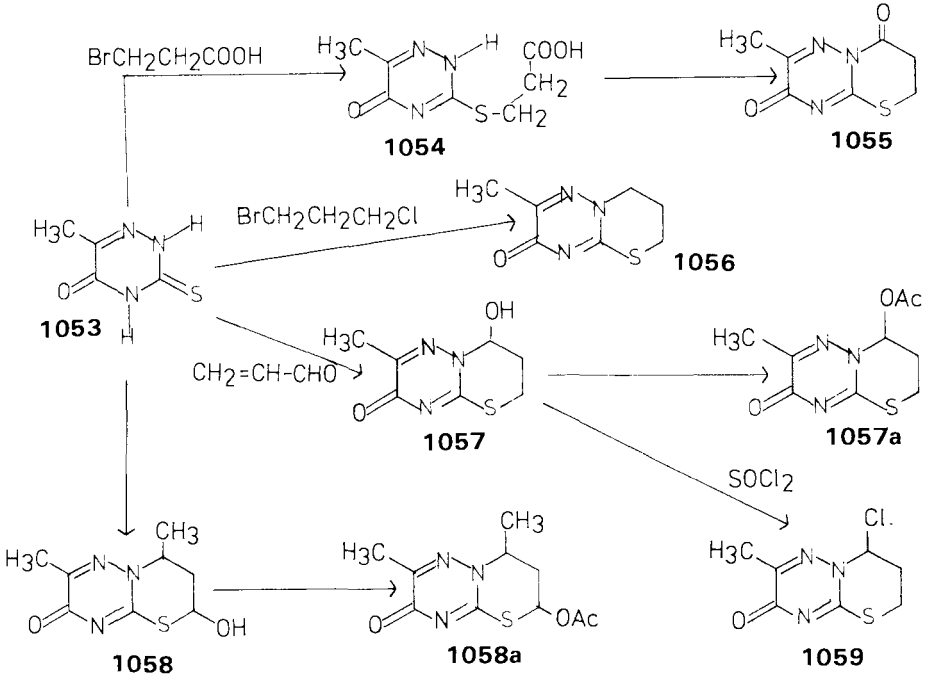
1051

oxazino[3,4-*c*]1,2,4-triazin-4(9*H*)-ones (**1052**) (181, 1390) ($R^3 = CH_3$, 116°C; $R^3 = C_6H_5$, 158°C; $R^3 = CH_2COOCH_3$, 120 to 123°C). Infrared, ultraviolet, and PMR spectroscopic study have shown that both tautomeric forms **1052a** and **1052b** exist the ratio of **a** to **b** depending on the polarity of the solvent. In the solid state the enamine, form **b**, predominates (1390).

XLIII. CONDENSED WITH THE 1,3-THIAZINE RING

A. 1,3-Thiazino[3,2-*b*]1,2,4-triazines

Reaction of 6-methyl-3-thioxo-1,2,4-triazin-5-one (**1053**) with β-bromopropionic acid yields **1054** which can be cyclized by heating in acetic anhydride and pyridine to give 2-methyl-6,7-dihydro-3H,8H-1,3-thiazino[3,2-*b*]1,2,4-triazine-3,8-dione (**1055**) (m.p. 155 to 156°C) (753). Condensation of **1053** with 1-bromo-3-chloropropane afforded 2-methyl-7,8-dihydro-3H,6H-1,3-thiazino[3,2-*b*]1,2,4-triazin-3-one (**1056**) (m.p. 182°C) (789, 781), whereas 7,8-dihydro-8-hydroxy-2-methyl-3H,6H-1,3-thiazino[3,2-*b*]1,2,4-triazin-3-one (**1057**) [m.p. 176 to 178°C (dec.), m.p. hydrochloride, 125 to 127°C (dec.)] and 7,8-dihydro-6-hydroxy-2,8-



dimethyl-3H,6H-1,3-thiazino[3,2-*b*]1,2,4-triazin-3-one (**1058**) (m.p. 152 to 154°C) were obtained from the reaction of **1053** with acrolein and crotonaldehyde (780), respectively. The hydroxy group in both compounds can be acetylated to give **1057a** (m.p. 189 to 191°C) and **1058a** (m.p. 200 to 202°C). The hydroxy group in **1057** is replaced by chlorine (**1059**) [m.p. 182 to 184°C (dec.)] when **1057** is treated with thionyl chloride (780).

XLIV. CONDENSED WITH THE 1,3,4-THIADIAZINE RING

A. 1,2,4-Triazino[3,4-*b*]1,3,4-thiadiazines

Reaction of 4-amino-3-thioxo-1,2,4-triazin-5-ones (**1060**) with α-halocarbonyl compounds afforded 4*H*,8*H*-1,2,4-triazino[3,4-*b*]1,3,4-thiadiazin-4-ones (**1061**) or 6,7-dihydro-4*H*,8*H*-1,2,4-triazino[3,4-*b*]1,3,4-thiadiazin-4-ones (**1062**) (R^3 = CH_3, R^7 = $CH_2COOC_2H_5$, R^8 = H, 147 to 148°C; R^3 = CH_3, R^7 = R^8 = H, hydrochloride 166 to 167°C) (935), whereas interaction of **1060** (R^3 = CH_3) and ethyl chloroacetate yields 3-methyl-4*H*,8*H*-1,2,4-triazino[3,4-*b*]1,3,4-thiadiazine-4,7-dione (**1063**) (m.p. 212 to 213°C), which is methylated by diazomethane to give 3,6-dimethyl-4*H*,8*H*-1,2,4-triazino[3,4-*b*]1,3,4-thiadiazine-4,7-dione (**1063a**) (m.p. 217 to 218°C) (935).

Table VI-27 lists the compounds of this group reported in the literature.

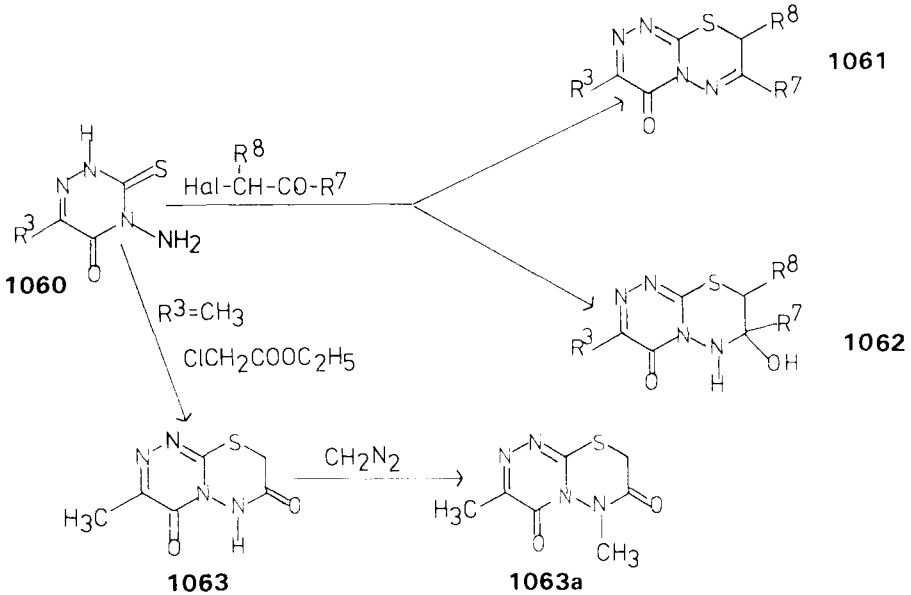


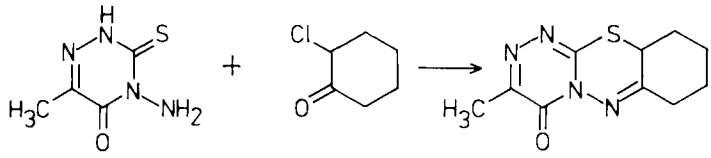
TABLE VI-27. 4*H*, 8*H*-1,2,4-TRIAZINO[3,4-*b*]1,3,4-THIADIAZIN-4-ONES (935)

1061				
R^3	R^7	R^8		m.p. (°C)
CH_3	CH_3	H		170–171
CH_3	CH_3	$CH_2CH_2OCOCH_3$		152–153
·HCl				186–187
CH_3	$CH_2COOC_2H_5$	H	·HBr	209
CH_3	$-(CH_2)_4-$			166–168
·HBr				268
CH_2CH_2OH	CH_3	H		178
$(CH_2)_3OH$	CH_3	H		154

XLV. CONDENSED WITH THE 4,1,2-BENZOTHIADIAZINE SYSTEM

A. 1,2,4-Triazino[4,3-*b*]4,1,2-benzothiadiazines

Interaction of 4-amino-6-methyl-3-thioxo-1,2,4-triazin-5-one (**1060a**) with 2-chlorocyclohexanone affords 8,9,10,10a-tetrahydro-3-methyl-4*H*,7*H*-1,2,4-triazino[4,3-*b*]4,1,2-benzothiadiazin-4-one (**1061a**) (m.p. 166 to 169°C; HBr 268°C) (935). Both compounds are included in Table VI-27.



1060a **1061a**

Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

VII

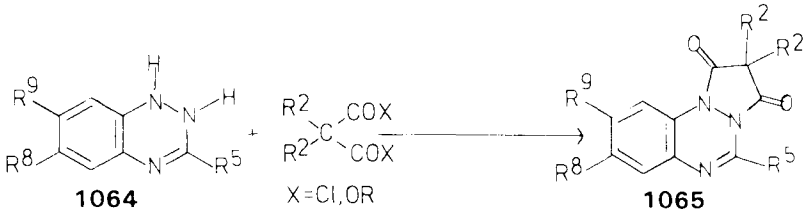
1,2,4-Triazine Rings Condensed with Heterocycles through Two Nitrogen Atoms

I. PYRAZOLO[1,2-*a*]1,2,4-BENZOTRIAZINES

Condensation of 1,2-dihydro-1,2,4-benzotriazines (**1064**) with malonates or malonyl chlorides affords 1*H*-pyrazolo[1,2-*a*]1,2,4-benzotriazine-1,3-diones (**1065**) (1173, 1174, 1197, 1198, 1531, 1532).

To study the chemistry of this class of condensed 1,2,4-triazines, the 9-methyl-5-(dimethylamino)-2-propyl-1*H*-pyrazolo[1,2-*a*]1,2,4-benzotriazine-1,3-dione (**1065a**), called azapropazone, was used. Reduction of **1065a** with lithium aluminum hydride affords one of the two isomers **1066** [m.p. 210 to 211°C (dec.)]; the 5-dimethylamino group is replaced by the hydroxy group when **1065a** is heated with acetic acid for 2 hr. The formed 5-hydroxy derivative (**1067**) gives the 5-chloro derivative (**1068**) when treated with phosphoryl chloride. Interaction of **1065a** with ammonia or hydrazine yields the 5-amino (**1069a**) and the 5-hydrazino derivative (**1069b**). Treatment of **1065a** with formic acid and acetic anhydride affords the 5*H*-derivative (**1070**) and reaction of **1065a** with acetic acid/acetic anhydride yields the 5-acetoxy derivative (**1071**).

The proton in position 2 can be substituted by a methyl group (**1072**) when **1065a** is reacted with methyl iodide in alkaline media. Prolonged reaction of



1064 **1065**

1065a with formic acid, acetic acid, or hydrogen peroxide in acetic acid or aqueous sodium hydroxide solution led to the opening of the pyrazole ring. The 6-hydroxy derivative (**1073**) was isolated as a metabolite of azapropazone.

Table VII-1 lists the known compounds of this group.

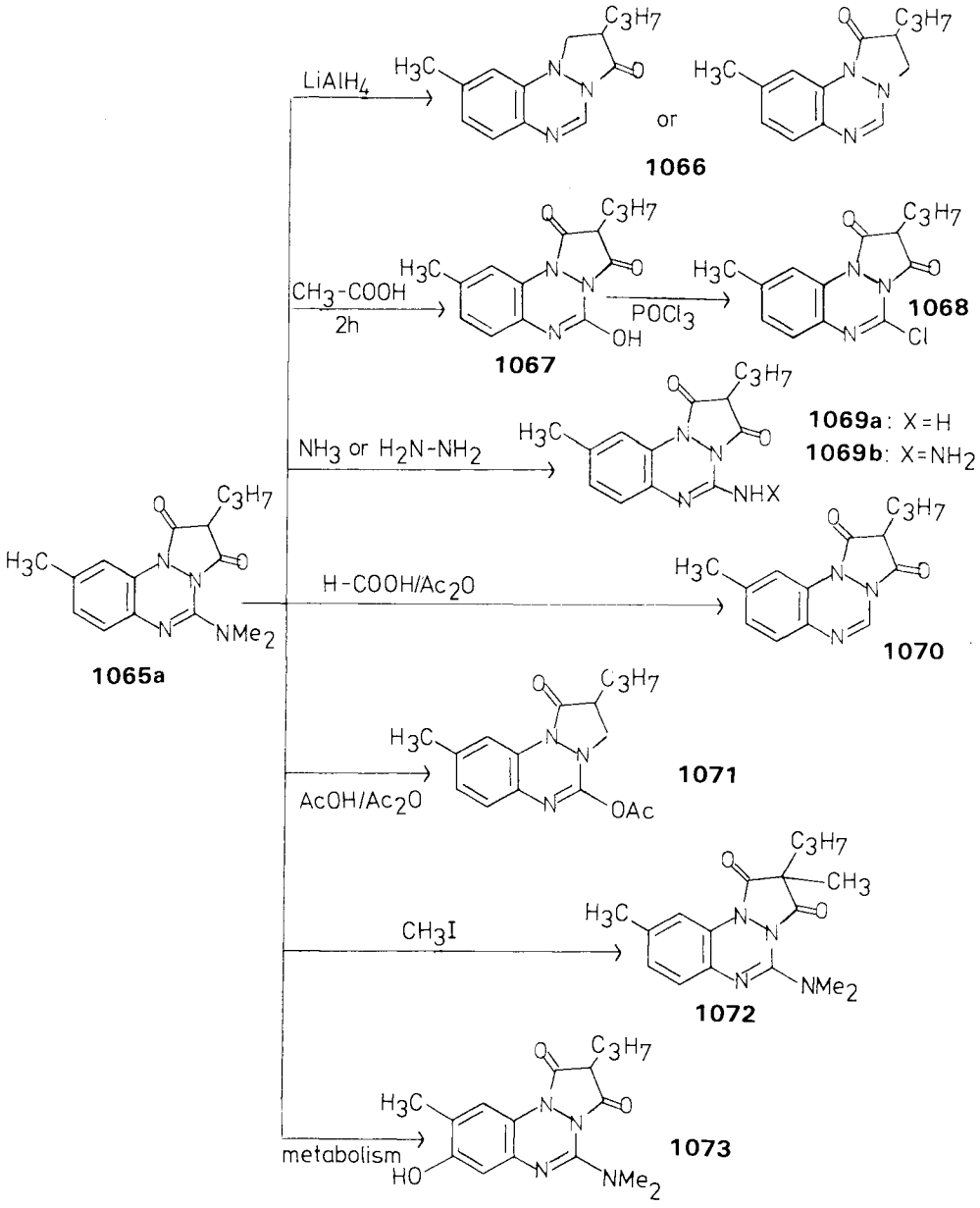
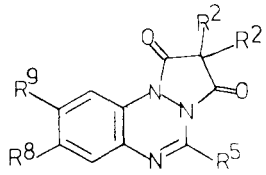


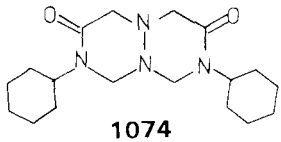
TABLE VII-1. 1*H*-PYRAZOLO[1,2-*a*]1,2,4-BENZOTRIAZINE-1,3-DIONES



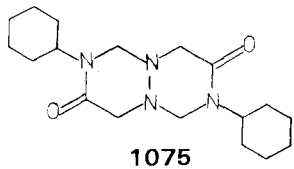
R^2	R^2	R^5	R^8	R^9	m.p. (°C)	Refs.
H	C_3H_7	H	H	CH_3	262–264	1174
H	C_3H_7	OH	H	CH_3	242–244	1174
H	C_3H_7	CH_3COO	H	CH_3	275–277	1174
H	C_3H_7	Cl	H	CH_3	215–217	1174
H	C_3H_7	NH_2	H	CH_3	295 (dec.)	1174
H	C_3H_7	$NHNH_2$	H	CH_3	209–211 (dec.)	1174
H	C_3H_7	$N(CH_3)_2$	H	H	207	1198
H	C_3H_7	$N(CH_3)_2$	H	CH_3	215	1198
	$\cdot 2H_2O$				247–248 (dec.)	1531, 1532
H	C_3H_7	$N(CH_3)_2$	H	CF_3		1197
H	C_3H_7	$N(CH_3)_2$	H	F		1197
H	C_3H_7	$N(CH_3)_2$	OH	CH_3	242–245	1173
H	C_3H_7	$N(CH_3)_2$	C_6H_5COO	CH_3	189–191	1173
H	C_3H_7	$N(CH_3)_2$	Cl	H	195	1198
H	*i*-C_3H_7	$N(CH_3)_2$	H	CF_3		1197
H	C_4H_9	OC_2H_5	H	Cl	105	1198
H	C_4H_9	$N(CH_3)_2$	H	H	187	1198
H	C_4H_9	$N(CH_3)_2$	H	CH_3	212–213	1198
H	C_4H_9	$N(CH_3)_2$	H	CF_3		1197
H	C_4H_9	$N(CH_3)_2$	H	OCH_3	207	1198
H	C_4H_9	$N(CH_3)_2$	H	Cl	107	1198
					203–205	1198
H	C_4H_9	$N(CH_3)_2$	CH_3	CH_3	216	1198
H	C_4H_9	$N(CH_3)_2$	OCH_3	Cl	206	1198
H	C_4H_9	$N(CH_3)_2$	Cl	H	202–203	1198
H	C_4H_9	$N(CH_3)_2$	$N(CH_3)_2$	Cl	117–118	1198
H	*i*-C_4H_9	$N(CH_3)_2$	H	CF_3		1197
H	C_5H_{11}	$N(CH_3)_2$	H	H	188	1198
H	C_5H_{11}	$N(CH_3)_2$	Cl	H	200	1198
H	Cyclopentyl	$N(CH_3)_2$	Cl	H	191	1198
CH_3	C_3H_7	$N(CH_3)_2$	H	CH_3	94.5–95.5	1174

II. 1,2,4-TRIAZINO[1,2-*a*]1,2,4-TRIAZINES AND 1,2,4-TRIAZINO[2,1-*a*]1,2,4-TRIAZINES

The reaction of hydrazine, 4 moles of formaldehyde, and cyclohexylisocyanide afforded a compound of m.p. 275 to 276°C (dec.), which is formulated as either 2,8-dicyclohexyl-1,4,6,9-tetrahydro-1,2,4-triazino[1,2-*a*]1,2,4-triazine-3,7-dione (**1074**) or 2,7-dicyclohexyl-1,4,6,9-tetrahydro-1,2,4-triazino-[2,1-*a*]1,2,4-triazine-3,8-dione (**1075**) (1533).



1074



1075

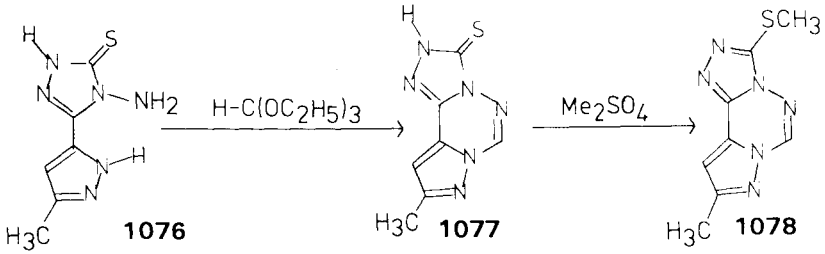
Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

VIII

1,2,4-Triazine Rings Condensed with Two Heterocycles

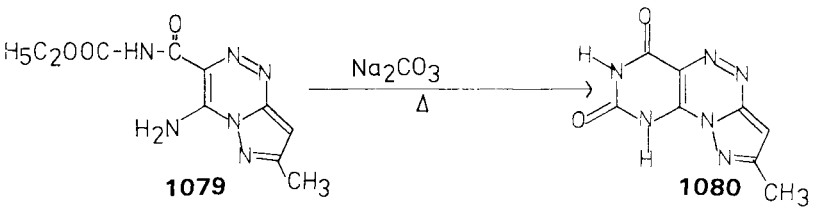
I. PYRAZOLO[1,5-*d*]1,2,4-TRIAZOLO[3,4-*f*]1,2,4-TRIAZINES

Cyclization of 5-methyl-3-(3-thioxo-4-amino-1,2,4-triazol-5-yl)pyrazole (**1076**) with triethyl orthoformate yields 9-methylpyrazolo[1,5-*d*]1,2,4-triazolo[3,4-*f*]1,2,4-triazine-3-thione (**1077**) (m.p. 318°C), which is methylated by dimethyl sulfate to give 3-(methylmercapto)-9-methylpyrazolo[1,5-*d*]1,2,4-triazolo[3,4-*f*]1,2,4-triazine (**1078**) (m.p. 214°C) (1398).



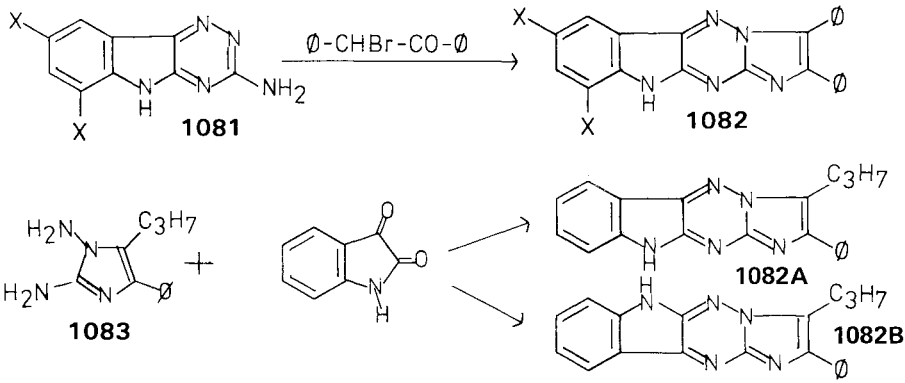
II. PYRAZOLO[5,1-*c*]PYRIMIDO[4,5-*e*]1,2,4-TRIAZINES

Heating ethyl 4-amino-7-methylpyrazolo[5,1-*c*]1,2,4-triazine-3-carbonylcarbaminate (**1079**) with sodium carbonate in water affords the light yellow 8-methylpyrazolo[5,1-*c*]pyrimido[4,5-*e*]1,2,4-triazine-2,4-dione (**1080**) (m.p. > 360°C) (893).

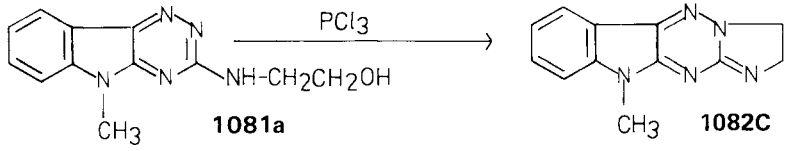


III. IMIDAZO[1′,2′:2,3]1,2,4-TRIAZINO[5,6-*b*]INDOLES AND IMIDAZO[1′,2′:2,3]1,2,4-TRIAZINO[6,5-*b*]INDOLES

Rossi and Trave (619) cyclized the two 3-amino-1,2,4-triazino[5,6-*b*]-indoles (**1081**) (X = H or Br) with desyl bromide and isolated 2,3-diphenyl (**1082a**) (X = H, m.p. 364°C) and 2,3-diphenyl-7,9-dibromo-10*H*-imidazo[1′,2′:2,3]1,2,4-triazino[5,6-*b*]indole (**1028b**) (X = Br, m.p. 345 to 346°C) (RRI 8795). Condensation of 1,2-diamino-4-phenyl-5-*n*-propylimidazole (**1083**) with isatin by heating together in benzene for 2 hr yields a homogeneous substance (m.p. 288 to 290°C) which is either 2-phenyl-3-*n*-propyl-10*H*-imidazo[1′,2′:2,3]1,2,4-triazino[5,6-*b*]indole (**1082A**) or 2-phenyl-3-*n*-propyl-6*H*-imidazo[1′,2′:2,3]1,2,4-triazino[6,5-*b*]indole (**1082B**) (1534).



Treatment of 3-[(2-hydroxyethyl)amino]-5-methyl-1,2,4-triazino[5,6-*b*]-indole (**1081a**) with phosphorus chloride yields 10-methyl-2,3-dihydroimidazo-[1′,2′:2,3]1,2,4-triazino[5,6-*b*]indole (**1082C**) (1309).

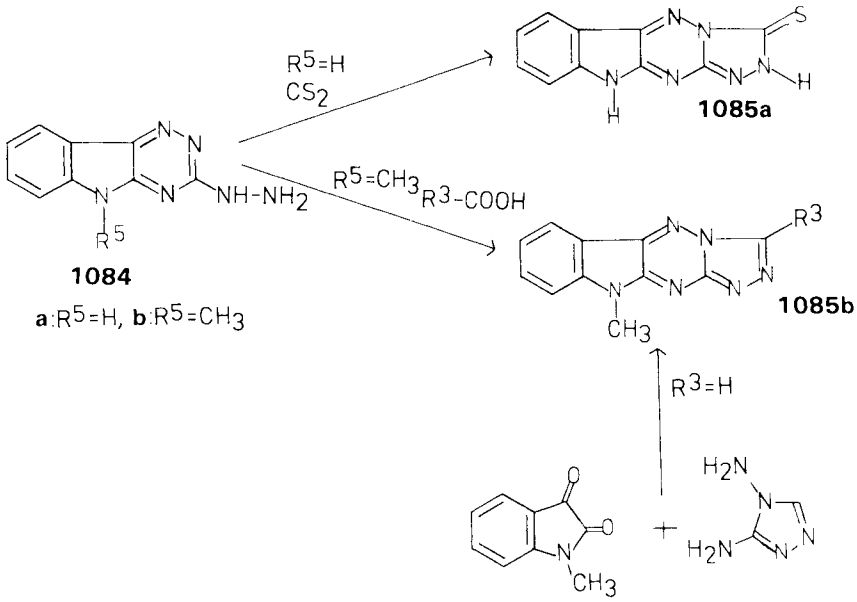


IV. 1,2,4-TRIAZOLO[4′,3′:2,3]1,2,4-TRIAZINO[5,6-*b*]INDOLES

Interaction of 3-hydrazino-5*H*-1,2,4-triazolo[5,6-*b*]indole (**1084a**) and carbon disulfide affords 10*H*-1,2,4-triazolo[4′,3′:2,3]1,2,4-triazino[5,6-*b*]-indole-3-thione (**1085a**) (m.p. 320°C) (1314).

Cyclization of 3-hydrazino-5-methyl-1,2,4-triazino[5,6-*b*]indole (**1085b**) with carboxylic acids yields 10-methyl-1,2,4-triazolo[4′,3′:2,3]1,2,4-triazino-[5,6-*b*]indoles (**1085b**) (R = H, m.p. 308 to 309°C; ·HCl 299.5 to 300°C; R = CH_3, m.p. 331 to 332°C; R = C_6H_5, m.p. 336 to 337°C; R = 4-Cl-C_6H_4, m.p. 347 to 348°C; R = OH, 336°C) (1309).

Condensation of *N*-methylisatin and 3,4-diamino-1,2,4-triazole was used for the synthesis of 10-methyl-1,2,4-triazolo[4′,3′:2,3]1,2,4-triazino[5,6-*b*]indole (**1085b**) (R^3 = H) (1309).

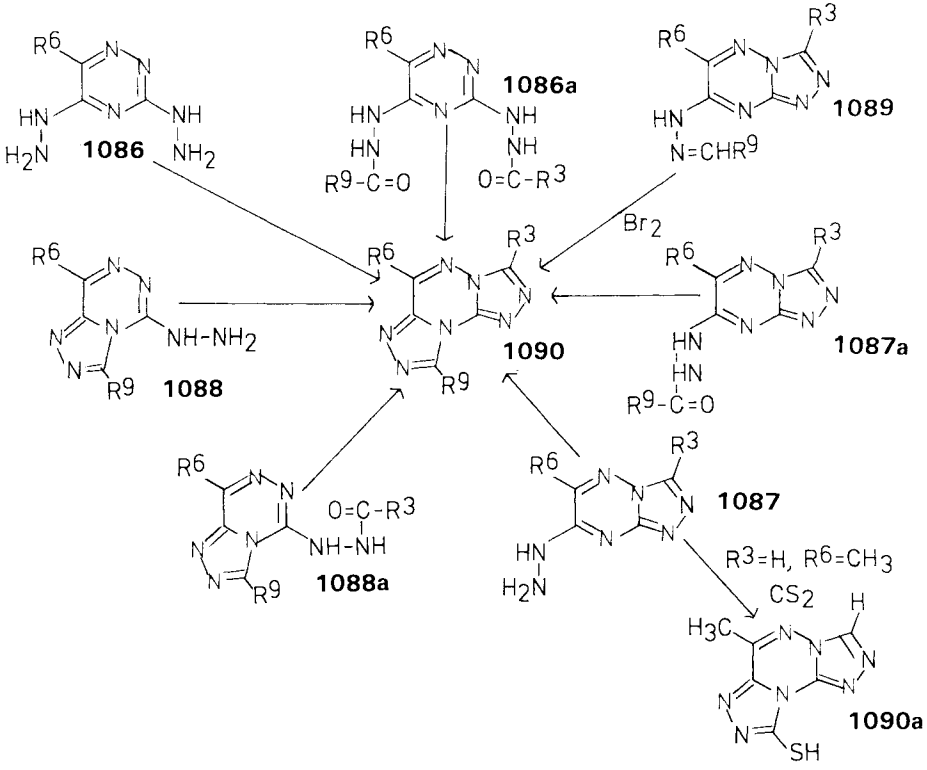


V. 1,2,4-TRIAZOLO[4,3-*b*]1,2,4-TRIAZOLO[4,3-*d*]-1,2,4-TRIAZINES

1,2,4-Triazolo[4,3-*b*]1,2,4-triazolo[4,3-*d*]1,2,4-triazines (**1090**) were prepared by condensation of 3,5-dihydrazino-1,2,4-triazines (**1086**) (595, 832), 7-hydrazino-1,2,4-triazolo[4,3-*b*]1,2,4-triazines (**1087**) (595, 832, 1474) or 5-hydrazino-1,2,4-triazolo[4,3-*d*]1,2,4-triazines (**1088**) (595) with carboxylic

acids, through cyclization of the corresponding acylhydrazino derivatives **1086a** to **1088a** (595, 832, 1474) and by oxidation of 7-(benzalhydrazino)-1,2,4-triazolo[4,3-*d*]1,2,4-triazines (**1089**) with bromine (832). The reaction of **1087** (R^3 = H, R^6 = CH_3) with carbon disulfide affords 6-methyl-1,2,4-triazolo[4,3-*b*]-1,2,4-triazolo[4,3-*d*]1,2,4-triazine-9-thione (**1090a**) (1474). Oxidation of 6-methyl-1,2,4-triazolo[4,3-*b*]1,2,4-triazolo[4,3-*d*]1,2,4-triazine with potassium permanganate yields the corresponding carboxylic acid (832).

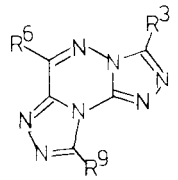
Table VIII-1 lists the compounds of this group reported in the literature.



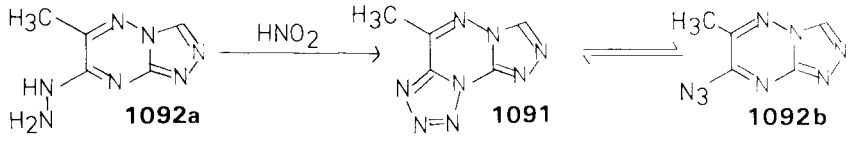
VI. TETRAZOLO[1,5-*d*]1,2,4-TRIAZOLO[4,3-*b*]-1,2,4-TRIAZINES

The reaction of 6-methyl-7-hydrazino-1,2,4-triazolo[4,3-*b*]1,2,4-triazine (**1092a**) with nitrous acid yields 4-methyltetrazolo[1,5-*d*]1,2,4-triazolo-[4,3-*b*]1,2,4-triazine (**1091**) (m.p. 185 to 187°C) (1474, 1484). The tetrazolo-azido equilibrium **1091** ⇌ **1092b** can be observed in solution but the tetrazolo form (**1091**) is predominant (1484).

TABLE VIII-1. 1,2,4-TRIAZOLO[4,3-*b*]1,2,4-TRIAZOLO[4,3-*d*]1,2,4-TRIAZINES



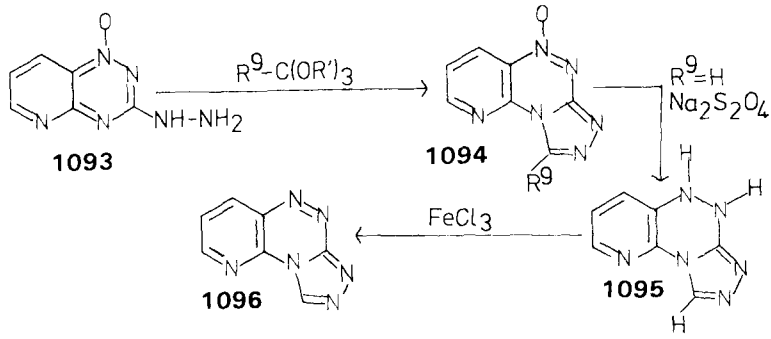
R^3	R^6	R^9	m.p. (°C)	Refs.
H	H	H	225–235	1474
H	H	CH_3	237–239	1474
H	H	C_6H_5	237–240	1474
H	CH_3	H	196–197	595
			197–198	832
			207–208	1474
H	CH_3	CH_3	210–211	832
			213–214	1474
H	CH_3	C_6H_5	201–202	832
			204–205	1474
H	CH_3	4-Cl–C_6H_4	208–209	832
H	CH_3	4-CH_3O–C_6H_4	209–211	832
H	CH_3	SH	300	1474
H	COOH	H	227 (dec.)	832
CH_3	CH_3	H	255–258	832
CH_3	CH_3	CH_3	168–169	832
C_6H_5	CH_3	C_6H_5	275–277	832
C_6H_5CO	CH_3	C_6H_5	265–267	832
C_6H_5CO	CH_3	C_6H_5CO	273–275	832
C_6H_5–C=NOH	CH_3	C_6H_5	266–268	832



VII. PYRIDO[2,3-*e*]1,2,4-TRIAZOLO[3,4-*c*]1,2,4-TRIAZINES

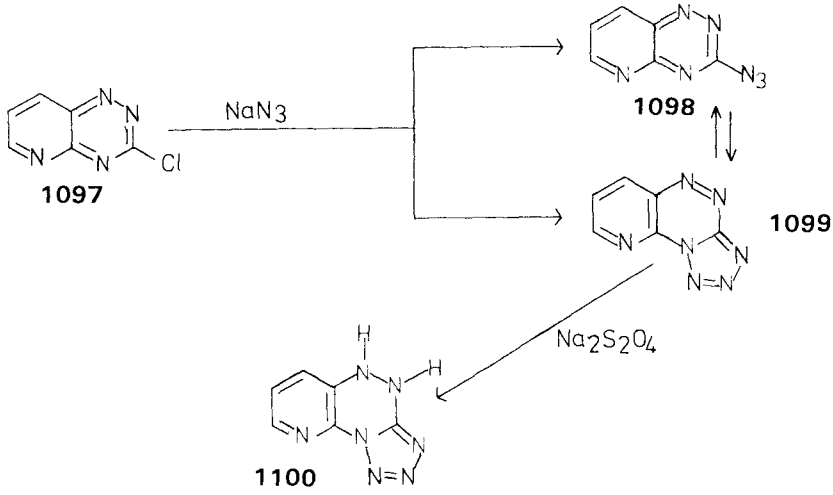
3-Hydrazinopyrido[2,3-*e*]1,2,4-triazine 1-oxide (**1093**) reacts with orthoesters to give 9-substituted pyrido[2,3-*e*]1,2,4-triazolo[3,4-*c*]1,2,4-triazine 5-oxides (**1094**) (R^9 = H, 278°C; R^9 = CH_3, 260 to 261°C). Sodium dithionite reduction of compounds **1094a** (R^9 = H) yields 5,6-dihydropyrido[2,3-*e*]1,2,4-

triazolo[3,4-*e*] 1,2,4-triazine (**1095**) (m.p. 196 to 198°C) which, on oxidation with ferric chloride, gives the heteroaromatic pyrido[2,3-*e*] 1,2,4-triazolo[3,4-*c*]-1,2,4-triazine (**1096**) (m.p. 226 to 228°C) (1267).



VIII. PYRIDO[2,3-*e*]TETRAZOLO[5,1-*c*]1,2,4-TRIAZINES

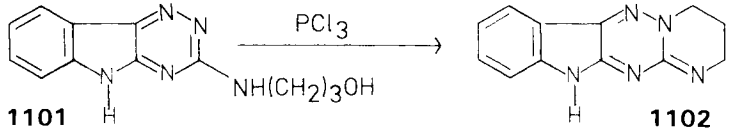
Treatment of 3-chloropyrido[2,3-*e*] 1,2,4-triazine (**1097**) with sodium azide gave rise to the formation of two crystalline products of identical composition. The aqueous acetone reaction medium deposited pale yellow crystals melting at 129°C (dec.), and extraction of the filtrate with dichloromethane and treatment of the partially concentrated extract with petroleum ether gave bright yellow crystals of melting point 62°C. The infrared spectrum of the lower melting product had a strong azide band both in the solid phase and in solution;



accordingly, the structure of 3-azidopyrido[2,3-*e*]1,2,4-triazine (**1098**) was assigned to it. The other product, which contains no azide band in the infrared, should thus be regarded as pyrido[2,3-*e*]tetrazolo[5,1-*c*]1,2,4-triazine (**1099**). The two isomers are interconvertible. In the solid phase, the tetrazole isomer (**1099**) is the more stable, and in solution, the azide isomer (**1098**), but the latter is stable enough to exist for a few days in the crystalline form (1267). The tetrazole (**1099**), dissolved carefully in cold dimethylformamide and treated with aqueous sodium dithionite solution, is converted to 4,5-dihydropyrido[2,3-*e*]tetrazolo[5,1-*c*]1,2,4-triazine (**1100**).

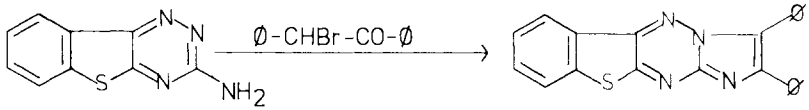
IX. PYRIMIDO[1′,2′:2,3]1,2,4-TRIAZINO[5,6-*b*]INDOLES

Reaction of 3-[(3-hydroxypropyl)amino]-1,2,4-triazino[5,6-*b*]indole (**1101**) with phosphorus chloride was used for the synthesis of 2,3,4,11-tetrahydropyrimido[1′,2′:2,3]1,2,4-triazino[5,6-*b*]indole (**1102**) (m.p. 311 to 312°C, ·HCl 395 to 395.5°C) (1309).



X. [1]BENZOTHIENO[2,3-*e*]IMIDAZO[1,2-*b*]1,2,4-TRIAZINES

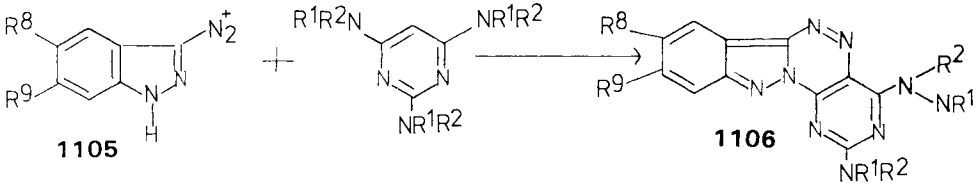
Condensation of 3-amino[1]benzothieno[2,3-*e*]1,2,4-triazine (**1103**) with desyl bromide was used by Rossi and Trave (619) for the synthesis of 2,3-diphenyl-[1]benzothieno[2,3-*e*]imidazo[1,2-*b*]1,2,4-triazine (**1104**) (m.p. 292°C) (RRI 8799).



XI. PYRIMIDO[4′,5′:5,6]1,2,4-TRIAZINO[4,3-*b*]INDAZOLES

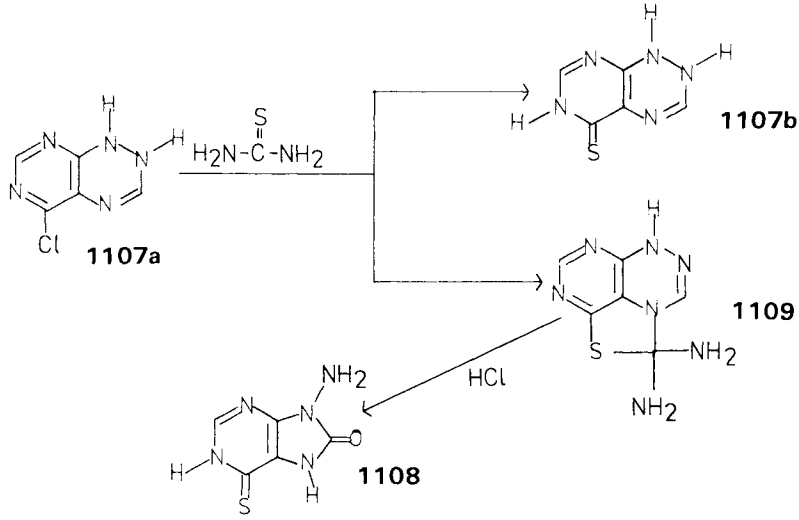
Coupling of diazotized 3-aminoindazoles (**1105**) and 2,4,6-triaminopyrimidines affords pyrimido[4′,5′:5,6]1,2,4-triazino[4,3-*b*]indazoles (**1106**)

which can be used as dyes (1535–1537, 2297) (m.p.: $R^1 = H$, $R^2 = C_2H_5$ $R^8 = R^9 = H$, m.p. 289 to 291°C; $R^1 = H$, R^2 = cyclohexyl, $R^8 = NO_2$, $R^9 = H$, m.p. 290 to 292°C; $R^1 = R^2 = CH_3$, $R^8 = NO_2$, $R^9 = H$, 350°C; $R^1 = R^2 = CH_3$, $R^8 = H$, $R^9 = Cl$, m.p. 288 to 289°C).



XII. 2*H*,5*H*-1-THIA-2a,4,5,6,8-PENTAAZAACENAPHTHYLENES

Reaction of 5-chloro-1,2-dihydropyrimido[5,4-*e*] 1,2,4-triazine (**1107a**) with thiourea gave 1,2-dihydropyrimido[5,4-*e*] 1,2,4-triazine-5-thione (**1107b**) and a 2-thiopseudourea addition product that was rearranged in hydrochloric acid to give 9-amino-6-thioxo-9*H*-purin-8-one (**1108**). This result suggested that the second product was the hydrochloride of 2,2-diamino-2*H*,5*H*-1-thia-2a,4,5,6,8-pentaazaacenaphthylene (**1109**) [(m.p. 190°C (dec.)] (1348).



Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

IX

1,2,4-Triazine Rings as Part of a Bicyclic System

I. 2,3,5-TRIAZABICYCLO[2.2.2]OCTENES

(4 + 2)-Cycloaddition reaction of *N*-substituted 1,2-dihydropyridines with the highly reactive 1,2,4-triazoline-3,5-dione provided a quantitative route to 2,3,5-triazabicyclo[2.2.2]oct-7-ene-2,3-dicarboxylic acid imides (**1110**) (1538). Reduction of **1110a** ($R^1 = R^3 = C_6H_5$, $R^2 = CH_3CO$) in methanol using palladium–charcoal for 2.5 hr with hydrogen at 30 psi afforded the reduced product (**1111**). Table IX-1 lists the known compounds.

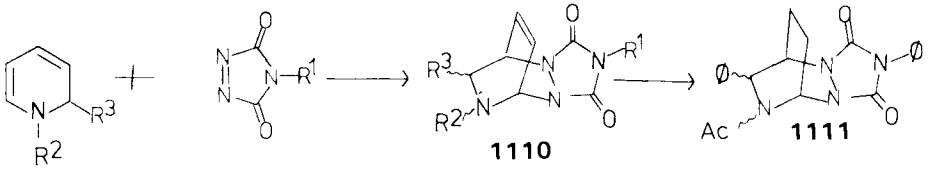
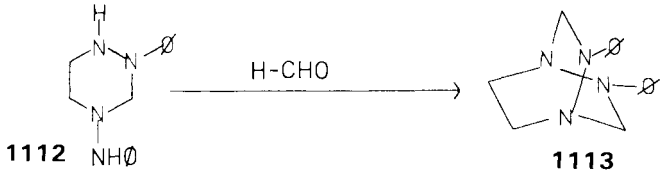


TABLE IX-1. 2,3,5-TRIAZABICYCLO[2.2.2]OCT-7-ENES (1538)

(1110)			
R^1	R^2	R^3	m.p. (°C)
C_2H_5	CH_3CO	C_6H_5	70
C_2H_5	CH_3SO_2	H	
C_6H_5	CH_3CO	C_6H_5	181–183
C_6H_5	C_6H_5CO	C_6H_5	202–204
C_6H_5	$COOCH_3$	H	152–156 (dec.)
C_6H_5	$COOC_2H_5$	C_6H_5	150–154
C_6H_5	CH_3SO_2	H	170–175 (dec.)
C_6H_5	$C_6H_5SO_2$	H	145

II. 1,2,4,5-TETRAAZABICYCLO[2.2.2]OCTANES

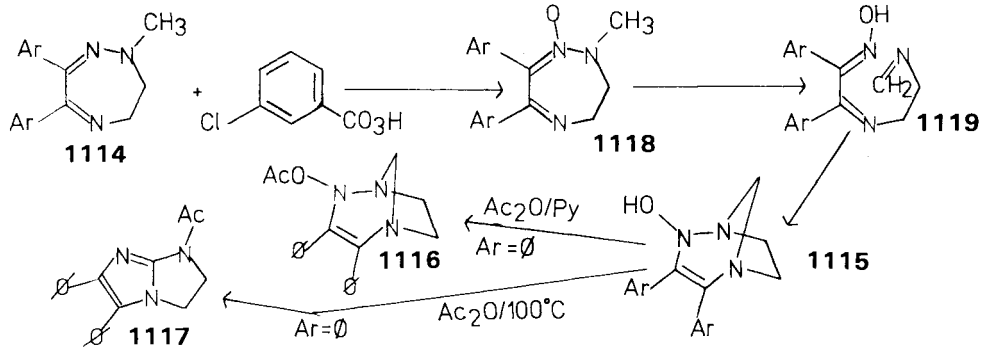
Reaction of 4-anilino-2-phenylhexahydro-1,2,4-triazine (**1112**) with formaldehyde yields 2,5-diphenyl-1,2,4,5-tetraazabicyclo[2.2.2]octane (**1113**) (m.p. 144 to 145°C) (1048)(RRI 10029).



III. 1,2,5-TRIAZABICYCLO[3.2.1]OCTENES

3,4-Diaryl-6,7-dihydro-1-methyl-1*H*-1,2,5-triazepines (**1114**) gave 3,4-diaryl-2-hydroxy-1,2,5-triazabicyclo[3.2.1]oct-3-enes (**1115**) (Ar = C_6H_5, m.p. 184 to 185°C; Ar = 4-CH_3-C_6H_4; 4-CH_3O-C_6H_4; 3,4-$(CH_2O_2)C_6H_3$), when treated with *m*-chloroperbenzoic acid. The diphenyl derivative can be acetylated with acetic anhydride and pyridine to give 2-acetoxy-3,4-diphenyl-1,2,5-triazabicyclo[3.2.1]oct-3-ene (**1116**) (m.p. 122 ro 124°C), and treating the same compound with acetic anhydride at 100°C affords the imidazo[1,2-*a*]imidazole derivative (**1117**) (1539).

A reasonable mechanism for the formation of **1115** involves initial electrophilic attack by the peracid on **1114** to generate **1118** which is constrained to undergo a [2.3] sigmatropic shift leading to **1119** which may then give **1115** by a conventional Diels–Alder reaction.



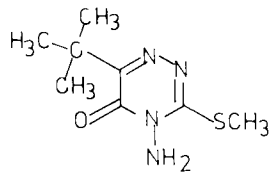
Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

X

Uses and Biochemical Aspects of 1,2,4-Triazine Derivatives

A large number of suggested uses for 1,2,4-triazines, reduced 1,2,4-triazines, and condensed 1,2,4-triazines have been reported in the literature. These claims seem to have been mostly for the purpose of obtaining patents on the compounds involved and it seems to us that only a few significant uses are known. Since most of the claimed uses of 1,2,4-triazine derivatives result from their biochemical properties we discuss these problems together.

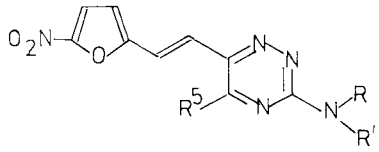
4-Amino-1,2,4-triazines are biochemically highly active compounds and their synthesis and use as herbicides is claimed by different groups (185, 921–928, 1568, 1590). From this group the 4-amino-6-*tert*-butyl-3-(methylmercapto)-1,2,4-triazin-5-one (**1120**) (sencor, metribuzin, BAY 94337) is the best known and most widely used herbicide.



1120

Owing to the use of this compound as a herbicide a large number of publications (1569–1649, 2310, 2311) have appeared, dealing with its biochemical properties or with the problems of its use, such as tolerances for residues (1647) or the analytical determination of **1120** (929, 939, 1648). A review on the biochemical properties of these compounds was given by Eue in 1972 (1649). For the synthesis, the chemical properties and reactions of 4-amino-1,2,4-triazines see Chapter II, Sections XII-B to XII-I.

Another group of biochemically active 1,2,4-triazine derivatives are 5-nitro-2-furyl substituted 1,2,4-triazines, especially 3-amino-6-[2-(5-nitro-2-furyl)vinyl]-1,2,4-triazines (**1121**) (panfuran) (1650–1685). These compounds were tested



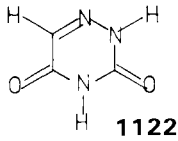
1121

for their pharmacological, antibactetrial, or tuberculostatic activities, and various uses were suggested or claimed.

Other 1,2,4-triazine derivatives, the biochemical properties of which were tested and for which uses due to these properties were suggested or claimed are 3-amino-1,2,4-triazines (1686, 1702, 2314), 1,2,4-triazinothiamine (1687–1691), pyrazolo[3,2-*c*] 1,2,4-triazines (1692–1694), 1,2,4-triazino[5,6-*b*] indoles (1695–1701), 3-mercapto-1,2,4-triazines (1702), 1,2,4-benzotriazine 1-oxides (1703), thiazolo[4,3-*c*] 1,2,4-triazines (1704), dihydro-1,2,4-triazines (1705–1710), tetrahydro-1,2,4-triazines (1711, 1712), pyrimido-1,2,4-triazines (1713–1718), and 1,2,4-triazolo[1,5-*d*] 1,2,4-triazines (936, 937).

By far the greatest number of papers dealing with biochemical aspects or uses of 1,2,4-triazine derivatives were published for 1,2,4-triazines with hetero-substituents in the 3- and 5-positions, (420, 453, 1561, 1666, 1720–2257, 2313). From this group of compounds the derivatives of 1,2,4-triazine-3,5-dione (**1122**) (6-azauracil), its 6-methyl derivative (**1123**) (6-azathymine), the 2-ribofuranosyl derivatives of **1122** (**1124**) (6-azauridine), and the 2-desoxyribofuranosyl derivative of **1123** (**1125**) (6-azathymidine) have been most intensively studied.

Nearly every possible biochemical property has been tested for these compounds, such as antitumor activity, antimetabolic activity, coccidiostatic activity, antiviral activity, their renal excretion in man, their metabolism in man, their determination in blood or serum, their use in anticancer therapy, their use as an oral agent to control human pregnancy with minimal toxic effects, their effect on protein synthesis, their use in tetracycline production, their effect on the growth and development of plants, their pharmacological activities, their inhibition of the growth of *E. coli*, their stabilization against ultraviolet light, and many other properties. A detailed enumeration of all reported tests is far beyond the scope of this book.



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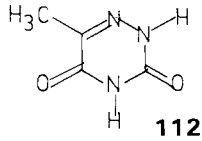

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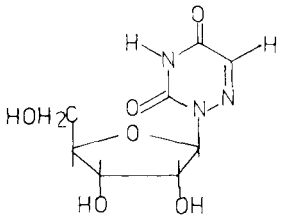
Besides the above mentioned compounds the following 3,5-disubstituted 1,2,4-triazines were tested for their biochemical properties and uses were



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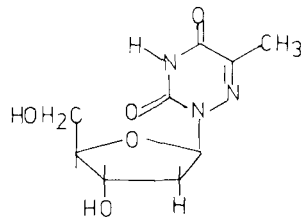
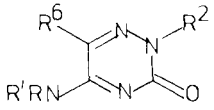


1125

suggested or claimed: 5-amino-1,2,4-triazin-3-ones (**1126**) (6-azacytosin, 6-azacytidine) (1738, 1742, 1774, 1777–1781, 1787, 1816, 1890, 1907, 1908, 1911, 1920, 1940, 1956, 1957, 1972, 1973, 1997, 2007, 2020, 2052, 2072, 2102, 2104, 2124, 2129–2134, 2142, 2143, 2152, 2168, 2169, 2172, 2200); 1,2,4-triazin-one-thiones (**1127**, **1128**) (420, 1782, 1788, 1828–1830, 1882, 1892–1895, 1910, 1974, 1993, 2085, 2125, 2149, 2153–2155, 2157, 2158, 2176); 1,2,4-triazine-3,5-dithiones (**1129**) (1728, 1788, 1806, 1813, 2202); 3,5-diamino-1,2,4-triazines (**1130**) (1744, 2194); 5-amino-3-(methylmercapto)-1,2,4-triazines (**1131**) (1782); and dihydro derivatives of the enumerated compounds (1806, 2098).



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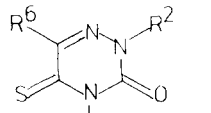

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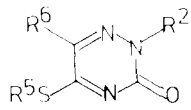

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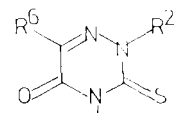

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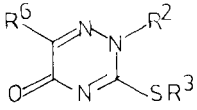

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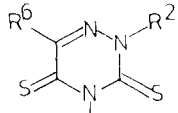

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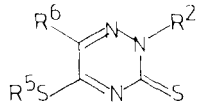

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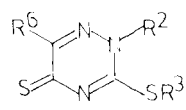

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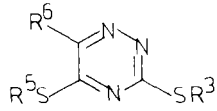

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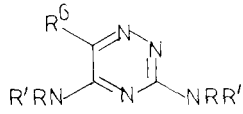

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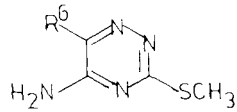


1131

In a large number of papers or patents the biological ribosidation of these 1,2,4-triazine derivatives, mainly by *Escherichia coli*, the phosphorylation of the ribofuranosyl 1,2,4-triazine derivatives, and the isolation of the biological synthetized compounds are reported or claimed (1783, 1797, 1980, 1992, 2009, 2018, 2209–2228, 2249, 2312).

The biological introduction of these compounds in RNA is reported in one paper (2221).

In a large number of publications the synthesis of labeled compounds or the testing of the labeled compounds of the discussed class of 1,2,4-triazine derivatives was reported or claimed (1797, 2229–2247, 2255).

Reviews on various biochemical aspects of 1,2,4-triazines with heterosubstituents in the 3- and 5-positions were presented by various groups (1719, 2121, 2248–2257, 2113).

1,2,4-Triazines with 2-pyridyl substituents in the 3- and/or 5-positions form stable complexes with metal ions (31, 34, 39, 1068, 1069, 2259–2268) such as iron(II), cobalt(II), nickel(II), zinc(II), and copper(I). Owing to the stability of these complexes the use of these 1,2,4-triazine derivatives was suggested for the determination of the mentioned ions, especially for iron(II) ions and the use of these substances as corrosion inhibitors (31).

6-Phenyl- and 5,6-diphenyl-1,2,4-triazine-3-thione can be used for the gravimetric determination of thallium and palladium (2269).

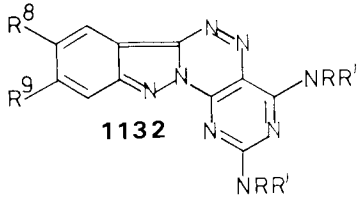
For the determination of osmium the use of the following 1,2,4-triazine derivatives is mentioned: 3-thioxo-1,2,4-triazin-5-ones (2270–2273), dihydro-3-thioxo-1,2,4-triazin-5-ones (2270), 6-mercapto-1,2,4-triazine-3,5-diones (2270), 6-mercapto-5-thioxo-1,2,4-triazin-3-ones (2273), and 3,5-dithioxo-1,2,4-triazine-6-carboxylates (2274, 2275).

Sanyal and Mushran (200, 2276) reported the possibility of using 5-alkylidene-1,2,4-triazin-6-ones as indicators for the determination of halogens.

Stransky, Cap, and Slouka suggested 1,2,4-triazine-3,5-diones or pyrrolo[3,4-*e*]1,2,4-triazinediones as indicators for the determination of N-H acids in acetonitrile (2277).

The use of pyrimido[4′,5′:5,6]1,2,4-triazino[4,3-*b*]indazoles (**1132**) or derivatives of 1,2,4-benzotriazine-7-carboxylic acid 1-oxide (**1133**) as dyes is claimed by different groups (1535–1537, 2279, 2280).

The addition of 1,2,4-triazine derivatives to fuels is claimed in one patent (2282).



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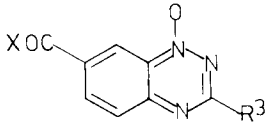


1133

The use of various 1,2,4-triazine derivatives as additives to photographic layers, developer bath, as photoconductors, or in direct writing emulsions is claimed (54, 972, 2281, 2283–2299).

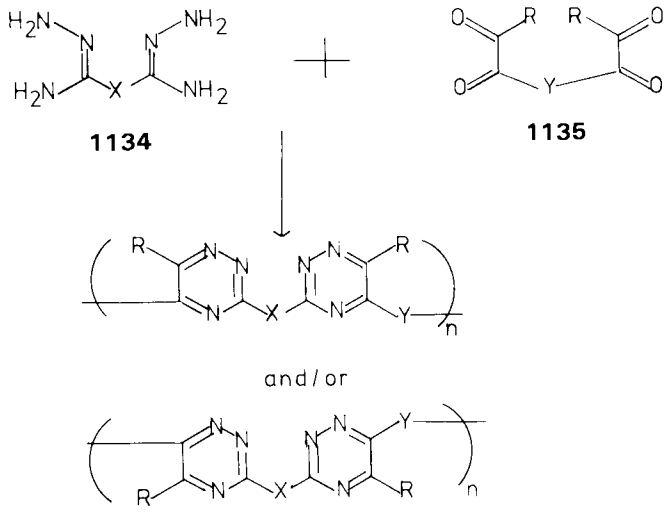
1,2,4-Triazines can be used as ultraviolet absorbers for textiles, plastics, resins, rubbers, or papers (53).

Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

XI

Polymers Containing the 1,2,4-Triazine Nucleus

At present only a few publications are known, which deal with polymers containing the 1,2,4-triazine nucleus (30, 2300–2304). They were all prepared by reaction of bisamidrazones (**1134**) with bis-1,2-dicarbonyl compounds (**1135**). A review on the synthesis and uses of poly-1,2,4-triazines is given by Hergenrother and Kiyohara (2301).



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Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

1,2,4,5-Tetrazines

PAUL F. WILEY

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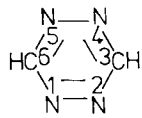
I

Introduction

In 1956 a comprehensive review of the 1,2,4,5-tetrazines appeared (141) and about 10 years later another review was published (585). Since the appearance of the first review and, to a lesser degree, of the second, research on this subject has increased to such an extent that a complete revision of the earlier material seems warranted. This discussion represents a totally rewritten review covering the entire field of research in the 1,2,4,5-tetrazines.

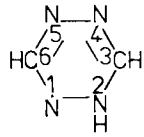
The parent compound of the 1,2,4,5-tetrazine series has structure **1** and is



1

numbered as indicated. The preferred name in *Chemical Abstracts* is 1,2,4,5-tetrazine, but the compound was formerly called *s*-tetrazine (indicating symmetrical tetrazine) as it still is in *The Ring Index*, in which it is No. 178. There is considerable evidence for some degree of electron delocalization in 1,2,4,5-tetrazines, but the chemical behavior of this class of compounds is such that it is misleading to draw the system as fully aromatic. Consequently the structures given here contain localized double bonds, although these too are inaccurate.

In addition to the completely unsaturated 1,2,4,5-tetrazines, dihydro-, tetrahydro-, and hexahydro-1,2,4,5-tetrazines are well-known. There are four possible isomeric dihydro-1,2,4,5-tetrazines. These are 1,2-, 1,4-, 1,6-, and 3,6-dihydro, examples of all of which are known, although the 1,2-, and 1,4-dihydro isomers are much more numerous than the others. 1,2,3,4- and 1,2,3,6-tetrahydro compounds are possible; both series are known although examples of the latter are few. In recent years a new class of 1,2,4,5-tetrazines has been reported, which has been given the trivial name of verdazyls and is named by *Chemical Abstracts* as derivatives of 1,2,4,5-tetrazin-1(2*H*)-yl (**2**).



2

Verdazyls are free radicals, and only substituted 3,4-dihydro compounds are known. Because verdazyls do not fit into any of the already mentioned categories of 1,2,4,5-tetrazines, they are discussed separately.

In the earlier literature 1,2,4,5-tetrazines were frequently referred to as tetrazines, with qualifiers being used for the other two types of tetrazines, and in this discussion also the term tetrazine with no indication of the nitrogen arrangement refers to the 1,2,4,5-tetrazines. Considerable confusion has been introduced into the literature by the use of the term *p*-urazine. The compound referred to was earlier believed to be hexahydro-1,2,4,5-tetrazine-3,6-dione although it actually was 4-amino-4*H*-1,2,4-triazole. Therefore the term *p*-urazine is avoided as much as possible here, although it is still encountered in the literature. In general trivial names are not used here except in the case of verdazyls, for which the systematic nomenclature is quite cumbersome. In some cases, mainly those involving substitution of hetero atoms and functional groups on the ring, nomenclature differs from that of *Chemical Abstracts.* It also differs from *Chemical Abstracts* in naming the hydro derivatives, except for the verdazyls, totally on the basis of ring unsaturation.

Organization of the discussion is based on the degree of saturation of the 1,2,4,5-tetrazine ring. However, the condensed systems, polymers, and uses are discussed separately. A second division is based on type of substitution in that two classes are set up in which one is devoted to compounds having carboxyl groups, carboxyl derivatives, or hetero atoms substituted on the ring; the other is concerned with compounds having alkyl, arylalkyl, aryl, and heterocyclic groups attached to the ring. However, it was not possible to divide the material completely on this basis so there is some overlay such as heterocyclic rings, which, even though they are attached by a nitrogen atom to a carbon atom of the 1,2,4,5-tetrazine system, are considered under heterocyclic substituents.

No naturally occurring 1,2,4,5-tetrazines or hydro-1,2,4,5-tetrazines are known.

Chemistry of Heterocyclic Compounds, Volume 33
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II

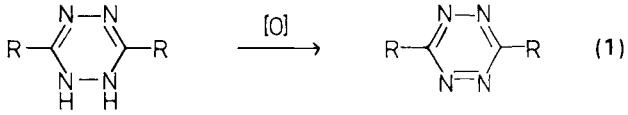
Uncondensed Aromatic Systems

I. ALKYL-, ARYLALKYL-, ARYL-, AND HETEROCYCLIC-SUBSTITUTED 1,2,4,5-TETRAZINES

A. Preparation

The number of 1,2,4,5-tetrazines of this type reported in the literature have been relatively few, surprisingly so in view of the large number of synthetic methods reported and the extensive variations of some of these methods.

By far the most widely used and important procedure for preparing 1,2,4,5-tetrazines is by oxidation of 1,2-dihydro-1,2,4,5-tetrazines using a variety of common oxidizing agents, as indicated in eq. II-1. The agent most

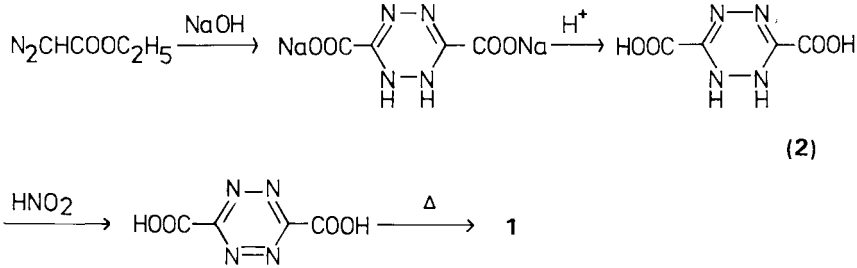


(1)

frequently used has been nitrous acid (14, 18, 19, 20, 109, 150, 168, 267, 293, 299, 347, 349, 446, 522), and at present it is the standard reagent for this purpose. The use of halogens (chlorine and bromine), ferric chloride, nitric acid, hydrogen peroxide, and isoamyl nitrite has also been frequent (48, 49, 70, 77, 80, 109, 117, 179, 208, 238, 241, 296, 297, 310, 349, 403, 407, 467, 478, 480, 575, 583, 591). In one case (259) lead tetraacetate was the oxidant. Although not strictly speaking an oxidation procedure, pyrolysis has been used to bring about the reaction in eq. II-1 using both 1,2-, and 1,4-dihydro-1,2,4,5-tetrazines (84, 220, 561), and irradiation of 3,6-diphenyl-1,4-dihydro-1,2,4,5-tetrazine also has been reported to form the 1,2,4,5-tetrazine (83). The oxidation procedures vary considerably in yield depending upon compounds being oxidized, oxidant, and conditions. However, in most cases they are quite good, 80 to 100% with frequent reports of quantitative yields. The 1,6-dihydro-1,2,4,5-tetrazines have also been oxidized chemically to 1,2,4,5-tetrazines (510, 511), and most of the

simple 3,6-dialkyl-1,2,4,5-tetrazines known have been derived from the corresponding 1,6-dihydro compounds by oxidation.

The preparation of 1,2,4,5-tetrazines by modification of substituents at the 3- and 6-positions is not an important preparative method, but it was the procedure used for the original synthesis of 1,2,4,5-tetrazine and is still the best preparative method for that compound. Hantzsch and Lehmann (200) in 1900 dimerized ethyl diazoacetate in base to give a 1,2-dihydro-1,2,4,5-tetrazine (eq. II-2) which was then neutralized, oxidized, and decarboxylated to 1,2,4,5-tetrazine. The yield of impure product (1) was only 1 to 2% and an erroneous structure was

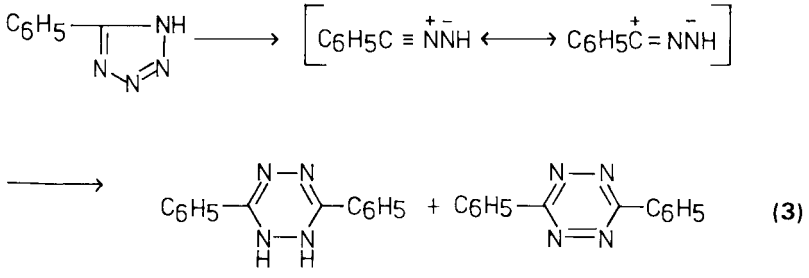


(2)

proposed. A few years later Curtius, Darapsky, and Müller (102, 107) improved the yield, as did other workers (349, 581), and proposed the correct structure (100). Spencer, Cross, and Wiberg (522) have improved the procedure sufficiently to obtain an 11% overall yield from the diazoacetic ester. Fridh and co-workers (158) proposed an improvement in the last step which increases the yield still further. The latter workers carried out the decarboxylation in a vacuum and condensed the 1,2,4,5-tetrazine in a trap cooled with liquid air.

About 20 other procedures have been reported for preparing 1,2,4,5-tetrazines, but none of these methods has been applied more than a few times. In most cases they involve the intermediacy of a dihydro-1,2,4,5-tetrazine which is not isolated as such but loses hydrogen under the conditions of the reaction, and the end result is the isolation of the completely unsaturated ring system directly.

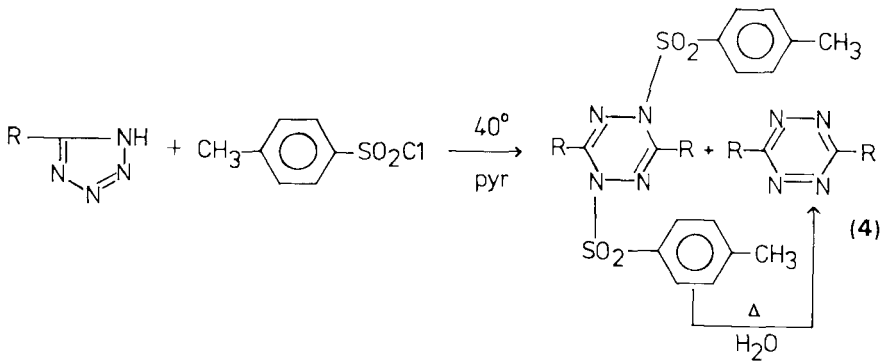
Conversion of 5-phenyltetrazoles to 1,2,4,5-tetrazines is the minor synthetic procedure which has been most frequently used (eq. II-3). It occurs by



(3)

application of thermal (219) or photochemical (478, 499) energy to 5-phenyltetrazoles. It has been proposed by Huisgen *et al.* (219) and Scheiner (478) that the reaction proceeds by the 1,3-dipolar nitrilimine intermediate indicated in eq. II-3, although this view was subsequently modified by Scheiner (480). One of the products of the reaction is usually the 1,2-dihydro-1,2,4,5-tetrazine, and it is frequently the principal one. It is generally considered that the 1,2-dihydro-1,2,4,5-tetrazine is the precursor of the 1,2,4,5-tetrazine product. In both the thermal and photochemical reactions a number of other products are produced, such as 3,5-diphenyltriazole and benzonitrile. The quite limited use of 5-substituted tetrazoles to prepare 1,2,4,5-tetrazines is probably because of the low yield (usually under 20%) and the multiplicity of products formed.

A closely related procedure has been reported by Huisgen *et al.* (220) and is indicated in eq. II-4. The reaction was run in cases in which R = C_6H_5 and CH_3, and only in the former case did the reaction give the 1,2,4,5-tetrazine as one of

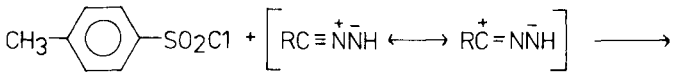


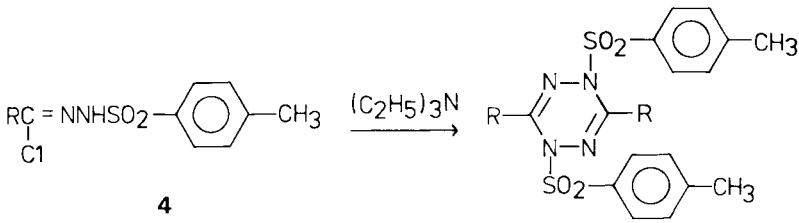
(4)

the products or was it obtained by heating the 1,4-bis(4-toluenesulfonyl)-1,4-dihydro-1,2,4,5-tetrazine. The reaction was interpreted as a 1,3-dipolar dimerization of **3**. However, Wawzonek and Kellen (568) have questioned such

3

an interpretation on the basis of the reaction of *N*-4-toluensulfonylarylhydrazidoyl chlorides (**4**, R = Ar) with base to give the same type of products and suggest the sequence of events shown in eq. II-5 with the 1,3-dipolar nitrilimine being formed from 5-phenyltetrazole. It was found that 2-(4-toluenesulfonyl)-5-phenyltetrazole gave only traces of 3,6-diphenyl-1,2,4,5-tetrazine after being heated in solvents. Since it would be expected that **3** would arise under such conditions, it was inferred that the actual course of the reaction was that shown in eq. II-5.

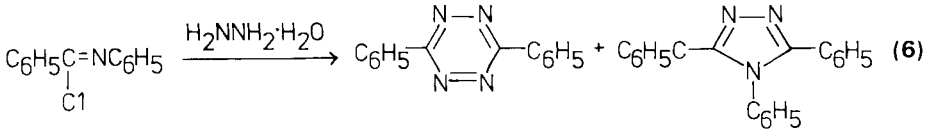




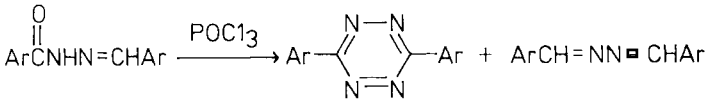
(5)

4

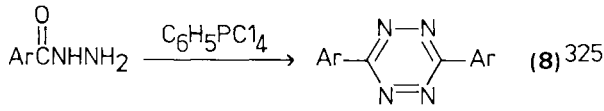
A number of methods of preparing 1,2,4,5-tetrazines involve the use or intermediacy of arimidyl chloride derivatives as, for example, the reaction of *N*-phenylbenzimidyl chloride with hydrazine hydrate to give 3,6-diphenyl-1,2,4,5-tetrazine (eq. II-6) (67). It seems likely that these all involve dihydro-1,2,4,5-tetrazine intermediates. The procedures are shown in eqs. II-6 to II-11.



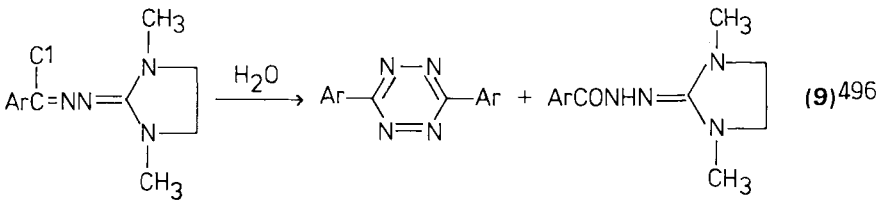
(6)



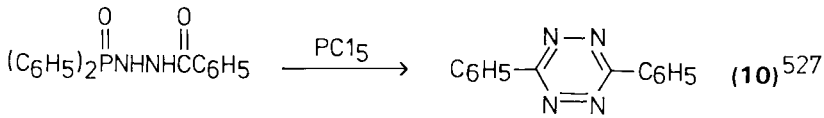
(7) 222



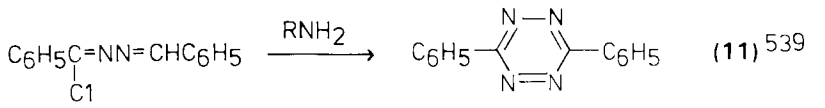
(8) 325



(9) 496



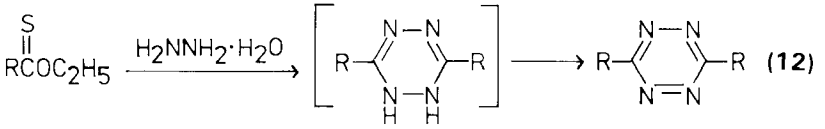
(10) 527



(11) [539]

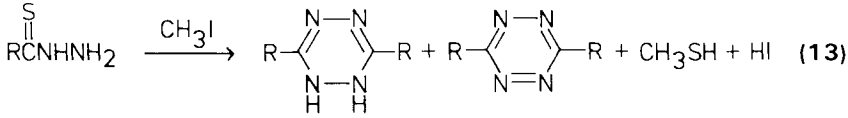
In most cases the yields are quite poor, but the method indicated in eq. II-8 gives 40–60% yields, and the very similar procedure shown in eq. II-10 results in a 33% yield. Steininger (527), in a modification of the method of eq. II-10, treated methylphenylphosphoroylhydrazide with ethyl orthobenzoate and obtained traces of 3,6-diphenyl-1,2,4,5-tetrazine. In most cases these reactions require elevated temperatures, and there is considerable conversion to triazoles.

Two methods for the synthesis of 1,2,4,5-tetrazines, one starting with thiono esters and the other with thiohydrazides, which are quite closely related and no doubt proceed through similar intermediates, are illustrated in eqs. II-12 and II-13. The procedure (30) shown in eq. II-12 involves treatment of a thiono ester with hydrazine hydrate, resulting in isolation of a 1,2,4,5-tetrazine. In some cases the dihydro intermediate was isolable. When aliphatic thiono esters were



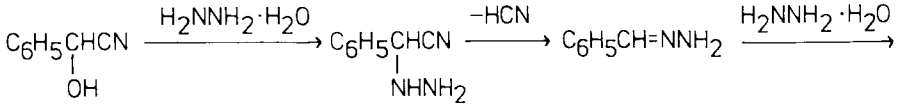
(12)

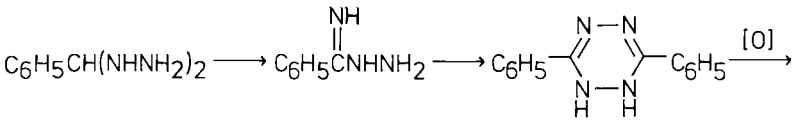
used, the only products were 3,5-dialkyl-4-amino-4*H*-1,2,4-triazoles. The second procedure (230) utilized thiohydrazides and added methyl iodide which probably formed an imino thio ester as an intermediate. In most cases the product was a 1,2-dihydro-1,2,4,5-tetrazine, but in the case in which R = $C_6H_5CH_2$ the 1,2,4,5-tetrazine was isolated.

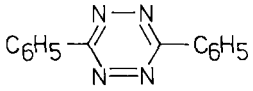


(13)

In an attempt to prepare a 1,2-dihydro-1,2,4,5-tetrazine by the reaction of mandelonitrile with hydrazine Darapsky and Adamczewski (119) obtained an unidentified intermediate which was oxidized with amyl nitrite to 3,6-diphenyl-1,2,4,5-tetrazine. It was suggested that the reaction followed the rather complicated sequence indicated in eq. II-14, with the benzhydrazidine formed dimerizing to a 1,2-dihydro-1,2,4,5-tetrazine, which was the unidentified intermediate. Such a course seems most unlikely.

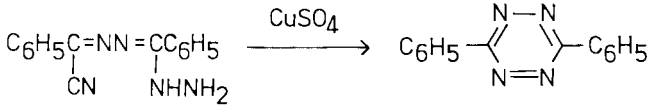






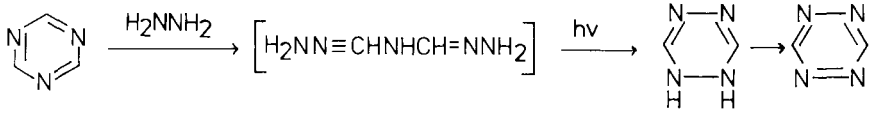
(14)

Fusca and Rossi (165) have used the azine shown in eq. II-15 to prepare 3,6-diphenyl-1,2,4,5-tetrazine by an oxidative procedure. Again this would appear to have a dihydro intermediate.



(15)

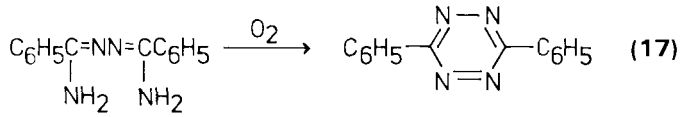
One of the more interesting 1,2,4,5-tetrazine syntheses is the reaction of 1,3,5-triazine with hydrazine followed by photolysis (eq. II-16) (187), although no 1,2,4,5-tetrazine was actually isolated. The triazine is believed to be only a



(16)

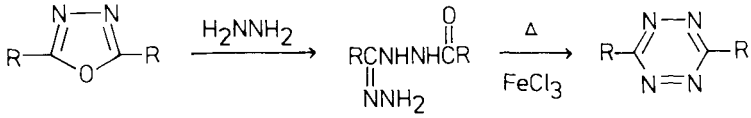
source of CH. The product actually isolated from the reaction was 1,2-diacetyl-1,2,-dihydro-1,2,4,5-tetrazine, but 1,2,4,5-tetrazine was believed to be present because a red color was observed.

Two procedures for preparing 1,2,4,5-tetrazine which differ quite markedly from those already discussed are illustrated in eqs. II-17 and II-18. One method (583) involves oxidation of arylamide azines to give 3,6-diaryl-1,2,4,5-tetrazines. Lutz has been unable to repeat this preparation (585). A somewhat



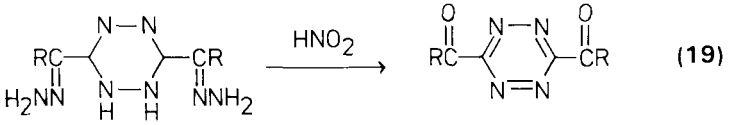
(17)

similar procedure was used by Brown and co-workers (49) to prepare fluorinated dialkyl-1,2,4,5-tetrazines (eq. II-18). Acylhydrazonohydrazides prepared by treatment of oxadiazoles with hydrazine were cyclized thermally under oxidizing conditions to give poor yields of 1,2,4,5-tetrazines.



(18)

Only two 3,6-diacyl-1,2,4,5-tetrazines have been reported, and these were prepared from the bishydrazones of 3,6-diacyl-1,2-dihydro-1,2,4,5-tetrazines by nitrous acid oxidation (eq. II-19) (15). The preparation of the dihydro compounds is discussed in the section devoted to such compounds.



(19)

Most of the synthetic procedures for preparing 1,2,4,5-tetrazines can form only the symmetrical compounds having both substituents the same, and most of the 1,2,4,5-tetrazines reported are symmetrical. However, oxidation of unsymmetrical 1,2-dihydro- (48, 332) and 1,6-dihydro-1,2,4,5-tetrazines (513) has given the unsymmetrical 1,2,4,5-tetrazines. The procedure of Brown and co-workers (49) (eq. II-18) can give unsymmetrical products when different substituents are present in the 2,5-disubstituted oxadiazoles used as starting materials. Also modification of substituents in already formed 1,2,4,5-tetrazines (18, 19) can give unsymmetrical end products. These methods are discussed in the section dealing with reactions of 1,2,4,5-tetrazines.

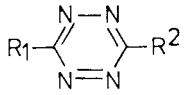
B. Compound Survey

The compounds of this class that have been reported in the literature are listed in Table II-1.

C. Physical Properties and Theoretical Considerations

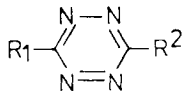
1,2,4,5-Tetrazines are strongly colored compounds, being red, bluish red, or violet-red. 1,2,4,5-Tetrazine is quite unstable and can be stored only out of contact with air and at reduced temperatures. The 3,6-dialkyl-1,2,4,5-tetrazines are also rather unstable unless their substituents contain an electron-rich group such as fluorine, but aromatic and heterocyclic substituents confer stability. Most of the 3,6-dialkyl-1,2,4,5-tetrazines are red oils, some of the more stable of which can be distilled under atmospheric pressure. No boiling points are reported for those containing only unsubstituted saturated alkyl groups, probably indicating that they are too unstable to distill. The few solid

TABLE II-1. 1,2,4,5-TETRAZINES WITH ALKYL, ARYLALKYL, ARYL, AND HETEROCYCLIC SUBSTITUENTS



R^1	R^2	m.p. (°C)	Refs.
1. *Alkyl and alicyclic*			
H	H	99	102, 107, 200, 522
CH_3	CH_3	74	109, 267, 289, 480, 511, 513
CH_3	C_2H_5	n_D^{20} 1.504	513
CH_3	$(CH_3)_2CH$	n_D^{20} 1.495	513
CH_3	$(CH_3)_3C$	n_D^{20} 1.485	513
CH_3CH_2	CH_3CH_2	n_D^{20} 1.497	289, 349, 511, 513
CH_3CH_2	$(CH_3)_2CH$	n_D^{20} 1.489	513
$CH_3CH_2CH_2$	$CH_3CH_2CH_2$	n_D^{20} 1.488	289, 511, 513
$(CH_3)_2CH$	$(CH_3)_2CH$	n_D^{20} 1.485	289, 511, 513
$(CH_3)_3C$	$(CH_3)_3C$	95–99	289, 513
$CH_3(CH_2)_{10}$	$CH_3(CH_2)_{10}$	64	511, 513
$CH_2=CHCH_2$	$CH_2=CHCH_2$	–	480
F_2CH	F_2CH	103	77, 591
CF_3	$CF_3CF_2CF_2$	b.p. 123	49
CF_3CHF	CF_3CHF	67	75, 77, 591
$CF_3CF_2CF_2$	$CF_3CF_2CF_2$	b.p. 150	49
$CF_2=CHCH_2$	$CF_2=CHCH_2$	b.p. 75–80	75
$C_6H_5CH=NN=C(CH_3)$	$C_6H_5CH=NN=C(CH_3)$	164	14
		42	480
2. *Arylalkyl*			
$C_6H_5CH_2$	$C_6H_6CH_2$	74	230, 238, 406, 409, 581
4-$H_2NC_6H_4CH_2$	4-$H_2NC_6H_4CH_2$	166	239
4-$CH_3CONHC_6H_4CH_2$	4-$CH_3CONHC_6H_4CH_2$	205	239
4-(2-$HOC_{10}H_7N=N)C_6H_4CH_2$	4-(2-$HOC_{10}H_7N=N)C_6H_4CH_2$	200d	239
4-$CH_3C_6H_4C(OH)(CH_3)$	CH_3	83–86 rac.	48

TABLE II-1. (continued)



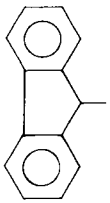
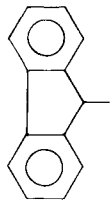
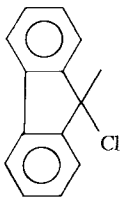
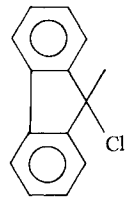
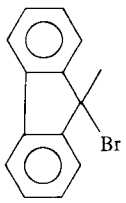
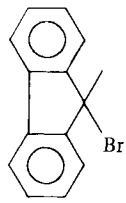
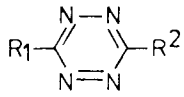
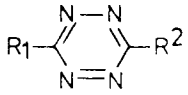
R^1	R^2	m.p. (°C)	Refs.
$C_6H_5C(CH_3)(OH)$	$C_6H_5C(CH_3)(OH)$	133 rac.	353
		186 meso	353
		121 (+ or −)	353
$C_6H_5C(C_2H_5)(OH)$	$C_6H_5C(C_2H_5)(OH)$	101 rac.	150, 353
		161 meso	150, 353
		191 (+ or −)	150, 353
4-$CH_3C_6H_4C(CH_3)(OH)$	4-$CH_3C_6H_5C(CH_3)(OH)$	139 rac.	48, 353
		166 meso	48, 353
		117 (+ or −)	353
$(C_6H_5)_2CH$	CH_3	108	20
$(C_6H_5)_2CH$	$(C_6H_5)_2CH$	172	18, 20, 540
$(C_6H_5)_2C(Cl)$	$(C_6H_5)_2C(Cl)$	162 (dec.)	542
$(C_6H_5)_2C(Br)$	$(C_6H_5)_2C(Br)$	162	542
$C_6H_5SO_2CH_2$	$C_6H_5SO_2CH_2$	244	30
		225	541
		206 (dec.)	541
		206 (dec.)	541

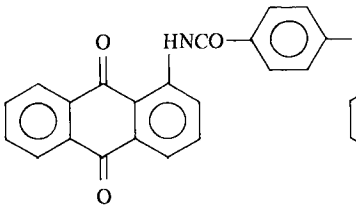
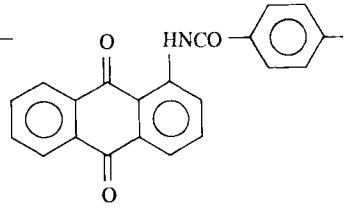
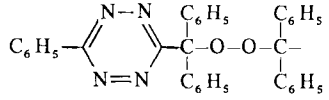
TABLE II-1. (continued)



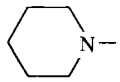
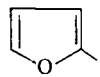
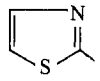
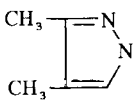
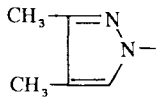
R^1	R^2	m.p. (°C)	Refs.
C_6H_5CO	C_6H_5CO	196	15
4-$CH_3C_6H_4CO$	4-$CH_3C_6H_4CO$	173	15
3. *Aryl*			
C_6H_5	H	195	48, 332
C_6H_5	CH_3	75	48
4-$CH_3C_6H_4$	H	84.5	332
C_6H_5	$C_6H_5CH_2$	110	48
C_6H_5	$(C_6H_5)_2CH$	136	18, 19
C_6H_5	$(C_6H_5)_2C(OH)$	137	19
C_6H_5	$(C_6H_5)_2C(OC_2H_5)$	161	19
C_6H_5	$(C_6H_5)_2C(Br)$	126	19
C_6H_5	C_6H_5	175, 193	67, 165, 208, 222, 238, 241, 304, 325, 349, 403, 407, 478, 479, 561, 583
3-$CH_3C_6H_5$	3-$CH_3C_6H_5$	150	349
4-$CH_3C_6H_5$	4-$CH_3C_6H_5$	235	325, 349, 407, 409, 583
4-$(CH_3)_2CHC_6H_4$	4-$(CH_3)_2CHC_6H_4$	156	89
4-$C_6H_5C_6H_4$	4-$C_6H_5C_6H_4$	257	575
4-FC_6H_4	4-FC_6H_4	–	241
3-ClC_6H_4	3-ClC_6H_4	215	398, 496
4-ClC_6H_4	4-ClC_6H_4	298, 315	325, 496, 544
4-BrC_6H_4	4-BrC_6H_4	288, 337	241, 325, 496, 544
3-$NO_2C_6H_4$	3-$NO_2C_6H_4$	215	496
4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	215	409
3,4-$(OCH_2O)C_6H_3$	3,4-$(OCH_2O)C_6H_3$	270	117
3-$H_2NC_6H_4$	3-$H_2NC_6H_4$	295	239
3-$CH_3CONHC_6H_4$	3-$CH_3CONHC_6H_4$	295	239

TABLE II-1. (continued)



R^1	R^2	m.p. (°C)	Refs.
3-$HOOCC_2H_4$	3-$HOOCC_6H_4$	270–280 (dec.)	113
Acid hydrazine salt		>277	113
Dipyridinium salt		300–301 (dec.)	113
4-$HOOCC_6H_4$	4-$HOOCC_6H_4$	–	463
			463
1-$C_{10}H_7$	1-$C_{10}H_7$	185	239
2-$C_{10}H_7$	2-$C_{10}H_7$	240	239, 349, 406, 409, 583
C_6H_5		–	19

4. *Heterocyclic*

C_6H_5		121	179
C_6H_5		134	179
		195	408, 409
		226	117, 301
		223	70

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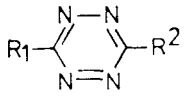


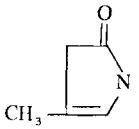
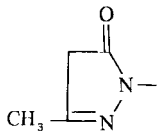
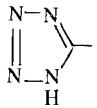
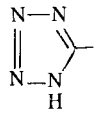
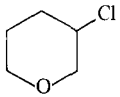
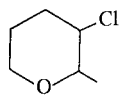
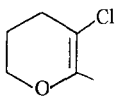
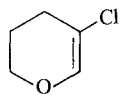
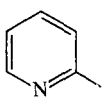
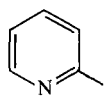
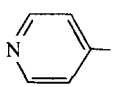
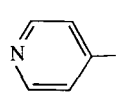
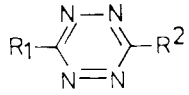
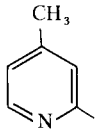
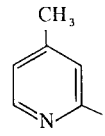
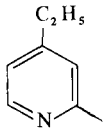
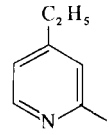
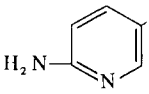
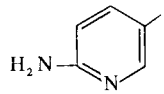
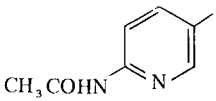
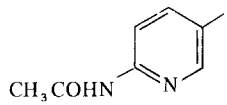
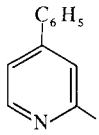
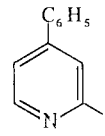
R^1	R^2	m.p. (°C)	Refs.
		–	314
		dec.	109, 296–298
Ammonium salt		210	298
Potassium and sodium salts		–	298
		161	446
		175	446
		198	446
		222 (dec.), 230	71, 117, 168, 567
		198	117
		258, 262, 275	84, 117,
Dimethyl sulfate salt		200	293

TABLE II-1. (continued)



R^1	R^2	m.p. (°C)	Refs.
		244	80
		134	80
		312	301
		277	301
		247	80

compounds of this type melt at fairly low temperatures. All the 1,2,4,5-tetrazines substituted with arylalkyl, aryl, and heterocyclic groups are solids with medium to high melting points. 1,2,4,5-Tetrazine is soluble in water and most organic solvents, and the higher homologues are also soluble in organic solvents. Salts of 1,2,4,5-tetrazines with potassium, silver nitrate, mercuric chloride, auric chloride, and chloroplatinic acid have been reported, but they are of no definite composition and are unstable (102, 581). The nitrogen atoms of 1,2,4,5-tetrazines are not basic.

The electronic spectra of 1,2,4,5-tetrazines and a few higher members of the series have been of great interest to physical chemists and physicists and have been studied extensively both by using molecular orbital calculations and by experimental observations. All 1,2,4,5-tetrazines are colored and so must absorb visible light. The usual wavelength of absorption is in the region of 520 to 570 nm (49, 77, 84, 117, 180, 181, 255, 299, 319, 320, 349, 446, 511, 513) with an absorptivity of a few hundred. The peak in this region is usually considered to be due to $n \rightarrow \pi^*$ transitions with an electron of a lone pair being promoted into a π^* bond (137, 176, 177, 243, 255, 319, 320, 389, 390, 519–521, 555). The energy required is of the order of 2.25 eV (177, 555). The effect of various chemicals on this transition state has been studied in 1,2,4,5-tetrazines when the tetrazine was absorbed on glass (29). The $n \rightarrow \pi^*$ transition has been considered (176, 177) using the LCAO MO method for calculating transition energies and also by the semiempirical theory of electronic spectra of Parisier and Parr (390). Various workers (50, 226, 322, 519–521) have investigated the fine structure of the visible absorption spectrum. 1,2,4,5-Tetrazines also have a maximum in their ultraviolet spectra at about 250–300 nm with absorptivities of 2000 to 4000 (49, 77, 84, 117, 180, 181 299 319, 320, 446, 511, 513). The position of the maximum can be substantially modified by the presence of aromatic or heterocyclic substituents (117, 446). The short-wavelength maximum is due to a $\pi \rightarrow \pi^*$ transition. Weak absorption can also occur as a shoulder at about 320 nm (320). Molecular orbital studies using the Parisier–Parr–Pople modification (148, 149, 155) as well as the LCAO SCF MO (323) and the Hückel molecular orbital (HMO) (373) treatments have been used to calculate transition energies and intensities of $\pi \rightarrow \pi^*$ bands. The HMO calculation (254 nm) agreed very well with the observed maximum at 252 nm.

There has been a great deal of interest in the fluorescence of 1,2,4,5-tetrazines and considerable discussion of its source (45, 87, 88, 137, 139, 245). It seems most reasonable to consider that the effect is due to the singlet (n, π^*) state (137) although it has been suggested (139) that fluorescence results from an $S\ (n, \pi^*) \rightarrow T\ (\pi, \pi^*)$ process. The quantum efficiency of fluorescence has been found to be low, and this may be due to decomposition (563).

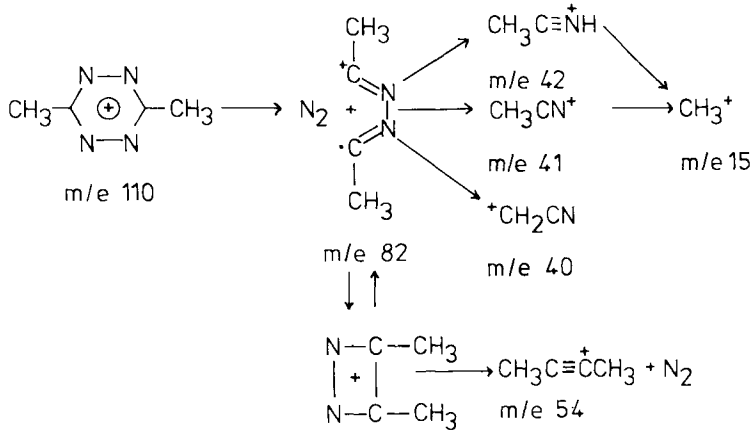
Murrell (350) has discussed the electronic spectra of 1,2,4,5-tetrazines from the standpoint that such spectra can be derived by considering them to be the result of perturbation in benzene spectra.

The absorption of 1,2,4,5-tetrazines in the infrared region are those expected for the system present in addition to which any substitutents contribute their own absorption. In the infrared spectra there are usually bands due to N–N stretching at 1650 cm^{-1}, C=N vibrations at 1430 cm^{-1}, and C–N vibrations at 1375 to 1400, 1140 to 1000, and 930 to 910 cm^{-1} (117, 245, 313, 513, 575). A number of investigations of the IR spectrum of 1,2,4,5-tetrazine, of its

deuterated analogues, and of the ring system containing a few simple substituents have been made in which theoretical calculations and, in some cases, experimental evidence were used to assign fundamental vibrational frequencies (37, 38, 45, 157, 351, 505, 520, 521). Several vibrational spectra investigations have also included Raman spectra (37, 157, 245, 505).

The NMR spectra of the 1,2,4,5-tetrazine nucleus have been reported for ^{1}H, ^{13}C, and ^{14}N. In the case of the proton spectra for the parent compound no chemical shifts have been published, but a calculated chemical shift of 10.48 ppm has been reported by Nicholson (372). This value was derived from the values of benzene, pyridine, pyridazine, and pyrimidine. 3,6-Dialkyl-1,2,4,5-tetrazines have the expected downfield shift (2.97 to 3.60 ppm) for α-protons (513). 3,6-Diaryl- and 3,6-diheterocyclic-1,2,4,5-tetrazines show a strong interaction of the protons with the nitrogen atoms of the tetrazine ring (43, 81, 189). The chemical shifts of the carbon atoms of the rings of 1,2,4,5-tetrazine and 3,6-dimethyl-1,2,4,5-tetrazine are 161.2 and 166.6 ppm, respectively, and the ^{13}C of the methyl substituent gives rise to a signal at 20.8 ppm (3, 290). Attempts have been made to calculate ^{13}C chemical shifts (3, 555), but the values obtained were in poor agreement with the experimental results. Witanowski and co-workers (580) have reported calculated values for the ^{14}N NMR chemical shift.

The mass spectrum of 1,2,4,5-tetrazine is a fairly simple one showing the expected ions (158, 245, 513, 569). The molecular ion (*m/e* 82) is obtained, but the most abundant ions (*m/e* 28) result from fragmentation to N_2 and H_2CN^+. Other fragments are *m/e* 54 arising from $H_2C_2N_2^+$, *m/e* 29 from N_2H^+, *m/e* 27 from HCN^+, and *m/e* 24 from C_2^+, which is derived from a cyclic four-membered ion. Weininger and Thornton (569) have proposed the scheme given in eq. II-20 to account for ions obtained in the mass spectrum of



(20)

3,6-dimethyl-1,2,4,5-tetrazine. The mass spectra of a series of 3,6-dialkyl-1,2,4,5-tetrazines have been studied, and it was stated that among the principal ions were those arising by loss of N_2 and cleavage to give RCN^+ or one H more or less (289). Yates and Meresz (588) have studied the mass spectra of a number of 3,6-diaryl- and 3,6-diarylalkyl-1,2,4,5-tetrazines. It was found that there was an excess of $M+2$ ions, which was believed to be due to reduction of the tetrazines to dihydrotetrazines in the ion source of the mass spectrometer.

A number of crystallographic studies of the structure of 1,2,4,5-tetrazine have been published (35, 39, 40, 302), and also one of 3,6-diphenyl-1,2,4,5-tetrazine (5). The unit cell of 1,2,4,5-tetrazine contains two molecules and is monoclinic with the following dimensions: $a = 5.23$, $b = 5.79$, $c = 6.63 \pm 0.01$ Å; $\beta = 115°30' \pm 15'$. The bond distances are 1.334 Å for the C–N bond and 1.321 Å for the N–N bond. The bond angles were found to be 115°27′ for the C–N–N bond angle and 127°22′ for the N–C–N bond angle. The molecule is planar, which is consistent with the view that the nitrogen atoms are sp^2 hybridized and one of the nitrogen p electrons takes part in the π-bond system of the ring. Molecular orbital calculations of bond lengths using the LCAO MO method (302, 303) and the LCAO SCF MO method (411) have agreed well with experimental results. Theoretical calculations of bond angles (92, 93, 123, 195, 253) have also given good agreement with experimental values.

Calculations of the resonance energy of 1,2,4,5-tetrazine have been made by Maccoll (311) and by Liquori and Vaciago (302). A value of 20 kcal/mole was found by Maccoll, but it is now known that his method of calculation gives erroneous results. The latter authors report 40 kcal/mole. These values indicate a substantial resonance stabilization and are such that aromaticity would be expected. Furthermore, bond orders calculated by variants of the LCAO MO method (303, 411) are 0.66 for both the C–N and N–N bonds, and bond lengths measured experimentally are consistent with aromaticity. However, the instability of 1,2,4,5-tetrazine and the chemical reactivity of this class of compounds indicate a lack of aromaticity.

A number of publications (31, 43, 44, 122, 285, 292, 427, 432, 570) have discussed a variety of molecular orbital calculations and other procedures for calculating electron densities on the various atoms of 1,2,4,5-tetrazines and a few of its substituted analogues. These have been expressed in several different ways, but in general it was concluded that the carbon atoms of 1,2,4,5-tetrazine have a slight positive charge whereas the nitrogen atoms are negative. Kwiatkowski and Zurawski (285) have used these values to predict reactivity sites in electrophilic, nucleophilic, and free-radical reactions.

The Parisier–Parr–Pople MO method has been used to calculate ionization potentials for 1,2,4,5-tetrazine (155, 432, 548, 582). Flurry, Stout, and Bell (155) have reported a value of 11.18 eV, which is in good agreement with results reported by Sundbom (548). It was concluded from these studies that the lowest

ionization potential is derived from nonbonding orbitals. Fridh and co-workers (158) derived ionization potentials from photoelectron spectroscopy and also conclude that the lowest ionization potential is derived from lone-pair electrons but having some bonding properties.

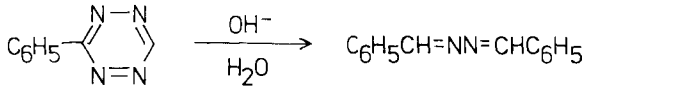
The electron spin resonance of 1,2,4,5-tetrazine radicals and its 3,6-dialkyl analogues have been investigated by several workers (147, 169, 312, 545). Both anion and cation radicals generated by several procedures have been studied. The ESR spectra of 3,6-dialkyl-1,2,4,5-tetrazine radicals contained 63 well-defined lines (312). Coupling constants have been reported by Stone and Maki (545) for 1,2,4,5-tetrazine anion radicals, and by Gerson and Skorianetz (169) for both anion and cation radicals of 3,6-dimethyl-1,2,4,5-tetrazine. In both cases the N–N values were about 5.3 with H on the ring giving about 0.21 and H in CH_3 about 1.6. The LCAO SCF MO method has been used to calculate ESR spectra (342), and other molecular orbital calculations have been applied to determine hyperfine splitting constants (427, 546).

Many other physical properties of 1,2,4,5-tetrazine lacking sufficient significance to be discussed in detail have been reported in the literature and are listed below for the sake of complete literature coverage. Berezin (36) has discussed coefficients of influence from the standpoint of measurement of aromaticity. Bond polarizabilities have been treated by the LCAO MO method (121). Calculated dipole moments have been reported (122, 432). The asymmetric parameter of 1,2,4,5-tetrazine has been determined from IR bands (156). Photoelectron spectra have been investigated (174). Matrix elements have been determined and applied to the elucidation of various parameters (207, 291, 351). Innes and co-workers (223, 224, 227) have discussed orbital configurations symmetry of excited states. The same workers (225, 226) have considered contour analysis of $n \rightarrow \pi^*$ transition states. Systems of force constants and coefficients of effect have been derived from vibrational spectra (351). The orbital energies of 1,2,4,5-tetrazine have been calculated by the LCAO SCF MO method (411). Zorkii and Bel'skii (594) have considered 1,2,4,5-tetrazine as a centrosymmetric molecule and classified it within the family of such compounds. Molecular orbital calculations have been used to investigate electron position and bond character (318, 324, 589).

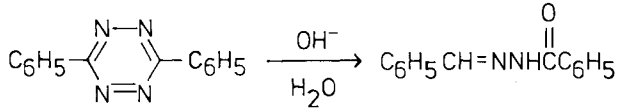
D. Reactions

1,2,4,5-Tetrazines are unstable to both acids and bases. Resistance to hydrolysis depends upon substituents present with 3,6-diaryl-1,2,4,5-tetrazines being the most stable. In the case of acid hydrolysis hydrazine and nitrogen are always formed (104, 111, 349). In some publications the only other product mentioned has been acids, but in others aldehyde formation has been reported.

Only a few examples of base hydrolysis have been published. Mester (333) has discussed the aqueous base hydrolysis of 1,2,4,5-tetrazine, but none of the direct hydrolysis products were mentioned. 3-Phenyl-1,2,4,5-tetrazine has been hydrolyzed with base to give benzaldehyde azine in 80% yield (eq. II-21) (428). The formation of benzaldehyde azine indicates that hydrazine and benzaldehyde were hydrolysis products. Pinner (404) treated 3,6-diphenyl-1,2,4,5-tetrazine with aqueous potassium hydroxide to form benzoylphenylhydrazone (eq. II-22).



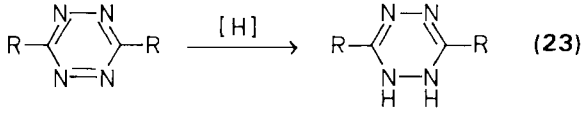
(21)



(22)

Libman and Slack (293) obtained the analogous acylhydrazone by hydrolysis of 3,6-bis(3-pyridyl)-1,2,4,5-tetrazine with sodium carbonate solution. A completely analogous reaction occurred by the action of alcoholic sodium hydroxide on 3,6-bis(2,3-dihydro-5-chloro-6-pyranyl)-1,2,4,5-tetrazine. The fate of the remaining nitrogen in these reactions was not reported, but presumably it was evolved as nitrogen. In some of the acid hydrolyses and in all of the base hydrolyses it was established that one of the carbon atoms derived from the tetrazine ring was reduced from an acid oxidation level to an aldehyde level. Libman and Slack (293) have proposed a mechanism for hydrolysis which involves a diazo hydroxide as an intermediate, but such a mechanism appears highly improbable. It seems more likely that diimide or its equivalent is formed in the reaction and brings about the reduction with concomitant nitrogen formation. In those cases of acid hydrolysis in which aldehyde was not reported as a product it is probable that it was formed and was not isolated.

Reduction of 1,2,4,5-tetrazines with mild reducing agents occurs quite easily with the usual product being the corresponding 1,2,-dihydro-1,2,4,5-tetrazine (eq. II-23). Such reduction has been done with hydrogen sulfide (49, 103),

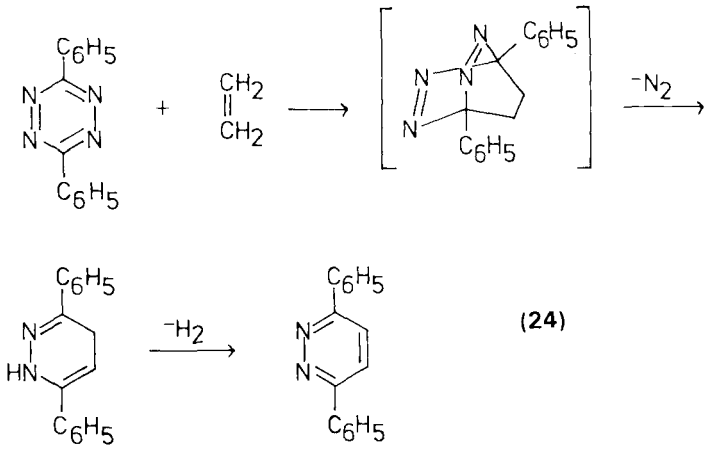


(23)

sodium dithionite (150, 559), photochemically in the presence of methanol (204), and with a 1,4-dihydropyridazine obtained as a reaction intermediate (41). In the photochemical reduction it was hypothesized that the excited triplet

state of the tetrazine abstracted protons from the solvent. Electrochemical reductions have been carried out, but the product was not specified (379, 570). Presumably it was a 1,2-dihydro-1,2,4,5-tetrazine. 3,6-Dimethyl-1,2,4,5-tetrazine has been reduced with the corresponding hexahydro-1,2,4,5-tetrazine to 3,6-dimethyl-1,4-dihydro-1,2,4,5-tetrazine in 36% yield (514). The use of lithium aluminium hydride and sodium borohydride to reduce 3,6-diphenyl-1,2,4,5-tetrazine formed benzaldehyde azine and hydrazine (559).

Carboni (75) first reported in a 1957 patent the important reaction of 1,2,4,5-tetrazines with olefins in a Diels–Alder type of reaction with the tetrazine acting as the diene. The reaction was subsequently elaborated by Carboni and Lindsey (76, 78) and has been investigated extensively by others. The reaction is illustrated in eq. II-24 using 3,6-diphenyl-1,2,4,5-tetrazine and ethylene, but it is a very general reaction for olefins of almost all types and

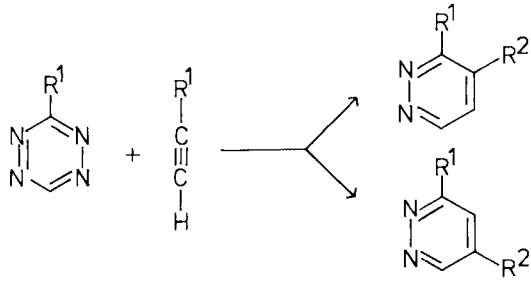


(24)

occurs with many tetrazines. Olefins react with 1,2,4,5-tetrazines quite readily and in many cases give quite high yields, although the yield varies considerably with the reactants used. The first product is normally the 1,4-dihydropyridazine, as has been shown by ultraviolet and infrared spectra (78). The dihydro compound can then be oxidized to the pyridazine, although frequently the 1,4-dihydropyridazine is not isolable and the first product obtained is the pyridazine. When an acetylenic dienophile is used, a pyridazine is formed directly with no dihydropyridazine intermediate. The reaction of a cyclic olefin normally gives a 4,5-dihydropyridazine (78, 205, 473, 553) but occasionally hydrogen is lost spontaneously forming a pyridazine (471).

Only a limited number of 1,2,4,5-tetrazines have been used as dienes, and almost all of these have been symmetrical compounds. In the earliest work (78) the 1,2,4,5-tetrazines were substituted in the 3- and 6-positions with fluorinated

alkyl groups. The most popular tetrazine has been 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine (71, 328, 384, 385, 431, 471, 553, 567, 578, 579), followed by the 3,6-diphenyl compound (75, 76, 78, 205, 316, 391, 473, 526). 3,6-Bis(4-bromophenyl)-1,2,4,5-tetrazine has been used, as have dialkyl-substituted tetrazines, primarily methyl (75, 76, 78, 316, 473, 513). In addition 3-phenyl- and 3-(4-tolyl)-1,2,4,6-tetrazine were reported to undergo reaction with olefins (332). It has been shown that the 1,2,4,5-tetrazines having fluoroalkyl substituents react more readily than tetrazines substituted with methyl or phenyl groups (78). The greater reactivity was attributed to an electron-withdrawing effect making for a more positive charge at the reaction site. The superior reactivity of 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine has been rationalized on the same basis (71). When unsymmetrical 1,2,4,5-tetrazines and unsymmetrical olefins are used, the possibility exists that addition can occur to give two different products (eq. II-25). In the three cases studied the reaction gave

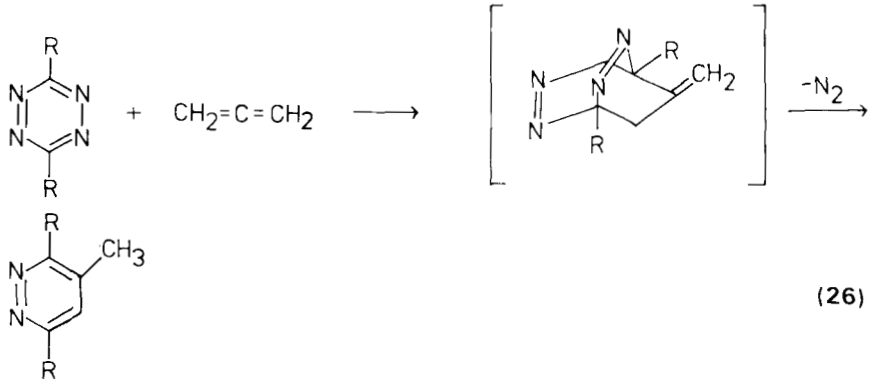


(25)

examples of addition in both possible ways in the same reaction, addition to give *ortho* substituents and addition to give *meta* substituents (332).

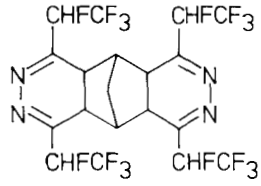
A large number of olefins have been shown to react with 1,2,4,5-tetrazines starting with the simplest, ethylene (21, 474). Monosubstituted olefins such as acrylonitrile, styrene, and isobutylvinyl ether have been used (71, 78). Disubstituted olefins, both 1,1 and 1,2, have been found reactive, for example, α-methylstyrene, β-methylstyrene, and ketene acetal (78, 473). The conjugated dienes butadiene and isoprene and the 1,2-diene allene are quite suitable reactants (78). A large number of cyclic olefins have been used in the tetrazine Diels–Alder reaction. Among them have been many substituted cyclopropenes (205, 473, 526), cyclobutenes (391, 567, 578), cyclopentenes (78, 316), cyclohexene (78), norbornene, and norbornadiene (78, 473, 579), as well as a number of quite complex polycyclic olefins (328, 384, 385) related to norbornadiene for the most part (328, 384, 385, 553) but including others (431, 471, 567, 578). The few acetylenes that have been used are acetylene, methylacetylene, phenylacetylene, 1,2-diphenylacetylene, benzyne, cyclopentyne (78, 316, 332, 473), and (trimethylsilyl)acetylenes (41). Paquette and co-workers (391) have used cyclobutadiene formed *in situ*.

The usual result of reaction has already been mentioned, but some dienophiles give rise to somewhat different products or can react in more than one way. For example, allene reacts to give a methyl-substituted pyridazine by proton rearrangement of the intermediates rather than oxidation (eq. II-26) (78). Norbornadiene has been reported to react in several different ways.



(26)

Carboni (78) has found that reaction occurs with 3,6-bis(fluoroalkyl)-1,2,4,5-tetrazines at both of the double bonds in norbornadiene to give a product containing two pyridazine rings (**5**). Wilson and Warrener (579) have reported the normal reaction in quantitative yield using 3,6-bis(2-pyridyl)-1,2,4,5-



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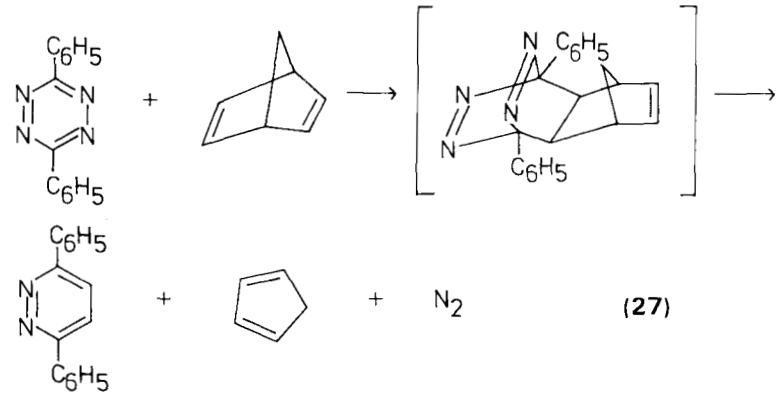
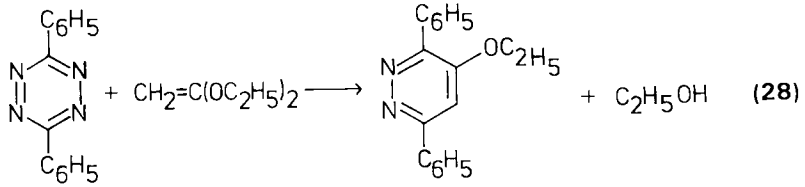


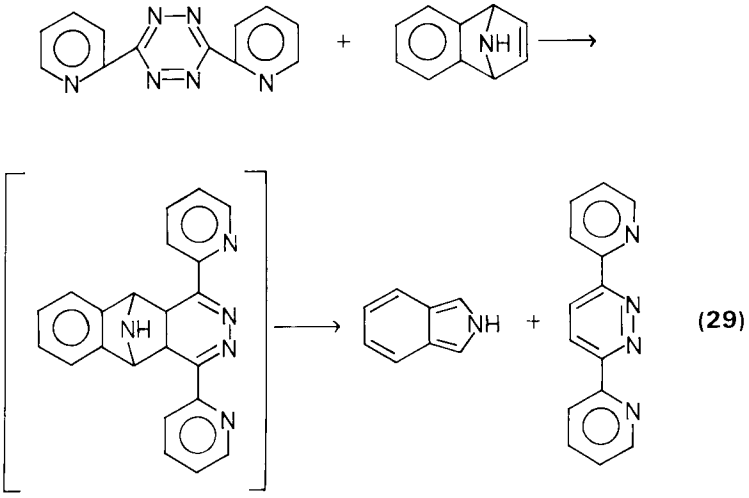
(27)

tetrazine. Sauer and Heinrichs (473) have discovered a third pathway of reaction with 3,6-diphenyl-1,2,4,5-tetrazine in which the first 1:1 adduct loses nitrogen and undergoes a reverse Diels–Alder reaction to give 3,6-diphenylpyridazine and cyclopentadiene (eq. II-27). In the reaction of olefins having two alkoxy or amino substituents on one carbon atom, the intermediate dihydropyridazine is not isolable, and the product is the pyridazine with loss of an alcohol or an amine (eq. II-28) (473). The Diels–Alder reaction has been used with advantage



(28)

being taken of a very unstable intermediate to synthesize isoindole as shown in eq. II-29 (431). This reaction also involves a reverse Diels–Alder reaction. The isoindole was best isolated as an adduct with dienophiles because of its instability.

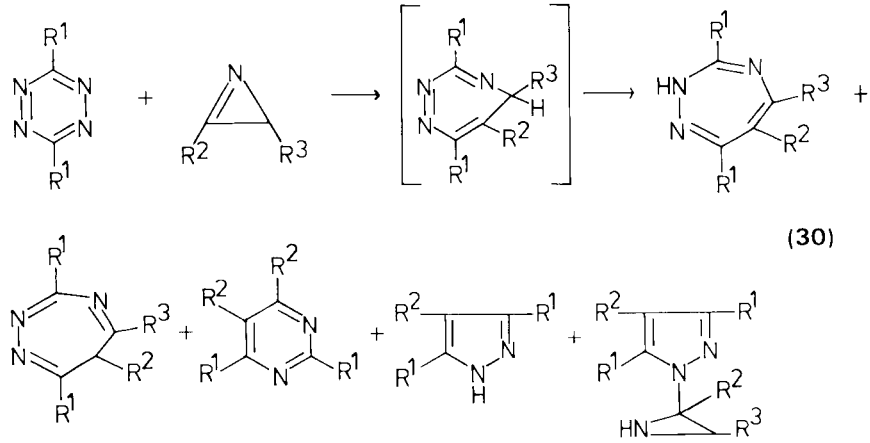


(29)

Olefins having electron-releasing groups, such as isobutylvinyl ether and butadiene, react more rapidly than those having electron-attracting groups such as acrolein and acrylonitrile (78, 385, 473). A difference of 47000-fold in reaction rate has been reported for α-(4-morpholino)styrene over acrylonitrile. The reaction of 1,2,3,4,7-hexachloronorbornadiene with 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine requires 7 days at 80°C as compared to room temperature in a few hours for many olefins (578). Terminal olefins react more rapidly than do

nonterminal compounds as shown by comparison of the reactivities of α- and β-methylstyrene (78).

A reaction very similar to the Diels–Alder reaction of 1,2,4,5-tetrazines is their reaction with Δ^1-azirines to give 1,2,4-triazepines (7). With the Δ^1-azirine the reaction that presumably occurs (eq. II-30) is normally followed by loss of nitrogen and opening of the three-membered ring. The resulting intermediate



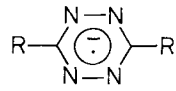
(30)

then undergoes further reaction to give the two triazepines by rearrangement and the pyrimidine and pyrazole by loss of fragments of the intermediate. The pyrazole–aziridine compound is formed by reaction of aziridine still present with pyrazole formed in the reaction (331). A similar reaction occurs with cyclopropenes under the influence of heat giving 1,2-diazepines (205).

Although examples of thermal degradation of 1,2,4,5-tetrazines in which the products were identified are few, the cases reported suggest that the products are largely nitriles and nitrogen. At least this is the case with 1,2,4,5-tetrazine, whose decomposition occurs readily at room temperature, and with 3,6-diphenyl-1,2,4,5-tetrazine, which requires an elevated temperature (225°C) to form benzonitrile and nitrogen (78). Photolysis gives a similar decomposition (480).

A series of 1,2,4,5-tetrazines having 2-pyridyl and substituted 2-pyridyl substituents at the 3- and 6-positions have been found to form complexes with salts of the *3d* subgroup elements (193, 483). The salts used were $FeCl_2$, $ZnCl_2$, $CrBr_2$, $CuCl_2$, $NiBr_2$, $NiCl_2$, $CoBr_2$, $CoCl_2$, and $MnCl_2$. These salts all reacted in a 1:1 ratio with the tetrazines. It was proposed that such complexes could be used as a method of determining the metals by extracting the complexes with solvents and determining by photometric methods (483) the amount of 1,2,4,5-tetrazine bound.

3,6-Dialkyl-1,2,4,5-tetrazines readily form radical anions (**6**) with potassium

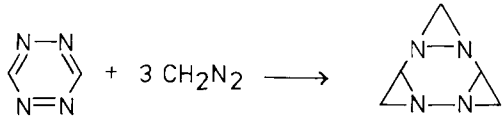


6

tert-butoxide (312, 462) or a sodium–potassium amalgam (312). The radicals were detected by ESR spectroscopy. 3,6-Diphenyl-1,2,4,5-tetrazine forms radical anions only in the presence of some suitable electron donor such as a dihydro-1,2,4,5-tetrazine. Skorianetz and Kováts (514) have shown that 3,6-dimethyl-1,2,4,5-tetrazine forms a charge-transfer complex with 3,6-dimethyl-1,4-dihydro-1,2,4,5-tetrazine, in which it is thought that the 1,2,4,5-tetrazine is a radical anion and the 1,4-dihydro compound is a radical cation. The radical anion of 3,6-dimethyl-1,2,4,5-tetrazine has been prepared by the reaction of the tetrazine with 3,6-dimethyl-1,4-dihydro-1,2,4,5-tetrazine in the presence of base (169).

1,2,4,5-Tetrazines form five-membered rings under either oxidizing or strongly reducing conditions. Oxidation with peracetic acid gives a 2,5-disubstituted 1,3,4-oxadiazole (6, 353), whereas reduction with zinc and acetic acid under suitable conditions forms a 2,5-disubstituted 1,3,4-triazole (559). The latter reaction undoubtedly proceeds through a 1,2-dihydro-1,2,4,5-tetrazine, which rearranges to the 4-aminotriazole followed by removal of the amino group by reduction.

Müller (348) has claimed that diazomethane reacts with 1,2,4,5-tetrazine to form a polycyclic saturated tetrazine (7). This product is rather unlikely, and



(31)

7

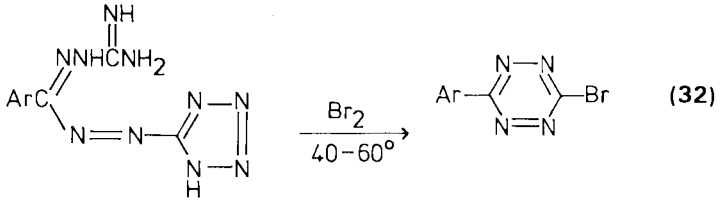
very few data were reported to substantiate the structure. Meerwein (330) stated that the presence of 1,2,4,5-tetrazine in small quantities retards the polymerization of diazomethane.

II. 1,2,4,5-TETRAZINES SUBSTITUTED BY CARBOXYL GROUPS, DERIVATIVES OF CARBOXYL GROUPS, AND HETERO ATOMS

A. Preparation

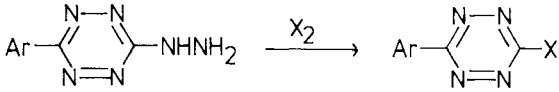
Only a few halogenated 1,2,4,5-tetrazines are known, and all of them have only one halogen substituent. Two methods are known for preparing such

compounds. One method involves cyclization of a *C*-arylguanyl-N^1-(5-tetrazolyl)formazan to a 1,2,4,5-tetrazine ring with bromine (eq. II-32) and must involve considerable oxidation of the formazan substituents (179). The yields are 35 to 40% when the *C*-substituent is phenyl or a substituted phenyl group,



(32)

but no tetrazines were obtained when 3-pyridyl or thienyl formazans were used. Ershov and Postovskii (143, 144) have replaced the hydrazino substituent in 3-hydrazino-6-aryl-1,2,4,5-tetrazines with chlorine and bromine in excellent yields to form 3-halogenated 1,2,4,5-tetrazines (eq. II-33). When the halogen was iodine, the hydrazino substituent was not replaced but oxidized instead.



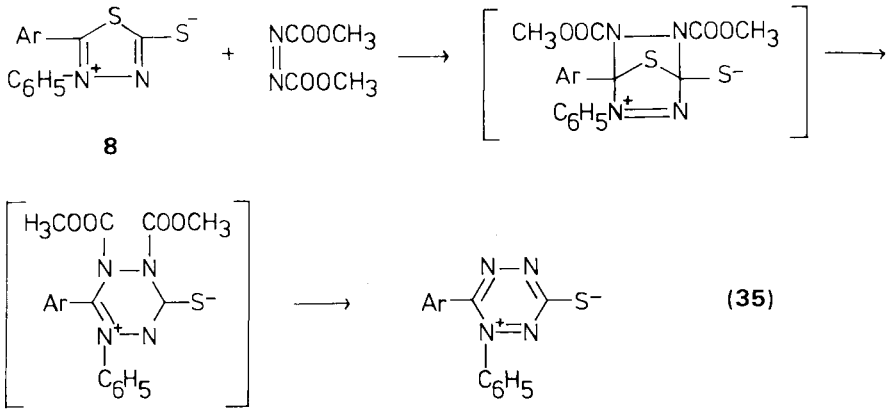
$X_2 = Cl_2$ or Br_2 (33)

Only four 1,2,4,5-tetrazines having oxygen attached at one or both of the 3- and 6-positions have been reported, and the evidence for one of them is very weak. Gryskiewicz-Trochimowski and Bousquet (188) prepared 3,6-dicyano-1,2,4,5-tetrazine and suggested that a solution of the dicyano compound in ether exposed to air formed 3,6-dihydroxy-1,2,4,5-tetrazine (eq. II-34). There was very little evidence for such a product since it was not isolated. Two

(34)

3-hydroxy-6-aryl-1,2,4,5-tetrazines have been prepared by treatment of 3-bromo analogues with aqueous base (179). Oxidation of 3,6-diphenoxy-1,2-dihydro-1,2,4,5-tetrazine (eq. II-1) has been used to prepare 3,6-diphenoxy-1,2,4,5-tetrazine.

1,2,4,5-Tetrazines substituted with sulfur at both the 3- and 6-positions were also prepared by oxidation of the corresponding 1,2-dihydro compounds using ferric chloride (308, 310, 467). Compounds having only one sulfur substituent have been prepared by a *de novo* 1,2,4,5-tetrazine ring synthesis starting with mesionic thiadiazoles (8) and allowing them to react with dimethyl azodicarboxylate (eq. II-35) (341). The proposed structure of the product was supported



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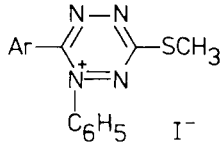
9

(35)

by considerable spectral data and by reactions. The structure was published as **9** but it seems probable that it actually has a mesionic electron delocalized structure which can only formally be considered as a 1,2,4,5-tetrazine. The yields are about 60%. Reaction of **9** with methyl iodide gives what were described as methiodides but may be 3-(methylmercapto)-6-aryl-1,2,4,5-tetrazines as quaternary salts (**10**).



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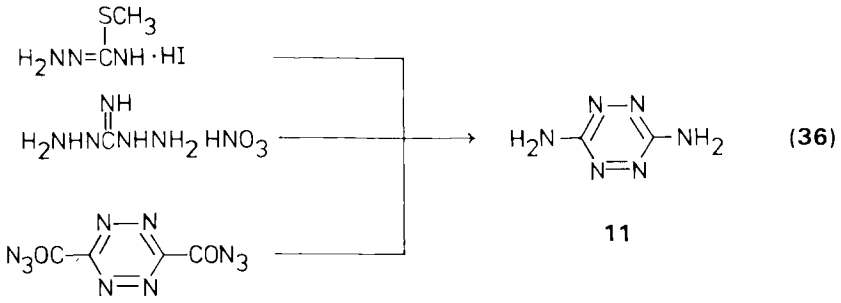
The synthesis of 3,6-diamino-1,2,4,5-tetrazine has been accomplished both by reactions forming the 1,2,4,5-tetrazine ring carrying the proper substituents (299) and by Curtius rearrangement of the 3,6-bis(azidocarbonyl)-1,2,4,5-tetrazine system (eq. II-36) (299). Scott and Reilly (497) have also cyclized *S*-methylisothiosemicarbazide, and their discussion indicates that the product was **11** but they give the structural formula for 3,6-diamino-1,4-dihydro-1,2,4,5-tetrazine. However, because Lin and co-workers (299) found that the product has the typical 1,2,4,5-tetrazine maximum in the visible spectrum at 528 nm, log ϵ_{max} 2.77, it seems safe to conclude that the product was **11**. McKay and co-workers (329) have also cyclized *S*-methylisothiosemicarbazide using dodecylamine. The yield of **11** was very low, the principal product being 4′-(dodecylamino)guanidine. In addition a 25% yield of 3,4,5-triamino-1,2,4-triazole was obtained. Since the reaction was run at 80°C this product would be consistent

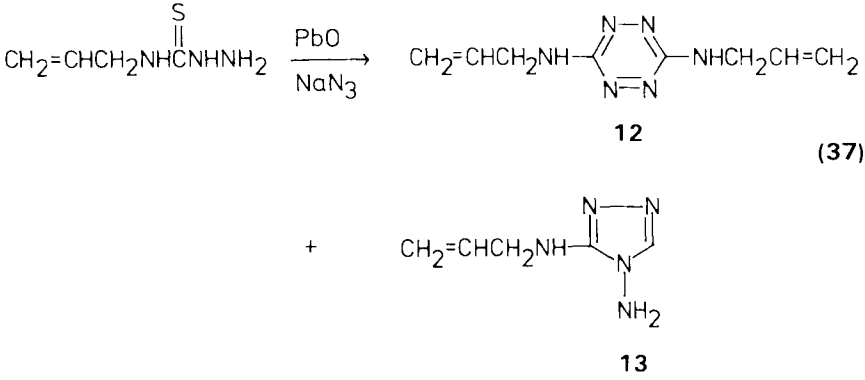


(36)

11

with formation of 3,6-diamino-1,2-dihydro-1,2,4,5-tetrazine followed by rearrangement to triazole. Ponzio and Gastaldi (422–425) claimed to have synthesized **11**, but Lin, Lieber, and Horowitz (299) and Scott and Reilly (497) have shown that the product was not **11**. Marcus and Remanick (315) have reported hat 3,6-diamino-1,2,4,5-tetrazine is formed when the 1,2-dihydro analogue is treated with base.

Only a few procedures are known for synthesizing symmetrical 3,6-diamino-1,2,4,5-tetrazines having substituents on the amino groups. Stollé and Gärtner (538) have reported the preparation of 3,6-bis(allylamino)-1,2,4,5-tetrazine (**12**) by the action of lead monoxide and sodium azide on 4-allylthiosemicarbazide (eq. II-37). The 1,2,4,5-tetrazine was a minor by-product probably formed by dimerization of the thiosemicarbazide; the main product was the triazole **13**

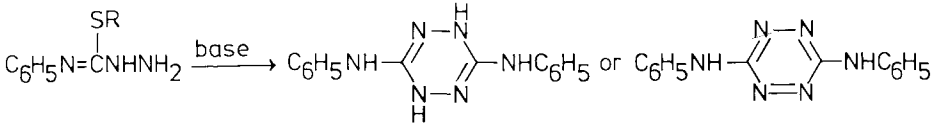


(37)

12

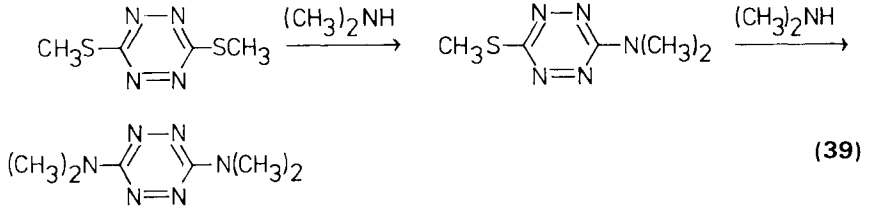
13

which was formed in an entirely different process. A similar reaction has been studied by Scott (493) who treated *S*-alkyl-4-phenylisothiosemicarbazide nitrates with various aliphatic and aromatic bases to give triazoles and small amounts of a 1,2,4,5-tetrazine (eq. II-38). The product, reported to have a molecular formula of $C_{14}H_{14}N_6$, was described as 1,4-dianilinotetrazine, and the structural formula given was **14**. However, the melting point and color, which was described as being a dark red-purple, would more nearly fit **15**. Also



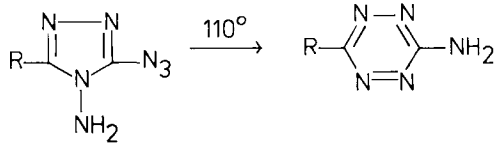
14 **15** **(38)**

the analogous reaction (eq. II-36) with no substituent on nitrogen in the starting material has been shown to give 3,6-diamino-1,2,4,5-tetrazine, so it appears probable that **15** was actually obtained. Lutz, Child, and Walworth (308) have prepared 3,6-bis(dimethylamino)-1,2,4,5-tetrazine in an analogous way but using an aqueous system at about pH 9. A modification of the same procedure in which a 4,4-dialkylthiosemicarbazide was treated with methyl iodide and base to give a series of 3,6-bis(dialkylamino)-1,2,4,5-tetrazines has been reported (288, 289). The yields were less than 5%. 3,6-Bis(dialkylamino-1,2,4,5-tetrazines have also been prepared starting with 3,6-bis(methylmercapto)-1,2,4,5-tetrazine (308). Successive replacement of the methylmercapto groups with dimethylamine (eq. II-39) gave the diaminotetrazine in good yield.



(39)

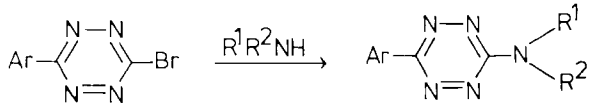
1,2,4,5-Tetrazines having one amino substituent have been prepared by thermal conversion of 3-azido-4-amino-4*H*-1,2,4-triazoles to 1,2,4,5-tetrazines (eq. II-40) (551). A yield of 95% was claimed when R = CH_3. The mechanism is probably loss of N_2 with nitrene formation, ring opening to an acyclic nitrile,



(40)

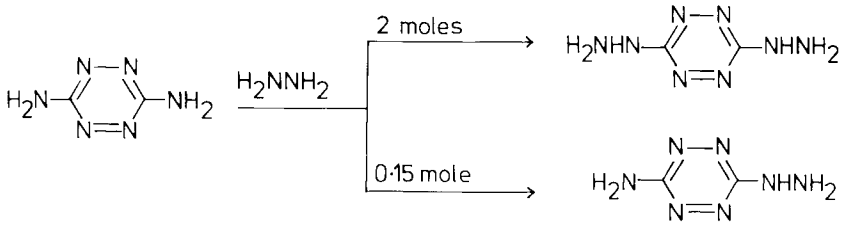
R=H, CH_3, C_2H_5, C_6H_5

and recyclization by addition of the NH_2 group to CN followed by proton rearrangement to give the 3-amino substituent. Similar tetrazines have been prepared by treatment of a 3-bromo-1,2,4,5-tetrazine with an amine (eq. II-41) (179, 309). The only compounds prepared in this way have had an aryl group in the 6-position.



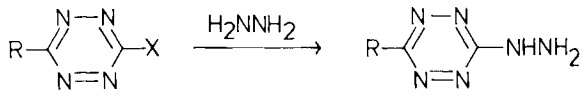
(41)

Most 1,2,4,5-tetrazines having hydrazino substituents have been prepared by the reaction of amino-1,2,4,5-tetrazines with hydrazines (314, 315, 429). When the amine participating in the reaction is 3,6-diamino-1,2,4,5-tetrazine, two products are obtained (eq. II-42) depending on whether or not an excess of hydrazine is used (314, 315). The yield of dihydrazine is 38%. Treatment of



(42)

3-alkyl- or 3-aryl-6-amino-1,2,4,5-tetrazine with hydrazine gives replacement as indicated in eq. II-43 ($X = NH_2$). In the cases in which X = halogen a



(43)

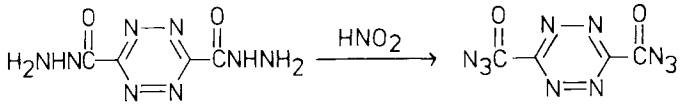
$X=NH_2$ or halogen

3-hydrazino-1,2,4,5-tetrazine is also obtained (179). Both the 3,6-dihydrazino- and 3-hydrazino-6-R-1,2,4,5-tetrazines are converted to azides by the action of nitrous acid (144, 314, 315). Azides can also be prepared by reaction of 3-bromo-6-aryl-1,2,4,5-tetrazines with sodium azide (144).

As mentioned earlier (eq. II-39) mixed 3-(alkylmercapto)-6-amino-1,2,4,5-tetrazines are prepared by reaction of the bis(alkylmercapto) compounds with amines (308).

The preparation of 1,2,4,5-tetrazine-3-6-dicarboxylic acid has already been indicated (eq. II-2) in discussing the preparation of 1,2,4,5-tetrazine. The process involved oxidation of 1,2-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic acid using mild oxidizing agents such as nitrous acid, ferric chloride, and halogens. The esters have been prepared in the same way (299, 346) as have the amides (100, 185, 347).

The only preparation of 3,6-dicyano-1,2,4,5-tetrazine reported was dehydration of the 3,6-dicarboxamide with phosphorus pentoxide in a yield of 12 to 18% (188). Treatment of 1,2-dihydro-1,2,4,5-tetrazine-3,6-dicarboxyhydrazide with nitrous acid has given the 1,2,4,5-tetrazine azide **16** (eq. II-44) (299).



(44)

16

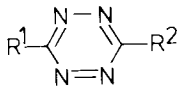
B. Compound Survey

The compounds in this group that have been reported in the literature are listed in Table II-2.

C. Physical Properties and Theoretical Considerations

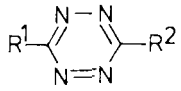
As with the 1,2,4,5-tetrazines already discussed, those substituted by hetero atoms and carbonyl groups attached to the tetrazine ring are strongly colored, usually red. Such a diverse group of substituents would be expected to modify electronic spectra from those seen for the types of 1,2,4,5-tetrazines already discussed, and this is what happens. However, the basic pattern remains much the same with a maximum at 500 to 550 nm with a low extinction coefficient with absorption due to $n \rightarrow \pi^*$ transitions (179, 299, 315, 320, 389). There is also a maximum at about 250 nm with a much higher extinction coefficient arising from $\pi \rightarrow \pi^*$ transitions (320 , 389). In addition many of the compounds exhibit other maxima such as those at 428 nm (ϵ 2000) shown by 3,6-diamino-1,2,4,5-tetrazine (299, 389) and at 454 nm (ϵ 1110) shown by the 3,6-dihydrazino compound (315). The origin of the 428 nm maximum in 3,6-diamino-1,2,4,5-tetrazine has been suggested as being due to isomerization to 3-amino-1,6-dihydro-1,2,4,5-tetrazin-6-imine and 1,2-dihydro-1,2,4,5-tetrazine-3,6-diimine (299), but Paoloni (389), on the basis of theory, suggests that it originates in $\pi \rightarrow \pi^*$ excitation. The ultraviolet spectra of sulfur-substituted 1,2,4,5-tetrazines have been reported and discussed by Sandström (467) and by Moriarity, Kliegman, and Desai (341). The latter group has published the spectra of mesionic sulfur containing 1,2,4,5-tetrazines (**9**). These compounds exhibit their longer-wavelength maxima at about 370 nm (ϵ 10,000). The mass spectrum of 3,6-dicyano-1,2,4,5-tetrazine has intense peaks arising from N_2^+ and $(CN)_2^+$ (569). Dialkylamino-substituted 1,2,4,5-tetrazines form ions of the type R_2NCN^+ or one hydrogen more or less (289). Carrington and collaborators (79) have discussed the radical anion of 3,6-dicyano-1,2,4,5-tetrazine and its ESR spectrum.

TABLE II-2. 1,2,4-TETRAZINES WITH CARBOXYL, CARBOXYL-DERIVATIVE, AND HETERO-ATOM SUBSTITUENTS



R^1	R^2	m.p. (°C)	Refs.
C_6H_5	Cl	–	143
C_6H_5	Br	131	143, 144, 179
4-ClC_6H_4	Br	176	144, 179
3-$NO_2C_6H_4$	Br	197	144, 179
4-$NO_2C_6H_4$	Br	276	144, 179
4-$CH_3OC_6H_4$	Br	159	179
C_6H_5	HO	184 (dec.)	179
4-ClC_6H_4	HO	175 (dec.)	179
HO	HO	–	188
C_6H_5O	C_6H_5O	168	480
C_6H_5	S^- (phenonium)	175	341
4-ClC_6H_4	S^- (phenonium)	176	341
C_6H_5	CH_3S (C_6H_5I salt)	170	341
4-ClC_6H_4	CH_3S (C_6H_5I salt)	205	341
CH_3S	CH_3S	83.5	308, 310, 467
C_2H_5S	C_2H_5S	–	308
$C_6H_5CH_2S$	$C_6H_5CH_2S$	139	467
$HOOCCH_2S$	$HOOCCH_2S$	255 (dec.)	467
$H_5C_2OOCCH_2S$	$H_5C_2OOCCH_2S$	84	467
H	H_2N	–	551
CH_3	H_2N	171	429, 551
C_2H_5	H_2N	–	551
C_6H_5	H_2N	226	179, 551
4-ClC_6H_4	H_2N	243	179
C_6H_5	$HOOCCH_2NH$	219	179
4-ClC_6H_4	CH_3CH_2NH	189	179
4-ClC_6H_4	C_6H_5NH	244	179
3-ClC_6H_4	$(CH_3)_2N$	–	309
4-ClC_6H_4	$(CH_3)_2N$	154	179, 309
C_6H_5	$(CH_3CH_2)_2N$	60	179
4-ClC_6H_4	$(CH_3CH_2)_2N$	–	309
3-$NO_2C_6H_4$	$(CH_3CH_2)_2N$	118	179
4-$NO_2C_6H_4$	$(CH_3CH_2)_2N$	215	179
4-$CH_3OC_6H_4$	$(CH_3CH_2)_2N$	91	179
C_6H_5	$(HOCH_2CH_2)_2N$	118.5	179
4-ClC_6H_4	$(HOCH_2CH_2)_2N$	179	179
C_6H_5	$(CH_3SO_3CH_2CH_2)_2N$	116 (dec.)	179
H_2N	H_2N	>300, 360	299, 314, 315, 497
CH_2=$CHCH_2NH$	CH_2=$CHCH_2NH$	118	538

TABLE II-2. (continued)



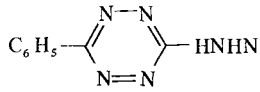
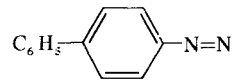
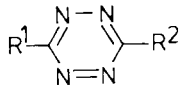
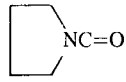
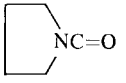
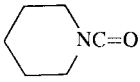
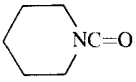
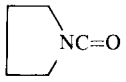
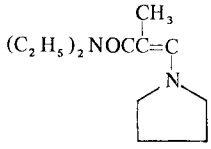
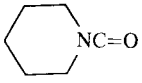
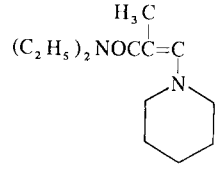
R^1	R^2	m.p. (°C)	Refs.
H_2N	$(CH_3)_2NCH{=}N$	–	244
Hydrochloride		–	244
C_6H_5NH	C_6H_5NH	298	493
$(CH_3)_2N$	$(CH_3)_2N$	121	288, 289, 308
$(C_2H_5)_2N$	$(C_2H_5)_2N$	40	289
$(C_3H_7)_2N$	$(C_3H_7)_2N$	Oil	289
$[(CH_3)_2CH]_2N$	$[(CH_3)_2CH]_2N$	133	289
CH_3CONH	CH_3CONH	156	299
$Cl_2CHCONH$	$Cl_2CHCONH$	–	244
$4\text{-}CH_3C_6H_4SO_2NH$	$4\text{-}CH_3C_6H_4SO_2NH$	227	299
H_2N	$(CH_3CO)_2NN(COCH_3)$	–	314
H_2N	$(C_2H_5)_2NNH$	–	314
CH_3	H_2NHN	–	429
CH_3	$C_6H_5CH{=}NHN$	198	429
CH_3	$C_6H_5C(N{=}NC_6H_5){=}NHN$	180	429
C_6H_5	H_2NHN	211	143, 144, 429
$4\text{-}ClC_6H_4$	H_2NHN	200 (dec.)	179
C_6H_5	$C_6H_5CH{=}NHN$	–	429
$4\text{-}ClC_6H_4$	$C_6H_5CH{=}NHN$	237 (dec.)	179
$4\text{-}ClC_6H_4$	C_6H_5HNHN	198 (dec.)	179
C_6H_5	$C_6H_5C(N{=}NC_6H_5){=}NHN$	179	429
C_6H_5	$C_6H_5C(N{=}NC_6H_4\text{-}4\text{-}NO_2){=}NHN$	168	429
$4\text{-}ClC_6H_4$	$H_2NC(=S)HNHN$	227.5	179
C_6H_5		–	143
C_6H_5		–	143
H_2NHN	H_2NHN	160	314, 315
Dihydrochloride		180	314
$(C_2H_5)_2NHN$	$(C_2H_5)_2NHN$	–	314
$CH_3CH{=}NHN$	$CH_3CH{=}NHN$	168 (dec.)	314, 315
$C_6H_5CH{=}NHN$	$C_6H_5CH{=}NHN$	256 (dec.)	314, 315
$2\text{-}HOC_6H_4CH{=}NHN$	$2\text{-}HOC_6H_4CH{=}NHN$	266	314, 315
$CH_3COHNHN$	$CH_3COHNHN$	265	314, 315

TABLE II-2. (continued)



R^1	R^2	m.p. (°C)	Refs.
$(CH_3CO)_2NN$ $CH_3\dot{C}=O$	$(CH_3CO)_2NN$ $CH_3\dot{C}=O$	226–232 (dec.)	314, 315
$(C_5H_{11}CO)_2NN$ $C_5H_{11}\dot{C}=O$	$(C_5H_{11}CO)_2NN$ $C_5H_{11}\dot{C}=O$	–	314
CH_3	N_3	159	144
C_6H_5	N_3	131	144
4-ClC_6H_4	N_3	154	144
3-$NO_2C_6H_4$	N_3	149	144
4-$NO_2C_6H_4$	N_3	159	144
N_3	N_3	130 (dec.)	314, 315
CH_3S	$(CH_3)_2N$	38.5	308
C_2H_5S	$C_2H_5\dot{N}$ CH_3	–	308
HOOC	HOOC	148 (dec.)	100, 107, 200, 346, 522, 581
Monohydrazino salt		185 (dec.)	100
CH_3OOC	CH_3OOC	–	299
H_5C_2OOC	H_5C_2OOC	135	346
CN	CN	–	188
H_2NOC	H_2NOC	210–280 (dec.)	100, 188
CH_3HNOC	CH_3HNOC	237	347
H_5C_2HNOC	H_5C_2HNOC	195	347
		215	185
		196 (dec.)	185, 347
		126	185
		90	185
N_3OC	N_3OC	–	299

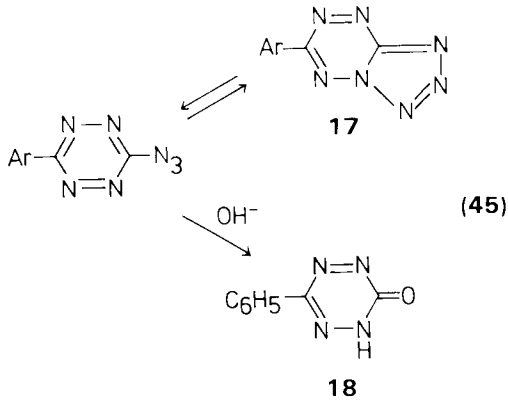
D. Reactions

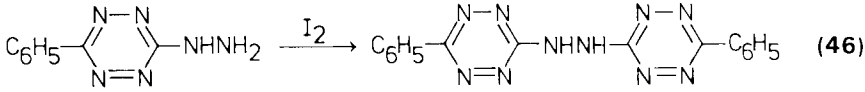
1. *Reactions of the* 1,2,4,5-*Tetrazine Ring*

1,2,4,5-Tetrazines of the type discussed in this section are very similar chemically to those already mentioned. The usually very easy chemical reduction to the 1,2-dihydro compounds occurs (eq. II-23) using such reducing agents as stannous chloride (314, 315), zinc and acetic acid (179), sodium borohydride (179) and hydrazine (315, 442). Only a few examples of base or acid hydrolysis resulting in destruction of the ring system have been reported. 3,6-Dicyano-1,2,4,5-tetrazine has been hydrolyzed with acid to give hydrogen cyanide and nitrogen, but other products must have been formed. Hydrolysis of 1,6-diphenyl-1,2,4,5-tetrazinium-3-mercaptide (**9**) resulted in the formation of 2-phenyl-5-amino-1,3,4-thiadiazole (341). Base hydrolysis of 3-azido-6-phenyl-1,2,4,5-tetrazine has given benzaldehyde azine (144). Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate reacts particularly readily as a dienophile with olefins (21, 474) in the same manner as was indicated in eq. II-24. A series of 3-acetamido-1,2,4,5-tetrazines have also been reported to undergo this reaction (551). Johnson and Levin (233) have prepared a 1,2,4-triazaheptatriene by the reaction of 2,3-diphenylazirine with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (eq. II-30, $R^1 = COOCH_3$, $R^2 = R^3 = C_6H_5$). The previous discussion of Diels–Alder reactions applied to 1,2,4,5-tetrazines also applies to the tetrazine types discussed in this section.

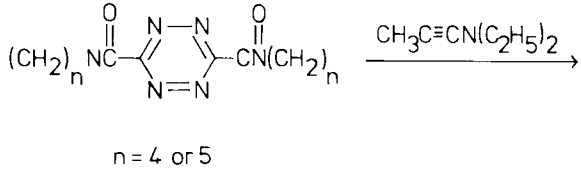
2. *Reactions Involving Functional Groups*

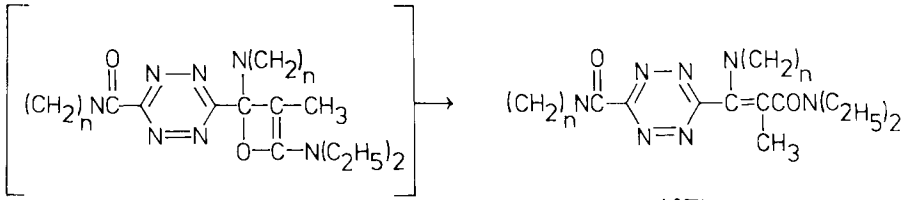
It is unnecessary to discuss the reactions of various 1,2,4,5-tetrazine substituents in great detail because most of them are the expected reactions and many have been covered in the section dealing with synthesis. For the former case reactions such as hydrazone formation between aldehydes and hydrazine compounds and acylation of amino 1,2,4,5-tetrazines are examples. For the latter case preparation of the hydrazino 1,2,4,5-tetrazines by replacement of halogen and amino groups might be mentioned. However, a few cases of functional group reaction are discussed here. 3-Azido-6-aryl-1,2,4,5-tetrazines are converted quite readily to 6-aryl-1,2,3-triazolo[4,3-*b*]1,2,4,5-tetrazines (**17**) and exist in equilibrium with the bicyclic system in solution (eq. II-45) (144). The same type of compound ($Ar = C_6H_5$) undergoes nucleophilic replacement of the azide group with base to give 3-phenyl-1,6-dihydro-1,2,4,5-tetrazin-6-one (**18**) (144). 3-Hydrazino-6-phenyl-1,2,4,5-tetrazine reacts with iodine at 50°C to give 1,2-bis(6-phenyl-1,2,4,5-tetrazin-3-yl)hydrazine (eq. II-46) (143). Although





1,2,4,5-tetrazines with carbomethoxy substituents react with unsaturated compounds as dienophiles, it has been reported (185) that certain 1,2,4,5-tetrazine-3,6-dicarboxamides react with (diethylamino)methylacetylene in an entirely different way. There is a 2 + 2 cycloaddition of the acetylene to one of the tetrazine carbonyl groups, with the ultimate result being that shown in eq. II-47.





Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

III

Uncondensed Reduced Systems

I. DIHYDRO-1,2,4,5-TETRAZINES

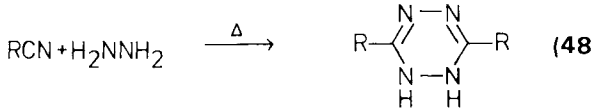
A. Alkyl-, Arylalkyl-, Aryl-, and Heterocyclic-Substituted Dihydro-1,2,4,5-tetrazines

1. *Preparation*

a. 1,2-DIHYDRO-1,2,4,5-TETRAZINES. In discussing 1,2-dihydro- and 1,4-dihydro-1,2,4,5-tetrazines considerable confusion arises from the failure of investigators to specify which compound is meant. Also in many cases the same compound is referred to as both 1,2-dihydro and 1,4-dihydro. As a consequence some uncertainty exists and leads to difficulties in interpreting the literature. Dihydro-1,2,4,5-tetrazines are classified here into the two broad classes according to substituents only on the carbon atoms, not on the nitrogen atoms.

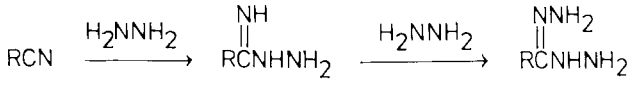
The parent compound of this series, 1,2-dihydro-1,2,4,5-tetrazine, has been prepared by three of the standard procedures used for preparing other 1,2-dihydro-1,2,4,5-tetrazines and is discussed further with the methods used for its preparation.

The most frequently used method for preparing 1,2-dihydro-1,2,4,5-tetrazines is the reaction of nitriles with hydrazine (eq. III-1) at a moderate temperature, such as that of boiling alcohol. As a rule the hydrazine is used as the hydrate and a solvent is employed. The products have usually been considered to be 1,2-dihydro-1,2,4,5-tetrazines, although a number of publications have reported the synthesis of 1,4-dihydro-1,2,4,5-tetrazines using this procedure (83, 84, 293). In fact Charbonnat and Fabriani (84) have claimed that

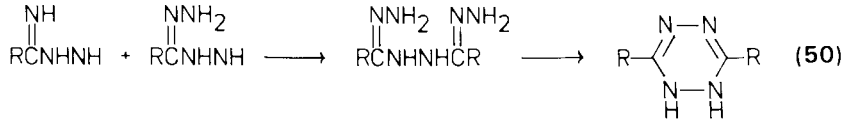


(48)

a 45% yield of 3,6-bis(4-pyridyl)-1,4-dihydro-1,2,4,5-tetrazine was obtained by the reaction of 4-cyanopyridine with hydrazine. Others (117, 590) have found that the same reaction gives the 1,2-dihydro product, but conditions were not comparable so the matter remains unresolved. All types of substituent groups have been used, including R = H to give 1,2-dihydro-1,2,4,5-tetrazine (349), alkyl (1, 109, 349), arylalkyl, aryl (1, 48, 113, 117, 208, 349), and heterocyclic (71, 80, 117, 168, 293, 296, 298, 301, 446, 590). When alkyl nitriles are used, the yields are only a few percent. Aryl nitriles usually react to give fairly good yields (as high as 75%) of dihydrotetrazines although *ortho* substituents diminish yields (1, 349), as do *meta* substituents (349). Recently it has been reported that the presence of sulfur or sulfur-containing compounds such as mercaptans in the reaction mixture enhances yields (1, 260), but Bowie and co-workers (48) have disputed this claim. They found that when acetonitrile and phenylacetonitrile were used, the product was not the reported 3,6-disubstituted 1,2-dihydro-1,2,4,5-tetrazine but the isomeric 3,5-disubstitued 4-amino-4*H*-1,2,4-triazole. The yields of heterocyclic-substituted 1,2-dihydro-1,2,4,5-tetrazines are usually 50% or better (80, 446), although they vary considerably with different heterocyclic nitriles. 3,6-Dipyridyl-1,2-dihydro-1,2,4,5-tetrazines have been obtained in excellent yield by treating the corresponding nitriles with hydrazine hydrate in the presence of Raney nickel (117, 590). Others have found that the use of Raney nickel does not improve the yield (71). The use of two different nitriles to give different substituents on the carbon atoms of the resulting product has been studied using the procedure involving sulfur. A low yield of 3-benzyl-6-phenyl-1,2-dihydro-1,2,4,5-tetrazine was obtained, but the procedure failed with other nitrile pairs. Müller and Herrdegen (349) have proposed a mechanism for the reaction which involves an initial nucleophilic attack of hydrazine on the carbon atom of the nitrile (eq. III-2) to give an imine hydrazine (**19**) which could then react further with hydrazine to give the hydrazide hydrazone (**20**). The next step was believed to be reaction of **20** with **19** to give a product (**21**) that cyclizes (eq. III-3). It has been shown that imine hydrazides such as **19** react with hydrazine to give dihydrotetrazines (298). However, there is very little evidence for such a mechanism, and it seems an



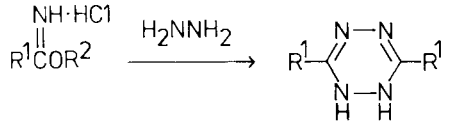
19 **20** **(49)**



(50)

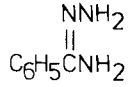
unduly complicated process. Several simpler pathways are theoretically possible and are more likely to fit the actual process. For example, **19** could dimerize to a product which could lose ammonia to give a 1,2-dihydro-1,2,4,5-tetrazine. However, it has been shown that a similar reaction of hydrazides requires conditions that result in triazole formation (393, 455, 506).

The first synthesis of 1,2-dihydro-1,2,4,5-tetrazines was carried out by Pinner (403, 404, 407) and was achieved by treating an imino ether hydrochloride with hydrazine (eq. III-4), and this is still a frequently used process.



(51)

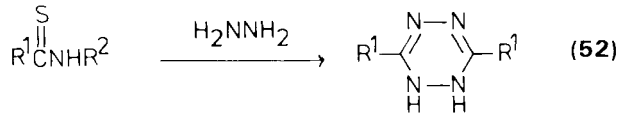
Early work using this reaction was done with a salt of hydrazine and was run in aqueous alcohol under very mild conditions. The reaction has been limited almost exclusively to preparation of aryl (403, 404, 406, 407, 575, 583), arylalkyl (150, 238, 406, 409), and heterocyclic (84, 293, 408, 409) 1,2-dihydro-1,2,4,5-tetrazines, although it has been used to prepare 1,2-dihydro-1,2,4,5-tetrazine (581). Yields have usually been poor, but Wiley, Jarboe, and Hays (575) have succeeded in obtaining yields of about 50% operating under strictly anhydrous conditions and starting with aromatic imino ethers. The procedure was unsuccessful with aromatic compounds having electron-attracting substituents or with pyridyl imino ethers. Libman and Slack (293) have used a procedure very similar to that of Wiley and co-workers. A mechanism much like that proposed for the formation of 1,2-dihydro-1,2,4,5-tetrazines from nitriles was proposed by Pinner (404, 406) for the imino ether process. The mechanism was based on the fact that benzamide hydrazone **22**, which is a side product



22

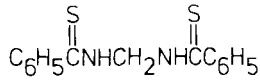
obtained in the preparation of 3,6-diphenyl-1,2-dihydro-1,2,4,5-tetrazine by the imino ether method, reacts with hydrazine to give a dihydrotetrazine. The same objections can be voiced to this proposed mechanism as to the mechanism suggested for nitriles.

The reaction of thioamides with hydrazine has been used to prepare 1,2-dihydro-1,2,4,5-tetrazines (eq. III-5). The procedure has been reported to give good yields with aromatic amides and a yield of 45% where $R^1 = C_6H_5CH_2$ (238, 239). It has also been used to prepare heterocyclic 1,2-dihydro-1,2,4,5-tetrazines (517, 518, 550). The use of pyruvoyl thioamide gave the bishydrazone of 3,6-diacetyl-1,2-dihydro-1,2,4,5-tetrazine (14). Thioanilides



(52)

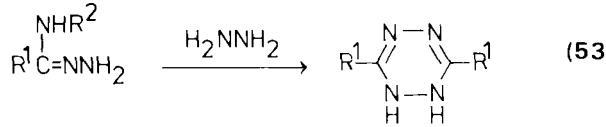
(R^2 = Ar, eq. III-5) have also given satisfactory results with a yield of 84% being reported for the preparation of 3,6-bis(2-pyridyl)-1,2-dihydro-1,2,4,5-tetrazine (517, 518). A rather unusual example of the use of thioamide was that reported by Ueda and Ohta (561) in which the amide was bis(benzothioamido)methane (**23**), but otherwise reactants and results were the same as with other thioamides.



23

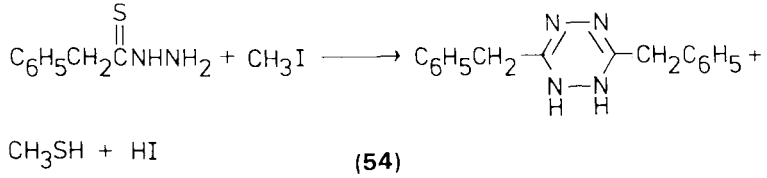
Chabrier and Renard (82) have included methyl iodide in the reaction of benzothiomorpholide with hydrazine to give 1,2-dihydro-1,2,4,5-tetrazines. The function of the methyl iodide is not clear, and it may be that an *S*-methyl derivative involving quaternization of the nitrogen atom is involved. The reaction of thioamides with hydrazine must have a very similar mechanism to the reactions of nitriles and imino ethers in that the first step is probably a nucleophilic attack at the thione carbon although subsequent steps may be different.

A number of procedures using hydrazides and hydrazones have been reported for synthesis of 1,2-dihydro-1,2,4,5-tetrazines (eq. III–6). Such intermediates are almost certainly involved in some of the previously discussed processes (for example eq. III-3). Several reports have appeared stating that amidehydrazones (tautomers of **19**) react with hydrazine to give 1,2-dihydro-1,2,4,5-tetrazines (168, 404, 406, 517, 518). R^2 has been either H or an aromatic moiety.



(53)

Thiohydrazides undergo a similar reaction with hydrazine (583). In a variant of this Jensen and Pedersen (230) have used a thiohydrazide and methyl iodide without added hydrazine to give a 1,2-dihydro-1,2,4,5-tetrazine (eq. III-7).

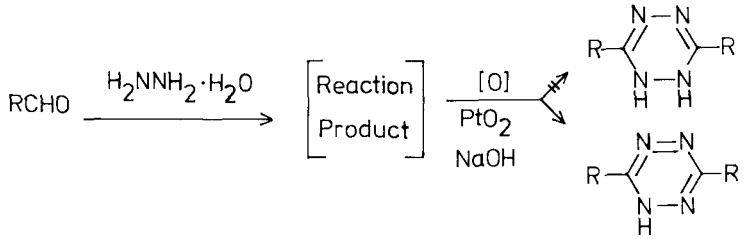


(54)

Presumably the first product of the reaction is a (methylmercapto)hydrazone which cyclizes.

The reduction of 1,2,4,5-tetrazines has been mentioned previously in connection with the reactions of those compounds (eq. II-23). Obviously this can be a procedure for preparing 1,2-dihydro-1,2,4,5-tetrazines, but in most cases it is not a practical method because the 1,2,4,5-tetrazines are usually prepared from the 1,2-dihydro compounds. However, it has been useful occasionally, as in the hydrogen sulfide reduction of 1,2,4,5-tetrazine to its 1,2-dihydro analogue (103). In some cases a 1,2-dihydro-1,2,4,5-tetrazine may be an intermediate in 1,2,4,5-tetrazine synthesis, but the latter is the only material isolable and is converted back to the dihydro compound with hydrogen sulfide (49).

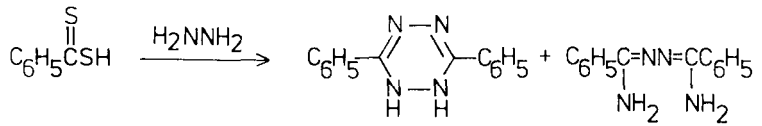
A few miscellaneous preparations of 1,2-dihydro-1,2,4,5-tetrazines are based on the reaction of hydrazine with compounds having an appropriate electrophilic center owing to the presence of $>C=X$ in which X is O, S, or NH. Reaction of an aldehyde with hydrazine with catalytic oxidation of the intermediate has been reported to give 1,2-dihydro-1,2,4,5-tetrazine in yields of about 60% (eq. III-8) (267), but the same authors in other publications



(55)

(511–514) state that the products are 1,6-dihydro-1,2,4,5-tetrazines and this seems to be the case. In the later publications it is indicated that the intermediate is a hexahydro-1,2,4,5-tetrazine. Amidine hydrochlorides react readily with hydrazine to form 1,2-dihydro-1,2,4,5-tetrazines (150, 353). The yields reported were usually 50 to 60%, although in one case the yield was 90%. Thiono esters react with hydrazine, with the product usually being the 1,2,4,5-tetrazine, but in at least one case the 1,2-dihydro compound was isolated (30). Dithio acids have been found to react with hydrazine to give 1,2-dihydro-1,2,4,5-tetrazines and amide azines (eq. III-9) (583).

A small number of procedures used by only one or two workers have been reported. One such method was the reaction of an acid chloride azine (**24**) with



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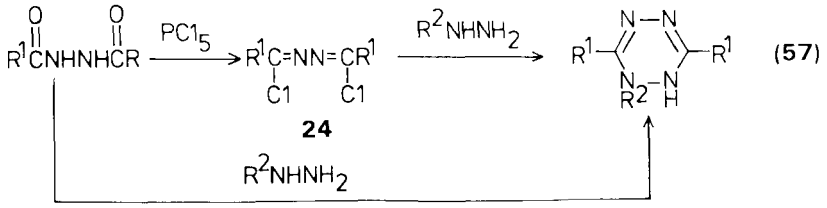


(57)

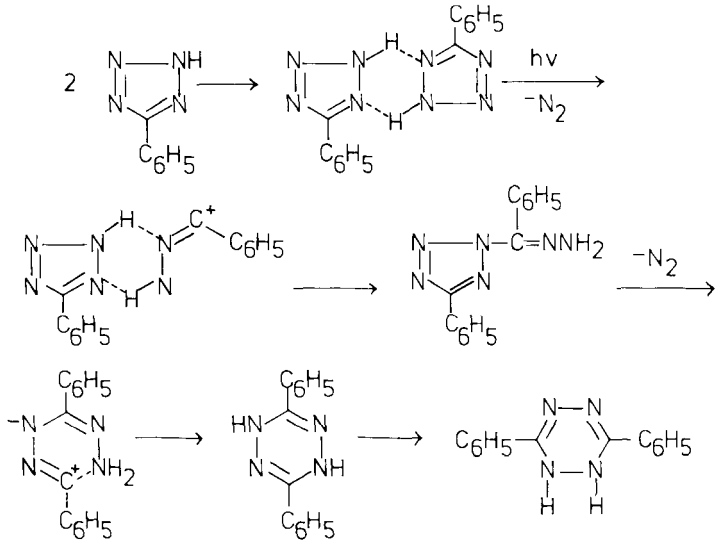
24

hydrazine (eq. III-10) (19, 20, 532, 534, 540) to give the dihydro compound in yields of 20 to 30%. The chloro compounds were prepared from 1,2-diacylhydrazides. The use of a substituted hydrazine gives a product with a substituent at N-1 (534, 536, 544). Stollé has obtained the same result by treatment of a 1,2-diacylhydrazide with a substituted hydrazine (534, 536, 543, 544).

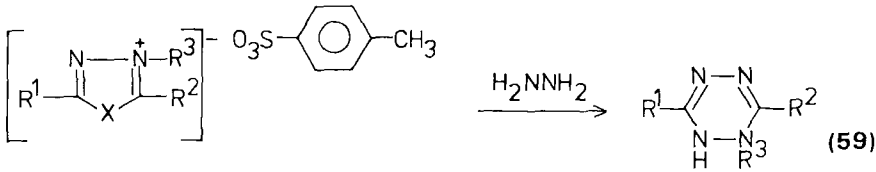
A second such procedure is the thermolysis or photolysis of 5-alkyl- or 5-aryltetrazoles to give 1,2-dihydro-1,2,4,5-tetrazines and the analogous 1,2,4,5-tetrazine (eq. II-3) (219, 478–480). In addition to the two products already mentioned several others are formed. A yield of 52% has been claimed for the preparation of 3,6-diphenyl-1,2-dihydro-1,2,4,5-tetrazine. Huisgen and collaborators (219) consider that the thermal reaction occurs by formation of dipolar nitrilimines (**25**) and dimerization of these. Scheiner and Dinda (480) have studied the mechanism of the photolysis reaction by ^{15}N labeling of the

25

reactants and using nuclear magnetic resonance. From these studies it was concluded that the sequence of reactions is that shown in eq. III-11. The first



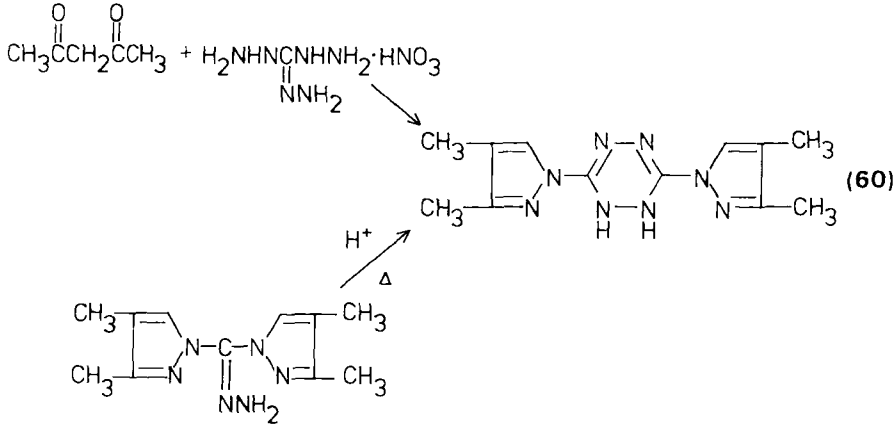
step is a dimerization followed by loss of nitrogen with concomitant acylation of one of the tetrazole nuclei of the dimer by the remaining fragment of the second tetrazole molecule. Subsequent loss of the nitrogen and cyclization occurs. The suggested mechanism also requires 1,3-dipolar intermediates but differs from the mechanism proposed for the thermolytic reaction. however, Chae and co-workers (83) have reported that photolysis of 5-phenyltetrazole forms 3,6-diphenyl-1,4-dihydro-1,2,4,5-tetrazine. Since no details of Chae's work are available it is difficult to determine the reason for the discrepancy between his work and that of Scheiner (478). Shvaika and Fomenko (502–504) have found that quaternary salts of 1,3,5-oxadiazoles or thiadiazoles react with hydrazine to form 1,2-dihydro-1,2,4,5-tetrazines (eq. III-12) in yields of 60 to 90%. This



X = O or S

(59)

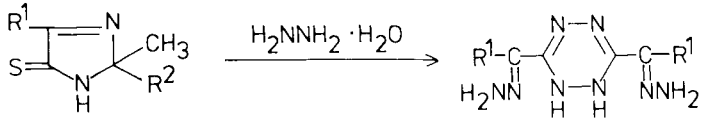
reaction affords a method of introducing substituents on nitrogen and different substituents at C-3 and C-6. Scott and co-workers (70, 494) have allowed acetylacetone to react with triaminoguanidine as its salt with nitric acid to give a product which was first thought to be a 1,4-dihydro-1,2,4,5-tetrazine but was later considered to be the 1,2-dihydro isomer (eq. III-13). The yield was 32%.



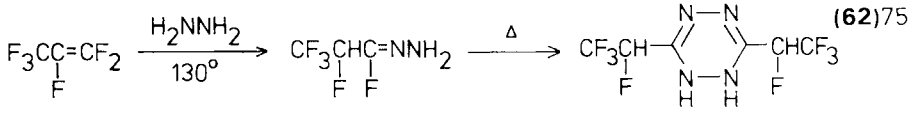
(60)

This reaction probably has as an intermediate the dipyrazolyl ketone hydrazone shown in eq. III-13 because that compound gives the same 1,2-dihydro-1,2,4,5-tetrazine. Three procedures having limited application are indicated in eqs. III-14 to III-16. The reaction shown in eq. III-14 results in 3-hydrazino-2*H*-imidazoles

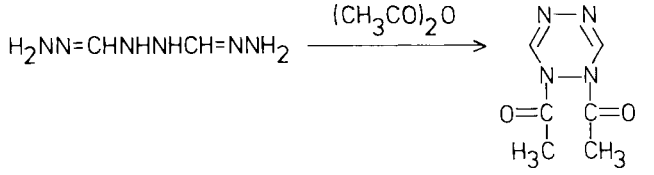
if R^1 and R^2 are comparatively small alkyl groups, except that if $R^1 = R^2 = CH_3$ the dihydro-1,2,4,5-tetrazine is formed. In the case represented by eq. III-15 other fluorinated hydrocarbons have been used.



(61) 14



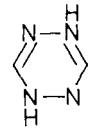
(62) 75



(63) 187

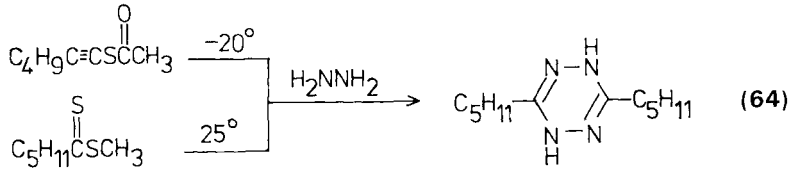
b. 1,4-DIHYDRO-1,2,4,5-TETRAZINES. The literature on the synthesis of 1,4-dihydro-1,2,4,5-tetrazines is quite confusing because of two factors. One of these is that 1,4-dihydro-1,2,4,5-tetrazines having no substituents or only one substituent on nitrogen have been reported, but the compounds actually prepared were probably in most cases the 1,2-dihydro isomers. In only four instances has there been sufficient investigation of the products to establish with certainty that they were the claimed 1,4-dihydro compounds. In many procedures used for the preparation of 1,2-dihydro-1,2,4,5-tetrazines it would be expected that the 1,4-dihydro isomer would be the product. The isolation of 1,2-dihydro compounds is most likely due to facile isomerization of 1,4- to 1,2-isomers (480, 504), although no study of such a proton shift has been made. The second source of confusion is the ready isomerism of 1,2- and probably 1,4-dihydro-1,2,4,5-tetrazines to 4-amino-4*H*-1,2,4-triazoles (48, 59, 103, 105, 107, 394, 455, 532–534) under the influence of acid or heat and to iminotriazoles with base (216, 256). Almost all the compounds reported in the earlier literature to be 1,4-dihydro-1,2,4,5-tetrazines with only hydrogen on nitrogen are 4-amino-4*H*-1,2,3-triazoles. Because of difficulties arising from the aforementioned factors, our discussion of the preparative procedures reported for 1,4-dihydro-1,2,4,5-tetrazines having only hydrogen on the nitrogen atoms is organized according to substituents rather than type of reaction.

The synthesis of 1,4-dihydro-1,2,4,5-tetrazine (**26**) has been reported by several groups of workers. Curtius and Lang (115) and Hantzsch and Silberrad



26

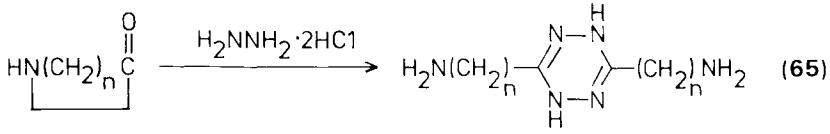
(202) reported the synthesis of **26** by treatment of 1,2-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic acid with hot potassium hydroxide. The thermal cyclization of biurea at 160°C (393) and heating formohydrazide (457) also were claimed to give **26**, as was the reaction of ethyl orthoformate with hydrazine (532). The reaction of the product with 1,4-diketones to give a pyrrole indicated the presence of an amino group (54, 55) and the 4-amino-4*H*-1,2,4-triazole structure was proposed. This proposal was supported by Curtius and co-workers (103, 105, 107), who demonstrated the isomerization of 1,2-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic acid to 4-amino-4*H*-1,2,4-triazole-3,5-dicarboxylic acid by heat and by hot potassium hydroxide solution. The synthesis of 3,6-dialkyl-1,4-dihydro-1,2,4,5-tetrazines by heating acetohydrazide (393, 455), butyrylhydrazide (532), and undecoylhydrazide (532) has been claimed. However, it was later found (394) that the reaction of acetohydrazide actually gave a triazole, and no doubt the other reactions also give triazoles. Silberrad (506) heated diacetylaniline with hydrazine at 260°C to give a product claimed to be 3,6-dimethyl-1,4-dihydro-1,2,4,5-tetrazine, but it is actually 3,5-dimethyl-4-amino-4*H*-1,2,4-triazole. Wijers and co-workers (573) have reported the synthesis of 3,6-dialkyl-1,4-dihydro-1,2,4,5-tetrazines by the reaction of hydrazine hydrate with acetylenic thio esters and with esters of alkyldithio acids at room temperature or below (eq. III-17). In the case of the acetylenic compounds the yield was about 35%. It was proposed that the acetylene reacted first with hydrazine to form acetohydrazide and a thioketene,



(64)

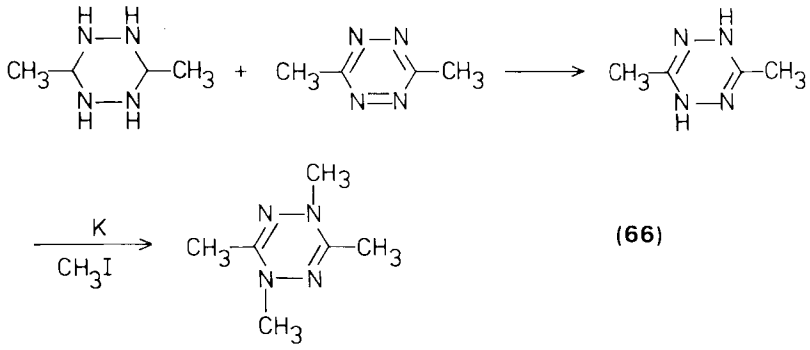
which then formed a thioacylhydrazide followed by dimerization. Presumably the dithio ester reacted directly to form the thioacylhydrazide. There was considerable spectral evidence for the nature of the product, but only the finding that the ultraviolet spectrum showed no maximum above 210 nm indicated a 1,4-dihydro rather than a 1,2-dihydro compound. The reaction of 2-undecyl-4,5-dimethyloxazole with hydrazine at elevated temperatures has been claimed to give 3,6-diundecoyl-1,4-dihydro-1,2,4,5-tetrazine (194), but no proof was offered for the structure. Pinner (406, 409) has reported that acid

isomerizes 3,6-dibenzyl-1,2-dihydro-1,2,4,5-tetrazine to 1,4-dihydro, but it has been shown (59) that such isomerization actually forms 4*H*-1,2,4-triazoles. Otsuka and co-workers (381, 382) have studied the reaction of ω-amino acids and ω-lactams with hydrazine hydrochloride at elevated temperatures (180 to 210°C) and proposed that the products were 1,4-dihydro-1,2,4,5-tetrazines (eq. III-18). It is very doubtful that the proposed products were obtained, because the conditions would probably give triazoles, and no study of the



n = 3, 5, 10, 16 **(65)**

structure of the products was mentioned. 3,6-Dimethyl-1,4-dihydro-1,2,4,5-tetrazine has been prepared by the reaction of 3,6-dimethylhexahydro-1,2,4,5-tetrazine with 3,6-dimethyl-1,2,4,5-tetrazine (eq. III-19) (514). The structure of the product was confirmed by methylation to be 1,3,4,6-tetramethyl-1,4-



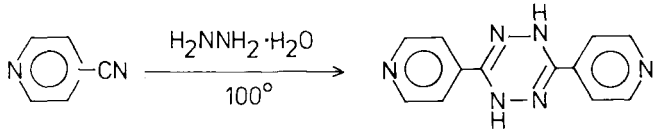
(66)

dihydro-1,2,4,5-tetrazine. These authors expressed the opinion that the 1,4-dihydro compound is thermodynamically more stable than the 1,2 isomer.

Holmberg (211, 212) has treated thiobenzohydrazide with base in the presence of methyl iodide or benzyl bromide and obtained what was claimed to be 3,6-diphenyl-1,4-dihydro-1,2,4,5-tetrazine. The melting point was the same as that reported for the 1,2 isomer, at least in most cases, and it may be that the two compounds are the same. However, since the melting points reported in most cases for both 1,2-dihydro- and 1,4-dihydro-3,6-diphenyl-1,2,4,5-tetrazines are the same as that of 3,6-diphenyl-1,2,4,5-tetrazine, it is possible that oxidation occurs during heating of the dihydro compounds, and the melting point of 3,6-diphenyl-1,2,4,5-tetrazine is the only one being seen. Steininger (527) has claimed an 11% yield of 3,6-diphenyl-1,4-dihydro-1,2,4,5-tetrazine along with several other products from the reaction of methylphenylphos-

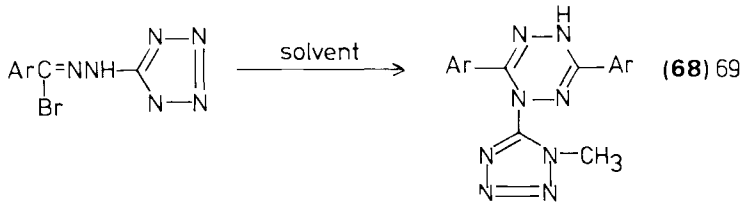
phinoylhydrazide with ethyl orthobenzoate. Only melting point and analyses were used to characterize the product. A number of other workers have reported the formation of the same compound as an intermediate in the preparation of 3,6-diphenyl-1,2,4,5-tetrazine. The reactions used were treatment of *N*-(diphenylphosphinoyl)-*N'*-benzoylhydrazide with phosphorus pentachloride (527), reaction of 3,6-diphenyl-1,4-bis(4-toluenesulfonyl)-1,2,4,5-tetrazine with base (220), and photolysis of 5-phenyltetrazole (479, 480). The latter reaction has been reported by Chae and co-workers (83) to give 3,6-diphenyl-1,4-dihydro-1,2,4,5-tetrazine as the isolable product. These workers also claimed the same product was formed by reaction of benzonitrile with hydrazine, but both reactions have been stated to form the 1,2-dihydro isomer (see eqs. II-3, III-2, and III-3). In the preparation of 1,3,6-triphenyl-1,2-dihydro-1,2,4,5-tetrazine from 1,2-dibenzoylhydrazine (eq. III-10) it was thought that a second product was the 1,4-dihydro isomer (534, 536, 543, 544), but it was later found to be 3,5-diphenyl-4-anilino-4*H*-1,2,4-triazole.

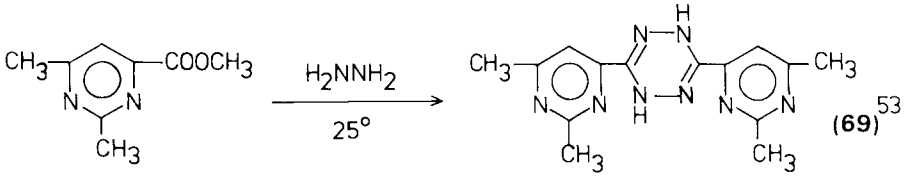
Warrener, Felix, and Wilson (567) have stated that 2-cyanopyridine and hydrazine hydrate at 100°C react to form 3,6-bis(2-pyridyl)-1,4-dihydro-1,2,4,5-tetrazine, but no evidence was presented for the structure. Charbonnat and Fabriani (84) reported an analogous reaction with 4-cyanopyridine (eq. III-20). The product was obtained in a yield of 45% and differed from the



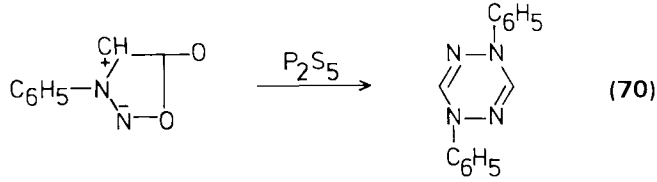
(67)

compound believed to be the 1,2-dihydro isomer, which was obtained from the 4-pyridyl imino ether hydrochloride and hydrazine. These same workers also prepared the same 1,4-dihydro-1,2,4,5-tetrazine in low yield from the reaction of pyridine-4-thiocarboxamide and hydrazine. Scott (494) claimed the preparation of a 1,4-dihydro-1,2,4,5-tetrazine with substituted pyrazolyl groups at C-3 and C-6 but in a later publication (70) reported it as the 1,2-dihydro isomer. It has been proposed that 3,6-bis(5-tetrazolyl)-1,2-dihydro-1,2,4,5-tetrazine prepared by the reaction of nitrile with hydrazine is the 1,4-dihydro compound, but there was no direct evidence for this proposal (298). Santoro (470) studied this reaction and obtained four isomeric compounds as products. The four compounds had different colors and ultraviolet spectra. The results were explained by equilibria among the possible isomeric tetrazole rings and possibly between the two possible dihydro-1,2,4,5-tetrazine rings. However, no structures were assigned. Other compounds thought to be 3,6-disubstituted 1,4-dihydro-1,2,4,5-tetrazine have been prepared as shown in eqs. III-21 and III-22. The evidence given for the structures proposed was not conclusive in either case.





The first reported synthesis of 1,4-diaryl-1,4-dihydro-1,2,4,5-tetrazines was by Ruhemann (449–452), who prepared a compound first called *carbohydrazide* by the reaction of phenylhydrazine with chloroform and potassium hydroxide and subsequently proposed the 1,4-diphenyl-1,4-dihydro-1,2,4,5-tetrazine structure (**27**) for it. A short time later the same compound was synthesized by heating formylphenylhydrazine (23, 392). Baker, Ollis, and Poole (22) treated *N*-phenylsydnone with phosphorus pentasulfide and obtained a compound which had the appropriate molecular formula for **27**, but it was not the same as the compound previously reported to be **27**. The yield was 27%. This reaction probably occurs through loss of carbon dioxide from the sydnone to form a

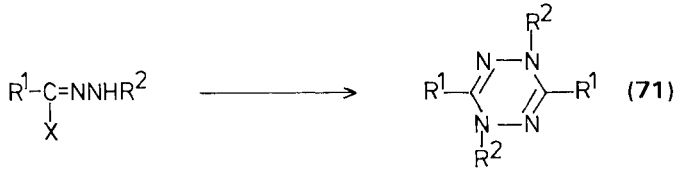


27

1,3-dipolar nitrilimine which dimerizes. The same compound was then prepared in 43% yield by the action of sodium methoxide on thioformylphenylhydrazine. Analogous aromatic compounds were prepared in the same fashion starting with various thioformylarylhydrazines. Treatment of formylphenylhydrazine with phosphorus pentasulfide also gave **27** but in very poor yield. Hydrolysis with acid of the compound obtained by these later procedures gave two molar equivalents of phenylhydrazine and two of formic acid. The dipole moment was essentially zero (136), and the properties of **27** were very similar to those of the previously prepared 1,3,4,6-tetraaryl-1,4-dihydro-1,2,4,5-tetrazines (24, 86). Subsequently Huisgen and co-workers (216) confirmed by infrared and NMR

spectra that the compounds prepared by Baker and his colleagues (22) were 1,4-diaryl-1,4-dihydro-1,2,4,5-tetrazines. Consequently it is now considered that those compounds reported previously (23, 392, 449–451, 454) do not have the proposed 1,4-diaryl-1,4-dihydro-1,2,4,5-tetrazines although two of them are included in Table III-1. Huisgen (216) has suggested that they are 1-aryl-3-(arylamino)-4*H*-1,2,4-triazoles. A variant of the sydnone process (eq. III-23) in which the sydnone is treated with phosphorus oxychloride and dimethylformamide or *N*-methylformanilide has been used subsequently (118) to prepare 1,4-diaryl-1,4-dihydro-1,2,4,5-tetrazines in yields of 20 to 40%. Sato and Ohta (472) have claimed the preparation of **27** by heating thioformylphenylhydrazine and also by heating a sulfide formed from the enolic form of thioformylphenylhydrazine.

One of the most widely used procedures for preparing 1,4-disubstituted 1,4-dihydro-1,2,4,5-tetrazines is the reaction of α-substituted hydrazones with or without base as indicated in eq. III-24. In most cases the substituents have been aryl, but other substituents can be present. In one of the earliest versions of this

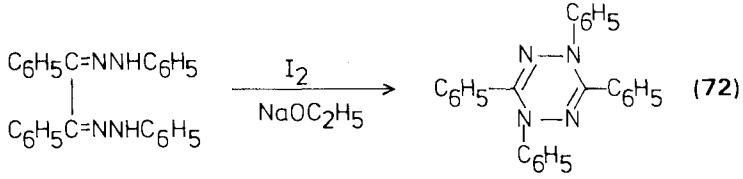


28
X = halogen

(71)

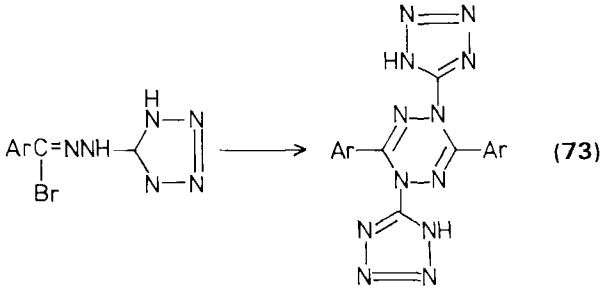
procedure (24, 86, 557, 562) arylhydrazones of arylaldehydes were treated with bromine or iodine to give α-halo-substituted hydrazones which then cyclized without the use of base. Yields as good as 50% have been reported (86). Buzykin and co-workers (72) have treated compounds of the type **28** in which R^1 and R^2 = Ar and X = Cl with oxidizing agents such as benzoyl peroxide, *tert*-butyl peroxide, lead dioxide, and *N*-bromosuccinimide and obtained 1,3,4,6-tetraaryl-1,4-dihydro-1,2,4,5-tetrazines. In addition the corresponding radical cations, which could be converted thermally to 1,4-dihydro-1,2,4,5-tetrazines, were obtained as chlorides. Vanghelovitch (562) has claimed that sunlight is necessary to cause the conversion of compounds of type **28** to the 1,4-dihydro-1,2,4,5-tetrazines, but others have not found this to be the case. When hydrazones are treated with bromine, the aryl groups attached to nitrogen are usually brominated. In most cases the dihydro-1,2,4,5-tetrazine is prepared by treating the preformed halogenated hydrazone with base at the temperature of boiling alcohol (90, 214, 215, 305, 386), but the reaction has been done solely by heating (476). A yield as high as 72% has been recorded. A variation of this used α-nitro hydrazones (eq. III-24, X = NO_2) (24–27, 215, 420, 421). In this

version low yields are the rule, with none exceeding 40%. In only a few cases have the substituents been other than aryl groups, but tosylhydrazones (R^2 = tosyl) (386, 568) have been used, and in one case R^1 has been CH_3. What seems to be 1,3,4,6-tetraphenyl-1,4-dihydro-1,2,4,5-tetrazine has been prepared by a reaction (eq. III-25) which is probably a version of that shown in eq. III-24 and in which a probable intermediate is **28** with X = I (516). A modification of the acid chloride hydrazone reaction involves the use of an aryl hydrazone



(72)

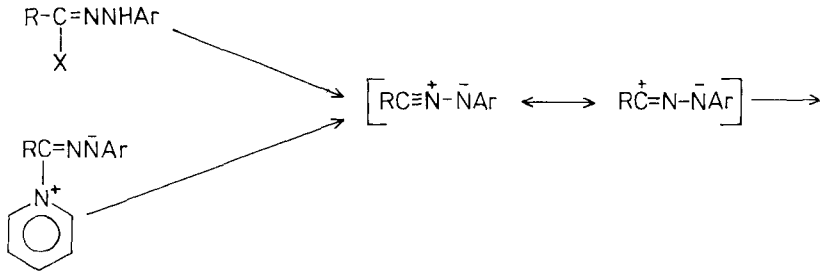
having as R^1 a carboxyl group which is lost during cyclization (eq. III-24 in which R^1 in **28** = COOH but in the dihydrotetrazine = H). The yields reported in this reaction were only 10 to 20%, but in all cases the aryl groups (R^2 = Ar) had *ortho* substituents which may have reduced the yield. The reaction has occurred as a side reaction when *N*-phenylbenzohydrazidoyl chloride (**28**, $R^1 = R^2 = C_6H_5$) was allowed to react with nitriles in the presence of a Lewis acid (90). The main product was produced by reaction of the nitrile with the hydrazone to give a triazole, but yields of 1,4-dihydro-1,2,4,5-tetrazine as high as 47% were reported when the nitrile was that of a negatively substituted aryl group. Scott (69, 495) (as already mentioned) has proposed that *N*-(5-tetrazolyl)aryl-hydrazidoyl chlorides are converted under neutral conditions at low temperatures to 1,4-dihydro-1,2,4,5-tetrazines (eq. III-26). However, the products were not colored, which would indicate that they do not have the proposed structure,



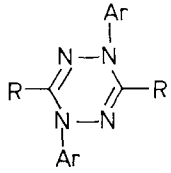
(73)

and Scott (495) emphasizes that the structures are only provisional. Huisgen (214, 215) has proposed that the reaction of compounds of the type **28** to form dihydrotetrazines proceeds through nitrilimines, as shown in eq. III-27, although Wawzonek and Kellen (568) have questioned this (see the 1,2,4,5-

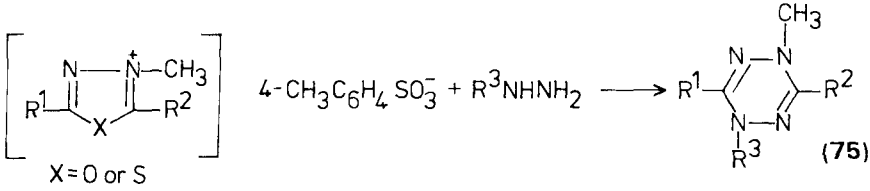
tetrazine discussion). Support for Huisgen's proposal was derived from the preparation of 3,6-diacyl-1,4-diphenyl-1,2,4,5-tetrazines through pyridinium compounds which must pass through nitrilium intermediates (eq. III-27) (268, 354).



R=Ar or acyl **(74)**



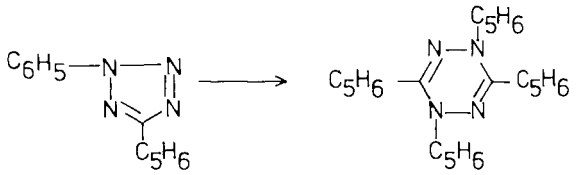
Shvaika and Fomenko (502–504) have discovered a procedure for preparing 1,3,5,6-tetrasubstituted 1,4-dihydro-1,2,4,5-tetrazines which are unsymmetrical with respect to both the 1- and 4-substituents and the 3- and 6-substituents. It is the only method for preparing such compounds. The method consists of treating quaternary salts, usually tosylates, of 3,5-disubstituted 1,3,4-oxadiazoles or thiadiazoles with substituted hydrazines (eq. III-28). Yields in the range of 70 to



X=O or S **(75)**

99% were reported. R^1 and R^2 have been aromatic groups, and groups other than methyl can be attached to the quaternary nitrogen atom of the starting material. Side products are 4-amino-4*H*-1,2,4-triazoles (502).

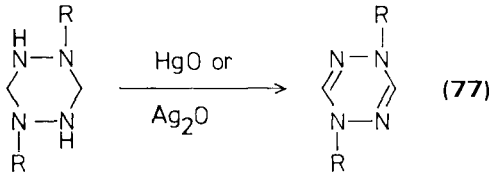
Huisgen and co-workers (218) have found that 3,5-disubstituted tetrazoles on heating are converted to tetrasubstituted 1,4-dihydro-1,2,4,5-tetrazines (eq. III-29). In a closely related reaction (220) it was found that treatment of 5-phenyltetrazole with tosyl chloride in pyridine at 40°C gave 3,6-diphenyl-1,4-bis(4-toluenesulfonyl)-1,4-dihydro-1,2,4,5-tetrazine. Presumably the tetra-



(76)

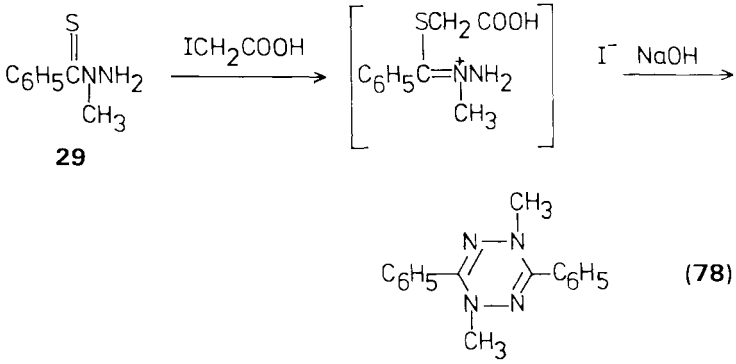
zole was first tosylated at the 3-position, and then underwent the reaction shown in eq. III-29. It was proposed that the reaction passes through a nitrilimine intermediate, as indicated in eq. III-27, but here again the report of Wawzonek and Kellen (568) (already discussed in the 1,2,4,5-tetrazine section) should be considered.

Tolles and co-workers (557) and Schmitz and Ohme (486, 490) have prepared 1,4-dimethyl- and 1,4-diphenyl-1,4-dihydro-1,2,4,5-tetrazines by oxidation of appropriate hexahydro-1,2,4,5-tetrazines (eq. III-30) with metal oxides using mercuric oxide for the dimethyl compound and silver oxide for the diphenyl



(77)

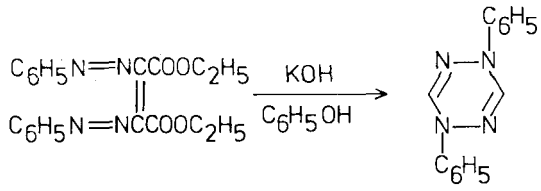
one. Oxidation of 3,6-disubstituted hexahydro-1,2,4,5-tetrazines with metal oxides or catalytically with oxygen does not follow this course (514). Two cyclizations rather similar to each other involve treatment of monosubstituted hydrazine with either ethyl orthoformate to give 1,4-diphenyl-1,4-dihydro-1,2,4,5-tetrazine (459) or with ethyl iminoformate hydrochloride to form the analogous 1,4-dimethyl compound in 38% yield (256). Holmberg (212) has treated the thiohydrazide **29** with iodoacetic acid forming an intermediate which, upon base treatment, cyclized to a 1,4-dihydro-1,2,4,5-tetrazine (eq. III-31). Treatment of diethyl α,α'-bis(phenylazo)maleate or fumarate with



29

(78)

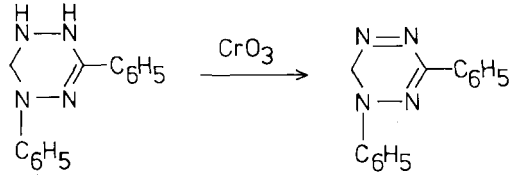
base in alcohol has been reported (448) to cause decarbethoxylation and cyclization to 1,4-diphenyl-1,2,4,5-tetrazine (eq. III-32). The latter reaction seems somewhat improbable.



(79)

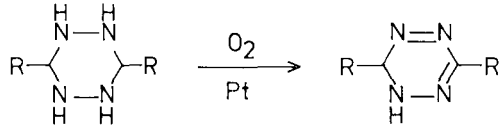
c. 1,6-DIHYDRO-1,2,4,5-TETRAZINES. Only a few compounds that might be considered as normal 1,6-dihydro-1,2,4,5-tetrazines (**30**) are known, and a somewhat larger number, but still not many, of quaternary (onium) salts, in which N-2 is quaternary, of 1,6-dihydro-1,2,4,5-tetrazines (**31**) have been reported. The latter compounds are derived from a class of 1,2,4,5-tetrazines called verdazyls, which are discussed separately because they do not fit well into any of the other classes.

Uncharged 1,6-dihydro-1,2,4,5-tetrazines (**30**) are prepared by oxidation of either 4,6-disubstituted 1,2,3,4-tetrahydro-1,2,4,5-tetrazines with chromic oxide (426) (eq. III-33) or oxidation of hexahydro-1,2,4,5-tetrazines with oxygen in the presence of a platinum catalyst (eq. III-34) (511–514). The only compounds prepared by the tetrahydro route have been substituted by aromatic groups but



(80)

30

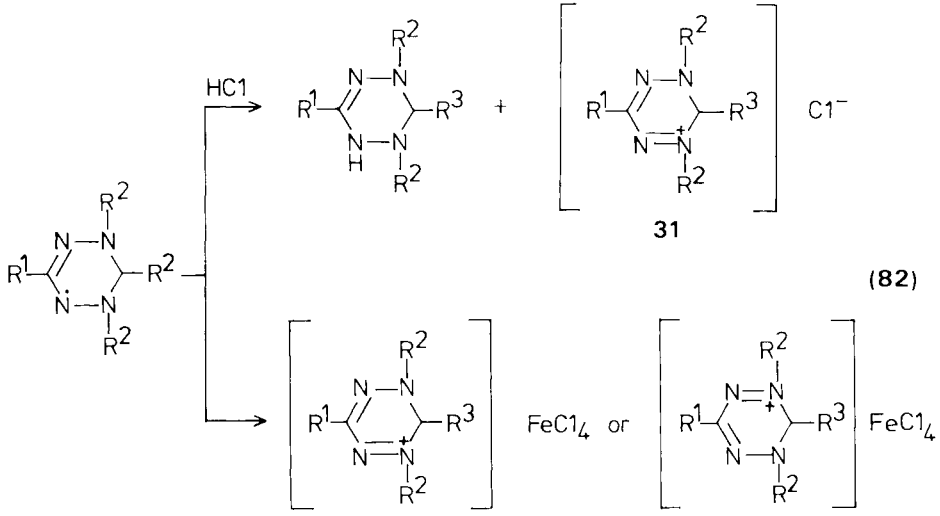


(81)

compounds prepared by the second method have had aliphatic substituents. A yield of 80% was reported for the preparation of 3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazine, but as R becomes more complex the yields were substantially reduced. These same authors reported (267) in a patent that the products of this reaction are 1,2-dihydro-1,2,4,5-tetrazines, but this does not seem to be the case.

The onium salts mentioned above are always prepared from verdazyls by some reaction involving oxidation and reduction. The most commonly used

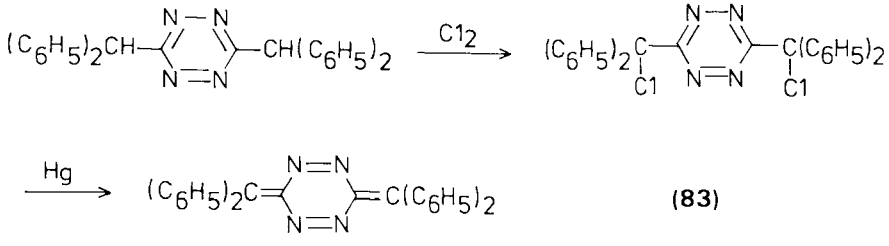
procedures have been treatment of verdazyls with acids (270, 274, 278) or with transition metal halides (278) as shown for both methods in eq. III-35. Oxidation has also been done polarographically (269) and anodically (274). Two moles of transition metal salt are required per mole of verdazyl. The complexes probably exist as resonance intermediates of the two degenerate canonical forms



(82)

indicated. Verdazyls have been found to react with benzoyl peroxide, and the products may be salts similar to those indicated in eq. III-35 (586, 587).

d. 3,6-DIHYDRO-1,2,4,5-TETRAZINES. A number of reports (115, 202, 452) claimed the synthesis of 3,6-dihydro-1,2,4,5-tetrazine, originally called *bisdiazomethane,* from the treatment of 1,2-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic acid with hot potassium hydroxide solution. After the base-induced isomerization of dihydro-1,2,4,5-tetrazines became clear, it was found (103) that *bisdiazomethane* was 3-amino-1,2,4-triazole. Hantzsch and Lehmann (201) reported the dimerization of diazomethane under the influence of light to give



32

(83)

3,6-dihydro-1,2,4,5-tetrazine, but later workers obtained only ethylene and nitrogen (103).

The only authentic reported 3,6-dihydro-1,2,4,5-tetrazines of the class under discussion in this section are 3,6-bis(diphenylmethylidene)-3,6-dihydro-1,2,4,5-tetrazine (312, 542) (**32**), m.p. 170°C (dec.), and 3,6-bis(9-fluorenylidene)-3,6-dihydro-1,2,4,5-tetrazine (541) both prepared by the procedure indicated in eq. III-36.

2. *Compound Survey*

The derivatives of 1,2-, 1,4-, and 1,6-dihydro-1,2,4,5-tetrazines reported in the literature are listed in Table III-1.

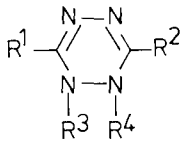
3. *Physical Properties and Theoretical Considerations*

The solubility and melting points of the dihydro-1,2,4,5-tetrazines vary enormously not only among 1,2-dihydro and 1,4-dihydro and other dihydro forms but also depending on substitution. A loose generalization is that they are high-melting compounds which are soluble in polar organic solvents but not in water or solvents such as benzene and petroleum ether. 1,2-Dihydro-1,2,4,5-tetrazines usually are reported to have the same melting point as the corresponding 1,2,4,5-tetrazine, indicating a loss of hydrogen under the influence of heat. Almost all of the dihydro-1,2,4,5-tetrazines are colored, with most being a light to moderate yellow, although substitution can deepen the color. Junghahn (238, 239) has reported that 3,6-diarylalkyl-1,2-dihydro-1,2,4,5-tetrazines are colorless, but this is inconsistent with the findings of others. The 3,6-disubstituted 3,6-dihydro-1,2,4,5-tetrazines (**32**) are black, but these compounds have quite extended conjugated systems. The dihydro-1,2,4,5-tetrazines usually do not dissolve in acids and are very weakly basic although hydrochlorides have been reported (543, 544).

Most of the ultraviolet studies reported on dihydro-1,2,4,5-tetrazines are those on the 1,2-dihydro compounds. There is considerable variation in ultraviolet spectra owing to substitution. 3,6-Bis(polyfluoroalkyl)-1,2-dihydro-1,2,4,5-tetrazines have ultraviolet spectra maxima at about 230 (ϵ 3000) and 330 nm (ϵ 77) (49, 77). The maxima in 3,6-diaryl-1,2-dihydro-1,2,4,5-tetrazines are at 273 and 325 nm with ϵ values of about 4000 (180, 181). Heterocyclic substitution induces shifts in the ultraviolet maxima as 3,6-dipyridyl compounds give strong maxima at about 240 nm and shoulders in the 270 and 310 nm regions (84). Santoro (470) reported the synthesis of 3,6-bis(5-tetrazolyl)-1,4-dihydro-1,2,4,5-tetrazine, but it appears more probable that it was the 1,2-dihydro isomer so its

TABLE III-1. DIHYDRO-1,2,4,5-TETRAZINES WITH ALKYL, ARYLALKYL, ARYL, AND HETEROCYCLIC SUBSTITUENTS

A. 1,2-Dihydro-1,2,4,5-Tetrazines

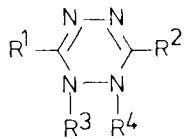


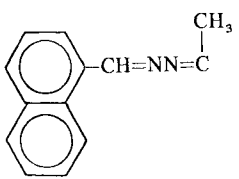
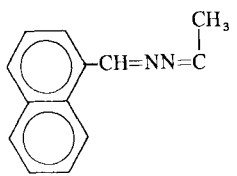
R^1	R^2	R^3	R^4	m.p. (°C)	Refs.
1. *Alkyl*					
H	H	H	H	117, 125	103, 187, 349, 581
H	H	CH_3CO	CH_3CO	149	187
CH_3	CH_3	H	H	180	1, 109
C_2H_5	C_2H_5	H	H	–	349
$CH_3CH_2CH_2$[a]	$CH_3CH_2CH_2$	H	H	72	267
CHF_2	CHF_2	H	H	–	591
CF_3	CF_3	H	H	95	75
CF_3	$CF_3CF_2CF_2$	H	H	98	49
CF_3CHF	CF_3CHF	H	H	106, 126	75, 591
$CF_3CF_2CF_2$	$CF_3CF_2CF_2$	H	H	117.5	49
$CF_2=CHCH_2$	$CF_2=CHCH_2$	H	H	130	75
$C_6H_5CH=CHCH=NN=C(CH_3)$	$C_6H_5CH=CHCH=NN=C(CH_3)$	H	H	196	14
$2\text{-}HOC_6H_4CH=NN=C(CH_3)$	$2\text{-}HOC_6H_4CH=NN=C(CH_3)$	H	H	254	14

[a]This compound is probably 3,6-bis(*n*-propyl)-1,6-dihydro-1,2,4,5-tetrazine.

TABLE III-1. (continued)

A. 1,2-Dihydro-1,2,4,5-Tetrazines



R^1	R^2	R^3	R^4	m.p. (°C)	Refs.
1. *Alkyl*					
4-$CH_3OC_6H_4CH{=}NN{=}C(CH_3)$	4-$CH_3OC_6H_4CH{=}NN{=}C(CH_3)$	H	H	202	14
4-$BrC_6H_4CH{=}NN{=}C(CH_3)$	4-$BrC_6H_4CH{=}NN{=}C(CH_3)$	H	H	206	14
4-$NO_2C_6H_4CH{=}NN{=}C(CH_3)$	4-$NO_2C_6H_4CH{=}NN{=}C(CH_3)$	H	H	244	14
4-$(CH_3)_2NC_6H_4CH{=}NN{=}C(CH_3)$	4-$(CH_3)_2NC_6H_4CH{=}NN{=}C(CH_3)$	H	H	241	14
4-$CH_3CONHC_6H_4CH{=}NN{=}C(CH_3)$	4-$CH_3CONHC_6H_4CH{=}NN{=}C(CH_3)$	H	H	262	14
		H	H	196	14

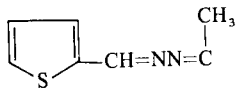
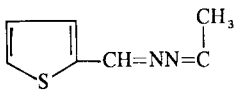
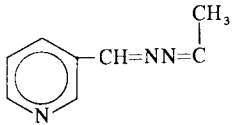
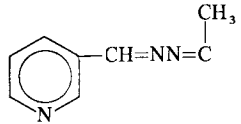
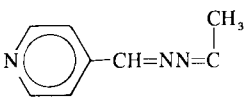
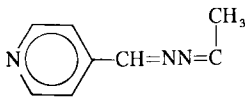
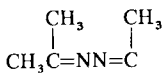
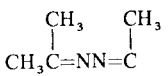
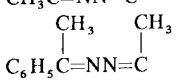
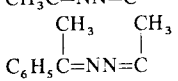
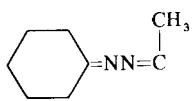
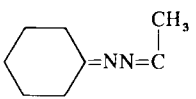
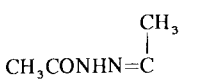
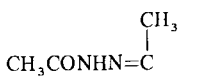
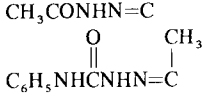
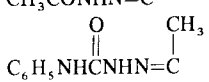
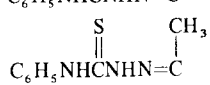
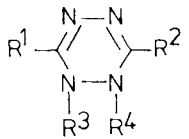
		H	H	158	14
		H	H	192	14
		H	H	190	14
		H	H	134	14
		H	H	195	14
		H	H	124	14
		H	H	317 (dec.)	14
		H	H	258	14
		H	H	239	14

TABLE III-1. (continued)

A. 1,2-Dihydro-1,2,4,5-Tetrazines



R^1	R^2	R^3	R^4	m.p. (°C)	Refs.
2. *Arylakyl*					
$C_6H_5CH_2$	$C_6H_5CH_2$	H	H	158	1, 230, 255, 406, 409
4-$H_2NC_6H_4CH_2$	4-$H_2NC_6H_5CH_2$	H	H	212	239
$C_6H_5SO_2CH_2$	$C_6H_5SO_2CH_2$	H	H	238	30
$C_6H_5CH(OH)$	$C_6H_5CH(OH)$	H	H	193	406, 409
$C_6H_5C(CH_3)(OH)$	$C_6H_5C(CH_3)(OH)$	H	H	154 rac. 180 meso 122 (+ or −)	150, 353 150, 353 150, 353
$C_6H_5C(C_2H_5)(OH)$	$C_6H_5C(C_2H_5)(OH)$	H	H	107.5 rac. 159 meso 118 (+ or −)	150, 353 150, 353 150, 353
4-$CH_3C_6H_4C(CH_3)(OH)$	4-$CH_3C_6H_4C(CH_3)(OH)$	H	H	188 rac. 174 meso 139 (+ or −)	353 353 353

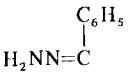
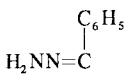
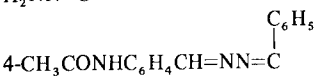
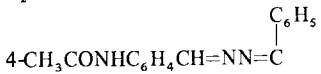
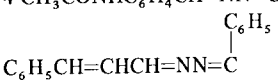
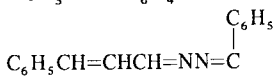
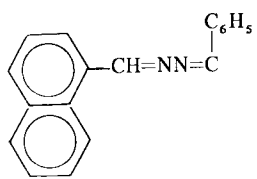
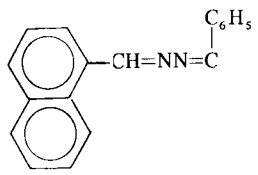
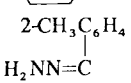
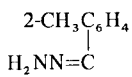
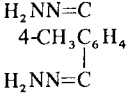
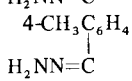
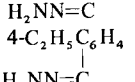
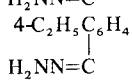
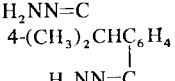
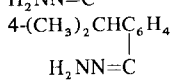
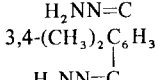
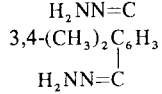
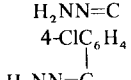
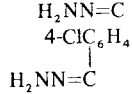
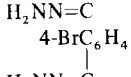
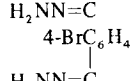
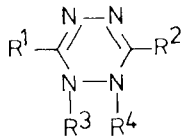
		H	H	273	15
		H	H	–	15
		H	H	–	15
		H	H	–	15
		H	H	286	15
		H	H	256–264	15
		H	H	269	15
		H	H	275	15
		H	H	245	15
		H	H	260	15
		H	H	217	15

TABLE III-1. (continued)

A. 1,2-Dihydro-1,2,4,5-Tetrazines



R^1	R^2	R^3	R^4	m.p. (°C)	Refs.
2. *Arylakyl*					
4-$CH_3OC_6H_4$ | $H_2NN{=}C$	4-$CH_3OC_6H_4$ | $H_2NN{=}C$	H	H	258	15
4-$H_2NC_6H_4$ | $H_2NN{=}C$	4-$H_2NC_6H_4$ | $H_2NN{=}C$	H	H	256	15
2-$C_{10}H_7$ | $H_2NN{=}C$	2-$C_{10}H_7$ | $H_2NN{=}C$	H	H	230	15
3. *aromatic*					
CH_3	C_6H_5	H	H	192	48
CH_3	C_6H_5	C_6H_5	H	143	504
C_6H_5	C_6H_5	H	H	160, 195	1, 54, 82, 160, 204, 219, 238, 403, 404, 407, 443 478, 480, 502, 532, 534, 543, 559, 561, 583
C_6H_5	C_6H_5	CH_3	H	159	502
C_6H_5	C_6H_5	C_2H_5	H	151	502

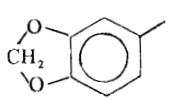
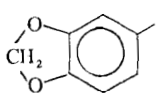
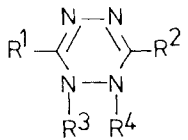
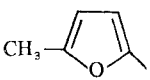
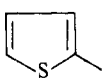
C_6H_5	C_6H_5	C_6H_5	H	125	504, 534, 536, 541
Hydrochloride				180	543
C_6H_5	C_6H_5	C_6H_5	CH_3CO	186	536
C_6H_5	C_6H_5	$4\text{-}BrC_6H_4$	H	176	504
C_6H_5	C_6H_5	$4\text{-}NO_2C_6H_4$	H	197	504
C_6H_5	C_6H_5	C_6H_5CO	H	208	534
C_6H_5	C_6H_5	CH_3CO	CH_3CO	228	238, 403
C_6H_5	C_6H_5	C_6H_5	CH_3CO	186	536
C_6H_5	$1\text{-}C_{10}H_7$	CH_3	H	143	504
C_6H_5	$4\text{-}CH_3O_6H_4$	CH_3	H	152	504
$4\text{-}CH_3OC_6H_4$	C_6H_5	CH_3	H	151	504
$4\text{-}CH_3OC_6H_4$	C_6H_5	C_6H_5	H	124	504
$3\text{-}CH_3C_6H_4$	$3\text{-}CH_3C_6H_4$	H	H	194	349
$4\text{-}CH_3C_6H_4$	$4\text{-}CH_3C_6H_4$	H	H	235, 235	260, 349, 407, 409, 583
$4\text{-}C_6H_5C_6H_4$	$4\text{-}C_6H_5C_6H_4$	H	H	160	575
$4\text{-}ClC_6H_4$	$4\text{-}ClC_6H_4$	H	H	215	1, 260, 544
$4\text{-}BrC_5H_4$	$4\text{-}BrC_6H_4$	H	H	235	1, 544
$4\text{-}BrC_6H_4$	$4\text{-}BrC_6H_4$	C_6H_5	H	167	534, 544
$4\text{-}BrC_6H_4$	$4\text{-}BrC_6H_4$	C_6H_5CO	C_6H_5CO	248	544
$4\text{-}NO_2C_6H_4$	$4\text{-}NO_2C_6H_4$	H	H	215	260, 409
$2\text{-}H_2NC_6H_4$	$2\text{-}H_2NC_6H_4$	H	H	206	48
$3\text{-}H_2NC_6H_4$	$3\text{-}H_2NC_6H_4$	H	H	179–190	239
$4\text{-}HOC_6H_4$	$4\text{-}HOC_6H_4$	H	H	–	260
$4\text{-}CH_3OC_6H_4$	$4\text{-}CH_3OC_6H_4$	H	H	242, 258	181, 260
$4\text{-}CH_3OC_6H_4$	$4\text{-}CH_3OC_6H_4$	CH_3	H	173	502
		H	H	242	117
$3\text{-}HOOCC_6H_4$	$3\text{-}HOOCC_6H_4$	H	H	>285	113

TABLE III-1. (continued)

A. 1,2-Dihydro-1,2,4,5-Tetrazines



R^1	R^2	R^3	R^4	m.p. (°C)	Refs.
3. *Aromatic*					
4-$HO_3SC_6H_4$	4-$HO_3SC_6H_4$	H	H	–	260
1-$C_{10}H_7$	1-$C_{10}H_7$	H	H	–	260
2-$C_{10}H_7$	2-$C_{10}H_7$	H	H	–	260
4-Cl–1-$C_{10}H_6$	4-Cl–1-$C_{10}H_6$	H	H	–	260
5-NO_2–2-$C_{10}H_6$	5-NO_2–2-$C_{10}H_6$	H	H	–	260
4. *Heterocyclic*					
C_6H_5		CH_3	H	183	504
C_6H_5		CH_3	H	182	504
C_6H_5		CH_3	H	178	504
		H	H	214	230

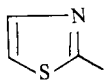
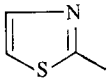
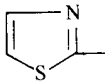
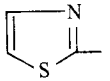
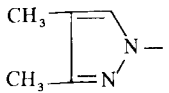
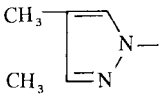
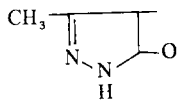
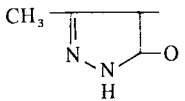
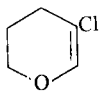
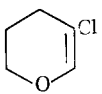
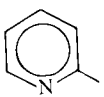
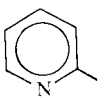
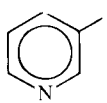
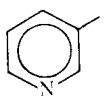
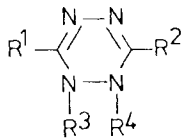
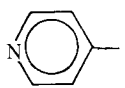
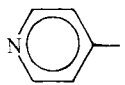
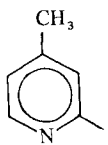
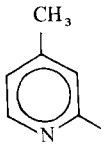
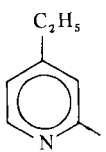
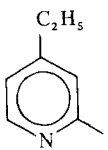
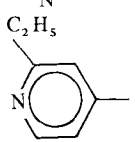
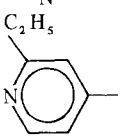
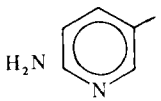
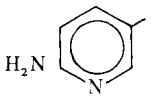
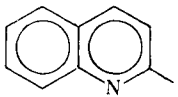
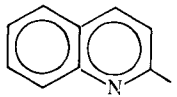
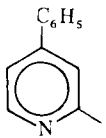
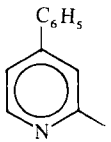
		H	H	209, 247	293, 301
		CH_3CO	CH_3CO	248	301
		H	H	144	70, 494
		H	H	–	314
		H	H	170	446
		H	H	215	446
		H	H	193	71, 117, 168, 517, 518, 590
		H	H	235	117, 260, 590

TABLE III-1. (continued)

A. 1,2-Dihydro-1,2,4,5-Tetrazines

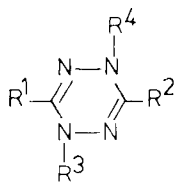


R^1	R^2	R^3	R^4	m.p. (°C)	Refs.
4. *Heterocyclic*					
		H	H	272	84, 117, 260, 293, 590
		H	H	210	80
		H	H	134	80
		H	H	168	550

		H	H	297	301
		H	H	–	260
		H	H	189	80

B. 1,4-Dihydro-1,2,4,5-tetrazines

1. *Neutral*

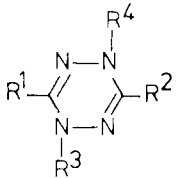


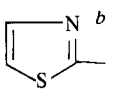
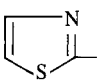
R^1	R^2	R^3	R^4	m.p. (°C)	Refs.
H	H	CH_3	CH_3	44	256, 557
Methylfluoroborate				–	256
Ethylfluoroborate				–	256
H	H	C_6H_5	C_6H_5	189, 198	22, 118, 216, 448, 459, 472, 557

TABLE III-1. (continued)

B. 1,4-Dihydro-1,2,4,5-tetrazines

1. *Neutral*



R^1	R^2	R^3	R^4	m.p. (°C)	Refs.
H[b]	H	2-$CH_3C_6H_4$	2-$CH_3C_6H_4$	141	451
H	H	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	102	22
H[b]	H	4-$(CH_3)_2CHC_6H_4$	4-$(CH_3)_2CHC_6H_4$	234	451
H	H	4-ClC_6H_4	4-ClC_6H_4	178, 185	22, 118
H	H	2-$NO_2C_6H_4$	2-$NO_2C_6H_4$	166	305
H	H	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	286	118
H	H	2-CH_3O–4-$NO_2C_6H_3$	2-CH_3O–4-$NO_2C_6H_3$	191	305
H	H	2-CH_3O–5-$NO_2C_6H_3$	2-CH_3O–5-$NO_2C_6H_3$	212	305
CH_3	CH_3	H	H	160	514
n-C_5H_{11}	n-C_5H_{11}	H	H	106	573
$H_2N(CH_2)_3$[c]	$H_2N(CH_2)_3$	H	H	–	381, 382
$H_2N(CH_2)_5$[c]	$H_2N(CH_2)_5$	H	H	–	381, 382
$H_2N(CH_2)_{10}$[c]	$H_2N(CH_2)_{10}$	H	H	–	381, 382
$H_2N(CH_2)_{16}$[c]	$H_2N(CH_2)_{16}$	H	H	–	381, 382
C_6H_5	C_6H_5	H	H	191	211, 212, 220
 [b]		H	H	209	293

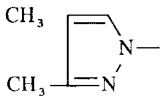
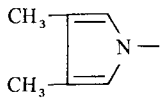
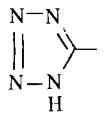
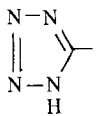
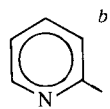
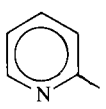
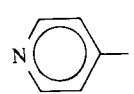
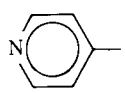
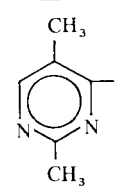
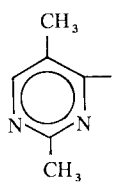
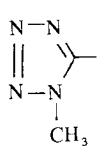
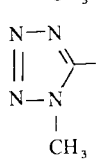
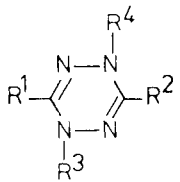
		H	H	148	494
		H	H	4 isomers	470
 [b]		H	H	194	567
		H	H	242	84
		H	H	207	53
C_6H_5 [b]	C_6H_5 		H	262	69
4-$CH_3C_6H_4$ [b]	4-$CH_3C_6H_4$ 		H	272	69

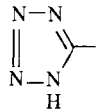
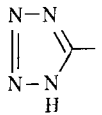
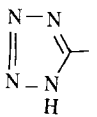
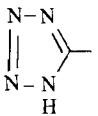
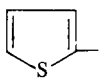
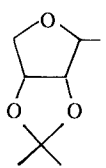
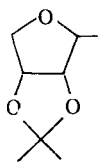
TABLE III-1. (continued)

B. 1,4-Dihydro-1,2,4,5-tetrazines

1. *Neutral*



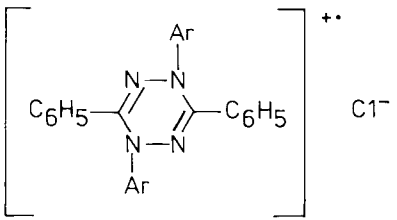
R^1	R^2	R^3	R^4	m.p. (°C)	Refs.
CH_3	CH_3	CH_3	CH_3	91	514
CH_3	CH_3	4-$CH_3C_6H_4SO_2$	4-$CH_3C_6H_4SO_2$	182	220, 386
$CH_3CH(OH)$	$CH_3CH(OH)$	C_6H_5	C_6H_5	182	216
CH_3CO	CH_3CO	C_6H_5	C_6H_5	168	216, 354
C_6H_5CO	C_6H_5CO	C_6H_5	C_6H_5	198	216, 268
C_6H_5	C_6H_5	CH_3	CH_3	94	212, 504
C_6H_5	C_6H_5	C_2H_5	CH_3	148	504
C_6H_5	C_6H_5	C_6H_5	CH_3	119, 169	502, 504
C_6H_5	C_6H_5	C_6H_5	C_6H_5	205	24, 72, 215, 218, 516, 557
C_6H_5	C_6H_5	4-$CH_3C_6H_4SO_2$	4-$CH_3C_6H_4SO_2$	156	220, 568
C_6H_5	C_6H_5	4-BrC_6H_4	4-BrC_6H_4	264	86, 557
C_6H_5	C_6H_5	2,4-$Br_2C_6H_3$	2,4-$Br_2C_6H_3$	255	72, 86
C_6H_5	C_6H_5	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	300, 305	24, 26, 72, 420, 421
C_6H_5	C_6H_5	2-Br–4-$NO_2C_6H_3$	2-Br–4-$NO_2C_6H_3$	–	72

C_6H_5[b]	C_6H_5			188	495
3-$NO_2C_6H_4$[b]	3-$NO_2C_6H_4$			194	495
4-$CH_3OC_6H_4$	C_6H_5	C_6H_5	CH_3	171	504
C_6H_5		CH_3	CH_3	102	504
2,4,6-$(CH_3)_3C_6H_2$	2,4,6-$(CH_3)_3C_6H_2$	4-$CH_3C_6H_4SO_2$	4-$CH_3C_6H_4SO_2$	230 (dec.)	568
4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	C_6H_5	C_6H_5	173	25, 27
4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	4-BrC_6H_4	4-BrC_6H_4	150	562
4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	303	215
4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	340	215
		4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	251	558

[b]These may be 1,2-dihydro-1,2,4,5-tetrazines.
[c]May not be 1,2,4,5-tetrazines.

TABLE III-1. (continued)

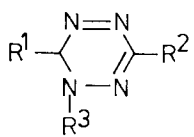
2. *Radical cations*



Ar	Refs.
C_6H_5	72
4-$NO_2C_6H_4$	72
2,4-BrC_6H_3	72
2-Br–4-$NO_2C_6H_3$	72

C. 1,6-Dihydro-1,2,4,5-tetrazines

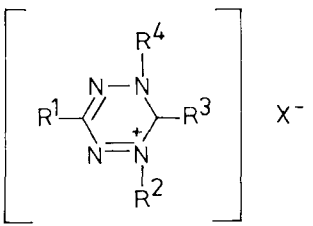
1. *Neutral*



R^1	R^2	R^3	m.p. (°C)	Refs.
CH_3	CH_3	H	114	511–514
C_2H_5	C_2H_5	H	44	511, 513

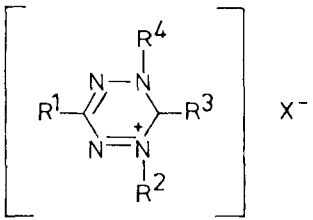
C_3H_7	C_3H_7	H	74	511, 513
$(CH_3)_2CH$	$(CH_3)_2CH$	H	–	511
n-$C_{11}H_{23}$	n-$C_{11}H_{23}$	H	91	511, 513
CH_3	CH_3	CH_3	n_D^{20} 1.5181	514
CH_3	CH_3	$HOCH_2$	76	514
H	C_6H_5	C_6H_5	86	426
H	4-$CH_3C_6H_4$	C_6H_5	104	426

2. *Onium salts*



R^1	R^2	R^3	R^4	X	m.p. (°C)	Refs.
H	C_6H_5	H	C_6H_5	$FeCl_4$	133	276
H	C_6H_5	H	C_6H_5	ClO_4	153	276
$(CH_3)_3C$	C_6H_5	H	C_6H_5	$FeCl_4$	165	361
$(CH_3)_3C$	4-$CH_3C_6H_4$	H	4-$CH_3C_6H_4$	$FeCl_4$	150	361
$(CH_3)_3C$	4-$CH_3OC_6H_4$	H	4-$CH_3OC_6H_4$	$FeCl_4$	151	361
$(CH_3)_3C$	4-$NO_2C_6H_4$	H	4-$NO_2C_6H_4$	$FeCl_4$	169	361
$(CH_3)_3C$	4-$CH_3OOCC_6H_4$	H	4-$CH_3OOCC_6H_4$	$FeCl_4$	175	361
$(CH_3)_3C$	4-NCC_6H_4	H	4-NCC_6H_4	$FeCl_4$	168	361
C_6H_5	C_6H_5	H	C_6H_5	$FeCl_4$	162	276
C_6H_5	C_6H_5	H	C_6H_5	1/2 $PdCl_4$	183	276
C_6H_5	C_6H_5	H	C_6H_5	1/2 $PtCl_6$	183	276

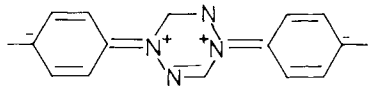
TABLE III-1. (continued)



C_6H_5	C_6H_5	H	C_6H_5	$AuCl_4$	163	276
C_6H_5	C_6H_5	H	C_6H_5	$C(NO_2)_3$	123	276
C_6H_5	C_6H_5	H	C_6H_5	NO_3	141	276
C_6H_5	C_6H_5	H	C_6H_5	ClO_4	177	276
C_6H_5	C_6H_5	H	C_6H_5	Cl	–	278
C_6H_5 [d]	C_6H_5	H	C_6H_5	C_6H_5COO	–	586, 587
C_6H_5	$4\text{-}CH_3OC_6H_4$	H	C_6H_5	$FeCl_4$	147	276
C_6H_5	$4\text{-}CH_3OC_6H_4$	H	$4\text{-}CH_3OC_6H_4$	$FeCl_4$	143	276
$4\text{-}CH_3OC_6H_4$	C_6H_5	H	C_6H_5	$FeCl_4$	145	276
$4\text{-}CH_3OC_6H_4$	$4\text{-}CH_3OC_6H_4$	H	C_6H_5	$FeCl_4$	128	276
$4\text{-}CH_3OC_6H_4$	$4\text{-}CH_3OC_6H_4$	H	$4\text{-}CH_3OC_6H_4$	$FeCl_4$	150	276
$4\text{-}NO_2C_6H_4$	C_6H_5	H	C_6H_5	$FeCl_4$	161	276
$4\text{-}CH_3OOCC_6H_4$	C_6H_5	H	C_6H_5	$FeCl_4$	162	276
C_6H_5	C_6H_5	HC≡C	C_6H_5	$FeCl_4$	124	276
C_6H_5	C_6H_5	C_6H_5	C_6H_5	$FeCl_4$	139	276
C_6H_5	C_6H_5	C_6H_5	C_6H_5	Cl	–	282

[d] There is some doubt as to the structure of this compound.

ultraviolet spectrum will be discussed here. Four isomers were claimed to be present, with all having different ultraviolet spectra. The maxima were at 234 to 278 nm, with ϵ values varying from 17,800 to 23,000. It may be that both 1,2-dihydro and 1,4-dihydro isomers are present, but most of the isomerism must be a result of the presence of 1*H* and 2*H* forms of the tetrazole rings. The



33

ultraviolet spectrum of only one 1,4-dihydro-1,2,4,5-tetrazine having hydrogen on the nitrogen atoms is reported, and it was stated to have a maximum at 240 nm with shoulders in the region of 270 to 310 nm (84). 1,4-Dialkyl-1,4-dihydro-1,2,4,5-tetrazines have a single maximum in the ultraviolet at 237 nm (ϵ = 8000) (557). The 1,4-diaryl analogues have a single maximum at 290 to 300 nm and are bright yellow in color (22). The 1,3,4,6-tetraaryl analogues have two strong maxima at 270 to 280 and 330 to 340 nm with molar absorptivities of 15,000 to 20,000 (557). It is apparent that there is electron delocalization into the aromatic rings with contributions from such polar forms as **33**. The 1,6-Dihydro-1,2,4,5-tetrazines have $\pi \rightarrow \pi^*$ transitions at 310 nm giving ϵ values of about 3000. There are also $n \rightarrow \pi^*$ transitions at 426 nm with quite low molar absorptivities (about 400) (511). The 1,6-dihydro quaternary nitrogen salt forms are strongly colored, having maxima in the visible region at 500 to 580 nm and ϵ about 2000. Ultraviolet spectra maxima are present at 348 to 410 nm (ϵ 8000 to 10,000) and 240 to 268 nm (361, 481). Though almost all, if not all, dihydro-1,2,4,5-tetrazines are colored, very little has been published concerning their visible spectra with the exception of the 1,6-dihydro compounds. A dihydro-1,2,4,5-tetrazine of somewhat dubious structure (1,2- or 1,4-dihydro) has been reported to have a very weak maximum at 525 nm (494). However, it was a 3,6-bis(3,5-dimethyl-1-pyrazolyl) compound, which would probably have a visible spectrum different from that of most dihydro-1,2,4,5-tetrazines.

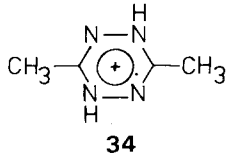
The infrared spectra of dihydro-1,2,4,5-tetrazines are consistent with the different moieties present and are not characteristic of the dihydrotetrazine ring systems. For example, the 1,2-dihydro-1,2,4,5-tetrazines have bands at about 3300 and 1650 cm^{-1} arising from NH, at about 1550 cm^{-1} from N—N stretching, at 1300 to 1500 cm^{-1} from C=N stretching, and at 1000 to 1450 cm^{-1} from C—N stretching. In addition there are bands due to substituents present. It has been proposed (117) that 1,2-dihydro-1,2,4,5-tetrazines can be distinguished from isomeric 4-amino-4*H*-1,2,4-triazoles by the NH bands in the infrared spectra. The former exhibit a singlet at about 3300 cm^{-1}, and the latter show a doublet at 3270 and 3290 cm^{-1}.

The PMR spectra of dihydro-1,2,4,5-tetrazines are as expected (48, 467).

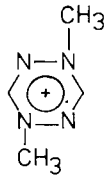
Bowie and co-workers (48) have found that the protons on nitrogen in 1,2-dihydro-1,2,4,5-tetrazines resonate at 0.9 ppm lower field than do those on nitrogen in the isomeric 4-amino-4*H*-1,2,4-triazoles. This affords a second spectral method for distinguishing between the two series of compounds. 1,4-Disubstituted 1,4-dihydro-1,2,4,5-tetrazines have a singlet in their PMR spectra at δ6.38 to 6.88 arising from the protons on the carbon atoms of the tetrazine ring (216, 256).

There has been little published on the mass spectra of dihydro-1,2,4,5-tetrazines (199, 588). 1,3,4,6-Tetraphenyl-1,4-dihydro-1,2,4,5-tetrazines fragment to give the ions $C_6H_5CNC_6H_5]^+$ and $C_6H_5CN]^+$.

The ESR spectra of the two isomeric radical cations **34** and **35** have been



34



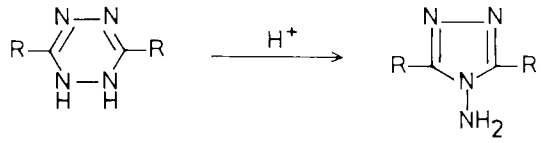
35

reported along with the coupling constants (169, 557). The ion **34** was prepared by reaction of 3,6-dimethyl-1,4-dihydro-1,2,4,5-tetrazine with 3,6-dimethyl-1,2,4,5-tetrazine in acid. The second cation (**35**) was the product of iodine oxidation of 1,4-dimethyl-1,4-dihydro-1,2,4,5-tetrazine. The ESR spectrum of a material which was not isolated but was believed to be the radical cation of a dihydro-1,2,4,5-tetrazine prepared by iodine oxidation of benzaldehyde β-methylhydrazone has been reported (557). A series of radical cations similar to **34** and **35** but having 1,2,4,6-tetraaryl substituents has been prepared (72) by oxidation of hydrazones of type **28**. These compounds presumably arise *in situ* by oxidation of the initially formed 1,3,4,6-tetraaryl-1,4-dihydro-1,2,4,5-tetrazines. They are deeply colored compounds existing as chlorides and presumably giving ESR spectra.

Circular dichroism studies have been reported on various 1,2-dihydro-1,2,4,5-tetrazines containing substituents having asymmetric carbon atoms (150). Molecular orbital parameters for 1,4-dimethyl-1,4-dihydro-1,2,4,5-tetrazine have been determined by Tolles, McBride, and Thum (557).

4. *Reactions*

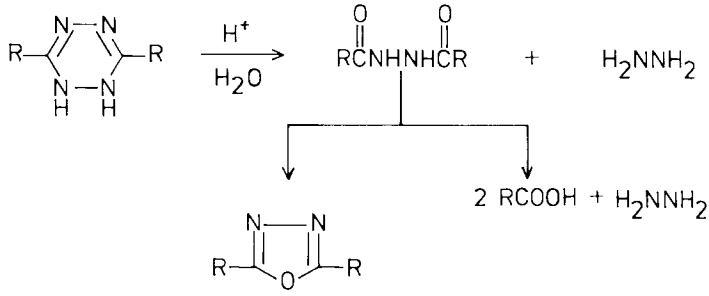
The most commonly reported reaction of 1,2-dihydro-1,2,4,5-tetrazines is oxidation to the corresponding 1,2,4,5-tetrazine. This reaction has already been discussed in some detail in the section on 1,2,4,5-tetrazine synthesis (eq. II-1).



(84)

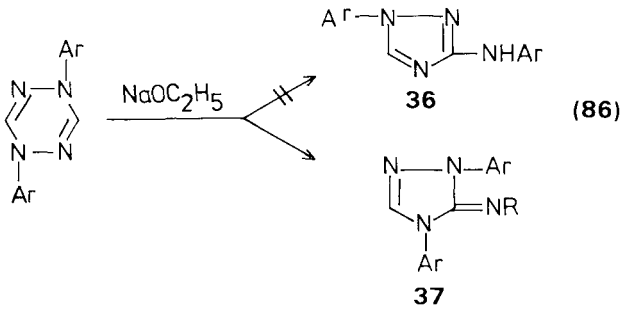
The 1,2-dihydro-1,2,4,5-tetrazines can react with mineral acids by isomerization to 4-amino-4*H*-1,2,4-triazoles (eq. III-37), as has already been mentioned, or by degradation of the tetrazine ring system. In the early work on the synthesis of 3,6-diphenyl-1,2-dihydro-1,2,4,5-tetrazine a by-product was isolated which was isomeric with 3,6-diphenyl-1,2-dihydro-1,2,4,5-tetrazine, and the tetrazine could be converted to the isomeric by-product by acid treatment (98, 110, 403, 404, 506, 532–534, 543). The compound was called *benzyliminonitrile*, *diphenylisodihydrotetrazine*, and *hydrazicarbamine*, and it was suggested that the compound was 3,6-diphenyl-1,4-dihydro-1,2,4,5-tetrazine. Stollé (532–534), on the basis of failure to obtain the 1,2,4,5-tetrazine by oxidation, suggested the 4-amino-4*H*-1,2,4-triazole structure. A short time later the proposed triazole structure was confirmed by Bülow and Weber (59), who showed that the compound underwent reactions very similar to those of other amino triazoles. It appears that all types of 1,2-dihydro-1,2,4,5-tetrazines isomerize readily with acid including alkyl-substituted (49), arylalkyl-substituted (406, 409), aryl-substituted (117, 219), 1,2-dihydro-1,2,4,5-tetrazines substituted with heterocyclic rings (117, 168, 301), and 1,2-dihydrotetrazines substituted on nitrogen (543, 544). Although it has been suggested many times that 1,2-dihydro-1,2,4,5-tetrazines isomerize to the 1,4-dihydro isomers under the influence of acid, this does not occur. Also there seem to be no authentic cases of isomerization of 1,4-dihydro-1,2,4,5-tetrazines to aminotriazoles as a result of acid treatment. The effect of acid on 1,6-dihydro- and 3,6-dihydro-1,2,4,5-tetrazine has not been reported.

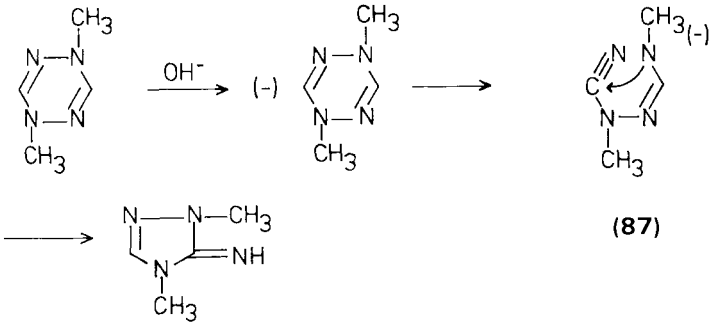
Acid hydrolysis of 1,2-dihydro-1,2,4,5-tetrazines has been found to give a variety of products (eq. III-38). The products reported have been hydrazides (77, 117), acids (103, 349), hydrazine (103, 349), and oxadiazoles (117, 168, 349, 403, 404, 407, 543, 544). A probable reaction sequence is the initial



formation of hydrazine and diacylhydrazides which are then converted to acids and hydrazine or to oxadiazoles as indicated in eq. III-38. The factors responsible for the varied products obtained by acid hydrolysis of 1,2-dihydro-1,2,4,5-tetrazines have not been identified. 1,4-Dipehnyl-1,4-dihydro-1,2,4,5-tetrazine has been hydrolyzed with acid to phenylhydrazine and formic acid (22). The same compound on treatment with ethanolic hydrogen chloride gave 1,5-diphenylformazan (216). It was hypothesized that the product arose from intermediate formation of phenylhydrazine and ethyl orthoformate derived from formic acid.

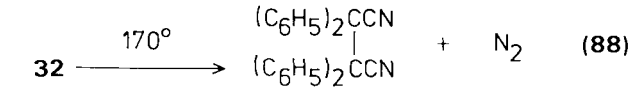
Alkaline treatment of dihydro-1,2,4,5-tetrazines has been discussed only sparingly in the literature. Baker, Ollis, and Poole (22) treated 1,4-diaryl-1,4-dihydro-1,2,4,5-tetrazines with sodium ethoxide in ethanol and postulated that the products were 1-aryl-3-(arylamino)-4*H*-1,2,4-triazoles (**36**). A subsequent study by Huisgen and co-workers (216) established, as a result of independent synthesis in the case of the 1,4-diphenyl compounds, that the products were 5-imino-1,4-diaryl-Δ^2-1,2,4-triazolines (**37**). Treatment of 1,4-diphenyl-1,4-dihydro-1,2,4,5-tetrazine with sodium methoxide degraded it to phenylcyanamide presumably through a compound of type **37** as an intermediate. Kohn and Olofson (256) report results quite similar to those of Huisgen and his collaborators when 1,4-dimethyl-1,4-dihydro-1,2,4,5-tetrazine was treated with aqueous sodium hydroxide and suggested the mechanism shown in eq. III-40.



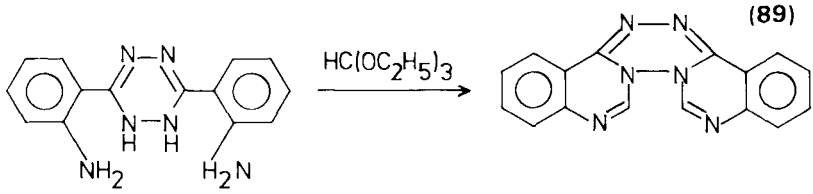


Treatment of 3,6-bis(4-pyridyl)-1,2-dihydro-1,2,4,5-tetrazine with alcoholic potassium hydroxide forms 3,5-bis(4-pyridyl)-4*H*-1,3,4-triazole (293). The result from the 1,2-dihydro-1,2,4,5-tetrazine is markedly different from that with the 1,4-dihydro-1,2,4,5-tetrazines. Whether or not this difference is a result of differences inherent in the 1,2-dihydro and 1,4-dihydro isomers or whether it arises from differences in substitution at the 3- and 6-positions is not known.

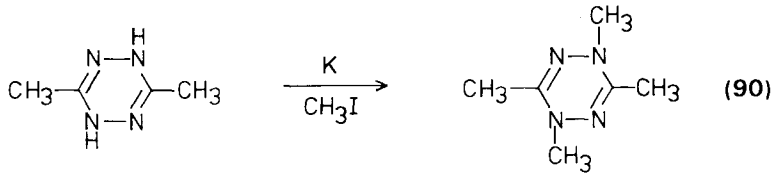
There are a number of reports of pyrolysis of 1,2-dihydro- and 1,4-dihydro-1,2,4,5-tetrazines (84, 220, 561) to give 1,2,4,5-tetrazines. These have been done without solvent and with solvents, but there was not a rigorous exclusion of oxygen so it is probable that these were actually oxidations. 3,6-Dimethyl-1,2-dihydro-1,2,4,5-tetrazine isomerizes at its melting point to 3,5-dimethyl-4-amino-4*H*-1,2,4-triazole (109). Huisgen and co-workers (219) found that heating 3,6-diphenyl-1,2-dihydro-1,2,4,5-tetrazine at 190°C without solvent formed 2,4,6-triphenyl-1,3,5-triazine, 3,5-diphenyl-4*H*-1,2,4-triazole, benzonitrile, and ammonia. Pyrolysis of 3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazine forms acetaldehyde azine and nitrogen (514). Heating 3,6-bis(diphenylmethylidene)-3,6-dihydro-1,2,4,5-tetrazine (**32**) at 170°C gave tetraphenylsuccinonitrile and nitrogen (eq. III-41) (542). The product probably arises from the free-radical intermediate $(C_6H_5)_2\dot{C}CN$, although there is no evidence for this.



Although the nitrogen atoms in 1,2-dihydro-1,2,4,5-tetrazines are only very weakly basic, they react very much as do ordinary amines. 3,6-Diphenyl-1,2-dihydro-1,2,4,5-tetrazine forms a bismethiodide (404). Acylation occurs readily to form both mono- and diacyl derivatives using acetic anhydride or benzoyl chloride as the acylating agents (301, 403, 404, 406, 407). Reaction of 3,6-bis(2-aminophenyl)-1,2-dihydro-1,2,4,5-tetrazine with ethyl orthoformate gave a pentacyclic compound (eq. III-42) (48). 3,6-Dimethyl-1,4-dihydro-1,2,4,5-tetrazine can be methylated on the nitrogen atoms with potassium and

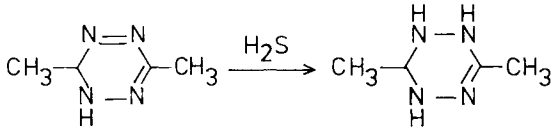


methyl iodide in 52% yield (eq. III-43) (514). The proton on nitrogen in 1,6-dihydro-1,2,4,5-tetrazine is acidic enough to react with diazomethane to give an *N*-methyl compound, and it reacts with formaldehyde to form a hydroxymethyl group on nitrogen (514).



(90)

Vigorous reduction of 3,6-diaryl-1,2-dihydro-1,2,4,5-tetrazines with zinc in acetic acid (219, 403, 404, 407, 559) forms 3,6-diaryl-4*H*-1,2,4-triazoles. The same products are obtained using sodium in ethanol (219) and diimide for the reduction. Reductions of 1,3,4,6-tetraphenyl- and 1,4-bis(4-bromophenyl)-3,6-diphenyl-1,4-dihydro-1,2,4,5-tetrazines by means of zinc dust distillation gave benzonitrile and aniline (24, 86), but reduction of the bromo compound with zinc and hydrochloric acid formed *p*-bromoaniline (86). Hydrogen sulfide reduces 3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazine to 3,6-dimethyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (eq. III-44) (514).



(91)

The formation of radical cations of 1,4-dihydro-1,2,4,5-tetrazines (**34** and **35**) has already been discussed, as has the formation of radical anions of 1,2,4,5-tetrazines (**6**) by reaction of 1,4-dihydro-1,2,4,5-tetrazines with 1,2,4,5-tetrazines in the presence of base. In the absence of base a charge-transfer complex is formed in which the 1,4-dihydro-1,2,4,5-tetrazine is a radical cation and the 1,2,4,5-tetrazine is a radical anion (514).

Scheiner and co-workers (478, 480) have studied the photolysis of 3,6-diphenyl-1,2-dihydro-1,2,4,5-tetrazine and found that the product was 3,5-diphenyl-4*H*-1,2,4-triazole. A mechanism for the reaction was suggested. However, a very different course was reported for the photolysis of 3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazine by Skorianetz and sz. Kováts (514). Acetaldehyde azine and nitrogen were the products.

A series of 1,2-dihydro-1,2,4,5-tetrazines substituted in the 3- and 6-positions with substituted pyridines or 5-tetrazolyl rings were found to form complexes with Cu^{+}, Cu^{2+}, Fe^{2+}, Fe^{3+}, Ni^{2+}, Ca^{2+}, Co^{2+}, Al^{3+}, and Cr^{3+} (469, 483). The complexes contained one metal ion for each dihydro-1,2,4,5-tetrazine molecule.

Treatment of 3,6-disubstituted 1,2-dihydro-1,2,4,5-tetrazines in which the substituents were polyfluorinated alkyl groups with cobalt trifluoride, copper, potassium hydrogen fluoride, fluorine, or oxygen at 150°C resulted in complete destruction of the ring with formation of fluorinated alkanes and fluorinated alkylhydrazines (591).

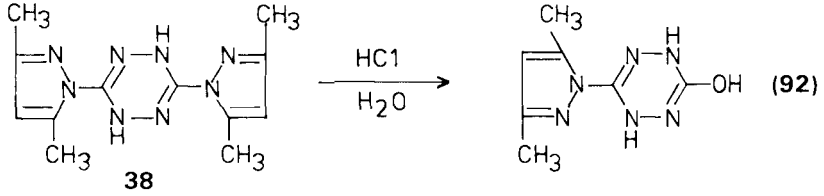
3,6-Diacetyl-1,4-diphenyl-1,2,4,5-tetrazine reacts as do normal methyl

ketones undergoing sodium borohydride reduction and the iodoform reaction (216). Hydrazones of 3,6-diacetyl-1,2-dihydro-1,2,4,5-tetrazines are known (eq. III-14) and react normally with aldehydes and ketones to form azines (14, 15). The hydrazones are readily acylated using acetic anhydride, phenyl isocyanate, or phenyl isothiocyanate (14). Reaction with nitrous acid converts the hydrazones back to the ketones (14, 15).

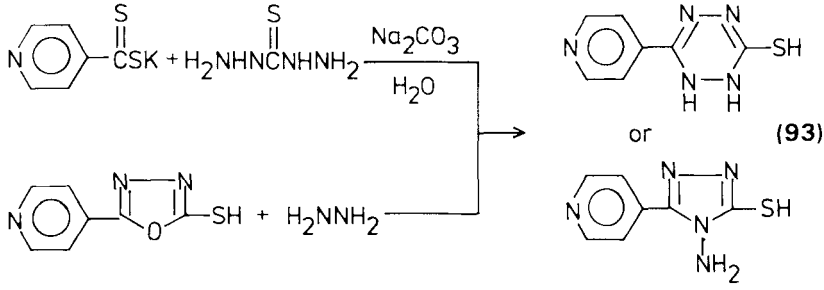
B. Dihydro-1,2,4,5-tetrazines Substituted by Carboxyl Groups, Derivatives of Carboxyl Groups, and Hetero Atoms

1. *Preparation*

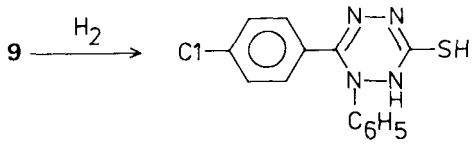
a. 1,2-DIHYDRO-1,2,4,5-TETRAZINES. 3-Bromo-6-phenyl-1,2-dihydro-1,2,4,5-tetrazine was prepared by zinc and acetic acid reduction of the corresponding 1,2,4,5-tetrazine prepared as shown in eq. II-32 (179). Scott has reported the preparation of 3-hydroxy-6-(3,5-dimethyl-1-pyrazolyl)-1,4-dihydro-1,2,4,5-tetrazine by acid hydrolysis of the symmetrically substituted compound **38** (eq. III-45) (494). However, as has already been discussed, it seems likely that



the product is the 1,2-dihydro-1,2,4,5-tetrazine (70). The preparation of only a few mercapto-1,2-dihydro-1,2,4,5-tetrazines has been reported. König and co-workers (257, 258) have prepared a compound which is either 3-mercapto-6-(4-pyridiyl)-1,2-dihydro-1,2,4,5-tetrazine or the isomeric 4-aminotriazole by two procedures (eq. III-46); one of these involved the reaction of potassium

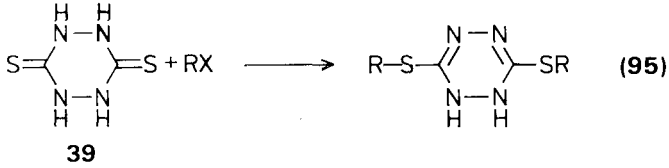


dithioisonicotinate with thiocarbazide, and the other consisted of treatment of 2-mercapto-5-(4-pyridiyl)-1,3,4-oxadiazole with hydrazine. It was stated (258) that the product melts at about 210°C, solidifies, and remelts at 248 to 250°C, possibly indicating that the original product was a 1,2-dihydro-1,2,4,5-tetrazine which isomerizes to a triazole at its melting point and then solidifies. There is some precedent for the oxadiazole reaction with hydrazine as such a reaction has been reported by Brown and co-workers (49) to give an acylhydrazonohydrazide, which can be converted to a 1,2,4,5-tetrazine in the presence of oxidizing agents. The inner ammonium salt **9** in which aryl is *p*-chlorophenyl has been reduced catalytically to a mercapto compound (eq. III-47) (341). The preparation of a compound which might be a 3-mercapto-1,2-dihydro-1,2,4,5-tetrazine has been reported (65), but it seems more probable that it is a



(94)

1,2,3,4-tetrahydro-1,2,4,5-tetrazine-3-thione (183, 184). The synthesis is discussed in the section dealing with 3-thio-1,4-dihydro-1,2,4,5-tetrazines (eq. III-57). The usual procedure for preparing 3,6-dimercapto-1,2-dihydro-1,2,4,5-tetrazines has been alkylation of hexahydro-1,2,4,5-tetrazine-3,6-dithione as indicated in eq. III-48 (310, 467). The preparation of the dithione will be

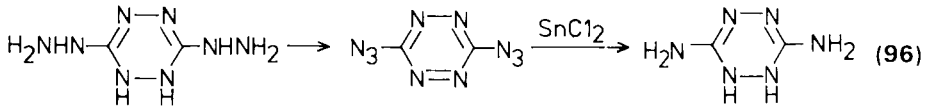


(95)

X = halogen

discussed in the section devoted to hexahydro-1,2,4,5-tetrazines. The yields reported have been about 50%. Mixed alkylthio compounds have been prepared by a stepwise alkylation involving alkylation at one sulfur atom only, followed by alkylation with a different alkyl group at the second sulfur atom. A series of bis(6-aryl-1,2-dihydro-1,2,4,5-tetrazin-3-yl) disulfides prepared from hexahydro-1,2,4,5-tetrazine-3-thiones by oxidation have been reported (145).

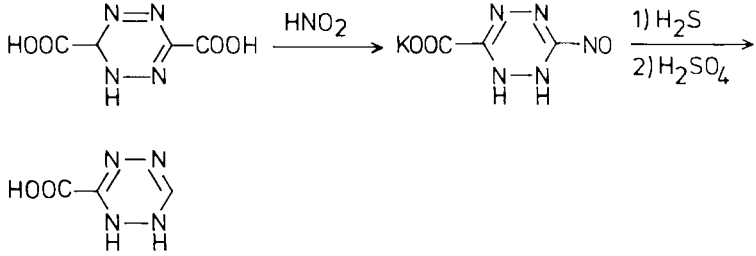
3-Amino-1,2-dihydro-1,2,4,5-tetrazines are prepared by reduction of the corresponding 1,2,4,5-tetrazines (551). Reduction of 3,6-diazido-1,2,4,5-tetrazine with stannous chloride forms 3,6-diamino-1,2-dihydro-1,2,4,5-tetrazine (eq. III-49) (315). 3,6-Dihydrazino-1,2-dihydro-1,2,4,5-tetrazine, as well as 3-amino-6-hydrazino-1,2-dihydro-1,2,4,5-tetrazine, arises from the action of



(96)

hydrazine on 3,6-diamino-1,2,4,5-tetrazine in the absence of air (315, 442), and also by stannous chloride reduction of 3,6-dihydrazino-1,2,4,5-tetrazine (314).

Both 1,2-dihydro-1,2,4,5-tetrazine-3-carboxylic acid and the corresponding 3,6-dicarboxylic acid are known as well as many derivatives of the latter including esters, amides, hydrazides, and azides. 1,2-Dihydro-1,2,4,5-tetrazine-3-carboxylic acid was derived from 1,6-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic acid through treatment with nitrous acid to give 3-nitroso-1,2-dihydro-1,2,4,5-tetrazine-6-carboxylic acid, isolated as the potassium salt, followed by treatment with hydrogen sulfide and sulfuric acid (eq. III-50) (346). The preparation of the dicarboxylic acid is carried out by dimerization of ethyl diazoacetate in base (522) and has already been discussed (eq. II-2).

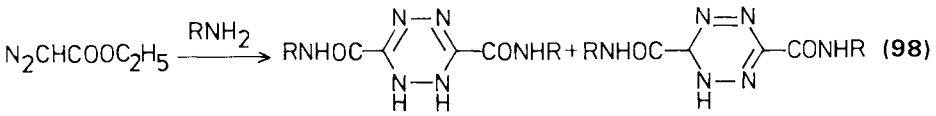


(97)

Such a reaction no doubt occurs via a 1,3-dipolar nitrilimine intermediate. The potassium salt of 1,2-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic acid has been claimed to react with bromine to give the corresponding 1-bromo compound as a bromine complex, but characterization of the product was almost nonexistent, and the structure of the product should be considered as unproved (346).

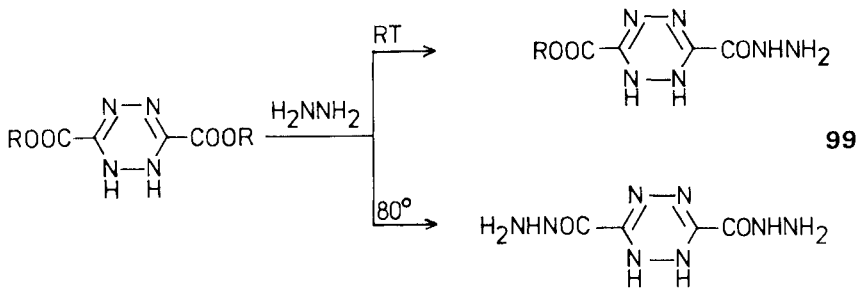
A limited number of esters of 1,2-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic acid have been prepared by standard procedures for the most part, such as treatment of metal salts with alkyl halides (115, 202) and reaction of the acid with diazoalkanes (116, 299). Reaction of the acid with diazomethane forms not only the dimethyl ester but also causes *N*-methylation to give dimethyl 1-methyl-1,2-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate (298). In the reaction of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate with trimethylsilylethylene (eq. II-24) the dihydropyridazine intermediate was dehydrogenated by addition of an equivalent of the starting tetrazine ester, which was reduced to dimethyl 1,2-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate (41).

Amides, hydrazides, and azide derivatives of 1,2-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic acid are known. The amides have been prepared by the reaction of diazoacetic ester with ammonia and with amines as indicated in eq. III-51 (95,



(98)

100, 108, 185, 347, 507). The products are claimed to be in most cases either the 1,2-dihydroamides or the 1,6-dihydroamides, or a mixture of both as shown in the above equation. In some cases (507) the products were described only as dihydro without specifying the position of the hydrogen atoms but giving a reference to the earlier publication of Müller (347). It is assumed that these are 1,2-dihydro compounds. The earlier reports on the dimerization of ethyl diazoacetate in the presence of ammonia and amines was done without any knowledge of the structure of the products. Two series of compounds were isolated, and these were referred to as *bisdiazoacetamide, pseudodiazoacetamide,* and *iminoazoacetamide.* Although the earlier work is not conclusive, on the basis of results reported the best interpretation seems to be that *pseudodiazoacetamide* and *iminoazoacetamide* are 1,6-dihydro-1,2,4,5-tetrazine-3,6-dicarboxamide, and *bisdiazoacetamide* is the 1,2-dihydro isomer. The dimerization is usually run in alcoholic solution at various temperatures from cold to 100°C, and a lower temperature promotes the formation of the 1,6 isomer. Warming the 1,6-dihydroamides with amines isomerizes the amides to the 1,2-dihydro isomer. Reaction of esters with ammonia or amines has also been used to prepare amides (115). Two series of 1,2-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic acid hydrazides are known. One series has one carbalkoxy substituent and one hydrazide substituent, whereas the other has hydrazide substituents at both the 3- and 6-positions (eq. III-52) (116, 299). The monohydrazides are prepared by reaction of the appropriate ester with hydrazine in alcohol at room temperature. Reaction at 80°C forms the dihydrazide. Both series of hydrazides have been converted by nitrous acid treatment to what was



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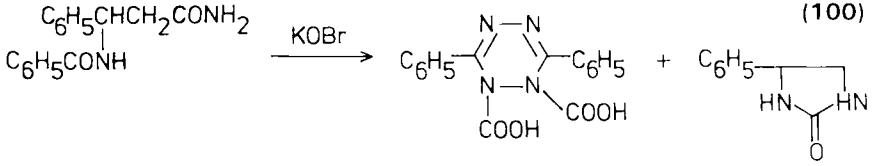
believed to be 1,2-dihydro-1,2,4,5-tetrazine azides (116). However, Lin, Lieber, and Horwitz (299) reported that such treatment results in oxidation with formation of 1,2,4,5-tetrazine-3,6-dicarboxazide.

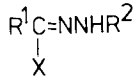
The preparation of 3,6-diphenyl-1,2-dihydro-1,2,4,5-tetrazine-1,6-dicar-



(100)

boxylic acid by the action of potassium hypobromite on β-benzoylaminohydrocinnamide has been claimed (eq. III-53) (447). The dihydrotetrazine was obtained in 29% yield with the principal product being 4-phenyl-2-imidazolidone. Proof of structure for the 1,2-dihydro-1,2,4,5-tetrazine was not extensive, and it is difficult to see how such a product could arise by the reaction used. Consequently it seems best to question the proposed structure.

b. 1,4-DIHYDRO-1,2,4,5-TETRAZINES. Only one general method is known for synthesizing 1,4-dihydro-1,2,4,5-tetrazines having substituents at positions 3 and 6 which are not carbon or which are carboxyl groups or their derivatives, but it is capable of such variation that halogens, nitro groups, carbalkoxy groups, and acyl groups can be introduced into the product. The reaction is that indicated in eq. III-24, using compounds of the type of **28**, in



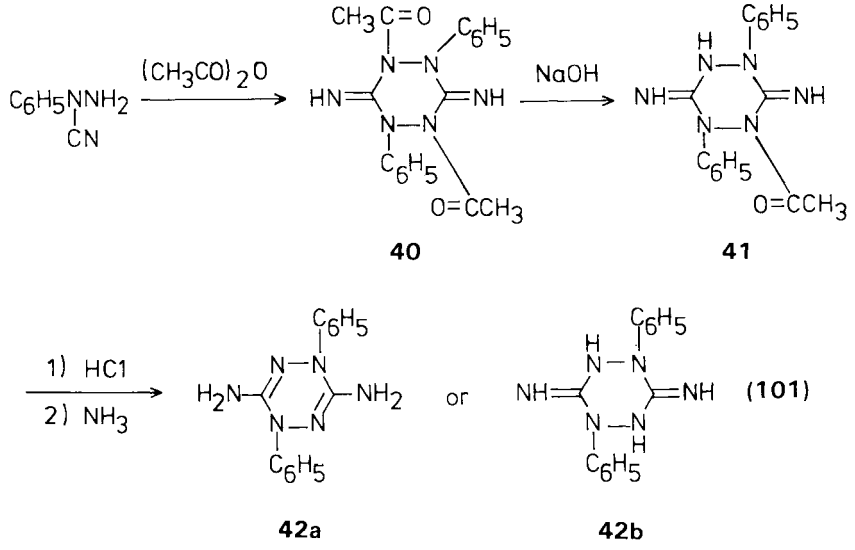
28

which X is chlorine or bromine, R^1 is chlorine, nitro, or carbethoxy, and R^2 is an aryl group. Moon (340) has prepared 3,6-dichloro-1,4-bis(2-methyl-4,6-dichlorophenyl)-1,4-dihydro-1,2,4,5-tetrazine by this reaction using sodium methoxide as the base. A similar reaction using sodium acetate has been used to prepare 3,6-dinitro-1,4-dihydro-1,2,4,5-tetrazines (433). The yields in these reactions were quite good, varying from 63 to 95%.

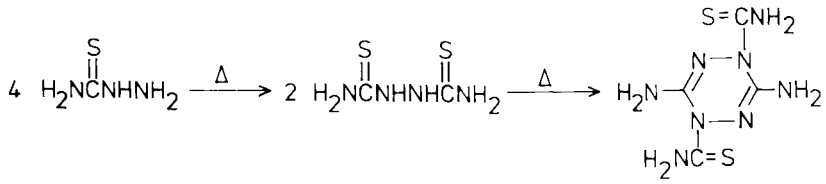
Bowack and Lapworth (47) and Bülow and co-workers (56, 59) have used the same reaction, in which R^1 of **28** is $COOC_2H_5$ and the bases are hydroxides and carbonates of alkali metals, to prepare what they believed to be diethyl 1,4-diaryl-1,4-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylates. In the case in which the aryl substituents were phenyl, the ester was hydrolyzed to an acid. However, Baker, Ollis, and Poole (22) concluded that the products obtained were not 1,4-dihydro-1,2,4,5-tetrazines on the basis of their ultraviolet spectra. The maximum at 375 nm was not considered by Baker and co-workers to be consistent with the proposed structure. Subsequently Huisgen and his collaborators (215, 216) used essentially the same reaction to prepare similar compounds but using triethylamine as base. It was shown that the compound prepared by the latter group differed from those prepared earlier, and that

Huisgen's product was diethyl 1,4-diphenyl-1,4-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate. The proof of structure was spectral data and degradation to 1,4-diphenyl-1,4-dihydro-1,2,4,5-tetrazine. Consequently, it now is clear that the compounds prepared earlier did not have the proposed structures. Since the starting material was the same in all these cases, and the conditions were quite similar, the failure to obtain the same products is surprising. This is particularly true in light of the fact that Ruccia and Vivona (448) have used sodium hydroxide in ethanol to dimerize **28** ($X = Cl$, $R^1 = COOC_2H_5$) to give diethyl 1,4-diphenyl-1,4-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate. These conditions were even more similar to those of Bowack and Lapworth and Bülow and co-workers than were those of Huisgen and his group.

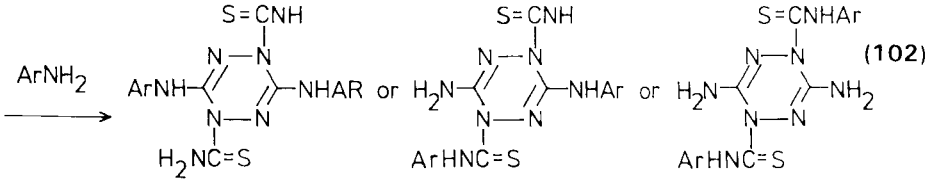
Walter (566) has claimed the preparation of 3,6-diamino-1,4-dihydro-1,2,4,5-tetrazine by the reaction of ethyl carbonate with hydrazine at 120–175°C. No proof of structure was presented so it is most likely that the product did not have the proposed structure. Scott and Reilly (493) have reported the preparation of 3,6-diamino-1,4-dihydro-1,2,4,5-tetrazines by the reaction of *S*-methylisothiosemicarbazide with organic bases (eq. II-38). However, it is more probable that these are 3,6-diamino-1,2,4,5-tetrazines as already discussed. Pellizzari (395) has treated 1-cyano-1-phenylhydrazine with acetic anhydride (eq. III-54) to form 3,6-diimino-1,4-diphenyl-2,5-diacetylhexahydro-1,2,4,5-tetrazine (**40**). Deacetylation with base followed by acid results in formation of either the 1,4-dihydro-1,2,4,5-tetrazine **42a** or the hexahydro compound **42b**. A series of compounds believed to be 3,6-diamino-1,4-bis(thiocarbamoyl)-1,4-dihydro-1,2,4,5-tetrazines have been prepared by Mazourewitch (326) by the



thermal condensation of thiosemicarbazide or dithiobiurea with aromatic amines. The products were thought to arise by the series of reactions indicated in eq. III-55, and the final products were considered to have one of the three



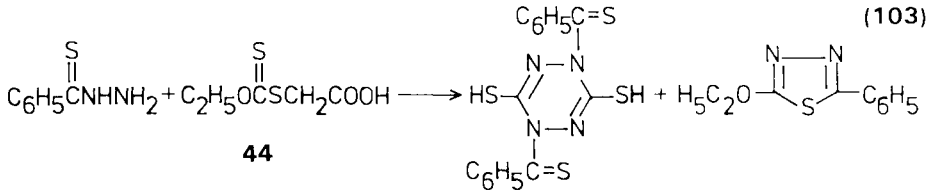
43



(102)

possible structures shown. In every case a high-melting white solid, m.p. 297–300°C (dec.), was obtained, which was thought to have structure **43**. A series of five compounds derived from aniline and the three toluidines was reported. However, in a subsequent publication it was shown that the products were actually 1,2,4-triazoles (327).

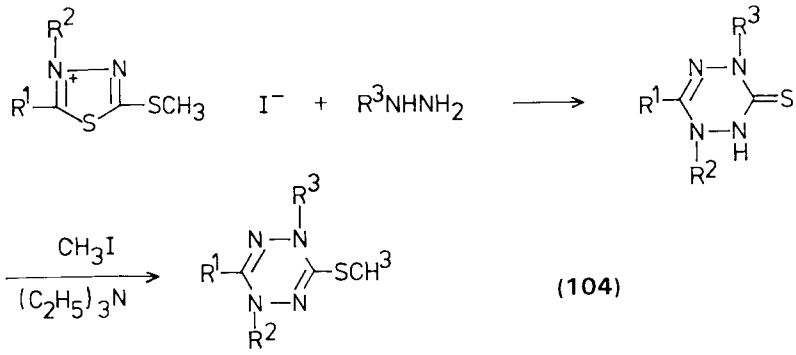
Holmberg (211) has found that 3,6-dimercapto-1,4-dithiobenzoyl-1,4-dihydro-1,2,4,5-tetrazine is formed as a by-product in the reaction of thiobenzohydrazide with the dithiocarbonate **44** (eq. III-56). This product involves some



(103)

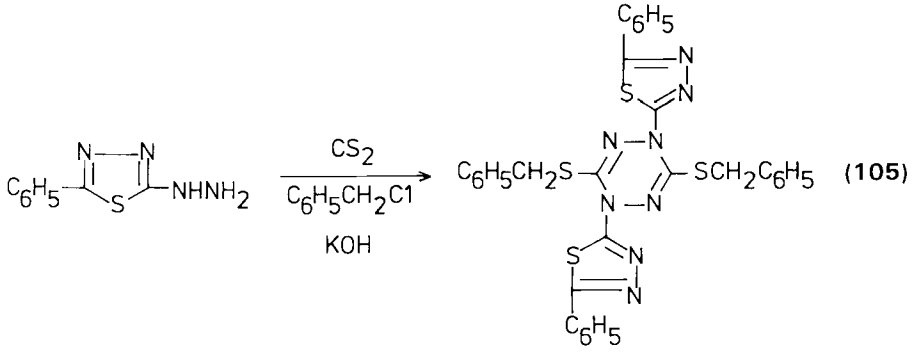
44

intermediate which dimerizes, whereas the principal product (2-ethoxy-5-phenyl-1,3,4-thiodiazole) arises by cyclization of the intermediate monomer. Busch and co-workers (65) have treated quaternary salts of 2-(methylmercapto)-5-phenyl-1,3,4-thiadiazole with hydrazine and report the formation of either 1,6-diphenyl-3-mercapto-1,4-dihydro-1,2,4,5-tetrazine or its 1,2-dihydro isomer. Subsequently Grashey and collaborators (183, 184) using essentially the same reaction (eq. III-57) obtained a series of products which were considered to be 1,4-dihydro-1,2,4,5-tetrazine-3-thiones. These were then treated with methyl iodide and base to form 3-(methylmercapto)-1,4-dihydro-1,2,4,5-tetrazines in



(104)

yields of 91 to 99%. Sandström (468) has treated 5-phenyl-1,3,4-thiadiazol-2-ylhydrazine with carbon disulfide and benzyl chloride in the presence of base to form the 3,6-dimercapto-1,4-dihydro-1,2,4,5-tetrazine **45**.



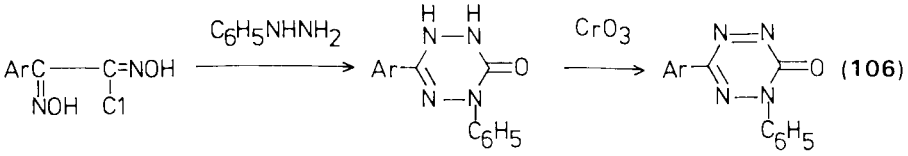
(105)

45

The dimerization of ethyl diazoacetate in the presence of amines to form *N*-substituted dihydro-1,2,4,5-tetrazine-3,6-dicarboxamides in which the compounds may be 1,4-dihydro (185) has already been discussed in the section concerning 1,2-dihydro compounds.

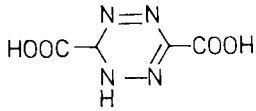
c. 1,6-DIHYDRO-1,2,4,5-TETRAZINES. 1-Phenyl-3-aryl-1,6-dihydro-1,2,-4,5-tetrazine-6-ones have been prepared by Ponzio and Perolio (426) by chromic oxide oxidation of the correponding tetrahydro compound (**47**) derived from oximes of type **46** (eq. III-59). The compound 3-phenyl-1,6-dihydro-1,2,4,5-tetrazin-6-one has been reported (146), but its method of synthesis was not mentioned.

1,3-Dihydroxyguanidine in the presence of base reacts to give a product claimed to be 3-amino-1,6-dihydro-1,2,4,5-tetrazin-6-one oxime (572). The evidence presented for the structure was insufficient to establish that the



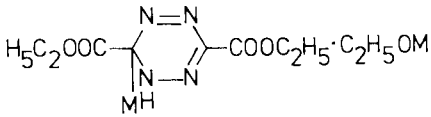
46 **47**

proposed structure was correct. The reaction of ethyl diazoacetate with base formed a second acid in addition to 1,2-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic acid (346). The second acid was isolated as a tripotassium salt and called *pseudodiazoacetic* acid. It was soon observed that analogous diamides arose from treatment of ethyl diazoacetate with amines, and it was proposed (101), largely on the basis of the hydrolysis of the amides to glyoxylic acid amide, hydrazine, and nitrogen, that *pseudodiazoacetic* acid was 3,6-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic acid. However, the ready oxidation of the acid to 1,2,4,5-tetrazine-3,6-dicarboxylic acid, the presence of three acidic hydrogens in the acid, and the fact that only one nitrogen atom can be alkylated (108) in the amide series all indicated that *pseudodiazoacetic* acid was 1,6-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic acid (**48**).



48

Curtius and co-workers (106) have prepared a compound, by reaction of sodium or potassium ethoxide with ethyl diazoacetate, that was claimed to be the salt **49**. The structure was proposed because the compound could be



49

hydrolyzed to hydrazine and ethyl glyoxylate, and aqueous base converted it to 1,6-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic acid. This is probably the same compound prepared by Hantzsch and Lehmann (201) and thought to be a salt of ethyl isodiazoacetate. The latter workers converted the salt to an ester which may be the diethyl ester of **48**.

Amides of 1,6-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic acid (**48**) have been prepared by treatment of ethyl diazoacetate with ammonia (95, 100, 507) or amines (347) as shown in eq. III-51. The preparation has already been discussed in the section dealing with the 1,2-dihydro isomers.

d. 3,6-DIHYDRO-1,2,4,5-TETRAZINES. Only a few compounds in this class have been reported, and it is highly doubtful that any have the structures claimed. Because of the doubt connected with the few compounds claimed to have hetero atoms at the 3- and 6-positions in 3,6-dihydro-1,2,4,5-tetrazine rings, none of them are included in the tables. The synthesis of 3,6-dihydro-1,2,4,5-tetrazine-3,6-dione by oxidation of *p*-urazine, which was assumed to be hexahydro-1,2,4,5-tetrazine-3,6-dione, has been claimed. However, as is discussed later, the compound ordinarily called *p*-urazine is a triazole so the product of its oxidation can hardly be the proposed one. Spectral data derived from the product were given. 3,6-Diamino-3,6-dihydro-1,2,4,5-tetrazine has been mentioned in the literature (153, 498), but neither the method of preparation nor characterization data were given. In one case (498) 3,6-diamino-3,6-dihydro-1,2,4,5-tetrazine was treated with formaldehyde and a methylol product, which may be 3,6-bis(hydroxymethyl)-3,6-dihydro-1,2,4,5-tetrazine, was mentioned. If such compounds actually have been prepared, they are the only examples of 3,6-dihydro-1,2,4,5-tetrazines having hydrogen atoms on the carbon atoms of the ring.

2. *Compound Survey*

Known compounds of this type are listed in Table III-2.

3. *Physical Properties and Theoretical Considerations*

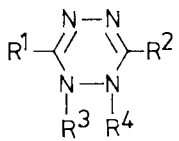
Very few data have been reported dealing with various spectra of dihydro-1,2,4,5-tetrazines having hetero atoms or carboxyl derivatives as substituents. As would be expected in such cases the ultraviolet and infrared spectra of 3,6-dinitro-1,4-diaryl-1,2,4,5-tetrazines are dominated by substituents rather than by the tetrazine system (433). 3,6-Bis(alkylthio)-1,2-dihydro-1,2,4,5-tetrazines have an ultraviolet maximum at 221.5 nm (ϵ 13,500), which is quite different from that of 3,6-dialkyl-1,2-dihydro-1,2,4,5-tetrazines. The circular dichroism of certain 3,6-arylalkyl-1,2-dihydro-1,2,4,5-tetrazines has been reported (150).

4. *Reactions*

Oxidation of both 1,2-dihydro- and 1,6-dihydro-1,2,4,5-tetrazines substituted with hetero atoms or carboxyl groups, or derivatives of carboxyl groups to tetrazines have been carried out (100, 101, 179, 185, 299, 522). Such oxidation

TABLE III-2. DIHYDRO-1,2,4,5-TETRAZINES WITH CARBOXYL, CARBOXYL-DERIVATIVE, AND HETERO-ATOM SUBSTITUENTS

A. 1,2-Dihydro-1,2,4,5-tetrazines



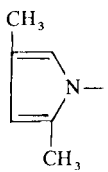
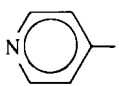
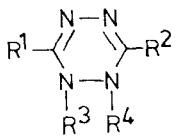
R^1	R^2	R^3	R^4	m.p. (°C)	Refs.
C_6H_5	Br	H	H	186–204	179
	HO	H	H	180	494
4-ClC_6H_4	HS	C_6H_5	H	205	341
	HS	H	H	210, 248	257, 258
CH_3S	CH_3S	H	H	194–198	310, 467
CH_3S	$CH_2{=}CHCH_2S$	H	H	107	310
$CH_2{=}CHCH_2S$	$CH_2{=}CHCH_2S$	H	H	86	310
$C_6H_5CH_2S$	$C_6H_5CH_2S$	H	H	165	467
$C_6H_5CH_2S$	$C_6H_5CH_2S$	CH_3CO	H	141	467
$H_5C_2OOCCH_2S$	$H_5C_2OOCCH_2S$	H	H	104	467

TABLE III-2. (continued)

A. 1,2-Dihydro-1,2,4,5-tetrazines



R^1	R^2	R^3	R^4	m.p. (°C)	Refs.
CH_3	H_2N	H	H	–	551
C_6H_5	H_2N	H	H	–	551
H_2N	H_2N	H	H	–	315
H_2N	H_2NHN	H	H	–	314, 442
H_2N	$C_6H_5CH{=}NHN$	H	H	–	314
H_2NHN	H_2NHN	H	H	170 (dec.)	314, 315, 442
$(CH_3)_2NN$ $\quad\quad\vert$ $\quad\quad CH_3$	$(CH_3)_2NN$ $\quad\quad\vert$ $\quad\quad CH_3$	H	H	–	314
$(CH_3)_2C{=}NHN$	$(CH_3)_2C{=}NHN$	H	H	176	314, 315
$C_6H_5CH{=}NHN$	$C_6H_5CH{=}NHN$	H	H	243	314, 315
$CH_3COHNHN$	$CH_3COHNHN$	H	H	–	314
HOOC	H	H	H	93–105	346
HOOC	NO	H	H	170	346
HOOC	HOOC	H	H	185	104, 115, 299, 522
Ammonium salt				217, 222	115, 116
Hydrazine salt				183–188	116
Ethylamine salt				179	347
CH_3OOC	CH_3OOC	H	H	167	41, 115, 299
CH_3OOC	CH_3OOC	CH_3	H	114	299
H_5C_2OOC	H_5C_2OOC	H	H	113	115, 116

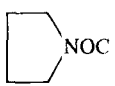
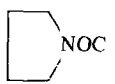
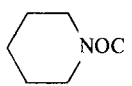
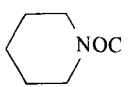
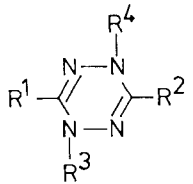
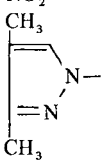
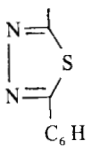
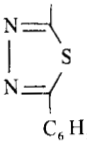
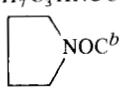
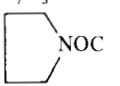
$(CH_3)_2CHOOC$	$(CH_3)_2CHOOC$	H	H	–	115
CH_3OOC	H_2NHNOC	H	H	211	116
H_5C_2OOC	H_2NHNOC	H	H	228	116
Hydrochloride				212	116
H_5C_2OOC	$C_6H_5CH{=}NHNOC$	H	H	233	116
H_5C_2OOC	4-$CH_3C_6H_4CH{=}NHNOC$	H	H	237	116
H_5C_2OOC	$(CH_3)_2C{=}NHNOC$	H	H	115	116
H_5C_2OOC	$C_6H_5C(CH_3){=}NHNOC$	H	H	182	116
H_5C_2OOC	$CH_3COHNHNOC$	H	H	166	116
H_5C_2OOC	N_3OC	H	H	dec.	116
H_2NOC	H_2NOC	H	H	>300	115
CH_3HNOC	H_2NOC	H	H	234 (dec.)	108
CH_3HNOC	CH_3HNOC	H	H	295 (dec.)	347
H_5C_2HNOC	H_5C_2HNOC	H	H	287 (dec.)	347
H_7C_3HNOC	H_7C_3HNOC	H	H	307 (dec.)	185
n-$H_{15}C_7HNOC$	n-$H_{15}C_7HNOC$	H	H	240	347
$(CH_3)_2NOC$	$(CH_3)_2NOC$	H	H	225	347
		H	H	218	185
		H	H	266	347
H_2NHNOC	H_2NHNOC	H	H	265, 275, 287	116, 299
$C_6H_5CH{=}NHNOC$	$C_6H_5CH{=}NHNOC$	H	H	290	116
N_3OC	N_3OC	H	H	–	116
C_6H_5	C_6H_5	HOOC	HOOC	137	447

TABLE III-2. (continued)

B. 1,4-Dihydro-1,2,4,5-tetrazines



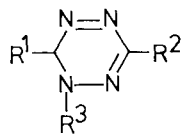
R^1	R^2	R^3	R^4	m.p. (°C)	Refs.
Cl	Cl	3,5-Cl_2–2-$CH_3C_6H_2$	3,5-Cl_2–2-$CH_3C_6H_2$	245	340
NO_2	NO_2	C_6H_5	C_6H_5	98	433
NO_2	NO_2	4-ClC_6H_4	4-ClC_6H_4	145	433
NO_2	NO_2	4-BrC_6H_4	4-BrC_6H_4	158	433
NO_2	NO_2	2,4-$Cl_2C_6H_3$	2,4-$Cl_2C_6H_3$	100	433
	HO	H	H	180	494
HS	HS	$C_6H_5C(=S)$	$C_6H_5C(=S)$	211	211
C_6H_5	HS	C_6H_5	H	208	65, 184

CH_3	CH_3S	C_6H_5	CH_3	–	184
C_6H_5	CH_3S	C_6H_5	H	–	65, 184
C_6H_5	CH_3S	CH_3	$C_6H_5CH_2$	–	184
C_6H_5	CH_3S	$C_6H_5CH_2$	CH_3	–	184
C_6H_5	CH_3S	C_6H_5	CH_3	–	184
C_6H_5	CH_3S	C_6H_5	C_6H_5	–	184
$C_6H_5CH_2S$	$C_6H_5CH_2S$			125	468
H_2N[a]	H_2N	H	H	360	497
H_2N	H_2N	C_6H_5	C_6H_5	198	395
C_6H_5HN[a]	C_6H_5HN	H	H	298	493
HOOC[a]	HOOC	C_6H_5	C_6H_5	206	47
H_5C_2OOC	H_5C_2OOC	C_6H_5	C_6H_5	91, 145	47, 216, 448
H_5C_2OOC[a]	H_5C_2OOC	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	158	47
H_5C_2OOC	H_5C_2OOC	2,4-$Cl_2C_6H_3$	2,4-$Cl_2C_6H_3$	196	57, 58
H_5C_2OOC	H_5C_2OOC	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	236	215, 216
H_5C_2OOC	H_5C_2OOC	4-$H_2NC_6H_4$	4-$H_2NC_6H_4$	110	216
H_7C_3HNOC[b]	H_7C_3HNOC	H	H	307	185
		H	H	218	185

[a]These compounds probably do not have the reported structure.
[b]These may be 1,2-dihydro-1,2,4,5-tetrazines or 1,2,3,4-tetrahydro-1,2,4,5-tetrazine-3-thiones.

TABLE III-2. (continued)

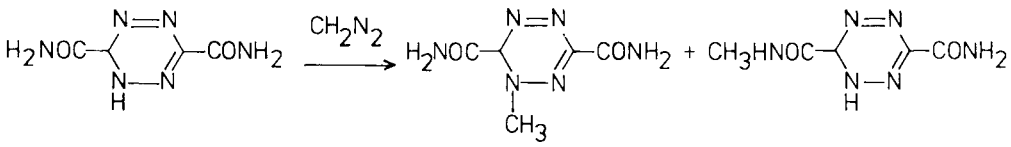
C. 1,6-Dihydro-1,2,4,5-tetrazines



R^1	R^2	R^3	m.p. (°C)	Refs.
=O	C_6H_5	H	–	146
=O	C_6H_5	C_6H_5	264	426
=O	4-$CH_3C_6H_4$	C_6H_5	265	426
=NOH	H_2N	H	>350	572
HOOC	HOOC	H (K salt)	–	346
H_5C_2OOC	H_5C_2OOC	H	–	201
H_2NOC	H_2NOC	H	170	95, 100, 507
H_2NOC	H_2NOC	CH_3	118 (dec.)	108
H_2NOC	H_2NOC	C_2H_5	125 (dec.)	108
CH_3HNOC	CH_3HNOC	$H(CH_3NH_2$ salt)	115 (dec.)	347
H_5C_2HNOC	H_5C_2HNOC	$H(C_2H_5NH_2$ salt)	–	347

has already been indicated in eq. II-2 for 1,2-dihydro-1,2,4,5-tetrazines-3,6-dicarboxylic acid. The usual oxidizing agents have been employed. Hydrolysis of 1,2-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic acid or its amides with acid forms oxalic acid, hydrazine, and, in the case of the amides, amines (101, 347). No nitrogen was isolated from this hydrolysis, which is further evidence that it is indeed the 1,2-dihydro rather than the 1,6-dihydro series. Mild acid hydrolysis of 1,6-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic acid amides forms glyoxylic acid amides, hydrazine, and nitrogen whereas more vigorous hydrolysis gives glyoxylic acid and ammonia or amines as well as nitrogen and hydrazine (101, 347). The absence of oxalic acid and the formation of nitrogen must indicate that diimide occurs as an intermediate and then reduces C-3 to the aldehyde level of oxidation. Those 1,6-dihydro-1,2,4,5-tetrazine-3,6-dicarboxamides having an alkyl substituent at N-1 give rise to an alkylhydrazine on hydrolysis (108). 3-Phenyl-1,6-dihydro-1,2,4,5-tetrazin-3-one is hydrolyzed by base to give benzaldehyde azine, presumably by way of benzaldehyde hydrazone as an intermediate (146). 1,6-Dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic acid and its amide derivatives rearrange to 1,2-dihydro compounds on warming with bases (101, 347). More vigorous treatment with base results in isomerization to a 1,2,4-triazole. Treatment of what was believed to be 1-bromo-1,2-dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic acid with potassium acetate is reported (346) to give 1,2,4,5-tetrazine-3,6-dicarboxylic acid. 1,6-Dihydro-1,2,4,5-tetrazine-3,6-dicarboxamide reacts with diazomethane to form two *N*-methylated products, **50** and **51**, as shown in eq. III-60 (108). Diazoethane also forms an *N*-ethyl compound analogous to **50**.

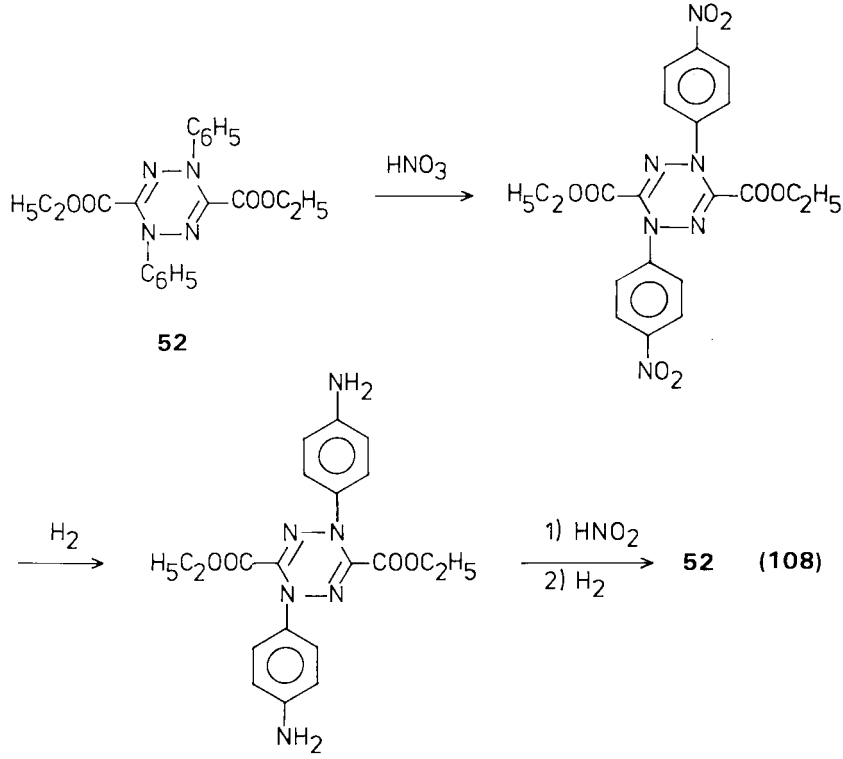
(107)



50 **51**

Many of the reactions undergone by functional groups substituted on dihydro-1,2,4,5-tetrazines have already been mentioned in connection with the synthesis of various types of 1,2,4,5-tetrazines. For the most part such reactions are the usual ones for the functional groups involved such as decarboxylation of acids (eq. II-2), ester formation of acids, hydrolysis of esters to acids, reaction of esters with ammonia or hydrazine (eq. III-52), and conversion of hydrazino groups to amines (eq. III-49). The reaction of amines with formaldehyde has already been mentioned, but reaction also occurs with other aldehydes. Benzaldehyde reacts with 3,6-diamino-1,4-diphenyl-1,4-dihydro-1,2,4,5-tetrazine to give the benzylidene derivative (395). 3,6-Dihydrazino-1,2-dihydro-1,2,4,5-

tetrazine reacts with acylating agents and aldehydes and ketones to give acylation on the amino nitrogen or hydrazones (116). The 1,4-diphenyl-1,4-dihydro-1,2,4,5-tetrazines are readily nitrated to give the corresponding *p*-nitrophenyl analogues which can then be reduced to amines, and the amines undergo normal amine reactions (eq. III-61) (216). The conversion of 3,6-diphenyl-1,4-bis(4-toluenesulfonyl)-1,4-dihydro-1,2,4,5-tetrazine to 3,6-diphenyl-1,2,4,5-tetrazine by pyrolysis or base has already been discussed (eq. II-4).



52 (108)

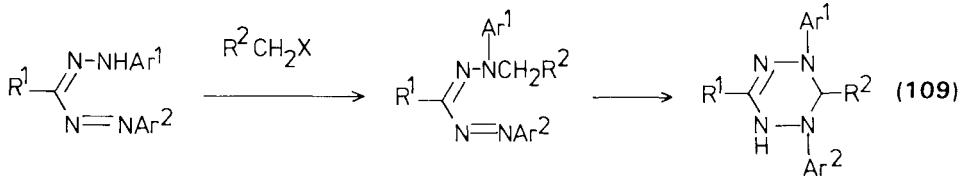
II. TETRAHYDRO-1,2,4,5-TETRAZINES

A. Alkyl-, Arylalkyl-, Aryl-, and Heterocyclic-Substituted Tetrahydro-1,2,4,5-tetrazines

1. *Preparation*

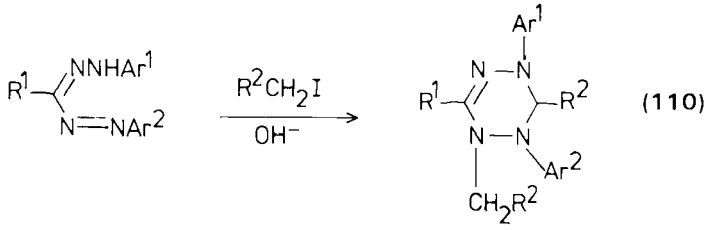
a. 1,2,3,4-TETRAHYDRO-1,2,4,5-TETRAZINES. The synthesis of 1,2,3,4-tetrahydro-1,2,4,5-tetrazines has been achieved in only a limited number

of ways, mostly involving the use of formazans as starting materials. The formazans are either converted directly to 1,2,3,4-tetrahydro-1,2,4,5-tetrazines or indirectly by processes involving verdazyls, which are 3,4-dihydro-1,2,4,5-tetrazines that are free radicals at N-1 (see **99** in the verdazyl section), as intermediates. The use of formazans has limited substituents on N-2 and N-4 to aryl or heterocyclic groups. Formazans can be alkylated and then converted to the 1,2,3,4-tetrahydro-1,2,4,5-tetrazines by pyrolysis or the complete reaction can be carried out without isolation of the intermediate alkylation products (274, 362, 366), as indicated in eq. III-62. The aryl groups can be the



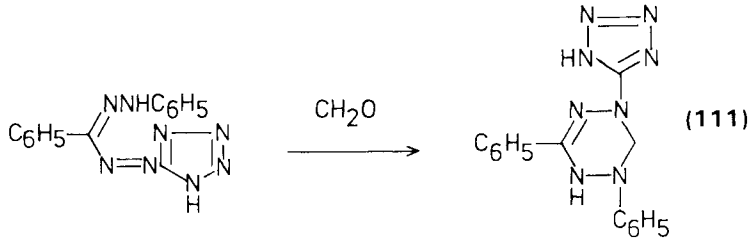
(109)

same or different but usually have been the same. R^1 can be alkyl, aryl, or groups containing hetero atoms attached to carbon. Presumably it would be possible to have almost any group as R^1. The alkylating agent has usually been an alkyl bromide or iodide. It can be varied considerably, but only primary halides have been successfully used. α,ω-Dihaloalkanes have been used (274), resulting in the formation of compounds containing two tetrahydro-1,2,4,5-tetrazine rings. Normally the 1,2,3,4-tetrahydro-1,2,4,5-tetrazines have not been isolated, but the reaction has been carried further so that the product is the corresponding verdazyl (eq. IV-1). The alkylations and cyclizations are run at room temperature in the presence of barium oxide and barium hydroxide octahydrate in dimethylformamide, and the tetrahydro compound is oxidized by air to the corresponding verdazyl (274, 362). The verdazyl can then be reduced to a 1,2,3,4-tetrahydro-1,2,4,5-tetrazine (eq. III-65). Cyclization of an isolated alkylated formazan to the tetrahydrotetrazine has been carried out at 150°C (366). A modification that results in the isolation of a product containing an alkyl group at N-1 involves carrying out the formazan alkylation in the presence of base and excess alkyl halide, with the resultant product being one that cannot be converted to a verdazyl as shown in eq. III-63 (367, 369). The



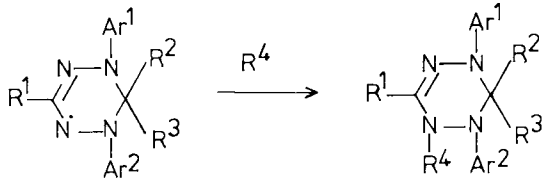
(110)

corresponding 1,2,3,4-tetrahydro-1,2,4,5-tetrazine with no substituent at N-1 is usually formed also. A variation of this procedure and also of one frequently used to prepare verdazyls is treatment of a formazan with formaldehyde (eq. III-64) (500, 501). The usual product of this reaction is the verdazyl, but in this case reduction by formaldehyde proceeds one step further.



(111)

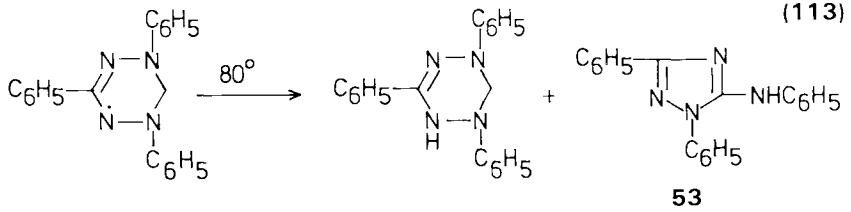
The reduction of verdazyls (eq. III-65, $R^4 = H$) has been used to prepare quite a number of 1,2,3,4-tetrahydro-1,2,4,5-tetrazines (274, 278, 279, 282, 367–369, 371). It is usually easier to prepare verdazyls and reduce them than it is to isolate the intermediate tetrahydro compounds. The overall yields are



(112)

R^4 = H or a free radical

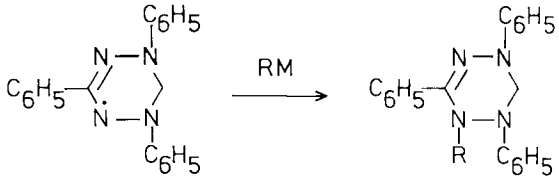
frequently quite good, although this depends on the yield of verdazyl. The usual reducing procedure is catalytic reduction with hydrogen (367, 369, 371). However, chemical reductions utilizing reductants such as sodium dithionite and zinc and acetic acid are also effective (279). One variant of the reduction procedure is treatment of a verdazyl with acid (eq. III-35) resulting in reduction of half of the verdazyl to the 1,2,3,4-tetrahydro-1,2,4,5-tetrazine and oxidation of the other half to a dihydro tetrazinium salt (278, 279, 282). Another procedure involving internal oxidation–reduction is the pyrolysis of 2,4,6-triphenylverdazyl at 80°C forming a tetrahydrotetrazine with concomitant formation of 1,3-diphenyl-5-anilino-1,2,4-triazole (**53**), as shown in eq. III-66 (368). A further procedure for conversion of verdazyls to 1,2,3,4-tetrahydro-1,2,4,5-tetrazines is their reaction with free radicals (247, 249, 250, 359, 367, 586). Neugebauer and Mannschreck (359, 367) first studied the reaction of verdazyls with free radicals using the isobutyronitrile free radical derived from azoisobutyronitrile [eq. III-65, $R^4 = (CH_3)_2C(CN)\cdot$]. The reaction was run at



(113)

53

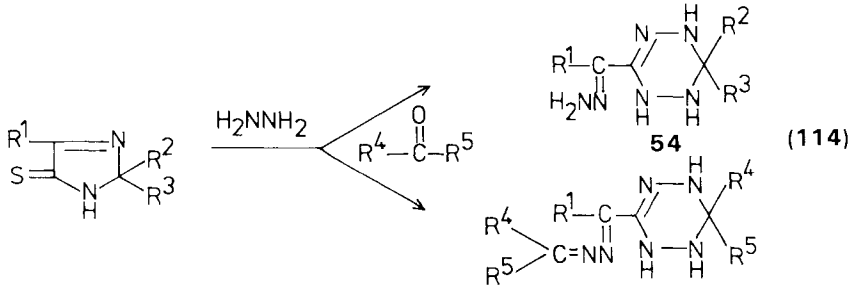
80°C. Kinoshita and collaborators (249, 250) have derived free radicals from the reaction of alkyl halides with such metals as silver and mercury and used them for verdazyl alkylation. Benzyl and diphenylmethyl free radicals attacked verdazyls but triphenylmethyl did not. The benzyloxy free radical derived from dibenzoylperoxide also reacts with 2,4,6-triphenylverdazyl (586, 587), but the product may be a verdazylium salt which would be a 1,6-dihydro-1,2,4,5-tetrazine. A somewhat similar reaction is that of 2,4,6-triphenylverdazyl with alkyllithium and Grignard reagents to give 1-alkyl-2,4,6-triphenyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazines (eq. III-67) (377a).



(113a)

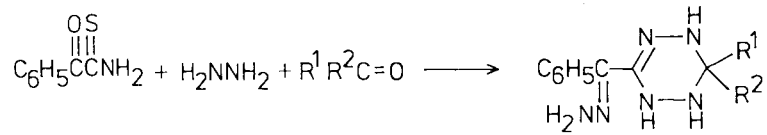
R = alkyl or benzyl; M = Li, MgCl, or MgBr

Two methods for synthesizing 1,2,3,4-tetrahydro-1,2,4,5-tetrazines have been developed by Asinger and Leuchtenberger (13), although it is probable that both involve the same intermediate. One procedure involves the reaction of an appropriately substituted imidazoline-4-thione with hydrazine hydrate either in the presence or absence of a ketone (eq. III-68). This reaction has already been discussed as a method for obtaining 1,2-dihydro-1,2,4,5-tetrazines (eq. III-14), but it gives as a side product the indicated tetrahydro compounds. Using a series



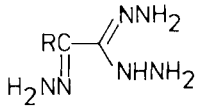
(114)

of imidazoline-4-thiones in which $R^2 = CH_3$ and $R^3 = Ar$ the tetrahydro-1,2,4,5-tetrazines were isolated in yields of 4 to 16%. In those cases in which $R^2 + R^3 = -(CH_2)_5-$ and $R^1 = Ar$ the yields of **54** were 60 to 85%, but when $R^1 = CH_3$ the yield was only 17%. When the reaction was run in the presence of acetone or cyclohexane, only the imidazoline-4-thione in which $R^1 = R^2 = (CH_3)_2CH$ and $R^3 = CH_3$ was used. The second procedure used was the reaction of α-ketothioamides with hydrazine in the presence of ketones (eq. III-69). In



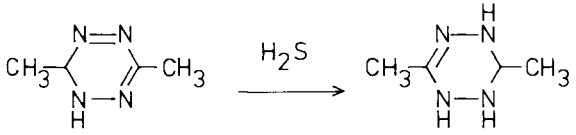
(115)

this case the ketones used were acetone and cyclohexanone. It was hypothesized by Asinger and Leuchtenberger that an intermediate hydrazono hydrazide compound, presumably such as **55**, was involved in both cases.

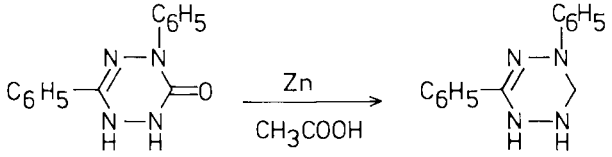


55

Only two other procedures have been reported for preparing the type of 1,2,3,4-tetrahydro-1,2,4,5-tetrazines under discussion. One of these is the hydrogen sulfide reduction of a 1,6-dihydro-1,2,4,5-tetrazine (eq. III-70) (514) which was obtained by oxidation of the corresponding hexahydro-1,2,4,5-tetrazine (eq. III-34). The reduction gave a yield of 85%. Ponzio and Perolio (426) have prepared 4,6-diphenyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine by chemical reduction of the corresponding 3-one (eq. III-71), which was prepared as shown in eq. III-59.

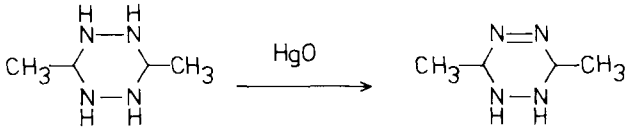


(116)



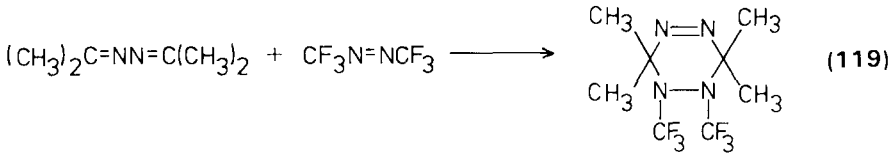
(117)

b. 1,2,3,6-TETRAHYDRO-1,2,4,5-TETRAZINES. Only four compounds of this type have been reported. One compound (514) has been prepared by oxidation of a hexahydro-1,2,4,5-tetrazine with mercuric oxide (eq. III-72). A



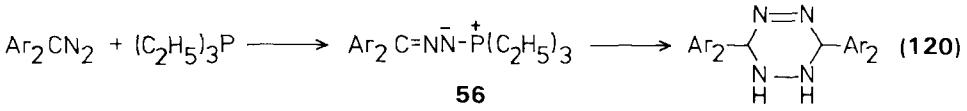
(118)

second preparative procedure involves the reaction of acetone azine with azotrifluoromethane (eq. III-73) (170). This latter reaction appears to be a variant of the Diels–Alder reaction. Staudinger and Meyer (525) have prepared



(119)

3,6-tetraaryl-1,2,3,6-tetrahydro-1,2,4,5-tetrazines by an interesting procedure (eq. III-74) in which azodiarylmethanes reacted with triethylphosphine to form an intermediate **56** which then in the presence of moisture gave the final product.



(120)

56

2. *Compound Survey*

Compounds of this group that have been reported in the literature are listed in Table III-3.

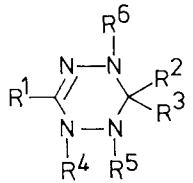
3. *Physical Properties and Theoretical Considerations*

All of the known tetrahydro-1,2,4,5-tetrazines are solids except 3,3,6,6-tetramethyl-1,2-bis(trifluoromethyl)-1,2,3,6-tetrahydro-1,2,4,5-tetrazine, which is a liquid. The 1,2,3,4-tetrahydro-1,2,4,5-tetrazines are colorless, but the 3,3,6,6-tetraaryl-1,2,3,6-tetrahydro-1,2,4,5-tetrazines are yellow or orange.

The spectral data on 1,2,3,4-tetrahydro-1,2,4,5-tetrazines are quite meager. Ultraviolet spectra are unreported except for cases in which there are nitro substituents. The 1,2,3,4-tetrahydro-1,2,4,5-tetrazine system would be expected

TABLE III-3. TETRAHYDRO-1,2,4,5-TETRAZINES WITH ALKYL, ARYLALKYL, ARYL, AND HETEROCYCLIC SUBSTITUENTS

A. 1,2,3,4-Tetrahydro-1,2,4,5-tetrazines with one tetrazine ring

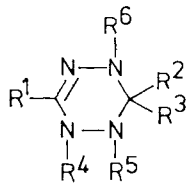


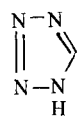
R^1	R^2	R^3	R^4	R^5	R^6	m.p. (°C)	Refs.
CH_3	CH_3	H	H	H	H	143	514
CH_3	H	H	H	C_6H_5	4-$NO_2C_6H_4$	166	366
$(CH_3)_3C$	H	H	H	C_6H_5	C_6H_5	–	369
$(CH_3)_3C$	H	H	CH_3	C_6H_5	C_6H_5	85	367, 369
$(CH_3)_3C$	H	H	$C_6H_5CH_2$	C_6H_5	C_6H_5	100	367
$(CH_3)_3C$	CH_3	H	$C_6H_5CH_2$	C_6H_5	C_6H_5	128	367
$(CH_3)_3C$	C_6H_5	H	$C_6H_5CH_2$	C_6H_5	C_6H_5	136	367
H	H	H	$(CH_3)_2C(CN)$	C_6H_5	C_6H_5	164 (dec.)	367
H	H	H	$C_6H_5CH_2$	C_6H_5	C_6H_5	145	367
$CH_3C(=NNH_2)$	CH_3	CH_3	H	H	H	–	13
$CH_3C(=NNH_2)$		$-(CH_2)_5-$	H	H	H	166	13
$(CH_3)_2CHC(=NN=C(CH_3)_2)$	CH_3	CH_3	H	H	H	–	13
$(CH_3)_2CHC(=NN=C_6H_4)$		$-(CH_2)_5-$	H	H	H	–	13

$C_6H_5CH_2$	H	H	$(CH_3)_2CH$	C_6H_5	C_6H_5	85	367
$C_6H_5CH_2$	H	H	$C_6H_5CH_2$	C_6H_5	C_6H_5	117	367
$C_6H_5C(=NNH_2)$	CH_3	C_6H_5	H	H	H	108	13
$C_6H_5C(=NNH_2)$		$-(CH_2)_5-$	H	H	H	194	13
$(CH_3)_2C{=}NN{=}C(C_6H_5)_2$	CH_3	C_6H_5	H	H	H	–	13
$(CH_3)_2C{=}N{-}N{=}C(C_6H_5)_2$		$-(CH_2)_5-$	H	H	H	–	13
$2\text{-}CH_3C_6H_4C(=NNH_2)$		$-(CH_2)_5-$	H	H	H	186	13
$4\text{-}H_5C_2C_6H_4C(=NNH_2)$	CH_3	$4\text{-}H_5C_2C_6H_4$	H	H	H	164	13
$4\text{-}(CH_3)_2CHC_6H_4C(=NNH_2)$	CH_3	$4\text{-}(CH_3)_2CHC_6H_4$	H	H	H	171	13
$4\text{-}ClC_6H_4C(=NNH_2)$	CH_3	$4\text{-}ClC_6H_4$	H	H	H	173	13
$4\text{-}BrC_6H_4C(=NNH_2)$	CH_3	$4\text{-}BrC_6H_4$	H	H	H	148–160	13
$4\text{-}CH_3OCH_4C(=NNH_2)$		$-(CH_2)_5-$	H	H	H	192	13
C_6H_5	H	H	H	H	C_6H_5	86	426
$4\text{-}CH_3C_6H_4$	H	H	H	H	C_6H_5	104	426
C_6H_5	H	H	H	C_6H_5	C_6H_5	–	247, 278, 368
C_6H_5	H	H	H	$4\text{-}H_5C_2C_6H_4$	$4\text{-}H_5C_2C_6H_4$	116	371
C_6H_5	H	H	H	$3\text{-}CH_3OC_6H_4$	$3\text{-}CH_3OC_6H_4$	140	371
C_6H_5	H	H	H	$4\text{-}CH_3OC_6H_4$	$4\text{-}CH_3OC_6H_4$	166	371

TABLE III-3. (continued)

A. 1,2,3,4-Tetrahydro-1,2,4,5-tetrazines with one tetrazine ring



R^1	R^2	R^3	R^4	R^5	R^6	m.p. (°C)	Refs.
C_6H_5	H	H	H	C_6H_5		–	500
C_6H_5	H	H	CH_3	C_6H_5	C_6H_5	138	279, 367
C_6H_5	H	H	C_2H_5	C_6H_5	C_6H_5	–	337a
C_6H_5	H	H	$(CH_3)_2CH$	C_6H_5	C_6H_5	124	337a, 367
C_6H_5	H	H	C_4H_9	C_6H_5	C_6H_5	–	337a
C_6H_5	H	H	$(CH_3)_2C(CH_3OOC)$	C_6H_5	C_6H_5	–	247
C_6H_5	H	H	$(CH_3)_2C(CN)$	C_6H_5	C_6H_5	149 (dec.)	359, 367
C_6H_5	H	H	$C_6H_5CH_2$	C_6H_5	C_6H_5	169	247, 249, 250, 337a, 367
C_6H_5	H	H	$(C_6H_5)_2CH$	C_6H_5	C_6H_5	160	249, 250
C_6H_5	H	H	C_6H_5COO	C_6H_5	C_6H_5	–	586, 587
C_6H_5	C_6H_5	H	H	C_6H_5	C_6H_5	–	282

4-$CH_3C_6H_4$	H	H	H	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	133	371
4-$(CH_3)_3CC_6H_4$	H	H	H	4-$(CH_3)_3CC_6H_4$	4-$(CH_3)_3CC_6H$	196	371
3,5-$[(CH_3)_3C]_2C_6H_3$	H	H	H	3,5-$[(CH_3)_3C]_2C_6H_3$	3,5-$[(CH_3)_3C]_2C_6H_3$	178	371
4-$CH_3OC_6H_4$	H	H	H	C_6H_5	C_6H_5	127	371
2,6-$(CH_3O)_2C_6H_5$	H	H	H	C_6H_5	C_6H_5	136	371
3,4-$(CH_3O)_2C_6H_5$	H	H	H	C_6H_5	C_6H_5	159	371

B. 1,2,3,4-Tetrahydro-1,2,4,5-tetrazines with two tetrazine rings

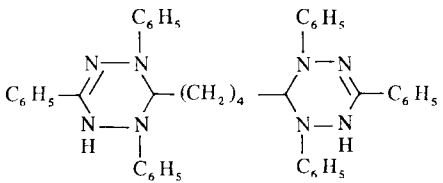
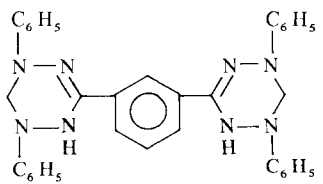
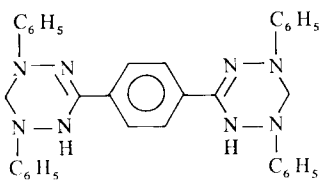
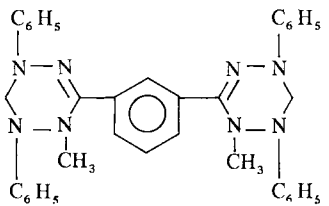
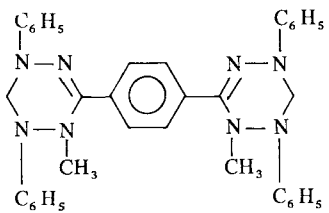
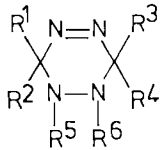
Compound	m.p. (°C)	Refs.
	–	274
	–	274
	–	274

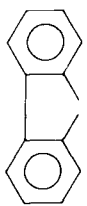
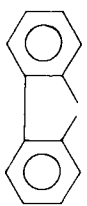
TABLE III-3. (continued)

B. 1,2,3,4-Tetrahydro-1,2,4,5-tetrazines with two tetrazine rings

Compound	m.p. (°C)	Refs.
	193	274
	239	274

C. 1,2,3,6-Tetrahydro-1,2,4,5-tetrazines

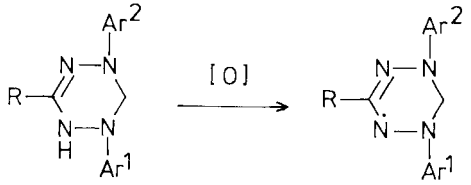


R^1	R^2	R^3	R^4	R^5	R^6	m.p. (°C)	Refs.
CH_3	H	CH_3	H	H	H	116	514
CH_3	CH_3	CH_3	CH_3	CF_3	CF_3	n_D^{20} 1.4220	170
C_6H_5	C_6H_5	C_6H_5	C_6H_5	H	H	204.5	525
				H	H	325	525

to exhibit maxima arising from the azomethine system, but such absorptions are very weak and so would not normally be reported. The infrared spectra of only a few of the known 1,2,3,4-tetrahydro-1,2,4,5-tetrazines have been reported (166, 279, 366). There is a band at 3400 to 3300 cm^{-1} due to NH if a proton is present on nitrogen. Bands in the 1635 cm^{-1} region have been considered to arise from the azomethine group. The dominant bands of the infrared spectrum are a result of thyaromatic rings usually present as substituents. The PMR spectra reported for this type of compound shows a signal at about $\delta 9$ arising from a proton on nitrogen if one is present (366). If two protons are present at C-3, they give rise to a broad band at room temperature, but at lower temperatures the broad band is resolved into a quartet with chemical shifts centred at $\delta 3.3$ to 4.0 and $\delta 5.4$ to 6 (366, 367). These results have been taken to indicate a slow inversion at N-2 for which free energies of activation for various compounds of 12 to 20 kcal/mole have been calculated (367). Kotorlenko and Gardenina (265) have done an expanded Hückel molecular orbital calculation on 2,4,6-triphenyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine.

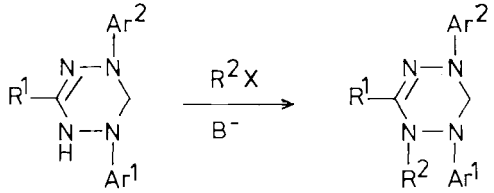
4. *Reactions*

The oxidation of 4,6-diphenyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine to the corresponding 1,6-dihydro compound (eq. III-33) has already been discussed. However, if there are substituents on both N-2 and N-4, oxidation to a verdazyl occurs (eq. III-75) (51, 279, 362, 366, 500). The oxidants used have been ferric chloride (51) air (279, 362), and lead dioxide (366, 500).



(121)

The alkylation of 1,2,3,4-tetrahydro-1,2,4,5-tetrazines in the course of formation from formazans has already been mentioned (eq. III-63) in connection with synthesis of such compounds. Such an alkylation can also be done readily using a base and an alkyl halide to attack a 1,2,3,4-tetrahydro-1,2,4,5-tetrazine having



(122)

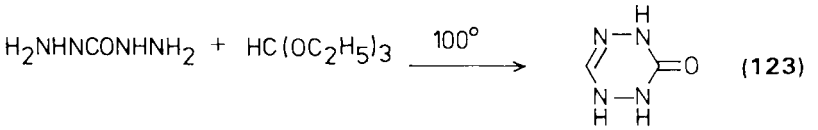
hydrogen at N-1 (eq. III-76) (274, 362, 367). The base used has usually been barium oxde, and alkyl iodides were the commonly used halides. Yields are quite good. It has been found that pyrolysis of some N-1 alkylated 1,2,3,4-tetrahydro-1,2,4,5-tetrazines causes the reversal of eq. III-65 giving a free alkyl radical and a verdazyl (359).

B. Tetrahydro-1,2,4,5-tetrazines Substituted by Carboxyl Groups, Derivatives of Carboxyl Groups, and Hetero Atoms

1. *Preparation*

In this class of compounds it is not certain that any 1,2,3,6-tetrahydro-1,2,4,5-tetrazines are known, so both types of tetrahydro compounds are discussed in this section. A few 6-nitro-2,4-diaryl-1,2,4,5-tetrahydro-1,2,4,5-tetrazines have been prepared by reaction of formazans with methyl iodide in the presence of base and followed by cyclization (eq. III-62) (362).

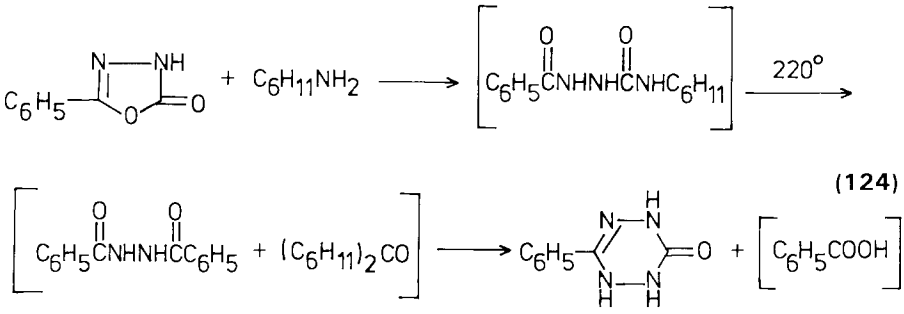
Several 1,2,3,4-tetrahydro-1,2,4,5-tetrazines having oxygen at the 3-position have been reported in the literature. Curtius and Heidenreich (111, 112) have allowed carbohydrazide to react with ethyl orthoformate at 100°C and have claimed that 1,2,3,4-tetrahydro-1,2,4,5-tetrazin-3-one (**57**) was isolated (eq. III-77). Busch (60–62) also claimed to have prepared this compound. However,



(123)

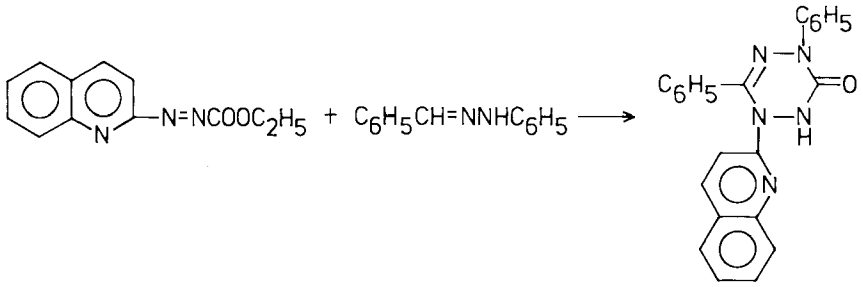
57

Stollé (536) has argued on the basis of the known rearrangement of hydro-1,2,4,5-tetrazines to triazoles that the product obtained was 3-hydroxy-4-amino-4*H*-1,2,4-triazole. Stollé's arguments were quite convincing, and it appears that the triazole rather than **57** was the actual product. Sampson (464) has claimed the formation of **57** by the reaction of hydrazine hydrate with carbon monoxide at high pressures and a temperature of 175°C. No characterization data were offered, and it seems certain that a tetrazine, even if formed, would isomerize to a triazole. The formation of 6-phenyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazin-3-one by a series of reactions starting with 2-phenyl-4*H*-1,3,4-oxadiazol-5-one and cyclohexylamine has been claimed (eq. III-78) (159). Since only a very sketchy abstract of the original paper was available it was impossible to reach any conclusion as to the validity of the claim. 4-Phenyl-6-aryl-1,2,3,4-tetrahydro-1,2,4,5-tetrazin-3-ones (**47**, eq. III-59) have been prepared by reaction



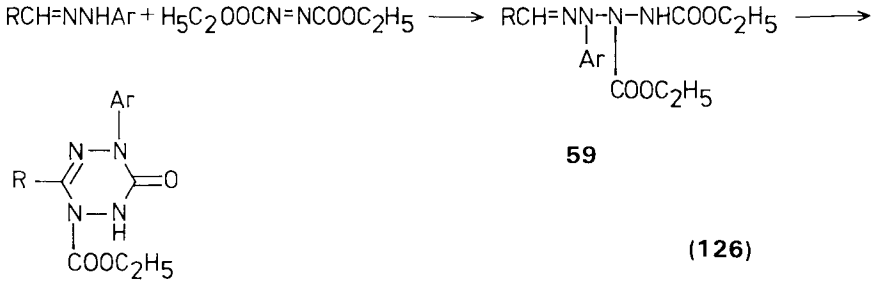
(124)

of phenylhydrazine with chlorinated dioximes of arylglyoxals (**46**) (426). Pentimalli and Bruni (397) have described the reaction of benzaldehyde phenylhydrazone with an azocarbonic ester (eq. III-79) to form the tetrahydrotetrazine **58**. Busch, Müller, and Schwarz (66) described what appears to be a



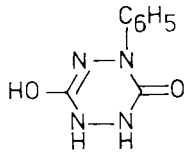
58

very similar reaction except that an intermediate is obtained in the first step. The intermediate is believed to be a tetrazane (**59**) derived by attack of a nitrogen atom in the phenylhydrazone on the N=N double bond of the azo compound (eq. III-80). Acid or base then brings about cyclization. R may be alkyl or aryl and Ar was phenyl or *o*-tolyl. It may be that the two reactions are completely analogous. Busch and Heinrichs (54) have proposed that a

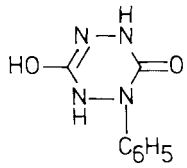


59

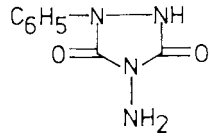
(126)



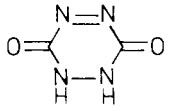
60



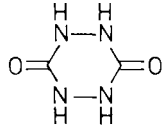
61



62



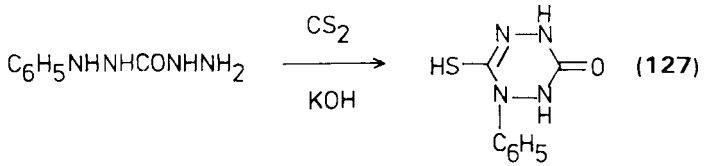
63



64

compound prepared by them was one of the two tetrahydro 1,2,4,5-tetrazines, **60** or **61**. However, Busch subsequently showed by unequivocal synthesis that it was 4-amino-1-phenyl-1*H*-1,2,4-triazole-3,5(2*H*,4*H*)-dione (**62**). Linch (300) claimed to have prepared 1,2,3,6-tetrahydro-1,2,4,5-tetrazine-3,6-dione (**63**) by oxidation of *p*-urazine (supposedly having the structure **64**, but whose actual structure is discussed in the section on hexahydro-1,2,4,5-tetrazines). The *p*-urazine was derived by oxidation of semicarbazide with sodium hypobromite. Stollé (537) disagreed with Linch and argued that the compound believed to be **64** was actually biurea, but he offered no experimental support for his arguments. Subsequent investigation (574) has established that the oxidation of semicarbazide as described by Linch gives biurea so he could not have obtained **63**.

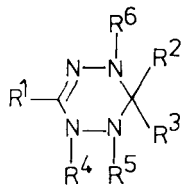
Neugebauer and Fischer (365) have treated a 3-(alkylthio)- or 3-(arylthio)-formazan with methyl iodide and a base and have obtained the corresponding 6-(alkylthio)- or 6-(arylthio)2,4-diphenyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine (eq. III-62). 6-Mercapto-1-phenyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazin-3-one was reported as the product of the reaction of 1-phenylcarbazide with carbon disulfide in the presence of base (III-81) (192). The reaction was run in boiling ethanol. Artemov and Shvaika (12) have treated 2-aryl-4*H*-1,3,4-oxadiazole-5-



(127)

thiones with methylhydrazine and obtained two isomeric products, a triazole and a tetrahydro-1,2,4,5-tetrazine (eq. III-82) substituted with sulfur at C–3.

TABLE III-4. TETRAHYDRO-1,2,4,5-TETRAZINES WITH CARBOXYL, CARBOXYL-DERIVATIVE, AND HETERO-ATOM SUBSTITUENTS



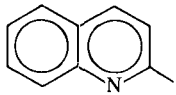
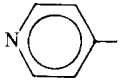
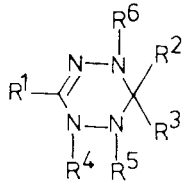
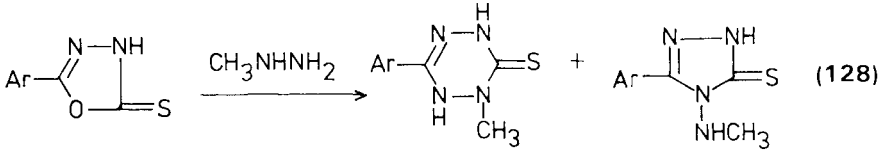
R^1	R^2	R^3	R^4	R^5	R^6	m.p. (°C)	Refs.
NO_2	H	H	CH_3	C_6H_5	C_6H_5	123	362
NO_2	H	H	CH_3	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	132	362
NO_2	H	H	CH_3	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	133	362
H	=O		H	H	H	–	464
C_6H_5	=O		H	H	H	–	159
C_6H_5	=O		H	H	C_6H_5	174	426
4-$CH_3C_6H_4$	=O		H	H	C_6H_5	190	426
C_6H_5	=O		H	H	4-BrC_6H_4	189	426
C_6H_5	=O			H	C_6H_5	–	397
C_6H_5	=O		CH_3CO or H	CH_3CO or H	C_6H_5	161	426
C_6H_5	=O		CH_3CO	CH_3CO	C_6H_5	174	426
4-$CH_3C_6H_4$	=O		CH_3CO	CH_3CO	C_6H_5	170	426
C_6H_5	=O		CH_3CO	CH_3CO	4-BrC_6H_4	169	426
CH_3	=O		H_5C_2OOC	H	C_6H_5	112	66
C_6H_5	=O		H_5C_2OOC	H	C_6H_5	149	66
C_6H_5	=O		H_5C_2OOC	H	2-CH_3C_6H	93	66
2-HOC_6H_4	=O		H_5C_2OOC	H	2-$CH_3C_6H_4$	178	66
4-HOC_6H_4	=O		H_5C_2OOC	H	C_6H_5	184	66
3-$NO_2C_6H_4$	=O		H_5C_2OOC	H	C_6H_5	179	66
$(CH_3)_2CHS$	H	H	H	C_6H_5	C_6H_5	91	365
CH_3S	H	H	CH_3	C_6H_5	C_6H_5	123	365
$(CH_3)_2CHS$	H	H	CH_3	C_6H_5	C_6H_5	79	365
$C_6H_5CH_2S$	H	H	CH_3	C_6H_5	C_6H_5	105	365
C_6H_5S	H	H	CH_3	C_6H_5	C_6H_5	124	365
C_6H_5	=S		H	CH_3	H	–	12
	=S		H	CH_3	H	–	12
C_6H_5	=S		CH_3	H	H	–	184
C_6H_5	=S		C_6H_5	H	H	–	183, 184
4-ClC_6H_4	=S		C_6H_5	H	H	–	183, 184

TABLE III-4. (continued)

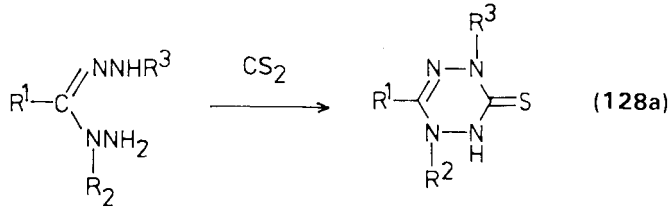


R^1	R^2	R^3	R^4	R^5	R^6	m.p. (°C)	Refs.
4-$CH_3OC_6H_4$	=S		C_6H_5	H	H	–	184
CH_3	=S		C_6H_5	H	CH_3	–	184
C_6H_5	=S		CH_3	H	CH_3	–	184
C_6H_5	=S		CH_3	H	$C_6H_5CH_2$	–	184
C_6H_5	=S		$C_6H_5CH_2$	H	CH_3	–	184
C_6H_5	=S		C_6H_5	H	CH_3	–	184
C_6H_5	=S		C_6H_5	H	C_6H_5	–	184
4-ClC_6H_4	=S		C_6H_5	H	C_6H_5	–	184
4-$CH_3OC_6H_4$	=S		C_6H_5	H	C_6H_5	–	184



(128)

Grashey and co-workers (183, 184) have prepared a series of 1,2,3,4-tetrahydro-1,2,4,5-tetrazine-3-thiones by the reaction of quaternary salts of 2-(methylmercapto)-5-aryl-1,3,4-thiadiazoles with excess hydrazines (eq. III-57). The yields were excellent, varying from 66 to 94%. Many years ago Busch and his collaborators (65) had carried out the same reaction and proposed that the product was a 3-mercaptodihydro-1,2,4,5-tetrazine. It is probable that the product of Busch, Kamphausen, and Schneider was similar to those obtained by Grashey. 1,3,6-Trisubstituted 1,2,3,4-tetrahydro-1,2,4,5-tetrazine-3-thiones have also been synthesized by the reaction of arylhydrazone hydrazides with carbon disulfide (eq. III-83) (184). The yields were 77 to 85%. Wieland (571) has



(128a)

obtained what was thought to be the ammonium salt of 1,2,3,6-tetrahydro-1,2,4,5-tetrazine-3,6-dione dioxime by the action of ammonia on 1,3-dihydroxyguanidine. Such a product seems quite unlikely and evidence for the proposed structure was lacking.

2. *Compound Survey*

The compounds of this class that have been reported are listed in Table III-4.

3. *Physical Properties and Theoretical Considerations*

The type of compounds discussed in this section has not been considered theoretically and very little has been reported concerning their physical properties, particularly their various spectra.

4. *Reactions*

The carbonyl groups of 1,2,3,4-tetrahydro-1,2,4,5-tetrazin-3-ones can be reduced to methylene as has already been mentioned (eq. III-71) (426). Oxidation of such tetrahydrotetrazines with chromium trioxide (eq. III-59) forms the 1,6-dihydro analogue (426). Methylation at N-1 with base and methyl iodide (365) occurs as readily as it does in the case of those 1,2,3,4-tetrahydro-1,2,4,5-tetrazines already discussed (eq. III-76).

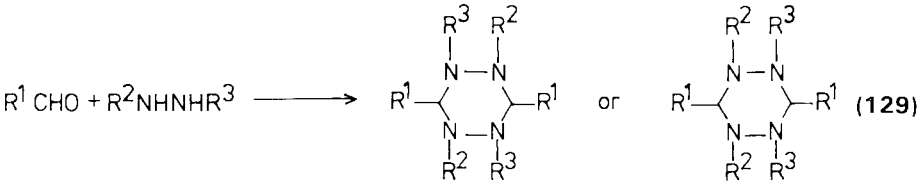
The 1,2,3,4-tetrahydro-1,2,4,5-tetrazine-3-thiones having hydrogen at N–2 react with methyl iodide in the presence of base to form 3-mercapto-1,4-dihydro-1,2,4,5-tetrazines (eq. III-57).

III. HEXAHYDRO-1,2,4,5-TETRAZINES

A. Hexahydro-1,2,4,5-tetrazines Substituted by Alkyl, Arylakyl, aryl, and Heterocyclic Substituents

1. *Preparation*

In the last quarter of a century the number of hexahydro-1,2,4,5-tetrazines prepared has multiplied many times. However, these results have mostly arisen from the work of only a few groups of investigators and by the preponderant use



(129)

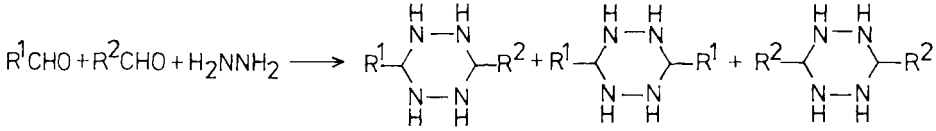
65 **66**

of only one method of synthesis. The method used almost exclusively has been the reaction of aldehydes with hydrazine and substituted hydrazines as shown in eq. III-84. If the hydrazines used are not symmetrical, the possibility arises of two different products having structures **65** and/or **66**. In no case, however, has it been established that any product other than those having the structure exemplified by formula **65** was obtained. In view of the mechanism of the reaction, which is discussed in detail subsequently, the structures of type **65** would be expected and would be the only ones possible. Friedheim (162, 163) has prepared a compound which was reported to have structure **66**. No supporting evidence was given, and it is probable that the structure claimed is incorrect. When formaldehyde is the aldehyde and it is used in excess with hydrazine or monosubstituted hydrazines, further reactions can occur to form condensed systems. These are discussed in a subsequent section devoted to 1,2,4,5-tetrazines having only condensed rings.

The aldehyde most frequently used has been formaldehyde. The first hexahydro-1,2,4,5-tetrazine was reported in 1898 by Bischoff (42) using the reaction of formaldehyde with hydrazobenzene ($R^1 = H$, $R^2 = R^3 = C_6H_5$, eq. III-84). Hammerum and co-workers (196, 197, 229) have studied the reaction of formaldehyde with various hydrazines in considerable depth and have given an excellent discussion of the best procedures and reaction conditions for optimum yields of hexahydro-1,2,4,5-tetrazines. The reaction of formaldehyde with various disubstituted unsymmetrical hydrazines has been extensively studied by Dorn and collaborators (127–131). Schmitz (486, 487, 490, 492) has also been quite active in this area. Hammerum (197, 229) recommends the use of aqueous formaldehyde with hydrazines at reduced temperatures (about 5°C) or paraformaldehyde with hydrazines in an organic solvent. The nature of the substitution on the hydrazine used affects the rate of the reaction in that the smaller the substituent the more rapid the reaction. In the case of such hydrazines as benzyl- or 2-phenylpropylhydrazine it is quite easy to isolate an intermediate hydrazone, but with smaller alkyl substituents the intermediates go very rapidly to hexahydro-1,2,4,5-tetrazines (197). The hydrazone derived from formaldehyde and α-methylbenzylhydrazine dimerizes to a hexahydro-1,2,4,5-tetrazine only over a period of months.

Several other aldehydes, mostly aliphatic, have been used although there seems to be no use of ketones. Such aldehydes as acetaldehyde (229, 242, 511–513, 547) propionaldehyde (242, 438, 511–513, 547, 592), and butyraldehyde (242, 511, 512, 592) have been used frequently and react with all types of hydrazines. Isobutyraldehyde reacts readily with hydrazine or 1,2-dialkylhydrazines (513, 592, 593), but it has been reported to fail with 1,2-diphenylhydrazine (438, 439). Higher aldehydes having straight chains of five to twelve carbon atoms react readily for the most part to form hexahydro-1,2,4,5-tetrazine (242, 438, 439, 512) although Rassow and Baumann (438, 439) have reported failure of valeraldehyde and chloral to give hexahydro-1,2,4,5-tetrazines with 1,2-diarylhydrazines. Five- and six-carbon branched-chain aldehydes also react with hydrazines to form hexahydro-1,2,4,5-tetrazine (547, 593). Only four aromatic aldehydes have been reported to give hexahydro-1,2,4,5-tetrazines, and in all cases these were reactions with 1,2-disubstituted hydrazines. Skorianetz and sz. Kováts (513) have attempted to prepare unsymmetrical hexahydro-1,2,4,5-tetrazines (eq. III-85) by the reaction of two aldehydes with hydrazine. The yields of unsymmetrical compounds were low, and both possible symmetrical products were obtained.

(130)

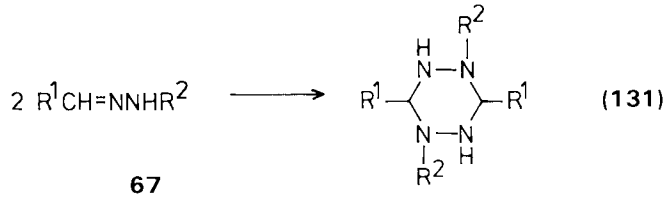


Hydrazines of varied types have been used to prepare hexahydro-1,2,4,5-tetrazines. Hydrazine has been used sparingly (242, 512, 513) but monosubstituted alkyl (229, 345, 512, 557), arylalkyl (127, 595), and aryl (229, 490) hydrazines form tetrazines. The most frequently used 1,2-disubstituted hydrazines have been those having two alkyl groups (130, 182, 355, 356, 486, 487, 492, 512, 547, 592, 593), but mixed hydrazines containing one alkyl group and an aralkyl group react readily to give hexahydro-1,2,4,5-tetrazines (128, 131), as do those having both alkyl and aryl groups (129, 131, 178, 254, 378). Diarylhydrazines have been found to react with aldehydes to form hexahydro-1,2,4,5-tetrazines (42, 162, 163, 437, 438, 440), but it seems that such reactions are limited by the complexity of the aldehyde (438, 439). Hydrazines substituted by acyl and thioacyl groups react with formaldehyde to form tetrahydro-1,2,4,5-tetrazines. Rink and Mehta (445) found that diethyl hydrazodicarboxylate (eq. III-84, $R^2 = R^3 = COOC_2H_5$) undergoes such reaction, as do 1-alkyl-2-(phenylacetyl)- (378), 1-arylalkyl-2-acyl- (237), and 1-(thioaryl)-2-phenylhydrazides (584).

The yields of hexahydro-1,2,4,5-tetrazines obtained by the reaction of aldehydes with hydrazines vary enormously, depending on a variety of factors.

As would be expected yields are most directly related to the particular aldehyde and hydrazine used, but reaction conditions also play an important part. The reported yields using apparently very similar reactants vary considerably so that generalizations are hazardous, but it seems that alkyl- and dialkylhydrazines give the poorest yields, possibly because of difficulties of isolation and instability of the products. However, yields of up to 90% have been reported, and most are in the range of 40 to 80%.

A modification of the aldehyde–hydrazine reaction to prepare hexahydro-1,2,4,5-tetrazines consists of dimerization of preformed hydrazones (eq. III-86) (175, 196, 197, 231, 242). Usually the hydrazones are prepared by

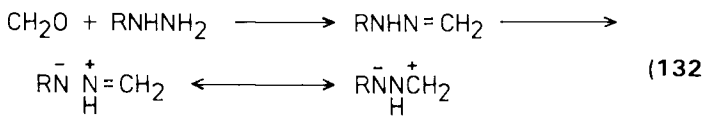


(131)

67

reaction of hydrazines with aldehydes, but acetaldehyde hydrazone has been prepared by dehydration of hydroxyethylhydrazine and dimerized (175). Hammerum (197) has stated that the hydrazones of the smaller straight-chained aldehydes cannot be isolated, but Kauffmann and collaborators (242) claim to have isolated hydrazones of acetaldehyde, propionaldehyde, butyraldehyde, and valeraldehyde and dimerized them. However, the properties reported by the latter group for the three lowest 3,6-dialkyl-hexahydro-1,2,4,5-tetrazines (R^1 = CH_3, C_2H_5, and C_3H_7, eq. III-84), which were prepared from the products they thought to be hydrazones, do not agree with those reported for the same compounds by others (229, 512). It may be that the claim of Kauffmann and co-workers to have isolated the hydrazones of lower-molecular-weight aldehydes is not valid.

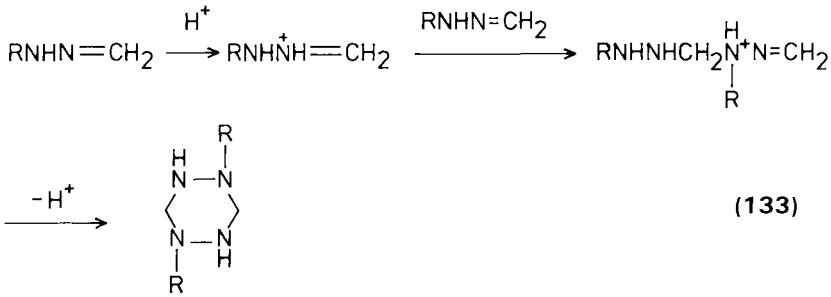
It is generally considered that the mechanism of formation of hexahydro-1,2,4,5-tetrazines by the reaction of aldehydes with hydrazines involves formation of a hydrazone intermediate (**67**) when possible, followed by dimerization. Hammerum (197) has presented NMR evidence for the intermediacy of such a compound. An intermediate of this type could not occur with 1,2-disubstituted hydrazines, however. Dorn and Dilcher (127) have proposed that formaldehyde reacts with monosubstituted hydrazines as indicated in eq.



(132)

68

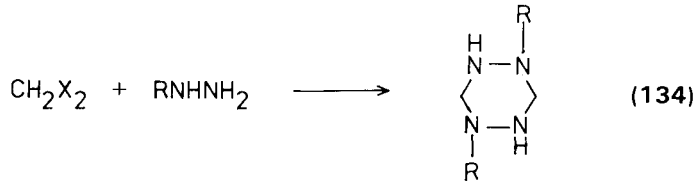
III-87. Such a course has also been proposed by Grashey and co-workers (182) and by Zinner and collaborators (593) for 1,2-disubstituted hydrazines. The proposed mechanism involves a 1,3-dipolar cyclodimerization which, if it were concerted, would be a forbidden proccess under the Woodward–Hoffman rules. An intermediate such as **68** should react with dipolarophiles present in the reaction mixture, but this has not been shown to occur. Oppolzer (378) presented evidence to show that 1,3-dipolar species are absent in the formation of 1,2,4,5-tetraalkylhexahydro-1,2,4,5-tetrazines from formaldehyde. Hammerum (197) and Skorianetz and sz. Kováts (512) have shown that the dimerization is acid catalyzed and suggest the process shown in eq. III-88. The



(133)

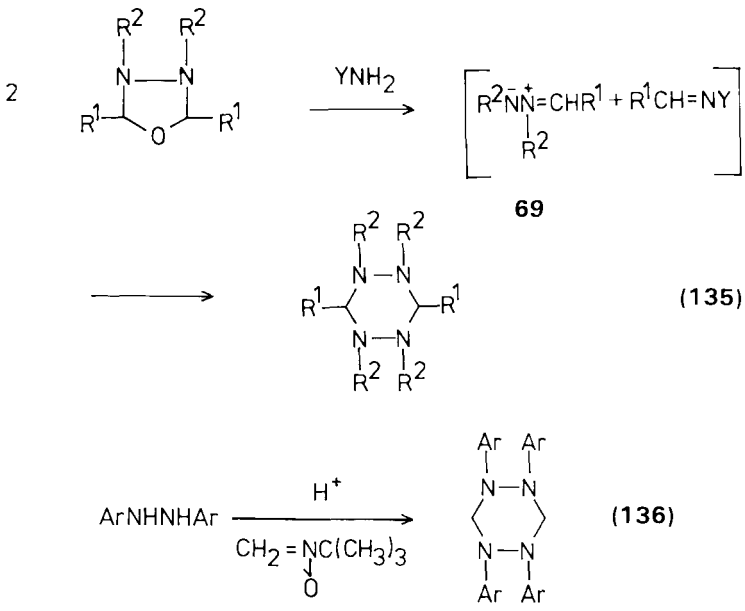
mechanism shown here would not apply to reactions involving 1,2-disubstituted hydrazines, but they could react by a similar mechanism.

Several other methods for preparing hexahydro-1,2,4,5-tetrazines are closely related to the aldehyde–hydrazine procedure in that it has been suggested or seems likely that they occur via a hydrazone type intermediate. For example, the reaction of methylene chloride and methylene bromide with hydrazines (eq. III-89) (197, 221, 229) has been suggested by Hammerum to involve the intermediate formation of methylal hydrazone. A very similar reaction is that of methylhydrazine with tris(chloromethyl)amine to give 1,4-dimethylhexahydro-1,2,4,5-tetrazine (154a). Zinner and Kilwing (592) have suggested that the

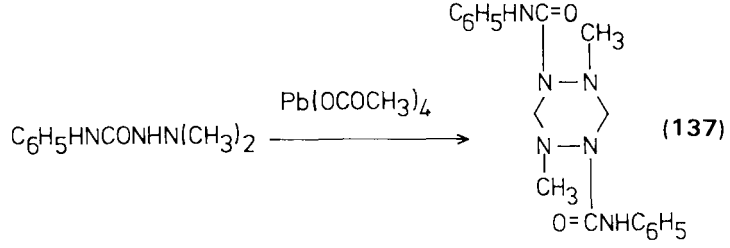


(134)

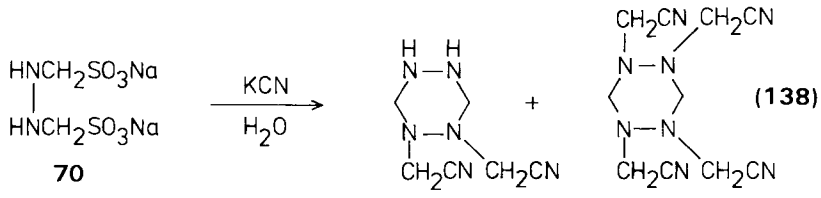
intermediate **69** occurs in the reaction of tetrasubstituted oxadiazolidines with hydrazines, hydroxylamine, or α-methylhydroxylamine to give hexahydro-1,2,4,5-tetrazines. The reaction of 1,2-diarylhydrazines with methylene *tert*-butylimine *N*-oxide to form hexahydro-1,2,4,5-tetrazines probably involves an intermediate somewhat similar to **69**, but in which R^1CH is CH_2 (eq. III-



91) (28). Cooley and Atchinson (91) have oxidized 1,1,-dimethyl-4-phenyl-semicarbazide with lead tetracetate to give 1,4-dimethyl-2,5-bis(*N*-phenylcarbamoyl)hexahydro,1,2,4,5-tetrazine (eq. III-92). It may be that the oxidation forms an intermediate similar to **69** which dimerizes. Disodium hydrazinemethanesulfonate (**70**) in an aqueous solution reacts with



potassium cyanide to give a small yield of two hexahydro-1,2,4,5-tetrazines (eq. III-93) (172). There is probably a complex series of reactions in which the substituted hydrazine breaks down to give formaldehyde and hydrazine, which then react further. Farina and Tieckelmann (151, 152) have reported a novel procedure for preparing hexahydro-1,2,4,5-tetrazines involving the reaction of dialkylnitrosamines with phenyllithium (eq. III-94). It was suggested that the first step was addition of phenyllithium to the NO group followed by loss of lithium hydroxide to form a dipolar compound such as **69**, which then



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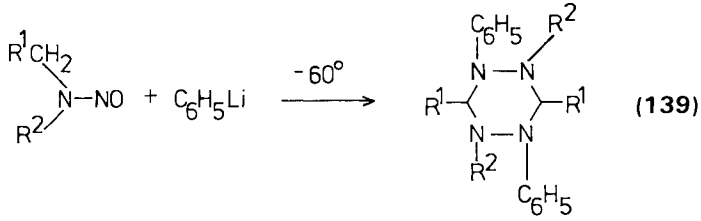
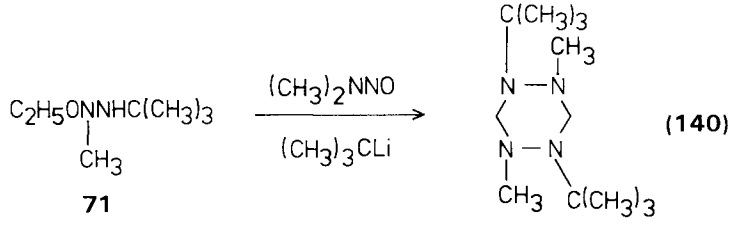


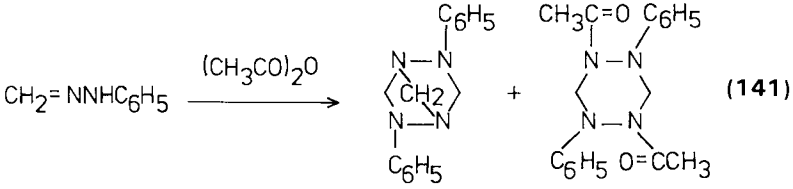
(139)

dimerizes. The yields were 30 to 40%. The same authors report that an adduct of dimethylnitrosamine with *tert*-butyllithium converts 1-methyl-1-(ethoxymethyl)-2-(*tert*-butyl)hydrazine (**71**) to 1,4-dimethyl-2,5-bis(*tert*-butyl)-hexahydro-1,2,4,5-tetrazine (eq. III-95). Here again an intermediate such as **69** is probable.



(140)

71



(141)

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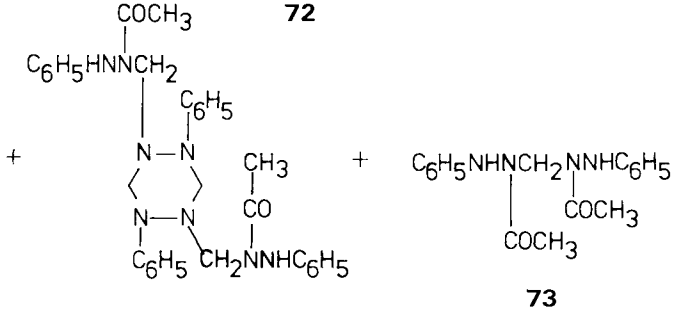
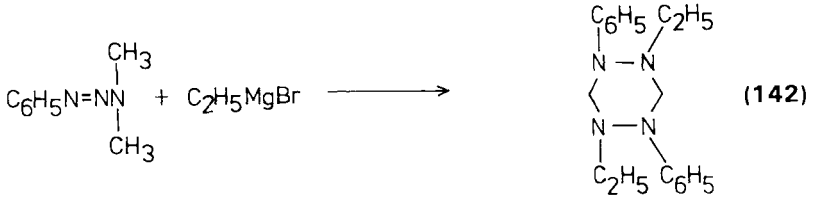
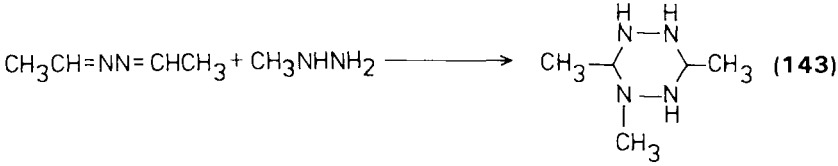


73

Lamberton, Nelson, and Triffitt (286) have prepared 1,5-diphenyl-2,4-diacetylhexahydro-1,2,4,5-tetrazine by reaction of 1,5-diphenyl-2,4-diacetyl-1,2,4,5-tetrazapentane (**73**) with formaldehyde. The compound **73** was formed in small yield by treatment of formal phenylydrazone with acetic anhydride (eq. III-96). In this same reaction traces of two hexahydro-1,2,4,5-tetrazines were formed, but the principal product was the condensed system 1,4-diphenyl-hexahydro-2,5-endomethano-1,2,4,5-tetrazine (**72**). The reactions indicated in



(142)



(143)

eqs. III-97 (252) and III-98 (512) have each been used to prepare one hexahydro compound, with the yield being low in each case.

2. *Compound Survey*

Compounds in this group that have been reported in the literature are listed in Table III-5.

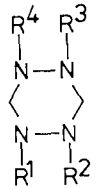
3. *Physical Properties and Theoretical Considerations*

Hexahydro-1,2,4,5-tetrazines are colorless compounds which are mostly solids with medium or high melting points although, if they have only alkyl substituents and are tetra- or hexasubstituted, they are high-boiling liquids. Most hexahydro-1,2,4,5-tetrazines are stable, but the lower members tend to hydrolyze in the presence of moisture and are oxidized by air. They also tend to dissociate into hydrazones on heating.

Electronic and vibrational spectra of hexahydro-1,2,4,5-tetrazines are unexceptional. Unless unsaturated substituents are present the ultraviolet spectra

TABLE III-5. HEXAHYDRO-1,2,4,5-TETRAZINES WITH ALKYL, ARYLALKYL, ARYL, AND HETEROCYCLIC SUBSTITUENTS

A. No substituent on ring carbon



R^1	R^2	R^3	R^4	m.p. (°C)	Refs.
CH_3	H	CH_3	H	123	154a, 196, 197, 221, 229
C_2H_5	H	C_2H_5	H	139	196, 197
$CH_3(CH_2)_3$	H	$CH_3(CH_2)_3$	H	135	196, 197
$(CH_3)_2CHCH_2$	H	$(CH_3)_2CHCH_2$	H	109	196, 198
n-C_6H_{13}	H	n-C_6H_{13}	H	128	196, 197
n-C_8H_{17}	H	n-C_8H_{17}	H	125	196, 197
$CH_2{=}CHCH_2$	H	$CH_2{=}CHCH_2$	H	103	196, 197
$HOCH_2CH_2$	H	$HOCH_2CH_2$	H	146	196, 197
$C_2H_5OCH_2CH_2$	H	$C_2H_5OCH_2CH_2$	H	93	196, 197
$NCCH_2CH_2$	H	$NCCH_2CH_2$	H	122	196, 197
$KO_3S(CH_2)_4$	H	$KO_3S(CH_2)_4$	H	261–265	131
$NCCH_2$	$NCCH_2$	H	H	208	172
$C_6H_5CH_2$	H	$C_6H_5CH_2$	H	165	127, 196, 197
$C_6H_5CH(CH_3)$	H	$C_6H_5CH(CH_3)$	H	102	196, 197
$C_6H_5CH_2CH_2$	H	$C_6H_5CH_2CH_2$	H	151	196, 197, 595
$C_6H_5CHCH_2(CH_3)$	H	$C_6H_5CHCH_2(CH_3)$	H	137	196, 197

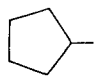
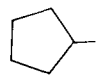
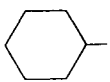
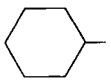
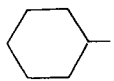
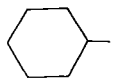
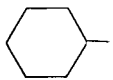
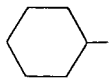
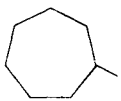
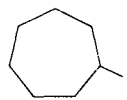
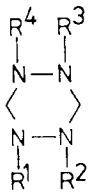
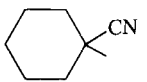
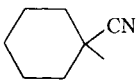
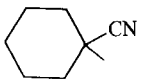
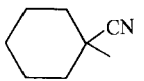
$C_6H_5CH_2CH_2CH_2$	H	$C_6H_5CH_2CH_2CH_2$	H	75	196, 197
4-$BrC_6H_4CH_2$	H	4-$BrC_6H_4CH_2$	H	143	127
4-$CH_3OC_6H_4CH_2$	H	4-$CH_3OC_6H_4CH_2$	H	173	127
3,4,5-$(CH_3O)_3C_6H_2CH_2$	H	3,4,5-$(CH_3O)_3C_6H_2CH_2$	H	154	127
C_6H_5	H	C_6H_5	H	210, 220	229, 490, 557
CH_3	CH_3	CH_3	CH_3	b.p. 66/12	229, 356, 486, 487
C_2H_5	C_2H_5	C_2H_5	C_2H_5	b.p. 165/100	355, 486
$(CH_3)_2CH$	$(CH_3)_2CH$	$(CH_3)_2CH$	$(CH_3)_2CH$	56	486, 487, 592
CH_3	$(CH_3)_3C$	CH_3	$(CH_3)_3C$	b.p. 59/0.05	152
CH_3	3-$ClC_6H_4O_3SCH_2CH_2$	CH_3	3-$ClC_6H_4O_3SCH_2CH_2$	137	131
$(CH_3)_2CH$	$KO_3S(CH_2)_3$	$(CH_3)_2CH$	$KO_3S(CH_2)_3$	>280	131
$(CH_3)_2CHCH_2$	$KO_3S(CH_2)_2$	$(CH_3)_2CHCH_2$	$KO_3S(CH_2)_2$	230 (dec.)	130
$(CH_3)_2CHCH_2$	3-$ClC_6H_4O_3S(CH_2)_2$	$(CH_3)_2CHCH_2$	3-$ClC_6H_4O_3S(CH_2)_2$	162	130
	$KO_3S(CH_2)_2$		$KO_3S(CH_2)_2$	>210	131
	3-$ClC_6H_4O_3S(CH_2)_2$		3-$ClC_6H_4O_3S(CH_2)_2$	161	131
	$KO_3S(CH_2)_2$		$KO_3S(CH_2)_2$	>242	131
	3-$ClC_6H_4O_3S(CH_2)_2$		3-$ClC_6H_4O_3S(CH_2)_2$	149	131
	$KO_3S(CH_2)_3$		$KO_3S(CH_2)_3$	220	131
	$KO_3S(CH_2)_3$		$KO_3S(CH_2)_3$	222	131

TABLE III-5. (continued)

A. No substituent on ring carbon



R^1	R^2	R^3	R^4	m.p. (°C)	Refs.
$NCCH_2$	$NCCH_2$	$NCCH_2$	$NCCH_2$	197	172
				161	492
$C_6H_5CH_2$	$NaO_3S(CH_2)_2$	$C_6H_5CH_2$	$NaO_3S(CH_2)_2$	242	128, 131
$C_6H_5CH_2$	$KO_3S(CH_2)_2$	$C_6H_5CH_2$	$KO_3S(CH_2)_2$	225	128, 131
$C_6H_5CH_2$	$C_6H_5O_3S(CH_2)_2$	$C_6H_5CH_2$	$C_6H_5O_3S(CH_2)_2$	171	131
$C_6H_5CH_2$	$3\text{-}ClC_6H_4O_3S(CH_2)_2$	$C_6H_5CH_2$	$3\text{-}ClC_6H_4O_3S(CH_2)_2$	158	131
$C_6H_5CH_2$	$4\text{-}ClC_6H_4O_3S(CH_2)_2$	$C_6H_5CH_2$	$4\text{-}ClC_6H_4O_3S(CH_2)_2$	170	131
$C_6H_5CH_2$	$NaO_3S(CH_2)_3$	$C_6H_5CH_2$	$NaO_3S(CH_2)_3$	–	128
$C_6H_5CH_2$	$KO_3S(CH_2)_3$	$C_6H_5CH_2$	$KO_3S(CH_2)_3$	–	128
$4\text{-}CH_3OC_6H_4CH_2$	$NaO_3S(CH_2)_2$	$4\text{-}CH_3OC_6H_4CH_2$	$NaO_3S(CH_2)_2$	232	128, 131
$4\text{-}CH_3OC_6H_4CH_2$	$KO_3S(CH_2)_2$	$4\text{-}CH_3OC_6H_4CH_2$	$KO_3S(CH_2)_2$	–	128
$4\text{-}CH_3OC_6H_4CH_2$	$KO_3S(CH_2)_3$	$4\text{-}CH_3OC_6H_4CH_2$	$KO_3S(CH_2)_3$	–	128
$4\text{-}CH_3OC_6H_4CH_2$	$3\text{-}ClC_6H_4O_3S(CH_2)_2$	$4\text{-}CH_3OC_6H_4CH_2$	$3\text{-}ClC_6H_4O_3S(CH_2)_2$	144	131
$C_6H_5CH_2CH_2$	$KO_3S(CH_2)_2$	$C_6H_5CH_2CH_2$	$KO_3S(CH_2)_2$	>255	131
$C_6H_5CH_2CH_2$	$3\text{-}ClC_6H_4O_3S(CH_2)_2$	$C_6H_5CH_2CH_2$	$3\text{-}ClC_6H_4O_3S(CH_2)_2$	133	131
$C_6H_5CH(CH_3)$	$KO_3S(CH_2)_2$	$C_6H_5CH(CH_3)$	$KO_3S(CH_2)_2$	>215	131
$C_6H_5CH(CH_3)$	$KO_3S(CH_2)_4$	$C_6H_5CH(CH_3)$	$KO_3S(CH_2)_4$	266	131

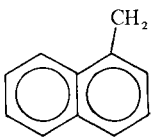
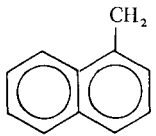
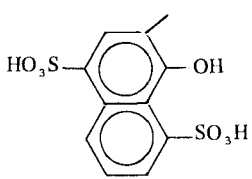
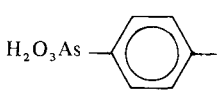
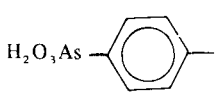
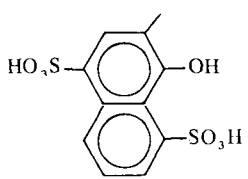
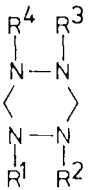
$C_6H_5CH(CH_3)$	$3\text{-}ClC_6H_4O_3S(CH_2)_2$	$C_6H_5CH(CH_3)$	$3\text{-}ClC_6H_4O_3S(CH_2)_2$	150	131
CH_3	C_6H_5	CH_3	C_6H_5	151	151, 152, 229, 254, 378
C_2H_5	C_6H_5	C_2H_5	C_6H_5	124	252, 254
$(CH_3)_2CH$	C_6H_5	$(CH_3)_2CH$	C_6H_5	163	178, 229
$KO_3S(CH_2)_3$	C_6H_5	$KO_3S(CH_2)_3$	C_6H_5	269	129
$C_6H_5CH_2$	C_6H_5	$C_6H_5CH_2$	C_6H_5	199	492
$C_6H_5CH_2CH_2$	C_6H_5	$C_6H_5CH_2CH_2$	C_6H_5	148	492
	C_6H_5		C_6H_5	228	492
C_6H_5	$C_6H_5NHNCH_2(CH_3CO)$	C_6H_5	$C_6H_5NHNCH_2(CH_3CO)$	240	286
$4\text{-}NO_2C_6H_4$	$C_2H_5OCH_2$	$4\text{-}NO_2C_6H_4$	H	–	231
C_6H_5	C_6H_5	C_6H_5	C_6H_5	200	229, 438
C_6H_5	$4\text{-}CH_3C_6H_4$	C_6H_5	$4\text{-}CH_3C_6H_4$	191	438, 439
$2\text{-}CH_3C_6H_4$	$2\text{-}CH_3C_6H_4$	$2\text{-}CH_3C_6H_4$	$2\text{-}CH_3C_6H_4$	187	438, 439
$3\text{-}CH_3C_6H_4$	$3\text{-}CH_3C_6H_4$	$3\text{-}CH_3C_6H_4$	$3\text{-}CH_3C_6H_4$	166	438, 439
$4\text{-}CH_3C_6H_4$	$4\text{-}CH_3C_6H_4$	$4\text{-}CH_3C_6H_4$	$4\text{-}CH_3C_6H_4$	213	438. 439
$4\text{-}ClC_6H_4$	$4\text{-}ClC_6H_4$	$4\text{-}ClC_6H_4$	$4\text{-}ClC_6H_4$	255	28
$4\text{-}BrC_6H_4$	$4\text{-}BrC_6H_4$	$4\text{-}BrC_6H_4$	$4\text{-}BrC_6H_4$	249 (dec.)	229
				--	162, 163

TABLE III-5. (continued)

A. No substituent on ring carbon

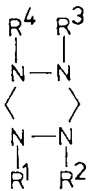


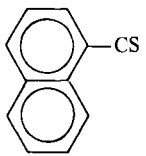
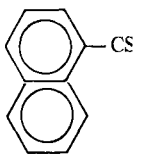
R^1	R^2	R^3	R^4	m.p. (°C)	Refs.
CH_3	CH_3CO	CH_3	CH_3CO	150–160, 219	127, 229
CH_3	F_3CCO	CH_3	F_3CCO	172	127
CH_3	$C_6H_5CH_2CO$	CH_3	$C_6H_5CH_2O$	203	378
C_2H_5	CH_3CO	C_2H_5	CH_3CO	169	197
C_4H_9	CH_3CO	C_4H_9	CH_3CO	103	197
C_4H_9	C_2H_5CO	C_4H_9	C_2H_5CO	83	197
$(CH_3)_2CHCH_2$	CH_3CO	$(CH_3)_2CHCH_2$	CH_3CO	139	197
C_6H_{13}	CH_3CO	C_6H_{13}	CH_3CO	91	197
C_8H_{17}	CH_3CO	C_8H_{17}	CH_3CO	97	197
$CH_2=CHCH_2$	CH_3CO	$CH_2=CHCH_2$	CH_3CO	184	197
$C_2H_5OCH_2CH_2$	CH_3CO	$C_2H_5OCH_2CH_2$	CH_3CO	128	197
$CH_3OOCCH_2CH_2$	CH_3CO	$CH_3OOCCH_2CH_2$	CH_3CO	164	197
$NCCH_2CH_2$	CH_3CO	$NCCH_2CH_2$	CH_3CO	286	197
$C_6H_5CH_2$	CH_3CO	$C_6H_5CH_2$	CH_3CO	207, 222	127, 197
$C_6H_5CH_2$	F_3CCO	$C_6H_5CH_2$	F_3CCO	228	127
$C_6H_5CH_2$[a]	$HOOCCH_2CH_2CO$	$C_6H_5CH_2$	$HOOCCH_2CH_2CO$	255	127, 128
$C_6H_5CH_2$	$KOOCCH_2CH_2CO$	$C_6H_5CH_2$	$KOOCCH_2CH_2CO$	359	127
$C_6H_5CH_2$	$CH_3OOCCH_2CH_2CO$	$C_6H_5CH_2$	$CH_3OOCCH_2CH_2CO$	145	127
4-$CH_3OC_6H_4CH_2$[a]	$HOOCCH_2CH_2CO$	4-$CH_3OC_6H_4CH_2$	$HOOCCH_2CH_2CO$	230	127, 128

4-$CH_3OC_6H_4CH_2$	$KOOCCH_2CH_2CO$	4-$CH_3OC_6H_4CH_2$	$KOOCCH_2CH_2CO$	360	127
4-$CH_3OC_6H_4CH_2$	$CH_3OOCCH_2CH_2CO$	4-$CH_3OC_6H_4CH_2$	$CH_3OOCCH_2CH_2CO$	142	127
4-$BrC_6H_4CH_2$	CH_3CO	4-$BrC_6H_4CH_2$	CH_3CO	283	127
$C_6H_5CH_2CH_2$	CH_3CO	$C_6H_5CH_2CH_2$	CH_3CO	152	197
$C_6H_5CH_2CH_2$	3-$CH_3OC_6H_4CHCO$ (C$_6$H$_5$)	$C_6H_5CH_2CH_2$	3-$CH_3OC_6H_4CHCO$ (C_6H_5)	175	237
$C_6H_5CH(CH_3)$	CH_3CO	$C_6H_5CH(CH_3)$	CH_3CO	267	197
$C_6H_5CH_2CH_2CH_2$	CH_3CO	$C_6H_5CH_2CH_2CH_2$	CH_3CO	110	197
$C_6H_5CH(CH_3)CH_2$	CH_3CO	$C_6H_5CH(CH_3)CH_2$	CH_3CO	160	197
C_6H_5	CH_3CO	C_6H_5	CH_3CO	257	229, 286
C_6H_5	CH_3CO	CH_3CO	C_6H_5	140	286
C_6H_5	C_2H_5CO	C_6H_5	C_2H_5CO	219	229
C_6H_5	$(CH_3)_2CHCO$	C_6H_5	$(CH_3)_2CHCO$	242	229
C_6H_5	C_6H_5CO	C_6H_5	C_6H_5CO	243, 257	229, 490
4-BrC_6H_4	CH_3CO	4-BrC_6H_4	CH_3CO	260–330 (dec.)	229
4-BrC_6H_4	C_6H_5CO	4-BrC_6H_4	C_6H_5CO	252	229
C_2H_5	CH_3CS	C_2H_5	CH_3CS	225	197
C_4H_9	CH_3CS	C_4H_9	CH_3CS	178	197
C_4H_9	C_6H_5CS	C_4H_9	C_6H_5CS	215	197
$(CH_3)_2CHCH_2$	CH_3CS	$(CH_3)_2CHCH_2$	CH_3CS	255	197
$CH_2=CHCH_2$	CH_3CS	$CH_2=CHCH_2$	CH_3CS	195	197
$HOCH_2CH_2$	CH_3CS	$HOCH_2CH_2$	CH_3CS	247	197
$C_2H_5OCH_2CH_2$	CH_3CS	$C_2H_5OCH_2CH_2$	CH_3CS	200	197
$C_6H_5CH_2$	CH_3CS	$C_6H_5CH_2$	CH_3CS	291	197
$C_6H_5CH_2CH_2$	CH_3CS	$C_6H_5CH_2CH_2$	CH_3CS	261	197
C_6H_5	CH_3CS	C_6H_5	CH_3CS	186	584
C_6H_5	$C_6H_5CH_2CS$	C_6H_5	$C_6H_5CH_2CS$	172	584
C_6H_5	C_6H_5CS	C_6H_5	C_6H_5CS	187	584
C_6H_5	4-$CH_3C_6H_4CS$	C_6H_5	4-$CH_3C_6H_4CS$	190	584

TABLE III-5 (continued)

A. No substituent on ring carbon



R^1	R^2	R^3	R^4	m.p. (°C)	Refs.
C_6H_5		C_6H_5		200	584
CH_3	C_6H_5NHCO	CH_3	C_6H_5NHCO	242	91
$C_6H_5CH_2$ [b]	$HOOCCH_2NHCO$	$C_6H_5CH_2$	$HOOCCH_2NHCO$	244	127, 128
$C_6H_5CH_2$	$KOOCCH_2NHCO$	$C_6H_5CH_2$	$KOOCCH_2NHCO$	329	127
$C_6H_5CH_2$	$H_5C_2OOCCH_2NHCO$	$C_6H_5CH_2$	$H_5C_2OOCCH_2NHCO$	185	127, 128
4-$CH_3OC_6H_4CH_2$ [b]	$HOOCCH_2NHCO$	4-$CH_3OC_6H_4CH_2$	$HOOCCH_2NHCO$	234	127, 128
4-$CH_3OC_6H_4CH_2$	$KOOCCH_2NHCO$	4-$CH_3OC_6H_4CH_2$	$KOOCCH_2NHCO$	335	127
4-$CH_3OC_6H_4CH_2$	$H_5C_2OOCCH_2NHCO$	4-$CH_3OC_6H_4CH_2$	$H_5C_2OOCCH_2NHCO$	231	127, 128
C_6H_5	H_5C_2NHCO	C_6H_5	H_5C_2NHCO	300	229
C_6H_5	C_6H_5NHCO	C_6H_5	C_6H_5NHCO	301	229
4-BrC_6H_4	4-BrC_6H_4NHCO	4-BrC_6H_4	4-BrC_6H_4NHCO	298 (dec.)	229
C_6H_5	$(CH_3)_2CHNHCS$	C_6H_5	H	215	229
C_6H_5	$(CH_3)_3CNHCS$	C_6H_5	H	189	229
CH_3	CH_3NHCS	CH_3	CH_3NHCS	284	229

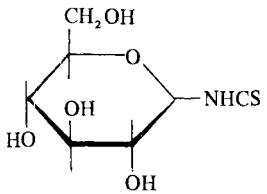
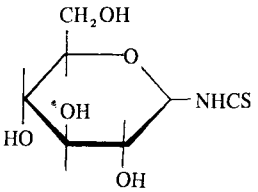
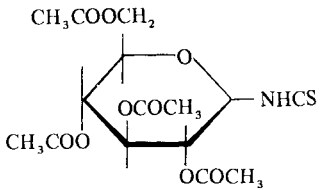
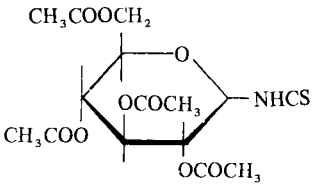
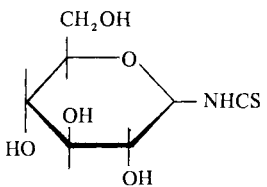
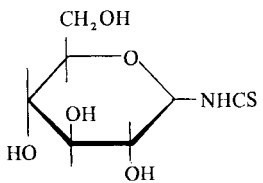
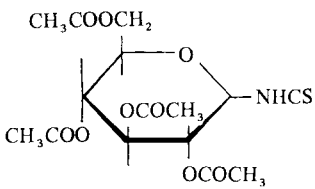
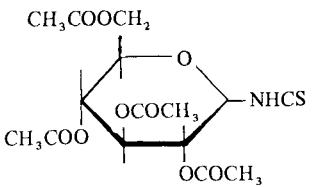
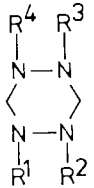
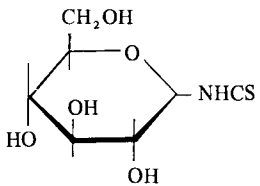
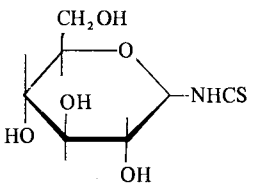
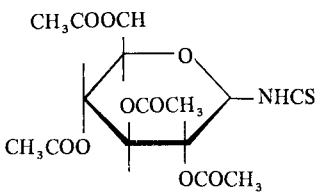
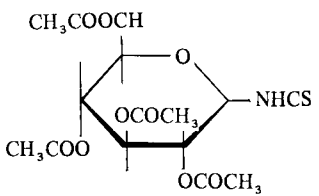
CH_3	$(CH_3)_3CNHCS$	CH_3	$(CH_3)_3CNHCS$	248	229
$C_6H_5CH_2$		$C_6H_5CH_2$		245	127
$C_6H_5CH_2$		$C_6H_5CH_2$		264	127
4-$CH_3OC_6H_4CH_2$		4-$CH_3OC_6H_4CH_2$		242	127
4-$CH_3OC_6H_4CH_2$		4-$CH_3OC_6H_4CH_2$		270	127

TABLE III-5 (continued)

A. No substituent on ring carbon

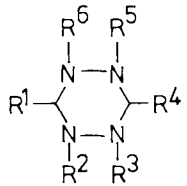


R^1	R^2	R^3	R^4	m.p. (°C)	Refs.
$3,4,5\text{-}(CH_3O)_3C_6H_2CH_2$			$3,4,5\text{-}(CH_3O)_3C_6H_2CH_2$		243	127
$3,4,5\text{-}(CH_3O)_3C_6H_2CH_2$			$3,4,5\text{-}(CH_3O)_3C_6H_2CH_2$		239	127
C_6H_5	CH_3NHCS		C_6H_5	CH_3NHCS	313	229
C_6H_5	C_2H_5NHCS		C_6H_5	C_2H_5NHCS	295	229
C_6H_5	$(CH_3)_2NHCS$		C_6H_5	$(CH_3)_2NHCS$	315	229
C_6H_5	C_6H_5NHCS		C_6H_5	C_6H_5NHCS	299 (dec.)	229
H_5C_2OOC	H_5C_2OOC		H_5C_2OOC	H_5C_2OOC	60	445

[a]This structure is probably incorrect.

[b]The 1-(methylamino)-1-desoxy-D-glucit salt of this compound is reported.

B. Substituents on nuclear carbon



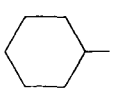
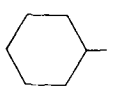
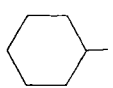
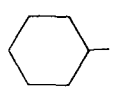
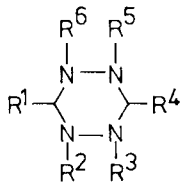
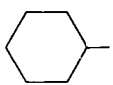
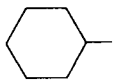
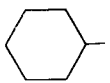
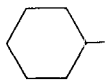
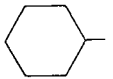
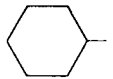
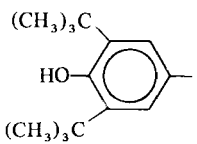
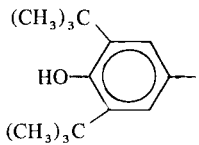
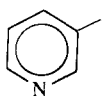
R^1	R^2	R^3	R^4	R^5	R^6	m.p. (°C)	Refs.
CH_3	H	H	CH_3	H	H	100, 163	175, 229, 242, 511–513
C_2H_5	H	H	C_2H_5	H	H	132, 193	242, 511–513
C_3H_7	H	H	C_3H_7	H	H	125, 153	242, 511–513
$(CH_3)_2CH$	H	H	$(CH_3)_2CH$	H	H	–	511
n-C_4H_9	H	H	n-C_4H_9	H	H	168	242
n-C_5H_{11}	H	H	n-C_5H_{11}	H	H	150	242
n-C_6H_{13}	H	H	n-C_6H_{13}	H	H	154	242
n-C_7H_{15}	H	H	n-C_7H_{15}	H	H	147	242
n-C_9H_{19}	H	H	n-C_9H_{19}	H	H	143	242, 465
n-$C_{11}H_{23}$	H	H	n-$C_{11}H_{23}$	H	H	66–110	511–513
CH_3	CH_3	H	CH_3	H	H	89–92	512
CH_3	CH_3	H	CH_3	CH_3	H	75–80	229, 512
CH_3	CH_3	CH_3	CH_3	CH_3	CH_3	31	511, 512, 547
C_2H_5	CH_3	CH_3	C_2H_5	CH_3	CH_3	62	547
C_2H_5			C_2H_5			b.p. 77/0.02	592

TABLE III-5 (continued)

B. Substituents on nuclear carbon



R^1	R^2	R^3	R^4	R^5	R^6	m.p.(°C)	Refs.
C_3H_7	CH_3	CH_3	C_3H_7	CH_3	CH_3	b.p. 54/0.05	592
$(CH_3)_2CH$	CH_3	CH_3	$(CH_3)_2CH$	CH_3	CH_3	94	547
$(CH_3)_2CH$	$(CH_3)_2CH$	$(CH_3)_2CH$	$(CH_3)_2CH$	$(CH_3)_2CH$	$(CH_3)_2CH$	b.p. 62/13	593
$(CH_3)_2CH$			$(CH_3)_2CH$			b.p. 79/0.03	592
$(C_2H_5)_2CH$	$(CH_3)_2CH$	$(CH_3)_2CH$	$(C_2H_5)_2CH$	$(CH_3)_2CH$	$(CH_3)_2CH$	b.p. 81/13	593
CH_3	C_2H_5	C_6H_5	CH_3	C_2H_5	C_6H_5	168, 184	151, 152
C_6H_5	CH_3	CH_3	C_6H_5	CH_3	CH_3	117	547, 592
4-ClC_6H_4	CH_3	CH_3	4-ClC_6H_4	CH_3	CH_3	146	182
4-$NO_2C_6H_4$	CH_3	CH_3	4-$NO_2C_6H_4$	CH_3	CH_3	188	182
4-$CH_3OC_6H_4$	CH_3	CH_3	4-$CH_3OC_6H_4$	CH_3	CH_3	114	182
4-$CH_3OC_6H_4$	C_2H_5	C_2H_5	4-$CH_3OC_6H_4$	C_2H_5	C_2H_5	–	199
CH_3	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	CH_3	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	150	438, 439
C_2H_5	C_6H_5	C_6H_5	C_2H_5	C_6H_5	C_6H_5	193	438, 439

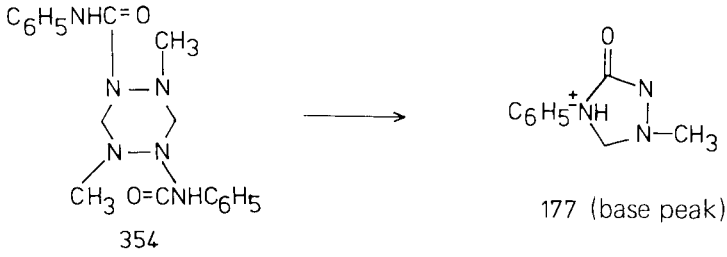
	C_6H_5	C_6H_5		C_6H_5	C_6H_5	133	438, 439
4-$CH_3C_6H_4$[c]	4-$CH_3C_6H_4$	H	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	H	–	281
CH_3	CH_3CO	H	CH_3	CH_3CO	H	260–270	229
CH_3	C_3H_7CO	H	CH_3	C_3H_7CO	H	218	229
CH_3	$(CH_3)_2CHCO$	H	CH_3	$(CH_3)_2CHCO$	H	270	229
CH_3	C_6H_5CO	H	CH_3	C_6H_5CO	H	252	229
CH_3	CH_3NHCS	H	CH_3	CH_3NHCS	H	240	229
CH_3	$(CH_3)_2CHNC$	H	CH_3	$(CH_3)_2CHNCS$	H	250 (dec.)	229
CH_3	$(CH_3)_3CNCS$	H	CH_3	$(CH_3)_3CNCS$	H	250	229
CH_3	$C_6H_5CH_2NHCS$	H	CH_3	$C_6H_5CH_2NHCS$	H	233	229
	C_6H_5NHCS	H		C_6H_5NHCS	H	–	465
	CH_3	CH_3		CH_3	CH_3	–	199

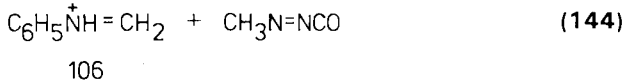
[c]The structure of this compound is not necessarily the one indicated here.

show only end absorption. The infrared spectra are as expected (175, 197, 512) in that the normal bands due to NH, if present, CH, and CN bonds, and the other groups in the molecule are present.

The PMR spectra of a large number of hexahydro-1,2,4,5-tetrazines have been reported (8, 9, 28, 196, 197, 229, 234–236, 511, 512). Many conformational studies have been based on NMR, but the two subjects will be discussed separately as much as possible though there is some overlap. If there are no substituents at C-3 and C-6, the methylene protons at those positions give rise to a singlet which normally appears at δ3.43 to 3.73 (8, 9, 196, 197, 229). However, if aromatic groups are attached to the nitrogen atom, the chemical shifts of the methylene protons move downfield. Jensen and Hammerum (229) have reported values of about δ4.4 for protons on C-3 and C-6 in compounds substituted with phenyl on the nitrogen atoms; Banthorpe and Winter (28) have found a value of δ5.57 for methylene protons in 1,2,4,5-tetra-(4-chlorophenyl)hexahydro-1,2,4,5-tetrazine. At lower temperatures, but varying considerably with the compound, the methylene proton singlet becomes an *AB* quartet (8, 9, 197). The singlet to quartet transformation has been used to support conformational arguments (8, 9). If there are acyl groups on the nitrogen atoms or thiocarbamoyl groups, there is a downfield shift of the methylene proton signals, and they appear as an *AB* quartet (196, 197). If the substituents are acyl groups, one doublet is centered at about δ5.0 and the other at about δ5.6 to 6.0. In the case of thiocarbamoyl substituents both doublets move upfield, but one moves to about δ4.0 whereas the other moves only to about δ5.5. The coupling constants are normally 13.5 Hz. Substitution of alkyl groups at C-3 and C-6 results in chemical shifts for the remaining protons of δ3.40 to 4.27. The signal appears as a quartet with $J = 6.0$ Hz if the substituents are methyl (511, 512). Protons on nitrogen give a signal at δ4.72 in $CDCl_3$. Methyl groups attached to nitrogen have proton chemical shifts at δ2.3 to 2.5. Substituents on either carbon or nitrogen give proton chemical shifts characteristic of such substituents in other systems.

Mass spectra of a limited number of hexahydro-1,2,4,5-tetrazines have been published (28, 91, 198, 199, 547). Molecular ions are usually obtained, but the parent peak is normally an ion representing one-half of the original molecule although in the case of 1,2,4,5-tetraalkylhexahydro-1,2,4,5-tetrazines $M/2 - 1$, $M/2 + 1$, and $M/2 + 2$ peaks are prominent (198). Similar compounds having 3,6-diaryl substituents give, in addition to the $M/2$ peak, peaks representing $ArCH{=}NR]^+$ and $ArCH^2]^+$ (199). Cooley and Atchinson (91) suggest fragmentation according to eq. III-99 for carbamoyl-substituted compounds. Sucrow and co-workers (547) have studied mass spectra at 150°C of 3,6-dialkyl-1,2,4,5-tetramethylhexahydro-1,2,4,5-tetrazines. Strong ions were found corresponding to pyrrole formation as indicated in eq. III-100. In addition





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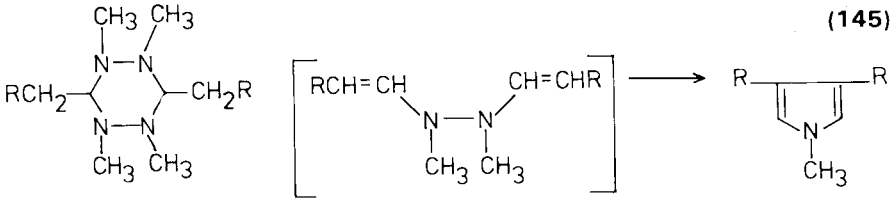
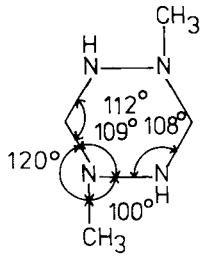


(145)

the $M/2$ fragments appeared, a $C_3H_7N]^+$ ion, and ions resulting from fragmentation of the pyrroles. 3,6-Diethylhexahydro-1,2,4,5-tetrazine and 3,6-diphenyl-1,2,4,5-tetramethylhexahydro-1,2,4,5-tetrazine did not form pyrroles.

There has been considerable interest in the conformation of hexahydro-1,2,4,5-tetrazines substituted on nitrogen. Ansell, Erickson, and Moore (9) have determined the structure of 1,4-dimethylhexahydro-1,2,4,5-tetrazine by X-ray crystallography and have also studied its conformation in solution by means of PMR. The bond angles are indicated in structure **74**. The methyl groups are equatorial and the protons on nitrogen are axial. The bond lengths are as

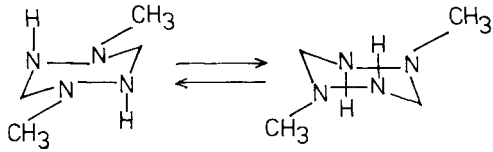


74

follows:

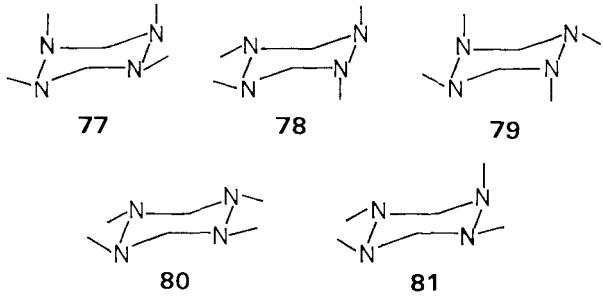
Bond	Bond length (A)
C–H(CH_3)	1.01, 1.02, 1.03
CH_3–N	1.45
CH_2–N(CH_3)	1.47
CH_2–N(H)	1.44
N–N	1.45
H–N	0.97

The PMR data were interpreted on the basis of a shift of the methylene from a singlet at higher temperatures to a quartet at lower temperatures to indicate a slow inversion between the forms **75** and **76** with a transition energy of 11.5 ± 0.05 kcal. Consistent with this is a dipole moment at 20°C in benzene of



75 **76** **(146)**

1.06 D. It was suggested that these conformations minimize 1,3-interactions between lone pair electrons. Anderson and Roberts (8) first considered the conformation of 1,2,4,5-tetraalkylhexahydro-1,2,4,5-tetrazines using the tetramethyl compound. This compound shows two singlets at 37°C, but at –87°C it gives rise to an *AB* quartet for the methylene protons and a doublet (δ 1.95 and δ2.36) for the N–CH_3 groups. It was considered that at 37°C the conformation was that of **79** with nitrogen inversion between two forms of the types **75** and **76**. Jones and co-workers (236) suggested on the basis of free



77 **78** **79** **80** **81**

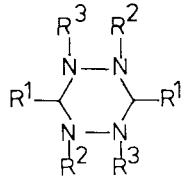
energy calculations that **78** would be more stable than **79**, and furthermore that **79** should have no dipole moment whereas 1,2,4,5-tetramethylhexahydro-1,2,4,5-tetrazine actually has a dipole moment of 1.45 D. Calculated dipole

moments for conformations **77** and **78** gave values of 2.47 and 1.31 D, respectively. Therefore the actual conformation must be **78**. Nelsen and Hintz (355) criticized the conclusion of Jones and co-workers because they felt that slight hydrolysis of hexahydro-1,2,4,5-tetrazines could give erroneous dipole moment values. As a result of PMR studies and theoretical considerations Nelsen and Hintz suggested that the tetramethyl compound has conformation **79**, but that 1,2,4,5-tetraethylhexahydro-1,2,4,5-tetrazine is 85% conformation **78** and 15% conformation **79**. Jones and coauthors (234, 235) then published extensive discussions of the conformation of these compounds considering the conformations **77** to **81**. The conformation **80** was dismissed because it would require the methyl substituents to be equivalent, and low-temperature PMR spectra indicate this is not the case. The conformation **77** was also excluded because of 1,3-diaxial interactions. After a thorough consideration of 220 Mg Hz PMR, dipole moments, and vibrational spectra, it was concluded that the tetramethyl compound exists as the interconverting forms **78** and **81** with about 30% as **78** and 70% as **81**. The tetraethyl compound was considered to be about 65% as conformation **79**, 33% as conformation **81**, and 2% as conformation **78** with interconversion occurring.

The electrochemical oxidation of 1,2,4,5-tetraalkylhexahydro-1,2,4,5-tetrazines to radical cations has been studied (356). The values of $E_{1/2}$ have been found to be 0.18 to 0.32 V.

4. *Reactions*

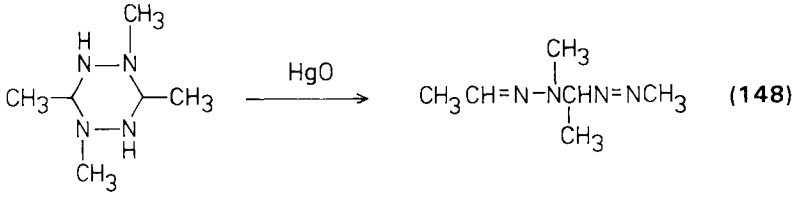
Hydrolysis of hexahydro-1,2,4,5-tetrazines occurs readily with destruction of the ring system and formation of an aldehyde and a hydrazine (eq. III-102) (128, 129, 182, 229, 242). Kauffmann and collaborators (242) have reported that some of the lower 3,6-dialkylhexahydro-1,2,4,5-tetrazines are largely



$$\xrightarrow{H_2O} R^1CHO + R^2NHNHR^3 \qquad \textbf{(147)}$$

hydrolyzed in water at 20°C and at higher temperatures complete hydrolysis occurs. However, since there is some uncertainty about their results (229, 512), perhaps this report should be accepted only with reservations. Alkaline solutions can cause hydrolysis at room temperature (128) as can acids (129, 182). Skorianetz and sz. Kováts (512) have studied the hydrolysis of 3,6-dimethylhexahydro-1,2,4,5-tetrazine at various pH's to form acetaldehyde hydrazone.

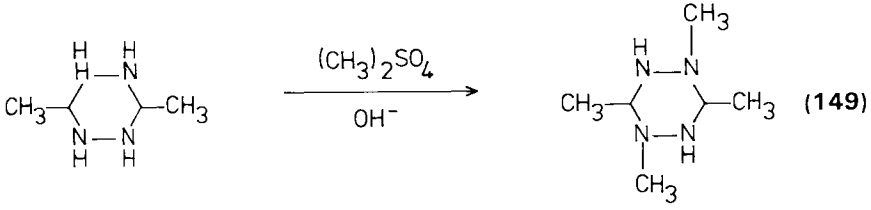
Oxidation of hexahydro-1,2,4,5-tetrazines with a number of reagents occurs readily, leading usually to more or less unsaturated 1,2,4,5-tetrazines. Oxidation of 1,4-disubstituted hexahydro compounds with metal oxides usually leads to 1,4-dihydro-1,2,4,5-tetrazines (eq. III-30) (486, 490, 557), but with a 3,6-disubstituted 1,4-dialkylhexahydro-1,2,4,5-tetrazine the product was 4,5-dimethyl-2,3,5,6-tetrazaocta-2,6-diene (eq. III-103) (514). In the only case reported in



(148)

which there was only hydrogen on the nitrogen atoms the product was a tetrahydro-1,2,4,5-tetrazine (eq. III-72) (514). Oxidation of 3,6-disubstituted hexahydro-1,2,4,5-tetrazines with oxygen catalyzed by platinum forms 1,6-dihydro-1,2,4,5-tetrazines (eq. III-34) (511–514). 1,4-Dihydro-1,2,4,5-tetrazines are the products of hexahydro-1,2,4,5-tetrazines oxidized with 1,2,4,5-tetrazines (eq. III-19) (514). Electrochemical oxidations (356) were discussed in the preceding section.

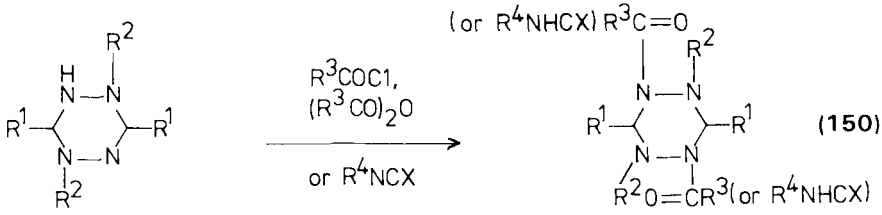
In those hexahydro-1,2,4,5-tetrazines having unsubstituted nitrogen atoms, the NH group reacts as an ordinary secondary amine does. Reaction with formaldehyde occurs readily, but usually reaction occurs at two nitrogen atoms, forming a bridge and resulting in condensed ring systems (490, 492). Since these are to be discussed in a subsequent section, they are not discussed here. The nitrogen atoms are readily alkylated with dimethyl sulfate (eq. III-104), resulting in 1,4-disubstitution in the only case reported (512).



(149)

Acylation occurs easily using acid chlorides (378) acid anhydrides (127, 229, 286), isocyanates (127, 229) and isothiocyanates (127, 229) (eq. III-105). For those compounds having no substituent on nitrogen, acylation and alkylation occur in the 1,4-positions.

Kauffmann and co-workers (242) have reported that 3,6-dialkylhexahydro-1,2,4,5-tetrazines having no substituents on nitrogen revert to the corresponding aldehyde hydrazone on being heated above their melting points. The pyrolysis of



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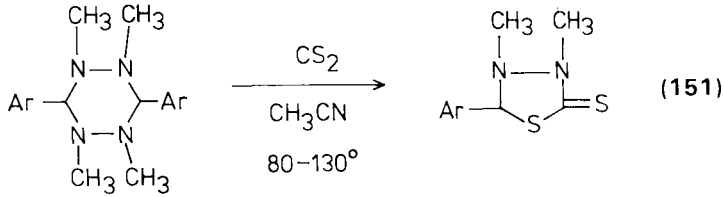
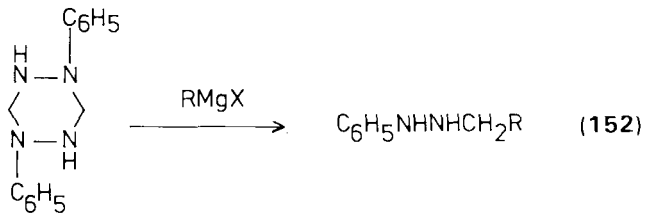
X = O or S



(151)

hexahydro-1,2,4,5-tetrazines in a mass spectrometer was discussed in the preceding section. 3,6-Diaryl-1,2,4,5-tetramethylhexahydro-1,2,4,5-tetrazines react with carbon disulfide at 80 to 130°C to form 2-aryl-3,4-dimethyl-1,3,4-thidiazolidine-5-thiones (eq. III-106) (182). The reaction did not occur if only hydrogen were at C-3 and C-6. Schmitz and Ohme (492) have treated 1,4-diphenylhexahydro-1,2,4,5-tetrazine with a series of Grignard reagents to form 1-arylalkyl-2-phenylhydrazines (eq. III-107). It seems that this must occur



(152)

by opening of the tetrazine ring to give formaldehyde phenylhydrazone or its equivalent.

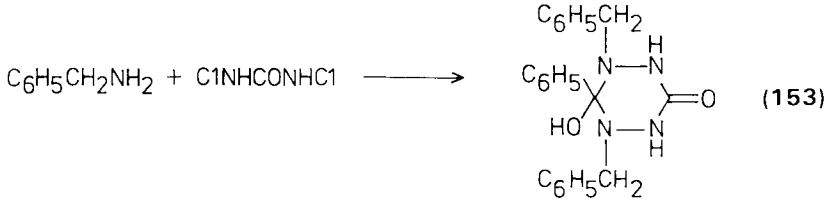
B. Hexahydro-1,2,4,5-tetrazines Substituted by Hetero Atoms

1. *Preparation*

Only a few hexahydro-1,2,4,5-tetrazines substituted by oxygen at C-3 and C-6 have been reported. It has been shown that some of the compounds claimed

to be of this type actually are not, and in some of the few remaining cases the structures are highly suspect.

Datta and Gupta (120) have found that the reaction of *N,N'*-dichlorourea with benzylamine results in two products. One of these was thought to have structure **82** (eq. III-108), and the other was the already mentioned *p*-urazine,

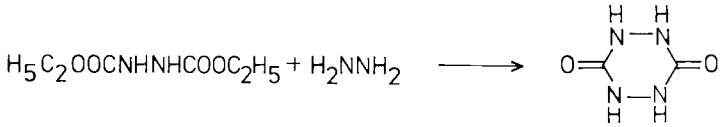


(153)

82

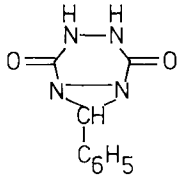
which was thought to be **64**. It was proposed that the first step was chlorination of benzylamine by the *N,N'*-dichlorourea. This was followed by reaction of one molecule of *N,N'*-dichlorourea, one molecule of benzylamine, two molecules of the *N*-chlorobenzylamine, and one molecule of water to give **82**, ammonium chloride, and hydrochloric acid. The only proof of structure was analysis, and, since the reaction is an unlikely one, it is probable that the proposed structure is incorrect.

A compound named *p*-urazine and believed to be hexahydro-1,2,4,5-tetrazine-3,6-dione (**64**) was prepared by Curtius and Heidenreich (111, 112) by the reaction of diethyl hydrazodicarboxylate with hydrazine (eq. III-109).

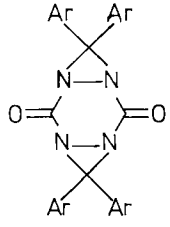


64

The product was a monoacidic base forming silver, ammonium, and barium salts, and it reacted with aldehydes to give compounds formulated as of the type **83**. Purgotti (434–436) prepared the same compound by heating biurea with hydrazine sulfate at 210°C. Purgotti and Vigano (437) reported a dimethiodide,

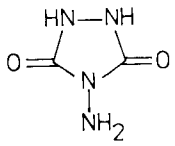


83

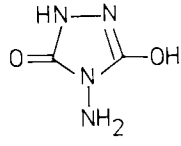


84

acetyl derivatives, and ketone derivatives, the latter of which were believed to be as shown in **84**. The same compound was reported as a result of several other reactions (52, 85, 190, 300). Busch and co-workers (60, 61, 63), Stollé (536), and Diels (126) contended that *p*-urazine actually was either 4-amino-1,2,4-triazolidine-3,5-dione (**85**) or its monoenolic isomer (**86**), but favored the latter



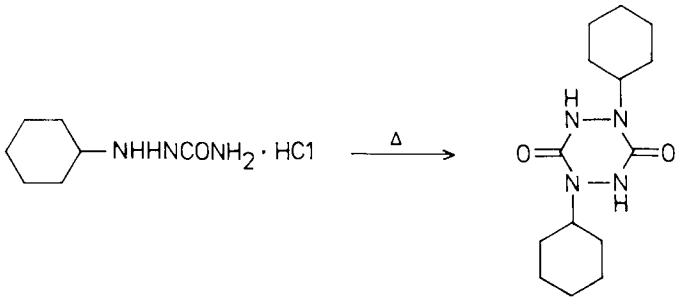
85



86

because *p*-urazine is acidic. It was argued that its reactions, such as those with one molecule of aldehyde, would be more reasonable for structure **85**, which would give a normal Schiff base. The products of *p*-urazine and two molecules of ketones were found to be azines derived from hydrazine and the ketone involved. It was found that many aryl-substituted *p*-urazines actually were triazoles, and this was a potent argument by analogy. Lutz (306) and Grove, Grillot, and Chang (186) have shown that the product obtained by the reaction of urea with carbohydrazide (190) is biurea, and it has been shown that Chattaway's procedure (85) also gives biurea. This same product rather than *p*-urazine was found (574) to arise from oxidation of semicarbazide with sodium hypobromite (300). Eloy and Moussebois (138) demonstrated that several of the reactions which had been purported to form *p*-urazine really gave biurea or similar compounds or 4-amino-1,2,4-triazolidine-3,5-dione (**85**). It is now believed that a compound of structure **64** has not been prepared (141, 585). However, from time to time there is mention of *p*-urazine in the literature with the assumption that it is hexahydro-1,2,4,5-tetrazine-3,6-dione (**64**) (73, 528).

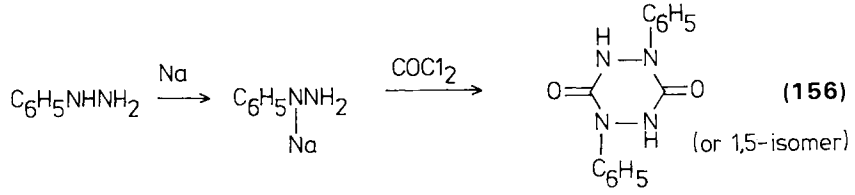
The cyclization of 1-cyclohexylsemicarbazide hydrochloride at 200 to 210°C has been claimed by Poth and Bailey (430) to form 1,4-dicyclohexylhexahydro-1,2,4,5-tetrazine-3,6-dione (eq. III-110). However, owing to the lack of rigorous structure proof and of the known tendency for 1,2,4,5-tetrazines to isomerize to



(155)

triazoles at high temperatures, it seems best to accept the reported structure with caution.

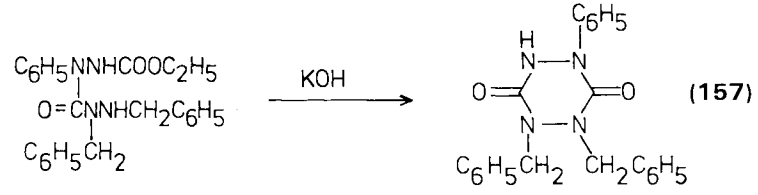
A number of workers (2, 68, 206, 400, 402, 460, 461, 510) prepared a compound called either *phenylurazole* or, later, *diphenylurazine*, which was believed to be 1,4-diphenylhexahydro-1,2,4,5-tetrazine-3,6-dione (**87**). The syntheses usually involved starting with 1-phenylsemicarbazide alone or 1-phenylsemicarbazide and some compound such as urea and heating. Busch (60) showed by independent synthesis that *diphenylurazine* is 4-anilino-1-phenyl-1,2,4-triazolidine-3,5-dione. The synthesis of **87** or its 1,5-diphenyl isomer starting with phenylhydrazine and involving reaction with phosgene (eq. III-111) has been done by Peratoner and Siringa (398).



(156)

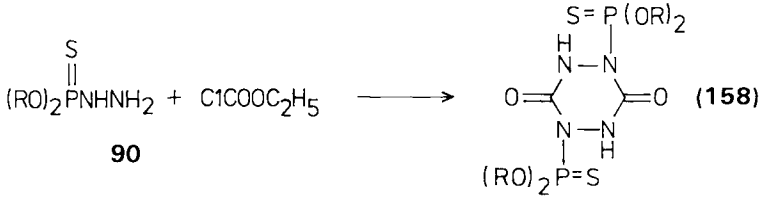
87

Busch (60) has synthesized 1,2-dibenzyl-4-phenylhexahydro-1,2,4,5-tetrazine-3,6-dione (**89**) by cyclization of the carbazide **88** with base (eq. III-112). The yield was 50%. The synthesis of phosphorylated hexahydro-1,2,4,5-tetrazine-3,6-diones (**91**) has been reported in a patent by Tolkmuth (556). The procedure was the reaction of ethyl chloroformate with *O,O*-dialkylphosphorohydrazidothioate (**90**) as shown in eq. III-113.



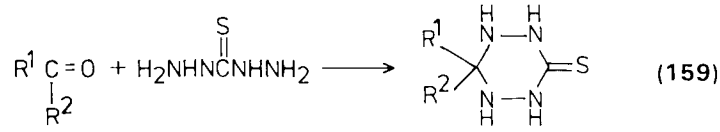
(157)

88 **89**



(158)

90 **91**

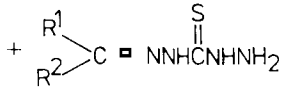


(159)

92

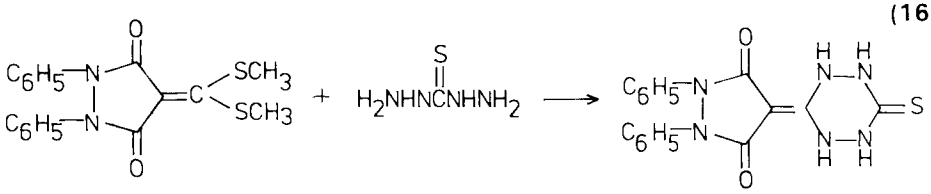
R^1 = H or alkyl

R^2 = Alkyl



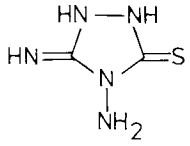
Lamon (287) has studied the reaction of aldehydes and ketones with thiocarbohydrazide (eq. III-114). In the reactions using aldehydes having no α-substituent good yields of the only product, the 1,2,4,5-tetrazine **92**, were obtained. Ketones and α-substituted aldehydes gave both products, although 1,2,4,5-tetrazines predominated. The structures of the 6-alkylhexahydro-1,2,4,5-tetrazine-3-thiones were established by spectral data. A somewhat similar procedure for preparing a similar compound, except that the thiomercaptal of a ketene was substituted for the ketone, has been used (eq. III-115) (549). Ershov

(160)

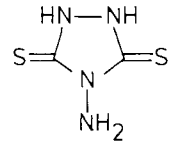


and Postovskii (145) have prepared compounds of type **92** in which R^1 is aryl and R^2 is ethoxy by starting with ethyl arylimidoates. The ethoxy group was removed by a subsequent oxidation followed by reduction giving 6-arylhexahydro-1,2,4,5-tetrazine-3-thiones (**92** in which R^1 = Ar and R^2 = H).

The synthesis of hexahydro-1,2,4,5-tetrazine-3,6-dithione (**39**) has been reported by a number of workers. It was originally called dithio-*p*-urazine (32, 191, 437). The compound was synthesized by a variety of procedures usually involving thiocarbohydrazide or an analogue either as such or as an intermediate. Arndt and Bielich (10) and Fromm and co-workers (164) attempted to repeat the procedure utilizing the reaction of dithiobiurea and hydrazine (437). It was found that the products were the triazoles **93** and **94** or



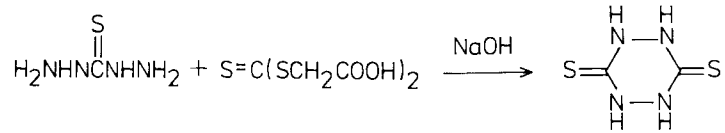
93



94

their enolic isomers. Subsequently Lutz (306), Petri (399), and Sandström (466) repeated the reactions used by Guha and De (191) to prepare dithio-*p*-urazine, among them the reaction of thiocarbohydrazide with potassium ethyl xanthoate and with carbon disulfide. The infrared spectrum of the product and its reaction with benzaldehyde to form a benzylidene derivative were taken to indicate that what had originally been thought to be hexahydro-1,2,4,5-tetrazine-3,6-dithione (**39**) actually was the aminotriazole **94.**

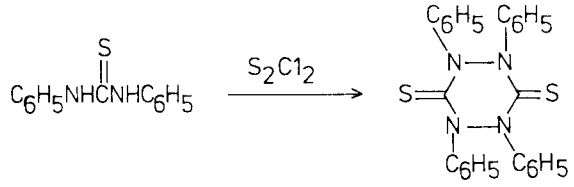
As final proof that the compounds previously claimed to be hexahydro-1,2,4,5-tetrazine-3,6-dithione (**39**) did not have that structure, it was synthesized by Sandström (467) and found to differ from products already reported. The synthesis was achieved by reaction of thiocarbohydrazide with bis(carboxymethyl) trithiocarbonate in basic solution at room temperature (eq. III-116).



(161)

39

The yield was 45%. The structure of the product was proved by spectral data and reactions. The NMR spectrum indicated absence of protons on sulfur but showed a broad NH signal. The infrared spectrum had no bands for SH or C=N. The ultraviolet spectrum had a maximum at 298.5 nm (ϵ 20,400) which is consistent with **39**. The compound **39** reacts readily with alkyl halides to form bis(alkylmercapto)-1,2-dihydro-1,2,4,5-tetrazines as already discussed (eq. III-48). The dihydro compounds were oxidized to 1,2,4,5-tetrazines and both series were well characterized. The dithione **39** has been mentioned in a patent as being useful as a stabilizer for photographic emulsions, but no method of preparation or characterization data were given (477). Naik (352) treated *N,N'*-diphenylthiourea with sulfur monochloride and obtained a crystalline solid which was thought to be 1,2,4,5-tetraphenylhexahydro-1,2,4,5-tetrazine-3,6-dithione (eq. III-117). However, the characterization data were poor and the

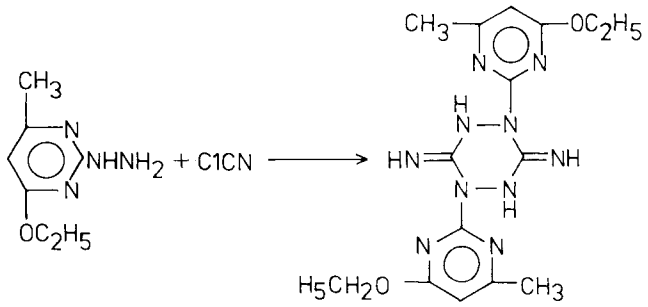


(162)

analyses were not good so there remains considerable question as to the compound's structure.

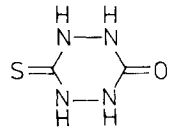
Pellizzari (395) has synthesized a series of 3,6-diimino-1,4-diphenylhexahydro-1,2,4,5-tetrazines by the reaction of 1-cyano-1-phenylhydrazine with

acetic anhydride (eq. III-54) as discussed above. Some of these (**40** and **41**) were considered to be hexahydro-1,2,4,5-tetrazines, but there was ambiguity about the structure of unacetylated material (**42a** and **42b**). By a very similar process, which must also involve dimerization of a cyanohydrazine, Bee and Rose (33) have prepared a 3,6-diimino 1,4-disubstituted hexahydro-1,2,4,5-tetrazine (eq. III-118) as the hydrochloride.



(163)

Guha and De (190) reported the preparation of hexahydro-1,2,4,5-tetrazin-3-one-6-thione (**95**) by the reaction of biurea with potassium ethyl xanthate.



95

The compound was reported again somewhat later although no preparative method was given (374). Lutz (306) attempted to repeat the earlier preparation by Guha and De and obtained only biurea so it seems probable that **95** has not yet been prepared, although it could probably be synthesized by a variation of Sandstrom's procedure for the 3,6-dithione **39**.

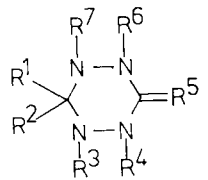
2. *Compound Survey*

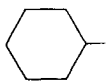
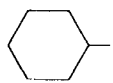
The hexahydro compounds of this class reported so far are listed in Table III-6.

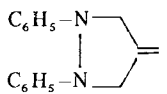
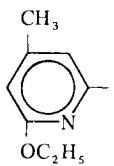
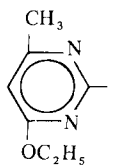
3. *Physical Properties and Theoretical Considerations*

All the compounds discussed in this section are stable and high melting. The dithiones are yellow, and at least one diimine is also yellow (33). The ultraviolet,

TABLE III-6. HEXAHYDRO-1,2,4,5-TETRAZINES WITH HETERO-ATOM SUBSTITUENTS



R^1	R^2	R^3	R^4	R^5	R^6	R^7	m.p. (°C)	Refs.
=O[a]			H	O		H	197	430
=O[b]		C_6H_5	H	O	C_6H_5	H	148	398
=O[b]		C_6H_5	H	O	H	C_6H_5	–	398
=O		$(CH_3O)_2P(=S)$	H	O	$(CH_3O)_2P(=S)$	H	201	556
=O		$(C_2H_5O)_2P(=S)$	H	O	$(C_2H_5O)_2P(=S)$	H	154	556
OH	C_6H_5	$C_6H_5CH_2$	H	O	H	$C_6H_5CH_2$	140	120
=O		$C_6H_5CH_2$	$C_6H_5CH_2$	O	H	C_6H_5	180	60
C_2H_5	H	H	H	S	H	H	161	287
$(CH_3)_2CHCH_2$	H	H	H	S	H	H	178 (dec.)	287
$(CH_3)_3C$	H	H	H	S	H	H	168	287

n-C_6H_{13}	H	H	H	S	H	H	159	287
$C_6H_5CH_2$	H	H	H	S	H	H	168	287
CH_3	CH_3	H	H	S	H	H	197	287
CH_3	C_2H_5	H	H	S	H	H	131	287
CH_3	$(CH_3)_2CH$	H	H	S	H	H	–	287
$-(CH_2)_4-$		H	H	S	H	H	179	287
$-(CH_2)_5-$		H	H	S	H	H	166	287
		H	H	S	H	H	226	549
=O[a]		H	H	S	H	H	–	374
=S		H	H	S	H	H	176	467, 477
=S		C_6H_5	C_6H_5	S	C_6H_5	C_6H_5	160	352
=NH		C_6H_5	H	NH	C_6H_5	H	198	395
=NH			H	NH		H	176 (dec.) (HCl)	33
=NH		C_6H_5	CH_3CO	NH	C_6H_5	H	228	395
=NH		C_6H_5	CH_3CO	NH	C_6H_5	CH_3CO	268	395
$=NCOCH_3$		C_6H_5	CH_3CO	NCOCH	C_6H_5	CH_3CO	188	395

[a]It is highly doubtful that this compound has the proposed structure.
[b]These compounds are the same, but it is not known which isomer was prepared.

infrared, and PMR spectra of **39** have already been discussed. The monothiones (**92**) have maxima in their ultraviolet spectra at about 250 nm with ϵ about 13,000. Protons on C-6 show chemical shifts of δ3.4 to 3.5, and the signals are multiplets. The protons on nitrogen adjacent to the saturated carbon atom (C-6) give rise to a doublet at δ4.7 to 4.8. The remaining two protons appear as a singlet at δ9.1 to 9.2. The diimine reported by Bee and Rose (33) shows ultraviolet maxima at 222 and 272 nm.

4. *Reactions*

The alkylation reactions of hexahydro-1,2,4,5-tetrazine-3,6-dithiones have been discussed in an earlier section (eq. III-48). The dithione shows the typical hydro-1,2,4,5-tetrazine acid-catalyzed rearrangement to an aminotrizole (**94**) or its dienolic form. 3,6-Diimino-1,4-bis(3-methyl-5-ethoxy-2-pyrimidinylhexahydro-1,2,4,5-tetrazine hydrochloride rearranges in hot water to a triazole (33). The amino groups as well as ring NH of such compounds are acetylated by acetic anhydride (395).

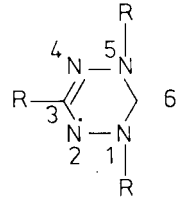
Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

IV

Verdazyls

I. INTRODUCTION

The first publication on verdazyls by Kuhn and Trischmann (278) appeared in 1963, and the development of the field has been largely due to the work of Kuhn and his successors who had originally been his collaborators. The verdazyls are very stable free radicals and in a formal sense could be considered as 2,3,4-trihydro-1,2,4,5-tetrazines. However, these compounds are theoretically and practically different enough from the other reduced 1,2,4,5-tetrazine systems that it is felt that they should be treated as a separate area of 1,2,4,5-tetrazine chemistry. The earlier workers in the verdazyl field numbered



96

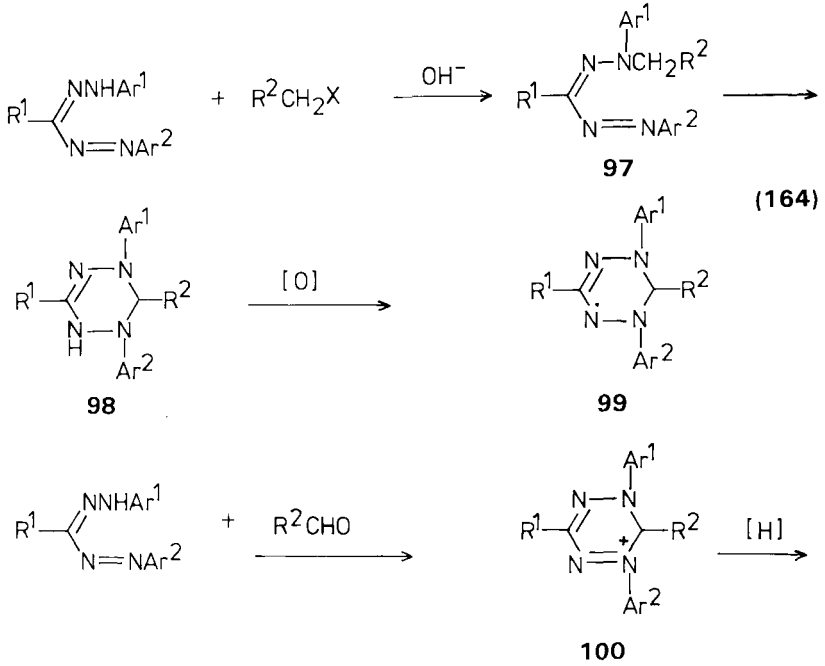
them as indicated in **96**, but this review uses the *Chemical Abstracts* numbering system (**2**), although the compounds are named as derivatives of verdazyl (**96**, R = H).

II. ALKYL-, ARYLALKYL-, ARYL-, AND HETEROCYCLIC-SUBSTITUTED VERDAZYLS

A. Preparation

Only a few methods for preparing verdazyls have been developed, and almost all of them start originally with 1,3,5-trisubstituted formazans. Verdazyl

preparation has already been discussed to some extent in the sections on 1,6-dihydro- and 1,2,3,4-tetrahydro1,2,4,5-tetrazines. The formazans are readily prepared by the reaction of arylhydrazones of aldehydes with diazonium salts. The basic procedures for preparing verdazyls are the reaction of alkyl halides or sulfates with formazans followed by oxidation (eq. IV-1) or reaction of aldehydes with formazans followed by reduction (eq. IV-2).

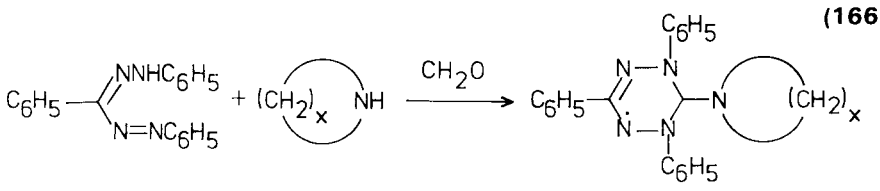


Syntheses exemplified by eq. IV-1 can be carried out in two ways. In one procedure the alkylation of the formazan is achieved by reaction of an alkyl halide or sulfate with a formazan at room temperature in the presence of barium oxide and barium hydroxide octahydrate in an appropriate solvent, usually dimethylformamide. Then without isolation of the intermediate **97** cyclization occurs, and a verdazyl is isolated. Oxidation of **98** occurs by exposure to air or oxygen (360). The other method consists of a two-step sequence in which the alkylation of the formazan is carried out much as in the first method, but the alkylated formazan (**97**) is isolated. It is then heated to about 150°C, and finally oxidation to **99** is done with ferric chloride (51). The overall yields from formazans are usually not high, normally 40 to 60%, but they may be substantially lower (51, 283, 360) or higher (278, 279). The substituents on the starting formazans have been for the most part aryl. As indicated in eq. IV-1 this is almost invariably the case for the substituents at N-1 and N-5. There is only

one exception, and that involved the use of 1-(5-tetrazolyl)-3,5-diphenylformazan giving rise to a heterocyclic-substituted verdazyl at N-2 or N-4 (500). A comparatively few examples are known in which R^1 in eq. IV-1 is hydrogen, alkyl, or arylalkyl (51, 248, 279, 363). Two or more formazan groups can be attached to various aromatic systems leading to compounds containing more than one verdazyl ring (269, 274). Such simple alkyl groups as methyl, ethyl, isopropyl, isobutyl, and tert-butyl have been reported at C-6 in verdazyls, and a series of polyhydroxylated alkyl substituents derived from sugars also have been the C-6 substituents (270). The alkylating agents (R^2CH_2X) commonly used have been methyl halides or sulfates so that the only substituent at C-3 has usually been hydrogen (270, 278–280, 335, 361). A few other alkyl halides have been used such as ethyl (279, 360), propyl (363), allyl (275), propargyl (275), isobutyl (363), and 1,6-diiodohexane (274), which results in verdazyls having two 1,2,3,4-tetrazine rings. Arylalkyl halides have also been used as the alkylating agents (279, 283). The alkyl and arylalkyl halides used to prepare verdazyls most commonly have been iodides (51, 270, 273, 279, 366), but bromides have been used frequently (275, 278, 279, 360), and even one chloride was reported (283). Methylene iodide has been used as an alkyl halide (279), but it would more properly be considered a reactant of the aldehyde type (eq. IV-2) leading to the same type of verdazylium intermediate (**100**). The commonly used base of eq. IV-1 has been a barium oxide–barium hydroxide octahydrate combination (273, 280, 283, 335, 363, 369), but sodium hydroxide has been used (369). Sodium hydroxide was not considered satisfactory because it led to alkylation of the intermediate **98** at N-1 (eq. III-63). Oxidation from stage **98** to the verdazyl (**99**) has frequently been with air or oxygen (278–280, 362), but ferric chloride (51, 363) and lead dioxide (366, 500) are effective.

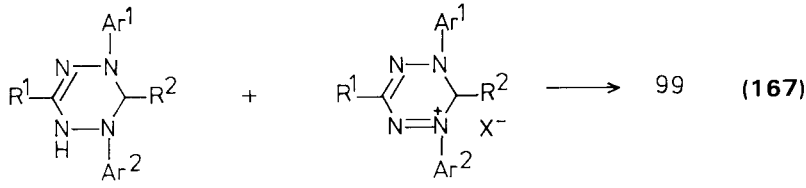
Preparation of verdazyls by reaction of aldehydes with formazans (eq. IV-2) first uses an acid catalyst (274, 280, 361). The reaction mixture is then made basic, and reduction of the verdazylium salt (**100**) occurs by the excess of aldehyde present. In almost all cases the aldehyde used has been formaldehyde, but acetaldehyde and propionaldehyde are satisfactory (51, 279). However, aromatic aldehydes do not give verdazyls (279). The most frequently used acid catalysts have been potassium bisulfate (274, 363) and boron trifluoride (51, 362, 363), but acetic acid has been used (280). The yields vary considerably but are usually below 50%. An interesting variation on the procedure is that reported by Kuhn and collaborators (275) in which a saturated cyclic amine was included in the cyclization reaction mixture (eq. IV-3). The product (**101**) contained a heterocyclic ring at C-3. The amines used were pyrrolidine, piperidine, and substituted piperidines.

Only two other procedures are known for the synthesis of verdazyls. In one of these 1,2,3,4-tetrahydro-1,2,4,5-tetrazines (**98**) react with quaternary salts of



(166)

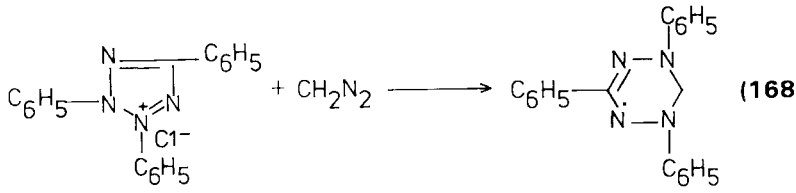
101



(167)

98 100

1,6-dihydro-1,2,4,5-tetrazines (**100**) in the presence of base to form verdazyls (eq. IV-4) (276). This method is only rarely practical because the starting materials are usually intermediates in verdazyl syntheses, and it is normally easier to obtain the desired verdazyls by one of the already mentioned procedures. The preparation of 2,4,6-triphenylverdazyl by the reaction of 2,3,5-triphenyltetrazolium chloride with diazomethane (eq. IV-5) was reported (275), but this method of synthesis has not been mentioned subsequently.



(168)

B. Compound Survey

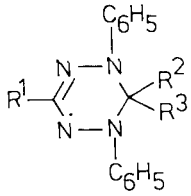
The verdazyls that have been reported in the literature are listed in Table IV-1.

C. Physical Properties and Theoretical Considerations

Kuhn and his associates (269–271, 279), in their earliest work on verdazyls, suggested that they were free radicals because they were paramagnetic and exhibited nine-line ESR spectra. It was also suggested (279) that verdazyls were

TABLE IV-1. VERDAZYLS

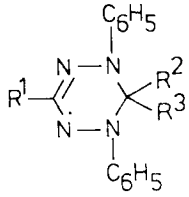
A. 2,4-Diphenylverdazyls with only one ring



R^1	R^2	R^3	m.p. (°C)	Refs.
H	H	H	93, 109	51, 279
CH_3	H	H	82, 99	51, 248
CH_3	D	D	101	51
CD_3	H	H	97	51
CD_3	D	D	101	51
C_2H_5	H	H	59	363
$(CH_3)_2CH$	H	H	72	363
$(CH_3)_2CHCH_2$	H	H	79	363
$(CH_3)_3C$	H	H	106,[a] 108	51
$C_2H_5CH(CH_3)CH_2$	H	H	64	367
$HOCH_2CH(OH)CH(OH)CH(OH)CH_2OH$	H	H	79	270
$HOCH_2CH(OH)CH(OH)CH(OH)CH_2OH$	H	H	99	270
$HOCH_2CH(OH)CH(OH)CH(OH)CH_2OH$	H	H	79	270
$CH_3CH(OH)CH(OH)CH(OH)CH_2OH$	H	H	79	270
$HOCH_2CH(OH)CH(OH)CH_2OH$	H	H	81	270
$HOCH_2CH(OH)CH(OH)CH_2OH$	H	H	60	270
$CH_3COOCH_2CH(OCOCH_3)CH(OCOCH_3)CH_2OCOCH_3$	H	H	90	270

TABLE IV-1. (continued)

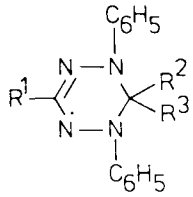
A. 2,4-Diphenylverdazyls with only one ring



R^1	R^2	R^3	m.p. (°C)	Refs.
$CH_3CH(OCOCH_3)CH(OCOCH_3)CH(OCOCH_3)_2$	H	H	70	270
$CH_3COOCH_2CH(OCOCH_3)CH(OCOCH_3)_2$	H	H	56	270
$CH_3COOCH_2CH(OCOCH_3)CH(OCOCH_3)_2$	H	H	66	270
$CH_3COOCH_2CH(OCOCH_3)CH(OCOCH_3)CH(OCOCH_3)_2$	H	H	85	270
$CH_3COOCH_2CH(OCOCH_3)CH(OCOCH_3)CH(OCOCH_3)_2$	H	H	70	270
CH_3	CH_3	H	109	51
CH_3	C_2H_5	H	81	363
CH_3	$(CH_3)_2CH$	H	114	363
$(CH_3)_3C$	CH_3	H	82	51
$(CH_3)_3C$	CD_3	D	88	51
$C_6H_5CH_2$	H	H	116	363
$C_6H_5CH(CH_3)$	H	H	127	363
$C_6H_5CH(CH_3)CH_2$	H	H	100	363
$C_6H_5CH{=}CH$	H	H	139	363
C_6H_5	H	H	140	275, 278–280, 364

TABLE IV-1. (continued)

A. 2,4-Diphenylverdazyls with only one ring



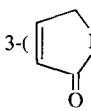
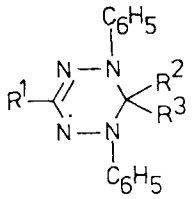
R^1	R^2	R^3	m.p. (°C)	Refs.
C_6H_5	D	D	160	364, 371
4-$CH_3C_6H_4$	H	H	143	481, 482
4-CH_2=CHC_6H_4	H	H	125	248
4-CH_2=$CHCOOCH_2C_6H_4$	H	H	–	337
4-CH_2=$C(CH_3)COOCH_2C_6H_4$	H	H	–	337
4-ClC_6H_4	H	H	146	416, 417, 481, 482
4-$CH_3OC_6H_4$	H	H	127	276, 363, 416, 417
4-$CH_3OC_6H_4$	D	D	138	371
4-$CD_3OC_6H_4$	D	D	138	371
2,6-$(CH_3O)_2C_6H_3$	H	H	141	371
3,4-$(CH_3O)_2C_6H_3$	H	H	127	371
4-$CH_3COOC_6H_4$	H	H	149	276, 417
4-CH_2=$C(CH_3)COOC_6H_4$	H	H	–	337
3-$NO_2C_6H_4$	H	H	167	335, 362
4-$NO_2C_6H_4$	H	H	205	279, 362, 416, 417
3-$H_2NC_6H_4$	H	H	149	335, 362
4-$H_2NC_6H_4$	H	H	158	362
3-(4-$NO_2C_6H_4CH$=N)C_6H_4	H	H	161	362
4-(4-$NO_2C_6H_4CH$=N)C_6H_4	H	H	181	362
4-[2,4,6-$(NO_2)_3C_6H_2NH]C_6H_4$	H	H	172	362
3-()C_6H_4	H	H	–	335
3-(HOOCCH=CHCOHN)C_6H_4	H	H	–	335
3-$C_6H_5CONHC_6H_4$	H	H	190	362
C_6H_5	CH_3	H	183	279
C_6H_5	C_2H_5	H	189	275, 279
C_6H_5	CH_2=CH	H	172	275
C_6H_5	HC≡C	H	183	275

TABLE IV-1. (continued)



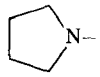
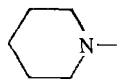
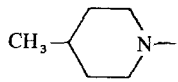
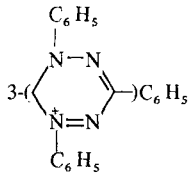
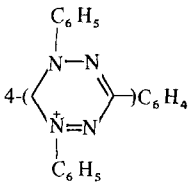
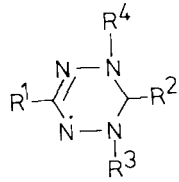
R^1	R^2	R^3	m.p. (°C)	Refs.
C_6H_5	$I(CH_2)_5$	H	105	275
C_6H_5	C_6H_5	H	180	278–280, 282, 283
C_6H_5	4-BrC_6H_4	H	198	278–280
C_6H_5		H	148	275
C_6H_5		H	170	275
Picrate			167	275
C_6H_5		H	154	275
	H	H	–	269
	H	H	–	269
NO_2	H	H	170	362
H_5C_2OOC	H	H	127	51, 360
H_5C_2OOC	D	D	132	360

TABLE IV-1. (continued)

B. All others with only one ring



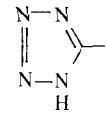
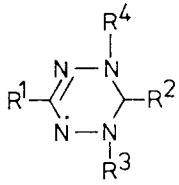
R^1	R^2	R^3	R^4	m.p. (°C)	Refs.
CH_3	H	C_6H_5	4-$NO_2C_6H_4$	158	366
$(CH_3)_3C$	H	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	120	361
$(CH_3)_3C$	H	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	86	361
$(CH_3)_3C$	H	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	195	361
$(CH_3)_3C$	H	4-$CH_3OOCC_6H_4$	4-$CH_3OOCC_6H_4$	130	361
$(CH_3)_3C$	H	4-NCC_6H_4	4-NCC_6H_4	204	361
C_6H_5	H	3-CH_2=CHC_6H_4	C_6H_5	--	284
C_6H_5	H	2-$CH_3OC_6H_4$	C_6H_5	--	280
C_6H_5	H	4-$CH_3OC_6H_4$	C_6H_5	119	276
C_6H_5	H	C_6H_5	3-$NO_2C_6H_4$	134	362
C_6H_5	H	C_6H_5	4-$NO_2C_6H_4$	153, 183	279, 362
C_6H_5	H	4-$H_5C_2C_6H_4$	4-$H_5C_2C_6H_4$	128	364, 371
C_6H_5	H	3-$CH_3OC_6H_4$	3-$CH_3OC_6H_4$	143	371
C_6H_5	H	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	143	276, 364
C_6D_5	H	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	144	364
C_6H_5	H	C_6H_5		–	500, 501
4-$CH_3C_6H_4$	H	C_6H_5	4-$CH_3C_6H_4$	116	343
4-$CH_3C_6H_4$	H	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	139	371
4-$H_5C_2C_6H_4$	H	4-$H_5C_2C_6H_4$	4-$H_5C_2C_6H_4$	146	371
4-$(CH_3)_3CC_6H_4$	H	4-$(CH_3)_3CC_6H_4$	4-$(CH_3)_3CC_6H_4$	202	371
3,5-$[(CH_3)_3C]_2C_6H_3$	H	3,5-$[(CH_3)_3C]_2C_6H_3$	3,5-$[(CH_3)_3C]_2C_6H_3$	183	371
4-$C_6H_5C_6H_4$ [b]	H	4-FC_6H_4	4-FC_6H_4	158	360
4-FC_6H_4 [b]	H	4-FC_6H_4	4-FC_6H_4	185	360
4-FC_6H_4	CH_3	4-FC_6H_4	4-FC_6H_4	163	360
4-FC_6H_4	C_6H_5	4-FC_6H_4	4-FC_6H_4	170	360
4-$CH_3OC_6H_4$	H	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	116	363
4-$CH_3OC_6H_4$	H	4-$H_5C_2C_6H_4$	4-$H_5C_2C_6H_4$	127	363
4-$CH_3OC_6H_4$	H	4-$(CH_3)_2CHC_6H_4$	4-$(CH_3)_2CHC_6H_4$	137	363
4-$CH_3OC_6H_4$	H	4-$(CH_3)_3CC_6H_4$	4-$(CH_3)_3CC_6H_4$	171	363
4-$CH_3OC_6H_4$	H	4-$CH_3OC_6H_4$	C_6H_5	147	279, 416, 417

TABLE IV-1. (continued)

B. All others with only one ring



R^1	R^2	R^3	R^4	m.p. (°C)	Refs.
4-$CH_3OC_6H_4$	H	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	124	279, 364
NO_2	H	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	169	362
NO_2	H	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	163	362
H_5C_2OOC	H	3,5-$Cl_2C_6H_3$	3,5-$Cl_2C_6H_3$	158	360
H_5C_2OOC	CH_3	3,5-$Cl_2C_6H_3$	3,5-$Cl_2C_6H_3$	121	51

C. Oligoverdazyls

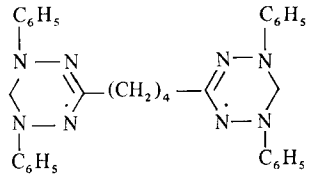
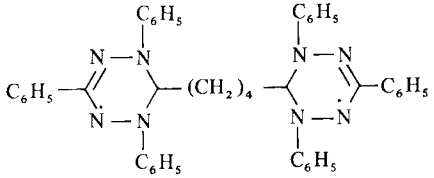
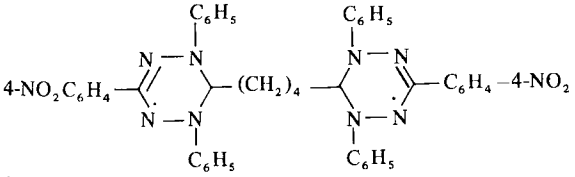
Compounds	m.p. (°C)	Refs.
	137	274
2 $FeCl_4$ salt	115	274
	192, 204	274, 275
2 $FeCl_4$ salt	171	274
$(ClO_4)_2$ salt	157	274
	226	362

TABLE IV-1. (continued)

C. Oligoverdazyls

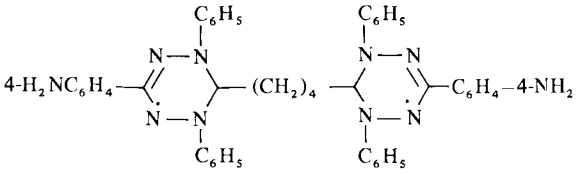
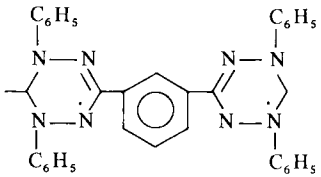
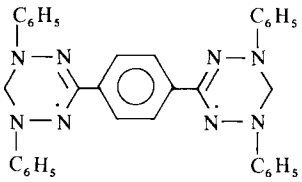
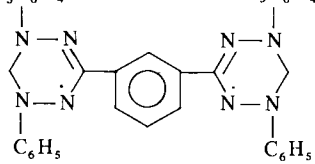
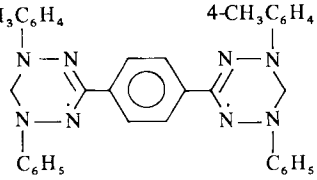
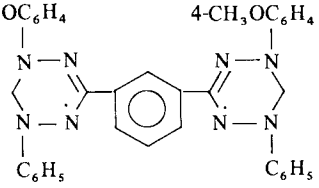
Compounds	m.p. (°C)	Refs.
	158	362
	184	269, 274
$2\ FeCl_4$ salt	181	274
Br_2 salt	143	274
	195	269, 274
$FeCl_4$ salt	171	274
[c] 4-$CH_3C_6H_4$ 4-$CH_3C_6H_4$ 	163	274
[c] 4-$CH_3C_6H_4$ 4-$CH_3C_6H_4$ 	164	274
[c] 4-$CH_3OC_6H_4$ 4-$CH_3OC_6H_4$ 	131	274

TABLE IV-1. (continued)

C. Oligoverdazyls

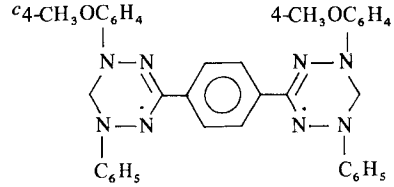
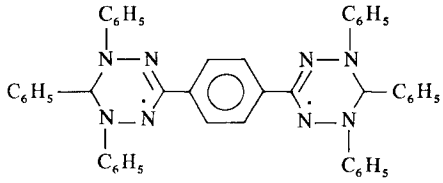
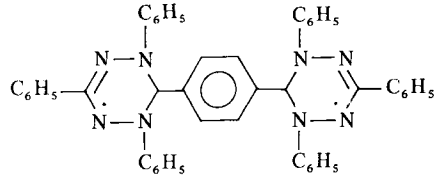
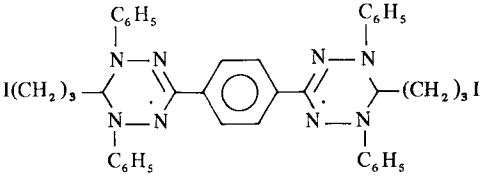
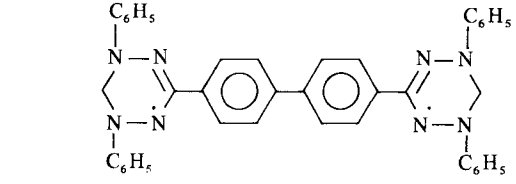
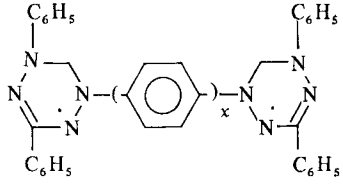
Compounds	m.p. (°C)	Refs.
	157	274
	183	283
	135	283
	–	283
	193	274
2 $FeCl_4$ salt	159	274
		

TABLE IV-1. (continued)

C. Oligoverdazyls

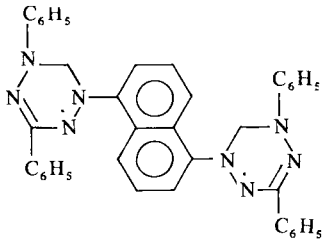
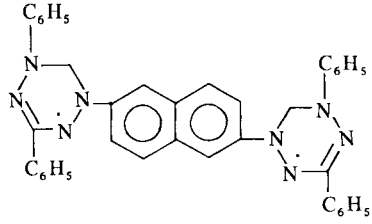
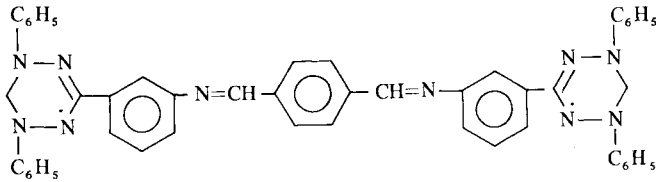
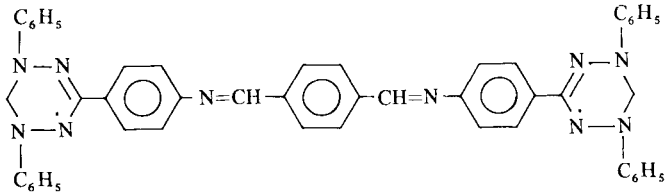
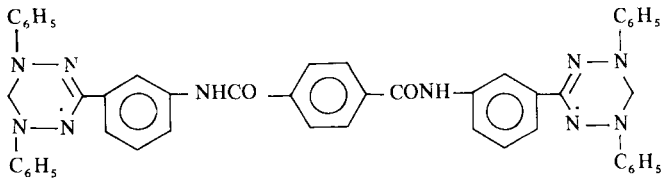
Compounds	m.p. (°C)	Refs.
$x = 2$	193	274, 370
$x = 3$	–	370
$x = 4$	–	370
	–	370
	–	370
	179	362
	221	362
	180	362

TABLE IV-1. (continued)

C. Oligoverdazyls

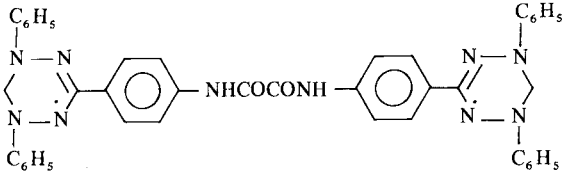
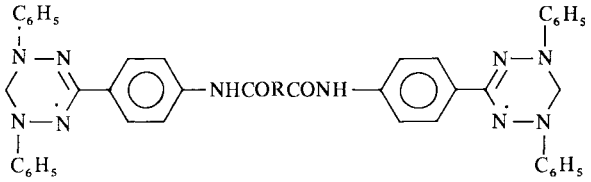
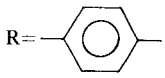
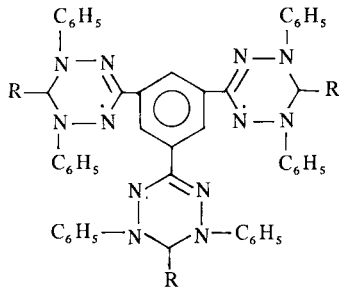
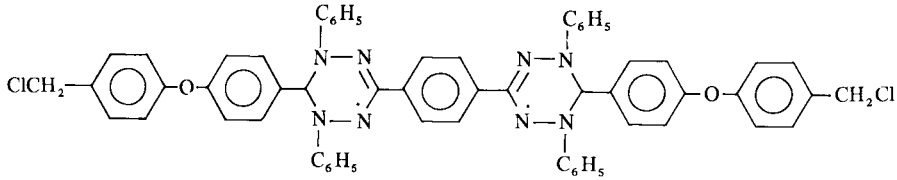
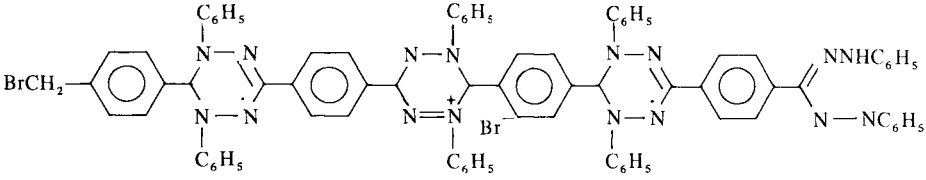
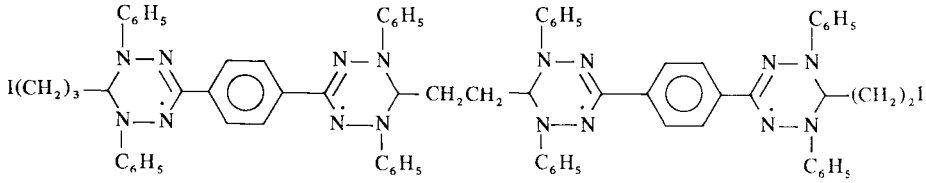
Compounds	m.p. (°C)	Refs.
	224	362
		
$R = (CH_2)_2$	183	362
$R = (CH_2)_4$	204	362
$R = (CH_2)_6$	182	362
	168	362
		
R = H	242 (dec.)	263, 272, 274
$R = CH_3$	279	274
$R = C_6H_5CH_2$	220	274
	--	283

TABLE IV-1. (continued)

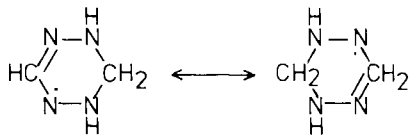
C. Oligoverdazyls

Compounds	m.p. (°C)	Refs.
	–	283
	–	283

[a]The phenyl groups are deuterated.

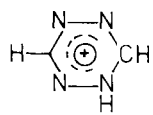
[b]Analogous compounds with deuterium replacing hydrogen at C-3 have been prepared. Melting points were 167 and 198°C.

[c]Compounds unsymmetrical at N-2 and N-4 could be the isomers having the free radical at the double bonded nitrogen or an intermediate of the two.



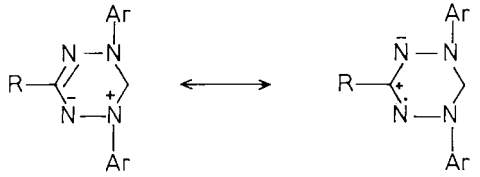
102 **103**

resonance hybrids of the degenerate canonical forms **102** and **103**. It was pointed out that the ring methylene group prevented the verdazyls from being fully aromatic, and thus their stability and ease of formation were due to other factors. Schiele and his co-workers (11, 481, 482) agreed with this representation of the structure and considered that form **104** in which the N-1 and N-5



104

atoms are completely equivalent would more truly represent the structure with verdazyl stability being a reflection of electron delocalization over a five-atom (N-2, N-1, C-6, N-5, N-4) system. On the basis of PMR studies in which it was found that the β coupling constant for protons on a methyl group was unusually high (−2.03 Gauss), suggesting a positive charge at C-6, and as a result of HMO calculations indicating substantial positive charges at N-2 and N-4, the forms **105** and **106** were suggested as resonance forms contributing strongly to the

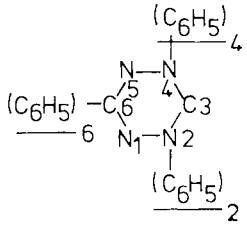


105 **106**

structure (51). In any case it was clear that no distinction could be made between the N-1 and N-5 atoms. Williams (576, 577) has determined the structure of 2,4,6-triphenylverdazyl by crystallography. It was found that the structure is very closely analogous to structure **104** with bond lengths and angles being as given in Table IV-2. The C-3 is displaced from the plane of the nitrogen atoms by 43° and C-6 is displaced by 9°. The phenyl substituents are out of the plane of the four nitrogen atoms, with the ones at N-2 and N-4 being on different sides of the ring.

The verdazyls are strongly colored compounds, as is to be expected for free radicals, being usually described as deep green, blue-black, or black. The ultraviolet spectra show a number of maxima from as low as 240 nm up to about 400 nm. A series of 2,4-diphenyl-6-arylverdazyls normally shows the strongest absorption at about 280 nm with ϵ being 20,000 to 30,000 (481, 482). When the aryl group at C-6 is replaced by an alkyl group, the strongest maximum is at about 350 nm with the ϵ value being 10,000 to 15,000 (361). All verdazyls show a strong maximum in the visible at 670 to 750 nm (ϵ = 3,500 to 10,000) (270, 279, 361, 481, 482). Depending on substituents there may be maxima in the 400 to 440 nm region to as high as 527 nm (361, 481, 482). These usually have extinction coefficients of about 10,000. The infrared spectra of a number of verdazyls have been given in the literature (279, 481, 482), and some have been studied in considerable detail with the aim of correlating spectra with structure (11, 166). Bands at 3060 and 1450 cm^{-1} have been reported for the carbon–hydrogen system at C-3 (279, 481, 482). The bands appearing at 1445 to 1450 cm^{-1} have been assigned to C–N bond stretching of the C-6 atom and its attached nitrogen atoms (481, 482). A number of other bands have been reported (279). The infrared spectra give no indication that a C=N system is present.

TABLE IV-2. STRUCTURE OF 2,4,6-TRIPHENYLVERDAZYL

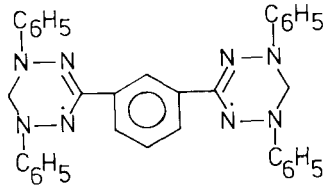


Bond	Bond length (Å)
C_6-N_1	1.34
C_6-N_5	1.33
N_1-N_2	1.35
N_4-N_5	1.37
C_3-N_2	1.45
C_3-N_4	1.43
$\underline{C_6H_5}-N_2$	1.42
$\underline{C_6H_5}-N_4$	1.42
$\underline{C_6H_5}-C_6$	1.48

Bond	Angle (°)
$\underline{C_6H_5}-C_6-N_1$	119
$\underline{C_6H_5}-C_6-N_5$	115
$C_6-N_1-N_2$	115
$C_6-N_5-N_4$	115
$C_3-N_2-N_1$	118
$C_3-N_4-N_5$	117
$N_2-C_3-N_4$	106
$\underline{C_6H_5}-N_2-N_1$	117
$\underline{C_6H_5}-N_4-N_5$	120

The free-radical nature of verdazyls is shown by their ESR spectra which are typically nine-line spectra with extensive hyperfine splitting (270, 279, 360–364). The ratio of line heights for 2,4,6-triphenylverdazyl was reported by Kuhn and Trischmann (279) to be 1:4:10:16:19:16:10:4:1. Neugebauer and collaborators (360, 361, 364) have studied the ESR spectra of a number of verdazyls with both aryl and alkyl substituents at C-6 and with various substituted aryl groups at N-2 and N-4. The effect of substituents in the aryl

groups and of the different types of substituents at C-6 on the number of lines obtained by resolution of the principal lines and on the hyperfine splitting constants (a) is substantial. In many cases g factors, which varied from 2.0030 to 2.0036, were also reported. The hyperfine splitting constants (a_N) for $a_{N_{1,5}}$ were 4.9 to 6.5 Gauss and for $a_{N_{2,4}}$ were 5.9 to 6.0 Gauss. A number of PMR spectra have been run also determining hyperfine splitting constants, but of protons, by making use of paramagnetic shifts (363, 364, 371). The ESR spectra of several compounds containing two verdazyl nuclei connected by an alkyl chain (262), by one benzene ring (262, 269, 344), or by multiaromatic ring systems (370) have been reported. In those cases such as **107** in which the verdazyls are substituted *meta* to each other on a benzene ring the normal nine-line ESR spectra with the usual a_N value were observed (269, 344), although only a single broad line was observed by Kopf and co-workers (262).

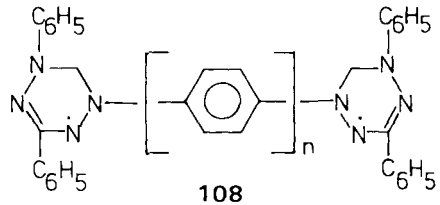


107

However, if the two verdazyl nuclei are attached *para* to each other, the ESR spectra are much more complicated indicating interaction between the two free radicals (262, 269, 344). The PMR spectra of such systems have also been reported (262) and also indicate interaction. The ESR spectra of compounds in which verdazyl nuclei are attached at opposite ends of biphenyl, terphenyl, and quaterphenyl systems (**108**) show that such compounds exist completely in the diradical form only at low temperatures (370). At ordinary temperatures an equilibrium exists between structure **108** and the ionic form **109** with the latter form predominating. Kuhn, Neugebauer, and Trischmann (272–274) reported the synthesis and ESR spectra of benzene nuclei substituted by three verdazyl rings (**110**). The ESR spectrum was interpreted as indicating that it is a triradical. In a later study (263) the ESR results were taken to indicate that the compound exists partially with the single electron spins parallel and partially with two parallel and one opposed, and thus is a monoradical.

The PMR spectra of 6-alkyl-2,4-diphenyl-verdazyls show only a single broad signal arising from methylene protons at C-3 (51). This was interpreted as indicating a slow equilibrium between structural forms having methylene above and below the plane of the four nitrogen atoms, a view that is consistent with crystallographic studies.

A number of Hückel molecular orbital calculations have been done in which various verdazyls were considered but usually 2,4,6-triphenylverdazyl (51, 154,



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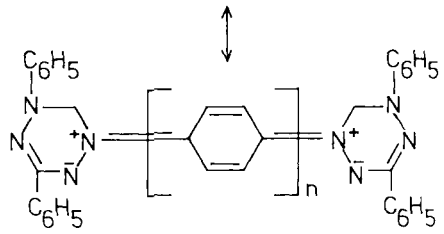

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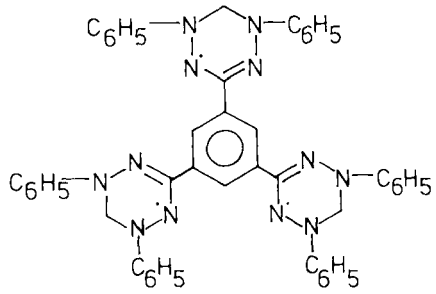


110

265). These calculations have indicated that N-2 and N-4 have an electron density of 1.52 to 1.55 with net positive charges of 0.45 to 0.48. N-1 and N-5 have an electron density of 1.48 to 1.52 and net negative charges of 0.48 to 0.52. The C-6 has an electron density of 0.81 with a net positive charge of 0.19. Bond lengths were also calculated, and the C_6-N_1 and C_6-N_5 bond lengths were found to be less than those of single C–N bonds. These calculations are in good agreement with the electron-delocalized structures such as **104** for verdazyls. Infrared spectra have also been used to study positions of electrons in verdazyls (166).

Fischer (154) has used Hückel molecular orbital calculations to find energy levels and optical transitions of verdazyls. Kopf and co-workers (262) have applied semiempirical molecular orbital (INDO) calculations to verdazyls.

The molar paramagnetic susceptibilities of verdazyls have been measured at various temperatures and have been found to approximate the linear Isinger model (273, 343). The redox potential of 2,3,4,6-tetraphenylverdazyl was

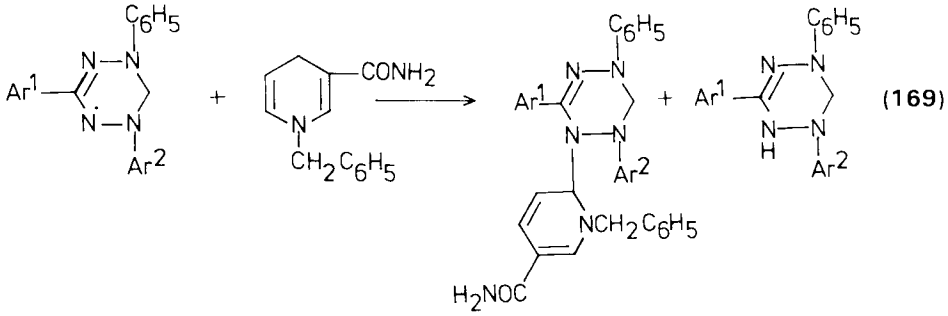
reported to lie between 0.39 and 0.45 eV (282). The dynamic nuclear polarization of verdazyls has been studied (173), as has the effect of verdazyls on the dynamic nuclear polarization of fluorine (410). Hartman, Brauer, and Schäfer (203) have related magnetic moment and atomic structure of verdazyls to specific conversion constants. Aslandi and collaborators (16) considered the mechanism of nonlinear optical absorption of 2,4,6-triphenylverdazyl.

D. Reactions

The reaction of verdazyls with mineral acids has already been discussed (eq. III-35) in the section dealing with the preparation of 1,6-dihydro-1,2,4,5-tetrazines. The products of this reaction result from reduction of one molecule of the verdazyl to give a 1,2,3,4-tetrahydro-1,2,4,5-tetrazine and oxidation of a second molecule with incorporation of the acid cation to form a verdazylium salt which is in reality a salt of a 1,6-dihydro-1,2,4,5-tetrazine (270, 274, 276, 279). Polumbrik and co-workers (412, 413, 416) have studied the kinetics and mechanism of the same reaction using organic acids instead of mineral acids. The mechanism suggested was that one molecule of verdazyl donates an electron to a second molecule which then accepts a proton from the acid. The donor molecule forms a salt with the acid anion. The products were analogous to those indicated in eq. III-35. 3-Piperidinoverdazyls behave somewhat differently, however. Either acid or base treatment converts them back to formazans (275).

The reduction of verdazyls to 1,2,3,4-tetrahydro-1,2,4,5-tetrazines occurs readily either catalytically or chemically, and the same effect can be obtained by reaction with free radicals. These reactions have already been discussed (eq. III-65) in the section devoted to preparation of 1,2,3,4-tetrahydro-1,2,4,5-tetrazines. Catalytic hydrogenation of 3-piperidinoverdazyls removes the amine before reduction of the verdazyl ring occurs (275). The mechanism of verdazyl and verdazyl cation reduction of 1,4-dihydropyridines has been studied by Polumbrik and his co-workers (134, 414, 415, 417–419). In the case of 2,6-dimethyl-3,5-bis(carbethoxy)-1,4-dihydropyridine reduction occurred as indicated in eq. III-65 to form the corresponding 1,2,3,4-tetrahydro-1,2,4,5-tetrazine (415, 417). Using 1-benzyl-1,4-dihydronicotinamide the same type of reaction was at first reported (419), but later the same reaction was claimed to give two products, the tetrahydro compound and compounds incorporating the pyridine ring (**111**, eq. IV-6) (417).

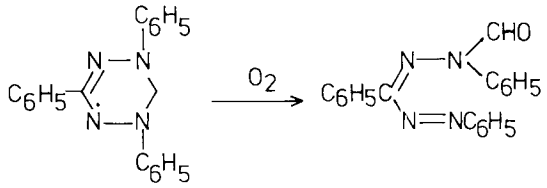
If any products were isolated, there was no mention of it. Miura and co-workers (337a) effected a formal reduction of verdazyls by treating them with alkyllithium compounds or Grignard reagents to give conversion to 1,2,3,4-tetrahydro-1,2,4,5-tetrazines with alkyl or arylalkyl groups at N-1 (eq. III-67).



(169)

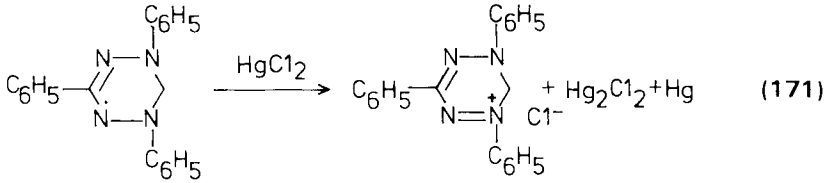
111

Oxidation of a verdazyl with oxygen catalyzed by activated charcoal converted the verdazyl back to a formazan (eq. IV-7) (277). Oxidation with lead dioxide has been discussed. It led only to oxidation of a tetrazolyl group on N-4 and not to oxidation of the verdazyl system (501). Electrolytic oxidation converts verdazyls to the 1,6-dihydroverdazylium salts (269, 274).



(170)

Verdazyls react with halogens (270, 279) and metallic halides (274, 276) to give salts of 1,6-dihydro-1,2,4,5-tetrazines (verdazylium salts) as shown in eq. III-35. The reaction with metallic halides has already been discussed. The halogen reactions occur by oxidation of verdazyls to the dihydro-1,2,4,5-tetrazine stage (**31**) and reduction of the halogens to anions. A somewhat similar reaction occurs with mercuric chloride (eq. IV-8) in that an onium salt such as **31** is formed, but the mercuric ion is reduced (132). Reaction with Lewis acids



(171)

such as aluminum chloride and boron trifluoride also gives rise to a salt, but the metallic halide remains as a free radical with only two halogen atoms ($\cdot MX_2$) (133).

Thermal degradation of verdazyls forms several products depending on the

temperature (279, 368). At lower temperatures 2,4,6-triphenylverdazyl forms 1,3-diphenyl-5-anilino-1*H*-1,2,4-triazole and 2,4,6-triphenyl-1,2,3,4-tetrahydro-1,2,4,5-tetrazine. At a temperature of 200°C the products were the same triazole, 1,3-diphenyl-1*H*-1,2,4-triazole, and aniline (368).

Functional groups in aromatic rings attached to verdazyl nuclei apparently react normally. A 3-nitrophenyl substituent has been reduced catalytically to an amine without verdazyl reduction, and the amino group was then acylated (335).

Polymerization of olefins initiated by free radicals is inhibited by verdazyls (247, 249, 338). Presumably the verdazyls react with the free radical initiators.

III. VERDAZYLS SUBSTITUTED BY NITRO GROUPS AND DERIVATIVES OF CARBOXYL GROUPS

Only a few verdazyls are known in which nitro groups are substituents, and all of them have the nitro group at C-6 with the usual aromatic groups at N-2 and N-4 (362). A few more are known having carbethoxy substituents at C-6 (51, 360). Both classes of compounds are prepared by the usual verdazyl syntheses as exemplified in eqs. IV-1 and IV-2. Their physical properties and reactions are analogous to those already discussed in the preceding section. The compounds of this type, because they are so few, are included in Table IV-1.

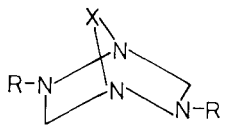
Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

V

Condensed Systems

I. CONDENSED WITH CARBOCYCLES

These condensed hexahydro-1,2,4,5-tetrazines are of two classes, bridged (**112**) and unbridged. The unbridged compounds may be of several different types. One of the two basic ones is the type **113** in which one or two rings are attached at two adjacent nitrogen atoms. The type **113** in which two rings are present is the more common, but the type having only one ring condensed with the 1,2,4,5-tetrazine ring is well known. The second basic unbridged type is as shown in **114** having rings attached at carbon and on



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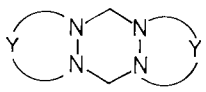
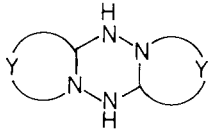


113

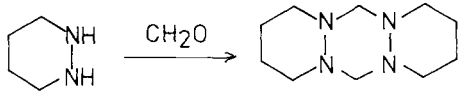


114

adjacent nitrogen atoms. In this type it is also possible to have only one ring attached. Furthermore the rings could be attached at N-1 to C-6 and N-2 to C-3 rather than to N-1 and N-4 as in **114**. The unbridged ring systems **113** are most common and are usually symmetrical as indicated. The moiety Y can be three or more carbon atoms, or it can be a polycyclic system. In the bridged cases X is usually $-CH_2-$, but it is in a few cases $-CH_2CH-$ and even other groups. Those types of **112** in which X contains oxygen are considered in the next section. The bridged system cannot strictly be considered as coming under the heading of this section, but are included for reasons of convenience. Other types of bridges (C to C or C to N) are possible but only the **116a** C to N type have been reported.

The most frequently used procedure for synthesis of condensed systems of type **113** has been the reaction of cyclic hydrazines with aldehydes, usually formaldehyde; an example of this is the condensation of piperidazine with formaldehyde (eq. V-1) to prepare 6*H*,13*H*-octahydrodipyridazino[1,2-*a*:1′2′-*d*]1,2,4,5-tetrazine (**115**) (235, 444, 445, 515). A series of aliphatic

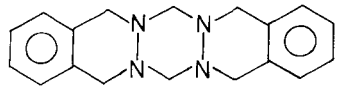
aldehydes (592) and benzaldehyde (444, 445) have also been used in similar syntheses. Other hydrazines consisting of six-membered rings undergo this reaction and have been used. Among these were methyl-substituted piperidazines (515) and 1,2,3,6-tetrahydropyridazine (235, 355). Five-membered rings



(172)

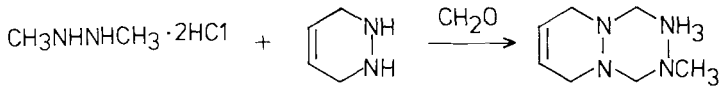
115

containing two adjacent NH groups also react to form condensed-system hexahydro-1,2,4,5-tetrazines (355, 592). 1,2,3,4-Tetrahydrophthalazine has been reported to react quantitatively with formaldehyde (129, 131, 375, 486) to form 1,2,4,5-bis(*o*-xylyl)hexahydro-1,2,4,5-tetrazine (**116**). This reaction has been suggested as a method for the quantitative determination of formaldehyde



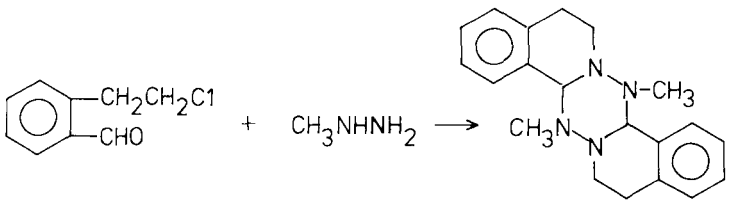
116

and also methanol which could be oxidized to formaldehyde and determined (375). Seven-membered cyclic hydrazines also have been used with formaldehyde (491). A mixture of hydrazines was condensed with formaldehyde in one instance (eq. V-2), but the yield of condensed system tetrazine was only 3.5% (235). A modification of the aldehyde procedure involves the use of an



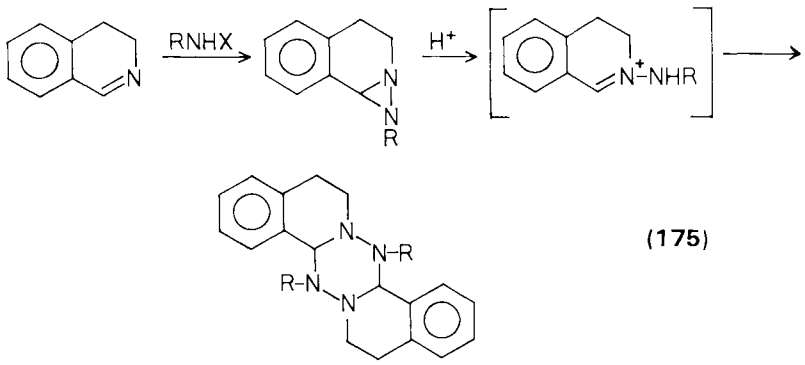
(173)

aldehyde having a second functional group which can react with a hexahydro-1,2,4,5-tetrazine initially formed to bring about cyclization to a condensed system (eq. V-3) (489). The product obtained is of the **114** type.



(174)

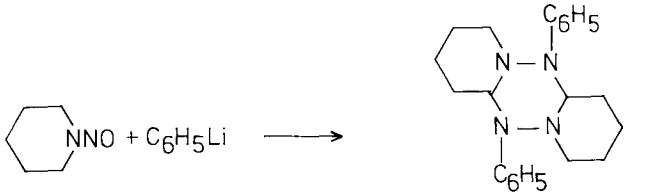
Schmitz and co-workers (484, 485, 489, 491) have dimerized quaternary salts of 3,4-dihydroisoquinolines to give condensed hexahyro-1,2,4,5-tetrazines (eq. V-4) in which the attached rings are from carbon to nitrogen (type **114**).



(175)

The starting material was 3,4-dihydroisoquinoline which, by reaction with a halogenated amine followed by acid treatment, formed a quaternary salt as an intermediate. The same type of reaction has been run using quaternary salts of quinoline (217, 377) and isoquinoline (4, 217) of the type indicated as an intermediate in eq. V-4. Yields as high as 95% have been reported. A closely related procedure for preparing such compounds is the reaction of isoquinoline methiodide with hydrazine in the presence of base (167).

Farina and Tieckelmann (151, 152) have treated nitrosamines derived from pyrrolidine and piperidine with phenyllithium and obtained cyclization to condensed hexahydro-1,2,4,5-tetrazines with loss of the elements of lithium hydroxide (eq. V-5).



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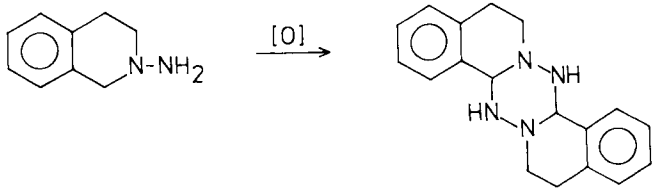

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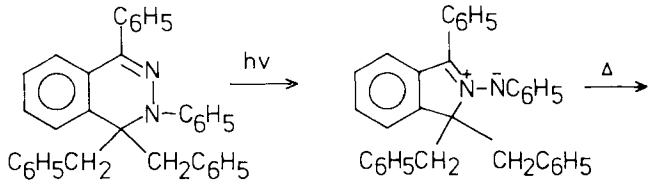
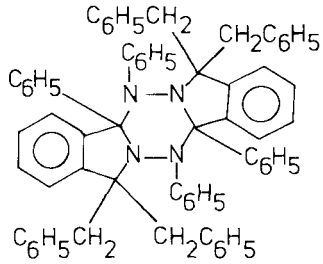
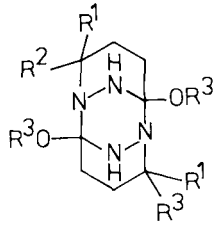




(178)

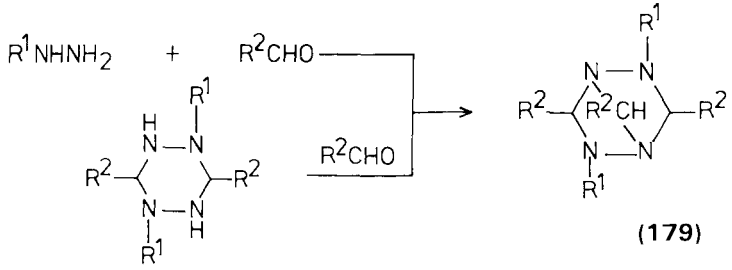
Two procedures which are probably basically 1,3-dipolar dimerizations are indicated in eqs. V-6 and V-7 (210, 509). The dimerization of 2-amino-1,2,3,4-tetrahydroisoquinoline also occurs with acid and photochemically.

Fukunishi and others (159a) have recently reported a dimerization of γ-hydroxyhydrazides to form compounds of the type **116a** in which R^1, R^2, and R^3 are H, alkyl, aryl, and aroyl.



116a

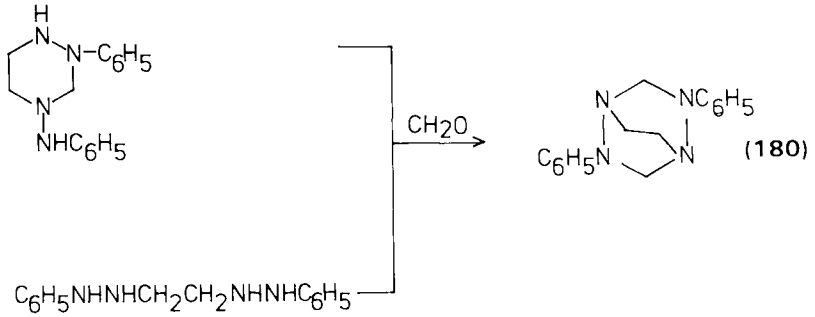
Bridged condensed hexahydro-1,2,4,5-tetrazines such as **112** have usually been prepared by reaction of hydrazines with excess formaldehyde (197, 232, 240, 490, 492) or acetaldehyde (240) or by reaction of an equivalent of formaldehyde with an already prepared hexahydro-1,2,4,5-tetrazine (eq. V-8) (355, 490). It is probable that formation of bridged compounds from the reaction of a hydrazine and an aldehyde passes through a hexahydro-1,2,4,5-tetrazine as an intermediate. Only a limited number of hydrazines have been used, but these have included alkyl, arylalkyl, and aromatic compounds.



(179)

Dimerization of hydrazones of formaldehyde (eq. III-86) in the presence of acetic anhydride (286) or in the presence of acetic acid and formaldehyde (231, 232) forms bridged compounds (**112**, X = CH_2). Some formaldehyde must be liberated in those reactions in which no formaldehyde was added. It has been suggested (232) that the first product is a hexahydro-1,2,4,5-tetrazine. Bridged compounds in which the bridge is methylene are named as 2,5-endomethanohexahydro-1,2,4,5-tetrazines or as derivatives of 1,2,4,5-tetrazabicylo[2.2.1]heptane.

Two procedures have been reported by Schmitz and Ohme (490, 492) to give bridged systems in which the bridge is $-CH_2CH_2-$. These are shown in eq. V-9. In

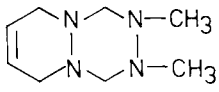


(180)

both instances the hydrazine moieties are first linked by what will later be the bridge, and the hexahydro-1,2,4,5-tetrazine rings are then formed.

Condensed hexahydro-1,2,4,5-tetrazines are colorless compounds for the most part which are soluble in organic solvents. Most of them are fairly high-melting solids, although a few are high-boiling liquids. Their electronic and vibrational spectra are not characteristic of the ring system.

The conformations of the condensed hexahydro-1,2,4,5-tetrazines **115**, **117**, **118**, and **119** have been discussed extensively (234, 235, 355). Conformations were first assigned by Nelsen and Hintz (355) chiefly on the basis of PMR data. However, Jones and co-workers (234, 235) disagreed with the assignments of



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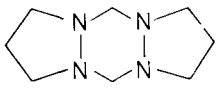

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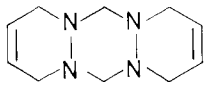
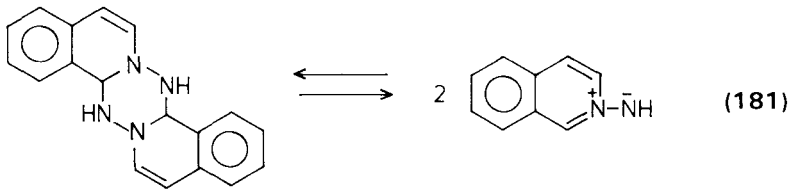


119

Nelsen and Hintz and advanced new proposals. Their proposals were also based mostly on PMR data, but vibrational spectroscopy and dipole moments were also considered. It was concluded that **117** exists to the extent of about 70% in conformation **81** and about 30% in conformation **78** (see Section III. A.3). The compound **119** was believed to be an equilibrium mixture of conformations **81**, **79**, and **80** in the ratio 7:2:1. The conformation of **115** was thought to be that

of **80** almost exclusively. The latter group did not discuss **118**, but Nelsen and Hintz proposed for it conformation **80**. Nelsen and Hintz (355) have also considered the conformations of some of the bridged compounds.

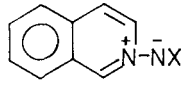
Reactions of only a few condensed hexahydro-1,2,4,5-tetrazines have been reported. In most cases reported reactions have involved cleavage of the hexahydro-1,2,4,5-tetrazine into two symmetrical halves followed by reaction with additional compounds present. It has been suggested (217) that there is normally present an equilibrium with a nitrilimine as indicated in eq. V-10 with the nitrilimine (**121**) being the reacting molecule. Compound **120** reacts with bromocyanogen to give **122** (4), phenylisocyanate to form **123** (4), phenyliso-

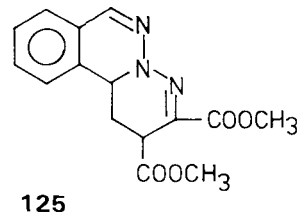


(181)

120 **121**

thiocyanate to give **124** (4), and dimethyl acetylenedicarboxylate to form the tricyclic compound **125** (217). A very similar reaction occurs with acid (eq. V-11) (489). Quite similar reactions also occur with condensed hexahydro-1,2,4,5-tetrazines derived from quinoline (217, 377). The analogue of **125** is



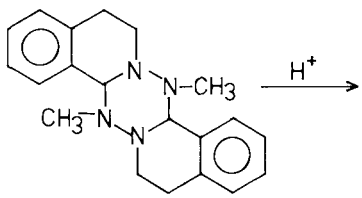


125

122 X = CN

123 X = C_6H_5NHCO

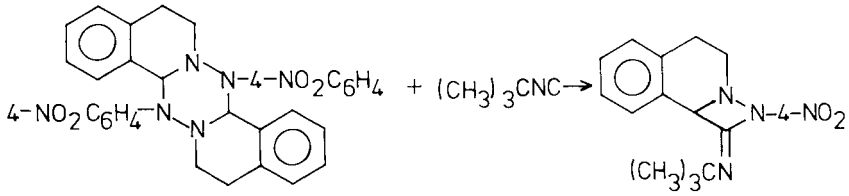
124 X = C_6H_5NHCS



(182)

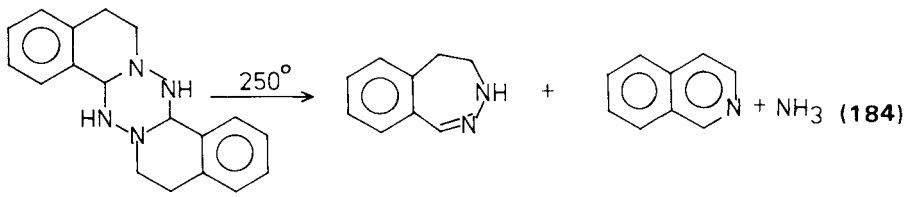
formed with dimethyl acetylenedicarboxlate, an acid reaction as shown in eq. V-11 occurs, and products similar to **122**, **123**, and **124** are formed by the action of acetic anhydride.

A reaction presumably involving a similar nitrilimine intermediate has been reported (eq. V-12) by Deyrup (125) with the suggestion that it may be an example of a (3 + 1) chelotropic addition. However, it is not certain that the reaction is concerted.



(183)

Schmitz (485) has reported that thermal decomposition of a condensed hexahydro-1,2,4,5-tetrazine resulted in formation of a diaziridine. Subsequently it was found (491) that the products were ammonia, isoquinoline, and 3,4-dihydro-5*H*-2,3-benzodiazepine (eq. V-13).

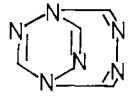


(184)

II. CONDENSED WITH HETEROCYCLES

Condensed hydro-1,2,4,5-tetrazine systems in which two or more of the ring systems are heterocyclic are derived from 1,2-dihydro-, 1,6-dihydro-, and hexahydro-1,2,4,5-tetrazines. Those derived from the hexahydro compounds can be bridged (**112**, X = COC) or unbridged of the type **113**, in which Y is either –C–N–N–C– or –C–O–O–C–. Again the bridged compounds do not fit well in this section but are included for convenience.

The earliest reported condensed 1,2,4,5-tetrazine was a compound prepared by heating formylhydrazide at 180°C (394). It was called *diazodimethine-tetrazoline* and was a colorless crystalline compound, m.p. 263°C. Analysis and hydrolysis to formic acid, hydrazine, and 4-amino-4*H*-1,2,4-triazole led to the proposal that it had either structure **126** or **127**. However, there is insufficient evidence to establish that the compound has either structure.



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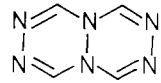
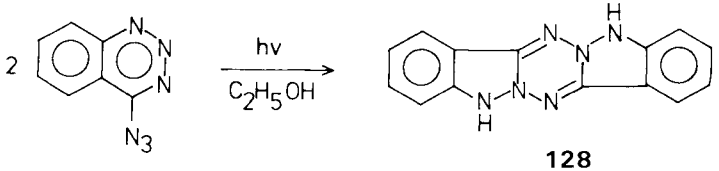


127

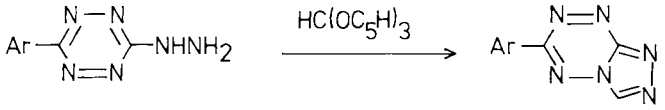
Only one condensed 1,2-dihydro-1,2,4,5-tetrazine is known (48). It was prepared by treatment of 3,6-bis(2-aminophenyl)-1,2-dihydro-1,2,4,5-tetrazine with ethyl orthoformate (eq. III-4). Stanovnik and Tišler (524) have reported that irradiation of an ethanolic solution of 4-azido-1,2,3-benzo triazine at 350 nm forms the condensed 1,4-dihydro-1,2,4,5-tetrazine **128** (eq. V-14). Analysis, infrared spectrum, and mass spectrum were the evidence for the structure **128**.



(185)

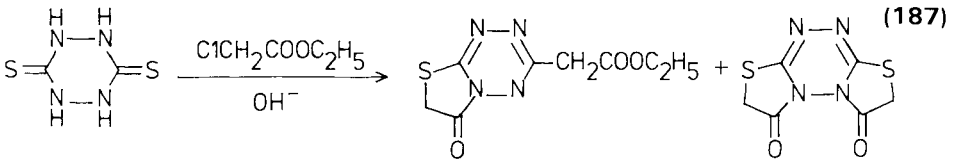
128

Ershov and Postovskii (142, 144) have prepared 1,6-dihydro-1,2,4,5-tetrazines fused with nitrogen containing rings. In both procedures reported the starting material was 6-aryl-3-hydrazino-1,2,4,5-tetrazine. Treatment with ethyl orthoformate gave a fused pyrazolo system (eq. V-15) and conversion to an azide resulted in formation of 6-aryl-*s*-triazolo[4,3-*b*]-1,2,4,5-tetrazine (**17**, eq. II-45). The azide apparently exists in equilibrium with the triazolotetrazine system.



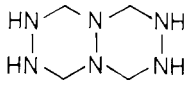
(186)

Alkylation of hexahydro-1,2,4,5-tetrazine-3,6-dithione with ethyl chloroacetate in the presence of base forms, in addition to the 3,6-dimercapto-1,2-dihydro-1,2,4,5-tetrazine, two condensed ring compounds (eq. V-16) (467).

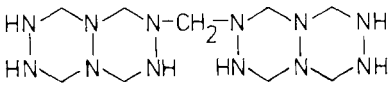


(187)

The reaction of formaldehyde with hydrazine under a variety of conditions leads to a number of condensed hexahydro-1,2,4,5-tetrazines and polymers which in one case appear to have hexahydro-1,2,4,5-tetrazine units. Hofmann

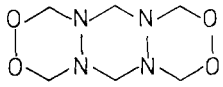


129



130

and Storm (209) have prepared a product called tetraformaltrisazine (**129**) by reaction of hydrazine hydrate with formalin. The systematic name for this compound is octahydro-1,2,4,5-tetrazino[1,2-*a*] 1,2,4,5-tetrazine. Mashima (317) prepared the same compound by addition of formalin to excess hydrazine hydrate with cooling and investigated its structure further. Under very similar conditions, but with an excess of formaldehyde, a product called methylenebis(tetraformaltrisazine) having structure **130** was obtained (339). The reaction of formaldehyde with hydrazine sulfate in the presence of hydrogen peroxide was reported by Girsewald and Siegens (171), and an incorrect structure was proposed for the product. It was later shown by Schmitz and collaborators (486–488) that the product was a condensed hexahydro-1,2,4,5-tetrazine peroxide having the structure **131**. The same product was obtained by



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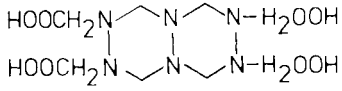
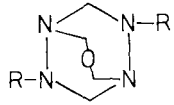


132

addition of tetraformaltrisazine (**129**) in an aqueous solution to a buffered solution of formaldehyde and hydrogen peroxide (488). However, the addition of the solid dihydrate of **129** gave the compound **132** which explodes upon heating and is readily decomposed by base. Yields of these condensed systems are quite good.

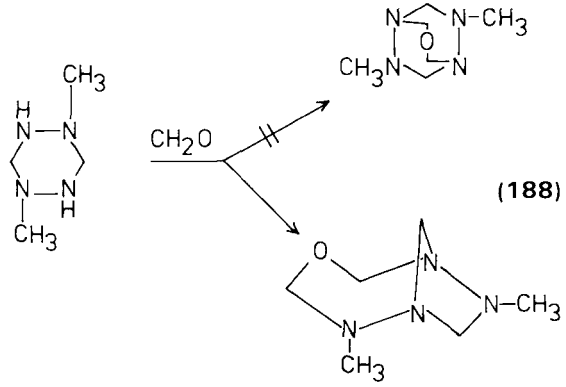
A few condensed hexahydro-1,2,4,5-tetrazines having *endo* bridged systems containing hetero atoms and conforming to the type **133** have been prepared.



133

Such compounds have been synthesized by reaction of a large excess of formaldehyde with 1,4-disubstituted hexahydro-1,2,4,5-tetrazines (490, 492). This reaction is very similar to the one (eq. V-8) used to prepare analogous compounds with methano bridges. Another method of preparation is the reaction of arylhydrazones of formaldehyde with formaldehyde in acetic acid or water at 100°C (231, 232). The latter process gives very poor yields. Hammerum (197) has proposed that treatment of 1,4-dimethylhexahydro-1,2,4,5-tetrazine

with formaldehyde results in the bicyclo compound indicated in eq. V-17 rather than the compound of type **133** as proposed by Schmitz and Ohme (492). This suggestion was based on the indication by the NMR spectrum of the product that the methyl groups are not equivalent.



(188)

III. COMPOUND SURVEY

The condensed 1,2,4,5-tetrazines reported in the literature are listed in Table V-1.

TABLE V-1. CONDENSED 1,2,4,5-TETRAZINES

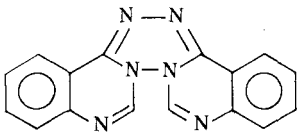
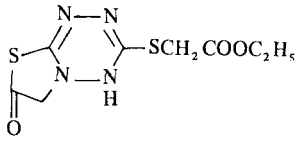
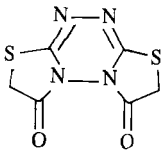
Compound	m.p. (°C)	Refs.
1. *1,2-Dihydro*		
	300	48
	123	467
	>300	467

TABLE V-1. (continued)

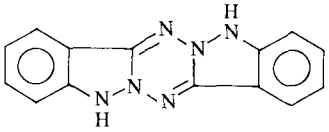
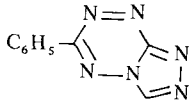
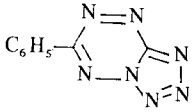
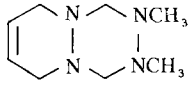
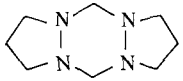
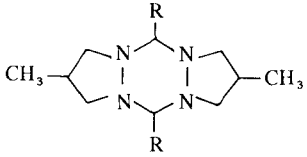
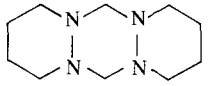
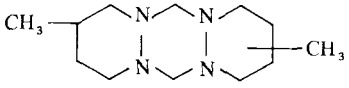
Compound	m.p. (°C)	Refs.
2. *1,4-Dihydro*		
	320	524
3. *1,6-Dihydro*		
	229	142
	–	144
4. *Hexahydro*		
	83	235
	131	355
		
R = C_2H_5	51/11	592
R = C_3H_7	35/1.5	592
R = $(CH_3)_2CH$	54/10	592
R = $(CH_3)_3C$	60/11	592
	170	235, 444, 445, 515
	188	515

TABLE V-1. (continued)

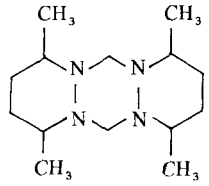
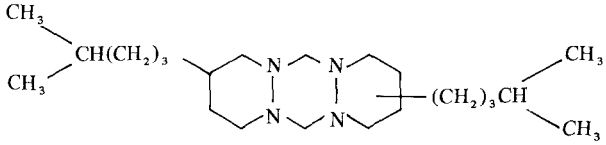
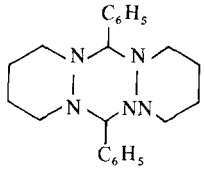
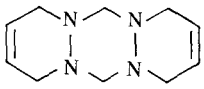
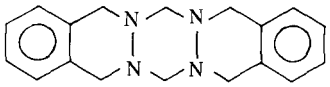
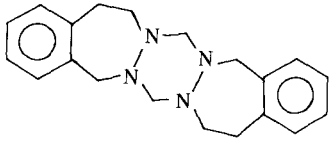
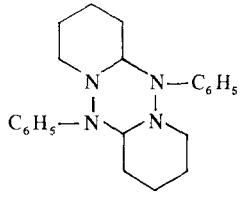
Compound	m.p. (°C)	Refs.
	132	515
	174	515
	245	444, 445
	151	235, 355
	265 (dec.)	129, 131, 375, 486, 488
	241	491
	151	151, 152

TABLE V-1. (continued)

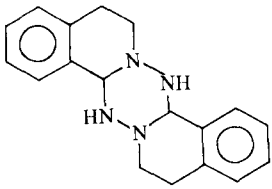
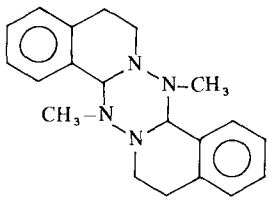
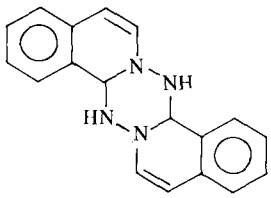
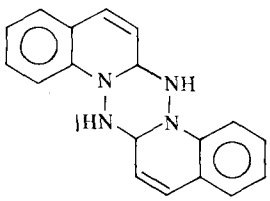
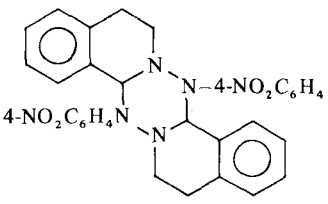
Compound	m.p. (°C)	Refs.
	249.5	210, 484, 491
	226	485, 489
	147	4, 217, 552
Picrate	182 (dec.)	552
HI salt	177 (dec.)	552
	155 (dec.)	167, 217, 377
Picrate	182 (dec.)	377
	–	125

TABLE V-1. (continued)

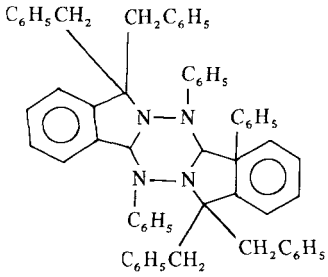
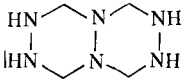
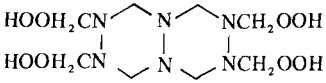
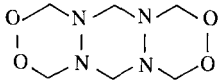
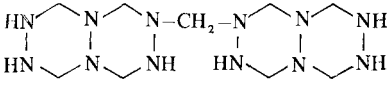
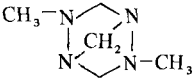
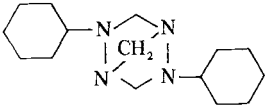
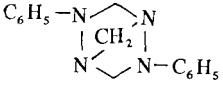
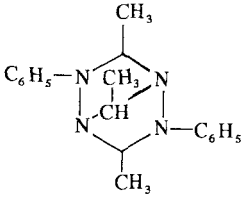
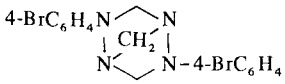
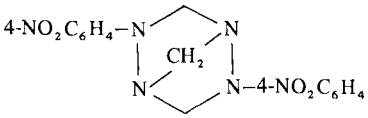
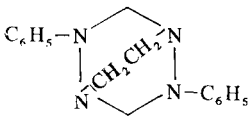
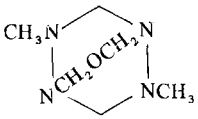
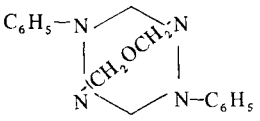
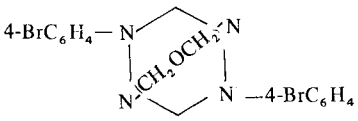
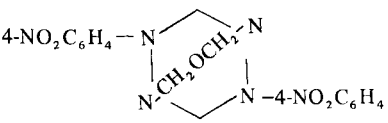
Compound	m.p. (°C)	Refs.
	235	509
	225	135, 209, 317, 339, 358, 488
	100 (expl.)	488
	–	171, 486–488
	285	339
	b.p. 86/25	355
	138	197, 492
	186	232, 240, 286, 490
	104	240

TABLE V-1. (continued)

Compound	m.p. (°C)	Refs.
	240	232
	269	231, 286
	144	490, 492
	b.p. 79/13	492
	139	232, 490
	204	232
	225	231

[a]Hammerum (197) suggests a different structure.

Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

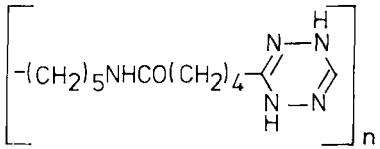
VI

Polymers

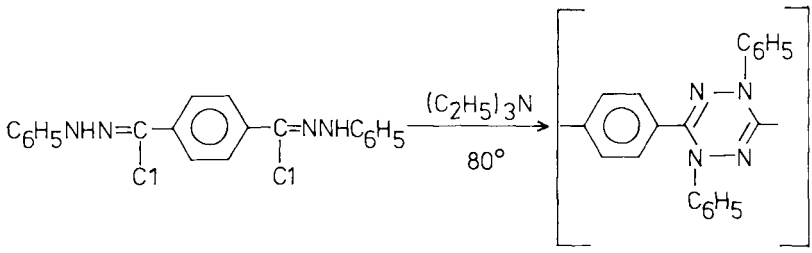
Several polymeric systems containing 1,2,4,5-tetrazine, 1,2-dihydro-1,2,4,5-tetrazine, 1,4-dihydro-1,2,4,5-tetrazine, verdazyl and hexahydro-1,2,4,5-tetrazine rings have been prepared. These polymers, with the exception of the ones containing verdazyl rings, are all the condensation type, and some of the verdazyl polymers were prepared by condensation.

Only a few 1,2-dihydro-1,2,4,5-tetrazine polymers have been prepared (264). The procedure used was condensation of a dinitrile with hydrazine as in eq. III-1. The groups connecting the 1,2-dihydro-1,2,4,5-tetrazine rings were spiro acetals or polymethylene units. The resulting polymer was then oxidized with nitrous acid to give polymers containing 1,2,4,5-tetrazine units. Polyamides containing 1,2,4,5-tetrazine rings prepared by reaction of 3,6-diamino-1,2,4,5-tetrazine with dicarboxylic acids have been reported (261). A number of polymers containing 1,4-dihydro-1,2,4,5-tetrazines have been prepared. A commonly used procedure has been condensation of 3,6-bis(aminoalkyl)-1,4-dihydro-1,2,4,5-tetrazines with dicarboxylic acids (380) and their esters (383) under relatively high temperatures. The conditions used bring about considerable rearrangement of the 1,4-dihydro-1,2,4,5-tetrazine rings to 4-amino-4*H*-1,2,4-triazoles. A somewhat similar procedure has been used by Honda and coworkers (213), but the hydrazine was condensed with a dicarboxylic acid (eq. VI-1) and the 1,4-dihydro-1,2,4,5-tetrazine ring is formed in the process. The procedures already mentioned form polymers with fairly lengthy connecting units between the tetrazine rings. Stille and Harris (529, 530) have used the nitrilimine condensation process (eq. III-24) with difunctional aromatic systems to give polymers whose units are a benzene ring attached to a 1,4-dihydro-1,2,4,5-tetrazine (eq. VI-2).

$$HOOC(CH_2)_5NHCO(CH_2)_4COOH + H_2NNH_2 \cdot H_2O \longrightarrow$$



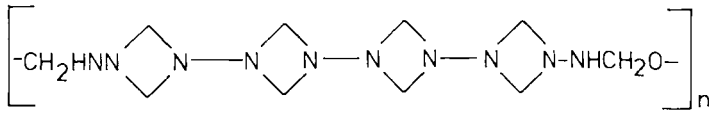
(189)



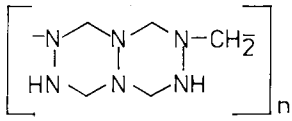
(190)

Polymeric verdazyls have been prepared by two variants of the standard procedure for preparing verdazyls (eq. IV-1). In one process polymeric 4-vinylbenzaldehyde was converted to a polymeric formazan by reaction with an aromatic hydrazine followed by reaction of the resulting hydrazone with a diazonium salt. The polymeric formazan was converted to a verdazyl-containing polymer by reaction with methyl iodide and cyclization with base (248). The final polymer contained approximately one verdazyl ring for each two units of the original polymer. The reverse method for obtaining verdazyl polymers has also been utilized. A chloromethylated polystyrene was allowed to react with 1,3,5-triphenylformazan to give polymers containing verdazyl units (282). Kinoshita and collaborators (248, 336) were unsuccessful in their first attempts to polymerize 2,4-diphenyl-6-(4-vinylphenyl)verdazyl but subsequently achieved success using *n*-butyllithium or sodium naphthalenes as the condensing catalyst. Polymers of approximately 2800 molecular weight were obtained. Copolymers with styrene and methyl methacrylate were also prepared. All these polymers contained about 63% free radical per polymeric unit. Verdazyl polymers were also obtained by vinyl polymerization of acrylate and methacrylate esters of 2,4-diphenyl-6-[4-(hydroxymethyl)phenyl] verdazyl, but analogous compounds containing similar esters of 2,4-diphenyl-6-(4-hydroxyphenyl)verdazyl did not polymerize (337). 2,4-Diphenyl-6-(3-maleimidophenyl)verdazyl was polymerized similarly giving a polymer containing about twelve molecules of monomer (335). Like monomeric verdazyls all these polymers are green.

Two polymers prepared from hydrazine and formaldehyde and formerly presumed to be polymeric hexahydro-1,2,4,5-tetrazines are known (317, 339, 358). The first of the two to be reported (and called formalazine) has recently been shown to have the repeating unit **134** (317). No definite structure has been claimed for the other, but because it can also be prepared by the reaction of formaldehyde with tetraformaltrisazine, it must have the structure **135** or something very similar (339).



134



135

The polymers that have been reported are listed in Table VI-1.

TABLE VI-1. POLYMERS

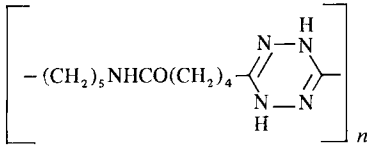
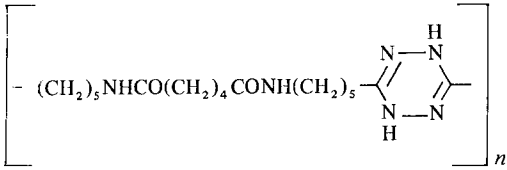
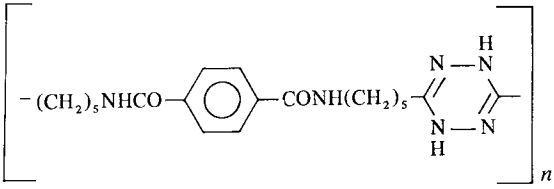
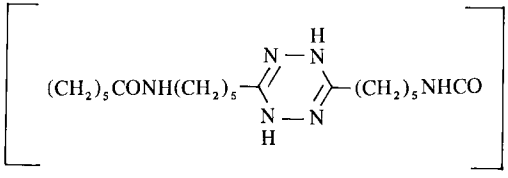
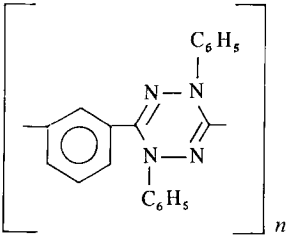
Compound	m.p. (°C)	Refs.
	91	213
	105	213
	153	213
	–	383
	–	529, 530

TABLE VI-1. (continued)

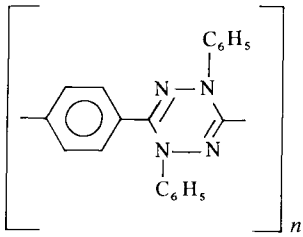
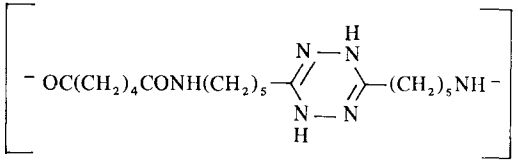
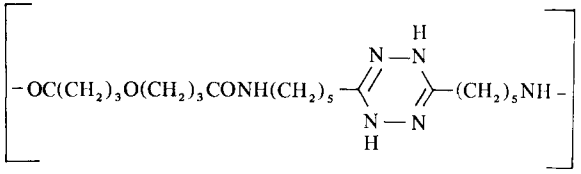
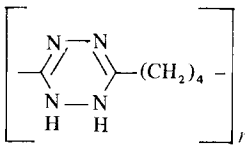
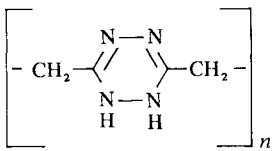
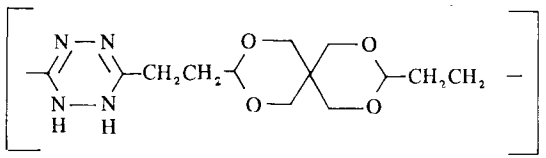
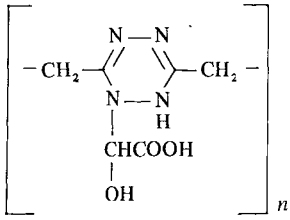
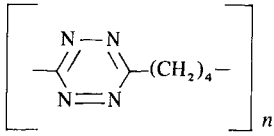
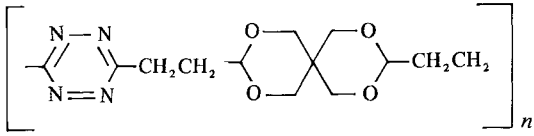
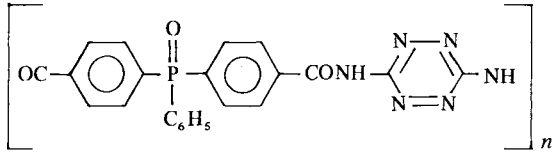
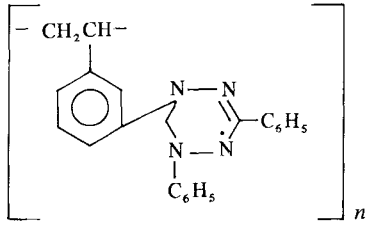
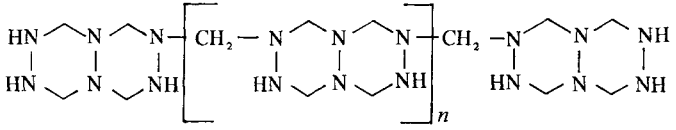
Compound	m.p. (°C)	Refs.
	–	529, 530
	–	380
	–	380
	–	259
	285 (dec.)	140
	–	264

TABLE VI-1. (continued)

Compound	m.p. (°C)	Refs.
	–	140
	145–150	259
	246–255	264
	–	261
	–	284
	–	339
Ill-defined polymers		248, 282, 335–337

Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

VII

Uses

A large number of suggested uses for 1,2,4,5-tetrazines and reduced 1,2,4,5-tetrazines have been recorded in the literature. These claims seem to have been mostly for the purpose of obtaining patents on the compounds involved, and it is doubtful that any significant uses are known. Claims for usefulness for *p*-urazine (523, 560) no doubt refer to 4-amino-1,2,4-triazolidine-3,5-dione and are not considered here. 2,4-Bis(4-methoxyphenyl)-6-phenylverdazyl has actually been used, because it is a free radical, to study the wear of knitted fabrics (475).

3,6-Diaryl-1,2,4,5-tetrazines substituted in the aromatic rings with amino-anthraquinones have been reported to be good yellow dyes (463). A number of uses have been claimed for 3-amino- and 3,6-diamino-1,2,4,5-tetrazines and their derivatives. Among these are use in treatment of salmonella and staphylococcal infections in animals (244), as herbicides (307–309), explosives (314), pharmaceuticals (314), photographic dyes (314), and photographic emulsion desensitizers (161), and for use in rocket propellants (376). Monoalkylthio- and bis(alkylthio)-1,2,4,5-tetrazines have also been reported to be effective herbicides (307–310).

1,2-Dihydro-1,2,4,5-tetrazines substituted at the 3- and 6-positions by amino, hydrazino, and 1-pyrazolonyl groups have been stated to be useful as explosives (314, 442), for conversion to polymers by reaction with aldehydes (314, 442), as pharmaceuticals (314), and as photographic dyes (314). A series of 3,6-bis(ω-aminoalkyl)-1,4-dihydro-1,2,4,5-tetrazines can be converted to polyamides which are fiber forming (381). The use of 3,6-diamino-3,6-dihydro-1,2,4,5-tetrazine as an intermediate in preparing resins has been suggested (498). Ficheroulle and Kovache (153) have considered the use of this compound as an explosive primer but concluded that it was unsuitable.

It has been proposed that 1,2,3,4-tetrahydro-1,2,4,5-tetrazin-3-one could be used as an intermediate for preparing synthetic resins, as a paper size, and to prevent shrinkage in wool or nylon (464).

1,4-Dimethylhexahydro-1,2,4,5-tetrazine has been reported to be useful as a fuel additive and as a reducing agent (221). The very similar 1,4-bis(2-phenyl-

ethyl)hexahydro-1,2,4,5-tetrazine is a monoamine oxidase inhibitor (595). 1,3,4,6-Tetrasubstituted hexahydro-1,2,4,5-tetrazines impart thermal and oxidative stability to natural rubber (465) and inhibit acid corrosion of steel (281).

Hexahydro-1,2,4,5-tetrazine-3,6-dione substituted in the 1- and 4-positions by thiophosphonate groups are insecticides and bactericides (556). It has been claimed (477) that hexahydro-1,2,4,5-tetrazine-3,6-dithione stabilizes photographic images. Friedheim (162, 163) has prepared hexahydro-1,2,4,5-tetrazines substituted at the 3- and 6-positions by aryl groups and claimed effectiveness against spirochetal and protozoal diseases.

Tetraformaltrisazine (**129**) mixed with various oxidizing agents is an effective rocket propellant (135, 339, 564, 565), as is its derivative **130** (339). Tetraformaltriasazine has also been claimed to be useful for tanning leather (334).

Polymers containing 1,2,4,5-tetrazine rings are reportedly suitable for use as pigments (259, 264). Polyamides have been prepared from 3,6-bis(ω-aminoalkyl)-1,4-dihydro-1,2,4,5-tetrazines and are transparent, spinnable, fiber-forming materials (383). 1,2,4,5-Tetrazine containing polymers in which the chain linking the 1,2,4,5-tetrazine rings contains pentavalent phosphorus are claimed to be fire and heat resistant (261).

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Other Six-Membered Nitrogen Heterocycles

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I

1,2,3,4-Tetrazines

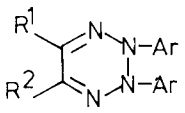
I. INTRODUCTION

The structure of 1,2,3,4-tetrazine and the numbering system used for it are indicated in **1** although, of course, the alternate Kekulé structure is possible, as is an electron-delocalized structure. At present compound **1** and its derivatives are

1

named in *Chemical Abstracts* as 1,2,3,4-tetrazines, but they were formerly named either *osotetrazines* or *v*-tetrazines. *The Ring Index* uses the name *v*-tetrazine and numbers it 177. The *Osotetrazine* name arose from the fact that compounds thought to be 1,2,3,4-tetrazines were derived by oxidation of osazones. The *v*-tetrazine nomenclature indicated that all the nitrogen atoms are neighboring. Two reviews have discussed 1,2,3,4-tetrazines (13, 29) although, as seen later in this discussion, most, if not all, of the 1,2,3,4-tetrazines reported in the literature prior to 1972 did not have the proposed tetrazine structure.

Almost all the compounds reported in the older literature as being 1,2,3,4-tetrazines fell into three classes. They were thought to be either 2.3-dihydro-1,2,3,4-tetrazines substituted at positions 2 and 3 with aryl groups (**2**) or aroyl groups (**3**), or were hydro-1,2,3,4-benzotetrazines (**4**). The compounds of type **2** were prepared by oxidation of bis(arylhydrazones) of



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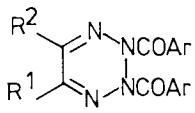

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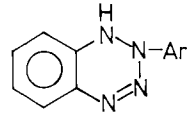
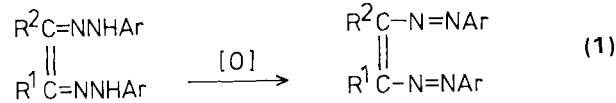


4

1,2-dicarbonyl compounds. The 2,3-diaroyl-2,3-dihydro-1,2,3,4-tetrazines (**3**) were similarly prepared from bis(aroylhydrazones).

At the time the earlier review was written, about 25 years ago, there was already considerable evidence to suggest that the course of the reaction claimed to produce compounds of structure **2** actually resulted in the formation of bis(arylazo) ethylenes (**5**) as shown in eq. I-1. The first suggestion that the products were of type **5** was made by Bucherer and Stickel (8) and indepen-

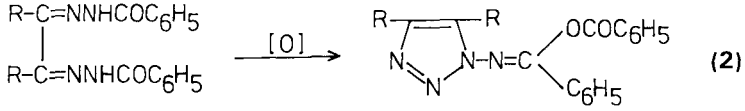


(1)

5

dently shortly thereafter by Stollé (27). The latter based his suggestion on the facts that the oxidations were reversible and that the 2,3-diaroyl-2,3-dihydro-1,2,3,4-tetrazines (**3**) are colorless, whereas the supposed 2,3-diaryl-2,3-dihydro-1,2,3,4-tetrazines are strongly colored. It was considered that these characteristics were inconsistent with structures such as **2**. Subsequently Bodforss (7) and Grammaticakis (15) studied the electronic and vibrational spectra of some of the compounds believed to be 2,3-diaryl-2,3-dihydro-1,2,3,4-tetrazines (**2**) and found that the spectra could arise only from bis(arylazo)-ethylenes (**5**) and not from the proposed structures.

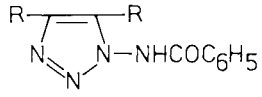
Until about 10 years ago it was generally considered that the reaction involving oxidation of bis(aroylhydrazones) of 1,2-dicarbonyl compounds formed 2,3-diaroyl-2,3-dihydro-1,2,3,4-tetrazines (**3**). However, at the time the later review (29) was written it had been shown by Curtin and Alexandrou (10) and was later developed by Alexandrou (2, 3) that the reaction (eq. I-2) actually resulted in formation of 1-amino-1*H*-1,2,3-triazoles (**6**). The proposed structure **6** was suggested on the basis of PMR spectra and infrared spectra. The former



(2)

6

indicated that the R groups were not equivalent when R = CH_3, and the latter showed a band at 1750 cm^{-1} which was interpreted as being consistent only with an ester carbonyl. The structure **6** also conforms to previously reported (27) preferential hydrolysis of one of the benzoyl groups to give the triazole **7** and thermal rearrangement to the triazole **8**. On the basis of these results it is now clear that none of the compounds prepared by oxidation of bis(aryl- or aroylhydrazones) of 1,2-dicarbonyl compounds or equivalent reactions are 1,2,3,4-tetrazines. Recent literature reports (4, 26) claiming the



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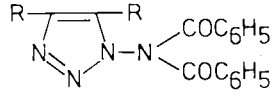
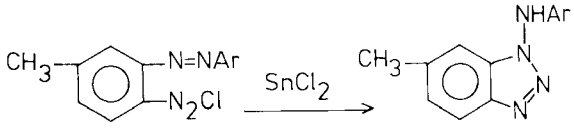


8

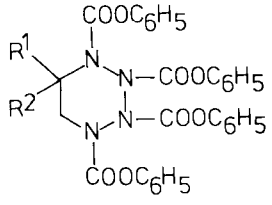
preparation of 1,2,3,4-tetrazines by such procedures must be considered with skepticism.

The preparation of hydrobenzo-1,2,3,4-tetrazines (**4**) was first reported by Zincke and Lawson (30). Synthesis was accomplished by stannous chloride reduction of 2-arylazobenzenediazonium salts (**9**). Bauer and Katritzky (5) studied the products of the reaction using infrared and ultraviolet spectroscopy. They found no indication in the infrared spectra of monoacetyl derivatives that NH was present, and the ultraviolet spectra were typical of benzotriazoles. The conclusion was reached that the reaction takes the course indicated in eq. I-3, and the products are benzotriazoles of type **10**.



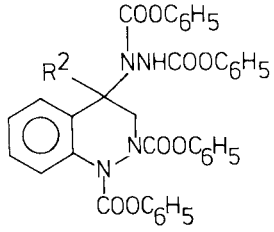
9 **10** **(3)**

Ingold and Weaver (16) found that styrene and 1,1-diphenylethylene react with diethyl azodicarboxylate in a ratio of 1 mole of hydrocarbon to 2 moles of ester and suggested a trimolecular reaction which formed a hexahydro-1,2,3,4-tetrazine (**11**). However, Alder and Niklas (1) showed that the product has structure **12** by degradation and analogy to other reactions of a similar nature.



11

$R^1=C_6H_5$; R^2=H or C_6H_5



12

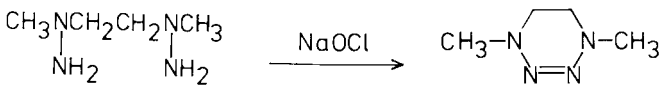
A small number of other hydro-1,2,3,4-tetrazines and fused ring 1,2,3,4-tetrazines have been reported in the literature. Because in all cases reported prior to 1972 the evidence for structure of such compounds is inadequate, and in most

cases there is considerable doubt that the reactions used for their preparation would give the structures claimed, they are not discussed further. The excellent review by Wystrach (29) can be consulted for complete information on the older literature concerning the few compounds, other that those already discussed, claimed to be 1,2,3,4-tetrazines.

II. REDUCED AND UNREDUCED 1,2,3,4-TETRAZINES

A. Synthesis

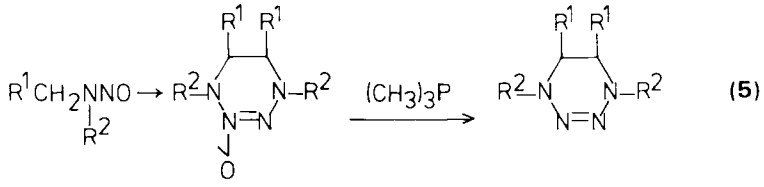
Completely unsaturated 1,2,3,4-tetrazines are unknown. As mentioned earlier a number of dihydro-1,2,3,4-tetrazines have been reported in the literature, but it is highly doubtful that any have the proposed tetrazine system present. One tetrahydro compound, 2,3-bis(2,4-dichlorophenyl)-5,6-diphenyl-1,2,3,4-tetrahydro-1,2,3,4-tetrazine, was purportedly prepared, but the proof of structure was inadequate, and it seems best to consider that the structure requires further corroboration. However, in 1972 Nelsen and Fibiger (20) published the preparation of a 1,4,5,6-tetrahydro-1,2,3,4-tetrazine, the first authentic 1,2,3,4-tetrazine. The next year three other groups of workers (17, 19, 24, 25) also reported syntheses of the same or similar compounds. One group used the same method as Nelsen and Fibiger, but two new methods were employed. The first such compound prepared was 1,4-dimethyl-1,4,5,6-tetrahydro-1,2,3,4-tetrazine (**13**), and it was synthesized by sodium hypochlorite oxidation of *N,N'*-dimethyl-*N,N'*-diaminoethylenediamine (eq. I-4) in a yield of about 4%. High-resolution mass spectroscopy and ultraviolet and infrared spectroscopy together with comparisons with the properties of 2-tetrazenes established the



(4)

13

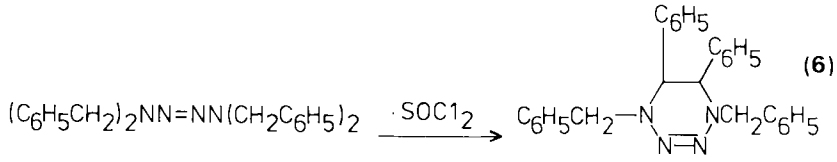
structure. A short time later Seebach and co-workers (24, 25) prepared the same compound and two other 1,4,5,6-tetrahydro-1,2,3,4-tetrazines by a markedly different synthesis. The starting point for the later synthesis was the reaction of alkylnitrosamines with lithium diisopropylamide to give the 2-oxides of 1,4,5,6-tetrahydro-1,2,3,4-tetrazines (**14**) in 30 to 45% yields. The *N*-oxides were then reduced to the corresponding tetrahydro-1,2,3,4-tetrazines quantitatively by means of trimethyl phosphite (eq. I-5). Here again such spectroscopic evidence as PMR, ultraviolet, and infrared spectra was used to establish the structures.



(5)

14

Analysis and conventional molecular weight determinations were also done. Seebach and his collaborators (24, 25) also synthesized **13** and reported properties very close to those found by Nelsen and Fibiger (20). Kreher and Wissmann (17) synthesized 1,4-diaryl-1,4,5,6-tetrahydro-1,2,3,4-tetrazines by oxidation of *N,N'*-diaminoethylenediamines with potassium hexacyanoferrate and potassium permanganate reporting yields of 10 to 59%. These workers also prepared 1,4-dicyclohexyl-1,4,5,6-tetrahydro-1,2,3,4-tetrazine and found its properties to be very similar to those reported by Seebach and others (24, 25). A third synthetic procedure, which consisted of the cyclization of 1,1,4,4-tetrabenzyl-2-tetrazene with thionyl chloride, was reported by Mataka and Anselme (19) (eq. I-6). In this case the product was a tetrasubstituted 1,4,5,6-tetrahydro-1,2,3,4-tetrazine (**15**).



(6)

15

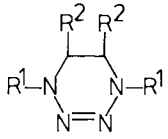
B. Compound Survey

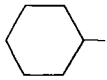
The 1,2,3,4-tetrazines and their *N*-oxides reported in the literature are given in Table I-1.

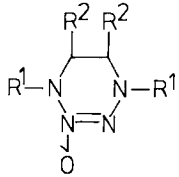
C. Physical Properties and Theoretical Considerations

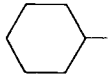
The known 1,4,5,6-tetrahydro-1,2,3,4-tetrazines are almost all colorless solids of low to medium melting point, as are their *N*-oxides. The 1,4-dialkyl-1,4,5,6-tetrahydro-1,2,3,4-tetrazines show maxima in their ultraviolet spectra at 265 to 280 nm (log ϵ 3.4 to 3.9) and at 220 to 235 nm (log ϵ 3.4 to 3.6). The 1,4-diaryl analogues show maxima at 323 to 327 nm with higher absorptivity with log ϵ for

TABLE I-1. 1,2,3,4-TETRAZINES AND SOME *N*-OXIDES



R^1	R^2	m.p. (°C)	Refs.
CH_3	H	b.p. 85/10	20, 24, 25
	H	92, 99	17, 24, 25
$-(CH_2)_4-$		67	24, 25
C_6H_5	H	176	17
$4\text{-}CH_3C_6H_4$	H	183	17
$C_6H_5CH_2$	C_6H_5	161	19



R^1	R^2	m.p. (°C)	Refs.
CH_3	H	60	24, 25
	H	83	24, 25
$-(CH_2)_4-$		79.5	24, 25

the longer wavelength being about 4.3. The *N*-oxides show a single maximum at 288 to 294 nm (log ϵ 4.08). The only infrared spectral data reported mention a 1450 cm^{-1} band for the 1,4,5,6-tetrahydro-1,2,3,4-tetrazines and bands at 1300 and 1480 cm^{-1} for their *N*-oxides. The chemical shift of the protons on the ring methylenes in the 1,4,5,6-tetrahydro-1,2,3,4-tetrazines and in the *N*-oxides tends to be about δ 3.12 to 3.3 in much the same position as signals from protons on carbons substituted at positions 1 and 4. However, the protons on methyl groups in 1,4-dimethyl-1,4,5,6-tetrahydro-1,2,3,4-tetrazine 2-oxide give signals at δ2.92 and 3.08. Protons not attached to the nitrogen atoms give their normal PMR chemical shifts. The 1,4,5,6-tetrahydro-1,2,3,4-tetrazines have mass spectra in which the most prominent ions arise by loss of a molecule of nitrogen

[$M^+ - N_2$ and $(M^+ - N_2)/2$ ions] although molecular ions were usually obtained. The *N*-oxides have a prominent peak due to the loss of an atom of oxygen from the molecular ion ($M^+ - O$).

Electrolytic oxidation of 1,4-dimethyl-1,4,5,6-tetrahydro-1,2,3,4-tetrazine (**13**) has been used to prepare the radical cation (20). The ESR spectrum was observed, and the hyperfine splitting constants were reported to be 17.5 G for the methylene hydrogen atoms. 10.5 G for the methyl hydrogen atoms, and 3.17 G for the N_2–N_3 nitrogen atoms.

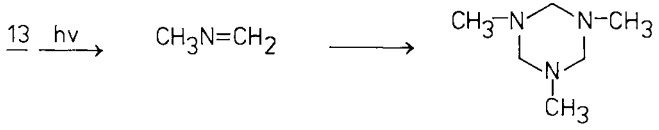
A number of authors have published various types of molecular orbital calculations applied to 1,2,3,4-tetrazine even though that compound has never been prepared. Carbo and Fraga (9) have used the AVE CI SCF MO method to calculate parameters such as ionization potentials, electron affinities, dipole moments, electron distribution, and electronic transitions. The SCF MO method was used by Dewar and Gleicher (12) to calculate the values of π-binding energies, bond lengths, resonance energies, and heat of formation. Using the same method Flurry and others (14) calculated ionization potentials and $\pi \rightarrow \pi^*$ transitions. Palmer, Gaskell, and Findlay (21, 22) used the LCGO method to calculate molecular orbital energies, total energy, and binding energy. From these values it was concluded (22) that 1,2,3,4-tetrazine probably cannot exist. Semiempirical molecular orbital calculations were made by Pukanic and collaborators (23), determining much the same parameters as have already been mentioned. de Giambiagi and Giambiagi (11) have used coulomb and exchange integrals together with the Kohlrausch nuclear effective charge to calculate electron densities, interatomic distances, dipoel moments, $n \rightarrow \pi^*$ transitions, and ionization potentials. Since there is considerable variation among values obtained for the same property depending on the type of molecular orbital calculations used, the particular variant of each type, and the approximations made, it does not seem worthwhile to list the values obtained. However, it is of interest that Dewar and Gleicher reported values for bond lengths indicating electron localization as in the structure **1** rather than as in **16** in spite of calculations indicating resonance stabilization (12, 18).

16

By a valence bond method Maccoll (18) has calculated that the electronic spectrum of 1,2,3,4-tetrazine should give a maximum at 530 nm. The chemical shifts of ^{14}N in the NMR of 1,2,3,4-tetrazine have been calculated on the basis of additivity of the 1,2, 1,3, and 1,4 interactions of nitrogen atoms (28). Black, Brown, and Heffernan (6) discussed proton chemical shifts and the ring contributions thereto as well as the diamagnetic anisotropy of 1,2,3,4-tetrazine.

D. Reactions

Nelsen and Fibiger (20) have reported that 1,4-dimethyl-1,4,5,6-tetrahydro-1,2,3,4-tetrazine is converted on irradiation to 1,3,5-trimethylhexahydro-1,3,5-triazine, presumably by way of the indicated intermediate (eq. I-7). The reduction of 1,4,5,6-tetrahydro-1,2,3,4-tetrazine *N*-oxides with trimethyl phosphite has already been mentioned (eq. I-5), as has the electrolytic oxidation of 1,4,5,6-tetrahydro-1,2,4,5-tetrazines.



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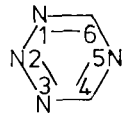
Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

II

1,2,3,5-Tetrazines

1,2,3,5-Tetrazine is a six-membered ring having three adjacent nitrogen atoms and one isolated nitrogen atom. The structure and numbering system is as indicated in **17**, although it is probable that considerable electron delocalization would occur, and the structure may not be well represented by **17**. The



17

presently used naming system in *Chemical Abstracts* is the 1,2,3,5-tetrazine system, but formerly **1** was called *as*-tetrazine. 1,2,3,5-Tetrazine is named *as*-tetrazine in *The Ring Index* and is assigned No. 178. No examples of this class of tetrazines are known. Attempts to prepare 1,2,3,5-tetrazines have been made and are discussed in a review (5) published some years ago.

Although no 1,2,3,5-tetrazines have been prepared, there have been many theoretical calculations, mostly molecular orbital, applied to 1,2,3,5-tetrazine to predict some of its properties. About 30 years ago Maccoll (7) applied relatively unsophisticated valence bond calculations to predict that the visible spectrum would exhibit a maximum at 520 nm and calculated a resonance energy of 10 kcal.

A number of publications (1–11) have used molecular orbital calculations modified in various ways such as the AVE CI SCF (2) and the VESCF (1) modification to calculate many of the parameters of 1,2,3,5-tetrazine. Such calculations determined values for electron densities on various atoms, ionization potentials, electron affinities, dipole moments, singlet and triplet electronic transitions, resonance energies, π-binding energies, bond lengths, heats of formation, π-ionization potentials, molecular orbital energies, total energies, and nonlocalized atom and bond charges. Values found for these properties mentioned are not listed because there is reason to believe that in most cases they are not very close to the actual values if these could be measured. However,

some points are worthy of mention. Palmer and collaborators (9) on the basis of LCGO calculations of total energy conclude that 1,2,3,5-tetrazine cannot exist. Dewar and Gleicher (4) have reported calculated bond lengths, and these are in agreement with considerable, if not total, electron delocalization indicating aromatic character for 1,2,3,5-tetrazine. These calculations would not be consistent with the conclusions of Palmer and co-workers.

Witanowski and others (11) have predicted the NMR chemical shifts of ^{14}N on the basis of additivities of 1,2, 1,3, and 1,4 interactions of nitrogen atoms.

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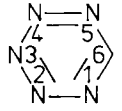
Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

III

Pentazines

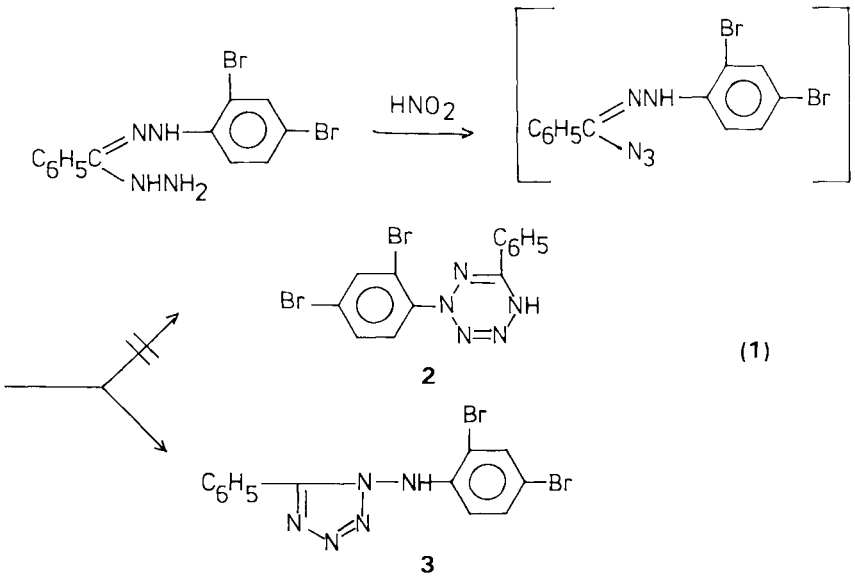
The parent compound (RI 160) of the pentazine series is shown in structure **18**. In pentazine the isomeric Kekulé form is degenerate suggesting considerable



18

electron delocalization. About 25 years ago the pentazines were reviewed (8), and in the intervening period there has been little change in knowledge of these compounds. One pentazine has been reported in the literature (4), but it proved to be a tetrazole rather than a pentazine (2). Chattaway and Parkes (4) treated the 2,4-dibromophenylhydrazone of benzhydrazide with nitrous acid and claimed to have isolated 2-(2,4-dibromophenyl)-6-phenyl-2,5-dihydropentazine (**19**, eq. III-1). The authors considered the possibility that the product might be an azide, but because heating with acetylene did not give a triazole (7), it was concluded that an azide was not present. Stollé and Helwerth (13) had run rather similar reactions and found that their products were tetrazoles. On the basis of analogy Stollé (12) challenged the structure proposed by Chattaway and Parkes. He preferred the tetrazole structure **20**. Approximately 40 years later the reaction was reinvestigated (2), and it was established that the product was **20**. The ultraviolet spectrum of **20** was so similar to that of other tetrazoles with the same type of substituents that compound **20** was necessarily a tetrazole. It was suggested that the azide intermediate indicated in eq. III-1 underwent a 1,3-dipolar internal addition to give the tetrazole. No other pentazines have ever been reported.

As with all of the parent tetrazine structures there have been a great many theoretical calculations applied to pentazine. Maccoll (9) has calculated by a valence bond method the maximum in the visible spectrum (865 nm) and the resonance energy. Witanowski and co-workers (14) have predicted ^{14}N NMR chemical shifts on the basis of additivity of 1,2, 1,3, and 1,4 nitrogen



interactions. A number of molecular orbital calculations using several variants have been made, and from them various properties of the pentazine molecule have been published (1, 3, 5, 6, 10, 11). Such parameters as electron density on the atoms, ionization potential, dipole moments, singlet and triplet electronic transitions, bond lengths, binding energies, resonance energies, heats of formation, orbital energies, and total energies have been calculated. Palmer, Gaskell, and Findlay (10, 11) used a standard Gaussian atomic orbital (LCGO) calculation to estimate total energy and concluded that pentazine could not exist. The many values reported from these calculations are not given here because it appears that they are not sufficiently reliable to make such a tabulation worthwhile.

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Chemistry of Heterocyclic Compounds, Volume 33
Hans Neunhoeffer, Paul F. Wiley

Index