PYRIDAZINES

This is the twenty-eighth 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

PYRIDAZINES

Edited by

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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 book attempts to cover all the literature references on pyridazines from the earliest references through those references appearing in *Chemical Abstracts* to mid-1971. There is some deviation in individual chapters by the different authors. Some authors have added selected references past mid-1971. We have attempted at least to list in the tables all the pyridazines known during the period covered. There are some differences in style in the different chapters, reflecting different approaches taken by the individual authors.

We trust that this volume will prove readable and useful to those engaged in research or development on the many phases of pyridazine chemistry. We also are hopeful that reading this volume may stimulate additional research in this simple heterocyclic ring system. Reference is made in this volume to very few condensed pyridazines. This forms the basis for a companion volume in this series, namely, *Condensed Pyridazines Including Cinnolines and Phthalazines*. We hope that these two volumes will be used together and serve as a starting point for research in these areas.

RAYMOND N. CASTLE

Provo, Utah
July 1972

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PYRIDAZINES

This is the twenty-eighth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

Chemistry of Heterocyclic Compounds, Volume 28
Edited by Raymond N. Castle

CHAPTER I

Physical Properties of Pyridazines

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I. Introduction

A. Historical

The pyridazine ring system is a 1,2-diazine or *o*-diazabenzene. The name pyridazine was suggested by Knorr (1), however, the first substituted pyridazines were prepared in 1886 by Fischer (2), and pyridazine itself was prepared by Taüber (3) in 1895.

Pyridazines have not been investigated as thoroughly as the other isomeric diazines because they are not known to occur in nature and are not easily produced by nitrogen biochemical transformations. Since some pyridazines have been found useful as growth inhibitors or as medicinals, the literature is expanding. For additional general information and recent reviews, see Tišler and Stanovnik (4), Ramage and Landquist (5), Druey (6), Jacobs (7), and Albert (8).

B. Structure

Pyridazine has been assumed to be a planar molecule for which two Kekulé structures (**1** and **2**) may be written.

1

2

These Kekulé forms have been shown to be nonequivalent (9, 10). In fact, the crystalline structures of several substituted pyridazines (11, 12) have been determined experimentally by x-ray crystallography, and these results indicate that the bond between the two nitrogen atoms possesses mostly single-bond character. The N—N bond distances were given as 1.3539 ± 0.0068 (11) and 1.346 ± 0.007 Å (12).

Numerous reports have been made on the various methods of calculating the N—N bond distance and bond angles in pyridazine (13–19), and most are in fair agreement with the experimental data. For example, Lofthus (14) obtained a value of 1.285 Å for the N—N bond distance in pyridazine using

the semiempirical linear combination atomic orbitals (LCAO) molecular orbital method.

Since structures **1** and **2** are not equivalent, one may consider pyridazine a resonance hybrid in which the greater contribution is made by the structure containing the =N—N= configuration. The resonance energy for the more stable form has been theoretically calculated as 22 kcal/mole by Maccole (10) and between 36.8 and 39.9 kcal/mole by Davis (20).

The conjugation energy has been experimentally determined by taking the difference between the value calculated for the heat of formation or heat of combustion of pyridazine (**1**) and the experimental value. Tjebbes (21) reported a value of 12.3 kcal/mole, and Cox (22) reported a value of $\approx$10 kcal/mole. These experimental values for the conjugation energy cannot be compared with the theoretical calculations as the amounts differ by an unknown compression energy.

An interesting note is that the calculated heat of combustion of the form **1** (N—N) was given as 1038.8 kcal/mole, whereas the less favored form **2** (N=N) had a value of 1014.6 kcal/mole (21).

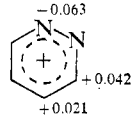
Albert (8) has suggested a framework in which the many heterocyclic compounds can be classed. First, the heterocycles are divided into heteroparaffinic, heteroethylenic, and heteroaromatic substances. The heteroaromatic substances are then subdivided on the basis of π-electron content into π-deficient heteroaromatics and π-excessive heteroaromatics. This division has been most useful in predicting reactivity of the general types.

Pyridazine is a representative of the π-deficient heteroaromatic class and has been derived from benzene by the replacement of two adjacent —CH= groups by two —N= groups. The hetero atoms attract π electrons from the ring and thus cause the other ring atoms to have partial positive charges. The nitrogen atoms are comparable to nitro groups attached to a benzene ring. In later sections the activity and properties are explained by this deficiency of π electrons. Pfleiderer (23) has also discussed the heteroaromatic character of six-membered nitrogen heterocycles in this light.

C. Theoretical Contributions to Structure

The distribution of the electrons in pyridazine has been calculated by several different methods and with various degrees of precision (8, 20, 25–55, 129).

Albert (8) has published a convenient electron distribution diagram (**3**) of pyridazine. The model was constructed from molecular orbital calculations by Brown and Coller (24) using the variable electronegativity self-consistent field (VESCF) method and uniform parameters.



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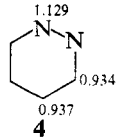
Earlier, Davies (20) had calculated charge densities in pyridazine using LCAO approximations of the molecular orbital theory. He reported two sets of values: one involving the overlap between adjacent atomic orbitals (**4**) and one without atomic orbital overlap (**5**). Good agreement with experimental data was observed. The values with overlap were similar to those reported by Chalvet and Sandorfy (25).



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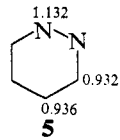

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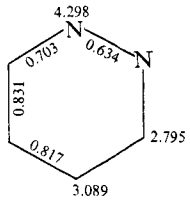
The magnitude of the charges varies somewhat with the method and parameters used. Thus the values of Brown (24) are smaller than those of Davies (20) or Chalvet and Sandorfy (25).

Other values for overpopulation and charge densities have been given by Pugmire and Grant (129) for unprotonated structure **6** and protonated structures **7** and **8**. The following diagrams give the overpopulations inside and the external charge densities (σ values).



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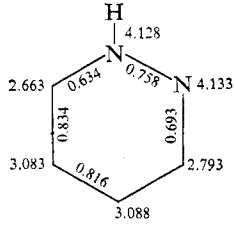

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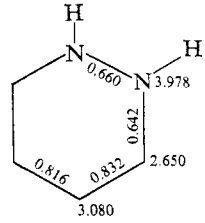

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Pyridazine has been extensively studied with respect to its electronic states, as have the other azines. A critical review has been presented by Innes, Byrne, and Ross (26). Considerable additional work has been done involving molecular orbital calculations for pyridazine using methods such as the Hückel method, EHT, CNDO, LCAO, LCAO-FE, SCMO, and so on. Yonezawa, Yamabe, and Kato (55) found that the Hückel method, which does not include direct interactions, gives an incorrect prediction for the symmetry of the energy levels of pyridazine. After comparative discussion it is concluded that the lone pairs couple with each other directly through space

as well as through bond. Many recent articles which have been often referred to and which are not discussed in other sections of this chapter are also available (27–55).

The calculation of electric dipole moments has been a problem in theoretical chemistry for a considerable period of time. Schneider (56) calculated the dipole moment for pyridazine by the vectorial sum method. Many molecular orbital calculations have also been used to determine the electric dipole moment (13, 20, 56–59). These calculated values have been shown to be in good agreement with the experimental value of 3.97 D. (62, 63).

Brown and Coller (24) made a survey of the computation of electric dipole moments of conjugated systems by the VESCF molecular orbital method. The theoretical and experimental values agreed within 0.4 D, which is notably better than most other procedures.

II. Physical Properties

A. Melting Point, Boiling Point, Density

Pyridazine, being a π-deficient heteroaromatic compound, can be compared with pyridine. At room temperature it is a colorless liquid with a pyridine-like odor and a melting point of $-8°$ C.

The boiling point has been reported as: 208° (760 mm) (3), 207.4° (762.5 mm) (20), 87° (14 mm), and 48° C (1 mm) (60). This unusually high boiling point compared to benzene (bp 80°) indicates the involvement of some type of intermolecular association. A similar situation was noted, to a lesser extent, in a comparison of benzene (bp 80°) with pyridine (bp 115°). Hückel and Jahnentz (60), using ebuliometric methods, reported that the association was due to the formation of a pyridazine dimer, while Coad, Coad, and Wilkins (61), using spectral data from ultraviolet (uv), visible, near infrared (ir), and nuclear magnetic resonance (nmr), showed a discrete dimer did not exist and concluded that the intermolecular attraction was not specific in nature and was due to the classic electrostatic forces arising from the high permanent dipole caused by the adjacent nitrogen atoms.

Some of the other physical properties of pyridazine are listed in Table I.

B. Solubility

π-Deficient nitrogen aromatic heterocycles are more readily soluble in water than their corresponding hydrocarbons because of the availability of

TABLE I. Physical Properties of Pyridazine

Density: $d_4^{20} = 1.1054$, $d_4^{23.5} = 1.1035$, $d_4^{18} = 1.107$
Index of refraction: $n_D^{23.5} = 1.52311$
Surface tension: 50.15 dynes/cm^2 at 0° C
Viscosity: $\lambda_{abs}\ 10^5 = 2049 \pm 1.8$ at 20°C
Salts:
Hydrochloride, yellow solid, mp 161–163°C
Monopicrate, yellow solid, dec. 170–175° C
Chloroaurate, yellow solid, dec. ~110° C

the lone-pair electrons on the double-bonded nitrogen atoms to form hydrogen bonds with water. Thus pyridazine is completely miscible with water and alcohol. It is also soluble in benzene and ether but insoluble in ligroin and cyclohexane.

The solubility of pyridazines containing substituents with bondable hydrogens (i.e. —OH, —SH, —NH_2) is decreased, and it appears that this increased insolubility is caused by intermolecular hydrogen bonding between the pyridazine molecules in preference to hydrogen bonding with water or a similar solvent. Blocking of the hydrogen atoms by using methyl groups causes an increase in solubility, thus supporting the above explanation.

C. Dipole Moments

Calculations of the dipole moments have been discussed in a previous section. Dipole moments have also been determined experimentally for pyridazine and many pyridazine derivatives containing chloro, methyl, carbethoxy, acetyl, and styryl groups in different positions (56, 62, 63). The magnitudes of the dipole moments showed that the two adjacent sp^2-hybridized nitrogen atoms in the pyridazine molecule possess an electron acceptor activity greater than the nitrogen in pyridine. This is reflected in the reactivity, for example, 3-chloropyridazine is easily decomposed (64), whereas 2-chloropyridine is quite stable.

The dipole moments of 3-acetylpyridazine and 3-carbethoxypyridazine indicated the predominance of the trans configuration in which the charges on the N and O atoms are furthest removed.

D. Molecular Optical Anisotropy

Bothorel et al. (65) examined the molecular optical anisotropy (γ^2) by Rayleigh depolarization diffusion for a series of heterocycles and compared

TABLE II (62, 63) Dipole Moments

Compound	μ(D)	
	Experimental	Calculated
Pyridazine	3.95	4.00
3-Methylpyridazine	3.86	3.96
4-Methylpyridazine	4.34	4.29
3-Chloropyridazine	4.42	4.24
3,6-Dichloropyridazine	4.11	3.94
3-Styrylpyridazine	5.82	
3-Acetylpyridazine	2.48	4.89[a]
		2.19[b]
3-Carbethoxypyridazine	3.33	4.34[a]
		2.30[b]

[a] Calculated allowing for free rotation
[b] Calculated trans configuration.

it to the carcinogenic activity of the compound. The introduction of a nitrogen atom into an aromatic skeleton generally decreased the molecular optical anisotropy; benzene had a higher value than pyridine. The value was higher for pyridazine (Table III). Craig and Bothorel (66) also observed this high value.

TABLE III (65, 66) Molecular Optical Anisotropy

Compound	γ^2 = Å6	Water solution (conc. M) γ^2	CCl_4 solution (conc. M) γ^2
Benzene	36.0	—	—
Pyridine	34.0	44 ± 1 (0.5–1)	34 ± 1 (0.5–1)
Pyridazine	38.0	46.5 ± 2 (0.15–0.35)	38 ± 1.5 (0.15–0.35)

E. Polarography

The polarographic reduction behavior of pyridazine has been reported by Vander Meer and Feil (67). According to their preliminary experimental results, pyridazine gave only one reduction wave. The addition of water caused the diffusion current to be increased. The $E_{1/2}$ values for the first wave were shown to correlate with the energy calculated for the lowest vacant π-molecular orbital by the Hückel molecular orbital approximation.

Millefiori (68) studied the polarographic reduction of pyridazine at different pH values and found that $E_{1/2}$ was pH-dependent. At pH 0–2.5 one

reduction curve was found, however, at pH 2.5–5.5 a second wave was present, and then at pH 8 the second wave disappeared. At pH 9.5 an interesting phenomenon was noted; the first wave split into two waves, which suggested that the reduction at this pH was occurring by a free-radical mechanism. The two earlier waves corresponded to an irreversible two-electron process.

$E_{1/2}$ values had been reported for pyridazine by Stone and Maki (141) and for pyridazine derivatives by Rogers et al. (150).

F. Gamma Radiolysis

Lahmani and Ivanoff (69) reported on the products obtained when pyridazine was irradiated in the liquid state at 25° C with a cobalt-60 γ-radiation source. The products, hydrogen, nitrogen, acetylene, and a polymer, indicated that the introduction of nitrogen into an aromatic ring increases the sensitivity toward ionizing radiation and that ring opening plays an important role in this irradiation. Photolysis (69) studies showed that pyridazine gives very different products compared with those obtained by γ irradiation. Lemal et al. (69a) found that 2,5-difluoro-3,6-dichloropyrazine was obtained by irradiation rearrangement of 3,6-difluoro-4,5-dichloropyridazine. The origin of the rearrangement is in the n, π^* singlet state.

III. Spectroscopic Properties

A. Ultraviolet Spectra

The theoretically calculated electronic spectra of pyridazine have been reported by many research groups using different methods and modifications (10, 29, 32, 83–93).

Experimentally determined ultraviolet spectra of pyridazine and many pyridazine derivatives have been reviewed and compared with benzene and the azabenzenes (70–73, 154). The electronic spectra of pyridazine in the vapor phase (74) or in solution (9, 61, 75) showed two bands: one strong band near 2460 Å (40,000 cm^{-1}) (ϵ_{max} 1300) composed of a series of rather widely spaced diffuse bands, and a weaker band, comparably sharp, near 3400 Å ($\sim$30,000 cm^{-1}) (ϵ_{max} 315). The difference in appearance of the two bands diminished when a solution was used. The long-wavelength absorption band (near 3400 Å) has been assigned to transitions due to the promotion of the nonbonding lone-pair electrons to an antibonding π orbital ($n \rightarrow \pi^*$). The band near 2500 Å has been assigned to transitions from the promotion of

a π-bonding electron to an antibonding π orbital ($\pi \rightarrow \pi^*$) (75, 76). The $n \rightarrow \pi^*$ transition is the better understood and the most extensively studied absorption band in heterocycles.

Pyridazine absorbs at longer wavelengths than its isomers. The reason appears to be that the lone-pair orbitals on the adjacent nitrogen atoms overlap appreciably, giving rise to a bonding and an antibonding lone-pair molecular orbital separated by approximately 12,000 cm^{-1}. The lowest energy transition ($n \rightarrow \pi^*$) takes place from the antibonding lone-pair molecular orbital.

A change in the solvent can cause a shift in the spectrum. In the pyridazine series the position of the $n \rightarrow \pi^*$ transition bands was shifted to shorter wavelengths on changing from a hydrocarbon to a hydroxylic solvent (77–80), which is referred to as a blue shift. This shift appeared to be due mainly to hydrogen bonding between the lone-pair nitrogen electrons and the hydroxylic solvent, which caused a greater stabilization of the ground state compared with the excited state of the molecule. This blue shift phenomenon has also been used to characterize the $n \rightarrow \pi^*$ transition from the $\pi \rightarrow \pi^*$ transition (77), as suggested by Kasha (81) and McConnell (82).

An association constant for hydrogen bonding has been obtained from uv data, and it has been shown to be in good agreement with the hydrogen association constant found by ir studies of pyridazine in ethanol (77). Launary and Wojtkowiak (80), by applying MacRae's theory, have used these frequency shifts due to solvent effects to obtain quantitatively a value for the excited-state dipole moment of pyridazine, 2.73 D.

The uv spectra of the sodium salt of the pyridazine anion in tetrahydrofuran has been reported to have two bands appearing at 28,450 cm^{-1} and 41,390 cm^{-1} (94).

The vacuum uv spectra of pyridazine vapors between 1550 and 2000 Å gave two strong diffuse systems and were correlated with the two $\pi \rightarrow \pi^*$ transitions of benzene observed in this spectral region (95).

Hochstrasser and Marzzacco (96, 97) reported the low-temperature electronic spectra of pyridazine at 4.2° K to have a relatively sharp band at 24,251 cm^{-1}, corresponding to the $3n\pi^* \leftarrow S_0$ transition. The higher-energy singlet–triplet transition was broadened to where it could not be identified. They also noted that pyridazine did not phosphoresce in spite of the short radiative half-times of their lowest triplet states.

Loustauneau and Nouchi (98) reported the absorption spectra of pyridazine in a crystalline solution at 77° K to have a primary band at 26,738 cm^{-1}.

The proton addition effect on the near uv and visible spectra was reported (99). The absorption spectra of the three diazines showed a two-step change owing to protonation, however, in the case of pyridazine the L_f bands were not shifted to longer wavelength.

An electronic field-induced spectra has been reported by Conrad (100).

The addition of substituents into the pyridazine nucleus led to shifts of the bands depending on the type and position of the group introduced. The major transfer of charge occurred when the groups were in position 4 and/or 5. Generally, the presence of an *ortho*-, *para*-, or *meta*-directing substituent tended to shift the $\pi \rightarrow \pi^*$ bands (lower-wavelength bands) toward increased wavelengths (red shift), whereas *ortho* and *para* directors (electron-releasing) shifted the $n \rightarrow \pi^*$ bands toward lower wavelengths (blue shift) and *meta* directors (electron-withdrawing) shifted the $n \rightarrow \pi^*$ bands toward longer wavelengths (red shift). The magnitude of the shifts depended mainly on the position. The behavior differences due to the direction group appeared to be caused by the π-electron system carrying an excess electronic charge in the excited state. Thus groups donating electrons tend to destabilize and electron-accepting groups tend to stabilize the system.

Das (101) theoretically calculated the shift in the longest wavelength absorption band caused by the substitution of a methyl substituent on the pyridazine ring. The calculated values showed fair agreement with experimental data.

B. Fluorescence Spectra

Early reports showed no fluorescence or luminescence spectra (102, 103); however, the fluorescence spectra of pyridazine has been reported recently in the vapor phase (104). In addition, fluorescence and excitation spectra have been reported for pyridazine in liquid and solid solutions (105–107).

Excitation spectra of pyridazine and substituted pyridazines resembled the corresponding absorption spectra in the $n \rightarrow \pi^*$ transition region, and the same blue shift phenomenon was noted with increasing polarity of the solvent (106).

The $n \leftarrow \pi^*$ fluorescence spectra of pyridazine gave a band in water at 2424 Å, in ether at 2381 Å, and in isooctane at 2353 Å. (For comparison, pyridine absorption: in water, 3358 Å; in ether, 3015 Å; in isooctane, 2974 Å.)

Solvent effects in the case of $n \leftarrow \pi^*$ fluorescence bands were clearly shown to differ from the absorption bands (106). In solvents with increasing dielectric constants, a red shift or a relatively small blue shift was shown and in hydrogen-bonding solvents there appeared to be no specific effect on the fluorescence bands. It was concluded from these results that the hydrogen bond was broken in the n, π^* singlet excited state (106).

The dipole moment of pyridazine in the excited state (n, π^*) was determined to be 1.1 D by using the frequency shifts of the absorption and

fluorescence spectra in nonhydrogen-bonding solvents. The relatively constant value of the dipole moment in the excited state in different solvents compared to the much greater difference of the dipole moment in the ground state suggested that the reorganization of the excited state arose in the π distribution.

C. Infrared and Raman Spectra

The ir spectra of a vast number of pyridazines have been given in the literature at the time the compounds were prepared. Only a few select examples are discussed here. For a comprehensive review and comparison of pyridazine with other heterocycles, Katritzky and Ambler (108) should be consulted.

The complete ir and Raman assignment of pyridazine was reported by Lord, Masterson, and Miller (28) in 1957, however, a partial assignment had been given earlier by Ito et al (109). The ir spectra of pyridazine exhibited CH stretching bands at 3043, 3075, and 3063 cm^{-1}; ring stretching at 1572, 1565, 1444, 1414, and 1283 cm^{-1}; CH in-plane bending at 1239, 1160, 1063, and 1052 cm^{-1}; ring breathing at 964 and 1009 cm^{-1}; CH out-of-plane bending at 936, 863, 760, and 696 cm^{-1}; ring in-plane bending at 619 and 664 cm^{-1} and ring out-of-plane bending at 751, 421, and 370 cm^{-1}

Raman and ir spectra of deuteriopyridazines and pyridazine have been reported by Tucci (110) and Stidham and Tucci (111).

Pyridazinones have been studied by Mason (112) and Kuraishi (113). The pyridazin-3-one showed characteristic NH stretching at 3387 cm^{-1} and carbonyl stretching at 1681 cm^{-1}. The pyridazin-4-one showed small shifts in the NH stretching band at 3430 cm^{-1} and the carbonyl stretching band at 1662 cm^{-1}.

Takahashi, Mamola, and Pleyler (114) recorded ir spectra of pyridazine in several hydrogen donor solvents to study the effect on the vibrations of the hydrogen bonds. However, no hydrogen bonds were detected for pyridazine, and the frequency shifts were comparatively small. It was noted that the band due to the hydrogen bonding (1564 cm^{-1}) could be overlapped by the band at 1572 cm^{-1}.

Dilution of pyridazine with chloroform produced an interesting phenomenon. The CH stretching band at 3057 cm^{-1} and the broad band with a shoulder at 3075 cm^{-1} of pure pyridazine changed upon dilution and the shoulder became intense, while the main peak decreased in intensity until almost undetectable. It was postulated that this could be due to the interaction between the pyridazine molecules, such as dipole–dipole interaction or possibly hydrogen bonding (114).

Low-frequency ir studies have been made on zinc, cadmium, and mercury complexes of pyridazine (115).

D. Nuclear Magnetic Resonance Spectra

The nmr spectra of pyridazine and some of its derivatives have been experimentally determined and in some cases calculated (61, 116–131). Tori and Ogata (118) reported that the nmr spectra of pyridazine consisted of two symmetrical quartets of an AAXX type; the higher part of the two quartets arose from the magnetically equivalent H-4 and H-5 protons. The chemical shifts were given as $\tau_3 = \tau_6 = 0.76$ and $\tau_4 = \tau_5 = 2.46$ Hz; the H—H coupling constants as $J_{3,4} = 4.9, J_{3,5} = 2.0, J_{3,6} = 3.5, J_{4,6} = 2.0, J_{4,5} = 8.4$, and $J_{5,6} = 4.9$ Hz; and the C—H coupling constants as $J_{C^{13}_{3 \text{ or } 6}} = 181.5$, and $J_{C^{13}_{4 \text{ or } 5}} = 168.5$ Hz.

A reinvestigation by Gil and Pinto (130, 131) of the proton coupling constants of pure liquid pyridazine gave four weak peaks, and analysis as a AA′ BB′ system gave proton coupling constants as $J_{3,4} = 5.07, J_{3,5} = 1.88$, $J_{3,6} = 1.38$, and $J_{4,5} = 8.34$ Hz. These values were in fair agreement with earlier reports (118, 119). The positive sign of $J_{3,6}$ was in accord with the approximate additivity of the nitrogen effect on the proton coupling constants of the azines. The values of $J_{3,6}$ was also found by Elvidge and Ralph (124) to be in the same range.

Substituted pyridazines have also been studied (118). 3-Methylpyridazine displayed no splitting of the methyl signal, and the coupling constants between the methyl group and ring protons were presumed very small. The spectrum was analyzed as an ABX system in which the chemical shifts were given as $\tau_4 = 2.62$, $\tau_5 = 2.60$, $\tau_6 = 0.94$, and $\tau_{CH_3} = 7.26$ Hz, and the proton coupling constants as $J_{4,6} = 1.8$, $J_{4,5} = 8.6$, and $J_{5,6} = 4.7$ Hz. In 4-methylpyridazine the methyl signal was split into a quartet, and the spectrum was analyzed as an $ABXY_3$ system in which the values for the chemical shift and for the proton coupling constants were given as $\tau_3 = 0.92$, $\tau_5 = 2.67$, $\tau_6 = 0.96$, $\tau_{CH_3} = 7.60$, $J_{3,4} \approx 0.5$, $J_{3,5} = 2.2$, $J_{3,6} = 3.0$, $J_{4,5} = 1.0$, and $J_{5,6} = 5.0$ Hz. Ohtsuru, Tori, and Watanabe (127) have suggested that the methyl substituent effect upon the signal of the *ortho* proton transmits more strongly through a C=C bond having more double-bond character than through a C=C bond with less double-bond character.

The 3-chloro derivative was similar to the 3-methyl derivative. Other pyridazine derivatives showed well-separated first-order patterns (118). Tori and Ogata (118) noted a small broadening in the peak from the protons H-3 and H-6 and stated that it results from spin coupling and nuclear quadrupole relaxation effects of the ^{14}N nucleus. Although the methyl group

or the chlorine atom showed only small shifts, a methoxy group produced large upfield shifts showing the predominant mesomeric effect since the large shifts were noted with *ortho* and *para* proton signals and not with *meta* proton signals.

Declerek et al. (122) studied 3-chloro-6-substituted pyridazines and found the $J_{4,5}$ coupling constant was dependent on the electron-releasing ability of the substituent in position 6 and paralleled the bond index $P_{4,5}$.

The spectral properties of tetrahydro-Δ^2-pyridazines (132) and of tetra- and hexahydropyridazines (133) have been reported. It was found that the spectra of 1,2,4,5-tetramethyl-1,2,3,6-tetrahydropyridazine, 1,2-dimethyl-1,2,3,6-tetrahydropyridazine, and 1,2-dideuteriomethyl-4,5-dimethyl-1,2,3,6-tetrahydropyridazine showed two distinct regions where coalescence of the peaks occurred, indicating that ring and nitrogen inversions were slow on the nmr time scale and that the barrier to ring inversion was smaller than to nitrogen inversion. The nmr spectral data for many other pyridazines have been reported, especially since many investigators are beginning to report the nmr characteristics at the time they report the preparations. Our review is not complete.

The ^{13}C magnetic shielding of pyridazine was reported as $\delta_{C_{3,6}} = 41.1$ and $\delta_{C_{4,5}} = 66.0$ ppm (123). The ^{13}C chemical shifts were shown to be critically dependent on both charge transfer features and variation in bond order parameters. Several sets of values have been given (120, 123, 129). The more recently reported values for pyridazine are: $\delta_{C^{13}_{3,6}} = -24.31$ and $\delta_{C^{13}_{4,5}} = +0.85$ ppm (129), and for the cation $\delta_{C^{13}_{3,6}} = -22.57$ ppm (120).

Elvidge and Ralph (124) found that the coupling constants were little affected by concentration and the chemical shifts were strongly concentration-dependent. The chemical shift values moved to lower fields as the concentration increased; this occurrence is in direct opposition to the shift normally encountered with aromatic compounds (134, 135).

The shifts in the nmr due to various solvents have been studied (121, 126). It was established that the shifts induced by aromatic solvents upon polar aromatic heterocycles such as pyridazine were additive. The ASIS (aromatic solvent-induced shift) values, experimental and calculated, for pyridazine and 3-methylpyridazine have been reported as: pyridazine, position 3: 0.33 ppm (expt.), 0.33 ppm (calc.); position 4: 0.98 ppm (expt.), 1.00 ppm (calc.); and 3-methylpyridazine, position 3-methyl: 0.35 ppm (expt.), 0.46 ppm (calc.); position 4 or 5: 0.82 ppm (expt.), 0.89 ppm (calc.); position 6: 0.24 ppm (expt.), 0.26 ppm (calc.) (126). The preliminary incremental solvent shift values have been reported (126) (see Table IV) and may be useful quantities for determining structures and for identifying proton resonance in similar molecules. For example, position 4 in 3-methylpyridazine contains a hydrogen atom which is affected by a *para* nitrogen, a *meta*

nitrogen, and an *ortho* methyl group. The ASIS value for this position can be obtained by adding the incremental solvent shift values: $N_{p,H} + N_{m,H} + Me_{o,H} = 0.56 + 0.44 - 0.11 = 0.89$ ppm.

TABLE IV. Incremental Solvent Shifts[126]

Nitrogen contributions (ppm):		
$N_{o,H} = -0.07$	$N_{m,H} = 0.44$	$N_{p,H} = 0.56$
$N_{o,Me} = 0.04$	$N_{m,Me} = 0.42$	$N_{p,Me} = 0.43$
Methyl contributions (ppm):		
$Me_{o,H} = -0.11$	$Me_{m,H} = -0.11$	$Me_{p,H} = -0.11$
$Me_{o,Me} = -0.01$	$Me_{m,Me} = -0.12$	$Me_{p,Me} = -0.10$

The nmr spectrum has become very useful for structure proof and identification; only a few references are cited: 3-acetylpyridazine (134), 3(2*H*)pyridazinones (135), 4,5-dihydropyridazine derivatives (136), 3-hydroxypyridazine 1-oxide and derivatives (proved predominance of the enol form tautomer) (137), 3,4,6-substituted 1,2-carbomethoxy-1,2,3,6-tetrahydropyridazine (which gave conformation equilibrium between *cis* and *trans* isomers) (138).

E. Electron Spin Resonance (Electron Paramagnetic Resonance) Spectra

The esr spectra of pyridazine anions have been observed and analyzed (139–142). Pyridazine in dimethoxyethane in low concentrations of potassium or sodium formed a colored solution which at $g = 2.0009 \pm 0.0002$ gave an esr spectra consisting of seven well-resolved lines with the intensity ratios of 1:4:8:10:8:4:1. The hyperfine splitting between each peak was about 6.05 G, with a total splitting of about 28 ± 1 G. These anion spectra were due to the interaction of the free electron with the equivalent nitrogen atoms and equivalent protons.

Word (140) assigned a coupling constant of 6.3 G to the two nitrogen atoms and a coupling constant of 6.3 G to the two protons. Later, Stone and Maki (141) obtained coupling constants for the anion of pyridazine as $N = 5.90 \pm 0.08$ G, $H = 6.47 \pm 0.08$ G, and $H = 0.16 \pm 0.01$ G. Their molecular orbital calculations indicated that the protons at the 3- and 6-positions were responsible for the 0.16 G coupling constant. Henning (142) has reported the coupling constants as position 1-N: 5.92 G; 3-H = 0 G; 4-H = 5.92 G.

F. Nuclear Quadrupole Resonance

Schempp and Bray (143, 144) have reported the nitrogen-14 nuclear quadrupole resonance (nqr) data for pyridazine. Four nqr lines were given for the resonance frequencies at: 4011.76, 3993.02, 3784.26, and 3777.73 kHz. These four lines were separated into pairs, and each pair was associated with a value of quadrupole coupling constant (5188.92 kHz) and asymmetry parameters ($n = 8.53\%$).

The nqr calculated values of the π-electron charge on nitrogen are in good agreement with values calculated by different methods (20, 29, 58).

Pyridazine had only a 0.24 electron σ-charge excess which was related to an averaging between the N—N bond and the C—N bond. This was expected since the charge density in the vicinity of the adjacent nitrogen atoms was reduced by the repulsive interaction of the lone-pair electrons.

G. Microwave Spectra

Electromagnetic radiation of pyridazine and three isotopic substituted pyridazines has given their rotational microwave spectra in the vibrational ground state (145). From the changes in rotational constants of the molecule induced by isotopic substitution, the r_s coordinates of the ring were calculated as:

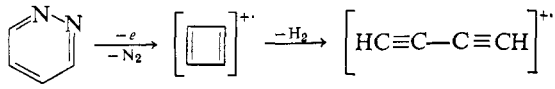
4-C (a) = 1.2277 Å	3-C	1-N (a) = 1.1830 Å
5-C (b) = 0.6871 Å	4-C (b) = 1.3212 Å	2-N (b) = 0.6650 Å

The quadrupole coupling constants were: −4.64, 1.34, and 3.27 MHz.

H. Mass Spectra

The electron impact on pyridazine and some derivatives has been reported (146–148). A review by Bowie et al. (148) showed the spectra diagrams for pyridazine, 3,6-dichloropyridazine, 3,6-dimethoxypyridazine, pyridazin-6-one, 3-methylpyridazin-6-one and 3,6-dihydroxypyridazine and listed the peaks for other derivatives.

Pyridazine was shown to reveal fragmentation modes M—N_2—H_2 (148).



Simple pyridazines containing groups such as chlorine, methyl, and amino groups easily lost nitrogen; however, when a methoxy group was present, the fragmentation proceeded first through the methoxy group (148).

The pyridazinones showed the decomposition modes M—CO—N_2—H, the initial fragmentation being the loss of carbon monoxide.

I. Magnetic Susceptibility

Francois (149) has reported the magnetic susceptibility of a large number of nitrogen-containing organic compounds, including pyridazine. The experimental value for magnetic susceptibility was given as $X_M = -44.9 \times 10^{-6}$ and the calculated value, obtained by a modified LCAO molecular orbital method was given as $X_M = -35.3 \times 10^{-6}$.

IV. Chemical Reactivity

A. Ionization Potentials

The ionization potentials of pyridazine have been calculated by various methods (29, 151–155) and experimentally determined by electron impact (156), by photoelectron (157), and by photoionization (158). The values that have been reported are summarized in Table V. The assignment of ionization

TABLE V. Ionization Potentials

eV	Method	Assignment	Reference
Observed			
9.86 ± 0.05	Electron impact	*n*	156
8.91 (1st)	Photoelectron		157
10.55 (2nd)			
11.13, 13.59, 15.69, 16.73			
8.71 ± 0.01	Photoionization	*n*	158
Calculated			
9.64			29
9.81			151
6.52		*n*	152
12.709		σ	153
10.99		π	155

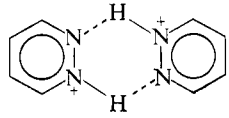
potentials varies from σ (153), π (155), or nonbonding electrons (152, 156). Although various possibilities were set forth and discussed (158), no definite

assignment was made because of lack of data. Part of the assignment problem was due to the strong interaction between the two adjacent nonbonding orbitals. If a nonbonding electron is assumed to give the lowest ionization potential, then tentatively the assignment of the second ionization potential could be a π electron (158).

B. Ionization Constants pK_a

The ionization constants of pyridazine and pyridazine derivatives have been reported many times (159–168).

Pyridine has a pK_a value of 5.23 (159). However, when a second nitrogen atom is introduced in place of the CH group into the pyridine nucleus, there is a reduction in the basic strength much like adding a nitro group to pyridine. This drop in pK_a value is due to the greater reluctance of the divalent nitrogen to accept a positive charge. Furthermore, the second nitrogen is electron-attracting and thus base-weakening. When comparing the three diazines, pyridazine has a much higher basic strength than would be expected if the only effect were inductive. In fact, the high basic strength has been attributed to the fact that the pyridazine cation is capable of forming a dimer (**9**) with two hydrogen bonds, which has extra resonance strength relative to the nonionized molecule (159, 166, 167).



9

The addition of a substituent on the pyridazine nucleus generally has an effect similar to that of the same substituent on benzene. The position of the substituent also has an effect, for example, an amino or an hydroxyl group can have a greater effect than on benzene if placed in a particular position. A 4-amino group has a greater base-strengthening effect on pyridazine than does a 3-amino group. The addition of a methyl group tends to have a base-strengthening effect, and the addition of an alkoxyl or an amino group has a similar but greater effect.

A glance at the pK_a values given in Table VI confirms the resonance and inductive effects of the substituents.

Joris and Von Rague Schleyer (167) tried to correlate the pK_a values with the ir spectral shifts (Δr). Although the values for a limited number of alkylpyridines showed a good linear relationship, the diazines did not show

TABLE VI. pK_a Values for Pyridazines

Compound	pK_a	Temperature (°C)	Reference
Pyridazine	2.33	20	159
4-Methylpyridazine	2.92	20	70
3-Methoxypyridazine	2.52	20	160
4-Methoxypyridazine	3.70	20	160
3,6-Dimethylpyridazine	1.61	20	160
3-Methylmercaptopyridazine	2.26		165
4-Methylmercaptopyridazine	3.26		165
3-Aminopyridazine	5.19	20	159
4-Aminopyridazine	6.69	20	166
3-Amino-6-methylpyridazine	5.32	20	164
Compound	**Proton lost**	**Proton gained**	
3-Hydroxypyridazine	10.46	−1.8	160
4-Hydroxypyridazine	8.68	1.07	160
3-Mercaptopyridazine	8.25	−2.73	165
4-Mercaptopyridazine	6.54	−0.75	165
4,5-Dicarboxypyridazine	3.30 (zwitterionic)		70

any correlation. For example, pyridazine has a larger pK_a value than would be predicted from the spectral shifts.

C. Reactions

Since the adjacent nitrogen atoms in pyridazine greatly increase the π deficiency on the carbon atoms, the pyridazine nucleus is resistant to attack by electrophilic reagents. The presence of an electron-releasing group, such as an amino or hydroxyl group, can counteract this effect and allow electrophilic substitution to take place.

Nucleophilic substitution can readily occur because of the π-deficient character of the pyridazine nucleus.

Crossland and Kofod (169) found that 3-chloro-6-dimethylaminopyridazine reacts with Grignard reagents to give 5-substituted products.

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CHAPTER II

The Pyridazinones, Alkoxy- and Aryloxypyridazines, and Related Compounds

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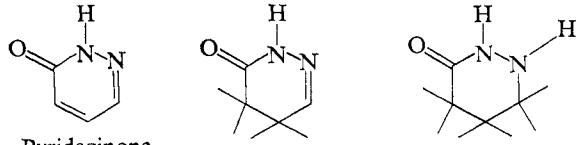
I. Nomenclature

The proper nomenclature for 1,2-diazine systems that contain a carbonyl group in the ring has been the subject of considerable debate and confusion. Fully unsaturated (aromatic) systems have been called by a variety of names, including pyridazinone, pyridazone, pyridazinol, oxopyridazine, and others. The confusion arises because partially saturated compounds have also been designated by quite similar or identical names. Moreover, it has often been difficult to determine the extent to which a given oxygen function exists in the keto or enol form. Some workers prefer to call all such compounds hydroxypyridazines, while others designate identical structures pyridazones or by some similar name, thus adding to the confusion.

In their review, Tišler and Stanovnik (1) adopt the name pyridazinone for the fully aromatic compounds. Reduced rings are then named as 4,5-dihydropyridazinones and 1,4,5,6-tetrahydropyridazinones (Eq. 1). This nomenclature preserves the basic ring system name and leads directly to logical names such as hydroxypyridazine in those cases in which the grouping is known to exist in the enol form. It is used throughout this chapter.



Pyridazinone | 4,5-Dihydropyridazinone | 1,4,5,6-Tetrahydropyridazinone (1)

II. Preparation

The methods for preparing pyridazines and pyridazinones can be grouped into three main categories: (1) ring closure of acyclic compounds, (2)

alteration of other heterocyclic ring systems, and (3) substitution and displacement on pyridazine and its derivatives. These methods are discussed in the following sections.

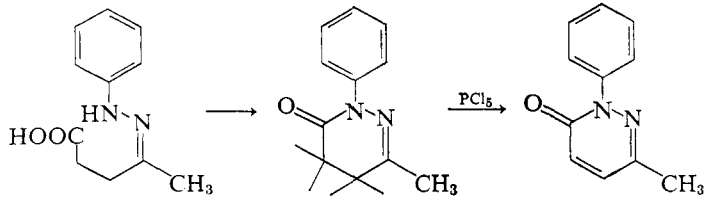
A. Ring Closure of Acyclic Compounds

Many of these methods employ a compound that has at least a four-carbon chain, the proper degree of unsaturation, and groups on carbons 1 and 4 that can undergo condensation with hydrazines or diazo groups. If carbon 1 or 4 is part of a hydrazone or hydrazide, intramolecular cyclization can readily occur and hydrazine is not needed.

When the four-carbon chain contains less than four degrees of unsaturation, dihydro- and tetrahydropyridazinones are formed. These compounds can be oxidized to the pyridazinones by a variety of reagents. Bromine in acetic acid is the most common reagent, but phosphorus oxychloride, phosphorus trichloride, and phosphorus pentachloride, alone or in various combinations, have also been used extensively. The phosphorus reagents can produce concurrent chlorination of the ring. Less frequently used reagents include potassium permanganate, chromic acid, and sodium or potassium dichromate in sulfuric acid. These more vigorous reagents may also oxidize susceptible side groups if any are present.

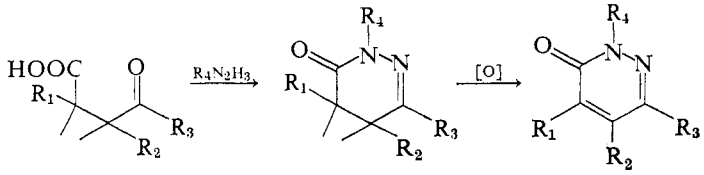
1. *1,4-Keto Acid Derivatives*

The first reported pyridazinone was prepared by the cyclization of levulinic acid phenylhydrazone followed by oxidation to 3-methyl-6(1*H*)pyridazinone (Eq. 2) (2, 3).



(2)

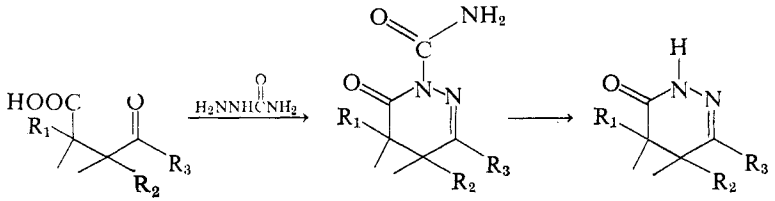
Through the years this and similar routes have been the most widely used methods for the preparation of such derivatives. The general scheme is outlined in Eq. 3.



(3)

A very wide variety of keto acids has been used. R_1 and R_2 are most often hydrogen, but alkyl and aryl derivatives have also been extensively employed. R_3 has been varied most widely. Alkyl and aryl groups predominate, but almost any functional group can be used, including carboxyl and related groups, various heterocyclic rings, and even the ferrocene residue (4). 1,4-Aldehydo acids can be cyclized similarly (5–8), often under very mild conditions.

The groups attached to the hydrazine moiety are also usually alkyl or aryl functions, but are not limited to these. For example, semicarbazides (9, 10) and semicarbazones (11–14) have been used (Eq. 4). The *N*-carboxamido group formed in these instances can be hydrolyzed during the reaction (15) or retained (16–18), depending upon the conditions of the reaction. Similar considerations apply to acid hydrazides (19) and to tosylhydrazones (20).



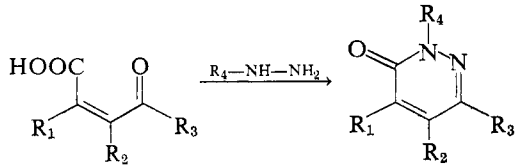
(4)

The cyclization is usually carried out in one step, but many workers have isolated the intermediate hydrazones. These compounds are also readily cyclized. Esters can be used, but the reaction is slower and gives smaller yields. In addition, acids are usually more available than their esters, and the former have been preferred.

Several reduced pyridazinones were prepared unintentionally during attempted Wolff–Kishner reductions of 1,4-keto acids (21). It has been shown that the ease of cyclization during these reactions depends upon the nature of aryl groups attached to the keto acid (21). This is consistent with much other experience which indicates that the ease with which keto acids cyclize is heavily dependent upon the number and nature of the functional groups attached to the reagents.

α,β-Unsaturated 1,4-keto acids have been cyclized to give pyridazinones directly (Eq. 5). This reaction has had limited application, however, because the unsaturated acids are often difficult to obtain, and oxidation of reduced

pyridazinones usually gives excellent yields. Halo derivatives of mucic acids (α,β-unsaturated 1,4-aldehydo acids) have been most used. They lead to 4,5-dihalopyridazinones which, because of the reactivity of the halogen substituents are very useful intermediates. Mucochloric acid (22–27), mucobromic acid (19, 24, 28, 29), and a mixed bromochloro acid (27, 30) have been cyclized.



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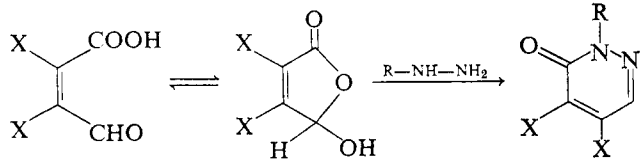
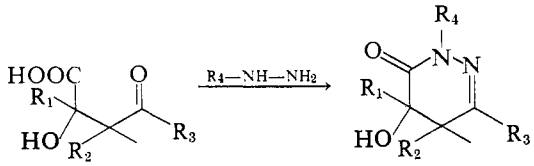


α- or β-bromo- (31), alkoxy- (32), alkylthio- (33), hydroxyl-1,4-keto acids (32, 34), and unsaturated γ-lactones (35–40) also cyclize to pyridazinones directly by elimination of the functional groups. Schreiber and his co-workers have claimed (41, 42) that in some cases the α-hydroxy compounds can be cyclized without the elimination of water (Eq. 6). However, the structures of the 4-hydroxypyridazinones have not been proved.

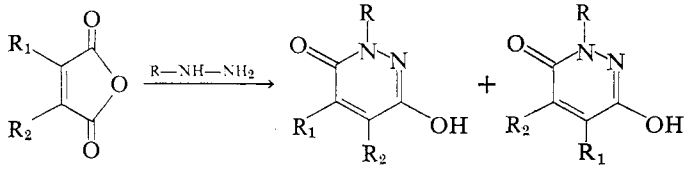


(6)

2. *1,4-Dicarboxylic Acids and Derivatives*

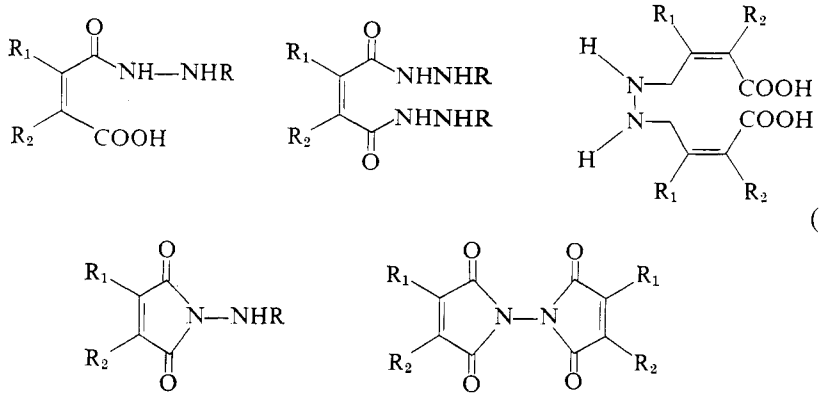
A common and versatile method for the preparation of pyridazinediones consists of the cyclization of maleic acid derivatives and their mono- and disubstituted analogs with hydrazines. Maleic anhydrides are used most often (Eq. 7), but the acids and other functional derivatives (esters, acid halides, imides, etc.) have also been employed. The reaction is applicable to nearly all derivatives of maleic anhydride and generally gives high yields when

proper conditions are employed. However, it is subject to numerous side reactions and can lead to difficult mixtures if precautions are not observed.



(7)

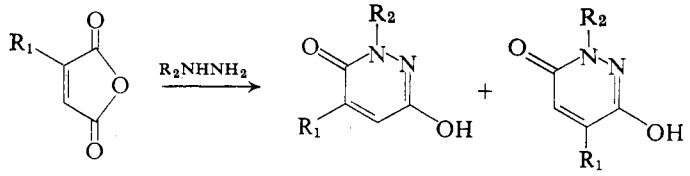
Among the side products observed are mono- and dihydrazides (43–45), linear hydrazides (46–48), *N*-aminomaleimides (49, 50), and *N*,*N*′-biimides (Eq. 8) (48). Fortunately, these compounds can usually be rearranged and cyclized to the desired pyridazines. The formation of such side products can be suppressed by a proper choice of reaction conditions (solvents, temperature, rate of addition of reactants, etc.), but no general rules for the production of high yields of pyridazinones can be formulated. Moreover, the relative quantities of the products are greatly influenced by steric effects in the maleimide (45, 51). Thus it is usually best to follow the literature preparation for any particular compound. This presents little difficulty because a wide variety of pyridazinones has been prepared (see tables at the end of the chapter), and nearly all the common substituent groups have been investigated. Within a narrow class, such as maleic anhydrides in which the double bond is part of a second ring, reasonable extrapolations can be made.



(8)

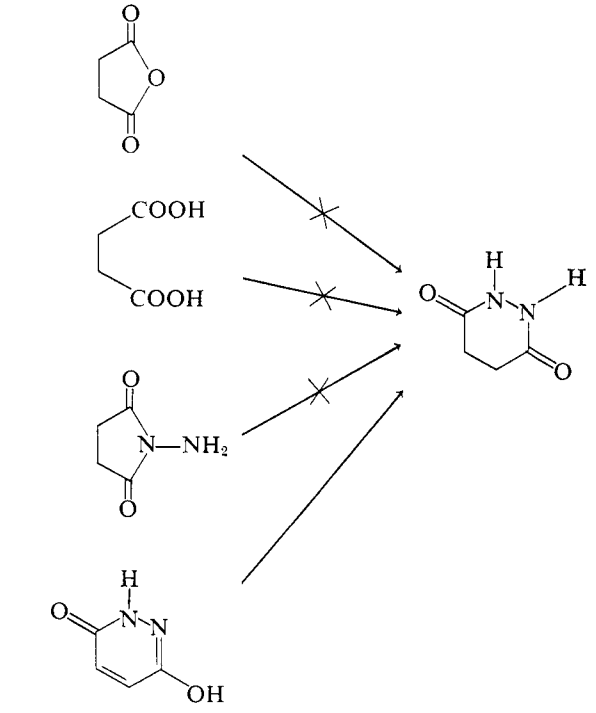
The reaction between a monosubstituted maleic anhydride and a monosubstituted hydrazine can produce two isomers (Eq. 9). In most cases the isomers are formed in approximately equal amounts, and reaction conditions appear to have little effect upon their distribution. Structural differences and steric effects seem to be the controlling factors, although no generally applicable rules can be stated. For example, citriconic anhydride gives nearly equal amounts of the isomers when cyclized with either methyl- or

phenylhydrazine (52). Chloromaleic anhydride gives predominantly the 5-chloro isomer with phenylhydrazine (49), but the 4-chloro isomer predominates with methylhydrazine (53, 54).



(9)

The saturated analogs of maleic acid derivatives (succinic acids) do not generally form dihydropyridazinones. For example, the reaction of succinic anhydride with hydrazine hydrate (Eq. 10) was thoroughly investigated



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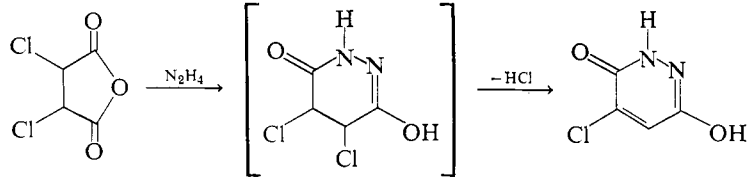
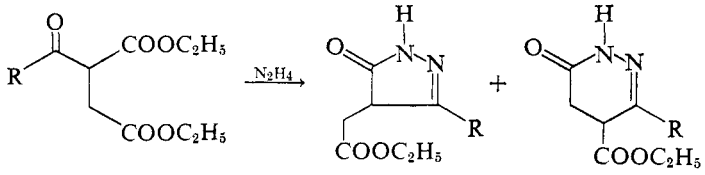


under varied conditions (55), but gave no cyclic products. Attempts to cyclize succinic acid (56) and to rearrange *N*-aminosuccinimide (57) also failed to produce succinhydrazide. The latter compound was finally prepared by the reduction of maleic hydrazide with aluminum amalgam (55, 58). In contrast, dichlorosuccinic anhydride cyclizes readily with hydrazine, giving the fully aromatic 4-chloromaleic hydrazide (Eq. 10) (59). The intermediate dichlorosuccinhydrazide cannot be isolated.

There has been much controversy concerning the products of the reaction of diethyl succinate and its monoacylated derivatives with hydrazines. Several investigators have claimed that the cyclic products are pyrazolones, while others claimed that dihydropyridazinones are formed (60–64). However, the structures of none of the compounds were proved. Finally, McMillan and King (65) demonstrated that the product was a mixture from which they isolated and identified examples of both structures (Eq. 11).



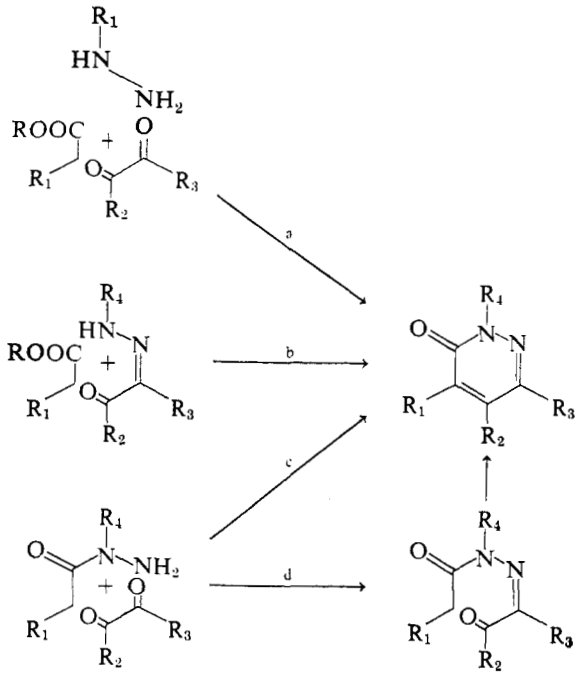
(11)

3. *1,2-Dicarbonyl Compounds*

In 1954, Schmidt and Druey (66, 67) described a very useful and versatile synthesis of pyridazinones. The reaction involves the condensation of a 1,2-dicarbonyl compound with a hydrazine and a compound containing a carboxyl derivative and an active methylene group. The reaction can be carried out by any of four pathways (Eq. 12) (68, 69). Many 3-, 4-, and 5-substituted 6(1*H*)pyridazinones have been made available in good yields by this method.

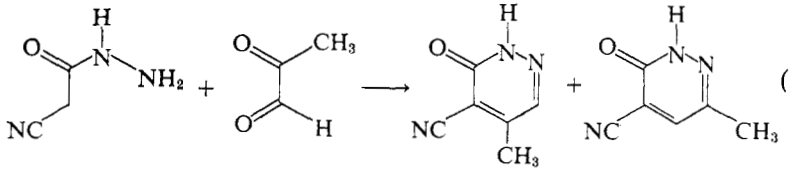
Although the one-step condensation of three compounds can be performed (pathway a), it is usually better to cyclize only two components to form the ring. Either the monohydrazone of the diketone (pathway b) or the hydrazide of the acid (pathway c) is formed first and cyclized with the third component. Basic catalysts (usually sodium ethoxide) are used most commonly, but glacial acetic acid–ammonium acetate can also be employed. If the components of pathway c are used without a catalyst, the intermediate hydrazidohydrazone is formed (pathway d). This compound can be cyclized by treatment with the catalysts mentioned above.

When unsymmetrical 1,2-dicarbonyl compounds are used in pathways c or d, isomeric products are possible (Eq. 13). That isomers are formed was



(12)

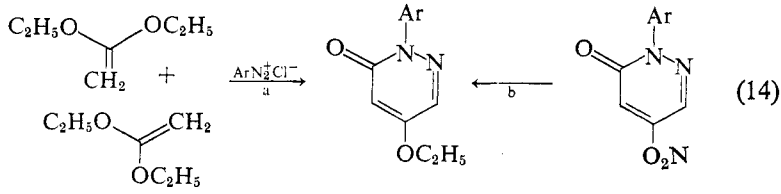
demonstrated by Schmidt and Druey (66). They condensed methyl glyoxal with cyanoacethydrazide and obtained the isomeric 5- and 6-methyl isomers in a ratio of 1:2.



(13)

4. *Miscellaneous Syntheses*

A few further examples of pyridazinone synthesis using acyclic compounds should be mentioned. Perhaps the most generally useful of these involves the reaction of an aromatic diazonium salt with ketene diethylacetyl (Eq. 14). The diazonium group adds across two molecules of the ketene and the adduct apparently cyclizes with elimination of ethanol to give a pyridazinone (70). The structure of the product was proved by an independent synthesis (b, Eq. 14).

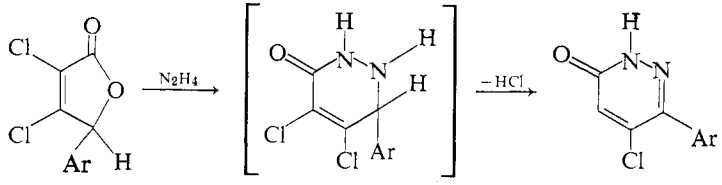


(14)

The isomerization of hydrazones formed in the Japp–Klingemann reaction of γ,δ-unsaturated β-keto esters has been reported to give pyridazinones (71), and the related decomposition of β,γ-unsaturated acid hydrazides gives reduced congeners (72). 4-Halo esters react with hydrazines to give related reduced pyridazinones (73).

B. From Other Ring Compounds

A second important method for the preparation of pyridazinones is the modification or rearrangement of other ring structures. Several of these involving cyclic anhydrides were described in the preceding section and need not be discussed further here. A closely related synthesis involves the treatment of aromatic γ-lactones of α,β-dihalocinnamic acids with hydrazine (Eq. 15) (74). Hydrazine adds across the lactone ring oxygen bridge, forming a dihydropyridazinone which loses the elements of hydrochloric acid spontaneously to yield the fully aromatic ring system. Somewhat surprisingly, the halogen adjacent to the carbonyl group is always lost, and no isomers are formed.



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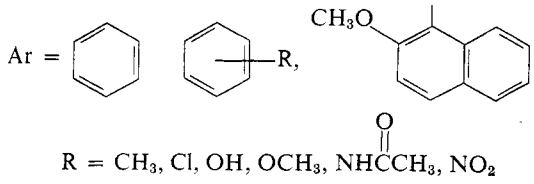
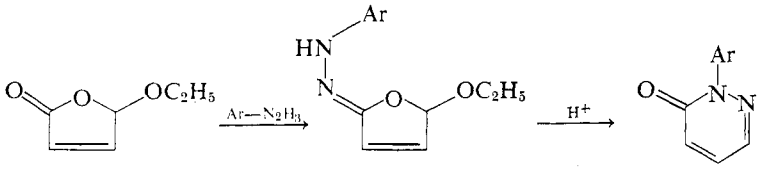


R = CH_3, Cl, OH, OCH_3, $NHCCH_3$, NO_2

A similar reaction in which the aromatic ring system is replaced by an ethoxy group is reported to give excellent yields (Eq. 16) (75). In this case the hydrazine adds to the carbonyl group first, followed by ring opening and elimination to the pyridazinone. The intermediate hydrazones can usually be isolated.



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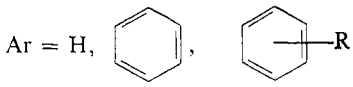
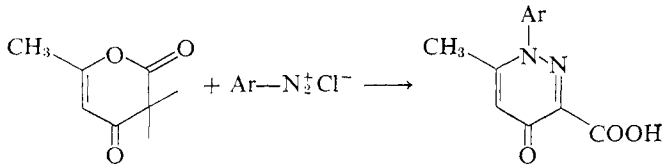


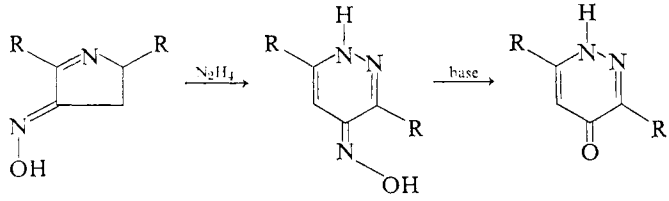
$R = CH_3, Cl, NO_2$

Certain six-membered oxygen heterocycles can be used to prepare pyridazinonecarboxylic acids (Eq. 17) (76–78). This reaction is of interest primarily as a method to prepare the acids and is discussed more fully in Chapter VIII.

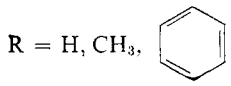


(17)

Nitrogen heterocyclic rings can also serve as starting materials for the preparation of pyridazinones. In one report the ring of a 3-oximino dihydropyrazole was opened with hydrazine (Eq. 18) (79). The intermediate 4(1*H*)-pyridazinone oximes were formed when the reaction was conducted in

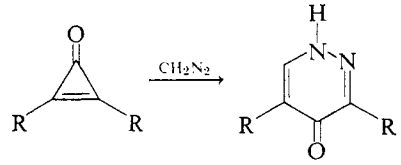


(18)



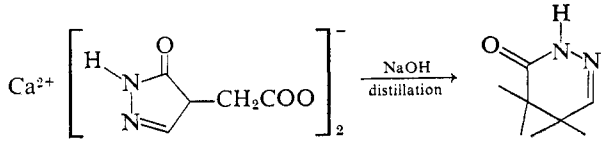
neutral media, but these were rapidly hydrolyzed to the 4(1*H*)pyridazinones by base.

The highly reactive cyclopropenone ring can be opened with diazomethane to give 4(1*H*)pyridazinones (Eq. 19) (80, 81). Both aliphatic and aromatic substituents on the cyclopropenone ring have been used successfully.



(19)

There is also one report in which a 3-keto-1,2-diazole ring was enlarged to yield dihydro-6(1*H*)pyridazinone (Eq. 20) (60).

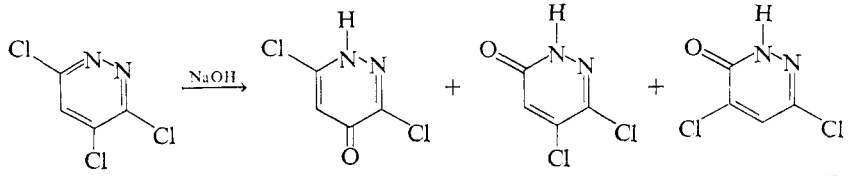


(20)

C. Modification of Pyridazine Derivatives

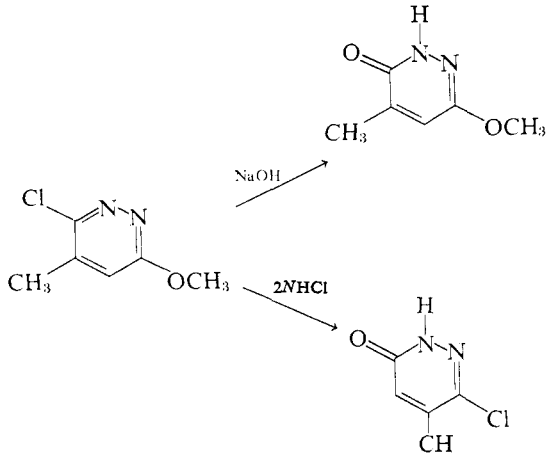
A third general method for the preparation of pyridazinones is the modification of pyridazines carrying other functional groups. The carbonyl group is often formed by hydrolysis of a labile group such as the halogen or alkoxyl functions. These reactions yield hydroxypyridazines which are tautomeric with pyridazinone structures.

The usual reagent for halogen hydrolyses is acetic acid, either alone or in combination with sodium or potassium acetate. Alcoholic hydrogen chloride (82) and sulfuric acid (83) have also been used. In one instance nitration with sodium nitrite in dimethylformamide was accompanied by hydrolysis of a secondary halogen substituent (84). Halogen substituents may also be replaced by dilute aqueous base (27, 62, 85–90), but acidic conditions are preferred where other sensitive groups are present. As with other reactions, halogens at the 4- and 5-positions are most labile to hydrolysis. This is illustrated by the hydrolysis of 3,4,6-trichloropyridazine with aqueous sodium hydroxide (Eq. 21) (91). The major product (90%) is 3,6-dichloro-4(1*H*)pyridazinone. Small amounts of the isomeric dichloro-6(1*H*)pyridazonones are also formed.



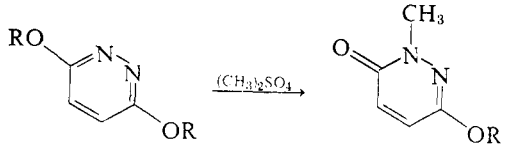
(21)

By contrast, alkoxy substituents can be hydrolyzed with dilute aqueous halogen acids (89, 92). Thus the selective replacement of groups in pyridazines carrying both types of substituents is possible. For example, treatment of 3-chloro-6-methoxy-4-methylpyridazine with dilute base yields 3-methoxy-5-methyl-6(1*H*)pyridazinone by hydrolysis of the methoxyl group (Eq. 22) (92).



(22)

Hydrolyses of alkoxyl groups by the following reagents have also been reported: acetic anhydride (93, 94), sodium ethoxide (95), (both of which require an *N*-oxide moiety adjacent to the alkoxyl group hydrolyzed), anhydrous sodium hydroxide (96–98), and concentrated ammonium hydroxide (88). In an interesting transformation *N*-alkylation of 3,6-dialkoxypyridazines brings about the displacement of one or both *O*-alkyl groups to form pyridazinones (Eq. 23) (99).



(23)

Nitrogen substituents can also be hydrolyzed to yield pyridazinones. This is most often done by diazotization with nitrous acid (85, 86, 100), but dilute hydrochloric acid can usually serve to hydrolyze hydrazine derivatives (86). Sodium hypochlorite has also been used with hydrazines (101). In one case pyridazinone oximes were formed and hydrolyzed to the parent pyridazinones in high yield with acetic acid (79).

Finally, a large number of pyridazinones and their derivatives have been prepared by the decarboxylation of pyridazinonecarboxylic acids. This reaction is discussed more fully in Chapter VIII, but it may be noted here that nearly all pyridazinecarboxylic acid derivatives are readily decarboxylated, usually merely by heating them above their melting points. Thus many pyridazinones are most conveniently prepared by cyclization to an acid derivative which can be hydrolyzed and decarboxylated.

III. Properties

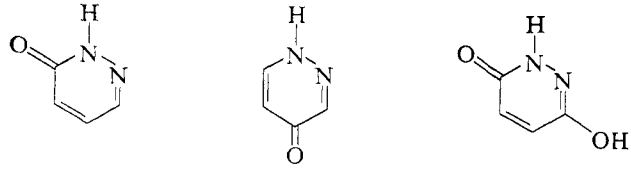
As with other hydroxyazines, pyridazinones exist predominantly in the oxo form. This has been demonstrated conclusively in the case of 6(1*H*)pyridazinone and several of its derivatives by correlations of ultraviolet (uv), infrared (ir), and nuclear magnetic resonance (nmr) spectra. In addition, the crystal structure of 1,6-dihydro-3-carboxamido-6(1*H*)pyridazinone has been examined by x-ray diffraction (82, 102). The bond lengths and hydrogen atom positions clearly indicate that the compound exists in the oxo form. Similarly, spectral considerations indicate that the 4(1*H*)pyridazinones also exist mainly in the oxo form (85, 103, 104).

The tautomeric equilibrium constants (K_t) of a few pyridazinones have been measured (104). As expected, they lie far on the side of the oxo form. Indeed, they are even smaller than those for the α- and β-pyridinones which also exist predominantly in the oxo form.

In contrast, maleic hydrazides have been shown to exist in a mixed oxo-hydroxyl form by uv and ir spectral evidence (105–108). Confirmation of this structure was obtained from nmr studies in which coupling constants strongly favor the hydrogen-bonded monohydroxy form both in the solid state and in weakly polar solvents (109–111). A state of dynamic equilibrium appears to exist between the lactam and enolyzed forms of the pair of amide groups. It is not possible to determine which group is in a given state in unsymmetrical 4- and 5-substituted maleic hydrazides (112).

As would be expected, ring nitrogen unsubstituted pyridazinones are weak acids (Eq. 24) (113). They all form salts with strong bases, and in some cases even with ammonia and the more basic amines (113). Maleic hydrazide is a rather strong organic acid (Eq. 24) (113–115) but forms only monometallic

salts with bases. This is to be expected from its monolactam structure as discussed above. Dimetallic salts of a few substituted maleic hydrazides have been reported, but they are unstable and difficult to prepare (116).



(24)

$pK_a = 3.44$ $pK_a = 5.32$ $pK_a = 1.00$

A few dielectric constants for pyridazinones and maleic hydrazides have been recorded (117–118), and some fairly extensive polarographic studies have been undertaken (114, 119–122).

Although many pyridazinones have been shown to have slight biological activity, only maleic hydrazide has been studied extensively. It was introduced as a plant growth regulator in 1949 (123), and numerous patents and papers covering its commercial production and use have appeared. A literature review (124) and two reviews of its herbicidal and growth regulatory properties (125, 126) have appeared.

IV. Reactions

A. Reactions of the Cyclic Amide Group

The reactions of the pyridazinone cyclic amide function may be divided into four main groups: (1) alkylations, (2) acylations, (3) replacement of the oxygen function by halogen, and (4) miscellaneous replacements. They are discussed in order.

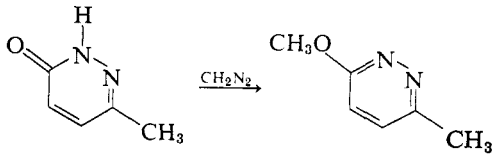
1. *Alkylations*

It is obvious that alkylation of pyridazinones results in either *O*- or *N*-substitution. In fact, both types of substitution have been observed, but the reaction is often quite complex and no simple explanation can account for all the observed results.

Methylations have been studied most extensively, but many other radicals have been used. When performed in the usual way with an alkyl halide or dialkyl sulfate in the presence of base, exclusive *N*-alkylation is generally observed (benzyl halides, discussed below, are the lone exceptions). Dialkyl

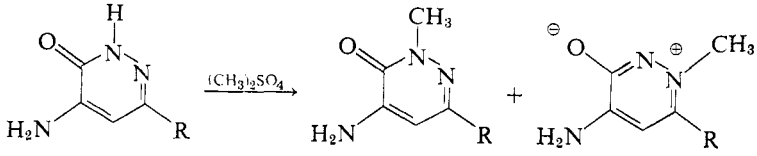
sulfates are said to be more efficient than the corresponding halides (127). Other alkylating agents such as alkylamino alkyl halides (128–130), α-halo acids and esters (130–135), and even 2-bromopyridine (130) have been used successfully, always producing *N*-substituted derivatives to the exclusion of the corresponding *O*-alkyl compounds.

In contrast, diazomethane reacts under the usual conditions with 3-methyl-6(1*H*)pyridazinone to give 3-methyl-6-methoxypyridazine (Eq. 25) (109). This reaction is also reported to give the *N*-methyl compound (133). Presumably, the different results were produced by different conditions, but they were not specified in the latter case.



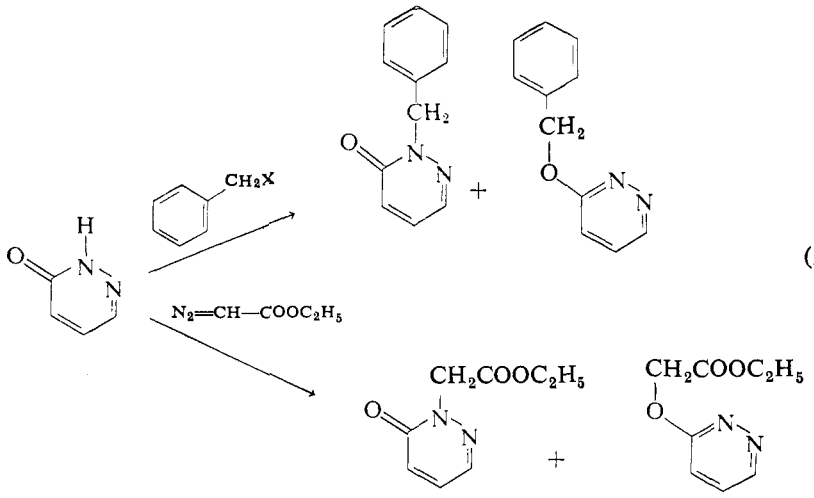
(25)

Methylation of more highly substituted pyridazinones is still more complex. For example, treatment of 3-substituted 5-amino-6(1*H*)pyridazinones with dimethyl sulfate (Eq. 26) yields a mixture of *N*-substituted products whose composition depends upon the bulk of the group at position 3 (136). If position 3 is unsubstituted, nearly equal quantities of the 1-methylpyridazinone and the 2-methylbetaine are formed. When a bulky substituent (CH_3, OCH_3, Cl) is present, the yield of betaine is depressed, and about 80% of 1-methylpyridazinone is obtained.



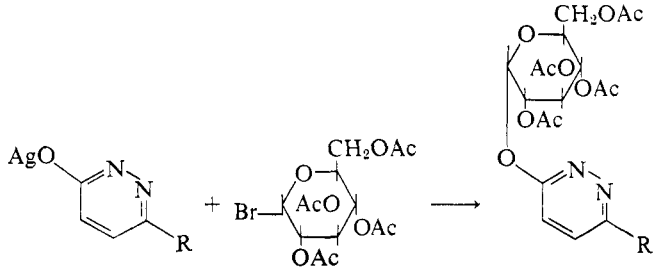
(26)

When large alkyl groups are employed, mixtures of the *N*- and *O*-substituted products are usually obtained. For example, benzylation of 6(1*H*)pyridazinone with a benzyl halide and base gives the *N*- and *O*-benzyl derivatives in a ratio of about 2:1 (Eq. 27) (137). However, if diazoacetic ester is used, the order is reversed, and the *N*- and *O*-carbethoxymethyl derivatives are obtained in a ratio of 1:10 (Eq. 27) (135, 138). Thus it is almost always necessary to examine each new case to determine whether *N*- or *O*-substitution will predominate.



(27)

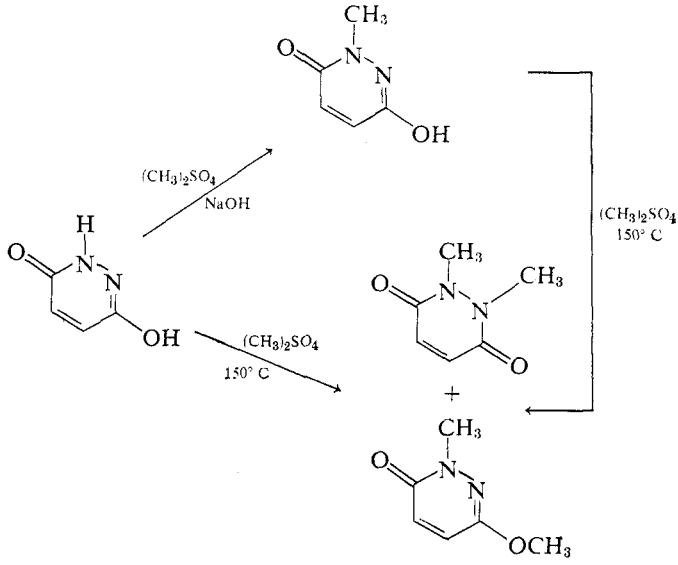
Under certain conditions it is possible to obtain *O*-alkylation exclusively. There have been several reports of the formation of pyridazine-*O*-glucosides by employing the silver salt of the pyridazinone as an intermediate (Eq. 28) (139–144). Treatment of the silver compound with a bromotetraacetyl glucoside gives the glucosyloxypyridazine in high yield. If the silver salt is not employed, exclusive *N*-substitution is observed (124). As yet, there are no reports of the use of this reaction to form other *O*-substitution products.



(28)

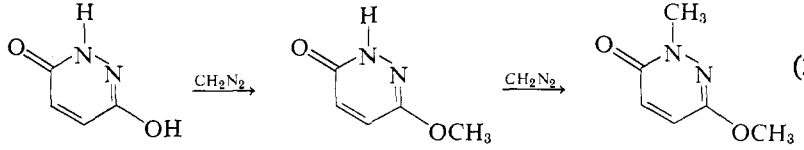
As may be expected, alkylation of maleic hydrazide is still more complex. However, many investigators have studied various aspects of the problem, and much is known about these reactions. Methylation with dimethyl sulfate can give three different products, depending on the reaction conditions. In the presence of aqueous base, exclusive *N*-methylation is observed (Eq. 29) (145). However, when a mixture of maleic hydrazide and dimethyl sulfate is heated at 150° C, mixtures of the 1,2-dimethyl and 1-methyl-3-methoxy derivatives are obtained (99). Longer heating times favor the

formation of the 1,2-dimethyl isomer. Similar mixtures are obtained when the monosubstituted product is heated at 150° C with dimethyl sulfate (99).



(29)

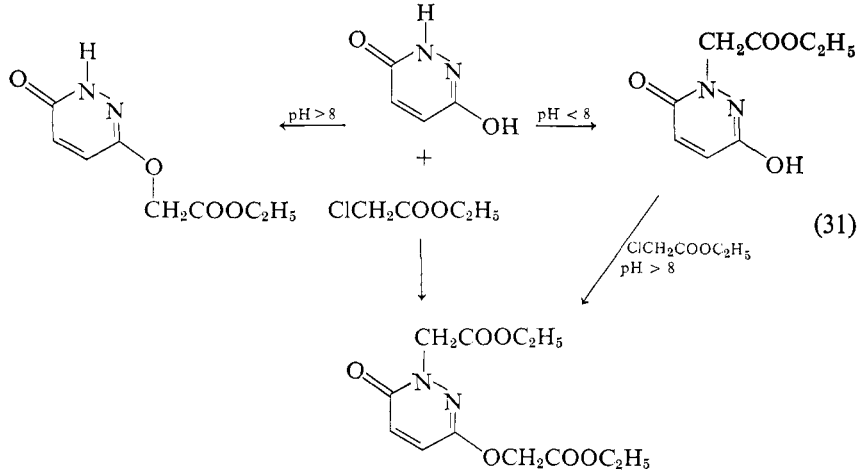
Methylation of maleic hydrazide with diazomethane gives a result opposite that of dimethyl sulfate and base; exclusive *O*-alkylation is observed (Eq. 30) (116, 146). If the monomethoxypyridazinone is further methylated with diazomethane or other methylating agents (methyl iodide, dimethyl sulfate), *N*-methylation occurs, producing the *N*,*O*-dimethyl compound.



(30)

Monoalkylation of maleic hydrazides with an alkyl halide usually produces a mixture of *N*- and *O*-alkylated products. One or the other of the products can sometimes be made to predominate by adjusting the pH of the reaction medium. An interesting example is the alkylation of maleic hydrazide with ethyl chloroacetate (Eq. 31) (147). At pH above 8, *O*-alkylation takes place to the exclusion of *N*-substitution. At lower pH only *N*-alkylation is observed. If 2 equivalents of the chloroacetate are used, the *N*,*O*-alkylated product is obtained under basic conditions (pH > 8); but if neutral or acid conditions are employed, only *N*-alkylation occurs. The *N*-carbethoxymethylmaleic

hydrazide may be *O*-alkylated under basic conditions to yield the same *N*,*O*-dialkyl compound obtained by the direct basic reaction.



(31)

Pyridazinones (148, 149), pyridazinethiones (150), maleic hydrazides (139, 151, 152), and succinhydrazide (153) undergo Michael-like additions with activated olefins. Only *N*-substitution has been observed (139). Maleic hydrazides yield the monosubstituted products exclusively. This is in contrast to succinhydrazide which yields mono- and disubstituted products (153). Good yields are obtained with acrylate esters, acrylonitrile, and methyl vinyl ketone, while dihydrofuran, dihydropyran, and dihydrothiopyran give poor yields.

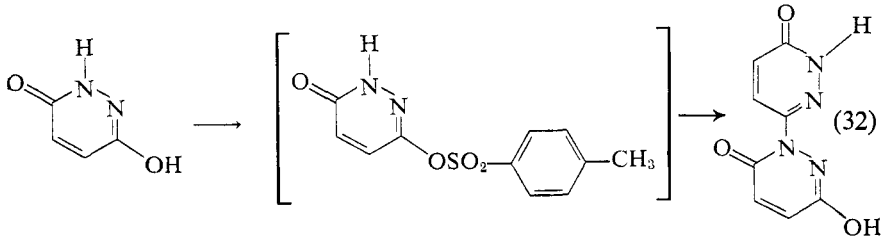
2. *Acylation*

Only a few direct acylations of the cyclic amide group of pyridazinones have been reported, and it is not possible to draw general conclusions. However, it appears that either the *N*- or *O*-substitution products can be obtained by proper control of the reaction conditions. Strongly basic conditions (i.e., the Schotten–Baumann reaction) yield *O*-acylation products (84, 154, 155), while weak base catalysts such as pyridine or sodium acetate favor *N*-substitution (109, 156, 157).

These results closely parallel those obtained with maleic hydrazide, which has been much more extensively studied, and therefore appear to be valid despite the small number of examples.

The extensive investigations of Stefonye and Howard (158) indicate that *O*-acylation is favored in maleic hydrazide. This fact was confirmed by Feuer and Rubinstein (139), who found that the acylation products differed from

N-acyl maleic hydrazides prepared by cyclization of acylated hydrazines. *O*-Acylations have been reported using acetic anhydride (139), acyl halides (52, 84, 139, 158, 159), a variety of sulfanyl halides (59, 160–163), phosphoryl halides (164–167), and trimethylsilyl chloride (168). An attempt to prepare the *O*-tosylate derivative of maleic hydrazide was reported to yield the first example of an *N*-acylation in the pyridazine series (Eq. 32) (59). Apparently, the excellent leaving-group properties of the tosylate moiety enable unreacted maleic hydrazide to displace it, yielding an *N*-pyridazinylpyridazinedione.

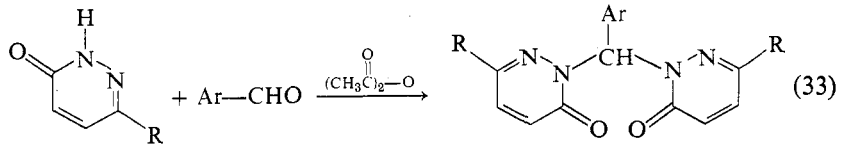


(32)

Several instances of *N*-acylation have also been reported. In general, treatment of maleic hydrazide with an acid halide in pyridine produces the *N*-substitution product (152, 169–171). In addition, unsaturated acid halides in boiling nitrobenzene (152) and chloromethylsulfonyl chloride (172) are reported to yield the corresponding *N*-acyl maleic hydrazides. These structures have been assigned on the basis of spectroscopic evidence (48) and by comparisons with known structures prepared by cyclization of acyl hydrazines (158) and rearrangement of acylated *N*-aminomaleimides (139, 173).

Pyridazinones and maleic hydrazides are acidic enough to undergo the hydroxymethylation and Mannich reactions. Substitution always occurs at the nitrogen atom. *N*-Hydroxymethyl derivatives are usually formed by reaction of pyridazinones and maleic hydrazides with formaldehyde in alcohol (174–176), but they are also reported to be the only products of attempted Mannich reactions with some pyridazinones (174, 176). The Mannich bases can be formed easily from the hydroxymethyl compounds (177). Mixtures of these two products are formed when the Mannich reaction is carried out on maleic hydrazides (175), but *N*-substituted derivatives fail to react (177).

Aromatic aldehydes react with 6(1*H*)pyridazinones in acetic anhydride to form a double adduct (Eq. 33) (174).



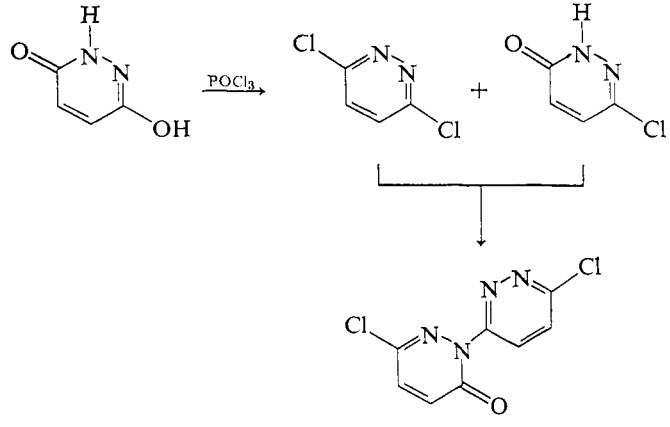
(33)

3. *Replacement of the Oxygen Function*

The most common reaction of the oxygen function in pyridazinones is replacement by halogen. The 3-halo- and 3,6-dihalopyridazines, which are among the most generally useful intermediates for the synthesis of pyridazines, are prepared almost exclusively by this reaction. A few 4-halopyridazines have been prepared by replacement of the oxo functions in the corresponding 4(1*H*)pyridazinones (178, 179), but such halo intermediates are more generally prepared by ring closure reactions. The preparation of halopyridazines is discussed more fully in Chapter III.

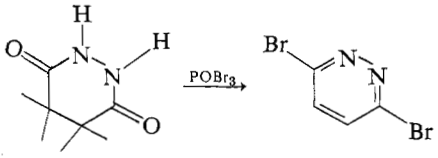
The most generally used halogenating reagent is phosphoryl chloride, either alone or in combination with phosphorus trichloride or phosphorus pentachloride. The phosphorus pentahalides can also be used alone to transform pyridazinones, but they are less successful with maleic hydrazides. The less reactive phosphoryl bromide has been used to prepare bromopyridazines from pyridazinones in some cases, but usually a combination of phosphoryl chloride and phosphorus tribromide is better. Apparently, the chloropyridazine forms first and the bromo analog is formed by *in situ* halogen exchange (180).

The reaction of phosphoryl chloride with maleic hydrazide yields two minor products in addition to the expected 3,6-dichloropyridazine (Eq. 34). The reaction has been investigated in some detail (59, 180, 181). As expected, one of the minor products is the monochlorinated derivative, 3-chloro-6(1*H*)-pyridazinone (Eq. 34). The second minor constituent is the product of reaction between the dichloropyridazine and the chloropyridazinone with the cyclic amide group acting as the attacking nucleophile. The relative quantities of the products can be controlled somewhat by the reaction conditions. This side reaction is similar to one discussed in Section IV.A.2.



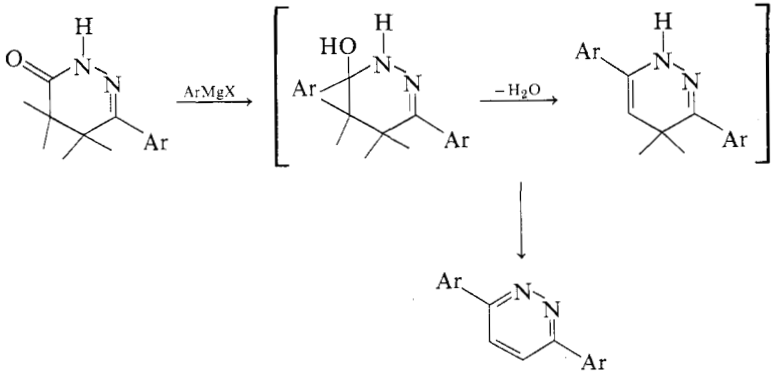
(34)

Phosphoryl bromide can be used to oxidize (dehydrogenate) hydropyridazines but can also produce simultaneous oxo group replacement. For example, treatment of succinhydrazide with phosphoryl bromide yields 3,6-dibromopyridazine (Eq. 35) (182).



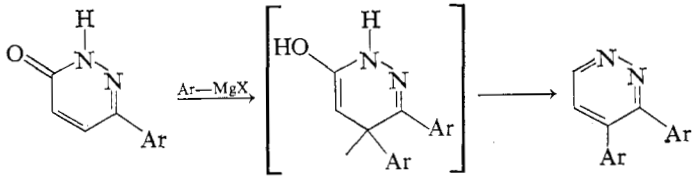
(35)

Although they do not normally react as ketone carbonyl groups, the oxo functions of both reduced and fully aromatic pyridazinones can be replaced by aromatic Grignard reagents. Reduced pyridazinones react by 1,2-addition, and apparently form diaryldihydropyridazines which dehydrogenate spontaneously. Only the fully aromatized products could be isolated (Eq. 36) (183–185).



(36)

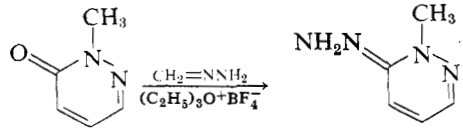
Fully aromatic pyridazinones react by 1,4-addition, giving the corresponding 4-arylpyridazines (Eq. 37) (184).



(37)

In at least one case, a pyridazinone has been converted to its hydrazone. Thus 1-methyl-6(1*H*)pyridazinone was treated with formylhydrazine and triethyloxonium fluoroborate to yield the 6-hydrazone (Eq. 38) (127). The hydrazone is reported to undergo oxidative coupling to yield azo dyes. Oximes

of several 4(1*H*)pyridazinones have also been reported (79), but these were formed by cyclization of the ring rather than replacement of the pyridazinone oxygen function.

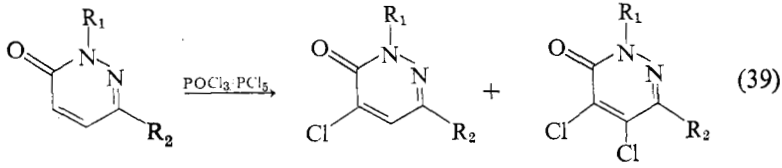


(38)

B. Reactions of the Nucleus

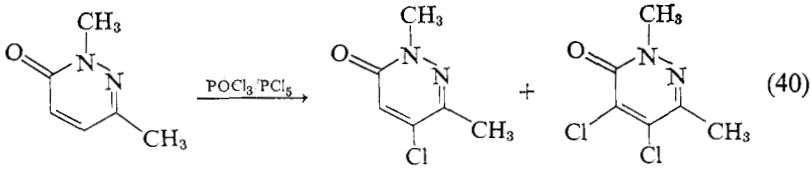
1. *Electrophilic Substitution*

Pyridazinones do not undergo electrophilic substitution readily, but several instances of such reactions have been reported. Halogenation has been reported most often. Many 1,3-disubstituted 6(1*H*)pyridazinones have been reported to yield the corresponding 5-chloro derivatives when treated with chlorine (22, 186), phosphorus pentachloride (3, 109, 187) or phosphoryl chloride–phosphorus pentachloride mixtures (Eq. 39) (22, 188, 189). The 4,5-dichloro compounds can be produced as by-products (188).



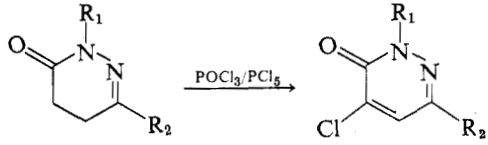
(39)

In most instances the halogen is reported to enter the ring at the position next to the ring carbonyl group. The case of 1,3-dimethyl-6(1*H*)pyridazinone may be an exception. Treatment of the molten compound with phosphoryl chloride–phosphorus pentachloride produced a mixture of four compounds, the major components of which were identified as the 4-chloro and the 4,5-dichloro derivatives (Eq. 40) (188). The other two compounds were not identified, but presumably some of the "normal" 5-chloro product was formed.



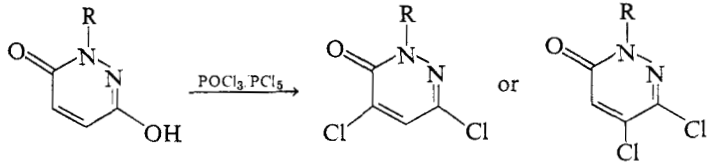
(40)

Ring chlorination has also been observed as a side reaction in the oxidation of dihydropyridazinones with phosphoryl chloride–phosphorus pentachloride mixtures (188, 190) and with phosphorus pentachloride alone (Eq. 41). (109, 187, 188, 191). The halogen always entered at position 5, next to the carbonyl group. It is probable that ring oxidation occurs first, but the timing of the substitution has not been determined.



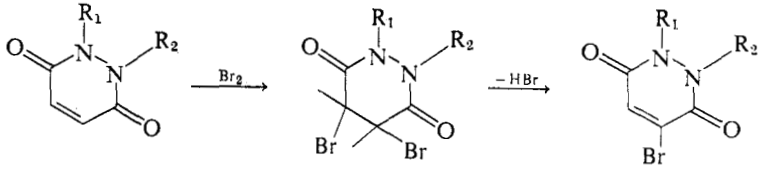
(41)

In a similar reaction ring halogenation was observed when 1-substituted maleic hydrazides were treated with phosphoryl chloride–phosphorus pentachloride or phosphorus tribromide to replace one of the hydroxyl groups (Eq. 42) (52, 192–194). Substitution can occur at either of the available positions in this case.



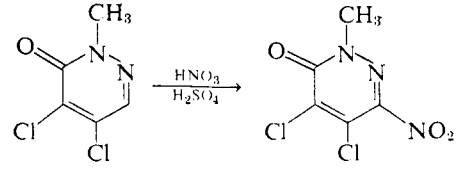
(42)

Disubstituted maleic hydrazides undergo a reaction with bromine or chlorine which appears to involve direct halogenation of the ring (Eq. 43). However, the actual mechanism has been shown to be addition of halogen to the 4,5-double bond, followed by dehydrohalogenation to the halopyridazinedione. This pathway was demonstrated by the isolation of several of the 4,5-dihalo adducts (99, 145, 195–197).



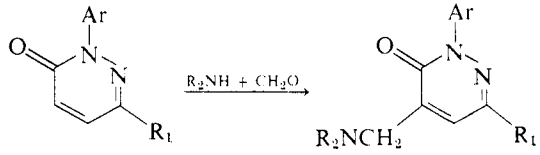
(43)

There are very few reports of the successful nitration of pyridazinones and of their alkoxy derivatives (Eq. 44). The success of such reactions is apparently due to the activating effect of halogen (198) or amino (199) substituents. Both halogenations and nitrations of the ring are common when the *N*-oxides of pyridazinones or alkoxypyridazines are used. The activating and directing influence of *N*-oxides is discussed more fully in Chapter IV.



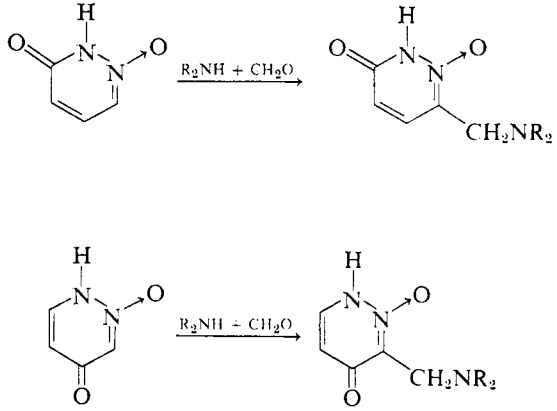
(44)

Direct ring substitution has also been realized through the Mannich reaction with 1-arylpyridazinones (Eq. 45) (200). Substitution always occurs at the 5-position, next to the activating carbonyl group.



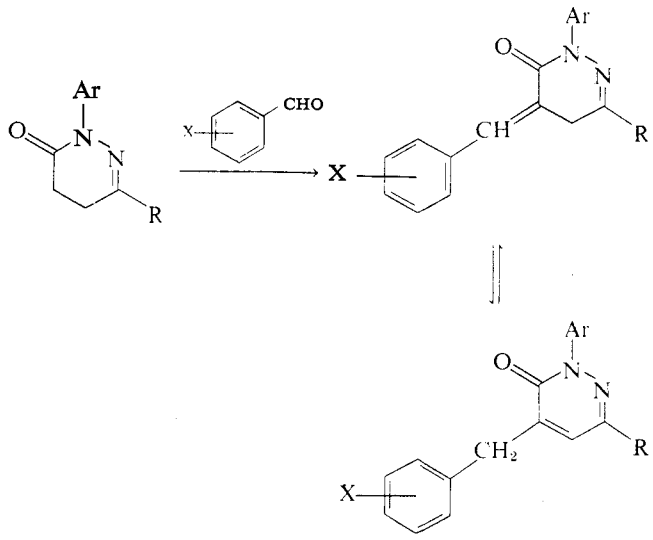
(45)

Similar reactions have been reported with 6(1*H*)pyridazinone 2-oxides (Eq. 46) (200–203). In this case the dominant activating group is the *N*-oxide, and substitution always occurs at the 3-position when 4(1*H*)pyridazinone 2-oxides are used (203).



(46)

A similar reaction can be used to produce ring-substituted pyridazinones. 1-Aryl-4,5-dihydro-6(1*H*)pyridazinones react with arylaldehydes to yield benzylpyridazinones (Eq. 47) (183). As with all such reactions, substitution occurs next to the activating carbonyl group.



(47)

2. *Nucleophilic Substitution*

As is true of all six-membered, aromatic nitrogen heterocycles, especially the diazines, electronegative substituents on the pyridazine ring are activated toward nucleophilic substitution. This lability toward nucleophiles is accentuated by the additional electron-withdrawing character of the carbonyl group in pyridazinones. Thus halopyridazinones, for example, react rapidly and smoothly with a wide variety of nucleophiles. Ammonia, amines, and hydrazine have been used most often (10, 20, 27, 30, 49, 54, 62, 157, 204–207). Other often used nucleophiles include aqueous inorganic bases (27, 53), alkali metal alkoxides and phenoxides (10, 49, 62, 189), and hydrosulfide and alkyl and aryl thiols (27, 208). There is also one report of nucleophilic displacement of chlorine by nitronium ion (20).

The most often used leaving group is chloride ion, but the other halogens have also been used extensively, and alkoxides and nitro groups can occasionally be replaced as well (30, 72, 141, 209–211).

When the nitrogen atom of the lactam moiety carries an alkyl or aryl substituent, strongly basic nucleophiles cause no difficulty (unless some susceptible side group is present). However, *N*-unsubstituted halopyridazinones react slowly or not at all with strongly basic nucleophiles (27, 30, 49, 54, 212). It is recalled that such pyridazinones are somewhat acidic (see Section III). Under strongly basic conditions they ionize, introducing a negative charge to the diazine system and deactivating it toward nucleophilic

substitution. In many cases this difficulty can be overcome by employing weakly basic catalysts such as sodium carbonate (212). Weakly basic nucleophiles (ammonia, amines, thiols, etc.) react normally with halopyridazinones.

The most reactive halogen of halo-6(1*H*)pyridazinones is that at the 4-position, meta to the activating carbonyl group. Thus 3,4-dihalo, 4,5-dihalo-, and 3,4,5-trihalo-6(1*H*)pyridazinones all react with most nucleophiles to yield the corresponding 4-substitution products. The difference in reactivity is great enough that the reaction can always be stopped at the monosubstitution stage. Indeed, vigorous conditions are usually needed to obtain disubstituted products (52, 54, 89, 213, 214).

Halogens at the 5-position of 6(1*H*)pyridazinones are less reactive than those at the 4-position but are much more easily displaced than those at the 3-position. Apparently, hydrogen-bonded intermediates (neighboring-group participating) play an important role in these displacements. For example, 3,5-dichloro-6(1*H*)pyridazinone reacts rapidly with excess dimethylamine at room temperature, yielding the 5-substituted product (54, 89). Introduction of the second dimethylamine moiety requires heating at 170–180° C for 60 hours (52). Similarly, heating 1-phenyl-3,4,5-trichloro-6(1*H*)pyridazinone with sodium methoxide yields some 3-chloro-4,5-dimethoxy-1-phenyl-6(1*H*)pyridazinone in addition to the expected 3,5-dichloro-4-methoxy compound, but the trimethoxy derivative was not detected (89).

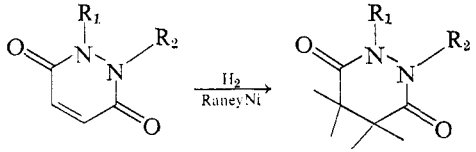
There are too few reports of nucleophilic substitutions in 4(1*H*)pyridazinones to draw any firm conclusions, but they appear to react normally (1). If the halo-4(1*H*)pyridazinones follow the pattern set by the 6(1*H*)pyridazinones, the most reactive halogen should be that at the 6-position. The 3- and 5-halogen substituents should be about equally reactive. These are, however, tentative conclusions which have not been confirmed by experiment.

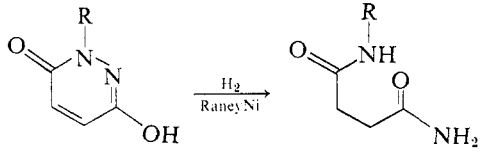
Halo-3,6-pyridazinediones appear to react by a hetaryne mechanism in some cases. Thus 4-chloro-1-methyl-2-phenyl-3,6-pyridazinedione reacts with piperidine to yield nearly equal amounts of the 4- and 5-piperidino isomers, suggesting a hetaryne intermediate (215, 216). An earlier report of the formation of the 5-methoxy isomer by treatment of this compound with sodium methoxide can also be interpreted as supporting a hetaryne mechanism (213).

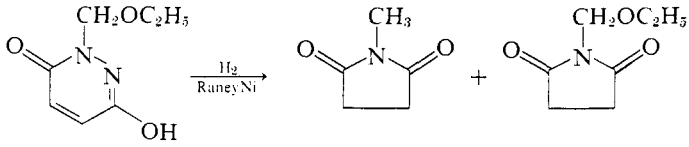
3. *Ring Reduction*

Maleic hydrazides have been reduced with hydrogen in the presence of several catalysts. Raney nickel has been used most often (99, 139, 175, 196), but platinum oxide (Adams catalyst) and palladium on calcium carbonate have also been employed (99). A variety of results has been observed. When

1,2-disubstituted maleic hydrazides are hydrogenated, the 4,5-double bond is reduced, yielding the corresponding succinylhydrazide derivative (Eq. 48) (99, 196). Reduction of the corresponding monosubstituted compounds produces either ring-opened (139) or ring-contracted compounds (Eq. 48) (175) by scission of the heterocyclic N—N bond.

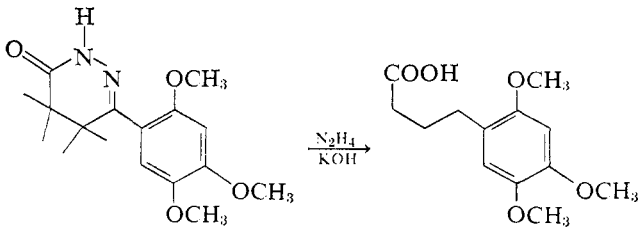






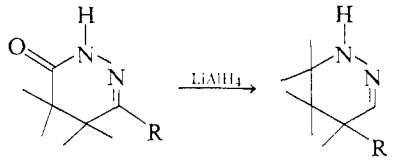
(48)

The similar reduction of pyridazinones has not been reported, but several 4,5-dihydropyridazinones have been reduced to the corresponding tetrahydro analogs (7). Hydrogenation over platinum oxide (Adam's catalyst) was used. There is also one report of an attempted Wolff–Kishner reduction of a 4,5-dihydropyridazinone, which yielded a ring-opened compound (Eq. 49) (217).



(49)

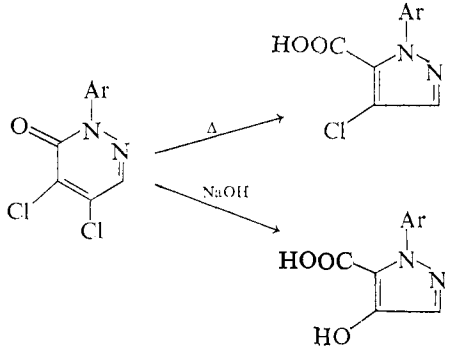
Lithium aluminum hydride has also been used to reduce 4,5-dihydropyridazinones. However, this reagent attacks the cyclic amide moiety and removes the carbonyl oxygen while leaving the ring structure intact (Eq. 50) (218, 219).



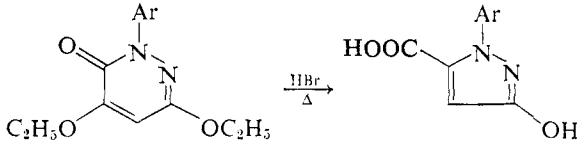
(50)

4. *Miscellaneous Ring Reactions*

There have been several reports of ring contraction reactions occurring in 1-aryl-6(1*H*)pyridazinones (Eq. 51) (53, 189, 207, 220). Pyrazole products were always reported, but their substituents were effected by the conditions employed in the reaction. For example, heating pure 4,5-dichloro-1-phenyl-6(1*H*)pyridazinone produced a chloropyrazolecarboxylic acid (53, 220). However, when it or its brominated analog was heated in aqueous base, the corresponding hydroxypyrazole resulted (207). A similar product was obtained from a quite different diethoxypyridazinone by heating in aqueous hydrobromic acid (Eq. 51) (189).



(51)



V. Alkoxy- and Aryloxypyridazines

The alkoxy- and aryloxypyridazines are a large heterogeneous subgroup of compounds, many of which are derivatives of other classes of pyridazine derivatives. Thus numerous methoxy, ethoxy higher alkyloxy acids, aminopyridazines, halopyridazines, and so on, have been reported. Nevertheless, the chemistry of these compounds is interesting in itself and is discussed in detail.

A. Preparation

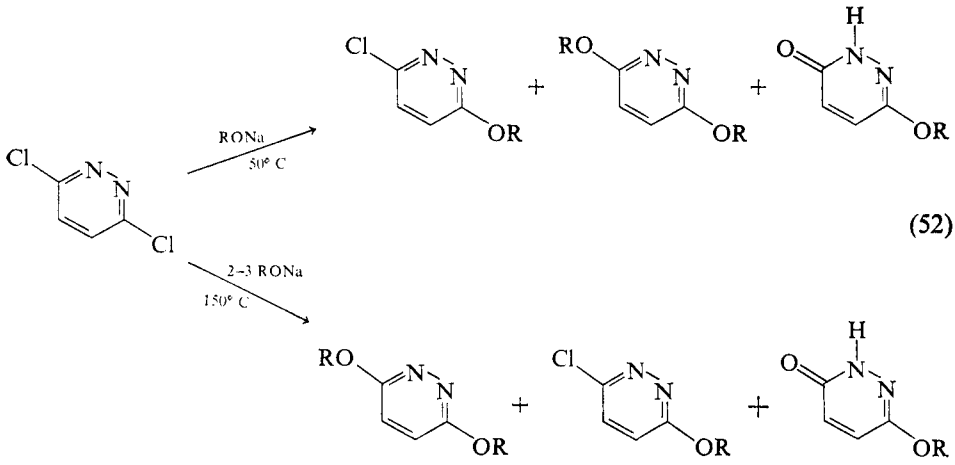
Direct alkylation of the oxygen function of pyridazinones was discussed in Section IV.A.1. While the reaction is general for pyridazinones, it is complicated by the competing alkylation of the ring nitrogen atoms. Mixtures of the *O*- and *N*-alkylation products are usually obtained, and it is difficult to determine in advance which reaction will predominate. In addition, the reaction is limited to the preparation of alkoxy derivatives because direct arylation of the pyridazinone oxygen function is not possible.

A more generally useful method for the preparation of alkoxy- and aryloxypyridazines is substitution of some displaceable group from the ring. The pyridazine ring system strongly activates electronegative substituents toward nucleophilic substitution. By using this fact the vast majority of alkoxy- and aryloxypyridazines have been prepared by nucleophilic displacement of halogen substituents (usually chlorine) with a sodium or potassium alkoxide or phenoxide. The reaction is generally straightforward and usually gives high yields.

Other nucleophilic reagents that have been used extensively include an alcohol with sodium or potassium hydroxide, or with aqueous base. Potassium carbonate can be used to activate phenols when more reactive halogens are present (221). These reagents usually give satisfactory results, but pyridazinones, produced by hydrolysis of the halogen atom, are often formed as by-productos.

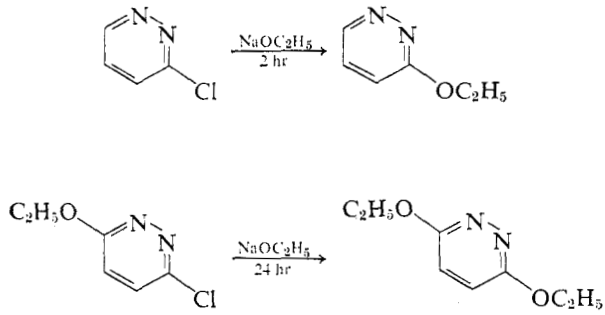
A few examples of unusual nucleophilic reagents have also been reported. An extensive series of oximes has been used to displace one halogen from 3,6-dichloropyridazine (222). Apparently, the oxime moiety supplies the needed basicity. Several potassium dialkylphosphorothionates have been used to substitute 4-chloropyridazinones (223). The extra activation of the cyclic lactam moiety is needed in this case, for the reaction failed with 4-chloropyridazines.

Only one product is possible when a single halogen atom is attached to the ring, but when two or more halogens are present complex mixtures of products often result. This difficulty is minimized by the use of alkoxides and phenoxides (which do not yield hydrolysis products), but even these reagents may produce mixtures that are difficult to separate. The case of 3,6-dichloropyridazine is typical, and it has been studied in detail (224). When the compound was treated with sodium alkoxides, the crude products were always found to contain several by-products. Lower temperatures and long reaction times favor the formation of 3-alkoxy-6-chloropyridazines, but some of the bisalkoxypyridazine unreacted starting material and some 3-alkoxy-6(1*H*)pyridazinone (apparently produced by hydrolysis during work up of the reaction) were always present (Eq. 52). Higher temperatures and excess alkoxide favor formation of the bisalkoxy derivative, but it too is always contaminated by the monoalkoxy compound and the pyridazinone (Eq. 52) (224, 225). Sodium and potassium phenoxides react similarly (226). Much larger amounts of the pyridazinone are formed when alcoholic hydroxides or aqueous/alcoholic bases are used.

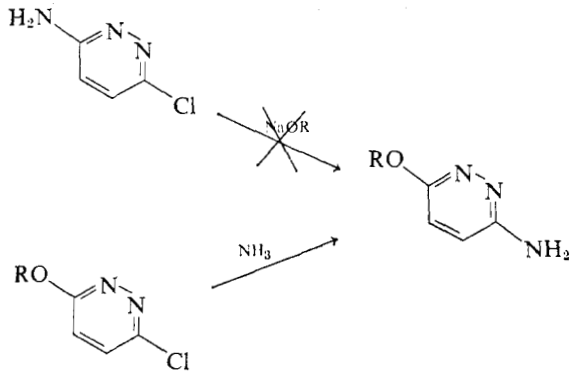


(52)

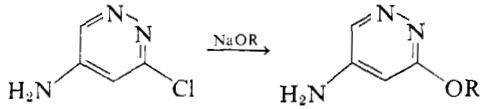
The activating influence of the pyridazine ring can be greatly reduced or eliminated by electron-donating substituents. Thus the halogen in 3-chloro-6-ethoxypyridazine is more difficult to replace than that of 3-chloropyridazine (Eq. 53) (103, 227). The amino group is one of the most potent electron donors, and it is often difficult to displace halogen substituents from aminopyridazines. For example, 3-amino-6-chloropyridazine is resistant to attack by sodium or potassium alkoxides (Eq. 53) (154, 181). Accordingly, 3-amino-alkoxypyridazines are prepared by ammination of the corresponding 3-alkoxy-6-chloropyridazines (Eq. 53).



(53)

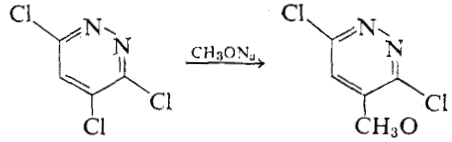


Halogens and other leaving groups are less affected by amine substituents at the meta position. Thus 4-amino-6-chloropyridazine yields 6-alkoxy derivatives with little difficulty (Eq. 54) (228).



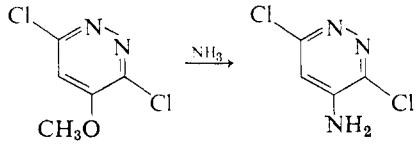
(54)

Halogens at the 4- and 5-positions of pyridazine are more susceptible to replacement by alkoxides and phenoxides than are those at the 3- and 6-positions. This is well illustrated by the reaction of 3,4,6-trichloropyridazine with sodium methoxide (Eq. 55). Substitution always occurs at the 4-position first, and any further replacements are sluggish (30).



(55)

In this connection it is of interest that alkoxy groups at the 4- (or 5-) position of pyridazines are transformed into better leaving groups than halogens at the 3- (or 6-) position by the activation of the ring. For example, treatment of 3,6-dichloro-4-methoxypyridazine with alcoholic ammonia yields 4-amino-3,6-dichloropyridazine by replacement of the methoxy group (Eq. 56) (227, 229). Many other 4- (and 5-) alkoxy- and phenoxypyridazines react similarly.



(56)

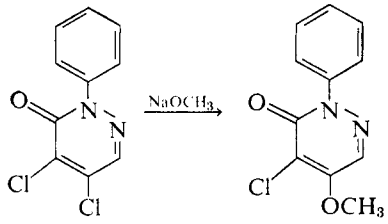
Halogen substituents on pyridazinones are more labile toward nucleophilic replacement than are those on pyridazines because of the additional activation of the carbonyl group. This activation affects all the available ring positions but is strongest in the meta position. Thus 4,5-dichloro-1-phenyl-6(1*H*)pyridazinone yields 5-chloro-4-methoxy-1-phenyl-6(1*H*)pyridazinone when treated with sodium methoxide (Eq. 57) (30, 49). Similarly, 3,4-dichloro-1-phenyl-6(1*H*)pyridazinone yields 3-chloro-4-methoxy-1-phenyl-6(1*H*)pyridazinone (49). 3,4,5-Trichloro-1-phenyl-6(1*H*)pyridazinone also reacts at the 4-position, demonstrating that the results with the dichloro compounds are not due to steric effects (49, 89).

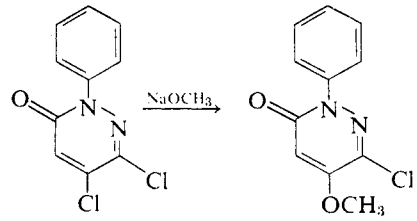
Halopyridazinones not substituted at the lactam nitrogen atom fail to react with alcohols under strongly basic conditions. The cyclic lactam moiety is somewhat acidic (see Section III) and is ionized by strong base. This introduces a negative charge to the ring system, strongly deactivating it toward nucleophilic substitution (Eq. 58) (212).

Alkoxypyridazines have also been produced by displacement of the nitro group from 4-nitropyridazine *N*-oxides (Eq. 59) (72, 94, 141, 209–211). Apparently, only the 4- (or 5-) position provides enough activation to allow the nitro function to act as a leaving group; treatment of 3-methoxy-4,6-dinitropyridazine 1-oxide with sodium methoxide yielded only the 3,4-dimethoxy compound (Eq. 59) (211).

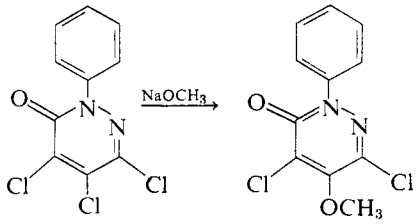
Alkoxide exchange can provide another route to alkoxypyridazines, although it is usually regarded as only a complicating side reaction in the synthesis of mixed dialkoxypyridazines. The reaction has been studied in detail with 3-alkoxy and 3,6-dialkoxypyridazines (230) and has been shown to be general for these compounds. The mechanism of the reaction (Eq. 60) clearly demonstrates the positive character of the pyridazine ring carbon atoms when attracted to more electronegative substituents.

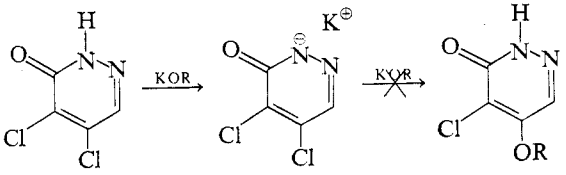
In a few instances alkoxypyridazines have been prepared by cyclization





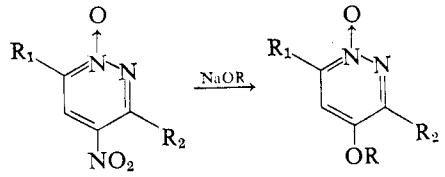
(57)



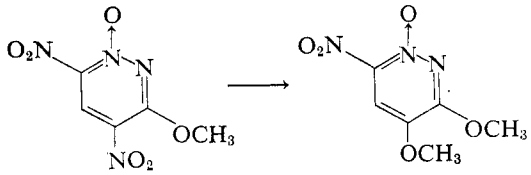


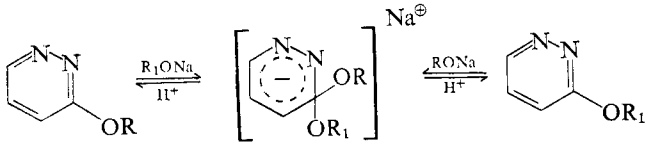
(58)

reactions. 1,1-Diethoxyethylene has been cyclized with several aromatic diazonium chloride salts (231) to yield 4-ethoxy-1-phenyl-6(1*H*)pyridazinones (Eq. 61). This compound has also been cyclized with 3,6-diphenyl-1,2,4,5-tetrazine to yield an ethoxypyridazine (Eq. 61) (232). Although similar reactions with other 1,1-dialkoxyethylenes have not been recorded, they should yield similar products.

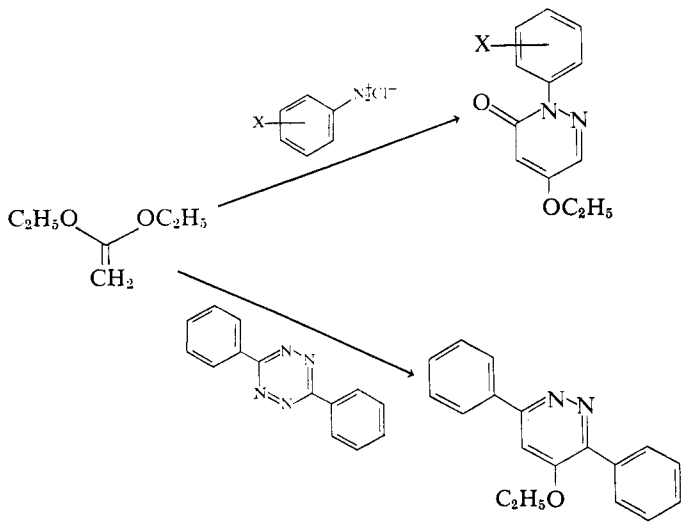


(59)





(60)



(61)

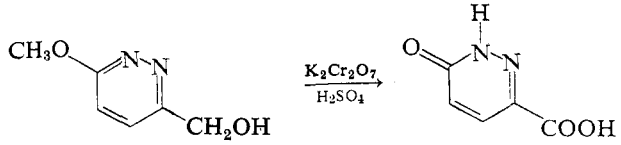
B. Reactions of Alkoxy- and Aryloxypyridazines

As mentioned above, most of the alkoxy- and aryloxypyridazines are derivatives of other classes of compounds. Therefore the effects of alkoxy and phenoxy substituents on the reactions and properties of the various classes of pyridazine derivatives are discussed in detail in the chapters of this

book that deal with them. The alkoxy- and aryloxpyridazinones, for example, have already been covered in earlier sections of this chapter. Accordingly, only those reactions of alkoxy- and aryloxypyridazines that are specific to these compounds are discussed here.

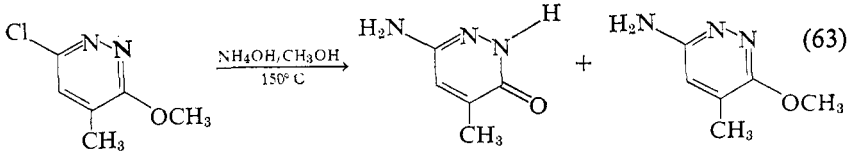
1. *Hydrolysis*

Alkoxy substituents at all available positions on pyridazines, pyridazinones, pyridazine *N*-oxides, and so on have been hydrolyzed to the corresponding hydroxypyridazines or pyridazinones. The most frequently used reagent is concentrated hydrochloric acid. Excellent yields are usually realized when the reaction is carried out in a sealed tube at 130–150° C. Hydrobromic acid (87, 89, 189) and hydriodic acid (49, 141, 233, 234) also give excellent results. In several instances formation of *N*-oxides of 3,6-dialkoxypyridazines with peroxide in acetic acid has been accompanied by hydrolysis of one of the alkoxy groups (141, 235, 236). Sulfuric acid has not been used directly, but the oxidation of 3-hydroxymethyl-6-methoxypyridazine with potassium dichromate in concentrated sulfuric acid was accompanied by hydrolysis of the methoxy group (Eq. 62) (72).



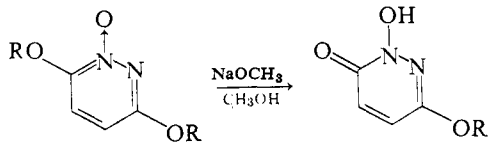
(62)

Hydrolysis may also be effected under basic conditions. Dilute solutions (1–2 *N*) of sodium or potassium hydroxide in boiling water are usually used, and the reaction can be fairly fast (1–2 hr). Basic hydrolysis is limited to pyridazines that do not carry other sensitive substituents or side chains. Thus acidic hydrolysis is usually preferred. Ammonium hydroxide may cause hydrolysis of methoxy groups when it is used to replace ring halogen substituents. An example is the reaction of 6-chloro-3-methoxy-4-methylpyridazine with concentrated ammonia (Eq. 63) (88). Prolonged heating at 150° C was required to produce any reaction, and the product was mainly the aminopyridazinone rather than the desired aminomethoxypyridazine.



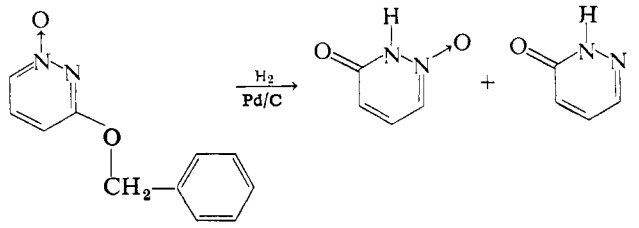
(63)

Sodium methoxide in anhydrous methanol is not usually considered a hydrolytic reagent. However, this reagent converts 3,6-dialkoxypyridazine *N*-oxides to 3-alkoxy-1-hydroxy-6(1*H*)pyridazinones very smoothly (Eq. 64) (95). Acetyl chloride and benzoyl chloride with silver nitrate are reported to give similar results (94). This reaction is closely related to the rearrangement of ring carbon *O*-alkyl groups, which is discussed in the following section.



(64)

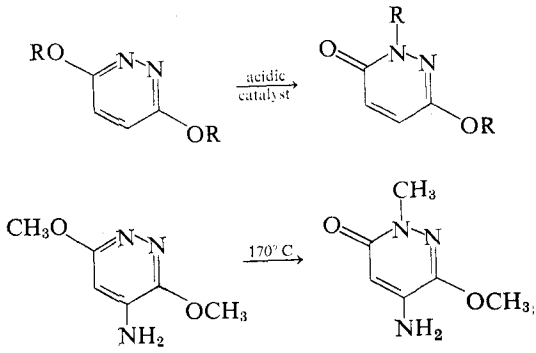
One "neutral hydrolysis" has also been reported (140). In this case the benzyl moiety was removed from 3-benzyloxypyridazine 1-oxide by hydrogenolysis over palladium (Eq. 65). Very short reaction times (1–5 min) left the oxide group intact, but it was removed when the reaction was continued to completion (15–20 min).



(65)

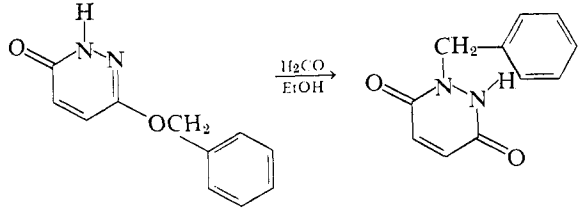
2. *Alkoxy Rearrangements*

a. O to N Rearrangements. Many 3,6-dialkoxypyridazines undergo rearrangement to the corresponding 3-alkoxy-1-alkyl-6(1*H*)pyridazinones (Eq. 66). The reaction can be carried out without a catalyst in some cases, but very high temperatures are required (300° C or more) and the yields are low (99). Strong mineral acids, organic acids such as toluenesulfonic acid (99), and Lewis acids such as aluminum chloride and ferric chloride catalyze the reaction. For example, pure 3,6-dimethoxypyridazine yields less than 5% of the rearranged product when heated at 300° C for several days but rearranges quantitatively when heated at 150° C for 3 hr with anhydrous aluminum chloride (99). Apparently, any source of electronic charge suffices, because 4-amino-3,6-dimethoxypyridazine rearranges at 170° C in 30 min without a catalyst (Eq. 66) (54).



(66)

Several 3-benzyloxy-6(1*H*)pyridazinones have been rearranged similarly (Eq. 67) (237). The reaction proceeds very smoothly under catalysis by formalin in alcohol at 100° C. Apparently, the great lability of the benzyl group is necessary, because there are no other reports of similar reactions.

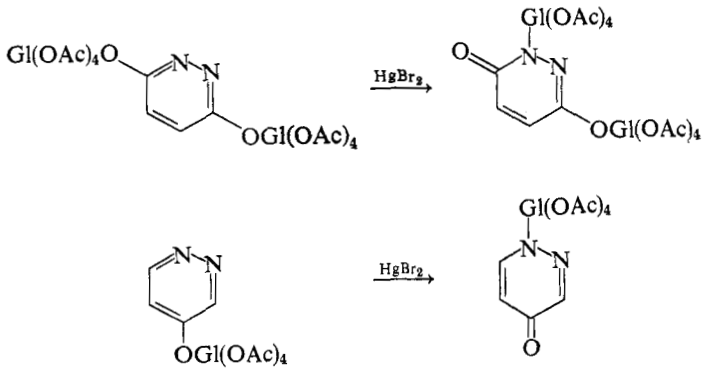


(67)

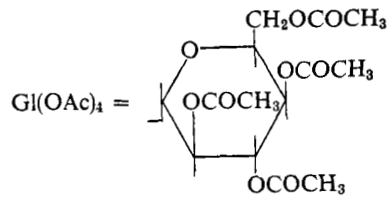
Pyridazine-*O*-glycosides can be rearranged to the *N*-glycosides in a similar reaction (Eq. 68). In addition to 3,6-diglycosides, 4-glycosyloxypyridazines can be rearranged (238). However, the *O*-glycosides are very susceptible to decomposition by acids, and the reactions are catalyzed by mercuric bromide, usually in boiling toluene (142, 143, 238–241). The preparation of the *O*-glycosides was discussed in Section IV.A.1.

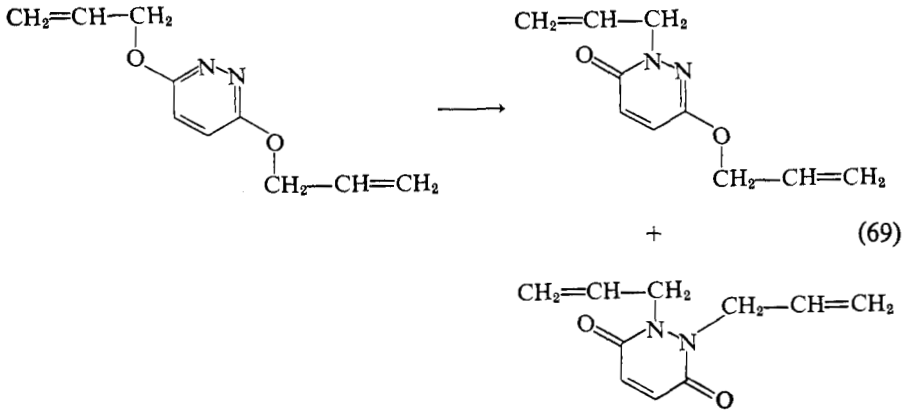
Claisen-type rearrangements occur when 3,6-diallyloxypyridazine is heated at 200° C (Eq. 69) (99). One or both allyl groups may migrate, and the reaction may be conducted with or without a catalyst.

A reaction that resembles *O*- to *N*-alkyl rearrangement occurs when 3,6-dialkoxypyridazines are treated with methyl iodide or dimethyl sulfate under mild conditions (Eq. 70) (99, 213, 243). In fact, the ring nitrogen atom of the product always carries a methyl group, and Eichenberger, Staehelin, and Druey (99) have proposed a mechanism for the reaction which involves formation of an intermediate quaternary pyridazinium compound (99). At higher temperatures with dimethyl sulfate, the bis-*N*-methylmaleic hydrazide may be formed. This reaction has been used to prepare mixed N_1,N_2-disubstituted maleic hydrazides (99, 243).



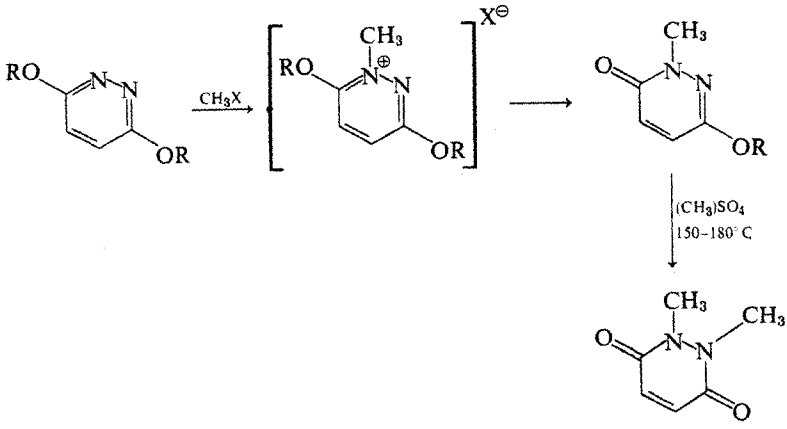
(68)



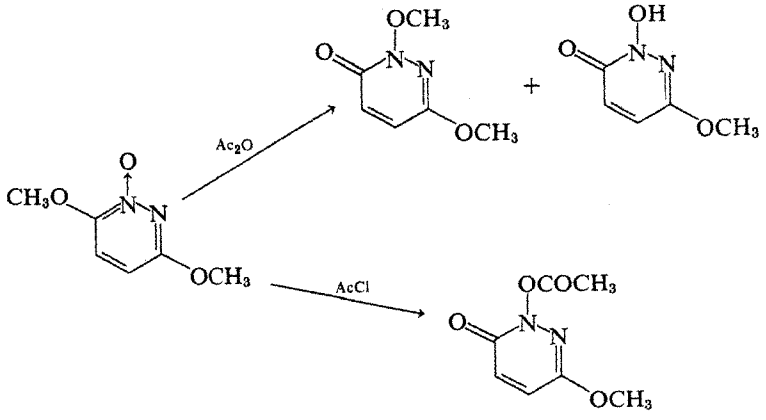


(69)

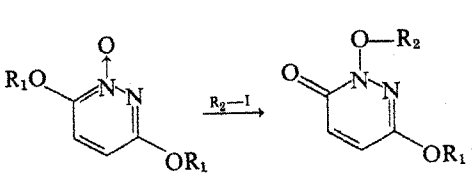
b. O TO O REARRANGEMENTS. The *N*-oxides of 3,6-dialkoxypyridazines undergo a rearrangement which is similar in many respects to the O to N rearrangements discussed in the previous section. For example, 3,6-dimethoxypyridazine 1-oxide yields 1,3-dimethoxy-6(1*H*)pyridazinone when fused alone at 150–160° C for 7 hr (93) or with acetic acid (236) or toluenesulfonic acid (236) in a neutral solvent (Eq. 71). The 1-hydroxy and 1-acetoxypyridazinones were formed as minor by-products when acetic anhydride was used as catalyst (93). The *N*-acetoxypyridazinone was formed exclusively when the *N*-oxide was treated with acetyl chloride (Eq. 71) (93).



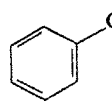
(70)

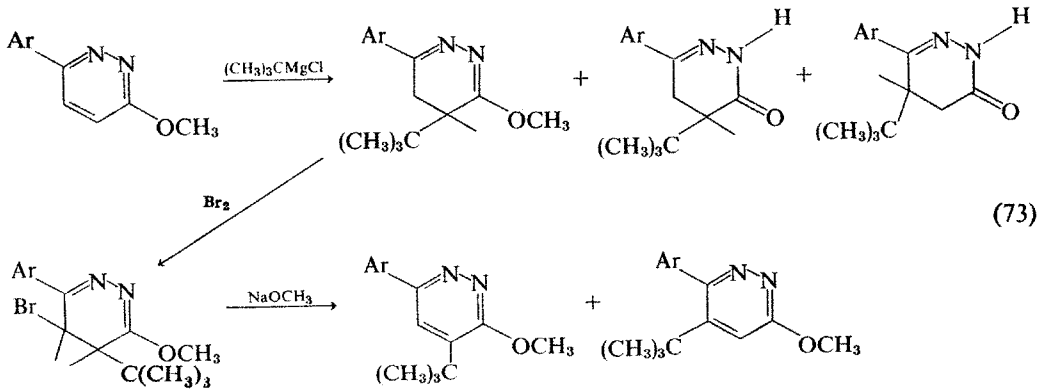


(71)



(72)

$R_1, R_2 = CH_3, C_2H_5,$  , and so on



(73)

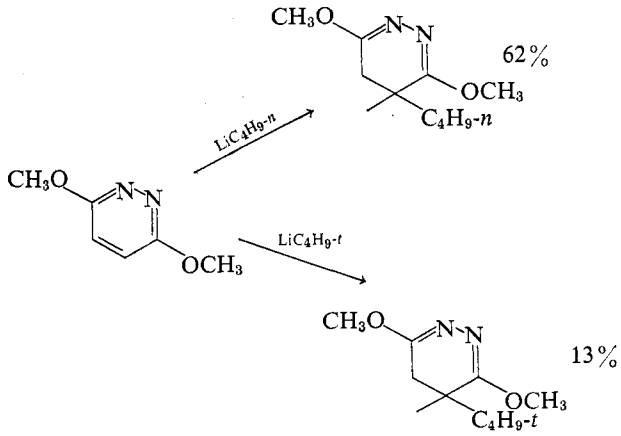
As may be expected, a mixture of rearranged and hydrolyzed products is formed during the preparation of the 3,6-dialkoxypyridazine 1-oxides with hydrogen peroxide in acetic acid (236). However, the *N*-oxides may be formed under very mild conditions (slight warming over several hours), which minimizes the side reactions.

The 3,6-dialkoxypyridazine 1-oxides also undergo an apparent rearrangement when treated with alkyl halides. This reaction is similar to the one discussed in Section V.B.2.a and gives an analogous result. The product always carries the alkyl group of the attacking halide, rather than the original alkoxy group residue (Eq. 72) (244).

3. *Miscellaneous*

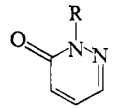
The electron-donating character of the methoxy group has been used to activate the pyridazine ring toward the strongly electrophilic alkyl Grignard and alkyl lithium reagents. For example, *tert*-butylmagnesium chloride attacks 2-methoxy-6-phenylpyridazine by 1,2-addition to the 4,5-double bond (245). The major product was shown to be the 4-butyl isomer of the methoxydihydropyridazine, although two isomeric pyridazinones were also formed. Bromination of the methoxypyridazine was straightforward, but dehydrohalogenation gave a mixture of 4- and 5-butyl-3-methoxy-6-phenylpyridazines, apparently by rearrangement of the butyl group (Eq. 73).

The reactions of *n*-butyl- and *tert*-butyllithiums with 3,6-dimethoxypyridazine are much less complex (Eq. 74) (246). Here too the organometallic reagent adds to the 4,5-double bond, but no displacement of the *O*-alkyl moiety was observed. As expected, the yield of the *n*-butyl adduct was considerably higher than that of the *t*-butyl analog because of steric effects.



(74)

TABLE I. 1-Substituted 6(1*H*)Pyridazinones



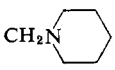
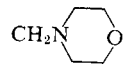
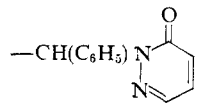
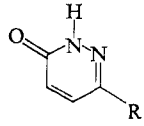
R	MP (°C)	Reference
H (H_2O)	70–71	29
	75	247
H	100–102	85
	102	248
	103	29, 65, 132, 177, 249
	103–104	247, 250, 251
	104–105	75
	No MP	184, 206, 208, 236, 252–256
OH	167–168	257
CH_3	35	258
	38–39	174, 248, 251, 258
	39–40	259
	42–43	260
CH_2OH	142	174
	148–152	261
CH_2COOH	168–170	131, 132, 147, 262
$CH_2COOC_2H_5$	52.5–53	131, 132, 262
$CH_2CONHNH_2$	208–209	132
	213–216	263, 264
	53	177
	82	177
CH_2COCH_3	98–99	131
CH_2COCH_3 (semicarbazone)	215–216	131
C_6H_5	107–109	52, 109
	110–111	75
	239	174
$C_6H_4Br(4)$	142	75
$C_6H_4Cl(3)$	93–95	75
$C_6H_4Cl(4)$	149–150	75
$C_6H_2Cl_3(2,4,5)$	177	75
$C_6H_4CH_3(4)$	101–103	75
$C_6H_4NH_2(4)$	238	75
$C_6H_4NO_2(3)$	178–179	75
$C_6H_4NO_2(4)$	206	75
$C_6H_4NO_2(4)$ (acetate)	189–190	75

TABLE I (*continued*)

R	MP (°C)	Reference
$C_6H_4NO_2(4)$ (benzoate)	268	75
β-L-Ribofuranosyl		239
β-D-Ribopyranosyl		239
β-D-Glucopyranosyl	153–154	265
β-D-Glucopyranosyl tetraacetate		240
	84–86	744

TABLE II. 3-Substituted 6(1*H*)Pyridazinones



R	MP (°C)	Reference
Br	157.5–158.5	154
	158–160	271
Cl	138–139	47, 87, 108, 272, 273
	138–140	181
	140	135
	141–142	274
	142–142.5	59
	No MP	164, 275–280
I	173	261
CH_3 (H_2O)	122–123	292, 293
	119–123	13
	112–116	29
CH_3	138	13
	138–140	66
	143	29, 294
	145–147	275
	No MP	100, 295
CH_3 (HCl)	176–176.5	13, 29
CH_3 (HBr)	184.5–185	13, 29
$CH_2SCH_2C_6H_5$	131.5–132	33
COOH	256–257	275
	257	249
	259–260	72, 176, 249, 302–306
$COOCH_3$	188–189	176, 302

TABLE II (*continued*)

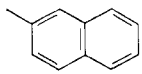
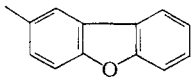
R	MP (°C)	Reference
$COOC_2H_5$	129–130	275
$CONH_2$	320 (dec)	72, 102, 302, 307
$CONHC_6H_5$	255–256	102
$CON(CH_3)C_6H_5$	158	308
$CONHNH_2$	>300 (dec)	302, 309, 310
C_2H_5	95	132, 264
C_2H_5 (HBr)	107–112	29
CH_2CH_2COOH (HBr)	222	297
$CH_2CH_2COOCH_3$	112	297
$CH_2CH_2COOC_2H_5$	92	297
$CH_2CH_2COOC_2H_5$ (HBr)	215	297
$CH_2CH_2CONH_2$	190	297
$(CH_2)_4CH_3$	32–34	298
	52–53	14
$CH_2CH_2CH(CH_3)_2$	63–64	14
$(CH_2)_5CH_3$	60	299
$(CH_2)_7CH_3$	65	124, 299
C_6H_5	201–202	300
	202	31, 129
	No MP	130, 301, 184
$C_6H_4Br(4)$	250–250.5	70, 311
$C_6H_4NH_2(4)$	200	745
$C_6H_3OCH_3(4)Br(3)$	263	312
$C_6H_3OC_2H_5(4)Br(3)$	240–243	312
$C_6H_4Cl(4)$	271–271.5	184, 311
$C_6H_3Cl_2(2,4)$	216–216.5	311
$C_6H_3Cl_2(3,4)$	258–259	311
$C_6H_4I(4)$	174–175	70, 311
$C_6H_4CH_3(4)$	225	184, 313
$C_6H_3(CH_3)_2(2,4)$		185
$C_6H_3(CH_3)_2(2,5)$		185
$C_6H_3(CH_3)_2(3,4)$		185
$C_6H_4OH(4)$	>290	312
$C_6H_4OCH_3(4)$	188–189	148, 184
$C_6H_4OCH_2C_6H_5(4)$	254	312
	256	314
	259–260	6
	144.5–145.5	315

TABLE II (*continued*)

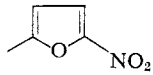
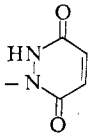
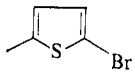
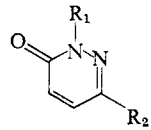
R	MP (°C)	Reference
	289–290	315, 316
	>300	59
		317
		317
NH_2		280, 318
NHC_6H_5	200–201	319, 320
$NHC_6H_4Br(4)$	262	319, 320
$NHC_6H_4Cl(4)$	254	319, 320
$NHC_6H_4OCH_3(4)$	215–216	319, 320
$NHC_6H_4OC_2H_5(4)$	208	319, 320
$NHCH_2C_6H_5$		319
$NHSO_2C_6H_4NH_2(4)$	243–244	321–323
$OCOCH_3$	125	324
$OCOC_2H_5$	106–108	154
$OCOCH_2CH_2Cl$	103.3–104.8	154
$OCOC_3H_7$	79.7–81	154
$OCOCH_2CH_2CH_2Cl$	99.2–100.7	154
$OCOC_4H_9$	84–85	154
$OCOCH_2CH(CH_3)_2$	76–77	154
$OCOC_6H_5$	162.5–164.5	154
OCH_3	161	236
	161–162	244
	162–163	140
	164–166	97
	165	325
	No MP	116, 295
OC_2H_5	175–176	97
OCH_2COOH	166.5	147
$OCH_2COOC_2H_5$	245	147
OC_3H_7	118–119	97
OC_4H_9	102–103	139
OC_6H_5	135	221
$OCH_2C_6H_5$	170	325–327
	174–175	327
$OCH_2C_6H_4Cl(4)$	193	319, 326, 327

TABLE II (*continued*)

R	MP (°C)	Reference
$OCH_2C_6H_4OCH_3(4)$	177	326, 327
$OCH_2C_6H_4NO_2(4)$	237 (dec)	326, 327
β-D-Glucopyranosyloxy	130 (dec)	143, 144
Tetra-*O*-acetyl-β-D-glucopyranosyloxy	183–184	143, 144
$OPO(OCH_3)NHCH(CH_3)_2$	n_D^{25} 1.463	167
$OPS(OCH_3)NH_2$	n_D^{25} 1.5040	167
$OPS(OCH_3)NHCH(CH_3)_2$	102–105	167
$OPS(OCH_3)NHCH(CH_3)C_2H_5$	109–111	167
$OPS(OCH_3)N(C_2H_5)_2$	n_D^{25} 1.5130	167
$OPS(OC_2H_5)NHC_2H_5$	n_D^{25} 1.5302	167
$OPS[OCH(CH_3)C_2H_5]NHCH_3$	99–102	167
$OPS[OCH(CH_3)_2]NHCH_3$	n_D^{25} 1.5308	167
OSO_2CH_3		163
$OSO_2C_2H_5$	112–114	162
$OSO_2CH_2CH_2Cl$		163
$OSO_2C_3H_7$	88–90	162
$OSO_2C_4H_9$	83–84	162
$OSO_2C_4H_9$-i	88	162
$OSO_2C_5H_{11}$-i	86–87	162
$OSO_2C_6H_5$	90	59, 162, 163
$OSO_2C_6H_4CH_3(4)$	140–142	160
	185–186	162
$OSO_2C_6H_4Cl(4)$	135–137	162
$OSO_2C_6H_4NO_2(4)$	190–191	162
$OSO_2CH_2C_6H_5$	128–130	162
$OSi(CH_3)_3$	63–64	168

TABLE III. 1,3-Disubstituted 6(1*H*)Pyridazinones



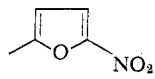
R_1	R_2	MP (°C)	Reference
CH_3	Cl	92–94	99
CH_3	CH_3	44–47	131
		50–51	109, 249
		81–82	328
CH_3	CH_3 (HBr)	150	109
CH_3	COOH	239	131, 176, 249
CH_3	$COOCH_3$	103	131, 176, 249
CH_3	$COOC_2H_5$	67–68	131, 249
CH_3	COCl	116	176, 329
CH_3	$CONH_2$	198–200	176, 329
CH_3	$CONHCH_3$	155–157	176, 329
CH_3	$CON(CH_3)_2$	73–75	176, 329
CH_3	$CON(CH_3)C_6H_5$	108	308
CH_3	C_6H_5	114–115	258
		116	258
		105–106	184
CH_3	$C_6H_4Cl(4)$	236–237	184
CH_3	$C_6H_4CH_3(4)$	116–117	184
		125	330
CH_3	$C_6H_4OCH_3(4)$	106–107	184
CH_3	$C_6H_4OC_2H_5(4)$		319
CH_3	NHC_6H_5	181–182	319
CH_3	$NHC_6H_4Br(4)$	249–250	319
CH_3	$NHC_6H_4Cl(4)$	248	319
CH_3	$NHC_6H_4OCH_3(4)$	200–201	319
CH_3	$NHCH_2C_6H_5$	146	319
CH_3		231	316, 331
CH_3	OCH_3	64–66	99, 332
CH_3	OC_2H_5	63–64	99
CH_3	$OC_2H_5OCH_3$	47–49	99
CH_3	$OC_2H_5OC_2H_5$	45–46	99
CH_3	$OC_2H_5OC_2H_5OCH_3$	bp 123 (0.06 mm)	99
CH_3	OC_3H_7	63–64	99
CH_3	$OCH(CH_3)_2$	115–117	99
CH_3	$OCH_2C_6H_5$	108–110	99
CH_3	$OPS(OCH_3)NHCH_3$	n_D^{25} 1.5205	333
CH_3	$OPS[OCH(CH_3)_2]_2$	37–38.5	164
CH_2Cl	Cl	87–90	334
CH_2Cl	CH_3	96–97	334
$CH_2N(CH_3)_2$	Cl	60–61	335

TABLE III (*continued*)

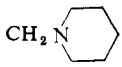
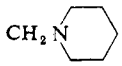
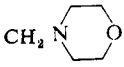
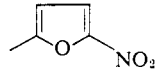
R_1	R_2	MP (°C)	Reference
$CH_2N(CH_3)_2$	I	137–145	261
	Cl	92–94 95–97	261 335
	I	148–152	261
	Cl	126	261
$CH_2N(C_2H_5)_2$	Cl	n_D^{20} 1.5402	335
$CH_2N(CH_2CH_2CN)_2$	Cl	67–71	335
CH_2OH	Cl	115–117	335
CH_2OH	I	163	261
CH_2OH	CH_3	142	174
CH_2OH	$COOC_2H_5$	106–107	176, 336
CH_2OH	C_6H_5	150–161	337
CH_2OH	OCH_3	162–166 (dec)	261
CH_2OCH_3	Cl	50–51	335
CH_2SCN	Cl	153–154	156
$CH_2SPS(OCH_3)_2$	Cl	bp 90 (0.3 mm)	334
$CH_2SPS(OC_2H_5)_2$	Cl	52.5–53.6	334
$CH_2SPO(OC_2H_5)_2$	Cl	bp 115–120 (1 mm)	334
$COCH_3$	Cl	126	338
$COOC_2H_5$	Cl	53–54	156
$COOC_4H_9$	Cl	146–147	156
$CON(C_2H_5)_2$	Cl	49–50	335
C_2H_5	CH_3	229–230 229–231	109 328
C_2H_5	$C_6H_4CH_3(4)$	96–97	330
C_2H_5		149–149.5	316, 331
C_2H_5	OCH_3	53–55	99
C_2H_5	OC_2H_5	31–32	99
C_2H_5	$OCH(CH_3)_2$	121–122	99
CH_2CH_2Cl	Cl	55–57	335
CH_2CH_2Cl	CH_3	141–142	129
CH_2CH_2OH	$COOC_2H_5$	173–176	272
CH_2CH_2CN	Cl	102–104	335
CH_2CH_2CN	C_6H_5		183
$CH_2CH_2N(CH_3)_2$	CH_3	bp 135–137 (15 mm)	128
$CH_2CH_2N(CH_3)_2$	$CH_3(CH_3I)$	270	128
$CH_2CH_2N(CH_3)_2$	$CH_3(C_6H_5CH_2Cl)$	216–217	128
$CH_2CH_2N(CH_3)_2$	$CH_3(C_6H_5CH_2Cl + NaI)$	220	128
$CH_2CH_2N(CH_3)_2$	CH_3 (cetyl bromide)	164–165	128

TABLE III (*continued*)

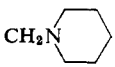
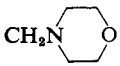
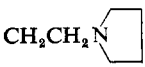
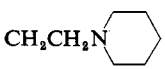
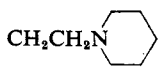
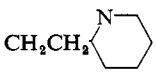
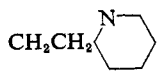
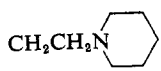
R_1	R_2	MP (°C)	Reference
$CH_2CH_2N(CH_3)_2$	C_6H_5	bp 166–168 (1 mm)	129
		bp 170–172 (3 mm)	301
$CH_2CH_2N(CH_3)_2$	$C_6H_5(HCl)$	195	130
		198	301
$CH_2CH_2N(CH_3)_2$	$C_6H_5(CH_3I)$	242	129
$CH_2CH_2N(C_2H_5)_2$	CH_3	bp 162–163 (16 mm)	128, 339
$CH_2CH_2N(C_2H_5)_2$	$CH_3(CH_3I)$	164	128
$CH_2CH_2N(C_2H_5)_2$	C_6H_5	bp 185–187 (1 mm)	301
$CH_2CH_2N(C_2H_5)_2$	$C_6H_5(HCl)$	81	301
$CH_2CH_2N(C_2H_5)_2$	C_6H_5 (picrate)	115–118	746
$CH_2CH_2CH_2N(CH_3)_2$	CH_3	bp 169.5–170 (17 mm)	129
$CH_2CH_2CH_2N(CH_3)_2$	$CH_3(CH_3I)$	231	129
$CH_2CH_2CH_2N(CH_3)_2$	C_6H_5	41–42	129
$CH_2CH_2CH_2N(CH_3)_2$	$C_6H_5(CH_3I)$	181	129
$CH_2CH_2CH_2N(C_2H_5)_2$	CH_3	bp 177–179 (20 mm)	129
$CH_2CH_2CH_2N(C_2H_5)_2$	$CH_3(CH_3I)$	174–175	129
	CH_3	82	177, 289
	CH_3	109	177, 289
	CH_3 (CH_3I)	207	128
	C_6H_5	84	129
	C_6H_5 (CH_3I)	190	129
	CH_3	bp 155–160 (20 mm)	129
	CH_3 (CH_3I)	227	128
		228	129
	C_6H_5	bp 179–181 (1 mm)	301
	C_6H_5 (HCl)	150–152	301
	C_6H_5	bp 179–181 (1 mm)	129
		77–78	340

TABLE III (*continued*)

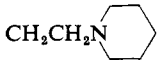
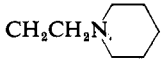
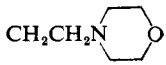
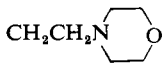
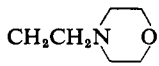
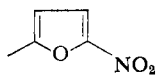
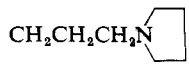
R_1	R_2	MP (°C)	Reference
	C_6H_5 (HCl)	150–152	340
	C_6H_5 (CH_3I)	211	129
	CH_3 (CH_3I)	245	128
	C_6H_5	64–65	129
	C_6H_5 (CH_3I)	227	129
CH_2CH_2OH	Cl	101–102	335
$CH_2CH_2OCOCH_3$	Cl	73–75	335
$CH_2CH_2OCOCH_2Cl$	Cl	58–59	335
$CH_2CH_2OCOCHCl_2$	Cl	97–99	335
$CH_2CH_2OCOCCl_3$	Cl	119–120	335
CH_2CH_2SCN	Cl	104–105	335
$CH_2CH{=}CH_2$	CH_3	bp 114–120 (16 mm)	339
$CH_2CH{=}CH_2$	$OCH_2CH{=}CH_2$	bp 74–81 (0.05 mm)	99
$CH_2CH_2CH_3$		106.5–107.5	316, 331
CH_2COCH_3	CH_3	bp 84 (0.05 mm) 99.5–100	262, 341 131
CH_2COCH_3	C_6H_5	140–142	341
$CH(CH_3)COCH_3$	CH_3	bp 90–100 (0.1 mm) bp 94–99 (0.4 mm)	341 131, 262
$CH(C_2H_5)COCH_3$	CH_3	bp 84 (0.05 mm)	341
$CH(CH_3)CH(OH)CH_3$	CH_3	73–76	341
$CH(CH_3)C(CH_3,OH)CH_3$	CH_3	57.5–58.5	341
CH_2CH_2COOH	Cl	106–109	335
CH_2CH_2COOH	CH_3		132, 264
$CH_2CH_2COOC_2H_5$	CH_3	bp 124 (0.5 mm)	132, 264
$CH_2CH_2CONHNH_2$	CH_3	151–153	132, 264
$CH_2CH_2CON(C_2H_5)_2$	Cl	60–62	335
$CH_2CH_2CON(C_2H_5)_2$	CH_3		342
$CH_2CH_2CH_2N(C_2H_5)_2$	$COOC_2H_5$ (HCl)	155–156	176
$CH_2CH_2CH_2N(C_2H_5)_2$	$COOC_2H_5$ (oxalate)	169–171	176
$CH_2CH_2CH_2N(C_2H_5)_2$	$COOC_2H_5$ (CH_3I)	233–234	176
	CH_3	bp 149–152 (2 mm)	129

TABLE III (*continued*)

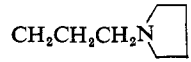
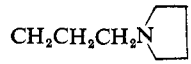
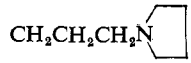
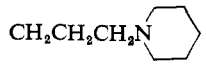
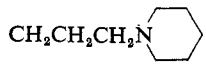
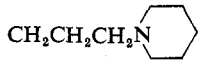
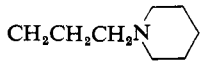
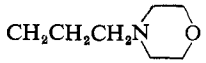
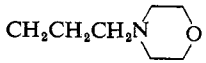
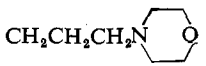
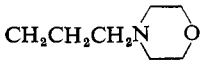
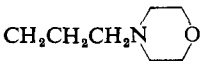
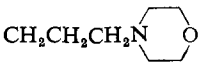
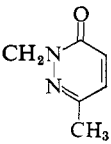
R_1	R_2	MP (°C)	Reference
	CH_3 (CH_3I)	197	129
	C_6H_5	56	129
	C_6H_5 (CH_3I)	137	129
	CH_3	bp 145 (1 mm)	129
	CH_3 (CH_3I)	195	129
	C_6H_5	78	129
	C_6H_5 (CH_3I)	212	129
	CH_3	60–62	129
	CH_3 (HCl)	190	129
	CH_3 (2HCl)	201–204	129
	CH_3 (CH_3I)	248	129
	C_6H_5	66	129
	C_6H_5 (CH_3I)	216	129
	CH_3	161–162	77

TABLE III (*continued*)

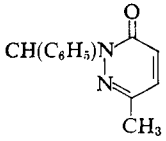
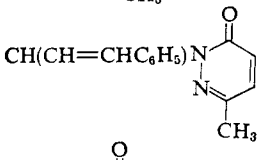
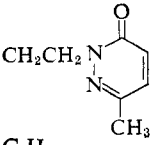
R_1	R_2	MP (°C)	Reference
	CH_3		343
	CH_3		343
	CH_3	180	77
C_4H_9	Cl	bp 67 (1.5 mm)	335
C_4H_9	COOH	119–121	176, 336
C_4H_9	$COOCH_3$	bp 85–90 (0.1 mm)	176, 336
$CH(COCH_3)CH_2CH_2CH_3$	CH_3	bp 96 (0.1 mm)	341
$CH_2COCH_2CH_3$	CH_3	95–97	341
$CH_2CH_2COCH_3$	CH_3	57–59	341
$CH_2CH_2COCH_3$	CH_3 (semicarbazone)	179–180	341
$CH_2COCH(CH_3)_2$	CH_3	126–127	341
C_5H_{11}	CH_3	bp 148–150 (16 mm)	77
$CH_2COC_3H_7$	CH_3	73–75	341
$CH_2COCH(CH_3)CH_2CH_3$	CH_3	92.5–93.5	341
$CH_2COCH_2CH(CH_3)_2$	CH_3	102–103	341
$CH(COCH_3)C_4H_9$	CH_3	bp 118 (0.35 mm)	341
$CH(COCH_3)C_5H_{11}$	CH_3	bp 135 (0.6 mm)	341
$CH_2COC_4H_9$	CH_3	84.5–86.0	341
C_7H_{15}	CH_3	bp 170–172 (16 mm)	77
$CH_2COC_5H_{11}$	CH_3	103–104	341
$CH_2COC_6H_5$	Cl	132–135	335
$CH_2COC_6H_{13}$	CH_3	92–95	341
$CH_2COC_7H_{15}$	CH_3	85–86	341
$(CH_2)_{10}COOH$	CH_3		264
$(CH_2)_{10}COOC_2H_5$	CH_3	bp 166–170 (0.04 mm)	132, 264
$(CH_2)_{10}CONHNH_2$	CH_3	85–87	132, 264
$C_{12}H_{25}$	CH_3	bp 126–127 (16 mm)	339
$C_{12}H_{25}$	$OPO(OC_2H_5)_2$	n_D^{25} 1.4843	164
$C_{16}H_{33}$	CH_3	45	339
β-D-Ribofuranosyl	Cl		239
β-D-Ribofuranosyl	OCH_3	122–123	325
2-Deoxy-D-*erythro*-pentofuranosyl	$OCH_2C_6H_5$	133	325
β-D-Ribofuranosyl	$OCH_2C_6H_5$	118	325

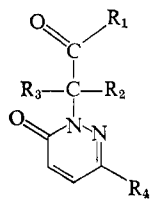
TABLE III (*continued*)

R_1	R_2	MP (°C)	Reference
β-D-Glucopyranosyl	Br		142
β-D-Ribopyranosyl	Cl		239
β-D-Glucopyranosyl	Cl		142
β-D-Glucopyranosyl	CH_3	154	265
β-D-Glucopyranosyl	OCH_3		142
β-D-Glucopyranosyl	β-D-Glucopyranosyloxy	117–118	143
β-D-Glucopyranosyltetra-acetate	β-D-Glucopyranosyloxy-tetraacetate	177–178	242
D	$OCH_2C_6H_5$		319
OH	Cl	173–174	338
$OCOCH_3$	Cl	126	338
OH	OCH_3	177–178	93, 141
		178	94, 338, 344
		178–179	95, 140, 345
$OCOCH_3$	OCH_3	127	338, 344
$OCOC_6H_5$	OCH_3	136–137	141
OH	OC_2H_5	120–121	346
		125–126	95
OH	OC_3H_7	113–114	95
OH	OC_4H_9	87–88	95
OH	OC_5H_{11}-*i*	96–97	95
OH	OC_6H_{13}	76–77	95
OCH_3	OCH_3	66–67	140
		68–69	244
		71–71.5	93, 236
		71–72	347
OCH_3	OC_2H_5	50	244
OC_2H_5	OCH_3	49–51	244
OC_2H_5	OC_2H_5	60–60.5	244
$OCH_2C_6H_5$	CH_3	133–134	94
$OCH_2C_6H_5$	OCH_3	82.5–83	244
$OCH_2C_6H_5$	OC_2H_5	99–99.5	244
$OCH_2COC_6H_5$	OCH_3	117–118	244
$OCH_2COC_6H_5$	OC_2H_5	113.5–115	244
$OCOCH_3$	OC_2H_5	135.5–136	244
$OCOC_6H_5$	OC_2H_5	106.5–107	244
$OSO_2C_6H_4CH_3(4)$	OCH_3	139–140	348
$SO_2C_6H_4NHCOCH_3(4)$	CH_3		348
	Cl	60–64	744
	C_6H_5	93–95	744

TABLE III (*continued*)

R_1	R_2	MP (°C)	Reference
	Br	129–130	744
	Cl	130–132	744
	CH_3	132–135	744
	C_6H_5	110–113	744
	Cl	57–60	744
	C_6H_5	60–63	744

TABLE IV. 3-Substituted 6-Oxo-1(6*H*)pyridazineacetic Acids



R_1	R_2	R_3	R_4	MP (°C)	Reference
OH	H	H	Cl	220	135, 138, 147, 349, 350
OCH_3	H	H	Cl	68	335
OC_2H_5	H	H	Cl	78	135, 138, 147, 350
OH	H	H	CH_3	273–274	131, 132, 262
OH	H	H	COOH	222–223	131
OC_2H_5	H	H	$COOC_2H_5$	82–83	131
$NHNH_2$	H	H	$CONHNH_2$	227–228	263
OC_2H_5	H	H	CH_3	bp 159–167 (5 mm)	131, 132, 262
OH	H	H	C_2H_5		132, 264
OC_2H_5	H	H	C_2H_5	48–50	132, 264
OH	H	H	C_6H_5	227–228	341

TABLE IV (*continued*)

R_1	R_2	R_3	R_4	MP (°C)	Reference
				230 (dec)	130
				No mp	132, 264
OC_2H_5	H	H	C_6H_5	89–92	130
				100–102	132, 264, 341
OH	H	H	$C_6H_4Br(4)$		132, 264
OC_2H_5	H	H	$C_6H_4Br(4)$	171–172	132, 264
OH	H	H	OCH_2COOH	205	147, 349
OC_2H_5	H	H	$OCH_2COOC_2H_5$	53	147
OH	H	H	SO_2CH_3		133
OC_2H_5	H	H	SO_2CH_3	96–96.5	133
OH	H	H	$SO_2C_2H_5$		133
OC_2H_5	H	H	$SO_2C_2H_5$	51.5	133
OH	H	H	$SO_2CH(CH_3)_2$		133
OC_2H_5	H	H	$SO_2CH(CH_3)_2$	88–89.5	133
OH	CH_3	H	CH_3	141–142	131
OC_2H_5	CH_3	H	CH_3	bp 97–101 (0.1 mm)	131
OC_2H_5	$COOC_2H_5$	H	Cl	bp 144 (0.2 mm)	335
OH	CH_3	CH_3	CH_3	214–214.5	131, 132, 262
OC_2H_5	CH_3	CH_3	CH_3	105–114 (0.3 mm)	131, 132, 262
OH	C_2H_5	H	CH_3	bp 92 (0.05 mm)	132, 264, 341
OH	C_3H_7	H	CH_3	162–163	132, 264, 341
OC_2H_5	C_3H_7	H	CH_3	bp 111 (0.15 mm)	132, 264
OH	$CH(CH_3)_2$	H	CH_3	148–150	341
OC_2H_5	$CH(CH_3)_2$	H	CH_3	bp 95–99 (0.01 mm)	341
OH	C_4H_9	H	CH_3	152–153	341
OC_2H_5	C_4H_9	H	CH_3	bp 117 (0.3 mm)	132, 264
OH	C_5H_{11}	H	CH_3	153–154.5	341
OC_2H_5	C_5H_{11}	H	CH_3	bp 129 (0.2 mm)	132, 264
OH	C_6H_5	H	CH_3		132, 264
OC_2H_5	C_6H_5	H	CH_3	121–123	132, 264
OC_3H_7	H	H	Cl	63–64	335
OC_4H_9	H	H	Cl	82–83	335
NH_2	H	H	Cl		280, 351
$NHCH_3$	H	H	Cl	134–136	335
$NHCH_2CH_2N(CH_3)_2$	H	H	Cl (HCl)	263	135, 352
$NHCH_2CH_2N(C_2H_5)_2$	H	H	Cl (HCl)	258	135, 352
NH_2	H	H	CH_3	224–225	262
NH_2	H	H	C_6H_5	216	130
$NHNH_2$	H	H	Cl		280, 351
$NHN{=}C(CH_3)_2$	H	H	Cl	216	353, 354
$NHNHCH(CH_3)_2$	H	H	Cl	311	353, 354
$NHNH_2$	H	H	CH_3	199–200	132
				199–201	263, 264

TABLE IV (*continued*)

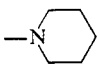
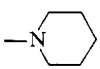
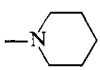
R_1	R_2	R_3	R_4	MP (°C)	Reference
$NHNH_2$	H	H	C_2H_5	170–171	132, 264
$NHNH_2$	H	H	C_6H_5	211–213	132, 264
$NHNH_2$	H	H	$C_6H_4Br(4)$	223–226	132, 264
$NHNH_2$	CH_3	H	CH_3	134.5–135.0	132, 264
$NHNH_2$	CH_3	CH_3	CH_3	165–166	132, 264
$NHNH_2$	C_2H_5	H	CH_3	125.5–127	132, 264, 341
$NHNH_2$	C_3H_7	H	CH_3	112–115	132, 264
$NHNH_2$	C_4H_9	H	CH_3	122–124	132
$NHNH_2$	C_5H_{11}	H	CH_3	108–109	132, 264
$NHNH_2$	C_6H_5	H	CH_3	191–192	132
				199–200	264
$OCH_2CH_2N(CH_3)_2$	H	H	Cl (HCl)	120	135, 138
$OCH_2CH_2N(CH_3)_2$	H	H	Cl (tartrate)	314	135, 138
$OCH_2CH_2N(C_2H_5)_2$	H	H	Cl (HCl)	118	135, 138
NHC_6H_5	H	H	Cl	169–170	335
NHC_6H_5	H	H	CH_3	203–204	131, 132, 262
				206	342
$N(CH_3)_2$	H	H	Cl	125–128	335
$N(CH_3)_2$	H	H	CH_3	158–159	342
				160	130, 355
$N(CH_3)_2$	H	H	C_6H_5	131	130, 301, 340 356
$N(C_2H_5)_2$	H	H	Br	123–124.5	357
$N(C_2H_5)_2$	H	H	Cl	96–99	357
$N(C_2H_5)_2$	H	H	CH_3	110.5–112	262
$N(C_2H_5)_2$	CH_3	H	Cl	78–80	335
$N(C_2H_5)_2$	C_6H_5	H	Cl	147	335
$N(CH_2CH{=}CH_2)_2$	H	H	CH_3	125	130, 355
$N(CH_2CH{=}CH_2)_2$	H	H	C_6H_5	102–104	130, 301, 340, 356
$N(C_3H_7)_2$	H	H	Cl	128–129	335
$N(C_3H_7)_2$	H	H	C_6H_5	144–146	135
				145	356
$N[CH(CH_3)_2]_2$	H	H	Cl	201–202	335
$N[CH(CH_3)_2]_2$	H	H	C_6H_5	144–146	301, 356
$N(C_4H_9)_2$	H	H	Cl	108	335
$N(C_2H_5)C_6H_5$	H	H	Cl	169–170	335
$N(C_6H_5)_2$	H	H	Cl	232	335
	H	H	Cl	130–134	357
	H	H	CH_3	171	130
				178	342, 355
	H	H	C_6H_5	158	130, 301, 340, 356

TABLE IV (*continued*)

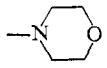
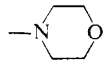
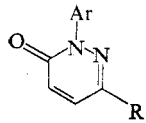
R_1	R_2	R_3	R_4	MP (°C)	Reference
	H	H	CH_3	185 195	355 130
	H	H	C_6H_5	175	130, 301, 340, 356

TABLE V. 1-Aryl-3-Substituted 6(1*H*)Pyridazinones



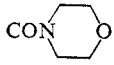
Ar	R	MP (°C)	Reference
C_6H_5	Br	122–124	52, 192, 194, 358
		226–228	194
C_6H_5	Cl	116–118	24, 52, 192, 194, 358
		117–118	27
C_6H_5	CH_3	79–80	187, 190, 191
		81–82	3
C_6H_5	COOH	210–212	362, 363
C_6H_5	$CONH_2$	224–225	362, 363
C_6H_5	$CON(CH_3)_2$	124–126	363
C_6H_5		134–135	363
C_6H_5	C_6H_5	150–151	359
		91–93	360, 361
C_6H_5	NH_2	149–151	192, 194
		153–154	52
C_6H_5	NH_2 (HCl)	170–171	192, 194
C_6H_5	$NHCH_3$	145–147	24, 52, 192
C_6H_5	NHC_4H_9	126–128	52
C_6H_5	$N(CH_3)_2$	130–132	24, 52, 192
C_6H_5	$N(C_2H_5)_2$	71–73	52
C_6H_5		161–163	52
C_6H_5		111–113	52

TABLE V (*continued*)

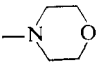
Ar	R	MP (°C)	Reference
C_6H_5		181–183	24, 192
C_6H_5	$OCOCH_3$	108–110	52
C_6H_5	OCH_3	76–77	49, 52
C_6H_5	OC_2H_5	85–86	52
		86–87	99, 196
C_6H_5	$OCH_2CH_2N(C_2H_5)_2$	bp 190–194 (0.4 mm)	52
C_6H_5	$OCH_2CH_2N(C_2H_5)_2$ (HCl)	141–143	52
C_6H_5	Tetra-*O*-acetyl-β-D-glucosyloxy	165–167	242
C_6H_5	β-D-Glucosyloxy	113–115	242
C_6H_5	$OPO(OCH_3)NHCH(CH_3)_2$	n_D^{25} 1.5247	167
C_6H_5	$OPO(OC_2H_5)_2$	n_D^{25} 1.5374	164, 165
C_6H_5	$OPS(OCH_3)_2$	46.5–47	164
C_6H_5	$OPS(OC_2H_5)_2$	56–57	164, 165
C_6H_5	$OPS(OCH_3)NHCH_3$	n_D^{25} 1.5401	167
C_6H_5	$OPS(OCH_3)NHC_3H_7$	n_D^{25} 1.5732	167
C_6H_5	$OPS(OCH_3)NHCH(CH_3)_2$	n_D^{25} 1.5692	167
C_6H_5	$OPS(OC_2H_5)NHC_2H_5$	n_D^{25} 1.5688	167
C_6H_5	$OSO_2C_2H_5$	145	162
C_6H_5	$OSO_2C_3H_7$	115	162
C_6H_5	$OSO_2C_4H_9$	160	162
C_6H_5	$OSO_2C_5H_{11}$-*i*	198	164
C_6H_5	$OSO_2C_6H_5$	78–80	164
C_6H_5	$OSO_2C_6H_4CH_3(4)$	69–70	164
C_6H_5	$OSO_2C_6H_4NO_2(4)$	112	164
C_6H_5	$OSO_2CH_2C_6H_5$	75	164
$C_6H_4Br(4)$	CH_3	72–73	109
$C_6H_4Br(4)$	C_6H_5	175–177	359
$C_6H_4Br(4)$	$OPO(OC_2H_5)_2$	67–67.5	164
$C_6H_4Br(4)$	$OPS(OCH_3)NHCH(CH_3)_2$	n_D^{25} 1.5786	167
$C_6H_4Cl(2)$	OC_2H_5	114–116	196
$C_6H_4Cl(4)$	Cl	138–140	192, 194, 358
$C_6H_4Cl(4)$	$N(CH_3)_2$	174–176	192, 194
$C_6H_4Cl(4)$		164–166	192, 194
$C_6H_4Cl(4)$	OC_2H_5	141–142	196
$C_6H_4CH_3(2)$	COOH	236	362
$C_6H_4CH_3(3)$	CH_3	68	188
$C_6H_4CH_3(4)$	Cl	108–109	194, 358
$C_6H_4CH_3(4)$	COOH	229–230	362
$C_6H_4CH_3(4)$	OC_2H_5	108–110	192
$C_6H_5NH_2(4)$	$N(CH_3)_2$	170–172	192, 194
$C_6H_4NH_2(4)$	$N(CH_3)_2$ (HCl)	252–255 (dec)	192, 194
$C_6H_4N(CH_3)_2(4)$	$N(CH_3)_2$	150–152	192, 194

TABLE V (*continued*)

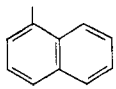
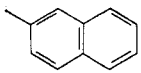
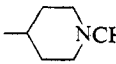
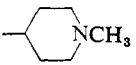
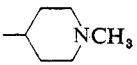
Ar	R	MP (°C)	Reference
$C_6H_4NO_2(4)$	Cl	195–199	192, 194, 747
$C_6H_4NO_2(4)$	CH_3	184–185	187, 191
$C_6H_4NO_2(4)$	$N(CH_3)_2$	210–212	192, 194
$C_6H_4NO_2(4)$	OCH_3	161–162	747
$C_6H_4NO_2(4)$	$OPO(OCH_3)NHCH_3$		167
$C_6H_4NO_2(4)$	$OPO(OC_4H_9)_2$	32–32.5	164
$C_6H_4NO_2(4)$	$OPS(OCH_3)NHCH(CH_3)_2$	n_D^{25} 1.5308	167
$C_6H_3(NO_2)_2(2,4)$	Cl	167	274, 358
$C_6H_4NO_2(3)$	Cl	188–189	748
$C_6H_4NO_2(3)$	OCH_3	158–160	748
$C_6H_4OCH_3(2)$	COOH	212–213	362
$C_6H_4OCH_3(4)$	CH_3	93–94	364
$C_6H_4OC_2H_5(4)$	CH_3	100–101	364
$CH_2C_6H_5$	Cl		319
$CH_2C_6H_5$	CH_3		137
$CH_2C_6H_5$	OCH_3	bp 131–133 (0.05 mm)	99
$CH_2C_6H_5$	$OCH_2C_6H_5$	81	319, 326, 327, 365
$CH_2C_6H_5$	$OCH_2C_6H_4Cl(4)$	118	326
$CH_2C_6H_5$	$OCH_2C_6H_4NO_2(4)$	81–83	326
$CH_2C_6H_4Cl(4)$	Cl		319
$CH_2C_6H_4Cl(4)$	$OCH_2C_6H_5$	74	326
$CH_2C_6H_4Cl(4)$	$OCH_2C_6H_4Cl(4)$	116	319, 326
$CH_2C_6H_4NO_2(4)$	$OCH_2C_6H_4NO_2(4)$	153	326, 327
$CH_2C_6H_4OCH_3(4)$	$OCH_2C_6H_4OCH_3(4)$	93	326
$CH_2CH(Cl)C_6H_5$	Cl	109–111	335
	Cl	118–120 126–128	194 358
	Cl	155–156	194, 358
	CH_3		188
	C_6H_5	140–142	130
	CH_3	87–89	345
	C_6H_5	122–125	68, 272, 366
	C_6H_5 (HBr)	310 (dec)	68, 272, 366

TABLE V (*continued*)

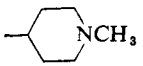
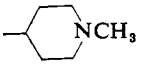
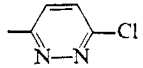
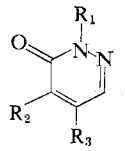
Ar	R	MP (°C)	Reference
	$C_6H_4OCH_3(4)$ (tartrate)	199–200	366
	(HCl)	286	366
	Cl	151–152	59
	Cl		150
	C_6H_5		150
	Br		150
	Cl		150
	C_6H_5		150
	Cl	57	149
	C_6H_5	60–63	149

TABLE VI. 1,4- and 1,5-Disubstituted 6(1*H*)Pyridazinones



1,5-Disubstituted derivatives

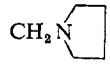
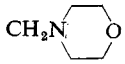
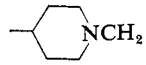
R_1	R_2	MP (°C)	Reference
H	Cl	176.5–177.5	236
H	CN	185–186	251, 281, 282
H	CH_3	134	86
		156	92
		157–158	88
		158–159	132, 264
H	COOH	199–200	251, 281–285
H	$COOCH_3$	159	88
H	$COOC_2H_5$	85	286
H	$CONH_2$	270	286
H	CONHCOOH	232	287, 288
H	$CSNH_2$	305	287, 288
H	*N*-Substituted amidines		287, 288
H	$CONHNH_2$	240 (dec)	286
H	NH_2	229–230	233
		230–231	234
H	NH_2 (picrate)	187–188	234
H	$NHCH_2CH_2OH$(HCl)	248–250	749
CH_3	CN	131–132	251, 258
CH_3	COOH	125–126	251, 258
CH_2COOH	CH_3		132
$CH_2COOC_2H_5$	CH_3	75–76	132
$CH_2CONHNH_2$	CH_3	203–204.5	132
$CH_2N(C_2H_5)_2$	CN	93–95	177, 289
	CN	129	177
C_6H_5	Cl		266
C_6H_5	CH_3	87–88	52
		89–90	267
C_6H_5	$N(CH_3)_2$	52–54	52
C_6H_5	OCH_3	99–101	189
C_6H_5		bp 189–193 (0.2 mm)	200
$C_6H_{11}O_5$	CN	236-238	240
$C_6H_{11}O_5$	CN (tetracetyl)	172–173	263

TABLE VI (*continued*)

R_1	R_2	MP (°C)	Reference
	CN	247–250 (dec)	272
	COOH	201–203	744
	$COOC_2H_5$	156–159	744

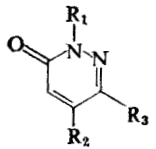
1,4-Disubstituted derivatives

R_1	R_3	MP (°C)	Reference
H	CH_3	152.5	86
		151–153	66
		154	88
		162	92
H	COOH	303 (dec)	65, 290, 750
H	$COOCH_3$	163	88
H	$COOC_2H_5$	127–128	65, 750
H	NH_2	286–287	30
		288 (dec)	205
H	NH_2 (diacetate)	253–254	268
H	$NHCOCH_3$	319–322	228, 268
H	$NH(CH_2)_3N(C_2H_5)_2$	147–149	749
H	$NH(CH_2)_3N(C_4H_9)_2$	137–138	749
H	$NHNH_2$		205
H	OC_2H_5	196–197	268
OCH_3	OCH_3		269
C_6H_5	Cl	83–85	49, 52
C_6H_5	CH_3	84–84.5	270
C_6H_5	COOH	180–181	291
C_6H_5	$N(CH_3)_2$	102–103	49
C_6H_5	$N(CH_3)_2$ (picrate)	191–191.5	49
C_6H_5		165–165.5	49
C_6H_5	 (picrate)	140–142	49
C_6H_5	ONa	229–230	231
C_6H_5	OCH_3	93–95	49
		92–93	89
C_6H_5	OC_2H_5	125–126	231
		124–125	62

TABLE VI (*continued*)

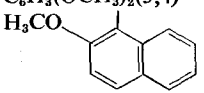
R_1	R_3	MP (°C)	Reference
$C_6H_4COOC_2H_5(4)$	OC_2H_5	131–132	231
$C_6H_4NH_2(4)$	OH	250–251	231
$C_6H_4NO_2(4)$	OH	299–300	231
$C_6H_4NO_2(4)$	OC_2H_5	249–250	231
$C_6H_4OC_2H_5(4)$	OC_2H_5	159–160	231
CH_2CH_2OH	COOH	173–176	750
CH_2CH_2OH	$COOC_2H_5$	85–88	750

TABLE VII. 1,3,4-Trisubstituted 6(1*H*)Pyridazinones



R_1	R_2	R_3	MP (°C)	Reference
H	Cl	Cl	169–171	30, 85
			203	87
H	CH_3	Cl	222	92, 283
			224	101
			224–225	436
			227	88
			231–232	141
H	COOH	Cl	245 (dec)	88
H	$COOCH_3$	Cl	99–101	88
H	$COOC_2H_5$	Cl	112	373
H	$CONH_2$	Cl	259–260	373
H	NH_2	Cl	278–280	30
H	$N(CH_3)_2$	Cl	127–128	49
H	$NHNH_2$	Cl		205
H	OH	Cl	282–283	335
H	OCH_3	Cl	286–288	335
H	OC_2H_5	Cl	240–241	268
H	Br	C_6H_5	235–236	74, 256
H	Cl	C_6H_5	230–231	74, 256
H	Cl	$C_6H_4CH_3(2)$	219–220	489
H	Cl	$C_6H_4Cl(4)$	211–212	74, 256
H	Cl	$C_6H_4NHCOCH_3$	265	74, 256
H	Cl	$C_6H_4NO_2(3)$	266–267	74, 256

TABLE VII (*continued*)

R_1	R_2	R_3	MP (°C)	Reference
H	Cl	$C_6H_4OH(4)$	296–298	74, 256
H	Cl	$C_6H_4OCOCH_3(4)$	221–222	74, 256
H	Br	$C_6H_4OCH_3(4)$	228–229	490
H	Cl	$C_6H_4OCH_3(4)$	219–220	256
			227–228	74
H	Cl	$C_6H_3(OCH_3)_2(3,4)$	237–238	74, 256
H	Cl		246–247	74
			247	256
H	Cl	$OPS(OC_2H_5)_2$	144–145	166
H	Br	$OSO_2C_6H_5$	202	751
H	CH_3	CH_3	221–222	66
			220–221	251
			230–231	51
			225–228	264
			232–233	132
H	CH_3	CH_3 (HBr)	183–185	51
H	COOH	CH_3	247 (dec)	65
H	$COOC_2H_5$	CH_3	114–116	65
			180–183	750
H	COOH	COOH	291	65
H	$COOC_2H_5$	$COOC_2H_5$	86–88	65
H	C_6H_5	CH_3	215–216	491
H	CH_3	$CH_2CH_2CH_3$	77–78	492
H	OCH_3	$CH(CH_3)_2$	207–208	493
H	CH_3	$C_6H_4Br(4)$	220	452
H	CH_3	$C_6H_3Cl_2(3,4)$	260–261	311
			260.2–263	70

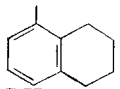
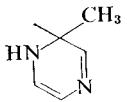
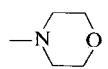
H	CH_3	$C_6H_4CH_3(4)$	217	452
H	CH_3	$C_6H_4C_6H_5(4)$	256	452
H	CH_3		245	452
H	C_6H_5	C_6H_5		181, 184
			177–178	450
H	$C_6H_4Cl(4)$	$C_6H_4Cl(4)$	202	251
H	C_6H_5	$CH_2C_6H_5$	142	494
H	OCH_3		181 (dec)	493
H	CH_3	OCH_3	210	244
			210–211	236
			214–215	93
			215–216	141
H	CH_3	$OSO_2C_6H_5$	143	751
H	COOH	OCH_3	259 (dec)	454
H	$COOCH_3$	OCH_3	178–179	454
H	$CONH_2$	OCH_3	265–266	454
H	CH_2Cl	OCH_3	213–214	93
H	$CH(CH_3)_2$	OCH_3	140–141	453
H	C_6H_5	OCH_3	214–215	453
H	NH_2	OCH_3	266	161, 454
H	NH_2	OCH_3(HCl)	217–218	454
H	$NHSO_2C_6H_4NH_2(4)$	OCH_3	266	454
H	CH_3	OC_2H_5	207	244
H	CH_3	NH_2	253	752
H	CH_3	Decahydro-2-hydroxy-2,5,5,8*a*-tetramethyl-1-naphthyl	212–213	38
OH	Cl	OCH_3	202–203	344, 488

TABLE VII (*continued*)

R_1	R_2	R_3	MP (°C)	Reference
OH	CH_3	OCH_3	203–204	93
			205–206	95
OH	OCH_3	OCH_3		347, 453
OH	CH_3	OC_2H_5	176–177	346
$OCOCH_3$	Cl	OCH_3	133–134	488
$OCOCH_3$	CH_3	OCH_3	98–99	244
			99–100	93
$OCOCH_3$	CH_3	OC_2H_5	114–115	435
$OCOC_6H_5$	Cl	OCH_3	177–178	488
$OCOC_6H_5$	CH_3	OCH_3	124.5–125.5	244
$OCOC_6H_5$	CH_3	OC_2H_5	122–123.5	244
$OCH_2COC_6H_5$	CH_3	OCH_3	109–110.5	244
OCH_3	CH_3	OCH_3	111–112	236
			114–115	244
OCH_3	OCH_3	OCH_3	156–157	214
			No mp	344, 347
OCH_3	CH_3	OC_2H_5	100–101	244
OC_2H_5	CH_3	OCH_3	54	244
OC_2H_5	OCH_3	OCH_3		344, 347
OC_2H_5	CH_3	OC_2H_5	83–84	244
			95–96	236
OC_2H_5	OC_2H_5	OCH_3		214
$OCH_2C_6H_5$	CH_3	OCH_3	66–67	244
$OCH_2C_6H_5$	CH_3	OC_2H_5	106–107	435
$OCH_2COC_6H_5$	CH_3	OC_2H_5	118–119	244
CH_3	CH_3	CH_3	92–93	251, 253, 444 495
CH_3	COOH	CH_3	183–185	249

CH_3	Cl	H	62–64	399
CH_3	Cl	Cl	97–98	53, 54, 268
CH_3	Cl	CH_3	80	22, 188
CH_3	Cl	COOH	188	22
CH_3	NH_2	Cl	168–169	54
CH_3	$N(CH_3)_2$	Cl	75–77	335
CH_3	NH_2	CH_3	163	188, 249
CH_3	NH_2	CH_3 (HCl)	245	188, 249
CH_3	NH_2	CH_3 (picrate)	130	188, 249
CH_3	$NHCOCH_3$	CH_3	227	188, 249
CH_3	$NHSO_2C_6H_4NHCOCH_3(4)$	CH_3	263	188, 249
CH_3	$NHSO_2C_6H_4NH_2(4)$	CH_3	207	188, 249
CH_3	Cl	OCH_3	85–87	482
CH_3	CH_3	$OPO(OC_2H_5)NHAm$		167
CH_3	NH_2	OCH_3	196–197	54
CH_3	OH	Cl	257–260	335
CH_3	OCH_3	Cl	174–175	335
CH_3	OC_2H_5	Cl	154–155	335
CH_3	OC_3H_5	Cl	108–109	335
CH_3	C_6H_5	C_6H_5	154–156	251, 285
CH_3	$C_6H_4Cl(4)$	$C_6H_4Cl(4)$	bp 220 (0.2 mm)	251, 285
$COOC_2H_5$	Cl	Cl	55–57	335
CH_2OH	Cl	Cl	106–108	335
CH_2Cl	Cl	Cl	92–94	335
CH_2SCN	Cl	Cl	108–109	335
$CH_2N(C_2H_5)_2$	Cl	Cl	36–38	335
$CH_2N(C_3H_5)_2$	Cl	Cl	50–52	335
$CH_2N(CH_2CH_2CN)_2$	Cl	Cl	104–107	335
C_2H_5	OH	Cl		260
C_2H_5	Cl	Cl	57–58	335
			213–214	260

TABLE VII (*continued*)

R_1	R_2	R_3	MP (°C)	Reference
CH_2CH_2Cl	Cl	Cl	90–92	335
CH_2CH_2OH	Cl	Cl	80	335
CH_2COOH	OH	Cl	242–245	335
CH_2COOH	Cl	Cl	235–237	335
CH_2COOH	CH_3	CH_3		132, 264
$CH_2COOC_2H_5$	Cl	Cl	82–83	335
$CH_2COOC_2H_5$	OCH_3	Cl	111–112	335
$CH_2COOC_2H_5$	CH_3	CH_3	bp 130 (0.2 mm)	132, 264
$CH_2CONHNH_2$	CH_3	CH_3	205–206	132, 264
$CH_2CON(CH_3)_2$	CH_3	CH_3	165	342
$CH_2CON(C_2H_5)_2$	Cl	Cl	112–113	335
CH_2COCH_3	Cl	Cl	80–81	335
CH_2OCH_3	OCH_3	Cl	115–116	335
$CH_2CH_2N(C_2H_5)_2$	Cl	Cl	Liquid	335
$CH_2CH{=}CH_2$	Cl	Cl	54–56	335
C_3H_5	OH	Cl	192	335
$CH_2CH_2CH_3$	Cl	Cl	38–40	335
C_6H_5	Br	Br	140–142	49, 194, 358
C_6H_5	$N(CH_3)_2$	Br	124.5–125.5	49, 358
C_6H_5		Br	171.5–172.5	49, 358
C_6H_5	Cl	H	83–85	49, 52
C_6H_5	Cl	Cl	135	189
			135–136	49
			138	193, 194, 358
			138–140	27, 192
C_6H_5	CH_3	$COOCH_3$	125–127	496, 497

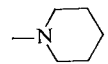
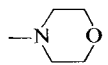
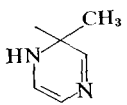
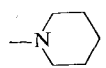
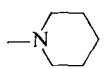
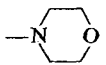
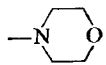
C_6H_5	CH_3	$COOC_2H_5$	102	497
C_6H_5	CH_3	$COCl$	135	497
C_6H_5	CH_3	$CON(CH_3)_2$	54	497
C_6H_5	CH_3	$CONHC_6H_5$	259	497
C_6H_5	CH_3	Cl	136–137	52, 194
C_6H_5	CH_3	COOH	230	270
C_6H_5	CH_2COOH	Cl	178–180	335
C_6H_5	NH_2	Cl	234–236	27
			236–238	49
C_6H_5	$NHCOCH_3$	Cl		402
C_6H_5	$N(CH_3)_2$	Cl	125–127	358
			127–128	193
C_6H_5		Cl	118.5–119.5	49, 194, 358, 499
C_6H_5		Cl	167	194, 499
			168–169	49, 358
C_6H_5	OCH_3	Cl	193–194	49
C_6H_5	OC_3H_5	Cl	148–149	335
C_6H_5	C_6H_5	C_6H_5	233–234	251, 285
C_6H_5	OCH_3		198–199	493
C_6H_5	NH_2	NH_2	263–266	49
C_6H_5	CH_3	NH_2	91–92	52
C_6H_5	$N(CH_3)_2$	$N(CH_3)_2$	132–133	49
C_6H_5	$N(CH_3)_2$	$N(CH_3)_2$ (HCl)	205.5	49
C_6H_5			170–171	49

TABLE VII (*continued*)

R_1	R_2	R_3	MP (°C)	Reference
C_6H_5			178–180	49
C_6H_5	OCH_3	OCH_3	224–225	189
			147–148	196
			152.5–154.0	195
C_6H_5	Cl	OCH_3	115–116	49, 482
C_6H_5	Cl	OCH_2COOH	150–151	335
C_6H_5	Cl	$OPS(OC_2H_5)_2$	82.5–83.0	166
C_6H_5	Cl	$OPO(OC_2H_5)_2$	82.5–83.0	164
C_6H_5	CH_3	OCH_3	117–118	195
C_6H_5	$N(CH_3)_2$	OCH_3	100–101	193
C_6H_5	Br	$OPS(OC_4H_9)N(C_2H_5)_2$		167
$C_6H_4Cl(4)$	Cl	Cl	173–174	358
$C_6H_4Cl(4)$	CH_3	COOH	216	496
$C_6H_4Cl(4)$	CH_3	$COOCH_3$	162	496
$C_6H_4Cl(4)$	CH_3	$CONHC_6H_5$	179	496
$C_6H_4Cl(4)$	CH_3	$CONHC_6H_4CH_3(4)$	165	496
$C_6H_4CH_3(4)$	CH_3	COOH	213	496
$C_6H_3(CH_3)_2(2,6)$	CH_3	COOH	224	496
$C_6H_4COOH(2)$	CH_3	COOH	231	496
$C_6H_4N(CH_3)_2(4)$	CH_3	COOH	251	496
$C_6H_4N(C_2H_5)_2(4)$	CH_3	COOH	187	496
$C_6H_4OCH_3(2)$	CH_3	COOH	234	270
$C_6H_4OCH_3(4)$	CH_3	COOH	221	496
$C_6H_3(OCH_3)_2(2,5)$	CH_3	COOH	206	496

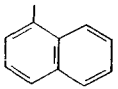
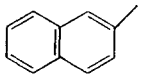
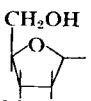
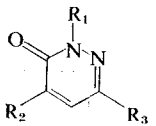
	CH_3	COOH	236	496
	CH_3	COOH	240	496
$C_6H_4NH_2(4)$	OH	COOH	297–299	231
$C_6H_4NO_2(4)$	OH	COOH		231
	C_6H_5	C_6H_5	124–129	149, 744
	C_6H_5	C_6H_5	134–137	150, 744
	C_6H_5	C_6H_5	178–182	150, 744
β-D-Ribofuranosyl	C_6H_5	C_6H_5	205–206	239, 500
 $(H_3C)_2HCO$ $OCH(CH_3)_2$	C_6H_5	C_6H_5	194–195	501
β-D-Ribopyranosyl	C_6H_5	C_6H_5	244–245	239, 500
Tribenzoyl-β-D-ribopyranosyl	C_6H_5	C_6H_5	140–142	500
$SO_2C_6H_4CH_3(4)$	NH_2	OCH_3	196–197	161
$SO_2C_6H_4NHCOCH_3(4)$	NH_2	OCH_3	215–217	161

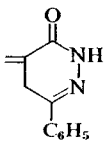
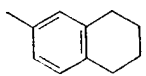
TABLE VIII 1,3,5-Trisubstituted 6(1*H*)Pyridazinones



R_1	R_2	R_3	MP (°C)	References
H	Cl	H	176–177	335
			176.5–177.5	236
H	Cl	Cl	203–204	372
H	CH_3	Cl	149–151	283
			148	86
			169–170	101
			170	92
			170–171	436
			171	88
			174–175	141
H	COOH	Cl	209–210	283
H	$COOCH_3$	Cl	132	88
H	$COOC_2H_5$	Cl	152.5	283
H	$CONH_2$	Cl	253	283
H	$CONHNH_2$	Cl	236–237 (dec)	283
H	NH_2	Cl	283	141, 373
H	$NHCOCH_3$	Cl	208–209	236, 437
H	$NHCOC_6H_5$	Cl	235	438
H	$NHSO_2C_6H_4NH_2(4)$	Cl	288–289	439
H	$N(CH_3)_2$	Cl	245–246	335
H	OCH_3	Cl	286 (dec)	235
H	SCH_3	Cl	190	335

H	CH_3	CH_3	124–125	298
			125	440
			130–131	132, 264
H	CN	CH_3	169–170	66, 251, 282, 426
H	COOH	CH_3	182–183	66, 249
H	$COOCH_3$	CH_3	161–162	249
H	$COOC_2H_5$	CH_3	171	286, 302
H	$CONH_2$	CH_3	286–287 (dec)	286, 302, 441
H	$CONHNH_2$	CH_3	220–221	286, 302
H	CH_3	COOH	275 (dec)	132, 264
H	CH_3	CH_3 (HCl)	255 (dec)	132
H	C_2H_5	CH_3	111–112	298
H	C_2H_5	CH_3 (HBr)	237	298
H	C_6H_5	CH_3	172–174	442
H	C_6H_5	CH_3 (HBr)	251–254 (dec)	442
H	NH_2	CH_3	259	141
			268	443
H	$NHCOCH_3$	CH_3	238	141
			242	443
H	$OP(S)(OCH_3)_2$	CH_3		223
H	CN	C_5H_9	207–209	444
H	CH_3	C_6H_5	189	445
			186	446
			183–184	447
			189–190	448
			190	449
H	$C(CH_3)_3$	C_6H_5	180–183	245
H	C_6H_5	C_6H_5	182	314
			183–184	450
			No mp	184, 451

TABLE VIII (*continued*)

R_1	R_2	R_3	MP (°C)	References
H		C_6H_5		39
H	Cl	$C_6H_4CH_3(2)$	219–220	74, 256
H	C_6H_5	$C_6H_4CH_3(4)$	218–219	753
H	CH_3	$C_6H_4Br(4)$	208	452
H	CH_3	$C_6H_3Cl_2(3,4)$	250–251	311
			251–251.8	70
H	CH_3	$C_6H_4CH_3(4)$	205	452
H	CH_3	$C_6H_3CH_3(4)OH(2)$	306	452
H	CH_3	$C_6H_4C_6H_5(4)$	279	452
H	$CH(OH)COOC_2H_5$	$C_6H_4Cl(4)$		40
H	CN	C_6H_{11}	240–241	282, 426, 444
H	CN	9,10-Phenanthro	290 (dec)	282
H	C_6H_5	$CH_2C_6H_5$	215	12
H	CH_2		214	452
H	CH_3	NH_2	213	88
H	CH_3	OCH_3	166	141
			161–162	236
H	$C(CH_3)_3$	OCH_3		453
H	NH_2	OCH_3	274–275	454
H	Cl	$OCOC_6H_5$	205–207	158
H	Cl	$OPS(OC_2H_5)_2$	91–92	166
H	CH_3	SCH_3	104	86
Cl	Cl	Cl	93–95	335
CH_3	Cl	Cl	75.5–76	54
CH_3	NH_2	Cl	248–248.5	455

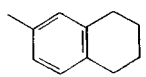
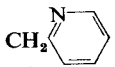
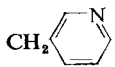
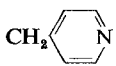
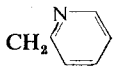
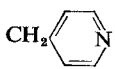
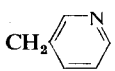
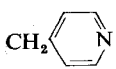
			144–145	136
CH_3	$NHCOCH_3$	Cl	208–209	456
CH_3	NO_2	Cl	129–130	754
CH_3	$NHSO_2C_6H_4NH_2(4)$	Cl	185–186	54, 456
CH_3	$NHSO_2C_6H_4NHCOCH_3(4)$	Cl	234.5–235	54
CH_3	Cl	CH_3	80	186
CH_3	Cl	NO_2	76–77	53
			75.5–76	54
CH_3	COOH	CH_3	150–153	249
CH_3	NH_2	CH_3	139–142	136
			141–142	457, 458
			166–167	186
CH_3	NH_2	CH_3 (HCl)	232	457, 458
CH_3	NH_2	CH_3 (picrate)	160–161	457, 458
CH_3	$NHCOCH_3$	CH_3	211	457
CH_3	$NHCOC_6H_5$	CH_3	124.5–125.5	457
CH_3	$N(CH_3)_2$	Cl	76–77	335
CH_3	$N(CH_3)_2$	CH_3 (HCl)	138 (dec)	186
CH_3	NO_2	CH_3	128–130	755
CH_3	OH	Cl	187–188	335
CH_3	OCH_3	Cl	105	335
CH_3	OC_2H_5	CH_3	98	186
CH_3	CN	C_5H_9	107–108	444
CH_3	CH_3	C_6H_5	75	446
CH_3	CN	C_6H_{11}	130–131	444
CH_3	CH_3	$C_6H_4Br(4)$	126	452
CH_3	CH_3		90	452
CH_3	NH_2	OCH_3	157–158	455
			159–160	459
CH_3	$NHCOCH_3$	OCH_3	204–205	437
CH_3	$NHSO_2C_6H_4NHCOCH_3(4)$	OCH_3	242–243	455
CH_3	$NHSO_2C_6H_4NH_2(4)$	OCH_3	215	455
CH_3	Cl	$OPO(OCH_3)NHCH_3$		167
CH_2Cl	Cl	Cl	78–80	335

TABLE VIII (*continued*)

R_1	R_2	R_3	MP (°C)	References
CH_2OH	Cl	Cl	119–121	335
CH_2SCN	Cl	Cl	112–113	335
	CH_3	C_6H_5	226–228	460
	CH_3	C_6H_5	226	460
	CH_3	C_6H_5	209	460
	C_2H_5	C_6H_5	237–238	460
	CH_3	$C_6H_4Cl(3)$	210	460
	CH_3	$C_6H_5OCH_3(3)$	165	460
	CH_3	$C_6H_5OCH_3(3)$	204	460
C_2H_5	Cl	Cl	141–142	335
C_2H_5	NO_2	Cl	48–50	754
C_2H_5	Cl	CH_3	53–54	186
C_2H_5	NHC_6H_5	CH_3	175	186
C_2H_5	NO_2	CH_3	68–70	754

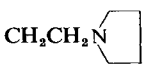
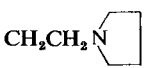
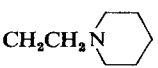
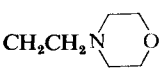
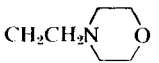
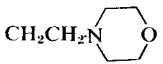
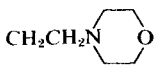
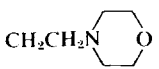
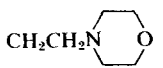
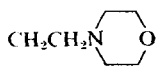
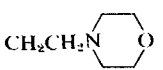
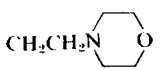
C_2H_5	$OCH(CH_3)_2$	CH_3	175	186
CH_2COOH	Cl	Cl	195–196	335
CH_2COOH	CH_3	CH_3		132, 264
CH_2COOH	SCH_3	Cl	190 (dec)	335
$CH_2COOC_2H_5$	Cl	Cl	86–87	335
$CH_2COOC_2H_5$	CH_3	CH_3	107-108	132, 264
$CH_2CON(C_2H_5)_2$	Cl	Cl	105–106	335
$CH_2CONHNH_2$	CH_3	CH_3	194–196	132, 264
$CH_2CH_2N(CH_3)_2$	CH_3	C_6H_5		428
$CH_2CH_2N(CH_3)_2$	CH_3	C_6H_5 (HCl)	218	449
			215	461
$CH_2CH_2N(CH_3)_2$	CH_3	$C_6H_4Cl(4)$	74	449
$CH_2CH_2N(CH_3)_2$	CH_3	$C_6H_4Cl(4)$ (HCl)	194	449
$CH_2CH_2N(CH_3)_2$	CH_3	$C_6H_4OH(4)$	140–143	449
$CH_2CH_2N(CH_3)_2$	CH_3	$C_6H_4OH(4)$ (HCl)	209–214	449
$CH_2CH_2N(CH_3)_2$	C_2H_5	C_6H_5 (HCl)	142	449
$CH_2CH_2N(C_2H_5)_2$	CH_3	C_6H_5 (HCl)	198	428, 449
$CH_2CH_2N(C_2H_5)_2$	C_2H_5	C_6H_5 (HCl)	152	449
$CH_2CH_2N(C_3H_7)_2$	CH_3	C_6H_5 (HCl)	222	449
$CH_2CH_2CH_2N(CH_3)_2$	CH_3	C_6H_5 (HCl)	201–203	449
	CH_3	C_6H_5 (HCl)	246	449
	C_2H_5	C_6H_5 (HCl)	215	449
	CH_3	C_6H_5 (HCl)	260	428, 449
			263–264	461
			268	746
	Br	C_6H_5 (HCl)	166	449

TABLE VIII (*continued*)

R_1	R_2	R_3	MP (°C)	References
	CH_3	C_6H_5	89 89–91	447 449
	CH_3	C_6H_5 (HCl)	224 225–226 228–230 No mp	461 447 449, 746 428, 462–464
	CH_3	$C_6H_4Cl(2)$ (HCl)	204–205	449
	CH_3	$C_6H_4Cl(3)$	131	449
	CH_3	$C_6H_4Cl(3)$ (HCl)	230	449
	CH_3	$C_6H_4Cl(4)$	106 108–109	449 746
	CH_3	$C_6H_4Cl(4)$ (HCl)	225	449
	CH_3	$C_6H_4OCH_3(2)$ (HCl)	213–215	449
	CH_3	$C_6H_4OCH_3(3)$	82–83	449

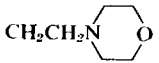
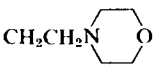
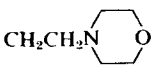
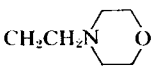
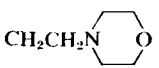
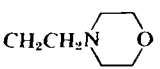
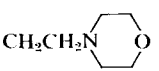
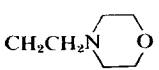
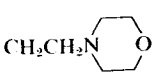
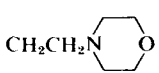
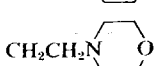
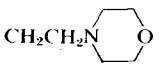
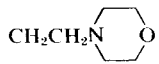
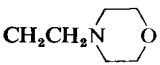
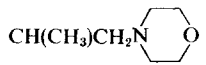
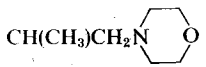
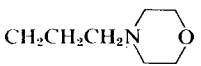
	CH_3	$C_6H_4OCH_3(3)$ (HCl)	175	449
	CH_3	$C_6H_4OCH_3(4)$	83	449
	CH_3	$C_6H_4OCH_3(4)$ (HCl)	210	449
	CH_3	$C_6H_4OH(2)$	160–163	449
	CH_3	$C_6H_4OH(2)$ (HCl)	245	449
	CH_3	$C_6H_4OH(3)$ (HCl)	232	449
	C_2H_5	$C_6H_4OCH_3(2)$ (HCl)	230–233	449
	C_2H_5	$C_6H_4OCH_3(3)$	67–68	449
	C_2H_5	$C_6H_4OCH_3(3)$ (HCl)	208–209	449
	C_2H_5	$C_6H_4OCH_3(4)$	92	449
	C_2H_5	$C_6H_4OCH_3(4)$ (HCl)	235–240	449

TABLE VIII (*continued*)

R_1	R_2	R_3	MP (°C)	References
	C_2H_5	C_6H_5 (HCl)	180–182	449
	C_3H_7	C_6H_5 (HCl)	178	449
	$CH(CH_3)_2$	C_6H_5 (HCl)	202	449
	CH_3	C_6H_5 (HCl)	162	449
	C_2H_5	C_6H_5 (HCl)	150–151	449
	CH_3	C_6H_5 (HCl)	252	449
C_6H_5	Cl	Cl	110–113	465
			111-112	52, 192-194, 229, 358
C_6H_5	CH_3	Cl	133–134	52, 194
C_6H_5	NH_2	Cl	179-180	52
C_6H_5	$NHCH_3$	Cl		466
C_6H_5	NHC_3H_7	Cl	142–143	466
C_6H_5	$NHNH_2$	Cl	204–205	467
C_6H_5	$N(CH_3)_2$	Cl	87.5–88.5	52, 193
C_6H_5	$N(C_2H_5)_2$	Cl	60–62	466

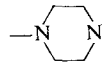
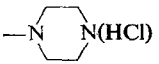
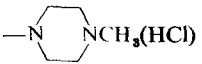
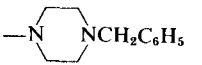
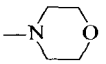
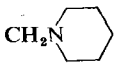
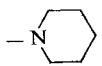
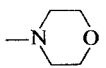
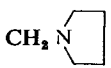
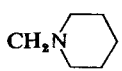
C_6H_5		Cl		468
C_6H_5		Cl	253–255	468
C_6H_5		Cl	97–99	468
C_6H_5		Cl	170 (dec)	468
C_6H_5		Cl	139.5–140.5	468
C_6H_5		Cl	121–122	52
C_6H_5	OCH_3	Cl	159–160	470
			159–161	189
C_6H_5	OC_2H_5	Cl	135–136	470
C_6H_5	SH	Cl	137–138	471
C_6H_5	SCH_3	Cl	135–136	471
C_6H_5	SO_2CH_3	Cl	174–175	419
C_6H_5	SC_2H_5	Cl	117–118	471
C_6H_5	Cl	CH_3	135–136	109, 187, 190, 191
			136–137	3
C_6H_5	CH_3	CH_3	80	440
			136	472
C_6H_5	$CH_2N(CH_3)_2$	CH_3	183–187	200
C_6H_5		CH_3	bp 185–191 (0.3 mm)	200

TABLE VIII (*continued*)

R_1	R_2	R_3	MP (°C)	References
C_6H_5	C_2H_5	CH_3	69–70	473
C_6H_5	C_3H_7	CH_3	43–44	473
C_6H_5	C_3H_7-*i*	CH_3	65–66	473
C_6H_5	NH_2	CH_3	167	187, 191
C_6H_5	NH_2	CH_3 (HCl)	176 (dec)	187, 191
C_6H_5	$NHCOCH_3$	CH_3	265	187, 191
C_6H_5	$NHCH_3$	CH_3	148–149	188, 190
C_6H_5	$N(CH_3)_2$	CH_3	61	188, 190
C_6H_5	$N(C_2H_5)_2$	CH_3	bp 196–198 (0.01 mm)	188, 190
C_6H_5	$N(C_2H_5)_2$	CH_3 (picrate)	107–108	188, 190
C_6H_5		CH_3	80	190
C_6H_5		CH_3	132	190
C_6H_5	OC_2H_5	CH_3	144–145	109
C_6H_5	CH_3	COOH	213–214	474–477
C_6H_5	CH_3	$COOC_2H_5$	125	469
C_6H_5	$N{=}NC_6H_5$	$COOC_2H_5$	163–164	478, 479
C_6H_5	Cl	C_2H_5	79–81	91, 480
C_6H_5	CH_3	C_2H_5	55–56	473
C_6H_5	$CH_2N(CH_3)_2$	C_2H_5	bp 168–172 (0.2 mm)	200
C_6H_5		C_2H_5	bp 189–195 (0.4 mm)	200
C_6H_5		C_2H_5	bp 170–175 (0.4 mm)	200

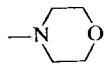
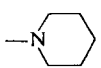
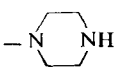
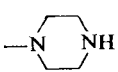
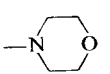
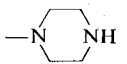
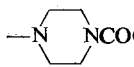
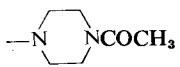
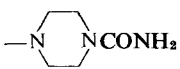
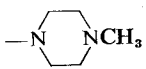
C_6H_5	C_2H_5	C_2H_5	43–44	473
C_6H_5	$N(CH_3)_2$	C_2H_5	52–53	91, 480
C_6H_5		C_2H_5	58–59	91, 480
C_6H_5		C_2H_5	78–79	91, 480
C_6H_5	$NH(CH_2)_5CH_3$	C_2H_5	bp 204–206 (1 mm)	91, 480
C_6H_5	$NHCH_3$	$CH_2CH_2OCH_3$	131–132	466
C_6H_5	$NHCH_3$	$CH_2CH_2OC_2H_5$	141–142	466
C_6H_5	CH_3	$CH_2CH_2CH_3$	98–100	473
C_6H_5	Cl	C_6H_5	186–187	130
			186–188	360, 361
C_6H_5	CH_3	C_6H_5		428
C_6H_5	$NHCH_2CH_2N(C_2H_5)_2$	C_6H_5	99–99.5	360, 361
C_6H_5	$NHCH_2CH_2N(C_2H_5)_2$	C_6H_5 (HCl)	203.5–205.0	360
C_6H_5	$N(CH_3)_2$	C_6H_5	120–121	130
			119–120	360, 361
C_6H_5	$N(C_2H_5)CH_2CH_2N(CH_3)_2$	C_6H_5	74–75	360, 361
C_6H_5	$N(C_2H_5)CH_2CH_2N(CH_3)_2$	C_6H_5 (HCl)	240–241	360
C_6H_5		C_6H_5	137–138	130
C_6H_5		C_6H_5	170–170.5	360, 361
C_6H_5		C_6H_5 (HCl)	190-192	360
C_6H_5		C_6H_5	149	130

TABLE VIII (*continued*)

R_1	R_2	R_3	MP (°C)	References
C_6H_5	$N(CH_3)_2$	$N(CH_3)_2$	83	192
			91.5–92	52
C_6H_5	$COOCH_3$	NO_2	128	481
C_6H_5	Cl	OCH_3	83–84	468, 482
C_6H_5	$NHCOCH_3$	OCH_3	121–122	466
C_6H_5	$NHCH_3$	OCH_3	141–142	466
C_6H_5	$N(CH_3)_2$	OCH_3	57–57.5	193
C_6H_5		OCH_3 (HCl)	228–230	468
C_6H_5		OCH_3	94–96	468
C_6H_5		OCH_3	118–119	468
C_6H_5		OCH_3	232–233	468
C_6H_5		OCH_3 (HCl)	241–243	468
C_6H_5		OCH_3	89.5–90.5	483
			90.5–91	468
C_6H_5		OCH_3 (HCl)	256–258	483

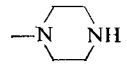
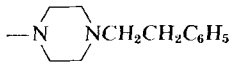
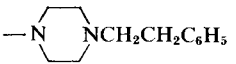
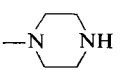
C_6H_5	OCH_3	OCH_3	136.5–137	195, 213
C_6H_5	$NHCH_3$	OC_2H_5	145–146	466
C_6H_5	NHC_3H_7	OC_2H_5		466
C_6H_5	$N(CH_3)_2$	OC_2H_5	74	229, 484
C_6H_5	$N(C_2H_5)_2$	OC_2H_5	41–43	466
C_6H_5		OC_2H_5 (HCl)	145–147	468
C_6H_5		OC_2H_5	95–96	483
C_6H_5		OC_2H_5 (HCl)	273–276	483
C_6H_5	OCH_3	OC_2H_5	119–120	484
C_6H_5	OC_2H_5	OC_2H_5	92–94	189, 229, 484, 485
C_6H_5	$NHCH_3$	OC_3H_7	115–116	466
C_6H_5	$N(CH_3)_2$	$OCH_2CH{=}CH_2$	42–43	439
C_6H_5	Cl	$OPO(OC_2H_5)_2$	n_D^{25} 1.5753	164
C_6H_5	Cl	$OPS(OC_2H_5)_2$	Liquid	166
$C_6H_4Br(2)$	$N{=}NC_6H_4Br(2)$	$COOC_2H_5$	166–167	486
$C_6H_4Br(3)$	$N{=}NC_6H_4Br(3)$	$COOC_2H_5$	149	486
$C_6H_4Br(4)$	CH_3	CH_3	127	440
$C_6H_4Br(4)$	$COOC_2H_5$	NO_2	128	481
$C_6H_4Br(4)$	$N{=}NC_6H_4Br(4)$	$COOC_2H_5$	229	486
$C_6H_4Cl(4)$	Cl	Cl	163–165	358, 468
$C_6H_4Cl(4)$	$N{=}NC_6H_4Cl(4)$	$COOC_2H_5$	208–209	486
$C_6H_4Cl(4)$		Cl	281–283	468
$C_6H_4Cl(4)$		OCH_3 (HCl)	250–251	468

TABLE VIII (*continued*)

R_1	R_2	R_3	MP (°C)	References
$C_6H_4CH_3(2)$	$N{=}NC_6H_4CH_3(2)$	$COOC_2H_5$	152	486
$C_6H_4CH_3(3)$	Cl	CH_3	109	190
$C_6H_4CH_3(3)$	NH_2	CH_3	153	188, 190
$C_6H_4CH_3(3)$	$NHCOCH_3$	CH_3	237	188, 190
$C_6H_4CH_3(4)$	Cl	CH_3	109	188, 190
$C_6H_4CH_3(4)$	$N{=}NC_6H_4CH_3(4)$	$COOC_2H_5$	157	486
$C_6H_3(CH_3)_2(2,4)$	$N{=}NC_6H_3(CH_3)_2(2,4)$	$COOC_2H_5$	155	486
$C_6H_4NH_2(4)$	Cl	Cl	164–165.5	53
$C_6H_4NO_2(4)$	Cl	Cl	237–238	747
$C_6H_4NO_2(4)$	Cl	CH_3	217–218	109, 187, 191
$C_6H_4NO_2(4)$	CH_3	CH_3	210	440
$C_6H_4NO_2(4)$	NH_2	CH_3	196	187, 191
$C_6H_4NO_2(4)$	$NHCOCH_3$	CH_3	190–191	187, 191
$C_6H_4NO_2(4)$	OC_2H_5	CH_3	138	109
$C_6H_4NO_2(3)$	Cl	Cl	182–184	747
$C_6H_3(NO_2)_2(2,4)$	CH_3	CH_3	192	472
$C_6H_3(NO_2)_2(3,5)$	CH_3	CH_3	144–146	440
$C_6H_4OCH_3(4)$	Cl	CH_3	129–130	364
$C_6H_4OCH_3(4)$	NH_2	CH_3	93–94	364
$C_6H_4OC_2H_5(4)$	Cl	CH_3	125–126	364
$C_6H_4OC_2H_5(4)$	NH_2	CH_3	156–157	364
C_6H_{11}	Cl	Cl	107–108	399
			111–112	487
	Cl	CH_3	123	188, 190
	NH_2	CH_3	172	188, 190
	$NHCOCH_3$	CH_3	216	188, 190

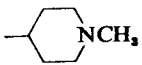
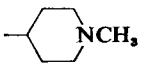
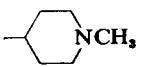
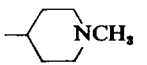
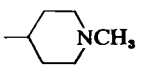
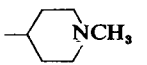
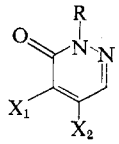
	$N(CH_3)_2$	CH_3	94	188, 190
	CH_3	CH_3	87–89	68, 272, 366
	CH_3	CH_3 (HCl)	252–254	68, 272, 366
	CH_3	CH_3 (HBr)	250–252	366
	C_6H_5	CH_3	140	68, 366
	C_6H_5	CH_3 (HCl)	228	366
	CH_3	C_6H_5 (HCl)	284	68, 272, 366
	CN	C_6H_5	223	68, 366
	CN	C_6H_5 (HCl)	280	68, 366
	C_6H_5	C_6H_5	243	68, 366
OH	CH_3	OCH_3	205–206	141
$OCOC_6H_5$	Cl	OCH_3	202–203	488
$OCOC_6H_5$	CH_3	OCH_3	126–127	141
OCH_3	CH_3	OCH_3	72–73	236
			71–72	141

TABLE IX. 4,5-Dihalo-1-Substituted 6(1*H*)Pyridazinones



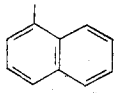
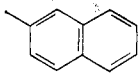
R	X_1	X_2	MP (°C)	References
H	Br	Br	215	367
			218	368
CH_3	Br	Br	92	157
CH_2CH_2CN	Br	Br		369
CH_2CH_2COOH	Br	Br		369
CH_2CH_2COCl	Br	Br		369
C_6H_5	Br	Br	142	370
			144–145	371
			145	207, 368
$C_6H_4Cl(4)$	Br	Br	183–184	207
$C_6H_4CH_3(4)$	Br	Br	129	370
$C_6H_4CF_3(3)$	Br	Br	103–105	756, 757
$C_6H_4NO_2(4)$	Br	Br	233–235	207
$C_6H_3(NO_2)_2(2,4)$	Br	Br	221	367
	Br	Br	226–228	207
	Br	Br	189–190	207
H	Cl	Br	208	30
			216–217	157
CH_3	Cl	Br	92	157
CH_2Cl	Cl	Br		334
CH_2OH	Cl	Br		334
C_6H_5	Cl	Br	156	27
H	Cl	Cl	198–199	371
			199–200	25, 87, 204, 372, 373, 374, 758
			201–202	157
			202	23, 375
			No mp	347, 369, 376
Br	Cl	Cl	200 (dec)	377
Cl	Cl	Cl	140–141	377
CH_3	Cl	Cl	78–79	371
			84–86	198, 758
			89–90	378, 759
			90	157
			90–91	22
CH_2Cl	Cl	Cl	67–68	335
			70–71	379

TABLE IX. (*continued*)

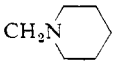
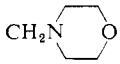
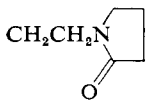
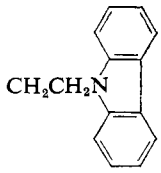
R	X_1	X_2	MP (°C)	References
$CH_2N(C_2H_5)_2$	Cl	Cl	n_D^{20} 1.5470	335
$CH_2N(C_3H_5)_2$	Cl	Cl	n_D^{20} 1.5555	335
$CH_2N(CH_2CH_2Cl)_2$	Cl	Cl	75–79	261
$CH_2N(CH_2CH_2CN)_2$	Cl	Cl	81–82	335
			114–115	379
$CH_2NHC_6H_5$	Cl	Cl	62–63	379
$CH_2NHC_6H_3Cl_2(3,4)$	Cl	Cl	165–166	379
CH_2N-4,5-dichloro-6-oxopyridazinyl	Cl	Cl	221–222	379
	Cl	Cl	86–89	261
	Cl	Cl	115–116	261
	Cl	Cl	125	379
			127–128	261
CH_2OH	Cl	Cl	104–105	379
			113–115	335
CH_2OCOCH_3	Cl	Cl	87–89	379
$CH_2OCOC_6H_5$	Cl	Cl	97–99	379
CH_2SCN	Cl	Cl	105–106	335
CN	Cl	Cl	103–104	379
$COOC_2H_5$	Cl	Cl	141	335
C_2H_5	Cl	Cl	49–51	379, 758
			54–55	379
			54–56	335
$CH_2C_6H_5$	Cl	Cl	87–89	379
$CH_2CH_2C_6H_5$	Cl	Cl	124–125	379
$CH_2CH(Cl)C_6H_5$	Cl	Cl		376
$CH_2CH_2NH_2$	Cl	Cl (HCl)	264–266	369
$CH_2CH_2N(C_2H_5)_2$	Cl	Cl		212
$CH_2CH_2N(C_2H_5)_2$	Cl	Cl (HCl)	193–194 (dec)	157
$CH_2CH_2N(C_2H_5)_2$	Cl	Cl (CH_3Br)	262–265 (dec)	157
$CH_2CH_2N(C_2H_5)_2$	Cl	Cl (C_2H_5Br)	242 (dec)	157
	Cl	Cl		376
	Cl	Cl		376

TABLE IX. (*continued*)

R	X_1	X_2	MP (°C)	References
CH_2CH_2OH	Cl	Cl	54–56	335
CH_2COOH	Cl	Cl	174–176	335
$CH_2COOC_2H_5$	Cl	Cl	94–95	335
$CH(CH_3)COOC_2H_5$	Cl	Cl	25–27	379
CH_2CONH_2	Cl	Cl	245	335
$CH_2CON(C_2H_5)_2$	Cl	Cl	123–124	335
$CH(CH_3)_2$	Cl	Cl	69–70	379
			72–74	335
			140–141	377
CH_2CH_2CN	Cl	Cl	85	369, 381
			100	382
			No mp	383–385
CH_2CH_2COOH	Cl	Cl	124–125	369
			127	381–385
CH_2CH_2COCl	Cl	Cl	Syrup	369, 382, 384, 386
$CH_2CH_2COC_6H_5$	Cl	Cl	100–101	379
$CH{=}CHCOC_6H_5$	Cl	Cl	161–162	379
$CH_2CH_2CONH_2$	Cl	Cl	166–168	379
$CH_2CH_2CONHCH_3$	Cl	Cl	146–148	379
$CH_2CH_2CONHC_6H_4NH_2(3)$	Cl	Cl		383
$CH_2CH_2CONHC_6H_4NO_2(3)$	Cl	Cl		383
$CH_2CH_2CONHC_6H_3OCH_3$ (2)$NH_2(4)$	Cl	Cl		383
$CH_2CH_2CONHC_6H_2OCH_3$ (2)Cl(5)$NH_2(4)$	Cl	Cl		383
$CH_2CH_2CONHC_6H_2(OCH_3)_2$ (2,4)$NH_2(5)$	Cl	Cl		383
$CH_3CH(Cl)CH_2Cl$	Cl	Cl		376
$CH_2C(Cl,CH_3)CH_3$	Cl	Cl		376
C_4H_9	Cl	Cl	Liquid	379
C_4H_9-*i*	Cl	Cl	37–38.5	379
C_4H_9-*s*	Cl	Cl	34–36	379
C_4H_9-*t*	Cl	Cl	67–68	379
$CH_3CH(Cl)C(OH,CH_3)CH_3$	Cl	Cl		376
$CH_2C(Cl,OH)C(OH,CH_3)CH_3$	Cl	Cl		376
$CH_2CH(Cl)C(OCH_3,CH_3)CH_3$	Cl	Cl		376
$CH_2C(Cl,CH_3)CH_2CH_3$	Cl	Cl		376
$C(CH_2Cl,CH_3)CH_2CH_2CH_3$	Cl	Cl		376
$CH_2C(Cl,CH_3)CH_2CH_2CH_3$	Cl	Cl		376
C_6H_5	Cl	Cl	150–155	387
			161	370
			162–163	27, 371, 388
			163–164	23
			No mp	53, 220, 374, 382, 384, 385, 387, 389

TABLE IX. (*continued*)

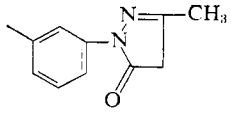
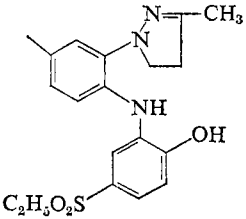
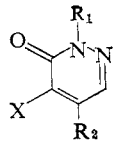
R	X_1	X_2	MP (°C)	References
$C_6H_4Cl(3)$	Cl	Cl	199–200	379
$C_6H_4Cl(4)$	Cl	Cl	270	379
$C_6H_3Cl_2(3,4)$	Cl	Cl	233 (dec)	379
$C_6H_4CH_3(3)$	Cl	Cl	119–120	379
$C_6H_4CH_3(4)$	Cl	Cl	164	370
$C_6H_4CF_3(3)$	Cl	Cl	92–94	756, 757, 760
$C_6H_4COOH(4)$	Cl	Cl	314–316	370
$C_6H_4COCl(4)$	Cl	Cl		386
$C_6H_3CH_3(4)NH_2(2)$	Cl	Cl		370
$C_6H_3CH_3(4)NO_2(2)$	Cl	Cl	166	370
$C_6H_4NH_2(3)$	Cl	Cl	132	370
$C_6H_4NHCOCH_3(3)$	Cl	Cl	185	370
$C_6H_4NHCOCH_3(4)$	Cl	Cl		370
$C_6H_4NO_2(3)$	Cl	Cl	208	370
	Cl	Cl		390, 391
	Cl	Cl		390
$C_6H_4SO_3H$	Cl	Cl	270	379
$C_6H_4SO_3Na$	Cl	Cl		379
$C_6H_4SO_2Cl$	Cl	Cl		386
$C_6H_4SO_2NH_2$	Cl	Cl	267–268	379
	Cl	Cl	62–63	379
C_6H_{11}	Cl	Cl	89–90	379
$C_6H_{10}Cl(2)$	Cl	Cl		376
$C_6H_{10}CH_3(4)$	Cl	Cl	70–71	379
C_7H_{13}	Cl	Cl	47–48	379
4-Chlorotricyclo[2,2,1,0]hept-3-yl	Cl	Cl	118–121	379
C_8H_{15}	Cl	Cl	58–59	379
$C_8H_{14}Br(2)$	Cl	Cl	162–163	379
$C_8H_{14}Cl(2)$	Cl	Cl		376
8-Chloro-4-cycloocten-1-yl	Cl	Cl		376
$C_{12}H_{22}Cl(2)$	Cl	Cl		379
Perhydro-4,7-methanoincenyl	Cl	Cl	92–100	379
Tetra-*O*-acetylglucosyl	Cl	Cl	164–165	379

TABLE IX. (*continued*)

R	X_1	X_2	MP (°C)	References
α-Naphthyl	Cl	Cl	198	379
CH_2-Furfuryl	Cl	Cl	78–80	379
CH_2CH_2-Pyrrolidinyl	Cl	Cl	80–81	379
N-Methyl-4-piperidinyl·HCl	Cl	Cl	310	379
N-Methyl-4-piperidinyl·CH_3I	Cl	Cl	280	379
2-Benzimidazolyl	Cl	Cl	259–260	379
2-Benzthiazolyl	Cl	Cl	216–218	379
C_6H_5	I	I	130–131	761

TABLE X. 5-Halo-1,4-Disubstituted 6(1*H*)Pyridazinones



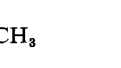
R_1	X	R_2	MP (°C)	References
H	Br	N_3	180–181	762
H	Cl	NH_2		393
H	Cl	$NHCOCH_3$	277–279	373
H	Cl	$NHCOC_6H_5$	244	373
H	Cl	$NHCH_3$	252–253	379
H	Cl	NHC_2H_5		157
H	Cl	$NHCH_2CH_2OH$	245–246	157, 749
H	Cl	$NHCH_2CH_2N(C_2H_5)_2$	149–150	157, 749
		(related compounds)		749
H	Cl	$NHCH_2CH_2N(C_2H_5)_2$ (CH_3Br)	252	157
H	Cl	NHC_6H_5	246–247	379
H	Cl	$NHC_6H_4CH_3$(4)	203–206	379
H	Cl	$NHC_6H_4OCH_3$(4)	242–243	379
H	Cl	NHC_6H_{11}		379
H	Cl	$NHCH_2C_6H_5$		157
H	Cl	$NHCH_2CH_2C_6H_5$		157
H	Cl	$N(CH_3)_2$	200–201	379
H	Cl	$N(C_2H_5)_2$		157
H	Cl	$N(CH_3)CH_2C_6H_5$	172–173	379
H	Cl			157
H	Cl			157

TABLE X (*continued*)

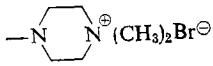
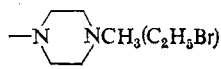
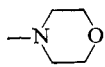
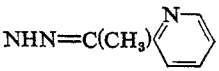
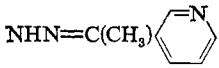
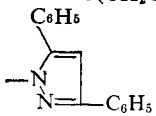
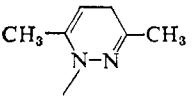
R_1	X	R_2	MP (°C)	References
H	Cl		290 (dec)	157
H	Cl		290 (dec)	157
H	Cl			157
H	Br	$NHNH_2$	180 (dec)	205
H	Br	$NHN{=}CHC_6H_5$	241 (dec)	205
H	Br	$NH{=}CHC_6H_4OH(3)$	267 (dec)	205
H	Br	$NHN{=}CHC_6H_3(OCH_3)_2(3,4)$	248 (dec)	205
H	Br	$NHN{=}C(CH_3)C_6H_5$	220 (dec)	205
H	Br	$NHN{=}C(CH_3)C_6H_3Cl_2(3,4)$	240 (dec)	205
H	Br	$NHN{=}C(CH_3)C_6H_4CH_3(4)$	224 (dec)	205
H	Br	$NHN{=}C(CH_3)C_6H_3(CH_3)_2(3,4)$	220 (dec)	205
H	Br	$NHN{=}C(CH_3)C_6H_4OH(2)$	234 (dec)	205
H	Br	$NHN{=}C(CH_3)CH{=}CHC_6H_5$	207 (dec)	205
H	Br	$NHN{=}C(CH{=}CHCOOH)C_6H_5$	233 (dec)	205
H	Br		251 (dec)	205
H	Br		267 (dec)	205
H	Br	$NHN{=}C(C_2H_5)C_6H_5$	182	205
H	Br	$NHN{=}C(C_3H_7)C_6H_5$	175–176	205
H	Br	$NHN{=}C(i\text{-}C_3H_7)C_6H_5$	221 (dec)	205
H	Br	$NHN{=}C(C_4H_9)C_6H_5$	151	205
H	Br	$NHN{=}C(C_6H_5)_2$	299 (dec)	205
H	Br	$NHN{=}C(C_6H_5)C_6H_4OCH_3(4)$	232	205
H	Br	$NHN{=}C(C_6H_5)C_6H_4N(CH_3)_2(4)$	213 (dec)	205
H	Br	$NHN{=}C(C_6H_5)CH(OH)C_6H_5$	240 (dec)	205
H	Br	$NHN{=}C(C_6H_5)COC_6H_5$	225	205
H	Br	$NHN{=}C(CH_2C_6H_5)C_6H_4CH_3(4)$	236 (dec)	205
H	Br	$NHN{=}C(CH_2C_6H_5)CH_2C_6H_5$	192 (dec)	205
H	Br		211–213	205
H	Br		264 (dec)	205

TABLE X (*continued*)

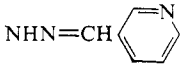
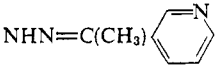
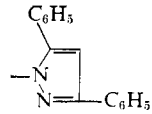
R_1	X	R_2	MP (°C)	References
H	Br	$SC_6H_4NH_2(2)$	196	395
			260–261 (dec)	208
H	Br	$SC_6H_4NHCOCH_3(2)$	238 (dec)	395
CH_3	Br	$NHC_6H_4SCH_3(2)$	161–162	397
CH_3	Br	$NHSO_2C_6H_4NH_2(4)$	198	396
CH_3	Br	$SC_6H_4NH_2(2)$	171–172	395
CH_3	Br	$SC_6H_4NHCOCH_3(2)$	216–217	395
H	Cl	$NHNH_2$	195 (dec)	205
H	Cl	$NHN{=}C(CH_3)C_2H_5$		394
H	Cl	$NHN{=}CHC_6H_5$	304 (dec)	205
H	Cl	$NHN{=}CHC_6H_4N(CH_3)_2(4)$	252 (dec)	205
H	Cl	$NHN{=}CHC_6H_4OH(3)$	300 (dec)	205
H	Cl	$NHN{=}CHC_6H_3(OCH_3)_2(3,4)$	276 (dec)	205
H	Cl	$NHN{=}C(CH_3)C_6H_5$	255 (dec)	205
H	Cl	$NHN{=}C(CH_3)C_6H_3Cl_2(3,4)$	314 (dec)	205
H	Cl	$NHN{=}C(CH_3)C_6H_4CH_3(4)$	280 (dec)	205
H	Cl	$NHN{=}C(CH_3)C_6H_3(CH_3)_2(3,4)$	263 (dec)	205
H	Cl	$NHN{=}C(CH_3)C_6H_4OH(2)$	289 (dec)	205
H	Cl		287 (dec)	205
H	Cl		280 (dec)	205
H	Cl	$NHN{=}C(C_2H_5)C_6H_5$	209–210	205
H	Cl	$NHN{=}C(C_3H_7)C_6H_5$	217–218	205
H	Cl	$NHN{=}C(i\text{-}C_3H_7)C_6H_5$	251	205
H	Cl	$NHN{=}C(C_4H_9)C_6H_5$	190	205
H	Cl	$NHN{=}C(CH{=}CHCOOH)C_6H_5$	255 (dec)	205
H	Cl	$NHN{=}C(CH_3)CH{=}CHC_6H_5$	214 (dec)	205
H	Cl	$NHN{=}C(C_6H_5)_2$	304 (dec)	205
H	Cl	$NHN{=}C(C_6H_5)C_6H_4N(CH_3)_2(4)$	258 (dec)	205
H	Cl	$NHN{=}C(C_6H_5)C_6H_4OCH_3(4)$	252	205
H	Cl	$NHN{=}C(C_6H_5)CH(OH)C_6H_5$	259 (dec)	205
H	Cl	$NHN{=}C(C_6H_5)COC_6H_5$	220 (dec)	205
H	Cl	$NHN{=}C(CH_2C_6H_5)C_6H_4CH_3(4)$	276 (dec)	205
H	Cl	$NHN{=}C(CH_2C_6H_5)_2$	207	205
H	Cl	$NHN{=}C[C_6H_4N(CH_3)_2(4)]_2$	253 (dec)	205
H	Cl	NHN=CH-2-Furyl	259 (dec)	205
H	Cl		209	205
H	Cl	$SCOOCH_3$	234–235	380
H	Cl	SC_2H_5	231–232	380
H	Cl	SC_6H_5	210–211	380

TABLE X (*continued*)

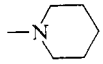
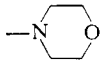
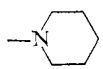
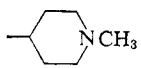
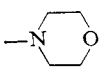
R_1	X	R_2	MP (°C)	References
H	Cl	$SC_6H_4NH_2(2)$	198 (dec)	208
Cl	Cl	OCH_3	159 (dec)	377
CH_3	Br	N_3	85–87	762
CH_3	Cl	NH_2	203–204	379
CH_3	Cl	$NHSO_2C_6H_4NH_2(4)$	208	396
CH_3	Cl	$NHSO_2C_6H_4NHCOCH_3(4)$	224	396
CH_3	Cl	$NHSO_2C_6H_4NHCH_3(4)$	198	396
CH_3	Cl			157
CH_3	Cl			157
CH_3	Cl	$NHNH_2$	153	393
CH_3	Cl	NO_2	97–99	392
CH_3	Cl	OCH_3	155–156	398
CH_3	Cl	$SCH_2C_6H_5$	112–113	759
CH_3	Cl	$SC_6H_4NH_2(2)$		399
CH_2Cl	Cl	Br	69–70	334
C_2H_5	Cl	NH_2	217	379
CH_2CH_2OH	Br	N_3	144–145	762
CH_2CH_2OH	Cl	NH_2	178–180	379
CH_2COOH	Cl	NH_2	245–250	335
			252	379
			253–255	379
CH_2COOH	Cl	OH	244–248	335
CH_2COOH	Cl	OCH_3	210	335
$CH_2COOC_2H_5$	Cl	OCH_3	134–135	335
$CH_2CH_2N(C_2H_5)_2$	Cl	$NHCH_2C_6H_5$ (HCl)	193–194	157
$CH_2CH_2N(C_2H_5)_2$	Cl	$NHCH_2C_6H_5$ (CH_3Br)	262–265 (dec)	157
$CH_2CH_2N(C_2H_5)_2$	Cl	$NHCH_2C_6H_5$ (C_2H_5Br)	242	157
$CH_2CH_2N(C_2H_5)_2$	Cl			157
$CH_2CH_2N(C_2H_5)_2$	Cl			157
$CH_2CH_2N(C_2H_5)_2$	Cl			157
$CH_2CH_2N(C_2H_5)_2$	Cl	OCH_3	60–61	212, 749
CH_2CH_2CN	Cl	NH_2	195–198	379
CH_2CH_2CN	Cl	NHC_3H_7-i	91–92	379
$CH_2CH_2CH_2OCH_3$	Cl	NH_2	137–138	379
C_6H_5	Br	COOH	247–248	403, 762
C_6H_5	Br	$COCH_3$	116–117	400

TABLE X (*continued*)

R_1	X	R_2	MP (°C)	References
C_6H_5	Br	NH_2	216–217	401, 402, 762
C_6H_5	Br	$NHCH_3$	158–159	62, 761
C_6H_5	Br	NHC_3H_7	128–129	762
C_6H_5	Br	$NHCH_2CCl_3$		401
C_6H_5	Br	$NHCH_2CH_2OH$	180–182	762
C_6H_5	Br	$NHCOOCH_3$	151–152	405
C_6H_5	Br	$NHCOOC_2H_5$	135–136	405
C_6H_5	Br	$NHCOOCH_2CH_2Cl$	102–104	405
C_6H_5	Br	$NHCOOCH_2CH_2OC_2H_5$	70–72	405
C_6H_5	Br	$NHCOO(CH_2)_{17}CH_3$	77–79	405
C_6H_5	Br	$NHCOSC_6H_5$	167–168	405
C_6H_5	Br	NHCOCOOH	183–184	406
C_6H_5	Br	$NHCON(CH_3)_2$	142–143	763
C_6H_5	Br	$NHCH(OH)CCl_3$	213–215 (dec)	407
C_6H_5	Br	$NHCH_2C_6H_5$	202	62
C_6H_5	Br	$NHSO_2C_6H_4NHCOCH_3(4)$	227	396
C_6H_5	Br	N=CHNHCH$_3$	175–175.5	404
C_6H_5	Br	N=CHNHCH$_3$ (HCl)	234–236	404
C_6H_5	Br	$N{=}CHN(CH_3)_2$	166–167	404
C_6H_5	Br	$N(CH_3)_2$	116	62
C_6H_5	Br	$N(C_2H_5)_2$	92–93	62, 762
C_6H_5	Br		151–152	49
C_6H_5	Br		140–141	762
C_6H_5	Br		151–152	49, 762
C_6H_5	Br	$NHNH_2$	161–162	207, 762
C_6H_5	Br	NHNHCOCH=CHCOOH	126–127	207
C_6H_5	Br	$NHNHCSNHC_6H_5$	175–176	207
C_6H_5	Br	N_3	98–100	762
C_6H_5	Br	N=C=O		401
C_6H_5	Br	NO_2	131–135	392
C_6H_5	Br	OH	270	62, 764
C_6H_5	Br	$OCOCH_3$	116–117	408
			124	764
C_6H_5	Br	OCH_3	153–154	400, 764
			152–154	49
			No mp	62, 402
C_6H_5	Br	OC_2H_5	129–130	400
			135	62, 764
$C_6H_4F(4)$	Br	OCH_3	170–171	400
C_6H_5	Br	SH	150	409

TABLE X (*continued*)

R_1	X	R_2	MP (°C)	References
C_6H_{11}	Br	NH_2		402
C_6H_{11}	Br	$NHCH(OH)CCl_3$	215–220 (dec)	407
C_6H_{11}	Br	$N{=}CHNHCH_3$	175	400
C_6H_{11}	Br	$N{=}CHN(CH_3)_2$	154–155	400
C_6H_{11}	Br	OCH_3	118–120	400
C_6H_5	Cl	Br	156	27
C_6H_5	Cl	NH_2	204–206	27, 410, 411
C_6H_5	H, Cl	H, NH_2		412, 413
C_6H_5	Cl	$NHCOCH_3$		402
C_6H_5	Cl	$NHCOCH_2Cl$		402
C_6H_5	Cl	$NHCOCHCl_2$	165.5–166.5	402
C_6H_5	Cl	$NHCOCCl_3$	194–195	414
C_6H_5	Cl	$NHCOCH_2CH_3$	127–128	414
C_6H_5	Cl	$NHCOCHClCH_3$	137–138	414
C_6H_5	Cl	$NHCOCH_2CH_2Cl$	119–120	414
C_6H_5	Cl	$NHCOCCl_2CH_3$	148–149	414
C_6H_5	Cl	$NHCOCH_2CH_2COOH$	160–162	406
C_6H_5	Cl	$NHCOCCl{=}CClCOOH$	158–161	406
C_6H_5	Cl	$NHCONHC_6H_5$	174–175	414
C_6H_5	Cl	$NHCONHC_6H_4Cl(3)$	210	414
C_6H_5	Cl	$NHCONHCH_2Cl$	124.5–125.0	415
C_6H_5	Cl	$NHCON(CH_3)_2$	141–142	763
C_6H_5	Cl	$NHCOOC_2H_5$	132–133	405
C_6H_5	Cl	$NHCOO(CH_2)_{17}CH_3$	75–77	405
C_6H_5	Cl	$NHCH_3$	213	27
C_6H_5	Cl	$NHCH_2OH$	179–181	415
C_6H_5	Cl	NHC_2H_5		402
C_6H_5	Cl	$NHCH_2CH_2OH$	170–171	415
C_6H_5	Cl	$NHCH(OH)CCl_3$		402
C_6H_5	Cl	NHCOCOOH	195–196	406
C_6H_5	Cl	NHCOCOONa	250	406
C_6H_5	Cl	$N(CH_3)COCOOH$	100–101	406
C_6H_5	Cl	NHC_3H_7	137–138	415
C_6H_5	Cl	$NHCH(CH_3)_2$	143	415
C_6H_5	Cl	$NHCH_2CH{=}CH_2$	163–164	415
C_6H_5	Cl	$NHCH_2CH_2CH_2OH$	115–117	415
C_6H_5	Cl	NHC_4H_9	83–84	415
C_6H_5	Cl	$NHCH_2CH(CH_3)_2$	80–82	415
C_6H_5	Cl	$NHCH(CH_3)CH_2CH_3$	169–170	415
C_6H_5	Cl	$NHSO_2C_6H_4NH_2(4)$	193	396
C_6H_5	Cl	$NHSO_2C_6H_4NHCOCH_3(4)$	226	396
C_6H_5	Cl	NH-Cyclooctyl	80–81	379
C_6H_5	Cl	$N(CH_3)_2$		402
C_6H_5	Cl	$N(C_2H_5)_2$	105-106	415
			107–108	379
C_6H_5	Cl	Pyrrolidinyl	148–149	379, 415

TABLE X (*continued*)

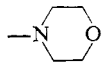
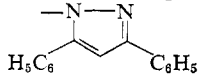
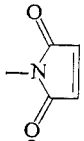
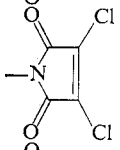
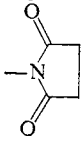
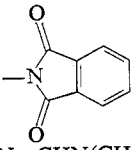
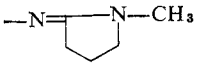
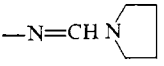
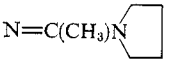
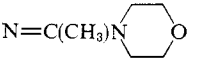
R_1	X	R_2	MP (°C)	References
C_6H_5	Cl		177	10
C_6H_5	Cl		157	10
C_6H_5	Cl	1-Piperazinyl	143–144	379, 415
C_6H_5	Cl	2,6-Dimethylmorpholino	126	379, 415
C_6H_5	Cl		176–178	205
C_6H_5	Cl		229–230	406
C_6H_5	Cl		245	406
C_6H_5	Cl		259–260	406
C_6H_5	Cl		204–206	406
C_6H_5	Cl	$N{=}CHN(CH_3)_2$	162–163	393
C_6H_5	Cl	$N{=}CHN(CH_3)_2(HCl)$	203–205 245–247	393 416
C_6H_5	Cl		121–122 152–153.5	393 416
C_6H_5	Cl		152–153.5	393
C_6H_5	Cl		169–171	393
C_6H_5	Cl		160–161	393

TABLE X (*continued*)

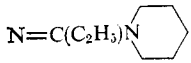
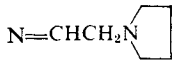
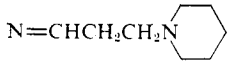
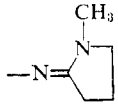
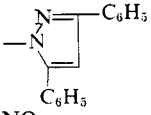
R_1	X	R_2	MP (°C)	References
C_6H_5	Cl		128–130	393
C_6H_5	Cl		169–171	416
C_6H_5	Cl		160–161	416
C_6H_5	Cl		128–130	416
C_6H_5	Cl		121–122	393
C_6H_5	Cl	$NHNH_2$	172 (dec)	205, 393, 417
C_6H_5	Cl	$NHNH_2$ (HCl)	150 (dec)	416
C_6H_5	Cl	$NHN{=}C(CH_3)_2$		393
C_6H_5	Cl	$NHN{=}C(CH_3)C_2H_5$		393
C_6H_5	Cl		176–178	205
C_6H_5	Cl	NO_2	124–126	392
C_6H_5	Cl	N_3	110–111	393, 417
C_6H_5	Cl	OH	247	89
			264	84
			266–270	27
C_6H_5	Cl	$OCOCH_3$	93.5–94	398
C_6H_5	Cl	OCH_3	156–157	398
			157–158	89
			160–161	10, 27
C_6H_5	Cl	OC_2H_5	133–134	10, 398
C_6H_5	Cl	$OCH_2CH_2N(CH_3)_2$ (HCl)	152–153	398
C_6H_5	Cl	$OCH_2CH_2OCH_3$	96–96.5	398
C_6H_5	Cl	$OCH_2CH{=}CH_2$	115–116	398
C_6H_5	Cl	$OCH_2CH_2CH_3$	118–120	398
C_6H_5	Cl	$OCH(CH_3)_2$	120–121	398
C_6H_5	Cl	OC_4H_9-*n*	119–120	398
C_6H_5	Cl	$OCH_2C_6H_5$	201–202	398
C_6H_5	Cl	SH	178–179	27
			180	409
C_6H_5	Cl	SCH_3		402
C_6H_5	Cl	$SCOOCH_3$	157–158	380
C_6H_5	Cl	SC_6H_5	117–118	380
C_6H_5	Cl	$SCH_2C_6H_4Cl(4)$	155–156	418

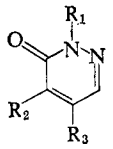
TABLE X (*continued*)

R_1	X	R_2	MP (°C)	References
C_6H_5	Cl	$SC_6H_4NH_2(2)$	209–210.5	421
C_6H_5	Cl	SCH_2-2-pyridyl	146	420
C_6H_5	Cl	SO_2CH_3	160–162	419
C_6H_5	I	CH_3	126–128	761
C_6H_5	I	SCH_3	138–140	761
C_6H_5	I	NH_2	150–152	761
C_6H_5	I	$NHCOCH_3$	198–200	761
C_6H_5	I	NHCOCOOH	182	761
C_6H_5	I	$NHCONHC_6H_5$	224–226	761
C_6H_5	I	NCO	105–106	761
		(Other related compounds)		761
$C_6H_4Cl(3)$	Cl	NH_2		402
$C_6H_4Cl(4)$	Cl	NH_2	254–256	379
				415
$C_6H_4Cl(4)$	Cl	NO_2	139–141	392
$C_6H_4CH_3(4)$	Cl	NH_2	226	379
$C_6H_4CF_3(3)$	Br	NH_2	172–174	760
$C_6H_4CF_3(3)$	Br	$NHCH_3$	156–158	757
$C_6H_4CF_3(3)$	Br	NHC_2H_5	138–140	756, 757
$C_6H_4CF_3(3)$	Br	$N(CH_3)_2$	159	756, 757
$C_6H_4CF_3(3)$	Br	OCH_3	145	760
$C_6H_4CF_3(3)$	Cl	NH_2	174–175	760
$C_6H_4CF_3(3)$	Cl	$NHCH_3$	183–185	757
$C_6H_4CF_3(3)$	Cl	NHC_2H_5	132	757
$C_6H_4CF_3(3)$	Cl	$N(CH_3)_2$	153	757
$C_6H_4CF_3(3)$	Cl	OCH_3	152–153	760
$C_6H_4NO_2(4)$	Br	N_3	155–160	762
$C_6H_2(NO_2)_3(2,4,6)$	Br	N_3	161–163	762
$C_6H_3NH_2(2)CH_3(4)$	Cl	NH_2	220–222	379
$C_6H_4OCH_3(4)$	Cl	NH_2	279–280	379
$C_6H_4COOH(4)$	Cl	NH_2		379
$C_6H_4SO_2NH_2(4)$	Cl	NH_2		379
$C_6H_4SO_2NHCH_3(4)$	Cl	NH_2	262–264	379
C_6H_{11}	Cl	NH_2		401, 402
			225-226	422
C_6H_{11}	Cl	$NHCON(CH_3)_2$	150–151	763
C_6H_{11}	Cl	NHCOCOOH	193–195	406
C_6H_{11}	Cl	NCO	121–123	763
C_6H_{11}	Cl	$NHNH_2$	148	393
C_6H_{11}	Cl	N_3		417
C_6H_{11}	Cl	OH	256–258	398
C_6H_{11}	Cl	OCH_3		401, 402
C_6H_{11}	I	$NHCOCH_3$	139–141	761
$C_6H_{10}Cl(2)$	Cl	OCH_3		376

TABLE X (*continued*)

R_1	X	R_2	MP (°C)	References
C_8H_{15}	Cl	NH_2	184–185	402, 422
C_8H_{15}	Cl	OH	178–179	398
N-Methylpiperidinyl	Cl	NH_2 (HCl)	296–297	379
Glucosyl	Cl	NH_2	178–180	379

TABLE XI. 1,4,5-Trisubstituted 6(1*H*)Pyridazinones



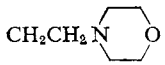
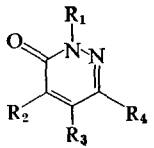
R_1	R_2	R_3	MP (°C)	References
H	CH_3	CH_3	147	427, 428
H	CH_3	C_2H_5	150	427, 428
H	CN	CH_3	228–230	66
H	CN	9-Fluorenyl	250–251	423
H	CN	4-Phenanthryl	284–287	423
H	COOH	CH_3	193–194	66
H	$COOC_2H_5$	NH_2	170 (dec)	424
H	$CH_2C_6H_5$	$CH_2C(OH,CH_2C_6H_5)COOH$		429
H	NH_2	Cl	292–294	204
H	OCH_3	COOH	184–186	290
H	OCH_3	$COOC_2H_5$	85–88	290
CH_3	CN	C_6H_5	165–167	425
CH_3	NH_2	SO_2NH_2	222–223	759
CH_3	NH_2	NO_2	220–222	430
CH_3	SO_2NH_2	NH_2	255–260	759
CH_3	SCH_3	SCH_3		402
CH_3	SO_3K	SO_3K	365–370	759
CH_2CH_3	CN	C_6H_5	66–67	426
$CH_2COC_6H_4NO_2(4)$	CN	C_6H_5	245	425
$CH_2CH_2N(CH_3)_2$	CH_3	C_2H_5	bp 106–120 (0.2 mm)	427 428
	CH_3	C_2H_5 (HCl)	198	427, 428
C_6H_5	NH_2	Cl	142–143.5	27
C_6H_5	NHC_2H_5	Cl		431
C_6H_5	NH_2	NO_2	212–214	430
C_6H_5	OCH_3	NO_2	94–96	84

TABLE XI. (*continued*)

R_1	R_2	R_3	MP (°C)	References
C_6H_5	OCH_3	OH	178–179	432
C_6H_5	OCH_3	$OCOCH_3$	117–118	432
C_6H_5	OCH_3	OCH_3	142	89
			144	402, 432
			144–146	433
C_6H_5	OCH_3	OC_2H_5	96–97	402, 432
C_6H_5	OC_2H_5	OC_2H_5	78	433
			79–80	402, 432
C_6H_5	OC_6H_5	Br	115	434
C_6H_5	$SCH_2C_6H_5$	Cl	76	435
C_6H_5	$SCH_2C_6H_4$-Cl(2)	Cl	88	435
C_6H_5	$SCH_2C_6H_4$-Cl(4)	Cl	106	435
$C_6H_4CH_3(4)$	NH_2	NO_2	200–201	430
$C_6H_4CH_3(4)$	OCH_3	OCH_3	95–96	402, 432
C_6H_{11}	OCH_3	OCH_3	60–61	402, 432

TABLE XII. 1,3,4,5-Tetrasubstituted 6(1*H*)Pyridazinones



R_1	R_2	R_3	R_4	MP (°C)	References
H	Br	Br	NO_2		502, 503
H	Br	Br	OAg		504
H	Br	Br	OBa		504
H	Br	Br	OC_2H_5	206	504
H	Br	Br	$OCOCH_3$	228	504
H	Br	Br	$OSO_2C_6H_5$	115	751
H	Br	Br	$OPS(OC_2H_5)_2$	120–123	166
H					
H	Br	Br	$OPO(OCH_3)N[(CH_2)_4CH_3]_2$		167
H	Cl	Cl	Cl	224–226	335
H	Cl	Cl	NO_2	184–186	502, 503
H	Cl	H	$OPS(OC_2H_5)_2$	91–92	165
H	Cl	Cl	$OPO(OC_2H_5)_2$		165
H	Cl	Cl	$OPS(OCH_3)NHCH_3$	120–122	167
H	F	F	F	129–131	765
H	F	OCH_3	F	162–164	765
H	OCH_3	F	F	134–136	765
H	OCH_3	OCH_3	F	139–141	765
H	CH_3	CH_3	CH_3	249.5–250	132, 264
H	CN	CH_3	CH_3	212–213	51, 66, 132, 251
H	COOH	CH_3	CH_3	172–173	51, 66, 132, 251

TABLE XII. (*continued*)

R_1	R_2	R_3	R_4	MP (°C)	References
H	$COOCH_3$	CH_3	CH_3	168–170	284
H	$COOC_2H_5$	CH_3	CH_3	173–174	284
H	CN	C_6H_5	CH_3	199–200	251, 281, 282, 426
H	$NHCOC_6H_5$	C_6H_5	C_6H_5	232–233	181
H	CN	C_6H_5	C_6H_5	274–275	251, 281, 282, 426
H	COOH	C_6H_5	C_6H_5	243–244	251
H	$COOC_2H_5$	C_6H_5	C_6H_5	217–220	251, 282
H	COC_6H_5	C_6H_5	C_6H_5	224–225	251, 282
H	$NHCOC_6H_5$	C_6H_5	C_6H_5	232–233	251, 282
H	C_6H_5	OH	C_6H_5		319
H	C_6H_5	C_6H_5	C_6H_5	272–273	181
				274–275	282
H	$COOC_2H_5$	$C_6H_4Cl(4)$	$C_6H_4Cl(4)$	235–236	251, 281, 282
H	COOH	$C_6H_4Cl(4)$	$C_6H_4Cl(4)$	274 (dec)	251
H	NH_2	NH_2	OCH_3	226–227	199
H	NH_2	NHCHO	OCH_3		199
H	$NHCOCH_3$	$NHCOCH_3$	OCH_3	270–273	199
H	$CH_3(H)$	$H(CH_3)$	OC_6H_5	184	505
Cl	Cl	Cl	Cl	103–104	335
CH_3	Br	Br	NO_2		506
CH_3	Br	Br	OCH_3	131–132	482
CH_3	Br	Br	$OPS(OC_2H_5)_2$	67–68	166
CH_3	Cl	Cl	Cl	102–103	335
CH_3	Cl	Cl	CH_3	116.5	22, 188
CH_3	Cl	Cl	COOH	203–204	22
CH_3	Cl	Cl	NH_2	191–193	758

CH_3	Cl	Cl	$NHSO_2C_6H_5$	164–166	766
CH_3	Cl	Cl	NO_2	97–99	198, 758
CH_3	Cl	Cl	OCH_3	127–130	482
CH_3	Cl	NH_2	CH_3	190–191	458
CH_3	NH_2	Cl	CH_3	169–171	458
CH_3	F	F	F	74–76	765
CH_3	OCH_3	F	F	57–59	765
CH_3	CN	CH_3	CH_3	115–116	251, 372
CH_3	COOH	CH_3	CH_3	107–108	251, 285, 444
CH_3	$COOCH_3$	CH_3	CH_3	59–60	444
CH_3	$CONH_2$	CH_3	CH_3	286–287	444
CH_3	$CSNH_2$	CH_3	CH_3	213–214	444
CH_3	COOH (*N*-hydroxyamidine)	CH_3	CH_3	187–189	444
CH_3	CH_3	CH_3	$OPS(OCH_3)NHC_2H_5$		167
CH_3	CN	C_6H_5	CH_3	187–188	251, 426, 444, 507
CH_3	C_6H_5	CH_3	CH_3	106–107	508
CH_3	CN	C_6H_5	C_6H_5	211–212	251, 426, 444, 507
CH_3	COOH	C_6H_5	C_6H_5	222	285, 444
CH_3	$COOC_2H_5$	C_6H_5	C_6H_5	158–159	251
				146–147	284, 507
CH_3	COONa	C_6H_5	C_6H_5	222	251
CH_3	COOH	$C_6H_4Cl(4)$	$C_6H_4Cl(4)$	241–242	251, 285
CH_3	$COOC_2H_5$	$C_6H_4Cl(4)$	$C_6H_4Cl(4)$	169–170	251
CH_2Cl	Cl	Cl	Cl	98–100	335
CH_2Cl	Cl	Cl	OCH_3	93–95	482
CH_2OH	Cl	Cl	Cl	130	355
CH_2SCN	Cl	Cl	Cl	120–122	355
$COOC_2H_5$	Cl	Cl	Cl	72–73	355
CH_2COOH	Cl	Cl	Cl	147–149	355

TABLE XII. (*continued*)

R_1	R_2	R_3	R_4	MP (°C)	References
CH_2CH_2N O	CH_3	CH_3	C_6H_5 (HCl)	245	449
$CH_2COOC_2H_5$	CH_3	CH_3	CH_3	122–126	132
				123–126	264
$CH_2CONHNH_2$	CH_3	CH_3	CH_3	217–221	132, 264
$CH_2CON(CH_3)_2$	CN	CH_3	CH_3	180	342
C_2H_5	Cl	Cl	NH_2	130–132	758
C_2H_5	Cl	Cl	NO_2	87–90	758
C_2H_5	F	F	F	75–77	765
C_2H_5	CN	CH_3	CH_3	66–67	251, 444, 507
CH_2CH_2Cl	Cl	Cl	OCH_3	83–84	482
CH_2CH_2OH	Cl	Cl	OCH_3	102–105	482
CH_2CH_2CN	Cl	Cl	OCH_3	98–100	482
$CH(CH_3)CH_2N(CH_3)_2$	CN	CH_3	CH_3 (HBr)	209–211	68
$CH_2CH_2N(C_2H_5)_2$	CN	C_6H_5	C_6H_5	95–96	444
C_6H_5	Cl	Cl	Cl	109–110	189, 767
C_6H_5	Br	Br	$OPO(OC_2H_5)_2$	67–68	164
C_6H_5	Cl	Cl	$OPS(OCH_3)NHCH_3$		167
C_6H_5	Cl	OH	Cl	253–254	89
C_6H_5	Cl	OCH_3	Cl	142–144	89
C_6H_5	OCH_3	OCH_3	Cl	119–120	89
C_6H_5	$N(CH_3)_2$	$N(CH_3)_2$	Cl	92–93	466
C_6H_5	$N(CH_3)_2$	$N(CH_3)_2$	OC_2H_5	bp 148–150 (0.2 mm)	466
C_6H_5	$N(CH_3)_2$	$N(CH_3)_2$	OC_3H_7	bp 160–164 (0.25 mm)	466
C_6H_5	$N{=}NC_6H_5$	CH_3	COOH	216	496
C_6H_5	$CH_2C_6H_5$	C_6H_5	CH_3	148–149	509
C_6H_5	$CH_2N(CH_3)_2$	$-(CH_2)_6-$		197–200	200
C_6H_5	COOH	C_6H_5	C_6H_5	248	251, 285
C_6H_5	COONa	C_6H_5	C_6H_5	285–286	251

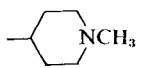
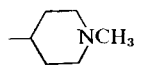
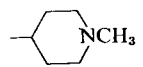
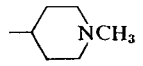
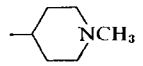
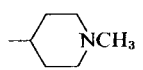
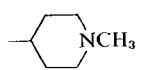
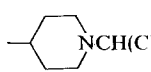
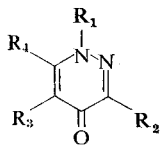
C_6H_5	$COOC_2H_5$	C_6H_5	C_6H_5	184	251
C_6H_5	NH_2	NO_2	$OCOC_6H_5$	163–164	430
C_6H_5	OCH_3	$H(OCH_3)$	$OCH_3(H)$		372
C_6H_5	OCH_3	OCH_3	OCH_3	102–103	89
$C_6H_{11}O_5$	CN	C_6H_5	C_6H_5	172–174	240
$C_6H_{11}O_5$	CN	C_6H_5	C_6H_5 (tetraacetyl)	223–224	240
$C_6H_4Cl(2)$	CH_3	CH_3	$OPO(OCH_3)NHCH_3$		167
$C_6H_4Cl(4)$	$N{=}NC_6H_4Cl(4)$	CH_3	COOH	209	496
$CH_2C_6H_5$	CH_3	CH_3	$OCH_2C_6H_5$	75–76	508
$CH_2C_6H_5$	Cl	NO_2	$OCH_2C_6H_5$	126–127	392
	CN	CH_3	CH_3 (HCl)	263–266	272
	CN	CH_3	CH_3 (HBr)	238–240	68
	CN	 (HCl)		247–250 (dec)	68
	C_2H_5	C_2H_5	C_6H_5 (HCl)	268–270	68, 272, 366
	C_2H_5	C_2H_5	C_6H_5 (HBr)	262–264	272, 366
			C_6H_5	179–180	68
			C_6H_5 (HBr)	220–222	68
	CN	CH_3	CH_5 (HCl)	276–278	68

TABLE XIII. 1,3,5,6-Tetrasubstituted 4(1*H*)Pyridazinones



R_1	R_2	R_3	R_4	MP (°C)	References
H	H	H	H	245–246	91
				247–249	179
				250–251	85
				252	235
				No mp	252, 253
H	H	H	H[CH_3Cl(2)]	115–117	85, 253
H	H	OH	H		302
H	H	H	CH_2OH	212 (dec)	510
H	H, H	H, COOH	$CH_3[C_6H_5(2)]$	203 (dec)	511
H	Cl	NH_2	H	259 (dec)	30
H	Cl	$NHCOCH_3$	H	258 (dec)	30
H	Cl	H	Cl	169–171	85
H	Cl	H	Cl (HCl)	199–200	85
H	Cl	OH	Cl	250	335
H	Cl	Cl	Cl	247–248	335
H	CH_3	H	H	238	324
H	CH_3	H	CH_3	249–250	172, 178
H	CH_3	H	CH_2Cl	206 (dec)	510
H	CH_3	H	CH_2OH	246–247 (dec)	510
H	CH_3	CH_3	CH_3		79
H	CH_3	H	C_6H_5		79
H	$CH_2C_6H_5$	OH	Cl	232–233	512
H	$CH_2C_6H_5$	OH	$CH_2C_6H_5$	>300	512

H	$CH_2C_6H_5$	OH	$CH_2C_6H_5$ (*monoacetate*)	215	512
H	$CH_2C_6H_5$	OH	$CH_2C_6H_5$ (diacetate)	147	512
H	$CH_2C_6H_5$	OH	H	252–253	512
H	COC_6H_5	OH	H	239–240	512
H	COC_6H_5	OH	$CH_2C_6H_5$	229–230	512
H	COC_6H_5	OH	$CH_2C_6H_5$ (monoacetate)	189–190	512
H	CH_2Cl	H	CH_2Cl	206	179
H	CH_2OH	H	CH_2OH	222–223	510
				223 (dec)	179, 513
H	$CH(OH)_2$	H	$CH(OH)_2$		514
H	COOH	H	COOH	219 (dec)	513
				251 (dec)	179
H	$CH_2OC_3H_7$	H	$CH_2OC_3H_7$	152	179
H	NH_2	H	CH_3	253	768
H	NH_2	H	$CH_2C_6H_5$	225	752, 768
H	NH_2	H	C_6H_5	264–266	752, 768
H	NH_2	CH_3	CH_3	284–284	752, 768
H	NH_2	$CH_2C_6H_5$	CH_3	249–250	752, 768
H	OCH_3	H	Cl	225–228	335
H	OCH_3	H	NH_2	130	515
H	C_3H_7	C_3H_7	H	138–140	80
H	C_6H_5	C_6H_5	H	326–328	80
				336–338	81
H	C_6H_5	C_6H_5	H (acetyl)	124–125	80
H	C_6H_5	H	C_6H_5	282	516
				>330	79
H	C_6H_5	C_6H_5	C_6H_5	275	83
CH_3	H	H	H	98–99	85, 252, 253
CH_3	H	H	H (HCl)	172–176	85, 252, 253
CH_3	Cl	H	Cl	153–155	85
CH_3	Cl	H	OCH_3	198–199	335
CH_3	OCH_3	H	CN	198–199	269

TABLE XIII. (*continued*)

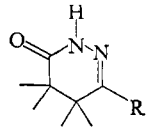
R_1	R_2	R_3	R_4	MP (°C)	References
C_2H_5	Cl	H	Cl	82–83	335
C_2H_5	OCH_3	H	CN	164–165	269
C_2H_5	C_6H_5	C_6H_5	C_6H_5	189	83
$CH_2COOC_2H_5$	Cl	H	Cl	102–103	335
$CH_2CON(C_2H_5)_2$	Cl	H	Cl	98–101	335
Tetra-*O*-acetyl-*β*-D-glucopyranosyl	H	H	H	110–115	238, 241
β-D-Glucopyranosyl	H	H	H	258–260	241
Tetra-*O*-acetyl-*β*-D-glucopyranosyl	Cl	H	Cl	160–163	238, 241
β-D-Glucopyranosyl	Cl	H	Cl	120–125	238
—N=O	CH_3	H	CH_3	238	178
OH	H	OH	$CH_2C_6H_5$	261 (dec)	512
OH	H	OH	COC_6H_5	245	512
OH	Cl	OH	COC_6H_5	190 (dec)	512
OH	COC_6H_5	OH	Cl	180	512
OH	COC_6H_5	OH	COC_6H_5	181–182	512
OCH_3	H	H	H (picrate)	130.5–131	236
OCH_3	CH_3	H	CH_3	102–104	517
OCH_3	CH_3	H	CH_3 (picrate)	132–134	517
OC_2H_5	H	H	H (picrate)	104–105	236
C_6H_5	H	H	CH_3	179–180	85
C_6H_5	H	Br	CH_3	177–178	85
C_6H_5	COOH	Br	CH_3	230–232 (dec)	85
C_6H_5	$COOCH_3$	Br	CH_3	222–223	426
C_6H_5	COOH	H	CH_3	183–185 (dec)	85, 518–520
C_6H_5	COOH	H	C_6H_5	330 (dec)	521

C_6H_5	$COOCH_3$	H	CH_3	210–212	85, 519, 520
C_6H_5	$COOC_2H_5$	H	CH_3	182–184	85, 519, 520
C_6H_5	$COOC_2H_5$	H	C_6H_5	104–105	71
C_6H_5	COO (other esters)	H	CH_3		85, 519, 520
C_6H_5	$CONH_2$	H	CH_3	229–231 (dec)	85, 519, 520
C_6H_5	$CONHCH_3$	H	CH_3	220–222	85, 519, 520
C_6H_5	$CONHNH_2$	H	CH_3	212–214 (dec)	85, 519, 520
C_6H_5	$COOC_2H_5$	H	$C_{13}H_{27}$	47–48	71
$C_6H_4Br(2)$	COOH	H	CH_3	216–217 (dec)	85, 519, 520
$C_6H_4Br(3)$	COOH	H	CH_3	221–222	85, 519, 520
$C_6H_4Br(4)$	COOH	H	CH_3	251–253	85, 519, 520
$C_6H_4Br(4)$	$COOC_2H_5$	H	CH_3	145–146	519
$C_6H_4Cl(2)$	COOH	H	C_6H_5	218	76
$C_6H_4Cl(3)$	COOH	H	CH_3	193	518
$C_6H_4Cl(4)$	COOH	H	CH_3	229	77
$C_6H_4Cl(4)$	COOH	H	C_2H_5	160	76
$C_6H_4CH_3(4)$	COOH	H	CH_3	154	518
$C_6H_4NO_2(2)$	COOH	H	CH_3	224	522
$C_6H_4NO_2(3)$	COOH	H	CH_3	224	76
$C_6H_4NO_2(3)$	COOH	H	C_6H_5	206	76
$C_6H_4NO_2(3)$	$COOC_2H_5$	H	CH_3	183–184	519
$C_6H_4NO_2(4)$	COOH	H	CH_3	209	76
$C_6H_4NO_2(4)$	$COOC_2H_5$	H	CH_3	161–162	519
$C_6H_4NO_2(4)$	COOH	H	OH	251	523
$C_6H_4NO_2(4)$	$COOC_2H_5$	H	OH	180	524
$C_6H_3CH_3(2)NO_2(4)$	COOH	H	CH_3	246	518
$C_6H_4COOC_2H_5(4)$	COOH	H	CH_3	156–157	519
$C_6H_4OCH_3(2)$	COOH	H	CH_3	170	518
$C_6H_4As(OH)_2(4)$	COOH	H	CH_3	252	77
$C_5H_4N(3)$	COOH	H	CH_3	202–203	85, 525
$C_5H_4N(3)$	$COOCH_3$	H	CH_3	169–171	85

TABLE XIII. (*continued*)

R_1	R_2	R_3	R_4	MP (°C)	References
$C_5H_4N(3)$	$COOC_2H_5$	H	CH_3	168–170	85
$C_3H_2NS(2)$	COOH	H	CH_3	176–178	525
$C_3H_2NS(2)$	$COOCH_3$	H	CH_3	152–154	525
C_6H_5	COOH	$N{=}NC_6H_5$	OH	260	526
C_6H_5	$COOC_2H_5$	$N{=}NC_6H_5$	OH	164–165	526
C_6H_5	COOH	H	OH	244–245	62
C_6H_5	$COOCH_3$	H	OH	138	62
C_6H_5	$COOC_2H_5$	H	OH	121–122	62
C_6H_5	$CONHC_6H_5$	H	OH	177–178	62
C_6H_5	$COOCH_3$	H	OCH_3	154	62
C_6H_5	COOH	$N{=}NC_6H_5$	H	235–236	527
C_6H_5	COONa	$N{=}NC_6H_5$	H	204–205	527
C_6H_5	NH_2	H	CH_3	218.5–220	85
C_6H_5	CH_3	H	CH_3	245	528
C_6H_5	CH_3	COOH	CH_3	220	528
C_6H_5	COOH	$COOCH_3$	$C_6H_4OCH_3(2)$	210	529
C_6H_5	CH_3	H	C_6H_5	225	528
C_6H_5	C_6H_5	H	CH_3	179	528
C_6H_5	C_6H_5	H	C_6H_5	207	528
C_6H_5	C_6H_5	C_6H_5	C_6H_5	220–221	528

TABLE XIV. 3-Substituted 4,5-Dihydro-6(1*H*)pyridazinones



R	MP (°C)	References
H	37	530
	41–43	248
	231–232	523
	No mp	183, 185
CH_3	102–103	531
	103–105	219
	104–105	532–534
	105	13
	104.5–105.5	36, 122, 275, 293
	No mp	535
		536
COOH	198 (dec)	64, 176, 247, 250, 302, 537–541
$COOCH_3$	136–137	329, 336, 537
$COOC_2H_5$	135–136	64, 302, 329, 537–541
$CONH_2$	250–251	64, 176, 302
$CONHNH_2$	190–191	64, 302
C_2H_5	43	29
CH_2CH_2COOH	184	542, 543
$CH_2CH_2COOC_2H_5$	62	542, 543
$CH_2CH_2CONH_2$	187	542, 543
C_5H_{11}	35	101
	37–38	299
	bp 150–152 (5 mm)	14
C_5H_{11}-*i*	bp 149–150 (5 mm)	14
C_6H_{13}	55–56	299
C_6H_{13}-*i*	54–55	299
C_7H_{15}	56–57	299
C_8H_{17}	62–63	299
C_9H_{19}	54–55	299
C_6H_5	149–150	218, 545, 546
	150	546
	151	547
	153	548
	No mp	40
$C_6H_4AsO_3H_2$(4)		549
C_6H_4Br(4)	168–168.5	70, 311
C_6H_4Cl(4)	178	548
	178.5–179	311
	No mp	40
$C_6H_3Cl_2$(2,4)	172–173	311

TABLE XIV (*continued*)

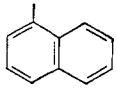
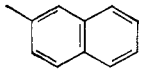
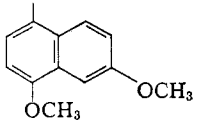
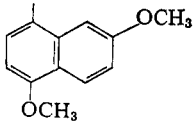
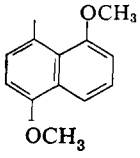
R	MP (°C)	References
$C_6H_3Cl_2(3,4)$	174–175	311
$C_6H_4I(4)$	199–199.5	311
$C_6H_4CH_3(4)$	154–156	550
	155	551, 552
	156	21
$C_6H_3(CH_3)_2(2,4)$	122	21
	No mp	185
$C_6H_3(CH_3)_2(2,5)$	105	21, 185
$C_6H_3(CH_3)_2(3,4)$		185
$C_6H_4C_3H_7(4)$	103.5–104.5	553
$C_6H_4C_6H_5(4)$	248	218
$C_6H_4NH_2(3)$	169	769
$C_6H_4NH_2(4)$	236	769
$C_6H_4NHC_4H_9(4)$	302	769
$C_6H_4NHCOCH_3(3)$	208	769
$C_6H_4NHCOCH_3(4)$	252	769
$C_6H_4NO_2(3)$		317
$C_6H_4OCH_3(4)$	146–147	218
	147–148	554
	153–154	148, 40
$C_6H_3(OCH_3)_2(2,5)$	139	555
$C_6H_2(OCH_3)_3(2,4,5)$	151–152	217
$C_6H_2(OCH_3)_3(3,4,5)$	139	556
$C_6H_4(OC_2H_5)4$	145–146	312
	205	219
	210	219
	205	314
	148	557
	172	21
	166	21
	164	21

TABLE XIV (*continued*)

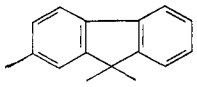
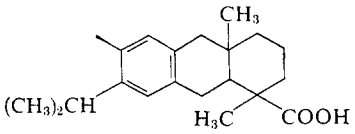
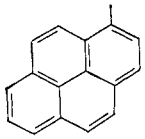
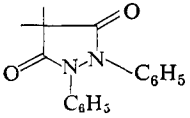
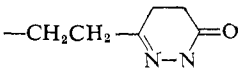
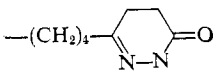
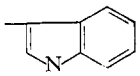
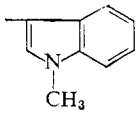
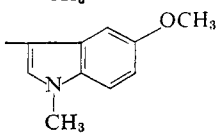
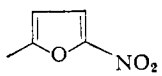
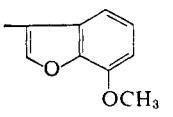
R	MP (°C)	References
		185
	190	558
	233	559
		26
	268 (dec)	37
	219–220 (dec)	560
	267 215	561 562
	210	562
	232	562
	143–145 145	563 564
	249.5–250 (dec)	563
	207	565

TABLE XIV (*continued*)

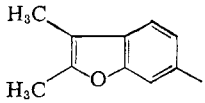
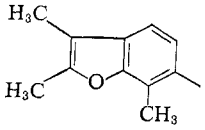
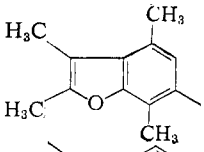
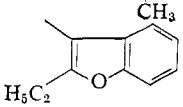
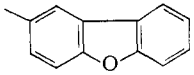
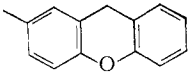
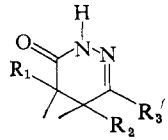
R	MP (°C)	References
	86–87	566
		567
	185	566
	148	21
	199–200	6
		185
		317

TABLE XV. 3,4,5-Trisubstituted 4,5-Dihydro-6(1*H*)pyridazinones



R_1	R_2	R_3	MP (°C)	References
H	$COOC_2H_5$	H	bp 125–130 (0.4 mm)	65
H	$C_6H_4CH(CH_3)_2(4)$	H	166–167	553
H	$C(CH_3)_3$	Cl	140–141	82
Br	H	CH_3	249–250	293
COOH, CH_3	H	CH_3	153–154	568
Br(H)	H(Br)	CH_3	190–192	275
H	$COOC_2H_5$	CH_3	92–93	65, 569
$COOC_2H_5$, CH_3	H	CH_3	43	568
H	CH_3	CH_3	108–110	51
			111.5–112.5	132
H	$COOC_2H_5$	$COOC_2H_5$	155–156	64, 65
CN	H	CH_3	97–100	570
COOH	H	CH_3	100	568
$COOC_2H_5$	H	CH_3	76–77	568, 571
$CONH_2$	H	CH_3	171–173	302, 572
$CONHNH_2$	H	CH_3	151–153	302, 568, 571, 572
$CONHN(CH_3)_2$	H	CH_3	183–184	572
CH_3	H	CH_3	62.5–63.5	132
			57–58	298
CH_3, CH_3	H	CH_3	97–98	258, 573
CH_3	CH_3	CH_3	85–86	132
COOH, C_2H_5	H	CH_3	137	568, 571
$COOC_2H_5$, C_2H_5	H	CH_3	73	568, 571
COOH, C_4H_9-*i*	H	CH_3	122–124	568
$COOC_2H_5$, C_4H_9-*i*	H	CH_3	80–81	568
C_2H_5	H	CH_3	bp 145–147 (13 mm)	298
C_6H_5	H	CH_3	121–123	442
OH	H	CH_3		302
CH_3	H	COOH		264
CH_3	H	$C_{13}H_{27}$	66	574
$C(CH_3)_3$	Br	C_6H_5		245
H	CH_3	C_6H_5	157	445
			157.5	575
COOH	H	C_6H_5	116–117 (dec)	576
$COOCH_3$	H	C_6H_5	179–180	576
$CONHNH_2$	H	C_6H_5	249–250	576
CH_3, CH_3	H	C_6H_5	167–168	577
CH_3, OH	H	C_6H_5	155	41

TABLE XV (*continued*)

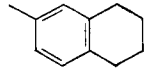
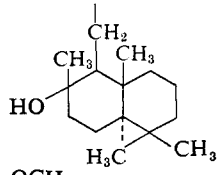
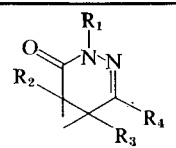
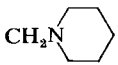
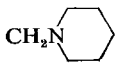
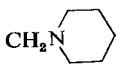
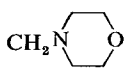
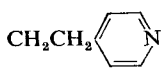
R_1	R_2	R_3	MP (°C)	References
CH_3, C_2H_5	H	C_6H_5	108	577
C_2H_5, OH	H	C_6H_5	163	41
H	$C(CH_3)_3$	C_6H_5	192–193	245
$C(CH_3)_3$	H	C_6H_5	161–162	245
$CH_2C(CH_3)_2C_6H_5$	H	C_6H_5	106.5–108.0	578
$CH_2C(C_6H_5)_2OH$	H	C_6H_5	195–196	579
$=CHC_6H_5$	H	C_6H_5	177	15, 39, 183
$=CHC_6H_4Cl(4)$	H	C_6H_5	169	183
$=CHC_6H_4NO_2(3)$	H	C_6H_5	189	183
$=CHC_6H_4OCH_2O(3,4)$	H	C_6H_5	182	183
H	C_6H_5	C_6H_5	217–218	450
			219–221	580
			No mp	40, 184
C_6H_5	H	C_6H_5	154–165	450
			164	184, 314
C_6H_5	OH	C_6H_5		319
C_6H_5	H	$C_6H_4Cl(4)$	163–164	184
CH_3	H	$C_6H_3Cl_2(3,4)$	167–168	70, 375
CH_3	H	$C_6H_4CH_3(4)$	141	452
$CH_2C[C_6H_4CH_3(4)]_2OH$	H	$C_6H_4CH_3(4)$	201–202	579
C_6H_5	H	$C_6H_4CH_3(4)$	176–177	184
$C_6H_4CH_3(4)$	H	$C_6H_4CH_3(4)$	165	493
C_6H_5	H	$C_6H_4OCH_3(4)$	167–168	184
$CH_2C_6H_5$	H	$C_6H_3(OCH_3)_2(3,4)$	173–174	581
$C_6H_3(OCH_3)_2(3,4)$	H	$C_6H_3(OCH_3)_2(3,4)$	196–198	582
H	C_6H_5	$CH_2C_6H_5$	115–116	494
CH_3, CH_3	H		202–203	44
C_6H_5, C_6H_5	H		256	44
CH_3	H		140	452
H	CH_3		206–207	38
Br	$C(CH_3)_3$	OCH_3	169.5–171	453
H	$CH(CH_3)_2$	OCH_3	116–117	453
H	C_4H_9	OCH_3	81–82	246
H	$C(CH_3)_3$	OCH_3	151.5–152.5	82
H	C_6H_5	OCH_3	197–198	453

TABLE XVI. 1,3,4,5-Tetrasubstituted 4,5-Dihydro-6(1*H*)pyridazinones



R_1	R_2	R_3	R_4	MP (°C)	References
H	H	H	H, H		
			C_6H_5(1)	130–131	583
CH_3	H	H	CH_3	bp 142–143 (15 mm)	109
CH_3	H	H	COOH	159–160	176, 538, 539
CH_3	H	H	$COOCH_3$	90–92	176, 329, 336, 540
CH_3	H	H	$CONH_2$	170–172	176, 329, 540
CH_3	H	C_6H_5	CH_3	52–53.5	584
CH_3	H	C_2H_5, C_6H_5	CH_3	87–88	584
CH_3	H	H	C_6H_5		585
CH_3	CH_3	H	C_6H_5	bp 138 (0.25 mm)	446
CH_2Cl	H	H	CH_3	83–84	535
CH_2Cl	H	H	C_6H_5	134–135.5	535
CH_2Cl	H	H	C_6H_4Cl(4)	28–29	535
$CH_2C_6H_5$	H	H	CH_3	56–57	586
$CH_2C_6H_5$	H	H	COOH	175–178	366, 539
$CH_2C_6H_3(CH_3)_2$(2,4)	H	H	CH_3	72	587
				79.5	588
$CH_2C_6H_3(CH_3)_2$(2,4)	H	H	C_6H_5	130	587

TABLE XVI (*continued*)

R_1	R_2	R_3	R_4	MP (°C)	References
$CH_2C_6H_3OCH_2O(3,4)$	H	H	CH_3	101	588
	H	H	C_6H_5		183
	$=CHC_6H_5$	H	C_6H_5		183
	$=CHC_6H_4NO_2(3)$	H	C_6H_5		183
	H	H	C_6H_5		183
CH_2OH	H	H	CH_3	100–101	535
CH_2OH	H	H	C_6H_5	119–120	183 535
CH_2OH	H	H	$C_6H_4Cl(4)$	114–116	535
CH_2SH	H	H	H		589
CH_2SH	H	H	CH_3		590
CSC_6H_5	H	H	CH_3		9
$CH_2CH_2C_6H_3OCH_2O(3,4)$	H	H	H	104	7
$CH_2CH_2C_6H_3OCH_2O(3,4)$	H	H	H, H[H(1)]	98.5	7
$CH_2CH_2C_6H_3OCH_2O(3,4)$	H	H	H, H[H(1)] (HCl)	195	7
	H	H	CH_3	91–92	591–593

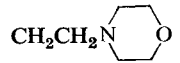
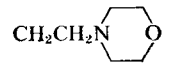
	OH, CH_3	H	C_6H_5	226	41, 42
	OH, CH_3	H	$C_6H_4OH(4)$	175	41, 42
CH_2CH_2OH	H	H	CH_3	99	129
CH_2CH_2OH	H	H	C_6H_5	97–99	746
CH_2CH_2CN	H	H	C_6H_5		183
$CH_2CH_2CH_2OH$	H	H	$C_6H_4OCH_3(4)$	117–118	770
C_4H_9	H	H	COOH	72	176, 336
C_4H_9	H	H	$COOCH_3$	38	176, 336
C_4H_9	H	H	$CONH_2$	172–174	102, 307, 308, 329, 479, 541
$COCH_3$	H	H	CH_3, H[$COCH_3(1)$]	bp 160 (0.005 mm)	109
C_6H_5	H	H	H, H	165	583
C_6H_5	H	COOH	H	178–179	291
C_6H_5	H	$COOC_2H_5$	H	111–112	291
C_6H_5	C_2H_5	H	H	159–160 (dec)	594
C_6H_5	C_2H_5	COOH	H	179	530
C_6H_5	C_2H_5	$COOC_2H_5$	H	bp 225–240 (15 mm)	530
C_6H_5	OH, CH_3	C_2H_5	H	193	595
C_6H_5	H	H	CH_3	107	187, 364, 584
				108	2
C_6H_5	H	H	COOH	170–172	366, 539, 596–599
C_6H_5	CH_3	H	CH_3	28–29	600
C_6H_5	H	CH_3	CH_3	47–48	600

TABLE XVI (*continued*)

R_1	R_2	R_3	R_4	MP (°C)	References
C_6H_5	CH_3, CH_3	H	CH_3	84	601
C_6H_5	CH_3, OH	H	CH_3	94	42
C_6H_5	C_2H_5	H	CH_3	bp 130–135 (0.01 mm)	473
C_6H_5	C_3H_7	H	CH_3	bp 135–140 (0.01 mm)	473
C_6H_5	$CH(CH_3)_2$	H	CH_3	bp 130–135 (0.01 mm)	473
C_6H_5	H	C_6H_5	CH_3	101.5–102.5	584
C_6H_5	CH_3	H	C_2H_5	bp 121–122 (0.13 mm)	473
C_6H_5	C_2H_5	H	C_2H_5	bp 108 (0.12 mm)	473
C_6H_5	CH_3	H	C_3H_7	bp 124–125 (0.12 mm)	473
C_6H_5	CH_3	H	$CH(CH_3)_2$	bp 121–122 (0.12 mm)	473
C_6H_5	H	H	C_5H_{11}	bp 186–187 (3 mm)	14
C_6H_5	H	H	C_5H_{11}-*i*	bp 183–184 (3 mm)	14
C_6H_5	H	H	C_6H_5	97–99	130, 602–605
C_6H_5	$=CHC_6H_5$	H	C_6H_5	123	183
C_6H_5	$=CHC_6H_4Cl(4)$	H	C_6H_5	140	183
C_6H_5	$=CHC_6H_4NO_2(3)$	H	C_6H_5	224	183
C_6H_5	$=CHC_6H_4OCH_3(4)$	H	C_6H_5	107	183
C_6H_5	CH_3, OH	H	C_6H_5	124	41

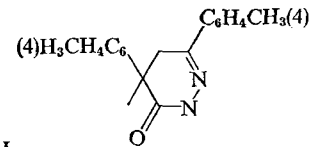
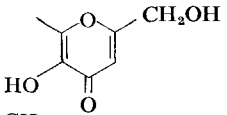
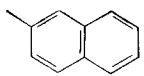
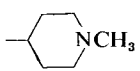
C_6H_5	C_2H_5, OH	H	C_6H_5	120	41
C_6H_5	C_2H_5, COOH	H	C_6H_5	134	606, 607
C_6H_5	$CH_2C(C_6H_5)$ $=NNHC_6H_5$	H	C_6H_5	164–166	608
C_6H_5	C_6H_5	H	C_6H_5	121–123	609–612
				122–124	584
C_6H_5	$C_6H_4CH_3(4)$; 	H	$C_6H_4CH_3(4)$	160	35
C_6H_5	H	H	$C_6H_4CH_3(4)$	103	554
C_6H_5	C_6H_5	H	$C_6H_4OCH_3(4)$	94–95	609
C_6H_5	$C_6H_4OCH_3(4)$	H	$C_6H_4OCH_3(4)$	123	609
C_6H_5	H	C_6H_5	$CH_2C_6H_5$	174–175	494
C_6H_5	H	H	OCH_3		116
$C_6H_4Br(4)$	H	H	CH_3	58–59	613, 614
$C_6H_4Cl(4)$	H	H	$C_6H_4Cl(4)$		317
$C_6H_4CH_3(2)$	H	H	CH_3	65	587
$C_6H_4CH_3(3)$	H	H	CH_3	68	190, 587
$C_6H_4CH_3(3)$	H	H	COOH	152	597–598
$C_6H_4CH_3(4)$	H	H	CH_3	59	587
$C_6H_4CH_3(2)$	H	H	C_6H_5	118	587
$C_6H_4CH_3(3)$	H	H	C_6H_5	84	587
$C_6H_4CH_3(4)$	H	H	C_6H_5	119	587
$C_6H_3(CH_3)_2(2,4)$	H	H	CH_3	81	587
$C_6H_3(CH_3)_2(2,4)$	H	H	C_6H_5	138	587
$C_6H_4COOH(4)$	H	H	CH_3	157–158	63
$C_6H_4COOH(4)$	H	H	C_6H_5	194–195	63
$C_6H_4NO_2(2)$	H	H	H	101.5–102	615
$C_6H_4NO_2(3)$	H	H	CH_2COOH	132	616

TABLE XVI (*continued*)

R_1	R_2	R_3	R_4	MP (°C)	References
$C_6H_4NO_2(4)$	H	H	H	125–127	613, 617
$C_6H_4NO_2(4)$	H	H	CH_3	118	187
				118–119	618
$C_6H_4NO_2(4)$	H	H	CH_2COOH	145–146	616
$C_6H_3(NO_2)_2(2,4)$	H	$C_6H(OCH_3)_3$ (2,3,4)COOH(6)	H	123	619
$C_6H_3(NO_2)_2(2,4)$	H	H		100–102	620
$C_6H_4OCH_3(4)$	H	H	CH_3	59–60	364
$C_6H_4OCH_3(4)$	H	H	$C_6H_4Cl(4)$	99–100	771
$C_6H_4OC_2H_5(4)$	H	H	CH_3	98–99	364
$C_6H_4SO_2NH_2$	H	H	COOH	258 (dec)	621
	H	H	CH_3	119	622
	H	H	CH_3	128	190
	H	H	CH_3		366
	CN	H	H	183–185	366

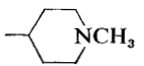
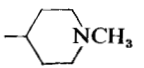
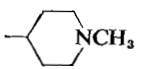
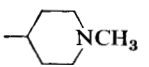
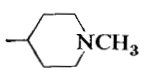
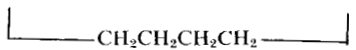
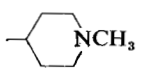
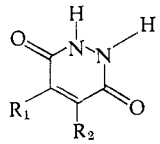
	CH_3	H	CH_3	107–111	366
	CH_3	H	CH_3 (HCl)	246–250	366
	H	H	C_6H_5	153–155	366
	CH_3	H	C_6H_5	124	366
			C_6H_5	146	68
			C_6H_5 (trans)	155	68
	C_6H_5	H	C_6H_5	138	366
	CN	H	C_6H_5	183–185	366
	H	H	$C_6H_4OCH_3$(4)	107–108	366
	H	H		103–105	366

TABLE XVII. 4,5-Disubstituted 3,6-Pyridazinediones



R_1	R_2	MP (°C)	References
H	H	>250	623
		256	308
		299–300	46, 624
		302 (dec)	502
		305.5 (dec)	166
		No mp	110, 114, 125, 144, 279, 333, 375, 625–641
H	H (glycine)	215–220	642
H	H [L-alanine ($Na \cdot H_2O$)]	227–230	642
H	H [L-asparagine (2 $Na \cdot 2\ H_2O$)]	209–211	642
H	H [L-glutamic acid (2 Na)]	230–238	642
H	H (L-histidine Na)	230–237	642
H	H (L-serine Na)	180–188	642
H	H (cysteine Na)	255–263	642
Br	H	251 (dec)	544
Br	Br	325	166
		330	544
		340	504
Br	Br (monoacetate)	228	504
Cl	H	254 (dec)	544
		263 (dec)	59
		265–268 (dec)	643
		269–272 (dec)	166
		285–288 (dec)	158
Cl	H (benzoate)	205–207	59, 544
Cl	Cl	296 (dec)	544
F	F	258 (dec)	633
CH_3	H	277	44, 644
		278–280	48, 225
		283–285	271
		284–285	498
		286.5–287	166, 620
		289–290	158, 181, 544
		No mp	279
CH_3	H (acetate)	174–176	48
CH_3	H (benzoate)	182.5–183.5	158, 181, 544
$CH{=}NNHC_6H_5$	H	165–170 (dec)	645
${=}CH_2$	H, H	276–278	646

TABLE XVII (*continued*)

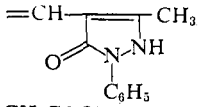
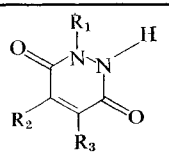
R_1	R_2	MP (°C)	References
	H	222–228	647
CH_2COOH	H	278–281 (dec)	498, 620
CH_2COOCH_3	H	190	498
$CH_2COOC_2H_5$	H	186–187	498
$CH_2COOC_3H_7$	H	187–188	498
$CH_2COOC_4H_9$	H	197–198	498
$C(COOH)=CHC_6H_5$	H	210 (dec)	645
CH_3	CH_3	>325	225, 271
		347–351	51
		No mp	648
CH_3	C_2H_5	260	298
C_6H_5	H	273	298
		279–280	166
NHC_2H_5	H	45–47	751
NHC_6H_5	H		649
$NHC_6H_4Br(3)$	H		649
$NHC_6H_4Br(4)$	H		649
$NHC_6H_4Cl(3)$	H		649
$HC_6H_4Cl(4)$	H		649
$NHC_6H_4F(3)$	H		649
$NHC_6H_4F(4)$	H		649
$NHC_6H_4CH_3(3)$	H		649
$NHC_6H_4CH_3(4)$	H		649
$NHC_6H_4C_2H_5(3)$	H		649
$NHC_6H_4C_2H_5(4)$	H		649
$NHC_6H_4OCH_3(3)$	H		649
$NHC_6H_4OCH_3(4)$	H		649
$NHC_6H_4OC_2H_5(3)$	H		649
$NHC_6H_4OC_2H_5(4)$	H		649
$OPS(OC_2H_5)_2$	H		223

TABLE XVIII. 2,4,5-Trisubstituted 3,6-Pyridazinediones



R_1	R_2	R_3	MP (°C)	References
CH_3	H	H	210–211	99
			213.5–215	166
			244	308
			No mp	110, 116, 243, 279, 332, 620, 650
CH_3	Br	Br	226–228	166
CH_3	Cl	H	185–186	54
CH_3	H	Cl	257	399
			262–263	651
CH_3	Cl	Cl	214–216	544
CH_3	NH_2	H		54
CH_2Cl	H	H	144	334
CH_2Cl	Cl	Cl	186	544
CH_2Cl	CH_3	CH_3	115	334
$CH_2NHC_{12}H_{25}$	H	H	111–115	652, 653
$CH_2NHC_6H_5$	H	H	200–205	653
$CH_2N(CH_3)_2$	H	H	168	177, 289
$CH_2N(C_2H_5)_2$	Cl	Cl	188–193	544
$CH_2N(CH_2CH_2Cl)_2$	H	H	143 (dec)	433
$CH_2N(CH_2CH_2OH)_2$	H	H		652
CH_2N 	H	H	178	177, 289
			180–181	261, 654

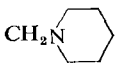
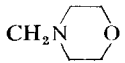
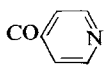
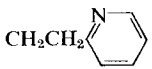
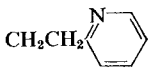
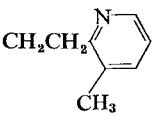
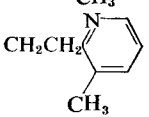
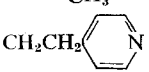
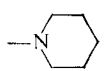
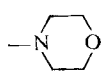
	H	CH_3	157	177, 289
	H	H	183	177, 289
			187–187.5	166
CH_2OH	H	H	169–170	261
			170 (dec)	166
			No mp	332, 652, 653
CH_2OH	Cl	Cl	245	544
CH_2OCH_3	H	H	153–154	175
$CH_2OC_2H_5$	H	H	142–143	175
$COC_{11}H_{23}$	H	H	159–163	169
$COC_6H_4NH_2(4)$	H	H	260	170
$COC_6H_4NO_2(4)$	H	H	246–247	170, 171, 655
$COC_6H_3Cl(2)NO_2(4)$	H	H	139	171
$COC_6H_3Cl(2)NO_2(4)$	CH_3	H	150	171
$COC_6H_4OH(2)$	H	H	192	171
$COC_6H_4OH(2)$	H	CH_3	155	171
	H	H	196	170
C_2H_5	H	Cl	210–212	651
CH_2CH_2Cl	Cl	Cl	176–177	544
CH_2CH_2OH	Cl	Cl	208–210	482
$COCH_3$	H	H	121–123	115
			160–162	169
			176	171
CH_2COOH	H	H	245	138, 147, 349
CH_2COOH	Cl	Cl	236–238	135, 482
$CH_2COOC_2H_5$	H	H	166–167	147, 349

TABLE XVIII (*continued*)

R_1	R_2	R_3	MP (°C)	References
$CH_2COOC_2H_5$	Cl	Cl	162–163	482
$CH_2COOCH_2CH_2N(CH_3)_2$	H	H	310	138
CH_2CONH_2	H	H	250–253 (dec)	357
CH_2CONH_2	Cl	Cl	273–275	482
$CH_2CON(CH_3)_2$	H	H	123–124.5	357
$COCH_2C_6H_3Cl_2(2,4)$	H	H	180–181	171
	H	H	216	151
	H	H (HCl)	191	151
	H	H	175	151
	H	H (HCl)	231	151
	H	H	199	151
$COCH_2OC_6H_3Cl_2(2,4)$	H	H	168–170	169
C_3H_7	Cl	Cl	140–141	482
COC_2H_5	H	H	111–113	169
$COC(CH_3)=CH_2$	H	H	169	152

$COCH{=}CHC_6H_5$	H	H	158	152
CH_2CH_2CN	H	H	209	151
			221–222	139
CH_2CH_2CN	Cl	Cl	188–190	482
CH_2CH_2COOH	H	H	217	152
			213–213.5	139
CH_2CH_2COOH	Cl	Cl	176–178	482
$CH(CH_3)CH_2COOH$	H	H	186	152
$CH_2CH(CH_3)COOH$	H	H	203	152
$CH(C_6H_5)CH_2COOH$	H	H	232	152
C_4H_9	H	H	125–126	139
			125–127	173, 633
$CH_2CH_2COCH_3$	H	H	148.5–149	139
$CH_2CH_2COCH_3$	H	H (2,4-dinitrophenylhydrazone)	225	139
$CH_2CH(NO_2)CH_2CH_3$	H	H	152–153	656
$CH_2CH(COOCH_3)CH_2COOCH_3$	H	H	171.5–172 (dec)	139
COC_5H_{11}	H	H	88–89	169
$COCH(C_2H_5)C_4H_9$	H	H	58–61	169, 332
C_6H_5	H	H	253.5–255.5	27
			255–256	52, 544, 767
			262–263	196
			268.5–269	166
			272–274	24, 164, 167, 189, 192, 194, 213
			No mp	279, 332, 358, 372, 657
C_6H_5	H	$H(OCOCH_3)$	110	52, 544
C_6H_5	H	$H[OCOCH(CH_3)_2]$	65–67	52, 544
C_6H_5	H	Br	259–261	49, 194, 358
C_6H_5	Cl	H	198–199.5	49
			199–200	166
			199–201	27

TABLE XVIII (*continued*)

R_1	R_2	R_3	MP (°C)	References
C_6H_5	H	Cl	250–252	27
			255–256	49
			270	194, 358
			274 (dec)	166
C_6H_5	Cl	Cl	226.5–227.5	27
			231–233	767
C_6H_5	CH_3	H	168–169.5	49, 194
C_6H_5	H	CH_3	220–221	52, 544
			226–228	192, 194, 279
C_6H_5	H	CH_2COOH	224	498
C_6H_5	H	CH_2COOCH_3	196–197	498
C_6H_5	H	$CH_2COOC_2H_5$	159–160	498
C_6H_5	H	$CH{=}NNHC_6H_5$	280–282	645
C_6H_5	H	$CH{=}NNHC_6H_4COOH(4)$	210–230 (dec)	645
C_6H_5	CH_3	CH_3	129	43
			No mp	279
C_6H_5	H	NH_2		197
C_6H_5	H	$N(CH_3)_2$ (HCl)	232–234	193
C_6H_5	H		252–253	49, 194, 358
C_6H_5	H		242.5–243	49, 194, 358
C_6H_5	H	OH	285–287	189
C_6H_5	H	OH (6-acetate)		189
C_6H_5	H	OH (diacetate)		189

C_6H_5	OCH_3	H	240–243	195
			248	484
			244–247	196
C_6H_5	H	OCH_3	260–262	195, 196
			270	189
C_6H_5	OC_2H_5	H	214–215	484, 485
$C_6H_4Br(4)$	H	H	275	166
$C_6H_4Br(4)$, $NO_2(2)$	Br	H	206–207	764
$C_6H_3Br(4)$, $NO_2(2)$	Br	Br	235–237	772
$C_6H_4Cl(2)$	H	H	242–244	196
$C_6H_4Cl(3)$	H	H	247–248	658
			249–251	196
			No mp	195
$C_6H_4Cl(4)$	H	H	280–282	192, 194, 196, 358
			No mp	319, 326
$C_6H_4Cl(4)$	H	Cl		358
$C_6H_4CH_3(4)$	H	H	230	658
			242–244	194–196, 358, 659
$C_6H_4NO_2(3)$	H	H	269–270	748
$C_6H_4NO_2(4)$	H	H	278–283	166
			289–291	192, 194, 358
			302–303	747
$C_6H_3(NO_2)_2(2,4)$	H	H	230–232	173
$C_6H_3(NO_2)_2(2,4)$	Br	H	270–272	764
$C_6H_3(NO_2)_2(2,4)$	Br	Br	329–330	772
$C_6H_4OCH_3(4)$	H	H	240–241	196, 658
$CH_2C_6H_5$	H	H	204–205	237
			206	367
			No mp	319, 326
$CH_2C_6H_5$	Cl	Cl	196–198	661
$CH_2C_6H_4Cl(4)$	H	H	250	237, 660
$CH_2C_6H_4NO_2(4)$	H	H	>280	237

TABLE XVIII (*continued*)

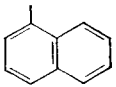
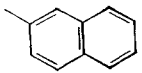
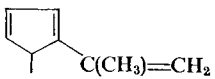
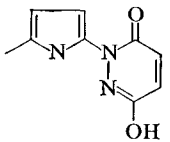
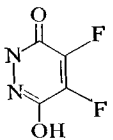
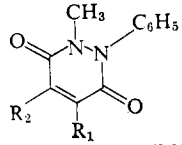
R_1	R_2	R_3	MP (°C)	References
$CH_2C_6H_4OCH_3(4)$	H	H	191–192	237, 660
C_6H_{11}	Cl	H	156–157	399
C_6H_{11}	H	Cl	277–278	399
	H	H	283–285 285 (dec)	358 194
	H	H	268–270	194, 358
	H	H		633
	H	H	315	633
	F	F	225 (dec)	633
β-D-Ribofuranosyl	H	H		325
2-Deoxy-D-*erythro*-pentofuranosyl	H	H		325
SO_2CH_2Cl	H	H	145–146	172
$SO_2CH(Cl)CH_3$	H	H	104	172
$SO_2C_6H_2Cl_3(2,4,5)$	H	H	194–200	172
$SO_2N(CH_3)_2$	H	H	164	172

TABLE XIX. 1-Methyl-2-phenyl-4,5-disubstituted 3,6-Pyridazinediones



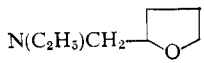
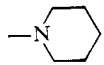
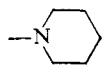
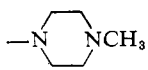
R_1	R_2	MP (°C)	References
H	H	173–175	196
		180–181	99, 215, 243
Br	H	159–161	195–197, 658, 662
H	Br	158.5–159	216
Br	Br	177–178.5	662
NH_2	Br	204–207	213
Cl	H	154–156	196
		156	662
		156–157	658
		156–157.5	195, 197
		No mp	216
H	Cl	150–152	195–197, 658
		No mp	216
Cl	Cl		661
CH_3	H	129–131	196
H	CH_3	111–113	196
H	NH_2	192–194	197, 213
H	$NHCH_3$	169–170	213
H	$NHCH_2CH_2N(C_2H_5)_2$	229–230	197
H	NHC_4H_9	130–131	197
H	NHC_6H_5	142	215
H	NHC_6H_{11}	184–186	197, 213
H	$N(CH_3)_2$	74.5–75.5	197, 213
H	$N(CH_3)CH_2CH_2OH$	103–104	197
H	$N(C_2H_5)_2$	115.5–116.5	197, 213
H	$N(C_2H_5)CH_2CH_2N(CH_3)_2$	88–88.5	197
H		bp 218–222 (0.15 mm)	197
H		140.5–142	197, 213
	H	64	215
H		182	215
		184–185	197
H		137.5–138	197

TABLE XIX (*continued*)

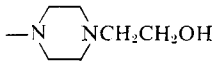
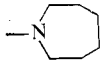
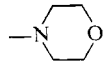
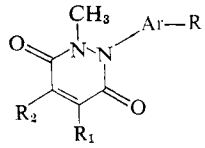
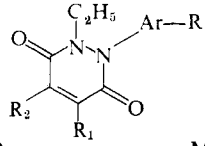
R_1	R_2	MP (°C)	References
H		136.5–137.5	197
H		129.5–130	197
H		175.5–177.5	213
		176–177.5	197, 658
H	OH		213
OCH_3	H	156.5–157.5	195, 196
		No mp	213, 372
H	OCH_3	117–118	213, 659
		118	372
		118.5–119.5	195, 196
		No mp	215
H	OC_2H_5	169–171	195, 213
H	OCH_2CH_2Cl	159.5–161.5	195
H	$OCH_2CH_2NH_2$	164–166	195
H	OCH_2CH_2OH	171–173	195, 213
H	$OCH_2CH_2OC_2H_5$	106–107	195
H	$OCH_2C{\equiv}CH$	151.5–152.5	195
H	$OCH_2CH{=}CH_2$	162–163	195
H	$OCH_2C(CH_3){=}CH_2$		195
H	OC_3H_7	144–146	195, 213
H	$OCH(CH_3)_2$	158–160	195
H	OC_4H_9		195, 213
H	$OCH_2CH(CH_3)_2$	151–152	195
H	$OCH_2CH_2CH(CH_3)OCH_3$		195
H	OC_5H_{11}	113–115	195, 213
H	OC_6H_{13}	109.5–111	195, 213
H	$OCH_2C_6H_5$	214–215	195

TABLE XX. 1-Methyl-2-substituted-4,5-disubstituted 3,6-Pyridazinediones



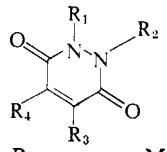
R—Ar	R_1	R_2	MP (°C)	References
$C_6H_4Cl(2)$	H	H	107–108	195, 196
$C_6H_4Cl(2)$	H	OC_4H_9	122–123	195
$C_6H_4Cl(3)$	H	H	139–141	195, 196, 658
$C_6H_4Cl(3)$	Br	H	169–170	195, 197, 658
$C_6H_4Cl(3)$	H	$N(CH_3)_2$	102–103	197
$C_6H_4Cl(3)$	H	OC_2H_5	179–180	195
$C_6H_4Cl(3)$	H	OC_3H_7	139–140	195
$C_6H_4Cl(4)$	H	H	145–146	195, 196, 658
$C_6H_4Cl(4)$	Br	H	158.5–159	195, 197, 658
$C_6H_4Cl(4)$	Cl	Cl		661
$C_6H_4Cl(4)$	H	$N(CH_3)_2$	159.5–160.5	197
$C_6H_4Cl(4)$	H		187.5–188.5	197
$C_6H_4Cl(4)$	H	OC_2H_5	164.5–165.5	195
$C_6H_4Cl(4)$	H	OC_3H_7	144.5–145.5	195
$C_6H_4Cl(4)$	H	OC_4H_9	116–118	195
$C_6H_4CH_3(4)$	H	H	132–134	195, 196, 658
$C_6H_4CH_3(4)$	Br	H	170–171	195, 197, 258
$C_6H_4CH_3(4)$	H	$N(CH_3)_2$	143–144	197
$C_6H_4CH_3(4)$	H	OC_2H_5	164–165	195
$C_6H_4CH_3(4)$	H	OC_3H_7	157–157.5	195
$C_6H_4CH_3(4)$	H	OC_4H_9	133–133.5	195
$C_6H_4NH_2(4)$	Br	H (HCl)	258–261	658
$C_6H_4NHCH_3(2)$	Cl	Cl		661
$C_6H_4NO_2(3)$	H	H	159–160	748
$C_6H_4NO_2(4)$	H	H	185–186	658, 747
$C_6H_4NO_2(4)$	Br	H	199–201	658, 747
$C_6H_4NO_2(4)$	H	Br	216–218	658, 748
$C_6H_4NO_2(4)$	H	$N(CH_3)_2$	175–177	197, 748
$C_6H_4NO_2(4)$	H		166–168	748
$C_6H_4NO_2(4)$	H		194–196	747, 748
$C_6H_4NO_2(4)$	H	OCH_3	239–240	747
$C_6H_4OCH_3(4)$	H	H	138.5–140	195
			139–140	658
$C_6H_4OCH_3(4)$	Br	H	155–157	658

TABLE XXI. 1-Ethyl-2-aryl(substituted aryl)-4,5-disubstituted 3,6-Pyridazinediones



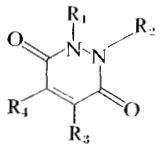
R—Ar	R_1	R_2	MP (°C)	References
C_6H_5	H	H	121–123	99, 196
C_6H_5	Br	H	142–144	197, 628
C_6H_5	Br	Br	176–177	195, 628
C_6H_5	H	NHC_6H_5	130–132	197
C_6H_5	H	$N(CH_3)_2$		197
C_6H_5	H		113–114	197
C_6H_5	H		78–79	197
C_6H_5	H		120–121	197
C_6H_5	H	OCH_3	110–112	195
C_6H_5	H	OC_2H_5	132–133.5	195, 213
C_6H_5	H	$OCH_2CH_2OCH_3$		195, 213
C_6H_5	H	OC_4H_9	116–118	195, 213
$C_6H_4Cl(2)$	H	H	100–102	196
$C_6H_4Cl(4)$	H	H	142.5–143	196
$C_6H_4CH_3(4)$	H	H	119–121	196, 658
$C_6H_4CH_3(4)$	Br	H	168–169	658
$C_6H_4NH_2(4)$	H	$N(CH_3)_2$	167–169	197
$C_6H_4NO_2(4)$	H	H	179–181	658
$C_6H_4NO_2(4)$	Br	H	199–201	197
$C_6H_4NO_2(4)$	H	Br	216–218	197
$C_6H_4NO_2(4)$	Br	Br	150–152	197
$C_6H_4NO_2(4)$	H	$N(CH_3)_2$	163–165	197

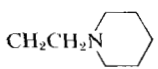
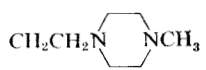
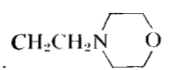
TABLE XXII. 1,2,4,5-Tetrasubstituted 3,6-Pyridazinediones



$R_1 = R_2$	R_3	R_4	MP (°C)	References
CH_3	H	H	137–138	99
			181–182	260
CH_3	Br	Br	209–211	661
CH_3	Cl	Br		661
CH_3	Cl	Cl	194.5–196	661
CH_3	Cl	NHC_6H_5	172–173	335
CH_3	Cl	OCH_3	120–121	335
CH_3	F	F	129.5–131	335
CH_3	I	I	209–210	335
$CH{=}CH_2$	H	H	bp 130–135 (15 mm)	8
CH_2CH_2N O	Cl	Cl	188–190	661
$CH_2CH{=}CH_2$	H	H	101–103	99
$CH(CH_3)_2$	Cl	Cl	200–205	661
$CH(C_2H_5)_2$	Cl	Cl	bp 155–160 (0.4 mm)	661
C_4H_9	H	H		153
C_7H_{15}	Cl	Cl	36.5–37.5	661
C_6H_{11}	Cl	Cl	158.5–161	661
$SCCl_3$	H	H		663
$SCCl_3$	Cl	Cl		663
$SCCl_3$	F	F		663
$SCCl_2CHCl_2$	H	H		663
$SCCl_2F$	H	H		663
SCF_2CHClF	H	H		663
$SCCl{=}CHCl$	H	H		663
$SCCl{=}CCl_2$	H	H		663

TABLE XXIII. 1,2,4,5-Tetrasubstituted 3,6-Pyridazinediones



R_1	R_2	R_3	R_4	MP (°C)	References
CH_3	CH_2COOH	Cl	Cl	206–207 (dec)	661
CH_3	CH_2COOCH_3	Cl	Cl	115–117	661
CH_3	$CH_2CH_2C_6H_5$	Cl	Cl	110–111.5	661
CH_3	$CH_2CH_2N(CH_3)_2$	Cl	Cl	81–83	661
CH_3	$CH_2CH_2N(CH_3)C_6H_5$	Cl	Cl	171–172.5	661
CH_3	$CH_2CH_2N(CH_3)CH_2C_6H_5$	Cl	Cl	70.5–72	661
CH_3	$CH_2CH_2N(C_2H_5)_2$	Cl	Cl	84.5–86.5	661
CH_3	$CH(CH_3)CH_2N(C_2H_5)_2$	Cl	Cl (HCl)	189–191	661
CH_3	$CH_2CH(CH_3)N(C_2H_5)_2$	Cl	Cl	91.5–93.5	661
CH_3	$CH_2CH(C_6H_5)N(C_2H_5)_2$	Cl	Cl		661
CH_3	$CH(C_6H_5)CH_2N(C_2H_5)_2$	Cl	Cl		661
CH_3	$CH_2CH_2N[CH(CH_3)_2]_2$	Cl	Cl	109.5–110.5	661
CH_3	$CH_2CH_2N(C_4H_9)_2$	Cl	Cl	78–80	661
CH_3		Cl	Cl	111–113	661
CH_3		Cl	Cl	102.5–104.5	661
CH_3		Br	Br	164.5–166	661

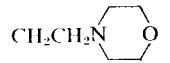
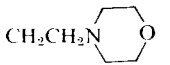
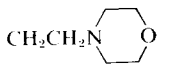
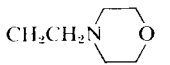
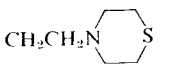
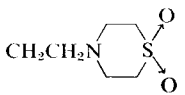
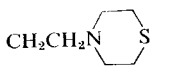
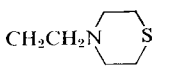
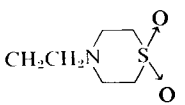
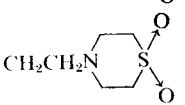
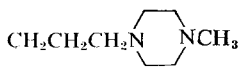
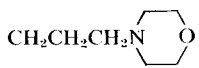
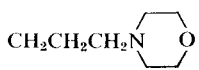
CH_3		Cl	Cl	126–128	661
CH_3		Cl	Cl (HCl)	239–241	661
CH_3		F	F	138–140	661
CH_3		F	F (HCl)	223.5–224.5	661
CH_3		Br	Br		661
CH_3		Br	Br	184–185	661
CH_3		Cl	Cl	119–221.5	661
CH_3		F	F		661
CH_3		F	F	164–165	661
CH_3		Cl	Cl	173.5–175	661

TABLE XXIII (*continued*)

R_1	R_2	R_3	R_4	MP (°C)	References
CH_3	$CH_2CH(CH_3)N(CH_3)_2$	Cl	Cl		661
CH_3	$CH_2CH_2CH_2N(CH_3)_2$	Cl	Cl		661
CH_3	$CH_2CH_2CH_2N(CH_3)_2$	Cl	Cl (oxalate)	154–156	661
CH_3	$CH_2CH(CH_3)CH_2N(CH_3)_2$	Cl	Cl	72.5–74.5	661
CH_3	$CH_2CH(CH_3)CH_2N(CH_3)_2$	Cl	Cl (HCl)	219–220.5	661
CH_3	$CH_2CH_2CH(CH_3)N(CH_3)_2$	Cl	Cl (CH_3I)	263.5–264.5	661
CH_3	$CH_2CH(CH_3)CH_2N(CH_3)_2$	F	F	62–64	661
CH_3	$CH_2CH(CH_3)CH_2N(CH_3)_2$	F	F (oxalate)	65–80	661
CH_3	$CH_2C(CH_3)_2NH\ H(CH_3)_2$	Cl	Cl	74.5–76.5	661
CH_3	$CH_2CH_2CH_2N(CH_3)CH_2C_6H_5$	Cl	Cl		661
CH_3	$CH_2CH_2CH_2N(CH_3)CH_2C_6H_5$	Cl	Cl (oxalate)	163–165 (dec)	661
CH_3	$CH_2CH_2CH_2N(C_2H_5)_2$	Cl	Cl	bp 208–216 (0.3 mm)	661
CH_3		Cl	Cl	121–123	661
CH_3		Cl	Cl		661
CH_3		Cl	Cl (HCl)	226–227.5	661
CH_3	$CH(CH_3)CH_2CH_2CH_2N(CH_3)_2$	Cl	Cl		661
CH_3	$CH(CH_3)CH_2CH_2CH_2N(CH_3)_2$	Cl	Cl (*p*-toluene-sulfonate)	122–123.5	661
CH_3	C_7H_{15}	Cl	Cl		661
CH_3	$CH_2C_6H_5$	Cl	Cl	104.5–106.5	661
CH_3	$CH_2C_6H_4Cl(4)$	Cl	Cl	148–150	661
CH_3	$CH_2C_6H_4COOH(4)$	Cl	Cl	245–247	661

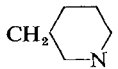
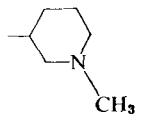
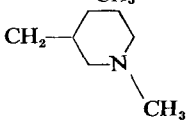
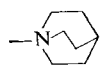
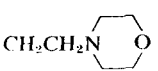
CH_3		Cl	Cl		661
CH_3	C_6H_{11}	Cl	Cl	103.5–105.5	661
CH_3	$C_6H_{10}N(CH_3)_2(2)$	Cl	Cl	148.5–151	661
CH_3	$C_6H_{10}CH_2N(CH_3)_2(2)$	Cl	Cl		661
CH_3		Cl	Cl	142.5–144	661
CH_3		Cl	Cl	80–83	661
CH_3		Cl	Cl		661
$CH(CH_3)_2$	CH_2CH_2OH	Cl	Cl	133–135	661
$CH(CH_3)_2$	$CH_2CH_2OCOCH_3$	Cl	Cl	81.5–83.5	661
$CH(CH_3)_2$	$CH_2CH_2OCOCH_2Cl$	Cl	Cl	68.5–70	661
$CH(CH_3)_2$	$CH_2CH_2OCOCH_2N(C_2H_5)$	Cl	Cl (HCl)	162.5–163.5	661
$CH(CH_3)_2$	C_6H_5	Br	Br	182–183	661
$CH(CH_3)_2$	C_6H_5	Cl	Cl	166–168	661
$CH(CH_3)_2$	$C_6H_4COOC_2H_4N(C_2H_5)_2(4)$	Cl	Cl (HCl)	187.189	661
$CH(CH_3)_2$	$C_6H_4COOH(4)$	Cl	Cl	246.5–248.5	661
$CH(CH_3)_2$	$C_6H_4CH_2N(CH_3)_2(4)$	Cl	Cl	108–109.5	661
$CH(CH_3)_2$	$C_6H_4OCH_3(3)$	Cl	Cl	153.5–157	661
$CH(CH_3)_2$	$SCCl_3$	H	H		663
C_6H_5	$CH_2CH_2N(C_2H_5)_2$	Cl	Cl	77.5–180	661
C_6H_5		Cl	Cl	142–144	661

TABLE XXIII (*continued*)

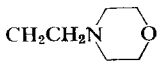
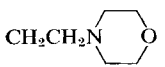
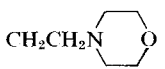
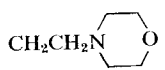
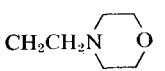
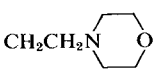
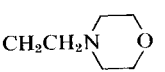
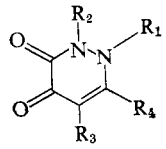
R_1	R_2	R_3	R_4	MP (°C)	References
C_6H_5		Cl	Cl (HCl)	256.5–259	661
C_6H_5	C_6H_{11}	Cl	Cl	134.5–136	661
C_6H_5	$SCCl_3$	H	H		663
C_6H_5	$SCCl_3$	Br	H		663
C_6H_5	$SCCl_3$	Cl	Cl		663
C_6H_5	$SCCl_3$	CH_3	H		663
C_6H_5	$SCCl_3$	C_2H_5	H		663
$C_6H_4Cl(2)$		Cl	Cl		661
$C_6H_4Cl(3)$		Cl	Cl	148–150	661
$C_6H_4Cl(3)$		Cl	Cl (HCl)	224–226	661
$C_6H_4F(4)$		Cl	Cl	133–135	661
$C_6H_4OCH_3(3)$		Cl	Cl		661
$C_6H_4OCH_3(3)$		Cl	Cl (HCl)	212.5–214	661

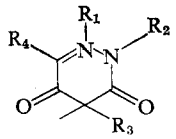
TABLE XXIV. 1,2,3,4-Tetrasubstituted 5,6-Pyridazinediones



R_1	R_2	R_3	R_4	MP (°C)	References
H	H	H	Cl	218–219	335
H	H	H	CH_3		302
H	H	H	SC_2H_5	225–227	664
H	H	NH_2	H	290	437
H	H	NO_2	H	242	84
H	CH_3	NH_2	H	234–235	437
H	CH_3	NH_2	H (HCl)	198	437
H	CH_3	NO_2	H	168–170	84, 392
H	CH_3	NO_2	H (Na salt)	345	84
H	CH_3	NH_2	C_6H_5	228–229	437
H	CH_3	NO_2	OCH_3	176–178	84
H	CH_2CH_2OH	NO_2	H		84
H	CH_2CH_2OH	NO_2	H (Na salt)	178–182	84
H	$CH(CH_3)COOC_2H_5$	NH_2	H	129–130	437
H	C_6H_5	H	H	174	189
H	C_6H_5	H	Cl	207–208	89
				199–201	189
H	C_6H_5	H	CH_3	200	109
				196	665
H	C_6H_5	H	OCH_3		465
H	C_6H_5	H	OC_2H_5	159–160	189, 465
H	C_6H_5	$CONH_2$, H	$CONH_2$, H	237–238	666
H	C_6H_5	NH_2	H	224–225	84, 437
H	C_6H_5	NO_2	H	184–186 (dec)	84
H	C_6H_5	NO_2	H (NH_4 salt)	260 (dec)	84
H	C_6H_5	NO_2	H (pyridinium salt	77–79	84
H	C_6H_5	NO_2	H (Na salt)	311	84
H	C_6H_5	OH	H	196–197	89
H	C_6H_5	OH	Cl	223–224	89
H	C_6H_5	OH	OH	230–231	89
H	$C_6H_4Cl(4)$	NH_2	H	176–177	437
H	$C_6H_4Cl(4)$	NO_2	H	140–142	84
H	$C_6H_4CH_3(4)$	NO_2	H	190 (dec)	84
H	$C_6H_4NO_2(3)$	NO_2	H	128–129	84
H	$C_6H_4OCH_3(4)$	NH_2	H	228–229	437
H	$CH_2C_6H_5$	NH_2	$OCH_2C_6H_5$	164–165	437
H	C_6H_{11}	NH_2	H	188–189	437
H	C_6H_{11}	NO_2	H	190–192	84

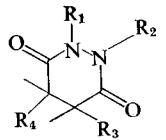
TABLE XXIV (*continued*)

R_1	R_2	R_3	R_4	MP (°C)	References
H	$C_6H_{10}OH(2)$	NO_2	H	223–225	84
H	$SO_2C_6H_4CH_3(4)$	NH_2	H	193–194	437
H	$SO_2C_6H_4CH_3(4)$	NO_2	H	194 (dec)	84
H	$SO_2C_6H_4CH_3(4)$	NO_2	H (Na salt)	190	84
C_6H_5	H	H	CH_3	222–224	85
C_6H_5	C_6H_5	C_4H_9	=O	134	667, 668
C_6H_5	C_6H_5	C_5H_{11}	=O	134	668
C_6H_5	C_6H_5	C_6H_5	=O	217–218	667, 668



R_1	R_2	R_3	R_4	MP (°C)	References
H	C_6H_5	H	H	220–222	49
				221–222	62
H	C_6H_5	Br	H	270	62
COC_6H_5	COC_6H_5	C_6H_5, C_6H_5	C_6H_5, C_6H_5	161	669

TABLE XXV. 1,2,4,5-Tetrasubstituted 4,5-Dihydro-3,6-pyridazinediones



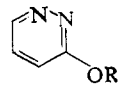
R_1	R_2	R_3	R_4	MP (°C)	References
H	H	H	H	277	55, 58, 99, 302, 585, 659, 670
H	H	H	H (diacetate)	130–132	55, 158, 670
H	H	Br	Br		671
H	H	Cl	H		671
H	H	Cl	Cl	225–240 (dec)	59
				260–263	671
H	H	Cl	NO_2		671, 672
H	H	COC_2H_5	H		672
H	H	COC_6H_5	H		672
H	H	$COCH_3$	COC_6H_5		672
H	H	NH_2	H		671, 672
H	H	NH_2	NO_2		672
H	H	$NHCH_3$	NO_2		671
H	H	$N(CH_3)_2$	H		672
H	H	NO_2	H		672
H	H	N=O	H		672
H	H	CH_2COOCH_3	H		773
H	H	OH	H		672
H	H	OH, CH_2COOH	H	92	673, 773
H	H	OH, CH_2COOCH_3	H	128–130	773
H	H	OH, CH_2COOEt	H	128	773
H	H	OH, $CH_2CONHNHC_6H_5$	H	274	673

TABLE XXV (*continued*)

R_1	R_2	R_3	R_4	MP (°C)	References
H	H	OH, $CH_2CONHNH_2$	H	200 (dec)	673
H	H	OH, $CH_2CONHC_6H_5$	H	267	673
H	H	OH	OH	220 (dec)	672
					673
H	H	$OCOCH_3$	$OCOCH_3$		671
H	H	$OC_6H_4CH_3(4)$	H		672
H	H	SH	N=O		671
H	H	$SCCl_3$	H		671
H	H	SC_4H_9	H		671
					672
H	H	3-Hydroxyergostatrien-6(7)-yl	H		674
H	C_2H_5	H	H	140–142	58
H	$CH_2CH_2COCH_3$	H	H		153
H	C_6H_5	H	H	196	675
				199	159
H	C_6H_5	OH, CH_3	C_2H_5	193	676
H	$C_6H_4Br(4)$	Br	Br, Br	167–169	772
H	$C_6H_4Cl(4)$	Br	Br	178	658
H	$C_6H_4NO_2(3)$	Br	Br, Br	172–174	772
H	$C_6H_4NO_2(4)$	Br	Br, Br	170–172	772
H	$C_6H_3NO_2(2)$, Br(4)	Br	Br	163–164	772
H	$COC_6H_3Cl(2)NO_2(4)$	H	H	156	171
H	$COC_6H_4NO_2(4)$	H	H	180	171
H	$COC_6H_4OH(2)$	H	H	204	171
CH_3	CH_3	H	H	104–105	58, 99
CH_3	CH_3	Br	Br	159.5–161.5	99
$CH_2CH_2COCH_3$	$CH_2CH_2COCH_3$	H	H		153

$CH(CH_3)_2$	$CH(CH_3)_2$	H	H	bp 75 (0.9 mm)	153, 774
CH_2CH_2CN	CH_2CH_2CN	H	H		153
$CH_2CH_2COOCH_3$	$CH_2CH_2COOCH_3$	H	H		153
C_4H_9	C_4H_9	H	H	bp 112 (0.5 mm)	153, 774
$CH_2CH_2C(SC_2H_5)_2CH_3$	$CH_2CH_2C(SC_2H_5)_2CH_3$	H	H		153
C_6H_5	C_6H_5	H	H	245	677, 774
C_6H_5	C_6H_5	CH_3	H	183–184	678
C_6H_5	C_6H_5	C_2H_5	H	144–144.5	678
C_6H_5	C_6H_5	C_3H_7	H	126–127	678
$C_6H_4CH_3(2)$	$C_6H_4CH_3(2)$	H	H	163–165	774
CH_3	C_6H_5	H	H	146–147.5	99
				144–147.5	196
				180	159
CH_3	C_6H_5	Br	Br	177–178.5 (dec)	195, 196, 197, 658
CH_3	C_6H_5	Br	NH_2	207–209	213
CH_3	C_6H_5	Cl	H	156–157	658
CH_3	C_6H_5	Cl	Cl	133–135	196
				134–136	658
CH_3	$C_6H_4Cl(2)$	Br	Br		195
CH_3	$C_6H_4Cl(3)$	Br	Br		658
CH_3	$C_6H_4Cl(4)$	Br	Br	178	195, 197
CH_3	$C_6H_4CH_3(4)$	Br	Br		658
CH_3	$C_6H_4NO_2(3)$	Br	Br	189–191	747
CH_3	$C_6H_4NO_2(4)$	Br	Br	183.5–184.5	658, 774
C_2H_5	C_6H_5	H	H	60.5	159
C_2H_5	C_6H_5	Br	Br	176–177 (dec)	658
C_2H_5	$C_6H_4CH_3(4)$	Br	Br		658
C_2H_5	$C_6H_4NO_2(4)$	Br	Br	150–152	658
$COCH_3$	C_6H_5	H	H	179	159
COC_6H_5	C_6H_5	H	H	185	159
$CH_2C_6H_5$	C_6H_5	H	H	159	159

TABLE XXVI. 3-Alkyl(aryl)oxypyridazines

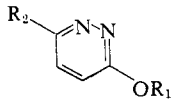


R	MP (°C)	References
CH_3	72–73	140, 230
	bp 86–87 (13 mm)	85
	bp 85–86 (3 mm)	679
	77–78	248
CH_3 (picrate)	111	140, 679
CH_2CH_3	34–35	97, 98
	35–36	248
CH_2COOH	189–192	147
$CH_2CH_2N(CH_3)_2$		224, 680
$CH(CH_3)_2$	96–101	680, 181
$CH(CH_3)_2$ (HCl)	115–117	180
C_4H_9-*n*	112–113	230
$CH_2CH_2CH(CH_3)_2$		224, 680
$CH_2C_6H_5$	147–150	97, 98, 140
C_6H_5	71	681
	74–75	679, 775
C_6H_5 (HCl)	156-157	681
C_6H_5 (H_3PO_4)	132–133	681
$C_6H_5(Cl_3CCOOH)$	74–75	681
$C_6H_4Cl(2)$	108	681, 775, 776
$C_6H_4Cl(3)$	90.5	681, 775–777
$C_6H_4Cl(4)$	106	681, 775–777
$C_6H_3Cl_2(2,4)$	98	681, 775–777
$C_6H_3Cl_2(2,6)$	87–88	681, 775–777
$C_6H_2Cl_3(2,4,5)$	134–136	681, 775
$C_6H_2Cl_3(2,4,6)$	153	681, 775, 776
C_6Cl_5		681
$C_6H_3Cl(2)F(4)$	114–116	778
$C_6H_3Cl(4)CH_3(2)$	98–99	775
$C_6H_3Cl(4)CH_3(3)$	83–86	681, 775–777
$C_6H_3Cl(6)$, $CH_3(2)$	89	775
$C_6H_2Cl_2(2,4)CH_3(6)$	128–130	681, 775
$C_6H_3Cl(2)CF_3(5)$	106	778
$C_6H_3Cl(4)CF_3(3)$	97–98	778
$C_6H_3Cl(2)C_6H_5(4)$	93–95	775
$C_6H_4F(2)$	57–58	778
$C_6H_4F(3)$	63–65	778
$C_6H_4F(4)$	87–89	778
$C_6H_4CH_3(2)$	78–80	681, 775
$C_6H_4CH_3(3)$	47	775, 776

TABLE XXVI (*continued*)

R	MP (°C)	References
$C_6H_4CH_3(4)$	94	775
$C_6H_4C_2H_5(2)$	47–48	775, 779
$C_6H_4C_3H$-*n*(2)	58–61	775, 776, 779
$C_6H_4C_3H_7$-*i*(2)	96–98	775, 776, 779
$C_6H_4C_4H_9$-*n*(2)	bp 127–136 (0.4 mm)	775, 779
$C_6H_4C_4H_9$-*s*(2)	53	775, 779
$C_6H_4C_4H_9$-*t*(2)	78–79	775, 779
$C_6H_4C_4H_9$-*t*(4)	121-123	775
$C_6H_3(CH_3)_2(2,3)$	88–90	775
$C_6H_3(CH_3)_2(2,4)$	66–68	775
$C_6H_3(CH_3)_2(2,5)$	77–79	775
$C_6H_3(CH_3)_2(2,6)$	94–95	775
$C_6H_3(CH_3)_2(3,4)$	88–91	681, 775
$C_6H_4CF_3(2)$	67–68	778
$C_6H_4CF_3(3)$	50–51	778
$C_6H_4C_6H_5(2)$	122–123	775–777
$C_6H_4NO_2(2)$	86	775–777
$C_6H_4NO_2(3)$	151	775–777
$C_6H_4OCH_3(3)$	88.5	775–777
$C_6H_2(OCH_3)_3(2,3,5)$		681
β-D-Glucosyloxytetraacetate		240

TABLE XXVII. 6-Substituted 3-Alkyl(aryl)oxypyridazines



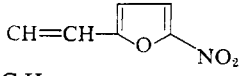
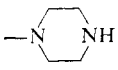
R_1	R_2	MP (°C)	References
CH_3	Br	103–104	180
CH_3	Cl	90	180
		91	679
		90.5	624
		88–89	274
		89–90	277, 682
		No mp	97, 683, 684
CH_3	Cl (HCl)	118–119 (dec)	274, 685
CH_3	CN	94–95	304, 305
CH_3	I	104–105	180
CH_3	OCH_3	bp 212–215	686
CH_3	OCH_3 (HCl)	bp 210	13, 109, 295
		137–138	13
		131–132	109
CH_3	OCH_3 (CH_3I)	160	258
CH_3	CH_2OH	55–56.5	687
CH_3	CH_3OCOCH_3	59–61	687
CH_3	$COOCH_3$	127–128	688
CH_3		202–203	689
CH_3	C_6H_5	116–117	245, 317, 690
CH_3	C_6H_5 (CH_3I)	153–154	258
CH_3	$C_6H_4CH_3$(4)	114–115	691
	(chlorplatinate)	177–179 (dec)	691
CH_3	NH_2	103–105	280, 692, 693
		107–108	233
CH_3	NH_2 (picrate)	222	233
CH_3	$NHCOCH_3$		694
CH_3	$NHCOOCH_3$	135.5	695
CH_3	$NHCH_2C_6H_5$	102	696
CH_3	$NHCOC_6H_4OH(2)$	253 (dec)	697
CH_3	$NHCOC_6H_3OH(2)NO_2(4)$	280–282 (dec)	697
CH_3	$NHSO_2C_6H_4NH_2(4)$	182–183	280, 692
CH_3	NO_2	142–143	233
CH_3			698
CH_3			698

TABLE XXVII (*continued*)

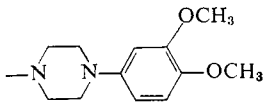
R_1	R_2	MP (°C)	References
CH_3			698
CH_3	$OCONHCH_3$	89	155
CH_3	$OSO_2C_6H_4CH_3(4)$	101–101.5	412
CH_3	$SO_2C_6H_4NHCOCH_3(4)$	218–219	693
β-D-Glucopyranosyloxy	CH_3O		142
CH_2CH_3	Br	68–70	699
CH_2CH_3	Cl	62	624
		60–62	234
		63	679, 683
CH_2CH_3	I	90–91	97, 699
CH_2CH_3	CH_3	bp 229–231	686, 700
		bp 114–115 (20 mm)	701
CH_2CH_3	CH_2OH	bp 142 (6 mm)	701
CH_2CH_3	CH_2OOCCH_3	42–43	701
CH_2CH_3	C_6H_5	100–102	240
CH_2CH_3	$C_6H_5CH_3(4)$	106	691
	(aurochlorate)	150–151	691
	(chloroplatinate)	146 (dec)	691
	(picrate)	118	691
CH_2CH_3	NH_2		280
CH_2CH_3	$NHCH_2CH_3$		683
CH_2CH_3	$NHC_{10}H_{21}$-*n*	89–91	749
CH_2CH_3	$NHCH_2C_6H_5$	122–123	696
CH_2CH_3	$NHSO_2C_6H_4NH_2(4)$	181–183	280
CH_2COOH	Cl	142–145	147
		145	135
$CH_2COOC_2H_5$	Cl	75–76	135, 138
$CH_2COO_4H_9$	Cl	48–49	147
CH_2CONH_2	Cl	210–212	335
$CH_2CONHNH_2$	Cl	169	353
$CH_2CONHN{=}C(CH_3)_2$	Cl	175	353, 354
$CH_2CONHNHCH(CH_3)_2$	Cl	138	353, 354
$CH_2COOCH_2CH_2N(CH_3)_2$	Cl (HCl)	120	135, 353
$CH_2COOCH_2CH_2N(C_2H_5)_2$	Cl (HCl)	118	135
$CH_2CH_2N(CH_3)_2$	Cl	46–47	230
$CH_2CH_2N(C_2H_5)_2$	Cl	bp 155–157 (9 mm)	679
$CH_2CH_2N(C_2H_5)_2$	Cl (picrate)	143	679
CH_2CH_2OH	Cl	102	700
$CH_2CH_2OC_2H_5$	NH_2		280
$CH_2CH_2OCH_2CH_2N(C_2H_5)_2$	Cl	bp 135 (5.5×10^{-5} mm)	271
		bp 135 (0.003 mm)	225
$CH_2CH_2OCH_2CH_2N(C_2H_5)_2$	Cl (oxalate)	91.5–92.5	271, 628

TABLE XXVII (*continued*)

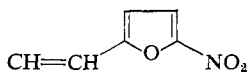
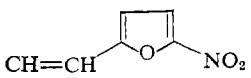
R_1	R_2	MP (°C)	References
$CH_2CH_2OC_6H_5$	Cl	74	226, 702
$CH_2CH_2OC_6H_4Cl(2)$	Cl	114–115	226
$CH_2CH_2OC_6H_4Cl(4)$	Cl		702
$CH_2CH{=}CH_2$	Cl	44	624
$CH_2CH{=}CH_2$	$NHCH(CH_3)_2$	80–81.5	703
$CH_2CH{=}CHC_6H_5$	Cl	118	226, 702
$CH_2CH_2CH_3$	Br	62–63	699
$CH_2CH_2CH_3$	Cl	65	97, 624, 683
$CH_2CH_2CH_3$	I	65–66	699
$CH_2CH_2CH_3$	NH_2		280
$CH_2CH_2CH_3$	$NHCH_2C_6H_5$	104	696
$CH_2CH_2CH_3$	$NHSO_2C_6H_4NH_2(4)$	184–185	692
$CH(CH_3)_2$	Br	64–65	699
$CH(CH_3)_2$	Cl	83	679
		83–84	181, 624
		82–84	230, 680
$CH(CH_3)_2$	I	95–97	699
$CH(CH_3)_2$	$NHSO_2C_6H_4NH_2(4)$	187–188	692
$CH_2CH(OH)CH_2OH$	CH_3	74–76	689
$CH_2CH(OH)CH_2OH$		147–148 (dec)	689
$CH_2CH(OAc)CH_2OAc$		Liquid	689
$CH_2CH_2CH_2N(C_2H_5)_2$	$NHCH_2CH_2CH_2N(C_2H_5)_2$	bp 175 (0.003 mm)	225
		bp 175 (1.8×10^{-5} mm)	271
n-C_4H_9	Br	59–62	699
n-C_4H_9	Cl	48	624
		47–48	230, 669
C_4H_9	I	65–66	699
C_4H_9	$=C(CN)_2$	273–274	704
C_4H_9	NH_2	178–180	280, 705
C_4H_9	NH_2 (HCl)	164–165	705
n-C_4H_9	$NHCOCH_3$	132–132.5	705
$CH(CH_3)CH_2CH_3$	Cl	110–112	703
$CH_2CH(CH_3)_2$	Cl	66	624
$C(CH_3)_3$	Cl	90–92	181
$(CH_2)_4N(C_2H_5)_2$	Cl	bp 110 (0.0015 mm)	225
		bp 110 (10^{-5} mm)	271
$(CH_2)_4N(C_2H_5)_2$	Cl (CH_3Br)	174–174.5	271
n-C_5H_{11}	Cl	61–63	680
C_5H_{11}	I	51–52	699
n-C_5H_{11}	NH_2		280
$CH_2CH_2CH(CH_3)_2$	Br	48–50	699
$CH_2CH_2CH(CH_3)_2$	Cl	58–59	624

TABLE XXVII (*continued*)

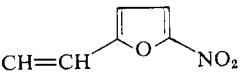
R_1	R_2	MP (°C)	References
$CH_2CH_2CH(CH_3)_2$	NH_2		280
$(CH_2)_5N(C_2H_5)_2$	Cl	bp 145 (0.002 mm)	225
		bp 145 (2×10^{-4})	271
C_6H_{13}	Cl	54–56	699
C_6H_{13}	I	56–57	699
n-C_6H_{13}	NH_2	25–30	280, 693
n-C_6H_{13}	$NHSO_2C_6H_4NH_2(4)$	140–141	692
n-C_6H_{13}	$NHSO_2C_6H_4NHCOCH_3(4)$	164.5–165.5	693
C_8H_{17}	Cl	34–36	335
n-C_8H_{17}	NH_2		280
$C_{10}H_{21}$	Cl	43–44	699
n-$C_{10}H_{21}$	NH_2		280
$(CH_2)_{11}CH_3$	Cl	107.5	226
3,6,9-Trioxydecyloxy		85–87	21
C_6H_5	Br	71	221
C_6H_5	Cl		221
		71	624, 679
		69–70	226
C_6H_5	$C_6H_4CH_3(4)$	135	691
C_6H_5	NHC_6H_5	133–136	221
C_6H_5	$NHC_6H_4Cl(3)$	150–151	221
C_6H_5	$NHC_6H_4Cl(4)$	182–183	221
C_6H_5	$NHSO_2C_6H_4NH_2(4)$	160–161	692
C_6H_5	$NHNH_2$		277
C_6H_5	SCH_3	99	226, 702
$C_6H_4Br(4)$	Cl	135–136	226, 702
$C_6H_4Cl(2)$	Cl	68–69	775
$C_6H_4Cl(4)$	Cl	119.5–120	274
		120–121	685, 702
$C_6H_3Cl_2(2,4)$	Br	88–89	221
$C_6H_3Cl_2(2,4)$	Cl	80–81	226, 702
$C_6H_3Cl_2(2,6)$	Br	126	221
$C_6H_3Cl_2(2,6)$	Cl	106–107	226, 702
$C_6H_2Cl_3(2,4,5)$	Cl	173–174	226, 702
$C_6H_2Cl_3(2,4,6)$	Cl	167–168	775
$C_6H_3CH_3(3)Cl(4)$	Br	94–95	221
$C_6H_3CH_3(2)Cl(4)$	Cl	92–94	775
$C_6H_3CH_3(2)Cl(6)$	Cl	101–102	775
$C_6H_3CH_3(3)Cl(4)$	Cl	92	226, 702, 775
$C_6H_2CH_3(6)Cl_2(2,4)$	Cl	147	775
$C_6H_3Cl(2)CF_3(5)$	Cl	106	778
$C_6H_3Cl(4)CF_3(3)$	Cl	78–79	778

TABLE XXVII (*continued*)

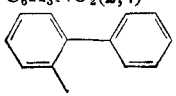
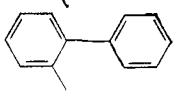
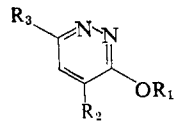
R_1	R_2	MP (°C)	References
$C_6H_4CH_3(2)$	Cl	85–85.5	226, 702
$C_6H_4CH_3(3)$	Cl	71	226, 702
$C_6H_4CH_3(4)$	Br	96–98	221
$C_6H_4CH_3(4)$	Cl	107–108	226, 702
$C_6H_4CH_3(4)$	NH_2		280
$C_6H_3(CH_3)_2(2,3)$	Cl	67	775
$C_6H_3(CH_3)_2(2,4)$	Cl	96	226, 702, 775
$C_6H_3(CH_3)_2(2,5)$	Cl	77–79	775
$C_6H_3(CH_3)_2(2,6)$	Cl	94–95	
$C_6H_3(CH_3)_2(3,4)$	Cl	135–135.5	280
		106	226, 702
$C_6H_3(CH_3)_2(3,5)$	Cl	135–135.5	685, 702
$C_6H_2(CH_3)_3(2,3,5)$	Cl	129–130	702, 775
$C_6H_2(CH_3)_3(2,4,5)$	Cl	129–130	226
$C_6H_4CF_3(2)$	Cl	bp 138–143 (1 mm)	778
$C_6H_4CF_3(3)$	Cl	63–65	778
$C_6H_4C_2H_5(2)$	Cl	bp 130–142 (0.4 mm)	775
$C_6H_4CH_2CH_3(4)$	Cl	75	226, 702
$C_6H_4CH_2CH_2CH_3(2)$	Cl	82–83	775
$C_6H_4CH(CH_3)_2(2)$	Cl	77–77.5	702
$C_6H_4CH(CH_3)_2(4)$	Cl	77–77.5	226
$C_6H_3OCH_3(2)CH_3(4)$	Cl	105–106	226
$C_6H_3OCH_3(3)CH_3(4)$	Cl		702
$C_6H_4C_2H_5(2)$	Cl	130–131	775
$C_6H_4OCH_3(2)$	Br	121–122	221
$C_6H_4OCH_3(2)$	Cl	98.5	226, 702
$C_6H_4OCH_3(2)$	NHC_6H_5	175–176	221
$C_6H_4OCH_3(2)$	$NHC_6H_4Cl(3)$	139–140	221
$C_6H_4OCH_3(2)$	SCH_3	133	226, 702
$C_6H_4OCH_3(3)$	Cl	73.5	226, 702
$C_6H_4OCH_3(4)$	Cl	98–99	226, 702
$C_6H_3NO_2(2)Cl(4)$	Br	168	221
$C_6H_4NO_2(2)$	Br	100–102	221
$C_6H_4NO_2(2)$	Cl	95	221
$C_6H_4NO_2(3)$	Br	125–126	221
$C_6H_4NO_2(3)$	Cl	114–115	221
$C_6H_4NO_2(4)$	Br	124–125	221
$C_6H_4NO_2(4)$	Cl	125–126	221
$C_6H_3NO_2(2,4)$	Br	165–166	221
$C_6H_3NO_2(2,4)$	Cl	151–152	221
	Br	112	221
	Cl	99.5	226, 702

TABLE XXVII (*continued*)

R_1	R_2	MP (°C)	References
C_6H_{11}	Cl	108–110	230
$CH_2C_6H_5$	Cl	77	679, 702
$CH_2C_6H_5$	CN	93–94	305
$CH_2C_6H_5$	CH_3	105	174
		106–107.5	137
$CH_2C_6H_5$	NH_2		280
$CH_2C_6H_5$	$NHCOCH_3$		280
$CH_2C_6H_5$	$NHC_6H_4Br(4)$	182	319
$CH_2C_6H_5$	$NHC_6H_4Cl(4)$	185	319
$CH_2C_6H_5$	$NHSO_2C_6H_4NH_2(4)$	200–201	692
$CH_2C_6H_5$	$NHCH_2C_6H_5$	135	696
$CH_2C_6H_4OCH_3(4)$	Cl	115	226, 702
$CH_2CH_2C_6H_5$	$NHSO_2C_6H_4NH_2(4)$	173–174	692
β-D-Ribofuranosyloxy tribenzoate	Cl		706
β-D-Glucopyranosyloxy	Cl		142, 190
β-D-Glucopyranosyloxy	Br		142

TABLE XXVIII. 3-Alkyl(aryl)oxy-4,6-disubstituted Pyridazines



R_1	R_2	R_3	MP (°C)	References
CH_3	Cl	Cl		97
CH_3	Cl	CH_3	121–122	72
CH_3	CH_3	Cl	116	93
			118.5–119.5	141
			113	92
			68–70	88
			68	86
CH_3	CH_2Cl	Cl	64–65	93
CH_3	CH_2OH	Cl	150–151	93
CH_3	COOH	Cl	158.5 (dec)	88
CH_3	$CONH_2$	CH_3	155–156	449
CH_3	NH_2	Cl	195	141
			190–191	199
CH_3	$NHCH_3$	Cl	178–179	335
CH_3	NHC_2H_5	Cl	95–97	335
CH_3	$NHSO_2C_6H_4NH_2(4)$	Cl	196	234
			207–208	707
CH_3	$N(CH_3)_2$	Cl	82–85	335
CH_3	NH_2	CH_3		210

TABLE XXVIII (*continued*)

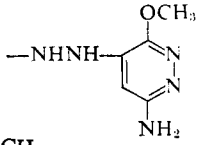
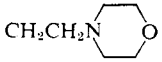
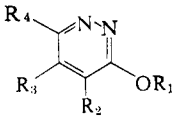
R_1	R_2	R_3	MP (°C)	References
CH_3	NH_2	COOH	188	449
CH_3	$N(C_2H_5)_2$	Cl	n_D^{20} 1.5585	335
CH_3	$SC_6H_4NH_2(2)$	Cl	133 (dec)	708
CH_3	$N(CH_3)NO_2$	CH_3	237 (dec)	137
CH_3	$NHNO_2$	CH_3	188 (dec)	137
CH_3	$NKNO_2$	CH_3	162	137
CH_3	Cl	NH_2	151–152	709
CH_3	Cl	$NHCOCH_3$	245–247 (dec)	709
CH_3	NH_2	NH_2		709
CH_3		NH_2	261–263	709
CH_3	CH_3	C_6H_5	60–61	710
CH_3	$C(CH_3)_3$	C_6H_5	73–75	245
CH_3	CH_3	NH_2	83–84	88
			125–125.5	141
CH_3	CH_3	NH_2 (picrate)	244–245	141
CH_3	NO_2	NO_2		273
CH_3	CH_3	SCH_3	58	86
$CH_2COOC_2H_5$	Cl	Cl	116–117	335
CH_2CH_3	CH_3	Cl	78	92
CH_2CH_3	CH_3	C_6H_5	103–104	710
CH_2CH_3	CH_3	C_6H_5 (picrate)	150	710
CH_2CH_3	NH_2	Cl	199	234
CH_2CH_3	$NHSO_2C_6H_4NH_2(4)$	Cl	155–155.5	234
CH_2CH_3	$N(CH_3)_2$	Cl	86–88	335
CH_2CH_2OH	$N(CH_3)_2$	Cl	112–113	335
	CH_3	C_6H_5 (HCl)		463
$CH_2CH_2CH_3$	$N(CH_3)_2$	Cl	48–50	335
$CH(CH_3)_2$	$N(CH_3)_2$	Cl	46–48	335
C_4H_9	NH_2	Cl	164–165	335
C_4H_9	$NHCH_3$	Cl	n_D^{20} 1.5590	335
C_4H_9	NHC_2H_5	Cl	n_D^{20} 1.5498	335
C_4H_9	$N(C_2H_5)_2$	Cl	n_D^{20} 1.5348	335
C_6H_5	C_6H_5	CH_3	96–98	442
C_6H_5	$N(CH_3)_2$	Cl	bp 190–195 (0.3 mm)	335
$CH_2C_6H_5$	$N(CH_3)_2$	Cl	62–64	335

TABLE XXIX. 3-Alkyl(aryl)oxy-4,5,6-trisubstituted Pyridazines



3-Alkyloxy-4-substituted

R_1	R_2	MP (°C)	References
CH_3	CH_3	34	92
		35–37	141
CH_3	CH_3 (HCl)	150	88
CH_3	CH_3 (picrate)	145–146	141
CH_3	NH_2		592
		127–128	234
		128–129	233
CH_3	$NH(CH_2)_3N(C_4H_9)_2$	76–78	749
CH_2CH_3	NH_2	75	234
CH_2CH_3	NH_2 (picrate)	192–193	234

3-Alkyloxy-5-substituted

R_1	R_3	MP (°C)	References
CH_3	CH_3	15 bp 105 (12 mm)	92
CH_3	NH_2	162–163	228
		161–162	268
CH_2CH_3	NH_2	bp 170–180 (0.1 mm)	268
CH_2CH_3	NH_2 (picrate)	61–63	268
C_4H_9-*n*	NH_2	bp 200 (0.5 mm)	268
C_4H_9-*n*	NH_2 (picrate)	124–126	268

3-Alkyloxy-4,5-disubstituted

R_1	R_2	R_3	MP (°C)	References
CH_3	Cl	NH_2	178–179	268
CH_2CH_3	Cl	NH_2	181	268
C_4H_9	Cl	NH_2	131–133	268

3-Alkyl(aryl)oxy-5,6-disubstituted

R_1	R_3	R_4	MP (°C)	References
CH_3	Cl	Cl	49–52	335
CH_3	CH_3	Cl	66	92
			71.5–72.5	141

TABLE XXIX (*continued*)

R_1	R_3	R_4	MP (°C)	References
CH_3	CH_3	Cl	112–116	88
			117–118.5	654
CH_3	COOH	Cl	159 (dec)	93
CH_3	COOH	OCH_3	156	93
$CH_2COOC_2H_5$	Cl	Cl	69–70	335
CH_3	CH_3	CH_3	70–71	647
CH_3	CH_3	SCH_3	100	86
CH_3	$C(CH_3)_3$	C_6H_5	69–70	245
CH_3	NH_2	CN	257–258	441
CH_3	NH_2	$OSO_2C_6H_4CH_3(4)$	171–172	692
CH_3	OCH_3	Cl	95	335
CH_2CH_3	CH_3	Cl	49	92
CH_2CH_3	C_6H_5	C_6H_5	55–60	240
C_6H_5	CH_3	Cl	142	505
Tribenzoylribopyranosyl	C_6H_5	C_6H_5	188–189	500

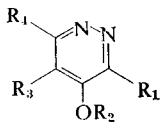
3-Alkoxy-4,6-disubstituted

R_1	R_2	R_4	MP (°C)	References
CH_3	$NH(CH_2)_2N(C_2H_5)_2$ (2 HCl)	Cl	157–158	749
CH_3	$NH(CH_2)_3N(C_2H_5)_2$ (2 HCl)	Cl	107–108	749
CH_3	$NH(CH_2)_3N(C_4H_9)_2$ (2 HCl)	Cl	110–112	749
CH_3		Cl	128–130	749

3-Alkoxy-4,5,6-trisubstituted

R_1	R_2	R_3	R_4	MP (°C)	References
CH_3	Cl	NH_2	CN	235–236	441
CH_3	F	F	F	54–56	765
CH_3	CN	CH_3	CH_3	93–94	444, 711
CH_3	$C(CH_3)_3$, H	H, Br	C_6H_5	134–136 (dec)	245
CH_3	NH_2	NH_2	CH_3	210–211	137
CH_3	NH_2	NO_2	CH_3	197–198	137
CH_3	NO_2	CH_3	CH_3		647
CH_3	OCH_3	OCH_3	OCH_3	47–49	765
CH_3	OCH_3	OCH_3	Cl	64–66	335
CH_3	F	F	OCH_3	115–117	765
CH_3	OCH_3	OCH_3	F	29–31	712, 765
CH_3	OCH_3	F	OCH_3	85–87	765
C_2H_5	Br	Br	OAg		504
C_2H_5	CN	CH_3	CH_3	76–78	444, 711
$CH(CH_3)_2$	CN	CH_3	CH_3	138–140	444, 711

TABLE XXX. 4-Alkyl(aryl)oxy-3,5,6-trisubstituted Pyridazines



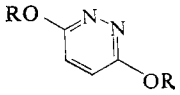
R_1	R_2	R_3	R_4	MP (°C)	References
H	CH_3	H	H	43–44	36, 85, 344
H	CH_3	H	H (HCl)	147–148	85
Cl	CH_3	H	H	129–130	236
Cl	CH_3	$NH(CH_2)_3N$ O	H	104–106	749
OCH_3	CH_3	H	H	55–57	235, 243, 273
OCH_3	CH_3	H	H (picrate)	151	235
H	CH_3	$NH(CH_2)_3N$ O	Cl	134–135	749
H	CH_3	OCH_3	H	98–100	344
H	CH_3	OCH_3	H (picrate)	165	344
H	CH_3	H	OCH_3	73–75	236, 344
Cl	CH_3	Cl	H		236
H	CH_3	Cl	Cl	101–102	344
Cl	CH_3	OCH_3	H	89–90	236
				91–92	344
H	CH_3	Cl	OCH_3	161–162	344
Cl	CH_3	H	Cl	130–131	85
F	CH_3	F	F	bp 74–76 (3 mm)	712, 713, 780
Cl	CH_3	OCH_3	Cl	103–105	335
F	CH_3	OCH_3	F	bp 78–80 (0.52 mm)	712, 780
C_6H_5	CH_3	C_6H_5	H	171–172.5	81

TABLE XXX (*continued*)

R_1	R_2	R_3	R_4	MP (°C)	References
NH_2	CH_3	H	CH_3	273–274	752, 768
OCH_3	CH_3	H	Cl	130	235, 236
OCH_3	CH_3	H	CN	200–201	269
CH_3	CH_3	H	CH_3	78–80	517
OCH_3	CH_3	H	OCH_3	121	209, 273
H	CH_2CH_3	H	H	bp 118–119 (5 mm)	87
H	CH_2CH_3	H	H (picrate)	93–94	87
Cl	CH_2CH_3	H	H	101–102	236
H	CH_2CH_3	H	Cl	100.5–102	268
Cl	CH_2CH_3	H	Cl	115–116	87
$COOCH_3$	CH_2CH_3	H	$COOCH_3$	75–76	714
C_6H_5	CH_2CH_3	H	C_6H_5		184, 232
C_6H_5	CH_2CH_3	C_6H_5	C_6H_5	145–146	83
Cl	CH_2CH_2Cl	H	Cl	119–122	335
Cl	$CH_2CH_2N(CH_3)_2$	H	Cl	79–80	335
Cl	CH_2CH_2OH	H	Cl	114–115	335
NH_2	CH_2CH_2OH	H	CH_3	194–196	752
Cl	$CH_2CH_2OCH_3$	H	Cl	68–70	335
NH_2	CH_2COOH	H	CH_3	194–196	768
Cl	$CH_2COOC_2H_5$	H	Cl	142–145	335
Cl	C_4H_9	H	Cl	76–77	335
H	C_6H_5	H	H	70–71	775
Cl	C_6H_5	H	Cl	84–85	335, 775
H	C_6H_5	Cl	Cl	68–69	775
Cl	$C_6H_4Cl(4)$	H	Cl	112–114	335
Cl	$C_6H_3Cl_2(3,4)$	H	Cl	125–126	335
Cl	$C_6H_4NH_2(2)$	H	Cl	118–119	715
Cl	$C_6H_4NHCOCH_3(2)$	H	Cl	164.5–165	715

Cl	$C_6H_4NO_2$(2)	H	Cl	164	221
				161.5–162.5	715
Cl	$C_6H_4NO_2$(3)	H	Cl	173–175	221
Cl	$C_6H_4NO_2$(4)	H	Cl	173	221
H	$C_6H_4OCH_3$(4)	H	H	81–84	775
Cl	$C_6H_4OCH_3$(2)	H	Cl	151	221
H	$C_6H_4OCH_3$(4)	Cl	Cl	60–64	775
H	$CH_2C_6H_5$	H	H		344
NH_2	$CH_2C_6H_5$	H	CH_3	163–166	752, 768
H	Tetra-*O*-acetyl-β-D-glucopyranosyloxy	H	H	167–168	240
H	β-D-Glucopyranosyloxy	H	H	165–168	240

TABLE XXXI. 3,6-Bisalkyl(aryl)oxypyridazines



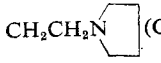
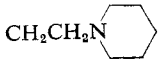
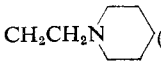
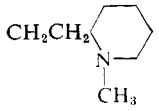
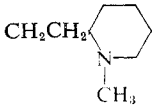
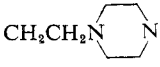
R	MP (°C)	References
CH_3	104.5–105	274
	106	679
	106–107	111, 230
	107–108	716
	108	99, 181, 277, 325 504, 685, 717
CH_2CH_3	48	679
	50	277
	51–52	97, 99, 181
$CH_2CH_2N(CH_3)_2$	bp 130–133 (0.4 mm)	225, 271
	bp 139–142 (0.1 mm)	181, 230, 680
$CH_2CH_2N(CH_3)_2$ $(HCl)_2$	211–212	181, 225
$CH_3CH_2N(CH_3)_2$ $(CH_3I)_2$	241–242 (dec)	225, 271
$CH_2CH_2N(C_2H_5)_2$	bp 190–200 (4 mm)	679
	bp 162–171 (0.1 mm)	181
	bp 132–137 (0.2 mm)	225, 271
	bp 85–90 (0.1 mm)	274
$CH_2CH_2N(C_2H_5)_2$ $(picrate)_2$	158–158.5	181, 225, 271
	159	679
$CH_2CH_2N(C_2H_5)_2$ $(CH_3I)_2$	215–220	181
	229–229.5	225, 271, 679
$CH_2CH_2N(n\text{-}C_4H_9)_2$	19 –195 (0.1 mm)	225
	192–195 (0.15 mm)	271
$CH_2CH_2N(n\text{-}C_4H_9)_2$ $(HNO_3)_2$	149.5–150.5	225, 271
	248–249	718
	bp 132 (6 mm)	718
	238–239	718
	bp 180 (0.02 mm)	271
	175 (3×10^{-4} mm)	275
	240–242 (dec)	271
	140–142	275
	107–109	271
	116–117	275

TABLE XXXI (*continued*)

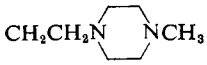
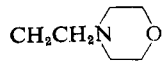
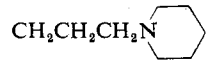
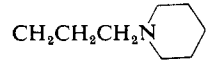
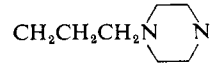
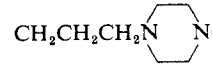
R	MP (°C)	References
	192–193	271, 275
	85.5–86	225, 271
CH_2CH_2OH	131–132	181
$CH_2CH_2OCH_3$	55.5–56.5	181
	55–56	277
$CH_2CH_2OCH_2CH_3$	71–73	181, 277
$CH_2CH_2OCH_2CH_2N(C_2H_5)_2$	bp 175 (0.003 mm)	225, 271
$CH_2CH_2OCH_2CH_2OCH_3$	44–45	181, 277
$CH_2CH{=}CH_2$	46–48	181
	48	277
	50	269
$CH_2CH_2CH_3$	41–43	181
	43	277
$CH(CH_3)_2$	108–111 (7 mm)	679
	112–113 (4 mm)	230
	120–122 (11 mm)	181
	122–124 (13 mm)	277, 680, 225
$(CH_2)_3N(CH_3)_2$	37.5–38	271
$(CH_2)_3N(CH_3)_2\ (HCl)_2$	222–223	225, 271
$(CH_2)_3N(CH_3)_2\ (CH_3Br)_2$	240–241	225, 271
$(CH_2)_3N(CH_3)_2\ [(4)NO_2C_6H_4CH_2Br]_2$	190–192	225, 271
$(CH_2)_3N(C_2H_5)_2$	130–132 (0.2 mm)	225
	130–132 (0.18 mm)	271, 275
$(CH_2)_3N(C_2H_5)_2\ (CH_3I)_2$	186–187	225, 271
$(CH_2)_3N(C_2H_5)_2\ (C_2H_5I)_2$	188–190	271
	186–187.5	275
$(CH_2)_3N(C_2H_5)_2\ (CH_3Br)_2$	162–164.5	275
$(CH_2)_3N(C_2H_5)_2\ [(4)NO_2C_6H_4CH_2Br]$	181–182	225, 271, 275
$CH(CH_3)CH_2N(CH_3)_2$	84–89 (10^{-3} mm)	225, 271
$CH(CH_3)CH_2N(CH_3)_2\ (CH_3I)_2$	198.5–200.5	225, 271
	70–72	271
	73.5–75.5	275
	196–198	271
	196.5–199	275
	99.5–100	271, 275
	222–224	271, 275

TABLE XXXI (*continued*)

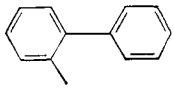
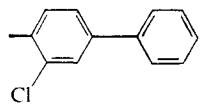
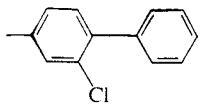
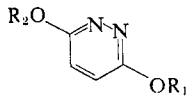
R	MP (°C)	References
n-C_4H_9	bp 163–166 (11 mm)	181
	bp 165 (11 mm)	717
	bp 155–156 (11 mm)	230, 680
$C(CH_3)_3$	76–78	181
$(CH_2)_4N(C_2H_5)_2$	bp 125 (0.001 mm)	225, 271
$CH(CH_3)CH_2CH_2N(CH_3)_2$	bp 80–84 (4.5×10^{-4} mm)	271
	bp 85 (0.004 mm)	275
$CH(CH_3)CH_2CH_2N(CH_3)_2$ $(CH_3Br)_2$	210 (dec)	271, 275
$CH(CH_3)CH_2CH_2N(CH_3)_2$ $(oxalate)_2$	157–159	275
$CH(CH_3)CH_2CH_2N(C_2H_5)_2$	bp 125 (0.001 mm)	275
$CH(C_6H_5)CH_2CH_2N(CH_3)_2$	bp 160 (0.001 mm)	275
$CH(C_6H_5)CH_2CH_2N(CH_3)_2$ $(CH_3I)_2$	160–165 (dec)	275
$CH_2CH_2CH(CH_3)_2$		224, 680
$(CH_2)_5N(C_2H_5)_2$	bp 145 (0.0002 mm)	225
	bp 165 (3×10^{-5})	271
$CH(CH_3)(CH_2)_3N(C_2H_5)_2$	bp 150–156 (2×10^{-4} mm)	271
$(CH_2)_3CHCH_3N(C_2H_5)_2$	bp 130–136 (0.001 mm)	225
$(CH_2)_5CH_3$	41–42	181
C_6H_5	140	679, 717
	140–141	181, 226, 702
$C_6H_4Br(2)$	196–197	226, 702
$C_6H_4Br(4)$	198–201	226, 702
$C_6H_4Cl(2)$	208–209	226, 702
$C_6H_4Cl(3)$	126.5	226, 702
$C_6H_4Cl(4)$		702
$C_6H_3CH_3(3)Cl(4)$	152	226, 702
$C_6H_3Cl_2(2,4)$	205	226, 702
$C_6H_3Cl_2(2,6)$	238–240	226
$C_6H_4CH_3(4)$	169–170	226, 702
$C_6H_4OCH_3(2)$	171	226
$C_6H_4OCH_3(3)$	112–114	226, 702
$C_6H_4OCH_3(4)$	176–177	226, 702
	137	226, 702
	198	226
		702

TABLE XXXI (*continued*)

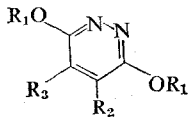
R	MP (°C)	References
C_6H_{11}	133–134	230
β-D-Glucopyranosyloxy	151–153	143, 144
Tetra-*O*-acetyl-β-D-glucopyranosyloxy	209–211	143, 144
$CH_2C_6H_5$	137–138	325
	134	181, 717
	136	679
	136.5–137	275
$CH_2C_6H_5$ $(CH_3I)_2$	202–204	275
$CH(C_6H_5)_2$	180–181	325, 364

TABLE XXXII. 3-Alkyl(aryl)oxy-6-alkyl(aryl)oxypyridazines



R_1	R_2	MP (°C)	References
CH_3	$CH_2CH_2N(CH_3)_2$	bp 120–123 (4 mm)	230, 680
CH_3	C_6H_5	100–101	181, 717
CH_3	$C_6H_3Cl_2$(2,4)	145	226, 702
CH_3	$C_6H_4OCH_3$(2)	92.5	226, 702
$CH_2CH_2CH_3$	$CH_2CH_2N(CH_3)_2$	bp 162–164 (8 mm)	224, 680
$CH(CH_3)_2$	$CH_2CH_2N(CH_3)_2$	bp 131–132 (4 mm)	230, 680
n-C_4H_9	$CH_2CH_2N(CH_3)_2$	bp 135–137 (3 mm)	230, 680
n-C_5H_{11}	$CH_2CH_2N(CH_3)_2$	bp 132–135 (2 mm)	224, 680
$CH_2CH_2CH(CH_3)_2$	$CH_2CH_2N(C_2H_5)_2$	bp 120–125 (2 mm)	224
C_6H_{11}	$CH_2CH_2N(CH_3)_2$	39–41	230, 680
C_6H_5	$C_6H_4NO_2$(4)	180	221
C_6H_5	$C_6H_3(NO_2)_2$(2,4)	141	221
$C_6H_4OCH_3$(2)	$C_6H_3(NO_2)_2$(2,4)	146	221

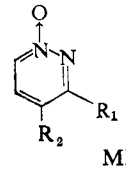
TABLE XXXIII. 3,6-Bisalkyl(aryl)oxy-4,5-disubstituted Pyridazines



R_1	R_2	R_3	MP (°C)	References
CH_3	Cl	H		633
CH_3	CH_3	H	83–84.5	93
			80–81	717
			83–84	181
CH_3	CH_2OH	H	161–161.5	93
CH_3	CH_2OCOCH_3	H	66	93
CH_3	CH_2CH_3	H		453
CH_3	$CH(CH_3)_2$	H		453
CH_3	H, C_4H_9-*n*	H, H	bp 94 (7 mm)	246
CH_3	$C(CH_3)_3$	H		453
CH_3	H, $C(CH_3)_3$	H, H	150–151	246
			bp 77 (0.5 mm)	82
CH_3	C_6H_5	H		453
CH_3	H, C_6H_5	H, H		453
CH_3	NH_2	H	177–178	141, 360, 514
			175	209, 719, 720
CH_3	$NHCOCH_3$	H	143	209
CH_3	$NHSO_2C_6H_4NH_2$(4)	H	189–190	719
CH_3	$NHSO_2C_6H_4NHCOCH_3$(4)	H		454
CH_3	$NHNH_2$	H		344
CH_3	N_3	H		347
CH_3	NH_2	NH_2	252–254 (dec)	199
CH_3	NH_2	NH_2 (picrate)	202–203	199

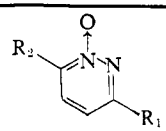
CH_3	NH_2	NH_2 (diacetate)	254	199
CH_3	NH_2	$NHCOCH_3$	202–203	199
CH_3	NH_2	NO_2	232–233	199
$CH_2CH_2N(C_2H_5)_2$	CH_3	H	bp 140 (0.005 mm)	225, 271
$CH_2CH_2N(C_2H_5)_2$	CH_3	$H(CH_3Br)_2$	145	225, 271
$CH(CH_3)_2$	CH_3	H	125–128	181
			127–128	717
$(CH_2)_3N(CH_3)_2$	CH_3	H	114–116 (5×10^{-4} mm)	271
$(CH_2)_3N(CH_3)_2$	CH_3	H (triphosphate)	155–165	271
$(CH_2)_3N(CH_3)_2$	CH_3	H [bis(4)$NO_2C_6H_4CH_2Br$]	191–192	271
$(CH_2)_3N(C_2H_5)_2$	CH_3	H	bp 129–132 (0.01 mm)	96, 271
$(CH_2)_3N(C_2H_5)_2$	CH_3	H[(4)$NO_2C_6H_4CH_2Br$]	187–189	225, 271
$(CH_2)_3N(CH_3)_2$	CH_3	CH_3	bp 120–122 (5×10^{-4} mm)	225, 271
$(CH_2)_3N(CH_3)_2$	CH_3	CH_3 (di-HCl)	250.5–251.5	225, 271
$(CH_2)_3N(CH_3)_2$	CH_3	CH_3 [di-(4)$NO_2C_6H_4CH_2Br$]	207–208	225, 271
$(CH_2)_3N(CH_3)_2$	$(CH_2)_3N(CH_3)_2$	$(CH_2)_3N(CH_3)_2$	bp 114–116 (5×10^{-5} mm)	225
$(CH_2)_3N(CH_3)_2$	$(CH_2)_3N(CH_3)_2$	$(CH_2)_3N(CH_3)_2$ (triphosphate)	155–156.5	225
$(CH_2)_3N(CH_3)_2$	$(CH_2)_3N(CH_3)_2$	$(CH_2)_3N(CH_3)_2$ [di-(4)$NO_2C_6H_4CH_2Br$]	191–192	225

TABLE XXXIV. 3,4-Disubstituted Pyridazine 1-Oxides



R_1	R_2	MP (°C)	References
H	OH	274–277	63
H	OH	283 (dec)	236
H	OCH_3	106–109	721
		121–122	236
		123–124	94, 210
H	OCH_3 (picrate)	90–91	236
H	OC_2H_5	91–92	722
		108–110	236
H	OC_2H_5 (picrate)	119–120.5	236
H	$OCH_2C_6H_5$		271
CH_3	OCH_3	105–106	210
		118–119	305
OH	H	197–198	305
		198–200	97, 98
		201–202	140, 271
OH	CH_3	194	141
		187 (dec)	346
OCH_3	H		723, 724
OCH_3	CH_3	125–126	141
OCH_3	NH_2		233, 273, 725
OCH_3	NO_2		273, 725
OCH_3	OCH_3		273
OC_2H_5	H	65–67	724
		70–71	234
		74–75	722
		74.5–75	346
		73–75	97
OC_2H_5	H (picrate)	86–87	346
		88–90.5	234
OC_2H_5	CH_3	125.5–126	346
OC_2H_5	NO_2	106–107	234
OC_3H_7	H	61–63	97
OC_6H_5	H		98, 271
$OCH_2C_6H_5$	H		271

TABLE XXXV. 3,6-Disubstituted Pyridazine 1-Oxides



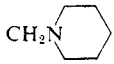
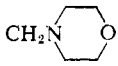
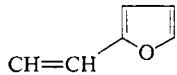
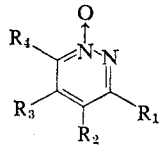
R_1	R_2	MP (°C)	References
Cl	OCH_3	187–188	683
Cl	OC_2H_5	138–139	683
OH	Cl	224–225 (dec)	97
OH	CH_3	200–202	345
		201–202	141, 687
OH	COOH	197–198	726
OH	$CON(CH_3)C_6H_5$	158	308
OH	$CH_2NHCH_2C_6H_5$		203
OH	$CH_2N(CH_3)_2$		202
OH			202
OH			202
OH	N_2^+		727
OCH_3	Cl	157–158	140, 345
OCH_3	CH_3	95–96	72
		96.5–97.5	137
		97–98	141, 394
		98–99	345
		NO mp	687, 728
OCH_3		244–245	689
OCH_3	NH_2	90–90.5	233
NH_2	OCH_3	135–135.5	233
OCH_3	NO_2		233, 592, 725
OCH_3	OH		140
OCH_3	OCH_3	150–151	346
		152	236, 273
OC_2H_5	Cl	115–116	346
OC_2H_5	CH_3		724
OC_2H_5	OCH_3	126–127.5	346
OC_2H_5	OC_2H_5	70.5–71.5	346
		71–72	632
OC_3H_7	Cl	83–84	683
OC_3H_7	OC_3H_7	54–55	632
OC_4H_9	OC_4H_9	52–53	632
$OCH_2C_6H_5$	CH_3	112–114	137
$CH_3(2)$, =O(3)	CH_3	111–112	394

TABLE XXXVI. 3,4,5,6-Tetrasubstituted Pyridazine 1-Oxides



R_1	R_2	R_3	R_4	MP (°C)	References
H	H	H	OCH_3		94, 233
H	H	NH_2	OCH_3	183 (dec)	233
H	H	NO_2	OCH_3		233
H	H	OH	CH_2NHCH_3		203
H	H	OH	$CH_2NHC_2H_5$		203
H	H	OH	$CH_2NHCH_2C_6H_5$		203
H	H	OCH_3	H	89.5–90.5	236
H	H	OCH_3	H (picrate)	81–82	236
H	H	OC_2H_5	H	61–62.5	236
H	Br	OH	Br	190–191	729
H	Br	OH	CH_2N 	193–194	729
H	OCH_3	H	CH_3	103–104	72
Cl	Cl	H	OCH_3	134	209
Cl	H	OCH_3	Cl	162.5–164.0	235
Cl	OCH_3	H	Cl	174–175	235, 680
CH_3	H	OCH_3	H	112	94
CH_3	H	OCH_3	CN	185	94
CH_3	H	OCH_3	CH_3	136–137	517
				142	94
CH_3	H	OH	CH_3	260 (dec)	517
CH_3	H	=O	COOH [C_6H_5(2)]	220–221	85, 520
$COOC_2H_5$	=O	=O	$COOC_2H_5$ [→O(2)]	70	512
CH_3	OH	H	CH_3	255 (dec)	517
CH_3	OH	NO_2	CH_3		347
CH_3	OCH_3	H	CH_3	148–149	517
CH_3	OCH_3	H	COOH	142 (dec)	726
CH_3	OCH_3	H	OCH_3	148–149	210
OH	H	CH_3	CH_3	215 (dec)	647
OH	Br	H	Br	220–221 (dec)	730
OH	Cl	H	CN	258 (dec)	305
OH	Cl	H	COOH	214	726
OH	CH_2N 	H	Cl	240–241	201
OH	CH_2N 	H	CH_3	162–164	201

TABLE XXXVI (*continued*)

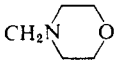
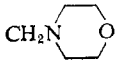
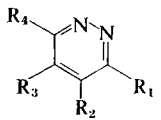
R_1	R_2	R_3	R_4	MP (°C)	References
OH		H	Cl	204–206	201
OH		H	CH_3	183–186	201
OH	NO_2	H	Cl	214–215	347
OCH_3	H	CH_3	Cl	152–153	141
OCH_3	H	CH_3	OCH_3	153.5–154	236
OCH_3	H	NO_2	H	135–136	94, 347
OCH_3	H	NO_2	OCH_3	61–62	214
OCH_3	H	OCH_3	H	131	94, 295
OCH_3	Cl	H	CH_3	138–139	726
OCH_3	Cl	H	CH=NH	112.5–113.5	305
OCH_3	Cl	H	CH=NOH	206	305
OCH_3	Cl	H	$CH=NOCOCH_3$	142–143	305
OCH_3	Cl	H	CN	174–175	305
OCH_3	Cl	H	NH_2	204 (dec)	709
OCH_3	Cl	H	NH_2 (HCl)	196 (dec)	709
OCH_3	Cl	H	$NHCOCH_3$	233–234	709
OCH_3	Cl	H	OCH_3	134	209
OCH_3	CH_3	H	Cl	205–206	93
OCH_3	CH_3	H	NH_2	184–185	141
OCH_3	CH_3	H	NO_2	116–117	141, 731
OCH_3	CH_3	H	OCH_3	163–164.5	236
				167–168	141
OCH_3	NH_2	H	CH_3	193 (dec)	137
OCH_3	NH_2	H	OCH_3 (picrate)	171	209
OCH_3	NO_2	H	Cl	144–145	97, 347
OCH_3	NO_2	H	CH_3	101–101.5	72
				101–103	137
				No mp	210, 650, 728
OCH_3	NO_2	H	NH_2	181	743
OCH_3	NO_2	H	$NHCOCH_3$		743
OCH_3	NO_2	H	NO_2		273
OCH_3	NO_2	H	OCH_3	114	209, 732
OCH_3	OCH_3	H	Cl	188–190	97
				190	235
OCH_3	OCH_3	H	CN	200–202	269
OCH_3	OCH_3	H	CH_3	150–151	72
OCH_3	OCH_3	H	NO_2	162 (dec)	211
OCH_3	OCH_3	H	OCH_3	116–118	97, 344
				117	209
				117–117.5	488
				No mp	235, 273

TABLE XXXVI (*continued*)

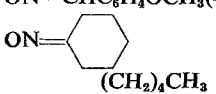
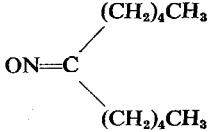
R_1	R_2	R_3	R_4	MP (°C)	References
OC_2H_5	H	CH_3	OC_2H_5	63–65	236
OC_2H_5	Cl	H	NH_2 (HCl)	187 (dec)	709
OC_2H_5	CH_3	H	NO_2	85–86	731
OC_2H_5	CH_3	H	OCH_3	115–116.5	346
OC_2H_5	CH_3	H	OCH_5	60–61.5	236
				80.5–82	346, 728
OC_2H_5	NO_2	H	CH_3		
OC_2H_5	NO_2	H	NH_2	156	743
OC_2H_5	NO_2	H	$NHCOCH_3$	209	743
OC_2H_5	NO_2	H	OC_2H_5	75–76	632
OC_3H_7	Cl	H	NH_2 (HCl)	169 (dec)	709
OC_3H_7	CH_3	H	NO_2	52	731
OC_3H_7	NO_2	H	NH_2	149	743
OC_3H_7	NO_2	H	$NHCOCH_3$	181	743
OC_3H_7	NO_2	H	OC_3H_7	67–68	632
OC_4H_9	Cl	H	NH_2 (HCl)	161 (dec)	709
OC_4H_9	NO_2	H	NH_2		743
OC_4H_9	NO_2	H	$NHCOCH_3$		743
OC_4H_9	NO_2	H	OC_4H_9	54–56	632
OC_5H_{11}	Cl	H	CH=NOH	112.5–113.5	733
OC_5H_{11}	NO_2	H	NH_2		743
OC_5H_{11}	NO_2	H	$NHCOCH_3$		743
OC_5H_{11}-*i*	NO_2	H	NH_2		743
OC_5H_{11}-*i*	NO_2	H	$NHCOCH_3$		743
OC_6H_{13}	NO_2	H	NH_2		743
OC_6H_{13}	NO_2	H	$NHCOCH_3$		743
OC_8H_{17}	NO_2	H	NH_2		743
OC_8H_{17}	NO_2	H	$NHCOCH_3$		743
$OC_{10}H_{21}$	NO_2	H	NH_2		743
$OC_{10}H_{21}$	NO_2	H	$NHCOCH_3$		743
COC_6H_5	OH	=O	COC_6H_5 [—OH(2)]	128	512
COC_6H_5	OH	=O	COC_6H_5 [—OH(2)] (diacetate)	Explodes	512
COC_6H_5	=O	=O	COC_6H_5 [→O(2)]		512

TABLE XXXVII. Other Oxygen-Containing Pyridazines



R_1	R_2	R_3	R_4	MP (°C)	References
H	H	H	H (1-OCH_3)	75–80	96
H	OH, OH	H	H (1-H)		734
H	H, $OCOCH_3$	H, $OCOCH_3$	H, H [1-$C_6H_3(NO_2)_2$(2,4)]	172–173	735
H, H	H, OH	H, OH	H, H (1-H, 2-H) (cis)	146	235, 736, 737
H, H	H, OH	H, OH	H, OH (1-H, 2-H) (trans)	246	235, 736, 737
H, H	H, OH	H, OH	H, H (1-CH_3, 2-H)	bp 135–155 (0.2 mm)	737
H, H	H, OH	H, OH	H, H (1-CH_3, 2-CH_3) (trans)	110	736
H, H	H, OH	H, OH	H, H (1-CH_3, 2-CH_3) (picrate)	125	736
H, H	H, OH	H, OH	H, H (1-CH_3, 2-CH_3) (diacetate)	bp 139–140 (9 mm)	736
H, H	H, OH	H, OH	H, H (1-CH_3, 2-CH_3) (diacetate–picrate)	202 (dec)	736
H, H	H, OH	H, OH	H, H (1-C_2H_5, 2-C_2H_5)	107	737
H, H	H, OH	H, OH	H, H (1-$COCH_3$, 2 $COCH_3$) (diacetate)	136	736
H, H	H, OH	H, OH	H, H (1-C_6H_5, 2-C_6H_5)	112	737
H, OC_2H_5	H, H	H, H	H [2-$SO_2C_6H_4CH_3$(4)]	98–99	738
Cl	$OPO(OC_2H_5)_2$	H	Cl	bp 100 (0.15 mm)	739
Cl	$OPS(OC_2H_5)_2$	H	Cl		223
CF_3	H, H	H, H	OH, OCH_2CH_3 [1-$C_6H_3(NO_2)_2$(2,4)]	105.5–106	740

TABLE XXXVII (*continued*)

R_1	R_2	R_3	R_4	MP (°C)	References
CF_3	H, H	H, H	OH, OC_3H_7 [1-$C_6H_3(NO_2)_2$(2,4)]	62	740
O^-	NH_2	H	H	246	136
O^-	NH_2	H	Cl (1-CH_3)	>300	136
O^-	NH_2	H	Cl (1-CH_3) (HCl)	237–238	136
O^-	NH_2	H	CH_3 (1-CH_3)	281–282	136
O^-	NH_2	H	CH_3 (1-CH_3) (picrate)	243.5	136
O^-	NH_2	H	OCH_3 (1-CH_3)	144–145	136
$OCOCH_3$	$OCOCH_3$	NO_2	H	150–151	84
$OCONHCH_3$	H	H	H	86	155
$OCONHCH_3$	H	H	$OCONHCH_3$	284 (dec)	155
ONHCOOH	H	H	Cl		741
$ON{=}C(CH_3)_2$	H	H	Cl	102–103	222
$ON{=}C(CH_3)CH_2CH_2COOC_2H_5$	H	H	Cl	89–90	222
$ON{=}CHC_6H_5$	H	H	Cl	144	222
$ON{=}C(CH_3)C_6H_5$	H	H	Cl	118–119	222
$ON{=}C(C_6H_5)_2$	H	H	Cl	113–115	222
$ON{=}CHC_6H_4Cl(2)$	H	H	Cl	93–95	222
$ON{=}CHC_6H_4NH_2(4)$	H	H	Cl	139–141	222
$ON{=}C(CH_3)C_6H_4NH_2(4)$	H	H	Cl	144–145	222
$ON{=}CHC_6H_4N(CH_3)_2(4)$	H	H	Cl	121–123	222
$ON{=}CHC_6H_4OCH_3(4)$	H	H	Cl	144–145	222
	H	H	Cl	86–88	222
	H	H	Cl	86–88	222

$OPO(OC_4H_9)_2$	H	H	Br		165
$OPO(OC_3H_7)_2$	H	H	Cl		165
$OPO(OC_3H_7\text{-}i)_2$	H	H	Cl		165
$OPS(OCH_3)_2$	H	H	Br		165
$OPS(OC_2H_5)_2$	H	H	Cl	48.5–49	165
$OPS(OC_2H_5)_2$	Br	Br	$OPS(OC_2H_5)_2$		165
$OPS(OC_2H_5)C_6H_5$	H	H	Cl		742
$OPS(OC_2H_5)C_6H_5$	H	H	OH	138–144	742
$OSCCl_3$	H	H	Cl	156–157	278
$OSO_2C_6H_4CH_3(4)$	H	H	Cl	185–186	160
$OSOC_6H_4NO_2(4)$	H	H	CH_3		348
$OSO_2C_6H_4NO_2(4)$	H	H	CH_3		348
$OSO_2C_6H_4OCH_3(4)$	NH_2	H	H	205–205.5	348

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CHAPTER III

Halopyridazines

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Because of the ease of preparation and reactivity of halopyridazines, they have found wide use in pyridazine chemistry. In addition to serving as intermediates for a wide variety of reactions, many halopyridazines have shown biological activity, such as herbicides, fungicides, and antituberculosis, antitumor, and antimicrobial agents.

I. The Preparation of Chloropyridazines

Although many means have been employed to introduce a chlorine atom on a pyridazine ring, the most widely used involves the action of phosphorus oxychloride on hydroxy derivatives. Other techniques involve the action of phosphorus pentachloride on hydroxypyridazines or pyridazinones, diazotization of amino groups followed by decomposition, oxidation of hydrazino groups with sodium hypochlorite, reaction of phosphorus oxychloride and other reagents on pyridazine *N*-oxides, and other more specific reactions. Another simple way to prepare chloropyridazines (or pyridazinones) is through ring closure of halogen-containing precursors with hydrazine or substituted hydrazines. Other specific types of ring closures that give chloropyridazines are also available.

A. Phosphorus Oxychloride on Hydroxypyridazines

The hydroxypyridazine is warmed or refluxed with phosphorus oxychloride to effect conversion to the chloro compound. Refluxing sometimes increases the amount of tars and undesirable side products of the reaction, hence the occasional use of lower temperatures (1–4). This reaction is quite versatile and can be carried out in the presence of many different types of functional groups. Among these are the following at the top of page 222.

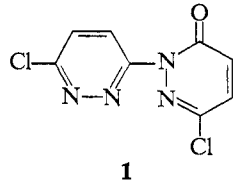
The presence of an amide group in addition to a hydroxy group under these conditions gives rise to cyano groups and chlorine atoms, respectively (17). Bromine attached directly to carbon undergoes elimination (23) or substitution for chlorine (24) upon treatment with phosphorus oxychloride.

Functional Group Attached to Carbon	References
Methyl	5–8
Ethyl	9, 10
Phenyl	11–14
Substituted phenyl	15
Benzyl and substituted benzyl	16
Cyano	5, 6, 7, 17
Ethyl carboxylate	17
Amino	18, 19
Acetamido	20
Morpholino	21
Ethoxy	20
Substituted benzylthio	22
Chloro	18, 19

Functional groups attached to the nitrogen atom of the pyridazine ring do not interefere with the conversion of a hydroxyl group to a chlorine atom, as illustrated by the following examples.

Functional Group Attached to Nitrogen	References
Methyl	25
Phenyl	21, 26, 27
Substituted phenyl (Cl, NO_2)	28, 29
Naphthyl (α, β)	21

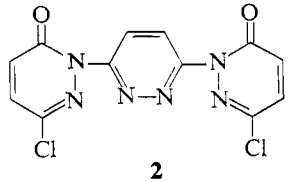
Side products in these replacement reactions sometimes occur. Druey, Meier, and Eichenberger (30), while preparing 3,6-dichloropyridazine, isolated a small amount of 3-[3′chloro-6′(1′*H*)pyridazinonyl]-6-chloropyridazine (**1**). Feuer and Rubinstein (31) found that **1** was not obtained



1

directly from the reaction of maleic hydrazide and phosphorus oxychloride but was the result of the work-up of the crude reaction mixture (heating for sublimation). Coad and Coad (32) obtained **1** in good yield (66%) by heating a 2:1 molar ratio of 3,6-dichloropyridazine and 3-chloro-6(1*H*)pyridazinone.

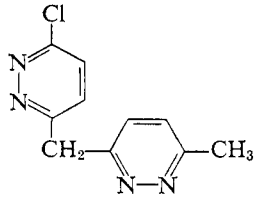
A small amount (11%) of 3,6-bis[3′-chloro-6′(1,4)pyridazinonyl]pyridazine (**2**) was also obtained. By reversing the molar ratio of 3,6-dichloropyridazine



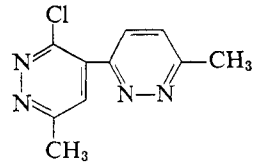
2

to 3-chloro-6(1*H*)pyridazinone from 2:1 to 1:2, a 75% yield of **2** was obtained.

Kumagai (33) isolated a condensation product $C_{10}H_9ClN_4$ in addition to 3-chloro-6-methylpyridazine from the reaction of 3-methyl-6-pyridazinone and phosphorus oxychloride. Structures **3** and **4** were proposed for this

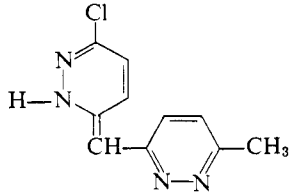


3



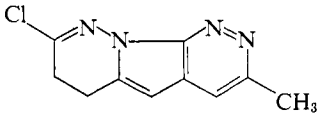
4

product. Basu and Rose (34) later isolated the same product and suggested



5

structure **5**. Lund and Gruhn (35), through degradation and spectroscopic data, have since shown this condensation product to be 8-chloro-6,7-dihydro-3-methyldipyridazino[2,3-*a*:4′,3′-*d*]pyrrole (**6**). Lehmann and Rasmussen (36) provided additional confirmatory evidence for **6** by x-ray diffraction. Another problem associated with the preparation of chloropyridazines

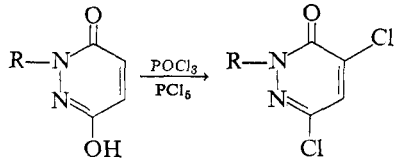


6

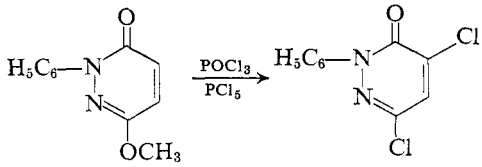
is the tendency of some of these compounds to hydrolyze during purification. From the results of over 200 runs, Coad and co-workers (3) devised a procedure using trituration in cold ammonium hydroxide and sodium hydroxide to prepare 3,6-dichloropyridazine, 3,6-dibromopyridazine, 4-methyl-3,6-dichloropyridazine, 4-methyl-3,6-dibromopyridazine, 3,4,6-trichloropyridazine, and 3,4,5,6-tetrachloropyridazine in high purity. Gordon and Dorf (37) describe an improved process for purifying 3,6-dichloropyridazine on a commercial scale by using aqueous bisulfite to solubilize the impurities.

B. Phosphorus Oxychloride and/or Phosphorus Petachloride on Pyridazines and Pyridazinones

Druey and co-workers (21, 38, 39) successfully used a combination of phosphorus oxychloride and phosphorus pentachloride on hydroxypyridazinones. This causes not only conversion of the hydroxyl group to a chlorine atom but substitution of chlorine directly on the ring as illustrated by the following general reaction.



Similarly, Takahashi (40) converted 3-methoxy-1-phenyl-6(1*H*)pyridazinone (**7**) into 3,5-dichloro-1-phenyl-6(1*H*)pyridazinone (**8**).



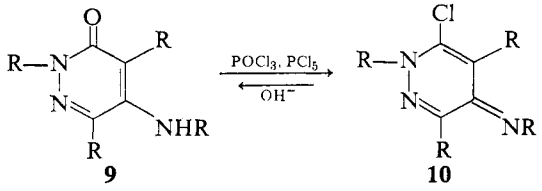
7 **8**

Nakagome (41) was also successful in replacing a methoxyl group with a chlorine atom, as shown by the conversion of 3-methoxy-6(1*H*)pyridazinone to 3,6-dichloropyridazine with phosphorus oxychloride.

Previously, Gregory and Wiggins (42) had introduced a chlorine atom directly into the 4-position of the pyridazinone ring by the action of phosphorus

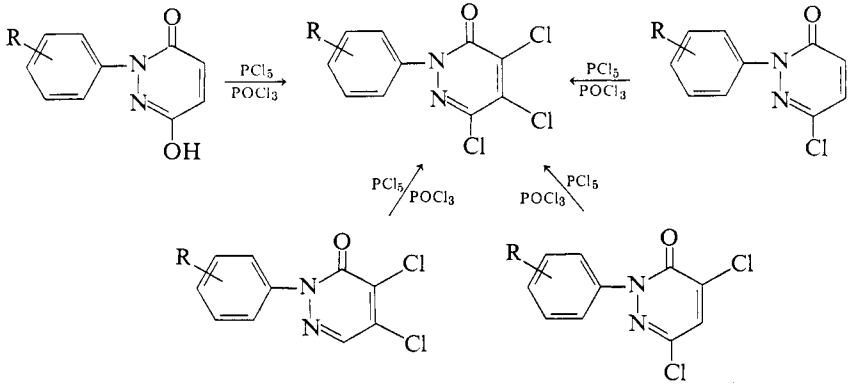
oxychloride and phosphorus pentachloride on 3-methyl-1-(*m*-tolyl)-6(1*H*)pyridazinone. Stevens (44) showed similar results with 1-(*p*-alkoxyphenyl)-3-methyl-6(1*H*)pyridazinones. Teotino and Cignarella (44), using phosphorus oxychloride and phosphorus pentachloride on 3-carbamyl-6(1*H*)pyridazinone, obtained 3-chloro-6-cyanopyridazine. Phosphorus oxychloride is not absolutely essential to the reaction. Several investigators (45–48) have introduced a chlorine atom into the 4-position of a 1,3-disubstituted 6(1*H*)pyridazinone by using phosphorus pentachloride by itself.

Dury (49) extended the use of phosphorus oxychloride and phosphorus pentachloride to 4-amino-1,3,5-trisubstituted-6(1*H*)pyridazinones (**9**). The oxygen is replaced by chlorine to form the very reactive strongly basic iminopyridazinones (**10**).



9 **10**

Takahashi (49a–c), starting with various 1-substituted-phenyl-6(1*H*)-pyridazinones, prepared the corresponding 3,4,5-trichloro derivatives through multiple additions of phosphorus oxychloride and phosphorus pentachloride according to the following scheme.



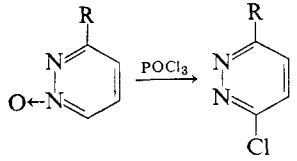
Maki (49d) carried out similar reactions starting with various 1-phenyl-6(1*H*)pyridazinones.

Chambers, McBride, and Musgrave (50–51) allowed phosphorus pentachloride to react with 3,6-dichloropyridazine in an autoclave to prepare the 3,4,5,6-tetrachloro derivative.

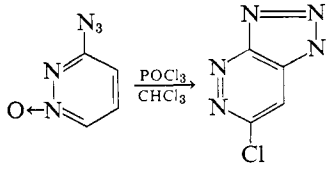
C. Addition of Active Chloro Compounds to Pyridazine *N*-Oxides

1. *Direct Substitution*

The reaction of an aromatic pyridazine *N*-oxide with phosphorus oxychloride allows direct substitution of a chlorine atom on the ring at a position alpha to the *N*-oxide function in the original compound. Should this position be blocked, substitution occurs gamma to the *N*-oxide function. The *N*-oxide function is also eliminated during the reaction. The presence of other



substituents on the pyridazine ring (methyl (52, 53), phenyl (54), alkoxy (55–58), acetamido (59)) does not interfere with this reaction. Itai and Kamiya (60) applied this reaction to 3-azidopyridazine 1-oxide (**11**). In addition to the direct substitution of a chlorine atom, the azido group cyclized to form a triazolopyridazine (**12**).



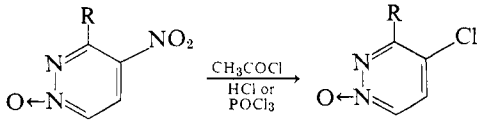
11 **12**

Kamiya, Okusa, and Hirakawa (60a) prepared 3-chloro-6(1*H*)pyridazinone from 3-hydroxypyridazine 1-oxide by the action of paraformaldehyde and hydrogen chloride.

2. *Replacement of Other Groups*

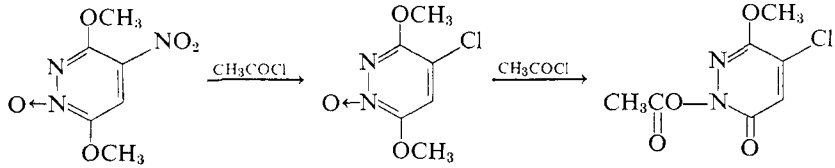
Another means of introducing chlorine into pyridazine *N*-oxides is through replacement of a nitro group. Pyridazine *N*-oxides readily undergo nitration gamma to the *N*-oxide group (**13**). The nitro group can then be exchanged for chlorine by the action of acetyl chloride, benzoyl chloride, hydrochloric acid, or phosphorus oxychloride with retention of the *N*-oxide function (**14**).

When Itai and Natsume (61) treated 4-nitropyridazine 1-oxide with phosphorus oxychloride, only 4-chloropyridazine 1-oxide was obtained. No direct substitution in the 6-position occurred. Other substituent groups on the ring (methyl (52, 53, 62, 63) chloro (62), alkoxy (46, 56, 64), amino (59),



13 **14**

or acetamido (60)) do not appear to limit the reaction. Yanai and Kinoshita (64) allowed 3,6-dimethoxy-4-nitropyridazine 1-oxide (**15**) to react with acetyl or benzoyl chloride, giving 1-acetoxy- (or benzoyloxy-) 3-methoxy-4-chloro-6(1*H*)pyridazinone (**17**). They found that 3,6-dimethoxy-4-chloropyridazine 1-oxide (**16**) was formed as an intermediate but further reacted with acetyl chloride to form the pyridazinone.

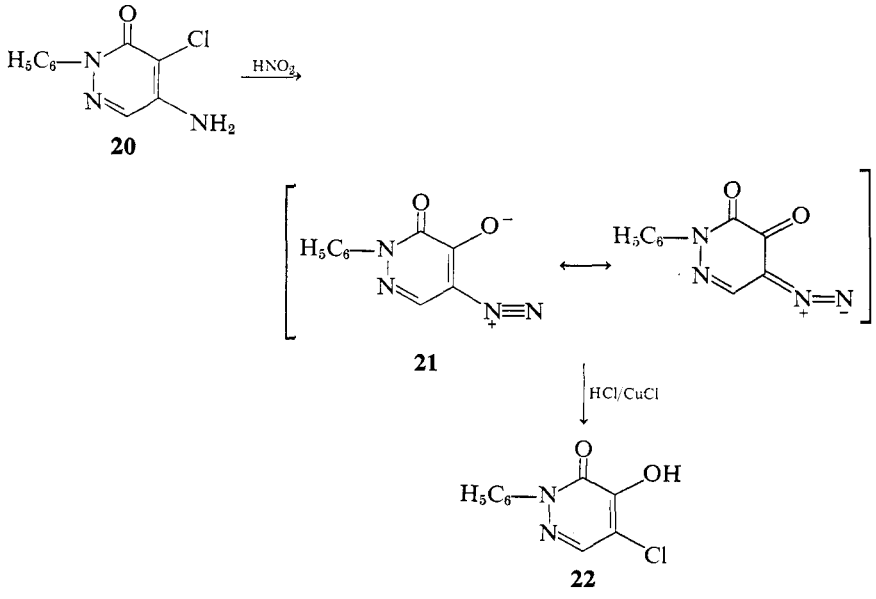


15 **16** **17**

D. Diazotization Followed by Replacement with Chlorine

Amino groups on the pyridazine ring undergo diazotization and subsequent replacement with chlorine, as shown by Becker and Böttcher (66) in the conversion of 3-amino-4,6-dimethylpyridazine into 3-chloro-4,6-dimethylpyridazine. Becker and Böttcher (65a) also used this same reaction on 3-amino-4-hydroxy-6-methyl- and 3-amino-4-methoxy-6-methylpyridazines to give the corresponding 3-chloro derivatives. Dury (49) found that the action of nitrous acid on 4-amino-5-chloro-1-phenyl-6(1*H*)pyridazinone (**20**) gave a yellow 4-diazonium-5,6-dioxo compound (**21**), which after the Sandmeyer reaction yielded 4-chloro-5-hydroxy-1-phenyl-6(1*H*)pyridazinone (**22**). It is noted that in this conversion the chlorine adjacent to the amino group is lost.

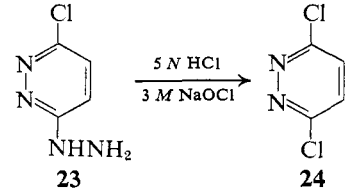
Aminopyridazine *N*-oxides also undergo diazotization and replacement without loss of the *N*-oxide function. Sako (67) converted both 5-amino-3,4-dichloropyridazine 1-oxide and 4-amino-3,5-dichloropyridazine 1-oxide into 3,4,5-trichloropyridazine 1-oxide, and also 5-aminopyridazine 1-oxide into



5-chloropyridazine 1-oxide. Sako (53) also converted 4-amino-3,6-dimethylpyridazine 1-oxide into 4-chloro-3,6-dimethylpyridazine 1-oxide by treatment with sodium nitrite and hydrochloric acid.

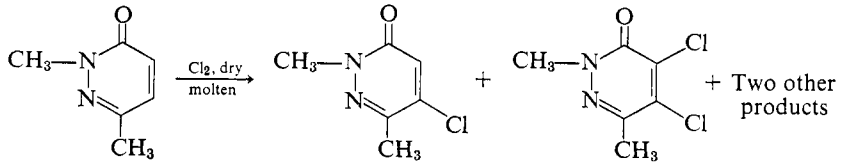
E. Other Methods of Preparing Chloropyridazines

Linholter, Rosenørn, and Vincents (68) devised an analytical oxidation procedure for hydrazinopyridazines (**23**) involving the use of sodium hypochlorite as the oxidant. The procedure probably involves an unstable diazonium intermediate. The reaction of this intermediate with the anions of the solution can be used for preparation of chloropyridazines (**24**) in good



yield. When 5 *N* sulfuric acid is used instead of hydrochloric acid, the corresponding hydroxy derivative is obtained. Methyl groups and halogen atoms on the ring do not interfere with this reaction.

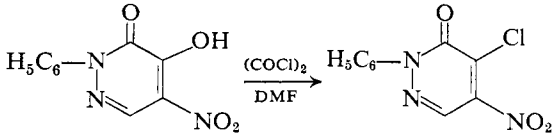
Homer, Gregory, and Wiggins (69), by chlorination of molten 1,3-dimethyl-6(1*H*)pyridazinone (**25**), introduced chlorine atoms at the unsubstituted carbon atoms remaining in the pyridazinone nucleus. Meyer (70) originally described this work claiming 5-chloro-1,3-dimethyl-6(1*H*)pyridazinone and an unknown dichloro derivative. Homer showed this compound to be the 4-chloro derivative (**26**) and also isolated and identified 4,5-dichloro-1,3-dimethyl-6(1*H*)pyridazinone (**27**) and two additional chlorine-containing compounds from this reaction.



25 **26** **27**

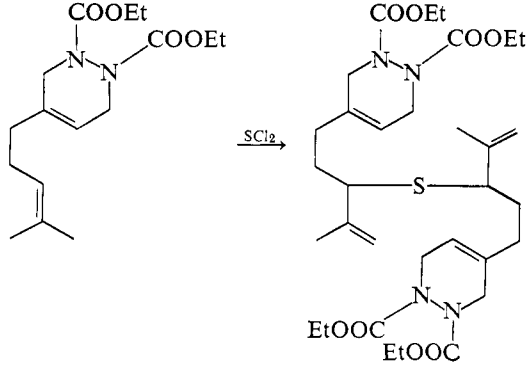
Bublitz (70a) has reported the direct chlorination (dry chlorine bubbled through the stirred melt) of 3,6-dichloropyridazine to give the 3,4,6-trichloro derivative with only a trace of the tetrachloro compound being obtained.

Dury (49) replaced the hydroxyl group of 5-hydroxy-4-nitro-1-phenyl-6(1*H*)pyridazinone (**28**) with chlorine (**29**) by the action of oxalyl chloride in dimethyl formamide. This chlorine atom is strongly activated and can easily undergo further reactions.



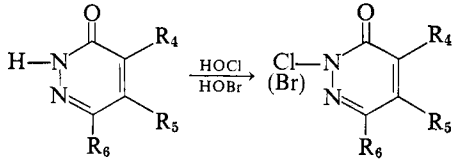
28 **29**

Sasaki (70b) described the reaction of sulfur dichloride with certain cyclic-acyclic 1,5-dienes (**29a** and **b**).



29a **29b**

Dury (49) reported the formation of *N*-halogenopyridazinones (**31**) by treating pyridazinones containing a hydrogen atom (**30**) on the 1-nitrogen atom with hypohalites. Either chlorine or bromine can thus be introduced. The products are surprisingly stable, especially when pure. Other ring substituents are noted in the equation.



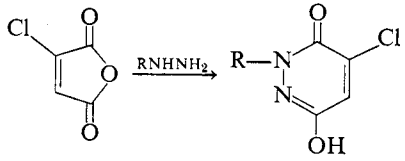
30 **31**

R_6 = H, *O*-alkyl, C_6H_5; R_5 = halogen; R_4 = OR, H

F. Ring Closure of Chlorine-Containing Precursors

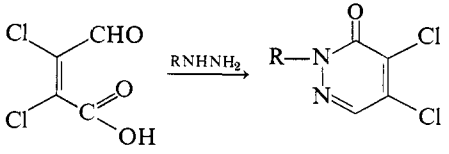
1. *Hydrazine or Substituted Hydrazine*

The action of hydrazine (71–74) and substituted (methyl (75, 76), phenyl (27)) hydrazines on chloromaleic anhydride (**32**) has been used by many investigators to prepare the corresponding 5-chloro-3-hydroxy-1-substituted 6(1*H*)pyridazinones (**33**).



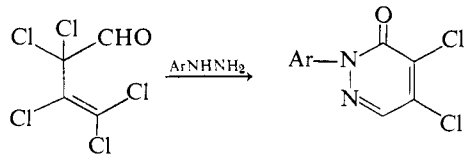
32 **33**

The use of hydrazine (49, 77, 78) and substituted hydrazines (49, 78–80) on mucochloric acid (**34**) provides a convenient means of preparing 4,5-dichloro-1-substituted 6(1*H*)pyridazinones (**35**).



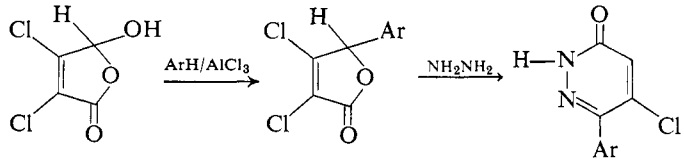
34 **35**

Roedig and Wenzel (80a) prepared several 1-aryl-4,5-dichloro-6(1*H*)-pyridazinones (**35b**) by the action of arylhydrazines on perchlorovinylacetaldehyde (**35a**). These compounds were obtained under mild conditions and in good yields.



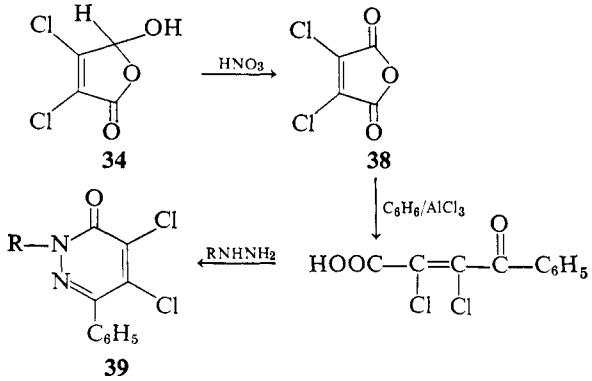
35a **35b**

Dury (49) prepared several halogenated pyridazinones from mucochloric acid (**34**) by Friedel–Crafts alkylation with aryl and substituted aryl groups leading to γ-aryldichlorocrotonolactones (**36**). These compounds in turn react in a complex manner with hydrazine hydrate, eliminating one atom of chlorine to give high yields of 3-aryl-4-chloro-6(1*H*)pyridazinones (**37**).



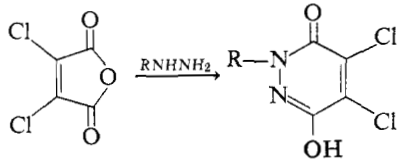
34 **36** **37**

Mucochloric acid can also be oxidized to dichloromaleic anhydride (**38**) with nitric acid (81). Friedel–Crafts acylation of benzene with dichloro maleic acid or its anhydride yields, after treatment with hydrazine or substituted hydrazines, 4,5-dichloro-3-phenyl-1-substituted-6(1*H*)pyridazinones (49) (**39**).



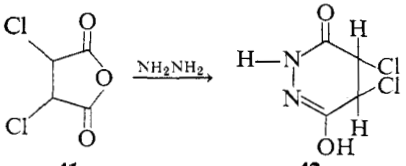
34 **38** **39**

The action of hydrazine or substituted hydrazines on dichloromaleic anhydride (**38**) has been widely used to prepare 4,5-dichloro-3-hydroxy-1-substituted 6(1*H*)pyridazinones (49, 82, 83) (**40**).



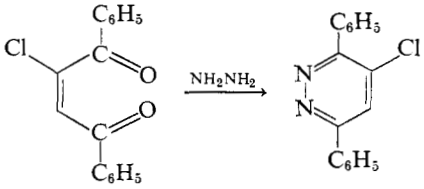
38 **40**

Ligett, Closson, and Wolf (84) prepared 4,5-dichloro-4,5-dihydro-3-hydroxy-6(1*H*)pyridazinone (**42**) by the action of hydrazine on 2,3-dichloro-succinic anhydride (**41**).



41 **42**

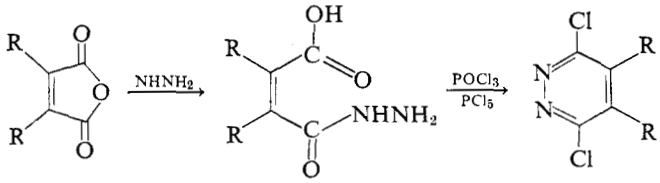
Chloro diketones have been cyclized with hydrazine to prepare the corresponding pyridazines. Ajello, Sprio, and Vaccaro (85) treated 2-chloro-1,4-diphenyl-2-butene-1,4-dione (**43**) with hydrazine to obtain 4-chloro-3,6-diphenylpyridazine (**44**).



43 **44**

2. *Novel Ring Closures*

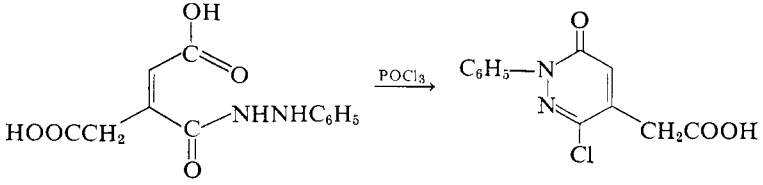
Horning and Amstutz (86) allowed 2,3-dialkyl maleic anhydride (**45**) to react with hydrazine, obtaining a monohydrazide (**46**). This in turn was



45 **46** **47**

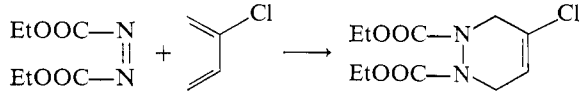
cyclized with phosphorus oxychloride and phosphorus pentachloride and both hydroxyl groups converted to chlorine atoms in a single step (**47**).

In a similar way Krbavčič and Tišler (87) cyclized the monophenylhydrazide of citraconic acid (**48**) with phosphorus oxychloride to form the 3-chloro-1-phenyl-6(1*H*)pyridazinonyl-4-acetic acid (**49**).



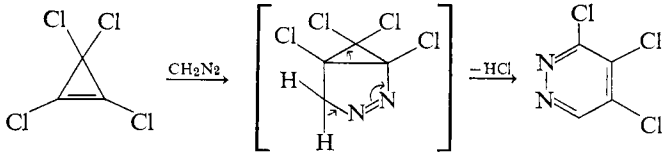
48 **49**

Snyder and Michels (88), as examples of 1,4-cycloaddition reactions, used 2-chloro-1,3-butadiene (chloroprene) and diethyl azodicarboxylate to prepare diethyl 4-chloro-2,3,5,6-tetrahydropyridazine-1,2-dicarboxylate (**50**).



50

Cohen (89) has reported a novel synthesis of 3,4,5-trichloropyridazine (**51**) in 51 % yield from the reaction of tetrachlorocyclopropene and diazomethane, proposing the following intermediate.



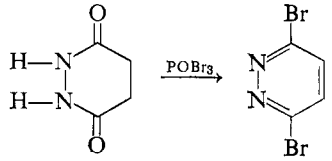
51

II. The Preparation of Bromopyridazines

A. Phosphorus Oxybromide on Hydroxypyridazines

As in the preparation of chloropyridazines with phosphorus oxychloride, the use of phosphorus oxybromide on hydroxypyridazines has proved to be an effective method of introducing a bromine atom on the ring. The 3-bromo (10, 90), 3,6-dibromo (91, 92), and 3,6-dibromo-4-methyl (68) derivatives have readily been prepared by this method. Pedrali and Mantegani (93) used this procedure on 3,6-dioxohexahydropyridazine (**52**) where

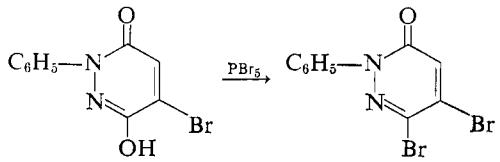
aromatization of the ring occurs in addition to replacement of the hydroxyl group with a bromine atom (**53**).



52 **53**

B. Phosphorus Oxybromide and/or Phosphorus Pentabromide on Pyridazines and Pyridazinones

Rogers and English (94) found either phosphorus oxybromide or phosphorus pentabromide to be satisfactory in the preparation of 3,6-dibromopyridazine from the dihydroxy derivative. Grundmann (10) used phosphorus pentabromide to prepare 3-bromo-6-methylpyridazine from 3-methyl-6(1*H*)pyridazinone. Druey and co-workers (21), with phosphorus pentabromide, prepared 3-bromo-1-phenyl-6(1*H*)pyridazinone from the corresponding hydroxy derivative and 3,4-dibromo-1-phenyl-6(1*H*)pyridazinone (**55**) from 4-bromo-3-hydroxy-1-phenyl-6(1*H*)pyridazinone (**54**).

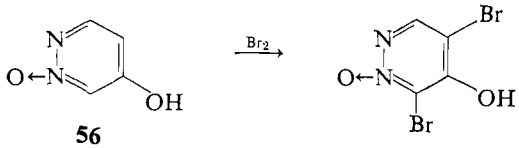


54 **55**

C. Addition of Active Bromo Compounds to Pyridazine *N*-Oxides

Okusa and Osada (95) demonstrated direct substitution of bromine into all unsubstituted ring carbons alpha and gamma to the *N*-oxide function. Elemental bromine is used, and no loss of the *N*-oxide function occurs. 5-Hydroxypyridazine 1-oxide (**56**) and 5-hydroxy-6-(1-piperidino)methylpyridazine 1-oxide (**57**) have been brominated by this procedure.

Similarly, Igeta and co-workers (95a) brominated 4-methyl-3-hydroxypyridazine 1-oxide to obtain the 6- and 4-bromo derivatives, respectively. Kamiya (60a) prepared 3-bromo-6(1*H*)pyridazinone from 3-hydroxypyridazine 1-oxide by the action of paraformaldehyde and hydrogen bromide.



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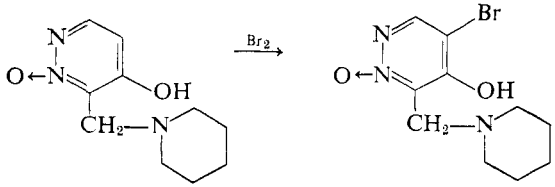
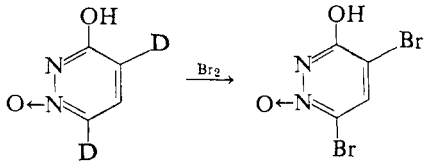


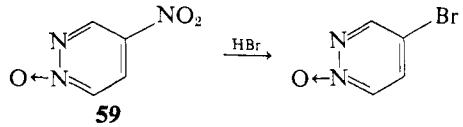
57

Igeta and co-workers (96) replaced the deuterio groups from 4,6-bis-deuterio-3-hydroxypyridazine 1-oxide (**58**) by the action of bromine.



58

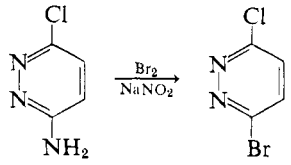
Sako (67) replaced the nitro group of 4-nitropyridazine 1-oxide (**59**) by reaction with hydrobromic acid.



59

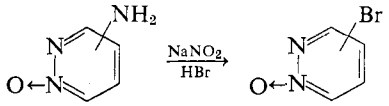
D. Diazotization Followed by Replacement with Bromine

Linholter, Rosenørn, and Vincents (68) converted 6-amino-3-chloropyridazine (**60**) into 6-bromo-3-chloropyridazine (**61**) by the action of bromine and sodium nitrite.



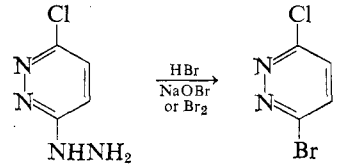
60 61

Sako (67) diazotized and replaced the 3-, 4-, 5-, and 6-aminopyridazine 1-oxides by the action of sodium nitrite and hydrobromic acid followed by the Gatterman reaction.



E. Oxidation of Hydrazinopyridazines

Linholter, Rosenørn, and Vincents (68) oxidized the hydrazino group of 3-chloro-6-hydrazinopyridazine (**23**) by reaction with hydrobromic acid and sodium hypobromite or bromine to yield the 3-chloro-6-bromopyridazine (**61**). The 6-bromo-3-chloro-4- and -5-methylpyridazines were also prepared by this method.

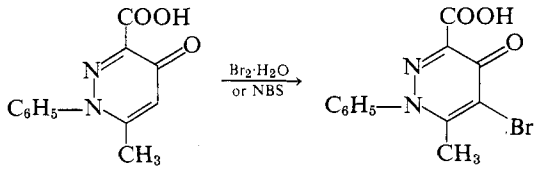


23 **61**

Yoneda, Ohtaka, and Nitta (97) oxidized 3,6-dichloro-4-hydrazinopyridazine with hydrobromic acid and sodium hypobromite to give 4-bromo-3,6-dichloropyridazine.

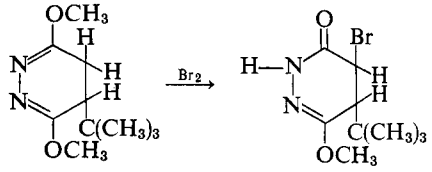
F. Other Methods of Preparing Bromopyridazines

Staehelin, Eichenberger, and Druey (98) introduced bromine directly into 6-methyl-1-phenyl-4(1*H*)pyridazinone-3-carboxylic acid (**62**) by means of bromine water or *N*-bromosuccinimide to give the 5-bromo derivative (**63**).



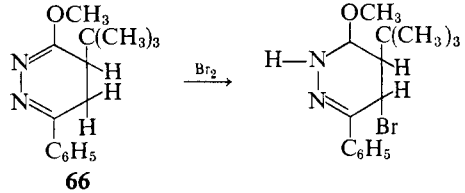
62 **63**

Christensen and Crossland (99) added bromine directly to 5-*t*-butyl-4,5-dihydro-3,6-dimethoxypyridazine (**64**). Bromine is substituted in the 5-position and the methoxyl group is lost from the 6-position to form 5-bromo-4-*t*-butyl-4,5-dihydro-3-methoxy-6(1*H*)pyridazinone (**65**). Crossland and



64 **65**

Rasmussen (100) brominated both the 4- (**66**) and 5-*t*-butyl-4,5-dihydro-3-methoxy-6-phenylpyridazines (**67**), obtaining the 5- and 4-bromo derivatives without cleavage of the 3-methoxy group.



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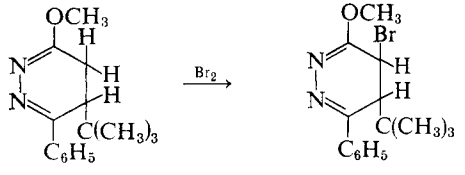
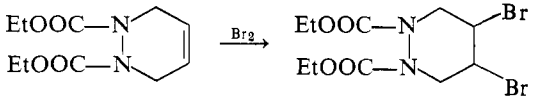


67

G. Addition of Bromine to Double Bonds of Pyridazines and Pyridazinones

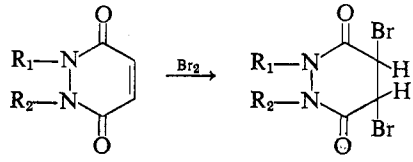
Rink, Mehta, and Grabowski (101) added bromine to diethyl 1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate (**68**), forming the diethyl 4,5-dibromohexahydropyridazine-1,2-dicarboxylate (**69**). Similarly, Gillis and



68 **96**

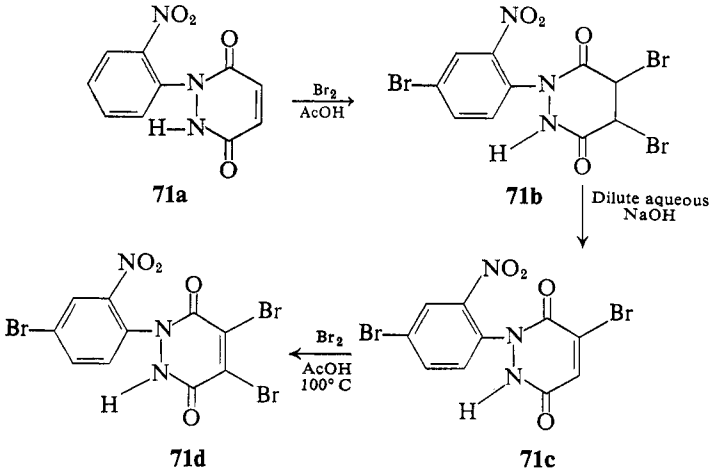
Beck (102) added bromine to diethyl 4,5-dimethyl-1,2,3-6-tetrahydropyridazine-1,2-dicarboxylate to obtain the 4,5-dibromo derivative.

The addition of bromine to 1,2-disubstituted pyridazine-3,6-diones (**70**) has been carried out by many investigators (26, 103–106, 106a, b). The product is a 4,5-dibromo-4,5-dihydro-1,2-disubstituted pyridazine-3,6-dione (**71**).



70 **71**

Baloniak (106c) also reported the addition and substitution of bromine to 2-(*o*-nitrophenyl)pyridazine-3,6-dione (**71a**) to give 2-(4-bromo-2-nitrophenyl)-4,5-dibromo-4,5-dihydropyridazine-3,6-dione (**71b**). Upon treatment with dilute aqueous sodium hydroxide, HBr was eliminated, giving 2-(4-bromo-2-nitrophenyl)-4-bromopyridazine-3,6-dione (**71c**). Upon further treatment with bromine in acetic acid at 100° C, 2-(4-bromo-2-nitrophenyl)-4,5-dibromopyridazine-3,6-dione (**71d**) was obtained.

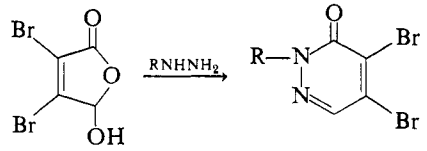


71a **71b** **71c** **71d**

Umio, Kazuo, and Kishimoto (106d) treated 1-(3-dimethylaminopropyl)-3-phenyl-6(1*H*)pyridazinone with bromine in chloroform to obtain the 5-bromo derivative.

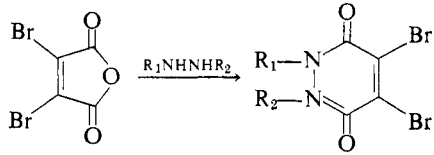
H. Ring Closure of Bromine-Containing Precursors with Hydrazine or Substituted Hydrazines

At the turn of the century, Bistrycki and co-workers (107–108) prepared 4,5-dibromo-6(1*H*)pyridazinone and its 1-phenyl derivative by treating mucobromic acid with hydrazine hydrate or phenylhydrazine, respectively. Rapos (83), using a mixed (bromine and chlorine) mucohalic acid and phenylhydrazine, prepared 4-bromo-5-chloro-1-phenyl-6(1*H*)pyridazinone. Similarly, Hensel et al. (79) allowed mucobromic acid (**72**) to react with β-cyanoethylhydrazine to prepare the 1-(β-carboxyethyl) derivative (**73**).



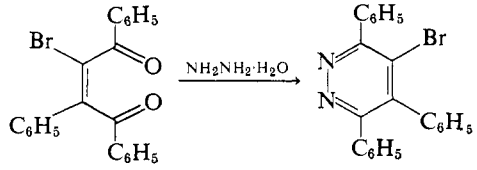
72 **73**

4,5-Dibromopyridazine-3,6-diones (109) and their 1,2-disubstituted derivatives (82) (**75**) have been prepared by the action of dibromomaleic anhydride (**74**) and hydrazine or substituted hydrazines, respectively.



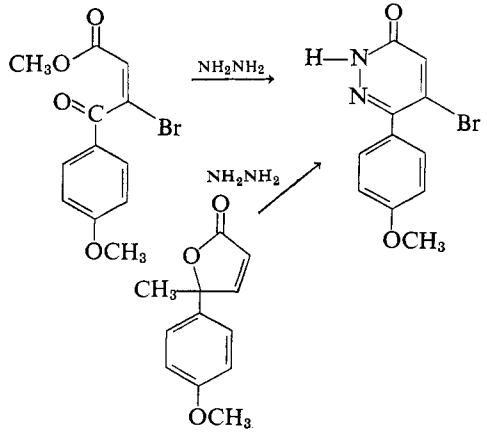
74 **75**

As an example of the action of hydrazine on a diketone, Sprio and Madonia (110) cyclized 2-bromo-1,3,4-triphenyl-2-butene-1,4-dione (**76**) with hydrazine hydrate to obtain 4-bromo-3,5,6-triphenylpyridazine (**77**).



76 **77**

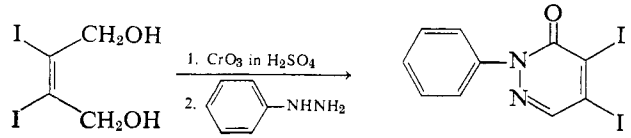
γ-Keto esters and lactones containing bromine have also been cyclized. Zekan and Semonsky (111) have reported the following conversions.



III. The Preparation of Iodopyridazines

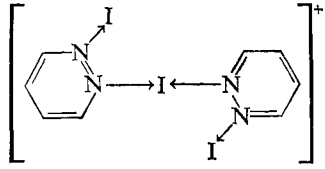
Only a few methods of introducing iodine into the pyridazine ring are known. Horning and Amstutz (86) reported the formation of iodopyridazines as by-products in the reduction of substituted chloropyridazines with red phosphorus and hydriodic acid. Coad and co-workers (3) prepared iodopyridazine from chloro or bromo pyridazine precursors by three different procedures. The most satisfactory procedure involved the use of sodium iodide in anhydrous acetone with a small amount of hydriodic acid as catalyst. Kano and Ogata (112, 113) reported the preparation of 3-iodo-6-methylpyridazine by treating both 3-bromo and 3-chloro precursors with hydriodic acid. Basu and Rose (34) reported the formation of 3-iodo-1,6-dimethylpyridazinium iodide as a result of quaternization of 3-chloro-6-methylpyridazine with methyl iodide. Lund and Lunde (114), from their extensive study of quaternization with methyl iodide, also reported the replacement of halogen from carbon adjacent to nitrogen with iodine.

Reicheneder and Fischer (114a) prepared 4,5-diiodo-1-phenyl-6(1*H*)-pyridazinone (**77b**) by the oxidation of 2,3-diiodo-2-butene-1,4-diol (**77a**) with CrO_3 in sulfuric acid followed by cyclization with phenylhydrazine.



77a **77b**

Hoare and Pratt (114b) found that aqueous solutions of potassium iodide, with carbon tetrachloride, benzene, or acetone solutions of pyridazine and iodine, react to form a black solid containing 1–1.4 I_2/1-pyridazine. Excess iodine could be accommodated within the lattice by the conversion of some I^- to I_3^-. Dratler and Laszlo (114c), in studying the nature of this pyridazine–

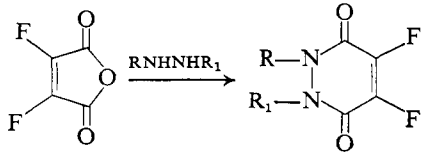


iodine complex through temperature-dependent pmr spectra, felt that the pyridazine rings are involved in a much larger assembly than simply a complex consisting only of one pyridazine and one iodine molecule.

Hoppe and Keene (114d) treated pyridazine with various ratios of iodine in carbon tetrachloride at room temperature and trituration with methanol to give 3 $(C_4H_4N_2)\cdot 2\ I_2$ (mp 240–242° C), which was stable to storage but dissociated in dimethylformamide and tetrahydrofuran. $C_4H_4N_2\cdot$ ICl (mp 54–55° C) and 2 $(C_4H_4N_2)\cdot Br_2$ (mp 75–77° C) were similarly prepared. They were unstable, and $C_4H_4N_2\cdot 2$ ICl decomposed to 3 $(C_4H_4N_2)\cdot 2\ I_2$ at room temperature. The stoichiometry of 3 $(C_4H_4N_2)\cdot 2\ I_2$ suggests a 1:1 mixture of $[(C_4H_4N_2)_2I]^+\ I^-$ and a cation $(C_4H_4N_2I)^+\ I^-$.

IV. The Preparation of Fluoropyridazines

Chambers, McBride, and Musgrave (50, 51), by the use of elevated temperatures and an autoclave, prepared 3,4,5,6-tetrafluoropyridazine from the reaction of potassium fluoride on the tetrachloro derivative. Kealy (115) reported the preparation of 4,5-difluoro-3,6-pyridazinedione from the reaction of hydrazine on difluoromaleic anhydride (**78**). Several similar examples (82) of 1,2-disubstituted-4,5-difluoropyridazine-3,6-diones (**79**) have also been reported.



78 **79**

V. The Properties of Halopyridazines

All nine of the possible chloropyridazines have been synthesized. Table I lists the melting points (all are low-melting solids, melting point ($<90°$ C) and literature references for their preparation.

Tables for chloro- bromo-, iodo-, and fluoropyridazines can be found at the end of the chapter.

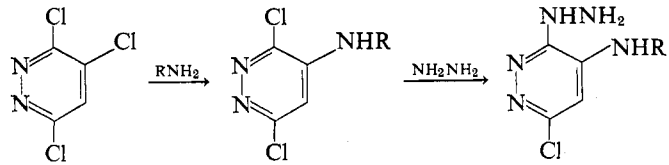
A. Reactivity and Reaction Rates

Chan and Miller (122) reported the reactivity of 3-chloropyridazine and 4-chloropyridazine to be nearly the same as measured by their reactivity with *p*-nitrophenoxide ion in methanol.

The chlorine atoms of 3,6-dichloropyridazine do not appear to be of equal reactivity. One chlorine atom is easily hydrolyzed if the necessary precautions are not observed during work-up of the product (3). This is also readily apparent from the many monosubstituted products (amino, substituted amino, hydrazino) obtained from reaction with 3,6-dichloropyridazine.

The 4- or 5-chlorine atom is replaced when 3,4,5-trichloropyridazine is allowed to react with ammonia (18, 19). If the resultant amino products are treated with hydrazine, attack takes place at the 3-position.

The 4-position is most active in 3,4,6-trichloropyridazine (**80**), as shown by the preference for substitution at this position by many reagents (ammonia, (18, 57, 123) methylamine (124), hydrazine (97, 125), sodium ethoxide (125), and alkali thiocyanate (126)). The treatment of 4-amino(methylamino)-3,6-dichloropyridazine (**81**) with hydrazine results in an attack upon the 3-chlorine atom to yield 4-amino(methylamino)-6-chloro-3-hydrazinopyridazine (19, 124) (**82**).



80 **81** **82**

Chambers, McBride, and Musgrave (51) showed the sequence of replacement of fluorine from 3,4,5,6-tetrafluoropyridazine by nucleophilic reagents to be 4, 5, (3 and 6).

Hill and Krause (127) derived kinetic data and thermodynamic parameters for the reaction of methoxide ion with 3-chloro-6-substituted pyridazines

(H, CH_3, OCH_3, SCH_3, SO_3^-, $SOCH_3$, COO^-, $COOCH_3$, Cl). Barlin and Brown (128), in a kinetic study of reactions of 3-methylsulfonyl and 3-chloropyridazines with methoxide ion, found the methylsulfonyl group to react ~90 times faster.

Sako (129–131) extensively studied the reactivity of 3-, 4-, 5-, and 6-chloropyridazine 1-oxides and other halopyridazine 1-oxides with sodium alkoxide, ethylamine, and piperidine. The rate order of position reactivity was $5 > 3 > 6 > 4$.

Duffin and Kendall (132) studied the rate and position of quaternization of substituted pyridazines. They found that methyl groups adjacent to nitrogen activated the ring, whereas methylthio groups similarly situated deactivated the ring. The quaternization of 6-chloro-3-methylpyridazine with methyl iodide produced the 6-chloro-2,3-dimethylpyridazinium iodide. Halverson and Hirt (133) earlier reported the preparation of 6-chloro-2-ethyl-3-methylpyridazinium iodide by the treatment of the 6-chloro-3-methyl derivative with ethyl iodide.

B. Infrared Spectra

Salisbury et al. (134) studied the ir absorption spectra of a large number of 3-halo- (chloro-, bromo-, iodo-) 6-alkoxypyridazines and reported pyridazine ring bands as occurring at 1600–1540, 1325–1295, and 1065–935 cm^{-1}. The change from chloro through bromo to iodo substituents shows a shift of about 10 cm^{-1} (toward lower energy) in the CH stretch frequency for each change. Other investigators (135–139) have also reported (ir) spectra for halopyridazines.

C. Ultraviolet Spectra

Ultraviolet (uv) absorption spectra of halopyridazine and halopyridazinones have been reported by many investigators. Eichenberger et al. (140) have given spectral data for several chloro (and chloro-substituted) pyridazines and halo (chloro and bromo) 6-(1*H*)pyridazinones. Levisalles (9) and Majee (141) have reported uv spectra for several chloro and alkylchloro pyridazines. Horning and Amstutz (142) have listed uv spectra of chloro and iodo pyridazines. Fujisaka et al. (139) reported uv data for several 3-chloro-6-amino and substituted aminopyridazines. Kuraishi (143) measured the uv absorption spectra of some 4-substituted (H, CH_3, Cl, OC_2H_5, NH_2, $NHNH_2$) 3,6-dichloropyridazines. Halverson and Hirt (133) compared the near-uv spectra of pyridazine and the 3-chloro-6-methyl and 3,6-dichloro derivatives. Other investigators (135, 144–146) have also reported uv spectra.

D. Nuclear Magnetic Resonance Spectra

Tori, Ogata, and Kano (147) applied nuclear magnetic resonance (nmr) in the determination of the position of the *N*-oxide group in pyridazine *N*-oxides. Several chloropyridazines containing other substituents as well have been investigated. Kawazoe and Natsume (148) prepared nmr spectra of pyridazines and their *N*-oxides. Declerck et al. (149) and Tori and Ogata (150) have reported nmr studies on chloropyridazines and pyridazines containing other groups (CH_3, OR) in addition to chlorine. Substituted pyridazines have very simple nmr spectra. Tori (150) found very little effect on ring proton shifts from methyl groups or chlorine atoms. Maki et al. (151) and Scapini et al. (151a) recorded the nmr spectra of several 1-substituted chloro-6(1*H*)pyridazinones. Price and co-workers (152), by the use of nmr, studied conformational changes in tetrahydro and hexahydrobromopyridazine derivatives. Ogden (152a) carried out nmr studies on 1,2-dimethyl-3,4,5,6-tetrafluoropyridazine.

Daniels and Rosman (153) used proton magnetic resonance (pmr) to determine the conformation of 1,2,3,6-tetrahydro-4-chloropyridazine in a study of the stereochemistry of the Diels–Alder reaction of heterodienophiles.

Stidham and Farrell (154), by the use of chlorine-35, measured the nuclear quadrupole resonance (nqr) of 3,6-dichloro- and 3,4,5,6-tetrachloropyridazine.

E. Other Properties

Weininger and Thornton (155) found in the mass spectral decomposition of pyridazines the probable formation of cyclobutadiene-type cations. After the electron impact molecular ions of 3,6-dichloropyridazine lose nitrogen to form $C_4H_2Cl_2^+$. Bowie and co-workers (156) have also reported and discussed the mass spectra of chloro-substituted pyridazines. Heiss and Zeller (156a) carried out mass spectrometric studies on 4-amino-5-chloro-6(1*H*)pyridazinone.

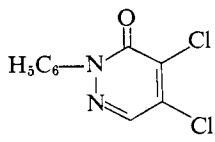
Cohen, Baba, and Goodman (157, 158) have discussed quantum yields, fluorescence, phosphorescence, and intersystem crossing of 3,6-dichloropyridazine.

Favini and Simonetta (159) noted electronic transitions (ΔE) of 3-chloropyridazine.

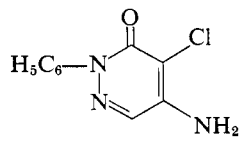
Dipole moments have been determined for chloropyridazine (160), substituted chloropyridazines (161), and *N*-oxide derivatives of substituted chloropyridazines (162).

Because 4-amino-5-chloro-1-phenyl-6(1*H*)pyridazinone (PCA) (**20**) is an

effective herbicide for sugar beets, it became necessary to find analytical procedures for the separation of PCA from another isomer, 5-amino-4-chloro-1-phenyl-6(1*H*)pyridazinone (iso-PCA) (**82**), and from the starting material, 4,5-dichloro-1-phenyl-6(1*H*)pyridazinone (PCC) (**83**). Ďulák,



PCC
83



PCA
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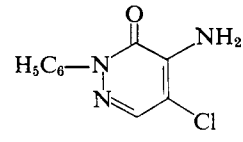
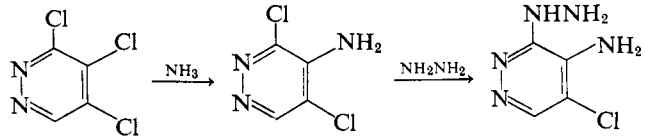


iso-PCA
84

Kováč, and Rapoš (163) and Gruca et al. (164) both developed techniques for separation of the mixture by thin-layer chromatography. Ďulák used spectrophotometric evaluation, while Gruca used polarography. Missala and Czulinska (165) did not separate PCA from iso-PCA but have developed a method for their analysis (combined) from other reaction materials. This involves diazotization of the amino group, splitting off the adjacent chlorine atom which is determined argentometrically.

VI. Reactions of Halopyridazines

Pyridazines with halogen substituents undergo a wide variety of reactions. Most of the reactions have been carried out with chloropyridazines because they are easier to make. Because of the difference in reactivity of the various chlorine atoms in pyridazines containing two or more chlorine atoms, derivatives can be prepared singly and with different reagents. For example, 3,4,5-trichloropyridazine (**51**) can be treated with ammonia to obtain the 4-amino-3,5-dichloropyridazine (**85**), which after treatment with hydrazine yields 4-amino-5-chloro-3-hydrazinopyridazine (19) (**86**).



51 **85** **86**

A. Removal of Halogens

The complete removal of halogen from pyridazines and pyridazinones has been accomplished primarily by reduction with hydrogen in the presence of either palladium on carbon (or some other substrate) or Raney nickel. Older

methods of reduction involving red phosphorus and hydriodic acid (65, 118) have largely been abandoned. Mosby (166), while investigating the use of hydrazine and palladium on charcoal for the reduction of nitro groups, found debromination took place as well as reduction. In attempts to expand the scope of this reaction, the dechlorination of 4,5-dichloro-6(1*H*)pyridazinone and its 1-phenyl derivative were undertaken. The reaction yielded only uncharacterized oily products.

1. *Hydrogen with Palladium on Charcoal*

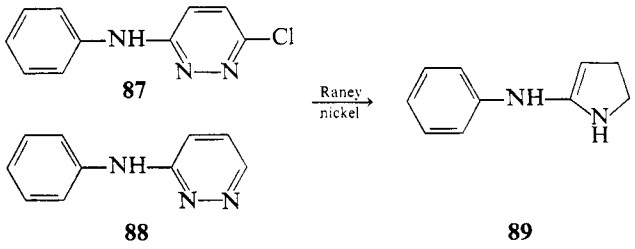
The presence of other functional groups on the pyridazine or pyridazinone ring besides halogen does not hinder the course of the dehalogenation reaction using palladium on charcoal. Several examples containing amino (18, 20, 57, 91, 121, 167, 168), substituted amino (57, 97, 169, 170), acetamino (171), hydrazino (125, 172), alkyl (9, 71), aryl (54), alkoxyl (125, 173–176), and carboxyl (177) are given in the literature. Pyridazine *N*-oxides substituted with amino (67, 178), methyl (168, 179), methoxy (61, 180–182), and carboxyl (62) groups also did not interfere with the dehalogenation by palladium on charcoal. It appears that the reaction can be stopped after dehalogenation but before reduction of the *N*-oxide function. The reduction of chloropyridazine *N*-oxides containing nitro groups involves the removal of chlorine, reduction of the nitro to amino (52, 183) and, if allowed to go to completion, removal of the *N*-oxide function (52, 184). Ogata (62) reported the reduction of an aldoxime to aminomethyl and removal of *N*-oxide and chlorine from the pyridazine ring. Mori (167) observed, during the dechlorination of both 4- and 5-carboxyl-6-chloro-3-hydroxypyridazine (palladium on charcoal using methanol as a solvent), that esterification of the carboxyl occurred as well. Igeta (185) obtained 6(1*H*)pyridazinone from the dechlorination reaction of 3-chloro-6-benzyloxypyridazine, indicating cleavage of the benzyl ether.

Hydrogen with palladium on charcoal has been used to prepare pyridazine from both the 3-chloro (2) and 3,6-dichloro derivatives (120, 186). Similar conditions have also been used to prepare 6(1*H*)pyridazinone from the 3-chloro (41) and 3,4-dichloro derivatives (125). The same conditions have produced 1-phenyl-6(1*H*)pyridazinone from the 3-chloro derivative.

2. *Hydrogen with Raney Nickel*

Hydrogen with Raney nickel is also used to dehalogenate pyridazines. Dehalogenation under these conditions has been satisfactory in the presence

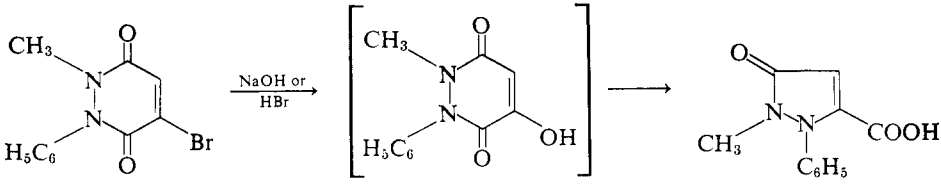
of the following functional groups: amino (49, 124), substituted amino (27, 187), methyl (187), alkoxyl (49, 176, 187), and carboxyl (1, 188). Krobevcic (189), on reductive dechlorination of 3-chloropyridazine-6-carboxylic acid with Raney nickel, found the carboxyl group had also undergone reduction to the hydroxymethyl derivative. Yoneda and co-workers (97) produced reductive ring contractions to 2-anilino-2-pyrrolene (**89**) when 3-anilino-6-chloropyridazine (**87**) or 3-anilinopyridazine (**88**) was refluxed with Raney nickel. A proposed intermediate is given.



87 **88** **89**

3. *Other Procedures*

The dehydrobromination of dihydropyridazines has been accomplished with methoxide ion (99, 100). Maki and Obata (26) debrominated 5-bromo-2-methyl-1-phenylpyridazine-3,6-dione (**90**) with either 10% sodium hydroxide or hydrobromic acid, causing ring contraction to 1-phenyl-2-methyl-4-pyrazol-3-one-5-carboxylic acid (**91**). Druey, Meier, and Staehelin (105, 106)



90 **91**

dehydrobrominated 4,5-dibromo-2-methyl-1-phenylpyridazine-3,6-dione by two methods. The first used pyridine in chloroform to obtain the 5-bromo (or chloro when the starting material was the 4,5-dichloro derivative) derivative. If the pyridine is replaced by morpholine, both dehydrobromination and substitution occur, producing the 5-morpholino derivative. Rink and co-workers (101) dehydrohalogenated diethyl 4,5-dibromohexahydropyridazine-1,2-dicarboxylate with the aid of potassium hydroxide to yield

both diethyl 1,2-dihydropyridazine-1,2-dicarboxylate and ethyl 1,2-dihydropyridazine-1-carboxylate.

DeLannoy, Gysen, and Nasielski-Hinkens (189a) described the Birch reduction (sodium in liquid ammonia) of 3-amino and 3-mercapto-6-chloropyridazines to give the corresponding dehalogenated compounds in good yields.

Igeta et al. (189b) prepared 3,3′-bipyridazine by the reaction of hydrazine hydrate in a basic mixture of $Pd/CaCO_3$. Equimolar mixtures of two 3-chloropyridazines with different substituents gave four unsymmetrical 3,3′-bipyridazines. Various 3-chloropyridazine *N*-oxides were also subjected to this condensation to give the expected 3,3′-bipyridazine di-*N*-oxides in low yields.

B. Replacement of Halogen by Amino and/or Substituted Amino Groups

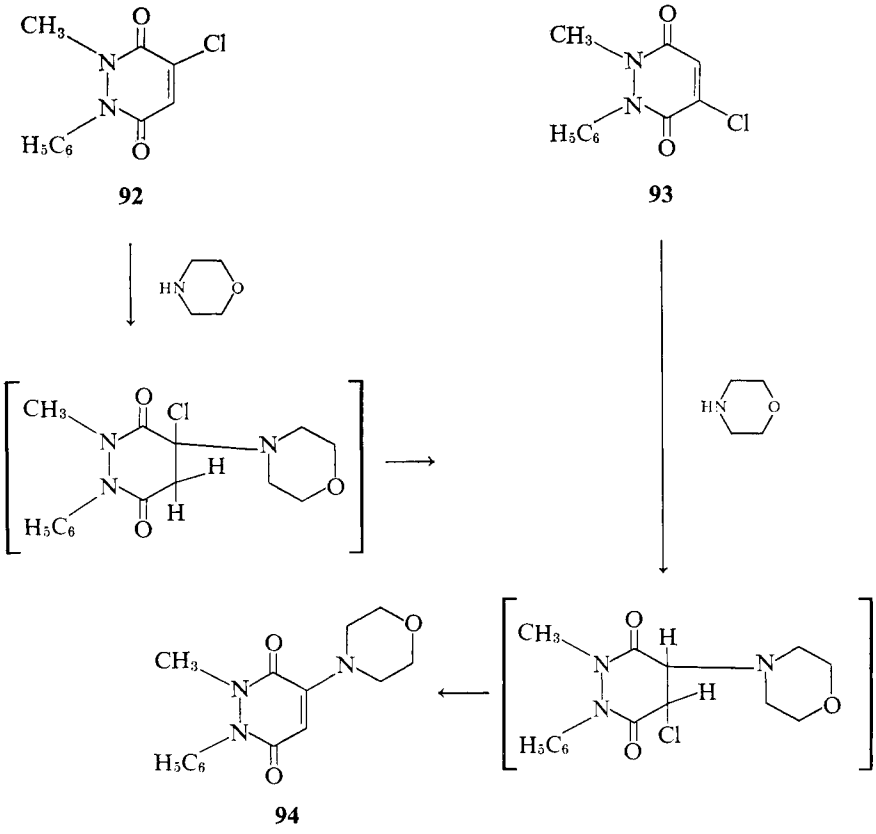
Examples of halogen (especially chlorine) being replaced by an amino or substituted amino group are legion.

1. *With One Halogen*

No particular problems arise during substitution. Although the majority of these reactions use a chloropyridazine or pyridazinone as starting material, monobromo compounds work equally as well. Examples of monoiodi- or monofluoropyridazines being converted into amino or substituted amino derivatives have not been found. Examples of *N*-substituted pyridazinones where N = methyl (25), phenyl (21, 38, 42), substituted phenyl (29, 43, 190), or cyclohexyl (25) have been reported. Druey, Meier, and Staehelin (191) found that when both 4- (**92**) and 5-halo-1-phenyl-2-methyl-3,6-dioxo-1,2,3,6-tetrahydropyridazines (**93**) react with morpholine only the 4-substituted product (**94**) is obtained. A possible mechanism follows (p. 249).

Pyridazine *N*-oxides containing halogen (192) have also been replaced by substituted amines.

Replacement of halogen by amino or substituted amino groups has also been accomplished with pyridazines containing the following substituents attached to carbon: methyl (4, 38, 42), phenyl (10, 13, 110), substituted phenyl (111), alkoxyl (193, 194), nitro (49), methylthio (195), methylsulfonyl (196), carboxyl (197), and carboxamido (197).

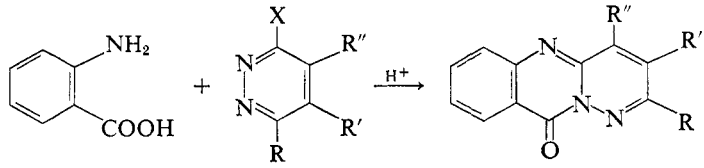


2. *With Two Halogens*

When dihalopyridazines or dihalopyridazinones are allowed to react with ammonia or primary or secondary amines, usually only one halo atom is replaced. The replacement of one halo atom serves to inactivate the other toward nucleophilic attack. The literature abounds with examples of monosubstitution occurring from dichloropyridazines. Dibromopyridazines have also been allowed to react with amines as well as a few examples of diiodopyridazines (198, 199). The reactions of amines with difluoro compounds have not been reported.

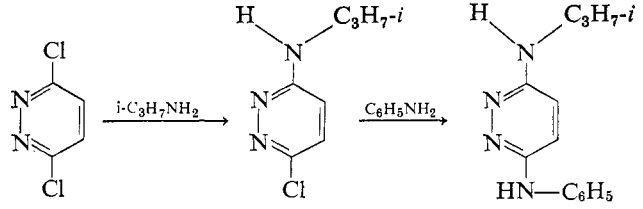
Beyer and Volcker (200), in reacting several 3,6-dihalopyridazines (including chloro, bromo, and iodo derivatives) or 3-halo-6-alkyl(aryl)pyridazine with anthranilic acid, found in addition to substitution of chloro with amino,

ring closure to form the 10*H*-pyridazino[3,2-*b*]quinazoline (**95**). Yanai and co-workers (201) observed similar results. The preparation of 3,6-diamino-



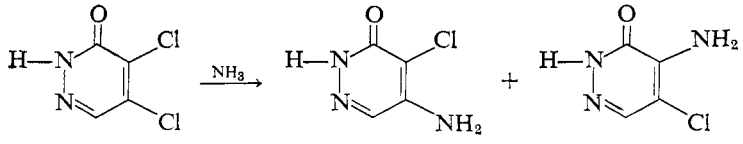
95

pyridazine from the 3,6-dichloro derivative has been reported (189, 202). It was necessary to use high temperatures, catalysts (copper bronze, copper salts), and an autoclave to effect the conversion. Secondary amines give 3,6-disubstituted pyridazines more readily. Examples of 3,6-bis- (lower dialkylamino (203, 204), piperidino (186), piperazino (205), pyrrolyl (188, 206)) pyridazines have been reported. A few primary amines (204, 207) have also given 3,6-bis-substitution products. Some investigators (208, 209) have made use of the lower reactivity of the second chlorine atom to prepare mixed amino derivatives. Usually, the lower-boiling amine is introduced first followed by reaction with the higher-boiling amine.

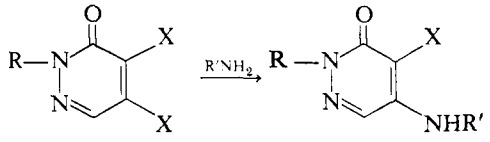


When 3,6-dichloro-4-methylpyridazine is treated with ammonia, two monosubstitution products are obtained, namely, the 3-amino-6-chloro-4-methyl- and the 6-amino-3-chloro-4-methylpyridazines (30, 167, 187).

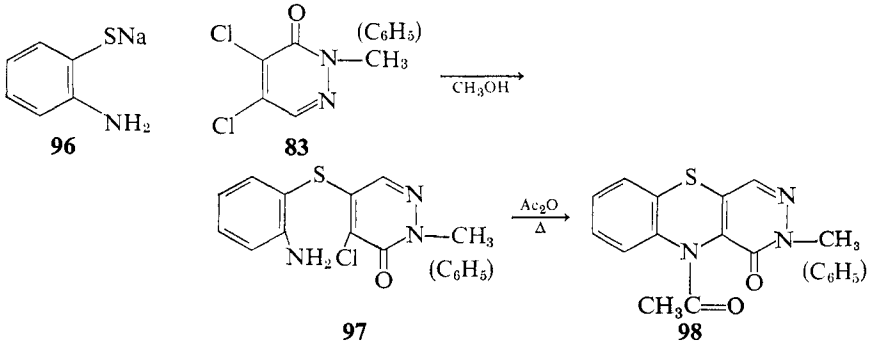
The reaction of 2-substituted (H, CH_3, C_6H_5) 4,5-dihalo- (Br, Cl) 6(*H*)-pyridazinones with ammonia or amines results exclusively in monosubstitution. Substitution of amino in either the 4- or 5-position of 4,5-dichlori-6(1*H*)pyridazinone has been observed (210), and Kuraishi (171) proved the position of the amino group. The treatment of 4,5-dichloro-1,3-dimethyl-6(1*H*)pyridazinone (75) and 4,5-dichloro-1-phenyl-6(1*H*)pyridazinone with



ammonia produces two monoamino-substituted isomers in each case. The reaction of amines (primary or secondary) with 2-substituted 4,5-dihalo-6(1*H*)pyridazinones results in monosubstitution in the 4-position (27, 211–

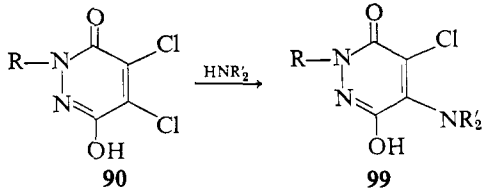


216). Druey, Meier, and Staehelin (217), upon reacting sodium 2-aminothiophenolate (**96**) with 4,5-dichloro-1-methyl(phenyl)-6(1*H*)pyridazinone (**83**), obtained 2-[2′-methyl(phenyl)-4′-chloro-3′-oxo-2′,3′-dihydropyridazinylthio]aniline (**97**) which upon heating with acetic anhydride (NaOH in dioxan for the 2-phenyl derivative) cyclized to 2-methyl(phenyl)-10-acetyl-1-oxo-1,2-dihydro-2,3-diazaphenothiazine (**98**). Yoneda (218) obtained similar



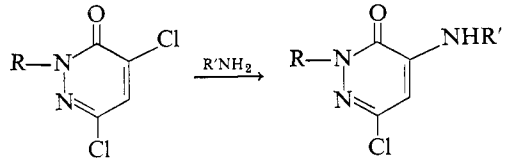
results starting with 4,5-dichloro-6(1*H*)pyridazinone. Scapini, Duro, and Pappalardo (219) and Cordorelli, Pappalardo, and Raspagliesi (219a) cyclized similar starting materials.

Dury (49) also has reported monosubstitution in the 5-position (**99**) when 4,5-dichloro-3-hydroxy-1-substituted-6(1*H*)pyridazinones (**90**) are allowed to react with amines.



When 3,5-dichloro-1-substituted (CH_3 (25, 75), C_6H_5 (25, 38, 220–222), substituted C_6H_5 (220), C_6H_{11} (25)) 6(1*H*)pyridazinones (**100**) are allowed to

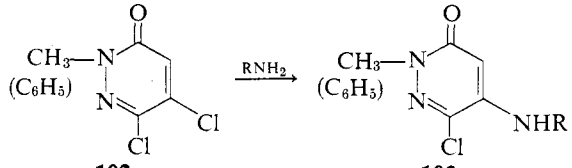
react with amines, monosubstitution in the 5-position (**101**) usually occurs. Druey et al. (38, 39) have reported the preparation of 3,5-bis(dimethyl-



100 **101**

amino)-1-phenyl-6(1*H*)pyridazinone using temperatures of 170–180° C for 60 hr.

Monosubstitution in the 4-position (**103**) is obtained from the reaction of 3,4-dichloro-1-methyl (25, 75) (phenyl) (83, 223) 6(1*H*)pyridazinone (**102**) with ammonia or amines. Druey et al. (224) reported the preparation of the

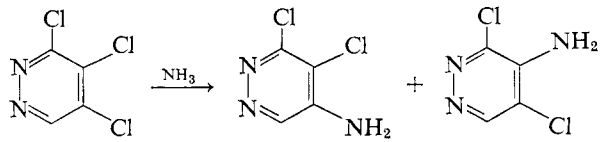


102 **103**

3,4-diamino derivative through the action of ammonium hydroxide with copper bronze at 150–160° C for 10 hr.

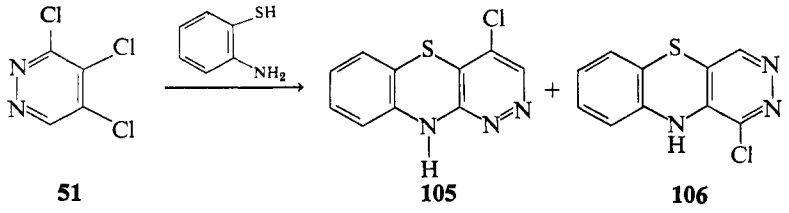
3. *With Three Halogens*

When 3,4,5-trichloropyridazine (**51**) is allowed to react with ammonia, two monoamino isomers are obtained (18, 19, 121). Kuraishi (19) showed these to be the 4- (**85**) and 5-amino (**104**) derivatives, as only 4-aminopyridazine was obtained from reductive dechlorination of the original mixture of



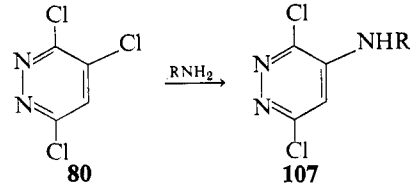
51 **104** **85**

isomers. Yoneda (225, 226) obtained both the 4-chloro-1,2-diazaphenothiazine (**105**) and 1-chloro-2,3-diazaphenothiazine (**106**) from the reaction of 3,4,5-trichloropyridazine (**51**) with 2-thioaniline.



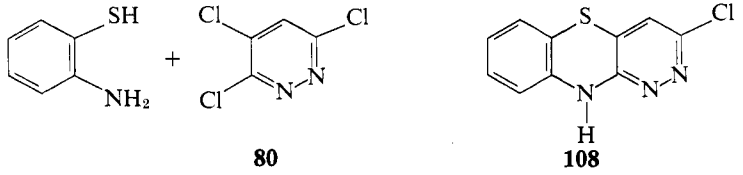
51 105 106

Monosubstitution in the 4-position (**107**) results from the action of ammonia (10, 18, 57, 123) or amines (124, 226a) on 3,4,6-trichloropyridazine (**80**). Yoneda (97) prepared 3-chloro-1,2-diazaphenothiazine (**108**) from



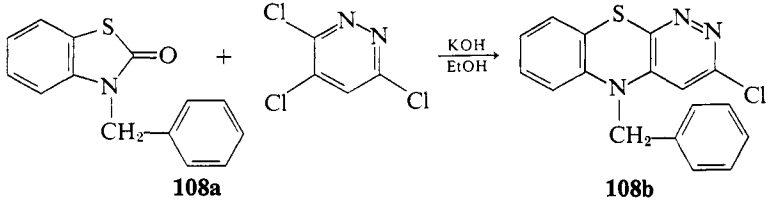
80 107

the reaction of 3,4,6-trichloropyridazine (**80**) and 2-thioaniline. The 10-methyl derivative was obtained in a similar fashion by starting with potassium



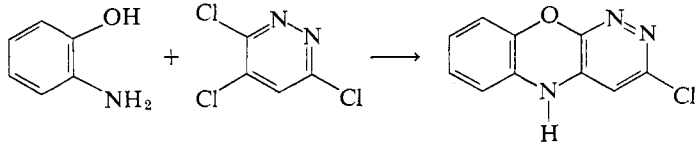
80 108

2-*N*-methylaminothiophenolate (97). Yoneda and Otaka (226b) also prepared *N*-benzyl-3-chloro-1,2-diazaphenothiazine (**108b**) by the reaction of 3-benzylbenzothiazol-2-one (**108a**) with 3,4,6-trichloropyridazine in the presence of ethanolic potassium hydroxide. Nyrkova and co-workers (227, 228,



108a 108b

228a) synthesized 2-chloro-3,4-diazaphenoxazine (**109**) by the reaction of 2-aminophenol with 3,4,6-trichloropyridazine (**80**).



80 109

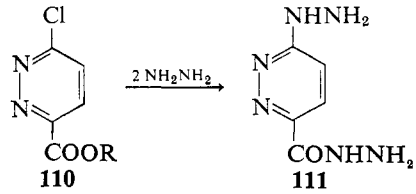
4. *With Four Halogens*

Three references to the reaction of ammonia or amines on tetrahalopyridazines were found. Chambers, McBride, and Musgrave (50, 51) describe the reaction of aqueous ammonia at 0° C on 3,4,5,6-tetrafluoropyridazine wherein they obtained the 4-amino derivative. The preparation of 4-diethylamino-3,5,6-trifluoropyridazine and a 3,6-difluoro-4,5-bisphthalimidopyridazine was also described. Beyer and Volcker (200) condensed tetrachloropyridazine with anthranilic acid to obtain 3,4-dichloro-10*H*-pyridazino[3,2-*b*]quinazolin-10-one.

C. Replacement of Halogen by Hydrazino Groups

1. *With One Halogen*

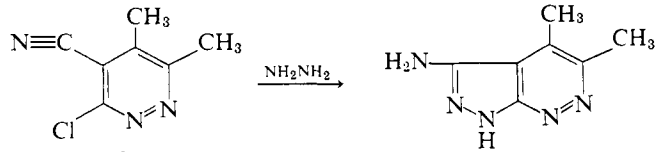
The replacement of a single halogen (chlorine or bromine) atom attached to a carbon of a pyridazine or pyridazinone can usually be accomplished by treatment with hydrazine. Other functional groups (substituted amino (229), amido (23, 230), methyl (66, 231), benzyl (16), substituted benzyl (16), phenyl (12, 23), substituted phenyl (15, 111), methoxy (182, 232), phenoxy (232), and methylsulfonyl) (232) do not interfere with this reaction. When hydrazine is added to a chloropyridazine containing an ester group (**110**), a hydrazide is formed in addition to the replacement of chlorine (**111**) (23, 197).



110 **111**

Takahayashi (232) obtained 6-chloro-3-hydrazinopyridazine from 6-chloro-3-thiopyridazine upon treatment with hydrazine hydrate, indicating preferential displacement of the thio group rather than the chlorine atom.

Schmidt, Eichenberger, and Wilhelm, (5) upon treatment of 3-chloro-4-cyano-5,6-dimethylpyridazine (**112**) with hydrazine, obtained 3-amino-4,5-dimethylpyrazolo[3,4-*c*]pyridazine (**113**). Dornow and Abele (17) carried



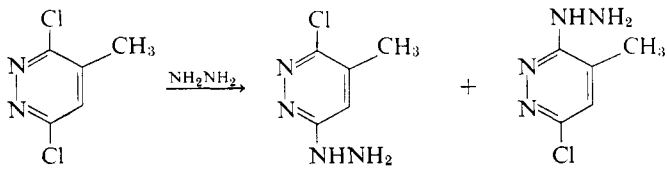
112 **113**

out similar ring closures starting with ethyl 3-chloro-6-alkylpyridazine-4-carboxylate, 3-chloro-4-hydroxymethyl-6-methylpyridazine, 3-chloro-4-cyano-6-methylpyridazine, and 3-chloro-4-cyanopyridazine.

2. *With Two Halogens*

The reaction of 3,6-dichloropyridazine with hydrazine yields a monohydrazino derivative (189, 202, 233, 234). Attempts to prepare the 3,6-bishydrazinopyridazine directly from the dichloro compound gave difficultly separable mixtures (202). This could be achieved, however, by first converting the 3,6-dichloro compound to the 3,6-dimethoxy compound which upon treatment with hydrazine produced the desired compound.

When 4-amino-3,6-dichloropyridazine (20, 123) and the 4-alkylamino derivatives (124, 226a) were treated with hydrazine, only the 3-hydrazino derivatives were obtained. However, when 3,6-dichloro-4-methylpyridazine (**114**) was similarly treated, both the 3-chloro-6-hydrazino-4-methyl- (**115**) and the 6-chloro-3-hydrazino-4-methylpyridazines (**116**) were obtained

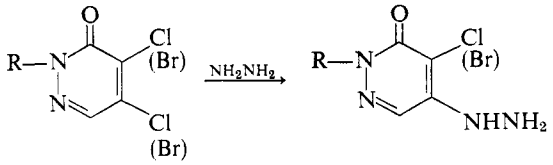


114 **115** **116**

(8, 68, 235, 236). Linholter (236) gave the assignment opposite that previously reported by Takahayashi (235).

The reaction of 4-amino-3,5-dichloropyridazine with hydrazine produced the 3-hydrazino derivative (19).

When 4,5-dibromo(dichloro)-1-(hydrogen (172), methyl (238), phenyl (172, 237–238), cyclohexyl (238))-6(1*H*)pyridazinone (**83**) is allowed to react with hydrazine, a 4-hydrazino derivative (**117**) is obtained (172, 237, 238).



83 **117**

A 5-hydrazino derivative is obtained from the treatment of 3,4-dichloro-6(1*H*)pyridazinone with hydrazine (172).

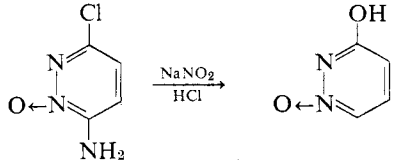
3. *With Three Halogens*

Kuraishi (125) reported the preparation of 3,6-dichloro-4-hydrazinopyridazine from the reaction of the 3,4,6-trichloro derivative with hydrazine.

D. Replacement of Halogen by Hydroxyl Groups

1. *With One Halogen*

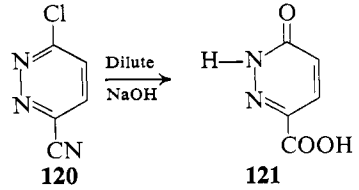
Reagents that cause conversion of a halogen atom to a hydroxyl group (hydrolysis) are generally either acidic or basic. Acetic acid alone or in combination with alkali metal acetates has proved effective (20, 59, 169). This same hydrolysis with acetic acid is sometimes seen as a side reaction in the preparation of pyridazine *N*-oxides using hydrogen peroxide and acetic acid (41, 179, 181, 239). Other acidic reagents that caused hydrolysis are hydrochloric acid (8) and dilute sulfuric acid (110). Itai and Nakashima (240), in the diazotization of 3-chloro-6-aminopyridazine-1-oxide (**118**) with sodium nitrite and hydrochloric acid, obtained 3-hydroxypyridazine 1-oxide (**119**).



118 **119**

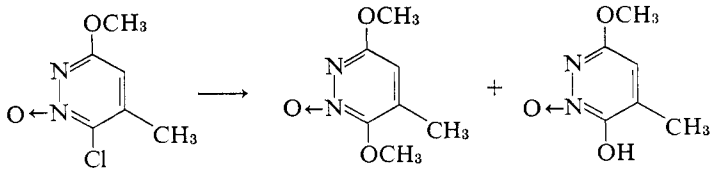
Several examples using aqueous solutions of alkali metal hydroxides to replace a chlorine atom with a hydroxyl group have been reported (61, 173, 185). Ogata (54), in treating 3-chloro-6-cyanopyridazine (**120**) with dilute

sodium hydroxide, hydrolyzed both groups, and 6(1*H*)pyridazinone-3-carboxylic acid (**121**) was obtained. Yanai and Kinoshita (58) observed

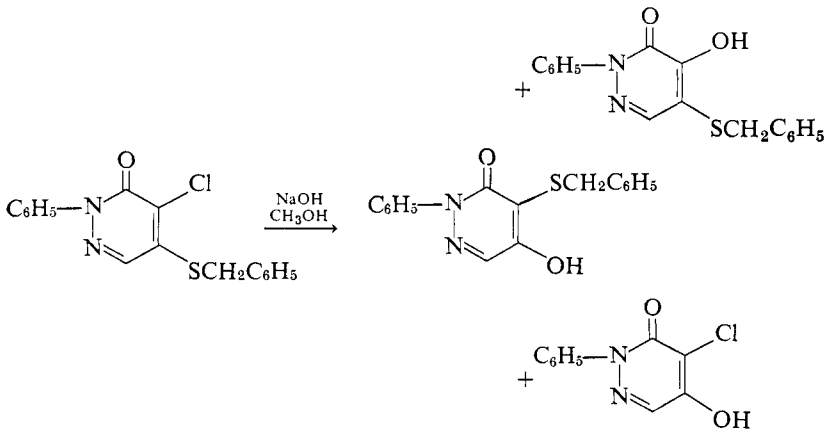


120 **121**

hydrolysis of the chlorine atom as a side reaction during the conversion of a chlorine atom to a methoxyl group using sodium methoxide.



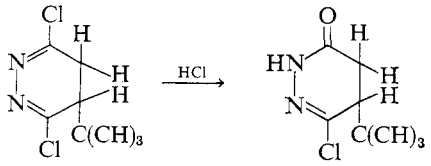
Kaji (240a) observed several hydrolysis products from the treatment of 4-benzylthio-5-chloro-1-phenyl-6(1*H*)pyridazinone with sodium hydroxide in methanol.



2. *With Two Halogens*

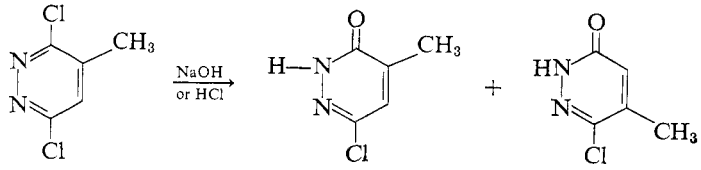
When subjected to hydrolysis conditions, pyridazines containing two halogen atoms usually replace only one with an hydroxyl group. 3,6-Dichloropyridazine, when allowed to react with sodium hydroxide (32, 41, 241) or potassium hydroxide (173), gave 3-chloro-6(1*H*)pyridazinone. Steck (242)

reported 5-amino-3-chloropyridazine from the reaction of sodium amide on the 3,6-dichloro derivative, but Taft, Adams, and Curran (243) have since shown the product to be 3-chloro-6(1*H*)pyridazinone from hydrolysis of the starting material during the work-up. Acidic reagents causing the hydrolysis of 3,6-dichloropyridazine include hydrochloric acid (32), acetic acid (with (232, 241) or without (125) hydrogen peroxide), and formic acid with hydrogen peroxide (244). Crossland (245), attempting to dehydrogenate 5-*t*-butyl-3,6-dichloro-4,5-dihydropyridazine (**122**) with hydrochloric acid, caused hydrolysis to 4-*t*-butyl-3-chloro-4,5-dihydro-6(1*H*)pyridazinone, (**123**).



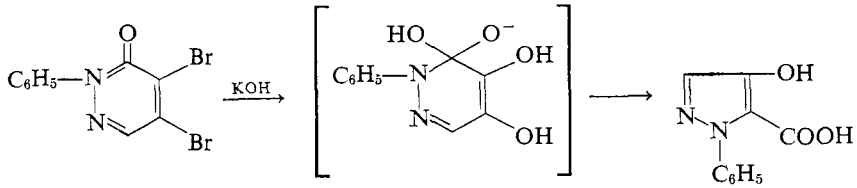
122 **123**

4-Amino-3,6-dichloropyridazine, when treated with aqueous (245) or methanolic (246) sodium hydroxide or sodium methoxide (170), gave 5-amino-3-chloro-6(1*H*)pyridazinone. When 3,6-dichloro-4-methylpyridazine (**114**) was treated with 15% sodium hydroxide (8) or constant-boiling hydrochloric acid (187), both 3-chloro-5-methyl- (**124**) *and* 3-chloro-4-methyl-6(1*H*)pyridazinones (**125**) were obtained.



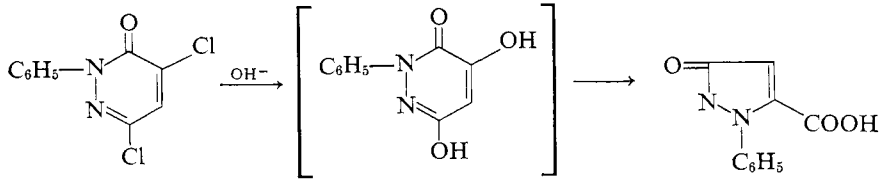
114 **124** **125**

The treatment of 4,5-dichloro-6(1*H*)pyridazinone with methanolic potassium hydroxide (49, 83) produced both the 4-hydroxy and the 4-methoxy derivatives. Sonn (211) obtained 5-bromo-4-hydroxy-1-phenyl-6(1*H*)-pyridazinone from the action of the 4,5-dibromo derivative and sodium hydroxide. Kuhel, Stanovnik, and Tišler (237), using aqueous potassium hydroxide, found that ring contraction had occurred to 1-phenyl-4-hydroxypyrazole-5-carboxylic acid (**126**). Maki et al. (26, 76, 247, 248) found that when 3,5-



126

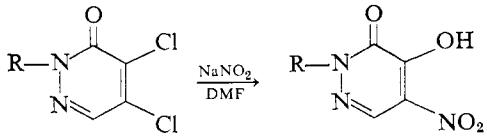
dichloro-1-phenyl-6(1*H*)pyridazinone (**100**) was treated with base, ring contraction occurred, forming 1-phenyl-3-pyrazolone-5-carboxylic acid (**127**). It was shown that 3,5-disubstituted derivatives which could form the



100 **127**

expected intermediate would also undergo ring contraction, whereas 3,4-disubstituted derivatives do not undergo rearrangement. The effect of substituents at the 1 position was also studied. *p*-Nitro, amino, or chlorophenyl groups produced ring contraction, whereas methyl or hydrogen substituents did not.

Dury (49) reported the replacement of a chlorine atom by a hydroxyl group by treatment of 1-substituted-4,5-dichloro-6(1*H*)pyridazinones (**35**) with sodium nitrite in dimethylformamide to produce 5-hydroxy-4-nitro-1-substituted-6(1*H*)pyridazinones (**128**). Kokosinski and Jankowska (249)



35 **128**

obtained 5-hydroxy-4-(2-hydroxy-1-naphthylazo)-1-phenyl-6(1*H*)pyridazinone from the treatment of 4,5-dichloro-1-phenyl-6(1*H*)pyridazinone with nitrous acid followed by the addition of *β*-naphthol.

Suszer (250) reported that labile halogens of 1-substituted 4,5-dichloro-6(1*H*)pyridazinones split off in alkaline media react with hydroxy groups of cellulose.

3. *With Three Halogens*

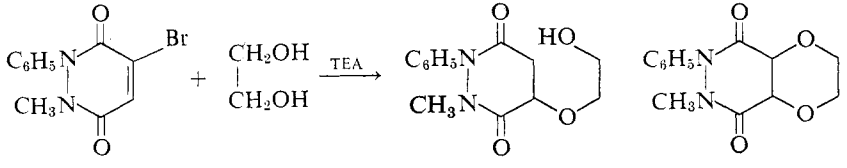
Kuraishi (125), studying the hydrolysis of 3,4,5- and 3,4,6-trichloropyridazines in glacial acetic acid, obtained 4,5-dichloro- and 3,5-dichloro-6(1*H*)pyridazinone, respectively. Maki and Obata (248) obtained 3,5-dichloro-4-hydroxy-1-phenyl-6(1*H*)pyridazinone from the treatment of 3,4,5-trichloro-1-phenyl-6(1*H*)pyridazinone with sodium hydroxide in methanol.

E. Replacement of Halogen by Aryloxy and Alkyloxy Groups

1. *With One Halogen*

From a preparative standpoint the activation or deactivation of the halogen is of little consequence. Replacement with an alkoxy or aryloxy group is easily accomplished by warming or refluxing the appropriate sodium alcoholate with the desired chloropyridazine in toluene or xylene. Examples are legion in which sodium methoxide has been allowed to react with chloropyridazines having the following substituents: *N*-oxide (60, 67, 174), alkyl (4, 16, 52, 179, 252), aryl (13, 110), 1-methyl-6-pyridazinone (103, 104), 1-phenyl-6-pyridazinone (38, 220), 2-methyl-1-phenyl-6-pyridazinone (191), amino (59, 75, 167, 178, 209), substituted amino (205, 253), substituted sulfonylamido (93, 254, 255), alkoxy (56, 58, 182), alkylthio (132, 232), methylsulfonyl (232), cyano (6, 7) and nitro (49). Several investigators (30, 119, 193, 233, 256) have prepared large numbers of various alkoxy derivatives.

In some cases other substituents have been affected in addition to the nucleophilic displacement of halogen by alkoxide ion. Horie (59) reported the loss of an acetyl group from 3-acetamino-5-chloro-6-methoxypyridazine during treatment with sodium methoxide to form 3-amino-5,6-dimethoxypyridazine. Ogata (62) noted the hydrolysis of a cyano group to a carboxylic acid in the conversion of 4-chloro-6-cyano-3-methylpyridazine 1-oxide to 4-methoxy-3-methylpyridazine-6-carboxylic acid 1-oxide with sodium hydroxide in methanol. Druey, Meier, and Staehelin (191) allowed 1-phenyl-2-methyl-5-bromo-3,6-dioxo-1,2,3,6-tetrahydropyridazine (**129**) to react with ethylene glycol and 2 moles of triethylamine (TEA) to give 1-phenyl-2-methyl-4-(β-hydroxyethoxy)-3,6-dioxo-1,2,3,6-tetrahydropyridazine (**130**) and 1-phenyl-2-methyl-4,5-ethylenedioxy-3,6-dioxohexahydropyridazine (**131**).

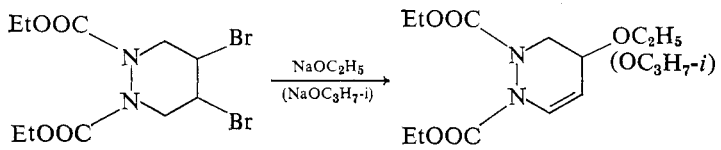


129 **130** **131**

2. *With Two Halogens*

When two halogen atoms are present on the pyridazine ring, one obtains replacement according to the number of moles of alkoxide ion used. One

mole of alkoxide provides a monohalo-monoalkoxide derivative, whereas the use of 2 moles of alkoxide results in the preparation of a dialkoxy derivative. The addition of a second alkoxide (different from the first) to a monoalkoxy monochloropyridazine allows the preparation of mixed dialkoxypyridazines. Several 3-alkoxy-6-chloropyridazines have been prepared (30, 175, 257–259). Tables listing 3-alkoxy-6-bromopyridazines (260) and 3-alkoxy-6-iodopyridazines (134) are given in the literature. Rink, Mehta, and Grabowski (101) describe the action of excess sodium ethoxide (isopropoxide) on diethyl 4,5-dibromohexahydropyridazine-1,2-dicarboxylate (**132**) to give diethyl 4-ethoxy(isopropoxy)-1,2,3,4-tetrahydropyridazine-1,2-dicarboxylate (**133**).



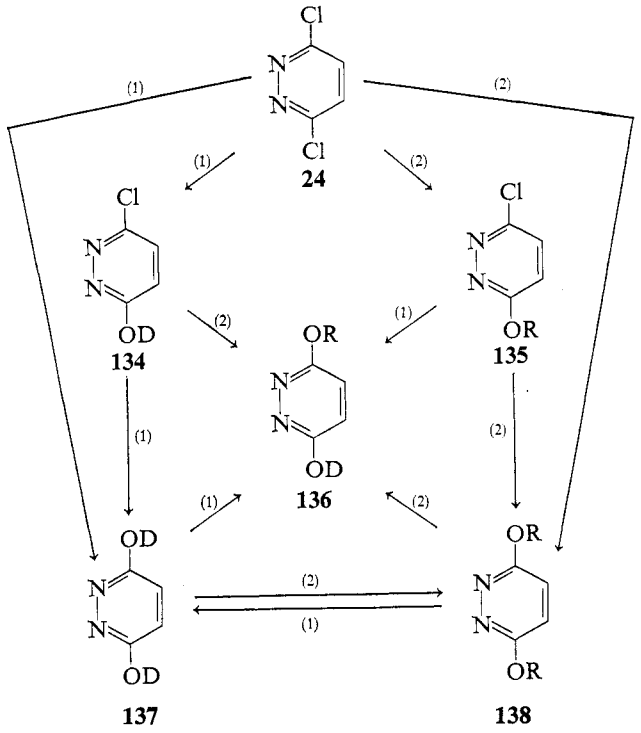
132 **133**

Several investigators (104, 186, 257) have prepared many 3,6-dialkoxypyridazines from the corresponding 3,6-dichloro derivatives.

Coad, Coad, and Hyepock (261) established the phenomenon of alkoxide exchange in the mono-, di-, and bisalkoxypyridazines according to the following scheme.

Yanai and Kinoshita (58) reported the preparation of 4-alkoxy (CH_3, C_2H_5)-3-chloropyridazine by the use of 1 molar equivalent of sodium alkoxide on 3,4-dichloropyridazine. Yanai, Kuraishi, and Kinoshita (57) obtained 4-amino-6-chloro-3-methoxypyridazine from 4-amino-3,6-dichloropyridazine and 1 molar equivalent of sodium methoxide. When two molar equivalents of sodium methoxide were used, both chlorine atoms were replaced. Nakagome and co-workers (170) reported the same results as those of Yanai when sodium methoxide was used. Earlier, Nakagome et al. (246) had isolated three products from the reaction of 4-amino-3,6-dichloropyridazine (**107**) with potassium hydroxide in methanol in an autoclave at 150° C for 1.5 hr.

In the case of 5-amino-3,4-dichloropyridazine and 1 molar equivalent of sodium alkoxide, Yanai and Kinoshita (20) found nucleophilic attack took place at position 3. When 4-amino-3,5-dichloropyridazine was similarly treated, the 3-methoxy derivative was also obtained. Originally, Takahayashi (8) reported the 6-chloro-3-methoxy-4-methylpyridazine from the treatment of 3,6-dichloro-4-methylpyridazine with 1 equivalent of sodium methoxide. Subsequently, Linholter et al. (187) showed that both the 6-chloro-3-methoxy- and the 3-chloro-6-methoxy-4-methylpyridazines are obtained in equal amounts. However, as the alkoxy group increases in size,

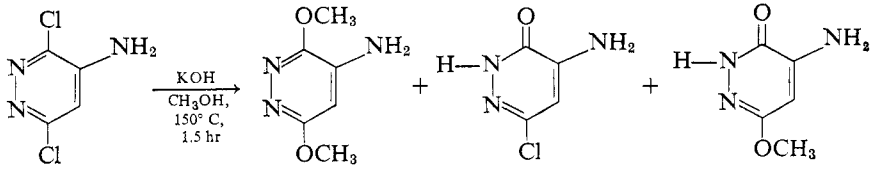


(1) Treatment with NaOD

134a–138a: R = —CH_3 **134d–138d:** R = cyclohexyl
134b–138b: R = —$CH(CH_3)_2$

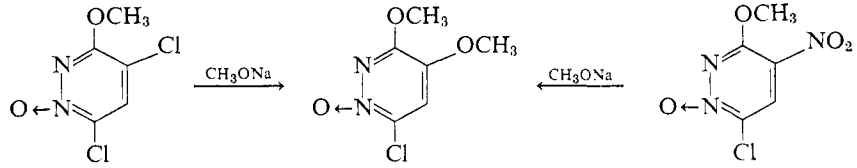
(2) Treatment with NaOR

134c–138c: R = —*n*—C_4H_9 **134–138:** D = —$CH_2CH_2N(CH_3)_2$



107

the 6-position is favored for attack. The 3-alkoxy derivatives were found to have higher melting points than the corresponding 6-alkoxy analogs. These results have also been confirmed by Mori (167) and Nakagome (239). Itai and Sako (183) obtained 6-chloro-3,4-dimethoxypyridazine 1-oxide (**139**) by treating both 4,6-dichloro-3-methoxypyridazine 1-oxide (**140**) or 6-chloro-3-methoxy-4-nitropyridazine 1-oxide (**141**) with an equimolar amount of sodium methoxide.



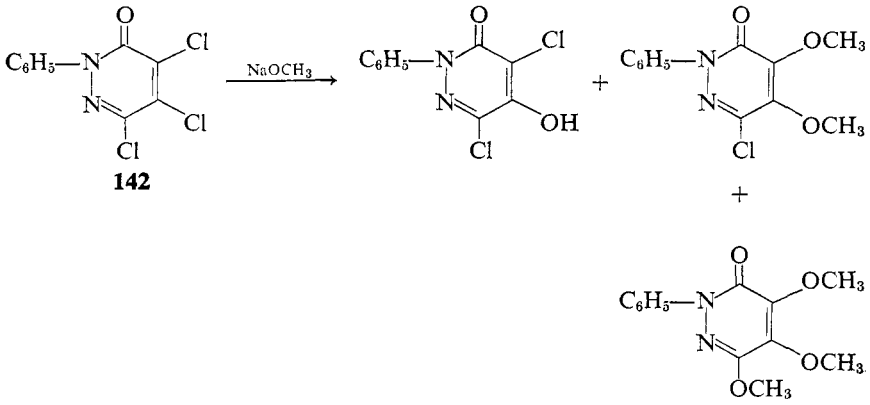
140 **139** **141**

The 4,5-dihalo-1-phenyl-6-pyridazinones, when treated with 1 equivalent of alkoxide, give the 4-alkoxy-5-halo-1-phenyl-6-pyridazinones exclusively, as reported by several investigators (27, 211, 212, 248). Maki and Obata (26) treated 3,5-dichloro-1-phenyl-6-pyridazinone with 1 equivalent of sodium methoxide and obtained 3-chloro-5-methoxy-1-phenyl-6-pyridazinone. Wagner and Heller (262) treated 1-β-D-glucosyltetraacetate-3,6-dichloro-4-pyridazinone with 1 equivalent of sodium methoxide and obtained 1-β-D-glucosyl-3-chloro-6-methoxyl-4-pyridazinone. Many 4,5-dialkoxy-1-alkyl(or aryl)-6(1*H*)pyridazinones have been prepared by Dury (49) and Reicheneder and Dury (256).

3. *With Three Halogens*

Itai and Kamiya (174), upon treating 3,4,5-trichloropyridazine with successive equivalents of sodium methoxide obtained first 3,4-dichloro-5-methoxypyridazine. Upon addition of the second equivalent, 4-chloro-3,5-dimethoxypyridazine and 3-chloro-4,5-dimethoxypyridazine were obtained. These two latter products were also obtained when 2 equivalents of sodium methoxide were allowed to react with the original trichloro derivative. When 3,4,6-trichloropyridazine is allowed to react with 1 equivalent of sodium alkoxide, 4-alkoxido-3,6-dichloro derivatives are obtained (125, 263). Maki and Obata (248) obtained three compounds from the reaction of 3,4,5-trichloro-1-phenyl 6(1*H*)pyridazinone (**142**) and excess sodium methoxide at room temperature.

Chambers, McBride, and Musgrave (263a) allowed 6-methoxy-3,4,5-trifluoropyridazine to react with 1 equivalent of sodium methoxide in



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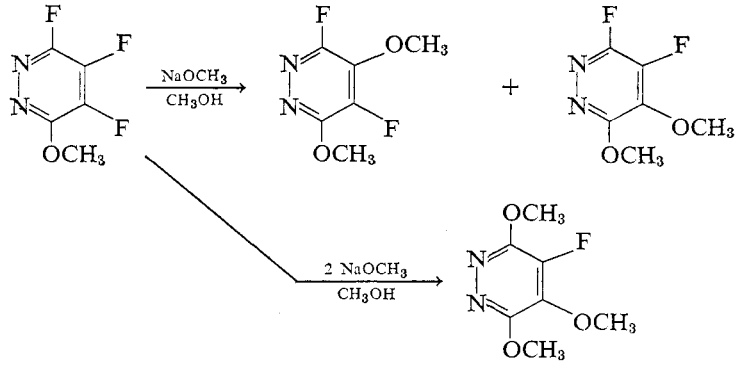
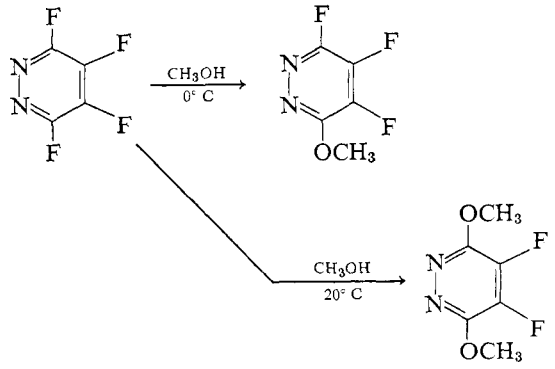
methanol to obtain the 4,6- and 5,6-dimethoxy derivatives. With 2 equivalents of sodium methoxide in methanol, the 3,5,6-trimethoxy compound was obtained.



4. *With Four Halogens*

Chambers, McBride, and Musgrave (50, 51) studied the sequential nucleophilic replacement of tetrachloro- and tetrafluoropyridazine by successive addition of equivalents of sodium methoxide. The order of replacement was 4 and then 5, with the positions 3 and 6 equivalent. With the addition of methanol only, Chambers, McBride, and Musgrave (263a–c) found the order of addition to be exactly opposite.

When tetrafluoropyridazine was allowed to react with aqueous sulfuric acid, 3,4,5-trifluoro-6(1*H*)pyridazinone was obtained. When chlorine is



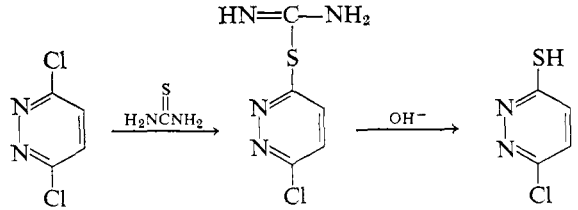
allowed to pass through an ether solution of tetrafluoropyridazine (18° C) the tetrachloro derivative is obtained.

F. Replacement of Halogen by Thio Groups

Thio groups can readily be introduced into the pyridazine ring by means of halogen displacement. This may be accomplished by the action of sodium (potassium) hydrogen sulfide; treatment with thiourea and alkaline hydrolysis of the thiouronium salt; reaction with sodium sulfide, sulfur, and sodium hydroxide; the action of hydrogen sulfide in pyridine or dimethylformamide; and finally through the action of phosphorus pentasulfide in pyridine.

1. *Using Thiourea*

The addition of thiourea to an alcoholic solution of the chloropyridazine results in the formation of a thiouronium derivative which may or may not be isolated prior to hydrolysis with alkali hydroxide. Several investigators (195, 257, 264, 265) have prepared 6-chloro-3-thiopyridazine from the dichloro derivative by this method. In addition, Kumagai (264) and Pollak,



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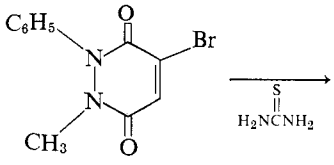
Stanovnik, and Tišler (265) have described the preparation of the 3,6-dithio derivative by this same route. The use of thiourea has been effective in the presence of the following functional groups: alkoxy (212, 266), alkyl (7, 264), aryl (264), amino (19, 264), and cyano (7). When Druey, Meier, and Staehelin (191) allowed thiourea to react with 4-bromo-1-methyl-2-phenyl-3,6-pyridazinedione (**129**) followed by alkaline hydrolysis 2,3,4,5,6,7-hexahydro-2,4,7-trioxo-5-phenyl-6-methylthiazolo[4,5-*d*]pyridazine (**143**) was formed.



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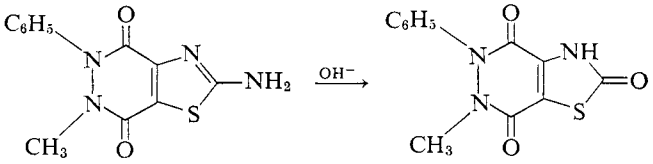

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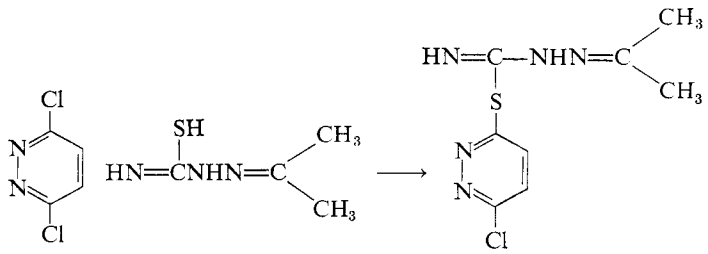
Pollak, Stanovnik, and Tišler also used acetone thiosemicarbazone and benzaldehyde thiosemicarbazone with 3,6-dichloropyridazine (**24**).



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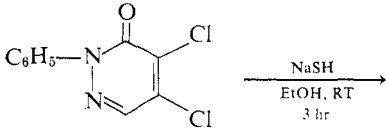
2. *Using Sodium (Potassium) Hydrogen Sulfide*

Sodium hydrogen sulfide in ethanol (aqueous or absolute; refluxing or in an autoclave) with a halopyridazine is an effective way of introducing a thio group. This has been accomplished with the following groups present on the pyridazine ring: alkoxy (59), amino (59, 193), and acetylamino (59). Kaji (267), upon stirring 4,5-dichloro-1-phenyl-6(1*H*)pyridazinone (**83**) with ethanolic sodium hydrogen sulfide (3 hr at room temperature), obtained 5-chloro-1-phenyl-4-thio-6(1*H*)pyridazinone. When the monothio compound (**144**) was heated in an autoclave with alcoholic sodium hydrogen sulfide,

the 4,5-dithio derivative (**145**) was obtained. Rapos, Synak, and Winternitz (83) also reported the preparation of 5-chloro-1-phenyl-4-thio-6(1*H*)pyrid-



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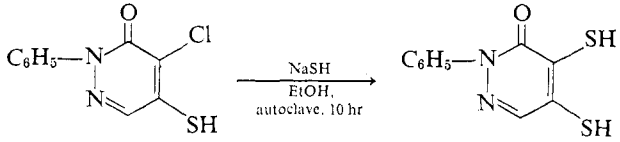
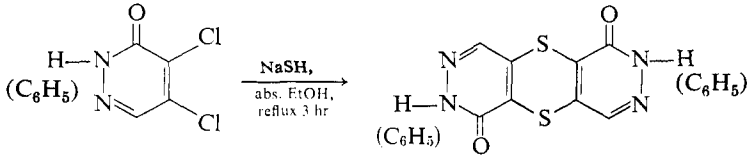


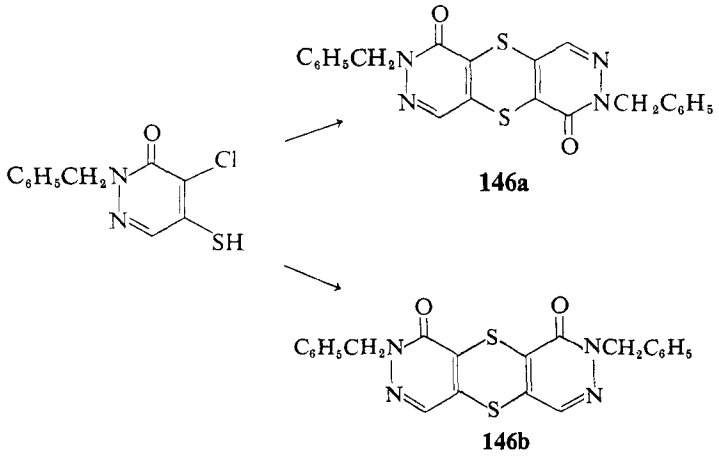
144 **145**

azinone using potassium hydrogen sulfide. When Castle, Kaji, and Wise (268) refluxed 4,5-dichloro-6(1*H*)pyridazinone (**35**) with sodium hydrogen sulfide in absolute ethanol, dipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,6-dione (**146**) was obtained. Under similar conditions 4,5-dichloro-1-phenyl-6(1*H*)pyridazinone gave the 2,7-diphenyl derivative.



35 **146**

Kaji (268a) refluxed 1-benzyl-5-chloro-4-mercapto-6(1*H*)pyridazinone in ethanol and obtained not only 2,7-dibenzyldipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,6-(2*H*,7*H*)dione (**146a**) but also the 2,8-dibenzyl derivative (**146b**).



146a

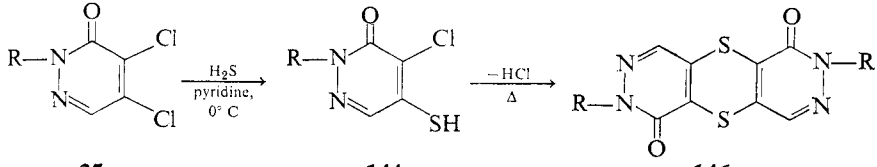
146b

Kazuya and Kaji (268b) carried out similar cyclizations starting with 3-chloro-5-ethoxy-4-thiopyridazine in absolute ethanol, obtaining not only the expected diethoxy derivatives but also the dione hydrolysis products.

Potassium hydrogen sulfide in ethanol has been used by Schönbeck (173) to prepare both 3-chloro-6-thio- and 3,6-dithiopyridazine from the 3,6-dichloropyridazine. Druey, Meier, and Eichenberger (30) and Takahayashi (233) also prepared 6-chloro-3-thiopyridazine by this method. Takahayashi (8, 232) successfully carried out this reaction in the presence of methoxy, methyl, and phenyl groups.

3. *Using Hydrogen Sulfide*

Dury (49) has described the nucleophilic displacement of the 5-chlorine atom from 4,5-dichloro-6(1*H*)pyridazinones (**35**) by the action of hydrogen sulfide in pyridine with cooling. Upon heating, hydrogen chloride is eliminated, giving rise to dipyridazo[4,5-*b*:4′,5′-*e*]-1,4-dithiin-1,6-diones (**146**). Dury (49) also treated acyl derivatives (**147**) or amines of 4-amino-5-



35 **144** **146**

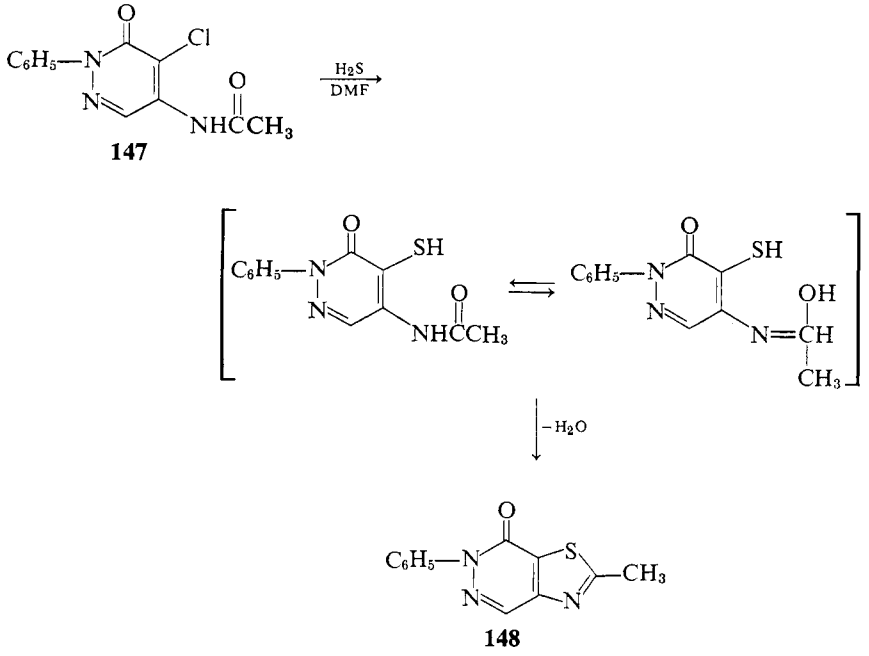
chloro-2-phenyl-6(1*H*)pyridazinone with hydrogen sulfide in dimethylformamide to form thiazolo[4,5-*d*]pyridazines (**148**).

4. *Using Sodium Sulfide, Sulfur, and Sodium Hydroxide*

Schönbeck and Kloimstein (119) prepared 6-chloro-3-thiopyridazine by warming 3,6-dichloropyridazine, sodium sulfide, sulfur, and sodium hydroxide.

5. *Using Phosphorus Pentasulfide in Pyridine*

The direct displacement of oxygen by sulfur using phosphorus pentasulfide has had wide application in heterocyclic systems in which the hydroxyl group is tautomeric with the cyclic amide structure. Castle et al. (19, 24, 266) have observed a novel nucleophilic displacement of halogen in activated



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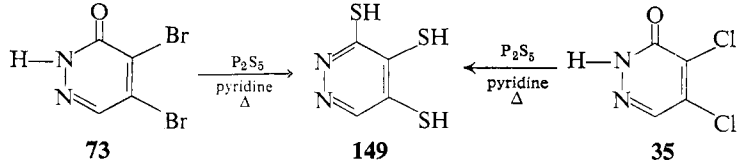
148

nitrogen heterocycles with phosphorus pentasulfide in refluxing pyridine. When either 4,5-dibromo- (**73**) or 4,5-dichloro- (**35**) 6(1*H*)pyridazinone was treated with phosphorus pentasulfide in boiling pyridine, 3,4,5-pyridazinetrithiol (**149**) was obtained. These same conditions have been used to prepare



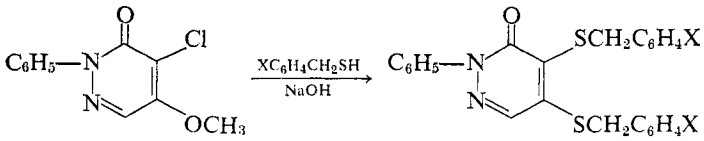
73 149 35

3,6-pyridazinedithiol (266), 3-amino-6-pyridazinethiol (266), 3-methyl-6-pyridazinethiol (266), and 3-isopropoxy-6-pyridazinethiol (266) from the corresponding chloro derivatives. 4,5-Dichloro-1-phenyl-6(1*H*)pyridazinone has also been converted to 4,5-dithio-1-phenyl-6(1*H*)pyridazinone under these same conditions.

G. Replacement of Halogen by Alkylthio or Arylthio Groups

Several procedures have been employed to prepare alkylthio or arylthio derivatives from corresponding halopyridazines. One of these methods uses

the desired thio- and halopyridazine in aqueous alkali hydroxide (173, 196, 269). Another uses an alkyl- or arylthiouronium salt in aqueous alkali hydroxide (24). Castle and Kaji (212) prepared several 4,5-bishalo-substituted benzylthio-3-chloropyridazines by the reaction of 2 equivalents of the appropriate halo benzylthio compound with 3,4,5-trithiopyridazine in the presence of aqueous alkali hydroxide. Kaji (270), under similar conditions, replaced not only a chlorine atom but also a methoxyl group from 5-chloro-4-methoxy-1-phenyl-6(1*H*)pyridazinone (**150**)



150

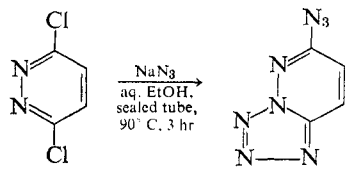
Another method uses a sodium alkyl(aryl)thiolate and a halopyridazine in dioxan (193, 271), benzene (24), toluene (263), xylene (272), or ethanol (273). Chambers, McBride, and Musgrave (51), upon treating tetrafluoropyridazine with 1 equivalent of sodium phenolthiolate in *N*-methyl-2-pyrrolidone at 0° C, obtained 4,5-bisphenylthio-3,6-difluoropyridazine and unreacted starting material. When 3 equivalents of sodium phenolthiolate were used (0° C) di-, tri-, and tetraphenylthio derivatives were obtained. At −10° C (3 equivalents), only the 4,5-bisphenylthio-3,6-difluoropyridazine was obtained.

A fourth method described by Castle and Kaji (212) involves the reaction of a halogen-substituted benzylthio compound with 4,5-dihalo-1-phenyl-6(1*H*)pyridazinone and sodium amide in dry benzene.

H. Miscellaneous Halogen Replacement Reactions

1. *Using Sodium Azide*

Itai and Kamiya (60), upon treatment of 3,6-dichloropyridazine (**24**) with sodium azide in a sealed tube with an ethanol–water solvent obtained a violently explosive azide. This compound was found to be 6-azidotetrazolo-[1,5-*b*]pyridazine (**151**). Under similar conditions, Itai and Kamiya prepared



24 **151**

3-azidopyridazine 1-oxide (60) and 4-azidopyridazine 1-oxide (174). Attempts to prepare 4-azido-3,6-dimethoxypyridazine 1-oxide from the action of sodium azide on the 4-chloro derivative were unsuccessful.

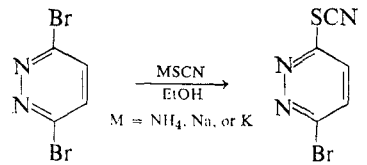
Gudriniece and Urbans (273a) treated 4,5-dichloro-1-phenyl-6(1*H*)-pyridazinone with sodium azide in an acetone–water solvent to obtain 4-azido-5-chloro-1-phenyl-6(1*H*)pyridazinone.

2. *Using Metallic Cyanide*

Robba (90) has reported the preparation of 3-cyanopyridazine from 3-bromopyridazine by the action of cuprous cyanide, benzonitrile, and anhydrous cupric sulfate. Homer, Gregory, and Wiggins (69) prepared 1,3-dimethyl-6(1*H*)pyridazinone-4-carboxylic acid from the reaction of 4-chloro-1,3-dimethyl-6(1*H*)pyridazinone and a mixture of cuprous chloride and potassium cyanide. Ogata (54) has described the preparation of 3-carboxamido-6-methylpyridazine from refluxing 3-iodo-6-methylpyridazine with potassium cyanide in aqueous ethanol.

3. *Using Alkali Metal Thiocyanate*

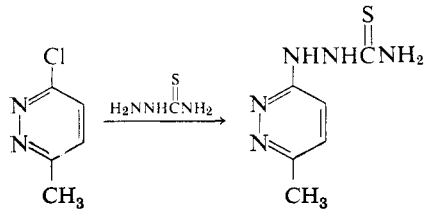
Kinugawa, Ochiai, and Yamamoto (126) prepared 6-chloro-3-thiocyanatopyridazine, 6-bromo-3-thiocyanatopyridazine (**152**), and 3,6-dichloro-4-thiocyanatopyridazine from the action of ammonium, sodium, or potassium thiocyanate in ethanol on the corresponding chloro- or bromopyridazines (**53**).



53 **152**

4. *Using Thiosemicarbazide*

Shiho and Takahayashi (231) allowed thiosemicarbazide to react with 3-chloro-6-methylpyridazine (**153**) to form 6-methyl-3-thiosemicarbazidopyridazine (**154**).



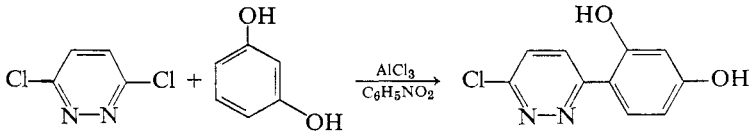
153 **154**

5. *Using n-Butyllithium*

Rosseels (188) has described the preparation of 6-chloro-3-pyridazinyllithium from the reaction of 3,6-dichloropyridazine and *n*-butyllithium in anhydrous benzene.

6. *Using Hydroquinone or Resorcinol in the Friedel–Crafts Reaction*

The inertness of halogenated heterocycles as alkylating agents in the Friedel–Crafts reaction is well known. However, Pollak, Stanovnik, and Tišler (274) were successful in the alkylation of resorcinol and hydroquinone with 3,6-dichloropyridazine (**24**) under the conditions of a Friedel–Crafts reaction.



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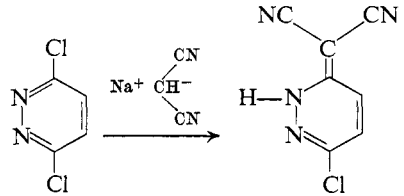
7. *Using Sodiomalonitrile*

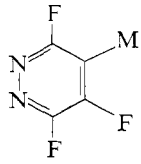
Kealy (275) reported the reaction of sodiomalononitrile with 3,6-dichloropyridazine (**24**) in refluxing tetrahydrofuran to give 3-chloro-6(1*H*)dicyanomethylene pyridazine (**155**) in 94% yield.



24 **155**

8. *Using Metal Carbonyl Anions*

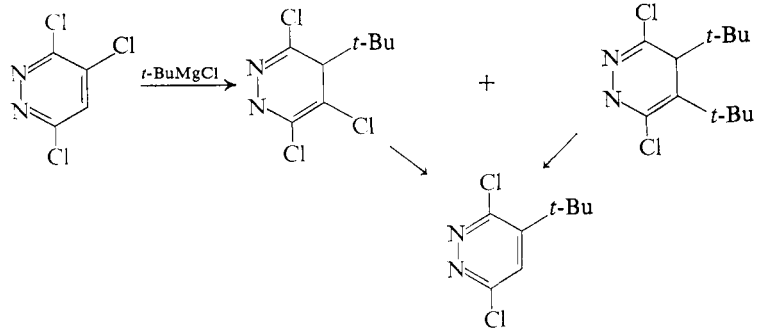
Cooke, Green, and Stone (276) have reported the reaction of perfluoropyridazine with metal carbonyl anions to form the following complexes:



M = π-$C_5H_5Fe(CO)_2$, $Re(CO)_5$, $Mn(CO)_5$, or π-$C_5H_5Mo(CO)_3$

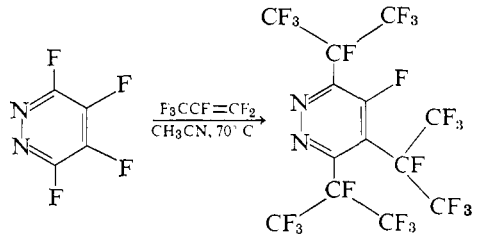
9. *Using t-Butylmagnesium Chloride*

Crossland (276a) allowed *t*-butylmagnesium chloride to react with 3,4,6-trichloropyridazine and obtained 4-*t*-butyl-3,5,6-trichloro-1,4-dihydropyridazine and 4,5-bis-*t*-butyl-3,6-dichloro-1,4-dihydropyridazine. Upon elimination both products gave 3,6-dichloro-4-*t*-butylpyridazine.

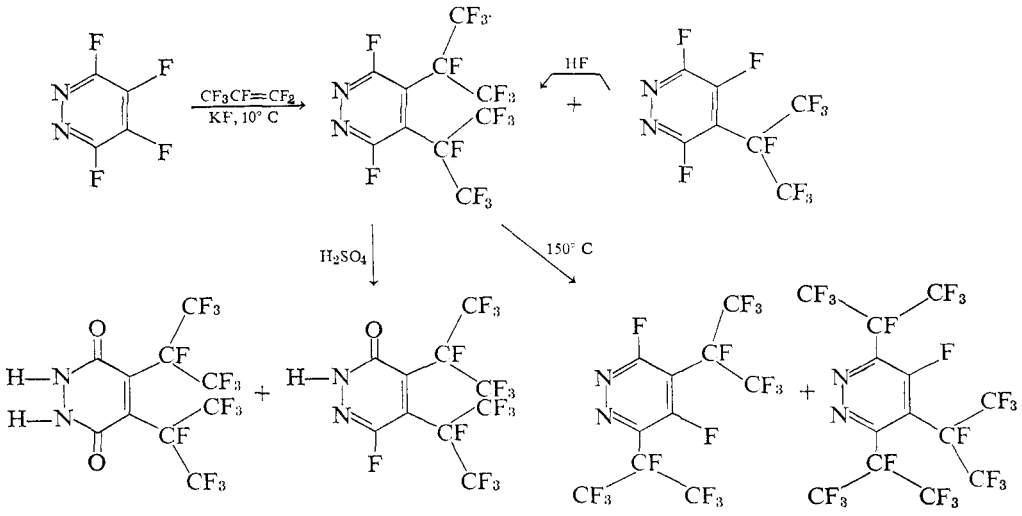


10. *Using Hexafluoropropene*

Drayton, Flowers, and Hazeldine (276b) treated tetrafluoropyridazine with hexafluoropropene at 70° C to obtain 4-fluoro-3,5,6-trisheptafluoroisopropylpyridazine. Chambers and co-workers (276c, d) extended the scope of

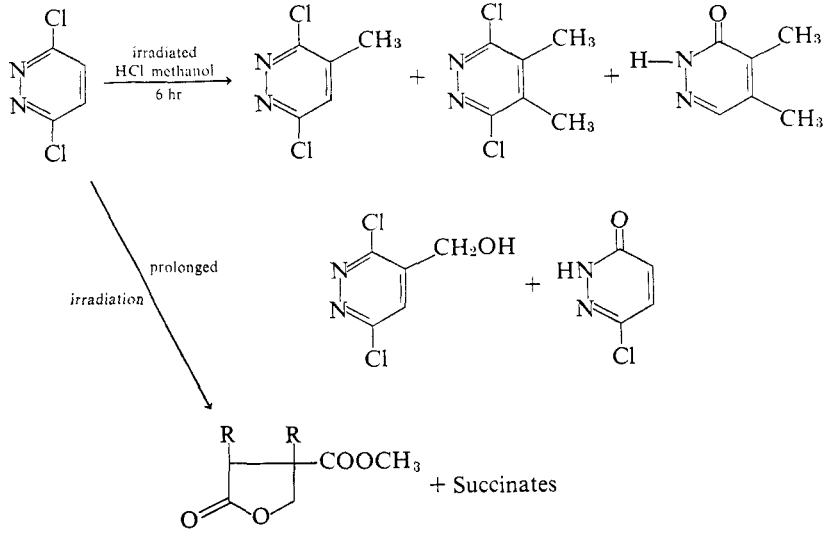


this reaction through the following scheme.



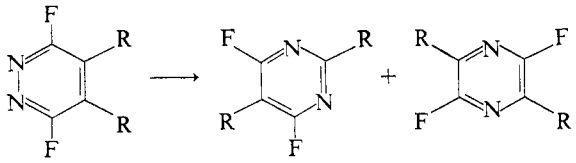
11. *Using Photolysis*

Tsuchiya, Arai, and Igeta (276e) obtained a series of products from the irradiation of 3,6-dichloropyridazine in HCl–methanol for 6 hr. Prolonged



irradiation of the same starting material gave methyl paraconates and succinates.

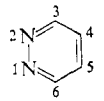
Allison et al. (276f) studied the isomerization of perfluoropyridazines to perfluoropyrimidines and perfluoropyrazines through the action of thermolysis and photolysis.



R = F
R = $F_3CCF(z)$

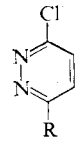
Starting with 4,5-dichloro-3,6-difluoropyridazine, Lemal and co-workers (276g), obtained 3,6-dichloro-2,5-difluoropyrazine through irradiation.

TABLE I. Chloropyridazines



Derivative	MP (°C)	References
3-Chloro	35	23, 116–118
4-Chloro	75–76	119
3,4-Dichloro	35–38	58
3,5-Dichloro	57–58	119
4,5-Dichloro	67–68	65
3,6-Dichloro	68–69	3, 30, 120
3,4,5-Trichloro	61	89, 121
3,4,6-Trichloro	57–58	3, 71, 74
3,4,5,6-Tetrachloro	85–86	3, 74
	87–89	51

TABLE II. 3-Chloro-6-substituted Pyridazines



R	MP (°C)	References
Br	93.5–94	68
CCl_3	99.5–101	277
CH_3	58	4
$CH_3 \cdot HBr$	220 (dec)	4
$CH_3 \cdot HCl$	250 (darkening)	4
COOH	146	188
COOLi		188
$COOCH_3$	104–105	127
$COOC_2H_5$	147–149	197
	152–153	230
$COOC_3H_7$	99–101	23, 197
$COOC_4H_9$	110–112	197
$CONH_2$	232–234	197
	249	23, 230
CN	94–95	54
C_2H_5	47	10
$=C(CN)_2$	258	275
$=C(CN)CONH_2$	214	275
$CH_2CH_2CH_2CH_2CH_3$	93–97 (dec)	9
C_6H_5	158–160	54
	144	23
$C_6H_4CH_3(4)$	153–154	278
$C_6H_3(OH)_2(2,4)$	225–226	274
$C_6H_3(OCOCH_3)_2(2,4)$	175–176	274
$C_6H_3(OH)_2(2,5)$	195–196	274
$C_6H_4OCH_3(4)$	160	15
$CH_2C_6H_5$	90–93	16
$CH_2C_6H_4CH_3(4)$	89–95	16
$CH_2C_6H_4Cl(2)$	64–67	16
$CH_2C_6H_4Cl(4)$	108–113	16
$CH_2CH_2C_6H_5$	77–80	16
Li		188
NH_2	210 (dec)	30
	213–214	92
$NHCH_3$	198–199	139
	199–201	119
	214–216	114
NHC_2H_5	125–126	129
$NHCH_2CH_2Cl$	120	279
$NHCH_2CH_2OH$	135.5	139
	135	208
$NHCHOHCCl_3$	215	139

TABLE II (*continued*)

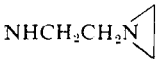
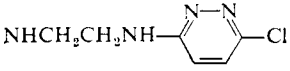
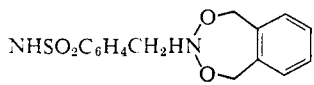
R	MP (°C)	References
$NHCH_2COOH$	200	139
	127–128	196
	268–269	208
NHC_3H_5	107–109	139
NHC_3H_7-*i*	107–110	204
		134
	110–112	280
$NHCH_2CH_2CH_2N(C_2H_5)_2 \cdot 2HCl$	223–224	272, 281
NHC_6H_5	191.2–192.2	209
	190	208, 282
	178–181	280
NHC_4H_9-*n*	108–109	49, 204
	110.9–111.5	209, 280
$NHC_6H_4Br(4)$	218–219	282
$NHC_6H_4Cl(2)$	124–125	282
$NHC_6H_4Cl(3)$	182–183	282
$NHC_6H_4Cl(4)$	201–203	282
$NHC_6H_4CH_3(4)$	189–190	208
$NHC_6H_4OCH_3(2)$	117–118	282
$NHC_6H_4OCH_3(3)$	183–184	282
$NHC_6H_4OCH_3(4)$	147–148	208
	148–149	282
$NHC_6H_4OC_2H_5(4)$	167–168	282
$NHC_6H_4NO_2(4)$	266–267	208
$NHCH_2C_6H_5$	162–163	208, 282
NHC_6H_{11}	160–161	208
	167.2–168.2	209, 280
$NHCOCH_3$	252–253	178
	268–271	114
$NHCOOC_2H_5$	201–202	178
	189.5–190.5	279
$NHCOC_6H_5$	196	283
$NHSO_2C_6H_4CH_3(4)$	154	283
	152	284
$NHSO_2C_6H_4NH_2(4)$	190–191	30, 94
	186–187	254, 285
	195 (dec)	193, 169
$NHSO_2C_6H_4NHAc(4)$	225 (dec)	169, 193, 285
$NHSO_2C_6H_4CH_2NH_2(4)$	280 (dec)	284
	222 (dec)	284

TABLE II (*continued*)

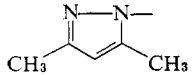
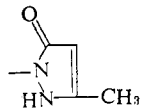
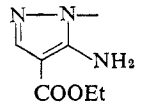
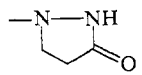
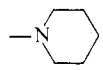
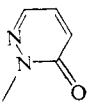
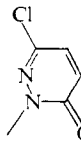
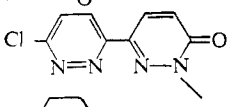
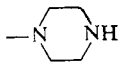
R	MP (°C)	References
$NH\text{-}P(O)Cl_2$	156–159	286
$NHP(O)(N\text{-}C_4H_4)_2$		287
$N(CH_3)_2$	104–106	139
	100–101	196
$N(C_2H_5)_2$	49–51	368
$N(CH_3)CH_2COOH$	186–188	139
$N(CH_3)CH_2COOC_2H_5$	50.5–53	368
$N(CH_3)C_6H_5$	89–91	229
$N(CH_2CH_2OH)_2$	96–98	229
$N(C_4H_9\text{-}n)_2$	57–58	209, 280
	127	288
N-Pyrrolo	183	188
N-Methyl-2-pyrrolo		188
	104–105	289
	232–233	237
	132–135	289
	156	290
	78 82–83	186 30
	173–174	32
	151–152	32
	239–240	32
	100–101.8 101	291 205

TABLE II (*continued*)

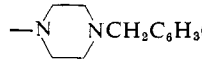
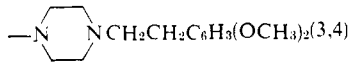
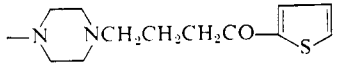
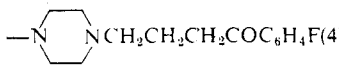
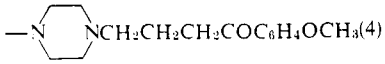
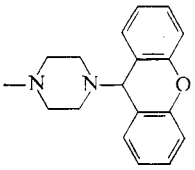
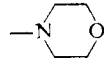
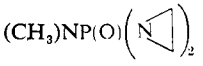
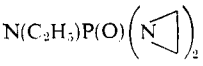
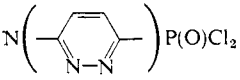
R	MP (°C)	References
	146	205
	120	253
	138–138.8	291
	152–153.9	291
	176–176.8	291
	216–218	292
	138–140	229
$N(CH_3)P(O)Cl_2$	71–73	286
	95–97	287
$N(C_2H_5)P(O)Cl_2$	66–69	286
	91–93	287
	122–124	286
$NHNH_2$	137–138	30
	140.5	233
$NHNO_2$	135	202
NHNHCHO	172	235
$NHNHC(=O)-CH_3$	77	235
NHNHCOCH=CHCOOH	188–190	237
$NHNHCOCH{=}CHCOOC_2H_5$	179–180	237

TABLE II (*continued*)

R	MP (°C)	References
$NHNHCOC_6H_5$	83–84	293
$NHNHCOC_6H_4COOH(2)$	200	237
$NHNHCOOC_2H_5$	157–158	237
$NHNHCSNHC_2H_5$	197–198	237
$NHN{=}CHCH_3$	205–206	293
$NHN{=}CHC_6H_5$	263–264	293
$NHN{=}CHC_6H_4Cl(4)$	295–296	293
$NHN{=}CHC_6H_4NO_2(4)$	288 (dec)	233
$NHN{=}CHC_6H_4OCH_3(4)$	225–226	293
OH	138–140	19, 204, 208, **263**, 368–371
$O^{\ominus}Ag^{\oplus}$		294
$O^{\ominus}Hg^{2+}O^{\ominus}$	198–199	295, 296
OCH_3	91	186, 233
	46–47	261
OC_2H_5	62	233
	63	186
OCH_2COOH	142–145	73, 297
	145	258
OCH_2CONH_2	210–212	119
	207–211	119
$OCH_2CONHNH_2$	169	298
$OCH_2CONHN{=}C(CH_3)_2$	175	298, 300
$OCH_2CONHNHCH(CH_3)_2$	138	298, 308
$OCH_2COOC_2H_5$	75–76	119
	211	298
$OCH_2COOCH_2CH_2N(CH_3)_2 \cdot HCl$	120	258, 297
$OCH_2COOCH_2CH_2N(C_2H_5)_2 \cdot HCl$	118	258
$OCH_2CH_2N(CH_3)_2$	42–44	261
$OCH_2CH_2N(C_2H_5)_2$ (picrate)	143	186
OCH_2CH_2OH	102	372
	67	126
$OCH_2CH_2OCH_2CH_2N(C_2H_5)_2$ (monooxalate)	135 (3×10^{-3} mm)	281
	bp 91.5–92.5	281
OC_3H_5	44–46	119, 233
OC_3H_7-*n*	65	233
	66–67	175
$OCH(CH_3)_2$	82–84	175, 186
	83–84	30, 233
$OC(CH_3)_3$	90–92	30
$OCH_2CH_2CH_2CH_3$	47–48	175, 233
	53–55	208
$OCH_2CH_2CH_2CH_2N(C_2H_5)_2$	bp 110 (1.5×10^{-3} mm)	281
$OCH_2CH_2CH_2CH_2CH_3$	61–63	134
OC_5H_{11}-*i*	58–59	233
	58–60	175

TABLE II (*continued*)

R	MP (°C)	References
$OCH_2CH_2CH_2CH_2CH_2N(C_2H_5)_2$	bp 145 (2×10^{-3} mm)	281
$O(CH_2)_5CH_3$	54–56	134
OC_6H_{11}	108–110	261
	46–47	175
$O(CH_2)_7CH_3$	34–36	119
$O(CH_2)_9CH_3$	43–44	134
OC_6H_5	69–70	257
	71	48, 186, 233
$OC_6H_4CH_3(2)$	85–85.5	257
$OC_6H_4CH_3(3)$	71	257
$OC_6H_4CH_3(4)$	107–108	257
$OC_6H_3(CH_3)_2(2,4)$	96, 97	257, 379
$OC_6H_3(CH_3)_2(3,4)$	106	257
$OC_6H_3(CH_3)_2(3,5)$	135–135.5	263
	132–133 (dec)	252
	132–134	301
$OC_6H_2(CH_3)_3(2,3,5)$	129–130	257, 379
$OC_6H_4(C_2H_5)(4)$	75	257
$OC_6H_4(i\text{-}C_3H_7)(2)$	77–77.5	257
$OC_6H_4(C_6H_5)(2)$	99.5	257
$OC_6H_4Br(4)$	135–136	257
$OC_6H_4Cl(4)$	115–116	257
	119.5–120	263
	120–121	301
$OC_6H_3Cl_2(2,4)$	80–81	257
	90	119
$OC_6H_3Cl_2(2,6)$	106–107	257
$OC_6H_2Cl_3(2,4,5)$	173–174	257
$OC_6H_3CH_3(3)Cl(4)$	92	257
$OC_6H_4OCH_3(2)$	98.5	257
$OC_6H_4OCH_3(3)$	73.5	257
$OC_6H_4OCH_3(4)$	98–99	257
$OC_6H_3OCH_3(2)CH_3(4)$	105–106	257
$OCH_2C_6H_5$	77	186, 257
$OCH_2C_6H_5OCH_3(4)$	115	257
$OCH_2CH_2OC_6H_5$	74	257
$OCH_2CH_2OC_6H_4Cl(2)$	114–115	257
$OCH_2CH{=}CHC_6H_5$	118	257
$OC_{12}H_{11}$	107.5	257
$OC_6H_4NO_2(2)$	95	263
$OC_6H_4NO_2(3)$	114–115	263
$OC_6H_4NO_2(4)$	125–126	263
$OC_6H_3(NO_2)_2(2,4)$	151–152	263
Tetraacetyl-1-β-D-glucosyloxy	159–161	294
1-β-D-Glucosyloxy	123–125	294
Tetraacetyl-1-β-D-glucosylthio	136–137	302, 303, 304
1-β-D-Glucosylthio	120–121	303, 304

TABLE II (*continued*)

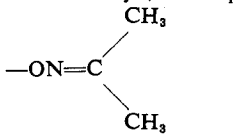
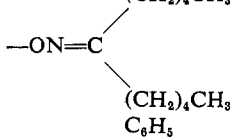
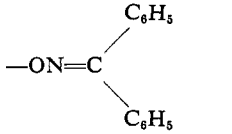
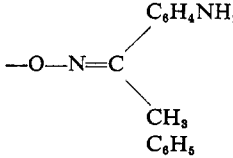
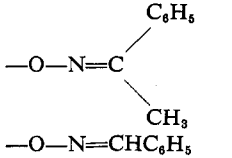
R	MP (°C)	References
2′,3′-Di-*O*-benzoyl-5′-diphenylphosphoryl-β-D-ribofuranosyloxy	137–141	305
Tri-*O*-benzoyl-β-D-ribofuranosyloxy	182–185	295
Tri-*O*-benzoyl-β-D-ribopyranosyl		295, 296
	102–103	259
	86–88	259
	113–115	259
—O—N=CHC$_6$H$_4$N(CH$_3$)$_2$(4)	121–123	259
—O—N=C—C$_6$H$_4$NH$_2$(4)	139–141	259
	144–145	259
	118–119	259
—O—N=CHC$_6$H$_5$	144	259
—O—N=CHC$_6$H$_4$Cl(2)	93–95	259
—O—N=CHC$_6$H$_4$OCH$_3$(4)	144–145	259
OPS(OC$_2$H$_5$)$_2$	48.5–49	306
OPO(OC$_3$H$_7$-*n*)$_2$		306
OPO(OC$_3$H$_7$-*i*)$_2$		306
—O—PSC$_6$H$_5$(OC$_2$H$_5$)		307
OSCCl$_3$	156–157	308
SH	136 (dec)	30, 173, 257, 259, 260, 298, 301, 369, 374, 375
SCH$_3$	101–102	195
	102	233
	103–104	132, 196
SOCH$_3$	110–112	127

TABLE II (*continued*)

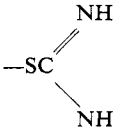
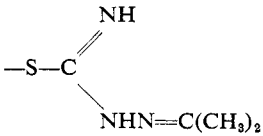
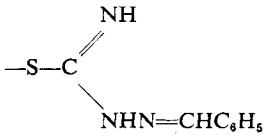
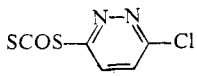
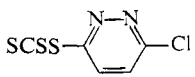
R	MP (°C)	References
SO_2CH_3	114	196, 309
	118–120	196
SCN	110–112 (dec)	126
	123–124	310
	158–159	264
	121	265
	159	265
$SCOC_6H_5$	112–114	119
$SCOOCH_3$	88–89	310
$SCOOC_2H_5$	49.5–50.5	310
$SCOOC_3H_7$	61–62	310, 311
$SCOOC_4H_9$	29–30	310, 311
$SCOOC_5H_{11}$	32–33	310, 311
$SCOOC_6H_{13}$	45–46	310, 311
$SCOOC_7H_{15}$	45–46	310, 311
$SCOOC_8H_{17}$	59–60	310, 311
$SCOOC_6H_5$	122–124	310, 311
$SCOOCH_2C_6H_5$	101–103	310, 311
	138 (dec)	311
	149–150 (dec)	311
SC_2H_5	65	233
SCH_2CH_2OH	79–80	119
SCH_2COOH	136 (dec)	173
	115–120	311
$SCH_2COOC_2H_5$	70–72	311
	73–74	173
$SCH_2COC_6H_4OH(2)$	134	119
$SCH_2COC_6H_4OCH_3(4)$	120	119
$SCH_2COC_6H_3(OCH_3)_2$	139	119
SCH_2CONH_2	180–183	312

TABLE II (*continued*)

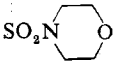
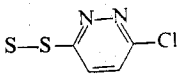
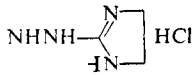
R	MP (°C)	References
$SCH_2CONHCH_3$	148–150	312
$SCH_2CONHCOCH_3$	168–170	119
$SCH_2CONHC_2H_5$	153–154	312
$SCH_2CON(CH_3)_2$	139–140	312
$SCH_2CON(C_2H_5)_2$	95–97	312
$SCH(CH_3)CON(C_2H_5)_2$	55–57	312
$SCH_2CON(CH_2CH{=}CH_2)_2$	56	312
$SCH_2CON(n\text{-}C_3H_7)_2$	55–56	312
$SCH_2CON[CH(CH_3)_2]_2$	91–92	312
$SCH_2CON(n\text{-}C_4H_9)_2$	Oil	312
$SCH_2CH{=}CH_2$	66	233
$SCH(CH_3)_2$	61	232
SCH_2CH_2COOH	153–156	119
$SCH_2CH_2CON(C_2H_5)_2$	Oil	312
$SCH(CH_3)COOH$	115–118	119
$SCH(CH_3)CONH_2$	130	119
$SCH(CH_3)CON(C_2H_5)_2$	55–57	119
SC_6H_5	82	186
$SC_6H_4Cl(4)$	96.5–97.5	263
$SCH_2C_6H_5$	107–108	311
$SHgCH_3$	196	313
SO_2Cl	50–55	314
$SO_2NH(CH_2)_3CH_3$	65	314
$SO_2NHCH_2CH_2CH_3$	127–128	314
$SO_2NHCH(CH_3)C_6H_5$	173–174	314
	210–211	314
SO_2NHNH_2	185–186	314
SO_3H	249 (dec)	309
$SSCCl_3$	94–95	308
	157.5 171	309 264
$NHSO_2C_6H_4N{=}CHC_6H_5(4)$		382
$NHSO_2C_6H_4N{=}CHC_6H_4N(CH_3)_2(4)$		382
$NHSO_2C_6H_4N{=}CH(5\text{-Nitro-2-furyl})(4)$		382
$N[(CH_2)_3COONa]SO_2C_6H_4NH_2(4)$		384
$N[(CH_2)_3SO_3Na]SO_2C_6H_4NH_2(4)$		384
$N(CH_2CH{=}CH_2)_2$		381
	285	388
$NHN{=}C(CH_3)_2$		380
$NHN{=}C(CH_3)CH_2CH_3$		380
$NHN{=}C(CH_3)C_6H_5$		380

TABLE II (*continued*)

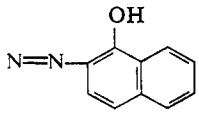
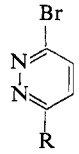
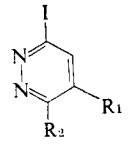
R	MP (°C)	References
		386
$OC_6H_3(CH_3)_2(2,3)$	95–96	379
$OC_6H_3(CH_3)_2(2,5)$	77–79	379
$OC_6H_3(CH_3)_2(2,6)$	94–95	379
$OC_6H_4C_2H_5(2)$	bp 130–142 (0.04 mm)	379
$OC_6H_4CH_2CH{=}CH_2$	bp 167–173 (1.0 mm)	383
$OC_6H_4C_3H_7$-*n*(2)	82–83	379
$OC_6H_4CH_2(CH_3)C{=}CH_2$	47	383
$OC_6H_4CH_2CH{=}CHCH_3$	bp 160–180 (0.4 mm)	383
$OC_6H_3CH_3(2)C_3H_7$-*i*(5)	bp 145–149 (0.12 mm)	379
$OC_6H_3CH_3(3)C_3H_7$-*i*(4)	84	379
$OC_6H_3CH_3(5)C_3H_7$-*i*(2)	85–87	379
$OC_6H_4C_4H_9$-*n*(2)	bp 156–165 (0.18 mm)	379
$OC_6H_4C_4H_9$-*sec*(2)	92–94	379
$OC_6H_3CH_3(5)C_4H_9$-*sec*(2)	72	379
$OC_6H_3CH_3(3)C_4H_9$-*sec*(4)	165–175 (0.4 mm)	379
$OC_6H_4C_4H_9$-*t*(2)	109–110	379
$OC_6H_4C_4H_9$-*t*(4)	112–114	379
$OC_6H_4C_7H_{15}$-*n*(2)	bp 178–187 (0.25 mm)	379
$OC_6H_4Cl(2)$	68–69	379
$OC_6H_2Cl_2(2,4)CH_3(6)$	147	379
$OC_6H_2Cl_3(2,4,6)$	167–168	379
$OC_6H_4Cl(4)CH_3(2)$	92–94	379
$OC_6H_3Cl(2)C_6H_5(4)$	102–106	379
2-Deoxy-3,5-di-*O*-(*p*-toluoyl)-D-*erythro*-pentofuranosyloxy		385
SO_2CH_2SCN	162–164.5	389
$OC_6H_3Cl(2)CF_3(5)$	106	390
$OC_6H_3Cl(4)CF_3(3)$	78–79	390
$OC_6H_4CF_3(2)$	138–143 (0.85 mm)	390
$OC_6H_4CF_3(3)$	63–65	390

TABLE III. 3-Bromo-6-substituted Pyridazines



R	MP (°C)	References
Br	115–116	3, 91
	117–118	30, 94
H	73–74	10
CH_3	78	10
C_6H_5	166–168	114
NH_2	180 (dec)	30
	210 (dec)	193
	205–206.5	91
NHC_6H_5	186–187	263
$NHSO_2C_6H_4CH_3(4)$	142	284
$NHSO_2C_6H_4NH_2(4)$	200 (dec)	30, 193
	243–244	93
$NHSO_2C_6H_4NHAc(4)$	194 (dec)	193
$N(CH_3)_2$	118	114
—N⟨ ⟩	145	288
OH		294, 60a
O^-Ag^+		294
OCH_3	103–104	30
	104–105	134
OC_2H_5	68–70	134
OC_3H_7-*n*	62–63	134
OC_3H_7-*i*	64–65	134
OC_4H_9-*n*	59–62	134
$OCH(CH_3)CH_2CH_2CH_3$	48–50	134
OC_6H_5	71	263
$OC_6H_4CH_3(4)$	96–98	263
$OC_6H_4C_6H_5(2)$	112	263
$OC_6H_4OCH_3(2)$	121–122	263
$OC_6H_3CH_3(3)Cl(4)$	94–95	263
$OC_6H_3Cl_2(2,4)$	88–89	263
$OC_6H_3Cl_2(2,6)$	126	263
$OC_6H_3NO_2(2)Cl(4)$	168	263
$OC_6H_4NO_2(2)$	100–102	263
$OC_6H_4NO_2(3)$	125–126	263
$OC_6H_4NO_2(4)$	124–125	263
$OC_6H_3(NO_2)_2(2,4)$	165–166	263
Tetraacetyl-1-β-D-glucosyloxy	170–178	294, 302
$OPO(OC_4H_9n)_2$		306
$OPS(OCH_3)_2$		306
SH	140–145 (dec)	311
$SCH_2CON(C_2H_5)_2$	87–89	312
SCN	110–115 (dec)	126

TABLE IV. 3-Iodo-5,6-disubstituted Pyridazines



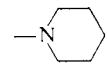
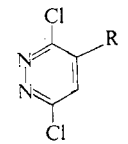
R_2	R_1	MP (°C)	References
I	H	157–158	3
I HI	H	171.5–172	3
CH_3	H	90.5	54, 113
NH_2	H	197–200	3
OCH_3	H	104–105	3, 134
OC_2H_5	H	90–91	134
OC_3H_7-*n*	H	65–66	134
OC_3H_7-*i*	H	95–97	134
OC_4H_9-*n*	H	65–66	134
OC_5H_{11}-*n*	H	51–52	134
OC_6H_{13}-*n*	H	56–57	134
H	$N(CH_2CH_2OH)_2$	176–178	398
H		117–119	398

TABLE V. 3,6-Dichloro-4-substituted Pyridazines



R	MP (°C)	References
Br	80–81	97
CH_3	83–84	3, 276e
	83.5–84	71
	85–87	30
$CH_2COOC_6H_5$	85–86	376
	106–107	87
COOH	144 (dec)	316
C_6H_5	92	9
NH_2	203	18, 73, 391, 121
	205	119
$NHSO_2C_6H_4NH_2(4)$	191	57
	200–201	170
$NHCH_3$	146–147	124
	154–156	119
NHC_2H_5	97–99	119
$NHCH_2COOH$	120	119
$N(CH_3)_2$	66–67	119

TABLE V (*continued*)

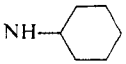
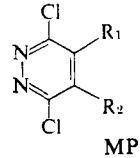
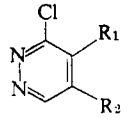
R	MP (°C)	References
$N(CH_3)CH_2COOH$	105–108	119
$N(C_2H_5)_2$	bp 154 (0.5 mm)	119
$N(CH_2CH_2OH)_2$	126–128	119
$N(C_3H_7)_2$-*i*	116–119	119
$N(CH_2CH_2CH_2CH_3)_2$	bp 158–162 (0.5 mm)	119
	96	119
NHC_6H_5	140	97
$NHC_6H_4OH(2)$	278–280	227, 228
$NHC_6H_4OCOCH_3(2)$	106–107	228
$NHC_6H_4OCH_3(2)$		227
$NHNH_2$	195–196	125
	199–200	145
OH	212	119
O^-Ag^+		262
OCH_3	130–131	145
	132	119
OC_2H_5	115–116	119, 125
OCH_2CH_2Cl	119–122	119
$OCH_2CH_2N(CH_3)_2$	79–80	119
OCH_2CH_2OH	114–115	119
$OCH_2CH_2OCH_3$	68–70	119
$OCH_2COOC_2H_5$	142–145	119
$OCH_2CH_2CH_2CH_3$	76–77	119
OC_6H_5	84–85, 87–88	119, 379
$OC_6H_4Cl(4)$	112–114	119
$OC_6H_3Cl_2(2,4)$	125–126	119
$OC_6H_4NH_2(2)$	118–119	227, 228
$OC_6H_4NH_2COCH_3(2)$	164.5–165	228
$OC_6H_4NO_2(2)$	161.5–162.5	227, 228
Tetraacetyl-1-β-D-glucosyl	128–130	262, 315
$OP(O)(OEt)_2$	bp 100 (0.15 mm)	317
SCH_3	126–128	119
SCN	115–117	119, 126
SC_2H_5	81–82	119
SCH_2COOH	135–136	119
$SCH_2COOC_4H_9$	90	119
SCH_2CONH_2	197	119
$SC_6H_4Cl(4)$	148–150	119
$SC_6H_4NH_2(2)$	150	97, 226
$SC_6H_4NHCH_3(2)$	120 (dec)	97
CH_2OH		276e
C_4H_9-*t*		276a, 392
$C_6H_4NH_2(4)$		393
$C_6H_4N{=}NR(4)$		393
3,5-Di-*O*-*p*-tolyl-2-deoxy-D-*erythro*-pentofuranosyloxy		394

TABLE VI. 3,6-Dichloro-4,5-disubstituted Pyridazines



R_1	R_2	MP (°C)	References
Cl	NH_2	203–204	119
Cl	$NHCH_3$	113–114	119
Cl	$NHCH(CH_3)_2$	73–75	119
Cl	NH–⬡	56–58	119
Cl	$N(CH_3)_2$	82–84	119
Cl	$N(C_2H_5)_2$	57–58	119
Cl	OH	247–248	119, 395
CH_3	C_2H_5	56–58	9
CH_3	C_6H_5	120–122	14
OH	OH	250	119
OCH_3	OCH_3	103–105	119
SCH_3	SCH_3	112–115	119
SC_2H_5	SC_2H_5	47–48	119
Cl	OCH_3		395, 396
Cl	OC_2H_5		395, 396
Cl	OC_3H_7		396
CH_3	CH_3		276e

TABLE VII. 3-Chloro-4,5-disubstituted Pyridazines



R_1	R_2	MP (°C)	References
Br	Cl	86	266
Cl	NH_2	151	121
		178	19
Cl	OCH_3	101–102	119
H	CH_3	139–140	8, 103, 168
H	NH_2	153–154	20
H	$NHCOCH_3$	180.5	20
H	$NHCH_3$	172–173	124
H	OC_2H_5	100–102	20
CH_3	H	46–47	168
		46.5–47.5	8
CH_3	CH_3	47–48	86
CN	H	41–42	17

TABLE VII (*continued*)

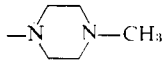
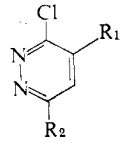
R_1	R_2	MP (°C)	References
$CONH_2$	H	72	17
$COOC_2H_5$	H	49	17
NH_2	Cl	151	19
		176–178	121
OH	NH_2	259 (dec)	18
OH	$NHCOCH_3$	258 (dec)	18
OCH_3	H	129–130	58
OCH_3	OCH_3	89–90	119
		91–92	174
OC_2H_5	H	101–102	58
$SCH_2C_6H_5$	$SCH_2C_6H_5$	113–114	212
$SCH_2C_6H_4Cl(2)$	$SCH_2C_6H_5Cl(2)$	135–136	212
$SCH_2C_6H_4Cl(4)$	$SCH_2C_6H_4Cl(4)$	120–121	212
$SCH_2C_6H_3Cl_2(3,4)$	$SCH_2C_6H_3Cl_2(3,4)$	130–131	212
Cl	SH		397
Cl	$SCH_2C_6H_5$		397
H	$N(CH_3)C_6H_5$		398
H	$N(CH_2CH_2OH)_2$		398
H	$N(CH_2CH_2OOCC_6H_5)_2$		398
H			398
SH	OC_2H_5		268b
Cl	OC_6H_5	68–69	379
Cl	$OC_6H_4OCH_3(4)$	60–64	379

TABLE VIII. 3-Chloro-4,6-disubstituted Pyridazines



R_1	R_2	MP (°C)	References
Cl	OCH_3	49–52	119
Cl	$OCH_2COOC_2H_5$	69–70	119
CH_3	Br	97	68
CH_3	CH_3	93–95	66
		98–100	9
CH_3	NH_2	186–187	187, 236
		188	8
		192	167
CH_3	$NHCOCH_3$	216	236

TABLE VIII (*continued*)

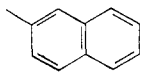
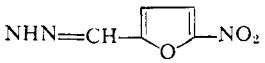
R_1	R_2	MP (°C)	References
CH_3	$NHSO_2C_6H_4NH_2(4)$	210–214	30
		230	169
CH_3	$NHSO_2C_6H_4NHCOCH_3(4)$	238 (dec)	169
CH_3	$NHNH_2$	158	236
		193	8
CH_3	$N(CH_3)_2$	122	187
CH_3	OH	220	187
		224	236
		227	167
CH_3	OCH_3	68–70	167
		71.5–72.5	24
CH_3	OCH_2CH_3	49	187
CH_2OH	CH_3	180	17, 401
		184.5–186	319
COOH	CH_3	181 (dec)	319
COOH	OH	245 (dec)	167
$COOC_2H_5$	CH_3	41	17
$COOC_2H_5$	OH	112	135
$CONH_2$	CH_3	206	17
$CONH_2$	OH	259–260	135
$CONHNH_2$	CH_3	125 (dec)	17
CN	CH_3	106 (dec)	17
C_2H_5	CH_3	38–40	9
$C(CH_3)_3$	CH_3	61.5–62.5	318
C_6H_5	CH_3	110–112	13
C_6H_5	C_6H_5	86–88	11
		102–103	12
NH_2	OH	301–302	119
OH	OH	282–283	119
OH	OCH_3	205–208	119
		286	180
OCH_3	OH	286–288	119
OCH_3	OCH_3	95	119
$OC_6H_4OCH_3(2)$	Cl	151	263
$OC_6H_4NO_2(2)$	Cl	164	263
$OC_6H_4NO_2(3)$	Cl	173–175	263
$OC_6H_4NO_2(4)$	Cl	173	263
CH_3			399
CH_3		136–139 (dec)	400
CH_2Cl	CH_3	86	401

TABLE VIII (*continued*)

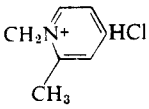
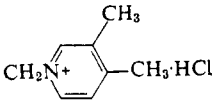
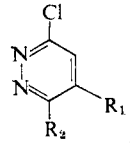
R_1	R_2	MP (°C)	References
	CH_3	202–204	401
	CH_3	218 (dec)	401
$COOC_2H_5$	CH_3	41	401
$NHCH_2CH_2OH$	$NHNH_2$		226a
$N(CH_2CH{=}CH_2)_2$	$NHNH_2$		402
$N(CH_2CH{=}CH_2)_2$	$NHN{=}CHC_6H_3Cl_2(2,6)$		402
OH	CH_3		65a
OCH_3	CH_3		65a
$CH(CH_3)_2$	$N(CH_3)_2$		403
$C(CH_3)_3$	$N(CH_3)_2$		403

TABLE IX. 3-Chloro-5,6-disubstituted Pyridazines

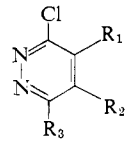


R_1	R_2	MP (°C)	References
Cl	$OCH_2COOC_2H_5$	116–117	119
CH_3	Br	98.5	68
CH_3	CH_3	50–51	320
CH_3	NH_2	111–113	8, 167
		137	187
CH_3	$NHNH_2$	149	8
		199–200	236
CH_3	OH	169–170	187, 236
		171	167
CH_3	OCH_3	113	187
		116–118	167
		118.5–119.5	239
CH_3	OCH_2CH_3	78	187
CH_2Cl	OCH_3	64–65	167
CH_2OH	OCH_3	150–151	167
COOH	OH	216 (dec)	167

TABLE IX (*continued*)

R_1	R_2	MP (°C)	References
COOH	OCH_3	158.5 (dec)	167
$C(CH_3)_3$	CH_3	43–43.5	318
C_6H_5	C_6H_5	110–111	11
NH_2	NH_2	186–187	123
NH_2	$NHCH_3$	241–242	124
NH_2	$NHNH_2$	209	20, 123
NH_2	OH	285	171
NH_2	OCH_3	190–191	57
		195	70
NH_2	OC_2H_5	177–178	57
NH_2	$OCH_2CH_2CH_2CH_3$	164–165	119
NH_2	SH	185–195 (dec)	124
$NHCOCH_3$	OH	255–256	171
$NHCOC_6H_5$	OH	235	245
$NHCH_3$	NH_2	201–202	124
$NHCH_3$	$NHNH_2$	217–218	124
$NHCH_3$	OCH_3	178–179	119
$NHCH_3$	$OCH_2CH_2CH_2CH_3$	n_D^{20} 1.5590	119
NHC_2H_5	OCH_3	95–97	119
NHC_2H_5	$OCH_2CH_2CH_2CH_3$	n_D^{20} 1.5498	119
$NHSO_2C_6H_4NH_2(4)$	OCH_3	196	57
		207–208 (dec)	170
$NHSO_2C_6H_4NH_2(4)$	OC_2H_5	155–155.5	57
$N(CH_3)_2$	OH	245–246	119
$N(CH_3)_2$	OCH_3	82–85	119
$N(CH_3)_2$	OC_2H_5	86–88	119
$N(CH_3)_2$	OCH_2CH_2OH	112–113	119
$N(CH_3)_2$	$OCH_2CH_2CH_3$	48–50	119
$N(CH_3)_2$	$OCH(CH_3)_2$	46–48	119
$N(CH_3)_2$	OC_6H_5	*bp* 190–195 (0.3 mm)	119
$N(CH_3)_2$	$OCH_2C_6H_5$	62–64	119
$N(CH_3)_2$	SCH_2COOH	160–163	119
$N(CH_3)_2$	$SCH_2COOC_2H_5$	83–84	119
$N(C_2H_5)_2$	OCH_3	n_D^{20} 1.5585	119
$N(C_2H_5)_2$	$O(CH_2)_3CH_3$	n_D^{20} 1.5348	119
OH	OH	218–219	119
OH	OCH_3	225–228	119
OCH_3	OH	195–196	119
		126	180
OCH_3	OCH_3	130	119
SCH_3	OH	190	119
$SC_6H_4NH_2(2)$	OCH_3	133 (dec)	97
C_2H_5	$N(CH_3)_2$		403
$CH(CH_3)_2$	$N(CH_3)_2$		403
C_6H_5	$N(CH_3)_2$		403
$NHCH_2CH_2OH$	$NHNH_2$		226a

TABLE X. 3-Chloro-4,5,6-trisubstituted Pyridazines



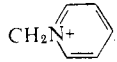
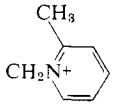
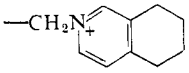
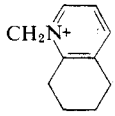
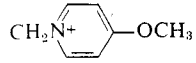
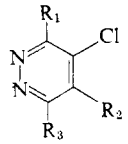
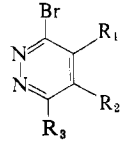
R_1	R_2	R_3	MP (°C)	References
CH_3	CH_3	Cl	120–121	281
CH_3	CH_3	NH_2	198–201	169
CH_3	CH_3	$NHSO_2C_6H_4NH_2(4)$	221	169
CN	CH_3	CH_3	79–80	6
			81–82	5
OH	OH	$CH_2C_6H_5$	232–233	65
OCH_3	OCH_3	OCH_3	64–66	119
SCH_3	SCH_3	SCH_3	82–83	119
CH_2Cl	CH_3	CH_3	90–92 (dec)	401
CH_2NH_2	CH_3	CH_3 (HCl)	281–282 (dec)	401
	CH_3	CH_3 (HCl)	144 (dec)	401
		CH_3 (perchlorate)	222 (dec)	401
	CH_3	CH_3 (HCl)	158 (dec)	401
	CH_3	CH_3 (HCl)	173 (dec)	401
	CH_3	CH_3 (HI)	162 (dec)	401
	CH_3	CH_3 (HCl)	168 (dec)	401

TABLE XI. 4-Chloro-3,5,6-trisubstituted Pyridazines



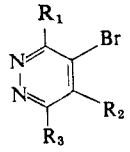
R_1	R_2	R_3	MP (°C)	References
Cl	OCH_3	H	101–102	174
H	NH_2	H	70–73	19
H	NH_2	NH_2	205	19
H	NH_2	$NHNH_2$	201–202 (dec)	19
H	NH_2	$NHNH_2$ (picrate)	199–200	19
H	NH_2	OCH_3	>310	20
CH_3	H	CH_3	63	322
C_6H_5	H	C_6H_5	138	85
OCH_3	H	CH_3	121–122	52
OCH_3	H	OCH_3	60–62	53
			86	56
OCH_3	H	NH_2	151–152	59
OCH_3	H	$NHCOCH_3$	245–247 (dec)	59
OCH_3	NH_2	H	178–179	20
OC_2H_5	NH_2	H	181	20
$OC_4H_9(n)$	NH_2	H	131–133	20
OCH_3	OCH_3	H	161–162	174
C_6H_5	C_6H_5	H	124–126	321

TABLE XII. 3-Bromo-4,5,6-trisubstituted Pyridazines



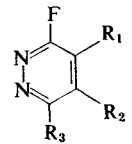
R_1	R_2	R_3	MP (°C)	References
H	CH_3	$NHNH_2$	179.5–180	68
CH_3	H	Br	103	68
			104–105	3
CH_3	H	$NHNH_2$	140–145	68
CH_3	H	$N(CH_3)_2$	118.5	68

TABLE XIII. 4-Bromo-3,5,6-trisubstituted Pyridazines



R_1	R_2	R_3	MP (°C)	References
C_6H_5	C_6H_5	C_6H_5	175	110
OAg	Br	OAg		109
OC_2H_5	Br	OAg		109
$OPS(OC_2H_5)_2$	Br	$OPS(OC_2H_5)_2$		306

TABLE XIV. 3-Fluoro-4,5,6-trisubstituted Pyridazines

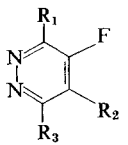


R_1	R_2	R_3	MP (°C)	References
OCH_3	OCH_3	OCH_3	29–31	51
SC_6H_5	SC_6H_5	SC_6H_5	140.5–143	51
OCH_3	OCH_3	F	*bp* 78–80 (0.52 mm)	51
SC_6H_5	SC_6H_5	F	97–99	51, 404
Phthalimido	Phthalimido	F	326–328	51
NH_2	F	F	89.5–91	50, 51, 404
$N(CH_2CH_3)_2$	F	F	*bp* 64–66 (0.005 mm)	51
OCH_3	F	F	bp 74–76 (3.0 mm)	50, 51
$Re(CO)_5$	F	F	144	120
$Mn(CO)_5$	F	F	121 (dec)	120
π-$C_5H_5Fe(CO)_2$	F	F	147	120
π-$C_5H_5Mo(CO)_3$	F	F	181	120
F	F	F	bp 117 (760 mm)	50
			58–60 (0.65 mm)	51
H	H	$NHCH{=}C(CN)COOC_3H_7$-*n*		387
F	OCH_3	OCH_3		263a
$CF(CF_3)_2$	F	$CF(CF_3)_2$		276c, 276d
OCH_3	F	OCH_3		263a
Cl	Cl	F		276g

TABLE XIV (*continued*)

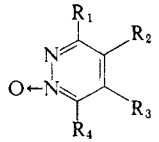
R_1	R_2	R_3	MP (°C)	References
$CF(CF_3)_2$	$CF(CF_3)_2$	F		276b, 276d
F	F	OH	129–131	404
F	F	OCH_3	54–56	263a, 263b
F	$CF(CF_3)_2$	F		276c, 276d
F	$NHC_6H_3CH_3(3)N{=}NR(4)$	F		405

4-Fluoro-3,5,6-trisubstituted Pyridazines



R_1	R_2	R_3	MP (°C)	References
OCH_3	F	OCH_3	105–108	404
			115–117	263a, 263b
OCH_3	OCH_3	OCH_3	85–87	263a
$CF(CF_3)_2$	$CF(CF_3)_2$	$CF(CF_3)_2$		276b, 276c

TABLE XV. Halopyridazine 1-Oxides



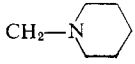
R_1	R_2	R_3	R_4	MP (°C)	References
Br	H	H	H	122–123	67
Br	NO_2	H	CH_3	123–124	328, 329
Cl	H	H	H	93	185
Cl	CH_3	H	H	148–149	168
Cl	H	CH_3	H	127–128	168
Cl	H	H	CH_3	160–161	179, 192
Cl	H	H	NH_2	255	271
Cl	H	H	NHC_2H_5	75–76	129
Cl	H	H	$NHCOCH_3$	203	271
Cl	H	H	OCH_3	187–188	129
Cl	H	H	OC_2H_5	138–139	129
Cl	NO_2	H	CH_3	103	327, 328
				103–103.5	192, 329
Cl	H	H	SCH_3	73	309
				198	
Cl	H	H	SC_2H_5	150	330
Cl	H	H	$SCH(CH_3)_2$	150	330
Cl	H	H	SC_6H_5	190–191	330
I	NO_2	H	CH_3	124–125	328, 329
H	Br	H	H	124–125.5	67
H	Br	OH		193–194	95
H	Cl	H	H	119–121	61
H	Cl	H	CH_3		62
CH_3	Cl	H	H	132.5–133	62
H	Cl	CH_3	H	61–62	62
CH_3	Cl	H	COOH	115 (dec)	62
CH_3	Cl	H	CN	150–151	62
CH_3	Cl	H	CH=NOH	224 (dec)	62
CH_3	Cl	H	CH_3	130–131	62
CH_3	Cl	H	CH_3	132–133	53
H	Cl	H	CH=NOH	218–219 (dec)	325
H	Cl	H	$CH=NOCOCH_3$	100	62
H	Cl	H	CN	205–206.5	67
OH	Cl	H	H	217	62
OH	Cl	H	CN	258 (dec)	62
OH	Cl	H	COOH	214	62
OCH_3	Cl	H	CH_3		62
OCH_3	Cl	H	CH=NOH	206 (dec)	325
OCH_3	Cl	H	$CH=NOCOCH_3$	142–143	67
OCH_3	Cl	H	CN	174–175	62

TABLE XV (*continued*)

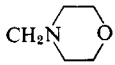
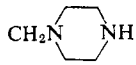
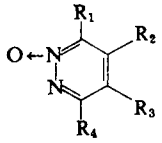
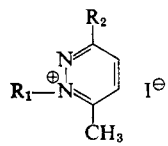
R_1	R_2	R_3	R_4	MP (°C)	References
$O(CH_2)_4CH_3$	Cl	H	CH=NOH	112.5–113.5	325
OCH_3	Cl	H	OCH_3	141–142	64
H	H	Br	H	117–119	67
H	H	Cl	H	119–120.5	67
CH_3	H	Cl	CH_3	126–127	53, 65
CH_3	H	Cl	CN	162–163	63
H	H	H	Br	111–113	67
H	H	H	Cl	157–158	130
CH_3	CH_3	H	Cl	184–184.5	324
NHC_2H_5	H	H	Cl	137–138	129
	H	H	Cl	124–125	192
N_3	H	H	Cl	153–154	60
OH	H	H	Cl	224–225 (dec)	183
OH	NO_2	H	Cl	214–215 (dec)	183
OH		H	Cl	204–206	326
OH		H	Cl	120–121	326
			HCl salt	233 (dec)	
OCH_3	Cl	H	Cl	153–154	183
OCH_3	OCH_3	H	Cl	188–190 (dec)	183
OCH_3	NO_2	H	Cl	144–145	183
OCH_3	H	H	Cl	160–161	129, 179
OCH_3	CH_3	H	Cl	138–139	239
OCH_3	H	CH_3	Cl	152–153	239
OC_2H_5	H	H	Cl	115–116	129
$OCH_2CH_2CH_3$	H	H	Cl	83–84	129
C_6H_5	H	H	Cl	151–151.5	54
CH_3	H	H	I	216	113
Cl	Cl	H	CH_3	165–166	62
Cl	Cl	H	CH=NOH	234 (dec)	62, 406
Cl	Cl	H	$CH=NOCOCH_3$	111–112	62
Cl	Cl	H	CN	132–133	62
Cl	Cl	NH_2	H	282 (dec)	67
Cl	Cl	H	OCH_3	134	46
Cl	NH_2	Cl	H	204 (dec)	67
Cl	H	H	Cl	110–112	41
				118–120	181
Cl	H	OCH_3	Cl	162.5–164	180
H	Br	OH	Br	190–191	95
Cl	Cl	Cl	H	124–125	67
OH	Br	H	CH_3		95a
OH	CH_3	H	Br		95a

TABLE XVI. Halopyridazine 2-Oxides



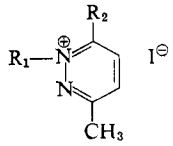
R_1	R_2	R_3	R_4	MP (°C)	References
Cl	H	OCH_3	OCH_3	190	180
CH_3	H	Cl	H	167–168	52
CH_3	H	Cl	OCH_3	138–139	52
NH_2	H	Cl	OCH_3	204 (dec)	59
NH_2	H	Cl	OCH_3 (HCl salt)	196 (dec)	59
NH_2	H	Cl	OC_2H_5 (HCl salt)	187 (dec)	59
NH_2	H	Cl	OC_3H_7 (HCl salt)	169 (dec)	59
NH_2	H	Cl	OC_4H_9 (HCl salt)	161 (dec)	59
$NHCOCH_3$	H	Cl	OCH_3	233–234 (dec)	59
CH_3	H	H	Cl	163–164	331
CH_3	H	NO_2	Cl	103–103.5	52
CH_3	CH_3	H	Cl	109–110	324
CH_3	CH_3	NO_2	Cl	105–106	184
NH_2	H	H	Cl	248 (dec)	279, 332
				253–255	178, 279
$NHCOOC_2H_5$	H	H	Cl	160–161	332
$NHCOCH_3$	H	H	Cl	202–203	178
C_6H_5	H	H	Cl	157.5–158.5	54
Cl	OCH_3	H	Cl	162.5–164	61
Cl	H	OCH_3	Cl	174–175	180

TABLE XVII. 3-Halo-6-methyl-1-substituted Pyridazinium Iodides



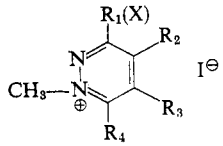
R_1	R_2	References
C_2H_5	Cl	114
i-C_3H_7	Cl	114
C_2H_5	I	114
i-C_3H_7	I	114

TABLE XVIII. 3-Halo-6-methyl-2-substituted Pyridazinium Iodides



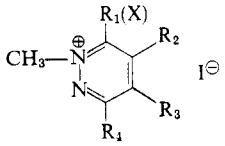
R_1	R_2	References
C_2H_5	Cl	114
i-C_3H_7	Cl	114
C_2H_5	I	114
i-C_3H_7	I	114

TABLE XIX. 3-Halo-1-methyl-4,5,6-trisubstituted Pyridazinium Iodides



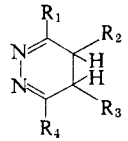
R_1	R_2	R_3	R_4	References
Cl	H	H	Cl	114
Cl	H	H	CH_3	114
Cl	H	H	C_2H_5	114
Cl	H	H	C_6H_5	114
Cl	H	H	$C_6H_4OCH_3$	114
Cl	H	H	NH_2	114
Cl	H	H	$NHCOCH_3$	114
Cl	H	H	$NHCH_3$	114
Cl	H	H	$N(CH_3)_2$	114
Cl	H	H	$N(CH_3)COCH_3$	114
Cl	H	H	OCH_3	114
Cl	H	CH_3	$N(CH_3)_2$	114
Cl	CH_3	H	$N(CH_3)_2$	114
Cl	C_6H_5	H	CH_3	114
Br	H	H	CH_3	114
Br	H	H	C_6H_5	114
Br	H	H	NH_2	114
Br	H	H	$NHCH_3$	114
Br	H	H	$N(CH_3)_2$	114
I	H	H	CH_3	114
I	H	H	C_6H_5	114
I	H	H	$N(CH_3)_2$	114

TABLE XX. 3-Halo-2-methyl-4,5,6-trisubstituted Pyridazinium Iodides



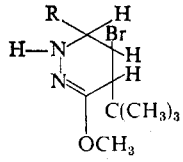
R_1	R_2	R_3	R_4	References
Cl	H	H	Cl	114
Cl	H	H	CH_3	114
Cl	H	H	C_2H_5	114
Cl	H	H	C_6H_5	114
Cl	H	H	$C_6H_4OCH_3$	114
Cl	H	H	NH_2	114
Cl	H	H	$NHCOCH_3$	114
Cl	H	H	$NHCH_3$	114
Cl	H	H	$N(CH_3)_2$	114, 408
			Cl^-	408
Cl	H	H	$N(CH_3)COCH_3$	114
Cl	H	H	OCH_3	114
Cl	H	CH_3	$N(CH_3)_2$	114
Cl	H	NH_2	OH	79
Cl	CH_3	H	$N(CH_3)_2$	114
Cl	C_6H_5	H	CH_3	114
Br	H	H	CH_3	114
Br	H	H	C_6H_5	114
Br	H	H	NH_2	114
Br	H	H	$NHCH_3$	114
Br	H	H	$N(CH_3)_2$	114
I	H	H	CH_3	114
I	H	H	C_6H_5	114
I	H	H	$N(CH_3)_2$	114

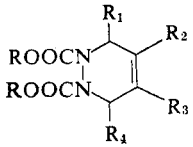
TABLE XXI. Halogenated Di-, Tetra-, and Hexahydropyridazines



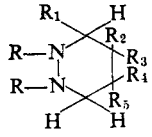
R_1	R_2	R_3	R_4	MP (°C)	References
Cl	$C(CH_3)_3$	H	Cl	bp 80 (1.0 mm)	323
Cl	$C(CH_3)_3$	H	OH	140–141	323
Cl	$C(CH_3)_3$	$C(CH_3)_3$	Cl		276a
Cl	CH_3	H	$C_6H_4Br(4)$	208	409
Cl	CH_3	H	$C_6H_4CH_3(4)$	97	409
Cl	H	CH_3	$C_6H_4CH_3(4)$	220	409
$C(CH_3)_3$	Br	$C(CH_3)_3$	$C(CH_3)_3$		392

TABLE XXI (*continued*)

R_1	R_2	MP (°C)	References
$C(CH_3)_3$	Cl		276a
$C(CH_3)_3$	$C(CH_3)_3$		276a
			
OH		169.5–171 (dec)	99
C_6H_5			100

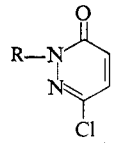


R_1	R_1	R_2	R_3	R_4	MP (°C)	References
CH_3	CH_3	Br	H	$COOCH_3$		410, 411
C_2H_5	H	Cl	H	H	bp 132–133 (1.25 mm)	88
C_2H_5	H	Cl	$CH_2CH{=}C(CH_3)_2$	H		70b

R_1	R_2	R_3	R_4	MP (°C)	References
					

R	R_1	R_2	R_3	R_4	R_5	MP (°C)	References
H	COOH	H	H	Cl	H		412, 413
$COOC_2H_5$	H	H	Br	H	Br	61–62	101
$COOC_2H_5$	H	CH_3	Br	CH_3	Br	90–92	102

TABLE XXII. 3-Chloro-1-substituted 6-(1*H*)pyridazinones



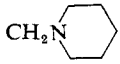
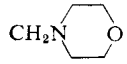
R	MP (°C)	References
CH_3	89–90	333
	90–91	119
	92–94	103
CH_2Cl	85–87	119
	89–90	333
$CH_2N(CH_3)_2$	60–61	119
	92–94	334, 416
	95–97	119
	123	416
	126	334
$CH_2N(C_3H_5)_2$	n_D^{20} 1.5402	119
$CH_2N(CH_2CH_2CN)_2$	67–71	119
CH_2OH	115–117	119
CH_2OCH_3	50–51	119
CH_2SCN	153–154	311
$CH_2SP(S)(OCH_3)_2$	bp 90 (0.3 mm) liq.	333
$CH_2SP(S)(OC_2H_5)_2$	52.5–53.6	333
$CH_2SP(O)(OC_2H_5)_2$	bp 115–120 (1 mm)	333
$COCH_3$	126	244
$COOC_2H_5$	53–54	311
	131–131.5 (0.25 mm)	
$COOC_4H_9$	146–147	311
$CON(C_2H_5)_2$	49–50	119
CH_2CH_2Cl	55–57	119
CH_2CH_2OH	101–102	119
$CH_2CH_2OCOCH_3$	73–75	119
$CH_2CH_2OCOCH_2Cl$	58–59	119
$CH_2CH_2OCOCHCl_2$	97–99	119
$CH_2CH_2OCOCCl_3$	119–120	119
CH_2CH_2SCN	104–105	119
CH_2COOH	142–145	173
	220	258
CH_2COOCH_3	68	119
$CH_2COOC_2H_5$	77–78	119
$CH_2COOCH_2CH_2N(CH_3)_2 \cdot HCl$	120	258, 297
$CH_2COOCH_2CH_2N(C_2H_5)_2 \cdot HCl$	118	258, 297
$CH_2COOCH_2CH_2CH_3$	63–64	119

TABLE XXII (*continued*)

R	MP (°C)	References
$CH_2COOCH_2CH_2CH_2CH_3$	82–83	119
CH_2CONH_2	220–222	335
	223	298
	165	298
$CH_2CONHNH_2$	161	298
	167–169	119
$CH_2CONHCH_3$	134–136	119
$CH_2CONHCH_2CH_2N(CH_3)_2 \cdot HCl$	263	258, 297
$CH_2CONHCH_2CH_2N(C_2H_5)_2 \cdot HCl$	258	258, 297
$CH_2CONHN{=}C(CH_3)_2$	216	298, 300
$CH_2CONHNH{-}CH(CH_3)_2$	311	298, 300
$CH_2CONHC_6H_5$	169–170	119
$CH_2CON(CH_3)_2$	125–128	119
$CH_2CON(C_2H_5)_2$	96–97	335
$CH_2CON(CH_2CH_2CH_3)_2$	128–129	119
$CH_2CONH(C_3H_7\text{-}i)$	201–202	119
$CH_2CON(CH_2CH_2CH_2CH_3)_2$	108	119
	130–134	335
$CH_2CON(C_2H_5)C_6H_5$	169–170	119
$CH_2CON(C_6H_5)_2$	232	119
CH_2CH_2CN	102–104	119
CH_2CH_2COOH	106–109	119
$CH_2CH_2CON(C_2H_5)_2$	60–62	119
$CH(CH_3)CON(C_2H_5)_2$	78–80	119
$CH(COOC_2H_5)_2$	bp 144 (0.2 mm)	119
$CH_2CH_2CH_2CH_3$	bp 67 (0.15 mm)	119
$CH_2CHClC_6H_5$	109–111	119
$CH_2COC_6H_5$	132–135	119
$CH(C_6H_5)CON(C_2H_5)_2$	147	119
C_6H_5	112–113	38
	117–118	83
$C_6H_4CH_3(4)$	108–109	21, 338
$C_6H_4Cl(4)$	138–140	28, 338, 49a
$C_6H_4NO_2(4)$	195–196	29, 338, 106a
$C_6H_3(NO_2)_2(2,4)$	167	263
1-Naphthyl	118–120	21
	126–128	338
2-Naphthyl	155–156	21, 338
Tetrahydrofuranyl	60–64	299, 414
Tetrahydropyranyl	130–132	299, 414
Tetrahydrothiopyranyl	57–60	337, 414
Tetraacetyl-1-β-D-glucosyl	148–149	294, 302
1-β-D-Glucosyl	230–232	294, 302
Tri-*O*-benzoyl-β-D-ribopyranosyl	205.5–206.5	295, 296
β-D-Ribopyranosyl		295, 296

TABLE XXII (*continued*)

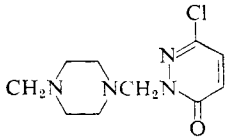
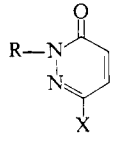
R	MP (°C)	References
Tri-*O*-benzoyl-β-D-ribofuranosyl		295, 296
β-D-Ribofuranosyl	152–153	295, 296
2′,3′-Isopropyliden-β-D-ribofuranosyl	127.5–128.5	305
2,3-Di-*O*-benzoyl-β-D-ribofuranosyl	Amorphous glass	305
2′,3′-Di-*O*-benzoyl-5′-*O*-diphenylphosphoryl-β-D-ribofuranosyl	Amorphous glass	305
β-D-Ribofuranosyl 5′-phosphate		305
β-D-Ribofuranosyl 5′-phenylphosphate		305
OH	173–174	244
Cl	130	308
$SCCl_3$		336
	227	416
$CH_2CON(CH_2CH{=}CH_2)_2$	139	415
$C_6H_4NO_2(3)$	188–189	106b
2-2-Deoxy-3,5-di-*O*-(*p*-toluoyl)-D-erythropentofuranosyl		385
2,3,5-Tri-*O*-benzoyl-D-xylofuranosyl		417

TABLE XXIII. 3-Bromo(iodo)-1-substituted 6(1*H*)pyridazinones



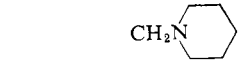
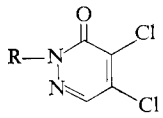
R	X	MP (°C)	References
$CH_2CON(C_2H_5)_2$	Br	123–124.5	335
C_6H_5	Br	122–124	21, 38, 338
1-β-D-Glucosyl	Br	224–225	294, 302
Tetraacetyl-1-β-D-Glucosyl	Br	159–161	294, 302
Tetrahydropyranyl	Br	129–130	299, 414
H	I	173	334
CH_2OH	I	163	334
$CH_2N(CH_3)_2$	I	137–145	334
	I	148–152	334

TABLE XXIV. 4,5-Dichloro-1-substituted 6(1*H*)pyridazinones



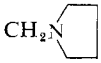
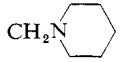
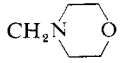
R	MP (°C)	References
H	202	78
	203–204	77
Cl	148–149	119
CH_3	70–71	49
	85–88	119
	89–90	119
	90–91	69
	134–144	49
CH_2Cl	67–68	119
	70–71	49
$CH_2N(C_2H_5)_2$	n_D^{20} 1.5470	119
$CH_2N(C_3H_5)_2$	n_D^{20} 1.5555	119
$CH_2N(CH_2CH_2Cl)_2$	75–79	334
$CH_2N(CH_2CH_2CN)_2$	81–82	119
	114–115	49
$CH_2NHC_6H_5$	62–63	49
$CH_2NHC_6H_3Cl_2(3,4)$	165–166	49
CH_2-N-4,5-Dichloro-6-oxopyridazinyl	221–222	49
	86–89	334
	115–116	334
	125	49
	127–128	334
CH_2OH	104–105	49
	113–115	119
CH_2OCOCH_3	87–89	49
CH_2-OCO-C_6H_5	97–99	49
CH_2SCN	105–106	119
CN	103–104	49
$COOC_2H_5$	141	119
	47–50	421
C_2H_5	49–51	49
	54–55	49
	54–56	119
$CH_2CH_2NH_2 \cdot HCl$	248 (dec)	49
$CH_2CH_2N(C_2H_5)_2 \cdot HCl$	193–194 (dec)	216
$CH_2CH_2\overset{\oplus}{N}(C_2H_5)_2(CH_3)Br^{\ominus}$	262–265 (dec)	216

TABLE XXIV (*continued*)

R	MP (°C)	References
$CH_2CH_2\overset{\oplus}{N}(C_2H_5)_3Br^{\ominus}$	242 (dec)	216
CH_2CH_2OH	54–56	119
CH_2COOH	174–176	119
	91–92	49
$CH_2COOC_2H_5$	94–95	119
CH_2CONH_2	245	119
$CH_2CON(C_2H_5)_2$	123–124	119
$CH(CH_3)_2$	69–70	49
	72–74	119
	140–141	378
$CH_2CH_2COC_6H_5$	100–101	49
$CH{=}CHCOC_6H_5$	161–162	49
CH_2CH_2CN	100	79
	102–103	49
CH_2CH_2COOH	124–125	79
	128–130	49
CH_2CH_2COCl	Syrup	79
$CH(CH_3)COOC_2H_5$	25–27	49
$CH_2CH_2CONH_2$	166–168	49
$CH_2CH_2CONHCH_3$	146–148	49
n-C_4H_9	Liquid	49
i-C_4H_9	37–38.5	49
sec-C_4H_9	34–36	49
t-C_4H_9	67–68	49
C_6H_5	161–162	49
	163–164	77, 78
$C_6H_4Cl(3)$	199–200	49
$C_6H_4Cl(4)$	270	49, 49a
$C_6H_3Cl_2(3,4)$	223 (dec)	49
$C_6H_4CH_3(3)$	119–120	49
$C_6H_4CH_3(4)$	147	49
$C_6H_4NO_2(3)$	210–212	49
$C_6H_4SO_3H(4)$	270	49
$C_6H_4SO_3Na(3)$		49
$C_6H_4SO_2NH_2(4)$	267–268	49
$CH_2C_6H_5$	87–89	49
$CH_2CH_2C_6H_5$	124–125	49
Cyclopentyl	62–63	49
Cyclohexyl	89–90	49, 423
4-Methylcyclohexyl	70–71	49
2-Chlorocyclohexyl	133–134	49
Cycloheptyl	47–48	49
4-Chlorotricyclo[2.2.1.0]hept-3-yl	118–121	49
Cyclooctyl	58–59	49, 423
2-Bromocyclooctyl	162–163	49
2-Chlorocyclooctyl	96–97	49

TABLE XXIV (*continued*)

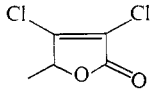
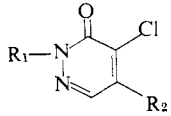
R	MP (°C)	References
Chlorocyclooct-5-enyl	151–153	49
2-Chlorocyclododecyl	87–89	49
Perhydro-4,7-methanoindenyl	92–100	49
Tetra-*O*-acetylglucosyl	164–165	49
α-Naphthyl	198	49
CH_2-Furfuryl	78–80	49
CH_2CH_2-pyrrolidinyl	80–81	49
N-Methyl-4-piperidinyl·HCl	310	49
N-Methyl-4-piperidinyl·CH_3I	280	49
2-Benzimidazolyl	259–260	49
2-Benzthiazolyl	216–218	49
$C_6H_4CF_3$(3)	90–91.5	418, 424
	92–94	419, 422
$C_6H_4CH{=}CH_2$		425
Cyclododecyl		423
		420

TABLE XXV. 5-Chloro-1,4-disubstituted 6-(1*H*)pyridazinones



R_1	R_2	MP (°C)	References
H	Br	208	18
H	NH_2	350–354	210
		352	49
H	$NHCH_3$	252–253	49
H	$NHCH_2C_6H_5$	209	216
H	NHC_2H_5	198–200	49
		205	216
H	$NHCH_2CH_2OH$	250–251	216
H	$NHCH_2CH_2N(C_2H_5)_2$	145	216
H	$NHCH_2CH_2\overset{\oplus}{N}(CH_3)(C_2H_5)_2Br^{\ominus}$	252	216
H	$NHCH_2CH_2C_6H_5$	163	216
H	NHC_6H_5	246–247	49
H	$NHC_6H_4CH_3$(4)	203–206	49
H	$NHC_6H_4OCH_3$(4)	242–243	49
H	NH-Cyclohexyl		49

TABLE XXV (*continued*)

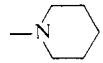
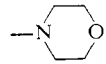
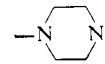
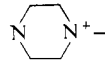
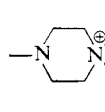
R_1	R_2	MP (°C)	References
H	$N(CH_3)_2$	200–201	49
H	$N(C_2H_5)_2$	119	49
		181–182	216
H	$N(CH_3)CH_2C_6H_5$	172–173	49
H		186–187	216
		192	212
H		229	216
		236	212
H		231	216
H		290 (dec)	216
H		290 (dec)	216
H	$NHCOCH_3$	277–279	171
H	$NHCOC_6H_5$	244	171
H	$—NHNH_2$	195 (dec)	172
H	$NHN{=}CHC_6H_5$	304 (dec)	172
H	$NHN{=}CHC_6H_4OH(3)$	300 (dec)	172
H	$NHN{=}CHC_6H_3(OCH_3)_2(3,4)$	276 (dec)	172
H	$NHN{=}C(CH_3)C_6H_5$	255 (dec)	172
H	$NHN{=}C(CH_3)C_6H_4CH_3(4)$	280 (dec)	172
H	$NHN{=}C(CH_3)C_6H_3(CH_3)_2(3,4)$	263	172
H	$NHN{=}C(CH_3)C_6H_4OH(2)$	289 (dec)	172
H	$NHN{=}C(CH_3)C_6H_3Cl_2(3,4)$	314 (dec)	172
H	$NHN{=}C(C_2H_5)C_6H_5$	209-210	172
H	$NHN{=}C(n\text{-}C_3H_7)C_6H_5$	217-218	172
H	$NHN{=}C(i\text{-}C_3H_7)C_6H_5$	251	172
H	$NHN{=}C(n\text{-}C_4H_9)C_6H_5$	190	172
H	$NHN{=}C(CH{=}CHCOOH)C_6H_5$	255 (dec)	172
H	$NHN{=}C(CH_3)CH{=}CHC_6H_5$	214 (dec)	172
H	$NHN{=}C(C_6H_5)_2$	304 (dec)	172
H	$NHN{=}C(C_6H_5)C_6H_4OCH_3(4)$	252	172
H	$NHN{=}C(CH_2C_6H_5)C_6H_4CH_3(4)$	276 (dec)	172
H	$NHN{=}C(CH_2C_6H_5)_2$	207	172
H	$NHN{=}C(C_6H_5)CH(OH)C_6H_5$	259 (dec)	172
H	$NHN{=}C(C_6H_5)COC_6H_5$	220 (dec)	172
H	NHN=CH—2-Furyl	259 (dec)	172

TABLE XXV (*continued*)

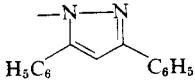
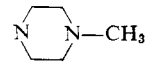
R_1	R_2	MP (°C)	References
H	NHN=C(CH_3)-3-Pyridyl	280 (dec)	172
H	NHN=CH-3-Pyridyl	287 (dec)	172
H	NHN=C(C_6H_5)$C_6H_4N(CH_3)_2$(4)	258 (dec)	172
H	NHN=C[$C_6H_4N(CH_3)_2$(4)]$_2$	253 (dec)	172
H	NHN=C$HC_6H_4N(CH_3)_2$(4)	252 (dec)	172
H		209	172
H	$SCOOCH_3$	234–235	343
H	SC_3H_5	231–232	343
H	SC_6H_5	210–211	343
H	$SC_6H_4NH_2$(2)	198 (dec)	225
CH_3	NH_2	203–204	49
CH_3	Morpholino	104–106	149
		132	216
CH_3		62	216
CH_3	$NHSO_2C_6H_4NH_2$(4)	208	215
CH_3	$NHSO_2C_6H_4NHCOCH_3$(4)	224	215
CH_3	$NHSO_2C_6H_4NHCH_3$(4)	198	215
CH_3	$SC_6H_4NH_2$(2)		25
CH_3	$NHNH_2$	153 (dec)	238, 340
CH_2Cl	Br	69–70	333
C_2H_5	NH_2	217	49
CH_2CH_2CN	NH_2	195–198	49
CH_2CH_2CN	NH-*i*-C_3H_7	91–92	49
CH_2CH_2OH	NH_2	178–180	49
CH_2COOH	NH_2	245–250	119
		252	49
		253–255	49
CH_2COOH	OH	244–248	119
CH_2COOH	OCH_3	210	119
$CH_2COOC_2H_5$	OCH_3	134–135	119
$CH_2CH_2N(C_2H_5)_2$·HCl	$NHCH_2C_6H_5$	154	216
$CH_2CH_2N(C_2H_5)_2$·HCl		149	216
$CH_2CH_2N(C_2H_5)_2$·HCl		161	216
$CH_2CH_2N(C_2H_5)_2$		62	216
$(CH_2)_3OCH_3$	NH_2	137–138	49
C_6H_5	Br	156	83

TABLE XXV (*continued*)

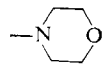
R_1	R_2	MP (°C)	References
C_6H_5	NH_2	205–206	49
C_6H_5	$NHCH_3$	212	213
		213	83
C_6H_5	$NHCH_2OH$	179–181	213
C_6H_5	$NHCOCH_3$	175–176	344
C_6H_5	$NHCOCHCl_2$	165.5–166.5	344
C_6H_5	$NHCOCCl_3$	194–195	344
C_6H_5	$NHCOCH_2CH_3$	127–128	344
C_6H_5	$NHCOCHClCH_3$	137–138	344
C_6H_5	$NHCOCH_2CH_2Cl$	119–120	344
C_6H_5	$NHCOCCl_2CH_3$	148–149	344
C_6H_5	$NHCOCH_2CH_2COOH$	160–162	345
C_6H_5	$NHCOCCl{=}CClCOOH$	158–161	345
C_6H_5	$NHCONHC_6H_5$	174–175	344
C_6H_5	$NHCONHC_6H_4Cl(3)$	210	344
C_6H_5	$NHCONHCH_2Cl$	124.5–125	213
C_6H_5	$NHCOOC_2H_5$	132–133	341
C_6H_5	$NHCOO(CH_2)_{17}CH_3$	75–77	341
C_6H_5	NHC_2H_5	156–157	213
C_6H_5	$NHCH_2CH_2OH$	170–171	213
C_6H_5	$NCH(OH)CCl_3$	163–166	344
C_6H_5	NHCOCOOH	195–196	345
C_6H_5	NHCOCOONa	>250	345
C_6H_5	$N(CH_3)COCOOH$	100–101	345
C_6H_5	$NHnC_3H_7$	137–138	213
C_6H_5	$NHCH(CH_3)_2$	143	213
C_6H_5	$NHCH_2CH{=}CH_2$	163–164	213
C_6H_5	$NHCH_2CH_2CH_2OH$	115–117	213
C_6H_5	$NHnC_4H_9$	83–84	213
C_6H_5	$NHCH_2CH(CH_3)_2$	80–82	213
C_6H_5	$NHCH(CH_3)CH_2CH_3$	169–170	213
C_6H_5	$NHSO_2C_6H_4NH_2(4)$	193	215
C_6H_5	$NHSO_2C_6H_4NHCOCH_3(4)$	226	215
C_6H_5	NH-Cyclooctyl	80–81	49
C_6H_5	$N(CH_3)_2$	89–90	213
C_6H_5	$N(C_2H_5)_2$	105–106	213
		107–108	49
C_6H_5	Pyrrolidinyl	148–149	49, 213
C_6H_5		177	212
C_6H_5		157	212
C_6H_5	1-Piperazinyl	143–144	49, 213
C_6H_5	2,6-Dimethylmorpholino	126	49, 213

TABLE XXV (*continued*)

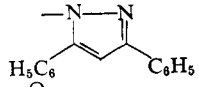
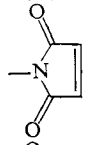
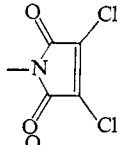
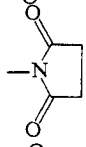
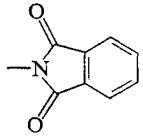
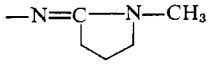
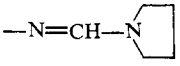
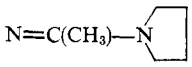
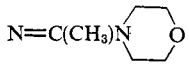
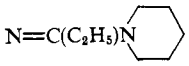
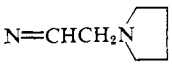
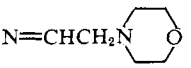
R_1	R_2	MP (°C)	References
C_6H_5		176–178	172
C_6H_5		229–230	345
C_6H_5		245	345
C_6H_5		259–260	345
C_6H_5		204–206	345
C_6H_5	$N{=}CHN(CH_3)_2$	162–163	340, 342
C_6H_5	$N{=}CHN(CH_3)_2{\cdot}HCl$	203–205	340
		245–247	342
C_6H_5		121–122	340
		152–153.5	342
C_6H_5		152–153.5	340
C_6H_5		169–171	340
C_6H_5		160–161	340
C_6H_5		128–130	340
C_6H_5		169–171	342
C_6H_5		160–161	342

TABLE XXV (*continued*)

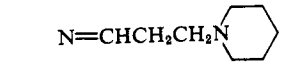
R_1	R_2	MP (°C)	References
C_6H_5		128–130	342
C_6H_5	—$NHNH_2$	164	172
		172	238, 340
C_6H_5	$NHNH_2$·HCl	150 (dec)	238
C_6H_5	$NHN{=}C(CH_3)_2$	120–121	238, 340
C_6H_5	$NHN{=}C(CH_3)C_2H_5$	107–109	238, 340
C_6H_5	N_3	110–111	340, 273a
C_6H_5	OH	247	248
		265	240a
C_6H_5	OCH_3	157–158	248
		160	240a
		165	212
C_6H_5	OC_2H_5	141	212
C_6H_5	SH	178–179	83
		180	339
C_6H_5	SCH_3	116–117	343
		120	432
C_6H_5	$SCOOCH_3$	157–158	343
C_6H_5	SC_6H_5	117–118	343
C_6H_5	$SCH_2C_6H_4Cl(4)$	155–156	346
C_6H_5	$SC_6H_4NH_2(2)$	209–210.5	217
C_6H_5	SCH_2-2-Pyridyl	146	267
C_6H_5	SO_2CH_3	160–162	347
$C_6H_4Cl(3)$	NH_2	214–216	49, 213
$C_6H_4Cl(4)$	NH_2	254–256	49, 213
$C_6H_4CH_2(4)$	NH_2	226	49
$C_6H_3NH_2(2)CH_3(4)$	NH_2	220–222	49
$C_6H_4OCH_3(4)$	NH_2	279–280	49
$C_6H_4COOH(4)$	NH_2		49
$C_6H_4SO_2NH_2(4)$	NH_2		49
$C_6H_4SO_2NHCH_3(4)$	NH_2	262–264	49
α-Naphthyl	NH_2	207–209	49
Cyclohexyl	NH_2	224–225	49, 429, 430
C_6H_{11}	NHCOCOOH	193–195	345
C_6H_{11}	$NHNH_2$	148 (dec)	238, 340
Cyclooctyl	NH_2	178–179	49
N-Methylpiperidyl·HCl	NH_2	296–297	49
Glucosyl	NH_2	178–180	49
CH_3	H		426
CH_3	$COOCH_3$		426
C_6H_5	H		426
C_6H_5	$COOCH_2CH{=}CH_2$		426
C_6H_5	$NHCON(CH_3)_2$	141–142	429, 430
C_6H_5	$NHCON(C_2H_5)_2$	137–138	429, 430
C_6H_5	$NHCON(CH_3)CH(CH_3)C{\equiv}CH$	142–143	429, 430

TABLE XXV (*continued*)

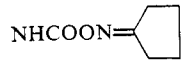
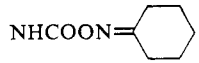
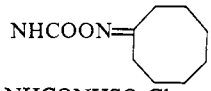
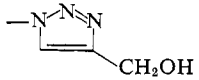
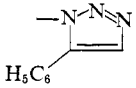
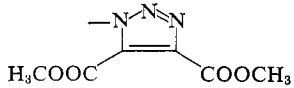
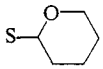
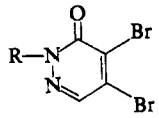
R_1	R_2	MP (°C)	References
C_6H_5	$NHCON(CH_3)OCH_3$	161–162	429, 430
C_6H_5		139–139.5	427, 428
C_6H_5		125	427, 428
C_6H_5		125–127	427, 428
C_6H_5	$NHCONHSO_2Cl$		431
C_6H_5	$NHCOOC_6H_4NHCOOC_2H_5(3)$		431
C_6H_5	NCO	154–155	427, 428
C_6H_5	$NHCOONC(CH_3)_2$	148–149	427, 428
C_6H_5		157	273a
C_6H_5		163–165	273a
C_6H_5		209–210	273a
C_6H_5		137	273a
C_6H_5	$SCH_2C_6H_5$		240a
C_6H_5		127	433
$C_6H_4F(4)$	NH_2		434
$C_6H_4F(4)$	$NHCH(OH)CCl_3$	228–229	434
$C_6H_4CF_3(3)$	NH_2	174–175	418
$C_6H_4CF_3(3)$	$NHCH_3$	183–185	419, 422
$C_6H_4CF_3(3)$	NHC_2H_5	132	419, 422
$C_6H_4CF_3(3)$	$N(CH_3)_2$	153	419, 422
$C_6H_4CF_3(3)$	OCH_3	152–153	418
$CH_2C_6H_5$	SH		268a
C_6H_{11}	NCO	121–123	429, 430
C_6H_{11}	$NHCON(CH_3)_2$	150–151	429, 430
$C_6H_4NO_2(4)$	SO_2CH_3	248–250	449
CH_3	$NH_2(CH_3)_2SO_4$	190–191	445
C_6H_5	$NH_2(CH_3)_2SO_4$	187–188	445
C_6H_5	$NHCOCH_3(CH_3)_2SO_4$	195–196	445
C_6H_5	$N(C_2H_5)_2$	152–154	445
$C_6H_3(NO_2)_2(2,4)$	SO_2CH_3	200.5–202.5	451

TABLE XXVI. 4,5-Dibromo-1-substituted 6(1*H*)pyridazinones



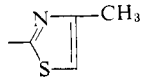
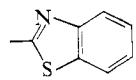
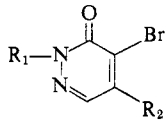
R	MP (°C)	References
H	218	348, 151a
CH_3	92	216, 151a
CH_2CH_2CN		79
CH_2CH_2COOH		79
CH_2CH_2COCl		79
C_6H_5	144–145	237
$C_6H_4Cl(4)$	183–184	237
	128	435
$C_6H_4CH_3(4)$	129–130	237
α-Naphthyl	226–228	237
β-Naphthyl	189–190	237
$C_6H_4NO_2(4)$	233–235	237
	236	435
$C_6H_3(NO_2)_2(2,4)$	221	348
$C_6H_4CF_3(3)$	103–105	419
$C_6H_4COOH(4)$	301	435
$C_6H_4NH_2(4)$		436
$C_6H_4NHCOCH_3(4)$	268–270	436
$C_6H_3OH(3)COOC_2H_5(4)$	157–158	436
$C_6H_4SO_3H(4)$	330	435
$C_6H_4COCH_3(4)$	213	435
	351	435
	216	435

TABLE XXVII. 5-Bromo-1,4-disubstituted 6(1*H*)Pyridazinones



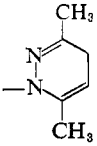
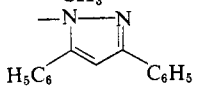
R_1	R_2	MP (°C)	References
H		157	212, 151a
H	$NHNH_2$	180 (dec)	172
H	$NHN{=}CHC_6H_5$	241 (dec)	172
H	$NHN{=}CHC_6H_4OH(3)$	267 (dec)	172
H	$NHN{=}CHC_6H_3(OCH_3)_2(3,4)$	248 (dec)	172
H	$NHN{=}C(CH_3)C_6H_5$	220 (dec)	172
H	$NHN{=}C(CH_3)C_6H_4CH_3(4)$	224 (dec)	172
H	$NHN{=}C(CH_3)C_6H_3(CH_3)_2(3,4)$	220 (dec)	172
H	$NHN{=}C(CH_3)C_6H_4OH(2)$	234 (dec)	172
H	$NHN{=}C(CH_3)C_6H_3Cl_2(3,4)$	240 (dec)	172
H	$NHN{=}C(C_2H_5)C_6H_5$	182	172
H	$NHN{=}C(n\text{-}C_3H_7)C_6H_5$	175–176	172
H	$NHN{=}C(i\text{-}C_3H_7)C_6H_5$	221 (dec)	172
H	$NHN{=}C(n\text{-}C_4H_9)C_6H_5$	151	172
H	$NHN{=}C(CH{=}CHCOOH)C_6H_5$	233 (dec)	172
H	$NHN{=}C(CH_3)CH{=}CHC_6H_5$	207 (dec)	172
H	$NHN{=}C(C_6H_5)_2$	299 (dec)	172
H	$NHN{=}C(C_6H_5)C_6H_4OCH_3(4)$	232	172
H	$NHN{=}C(CH_2C_6H_5)C_6H_4CH_3(4)$	236 (dec)	172
H	$NHN{=}C(CH_2C_6H_5)_2$	192 (dec)	172
H	$NHN{=}C(C_6H_5)CHOHC_6H_5$	240 (dec)	172
H	$NHN{=}C(C_6H_5)COC_6H_5$	225	172
H	$NHN{=}C(CH_3)$-3-Pyridyl	267 (dec)	172
H	$NHN{=}C(CH_3)$-2-Pyridyl	251 (dec)	172
H	$NHN{=}C(C_6H_5)C_6H_4N(CH_3)_2(4)$	213 (dec)	172
H		264 (dec)	172
H		211–213	172
H	$SC_6H_4NH_2(2)$	196 260–261 (dec)	273 225
H	$SC_6H_4NHCOCH_3(2)$	238 (dec)	273
CH_3	$NHC_6H_4SCH_3(2)$	161–162	219
CH_3	$NHSO_2C_6H_4NH_2(4)$	198	215
CH_3	$SC_6H_4NH_2(2)$	171–172	273

TABLE XXVII (*continued*)

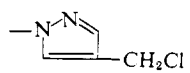
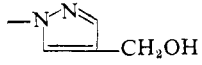
R_1	R_2	MP (°C)	References
CH_3	$SC_6H_4NHCOCH_3(2)$	216–217	273
C_6H_5	NH_2	220–221	75
		225–226	350
		214–215	213
		216–217	437
C_6H_5	$NHCH_3$	158–159	211, 437
C_6H_5	$NHCOOCH_3$	151–152	341
C_6H_5	$NHCOOC_2H_5$	135–136	341
C_6H_5	$NHCOOCH_2CH_2Cl$	102–104	341
C_6H_5	$NHCOOCH_2CH_2OC_2H_5$	70–72	341
C_6H_5	$NHCOO(CH_2)_{17}CH_3$	77–79	341
C_6H_5	$NHCOSC_6H_5$	167–168	341
C_6H_5	NHCOCOOH	183–184	345
C_6H_5	$NHCH(OH)CCl_3$	213–215 (dec)	351
C_6H_5	$NHCH_2C_6H_5$	203	211
C_6H_5	$NHSO_2C_6H_4NHCOCH_3(4)$	227	215
C_6H_5	$N(CH_3)_2$	116	211
C_6H_5	$N(C_2H_5)_2$	92–93	211
		93	437
C_6H_5	$NHNH_2$	161–162	237
		153–155	437
C_6H_5	NHNHCOCH=CHCOOH	126–127	237
C_6H_5	$NHNHCSNHC_6H_5$	175–176	237
		269	440
C_6H_5	OH	270	211
C_6H_5	$OCOCH_3$	116–117	349
		124	440
C_6H_5	OCH_3	153–154	211, 349, 440
C_6H_5	OC_2H_5	129–130	349
		135	211, 440
$C_6H_4F(4)$	OCH_3	170–171	349
C_6H_5	SH	150	339
C_6H_{11}	$NHCH(OH)CCl_3$	215–220 (dec)	351
C_6H_{11}	OCH_3	118–120	349, 441
H	$N(C_2H_5)_2$		151a
H	N_3	180–181	437
H	Cl	196–197 (dec)	438
H	OH	204	439
CH_3	N_3	85–87	437
CH_3		106–107	438
CH_3		159–160	438, 439
CH_2CH_2OH	N_3	144–145	437

TABLE XXVII (*continued*)

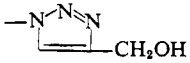
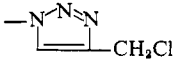
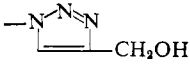
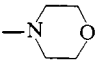
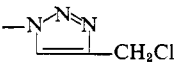
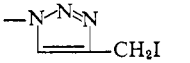
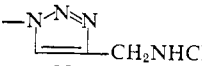
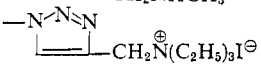
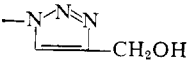
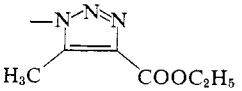
R_1	R_2	MP (°C)	References
CH_2CH_2OH		149–151	438, 439
CH_2CH_2CN		107–108	438
CH_2CH_2CN		115–116	438, 439
C_6H_5	Cl		440
C_6H_5		255–256	440
C_6H_5	CNS	155–156	440
C_6H_5	COOH	247–248	437
C_6H_5	$NHCON(CH_3)_2$	142–143	429
C_6H_5	$NHCON{=}CHC_6H_4Br(2)$	159–160 (dec)	427, 428
C_6H_5	NHCOCOONa		441
C_6H_5	$NHCOCOOCH_2CH_2N(CH_3)_2$		441
C_6H_5	$NHCH_2CH_2OH$	180–182	437
C_6H_5	NHC_3H_7-*n*	128–129	437
C_6H_5	NHC_4H_9-*n*	112	437
C_6H_5	$N(C_4H_9)_2$	39–41	437
C_6H_5		140–141	437
C_6H_5		150–151	437
C_6H_5	$NHN{=}CHC_6H_4NO_2(4)$	248–249	437
C_6H_5	N_3	98–100	437, 440
C_6H_5		186	438
C_6H_5		200–201 (dec)	438
C_6H_5		159–160	442
C_6H_5		229–230	442
C_6H_5		151–152	438, 439
C_6H_5			443

TABLE XXVII (*continued*)

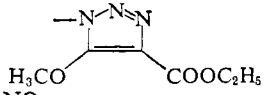
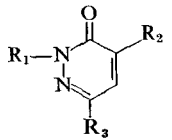
R_1	R_2	MP (°C)	References
C_6H_5			444
C_6H_5	NO_2		436
$C_6H_4CF_3(3)$	$CON(CH_3)_2$		418
$C_6H_4CF_3(3)$	NH_2	172–174	418
$C_6H_4CF_3(3)$	$NCOCHCl_2$		418
$C_6H_4CF_3(3)$	$NCOCH_3$		418
$C_6H_4CF_3(3)$	$NHCH_3$	156–158	419, 422
$C_6H_4CF_3(3)$	NHC_2H_5	138–140	419, 422
$C_6H_4CF_3(3)$	$N(CH_3)_2$	159	419, 422
$C_6H_4CF_3(3)$	$N(C_2H_5)_2$		418
$C_6H_4CF_3(3)$	OCH_3	145	418
$C_6H_4NO_2(4)$	N_3	155–160	437
$C_6H_2(NO_2)_3(2,4,6)$	N_3	161–163	437
C_6H_{11}	NH_2		441

TABLE XXVIII. Chloro-1,3,5-trisubstituted-6(1*H*)pyridazinones



R_1	R_2	R_3	MP (°C)	References
H	Cl	H	176–177	119
			176.5–177.5	58
H	Cl	$OCOC_6H_5$	205–207	72
H	Cl	$OPS(OC_2H_5)_2$	91–92	353
CH_3	Cl	$OPO(OCH_3)NHCH_3$		354
C_6H_5	Cl	$OPS(OC_2H_5)_2$	Liquid	353
C_6H_5	Cl	CH_3	135–136	45
C_6H_5	Cl	C_2H_5	79–81	47
C_6H_5	Cl	OCH_3	83–84	355, 356
C_6H_5	Cl	C_6H_5	186–187	48
$C_6H_4CH_3(3)$	Cl	CH_3	109	42
$C_6H_4OCH_3(4)$	Cl	CH_3	129–130	43
$C_6H_4OC_2H_5(4)$	Cl	CH_3	125–126	43
$C_6H_4NO_2(4)$	Cl	CH_3	217–218	45
$OCOC_6H_5$	Cl	OCH_3	202–203	64
2-Pyridyl	Cl	CH_3	123	42
H	CH_3	Cl	148	8
			149–151	172
H	COOH	Cl	209–210	177
			216 (dec)	167, 316
H	$COOC_2H_5$	Cl	152.5	177
H	$CONH_2$	Cl	253	177
H	$CONHNH_2$	Cl	236–237 (dec)	177

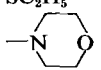
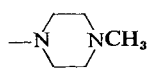
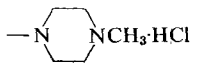
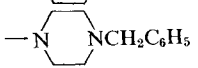
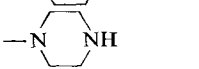
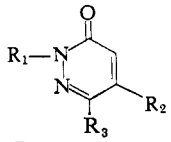
H	$COOCH_3$	Cl	132	167
H	$NHSO_2C_6H_4NH_2(4)$	Cl	288–289	357
CH_3	OH	Cl	187–189	119
CH_3	OCH_3	Cl	105	119
CH_2COOH	OH	Cl	233	119
CH_2COOH	SCH_3	Cl	190 (dec)	119
CH_3	NH_2	Cl	148–148.5	352
			145–145.5	75, 446
CH_3	$NHCOCH_3$	Cl	208–209	352
CH_3	$N(CH_3)_2$	Cl	76–77	119
CH_3	$NHSO_2C_6H_4NH_2(4)$	Cl	185–186	75, 352
CH_3	$NHSO_2C_6H_4NHCOCH_3(4)$	Cl	234.5–235	75
C_6H_5	OH	Cl	199–201	26
			207–208	248
C_6H_5	CH_3	Cl	133–134	21
C_6H_5	OCH_3	Cl	159–161	26
C_6H_5	NH_2	Cl	179–180	38
C_6H_5	$NHCH_3$	Cl	87.5–88.5	38
			182–183	222
C_6H_5	$N(CH_3)_2$	Cl	159–160	359
C_6H_5	$NHNH_2$	Cl	204–205	358
C_6H_5	SH	Cl	137–138	360, 448
C_6H_5	SCH_3	Cl	135–136	360, 448, 449
C_6H_5	SO_2CH_3	Cl	174–175	347
C_6H_5	SC_2H_5	Cl	117–118	360
C_6H_5		Cl	121–122	38
C_6H_5		Cl	253–255	220
C_6H_5		Cl	97–99	220

TABLE XXVIII (*continued*)

R_1	R_2	R_3	MP (°C)	References
C_6H_5		Cl	170 (dec)	220
C_6H_5		Cl	139.5–140.5	220
$C_6H_4Cl(4)$		Cl	281–283	220
H	Cl	Cl	169–171	145
			170–172	119
CH_3	Cl	Cl	75.5–76	75, 446
			76–77	76
CH_2Cl	Cl	Cl	78–80	119
CH_2OH	Cl	Cl	119–121	119
CH_2SCN	Cl	Cl	112–113	119
C_2H_5	Cl	Cl	141–142	119
CH_2COOH	Cl	Cl	195–196	119
$CH_2COOC_2H_5$	Cl	Cl	86–87	119
$CH_2CON(C_2H_5)_2$	Cl	Cl	105–106	119

C_6H_5	Cl	Cl	107–110	40, 49d, 448
			109–110	377
			111–112	21, 38
$C_6H_4Cl(4)$	Cl	Cl	163–165	220, 49a
$C_6H_4NH_2(4)$	Cl	Cl	164–165.5	76
C_6H_{11}	Cl	Cl	107–108	25
			111–112	39
Cl	Cl	Cl	93–95	119
CH_3	NO_2	Cl	129–130	447
C_2H_5	NO_2	Cl	48–50	447
C_4H_9n	NO_2	Cl		447
C_6H_5	$SOCH_3$	Cl	154–156	449, 451
C_6H_5	$SCH_2CONHNHCSNH_2$	Cl		450
$C_6H_4NO_2(4)$	$SOCH_3$	Cl	176	449
$C_6H_4NO_2(4)$	SO_2CH_3	Cl	221.5–223	449
$C_6H_3(NO_2)_2(2,4)$	$SOCH_3$	Cl	213.5–214.5	451
$C_6H_3(NO_2)_2(2,4)$	SO_2CH_3	Cl	213–214	451
$C_6H_4Cl(3)$	Cl	Cl		49c
$C_6H_4NO_2(3)$	Cl	Cl	182–184	106b
$C_6H_4NO_2(4)$	Cl	Cl	237–238	106a

TABLE XXIX. Chloro-1,3,4-trisubstituted 6(1*H*)Pyridazinones



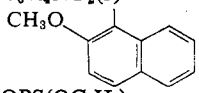
R_1	R_2	R_3	MP (°C)	References
H	Cl	C_6H_5	230–231	361
H	Cl	$C_6H_4OH(4)$	296–298	361
H	Cl	$C_6H_4OCOCH_3$	221–222	361
H	Cl	$C_6H_4OCH_3(4)$	227–228	361
H	Cl	$C_6H_3(OCH_3)_2(3,4)$	237–238	361
H	Cl	$C_6H_4CH_3(2)$	219–220	361
H	Cl	$C_6H_4Cl(4)$	211–212	361
H	Cl	$C_6H_4NHCOCH_3(4)$	265	361
H	Cl	$C_6H_4NO_2(3)$	266–267	361
H	Cl		246–247	361
H	Cl	$OPS(OC_2H_5)_2$	144–145	353
OH	Cl	OCH_3	206 (dec)	182
$OCOCH_3$	Cl	OCH_3	133–134	64
CH_3	Cl	H	62–64	25
CH_3	Cl	CH_3	80	69
CH_3	Cl	COOH	188	69
C_6H_5	Cl	H	83–85	27, 38
C_6H_5	Cl	OCH_3	115–116	27, 355
C_6H_5	Cl	OCH_2COOH	150–151	119
C_6H_5	Cl	$OPS(OC_2H_5)_2$	82.5–83	353
C_6H_{11}	Cl	Cl	92–93	25
H	CH_3	Cl	227	8
H	COOH	Cl	245 (dec)	177
H	$COOCH_3$	Cl	99–101	167
H	$NHNH_2$	Cl	268 (dec)	172
CH_3	OH	Cl	257–260	119
CH_3	OCH_3	Cl	174–175	119
CH_3	OC_2H_5	Cl	154–155	119
CH_3	OC_3H_5	Cl	108–109	119
CH_3	NH_2	Cl	168–169	75
CH_3	$N(CH_3)_2$	Cl	75–77	119
C_2H_5	OH	Cl		151
CH_2COOH	OH	Cl	242–245	119
$CH_2COOC_2H_5$	OCH_3	Cl	111–112	119
CH_2OCH_3	OCH_3	Cl	115–116	119
C_3H_5	OH	Cl	192	119
C_6H_5	CH_3	Cl	136–137	21
C_6H_5	OCH_3	Cl	198–200	27
C_6H_5	CH_2COOH	Cl	178–180	87

TABLE XXIX (*continued*)

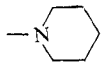
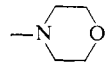
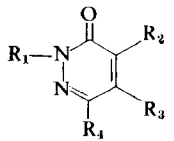
R_1	R_2	R_3	MP (°C)	References
C_6H_5	OC_3H_5	Cl	148–149	119
C_6H_5	NH_2	Cl	234–236	83
			236–238	27
C_6H_5	$N(CH_3)_2$	Cl	125–127	223
			127–128	27, 356
C_6H_5		Cl	118.5–119.5	27, 223, 338
C_6H_5		Cl	167	21, 338
			168–169	27
H	Cl	Cl	204	119
CH_3	Cl	Cl	97–98	20, 75, 76
CH_2OH	Cl	Cl	106–108	119
CH_2Cl	Cl	Cl	92–94	119
CH_2SCN	Cl	Cl	108–109	119
$COOC_2H_5$	Cl	Cl	55–57	119
$CH_2N(C_2H_5)_2$	Cl	Cl	36–38	119
$CH_2N(C_3H_5)_2$	Cl	Cl	50–52	119
$CH_2N(CH_2CH_2CN)_2$	Cl	Cl	104–107	119
C_2H_5	Cl	Cl	57–58	119
			213–214	151
CH_2CH_2Cl	Cl	Cl	90–92	119
CH_2CH_2OH	Cl	Cl	80	119
CH_2COOH	Cl	Cl	235–237	119
$CH_2COOC_2H_5$	Cl	Cl	82–83	119
$CH_2CON(C_2H_5)_2$	Cl	Cl	112–113	119
$CH_2CH_2N(C_2H_5)_2$	Cl	Cl	Liquid	119
$CH_2CH_2CH_3$	Cl	Cl	38–40	119
$CH_2CH{=}CH_2$	Cl	Cl	54–56	119
CH_2COCH_3	Cl	Cl	80–81	119
C_6H_5	Cl	Cl	135–136	27, 338
			138–140.5	83, 356
C_6H_5	$SOCH_3$	Cl	163–163.5	449
$C_6H_4NO_2(4)$	$SOCH_3$	Cl	205–205.5	449
$C_6H_4NO_2(4)$	SO_2CH_3	Cl	247–248	449
$C_6H_3(NO_2)_2(2,4)$	$SOCH_3$	Cl	229–230	451
$C_6H_3(NO_2)_2(2,4)$	SO_2CH_3	Cl	216–217.5	451

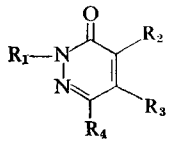
TABLE XXX. Chloro-1,3,4,5-tetrasubstituted 6(1*H*)Pyridazinones

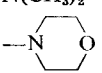


R_1	R_2	R_3	R_4	MP (°C)	References
H	Cl	H	$OPS(OC_2H_5)_2$	91–92	306
CH_3	Cl	NH_2	CH_3	190–191	75
H	NH_2	Cl	H	292–294	210
H	H	Cl	$OPS(OC_2H_5)_2$	144–145	306
CH_3	NH_2	Cl	CH_3	169–170	75
C_6H_5	NH_2	Cl	H	142–143.5	83
C_6H_5	$SCH_2C_6H_5$	Cl	H	76	22
C_6H_5	$SCH_2C_6H_4Cl(2)$	Cl	H	88	22
C_6H_5	$SCH_2C_6H_4Cl(4)$	Cl	H	106	22
H	CH_3	H	Cl	174–175	239
H	H	CH_3	Cl	231–232	239
H	$NHSO_2C_6H_4NH_4(4)$	H	Cl	288–289	170
C_6H_5	OCH_3	OCH_3	Cl	119–120	248
C_6H_5	H	CH_3	Cl	136–137	38
C_6H_5	CH_3	H	Cl	133–134	38
H	Cl	Cl	NO_2	184–186	363
H	Cl	Cl	$OPS(OCH_3)NHCH_3$	120–122	354
H	Cl	Cl	$OPO(OC_2H_5)_2$		306
CH_3	Cl	Cl	CH_3	116.5	69
CH_3	Cl	Cl	COOH	203–204	69
CH_3	Cl	Cl	OCH_3	127–130	355
				135	355
CH_3	Cl	Cl	NO_2	97–99	364
				99–100	454, 456

CH_2Cl	Cl	Cl	OCH_3	93–95	355
CH_2CH_2Cl	Cl	Cl	OCH_3	83–84	355
CH_2CH_2OH	Cl	Cl	OCH_3	101–103	355
				102–105	355
CH_2CH_2CN	Cl	Cl	OCH_3	98–100	355
C_6H_5	Cl	Cl	$OPS(OCH_3)NHCH_3$		354
C_6H_5	Cl	OH	Cl	253–254	248
C_6H_5	Cl	OCH_3	Cl	142–144	248
H	Cl	Cl	Cl	224–226	119
CH_3	Cl	Cl	Cl	102–103	119
CH_2Cl	Cl	Cl	Cl	98–100	119
CH_2OH	Cl	Cl	Cl	130	119
CH_2SCN	Cl	Cl	Cl	120–122	119
$COOC_2H_5$	Cl	Cl	Cl	72–73	119
CH_2COOH	Cl	Cl	Cl	147–149	119
C_6H_5	Cl	Cl	Cl	109–110	26, 119, 49d, 248, 362
Cl	Cl	Cl	Cl	103–104	119
C_6H_5	SH	Cl	H	128	452
C_6H_5	$SCH_2C_6H_3Cl_2(2,4)$	Cl	H	108	453
$CH_2C_6H_5$	SH	Cl	H		268a
CH_3	Cl	Cl	NH_2	191.5–193	421, 454, 455
CH_3	Cl	Cl	$NHSO_2C_6H_5$	164–166	455
CH_3	Cl	Cl	$NHSO_2C_6H_4Cl(4)$	178–180	455
CH_3	Cl	Cl	$N{=}NC_6H_3OH(2)N(C_2H_5)_2$		421
C_2H_5	Cl	Cl	NH_2	130–131.5	421, 454
C_2H_5	Cl	Cl	NO_2	87–89.5	421, 454, 456
$C_6H_4Br(4)$	Cl	Cl	Cl	185–186	457
$C_6H_4Cl(3)$	Cl	Cl	Cl	125–126	49c
$C_6H_4Cl(4)$	Cl	Cl	Cl	176–177	49a
$C_6H_3Cl_2(2,5)$	Cl	Cl	Cl	146–148	49a
$C_6H_4NH_2(4)$	Cl	Cl	Cl	170–171	458
$C_6H_4NO_2(4)$	Cl	Cl	Cl	198–200	49b, 458

TABLE XXXI. Bromo-, Iodo-, Fluoro-1,3,4,5-tetrasubstituted 6(1*H*)Pyridazinones



R_1	R_2	R_3	R_4	MP (°C)	References
			Bromo		
H	H	Br	C_6H_5	235–236	361
H	H	Br	$C_6H_4OCH_3(4)$	228–229	111
H	Br	Br	NO_2		363
H	Br	Br	OAg		109
H	Br	Br	OBa		109
H	Br	Br	$OCOCH_3$	228	109
H	Br	Br	OC_2H_5	206	109
H	Br	Br	$OPS(OC_2H_5)_2$	120–123	353
				121–122	306
H	Br	Br	$OPO(OCH_3)N(n\text{-}C_5H_{11})_2$		354
CH_3	Br	Br	NO_2		364
CH_3	Br	Br	OCH_3	131–132	355
CH_3	Br	Br	$OPS(OC_2H_5)_2$	67–68	353
C_6H_5	H	H	Br	122–124	38
C_6H_5	H	Br	Br	140–142	21, 27
C_6H_5	H	Br	$OPS(OC_4H_9)N(C_2H_5)_2$		354
C_6H_5	H	$N(CH_3)_2$	Br	124.5–125.5	27
C_6H_5	H		Br	171.5–172.5	27
H	Br	H	$OSO_2C_4H_9\text{-}n$	215	459

H	Br	H	$OSO_2C_5H_{11}$-*i*	230	459
H	Br	H	$OSO_2C_6H_5$	202	459
H	Br	H	$OSO_2CH_2C_6H_5$	228	459
H	Br	H	$OSO_2C_6H_4CH_3$	220	459
H	Br	H	$OSO_2C_6H_4Cl$	133	459
$CH_2CH_2CH_2Cl$	Br	H	C_6H_5		106d
$CH_2CH_2CH_2N(CH_3)_2$	Br	H	C_6H_5	Oil	106d
H	Br	Br	CH_2CH_2COOH		460
H	Br	Br	$C_6H_4COOH(4)$		460
H	Br	Br	$C_6H_4SO_3H(4)$		460
H	Br	Br	$OSO_2C_4H_9$-*n*	141	459
H	Br	Br	$OSO_2C_5H_{11}$-*i*	121	459
H	Br	Br	$OSO_2C_6H_5$	115	459
H	Br	Br	$OSO_2CH_2C_6H_5$	228	459
H	Br	Br	$OSO_2C_6H_4CH_3$	79	459
H	Br	Br	$OSO_2C_6H_4Cl$	133	459

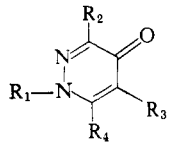
Iodo

C_6H_5	I	I	H	130–131	114a
C_6H_5	I	CH_3	H	126–128	114a
C_6H_5	I	NH_2	H	150–152	114a
C_6H_5	I	$NHCOCH_3$	H	198–200	114a
C_6H_5	I	$NHCOCH_2Cl$	H	167–168	114a
C_6H_5	I	NCO	H	105–110	114a
C_6H_5	I	NHOCCOOH	H	182	114a
C_6H_5	I	$N{=}CHN(CH_3)_2$	H	205–207	114a
C_6H_5	I	$NHCONHC_6H_5$	H	224–226	114a
C_6H_5	I	$NHCH(OH)CCl_3$	H	130 (dec)	114a
C_6H_5	I	$NHCH(OH)COOCH_3$	H	244–246	114a
C_6H_5	I	SCH_3	H	138–140	114a
C_6H_{11}	I	$NHCOCH_3$	H	139–141	114a

TABLE XXXI (*continued*)

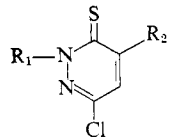
R_1	R_2	R_3	R_4	MP (°C)	References
		Fluoro			
H	$CF(CF_3)_2$	$CF(CF_3)_2$	F		276c
H	OCH_3	OCH_3	F	139–141	263a
H	F	OCH_3	F	162.5–164	263a
H	OCH_3	F	F	134–136	263a
CH_3	OCH_3	F	F	42–44	263a
H	F	F	F		263b
CH_3	F	F	F	74–76	263a
C_2H_5	F	F	F	bp 75–77 (10 mm)	263a

TABLE XXXII. Halo-1,3,5,6-tetrasubstituted 4(1*H*)Pyridazinones



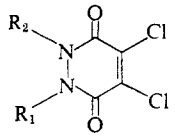
R_1	R_2	R_3	R_4	MP (°C)	References
CH_3	Cl	H	Cl	153–155	145
				153–154	145
C_2H_5	Cl	H	Cl	82–83	119
$CH_2COOC_2H_5$	Cl	H	Cl	102–103	119
$CH_2CON(C_2H_5)_2$	Cl	H	Cl	98–101	119
Tetraacetyl-1-β-D-Glucosyl	Cl	H	Cl	160–163	262, 315
1-β-D-Glucosyl	Cl	H	Cl	227–231	262
OH	Cl	OH	COC_6H_5	196–197	65
OH	COC_6H_5	OH	Cl	180	65
CH_3	Cl	H	OCH_3	198–199	119
C_6H_5	H	Br	CH_3	178–179	98
C_6H_5	COOH	Br	CH_3	230–232	98
C_6H_5	$COOCH_3$	Br	CH_3	222–223	98
3,5-Di-*O*-*p*-toluyl-2-deoxy-D-*erythro*-pentofuranosyl	Cl	H	Cl		394

TABLE XXXIII. 3-Chloro-1,5-disubstituted 6(1*H*)Thiopyridazinones



R_1	R_2	MP (°C)	References
C_6H_5	H	128–129	365
C_6H_5	NH_2	205–206	365
1-β-D-Glucosyl	H	192–194 (dec)	303
Tetraacetyl-1-β-D-Glucosyl	H	155–157	303
Tetrahydrofuranyl	H	92–93.5	299, 414
Tetrahydropyranyl	H	88–92	299, 414
Tetrahydrothiopyranyl	H	70–75	337, 414

TABLE XXXIV. 4,5-Dichloro-1,2-disubstituted Pyridazine-3,6-diones



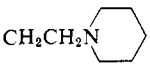
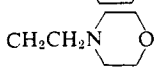
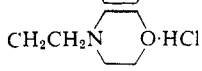
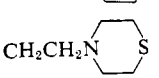
R_1	R_2	MP (°C)	References
H	H	290–292	296, 370, 355
H	CH_3	214–216	370
H	CH_2Cl	186	370
H	$CH_2N(C_2H_5)_2$	188–193	370
H	CH_2OH	245	370
H	CH_2CH_2Cl	176–177	370
H	CH_2CH_2OH	218–220	355
H	CH_2COOH	236–238	355
H	$CH_2COOC_2H_5$	162–163	355
H	CH_2CONH_2	273–275	355
H	$CH_2CH_2CH_3$	140–141	355
H	CH_2CH_2CN	188–190	355
H	CH_2CH_2COOH	176–178	355
H	C_6H_5	226–227	83
		226.5–227	83
		231–233	49d
H	$CH_2C_6H_5$	196–198	82
CH_3	CH_3	191–193	119
		194–196	82
CH_3	CH_2COOH	206–207 (dec)	82
CH_3	CH_2COOCH_3	115–117	82
CH_3	$CH_2CH_2N(CH_3)_2$	81–83	82
CH_3	$CH_2CH_2N(C_2H_5)_2$	84.5–86.5	82
CH_3	$CH_2CH_2N[CH(CH_3)_2]_2$	109.5–110.5	82
CH_3	$CH_2CH_2N(C_4H_9)_2$	78–80	82
CH_3	$CH_2CH_2N(CH_3)C_6H_5$	171–172.5	82
CH_3	$CH_2CH_2N(CH_3)CH_2C_6H_5$	70.5–72	82
CH_3	$CH_2CH(CH_3)N(C_2H_5)_2$	91.5–93.5	82
CH_3	$CH(CH_3)CH_2N(C_2H_5)_2 \cdot HCl$	189–191	82
CH_3	$CH_2CH(C_6H_5)N(C_2H_5)_2$		82
CH_3	$CH(C_6H_5)CH_2N(C_2H_5)_2$		82
CH_3		111–113	82
CH_3		126–128	82
CH_3		239–241	82
CH_3		119–121.5	82

TABLE XXXIV (*continued*)

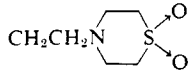
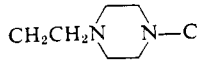
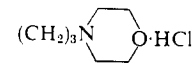
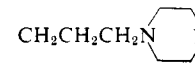
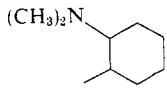
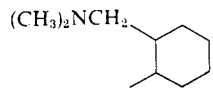
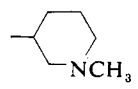
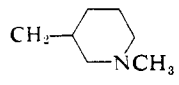
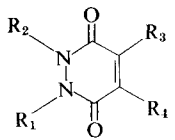
R_1	R_2	MP (°C)	References
CH_3		173.5–175	82
CH_3		102.5–104.5	82
CH_3	$CH_2CH_2CH_2N(CH_3)_2 \cdot H_2C_2O_4$	154–156	82
CH_3	$(CH_2)_3N(C_2H_5)_2$	bp 208–216 (0.3 mm)	82
CH_3	$(CH_2)_3N(CH_3)CH_2C_6H_5 \cdot H_2C_2O_4$	163–165 (dec)	82
CH_3	$CH_2CH_2\underset{\displaystyle CH_3}{\underset{\vert}{C}}HN(CH_3)_2 \cdot CH_3I$	263.5–264.5	82
CH_3	$CH_2CH(CH_3)CH_2N(CH_3)_2$	72.5–74.5	82
CH_3	$CH_2CH(CH_3)CH_2N(CH_3)_2 \cdot HCl$	219–220.5	82
CH_3	$CH_2C(CH_3)_2CH_2N(CH_3)_2$	74.5–76.5	82
CH_3		226–227.5	82
CH_3		121–123	82
CH_3	$CH(CH_3)(CH_2)_3N(CH_3)_2 \cdot p$-Toluenesulfonate	122–123.5	82
CH_3	$(CH_2)_6CH_3$		82
CH_3	C_6H_5	133–135	366
		145–147.5	82
CH_3	$CH_2C_6H_5$	104.5–106.5	82
CH_3	$CH_2C_6H_4Cl(4)$	148–150	82
CH_3	$CH_2C_6H_4COOH(4)$	245–247	82
CH_3	$CH_2CH_2C_6H_5$	110–111.5	82
CH_3	C_6H_{11}	103.5–105.5	82
CH_3		148.5–151	82
CH_3			82
CH_3		142.5–144	82
CH_3		80–83	82

TABLE XXXIV (*continued*)

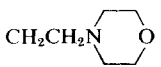
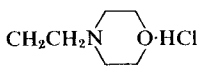
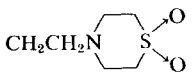
R_1	R_2	MP (°C)	References
CH_3			82
CH_2CH_2N O	CH_2CH_2N O	188–190	82
$CH(CH_3)_2$	$CH(CH_3)_2$	200–205	82
$CH(CH_3)_2$	CH_2CH_2OH	133–135	82
$CH(CH_3)_2$	$CH_2CH_2COCH_3$	81.5–83.5	82
$CH(CH_3)_2$	$CH_2CH_2COCH_2N(C_2H_5)_2$	162.5–163.5	82
$CH(CH_3)_2$	C_6H_5	166–168	82
$CH(CH_3)_2$	$C_6H_4OCH_3(3)$	153.5–157	82
$CH(CH_3)_2$	$C_6H_4COOH(4)$	246.5–248.5	82
$CH(CH_3)_2$	$C_6H_4COOC_2H_5N(C_2H_5)_2(4)\cdot HCl$	187.5–189	82
$(CH_3)_2CH$	$C_6H_4CH_2N(CH_3)_2(4)$	108–109.5	82
$CH(C_2H_5)_2$	$CH(C_2H_5)_2$	bp 155–160 (0.4 mm)	82
$(CH_2)_6CH_3$	$(CH_2)_6CH_3$	36.5–37.5	82
C_6H_5	$CH_2CH_2N(C_2H_5)_2$	77.5–80	82
C_6H_5	CH_2CH_2N O	142–144	82
C_6H_5	CH_2CH_2N O·HCl	256.5–259	82
$C_6H_4F(4)$	CH_2CH_2N O	133–135	82
$C_6H_4Cl(3)$	CH_2CH_2N O	148–150	82
$C_6H_4Cl(3)$	CH_2CH_2N O·HCl	224–226	82
$C_6H_4OCH_3(3)$	CH_2CH_2N O·HCl	212.5–214	82
C_6H_{11}	C_6H_5	134.5–136	82
C_6H_{11}	C_6H_{11}	158.5–161	82

TABLE XXXV. Halo-1,2,4,5-tetrasubstituted Pyridazine-3,6-diones



R_1	R_2	R_3	R_4	MP (°C)	References
H	H	Cl	H	252	353, 355
				265–268	71
H	H	F	F	258 (dec)	115
H	H	Br	Br	200 (dec)	340, 355
				325	353, 459
H	CH_3	Cl	H	185–186	75
				196–197	25
H	CH_3	H	Cl	262–263	25, 461
H	CH_3	Br	Br	226–228	353, 219a
H	C_6H_5	Cl	H	198–199.5	25, 27, 76
				199–201	83
C_6H_5	H	Cl	H	250–252	83, 119
				255–256	27, 76
				260–262	462
				270	338
H	C_6H_5	H	Br	259–261	27
H	C_6H_{11}	Cl	H	156–157	25
H	C_6H_{11}	H	Cl	277–278	25
H	3-Hydroxy-4,5-difluoro-6(1*H*)pyridazinyl	F	F	225 (dec)	115
CH_3	CH_3	F	F	129.5–131	82
CH_3	CH_3	Br	Cl		82
CH_3	CH_3	Br	Br	209–211	82
				212–213	219a
CH_3	CH_3	I	I	209–210	82

TABLE XXXV (*continued*)

R_1	R_2	R_3	R_4	MP (°C)	References
CH_3	CH_3	Cl	OCH_3	120–121	119
CH_3	CH_3	Cl	NHC_6H_5	172–173	119
	CH_3	F	F	138–140	82
	CH_3	F	F	223.5–224.5	82
$CH_2CH_2CH(CH_3)N(CH_3)_2$	CH_3	F	F	62–64	82
$CH_2CH_2CH(CH_3)N(CH_3)_2H_2C_2O_4$	CH_3	F	F	65–80	82
	CH_3	F	F	164–165	82
C_6H_5	CH_3	Cl	H	150–152	105, 106, 366
C_6H_5	CH_3	H	Cl	156–157.5	105, 106
C_6H_5	CH_3	H	Br	159–161	366
$C_6H_4Cl(4)$	CH_3	H	Br	158.5–159	105, 366
CH_3	$C_6H_4Cl(3)$	Br	H	169–170	105, 366
CH_3	$C_6H_4CH_3(4)$	Br	H	170–171	105, 366
CH_3	$C_6H_4NO_2(4)$	Br	H	199–201	366

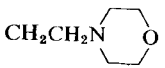
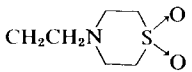
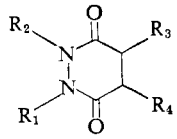
				203–204	106a
CH_3	$C_6H_4NO_2(4)$	H	Br	216–218	366
CH_3	$C_6H_4NH_2(4)HCl$	Br	H	258–261	366
CH_3	$C_6H_4OCH_3(4)$	Br	H	155–157	366
CH_3	C_6H_5	Br	Br	177–178.5	366
	CH_3	Br	Br	164.5–166	82
	CH_3	Br	Br	184–185	82
C_2H_5	C_6H_5	Br	H	142–144	366
C_2H_5	$C_6H_4CH_3(4)$	Br	H	168–169	366
C_2H_5	$C_6H_4NO_2(4)$	Br	H	179–181	105
C_6H_5	C_2H_5	Br	Br	176–177	366
C_6H_5	$CH(CH_3)_2$	Br	Br	182–183	82
H	H	Br	H		459
H	C_2H_5	H	Cl	210–212	461
H	$C_6H_3Br(4)NO_2(2)$	Br	H	206–207 (dec)	106c, 463
H	$C_6H_3Br(4)NO_2(2)$	Br	Br	235–237	106c
H	$C_6H_3(NO_2)_2(2,4)$	Br	H	270–272	463
H	$C_6H_3(NO_2)_2(2,4)$	Br	Br	329–330	106c
CH_3	$C_6H_4NO_2(3)$	Br	H	221–222	106b

TABLE XXXVI. Halo-4,5-dihydro-1,2,4,5-tetrasubstituted Pyridazine-3,6-diones



R_1	R_2	R_3	R_4	MP (°C)	References
H	H	Cl	Cl	260–263	84
H	$C_6H_4Cl(4)$	Br	Br	178	366
CH_3	CH_3	Br	Br	159.5–161.5	103, 104
CH_3	C_6H_5	Cl	H	156–157	366
CH_3	C_6H_5	Cl	Cl	134–136	106
CH_3	C_6H_5	Br	Br	175–177	106
				177–178.5	105, 367
CH_3	$C_6H_4Cl(4)$	Br	Br	178	366
				183.5–184.5	366
CH_3	$C_6H_4NO_2(4)$	Br	Br	181–182	106a
C_2H_5	$C_6H_4NO_2(4)$	Br	Br	150–152	105, 366
C_6H_5	CH_3	NH_2	Br	207–209	191
H	$C_6H_4Br(4)NO_2(2)$	Br	Br	163–164	106c
CH_3	$C_6H_4Br(4)$	Br, Br	Br	167–169	106c
CH_3	$C_6H_4NO_2(3)$	Br	Br	189–191	106b
CH_3	$C_6H_4NO_2(3)$	Br, Br	Br	172–174	106c
CH_3	$C_6H_4NO_2(4)$	Br, Br	Br	170–172	106c

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CHAPTER IV

Pyridazine Aldehydes, Ketones, and Alcohols

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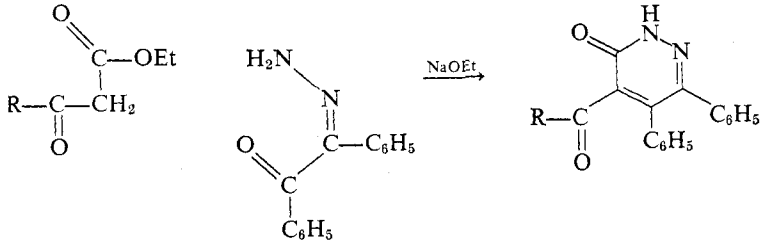
I. Synthesis of Aldehydes, Ketones, and Their Derivatives Attached to Carbon Atoms in Positions 3, 4, 5, or 6

A. By Ring Formation

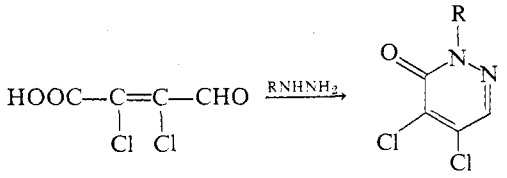
Schmidt and Druey (1) have developed a single-step synthesis using three components producing many 3-, 4-, and/or 5-substituted 6(1*H*)pyridazinones. The three components are: (1) α-diketone, α-ketoaldehyde, or glyoxal; (2) an ester of a carbonic acid with an active α-methylene group, such as malonic, acetoacetic, or benzoylacetic esters; and (3) hydrazine or a monosubstituted hydrazine. The preferred method is to condense two of the components and then form the pyridazine ring from the third component. The 5-benzoyl- and 5-acetyl-substituted pyridazines were formed from the monohydrazine of benzil and the ethyl ester of acetoacetic acid or benzoylacetic acid in the presence of sodium ethoxide.



1 **2** **3**

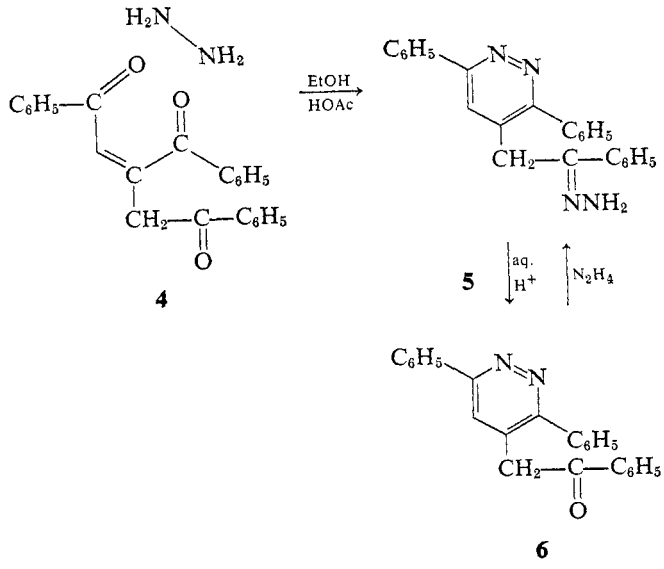
R = CH_3, C_6H_5

Recently, Zoller and Raff (1a) have reported in a German patent the reaction of substituted hydrazines which they prepared with $HO_2CCCl{=}CClCHO$ to give 1-substituted 4,5-dichloro-6(1*H*)pyridazinones (**3a**).



3a

The reaction of 1,2,3-tribenzoylpropene with hydrazine yields the hydrazone of 4-phenacyl-3,6-diphenylpyridazine as reported by Yates, Farnum, and Stout (2). The hydrazone could be hydrolyzed to the ketone, and the



4 5 6

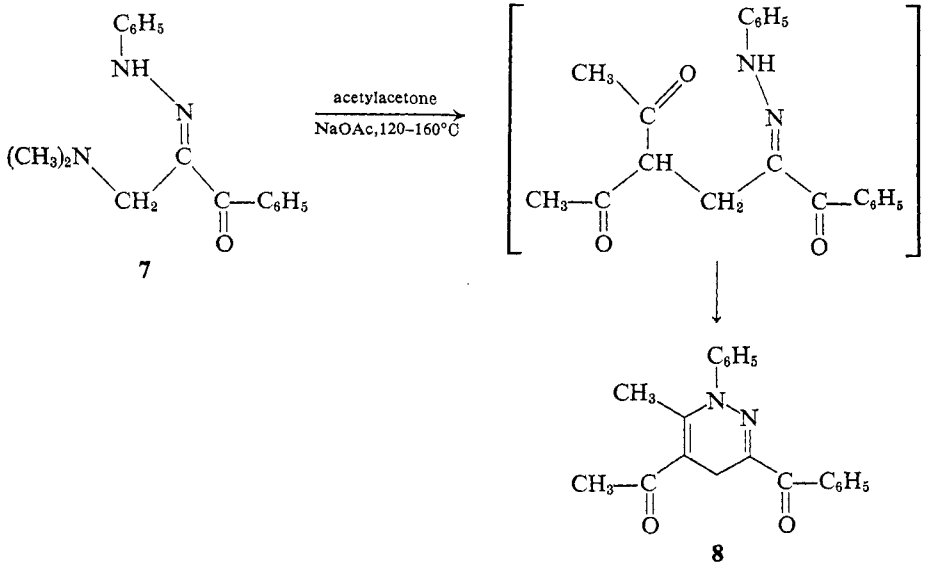
relationship between **5** and **6** was confirmed by regeneration of the hydrazone by treatment with hydrazine.

Many 3-hydroxy-1,4,5-trisubstituted 6(1*H*)pyridazinones were prepared (2a) by the reaction of maleic acids with hydrazines. After refluxing hydrazine with isobutyl methyl ketone, the product is treated with acid and maleic anhydride to give the pyridazinones in high yield.

Ried and Keil (3), during an investigation of various *N*- and *C*-alkylations by means of α-aminoketone arylhydrazones, synthesized a ketopyridazine. However, when the starting material contained a $=NNHCH_3$ group in place of the $=NNHC_6H_5$ group, a pyrazole was obtained.

In attempting to find synthetic routes to diphenyldiazatropones, Evans, Johns, and Markham (4) found that cyclization of 2-oximino-1,5-diphenyl-1,5-pentanedione with hydrazine gave substituted pyridazines as well as the triazolopyridazine (**12**). The dihydropyridazine (**11**) was isolated only when excess hydrazine was used. Since it is known that dihydropyridazines are sensitive to mild oxidizing conditions, warming of compound **11** in solvent produced the bicyclic system (**12**). Examination of the nuclear magnetic resonance (nmr) spectrum suggests that the structure of **11** is represented by **11a**. In deuteriochloroform, the nmr assignments were given as: τ 2.2–2.9 (10 phenyl protons); τ 0.5 (ring NH); τ 5–5.75 (NH_2 protons) with a superimposed multiplet at τ 5.63 (HC=C); doublet τ 6.87 (methylene at 5); τ 6.76 (methylene at 4).

When 1 equivalent of hydrazine was used in the cyclization, the fully aromatic ketone (**13**) and the bicyclic compound (**12**) were isolated. A yield



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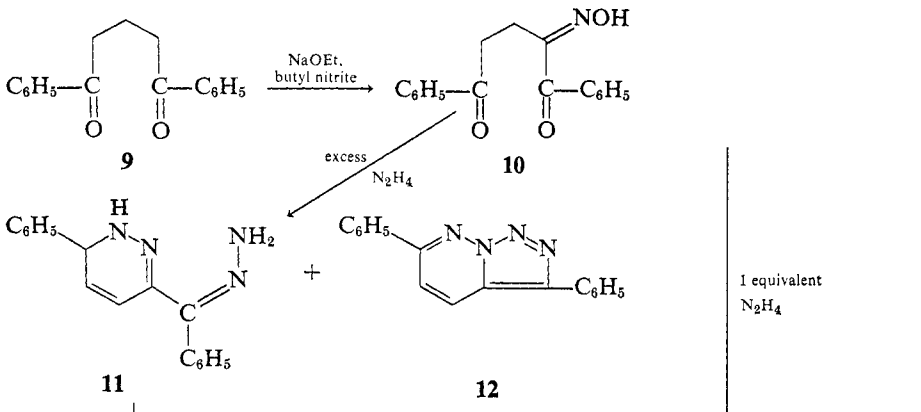
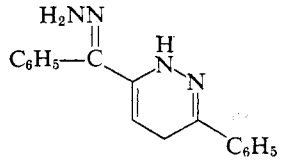


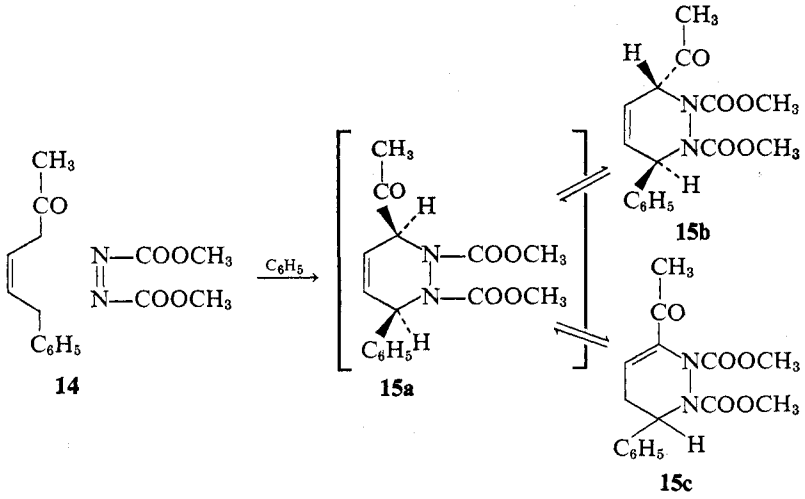
9 10 11 12 13



11a

of the 5,6-dihydro-4-oximino-3,7-diphenyl-4*H*-1,2-diazepine could be obtained along with the ketone **13**, the bicyclic compound, and the dioxime $C_6H_5C(=NOH)—CH_2—CH_2—C(=NOH)—COC_6H_5$ when acetic acid was substituted for the mineral acid in the cyclization reaction. The ketone **13** formed a hydrazone which reacted with benzaldehyde to give the same azine as the dihydropyridazine **11**.

Firl (5) prepared a series of tetrahydropyridazines by allowing substituted butadienes to react with the methyl esters of azidocarboxylic acid. A study (6) of the nmr spectra allowed assignment of the geometrical isomers. Only one substituted ketone was mentioned, 3-acetyl-6-phenyl-1,2-bis(methoxycarbonyl)tetrahydropyridazine (**15a–c**). The tetrahydropyridazine is reported to exist in several isomers, however, Firl showed that the cis form (**15a**) is unstable and changes into the trans form (**15b**), thus only data for the trans form are given. When the trans form of the 3-acetyl-6-phenyl-1,2-bis(methoxycarbonyl)-1,2,3,6-tetrahydropyridazine (**15b**) was allowed to stand for about 15 hr, isomerization occurred and the substituted 1,2,5,6-tetrahydropyridazine (**15c**) was formed.

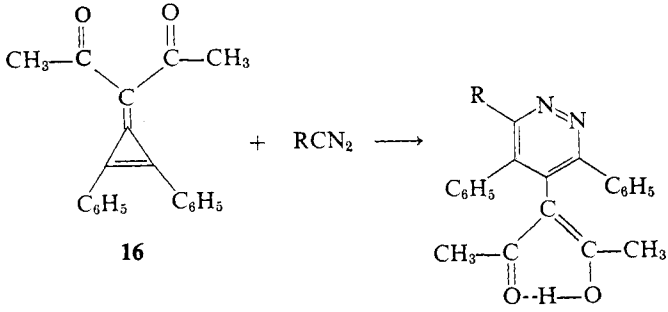


14 **15a** **15b** **15c**

B. By Rearrangement of Ring Systems

1. *Cyclopropenes*

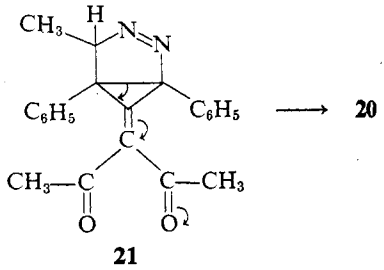
Eicher and Von Angerer (7) reported the reaction of a methylene cyclopropene with diazoalkenes. The products were dependent on the substituents on the cyclopropene, some leading to pyridazines and others to pyrazoles and condensed ring systems. The 1,2-diphenyl-3-diacetylmethylenecyclopropene with diazomethane, diazoethane, or diazopropane gave the enolized form of the 4-(diacetylmethyl)-3,5-diphenyl-6-substituted pyridaz-



16

R = H **17**
R = C_2H_5 **18**

ines. When diazoethane was used, the intermediate 2,7-dimethyl-4,7*a*-diphenyl-3-acetyl-7,7*a*-dihydrofuro[2,3-*d*]pyridazine (**19**) was isolated. This furopyridazine on treatment with base or fusion yielded the pyridazine (**20**). The mechanism is discussed and a possible step to the intermediate is



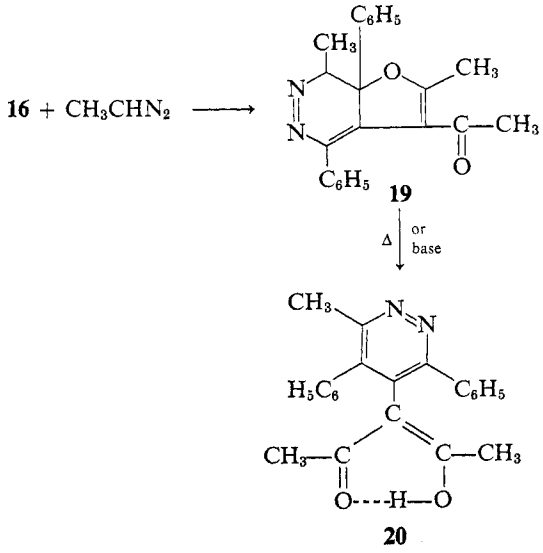
21

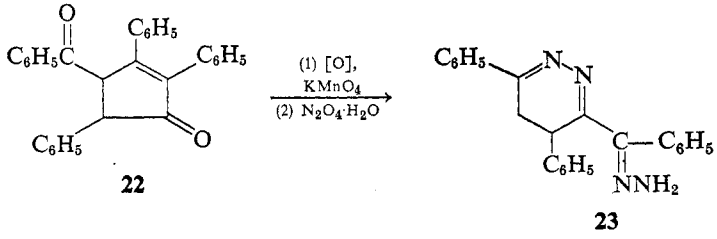
2. *Cyclopentenone*

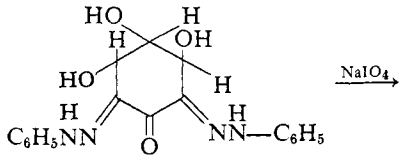
Kleinfeller and Trommsdorff (8) prepared a dihydropyridazine (**23**) by the oxidation of a cyclopentenone (**22**). The formation of this pyridazine was used as evidence for the structure of the cyclopentenone.

3. *Cyclohexanones*

Isbell and Fatiadi (9), while attempting to prove the structure of the crystalline bis(phenylhydrazone) of xylo-4,5,6-trihydroxycyclohexane-1,2,3-trione (**24**) provided a synthetic route to a new series of pyridazine derivatives.







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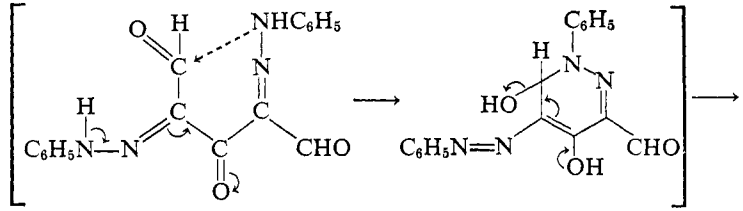
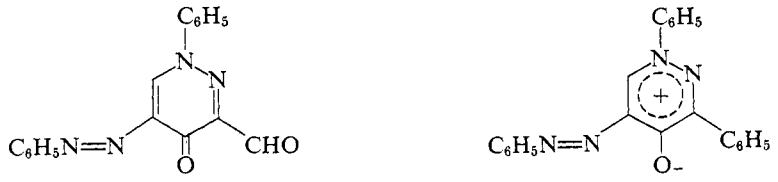




25 25a

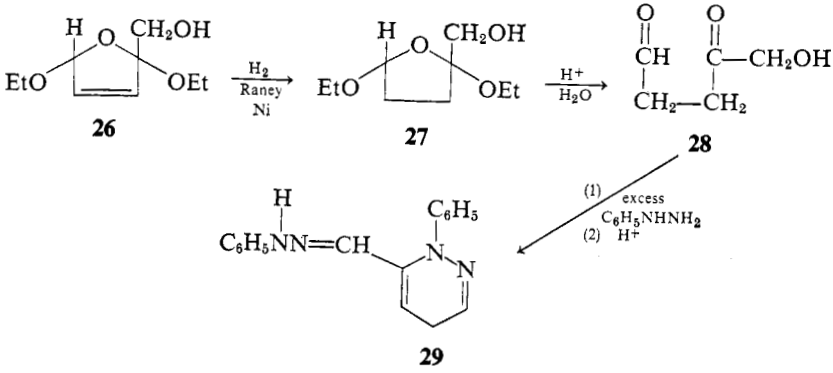
These investigators (9) state that examination of models indicates that the various compounds may have resonance structures involving a zwitterion (**25a**) and a quinonoid form (**25**). The electron shift from the pyridazine ring to the oxygen accounts for the fact that this group does not form normal carbonyl derivatives such as the phenylhydrazone.

4. *Furans*

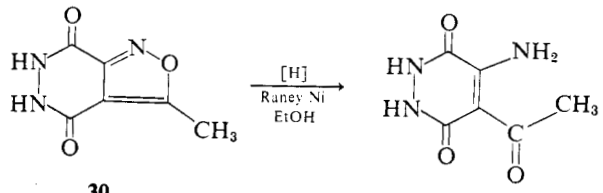
The 2-phenyl-3-formyldihydropyridazine phenylhydrazone (**29**) was prepared by Fakstorp, Raleigh, and Schniepp (10) to characterize the diethoxytetrahydrofurfuryl alcohol prepared in their study on dialkoxytetrahydrofurans.

5. *Isoxazolopyridazines*

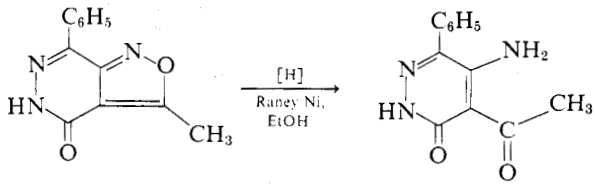
Fused isoxazolopyridazines have been shown to give various substituted pyridazines upon hydrogenation with Raney nickel in ethanolic solution (11, 12).



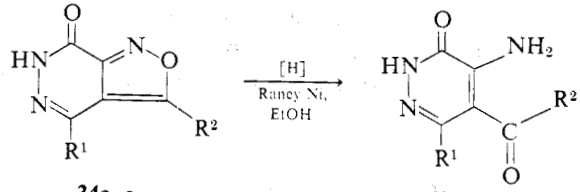
26 **27** **28** **29**



30 **31**



32 **33**



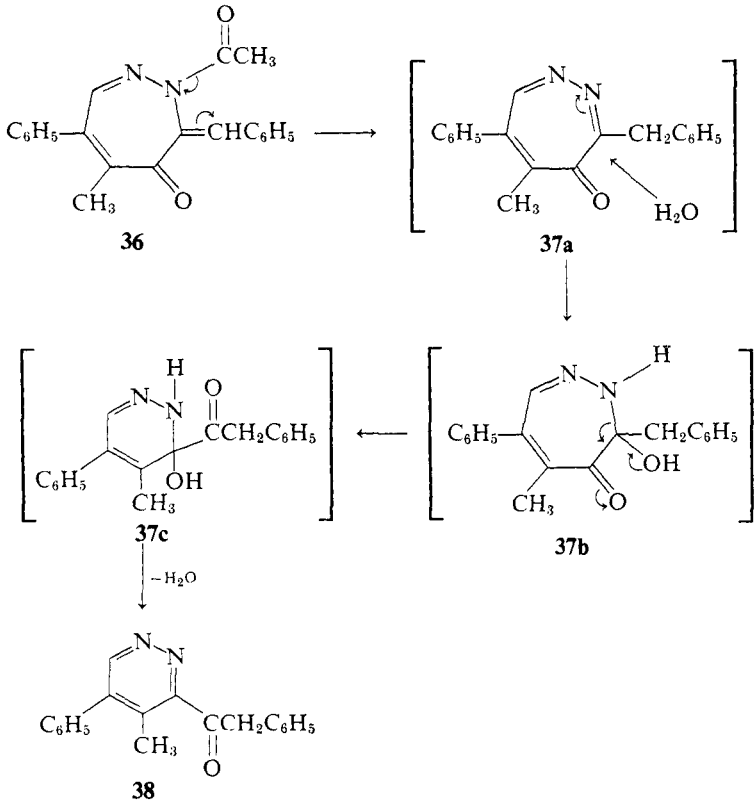
34a–c **35a–c**

34a and **35a**: $R^1,R^2 = CH_3$
34b and **35b**: $R^1,R^2 = C_6H_5$
34c and **35c**: $R^1 = C_6H_5$; $R^2 = CH_3$

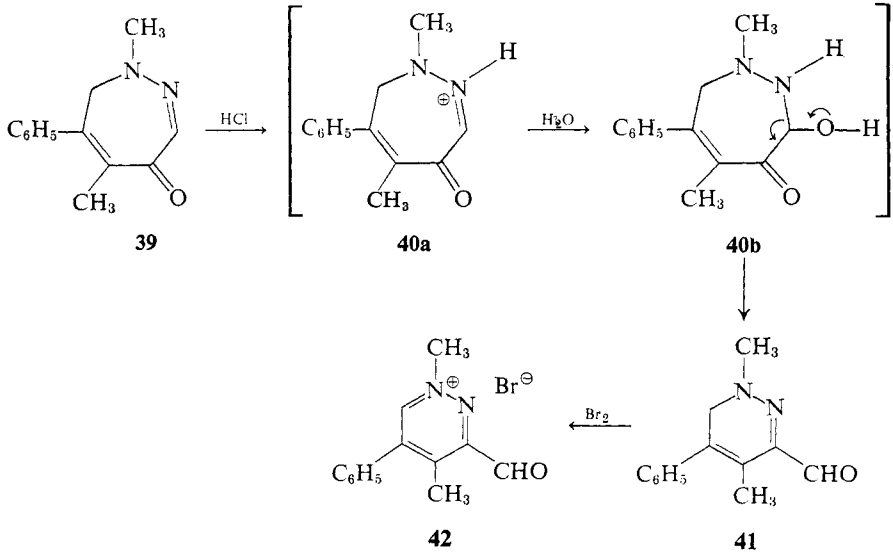
Isoxazolopyridazinones on hydrogenation gave 4(5)-acyl-5(4)-amino-pyridazinones.

6. *Diazepinone*

Bly, Zoll, and Moore (13) gave an additional example of heterocyclic rearrangement. This involves a solvolytic attack on the ring at a heteroatom to disrupt the ring, followed by reestablishment of a new heterocyclic or carbocyclic ring by participation of a reactive neighboring group. This type of reaction may occur with no change in ring size, ring expansion or, as in this case, ring contraction. The ring contraction of 2-acetyl-2,3-dihydro-3-benzylidene-5-methyl-6-phenyl-4*H*-1,2-diazepin-4-one (**36**) to benzyl-3-(4-methyl-5-phenylpyridazinyl) ketone (**38**) was shown by a simple sequence of steps (**37a–c**).



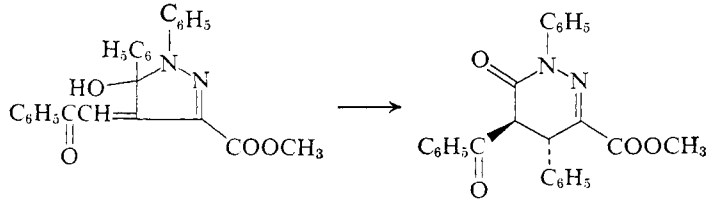
Moore and Theuer (14) found that the rearrangement of the diazepinone 2,5-dimethyl-2,3-dihydro-4-phenyl-6*H*-diazepin-6-one gave different products depending on the conditions. When the diazepine was treated with methanolic alkali, aminopyridines were formed, however, when warm 6 *N* hydrochloric acid was used, pyridazines were obtained. These conversions were explained in the same manner (solvolytic displacement) as the above example.



39 **40a** **40b** **42** **41**

7. *Pyrazole*

Fusco and Dalla Croce (14a) found that 1,5-diphenyl-3-methoxycarbonyl-4-benzoylmethylene-5-hydroxy-2-pyrazoline undergoes ring expansion in toluene to give 1,4-diphenyl-3-methoxycarbonyl-5-benzoyl-4,5-dihydro-6-(1*H*)pyridazinone (**42a**). Alkaline hydrolysis of this product gave the corresponding acid which was dehydrated.

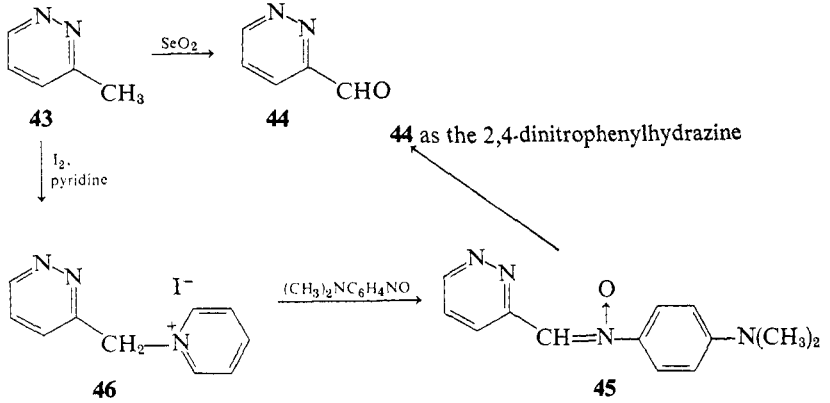


42a

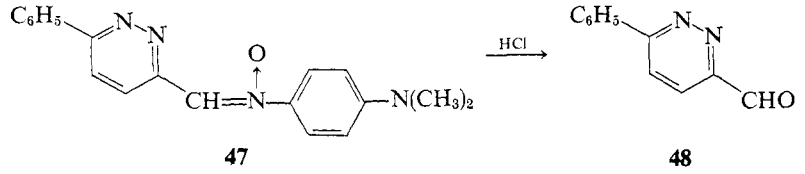
C. By Reactions of Substituted Pyridazines

1. *Methyl Group*

Oxidation of a methyl group in position 3 of pyridazine with selenium dioxide and ethanol yielded the 3-pyridazinecarboxaldehyde (15). Kumagai (15) prepared the 3-formylpyridazine (**44**), the 3-formyl-6-phenylpyridazine (**48**), and their derivatives by the routes shown in the scheme below. The 6-

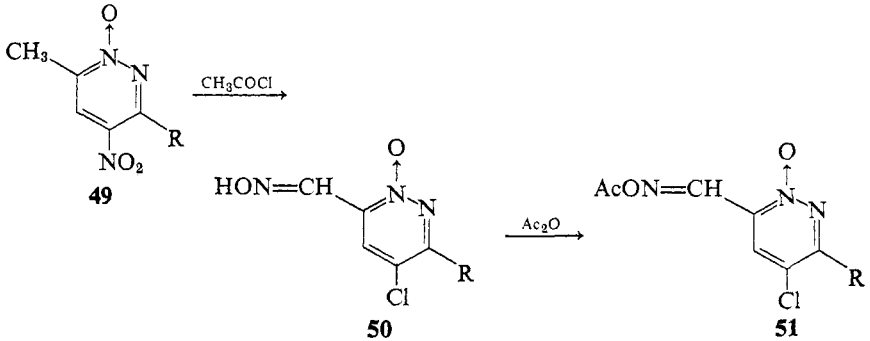


phenyl analog of **45** (**47**) was similarly prepared, and this in turn was decomposed with 10% HCl to give 6-phenyl-3-pyridazinecarboxaldehyde (**48**).



Ogata (16) reported that the methyl group present in the 3-substituted 4-chloro-6-methylpyridazine 1-oxides upon treatment with excess acetyl chloride yielded two products. These have been identified by spectral and chemical data to be the 3-substituted 4-chloro-6-methylpyridazine 1-oxides and the 3-substituted 4-chloro-6-formylpyridazine 1-oxide oximes. In addition, he found that the methyl group when placed in the 3- or 5-position under the same conditions was not converted to the formyl group. Thus the 3-methyl-4-nitropyridazine 1-oxide gave only 3-methyl-4-chloropyridazine 1-oxide, and the 4-nitro-5-methylpyridazine 1-oxide gave the 4-chloro-5-methylpyridazine 1-oxide.

The experimental procedure had previously been reported by Ogata and Kano (17).

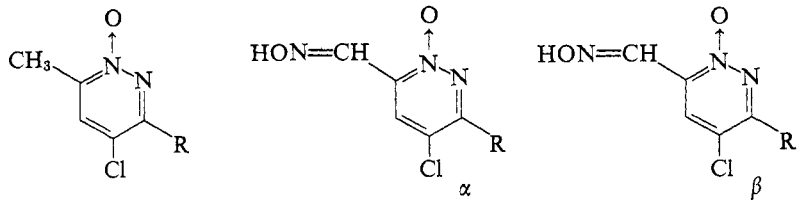


49 **50** **51**

49a and **50a**: R = H
49b and **50b**: R = CH_3
49c and **50c**: R = OCH_3
49d and **50d**: R = Cl

The most probable mechanism involves the formation of acetyl nitrite followed by nitrosation of the active methyl group. A similar situation has been observed in the nitropicoline 1-oxide and the nitroquinaldine 1-oxide series (18, 19).

Another method for converting a methyl group on a pyridazine *N*-oxide to an aldehyde *N*-oxide oxime was studied by Ogata (20). This method was modeled after the work done by Kato and Goto (21) on the methyl group in picolines and their *N*-oxides. It involved the formation of *syn*-aldoximes by the reaction of methylpyridazine *N*-oxides with amyl nitrite in the presence of sodium amide in liquid ammonia. It was found that treatment of the *syn*-aldoximes with hydrochloric acid or heat in some cases caused isomerization to the *anti*-aldoximes. The structures of the aldoximes were confirmed by



52a: R = H
52b: R = Cl
52c: R = OCH_3

53: R = OCH_3

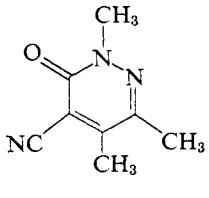
54a: R = H
54b: R = OCH_3

nmr and infrared (ir) spectra. When **52c** was allowed to react, the product **53** was obtained and surprisingly this was not identical to the 3-methoxy-4-chloro-6-formylpyridazine 1-oxide oxime (**50c**) derived from the reaction

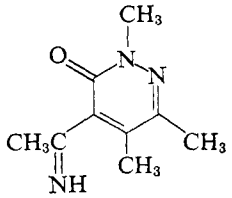
reported above using acetyl chloride. However, **53** could easily be isomerized to **50c** by warming with hydrochloric acid. Thus the stable isomers were labeled β and the unstable α. When **52a** underwent the reaction, only the β form (**54a**) was isolated and **52b** decomposed. The reactivity of the methyl group in various positions was compared by allowing the series to react under the same conditions. The 3-, 5-, and 6-methylpyridazine *N*-oxides yielded the α isomer, and only the 4-methyl compound formed the β isomer. When the 3,6-dimethyl compound was allowed to react with 1 molar equivalent of amyl nitrite and sodium amide, the starting material and the dioxime were found. This indicated that the reactivities of both methyl groups were equivalent.

2. *Cyano Group*

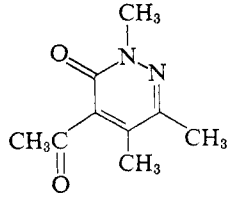
Schmidt and Druey (22) reported by the Grignard reaction the conversion of a cyano group to the acetyl group via the intermediate acetylimino compound. The 1,3,4-trimethyl-5-cyanopyridazin-6-one (**55**) was allowed to react with magnesium turnings and methyl iodide in absolute ether followed by ice and sulfuric acid, giving the crystalline acetylimino compound **56**. Hydrolysis of **56** gave the ketone **57**.



55



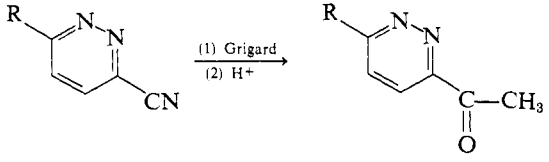
56



57

In 1960, Robba (23) used the Grignard reaction to prepare 3-acetylpyridazine (**59a**) from 3-cyanopyridazine (**58a**).

Nakagome and Castle (24) prepared 3-acetyl-6-methoxypyridazine (**59b**) from 3-cyano-6-methoxypyridazine (**58b**).



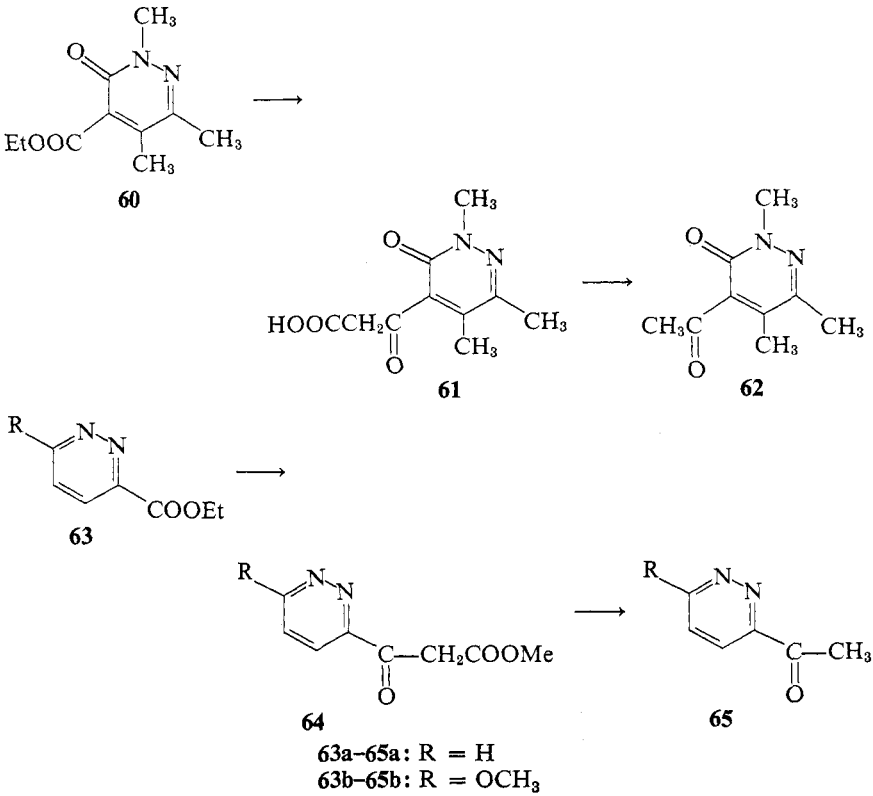
58a: R = H
58b: R = OCH_3

59a: R = H
59b: R = OCH_3

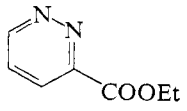
3. *Carbethoxy Group*

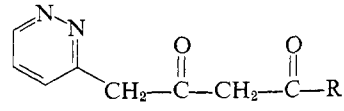
Several groups of investigators (22, 24, 25) have prepared acetylpyridazines via the Claisen condensation of a pyridazinecarboxylic ester with methyl acetate. The intermediate, methyl pyridazinoylacetate, which may or may not be isolated, could be hydrolyzed and decarboxylated in acid solution to give the desired acetylpyridazine.

Schmidt and Druey (22) prepared the 5-acetyl-1,3,4-trimethylpyridazin-6-one (**62**) from ethyl 1,3,4-trimethylpyridazin-6-one-5-carboxylate (**60**). Nakagome and Castle (24) prepared 3-acetylpyridazine (**65a**) and the 3-acetyl-6-methoxypyridazine (**65b**) from ethyl pyridazine-3-carboxylate (**63a**) and ethyl 6-methoxypyridazine-3-carboxylate (**63b**), respectively. They also prepared the *N*-oxides for the various substituted acetylpyridazines. These are discussed in detail in the section on oxidation of aldehyde and ketone pyridazines. Sokolov and Hiller (25) also reported the preparation of 3-acetylpyridazine (**65a**) by the same method.



Sokolov and Hiller (25) also reported the preparation of pyridazines with diketone groups in the side chain by using the appropriate methyl ketones with the pyridazinecarboxylic acid ester in a condensation reaction.

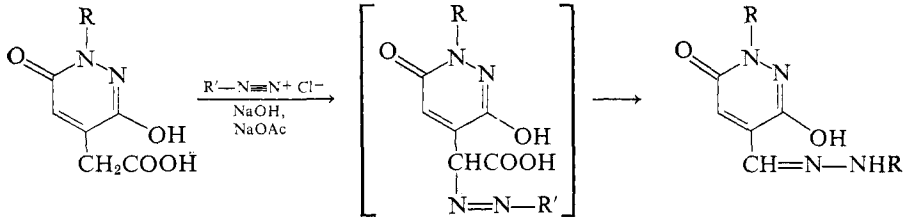




66a: R = CH_3
66b: R = C_2H_5
66c: R = C_4H_9

4. *Active Methylene Group*

The active methylene group present in pyridazinylacetic acid has been shown to condense with aldehydes and undergo the Japp–Klingeman reaction (26).



67 **68** **69**

a: R = H; R′ = C_6H_5
b: R = C_6H_5; R′ = C_6H_5
c: R = C_6H_5; R′ = *p*-HOOC—C_6H_4—

5. *Hydroxyl Group*

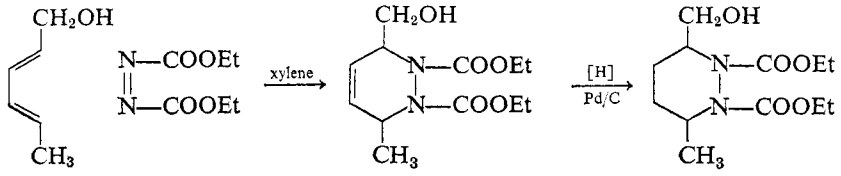
Nakagome (42) and Evans, Johns, and Markham (4) reported the oxidation of alcohols to the aldehyde or ketone by means of selenium dioxide–dioxan or chromic oxide–sulfuric acid.

II. Synthesis of Pyridazine Side-Chain Alcohols Attached to Carbon Atoms in the 3-, 4-, 5-, or 6-Positions of the Pyridazine Ring

A. By Ring Formation

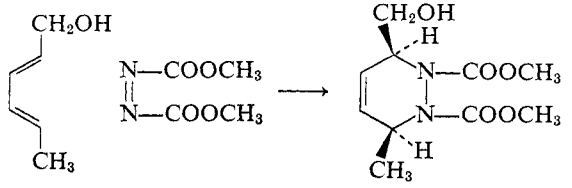
The Diels–Alder reaction is a good synthetic route for obtaining substituted (generally alkyl- and aryl-) 1,2,3,6-tetrahydropyridazines. Molnar (27)

reported the preparation of 1,2-dicarbethoxy-6-hydroxymethyl-3-methyl-1,2,3,6-tetrahydropyridazine (**70**) and the fully unsaturated compound (**71**).



70 **71**

Firl (5, 6), in studying the conformational analysis of the stereoisomers of tetrahydropyridazines, prepared the 3-hydroxymethyl-6-methyl-1,2-dicarbomethoxy-1,2,3,6-tetrahydropyridazine (**72**).

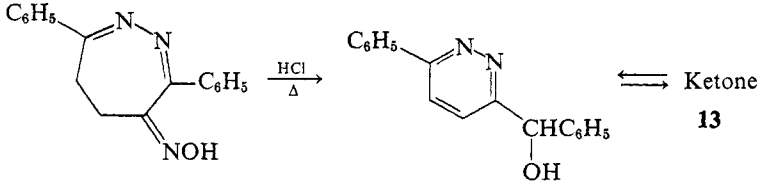


72

B. By Rearrangement of Ring Systems

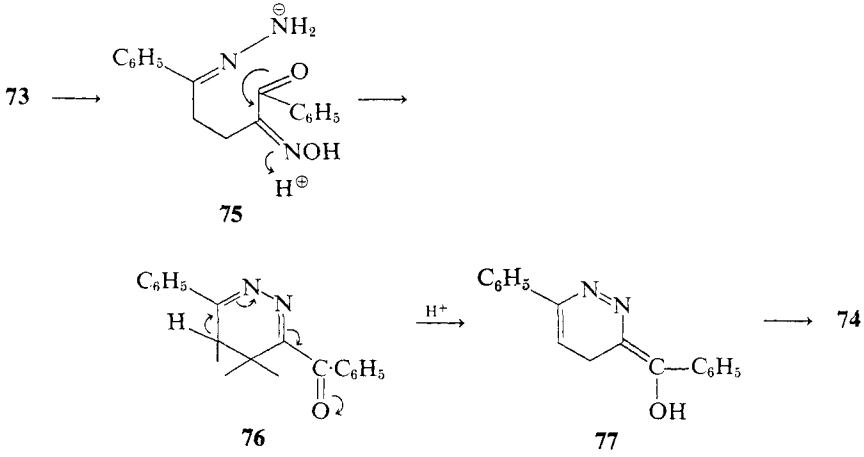
1. *Diazepinones*

Evans, Johns, and Markham (4) reported the unexpected formation of an alcohol when 5,6-dihydro-4-oximino-3,7-diphenyl-4*H*-1,2-diazepine was hydrolyzed with an acid. The nmr, ultraviolet (uv), and mass spectra were presented as evidence for the structure of the alcohol. Furthermore, the alcohol was oxidized to the ketone (4), and this ketone was readily reduced to the alcohol.



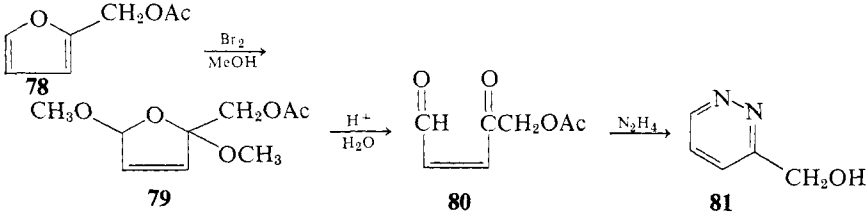
73 **74** **13**

The acid hydrolysis of the diazepinone to the fully oxidized pyridazine ring system with the secondary alcohol group was explained by the following steps.



2. *Furans*

The method of synthesis introduced by Clauson-Kaas and Limborg (28) has been very useful in preparing hydroxymethylpyridazines. In general, the substituted furans (**78**) are treated with a bromine–methanol solution to give the substituted dimethoxy-2,5-dihydrofurans (**79**) which when subjected to acid hydrolysis give the 2-en-1,4-dione intermediate (or aldehyde analog) (**80**). Without isolation, the intermediate is immediately allowed to react with hydrazine, giving the corresponding pyridazine (**81**). Leanza, Becker, and



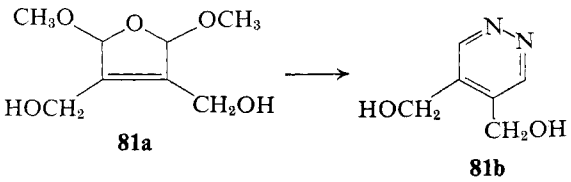
Rogers (28a) also prepared 3-hydroxymethylpyridazine in two steps from furfuryl acetate according to the method of Clauson-Kass and Limborg (28).

While studying the furfuryl esters, Edwards and Mitchell (29) prepared 3-hydroxymethylpyridazine in several steps from the reaction of difurfuryl oxalate with bromine and methanol. The chief products of the methoxylation reaction were methyl oxalate and presumably 2,5-dimethoxy-2,5-dihydrofurfuryl alcohol instead of the expected 2,5-dimethoxy-2,5-dihydrofurfuryl oxalate. To confirm that formation of the furfuryl alcohol had occurred, the

procedure of Clauson-Kaas and Limborg was followed and the 3-hydrox y methylpyridazine was readily identified.

Delaby, Damiens, and Robba (30) reduced furfural by a Cannizzaro reaction to furfuryl alcohol and then followed the procedure of Clauson-Kaas and Limborg (28) to produce the 3-hydroxymethylpyridazine. In 1960, Robba (23) again reported the synthesis of 3-hydroxymethylpyridazine from furfural.

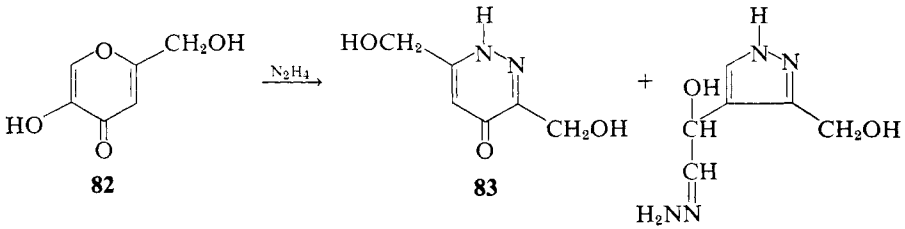
Novitskii and Kasyanova (30a) found that, upon electrolysis of 3,4-bis-(hydroxymethyl)furan in methanol with ammonium bromide, a product (**81a**) was obtained which upon heating with hydrochloric acid and hydrazine gave 4,5-bis(hydroxymethyl)pyridazine (**81b**).



81a **81b**

3. *Pyranone (Kojic Acid)*

In the 4-pyranone series kojic acid has been transformed into hydroxymethylpyridazine by hydrazine. Thomas and Marxer (31, 32) reported that the reaction between kojic acid and hydrazine gave two products: 3,6-dihydroxymethyl-1,4-dihydro-4(1*H*)pyridazinone (**83**) and 3-hydroxymethyl-5-pyrazolylhydroxyacetaldehyde hydrazone (**84**).

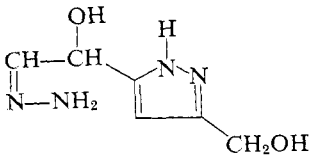


82 **83** **84**

Kotani and Tatsumi (33) reported a yield of 68% of the pyridazine **83** from treatment of kojic acid and hydrazine hydrate in the presence of alkali, whereas the yield reported by Thomas and Marxer (31) was 40%.

Ichimoto, Fujii, and Tatsumi (34) made an extensive study of kojic acid and related 4-pyranone compounds. They found that the structure (**84**) of the pyrazole reported by Thomas and Marxer (31) had not been fully

substantiated, and by using uv, ir, and nmr spectral data they proposed a different structure (**85**) for the pyrazole and also proposed a different mechanistic pathway.



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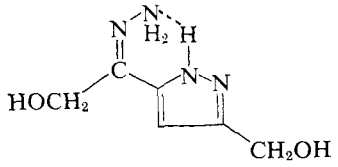
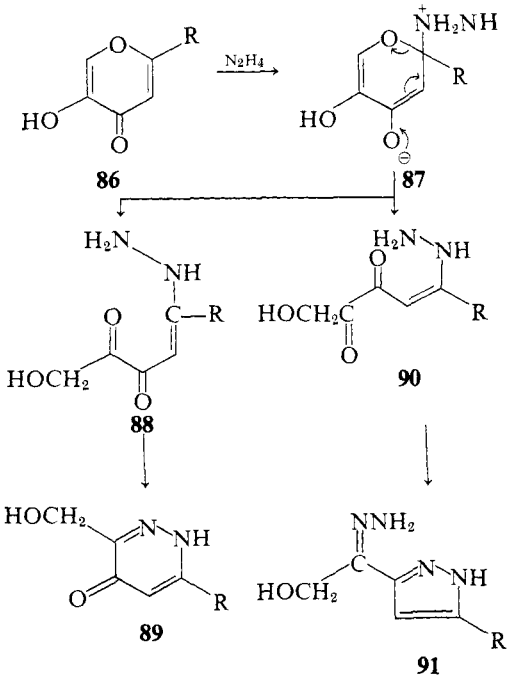


85

As support for their structure, several substituted kojic acids were used in the reaction.

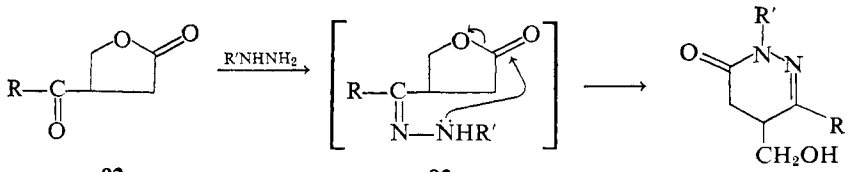
The products formed during the reaction suggested that the first step was the nucleophilic attack of hydrazine at position 2 of the pyrone ring to form **87** which could undergo various ring openings by shifts of electron pairs (**89–90**). These intermediates could immediately cyclize to give the pyridazine (**89**) or pyrazole (**91**) derivatives. The pyridazine formation was suggested to be the more favored in view of the steric effects. This was substantiated by the experimental results.



When the 5-methoxy-2-hydroxymethyl-4-pyranone was used in the reaction, only two products were obtained and neither product was the pyridazine. One product was 1-amino-2-hydroxymethyl-5-methoxy-4-pyridone and the other α-[3-hydroxymethylpyrazolyl-(5)]-α-methoxyacetaldehyde hydrazone.

4. *γ-Lactones*

Wamhoff and Korte (35) have reported that the reaction of β-acyl-γ-lactones (**92**) with hydrazine or phenylhydrazine gives the 4-hydroxymethyl-substituted 4,5-dihydro-6(1*H*)pyridazinones (**94**).



92 **93** **94**

	R	R′
92a–94a:	CH_3	H
92b–94b:	C_6H_5	H
92c–94c:	CH_3	C_6H_5
92d–94d:	C_6H_5	C_6H_5

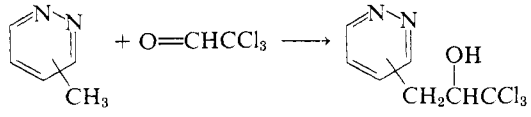
The ir and nmr spectra were given in some cases for the intermediate (**93**) formed as well as the pyridazine product (**94**). When the reaction was attempted with 2,4-dinitrophenylhydrazine, only the hydrazone intermediate was formed.

C. Reactions of Substituted Pyridazines

1. *Methyl Groups*

a. ALDOL-LIKE CONDENSATIONS. The methyl groups present in the pyridazine ring are similar to the methylpyridines and are capable of forming comparatively stable anions because of the electron-attracting properties of the ring nitrogen atoms. Thus the methylpyridazines undergo aldol-like condensations (36, 37). Jones, Kornfeld, and McLaughlin (38) allowed 3-methylpyridazine (**95a**) to react with chloral, giving 3-(2-hydroxy-3,3,3-trichloropropyl)pyridazine (**96a**). The reaction of different methyldiazines was studied in order to determine the optimum conditions for condensation. In the case of pyridazine, they obtained yields as high as 85%. Mizzoni and

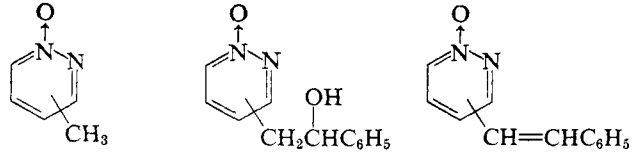
Spoerri (39) studied 4-methylpyridazine (**95b**) and found that it also underwent aldol-like condensations with chloral and anisaldehyde to yield 4-(3,3,3-trichloro-2-hydroxypropyl)pyridazine (**96b**) and the 4-(*p*-methoxystyryl)pyridazine, respectively.



95 **96**

95a and **96a**: 3-methyl
95b and **96b**: 4-methyl

Itai, Sako, and Okusa (40) examined the reactivity of a methyl group at various positions in the pyridazine 1-oxides. The 3- and 6-methyl groups were found to be almost identical in the reaction of 3,6-dimethylpyridazine 1-oxide with benzaldehyde. When the monomethylpyridazines were allowed to react with benzaldehyde in the presence of sodium methoxide, it was found that the 4- and 6-methyl groups had similar activity; the 5-methyl group was more active and the 3-methyl group was less active (5- > 4-, 6- > 3-).

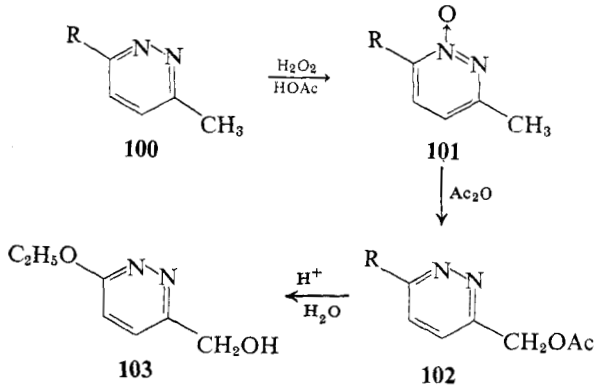


97 **98** **99**

97a and **99a**: 3-methyl (did not form **98**)
79b–99b: 4-methyl
79c–99c: 5-methyl
97d–99d: 6-methyl

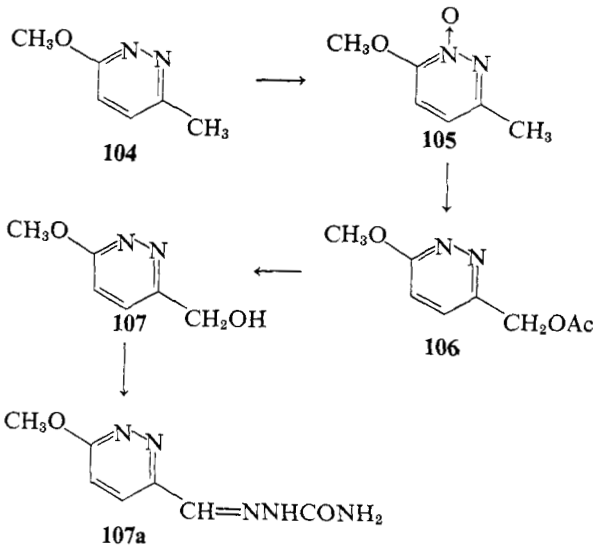
b. Acetates and Acetic Anhydride. Kumagai (41) reported the reaction of substituted 3-methylpyridazine 1-oxide (**101**) with acetic anhydride to yield the 3-acetoxymethyl-substituted pyridazines (**102**). Hydrolysis was carried out in the case of the 3-acetoxymethyl-6-ethoxypyridazine (**102c**) to give the 3-hydroxymethyl-6-ethoxypyridazine (**103**).

Nakagome (42) prepared the 3-hydroxymethyl-6-methoxypyridazine (**107**) by the same method as Kumagai (41), by treating the 3-methyl-6-methoxypyridazine (**104**) with hydrogen peroxide in acetic acid to obtain the *N*-oxide and then treatment with acetic anhydride followed by hydrolysis with hydrochloric acid.



100a–102a: R = H
100b–102b: R = C_6H_5
100c–102c: R = OC_2H_5

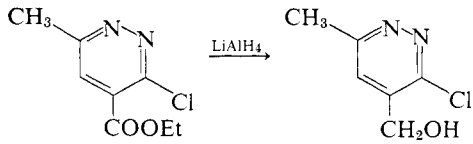
The semicarbazone of the methoxy ketone was formed by oxidation of the alcohol with selenium dioxide followed by treatment with semicarbazide.



Ogata and Kano (43) reported the synthesis of the 3-hydroxymethyl-6-methoxypyridazine by the method of Nakagome (42). However, they found that the 3-methylpyridazine 1-oxide, 3-methylpyridazine 2-oxide, or 3-methyl-6-chloropyridazine 2-oxide was not affected by treatment with acetic anhydride and only the starting materials were recovered.

2. *Esters*

Dornow and Abele (44) reported the reduction of an ester group with lithium aluminum hydride to give the alcohol. The ethyl ester of 3-chloro-6-methyl-4-pyridazinecarboxylic acid (**108**) was reduced to the 3-chloro-4-hydroxymethyl-6-methylpyridazine (**109**).

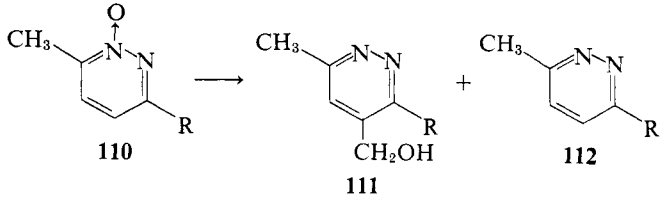


108 **109**

Ramuz, Spiegelberg, and Abele (45) reported the preparation of the 3-chloro-4-hydroxymethyl-6-methylpyridazine.

D. By Photochemical Reaction

Ogata and Kano (46) reported a novel photochemical reaction involving the hydroxymethylation of the pyridazine nucleus. The *N*-oxide derivatives of substituted pyridazines in methanol under an argon atmosphere were irradiated through Pyrex glass with a high-pressure mercury arc lamp at room temperature. Two products were isolated, one containing the hydroxymethyl group (**111a–d**); the other was the deoxygenated pyridazine (**112a–d**). When an unsubstituted pyridazine *N*-oxide was irradiated, only pyridazine and starting material were recovered.

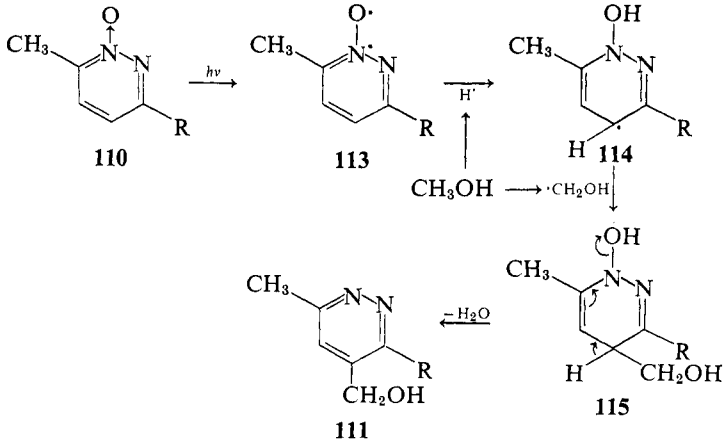


110 **111** **112**

110a–112a: R = H
110b–112b: R = CH_3
110c–112c: R = OCH_3
110d–112d: R = Cl

A mechanism was proposed that involved the excitation of the *N*-oxide to the excited state, followed by the removal of a hydrogen atom from the

solvent methanol; after this the hydrogen atom combines with the radical and the intermediate undergoes decomposition.



110 113 114 111 115

Cramer and Schlingloff (47) have reported a similar photochemical deoxygenation of purine *N*-oxides.

III. Reactions of Side-Chain Aldehydes and Ketones with Carbon Attachment

A. Ketone-Aldehyde Derivatives

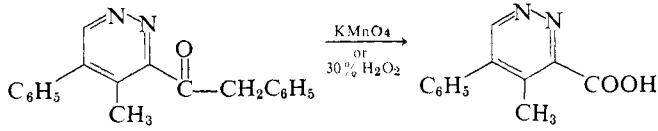
The pyridazine aldehydes and ketones give the reactions expected of aldehydes and ketone functions in side chains. The carbonyl moieties readily form phenylhydrazones, semicarbazides, 2,4-dinitrophenylhydrazones, and oximes, frequently being used for identification purposes. (See tables at end of this chapter.)

Ogata (16) prepared the oxime, reduced the oxime to the amine, converted the oxime to the oxime acetate and this into a cyano group.

B. Oxidation

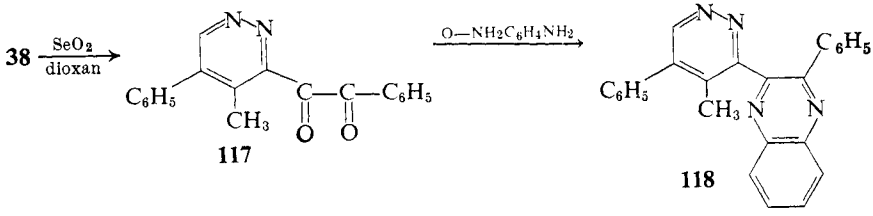
Oxidation of side-chain aldehydes occurs readily, as shown by Kumagai (15). 6-Phenylpyridazine-3-carboxylic acid was obtained by treatment of 3-formyl-6-phenylpyridazine with ethanolic silver nitrate.

As expected, groups containing the keto group in the side chain can also be oxidized to carboxylic acids (4, 13). One example is that reported by Bly, Zoll, and Moore (13).



38 **116**

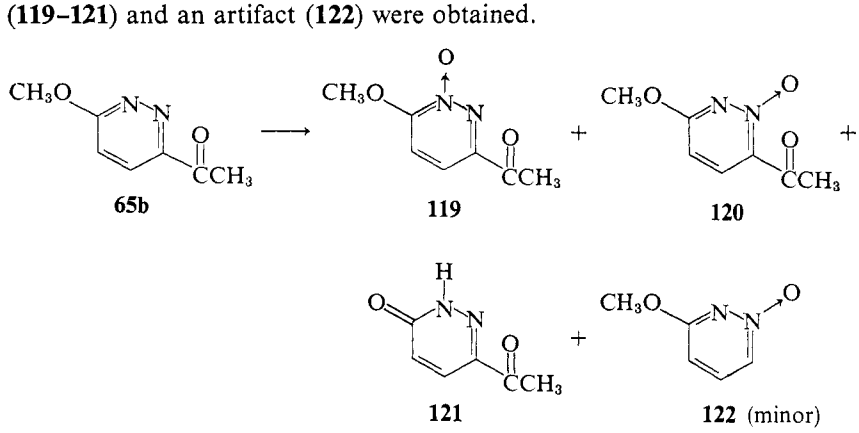
Bly, Zoll, and Moore (13) also prepared the α-diketone by oxidizing compound **38** with selenium dioxide. The diketone was characterized by conversion into a quinoxaline with *o*-phenylenediamine.



117 **118**

1. *N-Oxidation*

Nakagome and Castle (24) found that the *N*-oxidation of 3-acetylpyridazine with hydrogen peroxide and acetic acid gave only one product, 3-acetylpyridazine 1-oxide. However, when 3-acetyl-6-methoxypyridazine was allowed to react with hydrogen peroxide–acetic acid, three primary products (**119–121**) and an artifact (**122**) were obtained.



65b **119** **120**

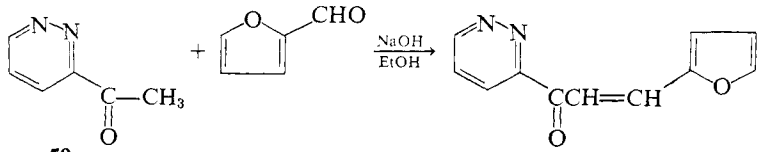
121 **122** (minor)

C. Reduction

The expected reductions have been carried out on the ketones. For example, 6-benzoyl-3-phenylpyridazine gives 3-benzyl-6-phenylpyridazine by Wolff–Kishner reduction (4). When 6-benzoyl-3-phenylpyridazine was allowed to react with sodium and ethanol, the corresponding alcohol was formed (4).

D. Condensation

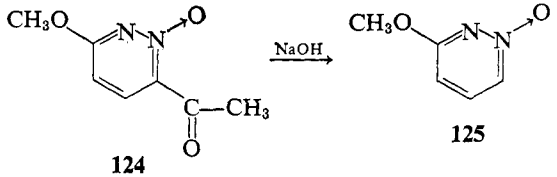
Sokolov and Hiller (25) reported an aldol-like condensation involving 3-acetylpyridazine and furfural.



59a 123

E. Deacylation

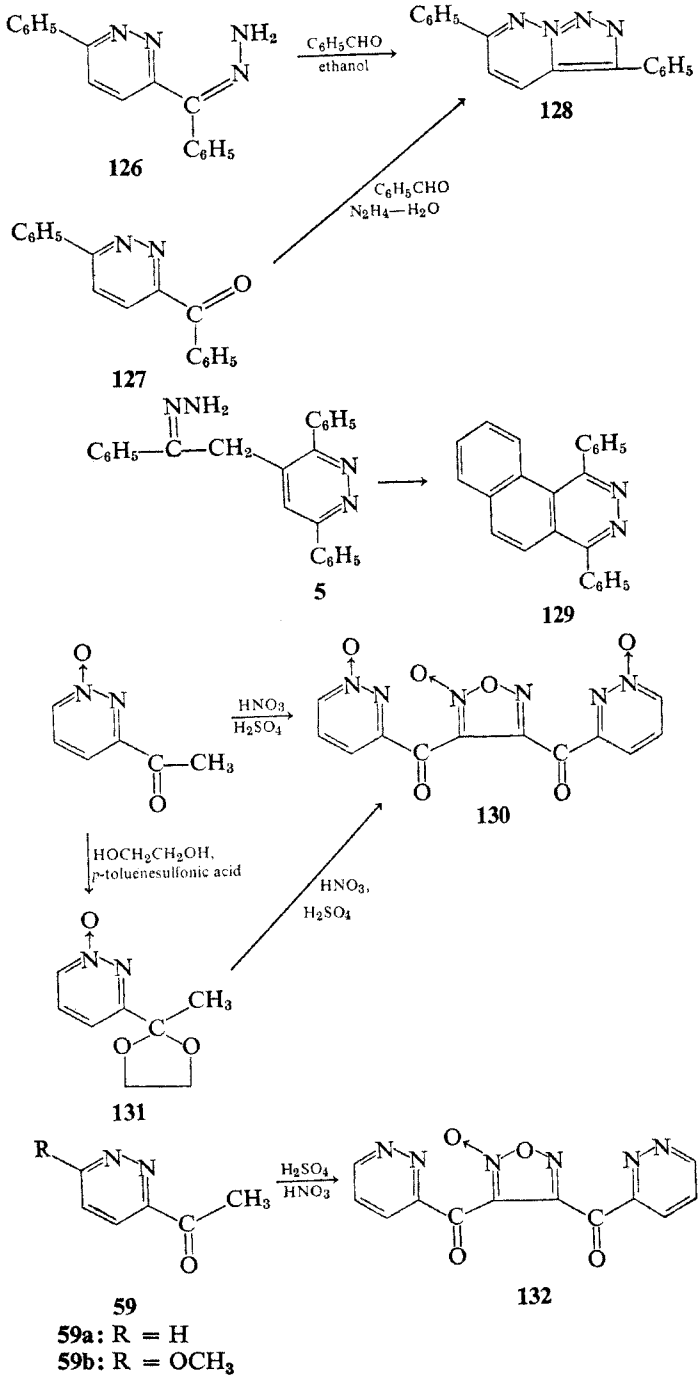
Nakagome and Castle (24) reported a novel alkali-catalyzed deacylation reaction. It was shown that 3-methoxypyridazine 1-oxide (**125**) could be obtained in quantitative yield by treatment of 3-acetyl-6-methoxypyridazine 2-oxide with dilute sodium hydroxide solution.



124 125

F. Cyclization

Several different types of cyclizations have been reported involving pyridazines with aldehyde or ketone moieties in the side chain. Evans, Johns, and Markham (4) reported the cyclization of a pyridazinyl ketone hydrazone with benzaldehyde to give a *v*-triazolo[3,4-*b*]pyridazine (**128**). Compound **128** arose from either 3-phenyl-6-benzoylpyridazine (**127**) or from the corresponding hydrazone (**126**).



59

59a: R = H

59b: R = OCH_3

Oxidation products of substituted pyridazine hydrazones have been shown to cyclize, as illustrated by Yates, Farnum, and Stout (2). Potassium permanganate oxidation of 4-phenacyl-3,6-diphenylpyridazine hydrazone gave a product with a formula $C_{24}H_{16}N_2$, together with benzoic acid. These investigators (2) proposed that a benzophthalazine was formed by oxidation of the hydrazone to an aliphatic diazo compound with elimination of nitrogen followed by oxidation.

Nitration of 3-acetylpyridazine 1-oxide and 3-acetylpyridazines under a variety of conditions were shown by Nakagome and Castle to lead to the formation of furoxanes and not the simple nitro compounds as would be expected. It was also found that the ethylene ketal (**131**) formed from 3-acetylpyridazine 1-oxide also cyclized upon nitration.

IV. Reaction of Side-Chain Alcohols Attached to the 3-, 4-, 5-, and 6-Positions of the Pyridazine Ring

A. Oxidation

Hydroxymethylpyridazines are readily oxidized to the corresponding pyridazine carboxylic acids with permanganate (23, 28a, 30, 31, 34). Ogata and Kano (43) used potassium dichromate and sulfuric acid in this same reaction.

The oxidation of the hydroxymethyl group to the aldehyde group was accomplished using SeO_2 in dioxan (42). Oxidation of a secondary alcohol, 3-(1-hydroxy-1-phenylmethyl)-6-phenylpyridazine, with chromic acid in aqueous sulfuric acid gives the corresponding ketone (4).

B. Chlorination

Hydroxymethyl groups are readily converted to chloromethyl substituents by treatment with thionyl chloride (31, 34) or phosphorus oxychloride (45).

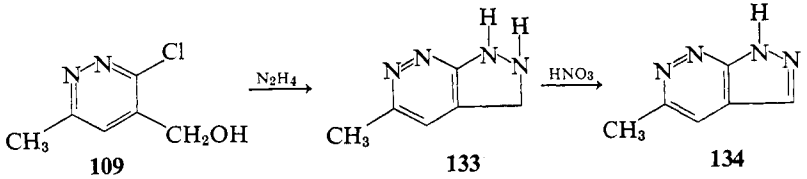
C. Styryl and Styryl-like Formation

β-Hydroxyphenethylpyridazine 1-oxides were converted to styrylpyridazine 1-oxides by heating in a sealed tube with methanolic sodium methoxide (40). The chlorohydroxypropyl compounds obtained from condensation of chloral

and methylpyridazines are readily converted into the acrylic acids by warming in sodium hydroxide followed by acidification (38, 39).

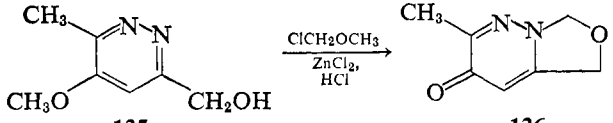
D. Cyclization

Two interesting cyclizations were observed with the side-chain alcohols. Dornow and Abele (44) found that treatment of 3-chloro-4-hydroxymethyl-6-methylpyridazine with hydrazine gives a pyrazolo[3,4-*c*]pyridazine.



109 **133** **134**

Suzuki, Nakadate, and Yoshida (48) have reported the formation of a new ring system which arose from the reaction of 3-methyl-4-methoxy-6-hydroxymethylpyridazine (**135**) with chloromethyl methyl ether in $ZnCl_2$–HCl. The product was an oxazolopyridazinone (**136**).



135 **136**

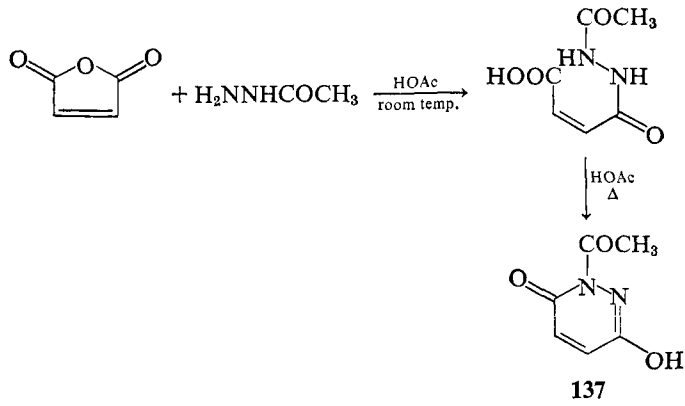
V. Synthesis of Nitrogen-Attached Side-Chain Aldehydes and Ketones

N-Alkylation and *N*-acylation have been reported to occur readily with maleic hydrazide and related pyridazines. The aldehyde and ketone groups attached to one of the ring nitrogen atoms have been prepared by different means. Some substituents are attached to the hydrazine moiety before cyclization to the pyridazine, and in other instances the group is attached to the amide-type nitrogen atom of the pyridazinone.

A. Ring Formation

In 1893, Capuano (49) reviewed the literature on the reaction of 1,4-diketones with hydrazine and its derivatives and reported the preparation of 1-benzoyl-3,4-diphenyl-1,2-dihydropyridazine by cyclization of the appropriate diketone with benzoylhydrazine.

Feuer and Rubinstein (50) undertook to establish the course of substitution in reactions between maleic hydrazide and acetic anhydride and related reactions. *N*-Acyl-substituted derivatives of maleic hydrazide were prepared by an unambiguous route.



137

The structure of 1-acetyl-3-hydroxy-6(1*H*)pyridazinone (**137**) is supported by ir, acidity characteristics, and reactions with acid and base.

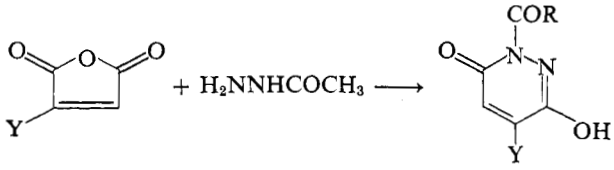
Shabarov, Vasil'er, and Levina (51) studied the possibility of using dibenzoyldiimide in a Diels–Alder-type reaction. The acidity of 1,4-diphenyl-1,3-butadiene was too low to cyclize with the diimide, although this diene has been known to cyclize with ethyl azocarboxylate. The activity of the 1-phenylbutadiene, 1,3-pentadiene, and the 2,4-hexadiene was sufficient to allow a reaction to take place with dibenzoyldiimide, giving 1,2-dibenzoyl-3-phenyl-1,2,3,6-tetrahydropyridazine, 1,2-dibenzoyl-3-methyl-1,2,3,6-tetrahydropyridazine, and the 1,2-dibenzoyl-3,6-dimethyl-1,2,3,6-tetrahydropyridazine, respectively.

1,2-Dibenzoylhexahydropyridazine was prepared by the cyclization of tetramethylene bromide with 1,2-dibenzoylhydrazine in basic solution (52).

The reaction between aliphatic dicarboxylic acid anhydrides and carboxylic acid hydrazides also leads to the formation of *N*-acyl derivatives of maleic hydrazide (53). Maleic anhydride, citraconic anhydride, and succinic anhydride are cyclized by reaction with different substituted hydrazides.

Carp, Dorneanu, and Zugravescu (54) cyclized mucobromic acid with benzoylmethylhydrazine and isolated 1-benzoylmethyl-4,5-dibromo-6(1*H*)-pyridazinone in a fashion similar to the work reported by Gudriniece and Karklins (55).

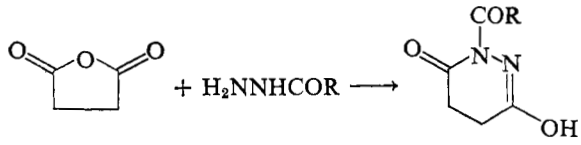
1-Phenyl-3-hydroxy-6(1*H*)pyridazinone was prepared from dichloromaleic anhydride and phenylhydrazine (55a). This pyridazinone when allowed to



138

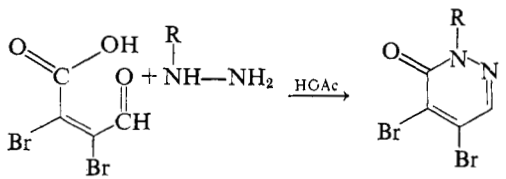
138a: R = CH_3^-; Y = H
138b: R = $4(NO_2)C_6H_4^-$; Y = H
138c: R = $2,4(Cl_2)C_6H_3^-$; Y = H
138d: R = $4(NO_2)2(Cl)C_6H_3^-$; Y = H
138e: R = $2(OH)C_6H_4^-$; Y = H

140a: R = $4(NO_2)2(Cl)C_6H_3^-$; Y = CH_3^-
140b: R = $2(OH)C_6H_4^-$; Y = CH_3^-



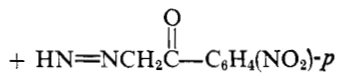
139

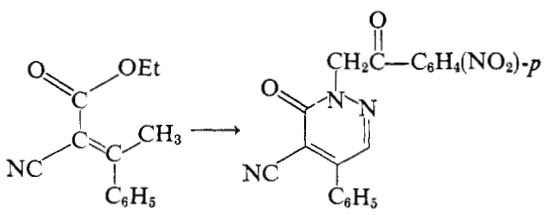
139a: R = $4(NO_2)C_6H_4^-$
139b: R = $2(OH)C_6H_4^-$



140 **141**

141a: R = $C_6H_5COCH_2^-$
141b: R = $HOCH_2CH_2^-$
141c: R = $NCCH_2CO^-$
141d: R = isonictinoyl





142

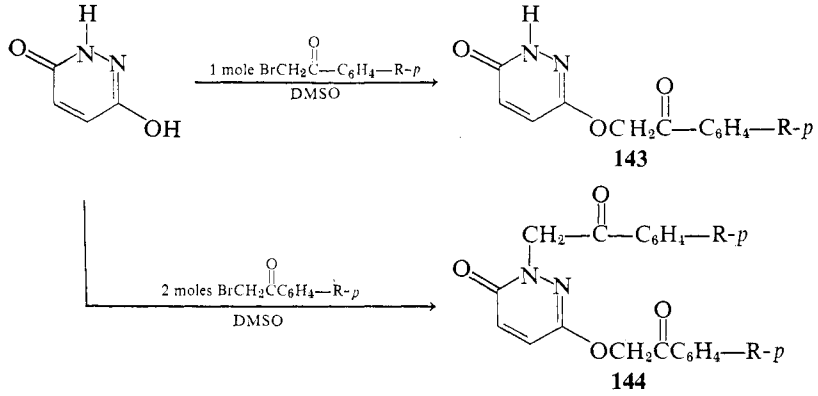
react with a mixture of phosphorus oxychloride and phosphorus pentachloride gives 1-phenyl-3,4,5-trichloro-6(1*H*)pyridazinone.

A cyclization of an alkylidenecyano ester with a diazocarbonyl compound has been reported recently by Fanghänel et al. (56).

B. By Reactions of Substituted Pyridazines

1. *N-Alkylation of Pyridazinones*

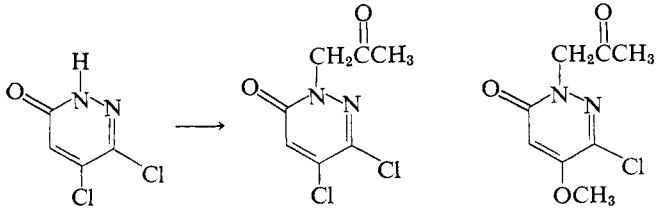
Usually, alkylations of pyridazinones lead to *N*-alkylated products. When phenacyl halides are the alkylating agents, the products contain a ketone carbonyl group in the side chain. However, Jaunin (57) reported that the reaction of 1 mole of substituted phenacyl halide with maleic hydrazide in dimethyl sulfoxide (DMSO) gave the *O*-alkylated product (**143**), while 2 moles of the phenacyl halide gave the disubstituted *O*,*N*-substituted pyridazinone (**144**).



143

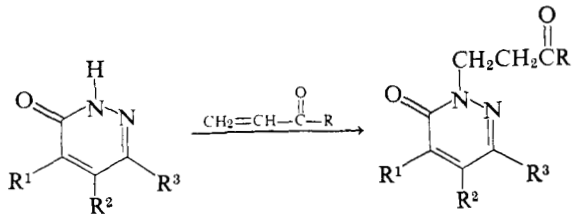
144

Schönbeck and Kloimstein (58) *N*-alkylated 3,4-dichloro-6(1*H*)pyridazinone with chloroacetone followed by replacement of the 4-chlorine atom with a methoxyl group.



145 **146**

Kamiya and Nakamura (59) reported a Michael-type addition of methyl vinyl ketone and maleic hydrazide. Similarly, acrolein gives the *N*-alkylation product.

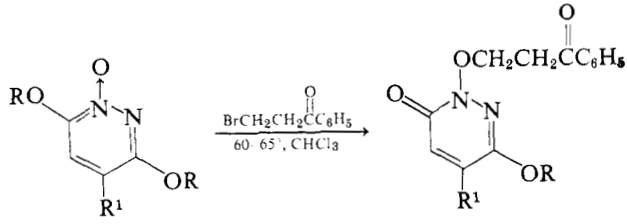


147 **148**

	R^1	R^2	R^3	R
147a and **148a**:	H	H	OH	H
147b and **148b**:	H	H	OH	CH_3
147c and **148c**:	Cl	Cl	H	CH_3
147d and **148d**:	H	H	Cl	CH_3

2. *O-Alkylations of Pyridazine N-Oxides*

The reactions of an α-iodoketone or a β-bromoketone with an alkoxypyridazine 1-oxide have been reported (60, 61) to occur at the *N*-oxide oxygen. The products are easily decomposed by heat, acid, or base.



149 **150**

149a and **150a**: R = CH_3; R^1 = H
149b and **150b**: R = C_2H_5; R^1 = H
149c and **150c**: R = CH_3; R^1 = CH_3
149d and **150d**: R = C_2H_5; R^1 = CH_3

3. *N-Acylation*

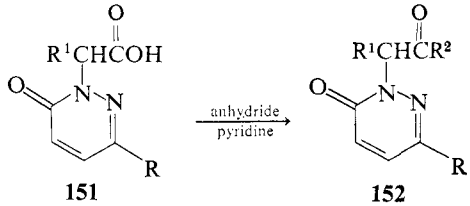
N-acylation of pyridazinones and hydropyridazines with at least one hydrogen atom on a nitrogen atom readily occurs to give, for example, the

N-acetyl or *N*-benzoyl derivative. Bacchette (62) prepared *N*-benzoyl and *N*-acetyl derivatives of 3,6-dimethyl-1,4-dihydropyridazine. Baranger, Levisalles, and Vuidart (63), Baranger and Levisalles (64), and Clement (65) characterized 1,2,3,6-tetrahydropyridazines by preparation of the dibenzoyl derivatives. Shabarov, Kux'min, and Levina (66) prepared the *N,N*-dibenzoyl derivatives of 3-methyl-1,2,3,6-tetrahydropyridazine. Overberger, Byrd, and Mesrobian (67) prepared the monobenzoyl derivative of 3,6-dimethyl-1,2-dihydropyridazine. Gillis and Beck (68) prepared the dibenzoyl derivative of 4,5-dimethylhexahydropyridazine. Hedaya, Hinman, and Theodoropulos (69) treated methylmaleic hydrazide with acetyl chloride and obtained a mixture of *N*- and *O*-acylated products.

Price, Sutherland, and Williamson (70) reported nmr studies of the conformational changes in diacyltetrahydropyridazines. The energy barriers to ring inversion were shown to be unusually high for six-membered rings. It is proposed that this was associated with the interaction between the *N*-acyl substituents.

4. *Methyl Ketones from Acids*

King and McMillan (71) and later McMillan et al. (72) allowed acetic anhydride in pyridine to react with pyridazinones with an *N*-alkylated function carrying a carboxyl group. The side-chain group was converted to a methyl ketone. Higher ketones are obtained by using the appropriate anhydride.



151 **152**

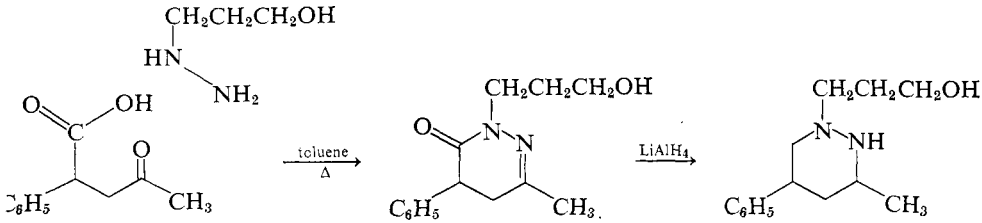
	R	R^1	R^2		R	R^1	R^2
151a and **152a**:	H	H	CH_3	**151i** and **152i**:	CH_3	H	C_2H_5
151b and **152b**:	CH_3	H	CH_3	**151j** and **152j**:	CH_3	H	*n*-C_3H_7
151c and **152c**:	CH_3	CH_3	CH_3	**151k** and **152k**:	CH_3	H	*i*-C_3H_7
151d and **152d**:	CH_3	C_2H_5	CH_3	**151l** and **152l**:	CH_3	H	*n*-C_4H_9
151e and **152e**:	CH_3	*n*-C_3H_7	CH_3	**151m** and **152m**:	CH_3	H	*i*-C_4H_9
151f and **152f**:	CH_3	*i*-C_3H_7	CH_3	**151n** and **152n**:	CH_3	H	*sec*-C_4H_9
151g and **152g**:	CH_3	*n*-C_4H_9	CH_3	**151o** and **152o**:	CH_3	H	*n*-C_5H_{11}
151h and **152h**:	CH_3	*n*-C_5H_{11}	CH_3	**151p** and **152p**:	CH_3	H	*n*-C_6H_{13}
				151q and **152q**:	CH_3	H	*n*-C_7H_{16}

VI. Synthesis of Side-Chain Alcohols Attached to a Nitrogen Atom

One of the most common methods for preparing *N*-pyridazinyl alcohols is by hydroxymethylation, however, several other methods have also been reported. These are cyclization, *N*-alkylation with reagents already containing a hydroxyl group, rearrangement from *O*-substitution to *N*-substitution, and reduction of ketones or esters to alcohols.

A. By Ring Formation

Gudriniece and Karklins (55) reported the preparation of 4,5-dibromo-1-hydroxyethyl-6(1*H*)pyridazinone by the cyclization of mucobromic acid and β-hydroxyethylhydrazine. Schönbeck and Kloimstein (58) allowed β-hydroxyethylhydrazine to react with mucochloric acid or with dichloromaleic acid to obtain 4,5-dichloro-1-(β-hydroxyethyl)-6(1*H*)pyridazinone and 4,5-dichloro-3-hydroxy-1-(β-hydroxyethyl)-6(1*H*)pyridazinone, respectively. Houlihan (73–75) cyclized substituted levulinic acids, or substituted and unsubstituted β-benzoylpropionic acids, with hydrazinopropanol. The substituted tetrahydropyridazinones are readily reduced with lithium aluminum hydride to the hexahydropyridazines.



153 154

Similarly, the substituted β-benzoylacrylic acids are cyclized and reduced to the hexahydropyridazines.

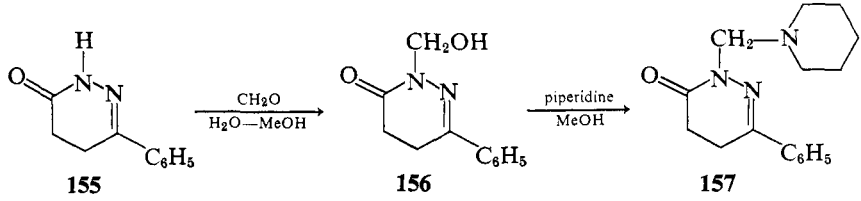
B. By Reactions of Substituted Pyridazines

1. *Hydroxymethylation*

The reaction of formaldehyde with pyridazinones has been shown to give the corresponding Mannich bases by Hellmann and Löschmann (76),

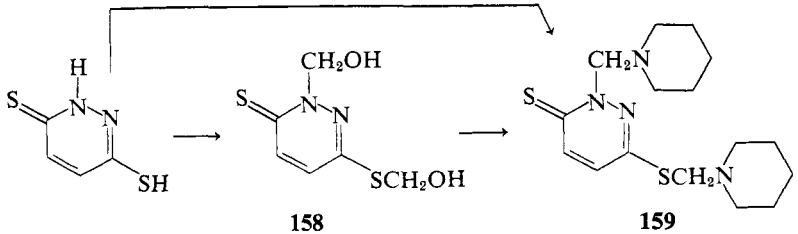
however, in the majority of instances the *N*-hydroxymethyl derivatives are formed. Gregory, Hills, and Wiggins (77) reported that neither 6(1*H*)-pyridazinone nor 3-methyl-6(1*H*)pyridazinone gave a Mannich base when allowed to react with formaldehyde and dimethylamine. Rather, 1-hydroxymethyl-6(1*H*)pyridazinones are produced. Teotino and Cignarella (78, 79) reported that, when 3-carbethoxy-6(1*H*)pyridazinone was heated with formaldehyde, the *N*-hydroxymethyl product was obtained. The *N*-hydroxymethyl product is also obtained when 3-phenyl-6(1*H*)pyridazinone is treated with dimethylamine and formaldehyde (80). Nishizawa and Nakagawa (81) reported that the reaction of 3-methyl-4,5-dihydro-6(1*H*)pyridazinone under similar conditions gives the expected 1-hydroxymethyl-3-methyl-4,5-dihydro-6(1*H*)pyridazinone.

The Mannich reaction on 4,5-dihydropyridazinones has been studied by Mustafa et al (82). The condensation of 5-arylidene-4,5-dihydro-3-phenyl-6(1*H*)pyridazinone with formaldehyde leads to the corresponding *N*-Mannich bases. When 3-phenyl-4,5-dihydro-6(1*H*)pyridazinone is allowed to react with formaldehyde and piperidine or morpholine, the corresponding *N*-Mannich base is formed; however, when 3-phenyl-4,5-dihydro-6(1*H*)-pyridazinone (**155**) is allowed to react with aqueous formaldehyde in methanol, the 1-hydroxymethyl-3-phenyl-4,5-dihydro-6(1*H*)pyridazinone (**156**) is formed. Further treatment of the hydroxymethyl compound with piperidine and methanol results in formation of the Mannich base (**157**).



155 **156** **157**

Polak and Tišler (83) reported a similar reaction using 3,6-dimethylmercaptopyridazine and 3-mercapto-6(1*H*)pyridazinethione. Formaldehyde and methanol give the bishydroxymethyl product (**158**) and treatment of this compound or the starting material with piperidine or morpholine gives the Mannich bases (**159**).



158 **159**

Schönbeck and Kloimstein (58) have reported numerous examples of the preparation of 1-hydroxymethyl chloro-substituted 6(1*H*)pyridazinones

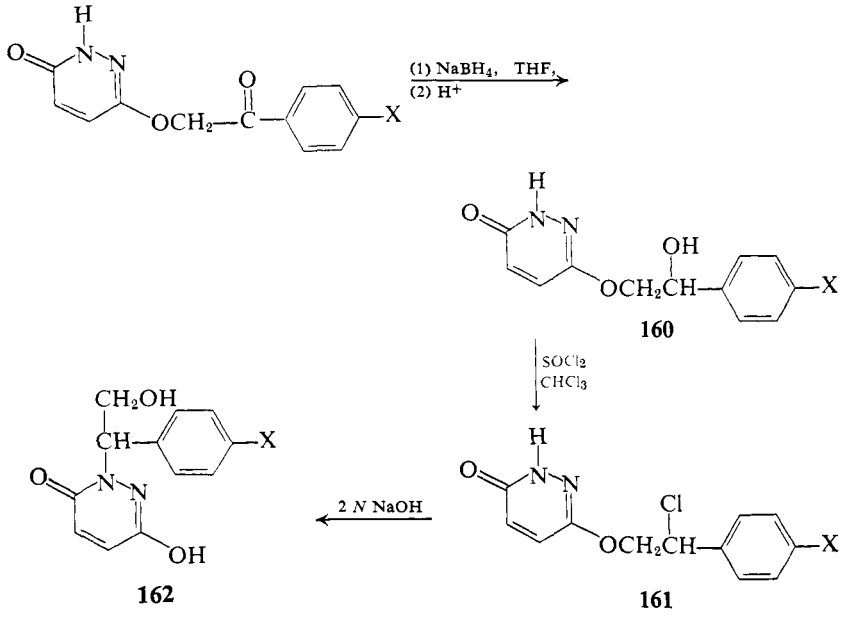
and 1-hydroxymethyl chloro- or hydroxy-substituted 6(1*H*)pyridazinones by the reaction of formaldehyde and sodium hydroxide on the corresponding pyridazinones.

2. *N-Alkylation*

N-Alkylations have been reported to occur on pyridazinones by reaction of halo-substituted aliphatic alcohols or styrene-like compounds. Schönbeck and Kloimstein (58) prepared a series of *N*-hydroxyethylchloropyridazinones by the reaction of 2-chloroethanol with the corresponding substituted chloropyridazinones. Umio, Kariyone, and Kishimoto (84) have also reported the preparation of 1-hydroxyethyl-3-phenyl-6(1*H*)pyridazinone and 1-hydroxyethyl-3-phenyl-5-methyl-6(1*H*)pyridazinone from the corresponding 3-phenyl-6(1*H*)pyridazinone. Molnar (27) allowed styrene oxide to react with 3-carbethoxy-6-methyl-1,4,5,6-tetrahydropyridazine and obtained 1-(2-hydroxy-2-phenylethyl)-3-carbethoxy-6-methyl-1,4,5,6-tetrahydropyridazine.

3. *O → N Rearrangement*

The rearrangement of simple alkoxypyridazines has been reported (85, 86) and occurs under relatively mild conditions. Jaunin (57) reported the reaction occurring with a derivative of maleic hydrazide.

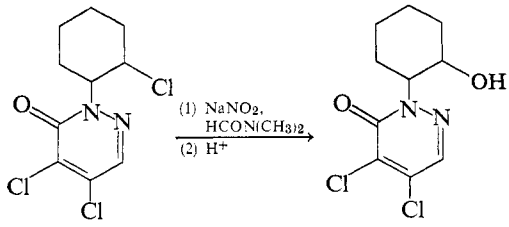


4. *Reductions*

Since the groups of interest are on the side chain, they undergo the reactions normal for aliphatic groups. McMillan et al. (72) prepared the alcohol by reduction of a ketone with dry 2-propanol and aluminum isopropoxide, thus 3-[1-(3-methyl-6(1*H*)pyridazinonyl)]-2-butanone gives 3-[1-(3-methyl-6(1*H*)pyridazinonyl)]-2-butanol.

5. *Chlorine → Hydroxyl*

The conversion of a side-chain chlorine atom to a side-chain hydroxyl group has been reported (87).



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VII. Reactions of Side-Chain Alcohols, Aldehydes, and Ketones Attached to a Ring Nitrogen Atom

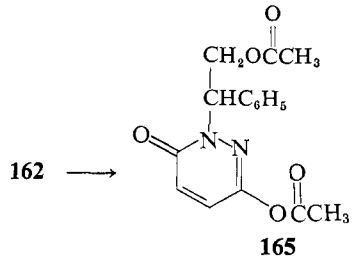
The alcohols and carbonyl groups undergo the normal reactions expected for most aliphatic alcohols, aldehydes, and ketones. Examples of some reactions have been given earlier in this chapter. A few additional examples are reported below.

Replacement of Side-Chain Hydroxyl Groups by Chlorine or Bromine

Thionyl chloride readily gives the chloro derivatives (57, 81, 88) and bromine gives the bromo derivatives (89).

A. Conversion of Alcohols into Esters

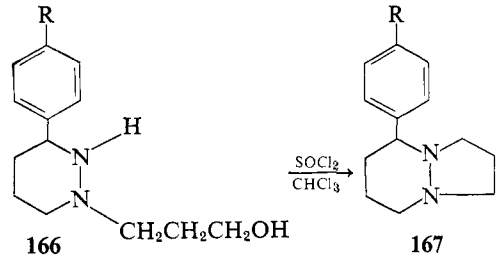
For example, Jaunin (57) prepared an ester by allowing acetic anhydride to react with a substituted maleic hydrazide to aid in the identification of a rearrangement product.



162 ⟶ **165**

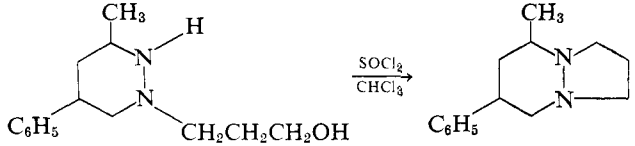
B. Cyclization of Alcohols

Houlihan (73–75) has reported the formation of cyclic products when *N*-(3-hydroxypropyl)pyridazines have been allowed to react with thionyl chloride in chloroform.



166 **167**

R = H, Cl, OCH_3



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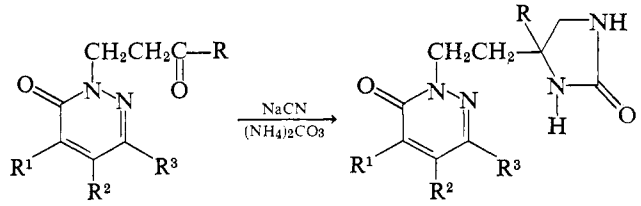
C. Conversion of Ketones to α-Amino Acids

Kamiya and Nakamura (59) treated the side-chain keto group with potassium cyanide and ammonium chloride followed by hydrolysis to obtain

the *dl*-1-(3-amino-3-carboxybutyl)-3-hydroxy-6(1*H*)pyridazinone and the *dl*-1-(3-amino-3-carboxypropyl)-3-hydroxy-6(1*H*)pyridazinone from the corresponding 1-(3-oxoalkyl)-3-hydroxy-6(1*H*)pyridazinone.

D. Cyclization of Ketones

Kamiya and Nakamura (59) reported the cyclization of the side-chain ketones, 1-(3-oxoalkyl)-substituted 6(1*H*)pyridazinones, to hydantoins with sodium cyanide and ammonium carbonate.



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R	R^1	R^2	R^3	
170a and **171a:**	H	H	H	OH
170b and **171b:**	CH_3	H	H	OH
170c and **171c:**	CH_3	H	H	Cl
170d and **171d:**	CH_3	H	H	Cl

TABLE I. Pyridazine Aldehydes and Ketones

Compound	Formula	MP (°C)	References
3,6-Diphenyl-4-phenacylpyridazine	$C_{24}H_{18}N_2O$	155–155.5	2
Hydrazone	$C_{24}H_{20}N_4$	155–156.5	2
5-Acetyl-3-benzoyl-6-methyl-1-phenyl-1,4-dihydropyridazine	$C_{20}H_{18}N_2O_2$	112–113	3
3-Benzoyl-6-phenylpyridazine	$C_{17}H_{12}N_2O$	126	4
Hydrazone	$C_{17}H_{14}N_4$	161	4
3-Benzoyl-6-phenyl-4,5-dihydropyridazine hydrazone	$C_{17}H_{16}N_4$	156–157	4
3-Hydroxymethyl-6-methyl-1,2-bismethoxycarbonyl-1,2,3,6-tetrahydropyridazine	$C_{10}H_{16}N_2O_5$	bp 126 (oil)	5
3-Acetyl-3-phenyl-1,2-bismethoxycarbonyl-1,2,3,6-tetrahydropyridazine	$C_{16}H_{18}N_2O_5$	121	5
3-Acetyl-6-phenyl-1,2-bismethoxycarbonyl 1,2,5,6-tetrahydropyridazine	$C_{16}H_{18}N_2O_5$	92	5

TABLE I (*continued*)

Compound	Formula	MP (°C)	References
4-Diacetylmethyl-3,5-diphenylpyridazine	$C_{21}H_{18}N_2O_2$	178–179	7
4-Diacetylmethyl-6-methyl-3,5-diphenyl-pyridazine	$C_{22}H_{20}N_2O_2$	207–208	7
4-Diacetylmethyl-6-ethyl-3,5-diphenylpyridazine	$C_{23}H_{22}N_2O_2$	152–153	7
3-Benzoyl-4,6-diphenyl-4,5-dihydro-pyridazine hydrazone	$C_{23}H_{20}N_4$	160–170	8
3-Formyl-5-phenylazo-1-phenyl-4(1*H*)-pyridazinone	$C_{17}H_{12}N_2O_2$	172–174	9
Oxime	$C_{17}H_{15}N_5O_2$	253–255	9
Semicarbazone	$C_{18}H_{15}N_7O_2$	241–243 (dec)	9
Phenylhydrazone	$C_{23}H_{20}N_6O$	244–246	9
Methyl hemiacetal	$C_{18}H_{16}N_4O_3$	134–136	9
2-Phenyl-3-formyl-2,5-dihydropyridazine phenylhydrazone	$C_{17}H_{16}N_4$	237	10
4-Acetyl-5-amino-3-methyl-6(1*H*)-pyridazinone	$C_7H_9N_3O_2$	234	11
Diacetyl	$C_{11}H_{13}N_3O_4$	202	11
Oxime	$C_7H_{10}N_4O_2$	249	11
5-Amino-4-benzyl-3-phenyl-6(1*H*)-pyridazinone	$C_{17}H_{13}N_3O_2$	229–230	11
Acetyl	$C_{19}H_{15}N_3O_3$	197	11
4-Acetyl-5-amino-3-phenyl-6(1*H*)-pyridazinone	$C_{12}H_{11}N_3O_2$	201–203	11
Acetyl	$C_{14}H_{13}N_3O_3$	237	11
4-Acetyl-5-aminopyridazine-3,6(1*H*,3*H*)-dione	$C_6H_7N_3O_3$	338 (dec)	11
5-Acetyl-4-amino-3-phenyl-6(1*H*)-pyridazinone	$C_{12}H_{11}N_3O_2$	302 (dec)	11
4-Methyl-5-phenyl-3-phenylacetylpyridazine	$C_{19}H_{16}N_2O$	125–126	13
2,4-Dinitrophenylhydrazone	$C_{25}H_{20}N_6O_4$	97–100	13
4-Methyl-5-phenyl-3-(2-phenyl-1,2-dioxoethyl)pyridazine	$C_{19}H_{14}N_2O_2$	134–135	13
Quinoxaline	$C_{25}H_{18}N_4$	187–190	13
1,4-Dimethyl-3-formyl-5-phenyl-1,6-dihydropyridazine	$C_{13}H_{14}N_2O$	98–100	14
Oxime	$C_{13}H_{15}N_3O$	160–162	14
Semicarbazone	$C_{14}H_{17}N_5O$	184–185 (dec)	14
1,4-Dimethyl-3-formyl-5-phenyl-pyridazinium bromide	$C_9H_{13}BrN_2O$	74–75	14
1,4-Dimethyl-3-formyl-5-phenyl-pyridazinium perchlorate	$C_{14}H_{16}ClN_5O_5$	215–216	14
3-Formylpyridazine	$C_5H_4N_2O$		15
2,4-Dinitrophenylhydrazone	$C_{11}H_8N_6O_4$	244–245	15
p-Dimethylaminophenylnitrone	$C_{13}H_{14}N_4O$	167–168	15

TABLE I (*continued*)

Compound	Formula	MP(°C)	References
3-Formyl-6-phenylpyridazine	$C_{11}H_8N_2O$	162	15
2,4-Dinitrophenylhydrazone	$C_{17}H_{12}N_6O_4$	272	15
Semicarbazone	$C_{12}H_{11}N_5O$	251	15
Thiosemicarbazone	$C_{12}H_{11}N_5S$	229–230	15
p-Dimethylaminophenylnitrone	$C_{19}H_{18}N_4O$	216	16
4-Acetyl-3,4-diphenyl-6(1*H*)pyridazinone	$C_{18}H_{14}N_2O_2$	231–232	1, 1a
5-Acetyl-1-methyl-3,4-diphenyl-6(1*H*) pyridazinone	$C_{19}H_{16}N_2O_2$	158–159	1a
5-Benzoyl-3,4-diphenyl-6(1*H*)pyridazinone	$C_{23}H_{16}N_2O_2$	224–225	1, 1a
5-Acetyl-1,3,4-trimethyl-6(1*H*)pyridazinone	$C_9H_{13}N_2O_2$	98–99	22
Imino derivative	$C_9H_{13}N_3O$	83–84	22
5-(1-Oxo-2-carboxyethyl)-1,3,4-trimethyl-6(1*H*)pyridazinone	$C_{10}H_{12}N_2O_4$	148–150	22
3-Acetylpyridazine	$C_6H_6N_2O$	89–90	24
Hydrazone	$C_6H_8N_4$	76–77.5	24
3-Acetyl-6(1*H*)pyridazinone	$C_6H_6N_2O_2$	173–174	24
3-Acetyl-1-hydroxy-6(1*H*)pyridazinone	$C_6H_6N_2O_3$	191–192 (dec)	24
3-Acetyl-6-methoxypyridazine	$C_7H_8N_2O_3$	97–98	24
3-(1,3-Dioxobutyl)pyridazine	$C_8H_8N_2O_2$	116–117	25
3-(1,3-Dioxopentyl)pyridazine	$C_9H_{10}N_2O_2$	71–72	25
3-(1,3-Dioxoheptyl)pyridazine	$C_{11}H_{14}N_2O_2$	53–54	25
3[3-(2-Furyl)-1-oxopropyl]pyridazine	$C_{11}H_{10}N_2O_2$	105	25
4-Formyl-3-hydroxy-6(1*H*)pyridazinone phenylhydrazone	$C_{11}H_{10}N_4O_2$	165–170	26
4-Formyl-3-hydroxy-1-phenyl-6(1*H*)-pyridazinone phenylhydrazone	$C_{17}H_{14}N_4O_2$	280–282	26
p-Carboxyphenylhydrazone	$C_{18}H_{14}N_4O_4$	210–230	26
3-Formyl-6-methoxypyridazine semicarbazone	$C_7H_9N_5O_3$	248 (dec)	42

TABLE II. Pyridazine Alcohols

Compound	Formula	MP (°C)	References
1-(1-Hydroxy-1-phenylmethyl)-6-phenylpyridazine	$C_{17}H_{14}N_2O$	161	4
Acetate	$C_{19}H_{16}N_2O_2$	158–159	4
3-(1-Hydroxy-2-phenylethyl)-4-methyl-5-phenylpyridazine	$C_{19}H_{18}N_2O$	111–112	13
Acetate	$C_{21}H_{20}N_2O_2$	93	13
1,2-Dicarbethoxy-6-hydroxymethyl-3-methyl-1,2,3,6-tetrahydropyridazine	$C_{12}H_{20}N_2O_5$	bp 131–141 (0.6–0.1 mm)	27
1,2-Dicarbethoxy-6-hydroxymethyl-3-methylhexahydropyridazine	$C_{12}H_{22}N_2O_5$	bp 147–150	27

TABLE II (*continued*)

Compound	Formula	MP(°C)	References
1,2-Dicarbethoxy-3-hydroxymethyl-6-methyl-1,2,3,6-tetrahydropyridazine	$C_{10}H_{16}N_2O_5$	bp 126	27
3-Hydroxymethylpyridazine	$C_5H_6N_2O$	66	28, 28a
p-Nitrobenzoate	$C_{12}H_9N_3O_4$	160	28
3,6-Bishydroxymethyl-4(1*H*)pyridazinone	$C_6H_8N_2O_3$	223 (dec)	31–34
3-Hydroxymethyl-4(1*H*)pyridazinone	$C_5H_6N_2O_2$	212 (dec)	34
3-Hydroxymethyl-6-methyl-4(1*H*)-pyridazinone	$C_6H_8N_2O_2$	246–247 (dec)	34
4-Hydroxymethyl-3-methyl-4,5-dihydro-6(1*H*)pyridazinone	$C_6H_{10}N_2O_2$	80	35
4-Hydroxymethyl-3-methyl-1-phenyl-4,5-dihydro-6(1*H*)pyridazinone	$C_{12}H_{14}N_2O_2$	118–121	35
4-Hydroxymethyl-3-phenyl-4,5-dihydro-6(1*H*)pyridazinone	$C_{11}H_{12}N_2O_2$	160–163	35
1,3-Diphenyl-4-hydroxymethyl-4,5-dihydro-6(1*H*)pyridazinone	$C_{17}H_{16}N_2O_2$	168–169	35
3-(2-Hydroxy-3,3,3-trichloropropyl)-pyridazine	$C_7H_7Cl_3N_2O$	138.5–139	38
4-(2-Hydroxy-3,3,3-trichloropropyl)-pyridazine	$C_7H_7Cl_3N_2O$	117–118	39
3-Hydroxymethyl-6-methoxypyridazine	$C_7H_{10}N_2O_2$	bp 142	41
3-Hydroxymethyl-6-methoxypyridazine	$C_6H_8N_2O_2$	55–56.5	42
		53–54	43
3-Chloro-4-hydroxymethyl-6-methyl-pyridazine	$C_6H_7ClN_2O$	180	44, 45
4-Hydroxymethyl-6-methylpyridazine	$C_6H_8N_2O$	78–79	46
3,6-Dimethyl-4-hydroxymethylpyridazine	$C_7H_{10}N_2O$	136–137	46
4-Hydroxymethyl-3-methoxy-6-methyl-pyridazine	$C_7H_{10}N_2O_2$	153–155	46
3-Chloro-4-hydroxymethyl-6-methyl-pyridazine	$C_6H_7ClN_2O$	184.5–186	46
6-Hydroxymethyl-4-methoxy-3-methyl-pyridazine	$C_7H_{10}N_2O_2$		48

TABLE III. Pyridazine Aldehydes and Ketones with *N*-Oxide Functions

Compound	Formula	MP (°C)	References
4-(2-Hydroxy-2-phenylethyl)-pyridazine 1-oxide	$C_{12}H_{12}N_2O_2$	147–148	40
5-(2-Hydroxy-2-phenylethyl)pyridazine 1-oxide	$C_{12}H_{12}N_2O_2$	146–147	40
6-(2-Hydroxy-2-phenylethyl) pyridazine 1-oxide	$C_{12}H_{12}N_2O_2$	152–153	40

TABLE III (*continued*)

Compound	Formula	MP(°C)	References
3-Formylpyridazine 1-oxide, oxime	$C_5H_5N_3O_2$	α 215 (dec)	20
		β 219 (dec)	20
4-Formylpyridazine 1-oxide, oxime	$C_5H_5N_3O_2$	β 258 (dec)	20
5-Formylpyridazine 1-oxide, oxime	$C_5H_5N_3O_2$	α 221 (dec)	20
		β 229 (dec)	20
6-Formylpyridazine 1-oxide, oxime	$C_5H_5N_3O_2$	α 212–213 (dec)	20
		β 213–214 (dec)	20
3,6-Diformylpyridazine 1-oxide dioxime	$C_6H_6N_4O_3$	224 (dec)	20
Diacetate	$C_{10}H_{10}N_4O_5$	183	20
3-Acetylpyridazine 1-oxide	$C_6H_6N_2O_2$	139–140	24
3-Acetyl-6-methoxypyridazine 1-oxide	$C_7H_8N_2O_3$	195–196	24
3-Acetyl-6-methoxypyridazine 2-oxide	$C_7H_8N_2O_3$	123–124	24
3-(α-Ethylenedioxyethyl)pyridazine 1-oxide	$C_8H_{10}N_3O_3$	104.5–105.5	24
4-Chloro-6-formylpyridazine 1-oxide, oxime	$C_5H_4ClN_3O_2$	β 218–219	20
Oxime acetate	$C_7H_6ClN_3O_3$	100	16
4-Chloro-3-methoxyformylpyridazine 1-oxide, oxime	$C_6H_6ClN_3O_3$	α 206	20
		β 211 (dec)	20
Oxime acetate	$C_8H_8ClN_3O_4$	142–143	16
4-Chloro-3-methyl-6-formylpyridazine 1-oxide, oxime	$C_6H_6ClN_3O_2$	224	16
4-Chloro-3-pentyloxy-6-formylpyridazine 1-oxide, oxime	$C_{10}H_{14}ClN_3O_3$	α 112.5–113.5	20
		β 136–137	20
3,6-Dichloro-6-formylpyridazine 1-oxide, oxime	$C_5H_3Cl_2N_3O_2$	234 (dec)	16
Oxime acetate	$C_7H_5Cl_2N_3O_3$	111–112	16

TABLE IV. Side-Chain Aldehydes and Ketones on Nitrogen

Compound	Formula	MP (°C)	References
3-Phenacyloxy-6(1*H*)pyridazinone	$C_{12}H_{10}N_2O_3$	232–234	57
3-(*p*-Chlorophenacyloxy)-6(1*H*)-pyridazinone	$C_{12}H_9ClN_2O_3$	220–222	57
3-(*p*-Methoxyphenacyloxy)-6(1*H*)-pyridazinone	$C_{13}H_{12}N_2O_3$	222–224	57
1-Phenacyl-3-phenacyloxy-6(1*H*)-pyridazinone	$C_{20}H_{16}N_2O_4$	147–149	57
1-Benzoyl-3,4-diphenyl-1,2-dihydro-pyridazine	$C_{29}H_{22}N_2O$	256	49
p-Nitrophenylhydrazone	$C_{35}H_{27}N_3O_2$	233–234	49

TABLE IV (*continued*)

Compound	Formula	MP (°C)	References
1-Acetyl-3-hydroxy-6(1*H*)pyridazinone	$C_6H_6N_2O_3$	160–162	50
1-Benzoyl-3-phenyl-1,4,5,6-tetrahydropyridazine	$C_{17}H_{16}N_2O$	111.5–112	51
1,2-Dibenzoyl-3-phenyl-1,2,3,6-tetrahydropyridazine	$C_{24}H_{20}N_2O_2$	143.5–144	51
2-Benzoyl-3-phenyl-1,2,3,6-tetrahydropyridazine	$C_{17}H_{16}N_2O$	119–119.5	51
1,2-Dibenzoyl-1,2,3,6-tetrahydropyridazine	$C_{18}H_{16}N_2O_2$	160	64, 65
1,2-Dibenzoyl-3-methyl-1,2,3,6-tetrahydropyridazine	$C_{19}H_{18}N_2O_2$	121–122	51, 63, 66
1,2-Dibenzoyl-4-methyl-1,2,3,6-tetrahydropyridazine	$C_{19}H_{18}N_2O_2$	121 126	63 64
1,2-Dibenzoyl-3,6-dimethyl-1,2,3,6-tetrahydropyridazine	$C_{20}H_{20}N_2O_2$	162–163 159	51 63, 64
1,2-Dibenzoyl-4,5-dimethyl-1,2,3,6-tetrahydropyridazine	$C_{20}H_{20}N_2O_2$	166	63, 64
1,2-Dibenzoylhexahydropyridazine	$C_{18}H_{18}N_2O_2$	130	52
1-Acetyl-3-hydroxy-6(1*H*)pyridazinone	$C_6H_6N_2O_3$	176	53
3-Hydroxy-1-(*p*-nitrobenzoyl)-6(1*H*)-pyridazinone	$C_{11}H_7N_3O_5$	185	53
3-Hydroxy-1-(*o*-hydroxybenzoyl)-6(1*H*)-pyridazinone	$C_{11}H_8N_2O_4$	192	53
1-(2-Chloro-4-nitrobenzoyl)-3-hydroxy-6(1*H*)pyridazinone	$C_{11}H_6ClN_3O_5$	139	53
3-Chloro-1-(3-oxobutyl)-6(1*H*)pyridazinone	$C_8H_9ClN_2O_2$	42–43	59
2,4-Dinitrophenylhydrazone	$C_{14}H_{13}ClN_6O_5$	155–156	59
3-Hydroxy-1-(3-oxobutyl)-6(1*H*)-pyridazinone	$C_8H_{10}N_2O_3$	144–146 148–149	59 90
2,4-Dinitrophenylhydrazone	$C_{14}H_{14}N_6O_6$	223–224 225	59 90
4,5-Dichloro-1-(3-oxobutyl)-6(1*H*)-pyridazinone	$C_8H_8Cl_2N_2O_2$	85–87	59
2,4-Dinitrophenylhydrazone	$C_{14}H_{12}Cl_2N_6O_5$	191–192	59
1-Benzoyl-3,6-dimethyl-1,4-dihydropyridazine	$C_{13}H_{14}N_2O$	238	62
1,2-Dibenzoyl-1,2,3,6-tetrahydropyridazine	$C_{18}H_{16}N_2O_2$	160.5	63
1,2-Dibenzoyl-3-methylhexahydropyridazine	$C_{19}H_{20}N_2O_2$	132–133	66
1-Benzoyl-3,6-dimethyl-1,2-dihydropyridazine	$C_{13}H_{14}N_2O$	184–184.5	67

TABLE IV (*continued*)

Compound	Formula	MP (°C)	References
1-(2,4-Dichlorophenoxyacetyl)-3-hydroxy-6(1*H*)pyridazinone	$C_{12}H_8Cl_2N_2O_4$	180–181	53
3-Hydroxy-1-(*p*-nitrobenzoyl)-4,5-dihydro-6(1*H*)pyridazinone	$C_{11}H_9N_3O_5$	180	53
3-Hydroxy-1-(*o*-hydroxybenzoyl)-4,5-dihydro-6(1*H*)pyridazinone	$C_{11}H_{10}N_2O_4$	204	53
3-Hydroxy-1-(*o*-hydroxybenzoyl)-4-methyl-6(1*H*)pyridazinone	$C_{12}H_{10}N_2O_4$	155	53
1-(2-Chloro-4-nitrobenzoyl)-3-hydroxy-4-methyl-6(1*H*)pyridazinone	$C_{12}H_8N_3O_5$	150	53
4,5-Dibromo-1-phenacyl-6(1*H*)-pyridazinone	$C_{12}H_8Br_2N_2O_2$	213	54
4,5-Dibromo-1,2-diphenacyl-6(1*H*)-pyridazinone bromidium	$C_{20}H_{15}Br_3N_2O_3$	130	54
5-Cyano-1-(*p*-nitrophenacyl)-4-phenyl-6(1*H*)pyridazinone	$C_{19}H_{12}N_4O_4$	245	56
3-Chloro-1-phenacyl-6(1*H*)pyridazinone	$C_{12}H_9ClN_2O_2$	132–135	58
1-Acetonyl-3-chloro-4-methoxy-6(1*H*)-pyridazinone	$C_8H_9ClN_2O_3$	115–116	58
1-Acetonyl-3,4-dichloro-6(1*H*)-pyridazinone	$C_7H_6Cl_2N_2O_2$	80–81	58
1-Acetyl-3,6-dichloro-1,4-dihydro-pyridazine	$C_8H_{12}N_2O$	75–80	62
1,2-Dibenzoyl-4,5-dimethylhexahydro-pyridazine	$C_{20}H_{22}N_2O_2$	190	68
1-Acetyl-5-methyl-6(1*H*)pyridazinone	$C_7H_8N_2O_3$	174–176	69
1,2-Diacetyl-4,5-dimethyl-1,2,3,6-tetrahydropyridazine	$C_{10}H_{16}N_2O_2$	106	70
1,2-Diacetyl-4,5-dimethylhexahydro-pyridazine	$C_{10}H_{18}N_2O_2$	67	70
1,2-Diacetyl-4,5-dibromo-4,5-dimethyl-hexahydropyridazine	$C_{10}H_{16}Br_2N_2O_2$	154	70
3-Methyl-1-(3-oxobutyl)-6(1*H*)-pyridazinone	$C_9H_{12}N_2O_2$	57–59	72
Semicarbazone	$C_{10}H_{15}N_5O_2$	179–180	72
1-Acetonyl-3-phenyl-6(1*H*)pyridazinone	$C_{13}H_{12}N_2O_2$	140–142	72
3-Methyl-1-(2-oxo-3-pentyl)-6(1*H*)-pyridazinone	$C_{10}H_{14}N_2O_2$	bp 84 (0.05 mm)	72
3-Methyl-1-(2-oxo-3-hexyl)-6(1*H*)-pyridazinone	$C_{11}H_{16}N_2O_2$	bp 96 (0.1 mm)	72
3-Methyl-1-(2-oxo-4-methyl-3-pentyl)-6(1*H*)pyridazinone	$C_{11}H_{16}N_2O_2$	bp 83.5 (0.02 mm)	72

TABLE IV (*continued*)

Compound	Formula	MP(°C)	References
3-Methyl-1-(2-oxo-3-heptyl)-6(1*H*)-pyridazinone	$C_{12}H_{18}N_2O_2$	bp 118 (0.35 mm)	72
3-Methyl-1-(2-oxo-3-octyl)-6(1*H*)-pyridazinone	$C_{13}H_{20}N_2O_2$	bp 135 (0.6 mm)	72
3-Methyl-1-(2-oxobutyl)-6(1*H*)-pyridazinone	$C_9H_{12}N_2O_2$	95–97	72
3-Methyl-1-(2-oxopentyl)-6(1*H*)-pyridazinone	$C_{10}H_{14}N_2O_2$	73–75	72
3-Methyl-1-(3-methyl-2-oxobutyl)-6(1*H*)-pyridazinone	$C_{10}H_{14}N_2O_2$	126–127	72
3-Methyl-1-(2-oxohexyl)-6(1*H*)-pyridazinone	$C_{11}H_{16}N_2O_2$	84.5–86	72
3-Methyl-1-(4-methyl-2-oxopentyl)-6(1*H*)-pyridazinone	$C_{11}H_{16}N_2O_2$	102–103	72
3-Methyl-1-(3-methyl-2-oxopentyl)-6(1*H*)-pyridazinone	$C_{11}H_{16}N_2O_2$	92.5–93.5	72
3-Methyl-1-(2-oxoheptyl)-6(1*H*)-pyridazinone	$C_{12}H_{18}N_2O_2$	103–104	72
3-Methyl-1-(2-oxooctyl)-6(1*H*)-pyridazinone	$C_{13}H_{20}N_2O_2$	92–95	72
3-Methyl-1-(2-oxononyl)-6(1*H*)-pyridazinone	$C_{14}H_{22}N_2O_2$	85–86	72
1-Acetonyl-6(1*H*)pyridazinone	$C_7H_8N_2O_2$	98–99	71
Semicarbazone	$C_8H_{11}N_5O_2$	215–216	71
1-Acetonyl-3-methyl-6(1*H*)pyridazinone	$C_8H_{10}N_2O_2$	99.5–100	71
Semicarbazone	$C_9H_{13}N_5O_2$	204–205 (dec)	71
3-Methyl-1-(3-oxo-2-butyl)-6(1*H*)-pyridazinone	$C_9H_{12}N_2O_2$	bp 94–99 (0.4 mm)	71

TABLE V. Side-Chain Alcohols on Nitrogen

Compound	Formula	MP (°C)	References
3-Carbethoxy-6-methyl-1-(2-hydroxy-2-phenylethyl)-1,4,5,6-tetrahydropyridazine	$C_{16}H_{22}N_2O_3$	bp 148–152 (0.01 mm)	27
4,5-Dibromo-1-(2-hydroxyethyl)-6(1*H*)-pyridazinone	$C_6H_6Br_2N_2O_2$	100–102	55
1-Cyanoacetyl-4,5-dibromo-6(1*H*)-pyridazinone	$C_7H_3Br_2N_3O_2$	162–165 (dec)	55

TABLE V (*continued*)

Compound	Formula	MP (°C)	References
4,5-Dibromo-1-(4-isonicotinoyl)-6(1*H*)-pyridazinone	$C_{10}H_5Br_2N_3O_2$	204	55
1-Hydroxymethyl-6(1*H*)pyridazinone	$C_6H_6N_2O_2$	142	77
1-Hydroxymethyl-3-methyl-6(1*H*)-pyridazinone	$C_6H_8N_2O_2$	131	77
3-Carbethoxy-1-hydroxymethyl-6(1*H*)-pyridazinone	$C_8H_{10}N_2O_4$	106–107	78
1-Hydroxymethyl-3-phenyl-6(1*H*)-pyridazinone	$C_{11}H_{10}N_2O_2$	150–161	80
1-Hydroxymethyl-3-phenyl-4,5-dihydro-6(1*H*)pyridazinone	$C_{11}H_{12}N_2O_2$	122 (dec)	82
1-Hydroxymethyl-3-hydroxymethylmercapto-6(1*H*)pyridazinethione	$C_6H_8N_2O_2S_2$	148–149	83
1-Hydroxyethyl-3-phenyl-6(1*H*)-pyridazinone	$C_{12}H_{12}N_2O_2$	106–107.5	84
1-Hydroxyethyl-5-methyl-3-phenyl-6(1*H*)pyridazinone	$C_{13}H_{14}N_2O_2$	108–110	84
5-Hydroxy-1-hydroxyethyl-4-nitro-6(1*H*)pyridazinone	$C_6H_7N_3O_5$	178–182 (dec)	87
5-Hydroxy-1-(2-hydroxycyclohexyl)-4-nitro-6(1*H*)pyridazinone	$C_{10}H_{13}N_3O_5$	223–225	87
1-Hydroxymethyl-3-methyl-4,5-dihydro-6(1*H*)pyridazinone	$C_6H_{10}N_2O_2$	100–101	81
1-Hydroxymethyl-3-phenyl-4,5-dihydro-6(1*H*)pyridazinone	$C_{11}H_{12}N_2O_2$	119–120	81
3,5-Dichloro-1-hydroxymethyl-6(1*H*)-pyridazinone	$C_5H_4Cl_2N_2O_2$	119–121	58
4,5-Dichloro-1-hydroxymethyl-6(1*H*)-pyridazinone	$C_5H_4Cl_2N_2O_2$	113–115	58
4,5-Dichloro-1-(2-hydroxyethyl)-6(1*H*)-pyridazinone	$C_6H_6Cl_2N_2O_2$	54–56	58
4,5-Dichloro-3-hydroxy-1-hydroxymethyl-6(1*H*)pyridazinone	$C_5H_4Cl_2N_2O_3$	245	58
4,5-Dichloro-3-hydroxy-1-(2-hydroxyethyl)-6(1*H*)pyridazinone	$C_6H_6Cl_2N_2O_3$	218–220	58
4,5-Dichloro-1-(2-hydroxyethyl)-3-methoxy-6(1*H*)pyridazinone	$C_7H_8Cl_2N_2O_3$	101–103	58
3-Chloro-1-hydroxymethyl-6(1*H*)-pyridazinone	$C_5H_5ClN_2O_2$	115–117	58
3-Chloro-1-(2-hydroxyethyl)-6(1*H*)-pyridazinone	$C_6H_7ClN_2O_2$	101–102	58
3-Hydroxy-1-(3-oxopropyl)-6(1*H*)-pyridazinone	$C_7H_8N_2O_3$	178–180	59
2,4-Dinitrophenylhydrazone	$C_{13}H_{12}N_6O_6$	225–226 (dec)	59
1-(3-Hydroxypropyl)-3-methyl-5-phenyl-4,5-dihydro-6(1*H*)pyridazinone	$C_{14}H_{18}N_2O_2$	Oil	73
1-(3-Hydroxypropyl)-3-methyl-5-phenyl hexahydro-6(1*H*)pyridazinone	$C_{14}H_{20}N_2O_2$	Oil	73

TABLE V (*continued*)

Compound	Formula	MP (°C)	References
1-(3-Hydroxypropyl)-3-(*p*-methoxyphenyl)-4,5-dihydro-6(1*H*)pyridazinone	$C_{14}H_{18}N_2O_3$	117–118	75
1-(3-Hydroxypropyl)-3-(*p*-methoxyphenyl)-hexahydropyridazine	$C_{14}H_{22}N_2O_2$	Oil	75
3-(*p*-Chlorophenyl)-1-(3-hydroxypropyl)-4,5-dihydro-6(1*H*)pyridazinone	$C_{13}H_{15}ClN_2O_2$	128–132	75
3-(*p*-Chlorophenyl)-1-(3-hydroxypropyl)-hexahydropyridazine	$C_{13}H_{19}ClN_2O$	65–67	75
1-(3-Hydroxypropyl)-3-phenyl-4,5-dihydro-6(1*H*)pyridazinone	$C_{13}H_{16}N_2O_2$	65–68	75
1-(3-Hydroxypropyl)-3-phenylhexahydropyridazine	$C_{13}H_{20}N_2O$	Oil	75
3-(2-Phenyl-2-hydroxyethoxy)-6(1*H*)-pyridazinone	$C_{12}H_{12}N_2O_3$ Acetate	150–151 195–196	57
3-[2-(*p*-Chlorophenyl)-2-hydroxyethoxy]-6(1*H*)pyridazinone	$C_{12}H_{11}ClN_2O_3$	182–183	57
3-[2-(*p*-Methoxyphenyl)-2-hydroxyethoxy]-6(1*H*)pyridazinone	$C_{13}H_{14}N_2O_3$	196–197	57
3-Hydroxy-1-(1-phenyl-2-hydroxyethyl)-6(1*H*)pyridazinone	$C_{12}H_{12}N_2O_3$	170–171	57
1-(*p*-Chlorophenyl-2-hydroxyethyl)-3-hydroxy-6(1*H*)pyridazinone	$C_{12}H_{11}ClN_2O_3$	187–188	57
3-Hydroxy-1-[1-(*p*-methoxyphenyl)-2-hydroxyethyl]-6(1*H*)pyridazinone	$C_{13}H_{14}N_2O_4$	172–173	57
3-Hydroxy-1-[1-phenyl-2-hydroxyethyl]-4,5-dihydro-6(1*H*)pyridazinone	$C_{12}H_{14}N_2O_3$	163	57
3-Methoxy-1-(1-phenyl-2-hydroxyethyl)-6(1*H*)pyridazinone	$C_{13}H_{14}N_2O_3$	115–116	57
3-Isopropoxy-1-(1-phenyl-2-hydroxyethyl)-6(1*H*)pyridazinone	$C_{15}H_{18}N_2O_3$	128–129	57
1,2-Dicarbethoxy-3-hydroxymethyl-6-methyl-1,2,3,6-tetrahydropyridazine	$C_{12}H_{20}N_2O_5$	bp 131–141 (0.6–1 mm)	27
1,2-Dicarbethoxy-3-hydroxymethyl-6-methylhexahydropyridazine	$C_{12}H_{22}N_2O_5$ $C_{12}H_{22}N_2O_5$	bp 147–150	27
3-Carbethoxy-6-methyl-1-(2-hydroxy-2-phenylethyl)-1,4,5,6-tetrahydro-pyridazine	$C_{15}H_{23}N_2O_3$	bp 148–152 (0.01 mm)	27
1-Hydroxymethyl-3,4,5-trichloro-6(1*H*)pyridazinone	$C_5H_3Cl_3N_2O_2$	130	58
3,4-Dichloro-1-hydroxymethyl-6(1*H*)pyridazinone	$C_5H_4Cl_2N_2O_2$	106–108	58
3,4-Dichloro-1-(2-hydroxyethyl)-6(1*H*)pyridazinone	$C_6H_6Cl_2N_2O_2$	~80	58
3-Methyl-1-(1-methyl-2-hydroxypropyl)-6(1*H*)pyridazinone	$C_9H_{14}N_2O_2$	73–76	72
1-(1,2-Dimethyl-2-hydroxypropyl)-3-methyl-6(1*H*)pyridazinone	$C_{10}H_{16}N_2O_2$	53–55	72

TABLE VI. Side-Chain Ketones N—O—R

Compound	Formula	MP (°C)	References
1-Benzoylethoxy-3-ethoxy-6(1*H*) pyridazinone	$C_{15}H_{16}N_2O_4$	89–90	61
1-Benzoylethoxy-3-ethoxy-4-methyl-6(1*H*)pyridazinone	$C_{16}H_{18}N_2O_4$	97–98.5	61
1-Benzoylmethoxy-3-methoxy-6(1*H*)pyridazinone	$C_{13}H_{12}N_2O_4$	117–118	60
1-Benzoylmethoxy-3-ethoxy-6(1*H*)pyridazinone	$C_{14}H_{14}N_2O_4$	113.5–115	60
1-Benzoylmethoxy-3-methoxy-4-methyl-6(1*H*)pyridazinone	$C_{14}H_{14}N_2O_4$	109–110.5	60
1-Benzoylmethoxy-3-ethoxy-4-methyl-6(1*H*)pyridazinone	$C_{15}H_{16}N_2O_4$	118–119	60

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CHAPTER V

Pyridazinecarboxylic Acids

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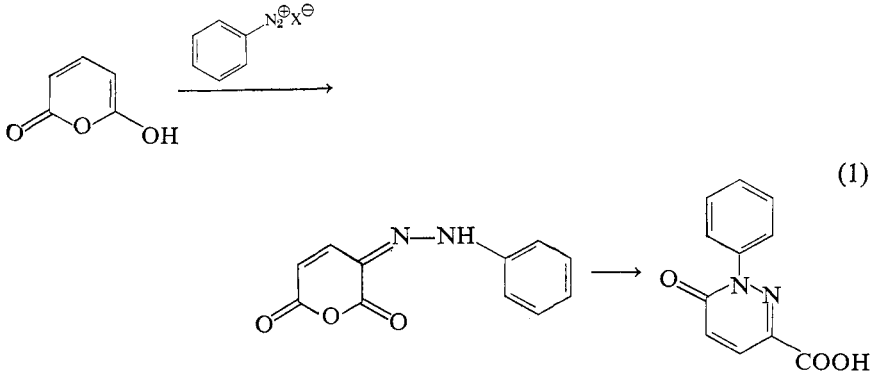
I. Preparation

A. From Nonpyridazine Starting Materials

The synthesis of the pyridazine ring system from nonpyridazine starting materials has been discussed in several previous chapters of this volume. Many of these methods have been adapted to the preparation of pyridazinecarboxylic acids and related compounds.

The standard preparations of the ring from γ-diketones to give pyridazines and from γ-keto acids and esters to give pyridazinones have been modified to yield acids, esters, amides, and nitriles. These methods often give dihydropyridazine and pyridazinone derivatives which are easily oxidized to the fully aromatic ring. Synthetic methods in which two or more compounds supply the carbon atoms of the ring have also been used to prepare pyridazinecarboxylic acids and related compounds. For example, α-diketones and β-keto esters can be condensed with hydrazine to yield 4-carboxypyridazines directly. β-Ketoamides and nitriles may be used in place of the keto ester to give the corresponding pyridazine amides or nitriles. Malonic ester and its derivatives can replace the β-keto ester in these reactions and the product will be a pyridazinone. Derivatives of malononitrile can also be used, the products being aminopyridazine nitilres (1).

Aromatic diazonium salts react with glutaconic anhydrides to yield hydrazones which readily rearrange to pyridazinonecarboxylic acids (Eq. 1) (2).

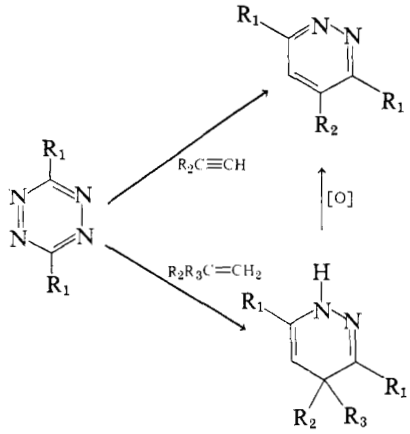


(1)

The esters, amides, and imides of glutaconic acid (2) and related compounds such as triacetic lactone (3, 4) may also be used. In some cases (particularly with glutaconic acid dimethyl ester), double addition occurs, and the product pyridazinone contains an aromatic diazo substituent (2, 5).

Diazo compounds also react with cyclopropene to yield the pyridazine nucleus (6). When ethyl diazoacetate is used, the product is a 3-carbethoxy dihydropyridazine which is easily oxidized to the fully aromatic ester.

Symmetrically substituted 1,2,4,5-tetrazines react with ethylenes and acetylenes to produce pyridazinones (Eq. 2). The reaction requires electron-withdrawing groups in the tetrazine ring (7). Ethylene derivatives give 1,4-dihydropyridazines which are easily oxidized to pyridazines when one of the substituents at position 4 is hydrogen. When vinyl ethyl ether or 1,1-diethoxyethylene are used, ethyl alcohol is eliminated during the reaction, giving a pyridazine directly (8). Acetylenes also yield pyridazines.



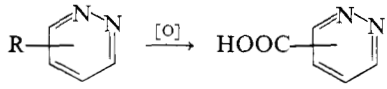
(2)

R_1 = aryl, $COOCH_3$
R_2, R_3 = H, alkyl, aryl, *O*-alkyl, $COOCH_3$, CN

B. From Pyridazine Starting Materials

1. *Oxidation of Alkyl- and Arylpyridazines*

Because of the great stability of the pyridazine ring, a large variety of derivatives yields pyridazinecarboxylic acids upon oxidation (Eq. 3). The



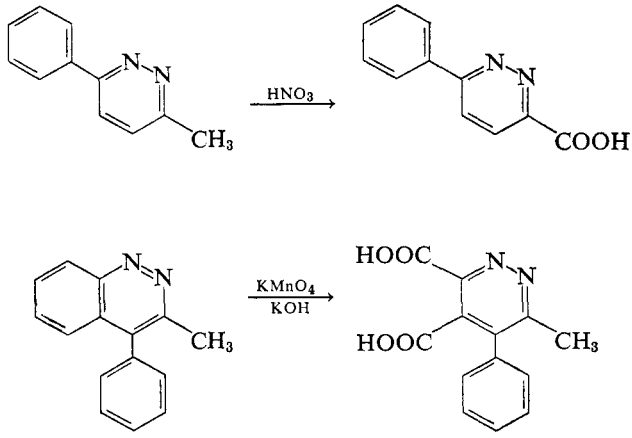
(3)

reaction is general for pyridazines and pyridazinones, and other ring substituents such as halogens and methoxyl groups are usually unaffected. However, it has had only limited use for the preparation of monocarboxylic

acids. Such compounds are often more conveniently prepared by condensation of the ring from compounds with carboxyl or nitrile side groups (see Section I.A.1) which can be hydrolyzed to carboxylic acids. Side-chain oxidation cannot be used to prepare hydropyridazine- and pyridazinonecarboxylic acids because oxidizing agents also convert these nuclei into fully aromatic compounds.

Intermediates with partially oxidized side chains, when available, are preferred to fully saturated groups. For example, oxidation of 3-methylpyridazine fails to yield pyridazine-3-carboxylic acid (9), and oxidation of 3-butylpyridazine with alkaline permanganate gives only 32% yield (10). However, 3-hydroxymethylpyridazine, which is readily available by simple ring condensations (11, 12), gives the acid in 81% yield upon similar treatment (12, 13). Pyridazine-4-carboxylic acid can be prepared by oxidation of 4-alkylpyridazines (10, 14, 15), but a better method is the partial decarboxylation of pyridazine-4,5-dicarboxylic acid (16) which is available by oxidation of phthalazine (17, 18). The latter method gives an overall yield of 56%, while the best side-chain oxidation reported gave a yield of 41% based upon the difficultly available 4-*n*-butylpyridazine (15).

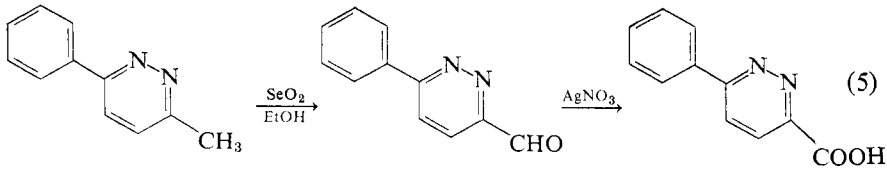
It is interesting that phenyl groups attached to pyridazines are more stable to oxidation than are alkyl groups, but that condensed aromatic rings are oxidized in preference to alkyl groups on the pyridazine nucleus. For example, 3-methyl-6-phenylpyridazine is converted to 6-phenylpyridazine-3-carboxylic acid upon oxidation with nitric acid (19). Yet, 3-methyl-4-phenylcinnoline, on treatment with alkaline permanganate, yields 3-methyl-4-phenylpyridazine-5,6-dicarboxylic acid (Eq. 4) (20).



(4)

The availability of many cinnolines and phthalazines has made them favored intermediates for the preparation of pyridazinepolycarboxylic acids. Generally, any benzopyridazine can be oxidized to the corresponding pyridazinedicarboxylic acid, with or without side-chain oxidation of alkyl groups attached to the pyridazine nucleus. The yields are usually good, in many cases approaching the theoretical.

Potassium permanganate in neutral, acid or, more commonly, alkaline medium, has been the most used oxidizing agent for these reactions, but several others have been employed. These include potassium or sodium dichromate in sulfuric acid solution, chromic acid in glacial acetic acid, and hot concentrated nitric acid. In contrast to 2- and 4-picoline, which are oxidized to the corresponding acids by selenium dioxide (21), 3-methylpyridazines are oxidized to the 3-aldehydes by selenium dioxide in ethanol (Eq. 5) (22, 23). The aldehydes can be converted to the acids by mild oxidation with silver nitrate.



(5)

2. *Hydrolysis of Functional Derivatives*

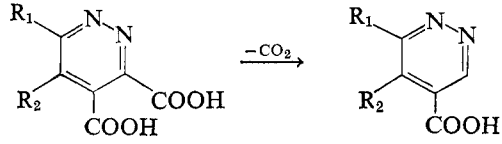
Esters and nitriles are the most common sources of pyridazinecarboxylic acids, but amides have also been used. The functional derivatives are usually formed in cyclization of the ring system and hydrolyzed to the carboxylic acids. The hydrolyses can be carried out by a variety of methods and often give high yields. Alkaline hydrolysis is generally preferred for the esters and nitriles, while acidic conditions are usually used to hydrolyze amides. The nitriles can also be partially hydrolyzed to amides, but this reaction has had only limited use in the pyridazine series. Ammination of esters is usually preferred for formation of amides. More complete discussions of these reactions are given in Sections IV.B and IV.D.

3. *Decarboxylation of Pyridazinepolycarboxylic Acids*

Pyridazinecarboxylic acids decarboxylate readily, and this property has been used to prepare derivatives which would be difficult to obtain by other

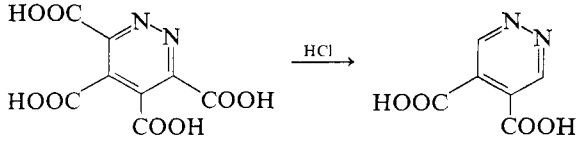
methods (see Section I.B.1). Pyridazine and pyridazinone acids prepared by any of the available methods can usually be decarboxylated in high yield under mild conditions. Pyridazinepolycarboxylic acids can be partially decarboxylated to yield mono- or dicarboxylic acids. An example is the partial decarboxylation of pyridazine-4,5-dicarboxylic acid to yield pyridazine-4-carboxylic acid which was mentioned previously.

Another interesting example is the partial decarboxylation of substituted pyridazine-3,4-dicarboxylic acids to the corresponding 4-carboxylic acids (Eq. 6) (9, 20, 24, 25). The 4-carboxylic acids are formed exclusively. Thus



(6)

carboxyl groups at the 3-position of pyridazine are lost more readily than are those at the 4-position. This is further demonstrated by the partial decarboxylation of pyridazine-3,4,5,6-tetracarboxylic acid. When the double potassium salt of this compound was warmed in dilute hydrochloric acid, 2 moles of carbon dioxide were evolved. The product was pyridazine-4,5-dicarboxylic acid, and no isomeric products could be isolated (Eq. 7) (26).



(7)

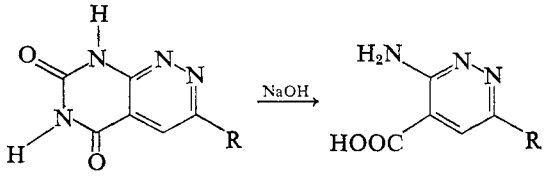
4. *Carbonation of 3-Pyridazinyllithium*

Rosseels recently reported that 6-chloro-3-pyridazinyllithium can be formed by metal–halogen interchange between butyllithium and 3,6-dichloropyridazine (27, 28). The pyridazinyllithium compound was carbonated to yield the carboxylic acid. This is the only reported instance in which a metalopyridazine has been carbonated, but if the reaction is general for halopyridazines, it may represent an efficient route to unusual pyridazinecarboxylic acids.

5. *Hydrolysis of Multiple-Ring Pyridazines*

Quite recently, Nakagome, Castle, and Murakami (29) reported the preparation of 3-aminopyridazine-4-carboxylic acid and its 6-methyl derivative by hydrolysis of pyrimidopyridazines (Eq. 8). This represents a new and

probably general route to aminopyridazinecarboxylic acids. The very interesting synthesis of the novel pyrimidopyridazines is discussed in Section IV.B.2.

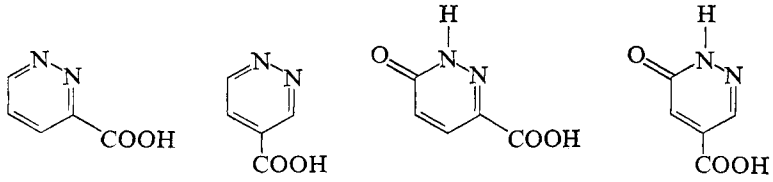


(8)

II. Properties

Both of the unsubstituted pyridazinecarboxylic acids are white, crystalline, high-melting solids. They can be crystallized from water but have only limited solubility in most organic solvents. Pyridazinepolycarboxylic acids are also high-melting solids and are practically insoluble in solvents other than water. Similar considerations apply to pyridazinonemono- and polycarboxylic acids.

Both of the unsubstituted pyridazine monocarboxylic acids are more acidic than benzoic acid (16), presumably because of the electronegativity of the pyridazine ring. The pyridazinone analogs are also fairly strong acids, but the acidity of the pyridazinone ring itself (see Chapter II) makes a significant contribution. When this was eliminated by addition of the *N*-methyl group (30), the pyridazinone acids were found to be weaker than the corresponding pyridazine derivatives (Eq. 9).



(9)

$pK_a = 3.0$ $pK_a = 2.8$ $pK_a = 3.2$ $pK_a = 3.7$

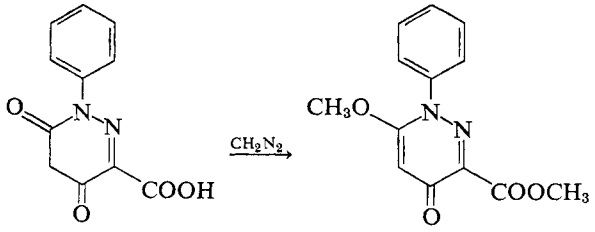
There have been numerous reports of biological effects attributed to pyridazinecarboxylic acids and their derivatives. The majority of the biologically active compounds are functional derivatives rather than carboxylic acids, and these are discussed in the following sections of this chapter. Both of the unsubstituted pyridazinecarboxylic acids have been reported to be antimetabolites in bacteria (15, 31). Pyridazine-3-carboxylic acid is an inhibitor of nicotinic acid metabolism (31), while the 4-acid is bacteriostatic, but its mode of action has not been specified (15). Similar but much weaker

activity has been reported for several of the pyridazinonecarboxylic acids, but none is sufficiently active to be clinically useful.

III. Reactions

A. Esterification

No difficulties are ordinarily encountered in the esterification of pyridazine and pyridazinone acids, and several good methods are available. These include direct esterification with diazomethane, or with an alcohol and an acid, or preliminary conversion to the acid chloride followed by reaction with an alcohol. These methods are generally satisfactory, and the choice in any particular case is influenced by the presence of other substituents. Thus esterification with an alcohol and a strong acid catalyst (usually hydrochloric or sulfuric acid) would be contraindicated if groups such as cyano or halogen were present, because they would be at least partially hydrolyzed. Diazomethane gives high yields (both 3- and 4-carbomethoxypyridazines are formed in quantitative yield from the acids (12) but may be contraindicated with the pyridazinone carboxylic acids. In one report esterification of 4,6-dioxo-1-phenyl-1,4,5,6-tetrahydropyridazine-3-carboxylic acid with diazomethane was accompanied by addition of the methyl group to the 6-oxo substituent (Eq. 10) (32).

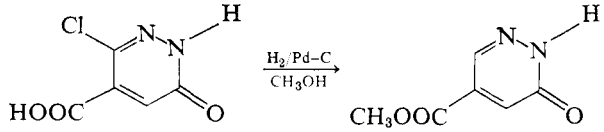


(10)

Although it requires an extra step, the best solution to such problems is usually to convert the acid to its acid chloride with thionyl chloride and then to react this chloride with an alcohol. The yields are generally good, and the two-step process can often be completed in less time than the long reflux required by the acid-catalyzed esterification. Thionyl chloride, under the conditions used to prepare acid chlorides (reflux in the pure reagent or in a solvent such as benzene), does not replace hydroxyl groups on the pyridazine ring (pyridazinones). However, care must be taken to insure that the temperature of the reaction does not go too high, or hydroxyl replacement can become a significant side reaction. If it is desired to replace hydroxyl groups

while forming the acid halide or ester, this can be done by using phosphorus trichloride (or tribromide) or a mixture of phosphorus oxychloride and phosphorus pentachloride. The halo-acid halide can be converted to an ester by reaction with alcohol without affecting halogen substituents on the ring.

Methyl esters of 6(1*H*)pyridazinone-4- and 5-carboxylic acids have been obtained when chlorine substituents were removed from the acids by hydrogenation in methanol over a palladium catalyst (Eq. 11) (33). This may be a general esterification method, but more study is needed.



(11)

The hydrolysis of pyridazinone nitriles with sulfuric acid in anhydrous ethanol has been reported to give esters in good yield (59%) (34). In those few cases in which the nitrile is more readily available than the ester or acid, this reaction provides a useful short cut to the ester. It is not, however, of great general interest.

B. Decarboxylation

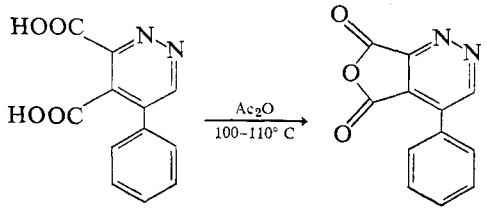
Nearly all pyridazinecarboxylic acids lose carbon dioxide when heated above 200° C, and the decarboxylated product can often be isolated in high yield. Thus the best preparative routes to many pyridazine derivatives involve the preparation of the appropriately substituted pyridazine- or pyridazinonecarboxylic acid followed by decarboxylation to the desired compound.

The partial decarboxylation of polycarboxylic acids was discussed previously (Section I.B.3), and it was noted that carboxyl groups at the 4-position are more stable to decarboxylation than those at the 3-position. This generalization also holds for the monocarboxylic acids. For example, pyridazine-3-carboxylic acid decarboxylates when heated at reduced pressure, giving pyridazine in nearly quantitative yield (35). The 4-carboxylic acid loses carbon dioxide only when heated at 200° C in hydrochloric acid solution at high pressure, and only small amounts of pyridazine can be isolated (9, 26).

Decarboxylation is most commonly carried out by heating the acid alone, because nearly all pyridazinecarboxylic acids lose carbon dioxide at their melting points or slightly above. Decarboxylation has also been carried out by heating dry silver salts as well as in solution in water, in dilute acid, and in dilute base. Catalysis by organic bases (aniline, dimethylaniline, quinoline) has been recommended for monodecarboxylation of pyridazine-4,5-dicarboxylic acid (15).

C. Dehydration of Pyridazinedicarboxylic Acids

Pyridazine acids cannot be dehydrated by heating because they decarboxylate too readily. Although many pyridazinedicarboxylic acids have been reported, only one has been converted to the corresponding acid anhydride (36). This was done by warming 5-phenylpyridazine-3,4-dicarboxylic acid at 100–110° C in acetic anhydride (Eq. 12). The product was stable under the conditions of vacuum sublimination used for purification, and it seems probable that many other anhydrides could be prepared similarly.



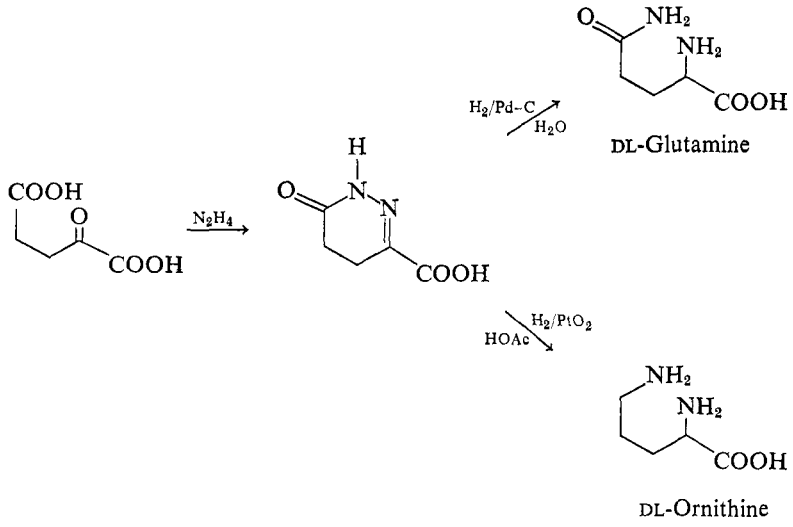
(12)

D. Ring-Opening Reactions

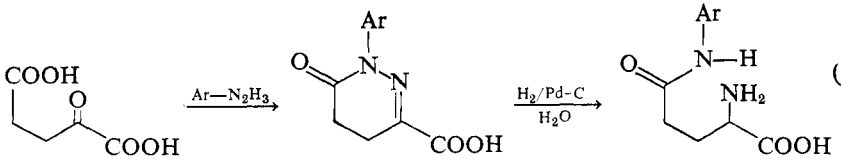
The catalytic hydrogenation of 4,5-dihydro-6(1*H*)pyridazinone-3-carboxylic acid represents a convenient method for the preparation of glutamine, a therapeutically useful natural product (37, 38). Until this route was devised, the clinical investigation of glutamine was restricted by the high cost and limited availability of the compound. The starting material for the synthesis was the readily available α-ketoglutaric acid which was cyclized with hydrazine to give the dihydropyridazinone acid in high yield. Hydrogenation of this intermediate at high pressure (70 atm of hydrogen) over a 5% palladium–carbon catalyst in water gave DL-glutamine in 63% yield (Eq. 13). When platinum oxide catalyst was used and the solvent was acetic acid, reduction of the amide function also occurred and DL-ornithine was isolated in 23% yield.

This ring-opening reaction has also made it possible to obtain *N*-substituted glutamines for therapeutic study. Such compounds are difficult to prepare by other routes but can be prepared in good yield by using monosubstituted hydrazines in the ring closure with α-ketoglutaric acid (Eq. 14) (38).

The hydrogenation of 6(1*H*)pyridazinone-3-carboxylic acid in acetic acid with a palladium–carbon catalyst has also been reported to give glutamine (Eq. 15) (39). In this instance the yields were low, and a less efficient



(13)



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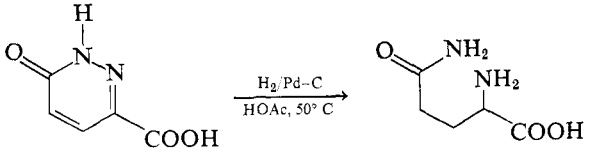
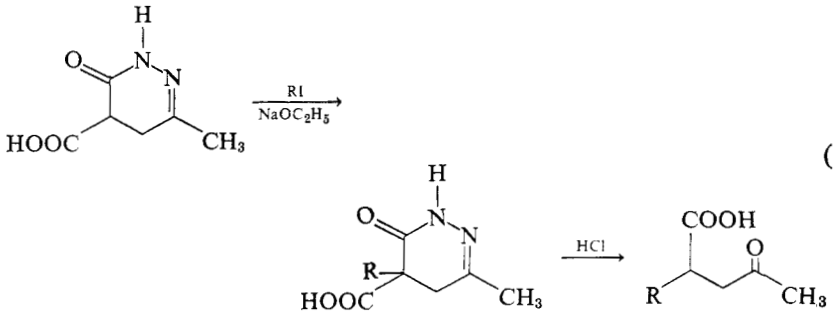


(15)

three-step synthetic process was required to obtain the pyridazinonecarboxylic acid intermediate. Thus the first method has a much higher overall efficiency.

Acid hydrolysis of 4-alkyl-6-methyl-4,5-dihydro-6(1*H*)pyridazinone-4-carboxylic acids also opens the ring to give α-substituted, γ-keto acids (Eq. 16) (40). Such compounds are difficult to prepare by other synthetic routes, but this method usually gives the γ-keto acid in good yield. The 4-alkyldihydropyridazinone acids are most easily prepared by replacement of the labile hydrogen atom at the 4-position of the unsubstituted pyridazinone ester as shown (Eq. 16). Hydrolysis to the acid occurs during the work-up of the product (40, 41).



(16)

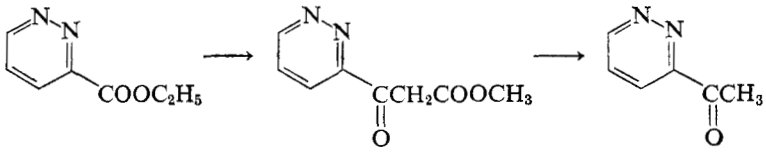
IV. Functional Derivatives

A. Esters

1. *Esters of Pyridazine-3- and 4-Carboxylic Acids*

The preparation of pyridazine esters has already been discussed (Section III.A). They are usually colorless, high-boiling liquids or relatively low-melting solids which are soluble in organic solvents but have only slight solubility in water. Their reactions (including hydrolysis and amide formation) do not differ significantly from their benzene counterparts. The special case of esters of hydropyridazine-1,2-dicarboxylic acids is discussed in the following section.

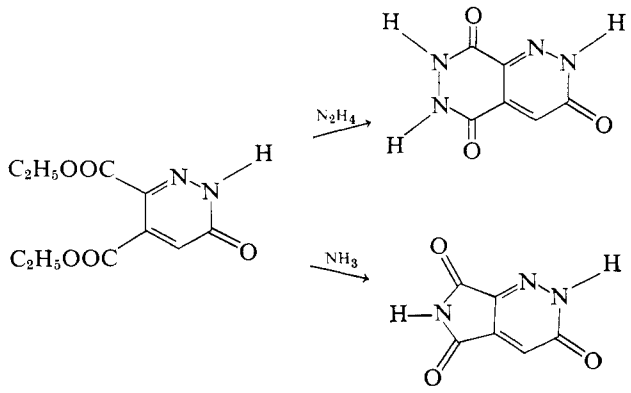
There have been few reports of ester condensations in the pyridazine series. One that is of particular significance is the Claisen condensation of methyl acetate with ethylpyridazine-3-carboxylate followed by hydrolysis to 3-acetylpyridazine (Eq. 17). The reaction was developed by two teams of workers independently (42, 43), but they obtained quite different yields of the product (28 and 77%). The reaction is particularly interesting because the high yields obtained (in one case) indicate that many of the well-known ester condensations can be employed with pyridazine esters.



(17)

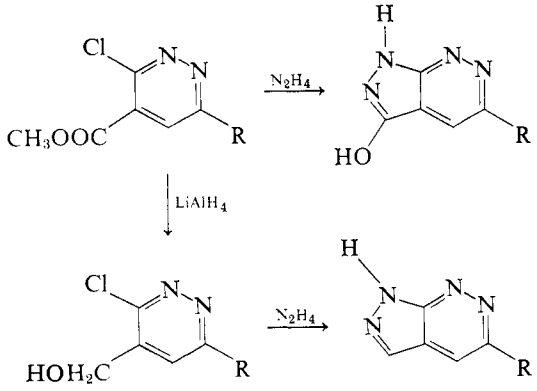
Esters of pyridazine- and pyridazinonecarboxylic acids are often good intermediates for ring closure reactions leading to unusual fused-ring systems.

For example, several pyridazinopyridazines have been prepared by cyclization of pyridazine- and pyridazinonedicarboxylic acid esters with hydrazine (Eq. 18) (23, 44–46). Pyridazinoimidazoles are similarly formed from pyridazinedicarboxylic acid esters and ammonia or amines (47, 48).



(18)

The cyclization of ethyl 3-chloropyridazine-4-carboxylate with hydrazine yields 3-hydroxypyrazolo[5,4-*c*]pyridazine (Eq. 19) (34). The 6-methyl ester reacts similarly. If the ester is first reduced to the carbinol (with lithium aluminum hydride), the unsubstituted ring system can be obtained (Eq. 19) (34).

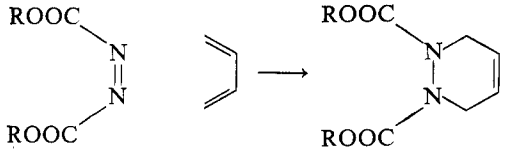


(19)

2. *Esters of Pyridazine-1,2-dicarboxylic Acids*

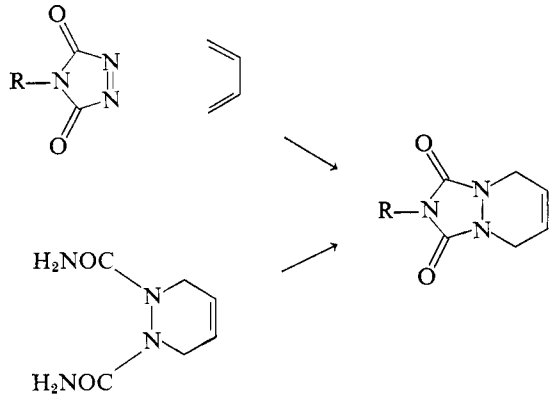
The dialkyl hydropyridazine-1,2-dicarboxylates and their related functional derivatives (amides, imides, nitriles) form a unique class of compounds which have been extensively studied since their discovery in 1925 by Diels

and his co-workers (49). The subject has been reviewed (50). Usually, these compounds are prepared by the Diels–Alder reaction between an alkyl azodicarboxylate (a strong dienophile) and a diene (Eq. 20). Other azo-



(20)

dienophiles have also been used, including azodicarboxamide (48, 51), azodicarboxamidine (52), azodinitrile (53, 54), dibenzoylazide (55), and azodicarboximides (Eq. 21) (56, 57). The diamides and diamidines can be cyclized by heating to yield imides corresponding to the adducts of azodicarboximides (Eq. 21) (47, 48, 51, 52).

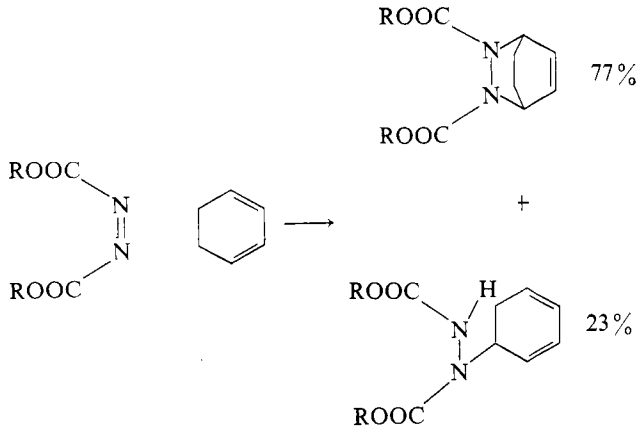


(21)

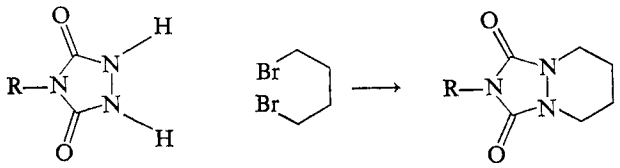
A wide variety of dienes react with azodicarboxylates, including cyclic dienes such as cyclopentadiene and cyclohexadiene which lead to diazabicyclo compounds. Allylic addition can be a significant side reaction, particularly when cyclic dienes are employed (Eq. 22).

Many related structures have been reported. For example, 1,4-dibromobutane reacts smoothly with urazoles to yield piperidazine-1,2-dicarboximides (Eq. 23) (57). Other related structures are formed when *N*-hydropyridazines are allowed to react with isocyanates, isothiocyanates, or benzoyl chlorides. These reactions are usually used to prepare solid derivatives of oils for purposes of identification and require no further discussion here.

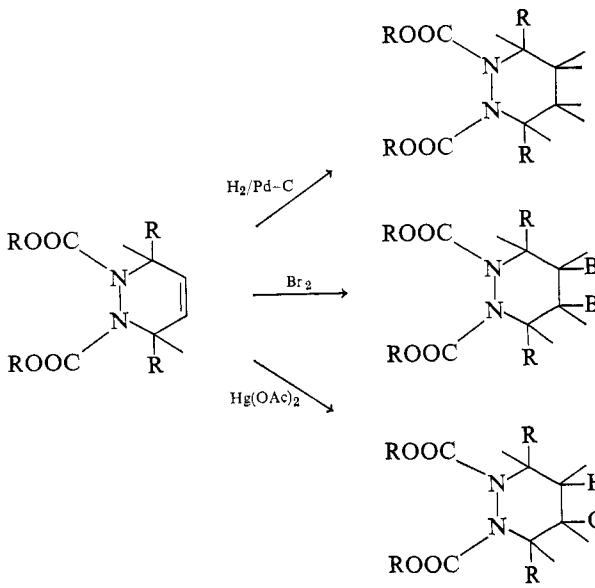
The carbon–carbon double bond of the adducts undergoes the usual reactions of cyclic double bonds. Thus the adducts can be hydrogenated to piperidazinedicarboxylates, and they add bromine readily (Eq. 24). Since most of the adducts are liquids, bromination is often used for their characterization. They also add mercury salts to the double bond (Eq. 24) (52). Many


ROOC
N
N
ROOC
77%
+
H
23%

(22)


O
H
N
R
N
N
H
O
Br
Br
O

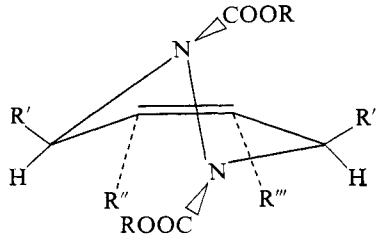
(23)


ROOC
R
N
N
ROOC
R
H2/Pd-C
Br2
Hg(OAc)2
Br
HgOAc
OAc

(24)

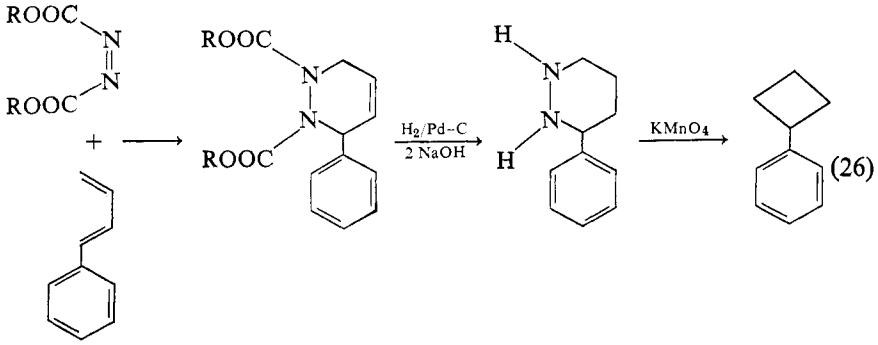
such mercurial adducts have been tested as diuretic agents (48, 58), and although they were active they have not been clincally useful.

The physical properties of the adducts and their derivatives are listed in the recent review by Gillis (50), and are not included here. They are usually high-boiling liquids or low-melting solids which are soluble in most organic solvents but insoluble in water. The conformation of the substituted adducts has been extensively studied by nuclear magnetic resonance (nmr) (59–66). Most workers agree that the carboxyl groups lie on opposite sides of the diazine ring while the substituents at the 3- and 6-positions lie on the same side of the ring (Eq. 25), and that ring inversion at room temperature is a relatively slow process.



(25)

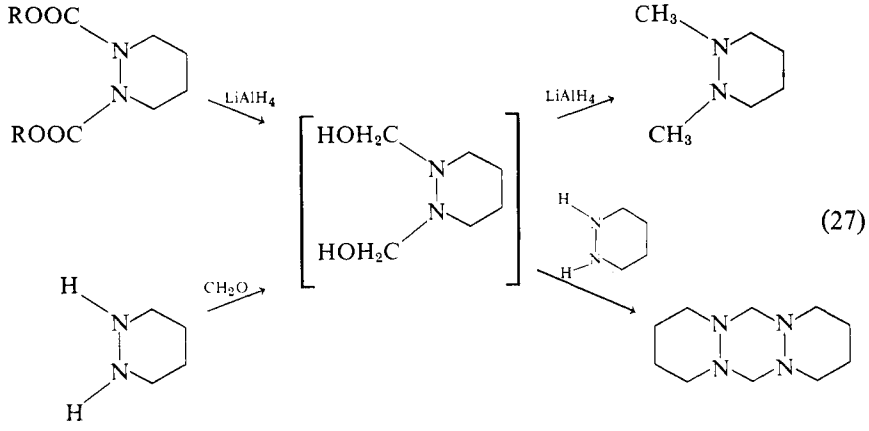
The 1,2-dicarboxylic acids decarboxylate so rapidly that they cannot be isolated, and basic hydrolysis of the adducts or their hydrogenated products always leads to the corresponding tetrahydropyridazine or piperidazine. Partial hydrolysis to monocarboxylates has been reported (67–69), but all attempts to isolate the acids have failed. Thus Diels–Alder addition, followed by hydrogenation and hydrolysis, is a facile method for preparing piperidazines. The latter lose nitrogen when oxidized, giving cyclobutane derivatives, and this sequence has been used to prepare cyclobutanes which are difficult to obtain by other methods (Eq. 26) (70–72).



(26)

The lithium aluminum hydride reduction of ethyl piperidazine-1,2-dicarboxylates has also been studied (73). The major products were the

expected 1,2-dimethylpiperidazines, but second products were obtained in small yield in each case. These proved to be 6*H*,13*H*-octahydrodipyridazino-[1,2-*a*:1′,2′-*d*]-*s*-tetrazines (Eq. 27). This unusual ring system was also synthesized by an alternate route from piperidazine and formaldehyde. Apparently both reactions proceed through a common intermediate.



(27)

B. Amides

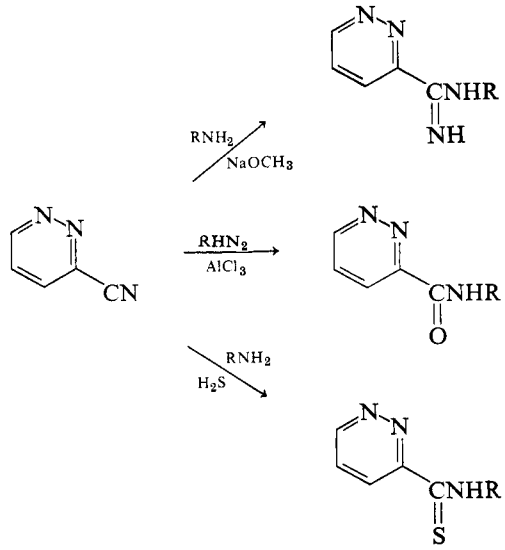
1. *Preparation*

Pyridazinecarboxamides are generally prepared by (1) the interaction of a pyridazine ester or acid chloride with ammonia or an amine, or (2) partial hydrolysis of a cyanopyridazine. Direct reaction between a pyridazine-carboxylic acid and an amine is often unsatisfactory because the acids decarboxylate too readily at the high temperatures required. However, conversion of acids to the corresponding esters and thence to the amides is generally satisfactory. Pyridazine-3-carboxylic acid can be converted quantitatively to the methyl ester with diazomethane, and this compound gives the amide in 90% yield upon treatment with methanolic ammonia. A similar sequence with the 4-isomer gives the amide in 65% overall yield (12).

Similar yields can be obtained with acid chlorides as intermediates, but they are unstable in storage, and esters are the generally preferred intermediates.

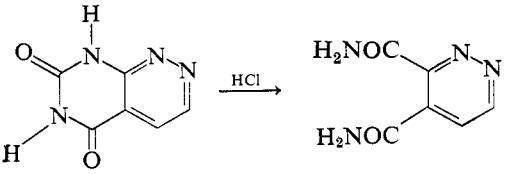
Pyridazine nitriles can be partially hydrolyzed to amides, usually in good yield, but this route has been little used because the nitriles are less available than are the esters and amides. Indeed, many of the reported pyridazine

nitriles were prepared by dehydration of amides. However, the preparation of substituted amidines by addition of amines to nitriles has been extensively studied (12, 74–77). Substituted amides and thioamides can also be formed by modifications of this reaction (Eq. 28) (12, 74, 77). Many of these compounds are biologically active (see below).



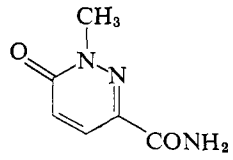
(28)

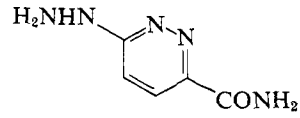
Pyridazinecarboxamides have been prepared by hydrolysis of 2,4-dioxopyrimido[4,5-*c*]- and [5,4-*c*]pyridazines (Eq. 29) (23, 29, 78). The yields are good, and unusual aminopyridazinecarboxamides and carboxylic acids can be prepared by this method. The formation of the pyrimidopyridazine ring systems is discussed in the following section.



(29)

The pyridazinecarboxamides, -thioamides, and -amidines are among the most biologically active derivatives in the pyridazine series. They have been tested as analgesics, antitussives, antibacterials, antihypertensives, and growth stimulants in mammals (12, 66, 74, 76, 77, 79–85). 1-ethyl-6(1*H*)pyridazinone-3-carboxamide has been introduced as an ethical antitussive agent under the name Medazonamide, (83) and 6-hydrazinopyridazine-3-carboxamide is used with chlorothiazide diuretics in antihypertensive formulations (Eq. 30) (66).





(30)

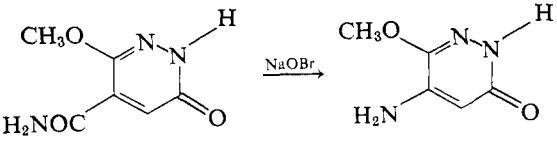
Medazonamide

2. *Reactions*

a. HYDROLYSIS. Pyridazinecarboxamides are converted to the corresponding acids by hot acid or alkaline hydrolysis (29, 86). Amide hydrolysis has been little used because of the ready availability of acids and esters by other routes.

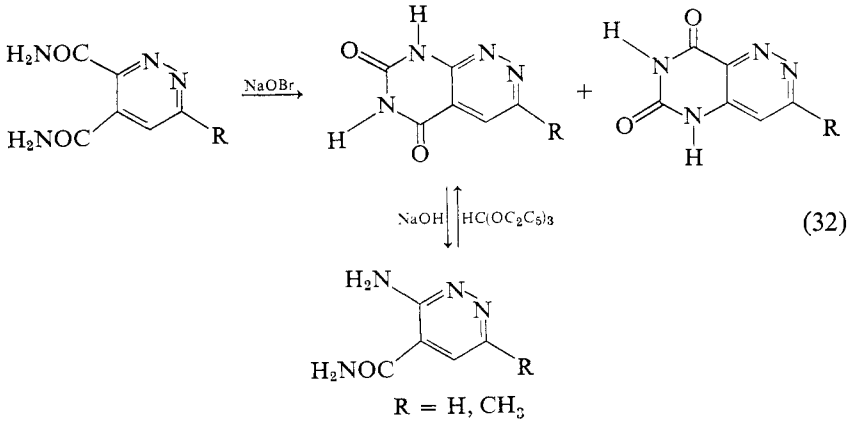
b. DEHYDRATION. Pyridazinecarboxamides are readily dehydrated to nitriles by heating with phosphorus oxychloride or phosphorus pentoxide. The yields are generally good, and many pyridazine nitriles containing a variety of substituents have been prepared by this method (see Section IV.D.1).

c. HOFMANN DEGRADATION. Pyridazinecarboxamides undergo Hofmann degradation to yield the corresponding amines (Eq. 31) (87). Good yields (69%) have been reported. When the reaction is applied to vicinal diamides,



(31)

pyrimidopyridazine ring systems are formed. Jones (88) first examined the reaction with a pyridazinediamide and isolated a polynuclear compound to which he tentatively assigned the pyrimido[4,5-*c*]pyridazine structure. Nakagome, Castle, and Muraami (29) reexamined the reaction and found that Jones had assigned the correct structure to the major product, and that one other ring system was also formed as well as another product. One of these is the pyrimido[5,4-*c*]pyridazine ring system, but no structural assignment has yet been possible for the third product (Eq. 32). Hydrolysis of these compounds yielded 3-aminopyridazine-4-carboxylic acids and 4-aminopyridazine-3-carboxylic acids and their amides (29), the compounds expected from normal Hofmann degradation. These reactions were mentioned previously (Section IV.B.1). The pyrimidopyridazine ring systems can be regenerated from the appropriate aminoamides by treatment with ethyl orthoformate (Eq. 32) (29).



(32)

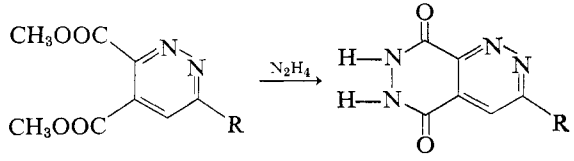
C. Hydrazines

The discovery that certain pyridinecarboxylic acid hydrazides are potent tuberculostatic agents (isonicotinic acid hydrazide, isoniazid or INH) and monoamine oxidase inhibitors has stimulated the study of similar derivatives in related ring systems. Thus an unusually large number of pyridazine acid hydrazides have been prepared and examined as possible therapeutic agents.

Pyridazinecarboxylic acid hydrazides are prepared by the same general methods used to prepare amides, that is, by reaction of an ester or acid chloride with hydrazine or a substituted hydrazine. As with amides, esters have been the preferred intermediates. The yields are generally excellent.

N^2-Substituted hydrazides may also be prepared by addition of aldehydes or ketones to preformed hydrazides followed by catalytic reduction (89, 90). Large groups of both the hydrazone and hydrazine derivatives have been tested as monoamine oxidase inhibitors, and most have shown some activity (90). However, none is as active as the corresponding pyridine derivatives.

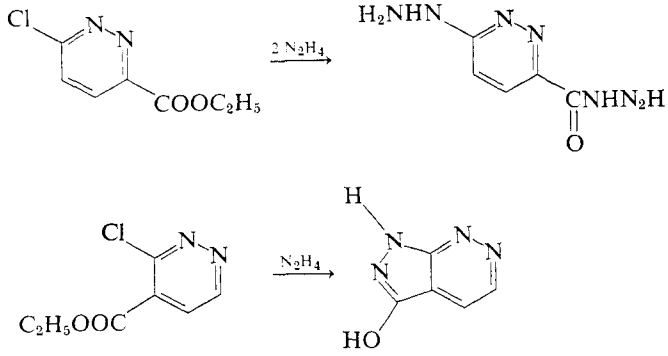
When vicinal pyridazine diesters are treated with hydrazine, cyclic hydrazides (pyridazinopyridazines) are formed (Eq. 33) (16, 23, 44, 47).



(33)

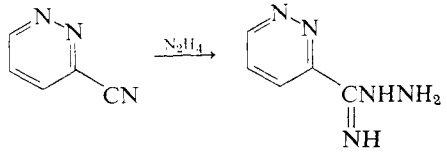
Halo substituents on the pyridazine ring may also be replaced by hydrazine in addition to its reaction with the ester. For example, ethyl 6-chloropyridazine-3-carboxylate reacts with 2 moles of hydrazine to yield 6-hydrazinopyridazine-3-carboxylic acid hydrazide (Eq. 34) (86, 91–94).This compound

and its bisthiosemicarbazide congener (prepared by reaction with potassium thiocyanate) (86) have antibacterial, antifungal, and antihypertensive activity. If the halo substituent is adjacent to the carboxyl group, cyclic compounds are formed (Eq. 34) (83).



(34)

The preparation of 3-pyridazylhydrazidine by reaction of 3-cyanopyridazine with hydrazine has been reported (Eq. 35) (95). This is the first such derivative reported in the pyridazine series.



(35)

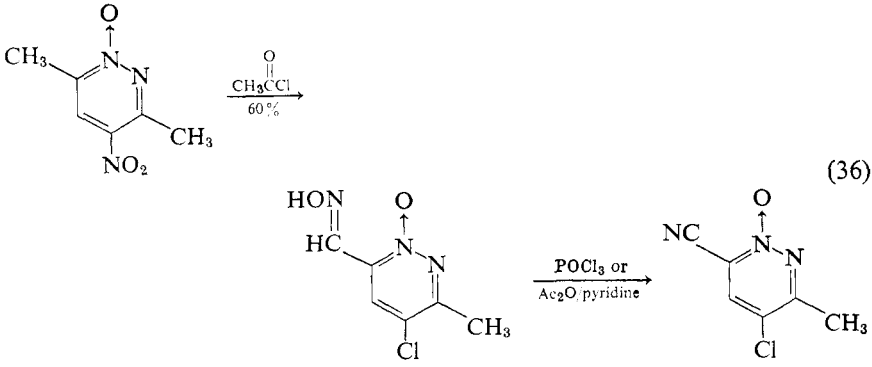
D. Nitriles

1. *Preparation*

Cyanopyridazines are generally prepared by (1) cyclization of the pyridazine ring from compounds containing cyano groups, (2) dehydration of pyridazinecarboxamides, and (3) substitution of the ring by sodium or potassium cyanide. Cyclizations of the pyridazine ring were discussed previously (Section I.A). Only minor modifications of the usual cyclization reactions are necessary to obtain pyridazine nitriles.

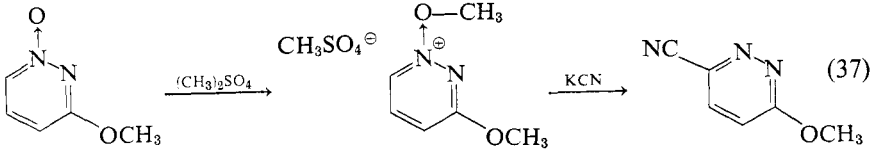
Dehydration of amides with phosphorus oxychloride is generally satisfactory and often gives high yields of the nitriles. When this reagent is used to dehydrate pyridazinonecarboxamides, oxo substituents in the ring are also replaced, yielding the corresponding chloropyridazine nitriles (34, 96, 97). Ring hydroxyl functions can be preserved by dehydrating with phosphorus pentoxide (98, 99). Comparable yields are obtained with either reagent.

In a similar reaction pyridazinecarboxaldoximes (carboxamidates) were dehydrated to yield the corresponding nitriles (96, 97). In addition to their usual preparation from aldehydes, pyridazinyl oximes have been generated by an interesting reaction in which 3-methyl-4- or 5-nitropyridazine 2-oxides were treated with acetyl chloride (Eq. 36). As expected, the nitro group was replaced by chloride ion, but in a major portion of the product the methyl group was also converted to the oxime. In the first report (96) the oxime was not isolated. A later study of the mechanism of the reaction (97) revealed this intermediate, and also the fact that only methyl groups next to the *N*-oxide function are affected in the reaction.



(36)

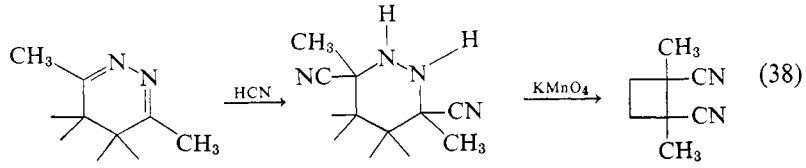
Cyanopyridazines can be prepared by substitution of pyridazine *N*-oxides with sodium or potassium cyanide after the ring has been activated by formation of a pyridazinium salt (Reinecke reaction). Methyl sulfate (29, 100, 101) and benzoyl chloride (100, 101) have been used to form the activated salts. The former gives the best yields (101). The nitrile function is always introduced at the position adjacent to the *N*-oxide moiety (Eq. 37).



(37)

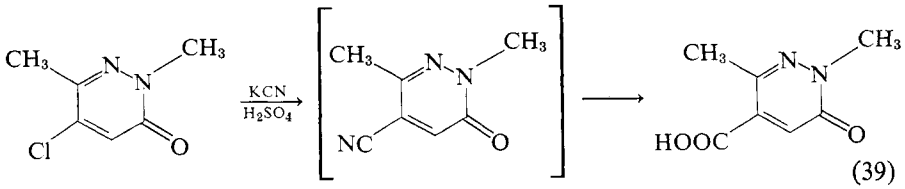
Cyanide ion can be introduced directly into partially reduced pyridazine rings. For example, 4,5-dihydro-3,6-dimethylpyridazine reacts smoothly with hydrogen cyanide to give 3,6-dicyano-3,6-dimethylpiperidazine in 84% yield (Eq. 38) (70, 71, 102, 103). The latter compound loses nitrogen upon mild oxidation with permanganate to yield 1,2-dicyano-1,2-dimethylcyclobutane (Eq. 38) (71, 102, 103).

Although the replacement of halogen substituents with cyanide ion is not a general preparative method for cyanopyridazines, it has been possible in a



(38)

few cases. For example, when 4-chloro-1,3-dimethylpyridazinone was treated with potassium cyanide in dilute sulfuric acid, the 4-carboxylic acid was isolated (Eq. 39) (30). Presumably, the nitrile intermediate formed, but it was not isolated.



(39)

2. *Reactions*

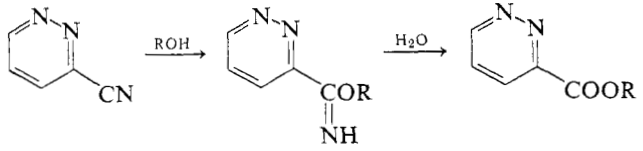
a. HYDROLYSIS. Cyanopyridazines can be hydrolyzed in either alkaline or acid solution and, depending on the conditions, the amide, acid, or decarboxylated acid may be isolated. Alkaline hydrolysis is usually somewhat more difficult than acid hydrolysis but is preferred for preparing acids because these products tend to decarboxylate under acidic conditions. Acidic hydrolysis is generally preferred for the preparation of amides and usually gives good yields.

b. ADDITION REACTIONS. Nitriles add hydrogen sulfide in the presence of ammonia in methanol solution to yield thioamides (74, 77). Excellent yields have been realized, and the reaction proceeds more rapidly than with the corresponding pyridine nitriles (1–2 hr versus 2–3 days) (77). This increased reactivity is apparently due to activation of the nitrile by the strongly electronegative pyridazine ring.

Nitriles add ammonia or a primary or secondary amine to yield amidines, again in excellent yields, and with unusually short reaction times (12, 74–77). Of particular interest are the hydroxamidines prepared by addition of hydroxylamine to cyanopyridazines (74, 77). These compounds have analgesic activity as do several of the nitriles (74). These reactions were discussed previously in Section IV.D.1.

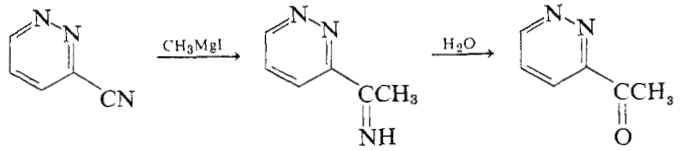
Addition of alcohols to cyanopyridazines yields carboximidates (Eq. 40) (77). These compounds are relatively stable (they can be isolated and characterized) but can be hydrolyzed to the corresponding esters with ease. Thus

this sequence represents a facile means for the direct conversion of nitriles to esters.



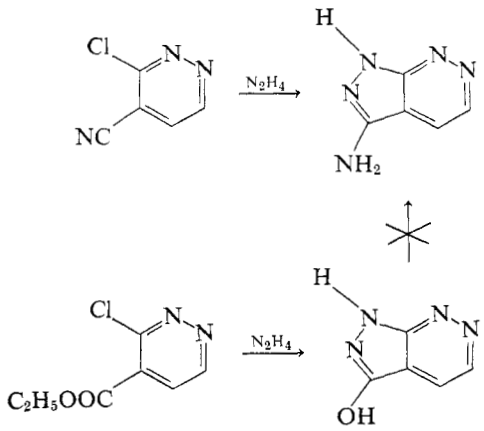
(40)

Methyl Grignard has been added to pyridazine nitriles, giving first the methyl pyridazinylimino ketones which are easily hydrolyzed to the corresponding pyridazinyl methyl ketones (Eq. 41) (12, 74). The yields in this method are low (27%), and a better route which employs the Claisen condensation with pyridazine esters has been devised (Section IV.A.1) (42, 43).



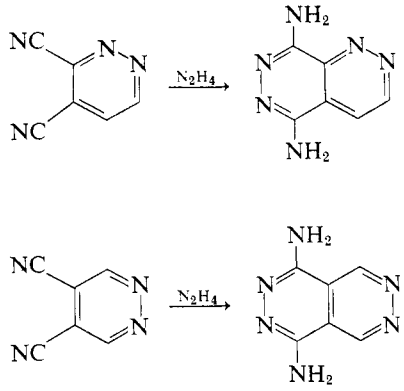
(41)

c. Formation of Polynuclear Ring Systems. Pyridazine nitriles and vicinal dinitriles have been used to prepare amino-substituted polynuclear ring systems that cannot be obtained in any other manner. For example, 3-chloro-4-cyanopyridazine reacts with hydrazine to yield 3-aminopyrazolo-[3,4-*c*]pyridazine (Eq. 42) (83). The 3-hydroxy derivative can be prepared similarly from the corresponding ester (Section IV.C) but cannot be converted to the chloride and thence to the amine. Thus the nitrile condensation represents the only source of the amine derivative.



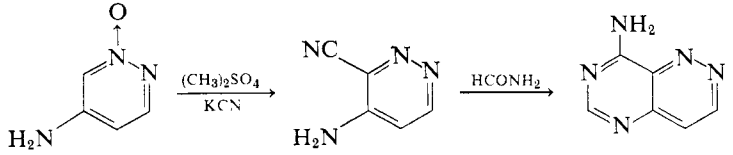
(42)

Similar condensations between hydrazine and pyridazine-3,4- and 4,5-dinitriles represent the only routes to amino-substituted pyridazino-[4,5-*d*]- and [4,5-*c*]pyridazines (Eq. 43) (23, 46).



(43)

Another related ring closure, but using formamide as the condensing agent rather than hydrazine, yields 8-aminopyrimido[4,5-*c*]pyridazine. 3-Cyano-4-aminopyridazine was prepared by the methylsulfate–potassium cyanide reaction discussed previously (Section IV.D.1) on 5-aminopyridazine 1-oxide. This nitrile condensed smoothly with formamide to yield the condensed ring system which could not be obtained otherwise (Eq. 44) (29).

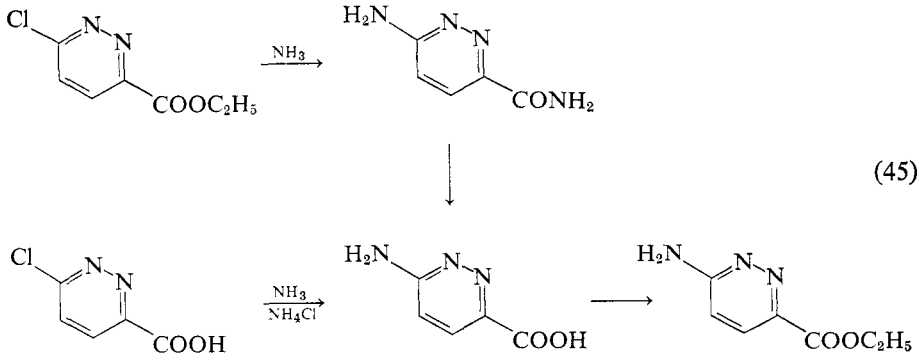


(44)

V. Substitution Reactions of the Pyridazine Ring

The methods by which reduced pyridazine and pyridazinone ring systems can be oxidized to fully aromatic compounds are thoroughly discussed elsewhere in this volume (see Chapter II). These methods work equally well with compounds containing carboxylic acid groups and their functional derivatives, but the choice of reagents and reaction conditions employed is sometimes dictated by the substituents present on the ring. For example, oxidation of 4,5-dihydro-6-methylpyridazine-3,4-dicarboxylic acid to the fully aromatic compound in hot acid solution is accompanied by loss of the carboxyl group at the 3-position. This can be overcome by oxidizing with alkaline permanganate, or by employing the diethyl ester followed by alkaline hydrolysis to the dicarboxylic acid (88).

Substitution reactions of the pyridazine and pyridazinone nuclei are also discussed elsewhere (see Chapter II). As with the ring oxidations, carboxylic acids and related substituents do not usually interfere but they may be converted to other functional derivatives by the reagents used in substitution reactions. For example, amination of ethyl 6-chloropyridazine-3-carboxylate yields 6-aminopyridazine-3-carboxamide, rather than the amino ester (Eq. 45) (86). The amide can be hydrolyzed to the acid and then converted to the ester, but a better method is direct amination of the 6-chloro acid and subsequent esterification (~10 versus 52% overall yield (Eq. 45) (86)).



(45)

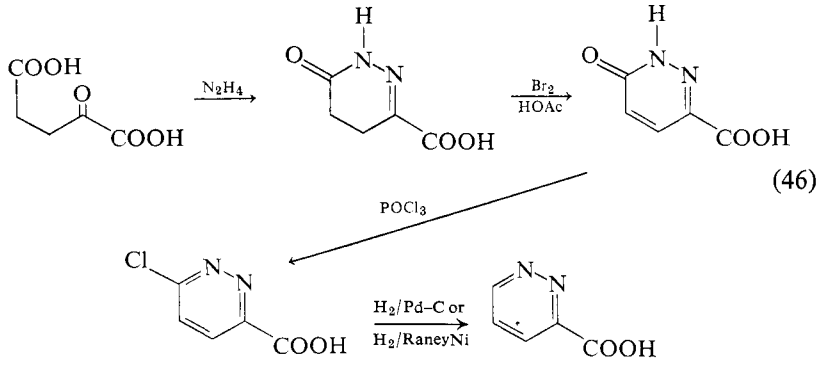
The conversion of ethyl 6-chloropyridazine-3-carboxylate to 6-hydrazinopyridazine-3-carboxylic acid hydrazide by mild reaction with hydrazine was noted previously (Section IV.C).

Halogen substituents are usually introduced by replacement of oxo groups in pyridazinones. Phosphorus oxychloride, the preferred reagent for this replacement, also affects carboxylic acids and amide functions. When a carboxylic acid group is present, care must be exercised in the work-up of the reaction, because many of the acid chlorides formed are unstable when isolated and must be maintained in solution until they are decomposed with water or an alcohol. Amide functions are converted to nitriles by phosphorus oxychloride and cannot be regenerated by partial hydrolysis because the halo substituents on the ring are also hydrolyzed. Haloamides are best prepared by converting the corresponding acid to its acid chloride and decomposing this intermediate with ammonia or an amine.

Halogen substituents on pyridazinecarboxylic acids have been replaced by hydroxyl and alkoxyl groups (33, 97, 101, 104, 105), amines (86), and hydrazine (91). A study of the kinetics of displacement of chlorine from 6-chloropyridazine-3-carboxylic acid by sodium methoxide has been reported (105).

Halogen substituents can also be replaced by hydrogen, and this reaction has been used as a convenient method for obtaining pyridazine acids. The

pyridazinonecarboxylic acids often obtained in cyclizations of the ring are converted to halopyridazine intermediates and dehalogenated to yield the pyridazinecarboxylic acids. For example, a convenient route to pyridazine-3-carboxylic acid begins with levulinic acid which is cyclized, oxidized to the pyridazinone acid, halogenated, and finally dehalogenated to the unsubstituted acid (Eq. 46). Dehydrohalogenation with Raney nickel (16) or palladium–carbon (43) catalysts gave essentially identical yields of the acid (80%).



(46)

Numerous examples of *N*-alkylation of pyridazinonecarboxylic acids and other functional derivatives have been reported. The usual conditions involve an alkyl halide and a strong base such as sodium ethoxide in alcoholic solution. With proper control of conditions, either the *N*-alkylated acid or the corresponding ester can be obtained (99, 106). Esters and amides can also be alkylated (30, 99), but the most general method of preparation for the *N*-substituted compounds involves cyclization of the pyridazinone ring from substituted hydrazines. Both *N*-alkyl- and *N*-arylpyridazinones are available by the cyclization method, but the latter cannot be prepared by direct substitution. Several *N*-hydroxymethylpyridazinonecarboxylic acids have been prepared by alkylation with formaldehyde (99, 106–108). Such compounds are difficult to prepare by other methods.

Acknowledgments

The author is grateful to Mr. R. G. Salisbury for assistance in searching the literature and for his comments on the manuscript. The advice of Drs. R. C. Bean and R. E. Kay has also been most helpful. Typing and proofing of the manuscript were provided by Mrs. Barbara Martin and Mrs. Edna King, whose contributions are also gratefully acknowledged.

TABLE I. Pyridazinemonocarboxylic Acids and Their Derivatives

Substituent position						
3	4	5	6	MP (°C)	Derivatives	References
COOH				200–201		10, 12, 13, 16, 27, 28, 35, 43
					Methyl ester: mp 139° C;	10, 12
					1-oxide: mp 195–196° C	43
					Ethyl ester: mp 68–69° C;	13, 16, 43
					1-oxide: mp 120° C	75, 43
					Other esters	10, 12, 13, 28
					Amide: mp 182–183° C	12, 13
					Carboxamide: mp 240° C	75–77
					Methyl carboxamidate: mp 79–80° C	77
					Thioamide: mp 168° C	76, 77
					N-Substituted amidines	75–77
					Hydrazide: mp 151–152° C	13, 16
					N^2-Substituted hydrazides	10, 90, 109
					Hydrazidine: mp 164–165° C	95
COOH			Cl	148		28, 30, 92, 94
					Ethyl ester: mp 152–153° C	30, 92, 93
					n-Propyl ester: mp 99–101° C	92
					n-Butyl ester: mp 110–112° C	92
					Other esters	58, 86, 93
					Amide: mp 249° C	93
COOH			OCH_3		Methyl ester: mp 127–128° C	43
COOH	NH_2			222 (dec)		29
					Amide: mp 187–188° C	29
COOH			NH_2		Hydrochloride: mp 243–245° C	86
					Methyl ester: mp 200–201° C	86

					Ethyl ester: mp 168–169° C	86
					Propyl ester: mp 141–142° C	86
					Amide: mp 260–262° C	86
COOH			$NHNH_2$		Amide: mp 251–252° C	58, 86, 91–94
					Hydrazide; dithioureide: mp 215–216° C	86
COOH			CH_3		Amide, 2-oxide: mp 204° C	101
COOH			C_6H_5	192		19, 22, 101
COOH		Cl	CH_3		2-Oxide: mp 115° C (dec)	97
COOH		OCH_3	CH_3		2-Oxide: mp 142° C (dec)	97
COOH		NH_2	OCH_3	188 (dec)		29
COOH	CH_3	C_6H_5		132–135		36
COOH	NH_2	Cl	Cl	273–274		29
	COOH			240–242		10, 12, 14–16
					Methyl ester: mp 63° C	12, 15, 16
					Ethyl ester: bp 125° C/13 mm	12, 15, 16
					Amide: mp 191–192° C	12, 15, 16
					Carboxamide: mp 209° C	76, 77
					Methyl carboxamidate: mp 102–103° C	77
					N-Benzylamide: mp 80–81° C	77
					Thioamide: mp 214–215 °C	76, 77
					N-Substituted amidines	76, 77
					Hydrazide: mp 124–125° C	12, 15, 16
Cl	COOH				Ethyl ester: mp 49° C	34
					Amide: mp 72° C	34
NH_2	COOH			261–262		29
	COOH	C_6H_5		222–224		20, 24, 25
					Methyl ester: mp 103–105° C	25
					Amide: mp 170–172° C	25
	COOH	*p*-HOC_6H_4		240		9
	COOH	*p*-$CH_3OC_6H_4$		206–208 (dec)		9, 25
	COOH	*o*-O_2N-*p*-$CH_3OC_6H_3$		232–234 (dec)		25
					Methyl ester: mp 151–153° C	25
					Amide: mp 233–234° C	25

TABLE I (*continued*)

Substituent position						
3	4	5	6	MP (°C)	Derivatives	References
Cl	COOH		Cl	144 (dec)		104
Cl	COOH		CH_3O	159 (dec)		104
CH_3O	COOH		CH_3O	156		104
Cl	COOH		CH_3		Ethyl ester: mp 41° C	29, 34, 211
					Amide: mp 206° C	29, 34
					Hydrazide: mp 190° C (dec)	29, 34
CH_3O	COOH		CH_3		Amide: mp 155–156° C	29
NH_2	COOH		CH_3	288 (dec)		29
					Methyl ester: mp 172–173° C	29
					Amide: mp 253–255° C	29
CH_3	COOH		CH_3		Ethyl ester: mp 108–110° C, bp 245–248° C/760 mm	111–115
CH_3	COOH		C_6H_5	201		116
					Ethyl ester: mp 53° C	116
$CH_2C_6H_5$	COOH		C_6H_5	200 (dec)		116
					Ethyl ester: mp 195–196° C	116
C_6H_5	COOH		C_6H_5	205–206		116, 122
					Ethyl ester: mp 100° C	116, 122
					N-Phenylamide: mp 20° C	116, 122
Cl	COOH	C_6H_5	C_6H_5		Ethyl ester: mp 134–135° C	124
Cl	COOH	*p*-ClC_6H_4	*p*-ClC_6H_4		Ethyl ester: mp 137–139° C	124
CH_3NH	COOH	C_6H_5	C_6H_5		*N*-Methylamide: mp 193–194° C	78

TABLE II. Pyridazinone-6(1*H*)carboxylic Acids and Their Derivatives

Substituent position						
1	3	4	5	MP (°C)	Derivatives	References
	COOH			259–260 (dec)		18, 30, 39, 99–101, 125–132
					2-Oxide: mp 197–198° C	97
					Methyl ester: mp 188–189° C	18, 99
					Ethyl ester: mp 129–130° C	30, 86, 92–94, 128–134
					Other esters	86
					Amide: mp 320° C (dec)	18, 132, 135, 136
					N-Phenylamide: mp 255–256° C	135
					N-Methyl-*N*-phenylamide: mp 158° C; 2-oxide: mp 221° C (dec)	137 137
					Hydrazide: mp >300° C (dec)	18, 91, 130
CH_3	COOH			239		30, 99, 128
					Methyl ester: mp 103° C	30, 99, 128
					Ethyl ester: mp 67–68° C	30, 128
					Acid chloride: mp 116° C	99, 139
					Amide: mp 198–200° C	99, 139
					N-Methylamide: mp 155–157° C	99, 139
					N,*N*-Diethylamide: mp 73–75° C	99, 139
					N-Methyl-*N*-phenylamide: mp 108° C	137
$HOCH_2$	COOH				Ethyl ester: mp 106–107° C	99, 106
$HOOCCH_2$	COOH			222–223		128
					Diethyl ester: mp 82–83° C	128
					Dihydrazide: mp 227–228° C	213

TABLE II (*continued*)

Substituent position						
1	3	4	5	MP (°C)	Derivatives	References
$(CH_3)_2NC_2H_4$	COOH				Ethyl ester, hydrochloride: mp 155–156° C; oxalate: mp 169–171° C; methiodide: mp 233–234° C	99
C_4H_9-*n*	COOH			119–121		99, 106
					Methyl ester: bp 85–90° C/0.1 mm	99, 106
C_6H_5	COOH			210–212		141, 142
					Amide: mp 224–225° C	
					N,*N*-Dimethylamide: mp 124–126° C	142
					Morpholinoamide: mp 134–135° C	142
o-$CH_3OC_6H_4$	COOH			212–213		141
o-$CH_3C_6H_4$	COOH			236		141
p-$CH_3C_6H_4$	COOH			229–230		141
	COOH		Cl		2-Oxide: mp 214° C	97
CH_3	COOH	Cl		188		30
CH_3	COOH	Cl	Cl	203–204		30
C_6H_5	COOH		$C_6H_5N{=}N$		Ethyl ester: mp 163–164° C	5a, 138
p-ClC_6H_4	COOH		*p*-$ClC_6H_4N{=}N$		Ethyl ester: mp 208–209° C	5b
o-BrC_6H_4	COOH		*o*-$BrC_6H_4N{=}N$		Ethyl ester: mp 166–167° C	5b
m-BrC_6H_4	COOH		*m*-$BrC_6H_4N{=}N$		Ethyl ester: mp 149° C	5b
p-BrC_6H_4	COOH		*p*-$BrC_6H_4N{=}N$		Ethyl ester: mp 229° C	5b
o-$CH_3C_6H_4$	COOH		*o*-$CH_3C_6H_4N{=}N$		Ethyl ester: mp 152° C	5b
p-$CH_3C_6H_4$	COOH		*p*-$CH_3C_6H_4N{=}N$		Ethyl ester: mp 157° C	5b
2,4-$(CH_3)_2C_6H_3$	COOH		2,4-$(CH_3)_2C_6H_3N{=}N$		Ethyl ester: mp 155° C	5b
C_6H_5	COOH	CH_3		230		147
					Methyl ester: mp 125–127° C	2, 148
					Ethyl ester: mp 102° C	148
					Acid chloride: mp 135° C	148
					N,*N*-Dimethylamide: mp 54° C	148
					N-Phenylamide: mp 259° C	148

p-ClC_6H_4	COOH	CH_3		216		2
					Methyl ester: mp 162° C	2
					N-Phenylamide: mp 179° C	2
					N-(*p*-Tolyl)amide: mp 165° C	2
o-$CH_3OC_6H_4$	COOH	CH_3		234		147
p-$CH_3OC_6H_4$	COOH	CH_3		221		2
2,5$(CH_3O)_2C_6H_3$	COOH	CH_3		206		2
p-$(CH_3)_2NC_6H_4$	COOH	CH_3		251		2
p-$(C_2H_5)_2NC_6H_4$	COOH	CH_3		187		2
o-$HOOCC_6H_4$	COOH	CH_3		231		2
p-$CH_3C_6H_4$	COOH	CH_3		213		2
2,6-$(CH_3)_2C_6H_3$	COOH	CH_3		224		2
α-$C_{10}H_7$	COOH	CH_3		236		2
β-$C_{10}H_7$	COOH	CH_3		240		2
C_6H_5	COOH	CH_3	$C_6H_5N{=}N$	216		2
p-ClC_6H_4	COOH	CH_3	*p*-$ClC_6H_4N{=}N$	209		2
	COOH		CH_3	275 (dec)		149, 150
C_6H_5	COOH		CH_3	213–214		151–153
					Ethyl ester: mp 125° C	154
			COOH	303 (dec)		45, 206
					Methyl ester: mp 163° C	33
					Ethyl ester: mp 127–128° C	45
					Ethyl ester: mp 173–176° C	206
$HOCH_2CH_2$		COOH				177
C_6H_5		COOH		180–181		33, 165
	Cl	COOH		245 (dec)		
					Methyl ester: mp 99–101° C	33
					Ethyl ester: mp 112° C	169
					Amide: mp 259–260° C	169
C_6H_5		COOH	Br	247–248		207
	CH_3O	COOH		259 (dec)		87
					Methyl ester: mp 178–179° C	87
					Amide: mp 265–266° C	87
	CH_3	COOH		247 (dec)		45
					Ethyl ester: mp 114–116° C	45, 206

TABLE II (*continued*)

Substituent position						
1	3	4	5	MP (°C)	Derivatives	References
CH_3	CH_3	COOH		183–185		30
		COOH	CH_3O	184–186		206
					Ethyl ester: mp 85–88° C	206
			COOH	199–200		164–168
					Methyl ester: mp 159° C	33
					Ethyl ester: mp 85° C, bp 186° C/1.5 mm	34
					Amide: mp 270° C	34
					Carboxamide: mp 232° C	76, 77
					Thioamide: mp 305° C	76, 77
					N-Substituted amidines	76, 77
					Hydrazine: mp 240° C (dec)	34
CH_3			COOH	125–126		166, 167
2-C_4H_7O			COOH	201–203		219
					Ethyl ester: mp 156–159° C	219
	Cl		COOH	216		33, 104, 165, 169
					Methyl ester: mp 132° C	33
					Ethyl ester: mp 152–153° C	165, 169
					Amide: mp 253° C	165, 169
					Hydrazide: mp 236–237° C	165, 169
		NH_2	COOH		Ethyl ester: mp 170° C (dec)	170
C_6H_5	NO_2		COOH		Methyl ester: mp 128° C	171

p-BrC_6H_4	NO_2		COOH		Ethyl ester: mp 128° C	171
	CH_3		COOH	182–183		14, 30
					Methyl ester: mp 161–162° C	30
					Ethyl ester: mp 171° C	18, 34
					Amide: mp 286–287° C	18, 29, 34
					Hydrazide: mp 220–221° C	18, 34
CH_3	CH_3		COOH	150–153		30
		CH_3	COOH	193–194		14, 167
	CH_3	CH_3	COOH	172–173		14, 166
					Methyl ester: mp 168–170° C	167
					Ethyl ester: mp 173–174° C	167
CH_3	CH_3	CH_3	COOH	109–110		74, 166–168
					Methyl ester: mp 59–60° C	74
					Amide: mp 286–287° C	74
					Thioamide: mp 213–214° C	74
					N-Hydroxyamidine: mp 187–189° C	74
	C_6H_5	C_6H_5	COOH	243–244 (dec)		164–168
					Ethyl ester: mp 219–220° C	164, 175
CH_3	C_6H_5	C_6H_5	COOH	222		74, 168
					Ethyl ester: mp 146–147° C	166, 167, 176
C_6H_5	C_6H_5	C_6H_5	COOH	285–286		74, 168
					Ethyl ester: mp 184° C	164, 166, 167, 175
	p-ClC_6H_4	*p*-ClC_6H_4	COOH	274 (dec)		168
					Ethyl ester: mp 235–236° C	166, 167, 175
CH_3	*p*-ClC_6H_4	*p*-ClC_6H_4	COOH	241–242		168
					Ethyl ester: mp 169–170° C	166, 167, 176

TABLE III. Pyridazinone-4(1*H*)carboxylic Acids and Their Derivatives

Substituent position						
1	3	5	6	MP (°C)	Derivatives	References
C_6H_5	COOH		CH_3O		Methyl ester: mp 154° C	32
C_6H_5	COOH	$C_6H_5N{=}N$		235–236		5c
					Sodium salt: mp 204–205° C (dec)	5c
C_6H_5	COOH		CH_3	183–185 (dec)		3, 156–158
					Methyl ester: mp 210–212° C	156–158
					Ethyl ester: mp 182–184° C	156–158
					Other esters	156–158
					Amide: mp 229–231° C (dec);	156–158
					2-Oxide: mp 220° C	96
					N-Methylamide: mp 220–222° C	156–158
					Hydrazide: mp 212–214° C (dec)	156–158
m-ClC_6H_4	COOH		CH_3	193		3
p-ClC_6H_4	COOH		CH_3	229		159
o-BrC_6H_4	COOH		CH_3	216–217 (dec)		156–158
m-BrC_6H_4	COOH		CH_3	221–222		156–158
p-BrC_6H_4	COOH		CH_3	251–253		156–158
					Ethyl ester: mp 145–146° C	157
o-$CH_3OC_6H_4$	COOH		CH_3	170		3

p-$O_2NC_6H_4$	COOH		CH_3	224		16
m-$O_2NC_6H_4$	COOH		CH_3	224		160
					Ethyl ester: mp 183–184° C	157
p-$O_2NC_6H_4$	COOH		CH_3	209		160
					Ethyl ester: mp 161–162° C	157
o-CH_3p-$O_2NC_6H_3$	COOH		CH_3	246		3
p-$HO_2CC_6H_4$	COOH		CH_3		Diethyl ester: mp 156–157° C	157
p-$HO_2AsC_6H_4$	COOH		CH_3	252		159
p-$CH_3C_6H_4$	COOH		CH_3	154		3
3-C_5H_4N	COOH		CH_3	202–203		156, 161
					Methyl ester: mp 169–171° C	156
					Ethyl ester: mp 168–170° C	156
2-C_3H_2NS	COOH		CH_3	176–178		161
					Methyl ester: mp 152–154° C	161
C_6H_5	COOH	Br	CH_3	230–232 (dec)		156
p-ClC_6H_4	COOH		C_2H_5	160		160
C_6H_5	COOH		$C_{13}H_{27}$		Ethyl ester: mp 47–48° C	4
C_6H_5	COOH		C_6H_5	330 (dec)		208
					Ethyl ester: mp 104–105° C	4
o-ClC_6H_4	COOH		C_6H_5	218		160
m-$O_2NC_6H_4$	COOH		C_6H_5	206		160
C_6H_5	CH_3	COOH	CH_3	220		180

TABLE IV. Pyridazine-4(1*H*),6(2*H*)dionecarboxylic Acids

Substituent position					
1	3	5	MP (°C)	Derivatives	References
C_6H_5	COOH		244–245		32
				Methyl ester: mp 138° C	32
				Ethyl ester: mp 121–122° C	32
				N-Phenylamide: mp 177–178° C	32
p-$O_2NC_6H_4$	COOH		251		162
				Ethyl ester: mp 180° C	163
C_6H_5	COOH	$C_6H_5N{=}N$	260		214
				Ethyl ester: mp 164–165° C	214

TABLE V. Pyridazinepolycarboxylic Acids and Their Derivatives

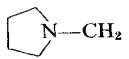
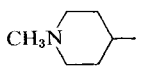
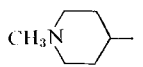
Substituent position						
3	4	5	6	MP (°C)	Derivatives	References
COOH	COOH				Diethyl ester: bp 117–119° C/0.5 mm	23
					Diamide: mp 220–221° C	23
COOH	COOH		CH_3	235–237		88
					Diethyl ester: mp 53–54° C	88
					Diamide: mp 245–246° C	23
COOH	COOH	C_6H_5		255–257		20, 24, 25, 36
					Dimethyl ester: mp 131–132° C	36
					Anhydride: mp 182–185° C	36
COOH	COOH	*p*-$CH_3OC_6H_4$		148–150 (dec)		9, 25
COOH	COOH	C_6H_5	CH_3	228–229 (dec)		20
	COOH	COOH		212–214		17, 18, 26, 46, 182, 205
					Diamide: mp 249–252° C	18, 46
CH_3	COOH	COOH	CH_3	226–228		112, 180, 183
					Ethyl ester: mp 155–156° C	112
					Diethyl ester: mp 22° C; bp 200/22 mm	112, 183
					Diamide: mp 240° C	47
					Imide: mp 240° C (dec)	47
C_6H_5	COOH	COOH	C_6H_5	202 (dec)		188
					Diethyl ester: mp 127–128° C	188
COOH			COOH		Dimethyl ester: mp 201–204° C (dec)	8, 189
COOH	C_2H_5O		COOH		Dimethyl ester: mp 75–76° C	8
COOH	CH_3		COOH		Dimethyl ester: mp 115–116° C	8
COOH	*n*-C_4H_9		COOH		Dimethyl ester: mp 55–56° C	8
COOH	C_6H_5		COOH		Dimethyl ester: mp 96–98° C	8
COOH	COOH	COOH	COOH	>300 (dec)		26
COOH	COOH		O(1*H*)	291		45
					Diethyl ester: mp 86–88° C	45
COOH	O(1*H*)		COOH	251 (dec)		190
COOH	O(1*H*)	COOH	*o*-CH_3 OC_6H_4		1-Phenyl,5-methyl ester: mp 210° C	191

TABLE VI. Cyanopyridazines and Their Derivatives

Substituent position						
3	4	5	6	MP (°C)	Derivatives	References
CN				43–44		12, 75, 95
CN		Cl			2-Oxide: mp 205–207° C	97
CN			Cl	94–95		99, 101
CN			CH_3O	94–95		100, 101
CN			$C_6H_5CH_2O$	93–94		101
CN			NH_2	222		29
CN			CH_3	90–91		101
					2-Oxide: mp 149–150° C	96
CN			C_6H_5	184–186		101
CN		Cl	Cl		2-Oxide: mp 132–133° C	97
CN		Cl	CH_3O		2-Oxide: mp 174–175° C	97
CN		CH_3O	CH_3O	200–201		209
					2-Oxide: mp 200–202° C	209
CN	NH_2		Cl	273		29
CN	NH_2		CH_3O	257–258		29
CN	Cl		CH_3		2-Oxide: mp 162–163° C	96
CN		Cl	CH_3		2-Oxide: mp 150–151° C	97

CN	CH_3O		CH_3		2-Oxide: mp 185° C	96
CN	NH_2	Cl	Cl	267–268		29
CN	NH_2	Cl	CH_3O	235–236		29
	CN			79–80		12
Cl	CN			41–42		34
Cl	CN		CH_3	106 (dec)		34
C_6H_5	CN		C_6H_5	162–163		195, 196
2-C_5H_4N	CN		2-C_5H_4N	206–207		27
Cl	CN	CH_3	CH_3	81–82		74, 124, 197, 198
CH_3O	CN	CH_3	CH_3	93–94		74, 197
C_2H_5O	CN	CH_3	CH_3	76–78		74, 197
$(CH_3)_2CHO$	CN	CH_3	CH_3	138–140		74, 197
NH_2	CN	CH_3	CH_3	162–164		74
	CN	CH_3	CH_3	77–78		74
$(C_2H_5)_2NC_2H_4NH$	CN	CH_3	CH_3	52–54		74
HS	CN	CH_3	CH_3	213–214		197
CH_3S	CN	CH_3	CH_3	66–67		74, 197
β-$C_6H_{11}O_6$	CN	C_6H_5	C_6H_5	206–209		215
CN	CN			61–63		23
CN	CN		CH_3	83–85		23
	CN	CN		136–137		46

TABLE VII. Cyano-6(1*H*)pyridazinones and Their Derivatives

Substituent position						
1	3	4	5	MP (°C)	Derivatives	References
			CN	185–186		164, 166, 175
CH_3			CN	131–132		74, 98, 166, 176
$(C_2H_5)_2NCH_2$			CN	93–95		199, 200
			CN	129		199
$C_6H_{11}O_5$			CN	236–238		215
					Tetraacetyl: mp 172–173° C	215
			CN	247–250 (dec)		204
	CH_3		CN	169–170		14, 98, 166, 175
	C_6H_5		CN		Hydrochloride: mp 280° C (dec)	140, 202
		CH_3	CN	228–230		14, 98, 175
CH_3		C_6H_5	CN	165–167		210
C_2H_5		C_6H_5	CN	66–67		98
p-$O_2NC_6H_4COCH_2$		C_6H_5	CN	245		210
		9-Fluorenyl	CN	250–251		201
		4-Phenanthryl	CN	284–287		201
	CH_3	CH_3	CN	212–213		74, 98, 164, 166, 175, 197, 198, 203

CH_3	CH_3	CH_3	CN	115–116		74, 98, 166, 176, 203
C_2H_5	CH_3	CH_3	CN	66–67		74, 166, 176
$(CH_3)_2NCH_2\underset{\displaystyle O}{\overset{\displaystyle CH_3}{\overset{\|}{\underset{\|}{CH}}}}$	CH_3	CH_3	CN		Hydrobromide: mp 209–211° C	202
$(CH_3)_2N\underset{\displaystyle O}{\overset{}{\underset{\|}{C}}}CH_2$	CH_3	CH_3	CN	180		216
Cyclic bases	CH_3	CH_3	CN			74, 91, 140, 202, 204
	CH_3	C_6H_5	CN	199–200		98, 164, 166, 175
CH_3	CH_3	C_6H_5	CN	187–188		74, 98, 166, 176
	C_6H_5	C_6H_5	CN	274–275		98, 164, 166, 175
CH_3	C_6H_5	C_6H_5	CN	211–212		74, 98, 166, 176
$(C_2H_5)_2NC_2H_4$	C_6H_5	C_6H_5	CN	95–96		74
$C_6H_{11}O_5$	C_6H_5	C_6H_5	CN	172–174		215
					Tetraacetyl: mp 223–224° C	215
	Cyclopentano		CN	207–209		74
CH_3	Cyclopentano		CN	107–108		74
	Cyclohexano		CN	240–241		74, 98, 175
CH_3	Cyclohexano		CN	130–131		74
	9,10-Phenanthro		CN	290 (dec)		175

TABLE VIII. 4,5-Dihydropyridazinecarboxylic Acids and Related Compounds

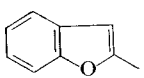
Substituent position				MP (°C)	Derivatives	References
3	4	5	6			
COOH					Ethyl ester: bp 90–100° C/0.4 mm	6
CH_3	COOH		C_6H_5		Ethyl ester: mp 98° C	116
CH_3	COOH		$C_6H_5C_6H_4$		Ethyl ester: mp 145° C	89
					Hydrazide: mp 200° C	89
					Benzalhydrazide: mp 180° C	89
CH_3	COOH				Ethyl ester: mp 189° C	121
$C_6H_5CH_2$	COOH		C_6H_5		Ethyl ester: mp 115° C	116
C_6H_5	COOH		C_6H_5	205–206		122
					Ethyl ester: mp 118° C	116, 122
CH_3	COOH	CH_3	CH_3		Ethyl ester: mp 112–114° C	123
COOH	COOH		CH_3		Diethyl ester: mp 86–87° C	23
CH_3	COOH	COOH	CH_3		Monoethyl ester: mp 205–207° C	112, 113
					Diethyl ester: mp 70–71° C	184–186
C_6H_5	CN		C_6H_5	190–191		197, 198
2-C_5H_4N	CN		2-C_5H_4N	137–138		7

TABLE IX. 4,5-Dihydro-6(1*H*)pyridazinonecarboxylic Acids and Related Compounds

Substituent position						
1	3	4	5	MP (°C)	Derivatives	References
	COOH			198 (dec)		12, 17, 18, 37, 38, 44, 99, 126, 127, 134, 138, 139
					Methyl ester: mp 136–137° C	12, 106, 139
					Ethyl ester: mp 135–136° C	12, 18, 38, 44, 134, 139
					Amide: mp 250–251° C	18, 44, 99
					Hydrazide: mp 190–191° C	18, 44
CH_3	COOH			159–160		37, 38, 99
					Methyl ester: mp 90–92° C	99, 106, 134, 139
					Amide: mp 170–172° C	99, 134, 139
C_4H_9-*n*	COOH			72		99, 106
					Methyl ester: mp 38° C	99, 106
					Amide: mp 172–174° C	134, 139
$C_6H_5CH_2$	COOH			175–178		38, 140
C_6H_5	COOH			170–172		38, 140, 143–146
$H_2NSO_2C_6H_4$	COOH			258 (dec)		217
m-$CH_3C_6H_4$	COOH			152		144, 145
		COOH			Ethyl ester: bp 125–130° C/0.4 mm	45
C_6H_5		COOH		178–179		177
					Ethyl ester: mp 111–112° C	177
	CH_3	COOH			Ethyl ester: mp 92–93° C	45, 178

TABLE IX (*continued*)

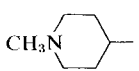
Substituent position						
1	3	4	5	MP (°C)	Derivatives	Reference
C_6H_5		COOH	C_2H_5	179		179
					Ethyl ester: bp 225–240° C/15 mm	179
	CH_3		COOH	130		40
					Ethyl ester: mp 76–77° C	40, 41
					Amide: mp 181–183° C	18, 129
					Hydrazide: mp 151–153° C	18, 40, 41, 129
					N^2,N^2-Dimethylhydrazide: mp 183–184° C	129
	C_6H_5		COOH	116–117 (dec)		172
					Methyl ester: mp 179–180° C	172
					Hydrazide: mp 249–250° C	172
	CH_3		COOH, CH_3	153–154		40
					Ethyl ester: mp 43° C	40
	CH_3		COOH, C_2H_5	137		40, 41
					Ethyl ester: mp 73° C	40, 41
	CH_3		COOH, *i*-C_4H_9	122–124		40
					Ethyl ester: mp 80–81° C	40
C_6H_5	C_6H_5		COOH, C_2H_5	134		173, 174
	COOH	COOH			Diethyl ester: mp 155–156° C	44, 45
			CN	183–185		140
	CH_3		CN	97–100		211

TABLE X. Miscellaneous Compounds

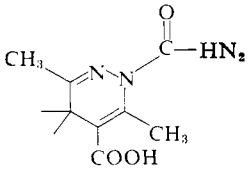
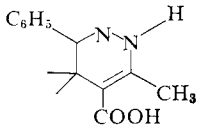
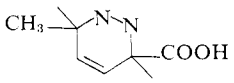
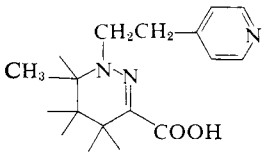
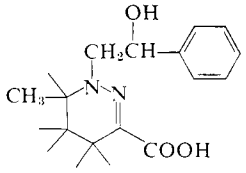
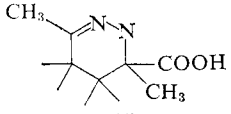
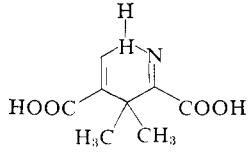
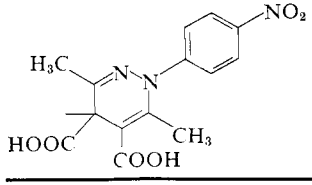
Structure	MP (°C)	Derivatives	References
	230		120
		Ethyl ester: mp 90–91° C 2-Phenyl: mp 185–186° C Ethyl ester: mp 114–116° C 2-Carbamoyl: mp 254° C *N*-Phenyl: mp 192° C	117–119 120 120 116, 120 120
		Methyl ester: bp 95–100° C/0.5 mm Ethyl ester: bp 85° C/0.5 mm Benzyl ester: bp 135–150° C/0.01 mm	 110 110 110
		Ethyl ester: bp 140–160° C/0.01 mm	 218
		Ethyl ester: 148–152° C/0.01 mm	218
	159–160		103
		Dimethyl ester: mp 122° C	212
	122–123		187

TABLE X (*continued*)

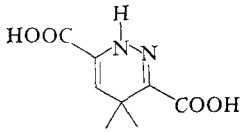
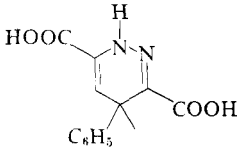
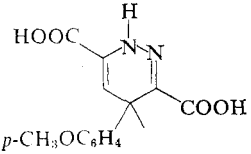
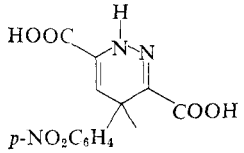
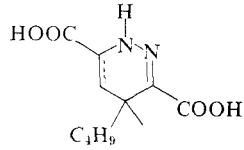
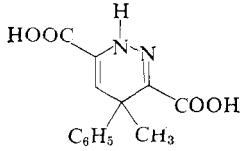
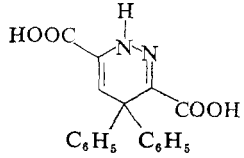
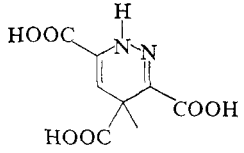
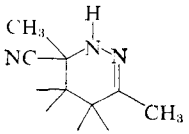
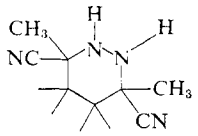
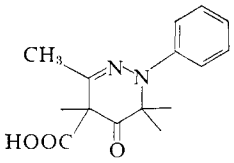
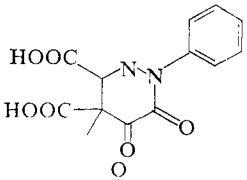
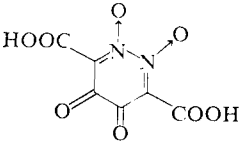
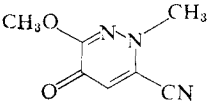
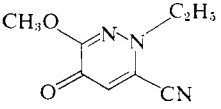
Structure	MP (°C)	Derivatives	References
	202		189
		Dimethyl ester: mp 114° C	59, 189
		Diethyl ester: mp 148–149° C	8, 189
		Dimethyl ester: mp 106–107° C	8
		Dimethyl ester: mp 112–114° C	8
		Dimethyl ester: mp 55–56° C	8
		Dimethyl ester: mp 140–142° C	8
		Dimethyl ester: mp 163–164° C	8
		Trimethyl ester: mp 109–111° C	8

TABLE X (*continued*)

Structure	MP (°C)	Derivatives	References
	57–59		70, 103, 194
		Hydrochloride: mp 151° C	70
	103–105		70, 71, 102, 103
	203 (dec)		181
		Diamide: mp 237–238° C	192
		Diethyl ester: mp 70° C	193
	198–199		209
	164–165		209

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CHAPTER VI

Aminopyridazines

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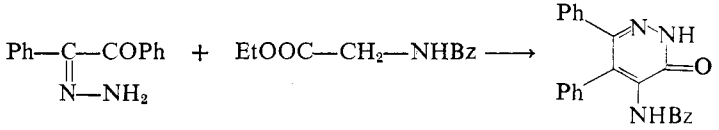
The study of aminopyridazines has been developed as a result of medicinal studies. Most primary aminopyridazines have been prepared as intermediates for sulfonamides; many secondary and tertiary aminopyridazines and aminopyridazinones were prepared in a search for compounds possessing analgesic, antipyretic, sedative, or antihistaminic activity.

I. Nuclear

A. Preparation

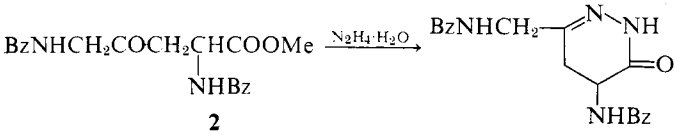
1. *From Nonpyridazine Starting Materials*

The first instance of the preparation of an aminopyridazine from nonpyridazine starting material was the condensation of benzilmonohydrazone with ethyl hippurate (1) (**1**). The condensation was effected by warming the reactants at 90° C in an ethanolic solution of sodium ethoxide.



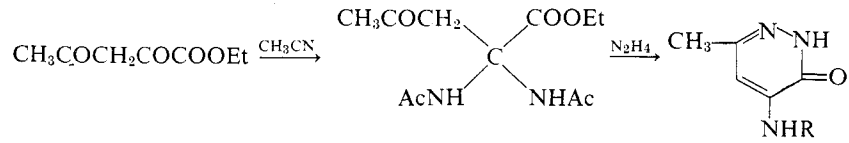
1

Amino ketones or amino keto esters also can serve as sources of nonpyridazine starting materials for aminopyridazines, even though they have not been thoroughly exploited. Methyl 2,5-bis(benzoylamino)-4-oxopentenoate (**2**) condenses with hydrazine hydrate to cyclize to 6-benzoylaminomethyl-4-benzoylamino-2,3,4,5-tetrahydro-3(2*H*)pyridazinone (**3**) in 97% yield (2). 1-Benzylamino-1,2-dibenzoylethene [BzCH=C(NHCH$_2$Ph)Bz] with hydrazine gave 4-benzylamino-3,6-diphenylpyridazine (360).



2 **3**

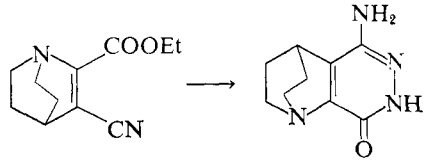
Druey (3) reported the formation of 4-amino-6-methyl-3(2*H*)pyridazinone (**4**) or its *N*-acetate from the addition product of acetopyruvic acid and acetonitrile followed by the action of hydrazine, however, no experimental details were reported.



R = H, Ac

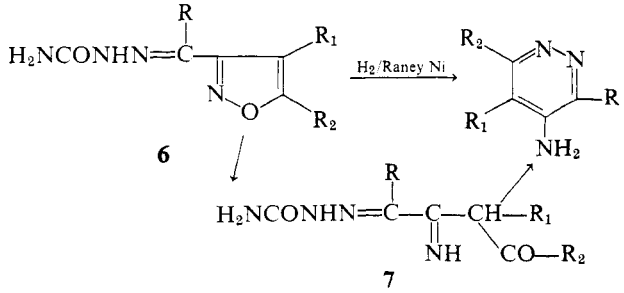
4

The reaction of ethyl 3-cyano-2,3-dihydroquinuclidine-2-carboxylate with hydrazine hydrate affords aminopyridazinone (4) (**5**).



5

The semicarbazones (**6**) of 3-acylisoxazoles were transformed into 4-aminopyridazine derivatives when they were hydrogenated catalytically in the presence of Raney nickel (5). The intermediate open-chain iminotrione semicarbazones (**7**) were isolated.



6 **7**

1-Diethylaminoprop-1-yne gave, by a Diels–Alder type of reaction with 3,6-disubstituted tetrazines or 3-substituted triazines, 3,6-disubstituted 4-dimethylamino-5-methylpyridazines (65–73%) (361) or 3-substituted 4-methyl-5-dimethylaminopyridazines (362), respectively. The intermediate Diels–Alder adduct spontaneously lost nitrogen in the former reaction and hydrogen cyanide in the latter to yield the aminopyridazines.

2. *The Displacement of Halogen Atoms by Amino Groups*

The majority of aminopyridazine derivatives has been synthesized by this method because of the accessibility of halogenated pyridazines and the ease with which the halogen atom is replaced.

3-Methyl-6-chloro-, 3,6-dichloro-, and 3,4,5- and 3,4,6-trichloropyridazines are among the most conveniently prepared halopyridazines and the most common intermediates for various aminopyridazines. A large number of 2-substituted amino-3(2*H*)pyridazinones was synthesized by the Ciba group in earlier days.

a. Preparation of Primary Aminopyridazines (Ammonolysis of Halopyridazines). The preparations of aminopyridazines and aminopyridazinones by ammonolysis reactions are listed in Tables I and II. As indicated in the tables, the reaction proceeded smoothly under mild conditions in most instances.

Ammonia usually can be used in the form of aqueous ammonia, methanolic or ethanolic ammonia, or liquid ammonia in the reaction with equal facility. However, in some instances one or the other reagent is to be preferred. For example, better results were obtained by using liquid ammonia rather than methanolic ammonia in the ammonolysis of 3-bromo-6-methoxypyridazine (6). 3-Amino-6-pyridazinecarboxylic acid has been prepared from the corresponding 6-chloro acid by the action of liquid ammonia in 40% yield, but the use of methanolic ammonia resulted in hydrolytic cleavage of the chlorine atom (7). Ethanolic ammonia was favored in the ammonolysis of 3,6-dichloro-4,5-tetramethylenepyridazine, where aqueous ammonia led to decomposition under vigorous conditions or to the recovery of the starting material under milder conditions (9).

It has been reported (9) that 3-chloropyridazine gave 3-aminopyridazine in 65–70% yield by treatment with liquid ammonia, however, when aqueous ammonia or ethanolic ammonia was employed in the same transformation, no reaction occurred below 130° C, and hydrolysis or resinification occurred at higher temperatures. However, two other groups reported that the ammonolysis of 3-chloropyridazine proceeded smoothly and afforded 3-aminopyridazine in fair yields by the action of methanolic (10) or ethanolic (11) ammonia. 3,6-Dichloropyridazine produced only a 7% yield of 3-amino-6-chloropyridazine on heating with liquid ammonia, whereas the same product was obtained in 70% yield by means of ethanolic ammonia (12). 4-Amino-3,6-dichloropyridazine was initially prepared by the treatment of 3,4,6-trichloropyridazine with ethanolic ammonia (13) which was more conveniently replaced by aqueous ammonia (14–17). Dudley (18) reported the preparation of ethyl 3-amino-5,6-diphenyl-4-pyridazinecarboxylate from the 3-chloro compound by the action of ethanolic ammonia. The action of liquid ammonia on the same starting material at a temperature of 125° or 190° C was also investigated and proved impractical (18). It is surprising that the ethoxycarbonyl group remained intact under the reaction conditions in view of the fact that the ethoxycarbonyl groups in other halo ester derivatives were more susceptible than the halogen atoms. The same investigator ascribes this to steric hindrance at the 4-position.

It is noteworthy that the solvent effects the ratio of the products in the ammonolysis of 4-methyl-3,6-dichloropyridazine (19). With ethanolic ammonia 3-chloro-4-methyl-6-aminopyridazine was produced predominantly

in 80% yield accompanied by a 10–15% yield of 3-amino-4-methyl-6-chloropyridazine, while with aqueous ammonia the yield of the former was decreased to 50% and that of the latter increased to 40–45%. In another article (20) the same ammonolysis reaction involving methanolic ammonia was reported and the same 3-amino and 6-amino compounds were separated in a ratio of 1:10 after the acetylation of the reaction mixture followed by hydrolysis.

The difference in reactivity between chloro and bromo substituents is not distinct in many instances. Marked differences were typically observed in the displacement of relatively unreactive halopyridazines. 3-Amino-6-methoxypyridazine was obtained from 3-bromo-6-methoxypyridazine, although in poor yield, but no product was obtained from 3-chloro-6-methoxypyridazine (6). When 2-phenyl-6-bromo-3(2*H*)pyridazinone was heated with aqueous ammonia in the presence of a copper catalyst, 2-phenyl-6-amino-3(2*H*)pyridazinone was obtained in 72% yield (21, 22). 2-Phenyl-6-chloro-3(2*H*)pyridazinone gave the same product in 13% yield under the same reaction conditions (21). The reactivity of the halogen atom increases as electron-attracting groups are introduced. Thus the reactivity of the halogen atoms in monochloro-, dichloro-, and trichloropyridazine derivatives increases in this order.

In the ammonolysis of polyhalopyridazines, the attempt to replace the second halogen atom proceeds with difficulty. There are not many examples available of the successful preparation of diaminopyridazine derivatives by direct ammonolysis. 2-Phenyl-5,6-dichloro-3(2*H*)pyridazinone produced the 5,6-diamino compound in 73% yield (23), and 3-amino-6-chloropyridazine gave 3,6-diaminopyridazine in poor yield on heating with aqueous ammonia, a copper catalyst being used in both instances. More 3,4- and 4,5-diaminopyridazines, which were expected to be key intermediates in the syntheses of purine isomers, were prepared after alternative preparative methods were devised (24, 25).

In both pyridazines and pyridazinones, the 4- and 5-halogen atoms are more reactive than the 3- and 6-halogen atoms as illustrated by the preparation of 4-amino-3,6-dichloropyridazine from the corresponding trichloropyridazine (13–17), 4-amino-3,5-dichloro- and 5-amino-3,4-dichloropyridazine from 3,4,5-trichloropyridazine (26), 4-amino-3,5,6-trifluoropyridazine from tetrafluoropyridazine (363, 364), 2-phenyl-4-amino-6-chloro-3(2*H*)-pyridazinone from the 4,6-dichloro derivative (21), 2-phenyl-5-amino-6-chloro-3(2*H*)pyridazinone from the 5,6-dichloro derivative (27), and 2-methyl-4-amino-6-chloro- and 2-methyl-5-amino-6-chloro-3(2*H*)pyridazinone from the corresponding 4,6- and 5,6-dichloro derivatives, respectively (28). The ammonolysis of 2-substituted-4,5-dihalopyridazinones gave the

5-amino derivatives (28–34) or a mixture of the 4- and 5-amino derivatives, the second product predominating when the 6-position was not substituted (28, 31, 32, 35, 36). Patents concerned with the separation technique of 2-phenyl-4-chloro-5-amino-3(2*H*)pyridazinone from the accompanying 4-amino isomer have been granted because of effectiveness of the former as a herbicide (37, 38). 2,6-Dimethyl-4,5-dichloro-3(2*H*)pyridazinone yields both of the possible 4- and 5-amino derivatives in almost equal quantities (28). Only 4-chloro-5-amino-3(2*H*)pyridazinone has been obtained by the ammonolysis of 4,5-dichloro- and 4-chloro-5-bromo-3(2*H*)pyridazinones (27, 39).

b. Displacement of Halogen Atoms by Amino Groups by Reagents Other Than Ammonia. Reagents other than ammonia have also been employed to effect the displacement of halogen atoms with amino groups, although the examples are few. 3-Chloro-4-phenyl-6-methylpyridazine was heated with urea at 190° C for 40 hr to give the 3-amino compound in 77% yield (40). The same starting material gave the 3-phenoxy derivative instead of the desired 3-amino derivative when gaseous ammonia was passed through the phenolic solution at 180° C (40). 3-Amino-4-X-nitrophenyl-6-chloropyridazine was likewise prepared in 48% yield. 3-Amino-6-chloropyridazine was obtained from 3,6-dichloropyridazine under mild conditions (41). Neither the chlorine atom nor the phenoxy substituent was replaced when 4- or 5-methyl-3-chloro-6-phenoxypyridazine was heated with ammonium acetate at 195° C for 8 hr. Only the hydrolysis product 4- or 5-methyl-6-chloro-3(2*H*)pyridazinone resulted (8).

3-Chloro-5-aminopyridazine was erroneously reported to have been produced from 3,6-dichloropyridazines by treatment with sodium amide in boiling xylene (356). The product was 6-chloro-3(2*H*)pyridazinone which was formed during the isolation process (42).

The action of potassium rhodanide in refluxing ethanol upon 4-bromo-3,5,6-triphenylpyridazine yielded the pyridazinylthiourethan, which in turn was hydrolyzed to 4-amino-3,5,6-triphenylpyridazine by boiling in ethanol containing dilute aqueous sulfuric acid (43).

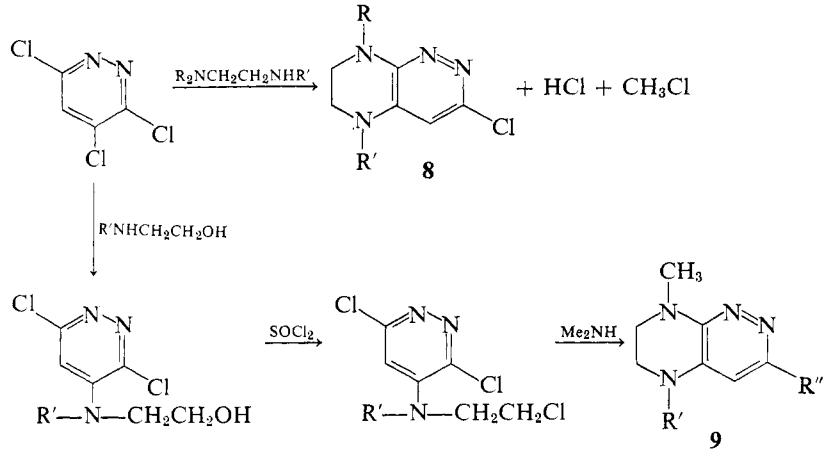
c. Preparation of Secondary and Tertiary Aminopyridazines. The reaction of amines and halopyridazines is the most common method for the preparation of *sec*- and *tert*-aminopyridazines and pyridazinones. The products are obtained in favorable yields under suitable conditions. Excess amines act as hydrogen halide acceptors. Sodium amide, sodium or potassium carbonate, triethylamine, and pyridine have been employed for the same purpose. These reactions are summarized in Tables III and IV.

Di- and trihalopyridazine derivatives give primarily monosubstituted derivatives. Under stronger conditions the second halogen atom is replaced without difficulty (23, 44–51, 365, 366). The replacement occurs

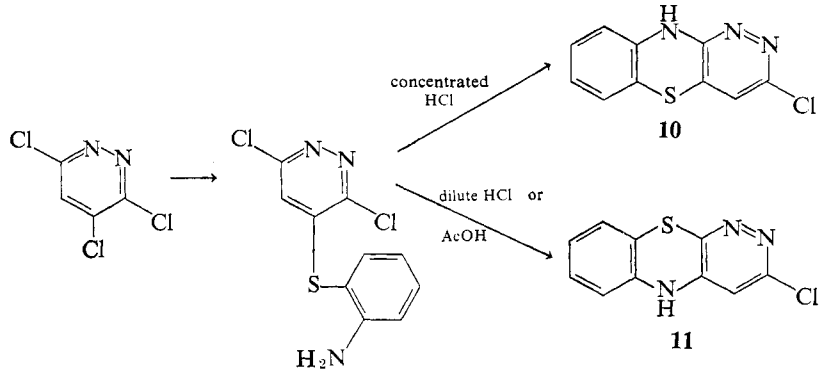
more easily when the amino residue introduced first is an arylamino group than when it is an aliphatic amino substituent. This is exemplified by the reaction carried out by Kumagai (47). When 3,6-dichloropyridazine was allowed to react with aromatic amines in boiling ethanol, benzene, or toluene, both mono- and disubstituted pyridazine derivatives were isolated from the product. With aliphatic amines no disubstituted compounds were produced under similar reaction conditions (47). Starting with 3-anilino-6-chloropyridazine, 3-anilinopyridazine derivatives substituted in the 6-position with a variety of amines were obtained by treatment with aromatic and aliphatic amines. However, no disubstituted derivatives except for 3-anilino-6-benzylaminopyridazine were obtained from the reaction of 3-benzylamino-6-chloropyridazine with various amines (47). Kumagai (47) has explained the different reactivities of the chlorine atoms on the basis of the higher electron-donating capacity of aliphatic amino groups compared with aromatic amino groups at the 3-position after monosubstitution has taken place.

The reactivity of halogen atoms in halopyridazine *N*-oxides was investigated in detail by Itai and Sako. Based on the kinetic studies of the displacement of halogen atoms in halopyridazine *N*-oxides with piperidine or sodium ethoxide, it was concluded that the order of position reactivity in halopyridazine 1-oxides is $5 > 3 > 6 > 4$ (52). The chlorine atom at the 3-position is more reactive than a chlorine atom at the 6-position toward nucleophilic substitution as shown in the reactions of 3,6-dichloropyridazine 1-oxide with sodium alkoxides, ethylamine, or piperidine (50). A comparison of the reactivity of halogen atoms of 3- or 4-halopyridazine with those of their *N*-oxides has also been made by the same investigator in reactions with piperidine or ethylamine (50, 53, 54). 3-Substituted 6-chloropyridazine 1-oxides are more reactive than 3-substituted 6-chloropyridazines (50). Both 3- and 6-chloropyridazine 1-oxides are also more reactive than their parent 3-chloropyridazines (54). 4-Chloro-3,6-dimethylpyridazine is more reactive than the 1-oxide and less reactive than the 2-oxide (53).

Examples of intramolecular diamination of 3,4,5-trichloropyridazine are syntheses of piperazopyridazines. When 3,4,6-trichloropyridazine is allowed to react with *N*,*N*′-dimethyl-*N*′-substituted ethylenediamines in ethanol under reflux, fair to good yields of 8-methyl-5-substituted 3-chloro-5,6,7,8-tetrahydropyrazino[2,3-*c*]pyridazines (**8**) are formed with the loss of 1 mole of hydrogen chloride and 1 mole of methyl chloride (55, 56). The 8-ethyl derivatives are similarly produced in the presence of triethylamine (55). The same type of compounds, 8-methyl-5-benzyl-3-dimethylmaino- and 8-methyl-5-(2-dimethylaminoethyl)-3-chloro-5,6,7,8-tetrahydropyrazino-[2,3-*c*]pyridazine (**9**), are prepared from 4-(*N*-benzyl-*N*-β-chloroethylamino)- and 4-*N*,*N*-bis(β-chloroethylamino)-3,6-dichloropyridazine, respectively, by the reaction with dimethylamine (55).



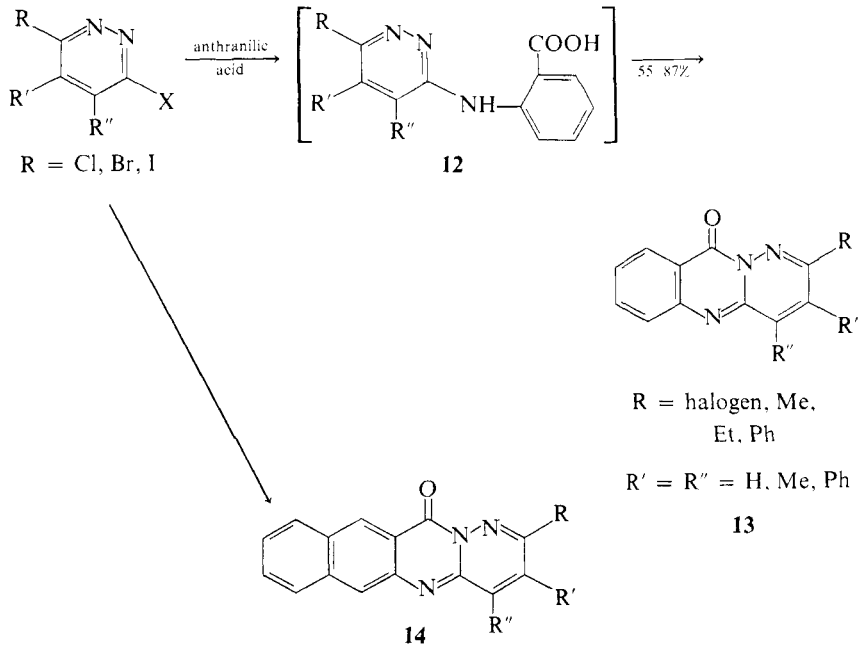
The reaction of polyhalopyridazines with aromatic amines substituted with a hydroxy or mercapto group at the ortho position often proceeds further, leading to diazaphenoxazines or diazaphenothiazines (**10** and **11**), respectively. The reaction of 3,4,6-trichloropyridazine with *o*-aminothiophenol in the presence of methanolic potassium hydroxide gives the 4-(2-aminophenylthio) derivative (56, 57) which cyclizes to 1,2-diaza-3-chlorophenothiazine (**10**) by the action of concentrated hydrochloric acid (56, 57)



or on heating at 140–150° C (57). The same diazaphenothiazine has also been obtained by the treatment of 4-(2-acetylaminophenylthio)-3,6-dichloropyridazine with sodium amide (56). When the 4-(2-aminophenylthio) compound is treated with dilute hydrochloric acid or acetic acid, rearrangement and cyclization occur, affording 2-chloro-3,4-diazaphenothiazine (**11**)

as the main product and the nonrearranged 1,2-diazaphenothiazine as a by-product (57, 58). In a similar fashion 4-chloro-1,2-diaza- and 1-chloro-2,3-diazaphenothiazine were obtained in a ratio of 3:1 from 3,4,5-trichloropyridazine (59). Likewise, 1-hydroxy- (59) and 4-hydroxy-2,3-diazaphenothiazine (60) were obtained from 4,5-dihalo-3(2*H*)pyridazinone, and 1,2-dihydro-1-oxo-2-methyl-2,3-diazaphenothiazine was obtained from 5-bromo-4-chloro-2-methyl-3(2*H*)pyridazinone (60). 2-Methylaminothiophenol and 3,4,5-trichloropyridazine lead to 4-chloro-10-methyl-1,2-diazaphenothiazine. With 2 equivalents of reagent, 3,4,5-trichloropyridazine gave 4-(2-aminophenylthio)-1,2-diazaphenothiazine and its 10-methyl derivatives (59).

The ring nitrogen is involved in cyclization when 3-halopyridazines are allowed to react with anthranilic acid or its ester in aqueous ethanol (61, 62), or by fusion (61–63); pyridazino[3,2-*b*]quinazolin-10-ones (**13**) are formed



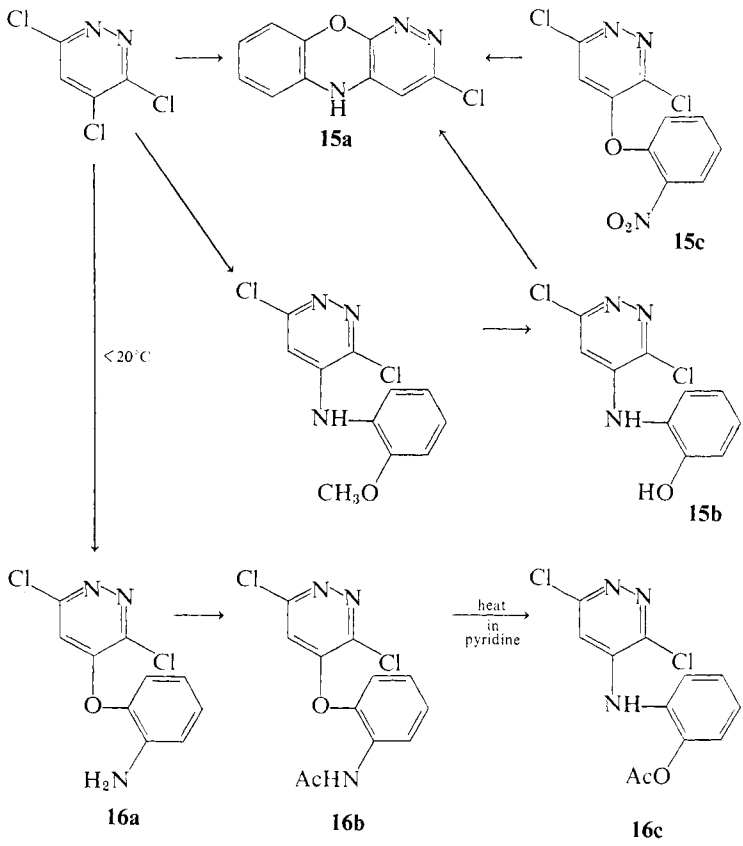
(62). A small amount of hydrochloric acid catalyzes the reaction (61). Beyer and Völcker (61, 62) prepared a series of substituted pyridazino[3,2-*b*]-quinazolin-10-ones (**13**) by this method in fair to good yields. *N*-(3-Pyridazinyl)anthranilic acids (**12**) are assumed to be intermediate, however, they were not isolated. The barium salts of the acids (**12**) were obtained when the pyridazino[3,2-*b*]quinazolinones were heated with aqueous barium hydroxide

solution (62). These salts of *N*-(3-pyridazinyl)anthranilic acids are immediately converted to the cyclized products upon acidification. 3-Amino-2-naphthoic acid instead of anthranilic acid provides pyridazino[3,2-*b*]benzo[*g*]quinazolin-12-ones (64) (**14**). Among the pyridazino[3,2-*b*]quinazolinones prepared by Beyer and Völcker (61, 62), the product from 4-methyl-3,6-dichloropyridazine was later shown to be 2-chloro-3-methyl-10*H*-pyridazino[3,2-*b*]quinazolin-10-one by Yanai and Kinoshita (63). The latter investigators carried out the reaction by the fusion method and isolated the isomeric 2-chloro-4-methyl compound as a minor product. Kuraishi and Castle (65) prepared 3-amino-4-chloro-10*H*-pyridazino[3,2-*b*]quinazolin-10-one by refluxing 5-amino-3,4-dichloropyridazine and anthranilic acid in dilute aqueous hydrochloric acid solution.

2-Chloro-3,4-diazaphenoxazine (**15a**) has been prepared by the condensation of *o*-amino- or *o*-acetaminophenol and 3,4,6-trichloropyridazine in the presence of triethylamine in ethanol (66, 67). The same product is also obtained by the action of alkali on 4-(2′-hydroxyphenylamino)-3,6-dichloropyridazine (**15b**) and by the catalytic hydrogenation of 4-(2′-nitrophenoxy)-3,6-dichloropyridazine (**15c**) over Raney nickel at room temperature. The intermediates in these reactions could not be isolated. However, the condensation of *o*-aminophenol with 3,4,6-trichloropyridazine in the presence of ethanolic sodium ethoxide at a temperature below 20° C yielded 4-(2′-aminophenoxy)-3,6-dichloropyridazine (**16a**). The *N*-acetate (**16b**), which was derived from **16a** on acetylation, was shown to rearrange on heating in pyridine to 4-(2′-acetoxyphenylamino)-3,6-dichloropyridazine (66, 67) (**16c**). These transformations suggest the reaction sequence in the formation of 2-chloro-3,4-diazaphenoxazine mentioned above (58). 9-Substituted 2-chloro-3,4-diazaphenoxazines were obtained in a similar fashion from 3,4,6-trichloropyridazine and *N*-substituted *o*-aminophenol (367).

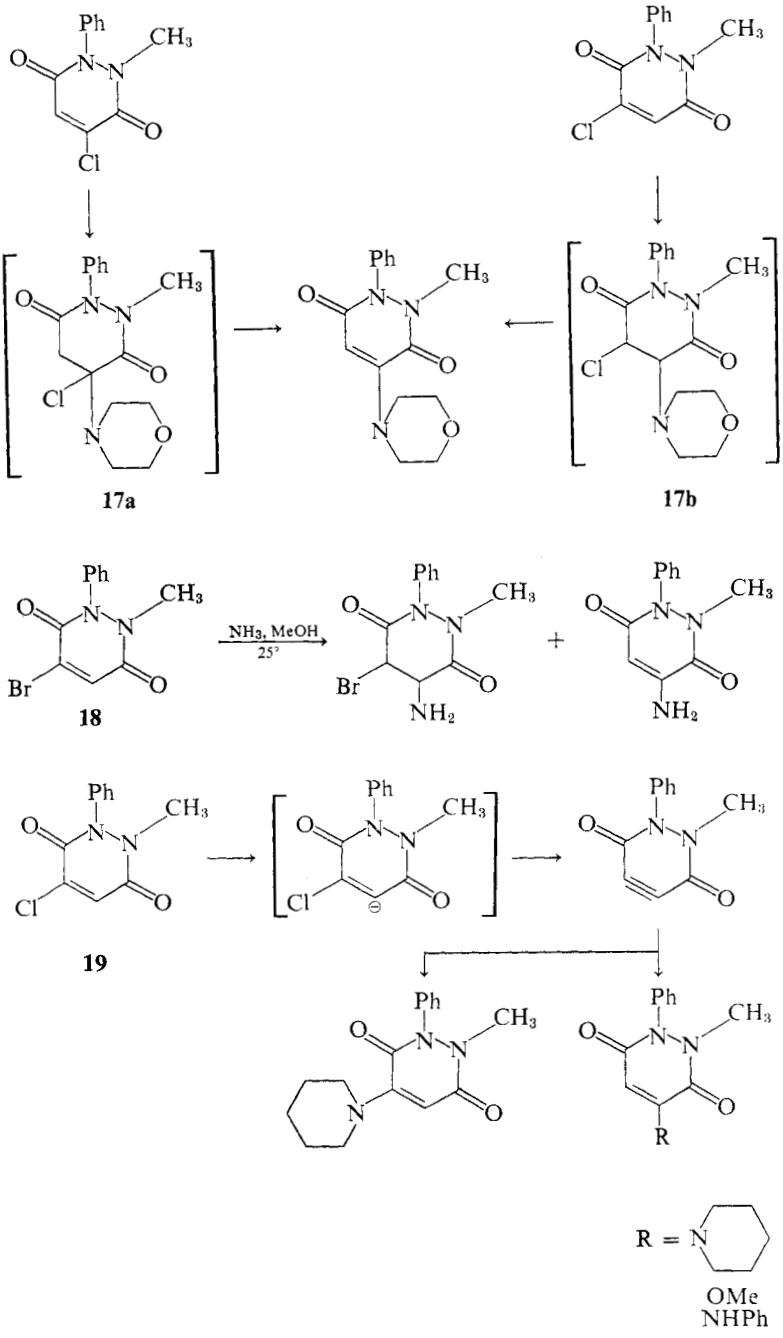
An interesting substitution reaction has been reported by Druey, Meier, and Staehelin (68–70). When 4-chloro-1-phenyl-2-methyl-3,6-dioxo-1,2,3,6-tetrahydropyridazine is treated with at least 2 moles of morpholine, 1-phenyl-2-methyl-4-morpholino-3,6-dioxo-1,2,3,6-tetrahydropyridazine is produced in a quantitative yield (68–70). The same product is also obtained from the isomeric 5-chloro and 5-bromo derivatives and also from the 4,5-dibromo-4,5-dihydro derivative by treatment with morpholine under mild conditions (68–70).

A large number of 1-aryl-2-alkyl-4-substituted 3,6-dioxo-1,2,3,6-tetrahydropyridazines have been prepared by a similar reaction with a variety of secondary and tertiary aliphatic amines (68–70). Based on the fact that in any of these reactions only 4-substituted products were obtained irrespective of the position of the halogen atom in the starting materials, an addition elimination mechanism was proposed for these reactions as shown in **17** (68).



Although the proposed intermediate **17a** or **17b** has not been isolated in the foregoing reactions with secondary and tertiary amines, the intermediate addition compound separated out in the reaction of 1-phenyl-2-methyl-5-bromo-3,6-dioxo-1,2,3,6-tetrahydropyridazine (**18**) with methanolic ammonia at 25° C (68).

Kauffmann and Risberg (71) later repeated Druey's work. In their laboratory both 4- and 5-substituted products were isolated in the reaction between 5-chlorodioxotetrahydropyridazine **(19)** and piperidine, the former predominating in a ratio of 25 : 1. They attributed the reaction to intermediate hetaryne formation as opposed to an addition elimination mechanism based upon the fact that the chloro compound, which is inert to methanol or aniline at 20° C reacts with these reagents in the presence of piperidine at 20° C to give the methoxy- or anilino-substituted product in addition to the piperidino derivatives, although the structural proof and experimental details have not yet been published.


Ph
CH3
O
N
Cl
17a
17b
18
NH3, MeOH
25°
Br
NH2
19
R = N
OMe
NHPh

3. *Preparation of Aminopyridazines by Nucleophilic Displacement of Groups Other Than Halogen Atoms*

In addition to halogen atoms, alkoxy, thio, alkylthio, alkylsulfonyl, hydroxy, and toluenesulfonyl groups can be replaced in nucleophilic substitution reactions in the pyridazine ring. However, halogen atoms are usually more readily replaced by ammonia or an amine than the above-mentioned substituents in the pyridazine ring. The preferential displacement of halogen atoms is observed in several instances. For example: the reaction of 3-bromo-6-methoxypyridazine with liquid ammonia or methanolic ammonia giving 3-amino-6-methoxypyridazine (6); the reaction of 3-chloro-6-methoxypyridazine 1-oxide with piperidine to yield 3-piperidino-6-methoxypyridazine 1-oxide; the reaction of 3-chloro-6-ethoxypyridazine 1-oxide with ethylamine to give 3-ethylamino-6-ethoxypyridazine 1-oxide (50); the reaction of 3-chloro-6-ethoxypyridazine with ethylamine to give 3-ethylamino-6-ethoxypyridazine (50), and the reaction of 2-phenyl-4-chloro-6-methoxy-3(2*H*)pyridazinone with piperazine to give 2-phenyl-4-piperazino-6-methoxy-3(2*H*)pyridazinone (72). 3-Chloro-6-methylthiopyridazine reacts with aniline (73) at boiling temperatures or with *N*-(γ-benzoylpropyl)piperazine (74) at 140–150° C in the presence of a catalytic amount of potassium iodide to give the 3-substituted derivatives in both cases, while 3-chloro-6-pyridazinethiol gives rise to 3-anilino-6-pyridazinethiol in poor yield by the action of aniline in boiling ethanol (73). The attempt to synthesize 3-aziridinyl-6-chloropyridazine from 3-chloro-6-methylsulfonylpyridazine by Nyberg and Cheng (75) failed to give the desired product, and the resulting product was found to be 3-aziridinyl-6-methylsulfonylpyridazine.

Similar treatment of the 3-chloro-6-methylfulfonylpyridazine with aliphatic and aromatic amines resulted in the formation of 3-dimethylamino-, 3-butylamino-, 3-cyclohexylamino-, and 3-anilino-6-methylsulfonylpyridazines (75). That these reactions proceed under moderate conditions and in favorable yields shows the activating effect of the methylsulfonyl group. Morren (76) obtained 3-amino-6-*p*-toluenesulfonylpyridazine by ammonolysis of the 3-chloro-6-*p*-toluenesulfonyl compound with aqueous ammonia in dimethylformamide at 70° C.

Only when an alkoxy group is located at a more active position than a halogen atom is it replaced preferentially by an amino group. Thus, by treatment with aqueous ammonia at 100° C, 3-chloro-4- and 3-chloro-5-ethoxypyridazines have been converted into the corresponding 3-chloro-4- and -5-aminopyridazines, respectively (77). 2-Phenyl-4-dimethylamino-6-chloro-3(2*H*)pyridazinone has similarly been obtained from 2-phenyl-4-methoxy-6-chloro-3(2*H*)pyridazinone by heating with dimethylamine in

methanol in the presence of sodium methoxide, although the yield was poor (78). In contrast, 2-phenyl-4-methylthio-6-chloro-3(2*H*)pyridazinone gave 2-phenyl-4-methylthio-6-dimethylamino-3(2*H*)pyridazinone by the reaction with dimethylamine (367). The reaction of 4-methoxy-3,6-dichloropyridazine with ethyleneimine was claimed in a patent (79) to produce 3-aziridinyl-4- or -5-methoxy-6-chloropyridazine without proof of the position of the substituents. However, contradictory results were later reported by the same investigators in another patent in which a description of the formation of 4-[β-(1-aziridinyl)ethylamino]-3,6-dichloropyridazine from 4-ethoxy-3,6-dichloropyridazine under the same reaction conditions was reported (80).

The replacement of alkoxy groups with amino functions is summarized in Table V. Sometimes this replacement is accompanied by cleavage of the alkoxy group. This side reaction has been observed in the conversion of 2-phenyl-4,5-diethoxy-3(2*H*)pyridazinone into the 4-dimethylamino derivative, which is accompanied by the simultaneous formation of an approximately 5% yield of 2-phenyl-4-hydroxy-6-ethoxy-3(2*H*)pyridazinone (81). The attempted ammonolysis of 3-methoxy-4-methyl-6-aminopyridazine (82) with aqueous ammonia at 120–140° C and of 3-phenoxy-4- or -5-methyl-6-chloropyridazine (8) with ammonium acetate at 195° C failed to give the amino derivatives and resulted in 4-methyl-6-amino-3(2*H*)pyridazinone and 4- or 5-methyl-6-chloro-3(2*H*)pyridazinone, respectively. 3-Chloro-6-methoxypyridazine undergoes cleavage on attempted ammonolysis with liquid or methanolic ammonia to yield 6-chloro-3(2*H*)pyridazinone, whereas 6-bromo-3-methoxypyridazine yields the aminomethoxypyridazine as discussed in Section I.A.2.a

When 2-phenyl-4-methoxy-5-nitro-3(2*H*)pyridazinone was hydrogenated catalytically over Raney nickel in the presence of aqueous ammonia, the methoxy group activated by an adjacent nitro group was replaced with an amino group. 2-Phenyl-4,5-diamino-3(2*H*)pyridazinone was thus obtained (83).

The reactivity of an alkoxy group at the 6-position is greater than the reactivity of an alkoxy group at the 3-position of a pyridazine 1-oxide. This has been demonstrated by the reaction between 6-ethoxy- or 3-ethoxypyridazine 1-oxide and ammonia. The former gave 6-aminopyridazine 1-oxide in 12% yield on heating with ammonia in aqueous ethanol at 90° C for 2 hr, but no reaction occurred in the case of 3-ethoxypyridazine 1-oxide (84).

Although only the starting materials were recovered when 3,6-pyridazinedithiol or 3,6-dimethylthiopyridazine was treated with refluxing aniline (73), the mercapto and the ethylthio groups in 6-methyl-3-pyridazinethiol and 3-methyl-6-ethylthiopyridazine were replaced by an amino group, giving 3-amino-6-methylpyridazine when treated with aqueous or methanolic

ammonia (85). However, the low yields make these replacement reactions of little practical value. Treatment of 4,5-dibenzylthio-3(2*H*)pyridazinone with ethanolic ammonia at 210° C for 30 hr yielded 5-amino-4-benzylthio-3(2*H*)-pyridazinone. However, the yield was not described (368).

3-Methylsulfonylpyridazine gives 3-aminopyridazine and 3(2*H*)pyridazinone in 11 and 60% yields, respectively, when it was heated with aqueous ammonia. The yield of 3-aminopyridazine was increased to 40% by the addition of ammonium chloride to the reaction mixture (86). The reactions of 3- and 4-methylsulfonylpyridazines with methylamine or *n*-propylamine similarly gave the corresponding 3- and 4-methylamino- or 3- and 4-*n*-propylaminopyridazines in good yields (86). Similar reactions of 3- and 4-methylsulfinylpyridazines with *n*-butylamine produced the corresponding *n*-butylaminopyridazines in 67 and 70% yields, respectively (369). The reaction of 4-methylsulfinylpyridazine was effected at a lower temperature.

One of the toluenesulfonyl groups of 3,6-bis(toluenesulfonyl)pyridazine can be replaced by the action of ethanolic ammonia at 150–170° C for 5 hr. 3-Amino-6-*p*-toluenesulfonylpyridazine was obtained in a satisfactory yield (76).

Dipotassium 2-methyl-3(2*H*)pyridazinone-4,5-disulfonate treated with phosphorus pentachloride and phosphorus oxychloride followed by liquid ammonia gave 2-methyl-5-amino-3(2*H*)pyridazinone-4-sulfonamide in 22% yield (370).

It has been shown that 6-methyl-3(2*H*)pyridazinone undergoes the Bucherer reaction to afford 3-amino-6-methylpyridazine (85). Because of the poor yield the reaction was never used as a preparative method. The hydroxy groups activated by the adjacent nitro group of 2,6-disubstituted-4-hydroxy-5-nitro-3(2*H*)pyridazinone are readily replaced by an amino group when the hydroxy compounds are heated with aqueous ammonia at 100° C (25, 87). 2,6-Disubstituted-4-amino-5-nitro-3(2*H*)pyridazinones are obtained by this method usually in good yields. 4-Amino-5-nitro-3(2*H*)pyridazinone has also been prepared in good yield at an elevated temperature (25, 87). These 4-amino-5-nitropyridazinones serve as starting materials for diaminopyridazinones as described in Section I.A.5.b

The replacement of the *N*-methyl-*N*-nitroamino group in 3-(*N*-methyl-*N*-nitramino)pyridazine and its 6-methyl derivative has been successful with benzylamine. The products were 3-benzylamino- and 3-benzylamino-6-methylpyridazine as reported by Dixon and Wiggins (88). The *N*-methyl-*N*-nitramino derivatives were prepared by methylation of the potassium salt of the nitramino compound. The amino group of 3-amino-4-hydroxy-6-methylpyridazine was replaced by a benzylamino or a methylamino group by the reaction with hydrochlorides of these amines to give 3-benzylamino- or 3-methylamino-4-hydroxy-6-methylpyridazine in 15–20% yield (371). When

1-methyl-3,6-bisdimethylaminopyridazinium iodide and its 5-methyl derivative were allowed to react with liquid dimethylamine, the 6-methylaminopyridazinium salts were formed (372).

4. *Hofmann and Curtius Reactions*

Although there are not many reports available, the Hofmann and Curtius reactions are successful methods for the syntheses of aminopyridazine derivatives.

5-Phenyl- and 5-(3-nitro-4-methoxyphenyl)-4-aminopyridazines have been prepared from the corresponding carboxamides by the Hofmann reaction in 80 and 50% yields, respectively (89). An attempt to obtain these amines directly from the carboxylic acid by using hydroxylamine hydrochloride in polyphosphoric acid failed (89). Pyridazinonecarboxamides also have been converted into the corresponding amines in good yield. These include 1-phenyl-6-methyl-1,4-dihydro-4-oxo-3-pyridazinecarboxamide (90), 6-chloro-2,3-dihydro-3-oxo-4-pyridazinecarboxamide (39), 6-methyl-2,3-dihydro-3-oxo-4-pyridazinecarboxamide (14, 91), and 6-methoxy-2,3-dihydro-3-oxo-5-pyridazinecarboxamide (92). 3,4-Pyridazinedicarboxamide cyclizes on treatment with potassium hypobromite to yield pyrimido[4,5-*d*]pyridazine-5,7-diol (373). 6-Methyl-3,4-pyridazinedicarboxamide, however, gave 3-methylpyrimido[4,5-*d*]pyridazine and isomeric 3-methylpyrimido[5,4-*c*]-pyridazine-6,8-diol (93, 373).

The Curtius reaction of 1-phenyl-6-methyl-4(1*H*)pyridazinone-3-carbohydrazide followed by treatment with ethanol gives the corresponding ethyl urethan (90). The intermediate carbonylazide has been isolated as a solid, (mp 135° C), in the Curtius reaction of 1,4,5,6-tetrahydro-6-oxo-3-pyridazinecarbohydrazide (94). The carbonylazide was further treated with ethanol to afford the ethyl ester (94).

Considering satisfactory yields in the Hofmann reaction of these pyridazinecarboxamides, it is rather surprising that this reaction has been less widely utilized in the pyridazine series.

5. *Reduction of Nitro Compounds*

Reduction of nitropyridazine derivatives and their *N*-oxides is next in importance to the displacement reactions of halopyridazine derivatives as a preparative method for aminopyridazines.

a. Reduction of Nitropyridazines and Their *N*-Oxides. Since Itai and Igeta (95) first prepared 4-nitro-3,6-dimethoxypyridazine 1-oxide by

nitration of 3,6-dimethoxypyridazine 1-oxide and reduced it catalytically to the amino derivatives, a wide variety of substituted nitropyridazine *N*-oxides, and as a result many aminopyridazines as well as aminopyridazine *N*-oxides, have been synthesized.

No instance of chemical reduction is known. Catalytic hydrogenation proceeds smoothly under atmospheric pressure and in most cases a good yield of aminopyridazine or aminopyridazine *N*-oxide is obtained depending upon the catalyst. These results are listed in Table VI.

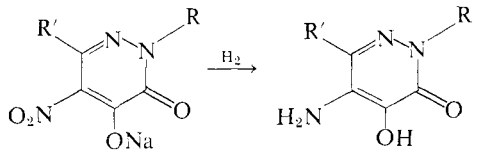
Starting with nitropyridazine *N*-oxides, the corresponding aminopyridazine *N*-oxides have been produced by catalytic hydrogenation over palladium–charcoal in neutral medium. Raney nickel (96) is the favored catalyst to effect the removal of the *N*-oxide function and the conversion of the nitro group to the amino group. A small amount of acetic acid is usually added to promote the reduction. Without acetic acid the reduction requires a long period of time for completion (97). Hydrogenation over palladium–charcoal in aqueous or alcoholic hydrochloric acid also causes reduction of the *N*-oxide function. The reduction is similar in acetic anhydride; the acetamino compound is obtained (91, 95). Halonitropyridazine *N*-oxides have been simultaneously reduced and dehalogenated to aminopyridazines (91, 98, 99) or aminopyridazine *N*-oxides (100).

Reduction of the nitro group to the hydroxylamino or the azo group is discussed in Chapter VII, Section III.

b. Reduction of Nitropyridazinones. The reduction of nitropyridazinones has been studied by Dury and Reicheneder. The starting 2-substituted 4-hydroxy-5-nitro-3(2*H*)pyridazinones were prepared by an interesting substitution reaction of 4,5-dichloro-3(2*H*)pyridazinones with sodium nitrite (see Chapter VII).

The reduction of these nitro compounds was performed under a variety of conditions (25, 101, 102). In a typical example the sodium salt of 2-phenyl-4-hydroxy-5-nitro-3(2*H*)pyridazinone was hydrogenated catalytically over Raney nickel in water at 40° C under 40 atm pressure for a period of 6 hr, and an 83% yield of the corresponding 5-amino derivative was obtained (102). The same compound was also reduced in such solvents as methanol, ethanol, tetrahydrofuran, or aqueous ammonia at various temperatures and pressures (25, 101, 102).

Other 4-hydroxy-5-nitro-3(2*H*)pyridazinones unsubstituted and/or substituted at the 2- and/or 6-positions have been hydrogenated similarly, Raney nickel, palladium–charcoal, or platinum catalyst being employed (102) (**20**). The reduction temperature ranges from room temperature to 100° C, and the pressure from 1 to 100 atm. The hydroxy group of the 4-hydroxy-5-nitro-3(2*H*)pyridazinone derivatives has been found to be replaced easily on



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R = H, alkyl, cycloalkyl, aryl, aralkyl, tosyl

R′ = H, phenyl, benzyloxy

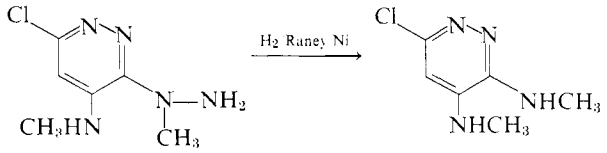
heating with ammonia or some amines, 4-amino-5-nitro-3(2*H*)pyridazinone derivatives being formed. These 4-amino-5-nitro-3(2*H*)pyridazinones were likewise reduced catalytically to the diaminopyridazinones (83, 25). These include 2-methyl-, 2-phenyl-, 2-unsubstituted 4-amino-5-nitro-3(2*H*)-pyridazinones and 2-phenyl-4-anilino-3(2*H*)pyridazinone with Raney nickel, 2-phenyl-4-(3,4-dichloroanilino)-, 2-*p*-toluenesulfonyl-4-anilino-5-nitro-3(2*H*)pyridazinones with palladium–charcoal, and 2-benzyl-4-amino-6-benzyloxy-, 2-*p*-tolyl-4-amino-, 2-phenyl-4-dimethylamino-, and 2-cyclohexyl-4-amino-5-nitro-3(2*H*)pyridazinones with platinum oxide (83); fair to good yields of the diamino derivatives are obtained. These compounds are said to also be reduced with zinc dust, although no experimental details have been reported (25).

When 2-phenyl-4-methoxy-5-nitro-3(2*H*)pyridazinone was subjected to catalytic reduction in tetrahydrofuran containing aqueous ammonia at 60° C and 40 atm, the replacement of the methoxy group occurred and 2-phenyl-4,5-diamino-3(2*H*)pyridazinone was obtained (83). 2-Alkyl-4,5-dichloro-6-nitro-3(2*H*)pyridazinones were reduced chemically by means of iron and hydrochloric acid in aqueous ethanol to give 2-alkyl-6-amino-4,5-dichloro-3(2*H*)pyridazinones which were also obtained by catalytic hydrogenation over Raney nickel (374, 375).

6. *Reduction of Compounds Other Than Nitro Compounds*

The catalytic reduction of 3-chloro-6-nitraminopyridazine over Raney nickel yielded 3-chloro-6-aminopyridazine (103), whereas the attempted reduction of 3-methyl-6-nitraminopyridazine by catalytic hydrogenation over Raney nickel, zinc and acetic acid, or by zinc and alkali resulted in decomposition (88). The catalytic reductive cleavage of the hydrazino group to an amino is of practical importance. Although halogen atoms of amino-halopyridazines show striking resistance to the ammonolysis reaction, they

have been found to be replaced readily by hydrazine to give aminohydrazinopyridazines which are converted to diaminopyridazines by catalytic hydrogenation over Raney nickel. In this reduction halogen atoms usually remain unaffected. By this method, Castle et al. synthesized 4,5-diamino- (24), 6-chloro-3,4-diamino- (104), 4-chloro-3,5-diamino- (24), and 3-amino-6-chloro-4-methylaminopyridazines (105) from 4-amino-5-hydrazino-, 4-amino-6-chloro-3-hydrazino-, 5-amino-4-chloro-3-hydrazino-, and 6-chloro-3-hydrazino-4-methylaminopyridazines, respectively, in fair yields. Likewise, 5-hydrazino-3(2*H*)pyridazinone has been reduced catalytically over Raney nickel in boiling ethanol to 5-amino-3(2*H*)pyridazinone in 60% yield (106). 4-Methylamino-6-chloro-3-(1′-methylhydrazino)pyridazine gives the 3-methylamino compound (**21**) in 33% yield (105).



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4-Azidopyridazine has been hydrogenated catalytically over palladium–charcoal in methanol to give a quantitative yield of 4-aminopyridazine (107). In a similar fashion 3- and 6-aminopyridazine 1-oxides are obtained from the corresponding azidopyridazine 1-oxides in 28 and 65% yield, respectively (84). Upon reduction of 3-azido-6-chloropyridazine 1-oxide, the chlorine atom was removed simultaneously to give 3-aminopyridazine 1-oxide (84). 5-Azido-4-bromo-2-phenyl-3(2*H*)pyridazinone gave 5-amino-4-bromo-2-phenyl-3(2*H*)pyridazinone in 15–93% yield when treated with compounds possessing an active methylene group, such as acetophenone, nitromethane, malonic dinitrile, ethyl cyanoacetate, dimedone, dibenzoylmethane, and acetoacetanilide (376).

7. *Cleavage of a Heterocyclic Ring Fused with the Pyridazine Ring System*

One of the interesting sources of aminopyridazine derivatives is condensed heterocyclic ring systems in which a pyridazine ring is fused with another heterocyclic ring. Thus it is possible to make some species of aminopyridazines by starting with more easily accessible heterocyclic rings than the pyridazine ring itself. A good yield of *N*-methyl-6-methylamino-3,4-diphenyl-5-pyridazinecarboxamide has been obtained by the ring-opening reaction of 6,8-dimethyl-3,4-diphenyl-5,7-dioxotetrahydropyrimido[4,5-*c*]pyridazine(**22**) in refluxing ethanolic sodium ethoxide (108).

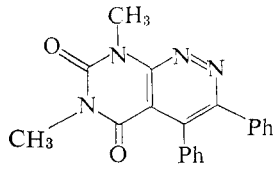
Pyrimido[4,5-*c*]pyridazine-5,7-dione and its 3-methyl derivative were heated with aqueous sodium hydroxide to form 3-amino- and 3-amino-6-methylpyridazine-4-carboxylic acid in 79 and 58% yield, respectively (373). Pyrimido[4,5-*d*]pyridazine-2,4-dione and aqueous sodium hydroxide gave rise to 5-hydroxypyridazine-4-carboxylic acid, and the desired 5-aminopyridazine-4-carboxylic acid was prepared in 98% yield by the use of aqueous ammonia (377). Cleavage of 3-methylpyrimido[4,5-*c*]pyridazin-5-one was effected more readily at room temperature to give 3-amino-6-methylpyridazine-4-carboxylic acid (373).

The oxazole ring of 2-phenyl-6-chlorooxazolo[5,4-*c*]pyridazine (**23**) is readily cleaved to 6-chloro-4-benzamido-3(2*H*)pyridazinone by hydrolysis with 15% aqueous hydrochloric acid under reflux, while the substitution of aqueous sodium hydroxide instead of the acid causes the cleavage of the benzoyl residue to form 4-amino-6-chloro-3(2*H*)pyridazinone (109). On treatment with ethanolic hydrochloric acid, 3-benzylideneamino-6-chloroimidazo[4,5-*c*]pyridazine (**24**) affords a 62% yield of 4-amino-6-chloro-3-benzylidenehydrazinopyridazine which in turn cyclizes to the former imidazopyridazine by heating with ethyl orthoformate (110, 378). Reductive cleavage of 4,7-diphenylfurazano[3,4-*d*]pyridazine (**25**) by catalytic hydrogenation over Raney nickel has given 4,5-diamino-3,6-diphenylpyridazine (111). Preparation of a series of amino ketone and aminocarboxamide derivatives of pyridazine by hydrogenation of isoxazolopyridazine and pyridazinones over Raney nickel has been reported (112, 113) (**26–28**).

The thiadiazolo ring of 4,7-dihydroxy-1,2,5-thiadiazolo[3,4-*d*]pyridazine (**56**) opens readily on heating with dilute aqueous sodium hydroxide, and 4,5-diaminopyridazine-3,6-diol is obtained (379).

1- or 3-Methyl-6-chloroimidazo[4,5-*c*]pyridazines have been reduced catalytically over palladium–charcoal to give 3-amino-4-methylamino- or 3-methylamino-4-aminopyridazine in 58 and 42% yield, respectively (105) (**29**). The reaction of 7-chloroimidazo[4,5-*c*]pyridazine and phosphorus pentasulfide in boiling pyridine solution caused the ring opening of the imidazole ring, yielding 5-mercapto-3,4-diaminopyridazine in low yield (105).

In the transformation of 6-chloroimidazo[4,5-*c*]pyridazine into the 6-mercaptoimidazo[4,5-*c*]pyridazine by treatment with sodium hydrosulfide, 6-mercapto-3,4-diaminopyridazine was isolated as a by-product (380).



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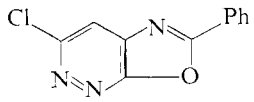

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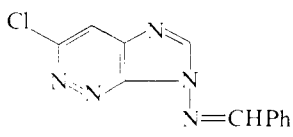

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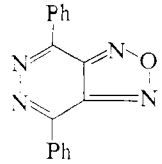

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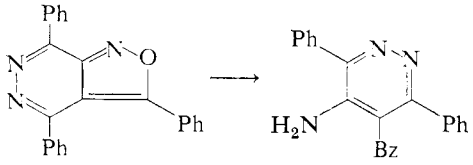

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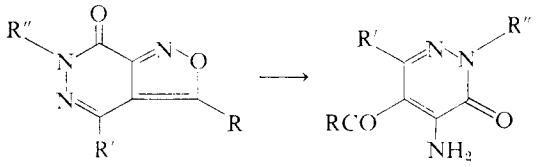
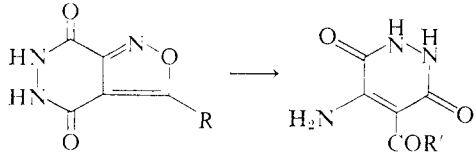


R, R′ = CH_3, Ph
R″ = H, Ph

27



R′ = CH_3, NH_2

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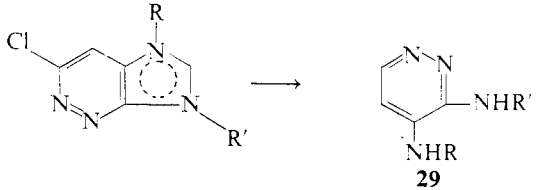
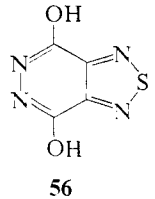


R = H, R′ = CH_3
or
R = CH_3, R′ = H

29



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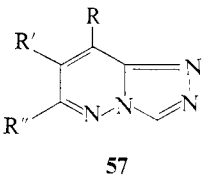

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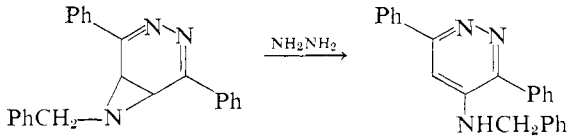
Several 3-aminopyridazine derivatives were prepared by Becker and Boettcher by catalytic hydrogenation of *s*-triazolo[4,3-*b*]pyridazines (**57**) under pressure at 190–200° C over Raney nickel (381, 382). *s*-Triazolo[4,3-*b*]-pyridazines were readily obtained from 4-amino-1,2,4-triazole and substituted *β*-dicarbonyl compounds. The conversion of *s*-triazolo[4,3-*b*]pyridazines (**57**) to 3-aminopyridazines was also effected by the same investigators by quaternizing the triazolopyridazines with halogeno ketones, nitriles, or esters and treating the quaternary salts with aqueous sodium hydroxide under reflux (383–385). The yields were satisfactory.

7-Benzyl-2,5-diphenyl-3,4,7-triaza-2,4-norcaradiene was isomerized into 4-benzylamino-3,6-diphenylpyridazine (**58**) in 50% yield when refluxed with hydrazine (360).



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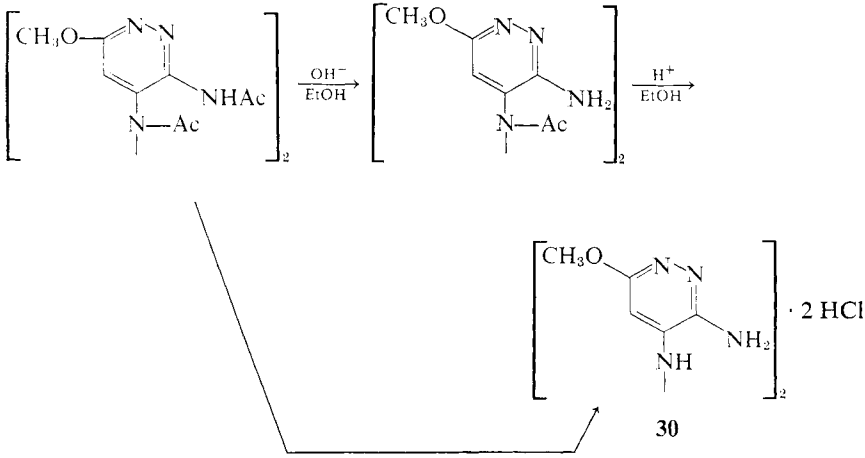
Potassium permanganate oxidation of pyrido[2,3-*d*]pyridazine in alkaline media yielded 5-aminopyridazine-4-carboxylic acid as a major product together with a small amount of quinolinic acid (386).

8. *Miscellaneous Methods*

Hydrolysis of acylaminopyridazine derivatives yields aminopyridazines. 2-Methyl-4-acetamido- (39), 2-methyl-4-acetamido-6-chloro- (29), 2-methyl-4-acetamido-6-methoxy-3(2*H*)pyridazinones (114, 115), and 5-acetamido-3-chloro-4(1*H*)pyridazinone (27) were boiled in dilute aqueous hydrochloric acid to give the corresponding aminopyridazinones in good yield. The acetyl group of 4-acetamido-3,6-dimethoxypyridazine has been readily removed by heating in dilute hydrochloric acid for a few minutes or even by boiling in water (95). 3-Amino-6-methoxypyridazine was detected by thin-layer chromatography in the solution of 3-sulfanilamido-6-methoxypyridazine treated with potassium bromide and hydrochloric acid in aqueous acetic acid solution (116). The treatment of 4-amino-5-formamido-3,6-dimethoxy-pyridazine with aqueous hydrochloric acid caused cleavage of one of the methoxy groups to form 6-methoxy-4,5-diamino-3(2*H*)pyridazinone (117). Alkaline hydrolysis with boiling dilute aqueous sodium hydroxide of 6-methoxy-4,5-diacetamido-3(2*H*)pyridazinone gave rise to the same diamine

(117). Aqueous or ethanolic sodium hydroxide hydrolyzed 3-methoxy-4-chloro-, 3-methoxy-4-methylthio-, and 3,4-dimethoxy-6-acetamidopyridazines to the corresponding 6-amino derivatives (118). Under the same conditions the tetraacetate of 3-methoxy-6-amino-4,4′-azopyridazine lost two of its acetyl groups to give 1,2-diacetylpyridazinyl hydrazine which was refluxed with ethanolic hydrochloric acid in order to remove the remaining two acetyl groups (118) (**30**).



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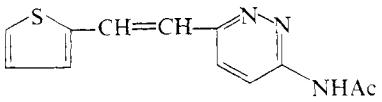
Although 3-chloro-5-acetamidopyridazine was converted to 3-methoxy-5-aminopyridazine by the action of methanolic sodium methoxide in 85% yield (119), an attempt to obtain 6-amino-3,4-dimethoxypyridazine 1-oxide from 3-alkoxy-4-nitro-6-acetamidopyridazine 1-oxide with the same reagent resulted in a black resinous product. Hydrolysis of the latter compound to 3-alkoxy-4-nitro-6-aminopyridazine 1-oxide was effected by heating with hydrochloric acid in aqueous ethanol solution (118). The use of aqueous hydrochloric acid for a longer period caused the nucleophilic replacement of the nitro group with a chlorine atom, yielding 3-alkoxy-4-chloro-6-aminopyridazine 1-oxides (118).

1-(5-Nitro-2-thienyl)-2-(6-acetamido-3-pyridazinyl)ethylene (**31**) is hydrolyzed to the amino compound with aqueous hydrochloric acid (134). 3-Amino-4-phenyl-6-methylpyridazine has been obtained as a by-product in the cyclization reaction of its 3-benzoylamino derivative into a triazaphenanthrene ring by fusion with aluminium chloride and sodium chloride at 220° C (40).

3,6-Dimethoxy-4,5-bis(α-ethoxyethylideneamino)pyridazine (**32**) is stable to alkaline reagents but sensitive to acid and is hydrolyzed to the 4,5-diamino derivative in 91% yield when treated with dry hydrochloric acid in ether or with picric acid (117).



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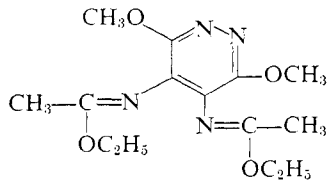

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4-Aminopyridazine 1-oxide has been produced as a by-product in 4% yield in the reaction of 4-chloropyridazine 1-oxide with sodium azide in aqueous alcohol at the boiling point of the solvents (107). 6-Aminopyridazine 1-oxide has been isolated in poor yield from an oily product when 6-azidopyridazine 1-oxide is heated in benzene (84).

A series of 2-phenyl-5- and/or 6-substituted-4-(*p*-dialkylaminophenylimino)-3(2*H*)pyridazinones has been prepared by the condensation of *p*-dialkylaminonitrosobenzene with 2-phenyl-5- and/or 6-substituted 4,5-dihydro-3(2*H*)pyridazinones in the presence of sodium ethoxide in ethanol (121). However, the yields are generally low (9–26%). No spectral data were given to support the imino structures.

Catalytic hydrogenation of pyrido[2,3-*d*]pyridazin-8-ol and its 5-chloro derivative over a large amount of palladium–charcoal in methanol containing aqueous ammonia to give 1,2,3,4-tetrahydropyrido[2,3-*d*]pyridazin-8-ol was reported by Nitta (122). This reaction was also later carried out by Kakimoto and Tonooka (123), who employed platinum as a catalyst in acetic acid, and the structure of the product was confirmed by the latter investigators. Good yields were reported. 1,2,3,4-Tetrahydropyrido[2,3-*d*]pyridazine-8(7*H*)one, the reduction product, was oxidized by chromic anhydride in acetic acid at room temperature to the original pyridopyridazinone (123).

Similarly, 7-phenylpyrido[2,3-*d*]pyridazin-8(7*H*)one and its 5-chloro compound were reduced over palladium–charcoal to 7-phenyl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyridazin-8(7*H*)one (124), while reduction over platinum also converted the same pyridopyridazinone, its 7-methyl analog, and 6-phenyl- and 6-methylpyrido[2,3-*d*]pyridazin-5(6*H*)one into the corresponding 1,2,3,4-tetrahydro compounds (123). Pyrido[2,3-*d*]pyridazine-5,8-(6*H*,7*H*)dione has likewise been hydrogenated over a platinum catalyst (123).

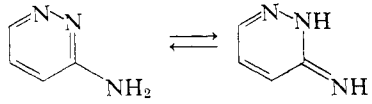
B. Properties

Aminopyridazines are generally more readily soluble in water and melt at higher temperatures than aminopyridines. Tables X–XIV give the physical constants of aminopyridazines and aminopyridazinones. Mason (125)

showed that in the tautomeric equilibria in chloroform solution 3-amino-6-methylpyridazine and 4-aminopyridazine exist predominantly as the amino form according to infrared (ir) spectroscopic studies.

Information supporting the amino structure of the simple 3- and 4-aminopyridazines was also provided later by a study (126) based upon the comparison of their ir spectra with those of aminopyridines.

Ultraviolet (uv) as well as ir absorption spectra of 3-amino-6-chloro-, 3-chloro-6-methylamino-, and 3-chloro-6-piperidinopyridazines were compared, and it was concluded that the amino and the methylamino groups may exist predominantly as such (127). This study, however, lacks data on 1-substituted 6-iminopyridazines.



C. Reactions

1. *Acylation*

a. Carbonyl Derivatives. The formylation of 4,5-diamino-3,6-dimethoxypyridazine has been reported in an article concerned with the syntheses of imidazo[4,5-*d*]pyridazine derivatives (117). The foregoing diamine yields the monoformyl derivative in 71% yield on boiling with formic acid for 15 min. Prolongation of the period of refluxing to 4 hr decreases the yield of the monoformyl compound (3%) and cyclized products predominate.

The attempted formulation of 3-amino-5,6-diphenyl-4-pyridazinecarboxamide and -carbonitrile with boiling formic acid resulted in recovery of the starting amines (18).

Acetylation has been successfully accomplished by heating with acetic anhydride. Acetic acid may be used as a solvent, with sodium acetate added in some instances. The use of other acetylating agents has seldom been reported. The acetylamino derivatives thus prepared include: 3- (128) and 4-acetamidopyridazines (26); 6-methyl- (9, 128, 129), 6-chloro (128, 130), 6-benzylthio- (131), and 6-alkoxy(C_{1-10})-3-acetamidopyridazines (103, 128); 3-acetamido-5,6-diphenyl-4-pyridazinecarbonitrile (18); 3-(2-benzylidenehydrazino)-4-acetamido-6-chloropyridazine (110); the diacetate of 4,5-diamino-3,6-dimethoxypyridazine (117); 4-acetamido-6-methyl-3(2*H*)pyridazinone (14) and its 2-phenyl, 2-(*p*-nitrophenyl) (132), 2-*m*-tolyl, and 2-(2′-pyridyl) (133) derivatives; 4-acetamido-2,6-dimethyl-3(2*H*)pyridazinone (10, 25); 5-acetamido-3(2*H*)pyridazinone (77, 119) and its 4-chloro derivative

(39); and ethyl 5-acetamido-4-pyridazinecarboxylate (377). The yields are generally good.

By catalytic hydrogenation over palladium–charcoal in acetic anhydride, 4-nitro-3,6-dimethoxypyridazine 1-oxide has been converted into 4-acetamido-3,6-dimethoxypyridazine (Section I.A.5.a.) (95), and 3-methoxy-4-nitro-6-acetamidopyridazine 1-oxide into 1,2-diacetyl-1,2-bis(3-acetamido-6-methoxy-5-pyridazinyl)hydrazine (118).

In the condensation reaction of 5-nitro-2-thienylcarboxaldehyde with 3-amino-6-methylpyridazine in acetic anhydride, 1-(5-nitro-2-thienyl)-2-(6-acetamido-3-pyridazinyl)ethylene is obtained (134). 4-Amino-3,6-dichloro- (39) and 5-amino-3,4-dichloropyridazines (27) undergo acetolysis of one of the chlorine atoms when boiled with acetic anhydride, yielding 4-acetamino-6-chloro-3(2*H*)pyridazinone and 5-acetamido-3-chloro-4(1*H*)pyridazinone, respectively. The cleavage of the methoxy group of 4,5-diamino-3,6-dimethoxypyridazine occurred on treatment with acetyl chloride in xylene, giving 6-methoxy-4,5-diacetamido-3(2*H*)pyridazinone (117).

4-Aminopyridazine 1-oxide was acetylated with acetic anhydride at 100° C to the *N*-acetate, which failed to rearrange to the expected 5-acetamido-3(2*H*)pyridazinone on being refluxed in acetic anhydride for 5 hr (135). However, under similar conditions 3-aminopyridazine 1-oxide gave the rearranged product which afforded 6-amino-3(2*H*)pyridazinone after hydrolysis with hydrochloric acid (128). The yield was not reported. Acetylation of 5-amino-3(2*H*)pyridazinone with boiling acetic anhydride gave the diacetate (77), however, whether the structure was an *N*,*O*-diacetate or a bis-*N*,*N*-diacetate was not specified. 3-Amino-4-hydroxy-6-methylpyridazine and acetic anhydride gave *O*-monoacetate, whereas the 4,5-diacetamide was obtained in addition to a small amount of cyclized product from 3-hydroxy-6-methyl-4,5-diaminopyridazine (387).

Both the mono- and diacetates of 1,2,3,4-tetrahydropyrido[2,3-*d*]-pyridazin-5(6*H*)one have been obtained by acetylation with boiling acetic anhydride, and these acetates formulated as the *O*-acetate and the N^1,*O*-diacetate, respectively, on the basis of their ir spectral data (123). The *O*-monoacetate and N^1,O^8-diacetate were prepared in a similar manner from 1,2,3,4-tetrahydropyrido[2,3-*d*]pyridazin-5,8(6*H*,7*H*)dione. The tetrahydropyrido[2,3-*d*]pyridazin-8(7*H*)one gave only the *O*-acetate under the same conditions.

Dudley (18) acetylated a series of 3-amino-5,6-diphenylpyridazines substituted at the 4-position with a cyano, ethoxycarbonyl, or acetyl group to yield their 3-acetamido derivatives by refluxing in acetic anhydride. The 4-carboxamide derivatives gave rise to 3-acetamido-5,6-diphenyl-4-pyridazinecarbonitrile on boiling with acetic anhydride. 3-Acetamido-5,6-diphenyl-4-pyridazinecarboxamide was prepared by allowing it to react with acetic anhydride at 90° C and hydrolyzing the reaction mixture with aqueous

ammonia at room temperature. The same investigator could not duplicate his results, and a diacetyl compound, tentatively formulated as the 3-*N*,*N*-diacetamido compound, was separated when the reaction mixture was hydrolyzed with water containing a small amount of hydrochloric acid at room temperature.

6-Amino-3-methoxypyridazine 1-oxide was readily acetylated at room temperature with acetic anhydride in acetic acid, while 6-amino-3-chloropyridazine 1-oxide required refluxing acetic anhydride in acetic acid (128) for acetylation.

The acetylation of 3-aminopyridazine 2-oxide has been effected by two Japanese groups under slightly different reaction conditions. Itai and Nakashima (136) acetylated the amino oxide by warming it with acetic anhydride at 50° C for ½ hr and represented the product as 3-acetamidopyridazine 2-oxide. Horie and Ueda (128), however, used acetic anhydride in acetone solution, warmed the reaction mixture for a few minutes, and assigned the structure of 2-acetoxy-3-imino-2,3-dihydropyridazine to the product on the basis of its ir absorption. The same products have been obtained by direct oxidation of 3-acetamidopyridazine. Hydrogen peroxide oxidation in acetic acid was effected at 65° for 3 hr by Itai and Nakashima (136) and at 100° C for 6 hr by Horie and Ueda (128) to afford the compounds in question as the main product and 3-acetamidopyridazine 1-oxide as a by-product in a ratio of approximately 3:1. The employment of ethereal peroxyphthalic acid solution as an oxidizing reagent at room temperature yielded an 82% yield of the former and a 2% yield of the latter compound (136). Although the reported melting points of the acetylated compounds of 3-aminopyridazine 2-oxide are close to each other, an examination of their properties has not been made to establish their identity.

The *N*-carboalkoxy derivatives have been readily obtained in good yields from 6-chloro- and 6-methoxy-3-aminopyridazines by the action of ethyl chlorocarbonate in pyridine (136) or in a mixture of pyridine and acetone (128).

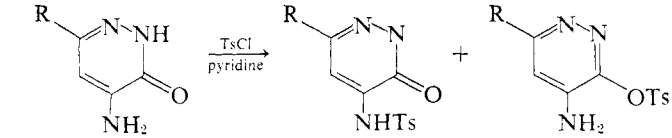
The amides and imides of dicarboxylic acids with 2-substituted 4-halo-5-amino-3(2*H*)pyridazinones have been prepared by miscellaneous methods by Fischer, Reicheneder, and Dury (137, 388) in the search for selective herbicides. They are monoamides of oxalic acid, succinic acid, and imides of succinic and maleic acids.

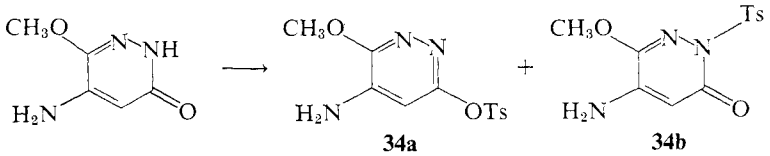
b. Sulfonyl Derivatives. 3-Amino-6-methylpyridazine treated with methanesulfonyl chloride in the presence of trimethylamine as an acid acceptor gave a bismethylsulfonyl compound which was converted to a monomethylsulfonamide by hydrolysis (120). Although the bis(methylsulfonyl) compound was represented as 3-(*N*,*N*-dimethylsulfonyl)-6-methylpyridazine, there was no proof whether it was an *N*,*N*-dimethylsulfonyl

derivative or a 2-methylsulfonyl-3-methylsulfonimido-1,2-dihydropyridazine.

The reaction of 3-aminopyridazines with arylsulfonyl chlorides has been accomplished in pyridine solution at room temperature or at slightly elevated temperatures. 3-Aminopyridazine gave 3-(*m*-nitrobenzenesulfonamido)pyridazine by the action of *m*-nitrobenzenesulfonyl chloride, although neither the melting point nor the yield was described (138). The action of toluenesulfonyl chloride on 6-halo, 6-alkylthio, and 6-alkoxy-3-aminopyridazines gives the corresponding 3-(toluenesulfonamido)pyridazines in good yield (130, 138–140). *p*-Nitrobenzenesulfonyl chloride similarly reacts with a variety of pyridazine derivatives to yield the pyridazinyl *p*-nitrobenzenesulfonamides as intermediates for pyridazinylsulfanilamides. These *p*-nitrobenzenesulfonamides prepared are 3-(*p*-nitrobenzenesulfonamido)pyridazine (141) and its 6-chloro (142, 143), 6-alkoxy (138, 143), 6-hydroxy (143, 144), 6-thiol (143), and 6-alkylthio (143, 145) derivatives. The reaction of amino-2-substituted 3(2*H*)pyridazinones with arylsulfonyl chlorides has similarly been conducted in the presence or absence of an acid acceptor (132, 355, 389).

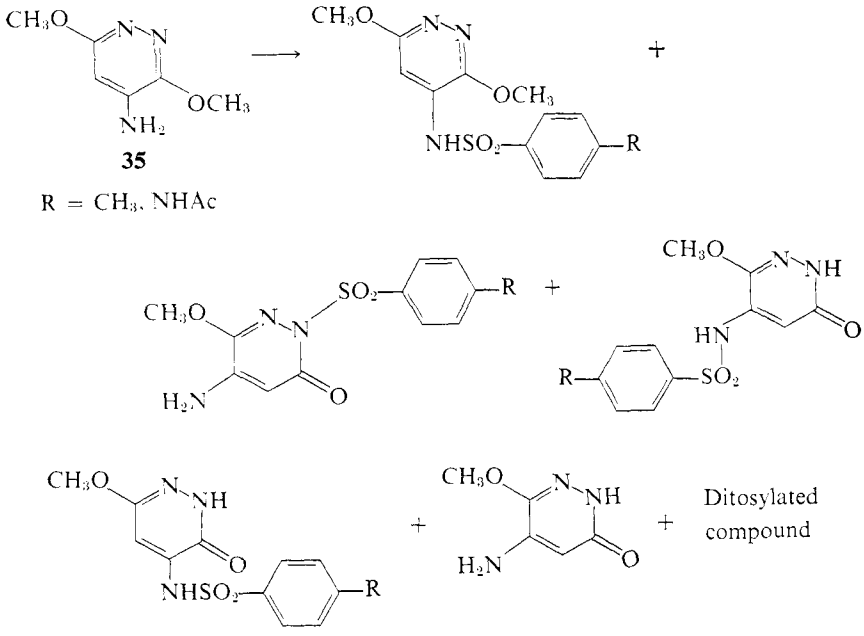
The reaction of 6-methoxy-4-amino-3(2*H*)pyridazinone with toluenesulfonyl chloride in pyridazine gives two isomeric products, the 4-toluenesulfonamido and the 3-*O*-toluenesulfonyl derivatives (146) (**33a,b**).





Since the latter compound rearranges in pyridine solution to the former, the yields are variable depending on the reaction period. Under Schotten–Baumann conditions, only the latter *O*-toluenesulfonyl compound is formed. Unsubstituted 4-amino-3(2*H*)pyridazinone likewise gives 4-toluenesulfonamide and the 3-*O*-toluenesulfonyl compound, the former product predominating. 4-Amino-3-methoxy-3(2*H*)pyridazinone, however, affords different types of products: 4-amino-3-methoxy-6-*p*-toluenesulfonyloxypyridazine(3-methoxy-4-amino-6-pyridazinyl *p*-toluenesulfonate) (**34a**) and 4-amino-3-methoxy-1-tosyl-6(1*H*)pyridazinone (**34b**). Tosylation of 4-amino-3,6-dimethoxypyridazine (**35**) in pyridine solution gives complicated results.

Four products have been isolated in addition to 4-toluenesulfonamido-6-methoxy-3(2*H*)pyridazinone and 4-amino-3-methoxy-6(1*H*)pyridazinone, as detected by thin-layer chromatography (146). Structure determination and the reaction sequence for each product have been discussed (92, 146).



3-Pyridazinylsulfanilamide, the first sulfanilamidopyridazine, was prepared by Roblin et al. in 1942 (11, 141). Not many sulfanilamides followed until Clark et al. (147–149) prepared 6-methoxy-3-pyridazinylsulfanilamide. Since the success of the methoxypyridazine as one of so-called long-acting sulfanilamides spurred interest in sulfanilamides in this field, a large number of pyridazinylsulfanilamides have been synthesized. Tables VII–IX list these pyridazinylsulfanilamides. The principal preparative procedures for them are: (1) the condensation of aminopyridazines with *p*-acylaminobenzenesulfonyl chloride in the presence of an acid acceptor followed by removal of the protecting group of the resulting pyridazinyl *p*-acylaminobenzenesulfonamides by hydrolysis, and (2) the reaction of halo- or other substituted pyridazines with sulfanilamide by fusion or by reaction in suitable solvents. (3) The reduction of *p*-nitrobenzenesulfonylamides is of less practical value.

Method (1) is the most commonly used for the preparation of pyridazinylsulfanilamides. *p*-Acetylaminobenzenesulfonyl chloride is the most preferred

sulfonyl chloride; *p*-ethoxycarbonylbenzenesulfonyl chloride is the next; others are of less practical value. The condensation reaction is effected most frequently in pyridine which serves as a solvent as well as an acceptor of hydrogen chloride liberated during the course of the reaction. Trialkylamines and potassium carbonate (150, 151) in indifferent solvents have rarely been employed.

The reaction generally proceeds even at low temperatures, but heating may be required when less reactive aminopyridazines are used. An instance has been reported in which pyridine causes the cleavage of an alkoxy group if the reaction is conducted at elevated temperatures (92).

The action of acetylsulfanilyl chloride on positions other than the primary amino group has been reported; 1-(*p*-acetylsulfonyl)-4-amino-3-methoxy-6(1*H*)pyridazinone is formed as a side product in the reaction of 4-amino-3,6-dimethoxypyridazine and *p*-acetylsulfanilyl chloride in pyridine (92) (**35**). Two bissulfonyl compounds of 3-amino-6-methoxypyridazine have been described in separate articles, one prepared by the action of acetylsulfanilyl chloride and sodium bicarbonate in aqueous acetone (150) and another in the presence of trialkylamine in methylene chloride solution (152). The physical constants reported by the different investigators do not agree. The former product is represented as *N*-acetylsulfanilyl-3-acetylsulfanilylimino-6-methoxypyridazine, and the latter as 3-*N*,*N*-bis(4-acetamidophenylsulfonyl)-amino-6-methoxypyridazine, although no confirmatory evidence was provided for either structure.

A bissulfonylated derivative of 3-amino-6-chloropyridazine has also been detected in the reaction on an industrial scale (6).

In the following step the acyl group attached to the amino group on the benzene ring should be removed in order to give the desired sulfanilamides. Alkaline hydrolysis is most favored. Refluxing in dilute aqueous sodium hydroxide solution for approximately 1 hr causes the complete removal of the acyl group. Under the circumstances such groups as alkoxy, alkylthio, and halogen do not undergo cleavage. Mineral acids are seldom used.

Satoda, Kusuda, and Mori (8) have reported the preparation of 6-chloro-4,5-tetramethylene-3-sulfanilamidopyridazine which was obtained by hydrolyzing the condensation product of the corresponding aminopyridazine and *p*-actamidobenzenesulfonyl chloride with methanolic hydrochloric acid. Aqueous sodium hydroxide failed to give the product. Methanolic sodium methoxide has also been used to effect the removal of the N^4-acyl group (153–157). At 120–130° C a halogen atom in a pyridazine ring also undergoes replacement with a methoxy group. Therefore this procedure has been utilized to make 6-methoxy-3-sulfanilamidopyridazine from 6-chloro-3-acylsulfanilamidopyridazine. Methyl acetate was formed during the reaction (156).

6-Alkoxy or halo-3-(homosulfanilamido)pyridazines have been prepared by method (1) from *p*-phthalylimidomethylbenzenesulfonyl chloride and the corresponding aminopyridazines (138, 158, 159). The phthalyl group of the resulting condensation product is hydrolyzed by heating with hydrazine hydrate.

Method (2) involves condensation of halopyridazines with sulfanilamide or acetylsulfanilamide and is also often utilized to prepare sulfanilamidopyridazines because of the reactivity of halogen atoms in the pyridazine ring and the availability of halopyridazines. The reaction proceeds easily and smoothly with polyhalopyridazines, and monosulfanilamidopyridazines are formed. There is a great deal of literature on this subject, including patents concerned with the preparation of 3-chloro-6-sulfanilamidopyridazine from 3,6-dichloropyridazine, because of the commercial value of 3-methoxy-6-sulfanilamidopyridazine. 3,6-Dichloropyridazine is usually mixed with sulfanilamide or acetylsulfanilamide, potassium carbonate, and sodium chloride; then the mixture is heated to a temperature of 110–150° C (6, 44, 154, 160–168). Yields are satisfactory (6, 154, 164). It is noted in one report (169) that the yield is increased from 56 to 84% when acetamide is employed as a fluidizing agent. Another report (170), however, denies the advantages of using a fluidizing agent because it requires excess amounts of sulfanilamide. 3-Bromo-6-sulfanilamido- (171) and 3-chloro-4- or 5-methyl-6-sulfanilamidopyridazines (174) have likewise been prepared from 3,6-dibromo- and 4-methyl-3,6-dichloropyridazines, respectively.

3,4,6-Trichloro- and tetrachloropyridazines react more readily with sulfanilamide or acetylsulfanilamide in a fused state (14, 172, 173) or in a fluidizing agent such as dimethylformamide (153) and acetamide (174), giving 4-sulfanilamido-3,6-dichloro- or 4-acetylsulfanilamido-3,6-dichloro- (14, 153, 172, 173) and 4-acetylsulfanilamido-3,5,6-trichloropyridazines (174).

3-Halo-6-substituted pyridazines react in a similar fashion to afford the corresponding 3-sulfanilamidopyridazine derivatives, although the yields are unsatisfactory or not specified. These 3-halopyridazines include 3-chloro- (9), 3-chloro-6-methyl- (85), 3-chloro-6-methylthio- (73), 3-chloro-6-methylsulfonyl- (73), 3-chloro-6-methoxy-, and 3-chloro-6-isopropoxypyridazines (176), and 6-chloro-3(2*H*)pyridazinone (177). It is noteworthy that the chlorine atom is always displaced in preference to any other substituent such as an alkoxy or a methylsulfonyl group. Only the methoxy group at the 4-position of 4-methoxy-3,6-dichloropyridazine, the position known to be more activated than the 3- or 6-position, is known to be replaced preferentially with acetylsulfanilamide (153). These findings correspond to those observed in the ammonolysis reaction of substituted halopyridazines (Section I.A.2.a.).

3,6-Bis(*p*-toluenesulfonyl)pyridazine reacted with the sodium salt of sulfanilamide in refluxing xylene to give the monosulfonamido derivative (178), while 3-benzylsulfonyl-6-methoxypyridazine gave rise to 3-benzylsulfonyl-6-sulfanilamidopyridazine accompanied by a demethylated product, 3-benzylsulfonyl-6(1*H*)pyridazinone, and methylated sulfanilamides through the interaction of the potassium salt of sulfanilamide in dimethyl sulfoxide at 140–150° C (179).

Much emphasis cannot be placed on the practicality of method (3). This preparative method aims principally at protecting the patents covering the syntheses of pyridazinylsulfanilamides. The starting pyridazinyl *p*-nitrobenzenesulfonamides are prepared in the same manner as in methods (1) and (2) for sulfanilamidopyridazines or by hydrogen peroxide oxidation of *p*-nitrobenzenesulfenamidopyridazine (180). These sulfonamides are reduced catalytically over Raney nickel (129, 132, 143, 178) or palladium–charcoal catalyst (142, 144, 181, 182), or with iron and acid (141, 180), or with hydrazine hydrate (180), and are listed in Tables VII–IX.

c. GUANIDINES. The action of *S*-methylisothiouronium sulfate upon 3-amino-6-anisylpyridazine in boiling aqueous solution yields the guanidine derivative (183).

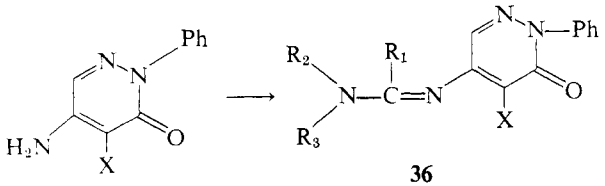
d. CARBAMATES. A series of carbamates or thiocarbamates has been prepared from 5-amino-4-halo-2-phenyl(cyclohexyl)-3(2*H*)pyridazinones by the action of phosgene or thionyl chloride to isocyanates or thioisocyanates followed by treatment with a variety of alcohols, glycols, thio alcohols, thiophenols (184), or oximes (390, 391).

e. UREAS. 5-Amino-4-chloro-2-methyl-3(2*H*)pyridazinone was treated with hydrogen chloride and phosgene at 130° C, and the isocyanate thus obtained was allowed to react with dimethylamine to afford the corresponding *N*,*N*-dimethylurea in good yield (391). In the same manner a series of urea derivatives of 4-halo-2-phenyl-3(2*H*)pyridazinones has been prepared. By the reaction of 3-amino-6-methoxypyridazine with *p*-ethoxyphenyl isothiocyanate, the assymmetric pyridazinylthiourea has been prepared (392).

2. *Condensation with Carbonyl Derivatives*

The reaction of 2-substituted 4-bromo-5-amino-3(2*H*)pyridazinones with mono- or dimethylformamide in the presence of phosphorus trichloride, thionyl chloride, phosgene, or benzenesulfonyl chloride leads to the mono- or dialkylaminomethyleneamino derivatives (185). A variety of other amidine derivatives has similarly been prepared by the condensation of 5-amino-4-chloro-2-phenyl-3(2*H*)pyridazinone and miscellaneous aliphatic amides in the presence of phosgene (186, 187) (**36**).

Trichloroacetaldehyde in dimethylformamide (335, 359, 393) and dimethyl mesoxalate in xylene (188) yield the addition products $Cl_3CCH(OH)NH$ and $(EtOCO)_2C(OH)NH$ derivatives of 2-substituted 4-halo-5-amino-3(2*H*)-pyridazinone, respectively.



X = Cl, Br

Condensation of aminopyridazine and an activated carbonyl compound has been reported. Thus 3-aminopyridazines react with 2-cyano-2-ethoxyacrylates in the presence of sodium ethoxide to give 2-cyano-3-(3-pyridazinylamino)acrylates (394).

3. *Diazotization Reactions*

Only a few examples of diazotization reactions of aminopyridazines are available in the literature. 3-Amino-6-chloro-4- and 5-methylpyridazines were treated with sodium nitrite and concentrated hydrochloric acid in the cold and then allowed to stand at room temperature, giving the 3-hydroxy compounds in good yields (19). The same transformations were later reported to be carried out in 50% sulfuric acid (20). 3-Amino-6-chloro-4-pyridazinecarboxylic acid is similarly converted to the 3-hydroxy compound by means of sodium nitrite and hydrochloric acid (18).

3-Amino-4-hydroxy-6-methylpyridazine was diazotized with sodium nitrite in dilute aqueous sulfuric acid to form the 3-hydroxy compound. In concentrated hydrochloric acid there was obtained as a by-product the 3-chloro compound which was the only product (73–75% yield) at higher hydrochloric acid concentrations (371). 3-Chloro-4-methoxy-6-methylpyridazine was obtained in a similar manner from the corresponding aminopyridazine.

3,4- and 4,5-Diaminopyridazines have been found to cyclize to triazolopyridazines when diazotized. 4,7-Dimethoxy-1*H*-*v*-triazolo[4,5-*d*]pyridazine has been obtained from 4,5-diamino-3,6-dimethoxypyridazine on diazotization with sodium nitrite and acetic acid followed by heating at 100° C (117), and 4- and 5-chloro-*v*-triazolo[5,4-*c*]pyridazines from 5- and 6-chloro-3,4-diaminopyridazines in dilute sulfuric acid in the cold (104).

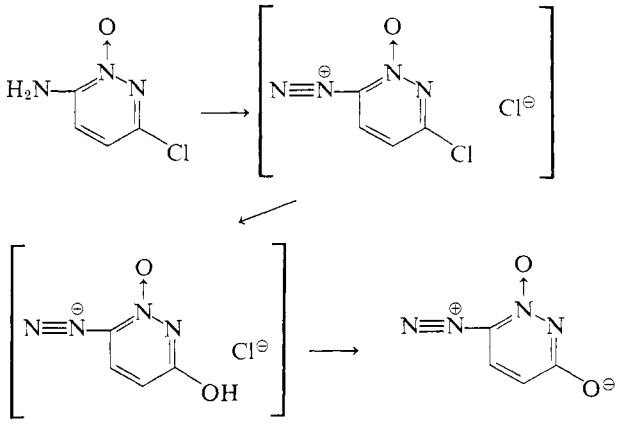
Under the diazotization reaction conditions, the hydrazino group of aminohydrazinopyridazine reacts first, the amino group remaining unaffected (65).

In contrast with aminopyridazines, each 3-, 4-, 5-, and 6-aminopyridazine 1-oxide can be diazotized and the diazo group replaced by halogen, although the yields are variable depending upon the position of the amino group.

It is noteworthy that 3- and 5-aminopyridazine 1-oxides, in which amino groups are present at positions beta to the *N*-oxide function, can be diazotized. Thus 3-, 4-, 5-, and 6-bromopyridazine oxides have been prepared by diazotization of the corresponding aminopyridazine oxide in aqueous hydrobromic acid in 8, 63, 40, and 20% yield, respectively (189). In hydrochloric acid 5-aminopyridazine 1-oxide has similarly been converted to 5-chloropyridazine 1-oxide (31%), and both 5-amino-3,4-dichloro- (37%) and 4-amino-3,5-dichloropyridazine 1-oxides (36%) were converted to 3,4,5-trichloropyridazine-1-oxide (189). 6-Aminopyridazine 1-oxide (61%) (54) and 4-amino-3,6-dimethylpyridazine 1-oxide (55%) (53) have been diazotized in hydrochloric acid and subsequently treated with copper powder, the corresponding chloro compounds being obtained.

Itai and Nakashima (136) diazotized 6-amino-3-chloropyridazine 1-oxide in either hydrochloric or sulfuric acid and obtained a 56% yield of 6-hydroxy-3-pyridazinediazonium 2-oxide (**37**) without regard to the acid used.

The compound is reduced on heating with methanol to 3-pyridazinol



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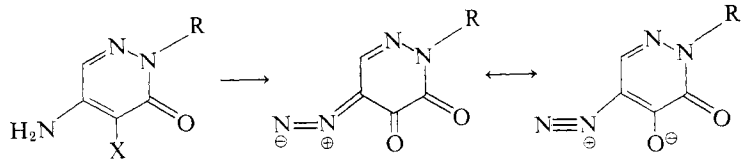
1-oxide and couples with β-naphthol to give a purple dye (136). The procedure could not be duplicated by Yoneda and Nitta (190), who obtained 3,6-dichloropyridazine 1-oxide instead by diazotization in concentrated hydrochloric acid. Compounds of similar type have been reported by Reicheneder

and Dury (191, 192), who diazotized 5-amino-4-halo-2-phenyl-3(2*H*)-pyridazinones with sodium nitrite and concentrated sulfuric acid or dilute hydrochloric acid to yield 5-diazo-4,5-dihydro-4-oxo-2-phenyl-3(2*H*)pyridazinone. The isomeric 4-diazo-4,5-dihydro-5-oxo compound has also been reported (192). These diazotized aminopyridazinones couple with a variety of aromatic amines and phenols to form the corresponding azo dyes (192, 193). The diazonium salt (**38**) can be converted to the chloro compound by the Sandmeyer reaction (192). Reduction of **38** is reported to yield 4-amino-5-



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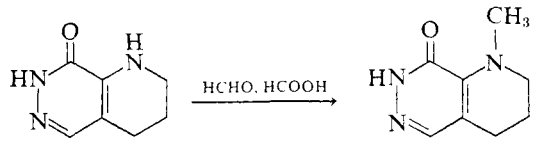
hydroxypyridazinones which can in turn be reconverted to the 4-diazonium pyridazinones by reaction with nitrous acid. However, the reducing agent is not specified (192). 6-Amino-4,5-dichloro-3(2*H*)pyridazinone and its 2-substituted derivatives have been diazotized and coupled with phenols, naphthols, heteroaromatic hydroxy compounds, or acetylacetone to produce a variety of azo dyes (375, 395). 3-Amino-6-methyl-1-phenyl-4(1*H*)pyridazinone gives the 3-hydroxy compound in 70% yield by diazotization followed by warming slightly (90).

4. *Alkylation of Aminopyridazines*

Methylation of the secondary amino group of tetrahydropyrido[2,3-*d*]-pyridazinol was effected by heating the amine with formalin and formic acid. In this manner 1-methyl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyridazin-8(7*H*)- and -5(6*H*)ones were prepared from their parent compounds (123) (**39** and **40**).

The reaction of 3-amino-, dialkylamino, and acetylaminopyridazines substituted with methyl, halogen, phenyl, and 4-methoxyphenyl groups in the 6-position and alkyl iodide in acetonitrile has been investigated and the reaction mixture analyzed using nuclear magnetic resonance (nmr) spectroscopy (194). No methylation at the exocyclic nitrogen atom has been observed and quaternization takes place exclusively in the nucleus. Only 3,6-bis-(dimethylamino)pyridazine formed two isomers, one of which was assigned by nmr study to the isomer quaternized at the exocyclic nitrogen. From the

methylation reaction of 4-amino-6-substituted (H, Me, Cl, OMe) 3(2*H*)-pyridazinone with dimethyl sulfate in alkaline medium, the 2-methyl-4-amino-3(2*H*)pyridazinones and the zwitterionic compounds methylated at the 1-position were separated (28, 195).



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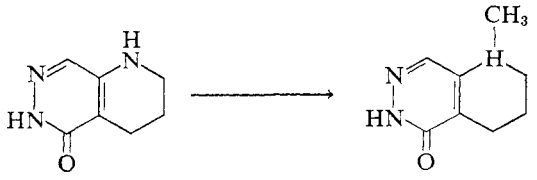

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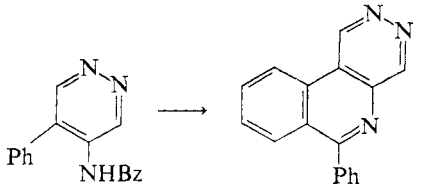
The reaction of aminopyridazines with halo ketone or halo aldehyde is discussed in the following section.

5. *Synthesis of Polycyclic Systems*

a. PYRIDOPYRIDAZINES (TRIAZAPHENANTHRENE). Atkinson and Rodway (89, 40) attempted cyclodehydration of phenylaroylaminopyridazines to aryltriazaphenanthrenes under a variety of reaction conditions, among which the use of phosphorus pentoxide in nitrobenzene, a mixture of phosphorus pentoxide and polyphosphoric acid, or a melt of aluminum chloride–sodium chloride, were found effective. The preparation of 6-phenylpyridazino[4,5-*c*]isoquinoline (**41**) from 4-benzamido-5-phenylpyridazine was



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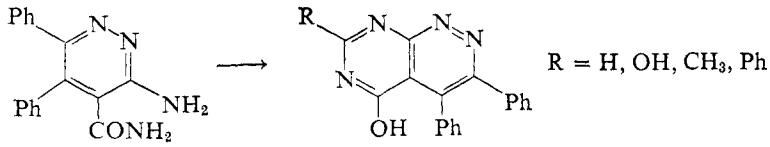
best effected with phosphorus pentoxide in nitrobenzene at 180° C, a yield of 53% being obtained (89). 6-(*m*-Nitrophenyl)- and 6-(*p*-nitrophenyl) analogs have likewise been obtained in 74 and 69% yield from the correspondingly

substituted 4-aroylamino-5-phenylpyridazines, respectively. The *o*-nitrobenzoylaminopyridazine resisted cyclization because of steric hindrance. 3-Benzamido-4-phenyl-6-methylpyridazine was also cyclized to 2-methyl-6-phenylpyridazino[3,4-c]isoquinoline (40). A melt of aluminium chloride and sodium chloride gave better results (50%) than phosphorus pentoxide in nitrobenzene. The *p*-nitrobenzamido derivative was, however, cyclized in only 15% yield by phosphorus pentoxide in nitrobenzene, other variations being useless.

b. PYRIMIDOPYRIDAZINES. 3-Amino-5,6-diphenyl-4-pyridazinecarboxamide was heated with diethoxymethyl acetate, urea, acetamidine, or benzamidine hydrochloride to give 5-hydroxy-, 5,6-dihydroxy-, 5-hydroxy-7-methyl-3,4-diphenylpyrimido[4,5-*c*]pyridazine, or 5-hydroxy-3,4,7-triphenylpyrimido[4,5-*c*]pyridazine, respectively (18) (**42**). The same aminopyridazinecarboxamide, however, did not cyclize with diethylcarbonate, triethylorthoacetate, ammonium rhodanide, guanidine carbonate, or *N*,*N*-dimethylcyanamide. 3-Amino-6-methyl-4-pyridazinecarboxamide and ethyl orthoformate yielded 5-hydroxy-3-methylpyrimido[4,5-*c*]pyridazine (273). Although 3-amino-5,6-diphenyl-4-pyridazinecarbonitrile reacted with formamide at refluxing temperatures to yield 5-amino-3,4-diphenylpyrimido-[4,5-*c*]pyridazine (**43**), the 5,6-dimethyl derivative failed to give a cyclized product. Other attempts to prepare the 5-amino derivatives of the same condensed ring system from either 5,6-diphenyl- or 5,6-dimethyl-3-amino-4-pyridazinecarbonitrile were not successful. Furthermore, the 5-mercapto-3,4-dimethylpyrimido[4,5-*c*]pyridazine could not be prepared.

Heating of 3-acetamido-5,6-diphenyl-4-pyridazinecarboxamide at 190–200° C gives rise to 5-hydroxy-7-methyl-3,4-diphenylpyrimido[4,5-*c*]pyridazine (18). The same investigator reported that no cyclization occurred when



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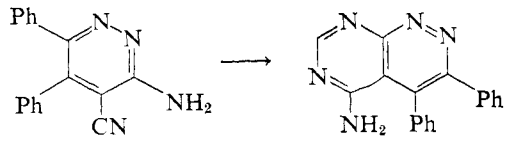

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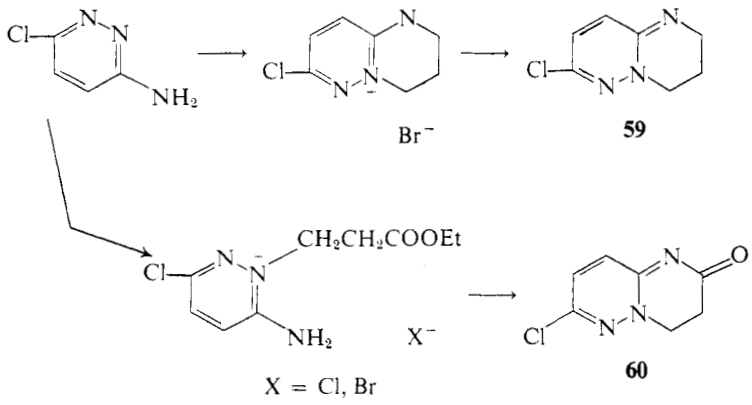
the 4-ethoxycarbonyl derivative of 3-amino-5,6-diphenyl-4-pyridazinecarbonitrile and formamide, or the 4-acetyl derivative and formamidine acetate, were allowed to react.

The formation of 5-hydroxy-3,4-dimethylpyrimido[4,5-*c*]pyridazine from 3-amino-5,6-dimethyl-4-pyridazinecarbonitrile has been reported in a review which gave no experimental details of the reactions (3). 8-Hydroxy- or 6,8-dihydroxy derivatives of the pyrimido[5,4-*c*]pyridazine ring system have been prepared from 4-amino-3-pyridazinecarboxamide by treatment with ethyl orthoformate or urea. 4-Amino-3-pyridazinecarbonitrile has been allowed to react with formamide to give 8-aminopyrimido[5,4-*c*]pyridazine (373). The same type of reaction with 5-amino-4-pyridazinecarboxamide and ethyl orthoformate gives 4-hydroxypyrimido[4,5-*d*]pyridazine (377). 2-Amino-4-hydroxypyrimido[4,5-*d*]pyridazine is obtained by the reaction of ethyl 5-amino-4-pyridazinecarboxylate with guanidine carbonate at high temperatures, while the 4-hydroxy-2-methyl derivative of the same ring system is formed from the acetate of the same aminopyridazinecarboxylate by treatment with ethanolic ammonia at room temperature (377).

As indicated earlier in Section I.A.4. the Hofmann reaction on 3,4-pyridazinedicarboxamide gives rise to 3,7-dihydroxypyrimido[4,5-*c*]pyridazine, while 6-methyl-3,4-pyridazinedicarboxamide gives a mixture of 3-methyl-5,7-dihydroxypyrimido[4,5-*c*]pyridazine and isomeric 6,8-dihydroxy-3-methylpyrimido[5,4-*c*]pyridazine (373).

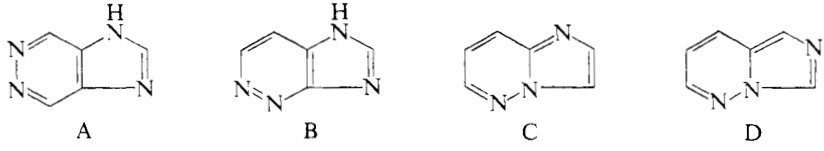
It seems to be easier to cyclize between an exocyclic nitrogen and one of the ring nitrogen atoms at the 2-position of a 3-aminopyridazine derivative in view of the high nucleophilicity of the ring nitrogen atom. However, these types of pyrimidopyridazines containing a bridgehead nitrogen are few. When 3-amino-6-chloropyridazine was heated with 1,3-dibromopropane in ethanolic solution, a 3% yield of 7-chloro-1,2,3,4-tetrahydropyrimido[1,2-*b*]-pyridazin-5-ium bromide was obtained, which was treated with alkali to form 7-chloro-2,3-dihydro-4*H*-pyrimido[1,2-*b*]pyridazine (**59**) (396). These bicyclic compounds were also prepared from 3-(3-bromopropylamino)-6-chloropyridazine. The quaternary salt of 3-amino-6-chloropyridazine and β-halogenopropionate was cyclized to 7-chloro-3,4-dihydropyrimido[1,2-*b*]-pyridazin-2-one (**60**) by means of polyphosphoric acid. The same sequence of reactions has been carried out with dibromopropane, and dihydroimidazo-[1,2-*b*]pyridazines have been obtained (396).

c. PYRAZINOPYRIDAZINE. The reaction of 6-chloro-3,4-diaminopyridazine with benzil at 160–175° C gave 6-chloro-2,3-diphenylpyrazino[2,3-*c*]pyridazine (104), while 4,5-diamino-3,6-diphenylpyridazine and diacetyl yielded 2,3-dimethyl-5,8-diphenylpyrazino[2,3-*d*]pyridazine (111). Unsubstituted

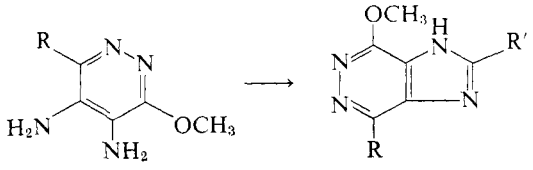


pyrazino[2,3-*d*]pyridazine was provided by the reaction of 4,5-diaminopyridazine with glyoxal in 22% yield (196). The use of methylglyoxal yielded the 2-methyl derivatives in 45% yield. 5-Hydroxypyrazino[2,3-*d*]pyridazine was obtained from 4,5-diamino-3(2*H*)pyridazinone and glyoxal (368).

d. IMIDAZOPYRIDAZINES. Of the four possible imidazopyridazine ring systems shown below, three (A–C) have been prepared starting with aminopyridazine derivatives.



Substituted imidazo[4,5-*d*]pyridazines (**44**) have been obtained from 3,6-dimethoxy- (117) or 3-methoxy-6-methyl-4,5-diaminopyridazine (97). 3,6-Dimethoxy-4,5-diaminopyridazine reacts with ethyl orthoformate in the presence of acetic anhydride and yields 4,7-dimethoxy-1*H*-imidazo[4,5-*d*]-pyridazine in 66% yield. Although attempts to prepare the 2-thiol analog by treatment with thiourea at 180° C failed, cyclization took place successfully on treatment with carbon disulfide and sodium hydroxide in hot pyridine to give the desired product in 32% yield (117). 4(7)-Methoxy-7(4)-methyl-1*H*-imidazo[4,5-*d*]pyridazine (59%) and its 2-thiol analog have been prepared in a similar fashion in quantitative yield (97). 3,6-Dimethoxy-4,5-diaminopyridazine was further treated with ethyl orthoacetate to give a poor yield of the appropriate 2-methylimidazo[4,5-*d*]pyridazine derivative, and with formic acid to give 4(7)-methoxy-1*H*-imidazo[4,5-*d*]pyridazin-7(6*H*) [or -4(5*H*)]one in 31% and its 6 (or 5)methyl derivative in 2% yield.



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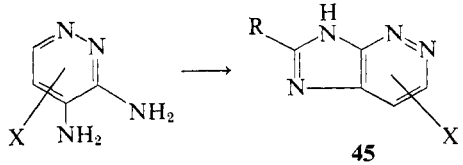
R = MeO, Me R′ = H, SH

4,5-Diamino-3(2*H*)pyridazinone was converted into 4-hydroxy-1*H*-imidazo[4,5-*d*]pyridazine by means of ethyl orthoformate in acetic anhydride (368), and 4,5-diamino-3,6-pyridazinediol into the 4,7-dihydroxy analog with formic acid (379). Subsequently, Yanai et al. (387) prepared several 1*H*-imidazo[4,5-*d*]pyridazines and their 2-methyl and 2-mercapto analogs according to the methods described above starting with 3,6-disubstituted 4,5-diaminopyridazines or 2,6-disubstituted 4,5-diamino-3(2*H*)pyridazinones. Condensation of diaminopyridazines possessing an alkoxy group with formamide led to the formation of dealkylated imidazopyridazines.

The reaction of 2-phenyl-4,5-diamino-3(2*H*)pyridazinone with *p*-methoxyphenylisothiocyanate failed to give an expected asymmetric thiourea. The product was 2-mercapto-5-phenyl-1*H*-imidazo[4,5-*d*]pyridazin-4(5*H*)one, instead (392).

3,4-Diaminopyridazines, however, give 7*H*-imidazo[4,5-*c*]pyridazines (**45**). Thus 3,4-diaminopyridazine and its halogenated derivatives have been treated with ethyl orthoformate or formic acid to give 7*H*-imidazo[4,5-*c*]pyridazine (68%) (105) and its 3- (93%) (110) and 4-chloro derivatives (84%) (65), with carbon disulfide and sodium hydroxide in pyridine to give imidazo[4,5-*c*]-pyridazine-6-thiol (53%) (105) and its 3-chloro (38%) (105) and 4-chloro derivatives (70%) (65), and with cyanogen bromide to give 6-amino-7*H*-imidazo[4,5-*c*]pyridazine (69%) (105). 3-Benzylidenehydrazino-4-amino-6-chloropyridazine and ethyl orthoformate yield 3-chloro-6-benzylideneamino-7*H*-imidazo[4,5-*c*]pyridazine in 52% yield (110). The 5- and 6-methyl derivatives of 7*H*-imidazo[4,5-*c*]pyridazines and their 6-thiols have also been prepared from the appropriate monoaminomonomethylaminopyridazines by the same treatment (105).



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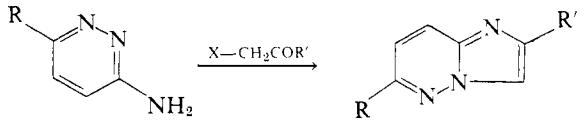
X = H, Cl

R = H, SH, NH_2

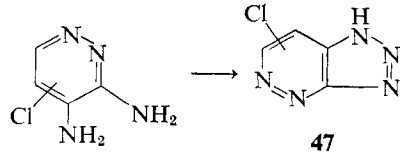
In the reaction of 3,4,5-triaminopyridazine and carbon disulfide, the 3- and 4-amino groups participate in the cyclization and the product is 4-amino-7*H*-imidazo[4,5-*c*]pyridazine-6-thiol (105).

The reactions between 3-aminopyridazines and haloketones or halo aldehydes yield imidazo[1,2-*b*]pyridazines (**46**). The reaction with halo ketones in most instances is conducted in boiling ethanol, while the reaction with halo aldehyde is at room temperature. Halo ketones employed are phenacyl bromide (197–200), para-substituted phenacyl bromides (197, 198), chloroacetone (201). Bromoacetone (200) and ethyl α-bromoacetoacetate (200), and haloaldehydes are bromoacetaldehyde (202, 203) and chloroacetaldehyde (397).



46

e. TRIAZOLOPYRIDAZINES. The treatment of substituted 3,4- (104) or 4,5-diaminopyridazines (97, 117) with nitrous acid gives the corresponding triazolopyridazines. The compounds thus prepared are 1*H*-*v*-triazolo[4,5-*d*]-pyridazine and its derivatives substituted with alkyl, alkoxy, hydroxy, mercapto, or alkylthio groups or halogen atom (60–90% yield) (97, 117, 368, 387), and 6- (47%) and 7-chloro-*v*-triazolo[4,5-*c*]pyridazines (83%) (104) (**47**).



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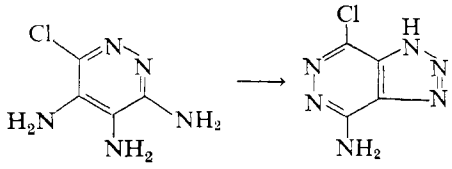
In the conversion of 6-chloro-3,4,5-triaminopyridazine to a triazolo-pyridazine, there are two possible ways of cyclization. The product has been proved to be 4-amino-7-chloro-1*H*-*v*-triazolo[4,5-*d*]pyridazine (**61**) (387).



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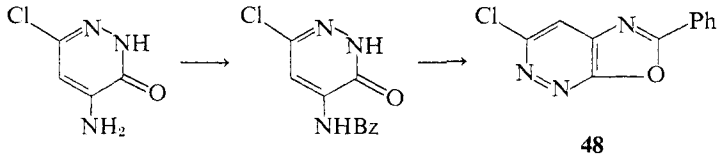
f. OXAZOLOPYRIDAZINES. 4-Amino-3,6-dichloropyridazine or 4-amino-6-chloro-3(2*H*)pyridazinone has been heated under reflux with benzoyl chloride to yield 6-chloro-2-phenyloxazolo[5,4-*c*]pyridazine (**48**) (39). When 4-amino-6-chloro-3(2*H*)pyridazinone is allowed to react with benzoyl chloride in boiling nitrobenzene or pyridine, the product is the 4-benzoylaminopyridazinone which can be cyclized to the oxazolopyridazine by heating with phosphoryl chloride (109) to **48**. A similar reaction with 5-amino-3,4-dichloropyridazine or 5-amino-3-chloro-4(1*H*)pyridazinone gives 7-chloro-2-phenyloxazolo[4,5-*d*]pyridazine (27).



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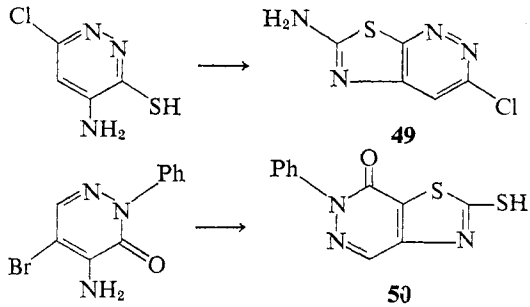
g. THIAZOLOPYRIDAZINES. Two thiazolopyridazines have hitherto been described. 3-Chloro-6-aminothiazolo[5,4-*c*]pyridazine (**49**) was prepared by the treatment of 4-amino-6-chloropyridazine-3-thiol with cyanogen bromide in alkaline medium at 8–10° C (204), and 2-mercapto-6-phenylthiazolo[4,5-*d*]-pyridazin-7(6*H*)one (**50**) by the reaction of 5-amino-4-bromo-2-phenyl-3(2*H*)pyridazinone with carbon disulfide and potassium in

$MeOCH_2CH_2OCH_2CH_2OH$ at 160° C (30).



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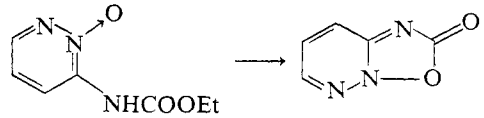
h. MISCELLANEOUS. The cyclization of ethyl 3-pyridazinecarbamate 2-oxide into 2*H*(1,2,4)oxadiazolo[2,3-*b*]pyridazin-2-one (**51**) on heating at



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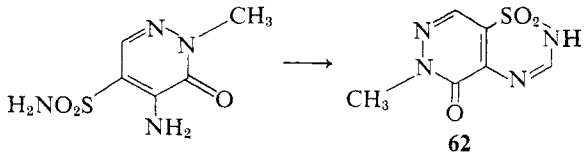
115° C has been reported (136). Meyer prepared 6-methyl-2*H*-pyridazino-[4,5-*e*][1,2,4]thiadiazin-5(6*H*)one 1,1-dioxide by the reaction of 4-amino-2-methyl-2,3-dihydro-3-oxo-5-pyridazinesulfonamide with ethyl orthoformate (**62**). The isomeric 7-methyl-2*H*-pyridazino[4,5-*e*][1,2,4]thiadiazine-8(7*H*)-one 1,1-dioxide was obtained on reversal of the positions of the amino and sulfonamide groups of the starting material (370).



62

A variety of condensed heterocyclic systems from aminopyridazinone intermediates was described in a review on the chemistry of pyridazinones (192, 205). However, no detailed report has been published as yet.

D. Nitraminopyridazines and Nitrosoaminopyridazines

Dixon and Wiggins (88) treated 3-aminopyridazine and its 6-methyl derivative with a mixture of nitric and sulfuric acids or fuming nitric acid at room temperature and obtained the corresponding nitramino compounds in 70% yield. 3-Amino-6-chloropyridazine likewise led to the nitramino derivative at 2–3° C (103).

Similar treatment of 4-amino-3-methoxy-6-methylpyridazine at 5–10° C for 2.5 hr yields the nitraminopyridazine, but at room temperature overnight a nuclear substituted aminonitropyridazine is produced along with an unidentified product (97). The nitramino compounds of 4-aminopyridazine and three diaminopyridazines have been prepared (24). The reactions are conducted at room temperature for ½ hr with 4-amino- and 3,5-diamino-pyridazines, or at 0° C with 3,4- and 4,5-diaminopyridazines. 4-Nitramino-, 4-nitramino-5-amino-, and 3,4-dinitraminopyridazines have thus been obtained under these conditions. The nitramino compound obtained from 3,5-diaminopyridazine has tentatively been designated 3-nitramino-5-aminopyridazine. However, no confirmatory evidence is given.

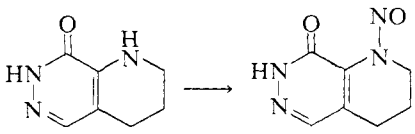
The nitraminopyridazines can rearrange upon heating only when activating groups are present in the molecule. Upon warming at 50–60° C in concentrated sulfuric acid, 3-methoxy-6-methyl-4-nitraminopyridazine was converted into 4-amino-3-methoxy-6-methyl-5-nitropyridazine (97), and the assumed 3-nitramino-5-aminopyridazine into 4-nitro-3,5-diaminopyridazine (24).

Reactions of the nitramino group have been studied with 3-methyl-6-nitraminopyridazine (88). Although the action of hot dilute hydrochloric acid on this compound resulted in the recovery of the starting material, the treatment with nitrous acid led to removal of the nitramino group, yielding 6-methyl-3(2*H*)pyridazinone (88). 3-Methyl-6-nitraminopyridazine and 3-nitraminopyridazine show acidic character, forming potassium salts by the action of ethanolic potassium hydroxide. These potassium salts are methylated with methyl iodide at the side-chain nitrogen atom to give the *N*-methylnitramino compounds. The *N*-methylnitramino groups can then be replaced by a benzylamino group with elimination of nitrous oxide to give 3-benzylaminopyridazine and its 6-methyl derivative (88). This fact eliminates the possibility of methylation on the ring nitrogen. The potassium salt of 4-nitramino-3-methoxy-6-methylpyridazine has also been treated with methyl iodide to give a methylated product which has been represented as the 4-*N*-methylnitramino derivative by analogy (97).

Attempts to reduce 3-methyl-6-nitraminopyridazine by catalytic reduction over Raney nickel, by reduction with zinc in acetic acid, and with zinc in sodium hydroxide or sodium hydrosulfite failed to give the product (88). Reduction over palladium–charcoal caused removal of the nitro group to give 3-amino-6-methylpyridazine (88). 3-Chloro-6-nitraminopyridazine (103), 4-nitramino-3-methoxy-6-methylpyridazine (97), and 3,4-dinitraminopyridazine (24) have similarly been hydrogenated over Raney nickel to their parent aminopyridazines.

The reduction of the nitramino to a hydrazino group is reported with 2-substituted 5-nitramino-3(2*H*)pyridazinones (192, 206). A procedure for the reduction was not reported. Hydrolysis of *N*-acylnitraminopyridazinones, prepared from acylaminopyridazinones and nitric acid, has also been described (206); nitroaminopyridazine derivatives are formed.

1,2,3,4-Tetrahydropyrido[2,3-*d*]pyridazin-8(7*H*)one has been treated with nitrous acid to yield the *N*-nitroso derivative (123) (**52**). It is reported that other 5-monoalkylamino-3(2*H*)pyridazinones also react smoothly with nitrous acid to form the *N*-nitroso derivatives (33). These *N*-nitrosoalkylaminopyridazinones can be reduced to *N*-alkylhydrazino derivatives (192).



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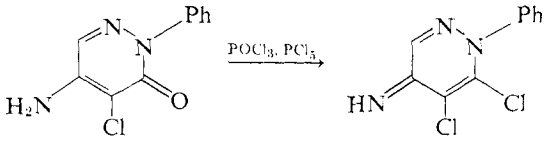
E. Pyridazinonimines

5-Imino-2,5-dihydro-2-phenyl-3,4-dichloropyridazine (**53**) has been formed by the action of a mixture of phosphorus pentachloride and phosphorus oxychloride at 60° C upon 5-amino-4-chloro-2-phenyl-3(2*H*)pyridazinone (207). 5-Monoalkylaminopyridazinones have similarly been converted to the 5-alkyliminopyridazines. Iminopyridazines thus prepared are 5-methylimino-, benzylimino-, ethylimino-, and β-chloroethylimino-2,5-dihydro-2-



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phenyl-3,4-dichloropyridazines, and 5-methylimino-2,5-dihydro-2-methyl-3-chloro-6-phenyl-, 5-ethylimino-2,5-dihydro-3-bromo-4-chloro-2-phenyl-, and 5-imino-2,5-dihydro-2-phenyl-3,6-dichloropyridazines. Iminopyridazinones thus prepared are listed in Table XXXIII.

These 5-imino-2,5-dihydropyridazines are much stronger bases than their parent aminopyridazinones, forming well-defined crystalline salts with aqueous acid. The chlorine atom at the 3-position undergoes hydrolysis rather than the imino group, giving the starting pyridazinones.

II. Side-Chain Amines

The Mannich reaction was first applied by Scheveren, Schlichting, and Amann (208) to 2-phenyl-3(2*H*)pyridazine derivatives in order to make a carbon–carbon linkage on the nucleus. The reaction was effected by heating a mixture of a 2-phenyl-3(2*H*)pyridazinone, a secondary amine, paraformaldehyde, and a catalytic amount of hydrochloric acid at 110–120° C. The reactive site is at the 4-position regardless of the presence of an alkyl group on the ring. A series of 4-(*N*,*N*-disubstituted aminomethyl)-6-alkyl (or 5,6-hexamethylene)-2-phenyl-3(2*H*)pyridazinones has been prepared (208).

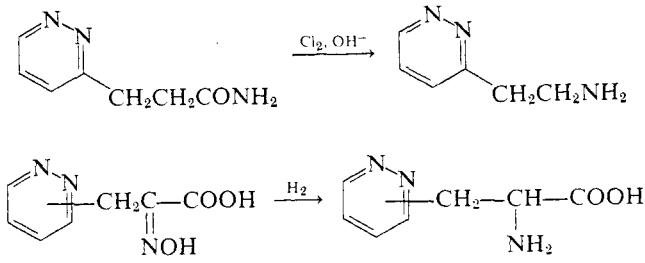
When 3(2*H*)- or 4(1*H*)pyridazinones unsubstituted at the 2-position are subjected to the reaction, *N*-aminoalkylation of the cyclic amide is favored to give the corresponding 2-(or 1-)aminoalkyl-3(2*H*) [or 4(1*H*)]pyridazinones (209–217).

Okusa, Kamiya, and Itai (218) found that 3-hydroxypyridazine 1-oxide, which is assumed to exist predominantly as the enol form, undergoes a Mannich reaction at the 6-position using dimethylamine, morpholine,

piperidine or bis(2-chloromethyl)amine, and aqueous formalin at room temperature. The yields range from 29 to 53%. With excess amounts of reagents, a 4,6-disubstituted derivative is formed (219). When the 6-position of 3-hydroxypyridazine 1-oxide is occupied by a chlorine atom or a methyl group, the morpholinomethyl or piperidinomethyl group enters the 4-position (219).

Co-workers of Itai continued the work and prepared 6-pyrrolidinomethyl and 6-(*N*-methylbenzylaminomethyl) derivatives from 3-hydroxypyridazine 1-oxide (398), and 6-dimethylaminomethyl, 6-piperidinomethyl, and 4,6-dipiperidinomethyl derivatives from 5-hydroxypyridazine 1-oxide (399). 5-Methoxypyridazine 1-oxide did not give a Mannich base. 3-Hydroxy-, 3-hydroxy-6-methyl-, and 5-hydroxypyridazine 1-oxides all reacted with primary amines under similar reaction conditions or at slightly elevated temperatures to yield 6-, 4-, and 6-*sec*-aminomethyl derivatives, respectively (400). The poor yields of 3-hydroxy-4-*sec*-aminomethyl-6-methylpyridazine 1-oxides were ascribed to the contribution of the alternative lactam form of the starting material.

In contrast to *N*-aminoalkyl-3(2*H*)pyridazinones which can be reduced to the parent 3(2*H*)pyridazinones by catalytic hydrogenation over palladium–charcoal (213) or Raney nickel (220), these *C*-aminoalkylpyridazines were found to resist reduction. On catalytic hydrogenation over palladium–charcoal, the 6-dimethylamino, 6-piperidinomethyl, and 6-morpholinomethyl derivatives of 3-hydroxypyridazine 1-oxides were converted to the 6-alkylaminomethyl-3(2*H*)pyridazinones which alternatively were derived from 3-chloromethyl-6-methoxypyridazine by the action of the corresponding secondary amines in ethanol (218). 4-Morpholinomethyl- or 4-piperidinomethyl-3(2*H*)pyridazinone, their 6-methyl derivatives, and 4,6-dimorpholino-3(2*H*)pyridazinones were similarly obtained by catalytic hydrogenation of their *N*-oxides over palladium–charcoal (219).



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Hofmann rearrangement of a side-chain amide to an amine has been carried out with 3-pyridazinepropionamide which gives a 73% yield of 3-(β-aminoethyl)pyridazine (221) (**54**).

DL-β-(3- and 4-pyridazinyl)alanines have been synthesized from the corresponding α-oximino-β-(3- and 4-pyridazinyl)propionic acids by low-pressure hydrogenation over palladium–charcoal in 65 and 58% yield, respectively (222) (**55**).

Catalytic reduction of the oxime of 4-chloro-6-pyridazinealdehyde 1-oxide at atmospheric pressure over palladium–charcoal resulted in the simultaneous reduction of all functional groups to yield 3-aminomethylpyridazine (223). 2,3-Dihydro-3-oxo-6-methyl-4-pyridazinecarbonitrile was reduced catalytically over palladium–charcoal in acidic medium to give 4-aminomethyl-6-methyl-3(2*H*)pyridazinone which was converted into 3-chloro-2-chloromethyl-6-methylpyridazinone by diazotization and subsequent treatment with phosphorus pentachloride and phosphorus oxychloride (401). The chlorine atom at the chloromethyl group is reactive, and the quaternary salts with miscellaneous pyridine derivatives have been prepared. 3-Chloro-4-chloromethyl-5,6-dimethylpyridazine forms the same type of pyridinium salts (401). 3-*Tert*-aminomethylpyridazines have been prepared by aminolysis of 3-chloromethylpyridazine in good yield (402). α-(2-Ketotropanyl)lactic acid condenses with hydrazine hydrate to form 1,3-dimethyl-5*H*-tropano[3,4-*e*]-pyridazin-4-one (**63**) in 12% yield (403).

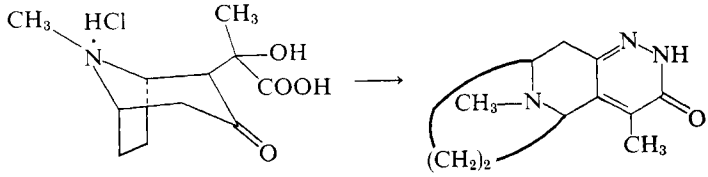

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TABLE I. Ammonolysis of Halopyridazines

Halopyridazine substituent				Conditions	Product	Yield	References
3	4	5	6				
Cl				NH_3, EtOH, 175° C, 3 hr	3-Aminopyridazine	58%	11
				NH_3, MeOH, 175° C, 2 days	3-Aminopyridazine	65%	10
				Liq. NH_3, 180–200° C, 8 hr	3-Aminopyridazine	65–70%	9, 224
Br				Aq. NH_3, 160–170° C, 5 hr	3-Aminopyridazine	44%	9
Cl			Me	Liq. NH_3, 180° C, 6–8 hr	3-Amino-6-methylpyridazine	65%	9, 224
				NH_3, MeOH, 175° C, 2 days	3-Amino-6-methylpyridazine and 3-methoxy-6-methylpyridazine	60%	129
				Aq. NH_3, 150° C, 2 days	3-Amino-6-methylpyridazine	49%	129
					6-Methyl-3(2*H*)pyridazinone	29%	
Br			Me	Aq. NH_3, 160–170° C, 7 hr	3-Amino-6-methylpyridazine	30–50%	9
Br			Et	Liq. NH_3, 180–200° C, 8 hr	3-Amino-6-ethylpyridazine	50%	9
Cl			Ph	Liq. NH_3, 190–200° C, 14 hr	3-Amino-6-phenylpyridazine	74%	9
Cl	Ph		Me	NH_3, PhOH, 180° C, 40 min	6-Methyl-3-phenoxy-4-phenylpyridazine	72%	40
Cl			$5,6(CH_2)_6$	NH_3, EtOH, 170° C, 72 hr	3-Amino-5,6,7,8,9,10-hexahydrocycloocta(*c*)-pyridazine	18%	225
Cl			*p*-$MeOC_6H_4$	Aq. NH_3, 120–130° C, 15 hr	3-Amino-6(4-methoxyphenyl)pyridazine		183

Cl			NH_2	35% Aq. NH_3, Cu, $CuSO_4$, 160° C, 6 hr	3,6-Diaminopyridazine	5 → 0.7 g	103
Br			OMe	Liq. NH_3, H_2O, Cu dust, 100° C, 10 hr	3-Amino-6-methoxypyridazine	4 → 1.6 g	6, 226
				NH_3, MeOH, 150–170° C, 24 hr	3-Amino-6-methoxypyridazine	4 → 0.8 g	6
Cl			OMe	Liq. NH_3, Cu, 100° C, 10 hr	Starting material		6
				NH_3, MeOH, 150–170° C, 24 hr	6-Chloro-3(2*H*)pyridazinone	4 → 2.8 g	6
Cl			*p*-$MeC_6H_4SO_2$	Aq. NH_3, dimethylformamide, 70° C, 6 hr	3-Amino-6(*p*-toluenesulfonyl)pyridazine	115 → 59 g	76
Cl			COOEt	NH_3, MeOH, room temp., 70 hr	3-Chloro-6-pyridazinecarboxamide		7
				Liq. NH_3, Cu, 100° C, 6 hr	3-Amino-6-pyridazinecarboxamide	43%	7
Cl			$CONH_2$	Liq. NH_3, NH_4Cl, 100° C, 8 hr	3-Amino-6-pyridazinecarboxamide		7
Cl			COOH	Liq. NH_3, NH_4Cl, 100° C, 8 hr	3-Amino-6-pyridazinecarboxylic acid	40%	7
				NH_3, MeOH, 100° C, 20 hr	3(2*H*)Pyridazinone-6-carboxylic acid (separated as ester)		7
Cl	COOEt			NH_3, EtOH, 0° C, 2 hr	3-Chloro-4-pyridazinecarboxamide	63%	227
Cl	COOEt		Me	NH_3, EtOH, 0° C, 2 hr	3-Chloro-6-methyl-4-pyridazinecarboxylic acid	70%	227
				NH_3, MeOH, 120–130° C, 24 hr	3-Amino-6-methyl-4- 3-Methoxy-6-methyl-4- 2,3-Dihydro-3-oxo-6-methyl-4-pyridazinecarboxamide	7% 28% 6%	373
Cl	CN	Ph	Ph	NH_3, EtOH, 130° C, 23 hr	3-Amino-5,6-diphenyl-4-pyridazinecarbonitrile	73%	18

TABLE I (*continued*)

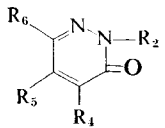
Halopyridazine substituent				Conditions	Product	Yield	References
3	4	5	6				
Cl	COOEt	Ph	Ph	NH_3, EtOH, 130° C, 23 hr	Ethyl 3-amino-5,6-diphenyl-4-pyridazinecarboxylate	49%	18
Cl	COMe	Ph	Ph	NH_3, EtOH, 130° C, 23 hr	Methyl 3-amino-5,6-diphenyl-4-pyridazinyl ketone	75%	18
Cl	$CONH_2$	Ph	Ph	NH_3, EtOH, 130° C, 23 hr	3-Amino-5,6-diphenyl-4-pyridazinecarboxamide	83–87%	18
Cl	CN	Me	Me	NH_3, EtOH, 130° C, 1.5 hr	3-Amino-5,6-dimethyl-4-pyridazinecarbonitrile	60%	18
Cl	COOH		Cl	NH_3, EtOH, 130° C, 24 hr	3-Amino-6-chloro-4-pyridazinecarboxylic acid	18%	18
Cl	(1-oxide)			Aq. NH_3, EtOH, 120° C, 4 hr	3-Aminopyridazine 1-oxide	0.2 → 0.05 g	228
Cl			Cl	Aq. NH_3, 100° C, 6 hr	3-Amino-6-chloro-pyridazine	5 → 4 g	44, 229
				NH_3, EtOH, 125–130° C, 10 hr	3-Amino-6-chloropyridazine	70%	12, 230
				Liq. NH_3, 120–125° C, 15 hr	3-Amino-6-chloropyridazine	7%	12
Br			Br	Aq. NH_3, 100° C, 6 hr	3-Amino-6-bromo-pyridazine		44, 229
Br			Br	NH_3, EtOH, 140–145° C, 10 hr	3-Amino-6-bromopyridazine	96%	12, 95
Cl	Me		Cl	NH_3, EtOH, 135–140° C, 8 hr	3-Amino-6-chloro-4-methyl-	10–15%	19
					3-Amino-6-chloro-5-methylpyridazine	80%	
				Aq. NH_3, 135–140° C, 8 hr	3-Amino-6-chloro-4-methyl-	40–45%	19

					3-Amino-6-chloro-5-methylpyridazine	50%	
				NH_3, MeOH, 120° C, 5hr	3-Amino-6-chloro-4-methyl- and 3-Amino-6-chloro-5-methylpyridazine (1:10 ratio)		20
				Aq. NH_3, 120–140° C, 20–24 hr	3-Amino-6-chloro-4-methyl- and 3-Amino-6-chloro-5-methylpyridazine		82
				Aq. NH_3, 100° C, 6 hr	3-Amino-6-chloro-4- or 5-methylpyridazine		44
Cl	Me	Me	Cl	Aq. NH_3, 120° C, 20 hr	3-Amino-6-chloro-4,5-dimethylpyridazine	10 → 6 g	8
Cl	$(CH_2)_4$		Cl	Aq. NH_3	Decomposition or starting material		8
				NH_3, EtOH, 160° C, 56 hr	3-Amino-6-chloro-4,5-tetramethylenepyridazine	5 → 3 g	8
				NH_3, EtOH, 160–170° C, 88 hr	3,6-Diamino-4,5-tetramethylenepyridazine	5 → 4 g	8
Cl	NH_2	NO_2	Cl	NH_3, EtOH, 95–100° C, 1.5 hr	3-Chloro-4,6-diamino-5-nitro- or	80%	
					6-Chloro-3,4-diamino-5-nitropyridazine		404
Cl	Cl		OH	Aq. NH_3, 150° C, 5 hr	4-Amino-3-chloro-6-hydroxypyridazine	15 → 8 g	405
Cl	Cl	Cl		NH_3, EtOH, 120–130° C, 5 hr	5-Amino-3,4-dichloro	8 → 2.8 g	26
					4-Amino-3,5-dichloropyridazine	8 → 2 g	
				NH_3, EtOH, 120–130° C, 5 hr	5-Amino-3,4-dichloro	38%	65
					4-Amino-3,5-dichloropyridazine	35%	

TABLE I (*continued*)

Halopyridazine substituent				Conditions	Product	Yield	References
3	4	5	6				
Cl	Cl		Cl	NH_3, EtOH, 100–105° C, 5 hr	4-Amino-3,6-dichloro-pyridazine	20 → 7 g	13
				NH_3, EtOH, 125° C, 7 hr	4-Amino-3,6-dichloro-pyridazine		104
				Aq. NH_3, 100° C (bath), 8 hr	4-Amino-3,6-dichloro-pyridazine	94%	14–17
F	F	F	F	Aq. NH_3, 0° C, 0.5 hr	4-Amino-3,5,6-trifluoropyridazine	90%	363, 364
Cl	Cl	Cl	Cl	Aq. NH_3, EtOH, 35–40° C, 30 min	4-Amino-3,5,6-trichloro-pyridazine	11 → 5.6 g	405

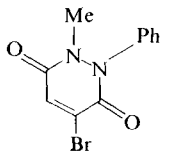
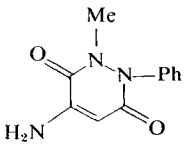
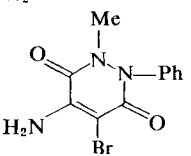
TABLE II. Ammonolysis of Halo-3(2*H*)pyridazinones



Halopyridazinone substituent						
R_2	R_4	R_5	R_6	Conditions	Product 3(2*H*)pyridazinone[a]	References
H	Me		Cl	Aq. NH_3, Cu, 130–160° C, 50 hr	4-Methyl-6-amino-	82
H	Cl	Cl		NH_3, EtOH, 150-160° C, 10hr	4-Chloro-5-amino-(3 → 1.9 g)	39
				NH_3, EtOH, 185° C, 60 hr	4 (or 5)-Amino-5 (or 4)-chloro-(30 → 15.7 g)	231
				NH_3, EtOH, 260° C, 84 hr	5 (or 4)-Amino-4 (or 5)-chloro-(49 → 1.8 g)	231
H		Cl	Cl	NH_3, EtOH, 150–160° C, 20 hr	5-Amino-6-chloro- (3.6 → 2.1 g)	27
H	Cl	Br		NH_3, EtOH, 160–170° C, 20 hr	4-Chloro-5-amino- (5 → 2.9 g)	27
Me		Cl	Me	Not specified	5-Amino-2,6-dimethyl-	232
				Aq. NH_3, 160° C, 60 hr	5-Amino-2,6-dimethyl-(58%)	10
				Aq. NH_3, 140–150° C, 50 hr	5-Amino-2,6-dimethyl-(80%)	28
Me			Cl	Aq. NH_3, 155–160° C (bath), 20 hr	2-Methyl-6-amino- (21%)	28
Me	Cl	SO_2Cl		Liq. NH_3, room temp.	2-Methyl-4-amino-2,3-dihydro-3-oxo-5-pyridazine sulfonamide	370
Me	Cl		Cl	Aq. NH_3, 140–150° C, 10 hr	2-Methyl-4-amino-6-chloro- (73%)	28, 406
Me		Cl	Cl	Aq. NH_3, 140–150° C, 10 hr	2-Methyl-5-amino-6-chloro- (66%)	28
Me	Cl	Cl		Aq. NH_3, 100° C, 1 hr	5-Amino-4-chloro-2-methyl-	407
Me	Cl	Cl	Me	Aq. NH_3, 140–150° C (bath), 10 hr	4-Amino-5-chloro-2,6-dimethyl- (42%) and 4-chloro-5-amino-2,6-dimethyl- (47%)	32
Et	Cl	Cl		Aq. NH_3, 125–128° C, 2 hr	2-Ethyl-4-chloro-5-amino-	33, 35

TABLE II (*continued*)

Halopyridazinone substituent						
R_2	R_4	R_5	R_6	Conditions	Product 3(2*H*)pyridazinone[a]	References
C_6H_{11}	Cl	Cl		Aq. NH_3, 125–128° C, 2 hr	2-Cyclohexyl-4-chloro-5-amino-	33, 35
CH_2COOH	Cl	Cl		Aq. NH_3, 115° C, 4 hr	5-Amino-4-chloro-2-carboxymethyl-	405
C_8H_{15}	Cl	Cl		Aq. NH_3, 125–128° C, 2 hr	2-Cyclooctyl-4-chloro-5-amino-	33, 35
	Cl	Cl		NH_3 (not further specified), 120° C, 6 hr	2-(Δ′-Cyclohexenyl)-4-chloro-5-amino-	233
Ph			Br	Aq. NH_3, Cu, 155–165° C, 10 hr	2-Phenyl-6-amino- (72%)	21, 22
Ph			Cl	Aq. NH_3, Cu, 155–165° C, 10 hr	2-Phenyl-6-amino- (13%)	21
Ph	Cl		Me	NH_3, MeOH, 125–130° C, 24 hr	2-Phenyl-4-amino-6-methyl- (88%)	129, 132
Ph	Cl		Cl	NH_3, EtOH, 150–160° C, 18 hr	2-Phenyl-4-amino-6-chloro- (60%)	21
Ph		Cl	Cl	Aq. NH_3, Cu, 150–165° C, 10 hr	2-Phenyl-5,6-diamino- (73%)	23, 234
Ph	Br	Br		Aq. NH_3, 130° C (bath), 10 hr	2-Phenyl-4-bromo-5-amino- (57%)	28
				Liq. NH_3, 100° C, 4 hr	2-Phenyl-4-bromo-5-amino (65%)	30
				NH_3, Me_2SO, 70° C	2-Phenyl-4-bromo-5-amino- (98%)	31
				Aq. NH_3, 125–128° C, 2 hr	2-Phenyl-4-bromo-5-amino-	33, 35
Ph	Cl	Cl		Aq. NH_3, 90–100° C, 6 hr	2-Phenyl-4-chloro-5-amino- (81%)	29
				Aq. NH_3, 125–128° C, 2 hr	2-Phenyl-4-chloro-5-amino- and 2-phenyl-4-amino-5-chloro- (total, 40.4 → 36 g) (ratio 92:7)	33, 35
				NH_3, Me_2SO, 120° C	2-Phenyl-4-chloro-5-amino- (94%)	31
				NH_3, ethylene glycol	2-Phenyl-4-chloro-5-amino- (quant.)	31
Ph	Cl	Cl		NH_3 (not further specified), 170–190° C, 3–4 hr	2-Phenyl-4-chloro-5-amino- (71%)	235
				Aq. NH_3, 100–110° C, 6 hr	2-Phenyl-4-chloro-5-amino- (71%)	34
				NH_3 gas passed, 210–220° C, 6–7 hr	2-Phenyl-4-chloro-5-amino- and 2-phenyl-4-amino-5-chloro- (ratio 73:27)	36

Ph	I	I		Aq. NH_3, 100° C, 6 hr	2-Phenyl-4-iodo-5-amino (10 → 6 g)	408
m-$CF_3C_6H_4$	Br	Br			5-Amino-4-bromo-2-*m*-trifluorotolyl	409
m-$CF_3C_6H_4$	Cl	Cl			5-Amino-4-chloro-2-*m*-trifluorotolyl	409
p-$NO_2C_6H_4$	Cl		Me	NH_3, MeOH, 125–130° C, 24 hr	2-*p*-Nitrophenyl-4-amino-6-methyl- (44%)	129, 132
p-$MeOC_6H_4$	Cl		Me	NH_3, MeOH, 125–130° C, 24 hr	2-*p*-Anisyl-4-amino-6-methyl- (48%)	236
p-$EtOC_6H_4$	Cl		Me	NH_3, MeOH, 125–130° C, 24 hr	2-*p*-Ethoxyphenyl-4-amino-6-methyl- (5%)	236
				NH_3, MeOH, CuO, 200° C, 18 hr	2-*p*-Ethoxyphenyl-4-amino-6-methyl- (32%)	236
p-MeC_6H_4	Cl	NO_2		Aq. NH_3, reflux, 3 hr	2-*p*-Tolyl-4-amino-5-nitro-	87
m-MeC_6H_4	Cl		Me	NH_3, MeOH, 150° C, 3 days	2-*m*-Tolyl-4-amino-6-methyl- (56%)	133, 237
2-Pyridyl	Cl		Me	NH_3, MeOH, 150° C, 3 days	2-(2-Pyridyl)-4-amino-6-methyl- (5 → 2.4 g)	133, 237
				NH_3, MeOH, room temp., 2 hr	 (5 → 1.2 g) and  (5 → 3.7 g)	68, 70

[a] Yield is given in parentheses.

TABLE III. Preparation of Secondary and Tertiary Aminopyridazines

Starting material substituents and positions	Amine	Conditions	Position of the r or product[a]
3-Chloro	$PhCH_2NHCH_2CH_2NBu_2$	$NaNH_2$, toluene, reflux, 18 hr	3
	$EtNH_2$	EtOH, 100° C, 1 hr	Starting materia recovered
	$EtNH_2$	EtOH, 120–130° C, 3 hr	3 (40%)
3-Chloro (1-oxide)	$EtNH_2$	EtOH, 100° C, 1 hr	3 (72%)
	$EtNH_2$	EtOH, 28° C, 5 hr	3 (3.5%)
	Piperidine	EtOH, 100° C	3
4-Chloro (1-oxide)	Piperidine	EtOH, 100° C	4
5-Chloro (1-oxide)	Piperidine	EtOH, 100° C	5
6-Chloro (1-oxide)	Piperidine	EtOH, 100° C	6
	$EtNH_2$	EtOH, 100° C, 1 hr	6 (79%)
	$EtNH_2$	EtOH, 28° C, 5 hr	6 (4%)
4-Chloro-3,6-dimethyl	$EtNH_2$	EtOH, 120–130° C, 6 hr	4 (11%)
4-Chloro-3,6-dimethyl (1-oxide)	$EtNH_2$	EtOH, 150° C, 6 hr	Starting materi recovered
	Piperidine	EtOH, 140–150° C	4
5-Chloro-3,6-dimethyl (1-oxide)	$EtNH_2$	EtOH, 120–130° C, 6 hr	5 (85%)
	Piperidine	EtOH, 100° C	5
3-Chloro-6-methyl	$PhCH_2NH_2$	Reflux, 6 hr	3 (29%)
	$PhCH_2NH_2$	100–130° C, 18 hr	3 (59%)
	$PhNH_2$	100° C, 1 hr	3 (56%)
	2-Furylamine	125° C, 24 hr	3 (66%)
	2-Thienylamine	130° C, 2 hr	3 (81%)
	p-Anisidine	125° C, 18 hr	3 (80%)

	$R_2NCH_2CH_2NHCH_2C_6H_4R'(p)$		135–140° C, 16 hr MeCOPh, K_2CO_3, reflux, 48–60 hr	3 (50%)	239
	R	R′			
	Me	H		3 (47%)	240
	Me	Cl		3 (26%)	240
	Me	OMe		3 (32%)	240
	Me	OEt		3 (45%)	240
	Me	OPr-n		3 (27%)	240
	Me	OPr-i		3 (37%)	240
	Et	H		3 (28%)	240
	Et	OMe		3 (31%)	240
	Me_2NH (40% aq. solution)		180° C, 10 hr	3 (2.35 → 1.1 g)	241
3-Chloro-6-methyl	Piperidine		H_2O, reflux, 17 hr	3	241
3-Chloro-4-hydroxy-6-methyl-	Morpholine		180° C, 3–10 hr	3	371
	Aniline		180° C, 3–10 hr	3	371
3-Chloro-4-hydroxy-6-methyl	Piperidine		180° C, 3–10 hr	3	371
	Benzylamine		180° C, 3–10 hr	3	371
	Phenethylamine		180° C, 3–10 hr	3	371
	$MeNH_2$		MeOH, 160° C, 8 hr	3	371
	Me_2NH		MeOH, 160° C, 8 hr	3	371
	Allylamine		MeOH, 160° C, 8 hr	3	371
3-Chloro-4-methoxy-6-methyl	Morpholine		180° C, 3–10 hr	3	371
	Aniline		180° C, 3–10 hr	3	371
	Piperidine		180° C, 3–10 hr	3	371
	Phenethylamine		180° C, 3–10 hr	3	371
	$MeNH_2$		MeOH, 160° C, 8 hr	3	371
	Me_2NH		MeOH, 160° C, 8 hr	3	371
	Allylamine		MeOH, 160° C, 8 hr	3	371

TABLE III (*continued*)

Starting material substituents and positions	Amine	Conditions	Position of the replacement or product[a]	References
3-Chloro-5,6,7,8,9,10-hexahydrocycloocta(*c*)-pyridazine	4-(3-Aminopropyl)morpholine	Not stated	3	225
	1-(2-Aminoethyl)hexamethyleneimine	Not stated	3	225
	N,*N*,*N*′Trimethyl-1,3-propanediamine	Not stated	3	225
3-Chloro-6-phenyl	Me_2NH	EtOH, 130° C, 3 hr	3	237
3-Chloro-6-anilino	$PhNH_2$	EtOH, reflux, 5 hr	3 (70%)	47
	p-Toluidine	EtOH, reflux, 5 hr	3 (15%)	47
	p-Toluidine	Xylene, reflux	3 (89%)	47
	Benzylamine	Reflux, 2 hr	3	47
	n-Butylamine	160–170° C, 8 hr	3 (80%)	47
	$HOCH_2CH_2NH_2$	170–180° C, 10 hr	3 (0.2 → 0.2 g)	47
3-Chloro-6-benzylamino	$PhNH_2$	Reflux, 1 hr	3 (60%)	47
3-Chloro-6-isopropylamino	$PhNH_2$	Xylene, reflux, 18 hr	3 (66%)	48
3-Chloro-6-piperidino	Piperidine	160° C, 5 hr	3 (62%)	51
3-Chloro-6-mercapto	$PhNH_2$	EtOH, reflux, 5 hr	3 (3 → 0.8 g)	73
3-Chloro-6-methylthio	$PhNH_2$	Reflux, 2 hr	3 (63%)	73
3-Chloro-6-methylthio	4-(γ-Benzoylpropyl)piperazine	Toluene, KI, 140–150° C, 48 hr	3	74
	4-(γ-*p*-Fluorobenzoylpropyl)-piperazine	Toluene, KI, 140–150° C, 48 hr	3	74
	4-(γ-*p*-Methoxybenzoylpropyl)-piperazine	Toluene, KI, 140–150° C, 48 hr	3	74
3-Chloro-6-methylsulfonyl	Ethyleneimine	Et_3N, (1) room temp., 15 hr, (2) 50° C, 0.5 hr	3 (60%)	75

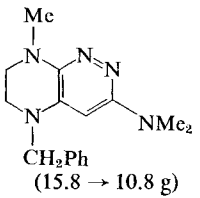
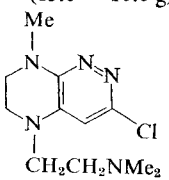
	Me_2NH	Aq. MeOH, room temp., 5 hr	3 (86%)	75
	$BuNH_2$	Et_3N, benzene, reflux, 20 hr	3 (92%)	75
	$PhNH_2$	EtOH, reflux, 18 hr	3 (77%)	75
	Cyclohexylamine	EtOH, reflux, 19 hr	3 (90%)	75
3-Methoxy-6-chloro (1-oxide)	Piperidine	EtOH, 130° C, 4 hr	6 (0.1 → 0.017 g)	50
3-Ethoxy-6-chloro (1-oxide)	$EtNH_2$	Aq. EtOH, 150° C, 5 hr	6 (32%)	50
3-Ethoxy-6-chloro	$EtNH_2$	Aq. EtOH, 160° C, 5 hr	No reaction	50
3-Chloro-4-nitro-6-methyl (1-oxide)	$i\text{-}PrNH_2$	Toluene, reflux, 0.5 hr	3 (5.7 → 4.0 g)	242
	Piperidine	Toluene, reflux, 0.5 hr	3	242
	$PhCH_2NH_2$	Toluene, reflux, 0.5 hr	3	242
	$PhOCH_2CH_2NH_2$	Toluene, reflux, 0.5 hr	3	242
3-Chloro-4,5-benzylthio	Morpholine	80° C, 5 hr	3 (66%)	410
3-Chloro-5-benzylthio-4-(2-tetrahydropyranylthio)	Morpholine	EtOH, reflux, 3 hr	3 (63%)	410
6-Chloro-3-dimethylamino (methiodide)	Liq. Me_2NH	In refrigerator, overnight	6-Methylamino (35%) (methiodide)	372
3-Dimethylamino-6-iodo-5-methyl (methiodide)	Liq. Me_2NH	In refrigerator, overnight	6-Methylamino (80%) (methiodide)	372
3-Dimethylamino-6-iodo-5-*t*-butyl (methiodide)	Liq. Me_2NH	In refrigerator, overnight	6-Methylamino (52%) (methiodide)	372
4-bromo-3,5,6-triphenyl	$PhNH_2$	Reflux, 0.5 hr	4	43
	Morpholine	EtOH, reflux, 2 hr	3 (75%)	412
	$HOCH_2CH_2NH_2$	120° C, 0.5 hr	4	43
6-Chloro-3-dimethyl-amino-4-methyl	Me_2NH	Aq. EtOH, 120° C, 24 hr	6 (90%)	366
3,6-Dichloro	Me_2NH	Aq. EtOH, 170° C, 10 hr	3,6 (19 → 9.5 g)	44
	Me_2NH	Aq. MeOH, 120–125° C, 24 hr	3,6 (44.7 → 49.8 g)	45
	Me_2NH	H_2O, 120–130° C, 5 hr	3 (64%)	75
	Me_2NH	Aq. EtOH, reflux, 45 min	3	366
	Me_2NH	EtOH, reflux, 3 hr	3 (60%)	405

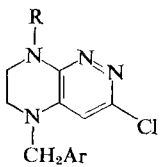
TABLE III (*continued*)

Starting material substituents and positions	Amine	Conditions	Position of the replacement or product[a]	References
	Me_2NH	Aq. EtOH, reflux, 0.5 hr, 120° C, 19 hr	3,6 (89%)	411
3,6-Dichloro	$MeNH_2$	H_2O, 120–130° C, 9 hr	3 (3.5 → 2.3 g)	243
	$MeNH_2$	EtOH, reflux, 3 hr	3 (62%)	405
	$EtNH_2$	Toluene, Cu, reflux, 18 hr	3	244
	Et_2NH	Toluene, Cu, reflux, 18 hr	3	244
	Et_2NH	EtOH, reflux, 3 hr	3	405
	i-$PrNH_2$	Benzene (or pyridine), reflux, 132 hr	3 (62%)	48
	$BuNH_2$	Benzene (or pyridine), reflux, 132 hr	3	48
	Bu_2NH	Benzene (or pyridine), reflux, 132 hr	3	48
	Cyclohexylamine	Benzene (or pyridine), reflux, 132 hr	3	48
	n-$BuNH_2$	BuOH, reflux, 5 hr	3	47
	Piperidine	Not stated	3	44
	Piperidine	180° C, 6 hr	3,6 (3 → 3.7 g)	44
	Piperidine	Benzene, reflux, 2.5 hr	3 (75%)	51
	Piperidine	180° C, 6 hr	3,6 (70%)	46
	Piperazine	H_2O, Me_2CO, conc. HCl, reflux, 3 hr	3 (54%) and *N*,*N*′-di(3-chloro-6-pyridazinyl)-piperazine (5%)	245
	Piperazine	Benzene, reflux, 2 hr	3	74
	$HOCH_2CH_2NH_2$	EtOH, reflux, 7.5 hr	3	47
	$HOCH_2CH_2NH_2$	Reflux, 10 hr	3,6	47

	Cyclohexylamine	Reflux, 10 hr	3	47
	Ethylenediamine	BuOH, reflux, 2 hr	3	47
	$Et_2NCH_2CH_2NH_2$	Me_2CO, conc. HCl, reflux, 24 hr	3 (89%)	246, 247
	$Et_2N(CH_2)_3NH_2$	Me_2CO, conc. HCl, reflux, 24 hr	3 (89%)	246, 247
	Ethyleneimine	Benzene, K_2CO_3, reflux, 5 hr	3 (11 → 16 g)[b]	248
	Ethyleneimine	Benzene, K_2CO_3, reflux, 11 hr	3-(β-Ethyleneiminoethyl-amino)-6-chloropyridazine (15 → 10 to 13 g)[b]	75
	$PhCH_2NH_2$	Benzene or EtOH, reflux, 5 hr	3	47
	$PhCH_2NH_2$	90° C, 4 hr	3 (quant.)	249
	$PhNH_2$	Benzene, reflux, 132 hr	3	48
	$PhNH_2$ (2 moles)	EtOH, reflux, 5 hr	3 (3 → 1.5 g) and 3,6 (3 → 1.5 g)	47
	p-Toluidine (2 moles)	EtOH, reflux, 3.5 hr	3 and 3,6	47
	p-Anisidine (2 moles)	Benzene, reflux, 5 hr	3	47
	p-Anisidine (4 moles)	Benzene, reflux, 5 hr	3,6	47
	p-Nitroaniline (2 moles)	Toluene, reflux 1 hr	3 and 3,6	47
	p-$RC_6H_4NH_2$(1 mole), (R = H, halogen, alkoxy)	EtOH, reflux, 2 hr	3	249, 250
	p-Dimethylaniline	pyridine, room. temp., 3 days	3,6 (75 → 64 g)	48, 49
	$EtNH_2$	Aq. EtOH, 100° C, 4 hr	3 (81%)	50
	Allylamine	EtOH, reflux, 3 hr	3 (72%)	405
	Diallylamine	EtOH, reflux, 118 hr	3	413
	$HO_2CCH_2CH_2NH_2$	Aq. propylene glycol, $NaHCO_3$, 100° C, 8 hr	3	414
	$HO_2CCH_2CH_2NH_2$	EtOH, reflux, 3 hr	3 (75%)	405
	$HO_2CCH_2NH_2$	EtOH, NaOH, reflux, 4 hr	3 (15 → 12 g)	405
	HO_2CCH_2NHMe	EtOH, NaOH, reflux, 4 hr	3 (45 → 43 g)	405
3,6-Dichloro (1-oxide)	$EtNH_2$	Aq. EtOH, 100° C, 4 hr	3 (54%) and 6 (14%)	50
	Piperidine	EtOH, 100° C, 4 hr	3 (60%) and 3,6 (12%)	50

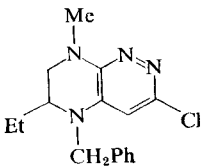
TABLE III (*continued*)

Starting material substituents and positions	Amine	Conditions	Position of the replacement or product[a]	References
3,6-Dibromo	Ethyleneimine	benzene, K_2CO_3, reflux, 5 hr	3 (12 → 8.6 g)[b]	247
4-Methyl-3,6-dichloro	Me_2NH	H_2O, 120° C, 20 hr	3 or 6 (83%)	20
	Me_2NH	Aq. EtOH, reflux, 30 min	3 and 6 (ratio 1:3)	366
	Me_2NH	Aq. EtOH, 120° C, 48 hr	3,6 (80%)	366
	Ethyleneimine	K_2CO_3, benzene, reflux, 3 hr	3 or 6	79
4-Methyl-3-chloro-6-bromo	Me_2NH	H_2O, 120° C, 20 hr	6 (90%)	251
4-Methyl-3-bromo-6-chloro	Me_2NH	H_2O, 120° C, 20 hr	6 (88%)	251
4-Methoxy-3,6-dichloro	Ethyleneimine	K_2CO_3, benzene, reflux, 3 hr	3 or 6	20
4-Amino-3,6-dichloro	$MeNH_2$	H_2O, 110–120° C, 8 hr	3 (55%)	105
4[*N*-Benzyl-*N*-(β-chloroethyl)amino]-3,6-dichloropyridazine	Me_2NH	EtOH, 120–130° C, 6 hr	 (15.8 → 10.8 g)	55
4-[*N*,*N*-Bis(β-dichloroethyl)]amino-3,6-dichloropyridazine	Me_2NH	EtOH, 120–130° C, 6 hr		55
3,4,5-Trichloro	Me_2NH	Aq. EtOH, 50–70° C, 5–10 min	5 (61%)	366
3,4,6-Trichloro	$MeNH_2$	EtOH, 85–95° C	4 (43%)	105
	$MeNH_2$	EtOH, reflux, 3 hr	4 (65%)	405
	$EtNH_2$	EtOH, reflux, 3 hr	4 (57%)	405

Cyclohexylamine	EtOH, reflux, 3 hr	4 (70%)	405
Me_2NH	Aq. EtOH, 50–70° C, 5–10 min	4 (78%)	366
Me_2NH	EtOH, reflux, 3 hr	4 (80%)	405
Et_2NH	EtOH, reflux, 3 hr	4 (90%)	405
i-Pr_2NH	EtOH, reflux, 3 hr	4 (55%)	405
$HO_2CCH_2NH_2$	Aq. EtOH, NaOH, reflux, 4 hr	4 (20 → 7.4 g)	405
HO_2CCH_2NHMe	Aq. EtOH, NaOH, reflux, 4 hr	4 (45%)	405
i-$PrNH_2$	Toluene, Cu powder, reflux, 18 hr	4	244
$PhCH_2NHCH_2CH_2OH$	EtOH, reflux, 20 hr	4 (184 → 224 g)	55
$HOCH_2CH_2NH_2$	EtOH, room temp., 1 hr	4	415
$CH_2{=}CHCH_2NH_2$	EtOH, room temp., 1 hr	4	415
$MeCH{=}CHCH_2NH_2$	EtOH, room temp., 1 hr	4	415
$PhNH_2$	EtOH, room temp.	4	415
$EtNH_2$	EtOH, room temp.	4	415
$(HOCH_2CH_2)_2NH$	EtOH, reflux, 6 hr	4	55
$(HOCH_2CH_2)_2NH$	EtOH, reflux, 3 hr	4 (82%)	405
o-Anisidine	EtOH, Et_3N, not further specified	4	66, 67
Diallylamine	EtOH, reflux, 25 hr	4	416
$R_2NCH_2CH_2NHCH_2Ar$	EtOH, (Et_3N), reflux, 15–20 hr		

R	Ar		
Me	Ph	(9.1 → 8.5 g)	55
Et	Ph	(102 → 97 g)	55

TABLE III (*continued*)

Starting material substituents and positions	Amine		Conditions	Position of the replacement or product[a]	References
	Me	Me		(7.1 → 8.1 g)	55
	Me	*p*-$Me_2NC_6H_4$		(18.3 → 14.4 g)	55
	Et	*p*-$MeOC_6H_4$			55
	Et	3-ClC_6H_4			55
	Et	Et			55
	Me	Et			55
	$Me_2NCH_2CH(Et)NHCH_2Ph$		EtOH, reflux, 16 hr		55
Tetrachloro	Me_2NH		Aq. EtOH, 50–70° C, 5–10 min	4 (73%)	366
	$MeNH_2$		EtOH, reflux, 3 hr	4 (65%)	405
	i-$PrNH_2$		EtOH, reflux, 3 hr	4 (70%)	405
	Cyclohexylamine		EtOH, reflux, 3 hr	4 (70%)	405
	Me_2NH		EtOH, reflux, 3 hr	4 (52%)	405
	Et_2NH		EtOH, reflux, 3 hr	4 (50%)	405
Tetrafluoro	Et_2NH		*N*-methylpyrrolidone, 18° C, 0.5 hr	4 (90%)	63, 364

[a] Yield is given in parentheses.

[b] The structure of the reaction product, which was represented to be 3-aziridino-6-chloropyridazine by Saijo and Inaba (248) was established later as 3-[β-(1-aziridinyl)ethylamino]-6-chloropyridazine by Nyberg and Cheng (75). Although Nyberg and Cheng have referred to Kumagai (47) concerning the same compound, this compound was not found in his article.

TABLE IV. Preparation of Secondary and Tertiary Amino-3(2*H*)pyridazinones

Halopyridazinone substituent				Amine	Reaction conditions	Position of replacement[a]	References
R_2	R_4	R_5	R_6				
H	Cl		OH	$RC_6H_4NH_2$ (R = 4-MeO, 4-Me, 4-Cl, 4-Et, 4-Br, 4-EtO, 3-MeO, 3-Me, 3-Et, 3-F, 3-Cl, 3-Br)	Cu powder, reflux, 25 min	4	252
H		Cl	4-Methoxyphenyl	Piperidine	Reflux, 7 hr	5 (98%)	253
				Morpholine	Reflux, 7 hr	5 (86%)	253
H	Cl	Cl		Piperidine	EtOH, reflux, 3 hr	5 (quant.)	13
				Morpholine	EtOH, reflux, 3 hr	5 (80%)	13
H	Br	Br		Morpholine	EtOH, reflux, 3 hr	5 (82%)	13
H	Cl	Cl		Me_2NH	Not stated	5	35, 36
				Piperidine	Not stated	5	35
				Morpholine	Not stated	5	35
				Pyrrolidine	Not stated	5	35
				$EtNH_2$	EtOH, reflux	5	254
				$HOCH_2CH_2NH_2$	EtOH, reflux	5	254
				$Et_2N(CH_2)_2NH_2$	EtOH, reflux	5	254
				Et_2CHNH_2	EtOH, reflux	5	254
				$PhCH_2CH_2NH_2$	EtOH, reflux	5	254
				$PhCH_2NH_2$	EtOH, reflux	5	254
				Piperidine	EtOH, reflux	5	254
H	Cl	Cl		Morpholine	EtOH, reflux	5	254
				4-Methylpiperidine	EtOH, reflux	5	254
Me		Cl	Me[b]	Me_2NH	100° C, not further specified	5 (23 → 16.5 g)	232
				$PhNH_2$	100° C, not further specified	5	232

TABLE IV (*continued*)

Halopyridazinone substituent							
R_2	R_4	R_5	R_6	Amine	Reaction conditions	Position of replacement[a]	References
Me	Cl	NO_2	Ph	$PhNH_2$	Reflux, 5 min	4	87
Me	Cl		OH	Me_2NH	EtOH, 100° C, 6 hr	4 (75%)	255
Me		Cl	OH	Me_2NH	EtOH, 100° C, 6 hr	5 (93%)	255
C_6H_{11}	Cl		OH	Me_2NH	EtOH, 100° C, 6 hr	4 (77%)	255
C_6H_{11}		Cl	OH	Me_2NH	EtOH, 100° C, 6 hr	5 (77%)	255
Me	Cl	Cl		Piperidine	EtOH, reflux	5	254
				Morpholine	EtOH, reflux	5	254
				Me_2NH	EtOH, 100° C, 6 hr	5 (2 → 2 g)	255
Me		Cl	Cl	Me_2NH	EtOH, 100° C, 4 hr	5 (2 → 1.6 g)	255
				Me_2NH	EtOH, reflux, 3hr	5 (75%)	405
Me		Cl	Cl	Me_2NH	EtOH, reflux, 3hr	4 (62%)	405
$Et_2N(CH_2)_2$	Cl	Cl		$PhCH_2NH_2$	EtOH, reflux	5	254
				Piperidine	EtOH, reflux	5	254
				Morpholine	EtOH, reflux	5	254
Et_2NCH_2	Cl	Cl		4-Methylpiperidine	EtOH, reflux	5	254
Ph	Cl		Me	$MeNH_2$	EtOH, 130° C, 3 days	4 (81%)	133, 237
				Me_2NH	EtOH, 140° C, 3 days	4 (52%)	133, 237
				Et_2NH	EtOH, 150° C, 3 days	4 (74%)	132, 237
				Piperidine	MeOH, 200–208° C, 3 days	4 (63%)	132
				Morpholine	MeOH, 200–208° C, 3 days	4 (83%)	132
	Cl		Me	Me_2NH	EtOH, 140° C, 3 days	4 (3.5 → 2 g)	132, 237
Ph	Cl		Et	Pyrrolidine	Toluene, reflux, 24 hr	4 (145 → 110 g)	256
				Me_2NH	MeOH, room temp., 20 hr, 45-50° C, 3 hr	4	256
				$C_6H_{11}NH_2$	MeOH, room temp., 20 hr, 45–50° C, 3 hr	4	256

				Morpholine	MeOH, room temp., 20 hr, 45–50° C, 3 hr	4	256
Ph	Cl		Ph	Piperazine	EtOH, 130–140° C, 6 hr	4	257
				N-Ethyl-*N*-β-dimethyl-aminoethylamine	EtOH, 130–140° C, 6 hr	4	257
				β-Diethylaminoethylamine	EtOH, 130–140° C, 6 hr	4	257
				Me_2NH	EtOH, 130–140° C, 6 hr	4	257
				Me_2NH	MeOH, 170° C, 10 hr	4 (2 → 1.5 g)	258
				Piperidine	EtOH, 150–160° C, 3 hr	4 (quant.)	258
Ph	Cl		Ph	Morpholine	EtOH, 150–160° C, 3 hr	4 (1 → 2 g)	258
Ph	Cl		OMe	*N*-(β-phenethyl)piperazine	EtOH, reflux, 20 hr	4	259
Ph	Cl		OEt	*N*-(β-phenethyl)piperazine	EtOH, reflux, 20 hr	4	259
Ph	Cl	NO_2		3-Amino-1,2,4-triazole	Reflux, 0.5 hr	4 (12.5 → 15 g)	87
				$PhNH_2$	Reflux, a few seconds	4 (5 → 5 g)	87
				3,4-Dichloroaniline	Reflux, 20 min	4 (12.5 → 8 g)	87
				p-Phenylenediamine	Reflux, a few seconds	4	87
				PhNHMe	Reflux, 10 min	4 (15 → 17 g)	87
				Me_2NH	100° C, 0.5 hr	4 (24 → 28 g)	87
				$Me_2NCH_2CH_2NH_2$	Reflux, 0.5 hr	4 (12.5 → 15 g)	87
Ph	Br	NO_2		2-Chloroaniline	$HCONMe_2$, Et_3N, 100° C, 5 hr	4 (5 → 3.6 g)	392
p-$MeC_6H_4SO_2$	Cl	NO_2		$PhNH_2$	Reflux, 10 min	4 (6 → 6 g)	87
Ph	Cl		OMe	Piperazine	EtOH, reflux, 12 hr	4 (1.18 → 1.24 g)	72
Ph		Cl		Me_2NH	EtOH, 80° C, 6 hr	5	23
				Morpholine	EtOH, reflux, 3 hr	5 (1.6 → 1.65 g)	23
Ph			Cl	Me_2NH	EtOH, 150–155° C, 6 hr	6	21, 260
				$MeNH_2$	EtOH, 150–155° C, 6 hr	6	21, 261
Ph			Cl	Et_2NH	EtOH, 150–155° C, 6 hr	6	21
				$BuNH_2$	EtOH, 150–155° C, 6 hr	6	21
				Pyrrolidine	EtOH, 150–155° C, 6 hr	6	21
				Piperidine	EtOH, 150–155° C, 6 hr	6	21
				Morpholine	EtOH, 150–155° C, 6 hr	6	21, 234
p-ClC_6H_4			Cl	Morpholine	150° C, 10 hr	6	262

TABLE IV (*continued*)

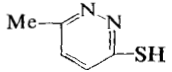
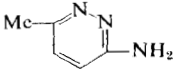
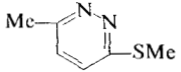
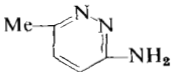
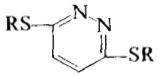
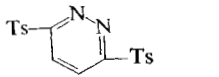
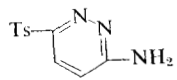
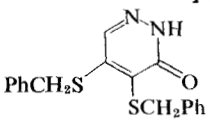
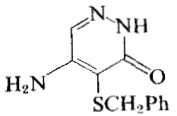
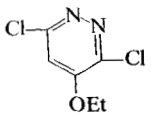
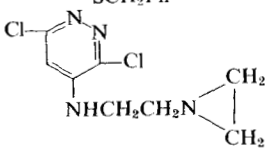
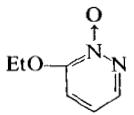
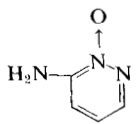
Halopyridazinone substituent							
R_2	R_4	R_5	R_6	Amine	Reaction conditions	Position of replacement[a]	References
				Me_2NH	EtOH, 150–155° C, 6 hr	6	263
p-$NO_2C_6H_4$			Cl	Me_2NH	EtOH, Et_3N, 165–175° C, 10 hr	6	264
Ph	MeS		Cl	Me_2NH	EtOH, 130° C, 21 hr	6	417
Ph	Cl	Cl		Morpholine	EtOH, reflux, 3 hr	5 (95%)	13
				Piperidine	EtOH, reflux, 3 hr	5 (95%)	13
				$MeNH_2$	Not stated	5	35, 36
				Et_2NH	Not stated	5	36
				$PhNH_2$	Not stated	5	35
				$MeNH_2$	170–190° C, 3–4 hr	5	235
				Me_2NH	170–190° C, 3–4 hr	5	235
				Me_2NH	170–190° C, 3–4 hr	4,5 (2 → 0.7 g)	365
				Et_2NH	170–190° C, 3–4 hr	5	235
				Pyrrolidine	EtOH, 170° C, 48 hr	5	235
Ph	Br	Br		$MeNH_2$	EtOH, 105–110° C, 5 hr	5	265
Ph	Br	Br		$PhCH_2NH_2$	Not specified	5	265
				Et_2NH	EtOH, 100° C, 5 hr	5	265
				Me_2NH	EtOH, 100–110° C, 4 hr	5	265
				Me_3N	EtOH, 100° C, 6 hr	5-Dimethylamino compound and a quaternary salt ($C_{13}H_{15}ON_3Br$)	265
				Morpholine	EtOH, reflux, overnight	5 (85%)	23
				Piperidine	EtOH, reflux, overnight	5 (81%)	23
				$HOCH_2CH_2NH_2$	EtOH, reflux, 20 hr	5	418

				Piperazine	EtOH, reflux, 25 hr	*N,N'*-Bis(1-phenyl)-5-bromo-6-pyridazon-4-yl)piperazine	418
Ph	Cl		Cl	Piperazine	EtOH, reflux, 20 hr	4	72
				$MeNH_2$	100°C, 6 hr	4 (71%)	365
				Et_2NH	EtOH, 100°C, 6 hr	4 (67%)	365
				i-$PrNH_2$	EtOH, 100°C, 6 hr	4 (86%)	365
				4-Benzylpiperazine	EtOH, reflux, 1 hr	4	72
p-ClC_6H_4	Cl		Cl	Piperazine	EtOH, reflux, 20 hr	4 (164 → 105 g)	72
Ph		Cl	Cl	Piperidine	EtOH, reflux	5 (73%)	23, 266, 267
				Me_2NH	EtOH, 200°C, 48 hr	5,6 (23%)	23, 266
				Me_2NH	EtOH, reflux	5 (84%)	23, 266
				Morpholine	EtOH, 200°C, 48 hr	5,6 (41%)	23, 266
				Morpholine	EtOH, reflux, 2 hr	5 (81%)	23, 266
				Piperidine	EtOH, 200°C, 48 hr	5,6 (42%)	23, 266
				Piperidine	EtOH, reflux, 2 hr	5 (73%)	23, 266
Ph		Br	Br	Me_2NH	EtOH, reflux, 4 hr	5 (75%)	23, 267
				Morpholine	EtOH, reflux, 4 hr	5	23, 267
				Piperidine	EtOH, reflux, 4 hr	5 (83%)	23, 267
m-$F_3CC_6H_4$	Cl	Cl		$MeNH_2$	EtOH, 85°C, 24 hr	4	419
				$EtNH_2$	EtOH, 85°C, 24 hr	4	419
				Me_2NH	EtOH, 85°C, 24 hr	4	419
m-$F_3CC_6H_4$	Br	Br		$MeNH_2$	EtOH, 85°C, 24 hr	4	419
				$EtNH_2$	EtOH, 85°C, 24 hr	4	419
				Me_2NH	EtOH, 85°C, 24 hr	4	419
Ph	Cl	Cl	Cl	Me_2NH	EtOH, 100°C, 6 hr	4,5 (48%)	365

[a] Yield is given in parentheses.

[b] The structure erroneously claimed by Meyer (232) to be the 4-chloro-2,6-dimethyl-3(2*H*)pyridazinone was revised subsequently by Wiggins et al. (10).

TABLE V. Displacement of Substituents Other Than Halogen Atoms with Amino Group

Starting material	Reagents and reaction conditions	Product[a]	References
	Aq. NH_3, 100°C, 1 day	 (0.65 → 0.08 g)	85
	NH_3, MeOH, 150°C, 3 days	 (18 %)	85
 R = H, Me	$PhNH_2$, reflux	No reaction	73
 Ts = $SO_2C_6H_4$-Me(*p*)	NH_3, EtOH, 150–170°C, 5 hr	 (30 → 16 g)	76
	EtOH, NH_3, 210°C, 30 hr		368
	Ethyleneimine, K_2CO_3, benzene, 7 hr		80
	Aq. NH_3, EtOH, 90°C, 2 hr		84

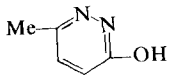
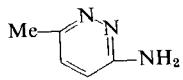
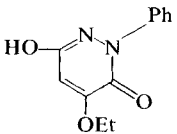
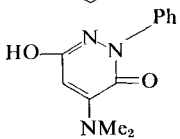
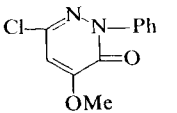
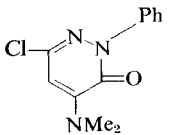
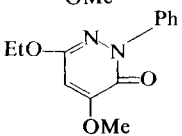
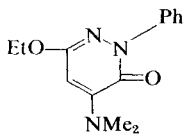
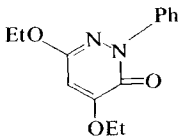
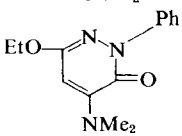
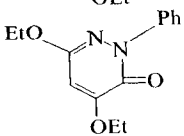
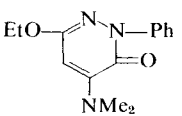
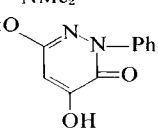
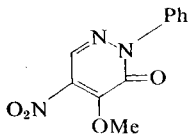
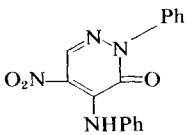
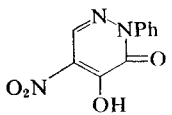
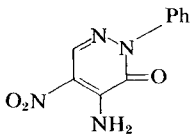
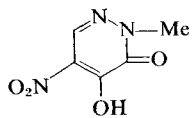
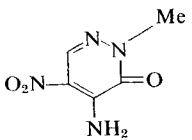
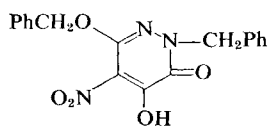
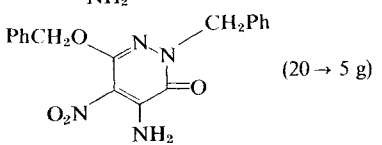
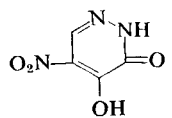
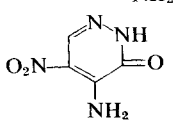
	Na_2SO_3, aq. NH_3, 240°C, 3 days		(7.3 → 0.2 g)	85
	Me_2NH, EtOH, NaOEt, 130–140°C, 8 hr		(1 → 0.8 g)	268
	Me_2NH, MeOH, NaOMe, 120–130°C, 5 hr		(2 → 0.6 g)	78
	Me_2NH, MeOH, NaOMe, 120–130°C, 8 hr		(0.1 → 0.04 g)	269
	Me_2NH, MeOH, NaOMe, 120–130°C, 8 hr		(5 → 1.3 g)	269, 270
	Me_2NH, MeOH, NaOMe, 120–130°C, 8 hr		(5 → 3 g)	81
		and 	(5 → 0.5 g)	

TABLE V (*continued*)

Starting material	Reagents and reaction conditions	Product[a]	References
	$PhNH_2$, reflux, 5 min	 (6 → 3.5 g)	87
	Aq. NH_3, 100° C, 3–10 hr	 (100 → 89 g)	87
	Aq. NH_3, 100° C, 3–10 hr	 (10 → 9 g)	87
	Aq. NH_3, 100° C, 3–10 hr	 (20 → 5 g)	87
	NH_3, MeOH, 120° C, 6 hr	 (10 → 5 g)	87

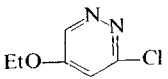
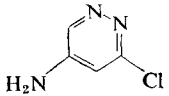
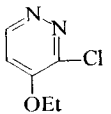
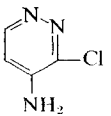
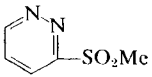
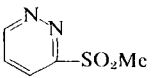
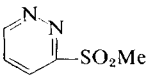
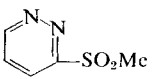
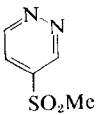
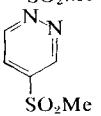
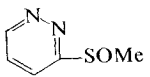
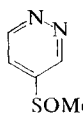
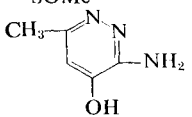
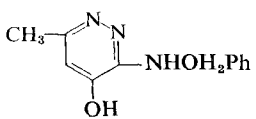
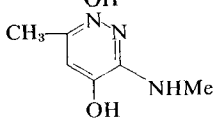
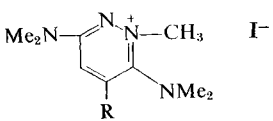
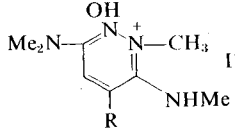
	Aq. NH_3, 100° C, 6 hr		77
	Aq. NH_3, 100° C, 6 hr		77
	Aq. NH_3, 100° C, 15 hr	3-Aminopyridazine (11%) and 3(2*H*)-pyridazinone (60%)	86
	Aq. NH_3, NH_4Cl, 100° C, 12 hr	3-Aminopyridazine (42%)	86
	$MeNH_2$, aq. HCl, 100° C, 18 hr	3-Methylaminopyridazine (65%)	86
	*n*-$PrNH_2$, 150° C, 12 hr	3-*n*-Propylaminopyridazine (93%)	86
	$MeNH_2$, aq. HCl, 100° C, 15 hr	4-Methylaminopyridazine (78%)	86
	*n*-$PrNH_2$, 111° C, 18 hr	4-*n*-Propylaminopyridazine (71%)	86

TABLE V (*continued*)

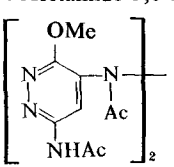
Starting material	Reagents and reaction conditions	Product[a]	References
	*n*-$BuNH_2$, 145° C, 20 hr	3-*n*-Butylaminopyridazine (67%)	369
	*n*-$BuNH_2$, 110° C, 18 hr	4-*n*-Butylaminopyridazine	369
	Benzylamine hydrochloride		371
	$MeNH_2$ hydrochloride		371
 I^-	Me_2NH	 I^-(R = H, Me)	372

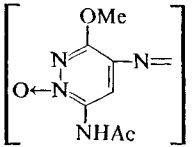
[a] Yield is given in parentheses.

TABLE VI. Catalytic Reduction of Nitropyridazines and Nitropyridazine *N*-Oxides

Starting material	Catalyst (adduct)	Product[a]	References
Pyridazine 1-oxide			
3-Nitro	Pd–C (HCl)	3-Aminopyridazine (31%)	228
	Pd–C, 2 moles H_2	3-Hydroxyaminopyridazine 1-oxide (76%)	228
	Pd–C, 3 moles H_2	3-Hydroxyaminopyridazine 1-oxide (21%), 3-aminopyridazine 1-oxide (32%), and 3-aminopyridazine (10%)	228
4-Nitro	Ni (R)(AcOH)	4-Aminopyridazine (59%)	228
	Ni (R)(AcOH)	4-Aminopyridazine (75%)	98
	Pd–C (HCl)	4-Aminopyridazine (0.1 → 0.01 g)	228
	Pd–C	4-Aminopyridazine 1-oxide (44%)	228
	Pd–C	4-Aminopyridazine 1-oxide (89%)	98
5-Nitro	Pd–C (HCl)	4-Aminopyridazine	228
5-Nitro-3-methyl	Pd–C (HCl)	3-Methyl-4-aminopyridazine (89%)	99
4-Nitro-5-methyl	Pd–C (HCl)	4-Amino-5-methylpyridazine (0.2 → 0.05 g)	271
4-Nitro-6-methyl	Ni (R)(AcOH)	4-Amino-6-methylpyridazine (70%)	98
	Pd–C (HCl)	4-Amino-6-methylpyridazine (0.5 → 0.11 g)	91
	Pd–C	4-Amino-6-methylpyridazine 1-oxide (87%)	98
	Pd–C	4-Amino-6-methylpyridazine 1-oxide (0.3 → 0.15 g)	91
4-Nitro-3,6-dimethyl	Ni (R)(AcOH)	4-Amino-3,6-dimethylpyridazine (91%)	98, 272
	Pd–C	4-Amino-3,6-dimethylpyridazine 1-oxide (80%)	98
4-Nitro-3,6-dimethyl	Pd–C	4-Amino-3,6-dimethylpyridazine 1-oxide (82%)	53
4-Nitro-3-chloro-6-methyl	(1) Pd–C (2) Ni (R)(AcOH)	4-Amino-6-methylpyridazine	98
	Pd–C	4-Amino-6-methylpyridazine (0.5 → 0.05 g)	91
	Ni (R)(AcOH)	4-Amino-3-chloro-6-methylpyridazine (43%) and its 1-oxide (2.5%)	404
4-Nitro-5,6-dimethyl	Ni (R)(AcOH)	4-Amino-5,6-dimethylpyridazine (82%)	99
4-Nitro-3-chloro-5,6-dimethyl	Pd–C (HCl)	4-Amino-5,6-dimethylpyridazine (84%)	99
6-Nitro-3,4-dimethyl	Pd–C (HCl)	6-Amino-3,4-dimethylpyridazine (57%)	99

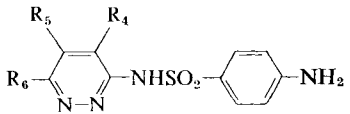
TABLE VI (*continued*)

Starting material	Catalyst (adduct)	Product[a]	References
		Pyridazine 1-Oxide (*continued*)	
3-Methoxy-4-nitro-6-methyl	Ni (R)(AcOH)	3-Methoxy-4-amino-6-methylpyridazine (70%)	98, 273
	(1) Pd–C in Ac_2O (2) 6*N* HCl	3-Methoxy-4-amino-6-methylpyridazine (0.5 → 0.18 g)	91
	Ni (R) 4 moles H_2	3-Methoxy-4-amino-6-methylpyridazine	97
	3 moles H_2	3-Methoxy-4-amino-6-methylpyridazine 1-oxide (98%)	97
	Pd–C	3-Methoxy-4-amino-6-methylpyridazine 1-oxide (90%)	98
3-Methoxy-4-nitro-5,6-dimethyl	Ni (R)(AcOH)	3-Methoxy-4-amino-5,6-dimethylpyridazine (81%)	99
3-Methoxy-4-methyl-6-nitro	Ni (R)(AcOH)	3-Methoxy-4-methyl-6-aminopyridazine (72%)	274
3-Methoxy-4-methyl-6-nitro	Pd–C	3-Methoxy-4-methyl-6-aminopyridazine 1-oxide (68%)	274
3-Methoxy-4-nitro	Ni (R)(AcOH)	3-Methoxy-4-aminopyridazine (0.2 → 0.09 g)	275
	Ni (R)(AcOH)	3-Methoxy-4-aminopyridazine (83%)	276, 277
	Pd–C (HCl)	3-Methoxy-4-aminopyridazine (70%)	172
	Pd–C	3-Methoxy-4-aminopyridazine (0.26 → 0.085 g)	275
	Pd–C	3-Methoxy-4-aminopyridazine (86%)	276
3-Ethoxy-4-nitro	Pd–C (HCl)	3-Ethoxy-4-aminopyridazine (1.4 → 0.4 g) and 4-amino-3(2*H*)pyridazinone	172
3-Methoxy-6-nitro	Ni (R)(AcOH)	6-Amino-3-methoxypyridazine	276
	Pd–C	3-Methoxy-6-aminopyridazine 1-oxide	276
3-Methoxy-4-nitro-6-chloro	Pd–C	3-Methoxy-4-aminopyridazine 1-oxide (54%)	100
4-Nitro-3,6-dimethoxy	Ni (R)(AcOH)	4-Amino-3,6-dimethoxypyridazine (quant.)	117
	Ni (R)(AcOH)	4-Amino-3,6-dimethoxypyridazine (20 → 15 g)	278
	Pd–C or Pd–C (HCl)	4-Amino-3,6-dimethoxypyridazine 1-oxide	95
	Pd–C in Ac_2O	4-Acetamido-3,6-dimethoxypyridazine (81%)	95
3-Methoxy-4-nitro-6-acetamido	Pd–C in Ac_2O		118

	(1) Pd–C in AcOH; (2) air oxidation	 (5 → 3.5 g)	118
3-Methoxy-4-nitro-6-amino	Pd–C (HCl)	3-Methoxy-4-hydroxyamino-6-aminopyridazine 1-oxide	118
	Pd–C (HCl)	3-Methoxy-4,6-diaminopyridazine 1-oxide	118
	Ni (R)(AcOH)	3-Methoxy-4,6-diaminopyridazine	118
Pyridazine			
3-Methoxy-6-nitro	Pd–C	6-Amino-3-methoxypyridazine	276
4-Nitro-3,5-diamino	Ni (R)	3,4,5-Triaminopyridazine (68%)	24
4-Amino-5-nitro-3,6-dimethoxy	Pd–C	4,5-Diamino-3,6-dimethoxypyridazine (80%)	117
3-Methoxy-4-amino-5-nitro-6-methyl	Ni (R)	3-Methoxy-6-methyl-4,5-diaminopyridazine (90%)	97
3-Methoxy-4-amino-5-nitro-6-chloro	Ni (R)	3-Chloro-6-methoxy-4,5-diaminopyridazine (70%)	404
	Pd–C	3-Methoxy-4,5-diaminopyridazine (66%)	404
3-Chloro-4-amino-5-nitro-6-methyl	Pd–C	3-Chloro-6-methyl-4,5-diaminopyridazine (68%)	404
3-Ethoxy-4-amino-5-nitro-6-methyl	Pd–C	3-Ethoxy-6-methyl-4,5-diaminopyridazine (85%)	404
4-Amino-5-nitro-3,6-diethoxy	Pd–C	4,5-Diamino-3,6-diethoxypyridazine (95%)	404
6-Chloro-5-nitro-3,4-diamino	Pd–C	6-Chloro-3,4,5-triaminopyridazine (56%)	404
3-Ethoxy-4-amino-5-nitro-6-chloro	Pd–C	3-Ethoxy-4,5-diaminopyridazine (35%)	404
4-Amino-5-nitro-3,6-dichloro	Pd–C	4,5-Diamino (16%) and 3-chloro-4,5-diamino-pyridazine	404

[a] Yield is given in parentheses.

TABLE VII. 3-Sulfanilamidopyridazines



Substituents	MP (°C)	Preparative method[a]	References
H	189–190	A, C	11, 141
	187–188	D	160–162
	297	A	9
	175	A	85
	N^4-Acetate (not specified)		161, 162
	106–107		85
	204–205		147
	N^1-Acetate 200–201		279
6-Me	Not specified	A	11, 141
	195–196	A, C	129
	190–191	A	9
		B	85
	N^4-Acetate (not specified)		11, 141
	247–247.5		129
	246–247		85
	N^1-Acetate 121–122		279
	2 HCl 215		129
6-Et	160	A	9
5-Me	262–264	D	8
4- or 5-Me	270–273	D	147
	254–255	D	147
4,5-di-Me	186	D	8
4,5,6-tri-Me	Not specified	A	11, 141
	N^4-Acetate (not specified)		11, 141

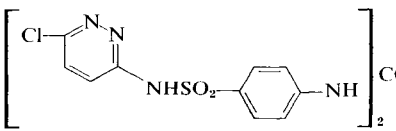
6-Ph	225	A	9
	Not specified	A	11, 141
6-Cl	190–191	A, B	44, 229
	Not specified	B	160–162
	Not specified	B	166, 167, 280
	192–193	B	165
	186–187	A	281
	Not specified	B	169
	Not specified	B	163
	Not specified	B	170
	195 (dec)	A, B	6
	195	C, D	144
	Not specified	A	8
	N^4-Acetate 225 (dec)		6, 144, 282
	218		164
	224–225		147
	Not specified		8, 161, 162
	218–219		154
	N^4-Ethoxycarbonate 198–200		229
	N^1-Acetate 221–223		279
	 CO 190–193 (dec)		157
	N^1-Carboxyethyl (not stated)		414
6-Br	>200 (dec)	A	44, 229
	200 (dec)	A, B	6
	243–244 (dec)	B	171
	N^4-Acetate 194 (dec)		6, 282
	N^4-Ethoxycarbonate 195–197		229
5-Me, 6-Cl	223	A	283

TABLE VII (*continued*)

Substituents	MP (°C)	Preparative method[a]	References
	N^4-Acetate 238		284
	230	A	284
5- or 4-Me, 6-Cl	234.5–235	B	147
4- or 5-Me, 6-Cl	224–225	B	147
4,5-di-Me, 6-Cl	221 (dec)	A	8
4-$CH_2CH_2CH_2CH_2$-5, 6-Cl	226 (dec)	A	8
6-MeO	182–183	A, D	147, 149
	181	A	6, 156
	Not specified	D	171, 165
	180	D	157, 286
	182	D	154–155
	182.5–183.5	A	148
	Not specified	B	175
		C	180
	180–181	D	282
	182	B	168
	Dimorphism		
	157.7–158.5	A	152
	179–180	A	152
	182–183	B	176
	182–183	A	285, 302
6-MeO	Dimorphism		
	182	D	8
	154	D	8
	180	C	182
	179–180	C	178
	182.5–184.5	D	287
	183	A	288

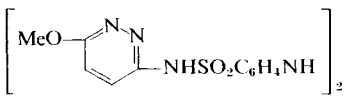
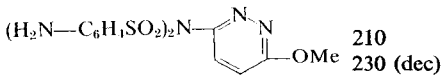
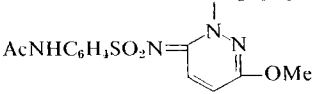
182–183	D	166, 167, 280
181–182	D	289, 290, 281
Monoethanolamine salt 87–89		291, 292
Diethanolamine salt 120–121		291, 292
N^4-Acetate 226–227		147
222 (dec)		6, 156
215–218		148
Not specified		175
N^4-Formate 200–203		293
N^1-Acetate 178–179 (dec)		279
174–175		294
Not specified		295–297
N^1-Ac, N^4-Ethoxycarbonyl 195–196		279
N^1-Ac, N^4-Benzal 201.5–202.9		295–297
N^1-Ac, N^4-Anisylidene (not specified)		295, 297
N^1-Ac, N^4-Benzyl 163–164		294
N^4-Maleate (HOOCCH=CHCO—) 172–172.5		298
N^4-Succinate ($HOOCCH_2CH_2CO$—) 213–214.5		298
N^4-Phthalate (amide) 246–247.5		298
(imide) 243–244.5		298
N^4-Benzyl 164–166		294
N^4-Methanesulfonate 194		291, 292
Na salt 208 (dec)		291, 292
di-Na salt 270		291, 292
N^4-Benzal 210–212 (dec)		294
205–207		299
N^4-Telephthalal (=CHC_6H_4CH=) 255–260		300
Mg salt of the addition compound with formaldehyde 198–202 (dec)		301
Ca salt of the addition compound with formaldehyde 207–209		301
 CO 215–220		302

TABLE VII (*continued*)

Substituents	MP (°C)	Preparative method[a]	References
	 210 230 (dec)		168 152
	 138		150
	N'-Carboxyethyl (not stated)		414
6-EtO	183–184	D	147, 149
	183	A	6, 156, 286
	184	A	288
	185.5–186.5	D	287
	N^4-Acetate 200 (dec)		6, 156, 286
6-*n*-PrO	184–185	D	147, 149
	185	D	288
6-i-PrO	187–188	B	176
	187–188	D	147, 149
	184	A	6, 156
	188	A	288
6-*n*-BuO	167	A	6
6-*n*-BuO	170–172	D	287
	170–172	C	178
	N^4-Acetate 185 (dec)		6
6-*n*-$C_6H_{13}O$	140–141	A, D	147–149
	139	A	6
	N^4-Acetate 164.5–165.5		148
6-*n*-$C_8H_{17}O$	133	A	6
6-$MeOCH_2CH_2O$	161	A	303
	161	C	178

	N^4-Acetate 182–183		303
6-$EtOCH_2CH_2O$	154–155	C	178
6-$HOCH_2CH_2OCH_2CH_2O$	137–139	C	178
6-$PhCH_2O$	200–201	D	147, 149
	197–199	D	287
	200	A	285
6-$PhCH_2CH_2O$	173–174	D	147, 149
6-PhO	139–140 resolidified and melted at 160–161	D	147, 149
4 or 5-Me, 6-MeO	199–202	B	147
	197–198.5	B	147
5-Me, 6-MeO	196–197	D	8
	182	A	283
5-Me, 6-EtO	174	A	283
	175	D	8
5-Me, 6-*n*-PrO	155.5	A	283
5-Me, 6-i-PrO	205	A	283
5-Me, 6-*n*-BuO	145	A	283
5-Me, 6-i-BuO	174.5	A	283
5-Me, 6-*sec*-BuO	184.5	A	283
5-Me, 6-$PhCH_2O$	217	A	283
6-AcO	210	A	6
	N^4-Acetate 222 (dec)		6
6-HO	243–244	B	177
	257 (dec)	A	6
	243–244	C, D	181
	240–243	C	178
	195	C, D	144
6-MeS	198–200	D	304
	198–200	C	143
	193–195	B	73
	198–200	A	305
	198	A	6
	N^4-Acetate 224		6

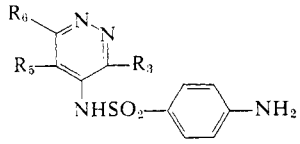
TABLE VII (*continued*)

Substituents	MP (°C)	Preparative method[a]	References
6-EtS	165–167	D	304
	162–163	A	305
	165–167	C	143, 142
	166	A	6
	N^4-Acetate 136–138		304
6-*n*-PrS	168	A	6
	N^4-Acetate 195		6
6-*n*-BuS	140	A	6
	N^4-Acetate 148		6
6-*n*-$C_5H_{11}S$	151	A	6
6-i-$C_5H_{11}S$	117–120	D	304
6-i-$C_5H_{11}S$	117–120	C	143
6-*n*-$C_6H_{13}S$	143	A	6
6-$PhCH_2S$	191–193	A	179
	N^4-Acetate 182–183		179
	N^1-Acetate 203–204		179
6-MeMgS	210 (dec)	D	306

6-HS	235 (dec)	D	304
	235 (dec)	C	143, 142
	285 (dec)	A	6
	229–230	D	73
6-MeSO	217–218	A	307–309
6-EtSO	237	A	309, 310
6-$MeSO_2$	196–199	D	311, 312
	196–199	C	142
	208–210	B	73
	197–199	A	305
6-$PhCH_2SO_2$	216–217	B	179
	215–216	A	179
	N^4-Acetate 229–231		179
6-*p*-$MeC_6H_4SO_2$	195	B	178
6-PhNH	254–256	D	73
4-OH, 6-Me	224–226	A	400
4-MeO, 6-Me	N^4-Acetate 242–244	A	400

[a] A: Condensation of aminopyridazines with *p*-acylaminobenzenesulfonyl chloride followed by hydrolysis. B: Condensation of halo and other substituted pyridazines with sulfanilamide or acetylsulfanilamide followed by hydrolysis. C: Reduction of pyridazinyl *p*-nitrobenzenesulfonamide. D: Miscellaneous methods.

TABLE VIII. 4-Sulfanilamidopyridazines



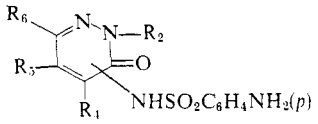
Substituents	MP (°C)	Preparative methods[a]	References
R_3=R_5=R_6=H	260–261	D	153
	240–242	A	172
	252 (dec)	D	14, 313
	N^4-Acetate, $\frac{1}{2}H_2O$ 196–196.5		172
6-Me	260–261	A	14
	217–217.5	A	151
3,6-di-Me	280	A	14, 272
3-MeO, 6-Me	174–175	A	14, 273
3,6-di-Cl	200–201	B, D	153
	191	B	172
	200–201	B	14, 173
	N^4-Acetate 255–260		153
3-MeO	$\frac{1}{2}H_2O$ 131–133.5	A	172
	Anhydrous 199–200	A	14, 358
	Anhydrous 201–202	D	314
	N^4-Acetate, H_2O 162–163		172
6-MeO	224–226	A	77
	237–238	A	119
	N^4-Acetate, $\frac{1}{2}H_2O$ 184–186		77
	N^4-Acetate 198–200		119
3-EtO	209	A	172
	N^4-Acetate, $\frac{1}{2}H_2O$ 150–152		172
6-EtO	226	A	77
	N^4-Acetate, $\frac{1}{2}H_2O$ 199		77
6-BuO	216–218	A	77
	N^4-Acetate, $\frac{1}{2}H_2O$ 179–180		77
3,6-di-MeO	189–190	A	172, 14, 278, 15, 92, 315
	190–193	D	174
	N^4-Acetate 207		14, 15, 92, 278, 315
	N^4-COOEt 176–177		316
	N^1-Acetate 194–196		316
3-MeO, 6-Cl	196	D	172
	207–208 (dec)	D	14
3- or 6-MeO, 3- or 6-Cl	200	D	153
3-EtO, 6-Cl	155–155.5	D	172
3,6-di-MeO, 5-Cl	200–203	D	174
3,5,6-tri-Cl	190–193	D	174
3-HO	237–238	A, D	14, 317, 318
	N^4-Acetate 253–254		14, 317, 318
3 or 6-HO	240–242	D	153
3-HO, 6-Me	273–274	A	14, 310

TABLE VIII (*continued*)

Substituents	MP (°C)	Preparative methods[a]	References
3-HO, 6-Cl	288–289	D	14, 319
3- or 6-HO, 3- or 6-Cl	262–265	D	153
3-HO, 6-MeO	248–248.5	A, D	92, 114
	N^4-Acetate 261 (dec)		92, 114
3-MeO, 6-HO	273	A, D	92, 114
	N^4-Acetate 274		92, 114

[a] For description of preparative methods, see footnote to Table VII.

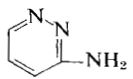
TABLE IX. 2-Substituted Sulfanilamido-3(2*H*)pyridazinone



Substituents	MP (°C)	Preparative method[a]	References
R_4 = *p*-$H_2NC_6H_4SO_2NH$-			
2-Ph, 6-Me	178	A, C	132
	N^4-Acetate 254		132
2-*p*-$NO_2C_6H_4$, 6-Me	190	A	132
	N^4-Acetate 238		132
2-Me	233 and 247–248	A	28, 320, 321
	N^4-Acetate 270–271		28, 320, 321
3,6-di-Me	200–201	A	28, 320, 321
2-Me, 6-Cl	185–186	A	28, 114
	N^4-Acetate 234.5–235		28, 114
2-Me, 6-MeO	215	A	28, 114
	N^4-Acetate 242–243		28, 114
R_5 = *p*-$H_2NC_6H_4SO_2NH$-			
2-Me	256–257	A	28
2,6-di-Me	H_2O 113–123	A	28
	Anhydrous 207	A	28
	N^4-Acetate 263		28
2-Me, 6-MeO	206.5	A	28
	N^4-Acetate 264		28
2-Ph	230–231	A	28
2-Me, 4-Cl	208–209	B	420
	N^4-Acetate 224–225	B	420
	N^4-Me: 198–201	B	420
2-Ph, 4-Cl	193–194	B	420
	N^4-Acetate 226–229	B	420
2-Me, 4-Br	198–200	B	420
	N^4-Acetate 227–229	B	420
R_6 = *p*-$H_2NC_6H_4SO_2NH$-			
2-Me	208	A	28

[a] For description of preparative methods, see footnote to Table VII.

TABLE X. 3-Aminopyridazines



Substituents and position			MP (°C)	References
4	5	6		
H	H	H	172	9, 224
			169–170	10, 421
			170–171	12, 230
			170	228
			168–170	11
			Hydrochloride 175.5–176.5	12
			Picrate 248–249 (dec)	9
			249–250 (dec)	12
			250–251	86
			3-AcNH 232	9
			226	128
			3-EtOCONH 189.5–190	136
			3-$Cl_3CCH(OH)NH$ 215	405
			$PhCOCH_2Br$ 219	197
		Me	224–225	129
			224	85
			225	88
			222–223	224
			226–227	381, 385
			Hydrochloride 237	129
			3-$MeSO_2NH$ 146–150	120
			3-$(MeSO_2)_2N$ 194–196	120
	Me		183–184	271
			Hydrochloride 264 (dec)	82
Me			193.5	322
			200	271

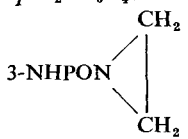
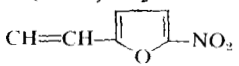
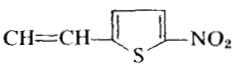
	Hydrochloride 194 (dec)	82
Et	150	9
Ph	152	9
4-Methoxyphenyl	162–164	183
	3-$H_2NC(=NH)NH$ 180	183
Cl	213–214 (dec)	12, 230
	210 (dec)	44, 229, 103, 405
	210	41
	3-AcNH 250 (dec)	323
	3-BzNH 196	323
	3-AcNH 252–253 (dec)	128
	3-EtOCONH 201–202	128
	3-*p*-$O_2NC_6H_4SNH$ (not specified)	180
	 (not specified)	324
	2-$Br(CH_2)_4$, bromide 202–208	396
	2-$EtOCOCH_2$, bromide 203–205	396
	2-$EtOCOCH_2CH_2$, bromide 185–188	396
	2-$EtOCOCH_2CH_2$, chloride 198–203	396
	2-$EtOCOCH_2$, chloride 190–195	396
Br	Above 180 (dec)	44, 229
	205–206.5 (dec)	12
	201–203	230
I	197–200 (dec)	325
OH[a]	243–244.5	422
	235–237 (dec)	422
	Hydrochloride 245–246 (dec)	144
MeO	103–105	147–148
	106–107	276

TABLE X (*continued*)

Substituents and position			MP (°C)	References
4	5	6		
			107	226
			104	288
			Picrate 222	276
			3-EtOCONH 106–108	128
			3-*p*-$O_2NC_6H_4SNH$ Not specified	180
			3-AcNH 222	128
			3-$CSNHC_6H_4OEt(p)$ 201–202	392
		EtO	183–184	147
			3-AcNH 178	128
		n-PrO	184–185	147
			3-AcNH 153	128
		i-PrO	187–188	147
			3-AcNH 173	128
		BuO	bp 178–180/8 mm	103
			Hydrochloride 164–165	103
			3-AcNH 132–132.5	103
			132	128
		n-$C_5H_{11}O$	3-AcNH 128	128
		i-$C_5H_{11}O$	3-AcNH 143	128
		n-Hexyloxy	140–141	147
			25–30	148
			3-AcNH 132	128
		n-$C_8H_{17}O$	3-AcNH 128	128
		n-$C_{10}H_{21}O$	3-AcNH 122	128
		PhO	139–140 (remelts at 160–161)	147
			Not specified	148

$PhCH_2O$	200–201	147
	Not specified	148
$PhCH_2CH_2O$	173–174	147
$MeOCH_2CH_2O$	Not specified	178, 303
SH	216–217 (dec)	130, 326
	285 (dec)	323
	250 (dec)	145
	3-AcNH >300	323
	3-BzNH 225	323
MeS	116–117	243
	117–118	145
	112	327
	Hydrochloride 216	327
EtS	53–54	145
EtS	92	327
	bp 192/1 mm	327
	Hydrochloride 164	327
BuS	84–85	145
PhS	136	145
$PhCH_2S$	99–101	179
	105	145
	3-AcNH 190–191	145
SO_2NH_2	3-AcNH 246–247	131
SOEt	143	310, 308
	Monohydrate 70	310, 308
SOMe	135.5	307, 308
	Monohydrate 70	307, 308
Ts	213–214	76
COOMe	200–201	7
COOEt	168–169	7
COOPr	141–142	7
$CONH_2$	260–262	7

TABLE X (*continued*)

Substituents and position			MP (°C)	References
4	5	6		
		$CS(=NH)NH_2$	Hydrochloride 159–160 (dec)	130
			264–266 (dec)	201
			N-oxide 275 (dec)	201
			Hydrochloride 290	120
			3-AcNH 292	120
			3-$MeSO_2NH$ 255–257	120
			3-$(MeSO_2)_2N$ 198–199	120
			286–288	134, 423
			$\frac{1}{2}(COOH)_2$ 259–261	225
			3-AcNH 305–306 (dec)	134, 423
	Me	Me	222–223	99
Meo		Me	271–273	371
			273–274	382, 384, 385
$PhCh_2O$		Me	163–166	382
HO_2CCH_2O		Me	194–196	382
Me (or H)	H (or Me)	Cl	70–75	44
Me		Cl	111–113	19, 82
			137	20
			3-AcNH 140	20
	Me	Cl	188	19
			187	20
			192	82
			186–187	322
			3-AcNH 216	20, 322

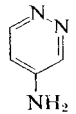
	Me	MeO	83–85	82
			125–125.5	274
			Picrate 224–225	274
Ph		Me	191–193	40
			184–186	382–385
			3-BzNH 208–210	40
			3-*m*-$NO_2C_6H_4CONH$ 216–218	40
			3-*p*-$NO_2C_6H_4CONH$ 227–229	40
x-$NO_2C_6H_4$		Me	221–223	40
			3-BzNH 208–210	40
x-$NH_2C_6H_4$		Me	3-BzNH 205–207	40
COOH		Cl	½ Hydrate 211–212 (dec)	18
	5-$(CH_2)_6$-6		½$(COOH)_2$ 259–261	225
4-$(CH_2)_4$-5		Cl	218 (dec)	8
CN	Me	Me	164–166	18
$CSNH_2$	Me	Me	195–197	18
COOEt	Ph	Ph	184–185	18
			3-AcNH 208–209	18
COMe	Ph	Ph	206–207	18
			3-AcNH 200–202	18
$CONH_2$	Ph	Ph	244–246	18
			3-AcNH 226–228	18
			Diacetate 247–248	18
CN	Ph	Ph	234–235	18
			3-AcNH 246.5–248.5	18
COOH			260–262 (dec)	373
COOH		Me	288 (dec)	373
COOMe		Me	185 (dec)	373
$CONH_2$		Me	254–255	373
OH		Me	253	381, 382
			3-BzNH 301–303	381
OH		Ph	264–266	381, 382, 384, 385

TABLE X (*continued*)

Substituents and position			MP (°C)	References
4	5	6		
OH	Me	Me	284–285	381, 382
OH	$PhCH_2$	Me	249–250	381, 382
OH		$PhCH_2$	225	381, 382
OH	5-$(CH_2)_4$-6		274–276	381, 382
Me	Me	Me	188	381–383
Me	Et	Me	124–125	381–383
OAc		Me	323 (dec)	381
SH		Me	188 (dec)	381
Me		Me	114	383–385
Ph		Ph	194–196	383–385
Me	$PhCH_2$	Me	139	383

[a] Although it has been shown that amino-3(2*H*)pyridazinones unsubstituted at the ring nitrogen exist in the pyridazinone form rather than pyridazinol form (92), they are classified as hydroxypyridazines for convenience.

TABLE XI. 4-Aminopyridazines



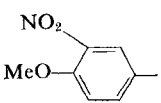
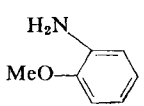
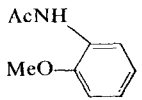
Substituents and position			MP (°C)	References
3	5	6		
H	H	H	129–131	13, 26
			130	135
			127–129	228
			129–130	107
			Picrate 228 (dec)	228
			4-AcNH 259–260	26
Me			166–166.5	99
			Picrate 223–224 (dec)	99
	Me		$\frac{1}{2}$ Hydrate 137–138	91
		Me	162–163	98
			$\frac{1}{2}$ Hydrate 162–163	91
	Ph		154–156	89
			4-BzNH 202–204	89
			4-*o*-$NO_2C_6H_4CONH$ 216–218	89
			4-*m*-$NO_2C_6H_4CONH$ 198–199	89
			4-*p*-$NO_2C_6H_4CONH$ 216–217	89
			199–201 (dec)	89
			4-BzNH 220–221	89
			4-BzNH 185–186	89

TABLE XI (*continued*)

Substituents and position			MP (°C)	References
3	5	6		
			4-BzNH 189–190	89
	Cl		70–73	65
			Picrate 210–212	65
Cl			141–142.5	77
		Cl	½ Hydrate 153–154.5	77
			153–156	415
			153–154	405
			4-AcNH 180.5	77, 405
			200–202	119
Me		Me	162–163	98, 273
			160–161	5
	Me	Me	196–197	99
			Picrate 239	99
Me		Ph	208	5
Ph		Ph	304	5
MeO		Me	158–159	98, 273
			159–160	91
			159–161	97
			156–157	404
EtO		Me	165–166	404
Cl		Me	179.5–180	404
OH		Me	260–261	91
Cl	Cl		150–151	26
			151	65, 405
Cl		Cl	203	13, 39, 104, 16
			205	405

	Cl	Cl	176–178	26
Cl	Br	Cl	178	405, 65
EtO	Br	Cl	202.5–203.5	404
F	F	F	147.5–148.5	404
H (or OH)	Cl	OH (or H)	89.5–91	363, 364
OH or H	Cl	H or OH	350–354	231
OH or H	Cl	H or OH	292–294	231
Cl		OH	>310	77
	Cl	OH	278–280	27
			301–302	405
			Above 300	39, 77
			352	33
			4-AcNH 277–279	39
			4-BzNH 244	39
	OH	Cl	259 (dec)	27
OH		Cl	4-AcNH 258 (dec)	27
			285	39
OH		Cl	286	109
			300–301	92
			4-AcNH 255–256	39
			4-BzNH 235	109
SH		Cl	185–195 (dec)	204
SH		SH	½ Hydrate above 350	65
	$PhCH_2S$	OH	248 (dec)	368
MeO		Cl	190–191	172
EtO		Cl	199	172
n-BuO		Cl	164–165	405
MeO	Cl		85	77
	Cl	MeO	178–179	77
	Cl	EtO	181	77
	Cl	*n*-BuO	131–133	77
MeO		MeO	175	95, 15, 17
			175–176	117
			177–178	172, 92, 278
			Picrate 177	95

TABLE XI (*continued*)

Substituents and position				
3	5	6	MP (°C)	References
			4-AcNH 143	95
EtO		EtO	145–146	404
OH		MeO	277–278	92
			275	328
MeO		OH	266	92
			Hydrochloride 217–218	92
p-AcNHC$_6$H$_4$SO$_2$O		MeO	167–169	92
TsO		MeO	171–172	146
OH			228–229	39
			230	275
			229–230	276
			230–231	172
			Picrate 187–188	172
			4-AcNH 272	39
		OH	286–287	39, 27
			288 (dec)	106
			4-AcNH 313–315	77
			319–320	119
			Diacetate 253–254	77
MeO			127–128	172
			127	275
			128–129	276, 277
			Picrate 208	276
TsO			205–205.5	146
EtO			75	172
			Picrate 192–193	172
		MeO	161–162	77
			162–163	119
		EtO	61–63	77
			bp 170–180/0.1 mm	77

		BuO	Picrate 144–146	77
			bp 200 (bath)/0.5 mm	77
			Picrate 124–126	77
MeO		TsO	166	146
Ph	Ph	Ph	210	43
			213	5
			4-EtOCS 180	43
MeO	Me	Me	182–183	99
OH	COMe	Me	234	113
			Diacetate 202	113
			Oxime 249	113
OH	COPh	Ph	229–230	113
			4-AcNH 197	113
OH	COMe	Ph	201–203	113
			4-AcNH 237	113
OH	COMe	OH	338	113
Ph	COMe	OH	302	113
			Oxime 242	113
	OH	OH	290	102
MeO	NO_2	MeO	232–233	117
$NHNH_2$			Dihydrochloride 281–283	415
$NHNH_2$		Cl	190	77
			209	104
$NHN{=}CMe_2$		Cl	158–162	415
MeO	NO_2	Me	197–198	97
			193–194	404
MeO	NO_2	Cl	181.5–182	404
EtO	NO_2	Cl	166–167	404
Cl	NO_2	Cl	118–119.5	404
Cl	NO_2	Me	155–155.5	404
EtO	NO_2	Me	173–174	404
EtO	NO_2	EtO	170.5–171.5	404
OH or Cl	NO_2	Cl or OH	291–293	404
$NHNH_2$	Cl		201–202	65, 110
			Picrate 199–200	65

TABLE XI (*continued*)

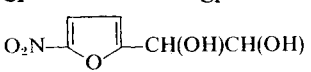
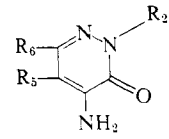
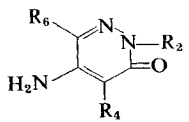
Substituents and position			MP (°C)	References
3	5	6		
		$NHNO_2$	Nitrate 259–260	24
	$NHNO_2$		>400 (darkens at 250–270)	24
	$NHNH_2$		150–150.5	24
		$NHNH_2$	169–176	424
			Dihydrochloride 220–222	415
NHN=CHPh		Cl	234	110
			4-AcNH 244	110
			4-BzNH 260 (dec)	110
$N(Me)NH_2$		Cl	163–164	105
	COOH		316 (dec)	377
			319–320	386
	COOEt		162–163	377
			4-AcNH 90	377
	$CONH_2$		293 (dec)	377
CN			222	373
CN		MeO	257–258	373
CN		Cl	273 (dec)	373
CN	Cl	Cl	267–268	373
CN	Cl	MeO	235–236	373
COOH			222 (dec)	373
COOH		MeO	188 (dec)	373
$CONH_2$			187–188	373
$CONH_2$	Cl	Cl	273–274	373
			Not stated	425
Cl	Cl	Cl	203–204	405

TABLE XII. 4-Amino-3(2*H*)pyridazinones



R_2	R_5	R_6	MP (°C)	References
Me			175–176	28
Me		Cl	145–145.5	28, 114, 406
			4-AcNH 208–209	114
Me		OH	250–251	28
Me		MeO	159–160	28, 338, 339
			157–158	114
			4-AcNH 204–205	114
Me	Cl	Me	169–170	28, 32
Me		Me	141–142	28, 32, 115
			Picrate 161–162	28, 32, 115
			Hydrochloride 232 (dec)	28, 32, 115
			4-AcNH 211	115
			4-BzNH 124.5–125.5	115
Me	SO_2NH_2		222–223	370
Ph	Cl		142–143.5	340
			143	37
Ph	Ph	Ph	4-BzNH 232–233	1
Ph		Me	169	132
			Hydrochloride 176 (dec)	132
			4-AcNH 265	132
Ph		Cl	179–180	21
3-Tolyl		Me	153	133, 237
			4-AcNH 237	133
2-Pyridyl		Me	172	133, 237
			4-AcNH 216	133
4-Methoxyphenyl		Me	161–162	236
4-Ethoxyphenyl		Me	156–157	236
4-Nitrophenyl		Me	196	132
			4-AcNH 190–191	132
4-Amino-6-chloro-2-phenyl-3(2*H*)pyridazine-thione			205–206	426

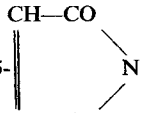
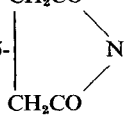
TABLE XIII. 5-Amino-3(2*H*)pyridazinones

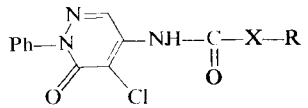


R_2	R_4	R_6	MP (°C)	References
Me			193.5–194.5	28
Me		Cl	168–169	28
Me		MeO	196–197	28
Me		OH	252–253	195
			Dihydrate 246–247	195
Me	Cl	Me	169–170	28, 32
Me		Me	163	10, 237
			168–169	28
			166–167	232
			Hydrochloride 245 (dec)	10
			266–267 (dec)	28
			Picrate 130	10
			163–164	28
			5-AcNH 227	10
			232–233	28
Me	SO_2NH_2		269	370
Et	Cl		108–109	191, 35
			217	33
Me	Cl		203–204	33
			195–198	407
Cyclohexyl	Cl		225–226	35, 341
			224–225	33
			5-NHCOOMe 104–106	184

			5-HOOCCONH 193–195	137
			5-O═C═N 121–123	184, 391
			5-Me_2NCONH 150–151	391
Cyclooctyl	Cl		184–185	35, 341
			178–179	33
Cyclohexen-1-yl	Cl		156–157	233
			5-HOOCCONH 176–178	233
			5-Cl_3CCH(OH)NH 136–138	233
Cyclohexen-1-yl	Br		165–167	233
Cyclohexyl	Br		5-MeNHCH═N 174–175	185, 353
			5-Me_2NCH═N 154–155	185, 353
			5-Cl_3CCH(OH)NH 215–220 (dec)	354
Cyclopentyl	Br		Me_2NCH═N (not specified)	353
			Cl_3CCH(OH)NH (not specified)	354
Cyclooctyl	Br		Me_2NCH═N, Cl_3CCH(OH)NH (not specified)	353, 354
CH_2CH_2CN	Cl		195–198	33
CH_2COOH	Cl		253–255	33
			245–250	405
CH_2CH_2OH	Cl		178–180	33
$(CH_2)_3OMe$	Cl		137–138	33
N-Methylpiperidyl	Cl		Hydrochloride 296–297	33
Glucosyl	Cl		178–180	33
			132–133	388
4-Acetamidobenzenesulfonyl		MeO	215–217	92
4-Toluenesulfonyl		MeO	200–201	146
Ph			209–211	28
Ph	Cl		198–200	34
			200–201	29
			204–206	340

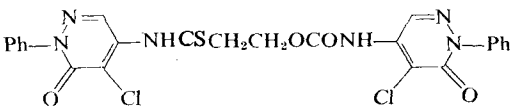
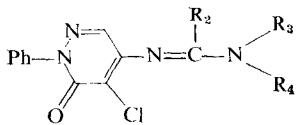
TABLE XIII (*continued*)

R_2	R_4	R_6	MP (°C)	References
			202–204	35
			205–206	33
			206–207	31
			205	36, 37
			210	191
			5-$(EtOOC)_2(OH)CNH$ 170–173	188
			5-HOOCCONH 195–196	137
			5-NaOOCCONH >250	137
			5-$HOOC(CH_2)_2CONH$ 160–162	137
			 229–230	137
			 259–260	137
			5-O=C=N 153–154	184
			154–155	390
			5-S=C=N 240–241	184
			5-MeN(OMe)CONH 161–163	391
			5-Me_2NCONH 141–142	391
			5-Et_2NCONH 137–138	391
			5-CH≡CMeCHNMeCONH 142–143	391



X = O	R = Me	142–143	184
	Et	110–111	184
		132–133	388
	$EtO(CH_2)_2$	67–71	184
X = O	R = C_8H_{17}	53–54	184
	i-C_9H_{19}	58–62	184
	$C_{18}H_{37}$	66–69	184
		75–79	388
	Ph	120–122	184
	(MeC≡C)EtMeC	143–145	184
	4-Hydroxyphenyl	196–198	184
	2,4-Dichlorophenyl	165–170	184
	Pentachlorophenyl	172–176	184
	5-Norbornen-2-ylmethyl	148–149	184
	3,3,4,4′-Tetrachlorotetrahydro-2-furyl	147–150	184
	3,4-Dichloro-2,5-dihydro-5-oxo-2-furyl	157–160 (dec)	184
	$Me_2C = N$	148–149	184
	Dimethylamino	148–149	390
	Cyclohexylideneamino	125–127	390
	Cyclooctylideneamino	125	390
	pentylideneamino	139–139.5	390
X = S	R = Ph	143–145	184
	4-Chlorophenyl	159–160	184
	4-Bromophenyl	165–168	184
	$Cl_2C{=}CClCH_2$	86–89	184
	CH_2CH_2COOH	165 (dec)	184
	$Et_2NCH_2CH_2$	174–177	184

TABLE XIII (*continued*)

R_2	R_4	R_6	MP (°C)	References
			194–195	184
	Condensation products with ketones			
				

R_2	R_3	R_4	MP (°C)	References
$-(CH_2)_3-$		Me	Hydrochloride 23	186
	Me	Me	162–163	
			Hydrochloride 203–205	
			Hydrobromide 227–229	
	$-(CH_2)_4-$		152–153.5	
Et	$-(CH_2)_5-$		128–130	
Me	$-(CH_2)_4-$		169–171	
Me	$-C_2H_4OCH_4-$		160–161	

R_2	R_4	R_6	MP (°C)	References
3-Chlorophenyl	Cl		214–216	33
4-Chlorophenyl	Cl		254–256	33

4-Fluorophenyl	Cl		5-$Cl_3CCHOHNH$ 228–229	393
4-Tolyl	Cl		226	33
4-Methyl-2-aminophenyl	Cl		220–222	33
4-Anisyl	Cl		279–280	33
4-Carboxyphenyl	Cl		Not specified	33
4-SO_2NH_2-phenyl	Cl		Not specified	33
4-SO_2NHMe-phenyl	Cl		262–264	33
α,α,α-Trifluoro-*m*-tolyl	Cl		174–175	409
	Br		172–174	409
1-Naphthyl	Cl		207–209	33
Ph		Cl	236–238	23
			234–236	340
Ph	Br		220–221	28
			214–215	35
			225–226	30
			216–217	427
			5-AcNH 204–205	30
			5-EtOCONH 106–107	184
			135–136	388
			5-MeOCONH 151–152	388
			5-$EtOCH_2CH_2OCONH$ 70–72	388
			5-$Me(CH_2)_{17}OCONH$ 77–79	388
			5-$ClCH_2CH_2OCONH$ 102–104	388
			5-PhSCONH 167–168	388
			5-HOOCCONH 183–184	137
			5-$HO(CH_2)_2OCONH$ 168–170	184
			5-MeNHCH=N 175–175.5	185, 353
			Hydrochloride 234–236 (dec)	185, 353
			5-Me_2NCH=N 166–167	353
			5-$Cl_3CCH(OH)NH$ 213–215 (dec)	354
			5-O=C=N 146–149	184
			5-$NHCOONCHC_6H_4Cl$(*o*) 159–160 (dec)	390

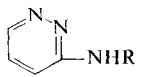
TABLE XIII (*continued*)

R_2	R_4	R_6	MP (°C)	References
			5-Me_2NCONH 142–143	391
Ph	I		150–152	408
			5-AcNH 198–200	408
			5-O=C=N 105–110	408
			5-$ClCH_2$CONH 167–168	408
			5-HOOCCONH 182	408
			5-Me_2NCH=N 205–207	408
			5-PhNHCONH 224–226	408
			5-Cl_3CCHOHNH 130 (dec)	408
			5-MeOOCCHOHNH 244–246	408
Cyclohexyl	I		5-AcNH 139–141	408
Me	OH		234–235	102
			Hydrochloride 198	102
Me	OH	Ph	Monohydrate 228–229	102
$PhCH_2$	OH	$PhCH_2O$	164–165	102
3-Chlorophenyl	OH		176–177	102
Ts	OH		193–194	102
Cyclohexyl	OH		188–189	102
4-Methoxyphenyl	OH		228–229	102
EtOCO(Me)CH	OH		129–130	102
Ph	OH		224–225	102, 101

TABLE XIV. 6-Amino-3(2*H*)pyridazinones

R_2	R_4	R_5	MP (°C)	References
Me			220–221	28
Ph			153–154	21, 22
			Hydrochloride 170–171	22
Me	Cl	Cl	191.5–193	374, 375
Et	Cl	Cl	130–131.5	374, 375

TABLE XV. 3-Alkylaminopyridazines



Substituent and position					
R	4	5	6	MP (°C)	References
Me				Picrate 209	86
Me			SH	234–237 (dec)	243
Me				194–198	428
Me			MeS	83–84	243
			Cl	198–199	243
				199–201	405
				N-PON (CH$_2$)$_2$ 95–97	243
Me	MeNHCO	Ph	Ph	193–194	108
				Dihydrate 96–98 (remelts at 182–183)	108
Me	OH		Me	237–238	371
Me	MeO		Me	183–184	371
Et				93–94	54
				Picrate 157–158	54
Et			Cl	125–126	50
				123–125	244

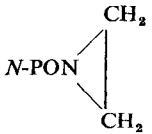
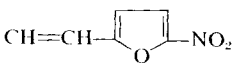
				324
n-Pr			85	86
n-Pr		SO_2NH_2	Not specified	131
i-Pr		Cl	107–110	48
			Picrate 174–176	48
i-Pr		$CH_2{=}CHCH_2O$	80–81.5	48
i-Pr		PhS	119–120	48
			Picrate 175–177	48
n-Bu			72–73	369
n-Bu		$MeSO_2$	117–118	75
n-Bu		Cl	108–109	47
			111	48
n-Bu		SO_2NH_2	Not specified	131
i-Bu		SO_2NH_2	Not specified	131
$(HOCH_2)_2CH$			170–172	120
	—$(CH_2)_6$—		Not specified, salt with 2$(COOH)_2$	225
$(CH_2)_6NCH_2CH_2$	—$(CH_2)_6$—		Not specified	225
$Et_2NCH_2CH_2$		Cl	87–87.5	247
			bp 130/5 × 10^{-5} m	247
			Dihydrochloride 223–224	247
$Et_2NCH_2CH_2$		$Et_2N(CH_2)_3O$	bp 175/1.8 × 10^{-5} mm	247
			n_D^{25} 1.5118	247

TABLE XV (*continued*)

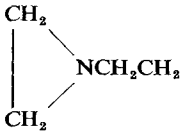
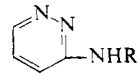
Substituent and position					
R	4	5	6	MP (°C)	References
			Cl	127–128	75
1,2-bis(6-Chloro-3-pyridazinyl)ethane				268–269 (dec)	47
$HOCH_2CH_2$			Cl	135	47
				135.5	405
$ClCH_2CH_2$			Cl	120	405
$BrCH_2CH_2$			Cl	133–138	396
$HO(CH_2)_3$			Cl	132.5–133	396
$Br(CH_2)_3$			Cl	135–141	396
$HOOCCH_2CH_2$			Cl	Not stated	414
Morpholino			Cl	138–140	412
Cyclohexyl			Cl	160–161	47
				167–168	48
$Et_2N(CH_2)_3$			Cl	bp $130/10^{-3}$ mm	246
				87–87.5	246
				Dihydrochloride 223–224	246
$Et_2N(CH_2)_3$			$Et_2N(CH_2)_3O$	bp $175/3 \times 10^{-3}$ mm	246
$HOOCCH_2$			Cl	200	405
Allyl			Cl	107–109	405
Allyl	OH		Me	176–178	371
Allyl	MeO		Me	139–140	371
EtOOCC(CN)=CH				193–194	394

TABLE XVI. 3-Aryl or Heteroarylaminopyridazines



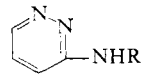
Substituent and position

R	4	5	6	MP (°C)	References
Ph				177–178	329, 249
Ph			OH	200–201	330, 249
Ph			PhO	149	331
Ph			$MeSO_2$	168–170	75
Ph			SH	184–185	73
Ph			SMe	179–180	73
Ph			$PhCH_2O$	154–155	249
Ph			Br	186–187	331
Ph			$4\text{-}MeOC_6H_4O$	175–176	331
Ph			Cl	190	47, 249
				191–192	48
				Hydrochloride 263 (dec)	47
Ph			Me	167.5–168	239
Ph	OH		Me	296–298	371
Ph	MeO		Me	178–180	371
4-Chlorophenyl			Cl	201–203	250, 249
4-Chlorophenyl			$PhCH_2O$	185	250, 249
4-Chlorophenyl				203–204	332, 249
4-Chlorophenyl			OH	254	330, 249
4-Chlorophenyl			SH	226–228	428
4-Chlorophenyl			PhO	182–183	331
4-Bromophenyl			Cl	218–219	250, 249
4-Bromophenyl			$PhCH_2O$	182	250, 249
4-Bromophenyl			OH	262	330, 249
4-Methoxyphenyl				117–118	332, 249
4-Methoxyphenyl			$PhCH_2O$	147–149	250, 249
4-Methoxyphenyl			OH	215–216	330, 249
4-Methoxyphenyl			Me	142–143	239
4-Methoxyphenyl			Cl	147–148	47, 249
4-Methoxyphenyl			SH	197–198	428
4-Ethoxyphenyl			$PhCH_2O$	151–152	250, 249
4-Ethoxyphenyl			OH	208	330, 249
4-Ethoxyphenyl			Cl	167–168	249
2-Chlorophenyl				165–166	332, 249
2-Chlorophenyl			Cl	124.5–125.5	334, 249
3-Chlorophenyl				189–190	332, 249
3-Chlorophenyl			SH	203–204	428
3-Chlorophenyl			Cl	182–183	334, 249
3-Chlorophenyl			PhO	150–151	331
3-Chlorophenyl			$4\text{-}MeOC_6H_4O$	139–140	331
2-Methoxyphenyl				109–110	332, 249
2-Methoxyphenyl			Cl	117–118	334, 249
2-Methoxyphenyl			SH	211–214	428

TABLE XVI (*continued*)

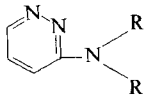
Substituent and position					
R	4	5	6	MP (°C)	References
3-Methoxyphenyl				115–117	332
3-Methoxyphenyl			Cl	183–184	334
2-Carboxyphenyl			Cl	Ba salt ($\frac{1}{2}$)	62
4-Tolyl			Cl	189–190	47
4-Nitrophenyl			Cl	266–267	47
2-Furyl			Me	161–162	239
2-Thenyl			Me	178–179	239
4-Chloro-2-methoxyphenyl			SH	245–250	428
2,3-Dichlorophenyl			SH	225–227	428
2,5-Dichlorophenyl			SH	232	328
3,4-Dichlorophenyl			SH	231	328

TABLE XVII. 3-Aralkylaminopyridazines



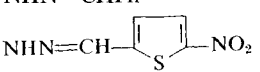
Substituent and position					
R	4	5	6	MP (°C)	References
Benzyl			MeO	102	333
Benzyl			EtO	122–123	333
Benzyl			PrO	104	333
Benzyl			Benzyloxy	135	333
Benzyl			OH	173	249
Benzyl			Cl	162–163	47
Benzyl			Me	138	88
				138.5–139	239
				Picrate 165	88
Benzyl				110	88
Benzyl				114	249
				Picrate 169–170	88
Benzyl	OH		Me	209–210	371
Benzyl	MeO		Me	174–176	371
3,4-Dimethoxybenzyl			Me	127–128	239
Phenethyl	OH		Me	204–205	371
Phenethyl	MeO		Me	159–161	371

TABLE XVIII. Tertiary 3-Aminopyridazines



Substituent and position					
RR'N	4	5	6	MP (°C)	References
Me_2N				bp 115–120/7 mm	366
				Methiodide 193–194	366
				Picrate 178–181	366
Me_2N			Me	65–66	241
Me_2N			Cl	100–101	75
				101–102	366
				104–106	405
Me_2N			$MeSO_2$	116–118.5	75
Me_2N			Ph	116	237
Me_2N	Me			Picrate 136–137	390
Me_2N	4 or 5-Me		Cl	122	20
				126	82
Me_2N	4 or 5-Me			90	20
Me_2N		Me	Br	118.5	251
Me_2N		Me	Cl	122	251
				121–122	366
Me_2N	Me		Cl	39–40	366
Me_2N	OH		Me	229–230	371
Me_2N	MeO		Me	88–90	371

TABLE XVIII (*continued*)

Substituent and position					
RR′N	4	5	6	MP (°C)	References
Me_2N			Me	Picrate 181–182	429
Et_2N			Cl	50.5–53.5	244
Ethyleneimino	4 or 5-MeO		Cl	141.5–143	79
				49–51	405
Ethyleneimino	4 or 5-Me		Cl	111–113	79
Ethyleneimino			Cl	126–127	248
Ethyleneimino			Br	145	248
Ethyleneimino			$MeSO_2$	147–148	75
Bu_2N			Cl	57–58	48
Piperidino				bp 180–181/14 mm	51
				Picrate 153	51
Piperidino			Cl	82–83	44
				78	51
Piperidino			Me	65–66	241
Piperidino			$MeSO_2$	160–162	75
Piperidino			SH	147–149	243
Piperidino	OH		Me	232–233	371
Piperidino	MeO		Me	93–95	371
Piperidino			$NHNH_2$	140–145	412
				Hydrochloride 222–226	406, 412
				Hydrochloride 187.5–188.5	412
Piperidino			NHN=CHPh	235–237	429
Piperidino				238–240	429
Piperidino			$NHN{=}CMe_2$	Hydrochloride 193–195	429
Piperidino			NHN=CMeCOOH	152–155	429

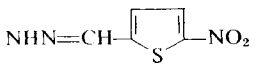
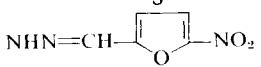
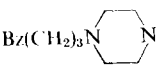
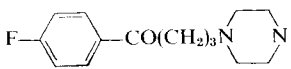
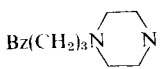
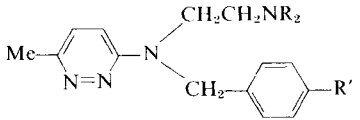
Piperidino			MeS	77–79	243
Morpholino	OH		Me	248–250	371
Morpholino	MeO		Me	158–159	371
Morpholino	2-Tetrahydropyranylthio	$PhCH_2S$		184	410
Morpholino	Cl	$PhCH_2S$		127	410
Morpholino	$PhCH_2S$	$PhCH_2S$		103–105	410
Morpholino			$NHNH_2$	145–150	412
				Hydrochloride 236	412
				234–236	406
Morpholino			$NHN{=}CMe_2$	187–190	429
Morpholino			NHN=CMeEt	125–127	429
Morpholino				244–246	429
Morpholino				Above 280	429
4-Methyl-1-piperazinyl			$NHNH_2$	165–167	412
4-Methyl-1-piperazinyl			$NHNH_2$	Hydrochloride 165	406
4-Methyl-1-piperazinyl			$NHN{=}CMe_2$	158–161	429
Piperazino				Dihydrochloride 275–278.8	74
Piperazino			Cl	101	245
				100–101.8	74
Piperazino			MeO	82	245
N-(3,4-Dimethoxybenzyl)-piperazino			Cl	146	245
Diallylamino			Cl	43–46	413
Diallylamino			$NHNH_2$	Dihydrochloride 211–214	413
Et_2N			NHN=CHPh	197–203	429
$(HOCH_2CH_2)_2N$			$NHNH_2$	Hydrochloride 185.5–188.5	406
$(HOCH_2CH_2)_2N$			$NHN{=}CMe_2$	Hydrochloride 196–197	429
$(HOCH_2CH_2)_2N$			NHN=CMeEt	Hydrochloride 200–202	429
PhNMe			$NHNH_2$	Hydrochloride 206–208	406, 412

TABLE XVIII (*continued*)

Substituent and position					
RR'N	4	5	6	MP (°C)	References
$Me_2N(CH_2)_3(Me)N$			—$(CH_2)_6$—	Not specified	225
			Cl	183	335
$Bu_2NCH_2CH_2(PhCH_2)N$				Not specified	238
N-(3,4-Dimethoxybenzyl)piperazino			MeO	121	245
			SMe	124–125	74
			Cl	176–176.8	74
			Cl	138–138.8	74
			MeO	98.8–99.8	74
			Cl	155–156	74
$HOOCCH_2MeN$				186–188	405
$EtOOCCH_2MeN$				104	405



Compound	R	R′	BP (°C/mm Hg)	References
	Me	H	168–170/0.003	240
	Me	Cl	168–170/0.01	240
	Me	MeO	180–185/0.005	240
	Me	EtO	190–195/0.015	240
	Me	*n*-PrO	190–195/0.02	240
	Me	i-PrO	196–200/0.05	240
	Et	H	144–150/0.0006	240
	Et	MeO	160–165/0.001	240

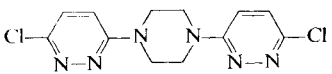
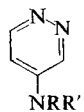
	MP (°C)	Reference
	352	245

TABLE XIX. Secondary or Tertiary 4-Aminopyridazines



Substituent and position					
3	NRR′	5	6	MP (°C)	References
	MeNH			77–78	86
				Picrate 192–193	86
	MeNH		Cl	172–173 (dec)	86
Cl	MeNH		Cl	146–147	105
				154–156	405
	MeNH	Cl	OH	252–253	33
$NHNH_2$	MeNH			Dihydrochloride 247–251	415
$NHNH_2$	MeNH		Cl	217–218	105
$NHN{=}CPr_2$	MeNH		Cl	94–96	415
MeO	MeNH		Cl	178–179	405
n-BuO	MeNH		Cl	n_D^{20} 1.5590	405
Cl	MeNH	Cl	Cl	113–114	405
Me	EtNH		Me	187–188	53
	EtNH	Cl	OH	205	254
				198–200	33
Cl	EtNH		Cl	97–99	415, 405
$NHNH_2$	EtNH		Cl	177–179	415
NHN=CMePr	EtNH		Cl	83–85	415
MeO	EtNH		Cl	95–97	405
n-BuO	EtNH		Cl	n_D^{20} 1.5498	405

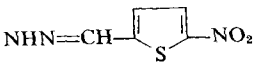
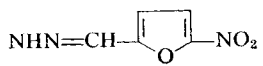
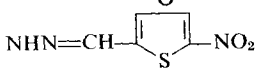
	n-PrNH			109	86
Cl	i-PrNH		Cl	bp 140–141/0.02 mm	244
Cl	i-PrNH	Cl	Cl	73–75	405
	n-BuNH			94–95	369
$NHNH_2$	i-BuNH			Hydrochloride 211–212	415
Cl	Cyclohexylamino		Cl	96	405
	Cyclohexylamino	Cl	OH	80–81	33
Cl	Cyclohexylamino	Cl	Cl	56–58	405
Ph	$HOCH_2CH_2NH$	Ph	Ph	190–191	43
	$HOCH_2CH_2NH$	Cl	OH	250–251	254
Cl	$HOCH_2CH_2NH$		Cl	146–146.5	415
Cl	$HOCH_2CH_2NH$		$NHNH_2$	Dihydrochloride (not stated)	415
$NHNH_2$	$HOCH_2CH_2NH$		Cl	168–172	415
				Dihydrochloride 204–208	415
Cl	$HOOCCH_2NH$		Cl	120	405
Cl	Allylamino		Cl	95–98	415
$NHNH_2$	Allylamino		Cl	168–172	415
				Dihydrochloride 199–202	415
Cl	$MeCH{=}CHCH_2NH$		Cl	172–175	415
$NHNH_2$	$MeCH{=}CHCH_2NH$		Cl	171–173	415
Cl	β-Ethyleneimino-ethylamino		Cl	142–143	80
	β-Diethylamino-ethylamino	Cl	OH	145	254
	Diethylamino-methylamino	Cl	OH	Methbromide 252 (dec)	254
	Benzylamino	Cl	OH	209	254

TABLE XIX (*continued*)

Substituent and position					
3	NRR′	5	6	MP (°C)	References
Ph	Benzylamino		Ph	Not stated	360
	Phenethylamino	Cl	OH	163	254
	Me_2N			47–48 (hydrate)	366
				Picrate 210–211	366
	Me_2N		Cl	115–116	366
	Me_2N	Cl	OH	200–201	35, 33
	Me_2N	Cl	Cl	89–90	366
Cl	Me_2N		Cl	70–71	366
				66–67	405
OH	Me_2N		Cl	245–246	405
MeO	Me_2N		Cl	82–85	405
EtO	Me_2N		Cl	86–88	405
$HOCH_2CH_2O$	Me_2N		Cl	112–113	405
n-PrO	Me_2N		Cl	48–50	405
i-PrO	Me_2N		Cl	46–48	405
PhO	Me_2N		Cl	bp 190–195/0.3 mm	405
$PhCH_2O$	Me_2N		Cl	62–64	405
$HOOCCH_2S$	Me_2N		Cl	160–163	405
$EtOOCCH_2S$	Me_2N		Cl	83–84	405
Cl	Me_2N	Cl	Cl	86–87	366
				82–84	405

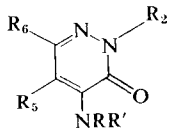
	Et_2N	Me		Picrate 110–112	362
	Et_2N	Me	Me	Picrate 156–157	362
	Et_2N	Me	Ph	45	362
	Et_2N	Me	4-Tolyl	58–59	362
	Et_2N	Cl	OH	181–182	254
				119	33
Cl	Et_2N		Cl	bp 154/0.5 mm	405
MeO	Et_2N		Cl	n_D^{20} 1.5585	405
n-BuO	Et_2N		Cl	n_D^{20} 1.5348	405
Cl	Et_2N	Cl	Cl	57–58	405
F	Et_2N	F	F	bp 64–66/0.005 mm	363
COOMe	Et_2N	Me	COOMe	98–101 (dec)	361
Ph	Et_2N	Me	Ph	120–121	361
Cl	i-Pr_2N		Cl	116–119	405
Cl	*n*-Bu_2N		Cl	bp 158–162/0.5 mm	405
Cl	$HOOCCH_2NMe$		Cl	105–108	405
Cl	$(HOCH_2CH_2)_2N$		Cl	126–128	405
	$(HOCH_2CH_2)_2N$		Cl	96–98	406
	$(HOCH_2CH_2)_2$		I	176–178	406
	$(PhCOOCH_2CH_2)_2N$		Cl	90–92	406
Cl	Diallylamino		Cl	52–54	416
Cl	Diallylamino		$NHNH_2$	95–97	416
Cl	Diallylamino		$NHN{=}CHC_6H_4Cl_2(2,6)$	Hydrochloride 195–204 (dec)	416
	Pyrrolidino	Cl	OH	247	35
	Piperidino		$NHN{=}CMeCOOH$	152–155	406
	Piperidino		I	117–119	406

TABLE XIX (*continued*)

Substituent and position					
3	NRR′	5	6	MP (°C)	References
	Piperidino			238–240	406
	Piperidino		NHN=CHPh	235–237	406
	Piperidino	Cl	OH	192	336
				183–185	35
				186–187	254
4-Methoxyphenyl	Piperidino		OH	212–214	253
	Morpholino			100–101	406
	Morpholino		OH	197–200	406
	Morpholino			Above 300	406
	Morpholino			244–246	406
	Morpholino		NHN=CMeCOOH	135	406
	Morpholino		$NHN{=}CHC_6H_4Cl$	265–270	406
	Morpholino		$NHN{=}CMe_2$	187–190	406
	Morpholino		NHN=CMeEt	125–127	406
	Morpholino		Cl	138–140	406
	Morpholino	Cl	OH	236	336
				229	254
				224–225	35
	Morpholino	Br	OH	157	336
	Morpholino	Benzylthio	OH	201	336
4-Methoxyphenyl	Morpholino		OH	268–269	253
	4-Methyl-1-piperazinyl		Cl	113–115	406

	4-Methyl-1-piperazinyl		$NHN{=}CMe_2$	159–161	406
	4-Methyl-1-piperazinyl		NHN=CHPh	248–252	406
	4-Methyl-1-piperazinyl	Cl	OH	231	254
				Methbromide 290 (dec)	254
				Ethbromide 290 (dec)	254
Cl	*N*-(β-Hydroxyethyl)-benzylamino		Cl	98–100	55
Cl	*N*-(β-Chloroethyl)-benzylamino		Cl	80–80.5	55
Cl	*N*,*N*-Bis(β-hydroxy-ethyl)amino		Cl	129–130	55
Cl	*N*,*N*-Bis(β-chloro-ethyl)amino		Cl	55–55.5	55
	N-Methylbenzyl-amino	Cl	OH	172–173	33
Ph	PhNH	Ph	Ph	191	43
Cl	PhNH		Cl	137–139	415
$NHNH_2$	PhNH		Cl	169–171	415
				Dihydrochloride 223–225	415
	PhNH	Cl	OH	246–247	33
	4-Toluidino	Cl	OH	203–206	33
	4-Anisidino	Cl	OH	242–243	33
Cl	2-Hydroxyanilino		Cl	160	66, 67
Cl	2-Anisidino		Cl	154–155	66, 67
Cl	2-Acetoxyanilino		Cl	106–107	67
Cl	PhNMe		Cl	89–91	406

TABLE XX. Secondary or Tertiary 4-Amino-3(2*H*)pyridazinones



Substituent and position

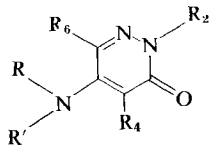
R_2	NRR′	R_5	R_6	MP (°C)	References
Me	Me_2N		OH	178–179	255
Me	Me_2N		Cl	76–77	405
Me	Me_2N		EtO	36–37	255
Cyclohexyl	Me_2N		OH	172–173	255
Cyclohexyl	Me_2N		EtO	112–113	255
Me	$—NHCH_2CH_2CH_2—$			115	123
Ph	$—NHCH_2CH_2CH_2—$			120	123
				130–131	124
Et	4- or 5-Anilino		Me	178	232
Ph	Me_2N			52–54	21
Ph	MeNH		Me	148–149	133, 237
Ph	Me_2N		Me	61	133, 237
Ph	MeNH		Cl	182–183	365
Ph	MeNH		MeO	141–142	365
				N-Acetate 121–122	365
Ph	MeNH		EtO	145–146	365
Ph	MeNH		$CH_2=CHCH_2O$	115–116	365
Ph	MeNH		$MeOCH_2CH_2O$	131–132	365
Ph	MeNH		$EtOCH_2CH_2O$	141–142	365
Ph	i-PrNH		Cl	142–143	365
Ph	i-PrNH		EtO	118–119	365
Ph	Et_2N		Me	bp 196–198/0.01 mm	133, 237
				Picrate 107–108	133

2-Pyridyl	Me_2N	Me	94	133, 237
Ph	Me_2N	Cl	179–180	21
Ph	Et_2N	Cl	60–62	365
Ph	Et_2N	EtO	41–43	365
Ph	Me_2N	Ph	120–121	258
			119–120	257
Ph	Me_2N	EtO	74	268–279
			73–74	81
Ph	Me_2N	OH	218–220	268
			226–228	81
Ph	Me_2N	$CH_2{=}CHCH_2O$	bp 170/0.2 mm	342
			42–43	342
			61–62	81
Ph	Me_2N	MeO	55–56	81
Ph	Me_2N	*n*-PrO	59–61	81
Ph	Me_2N	i-PrO	55–56	81
Ph	Me_2N	*n*-BuO	68–70	81
Ph	Me_2N	i-BuO	72–73	81
Ph	Me_2N	i-$C_5H_{11}O$	93–94	81
Ph	Me_2N	$PhCH_2O$	132–133	81
Ph	Me_2N	$EtOCH_2CH_2O$	74–76	81, 431
Ph	Me_2N	$MeOCH_2CH_2O$	76–80	81
			88–90	431
Ph	Me_2N	$Me_2NCH_2CH_2O$	72–74	81
Ph	Me_2N	$MeCH{=}CHO$	92–93	81, 343
Ph	Me_2N	Et	52–53	256
Ph	Pyrrolidino	Et	58–59	256
			bp 215–220/4 mm	256
Ph	Piperidino	Cl	118.5–119.5	344
Ph	Hexamethyleneimino	Et	bp 204–206/1 mm	256
Ph	Morpholino	Et	78–79	256
Ph	Piperazino	Cl	Hydrochloride 253–255	72
Ph	*N*-Methylpiperazino	Cl	97–99	72
			Hydrochloride 170 (dec)	72

TABLE XX (*continued*)

Substituent and position					
R_2	NRR′	R_5	R_6	MP (°C)	References
Ph	Piperazino		MeO	Hydrochloride 228–230	72
Ph	*N*-Methylpiperazino		MeO	Hydrochloride 241–243	72
Ph	Piperazino		EtO	Hydrochloride monohydrate 145–147	72
Ph	*N*-Benzylpiperazino		Cl	139.5–140.5	72
Ph	*N*-Benzylpiperazino		MeO	90.5–91	72
Ph	*N*-Formylpiperazino		MeO	141–142	72
Ph	*N*-Chlorocarbonylpiperazino		MeO	94–96	72
Ph	*N*-Aminocarbonylpiperazino		MeO	232–233	72
Ph	*N*-Acetylpiperazino		MeO	118–119	72
4-Chlorophenyl	Piperazino		Cl	Hydrochloride 281–283	72
4-Chlorophenyl	Piperazino		MeO	Hydrochloride 250–251	72
Ph	Piperazino		Ph	170–170.5	257
				Hydrochloride 190–192	257
Ph	$Et_2NCH_2CH_2NH$		Ph	99–99.5	257
				Hydrochloride 203.5–205	257
Ph	$Me_2NCH_2CH_2(Et)N$		Ph	74–75	257
				Hydrochloride 240–241	257
Ph	*N*-Phenethylpiperazino		MeO	89–90.5	259
				Hydrochloride 256–258	259
Ph	*N*-Phenethylpiperazino		EtO	95–96	259
				Hydrochloride 273–276	259
Ph	Piperidino		Me	80	133
Ph	Morpholino		Cl	121–122	21
Ph	Morpholino		Me	132	133
Ph	Piperidino		Ph	137–138	258
Ph	Morpholino		Ph	149	258

TABLE XXI. Secondary or Tertiary 5-Amino-3(2*H*)pyridazinones



Substituent and position

R_2	R_4	NRR′	R_6	MP (°C)	References
Me		Me_2N		119–120	255
Me	Cl	Me_2N		75–76	255
Me		Me_2N	Me	Hydrochloride 138 (dec)	232
Me		Me_2N	Cl	79–80	255
				75–77	405
Me		Me_2N	OH	213–214	255
Me		Me_2N	EtO	40–42	255
Me	Cl	Piperidino		62	254
Me	Cl	Morpholino		132	254
				104–106	33
$Et_2NCH_2CH_2$	Cl	$PhCH_2NH$		Hydrochloride 154	254
$Et_2NCH_2CH_2$	Cl	Piperidino		Hydrochloride 149	254
$Et_2NCH_2CH_2$	Cl	Morpholino		Hydrochloride 161	254
$Et_2NCH_2CH_2$	Cl	4-Methylpiperazino		62	254
Cyclohexyl		Me_2N	OH	227–228	255
Cyclohexyl		Me_2N	EtO	65–66	255
Me	$—CH_2CH_2CH_2NH—$			172–174	255
Ph	Cl	PrNH		137–138	35
Ph	Cl	Me_2N		92.5–94.5	235, 36
Ph	Cl	Et_2N		110–111	235, 36
				107–108	33

TABLE XXI (*continued*)

Substituent and position					
R_2	R_4	NRR′	R_6	MP (°C)	References
Ph	Cl	Pyrrolidino		150	235
				148–149	33
Ph	Cl	Morpholino		177	336
Ph	Cl	Piperidino		157	336
Ph	$PhCH_2S$	Morpholino		114	336
Ph	4-Chlorobenzylthio	Morpholino		125	336
Ph	$PhCH_2S$	Piperidino		138	336
Ph	Cl	Piperazino		143–144	33
Ph	Cl	2,6-Dimethylmorpholino		126	33
Ph	Cl	Cyclooctylamino		80–81	33
CH_2CH_2CN	Cl	i-PrNH		91–92	33
Ph	4-Chlorobenzylthio	Piperidino		164	336
Ph	Cl	MeNH		213	340, 235, 36
				212	35
(3)$F_3CC_6H_4$	Cl	MeNH		183–185	419
(3)$F_3CC_6H_4$	Cl	EtNH		132	419
(3)$F_3CC_6H_4$	Cl	Me_2N		153	419
Ph		Me_2N		102–103	23
Ph		Piperidino		131–132	23
Ph		Morpholino		165.5–166.5	23
Ph	Br	Morpholino		151–152	23
Ph	Br	Piperidino		133–134	23
				150–151	427
Ph	Br	MeNH		158–159	265, 427
Ph	Br	PrNH		128–129	427
Ph	Br	BuNH		112	427

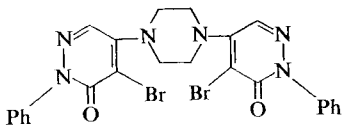
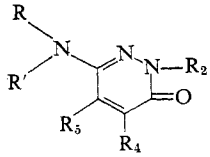
Ph	Br	$PhCH_2NH$		203	265
Ph	Br	$HOCH_2CH_2NH$		180–182	427, 418
Ph	Br	Et_2N		92–93	265
				93	427
Ph	Br	Bu_2N		39–41	427
Ph	Br	Me_2N		116	265
Ph	Br	Pyrrolidino		140–141	427
				200–204	418
$(3)F_3CC_6H_4$	Br	MeNH		156–158	419
$(3)F_3CC_6H_4$	Br	EtNH		138–140	419
$(3)F_3CC_6H_4$	Br	Me_2N		159	419
Ph		Me_2N	Cl	127–128	23, 266
Ph		Piperidino	Cl	118.5–119.5	23, 266, 267, 344
Ph		Morpholino	Cl	168–169	23, 266, 267
				167	344
Ph		Me_2N	Br	124.5–125.5	23, 267
Ph		Morpholino	Br	171.5–172.5	23, 267
Ph		Piperidino	OH	252–253	23, 267, 344
Ph		Morpholino	OH	242.5–243	23, 267, 344

TABLE XXII. Secondary or Tertiary 6-Amino-3(2*H*)pyridazinones



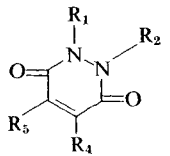
Substituent and position

R_2	R_4	R_5	NRR′	MP (°C)	References
Me			PhNH	181–182	249
Me			4-ClC_6H_4NH	248	249
Me			4-BrC_6H_4NH	249–250	249
Me			4-$MeOC_6H_4NH$	200–201	249
Me			4-$EtOC_6H_4NH$	183–184	249
Me			4-$C_6H_5CH_2NH$	146	249
Ph			MeNH	145–147	21, 261
Ph			Me_2N	130–132	21, 260
Ph			Et_2N	71–73	21
Ph			BuNH	126–128	21
Ph			Pyrrolidino	161–163	21
Ph			Piperidino	111–113	21
Ph			Morpholino	181–183	21, 234
Ph		Me	Me_2N	91–92	21, 345
Ph		MeS	Me_2N	179–181	367
4-Chlorophenyl			Morpholino	164–166	262
4-Chlorophenyl			Me_2N	174–176	263
4-Nitrophenyl			Me_2N	210–212	264, 346
4-Aminophenyl			Me_2N	170–172	264, 346
4-Dimethylaminophenyl			Me_2N	150–152	264, 346

TABLE XXIII. 3-Amino-4(1*H*)pyridazinones

Substituent and position					
R_1	R_3 (NRR′)	R_5	R_6	MP (°C)	References
Ph	NH_2		Me	218.5–220	90
Ph	EtOOCNH		Me	167–169	90

TABLE XXIV. 4 (or 5)-Amino-1,2,3,6-tetrahydro-3,6-dioxopyridazines



Substituent and position

R_1	R_2	R_4 (NRR')	R_5	MP (°C)	References
Ph	Me	Piperidino		182	71
				184–185	70
Ph	Me		Piperidino	118	71
Ph	Me	PhNH		142	71
Ph	Me	Morpholino		176–177.5	68, 69, 70
Ph	Me	NH_2		192–194.5	68, 70
Ph	Me	Et_2N		115.5–116.5	68, 70
Ph	Me	Me_2N		73–75	68
				74.5–75.5	70
Ph	Me	Pyrrolidino		140.5–142	68, 70
Ph	Me	MeNH		169–170	68
Ph	Me	Cyclohexylamino		184–186	68
Ph	Allyl		Me_2N	91–93	81
Ph	Me	BuNH		130–131	70
Ph	Et	Me_2N		bp 180–185/0.06 mm	70
Ph	Et	EtNH		130–132	70
Ph	Et	Pyrrolidino		113–114	70
Ph	Et	Morpholino		120–121	70
Ph	Et	Piperidino		78–79	70
Ph	Me	Cyclohexylamino		184–186	70

TABLE XXIV (*continued*)

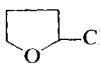
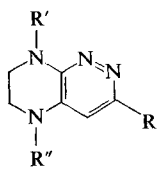
Substituent and position					
R_1	R_2	R_4 (NRR')	R_5	MP (°C)	References
Ph	Me			bp 218–222/0.15 mm	70
Ph	Me	4-Methylpiperazino		137–138	70
				Methiodide 275–277	70
Ph	Me	Hexamethyleneimino		129.5–130	70
Ph	Me	β-Diethylaminoethylamino		229–230	70
Ph	Me	4-(β-Hydroxyethyl)piperazino		136.5–137.5	70
Ph	Me	$Me_2NHCH_2CH_2(Et)N$		88–88.5	70
Ph	Me	$HOCH_2CH_2(Me)N$		103–104	70
4-Chlorophenyl	Me	Me_2N		159.5–160.5	70
4-Chlorophenyl	Me	Pyrrolidino		187.5–188.5	70
3-Chlorophenyl	Me	Me_2N		102–103	70
4-Tolyl	Me	Me_2N		143–144	70
4-Nitrophenyl	Et	Me_2N		163–165	70
4-Aminophenyl	Et	Me_2N		167–169	70
4-Nitrophenyl	Me	Me_2N		175–177	70
4-Nitrophenyl	Me		Me_2N	177–178	432
4-Nitrophenyl	Me		Piperidino	166–168	432
4-Nitrophenyl	Me		Morpholino	190–191	432
Me	Me	PhNH	Cl	172–173	405

TABLE XXV. Polyaminopyridazines

Substituent and position					
3	4	5	6	MP (°C)	References
NH_2	NH_2			Hydrochloride 200–201.5	24
NH_2	NH_2		Me	222–223	382
NH_2	NH_2	SH		200 (dec)	105
NH_2	NH_2	Cl		205	65
				½ Hydrate 194–196	65
				Picrate, $\frac{1}{2}H_2O$ 266	65
NH_2	NH_2		Cl	186–187	104
NH_2	NH_2		SH	Above 270	380
AcNH	AcNH			228–229	105
NH_2	MeNH			277–278 (dec)	105
MeNH	NH_2			½ Hydrate 222–223 (dec)	105
MeNH	NH_2		Cl	241–242	105
NH_2	MeNH		Cl	201–202	105



R′	R″	R	MP (°C)	References
Me	Benzyl	Cl	127–127.5	55
			Hydrochloride 206–208	55
Et	Benzyl	Cl	111.5–112.5	55

TABLE XXV (*continued*)

Substituent and position					
3	4	5	6	MP (°C)	References
Me	Benzyl		Me_2N	168–169	55
Me	β-Dimethylaminoethyl		Cl	116–117	55
				Hydrochloride 241–243	55
Et	4-Dimethylaminobenzyl		Cl	134–135	55
Et	3-Methoxybenzyl		Cl	108–109	55
Et	4-Chlorobenzyl		Cl	156.5–157.5	55
Et	Et		Cl	69–69.5	55
Me	Benzyl, 6-Et		Cl	145–146	55
Me	Et		Cl	80–80.5	55
Me	Me			Hydrochloride 293 (dec)	55
Et	Benzyl		MeO	126–127	55

Substituent and position					
3	4	5	6	MP (°C)	References
NH_2	NO_2	NH_2		291	24
NH_2		NH_2		Hydrochloride 268–269	24
NH_2	Cl	NH_2		198	24
	NH_2	NH_2		270–271	404
				Hydrochloride 234–235	24
Ph	NH_2	NH_2	Ph	361 (dec)	111
				Dihydrochloride 312	111

Me	NH_2	NH_2	MeO	210–211	97
				202–203	404
MeO	NH_2	NH_2	MeO	252–254 (dec)	117
				½ Hydrate 194–196	117
				Monopicrate 202–203	117, 404
MeO	AcNH	AcNH	MeO	254	117
MeO	Me(EtO)C=N	Me(EtO)C=N	MeO	101	117
MeO	NH_2	NH_2	OH	226–227	117
Cl	NH_2	NH_2	MeO	186.5–187.5 (dec)	404
Cl	NH_2	NH_2	Me	229–230 (dec)	404
EtO	NH_2	NH_2	Me	161–162	404
EtO	NH_2	NH_2	EtO	162–163	404
Cl	NH_2	NH_2	OH	314–318 (dec)	404
NH_2 or Cl	NH_2	NO_2	Cl or NH_2	258–259	404
MeO	NH_2	NH_2		182–183	404
EtO	NH_2	NH_2		155–156	404
Cl	NH_2	NH_2		207–208 (dec)	404
Cl	NH_2	NH_2	Cl	293–295	404
OH	NH_2	NH_2		224–226	404
SH	NH_2	NH_2		241–243	404
MeS	NH_2	NH_2		193.5–194	404
OH	NH_2	NH_2	Me	277–278 (dec)	404
OH	NH_2	NH_2	EtO	224–226.5	404
MeO	AcNH	AcNH	OH	270–273 (dec)	117
MeO	HCONH	NH_2	OH	202–203	117
NH_2			NH_2	235	103
NH_2	$—CH_2CH_2CH_2CH_2—$		NH_2	Hydrochloride 265 (dec)	8
	Phthalimido	Phthalimido	F	326–328	363

TABLE XXV (*continued*)

Substituent and position					
3	4	5	6	MP (°C)	References
Me_2N			Me_2N	132–134	44
				136–138.5	45
				135–138	411
				Methiodide 188	241
				178–180	411
				Picrate 179.5–180.5	430
				p-$NO_2C_6H_4CH_2Br$ 122.5–123	45
Me_2N	Me		Me_2N	52–53	366
				Methiodide 150–152	372
				Picrate 144–145	430
MeNH			Me_2N	Methiodide 181–184	372
MeNH	Me		Me_2N	Methiodide 192–193	372
MeNH	*t*-Bu		Me_2N	Methiodide 169–171	372
Piperidino			Piperidino	115–116	44, 46
				115	51
				Methiodide 189	46
1-Pyrryl			1-Pyrryl	213	335
i-PrNH			i-PrNH	175–175.6	48
				Picrate 212–215	48
4-Dimethylamino-anilino			4-Dimethylamino-anilino	234–236	48, 49

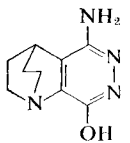
PhNH			PhNH	245	47
4-Toluidino			4-Toluidino	260	47
4-Anisidino			4-Anisidino	227–228	47
4-Nitroanilino			4-Nitroanilino	300	47
β-Hydroxyethyl-amino			β-Hydroxyethyl-amino	166–167	47
PhNH			4-Toluidino	225	47
PhNH			Benzylamino	165	47
				Hydrochloride 105–106	47
PhNH			*n*-BuNH	140	47
PhNH			β-Hydroxyethyl-amino	153	47
NH_2	NH_2	NH_2		Hydrochloride 214–215	24
NH_2	NH_2	NH_2	Cl	241–243	404
OH	NH_2	NH_2		224–225	83
				298–301	4
OH	NH_2	NH_2	OH	332 (dec)	379
OH	NHAc	NHAc	Me	235–236	387
Morpholino		Morpholino		175–176	406
Morpholino		Morpholino		Dihydrochloride 234–236	406

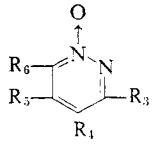
TABLE XXVI. Polyamino-3(2*H*)pyridazinones

Substituent and position					
2	4	5	6	MP (°C)	References
Ph		NH_2	NH_2	264–266 (dec)	23
				263–265 (dec)	347
Ph		Me_2N	Me_2N	132–134	23
Ph		Piperidino	Piperidino	170–171	23
Ph		Morpholino	Morpholino	178–180	23
Ph	Me_2N		Me_2N	91.5–92	21
				83	348
Me	NH_2	NH_2		210–211	83
Me	NH_2	NH_2	Me	Above 300	404
Ph	NH_2	NH_2		200–202	83
				Hydrochloride 194–196	83
Ph	PhNH	NH_2		234–235	83
Ph	3,4-Dichloro-anilino	NH_2		242	83
Ts	PhNH	NH_2		215–216	83
Benzyl	NH_2	NH_2	Benzyloxy	166	83
4-Tolyl	NH_2	NH_2		196–198	83
Ph	Me_2N	NH_2		185–187	83
Cyclohexyl	NH_2	NH_2		192–193	83
Ph	2-Chloroanilino	NH_2		233–235	392
Ph	Me_2N	Me_2N		78–80	365
Ph	Me_2N	Me_2N	Cl	92–93	365
Ph	Me_2N	Me_2N	EtO	bp 148–150/0.2 mm	365
Ph	Me_2N	Me_2N	i-PrO	bp 160–164/0.25 mm	365

TABLE XXVII. Nitroamino-3(2*H*)pyridazinones

Substituent and position					
2	4	5	6	MP (°C)	References
Ph	NH_2	NO_2		212–214	87
Me	NH_2	NO_2		220–222	87
$PhCH_2$	NH_2	NO_2	$PhCH_2O$	163–164	87
4-Tolyl	NH_2	NO_2		200–201	87
Ph	3-(1,2,4-Triazinyl)amino	NO_2		273 (dec)	87
Ph	PhNH	NO_2		194–195	87
Ph	3,4-Dichloroanilino	NO_2		198–199	87
Ph	4-Phenylenediamino	NO_2		200 (dec)	87
Ph	*N*-Methylanilino	NO_2		153–154	87
Ph	Me_2N	NO_2		93–94	87
Ph	$Me_2N(CH_2)NH$	NO_2		115–116	87
Ph	PhNH	NO_2		190	87
Ts	PhNH	NO_2		239–240	87
Me	PhNH	NO_2	Ph	218–219	87
H	NH_2	NO_2		303–305	87
Ph	2-Chloroanilino	NO_2		175–177	392

TABLE XXVIII Aminopyridazine *N*-Oxides

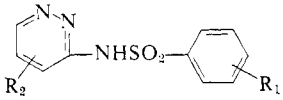


R_3	R_4	R_5	R_6	MP (°C)	References
NH_2				140–141	128
				140–142	84
				139–141	228
				3-AcNH 259 (dec)	136
				258–260 (dec)	128
	NH_2			229–230	98
				222–224 (dec)	135
				Nitrate 184	135
				4-AcNH 239	135
		NH_2		188.5–190	189
			NH_2	210–211	136
				214–215	128
				209	84
				6-AcNH 199–201	136
				6-EtOCONH 84–85	136
				124–125	128
				N^1-OAc 203–204	128
	NH_2		Me	260–261 (dec)	98
				258	91
MeO	NH_2			176 (dec)	275, 100
MeO	NH_2		MeO	168–169 (dec)	337
				Picrate 171	95
Me	NH_2		Me	291 (dec)	98
				295 (dec)	53
MeO	NH_2		Me	205 (dec)	98
				193	97
				Picrate 177	98
Cl	NH_2	Cl		204 (dec)	189
Cl	Cl	NH_2		282 (dec)	189
Cl			NH_2	248 (dec)	136
				253–255 (dec)	128
				6-AcNH 202–203	128
				6-EtOCONH 160–161	136
				161–162	128
MeO			NH_2	135–135.5	276
				Hydrochloride 207–208 (dec)	128
				6-AcNH 216–217	128
EtO			NH_2	6-AcNH 198	128
i-PrO			NH_2	6-AcNH 141	128
n-PrO			NH_2	6-AcNH 125	128
n-BuO			NH_2	6-AcNH 149	128

TABLE XXVIII (*continued*)

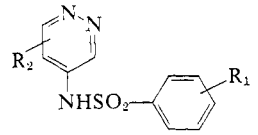
R_3	R_4	R_5	R_6	MP (°C)	References
i-$C_5H_{11}O$			NH_2	6-AcNH 155	128
n-$C_5H_{11}O$			NH_2	6-AcNH 144	128
n-$C_6H_{13}O$			NH_2	6-AcNH 146	128
n-$C_8H_{17}O$			NH_2	6-AcNH 131	128
n-$C_{10}H_{21}O$			NH_2	6-AcNH 129	128
MeO	Me		NH_2	184–185	274
MeO	NO_2		NH_2	181	118, 357
				6-AcNH 211	118, 357
EtO	NO_2		NH_2	156	118, 357
				6-AcNH 209	118, 357
n-PrO	NO_2		NH_2	150	118, 357
				6-AcNH 181	118, 357
n-BuO	NO_2		NH_2	132	118, 357
				6-AcNH 152	118, 357
i-$C_5H_{11}O$	NO_2		NH_2	126	118, 357
				6-AcNH 142	118, 357
n-$C_5H_{11}O$	NO_2		NH_2	112	118, 357
				6-AcNH 133	118, 357
$C_6H_{13}O$	NO_2		NH_2	120	118, 357
				6-AcNH 136	118, 357
$C_8H_{17}O$	NO_2		NH_2	92	118, 357
				6-AcNH 131	118, 357
$C_{10}H_{21}O$	NO_2		NH_2	110	118, 357
				6-AcNH 123	118, 357
EtNH				79–80	54
				Picrate 131–132	54
EtNH			Cl	137–138	50
EtNH			EtO	114–115	50
Me		EtNH	Me	177–178	53
			EtNH	113–114	54
Cl			EtNH	75–76	50
EtO			EtNH	92–93	50
i-PrNH	NO_2		Me	115–115.5	242
$PhCH_2NH$	NO_2		Me	221–224	242
$PhO(CH_2)_2NH$	NO_2		Me	127–128	242
Piperidino	NO_2		Me	104.2–104.7	142
Piperidino				83–84	52
	Piperidino			146–147	52
		Piperidino		151–152	52
			Piperidino	101–102	52
Piperidino			Cl	124–125	50
Piperidino			MeO	128–130	50
Piperidino			Piperidino	Picrate 160–161	50
Me	Piperidino		Me	72–73	52
Me		Piperidino	Me	130–131	52
MeO			Piperidino	107–108	50
		NH_2		190–191	373
MeO		NH_2		173–174	373
Cl		NH_2		215–216.5	373
MeO	Cl	NH_2		252 (dec)	373

TABLE XXIX. 3-(Arylsulfonyl)aminopyridazines



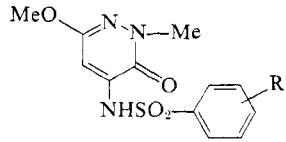
R_1	R_2	MP (°C)	References
4-Nitro		Not specified	141
4-Nitro	6-Chloro	180 (dec)	142, 143, 304
4-Nitro	6-Hydroxy	176	144
4-Nitro	6-Methoxy	155–156	178
		156–157 (dec)	182
4-Nitro	6-Methoxyethoxy	147–148	178
4-Nitro	6-Mercapto	220 (dec)	142, 143, 304
4-Nitro	6-Methylthio	174.5	145
4-Nitro	6-Ethylthio	161–162	145
4-Nitro	6-Butylthio	145	145
4-Nitro	6-Phenylthio	198	145
4-Nitro	6-Benzylthio	178	145
3-Nitro		Not specified	349
3-Amino		Not specified	349
4-Methyl	6-Chloro	152–153	140
		154	323
4-Methyl	6-Methylthio	129–130	139
4-Methyl	6-Ethylthio	144	139, 350
4-Methyl	4-Hydroxy-6-methyl	206–208	371
4-Methyl	6-Ethylsulfinyl	198	351
4-Methyl	6-Mercapto	209	323
3-Methyl	6-Chloro	Not specified	140
4-Aminomethyl	6-Methoxy	230–231	158
		Hydrochloride 242–243	158
4-Aminomethyl	6-Chloro	Not specified	158
4-Aminomethyl	6-Ethoxy	233–234	159
4-Acetamido-methyl	6-Chloro	228–230	158
4-Acetamido-methyl	6-Methoxy	218–220	158
4-Phthalamido-methyl	6-Chloro	220–222 (dec)	158
4-Phthalamido-methyl	6-Methoxy	215–216	158
H	6-Chloro	Not specified	140
4-Methyl	6-Hydroxy	243–245	140
4-Methyl	6-Ethoxy	Not specified	140

TABLE XXX. 4-(Arylsulfonyl)aminopyridazines



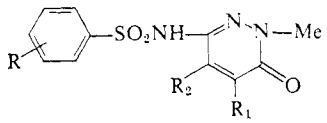
R_1	R_2	MP (°C)	References
4-Methyl	3,6-Dimethoxy	127–128	146
4-Methyl	3-Hydroxy-6-methoxy	215–216	146
4-Methyl	3-Methoxy-6-hydroxy	280–283	146
4-Methyl	3-Hydroxy	213–214	146

TABLE XXXI. 4-(Arylsulfonyl)amino-3(2*H*)pyridazinones



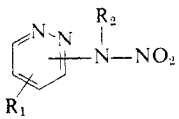
R	MP (°C)	References
4-Methyl	189.5–190	355
4-Chloro	213–214.5	355
3-Nitro	217–218.5	355
3-Methyl-4-chloro	183–184	355
2-Chloro-4-acetamido	246–247	355
2-Chloro-4-amino	231	355
4-Nitro	260–262	355
3-Amino	203–204	355
2,3,4-Trichloro	236.5–237.5	355
4-Methoxy	178–179	355
4-Carbobenzoxyamino	188–192	355
2-Methyl	194–195	355
4-Bromo	218.5–219	355
2-Methyl-4-chloro	192–193	355
2-Nitro	197.5–198.5	355
4-Ethyl	160–160.5	355
4-Fluoro	197.5–198.5	355
4-Cyclohexyl	230–233	355
2-Chloro-5-nitro	272.5–273.5	355
3-Methyl-4-bromo	177–178	355
H	200–201	355

TABLE XXXII. 6-(Arylsulfonyl)amino-3(2*H*)pyridazinones



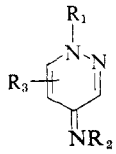
R	R_1	R_2	MP (°C)	References
H	Cl	Cl	164–166	389
4-Chloro	Cl	Cl	178–180	389
2,5-Dichloro	Cl	Cl	124–128	389
3,4-Dichloro	Cl	Cl	184–186	389
3,4,5-Trichloro	Cl	Cl	162–166	389
4-Methyl	Cl	Cl	150–152	389
4-Methoxy	Cl	Cl	187–189	389
4-Nitro	Cl	Cl	202–204	389
3-Nitro-4-chloro	Cl	Cl	128–132	389

TABLE XXXIII. Nitraminopyridazines



Position of —NR_2—NO_2	R_1	R_2	MP (°C)	References
3	6-Me	H	178 (dec)	88
			K salt 188	88
3	6-Me	Me	148	88
3	6-Cl	H	135 (dec)	103
4	3-MeO, 6-Me	H	188	97
			K salt 162	97
4	3-MeO, 6-Me	Me	237	97
3,4	H	H	144 (dec)	24
4	H	H	185 (dec)	24
3	5-NH_2		Nitrate 259–260	24
4	5-NH_2		>400 (darkens at 250–270)	24

TABLE XXXIV. 4(1*H*)Pyridazinonimines

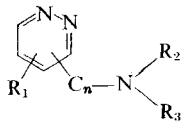


R_1	R_2	R_3	MP (°C)	References
Me	H	3-OH	246	195
Me	H	3-OH, 6-Me	281–282	195
			Picrate 243.5	195
Me	H	3-OH, 6-MeO	194–195	195
Me	H	3-OH, 6-Cl	>300	195
			Hydrochloride 237–238 (dec)	195
Ph	H	5,6-di-Cl	145–146	207
			Hydrochloride 223–224	207
Ph	Me	5,6-di-Cl	155–156	207
Ph	Benzyl	5,6-di-Cl	245–246	207
			Hydrochloride 260	207
Ph	β-Chloroethyl	5,6-di-Cl	Not specified	207
			Hydrochloride (not specified)	
Ph	Et	5,6-di-Cl	146–147	207
Me	Me	3-Ph, 6-Cl	78–80	207
Ph	Et	5-Cl, 6-Br	Not specified	207
			Hydrobromide (not specified)	207
Ph	H	3,6-di-Cl	105–106	207
			Hydrochloride 180–181	207

TABLE XXXV. 3(2*H*)Pyridazinonimines

R_1	R_2	R_3	MP (°C)	References
4-$AcNHC_6H_4SO_2$	4-$AcNHC_6H_4SO_2$	MeO	138 (dec)	150

TABLE XXXVI. Aminoalkylpyridazines



Position of aminoalkyl group	R_1	Aminoalkyl group	MP (°C)	References
3		β-Aminoethyl	Dihydrochloride 168–169	221
3		Aminomethyl	Dipicrate 179–180	223
3		—CH_2—$CH(NH_2)COOH$	224–226 (dec)	222
3		*N*-Methyl-2-pyrrolidyl	210	335
3		CH_2NEt_2	bp 124–125/6 mm	402
			Picrate 145.5–146	402
3		Morpholinomethyl	56–57	402
			bp 130–131/1.5 mm	402
			Picrate 169–170	402
3		Piperidinomethyl	51–52 bp 115/1.5 mm)	402
			Picrate 148–149	402
3	6-OH, N^2-oxide	Morpholinomethyl	185–186	218
3	6-OH	Morpholinomethyl	181–182	218
3	6-OH, N^2-oxide	Piperidinomethyl	Hydrochloride 222–223 (dec)	218
			Salt with 3-pyridazinol 1-oxide 84–85 (dec)	218
3	4-OH, 5-Br, N^2-oxide	Piperidinomethyl	193–194 (dec)	433
3	4-OH, N^2-oxide	Piperidinomethyl	175–176 (dec)	399
3	6-OH	Piperidinomethyl	147–148	218
3	6-OH, N^2-oxide	—CH_2NMe_2	Hydrochloride 229–230	218
			Salt with 3-pyridazinol 1-oxide 178 (dec)	218
3	6-OH	—CH_2NMe_2	104–105	218

TABLE XXXVI (*continued*)

Position of aminoalkyl group	R_1	Aminoalkyl group	MP (°C)	References
3	6-OH, N^2-oxide	$CH_2N(CH_2CH_2Cl)_2$	Hydrochloride 179–181 (dec)	218
3	4-OH, N^2-oxide	CH_2NMe_2	Salt with 4-pyridazinol 2-oxide 181–183	399
			Hydrochloride 203–204 (dec)	399
3	6-OH, N^2-oxide	Pyrrolidinomethyl	Hydrochloride 201–203	398
3	6-OH, N^2-oxide	CH_2NMeCH_2Ph	Hydrochloride 207–208	398
3	4-OH, N^2-oxide	CH_2NHCH_2Ph	209–210 (dec)	400
3	4-OH, N^2-oxide	$CH_2NHCH_2C_6H_4OMe(4)$	Hydrochloride 219–220	400
3	4-OH, N^2-oxide	CH_2NHEt	205	400
3	4-OH, N^2-oxide	CH_2NHMe	214–218	400
3	6-OH, N^2-oxide	CH_2NHCH_2Ph	Hydrochloride 226–227 (dec)	400
4		$CH_2CH(NH_2)COOH$	235–236 (dec)	222
4	3-OH, 6-Me	Aminomethyl	Hydrochloride 273 (dec)	401
4	3-Cl, 5,6-di-Me	Aminomethyl	Hydrochloride 281–282 (dec)	401
4	3-MeO, 5,6-di-Me	Aminomethyl	Hydrochloride 212 (dec)	401
4	3-OH, 6-Cl, N^1-oxide	Morpholinomethyl	204–206 (dec)	219
			Hydrochloride 233 (dec)	219
4	3-OH, 6-Me (N^1-oxide)	Morpholinomethyl	Salt with 6-methyl-3-pyridazinol 1-oxide 183–186 (dec)	219
4	3-OH	Morpholinomethyl	167–168	219
4	3-OH, 6-Me	Morpholinomethyl	176–178	219
4	3-OH, 6-Cl (N^1-oxide)	Piperidinomethyl	Hydrochloride 240–241 (dec)	219
			Salt with 3-pyridazinol 1-oxide monohydrate 120–121	219
4	3-OH, 6-Me (N^1-oxide)	Piperidinomethyl	Salt with 6-methyl-3-pyridazinol 1-oxide 162–164 (dec)	219
			Hydrochloride, ½ hydrate 214–217	219
4	3-OH, 6-Me	Piperidinomethyl	161–162	219
4	3-OH	Piperidinomethyl	134–136	219

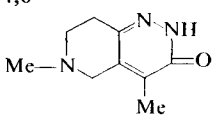
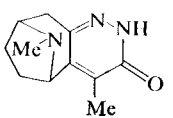
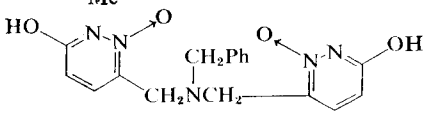
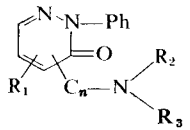
4	3-OH, 6-Me, N^1-oxide	CH_2NHCH_2Ph	219–220 (dec)	400
4	3-OH, 6-Me, N^1-oxide	CH_2NHMe	Salt with 6-methyl-3-pyridazinol 1-oxide 230	400
4	3-Cl, 6-Me	α-Picolinium, chloride	202–204 (dec)	401
4	3-Cl, 5,6-di-Me	Pyridinium, chloride	144 (dec)	401
		Pyridinium, perchlorate	222	401
4	3-Cl, 5,6-di-Me	5,6,7,8-Tetrahydroisoquinolinium, chloride	173 (dec)	401
4	3-Cl, 5,6-di-Me	4-Methoxypyridinium, chloride	168 (dec)	401
4	3-Cl, 5,6-di-Me	α-Picolinium, chloride	158 (dec)	401
4	3-Cl, 5,6-di-Me	5,6,7,8-Tetrahydroquinolinium, iodide	162 (dec)	401
4	3-MeO, 5,6-di-Me	α-Picolinium, chloride	197 (dec)	401
4	5,6-di-Me	4-Acetylpyridinium, iodide	151 (dec)	401
4,6	5-OH, N^1-oxide	Piperidinomethyl	192–193 (dec)	399
4,6	3-OH (N^1-oxide)	Morpholinomethyl	187–189 (dec)	219
			Dihydrochloride 205 (dec)	219
4,6	3-OH	Morpholinomethyl	165–167	219
			Dihydrochloride 232–235 (dec)	219
			204–205	352
			Hydrochloride 296 (dec)	352
			251–252	403
			Hydrochloride 224–226 (dec)	400

TABLE XXXVII. Aminoalkylpyridazinones



Position of aminoalkyl group	R_1	Aminoalkyl group	MP (°C)	References
4	6-Et	CH_2NMe_2	bp 168–172/0.2 mm	208
			Hydrochloride 128–130	208
4	6-Et	Pyrrolidylmethyl	bp 189–195/0.4 mm	208
4	6-Et	Piperidinomethyl	bp 170–175/0.4 mm	208
			Hydrochloride 174–175	208
4	6-Et	Morpholinomethyl	bp 189–193/0.2 mm	208
4	6-Me	CH_2NMe_2	bp 183–187/0.2 mm	208
4	6-Me	Morpholinomethyl	bp 185–191/0.3 mm	208
			Hydrochloride 178–180	208
4	5-$(CH_2)_6$-6	CH_2NMe_2	bp 197–200/0.2 mm	208

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CHAPTER VII

Nitropyridazines and Their Reduction Products (Except Amines)

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I. Nitropyridazines

A. Preparation

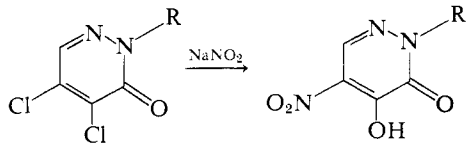
The unsubstituted pyridazine nucleus shows a remarkable resistance to nitration. The attempt by Dixon and Wiggins (1) to nitrate pyridazine using a mixed acid resulted in recovery of the starting material. Itai and Suzuki (2),

and later Aldous and Castle (3), found that only when the pyridazine nucleus is highly activated by electron-releasing substituents does it undergo nitration. Thus 4-amino-5-nitro-3,6-dimethoxypyridazine (2), 4-amino-3-methoxy-6-methyl-5-nitropyridazine (3), and 4-nitro-3,5-diaminopyridazine (4) are examples of the preparation of nitropyridazines by direct nitration. Yanai et al. (97) prepared additional 3,6-disubstituted-4-amino-5-nitropyridazines in a similar way. With nitrating agents aminopyridazine derivatives afford the corresponding nitraminopyridazines which failed to rearrange to nitroaminopyridazines with few exceptions (see Chapter VI, Section I.D).

3(2*H*)Pyridazinone resisted nitration under a variety of conditions, and its 6-methyl derivative underwent oxidation of the methyl group with hot dilute nitric acid to 3(2*H*)pyridazinone-6-carboxylic acid (1). However, 4,5-dichloro-3(2*H*)pyridazinone was nitrated at the 6-position with potassium nitrate in a mixture of fuming and concentrated sulfuric acid at 80–100° C to give 6-nitro-4,5-dichloro-3(2*H*)pyridazinone (5), and 2-methyl-4,5-dichloro-3(2*H*)pyridazinone, in which enolization by tautomerism is not possible, similarly nitrated to the 6-nitro derivative (6); the yields were fairly good in both instances.

The nitration of pyridazine derivatives bearing phenyl groups occurs exclusively on the phenyl ring (7, 8).

Dury and Reicheneder (9) discovered a new preparative method of nitropyridazinones by a replacement reaction with sodium nitrite (**1**). The reaction is effected by heating 4,5-dihalo-3(2*H*)pyridazinones with at least

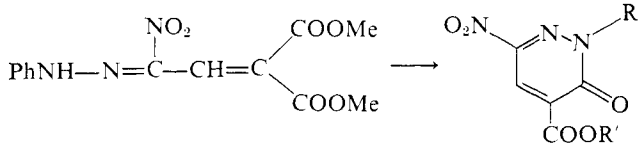


1

3 moles of sodium (or potassium) nitrite in such solvents as methylene glycol, dimethylformamide, ethylene glycol, dimethyl sulfoxide, and tetramethyl sulfone. The simultaneous replacements of one halogen atom with a nitro and of another halogen with a hydroxy group take place, 4-hydroxy-5-nitro-3(2*H*)pyridazinones being formed in fair to good yields. These products are listed in Table I. 4-Halo-5-hydroxy-3(2*H*)pyridazinones are other by-products separated. Although the isomeric 5-hydroxy-4-nitro compounds have not been isolated, subsequent studies have shown that these isomers are obtained in small quantities (9).

3-Methoxy-6-nitropyridazine has been isolated as a byproduct (0.5%) from the nitration of 3-methoxypyridazine 1-oxide, probably as a result of deoxygenation of the corresponding 1-oxide during the reaction (11).

Only one report of nitropyridazinones from aliphatic intermediates has been published (12). 3-Nitro-3-phenylhydrazino-1,1-bismethoxycarbonylpropene (1) was heated above its melting point (111° C) or heated under reflux in ethanol to cyclize to a 6-nitropyridazinone carboxylate in 65% yield (**2**: R = Ph, R′ = Me).



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The analogous diethyl ester substituted with bromine at the para position in the benzene ring was cyclized to the corresponding ethyl nitropyridazinonecarboxylate (**2**: R = *p*-BrC_6H_4, R′ = Et) in 68% yield.

In contrast to pyridazines their *N*-oxides readily undergo nitration, and a large number of nitropyridazine *N*-oxides have been prepared since Itai and Igeta (13) succeeded in their attempt to nitrate the first pyridazine *N*-oxide; 3,6-dimethoxypyridazine 1-oxide gave 4-nitro-3,6-dimethoxypyridazine 1-oxide. Pyridazine *N*-oxide itself can be nitrated to 3- (14), 4- (15, 16), or 5-nitropyridazine 1-oxide (14) by a choice of reagents. The nitro groups of nitropyridazine 1-oxide derivatives can be replaced with halogen, alkoxy, or hydroxy groups, and can also be reduced to amino groups. The reactions of nitropyridazine *N*-oxides with alkyl halides, ethyl chlorocarbonate, or ethyl bromoacetate have also been reported (98). The preparations and the reactions of nitropyridazine *N*-oxides are discussed in Chapter VIII. A comprehensive review on pyridazine *N*-oxides has been published (17).

The removal of the *N*-oxide function to yield nitropyridazines has not been reported except for the formation of 6-methoxy-3-nitropyridazine during the nitration reaction of 3-methoxypyridazine 1-oxide (11).

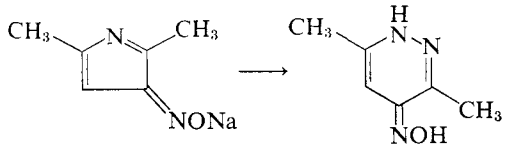
B. Reactions

The reduction of nitropyridazines and nitropyridazine *N*-oxides to amino compounds is discussed in Chapter VI.

Nucleophilic substitutions of nitro groups in nitropyridazine *N*-oxides are dealt with in Chapter VIII.

II. Hydroxylaminopyridazines

The treatment of 3-isonitroso-2,5-dimethylpyrrole with hydrazine yielded a product which was characterized as 4-isonitroso-3,6-dimethyl-1,4-dihydropyridazine (18) (**3**). The product gives the acetate with acetic anhydride, and



3

the dibenzoate with benzoyl chloride, however, conversion of **3** to any known pyridazine derivatives has not been reported.

Hydroxylaminopyridazine *N*-oxides have been prepared by partial reduction of nitropyridazine *N*-oxides. Catalytic hydrogenation of 3-nitropyridazine 1-oxide over palladium–charcoal in methanol yielded 3-hydroxylaminopyridazine 1-oxide in 76% yield when the reduction was stopped after the absorption of 2 moles of hydrogen (14). With 3 moles of hydrogen, 3-hydroxylaminopyridazine 1-oxide (21%) was accompanied by 3-aminopyridazine (10%) and 3-aminopyridazine 1-oxide (32%).

The same investigators further hydrogenated 3-hydroxylaminopyridazine 1-oxide under similar conditions and stopped the hydrogenation at the uptake of 1 mole of hydrogen, whereupon a mixture of 3-aminopyridazine (21%) and its 1-oxide (43%) was obtained (14).

6-Amino-3-methoxy-4-nitropyridazine 1-oxide was hydrogenated catalytically over 20% palladium–charcoal in 5% aqueous hydrochloric acid to the corresponding hydroxylamino compound (19).

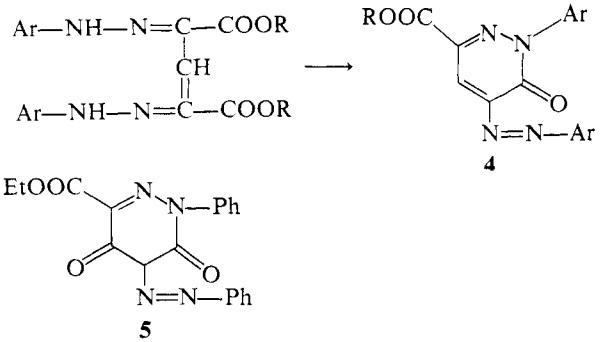
Chemical reduction has been employed to prepare hydroxylaminopyridazine *N*-oxides. 3-Methyl-5-nitropyridazine 2-oxide and its 6-methoxy derivative have been reduced with phenylhydrazine to the corresponding hydroxylamino compounds (20).

3-Hydroxylaminopyridazine 1-oxide has also been prepared, in poor yield, by the reaction of 3-chloropyridazine 1-oxide and hydroxylamine hydrochloride in methanol (14).

III. Azo- and Hydrazopyridazines

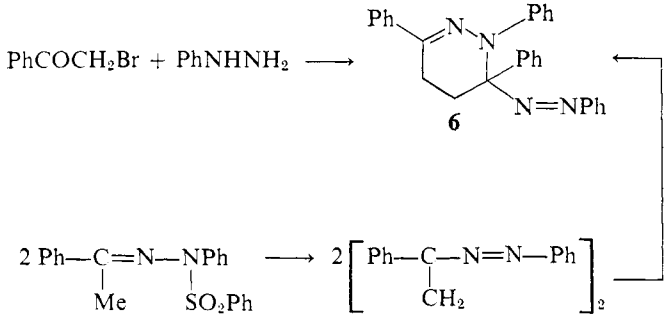
A series of ethyl 2-aryl-4-arylazo-2,3-dihydro-3-oxo-6-pyridazinecarboxylates (**4**: R = Et) has been prepared by intramolecular condensation of the arylhydrazones of ethyl 3-arylazoglutaconates which in turn are obtained by a coupling reaction of 2 moles of aryldiazonium chloride with ethyl glutaconate (21, 22). When the hydrazone is heated above its melting point or in ethanol, the reaction proceeds with more or less ease, depending upon the position of a substituent on the phenyl ring; ortho substituents greatly or entirely impede the reaction. The 5-methyl analogs of **4** (R = Me) have likewise been prepared from dimethyl β-methylglutaconate in low yields

without isolating the intermediate bisphenylazo compound (23). In a similar fashion the bisphenylazo compound of diethyl acetonedicarboxylate cyclized to ethyl 2-phenyl-4-phenylazo-2,3,4,5-tetrahydro-3,5-diketopyridazine-6-carboxylate (24) (**5**).

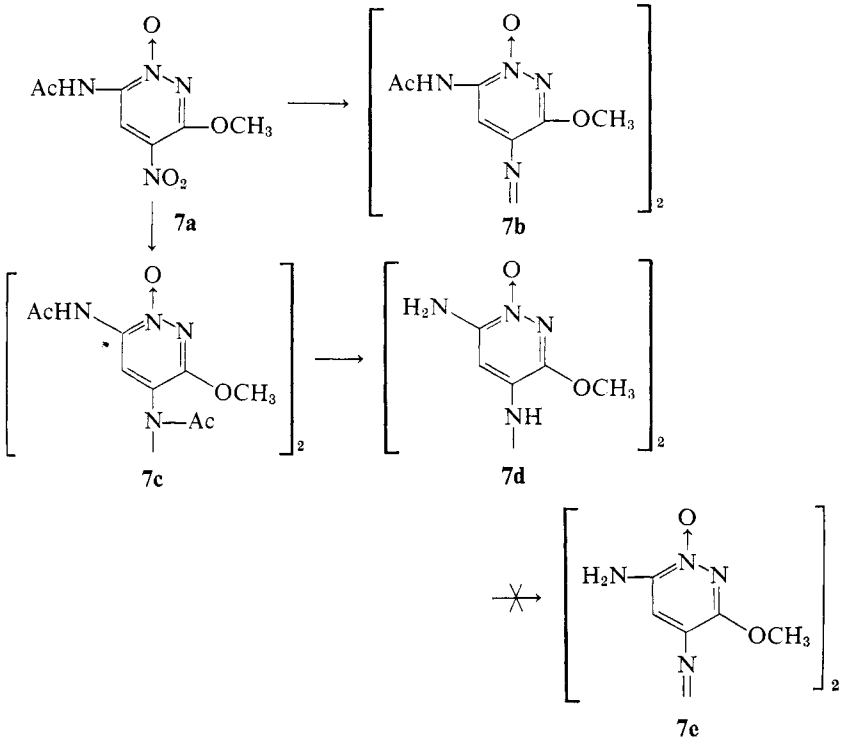


A yellow crystalline solid prepared by Hess (25) in the reaction of phenacyl bromide and phenylhydrazine, and erroneously formulated by Hess (25) and Culman (26), was shown to be 2,3,6-triphenyl-3-phenylazo-2,3,4,5-tetrahydropyridazine (**6**) by Curtin and Tristram (27). The procedure was also improved to increase the yield (27). Acetophenone *N*-phenyl-*N*-benzenesulfonyl hydrazone also gives the identical compound (**6**) by the action of sodium isopropoxide in 28% yield (28).

The phenylazo group of the compound is lost as phenyldiazonium ion on treatment with aqueous sulfuric acid (27).

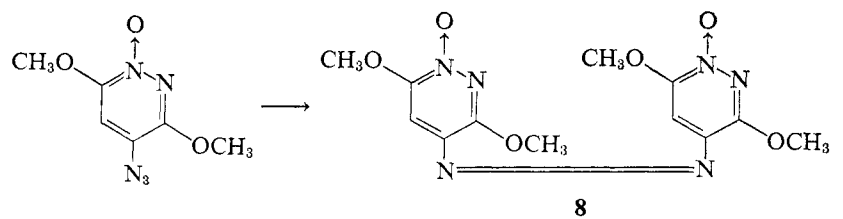


Catalytic reduction of 6-acetamido-3-methoxy-4-nitropyridazine 1-oxide (**7a**) over palladium–charcoal in acetic acid followed by oxidation with air formed a 4,4′-azodipyridazine 2,2′-dioxide (19) (**7b**). Air oxidation of the corresponding hydrazodipyridazine (**7d**) substituted with a free amino group failed to give the azodipyridazine. The hydrazodipyridazine (**7d**) was



prepared by hydrogenation of **7a** over palladium–charcoal in acetic anhydride followed by removal of the acetyl groups (19).

4-Azido-3,6-dimethoxypyridazine 1-oxide, when exposed to sunlight or refluxed in benzene solution, provided 3,3′,6,6′-tetramethoxy-4,4′-azopyridazine 1,1′-dioxide (29) (**8**).



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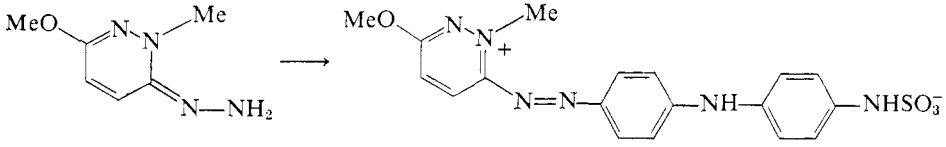
A coupling reaction of diazotized 6-amino-2-substituted 4,5-dichloro-3 (2*H*)-pyridazinone with a phenol or a naphthol to yield 6-phenylazopyridazinones is described in Chapter VI, Section I.C.3 (99). A mixture of 2-methyl-6-methoxy-3(2*H*)pyridazinone hydrazone and *N*-phenylphenylenediaminesulfonate was treated with sodium chlorite to form the 2-methyl-6-methoxy-3-phenylazopyridazinium salt (**21**) (100).



21

Diazotized aniline was coupled to 2-substituted-4,5-dihalo-3(2*H*)pyridazinones to give the 6-phenylazopyridazinones (101).

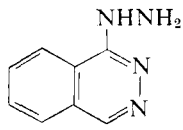
Condensation of 6-hydrazinopyridazines with aromatic or heteroaromatic quinones in acidic media gave a variety of 6-(2-hydroxyarylazo)pyridazines which dyed nickel-containing polypropylene fibers (102).

IV. Hydrazinopyridazines

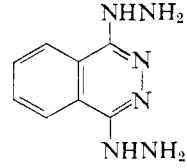
A. Preparation

1. *By Replacement Reaction*

The appearances of apresolin and nepresol as hypotensive agents stimulated the preparation of a variety of hydrazinopyridazines.



Apresolin (hydralazine)



Nepresol

Halopyridazines react much more readily with hydrazine than with ammonia, and the reaction proceeds under milder conditions as seen in Table V. As discussed in Chapter VI, Section I.A.2, 3,6-diaminopyridazine has been prepared by direct ammonolysis only under stringent conditions and in poor yield (30). In contrast, the replacement of both chlorine atoms of 3,6-dichloropyridazine is possible by heating with hydrazine hydrate under reflux (30). The difficulty has often been in the separation of the product from hydrazine hydrochloride. 3,6-Dihydrazinopyridazine could not be isolated from the reaction mixture of 3,6-dichloropyridazine and hydrazine (30). In the preparation of 3-azidopyridazine 1-oxide, 3-hydrazinopyridazine 1-oxide prepared from the 3-chloro compound was treated with nitrous acid without isolation (14). The difficulty, however, was avoided by substituting halopyridazines with alkoxy- or mercaptopyridazines. Thus Druey, Meier, and

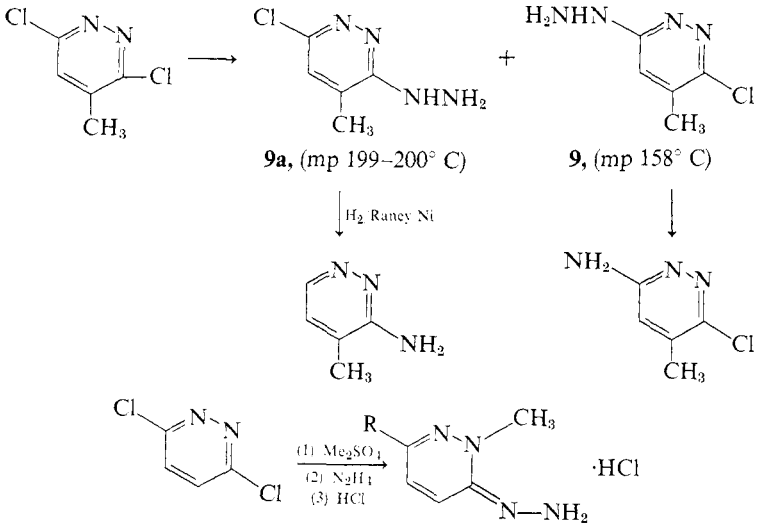
Eichenberger (31, 32) obtained 3,6-dihydrazinopyridazine by the reaction of dimercaptopyridazine with hydrazine hydrate, and Gortinskaya and Shchukina (30) later prepared the same compound from 3,6-dimethoxypyridazine. The yield reported by Druey et al. could not be repeated by Sato (33). Itai and Kamiya (34, 35) successfully prepared 3-, 4-, 5-, and 6-hydrazinopyridazine 1-oxides from the methoxy or ethoxy compounds in 26, 43, 55, and 56% yields, respectively.

As in the case of ammonolysis reactions of halopyridazines, a halogen atom reacts in preference to an alkoxy or methylsulfonyl group in the reaction of 3-halo-6-substituted pyridazines with hydrazine. Thus 3-chloro-6-methylsulfonylpyridazine reacts with hydrazine at room temperature (36), and 3-chloro-6-ethoxypyridazine at elevated temperature (37), giving 3-hydrazino-6-methylsulfonyl- and 3-hydrazino-6-ethoxypyridazine, respectively. The yield of the latter product is poor, and the product has been characterized as the *p*-nitrophenylhydrazone. The formation of 3-hydrazino-6-methoxypyridazine from 3-chloro-6-methoxypyridazine has been reported, but analytical values for the product were not given (36).

In the reaction of 3-chloro- or 3-phenoxy-6-pyridazinethiol with hydrazine, however, the replacement of the mercapto group is favored, 3-chloro- or 3-phenoxy-6-hydrazinopyridazine being formed (36). 3-Chloro-6-methylthio-, 3-chloro-6-phenylthio- (36), and 3-chloro-6-ethylthiopyridazines failed to give the hydrazino compounds.

Treatment of 4-methyl-3,6-dichloropyridazine with hydrazine provides two possible monohydrazino isomers (10, 38) (Tables VI and VIII). Takahayashi (10) assigned the high-melting isomer to 3-chloro-4-methyl-6-hydrazinopyridazine and the low-melting isomer to the 5-methyl compound by converting them to 4- and 5-methyl-6-chloro-3-(2*H*)pyridazinone, respectively, by the action of concentrated hydrochloric acid. However, the hydrolysis of these products could not be reproduced by Linholter and Rosenoern (38), who reduced these hydrazino isomers catalytically over Raney nickel. The low-melting hydrazino compound gave known 3-chloro-4-methyl-6-aminopyridazine, while the high-melting isomer yielded 3-amino-4-methylpyridazine, the structure of which was provided by nuclear magnetic resonance (nmr) studies. In addition, the conversion of the hydrazino compounds to the pyridazinone was further accomplished by treatment with hypochlorous acid. From these results, Linholter and co-workers concluded that the hydrazino compound of low melting point was 3-chloro-6-hydrazino-4-methylpyridazine (**9**) and the high-melting isomer was 3-chloro-6-hydrazino-5-methylpyridazine (**9a**).

Imino-type compounds of hydrazinopyridazine have been prepared by a replacement reaction of halo- or alkoxypyridazine with hydrazine. The

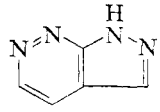


(10) R = Cl, MeO, *i*-PrO, PhO

methosulfates of 3,6-dichloro-, dialkoxy-, diphenoxy, or monochloromonoalkoxypyridazines react with aqueous hydrazine at low temperatures to yield 2-methyl-6-substituted 3(2*H*)pyridazinone hydrazones (39) (**10**).

Examples of the preparation of hydrazinopyridazines and pyridazinones by replacement are listed in Tables VI and VII.

The reaction of 3-chloropyridazine derivatives substituted with such groups as cyano, ethoxycarbonyl, and hydroxymethyl in the 4-position with hydrazine resulted in ring formation to give 1*H*-pyrazolo[3,4-*c*]pyridazine derivatives (40, 41) (**11**).



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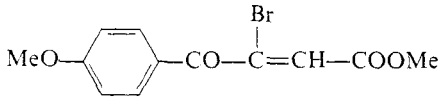
1*H*-Pyrazolo[3,4-*c*]pyridazine

One hydrazinopyridazinone has been obtained directly from a nonpyridazine source. When compound **12** or its cyclic form **13** is treated with



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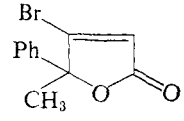


13

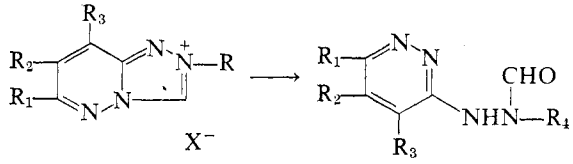
hydrazine hydrate at 130–135° C, 6-(*p*-methoxyphenyl)-5-hydrazino-3(2*H*)-pyridazinone is formed in good yields. At room temperature the reaction yields the 5-bromo compound (44).

2. *By Reduction of Nitramino or Nitrosoaminopyridazines*

The preparation of *N*-alkylhydrazino derivatives of the pyridazinones by means of catalytic hydrogenation of the *N*-alkyl-*N*-nitrosoaminopyridazinones over Raney nickel has been reported by Dury (42) in his review on the chemistry of pyridazinones. The same investigator has also reported the reduction of 2-substituted 4-chloro-5-nitraminopyridazinones to the 4-chloro-5-hydrazino derivatives in the same review (43). However, neither reagent nor reaction conditions for the reduction have been reported.

3. *By Cleavage of a Condensed Heterocyclic Ring System*

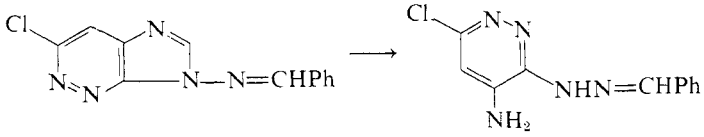
A series of N^1-alkyl- or benzyl-N^1-formyl-N^2-pyridazinylhydrazines has been prepared starting with 4-amino-1,2,4-triazole. 4-Amino-1,2,4-triazole was condensed with β-dicarbonyl compounds and the resulting *s*-triazolo-[4,3-*b*]pyridazines were quaternized at the 2-position by means of alkyl or benzyl halides. Treatment of the quaternary salts with an equivalent amount of aqueous potassium carbonate, sodium hydroxide, or ethanolic diethylamine yielded N^1-alkyl (or benzyl)-N^1-formyl-N^2-pyridazinylhydrazines in 60–90% yields (103–105) (**22**). When the quaternary salts were heated with an excess amount of sodium hydroxide for a longer period, the products were 3-aminopyridazines (see Chapter VI, Section I.A.7)



22 R_4 = Et or CH_2Ph

N^1-Benzyl-N^1-formyl-N^2-(4,6-dimethyl-3-pyridazinyl)hydrazine was hydrolyzed in boiling concentrated hydrochloric acid to yield the deformylated hydrazine in 85% yield (103, 105).

Ring opening of 3-benzylideneamino-6-chloroimidazo[4,5-*c*]pyridazine to 3-benzylidenehydrazino-4-amino-6-chloropyridazine (**23**) was effected by heating with ethanolic hydrochloric acid (56). When *N*-hydrochloric acid or acetic acid was used, the hydrazone was isolated as a by-product together with 8-amino-6-chloro-*s*-triazolo[4,3-*b*]pyridazine (106).



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B. Reactions

1. *Reactions with Aldehydes and Ketones*

Hydrazinopyridazines condense with aliphatic and aromatic aldehydes and ketones in a normal manner in neutral or acidic media. The hydrazones prepared are included in Tables XI and XIII. With bifunctional ketones cyclized derivatives can be formed (Tables XI and XIII). They are pyridazinylpyrazoles from acetylacetone (35) or benzoylacetophenone (45), pyridazinyl dihydropyridazine from 2,5-hexanedione (45), and pyridazinylpyrazolone from ethyl acetoacetate (46).

Benzaldehyde 4,6-dimethyl-3-pyridazinylhydrazone has also been prepared by air oxidation of the corresponding N^1-benzyl-N^2-pyridazinylhydrazine in aqueous alkali (103).

2. *Acylation*

3-Hydrazinopyridazines are acylated under mild conditions. The reaction may proceed further to form a condensed heterocyclic ring by participation of the ring nitrogen. This cyclization reaction is discussed later in this chapter (Section IV.B.4).

A typical example is observed in the acylation of 3-chloro-6-hydrazinopyridazine studied by Takahayashi (47). 3-Chloro-6-hydrazinopyridazine has been formylated by the action of ice-cold formic acid or by heating with methyl formate, and acetylated with acetic anhydride under cooling or by heating with ethyl acetate, to give the formyl or the acetyl derivative, respectively. Heating these acylated compounds with formic acid or acetic

anhydride on a water bath caused the cyclization to form the triazolopyridazines (Section IV.B.4). The same 3-chloro-6-hydrazinopyridazine and benzoyl chloride in pyridine solution at room temperature yield the benzoyl derivative which cyclizes to the triazolopyridazine when heated (48).

2,6-Dichloroisonicotinoyl derivatives have been prepared from 3-chloro- and 3-methyl-6-hydrazinopyridazines by the action of 2,6-dichloroisonicotinoyl chloride in the presence of pyridine (49).

The attempt to prepare another pyridazine ring by the condensation reaction of 3-chloro-6-hydrazinopyridazine with maleic anhydride in refluxing acetic acid solution did not give the desired cyclized product but resulted in the formation of a 56% yield of the maleinamic acid derivative (46). Phthalic anhydride similarly gave the phthalamide derivative at room temperature, and the *N*-carboethoxy derivative was obtained by the action of ethyl chloroformate in boiling ethanol solution (46). 4-Bromo-5-hydrazino-2-phenyl-3(2*H*)pyridazinone and maleic anhydride likewise give the maleinamic acid derivative.

The preparation of 5-nitro-2-imidofuroyl derivatives of 3-hydrazino- (107) or 6-chloro-5-methyl-3-hydrazinopyridazine (108) has been described.

3. *Thiosemicarbazides and Aminoguanidines*

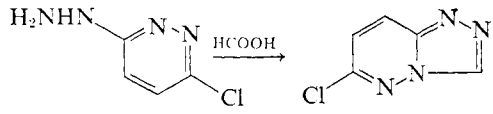
N-(Pyridazinyl)thiosemicarbazides have been prepared readily by treating hydrazinopyridazines with thiocyanates (34, 50, 51), or with alkyl and aryl isothiocyanates (46, 51), or by the action of thiosemicarbazide upon a halopyridazine (50). 3-Hydrazino-6-pyridazinecarbohydrazide and potassium isothiocyanate yield 3-thiosemicarbazidopyridazine-6-carbothiosemicarbazide (52).

N-Pyridazinylthiosemicarbazide reacts with γ-aceto-γ-chloropropanol or monochloroacetone to form the *N*-(2-thiazolyl)-*N'*-(3-pyridazinyl)hydrazines (50).

N-(Pyridazinyl)aminoguanidines have been obtained from hydrazinopyridazines by reaction with cyanamide (50) or *S*-methylisothioruea (51). 3-Chloro-6-hydrazinopyridazine condenses with 2-methylthioimidazoline to give the aminoguanidine-type compound (109).

4. *Synthesis of Polycyclic Systems*

a. *s*-Triazolo[4,3-*b*]pyridazines. Takahayashi (46) first prepared the *s*-triazolo[4,3-*b*]pyridazine ring system directly from 3-hydrazinopyridazines or from 3-acylhydrazinopyridazines. 3-Chloro-6-hydrazinopyridazine or its formyl derivative was treated with formic acid or ethyl orthoformate on a



14

water bath, forming 6-chloro-*s*-triazolo[4,3-*b*]pyridazine (**14**). 4-And 5-methyl derivatives of 3-chloro-6-hydrazinopyridazines (37), and 3-hydrazino-6-phenoxypyridazines (36), were similarly cyclized with formic acid to the corresponding *s*-triazolo[4,3-*b*]pyridazines. The assignment of the position of the methyl group in the former two compounds may be reversed from the reasons described in Section IV.A.1. By the substitution of acetic anhydride for formic acid, 3-methyl-6-chloro-, 6-chloro-3,7-dimethyl-, and 6-chloro-3,8-dimethyl-*s*-triazolo[4,3-*b*]pyridazines were prepared (37, 47). Using the same procedure, 4,6-dimethyl- (103) and 6-chloro-4,5-dimethyl-3-hydrazinopyridazine (110), and 3-hydrazino-6-chloro-4-pyridazinecarboxamide (106), have been cyclized with formic acid, and 6-chloro-4,5-dimethyl-3-hydrazinopyridazine with acetic anhydride (110), yielding the corresponding triazolopyridazines. Takahayashi investigated the cyclization of 6-acylhydrazino-3-chloropyridazine under a variety of reaction conditions and found that the reaction proceeds most readily in the presence of aqueous sodium hydroxide (53).

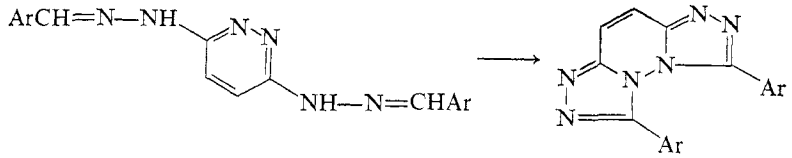
Later, Duffin, Kendall, and Waddington (54) heated 6-methyl- and 6-phenyl-3-hydrazinopyridazine with acetic anhydride in the presence of catalytic amounts of phosphoric acid, and Biniecki et al. (55) treated 3-hydrazino-6-phenylpyridazine with nicotinoyl or isonicotinoyl chloride in pyridine solution, the corresponding 3,6-disubstituted *s*-triazolo[4,3-*b*]-pyridazine being formed in each case.

The same general type of reaction has been accomplished with 3-hydrazinopyridazines substituted with a chlorine atom and an amino group (56, 57). Ring closure does not occur on the amino group but on the ring nitrogen. A variety of *s*-triazolo[4,3-*b*]pyridazines and their 3-phenyl derivatives has been prepared similarly from 4-amino-5-chloro-, 4-amino-6-chloro-, or 5-amino-4-chloro-3-hydrazinopyridazine (56, 57).

Another method for 3-alkyl or phenyl-*s*-triazolo[4,3-*b*]pyridazines has been reported separately by Kuraishi and Castle (56) and Pollak and Tišler (48). Kuraishi and Castle heated 4-amino-6-chloro-3-benzylidenehydrazinopyridazine with acetic acid, acetic anhydride, or benzoyl chloride and obtained 8-amino-6-chloro-3-phenyl-*s*-triazolo[4,3-*b*]pyridazine, its acetate, or its benzoate, respectively, while Pollak and Tišler prepared 3-phenyl-, 3-*p*-chlorophenyl-, and 3-*p*-methoxyphenyl-6-chloro-*s*-triazolo[4,3-*b*]pyridazine by treatment of the arylidenehydrazinopyridazine with bromine in

acetic acid at room temperature. The 3-phenyl compound was also formed by heating the benzylidenehydrazinopyridazine at 160° C. Ferric chloride in acidic ethanol solution and lead tetraacetate in acetic acid were employed in the cyclization of furfurylidene- or thienylidenehydrazinopyridazine to the corresponding 3-nitrofuryl- or 3-nitrothienyl-*s*-triazolo[4,3-*b*]pyridazines (107). These 3-(5-nitro-2-furyl)-*s*-triazolopyridazines were prepared alternatively by acid-catalyzed cyclization of 3-(5-nitro-2-imidofuroylhydrazino)-pyridazine or by thermal condensation of hydrazinopyridazines and 5-nitro-2-furoic acid. 3,6-Diaryl-bis-*s*-triazolo[4,3-*b*:3′,4′-*f*]pyridazines (**15**) have been obtained from 3,6-bisarylidenehydrazinopyridazines by similar treatment with bromine or lead tetraacetate in acetic acid (48). Pollak, Stanovnik, and Tišler (111) applied this oxidative cyclization successfully to the preparation of a *s*-triazolo[4,3-*b*]pyridazine 5-oxide. 3-Benzylidene-hydrazino-, 3-*p*-methoxybenzylidenehydrazino-, and 3-ethylidenehydrazino-pyridazine 1-oxides were treated with lead tetraacetate at room temperature, and the corresponding *s*-triazolo[4,3-*b*]pyridazine 5-oxides were obtained in 35–43% yield. Thermal condensation of 3-hydrazinopyridazine 1-oxide with diethoxymethyl acetate gave a poor yield of unsubstituted *s*-triazolo[4,3-*b*]-pyridazine 5-oxide. Attempted condensation of 3-hydrazinopyridazine 1-oxide with dimethylacetal in *N*,*N*-dimethylformamide gave no cyclized product, and 3-dimethylaminomethylenehydrazinopyridazine was obtained instead.

3-Chloro-6-hydrazino- and 3-hydrazino-6-methylpyridazines have been treated with chlorocyanide and sodium acetate in acetic acid at 0–5° C to give 3-amino-6-chloro- and 3-amino-6-methyl-*s*-triazolo[4,3-*b*]pyridazines (**16**) in good yields (58). 3-Allylamino-6-*p*-tolyl and 3-anilino-6-*p*-tolyl



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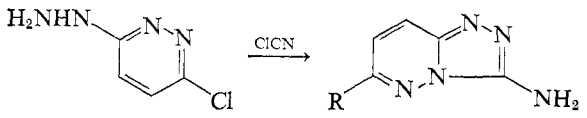

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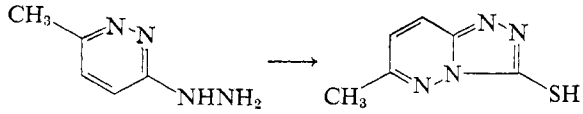
R = Cl, Me

derivatives of the same ring system have been obtained when 1-(*p*-tolyl-6-pyridazinyl)-4-allyl- or 4-phenylthiosemicarbazide is heated in acetic acid (51).

3-Hydrazinopyridazine 1-oxide reacts with bromocyanide in the presence of triethylamine at room temperature to provide 3-amino-*s*-triazolo[4,3-*b*]-pyridazine 5-oxide in 52% yield (111). The action of carbon disulfide in pyridine at 60° C upon 3-hydrazino-6-methylpyridazine gives the 3-mercapto derivative (58) (**17**).



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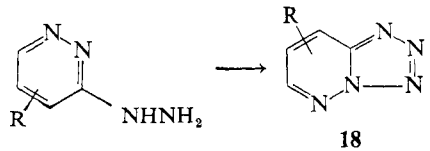
b. TETRAZOLO[1,5-*b*]PYRIDAZINES. 3-Hydrazinopyridazines are readily converted into tetrazolo[1,5-*b*]pyridazines (**18**) by the action of nitrous acid in acidic medium. The tetrazolo[1,5-*b*]pyridazines prepared by this method are 6-chloro- (47), 6-chloro-7- (73%), 6-chloro-8- (79%) (38), 7-chloro-8-amino (98%), 7-amino-8-chloro (51%) (57), 8-amino-6-chloro- (68%) (5), and 6-*p*-tolyl derivatives, in addition to the parent compound obtained from 3-hydrazinopyridazine in 55% yield (34).



18

c. 4*H*-PYRIDAZINO[3,2-*c*]-*as*-TRIAZINES. This ring system has been synthesized in two ways. The condensation products of 3-hydrazinopyridazines and α-halo ketones yielded 3- or 3,7-disubstituted 4*H*-pyridazino[3,2-*c*]-*as*-triazines as the hydro halides when heated in acetic acid (112). Parent 4*H*-pyridazino[3,2-*c*]-*as*-triazine was obtained by acid-catalyzed condensation of 3-chloro-6-hydrazinopyridazine with diethyl bromoacetal followed by catalytic hydrogenation. 3-Chloro-6-hydrazinopyridazine, however, was condensed with ethyl pyruvate, and the 3-(α-carbethoxyethylidenehydrazino)-6-chloropyridazine obtained was heated with polyphosphoric acid to yield 7-chloro-3-methylpyridazino[3,2-*c*]-*as*-triazin-4-one in 36% yield (113). Polyphosphoric acid cyclization was attempted with 3-(α-carboxyethylidene-hydrazino)-6-chloropyridazine. However, no cyclized product was obtained except for a small amount of the decarboxylated hydrazone.

d. MISCELLANEOUS. An attempt to prepare a pyridazinoindole derivative from 4-(2-cyclohexylidenehydrazino)pyridazine 1-oxide by means of Fisher's indole synthesis using sulfuric and acetic acid failed, and starting material was recovered (35).

5. *Replacement Reactions*

Whereas 3-hydrazinopyridazines form cyclized products with participation of the ring nitrogen (Section IV.B.4) by the action of nitrous acid, the 1- and 2-oxides of 3-hydrazinopyridazine give rise to azidopyridazine 1- and 2-oxides (35), respectively (14, 34). 4- And 5-hydrazinopyridazine 1-oxides (35), and 4-hydrazino-3,6-dimethoxypyridazine (29) similarly yield the corresponding azido compounds in 48, 74, and 47% yields, respectively. 2-Phenyl-4-chloro-5-hydrazino-3(2*H*)pyridazinone and nitrous acid have been reported to give the 5-azidopyridazinone (59).

Hydrazinopyridazines can be reduced catalytically over Raney nickel to aminopyridazines. In the presence of methanolic potassium hydroxide, 3-hydrazino-4-methyl-6-chloropyridazine is reduced to 3-amino-4-methylpyridazine, whereas the isomeric 5-methyl compound is reduced to 3-chloro-4-methyl-6-aminopyridazine with retention of the chlorine atom (38).

This reduction procedure has been applied to the preparation of diaminopyridazines that cannot be easily obtained by direct ammonolysis of halopyridazines or aminohalopyridazines. 5-Chloro-3,4-diamino- (57), 6-chloro-3,4-diamino- (60), 4,5-diamino-, and 4-chloro-3,5-diaminopyridazines (5) have been prepared from 5-chloro-4-amino-3-hydrazino-, 6-chloro-4-amino-3-hydrazino-, 4-amino-5-hydrazino-, and 5-amino-4-chloro-3-hydrazinopyridazine, respectively, by catalytic hydrogenation over Raney nickel in a neutral medium. The yields range from 47 to 53%. The vicinal diaminopyridazines have served as intermediates for condensed heterocycles. In these transformations the halogen atoms remain intact. 5-Hydrazino-3(2*H*)-pyridazinone has similarly been reduced to 5-amino-3(2*H*)pyridazinone (45).

The hydrazino group of 4-amino-6-chloro-3-hydrazino- (69), 5-amino-4-chloro-3-hydrazino- (57), or 4-methylamino-6-chloro-3-hydrazinopyridazine (62) has been replaced with hydrogen by oxidation with copper sulfate. 5-Hydrazino-4-chloro-3(2*H*)pyridazinone has been converted into 4-chloro-3(2*H*)pyridazinone by the same treatment in 9% yield (63). The hydrazino group of the 2-phenyl derivative is removed by the action of cupric oxide in aqueous sodium carbonate solution (42).

Takahayashi (37) has reported the hydrolysis of the hydrazino group of 4- and 5-methyl-3-chloro-6-hydrazinopyridazine into the hydroxy group, although in poor yields. The reaction could not be reproduced by Linholter and Rosenoern (38, 64), who carried out the same transformation using hypochlorite and sulfuric acid at 0° C. 3-Chloro-6-hydrazinopyridazine behaves similarly (64).

When Linholter, Rosenoern, and Vincents (64) conducted the reaction in hydrochloric acid instead of sulfuric acid, the replacement of the hydrazino

group with a chlorine atom occurred. Treatment with hypobromite in boiling hydrobromic acid caused replacement of the hydrazino group with a bromine atom. 3,6-Dichloro-, 4-methyl-3,6-dichloro- (92% from the 6-hydrazino, 74% from the 3-hydrazino compound), and 6-bromo-3-chloro-4-methylpyridazines have been prepared by chlorination, and 3-bromo-6-chloro- (41%) and both 4- (52%) and 5-methyl-6-bromo-3-chloropyridazine (65%) by bromination from the corresponding halohydrazinopyridazines. 6-Hydrazino-2,4-and 2,5-dimethyl-3(2*H*)pyridazinones fail to react with hypochlorite.

Dyes for polyacrylonitrile fibers have been prepared by the oxidative condensation of 2-methyl-6-substituted (chlorine, methoxy, phenoxy, or isopropoxy group) 3(2*H*)pyridazinone hydrazone with aromatic amines using hypochlorite in aqueous acetic acid (39). For example, the dye prepared from 6-chloro-2-methyl-3(2*H*)pyridazinone hydrazone and the monoacetate of *m*-phenylenediamine produces a red color on the fibers. Condensation of hydrazinopyridazines with aromatic orthoquinones also gives azo dyes (102).

V. Azidopyridazines

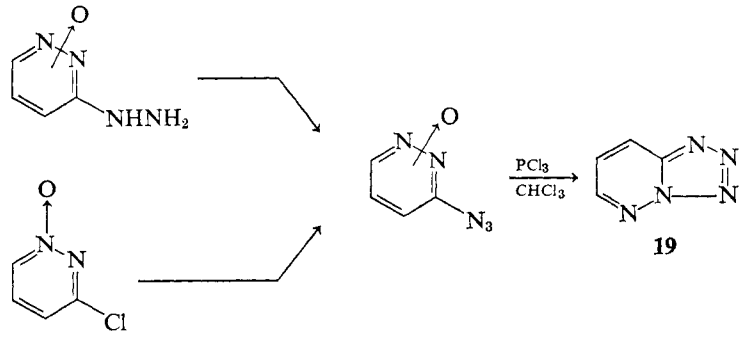
Azidopyridazines are obtainable by two methods: treatment of hydrazinopyridazines with nitrous acid and replacement of a halogen atom with sodium azide.

4-Azidopyridazine 1-oxide has been prepared in 48% yield from 4-hydrazinopyridazine 1-oxide under diazotization reaction conditions using sodium nitrite and dilute hydrochloric acid, or by the replacement reaction of 4-chloropyridazine 1-oxide and sodium azide in aqueous ethanol on a water bath (35). In the latter reaction a 4% yield of 4-aminopyridazine 1-oxide is formed in addition to a 51% yield of the main product. 5-Azidopyridazine 1-oxide is similarly produced by the first method in 74% yield. De-*N*-oxidation of 4-azidopyridazine 1-oxide by means of phosphorus trichloride in refluxing chloroform yields 4-azidopyridazine in 70% yield (35). 4-Hydrazino-3,6-dimethoxypyridazine gives a 47% yield of 4-azido-3,6-dimethoxypyridazine on treatment with sodium nitrite and hydrochloric acid (29).

The azide group at the 3-position of a pyridazine ring tends to cyclize to form a tetrazolo[1,5-*b*]pyridazine ring unless one of the ring nitrogens is occupied.

When a new hetero ring involving the nitrogen atom at the 5-position of a tetrazolo[1,5-*b*]pyridazine is formed, the tetrazolo ring opens spontaneously and an azido function is generated. The presumed valence isomerization has been studied in detail by Tišler, Stanovnik, and their co-workers (114–117). The formation of tetrazolo[1,5-*b*]pyridazines from 3-hydrazinopyridazines was discussed in Section IV.B.4. When 3-hydrazinopyridazine 1- or 2-oxide is

treated with nitrous acid, the corresponding azido *N*-oxides are formed (14, 34). 3-Azidopyridazine 1-oxide is also obtained in inferior yield by a replacement method using 3-chloropyridazine 1-oxide and sodium azide (34). These 3-azidopyridazine 1- and 2-oxides afford tetrazolo[1,5-*b*]pyridazine (**19**) when the *N*-oxide group is removed by treatment with phosphorus trichloride in chloroform solution (34). The use of phosphorus oxychloride instead of



phosphorus trichloride gives the 6-chloro derivative of the tetrazolopyridazine as a result of the concurrent removal of the *N*-oxide group and introduction of the chlorine atom. Again, introduction of an *N*-oxide function into the tetrazolopyridazine induces the isomerization of the tetrazolo ring into an azide group. Thus *N*-oxidation of tetrazolo[1,5-*b*]pyridazine with concentrated hydrogen peroxide in polyphosphoric acid produced 3-azidopyridazine 1-oxide in low yield (114). The attempt to obtain tetrazolo[1,5-*b*]-pyridazine 5-oxide by the action of hot concentrated sulfuric acid upon 3-azidopyridazine 1-oxide failed. In a patent the formation of 3,6-diazidopyridazine from the reaction between 3,6-dichloropyridazine and sodium azide is reported (65). The product from a similar reaction using 6-hydrazinotetrazolo[1,5-*b*]pyridazine and nitrous acid had been shown to be 6-azidotetrazolo[1,5-*b*]pyridazine from its chemical behavior and infrared (ir) spectrum (34).

The reaction of 3,6-dichloropyridazine 1-oxide and sodium azide gives 3-azido-6-chloropyridazine 1-oxide in poor yield (34). 5-Azido-4-chloro-2-phenyl-3(2*H*)pyridazinone has been prepared by the two conventional methods (59).

5-Azido-4-bromo-2-substituted 3(2*H*)pyridazinones have been prepared by the action of aqueous sodium azide upon the corresponding 4,5-dibromo-3(2*H*)pyridazinones (118). 5-(4-Chloromethyltriazolyl)-4-bromo-2-phenyl-3(2*H*)pyridazinone and sodium azide in aqueous sodium azide yield the 4-azido or the diazido compound (119).

The properties and reactions of azidopyridazine *N*-oxides have been investigated by Itai and Kamiya (29, 34, 35).

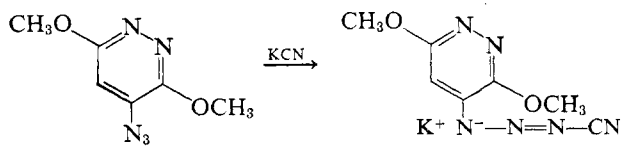
The azide groups of 3-, 4-, 5-, and 6-azidopyridazine 1-oxides can be replaced by alkoxy groups by treatment with sodium alkoxide at a variety of temperatures in fair to good yields. 4-Azido-3,6-dimethoxypyridazine 1-oxide and sodium methoxide give a 38% yield of 3,4,6-trimethoxypyridazine 1-oxide, accompanied by the formation of 1-hydroxy-3,4-dimethoxy-6(1*H*)pyridazinone in 14% yield.

The azido groups of 3- and 6-azidopyridazine 1-oxides and 4-azido-3,6-dimethoxypyridazine 1-oxide have been reduced by catalytic hydrogenation over palladium–charcoal in neutral medium, the corresponding aminopyridazine *N*-oxides being formed.

When 3-azidopyridazine 1-oxide was heated under reflux in xylene, it gave 3,3′-azodipyridazine 1,1′-dioxide, although in poor yield. In boiling benzene 4-azido-3,6-dimethoxypyridazine 1-oxide yielded the same type of azodipyridazine, whereas 6-azidopyridazine 1-oxide gave a small amount of 6-aminopyridazine 1-oxide and an unidentified oily product.

It has also been reported (34, 35) that 3- and 5-azidopyridazine 1-oxides are stable to sunlight but 4- and 6-isomers are sensitive. 3,3′,6,6′-Tetramethoxy-4,4′-azidopyridazine 1,1′-dioxide is formed when a benzene solution of 4-azido-3,6-dimethoxypyridazine 1-oxide is exposed to sunlight.

Not many reactions of simple 4-azidopyridazines have been reported. 4-Azidopyridazine was reduced by catalytic hydrogenation over palladium–charcoal to 4-aminopyridazine (35), and 4-azido-3,6-dimethoxypyridazine was converted into its potassium cyanotriazene derivative (**20**) by reaction with potassium cyanide (29).



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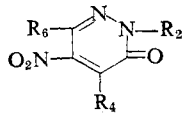
The azido group of 5-azido-4-bromo-3(2*H*)pyridazinone or its 2-substituted derivatives forms a 1,2,3-triazole ring on treatment with propargyl alcohol (120), acetylacetone, or ethyl acetoacetate (121). With acetoacetate in the presence of sodium ethoxide as the base, it is converted into an α-azoacetoacetylamino group (121). 5-Azido-4-bromo-2-phenyl-3(2*H*)pyridazinone is reduced by treatment with a variety of active methylene compounds and affords 4-amino-3-bromo-2-phenyl-3(2*H*)pyridazinone in variable yield (121).

TABLE I. Nitropyridazine[a] and Nitropyridazinones[b]

Nitropyridazine	MP (°C)	References
3-Nitro-6-methoxypyridazine	142–143	11



5-Nitro-3(2*H*)pyridazinones

R_2	R_4	R_6	MP (°C)	References
Ph	OH		184–186 (dec)	9
			NH_4 salt 260 (dec)	9
			Na salt 311 (dec)	9
			Pyridinium salt 77–79	9
Ph	MeO		94–96	9
4-Chlorophenyl	OH		140–142	9
4-Tolyl	OH		190 (dec)	9
3-Nitrophenyl	OH		128–129	9
Ts	OH		194 (dec)	9
			Na salt 190 (dec)	9
Cyclohexyl	OH		190–192 (dec)	9
Me	OH		168–170 (dec)	9
			Na salt 345 (dec)	9
$HOCH_2CH_2$	OH		Na salt 178–182 (dec)	9
2-Hydroxy-cyclohexyl	OH		223–225	9
H	OH		242 (dec)	9
			Diacetate 150–151	9
Me	OH	MeO	176–178 (dec)	9
Ph	Cl		124–126	66
Benzyl	Cl	Benzyloxy	126–127	66
Ph	Br		131–135	66
Me	Cl		97–99	66
4-Chlorophenyl	Cl		139–141	66
Ts	Cl		188–189	66

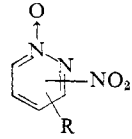
6-Nitro-3(2*H*)pyridazinones

R_2	R_4	R_5	MP (°C)	References
H	Cl	Cl	184–186	5
H	Br	Br	Not specified	5
Me	Cl	Cl	97–99	6
Et	Cl	Cl	87–89.5	99
Me	Br	Br	Not specified	6
Ph	COOMe		128	12
4-Bromophenyl	COOEt		128	12

[a] For nitroaminopyridazines, see Chapter VI, Tables XI and XXV.

[b] For nitroaminopyridazinones, see Chapter VI, Table XXVII.

TABLE II. Nitropyridazine Oxides[a]



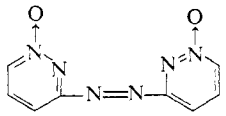
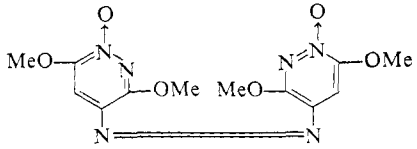
Position of nitro group	R	MP (°C)	References
3		169	14
4		150–151	15, 16
4	3-Methyl	72	67, 68
4	5-Methyl	144–145	69
4	6-Methyl	120–121	16, 67
		118–119	70
4	3-Methoxy	103	11, 73, 74
		Molecular compound with 3-methoxypyridazine 117–118	11, 72
4	3-Ethoxy	106–107	73
4	3-Chloro-6-methyl	103	16
		103–103.5	70
4	3-Methoxy-6-methyl	114–115	16
		101–101.5	70
		101–103	3
4	3,6-Dimethoxy	114	13
		114–115	71
4	3,6-Diethoxy	75–76	75
4	3,6-Di-*n*-propoxy	67–68	75
4	3,6-Di-*n*-butoxy	54–56	75
4	3,6-Dimethyl	117–118	75, 16
4	3-Methoxy-6-chloro	144–145	76
4	3-Methoxy-5-methyl	148–149	122
4	3-Hydroxy	124–126	122
4	3-Hydroxy-5-methyl	191–192	122
4	3-Hydroxy-6-methyl	200 (dec)	122
4	3-Hydroxy-6-chloro	214–215 (dec)	76
4	5,6-Dimethyl	97–97.5	67, 77
4	3-Chloro-5,6-dimethyl	105–106	67
4	3-Methoxy-5,6-dimethyl	106.5–107	67
5		142–143	14
5	6-Methyl	94	78
5	3,6-Dimethyl	85–86	78
5	6-Methoxy	135–136	78
6	3,4-Dimethyl	97–98	67, 79
6	3-Methoxy-4-methyl	116–117	80, 81
6	3-Ethoxy-4-methyl	85–86	81
6	3-*n*-Propoxy-4-methyl	52	81
6	3,4-Dimethoxy	162 (dec)	71
6	3-Methoxy	90–90.5	11, 72
6	3-Methoxy-5-methyl	113–115	122
6	3-Hydroxy-4-methyl	179 (dec)	122
4,6	3-Methoxy	130	74
4,6	3-Methoxy-5-methyl	175–177	122

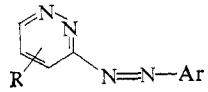
[a] For nitroaminopyridazine *N*-oxides, see Chapter VI, Table XXVIII.

TABLE III. Hydroxylaminopyridazines

Compound	MP (°C)	References
3-Hydroxylaminopyridazine 1-oxide	184 (dec)	14
4-Hydroxylamino-3,6-dimethylpyridazine	228–230	18
	Diacetate 142	18
	Dibenzoate 160	18
	N-nitroso 238	18
3-Methoxy-4-hydroxylamino-6-methylpyridazine 1-oxide	176 (dec)	20
4-Hydroxylamino-6-methylpyridazine 1-oxide	249 (dec)	20

TABLE IV. Azopyridazines

Compound	MP (°C)	References
	½ Hydrate >300	34
	248	29



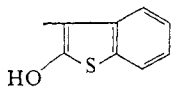
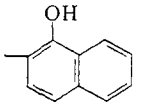
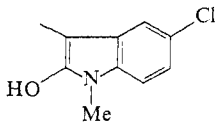
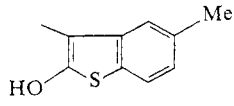
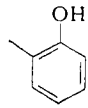
R	Ar	MP (°C)	References
H	 (X)	Not stated	102
H	 (Y)	Not stated	102
6-Cl		Not stated	102

TABLE IV. Azopyridazines (*continued*)

Compound		MP (°C)	References
6-Cl	X	Not stated	102
6-Cl		Not stated	102
6-Cl		Not stated	102
6-Br	X	Not stated	102
6-Me	X	Not stated	102
6-Ph	Y	Not stated	102
6-MeO	X	Not stated	102
6-MeO	Y	Not stated	102
6-EtO	Y	Not stated	102
4-Me, 6-Cl	X	Not stated	102
4-Me, 6-Cl	Y	Not stated	102
4,5,6-Cl_3	Y	Not stated	102
4,6-Cl_2	Y	Not stated	102

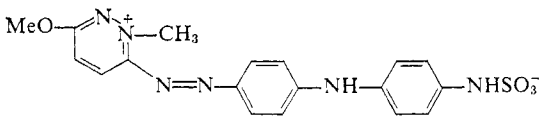
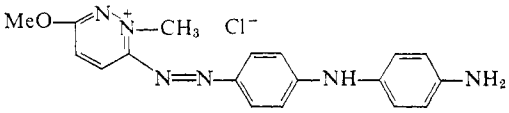
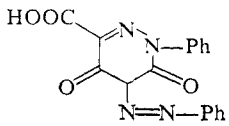
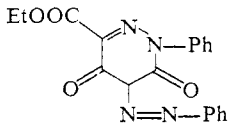
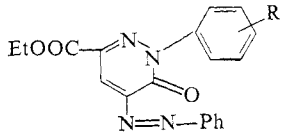
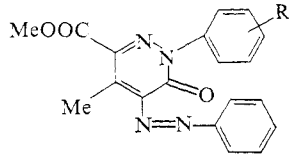
Compound	MP (°C)	References
	Not stated	100
	Not stated	100
	260	24
	164–165	24

TABLE IV Azopyridazines (*continued*)

	MP (°C)	References
R = 2-Methyl	152	22
4-Methyl	124–125	22
2,4-Dimethyl	155	22
4-Chloro	208–209	22
3-Bromo	149	22
2-Bromo	166–167	22
4-Bromo	229	22

	MP (°C)	References
R = H	216	23
4-Methyl	140	23
4-Methoxy	180	23

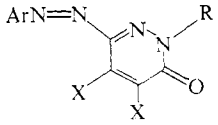
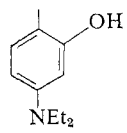
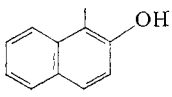
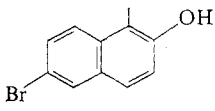
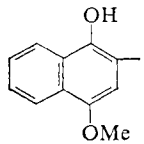
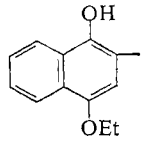
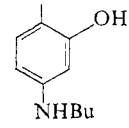
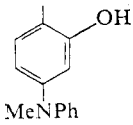
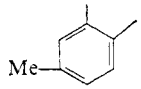
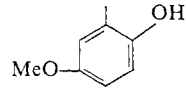
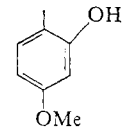
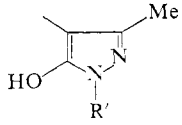
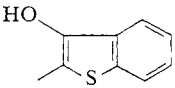
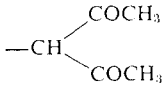
	MP (°C)	References
X = Cl R = Me, Et, Bu, $PhCH_2$, or Ph Ar =   	Not stated	99

TABLE IV. Azopyridazines (*continued*)

Compound	MP (°C)	References
        R′ = H, Ph, 2-tolyl, 2,5-dichlorophenyl, 3-nitrophenyl  		
X = Cl or Br Ar = Ph R = cyclohexyl, Ph, Bu, 4-chlorophenyl, Me, 3-tolyl	Not stated	101

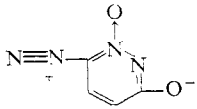
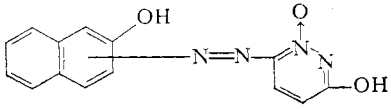
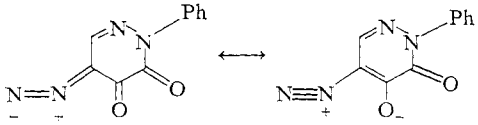
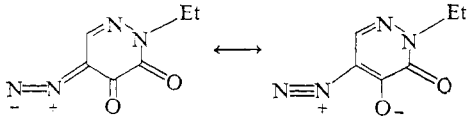
Compound	MP (°C)	References
	174 (dec)	82
	½ Hydrate 230 (dec) Not stated	82 99
	95 (dec)	83, 42
	81 (dec)	83, 42

TABLE V. Azidopyridazines and Azido-3(2*H*)pyridazinones

Azidopyridazines			
Position of azido group	Substituents	MP (°C)	References
3	(1-oxide)	155–156	14
		154–155	34
3	(2-oxide)	102–104 (dec)	34
3	6-Chloro (1-oxide)	153–154	34
4		62–64	35
4	(1-oxide)	123 (dec)	35
4	(2-oxide)	100–102 (dec)	35
4	3,6-Dimethoxy	77–79	29
4	3,6-Dimethoxy (1-oxide)	Hydrate 88–89 (dec, explosive)	29
3,6		129–130	65

Azido-3(2*H*)pyridazinones				
Position of azido group	Substituent at position 2	Substituents	MP (°C)	References
5	Phenyl	4-Chloro	110–111	59
			118–119	119
5	Phenyl	4-Bromo	Not stated	119
5	H	4-Bromo	180–181	118
5	Phenyl	4-Bromo	98–100	118
5	Me	4-Bromo	85–87	118
5	4-Nitrophenyl	4-Bromo	155–160	118
5	2,4,6-Trinitrophenyl	4-Bromo	161–163	118
5	Hydroxyethyl	4-Bromo	144–145	118
4,5	Phenyl		110	119

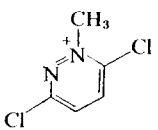
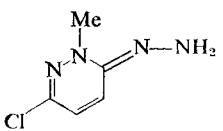
TABLE VI. Reaction of Substituted Pyridazines with Hydrazine

Starting material substituents				Reagents and conditions	Product[a]	References
3	4	5	6			
Cl				85% $N_2H_4 \cdot H_2O$, 100°C, 2–3 hr	3-$NHNH_2$ (3.5 → 2.25 g)	84, 85
				80% $N_2H_4 \cdot H_2O$, 100°C, 3 hr	3-$NHNH_2$ (60 → 36 g)	123
Cl			Me	80% $N_2H_4 \cdot H_2O$, 100°C, 3 hr	3-$NHNH_2$-6-Me (quant.)	50
				$N_2H_4 \cdot H_2O$, reflux, 5 hr	3-$NHNH_2$-6-Me (80%)	1
				$N_2H_4 \cdot H_2O$, reflux, 5 hr	3-$NHNH_2$-6-Me	54
				$N_2H_4 \cdot H_2O$, EtOH, reflux, 2 hr	3-$NHNH_2$-6-Me	86–88
				$H_2NNHCSNH_2$, H_2O, reflux, 6 hr	3-$NHNHCSNH_2$-6-Me	50
Cl			Ph	85% $N_2H_4 \cdot H_2O$, 100°C, 2–3 hr	3-$NHNH_2$-6-Ph	84
				$N_2H_4 \cdot H_2O$, EtOH, reflux, 6 hr	3-$NHNH_2$-6-Ph	86–88
				Not specified	3-$NHNH_2$-6-Ph	55
Cl			4-MeC_6H_4	$N_2H_4 \cdot H_2O$, EtOH, 120°C 3–5 hr	3-$NHNH_2$-6-*p*-tolyl (6 → 4 g)	89
Cl			4-$MeOC_6H_4$	$N_2H_4 \cdot H_2O$, EtOH, 120°C 3–5 hr	3-$NHNH_2$-6-*p*-methoxyphenyl	89
Cl			β-$C_{10}H_7$	$N_2H_4 \cdot H_2O$, EtOH, 120°C 3–5 hr	3-$NHNH_2$-6-β-naphthyl	86
Cl	Ph		Ph	$N_2H_4 \cdot H_2O$, EtOH, 120°C 3–5 hr	3-$NHNH_2$-4,6-di-Ph	86, 90
Cl		Ph	Ph	$N_2H_4 \cdot H_2O$, EtOH, reflux, 3 hr	3-$NHNH_2$-5,6-di-Ph	91
Cl			$CONH_2$	$N_2H_4 \cdot H_2O$, EtOH, reflux, 0.5 hr	3-$NHNH_2$-6-$CONH_2$ (105 → 58 g)	84, 92
Cl			COOEt	$N_2H_4 \cdot H_2O$, EtOH, reflux, 2 hr	3-$NHNH_2$-6-$CONHNH_2$ (92 → 122 g)	84, 85
Cl			COOEt	$N_2H_4 \cdot H_2O$, EtOH, 100°C, 2 hr	3-$NHNH_2$-6-$CONHNH_2$ (94%)	52
Cl			COOH	$N_2H_4 \cdot H_2O$, EtOH, reflux, 5 hr	3-$NHNH_2$-6-$CONHNH_2$ (3 → 2.1 g)	93

[a] Yield is given in parentheses.

TABLE VI (*continued*)

Starting material substituents						
3	4	5	6	Reagents and conditions	Product[a]	References
Cl			EtO	80% $N_2H_4 \cdot H_2O$, K_2CO_3, 145–150°C, 1 hr	3-$NHNH_2$-6-EtO	37
Cl			MeO	80% $N_2H_4 \cdot H_2O$, 110°C, 6 hr	3-$NHNH_2$-6-MeO (<10%)	36
Cl			$MeSO_2$	80% $N_2H_4 \cdot H_2O$, 30°C, 15 min	3-$NHNH_2$-6-$MeSO_2$	36
Cl			$PhCH_2$	$N_2H_4 \cdot H_2O$, *i*-PrOH, reflux, 4 hr	3-$NHNH_2$-6-benzyl (20 → 14.3 g)	94
Cl			2-Chlorobenzyl	$N_2H_4 \cdot H_2O$, *i*-PrOH, reflux, 4 hr	3-$NHNH_2$-6-(2-chlorobenzyl)	94
Cl			4-Chlorobenzyl	$N_2H_4 \cdot H_2O$, *i*-PrOH, reflux, 4 hr	3-$NHNH_2$-6-(4-chlorobenzyl)	94
Cl			4-Methylbenzyl	$N_2H_4 \cdot H_2O$, *i*-PrOH, reflux, 4 hr	3-$NHNH_2$-6-(4-methylbenzyl)	94
Cl			Phenethyl	$N_2H_4 \cdot H_2O$, *i*-PrOH, reflux, 4 hr	3-$NHNH_2$-6-phenethyl (51%)	94
MeO	Cl		MeO	80% $N_2H_4 \cdot H_2O$, EtOH, reflux, 0.5 hr	4-$NHNH_2$-3,6-di-MeO (25%)	29
	Cl	NH_2		95% N_2H_4, reflux, 3 hr	4-NH_2-5-$NHNH_2$ (47%)	4
Cl	NH_2	Cl		95% N_2H_4, 100°C, 3 hr	3-$NHNH_2$-4-NH_2-5-Cl (56%)	57
Cl	Cl	NH_2		95% N_2H_4, 100°C, 3 hr	3-$NHNH_2$-4-Cl-5-NH_2	57
Cl	NH_2		Cl	90% $N_2H_4 \cdot H_2O$, EtOH, reflux, 3 hr	3-$NHNH_2$-4-NH_2-6-Cl (80%)	61
Cl			Cl	80% $N_2H_4 \cdot H_2O$, EtOH, 100°C, 1 hr	3-$NHNH_2$-6-Cl (1.5 → 1.4 g)	37
				80% $N_2H_4 \cdot H_2O$, K_2CO_3, 110°C, 4 hr	3-$NHNH_2$-6-Cl	37
				$N_2H_4 \cdot H_2O$, EtOH, reflux	3-$NHNH_2$-6-Cl	49
				Not specified	3-$NHNH_2$-6-Cl	30
Cl	Me		Cl	80% $N_2H_4 \cdot H_2O$, 100°C, 1 hr	3-$NHNH_2$-4-Me-6-Cl (90%) and 3-$NHNH_2$-5-Me-Cl (10 → 0.4 g)	10
				80% $N_2H_4 \cdot H_2O$, MeOH or benzene, temp. not specified	3-$NHNH_2$-4-Me-6-Cl (10–25%) and 3-$NHNH_2$-5-Me-6-Cl (70–85%)	10

				50% $N_2H_4 \cdot H_2O$, reflux, 0.5 hr	3-$NHNH_2$-4-Me-6-Cl (81 → 15.7 g) and 3-$NHNH_2$-5-Me-6-Cl (81 → 34 g)	38
				80% $N_2H_4 \cdot H_2O$, not further specified	3-$NHNH_2$-4 or 5-Me-6-Cl	37
Br	Me		Br	85% $N_2H_4 \cdot H_2O$, 80°C, 20 min	3-$NHNH_2$-4-Me-6-Br	64
Cl	NHMe		Cl	95% N_2H_4, 90–100C, 2.5 hr	3-$NHNH_2$-4-NHMe-6-Cl (65%)	62
Cl	NH_2		Cl	95% $MeNHNH_2$, 90–100°C, 2.5 hr	3-$N(Me)NH_2$-4-NH_2-6-Cl (40%)	62
MeO			MeO	$N_2H_4 \cdot H_2O$, reflux, 5 hr	3,6-Dihydrazino (48%)	30
SH			SH	$N_2H_4 \cdot H_2O$, EtOH, reflux, 6 hr	3,6-Dihydrazino (2 → 1.5 g)	31, 32
				80% $N_2H_4 \cdot H_2O$, EtOH, reflux, 6 hr	3,6-Dihydrazino (poor)	33
	MeO (1-oxide)			80% $N_2H_4 \cdot H_2O$, EtOH, reflux, 3 hr	4-$NHNH_2$ (1-oxide) (43%)	35
	MeO (2-oxide)			80% $N_2H_4 \cdot H_2O$, EtOH, reflux, 3 hr	4-$NHNH_2$ (2-oxide) (55%)	35
MeO (1-oxide)				80% $N_2H_4 \cdot H_2O$, EtOH, reflux	3-$NHNH_2$ (1-oxide) (26%)	34
				100% $N_2H_4 \cdot H_2O$, 2-propanol, reflux, 1.5 hr	3$NHNH_2$ (1-oxide) (55%)	111
EtO (2-oxide)				80% $N_2H_4 \cdot H_2O$, EtOH, reflux	3-$NHNH_2$ (2-oxide) (56%)	34
				(1) $N_2H_4 \cdot H_2O$, H_2O, 5°C, 2 hr (2) HCl		39
Cl	$CONH_2$		Cl		3-$NHNH_2$-4-$CONH_2$-6-Cl	106
Cl		NH_2		N_2H_4, 100°C, 3 hr	3-$NHNH_2$-5-NH_2	107
Cl			Morpholino	98% $N_2H_4 \cdot H_2O$, reflux, 2 hr	3-$NHNH_2$-6-morpholino (75%)	124, 125

[a] Yield is given in parentheses.

TABLE VI (*continued*)

Starting material substituents				Reagents and conditions	Product[a]	References
3	4	5	6			
Cl			$N(CH_2CH_2OH)_2$	98% $N_2H_4 \cdot H_2O$, reflux, 2 hr	3-$NHNH_2$-6-$N(CH_2CH_2OH)_2$ (66%)	124, 125
Cl			NMePh	98% $N_2H_4 \cdot H_2O$, reflux, 2 hr	3-$NHNH_2$-6-NMePh (25%)	124, 125
Cl			Piperidino	98% $N_2H_4 \cdot H_2O$, reflux, 2 hr	3-$NHNH_2$-6-piperidino (75%)	124, 125
Cl			4-Methyl-piperazino	98% $N_2H_4 \cdot H_2O$, reflux, 2 hr	3-$NHNH_2$-6-(4-methyl-piperazino) (70%)	124, 125
Cl			$N(CH_2CH{=}CH_2)_2$	97% N_2H_4, reflux, 6 hr	3-$NHNH_2$-6-$N(CH_2CH{=}CH_2)_2$	126
Cl	Me	Me	Cl	80% N_2H_4, *n*-butanol, reflux, 3 hr	3-$NHNH_2$-4,5-Dimethyl-6-Cl (61%)	110
Cl	Me		Me	85% N_2H_4, 100°C, 3 hr	3-$NHNH_2$-4,6-dimethyl (62%)	103
Cl	$NHCH_2CH_2OH$		Cl	$N_2H_4 \cdot H_2O$, room temp., 20 hr	3-$NHNH_2$-4-R-6-Cl and 3-Cl-4-R-6-$NHNH_2$ (R = $NHCH_2CH_2OH$)	127
Cl	$NHCH_2CH{=}CH_2$		Cl	$N_2H_4 \cdot H_2O$, room temp., 20 hr	3-$NHNH_2$-4-R-6-Cl	127
Cl	$NHCH_2CH{=}CHMe$		Cl	$N_2H_4 \cdot H_2O$, room temp., 20 hr	R = $NHCH_2CH{=}CH_2$	
					R = $NHCH_2CH{=}CHMe$	127
Cl	NHPh		Cl	$N_2H_4 \cdot H_2O$, room temp., 20 hr	R = NHPh	127
Cl	NHEt		Cl	$N_2H_4 \cdot H_2O$, room temp., 20 hr	R = NHEt	127
Cl	$N(CH_2CH{=}CH_2)_2$		Cl	97% N_2H_4, reflux, 3 hr	3-Cl-4-$N(CH_2CH{=}CH_2)_2$-6-$NHNH_2$	128
SOMe				99% $N_2H_4 \cdot H_2O$, reflux, 1 hr	3-$NHNH_2$	129
	SOMe			99% $N_2H_4 \cdot H_2O$, reflux, 15 min	4-$NHNH_2$	129

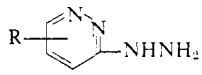
[a] Yield is given in parentheses.

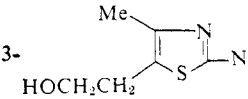
TABLE VII. Reaction of Substituted Pyridazinones with Hydrazine

Starting material substituent				Reagents and conditions	Position of replacement[a]	References
2	4	5	6			
H	Cl	Cl		95% $N_2H_4 \cdot H_2O$, MeOH, reflux, 1.5 hr	5 (62%)	45
H		Cl	Cl	95% $N_2H_4 \cdot H_2O$, MeOH, reflux, 1.5 hr	5 (94%)	45
H	Br	Br		95% $N_2H_4 \cdot H_2O$, MeOH, reflux, 1.5 hr	5	45
Ph	Cl	Cl		95% $N_2H_4 \cdot H_2O$, MeOH, reflux, 1.5 hr	5 (75%)	45
				$N_2H_4 \cdot H_2O$, EtOH, 60°C	5	59
Ph	Br	Br		$N_2H_4 \cdot H_2O$, pyridine, room temp.	5 (71%)	46
				$N_2H_4 \cdot H_2O$	5 (53%)	118
Ph	Cl		Cl	$N_2H_4 \cdot H_2O$, EtOH, reflux	4 (68%)	95

[a] Yield is given in parentheses.

TABLE VIII. 3-Hydrazinopyridazines[a]



Substituent			MP (°C)	References
4	5	6		
H	H	H	142	129
			Dihydrochloride 210–212 (dec)	84, 85
			Picrate 169 (dec)	34
		Me	74–75	86–88
			75–76	50
			121	54
			Monohydrate 71–72	1
			Hydrochloride 221–222 (dec)	86
			222	87, 88
			Dihydrochloride 231 (dec)	50
			3-HN=C(NH_2)NHNH-, dihydrochloride 205 (dec)	50
			3-  , picrate 242 (dec)	50
		Cl	137–138	31, 123
			140.5	37
			140	36
			135–137	49
			Hydrochloride >250 (dec)	49

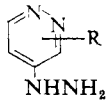
[a] For aminohydrazinopyridazines see Chapter VI, Tables X and XVIII.

TABLE VIII (*continued*)

Substituent				
4	5	6	MP (°C)	References
		Ph	143–144	86, 87
			144	87, 88
			151–152	84
			145–146	55
			Hydrochloride 231–233 (dec)	86, 87
			233 (dec)	87, 88
		2-Naphthyl	Hydrochloride 229–231 (dec)	86
		MeO	158–161	36
		PhO	120–130	36
		SO_2Me	163	36
		4-Tolyl	Hydrochloride 218–219	89
			3-HN=C(NH_2)NHNH, sulfate 245	51
		4-Methoxyphenyl	177	89
		Benzyl	119–123	94
			Hydrochloride 228–232 (dec)	94
		2-Chlorobenzyl	82–91	94
			Hydrochloride 230 (dec)	94
		4-Chlorobenzyl	155–157	94
			Hydrochloride 225–229	94
		4-Methylbenzyl	155–157	94
			Hydrochloride 241 (dec)	94
		Phenethyl	134–138	94
			Hydrochloride 218	94
		$NHNH_2$	193–195 (dec)	31–33
			Bisulfate (HSO_4) ~215 (dec)	31, 32
			Nitrate 191–192 (dec)	31, 32
			Hydrochloride 232–233	30
			Dihydrochloride 221–222	30
		$CONHNH_2$	228–230	52
			251–252 (dec)	84
			250–252	93, 85
			Dihydrochloride 224–225	93
		$CONH_2$	249–250	92
			249–250 (dec)	84
Ph		Ph	Dihydrochloride 205–208	86, 90
4 or 5-Me		Cl	149	37
Me		Cl	193	10
			158	38
	Me	Cl	149	10
			199–200	38
Me		Br	179.5–180	64
H	H	H (1-oxide)	158–160	34
			157–159	111
H	H	H (2-oxide)	160 (dec)	34
$CONH_2$		Cl	183–184	106
Me	Me	Cl	204–205	110
Me		Me	96–97	103

[a] For aminohydrazinopyridazines see Chapter VI, Tables X and XVIII.

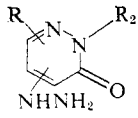
TABLE IX. 4-Hydrazinopyridazines[a]



Substituent			MP (°C)	References
3	5	6		
H	H	H	287–289 (dec)	129
			Hydrochloride 240–242 (dec)	96
Cl		Cl	195–196	96
MeO		MeO	177–178	29
H	H	H (1-oxide)	192–193 (dec)	35
H	H	H (2-oxide)	188 (dec)	35

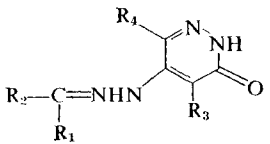
[a] For aminohydrazinopyridazines, see Chapter VI, Tables XI and XIX.

TABLE X. Hydrazino-3(2*H*)pyridazinones



Position of hydrazino group	R_2	R	MP (°C)	References
5	H		267 (dec)	45
5	H	4-Cl	195 (dec)	45
5	H	4-Br	180 (dec)	45
5	H	6-(4-Methoxyphenyl)	230–232	44
5	Ph	4-Cl	172 (dec)	59
			164 (dec)	45
5	Ph	4-Br	161–162	46
4	Ph	6-Cl	204–205	95

TABLE XI. Condensation Products of Hydrazinopyridazinones with Aldehydes or Ketones



R_1	R_2	R_3	R_4	MP (°C)	References
H	Ph		4-Methoxyphenyl	260–261	44
H	4-Methoxyphenyl		4-Methoxyphenyl	243–244	44
H	Ph	Br		241 (dec)	45
H	Ph	Cl		304 (dec)	45
H	3-Hydroxyphenyl	Br		267 (dec)	45
H	3-Hydroxyphenyl	Cl		300 (dec)	45
H	3,4-Dimethoxyphenyl	Br		248 (dec)	45
H	3,4-Dimethoxyphenyl	Cl		276 (dec)	45
Me	Ph	Br		220 (dec)	45
Me	Ph	Cl		255 (dec)	45
Me	4-Tolyl	Br		224 (dec)	45
Me	4-Tolyl	Cl		280 (dec)	45
Me	3,4-Xylyl	Br		220 (dec)	45
Me	3,4-Xylyl	Cl		263 (dec)	45
Me	2-Hydroxyphenyl	Br		234 (dec)	45
Me	2-Hydroxyphenyl	Cl		289 (dec)	45
Me	3,4-Dichlorophenyl	Br		240 (dec)	45
Me	3,4-Dichlorophenyl	Cl		314 (dec)	45
Et	Ph	Br		182	45
Et	Ph	Cl		209–210	45
n-Pr	Ph	Br		175–176	45
n-Pr	Ph	Cl		217–218	45

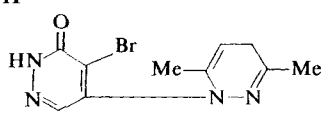
i-Pr	Ph	Br	221 (dec)	45
i-Pr	Ph	Cl	251	45
n-Bu	Ph	Br	151	45
n-Bu	Ph	Cl	190	45
2-Carboxyvinyl	Ph	Br	233 (dec)	45
2-Carboxyvinyl	Ph	Cl	255 (dec)	45
Me	Styryl	Br	207 (dec)	45
Me	Styryl	Cl	214 (dec)	45
Ph	Ph	Br	299 (dec)	45
Ph	Ph	Cl	304 (dec)	45
Ph	4-Methoxyphenyl	Br	232	45
Ph	4-Methoxyphenyl	Cl	252	45
Benzyl	4-Tolyl	Br	236 (dec)	45
Benzyl	4-Tolyl	Cl	276 (dec)	45
Benzyl	Benzyl	Br	192 (dec)	45
Benzyl	Benzyl	Cl	207	45
Ph	Phenylhydroxymethyl	Br	240 (dec)	45
Ph	Phenylhydroxymethyl	Cl	259 (dec)	45
Ph	Benzoyl	Br	225	45
Ph	Benzoyl	Cl	220 (dec)	45
H	2-Furyl	Cl	259 (dec)	45
Me	3-Pyridyl	Br	267 (dec)	45
Me	3-Pyridyl	Cl	280 (dec)	45
Me	2-Pyridyl	Br	251 (dec)	45
H	3-Pyridyl	Cl	287 (dec)	45
Ph	4-Dimethylaminophenyl	Br	213 (dec)	45
Ph	4-Dimethylaminophenyl	Cl	258 (dec)	45
4-Dimethylaminophenyl	4-Dimethylaminophenyl	Cl	253 (dec)	45
H	4-Dimethylaminophenyl	Cl	252 (dec)	45
			264 (dec)	45

TABLE XI (*continued*)

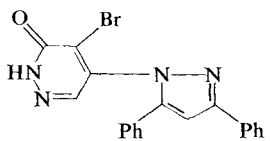
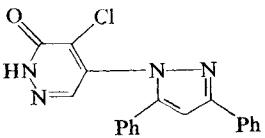
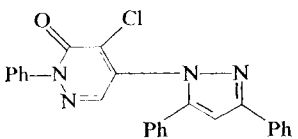
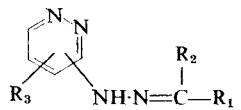
R_1	R_2	R_3	R_4	MP (°C)	References
				211–213	45
				209	45
				176–178	45

TABLE XII. Acylhydrazino- and Thiosemicarbazido-3(2*H*)pyridazinones

Position of hydrazino group	Acyl- or thiosemicarbazido group	R	MP (°C)	References
5	HOOCCH=CHCONHNH—	2-Ph-4-Br	126–127	46
5	EtNHCSNHNH—	2-Ph-4-Br	197–198	46
5	PhNHCSNHNH—	2-Ph-4-Br	175–176	46

TABLE XIII. Condensation Products of Hydrazinopyridazines with Aldehydes or Ketones



Position of hydrazone group	R_1	R_2	R_3	MP (°C)	References
3	Ph	H	(1-oxide)	246–247 (dec)	34
				255–256	111
3	Me	H	(1-oxide)	156–157	111
3	Me	Me	(1-oxide)	200	34
3	4-Methoxyphenyl	H	(1-oxide)	246–247	111
3	Me_2N	H	(1-oxide)	194	111
3	5-Nitro-2-thienyl	H	H	275–277	112
3	5-Nitro-2-furyl	H	H	Hydrochloride 235 (dec)	107
3	Ph	H	(2-oxide)	161–162 (dec)	34
3	2-Hydroxyphenyl	H	(2-oxide)	186 (dec)	34
3	CH_2CH_2COOH	Me	6-Me	175	1
3	2,4-Dihydroxyphenyl	H	6-Me	268 (dec)	50
3	3-Methoxy-4-hydroxyphenyl	H	6-Me	124 (dec)	50
3	2-Hydroxyphenyl	H	6-Me	243 (dec)	50
3	3,4-Methylenedioxyphenyl	H	6-Me	211 (dec)	50
3	4-Nitrophenyl	H	6-Me	250 (dec)	50
3	3-Nitrophenyl	H	6-Me	249 (dec)	50
3	5-Nitro-2-furyl	H	6-Me	236–237 (dec)	50
				242–243	107
3	5-Nitro-2-thienyl	H	6-Me	264–266 (dec)	107
3	Furyl	H	6-Me	254 (dec)	50
3	Ph	H	6-Cl	263–264	48
3	Ph	Me	6-Me	167–168	112
3	4-Tolyl	H	6-Cl	205–206	48
3	4-Chlorophenyl	H	6-Cl	295–296	48
3	4-Methoxyphenyl	H	6-Cl	225–226	48

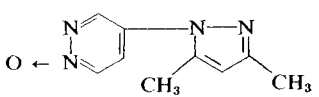
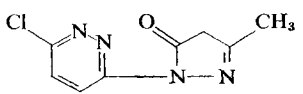
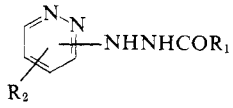
3	4-Nitrophenyl	H	6-Cl	288 (dec)	37
3	4-Acetamidophenyl	H	6-$NHNH_2$	280–281	30
3	Me	COOH	6-Cl	234	113
3	Me	COOEt	6-Cl	184	113
3	Me	H	6-Cl	Not stated	113
3	Ph	CH_2Br	6-Cl	Above 200	112
3	Me	CH_2Cl	6-Cl	Hydrochloride 169–170	112
3	4-Nitrophenyl	CH_2Br	6-Cl	320	112
3	Ph	Me	6-Cl	183–184	112
3	5-Nitro-2-furyl	H	6-Cl	295–296	112
				250–254	107
3	3-Methoxy-4-hydroxyphenyl	H	6-$NHNH_2$	244–245	30
3	4-Hydroxyphenyl	H	6-$NHNH_2$	259–260	30
3	4-Dimethylaminophenyl	H	6-$NHNH_2$	263–265 (dec)	30
3	Ph	H	4,6-di-Me	166–167	111
3	Ph	CH_2Br	$CONH_2$	273–276	112
3	Ph	Me	$CONH_2$	280–282	112
3	5-Nitro-2-furyl	H	$CONH_2$	300	112
3,6	Me	Me		~250 (dec)	31
3,6	Ph	H		261–262	48
3,6	4-Methoxyphenyl	H		225–226	48
3	Me	Me	6-Ph	163	86, 87
3	4-Nitrophenyl	H	6-EtO	275.5 (dec)	37
4	—$(CH_2)_5$—		3,6-di-MeO	143	29
4	Ph	H	(1-oxide)	252 (dec)	35
4	Me	Me	(1-oxide)	218	35
4	—$(CH_2)_5$—		(1-oxide)	196–199	35
4	Ph	H	(2-oxide)	280 (dec)	35
				155–156	35
				232–233	46

TABLE XIV. Acylhydrazinopyridazines



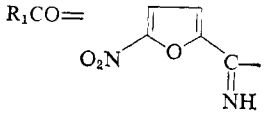
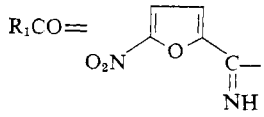
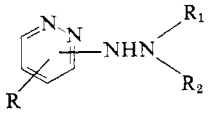
Position of acylhydrazino group	R_1	R_2	MP (°C)	References
3	2,6-Dichloro-4-pyridyl	6-Me	232–236	49
3	HOOCCH=CH	6-Cl	188–190	46
3	EtOOCCH=CH	6-Cl	179–180	46
3	2-Carboxyphenyl	6-Cl	200	46
3	EtO	6-Cl	157–158	46
3	H	6-Cl	172	47
3	Me	6-Cl	77	47
3	Ph	6-Cl	83–84	48
3	2,6-Dichloro-4-pyridyl	6-Cl	172–173	49
3	H	4 or 5-Me-6-Cl	189.5	47
3		H	215–218	107
3		6-Cl	214–216 (dec)	107

TABLE XV. Thiosemicarbazidopyridazines

Position of thiosemicarbazido group	R_1	R_2	MP (°C)	References
3	H	6-Me	137	50
3	H	6-(4-Tolyl)	210	51
3	Ph	6-(4-Tolyl)	156	51
3	Allyl	6-(4-Tolyl)	198–199	51
3	H	6-$CONHNHCSNH_2$	215–216	52
3	H	(1-Oxide)	232 (dec)	34

TABLE XVI. Alkyl- or Aralkylhydrazinopyridazines



Position of hydrazino group	R_1	R_2	R	MP (°C)	References
3	$PhCH_2$	H	4,5-di-Me	109–112	103, 105
				Dihydrochloride 210–215 (dec)	103, 105
3	$PhCH_2$	CHO	4,5-di-Me	124–127	103–105
3	Et	CHO	4-Ph, 6-Me	119–124 (dec)	103–105
3	$PhCH_2$	CHO	4-Ph, 6-Me	149–152	103–105
3	$PhCH_2$	CHO	4,5,6-tri-Me	121–124	103, 104
3	$PhCH_2$	CHO	4-OH, 6-Me	258–259	104, 105
3		H	6-Cl	Hydrochloride 285	109

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CHAPTER VIII

Pyridazine *N*-Oxides

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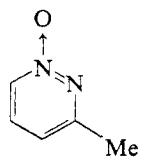
Pyridazine was first described in the chemical literature in 1885 by Knorr (1). Neither pyridazine nor any of the derivatives have been found in nature. Pyridazines are the least well-explored of the isomeric diazines. Hitherto, the methods of ring synthesis and nucleophilic substitution, and so on have been studied, but electrophilic substitution reactions such as nitration have not been reported (2).

In 1941, Ochiai (3) and his group began studies on pyridine 1-oxides and published a report on nitration. Subsequently, the studies were extended to not only pyridine and quinoline but also to the diazines. Ochiai (4) recently reviewed all aromatic amine oxides. Similar to the pyridine *N*-oxides, pyridazine 1-oxide and its derivatives have been studied mostly in Japan.

The nomenclature is in accordance with the rules suggested by *Chemical Abstracts*, however, the *N*-oxide ring nitrogen is designated as the 1-position. For instance, **1** is 3-methylpyridazine 1-oxide and **2** is 3-methylpyridazine



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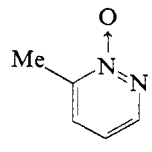


2

2-oxide according to *Chemical Abstracts* rules; however, in many cases the latter is designated 6-methylpyridazine 1-oxide for ease of understanding.

I. *N*-Oxidation

The history of heterocyclic *N*-oxides and other aromatic amine *N*-oxides has been reviewed in detail by Ochiai (5). In the pyridazine series 3,6-dimethoxypyridazine 1-oxide was reported for the first time by Itai and Igeta (6) in 1955. In 1958, Koelsch and Gumprecht (7) reported pyridazine 1-oxide, which Itai and Natsume (8) reinvestigated and improved the yield (89%). Subsequently, many pyridazine 1-oxides were synthesized by several groups. They were, however, entirely mono-*N*-oxides; no di-*N*-oxide was obtained. However, in 1966, Suzuki and Nakadate (9) obtained methylcinnoline di-*N*-oxide by carrying out the *N*-oxidation under more vigorous reaction conditions than previously used, followed by separation of the products. This success prompted the synthesis of pyridazine di-*N*-oxide and 3,6-dimethylpyridazine di-*N*-oxide (10). The yields were low, but the compounds are reasonably stable. More recently Nakadate, Sueyoshi, and Suzuki (48a) have reported the synthesis of pyridazine dioxide, 3,6-dimethylpyridazine dioxide, 3-methylpyridazine dioxide, and 4-methylpyridazine dioxide.

A. Synthetic Methods for *N*-Oxidation

In the earlier stages of *N*-oxidation studies, perbenzoic and monoperphthalic acids were used for *N*-oxidation (11), however, both of these reagents were unsuitable for large-scale preparation of *N*-oxides. Ochiai and Sai (12) overcame this difficulty by devising a method using hydrogen peroxide–glacial acetic acid solution. Synthetic methods are outlined in the order of decreasing frequency of use in the pyridazine 1-oxide series.

1. *Hydrogen Peroxide–Glacial Acetic Acid Solution*

In 1945, Ochiai and Sai (12) reported this most widely used method. The principal ingredient may be peracetic acid. The *N*-oxide may be prepared as follows. To a glacial acetic acid solution of a base, 1.5–2.0 equivalents of 30% hydrogen peroxide solution are added at room temperature in two or three portions at 2- to 8-hr intervals. After each addition the solution is usually warmed to 60–80° C. After assuring the existence of excess hydrogen

peroxide, most of the solvent is distilled off under reduced pressure. By repeating reduced pressure distillation after adding portions of water to the residue, excess hydrogen peroxide must be expelled. The residual solution is then basified with sodium carbonate, and the residue is extracted with chloroform. The combined extracts are dried over anhydrous sodium sulfate, and the solvent is removed by distillation under reduced pressure. The residue is purified by either recrystallization, distillation, or chromatography. Vacuum distillation should be carried out carefully because pyridazine 1-oxides seem less stable than pyridine *N*-oxides. If a compound is readily hydrolyzed, a highly concentrated hydrogen peroxide solution must be used. For this purpose the water in a mixture of 60% hydrogen peroxide–glacial acetic acid is calculated or determined and an equivalent amount of acetic anhydride is added; the mixture is then allowed to stand to decompose the water completely. Good results were obtained by using an anhydrous mixture of hydrogen peroxide and acetic acid prepared in this fashion (13). *N*-Oxidation of some very weak bases was successful for the first time through the use of a mixture of trifluoroacetic acid and hydrogen peroxide solution (14).

2. *Monoperphthalic Acid–Ether Solution*

This reagent was reported by Böhme (15). As *N*-oxidation proceeds under very mild conditions with this reagent, it may be the method of choice with easily hydrolyzable compounds (16). This method suffers from the disadvantages that the reagent must be prepared whenever it is needed (17), and the use of large quantities of ether may be dangerous in large-scale experiments. Although pyridine *N*-oxide phthalate separates out in crystalline form from an ethereal solution, the pyridazine *N*-oxides usually remain in solution.

3. *Perbenzoic Acid–Chloroform Solution*

Meisenheimer (18) reported a method using benzene as the solvent, however, in the pyridazine series *N*-oxides can be obtained in good yields by allowing chloroform solutions of perbenzoic acid to stand at room temperature (19, 20). A slight disadvantage is the preparation of perbenzoic acid (21, 22).

4. *Miscellaneous*

A solution of hydrogen peroxide and maleic acid has been used for pyridazines (23). Organic solvents, especially dichloromethane, were usually used.

This method often makes it possible to prepare *N*-oxides that cannot be obtained by other methods.

Formic acid was used as the organic acid for the *N*-oxidation of 3,6-dichloropyridazine (24) but with poor results.

B. The Relations between Substituents and the Position of the *N*-Oxide Group

The reaction mechanism of *N*-oxidation was described by Ochiai (25). It is proposed that, the higher the electron density of a ring nitrogen, the easier *N*-oxidation takes place. If an electron donor is present at a position adjacent to, or conjugated with, the ring nitrogen, the electron density is elevated and *N*-oxidation becomes easier. On the contrary, an electron-withdrawing substituent at these positions makes *N*-oxidation more difficult. Although the influence of a variety of factors in this reaction might be discussed, a review of the experimental facts is more informative. The greatest disadvantage of this approach is that all researchers did not necessarily determine quantitative yields of the products, thus it is difficult to assess exactly the effect of substituents on *N*-oxidation.

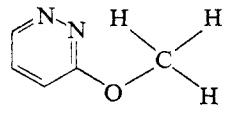
1. 3-*Substituted Pyridazines*

In 1961, Kano et al. (26, 27) reported that *N*-oxidation of 3-methylpyridazine (**3a**) provided the 1- (**4a**) and the 2-oxides (**5a**) in 8.2 and 22.4% yield, respectively (a ratio of 1:3). The products were separated by gas chromatography. In 1962, Nakagome (28) also examined the same reaction and reported that the yields were 46 and 45%, that is, in a ratio of 1:1. Prior to this, Kumagai (29) had isolated the 1-isomer (**4a**) but failed to separate the 2-isomer (**5a**). 3-Phenylpyridazine (**3b**) gave the 1- and 2-isomers in a ratio of 70.5:9.5, however, the ratio was described as 100:1 in another place in the report. In any event 3-phenylpyridazine (**3a**) produces overwhelmingly the 1-oxide (20).

3-Methoxy-, (**3c**) (30, 31) and 3-benzyloxypyridazine (**3d**) (19) are converted to the 1-oxides in good yields, while 3-chloropyridazine (**3e**) gives the 1-oxide although the yield is a somewhat low (32).

Although 3-aminopyridazine (**3f**) resinifies with monoperphthalic acid (method 2), 3-aminopyridazine 2-oxide (**5f**) is produced in 43% yield with hydrogen peroxide–glacial acetic acid (method 1). 3-Acetaminopyridazine (**3g**) is converted into *N*-oxides in a ratio of 2:82 by method 1, and of 10:33 by method 2 (33, 34). 3-Ethylaminopyridazine (**3h**) gives the 2-oxide (**5h**) only. These data are recorded in Table I.

The majority of these results can be explained by the electronic effects of a substituent on the ring. In the case of the methoxy group, it is somewhat difficult to explain the results by electronic effects. Otomasu (35, 36) studied the configuration of the methoxy group by dipole moment measurements and showed that the methoxy group is in a cis configuration which indicates some steric hindrance involving the 2-nitrogen as shown below (**6a**).



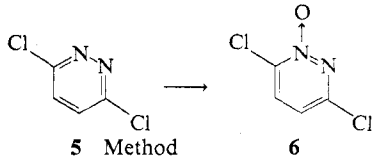
6a

2. *3,6-Disubstituted Pyridazines*

3,6-Dimethylpyridazine is *N*-oxidized somewhat easier in high yields (37) than pyridazine itself. In the instances involving methyl-phenyl groups or methyl-chloro groups at the 3,6-positions, *N*-oxidation takes place solely adjacent to the methyl group (29). However, 3-phenyl-6-chloropyridazine provides 1- and 2-oxides in a ratio of ca. 3:1 (20).

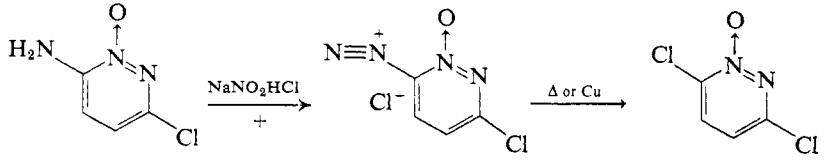
3-Methylpyridazines, which are substituted with an alkoxy or an hydroxy group at the 6-position, produce preferentially the corresponding 2-oxides (26–29).

Since the basicity of 3,6-dichloropyridazine (**5**) is low, *N*-oxidation is difficult. Furthermore, owing to the rather high activity of the chlorine atoms, 3-chloro-6 (1*H*) pyridazinone (**7**) was formed as a by-product by oxidation method 1, and the yield of 3,6-dichloropyridazine 1-oxide (**6**) is also low even by method 2 (9.1%) (16) or by method 3 (44.6%) (19). On using hydrogen peroxide in formic acid as the oxidizing agent, the results were similar to those mentioned above (24).



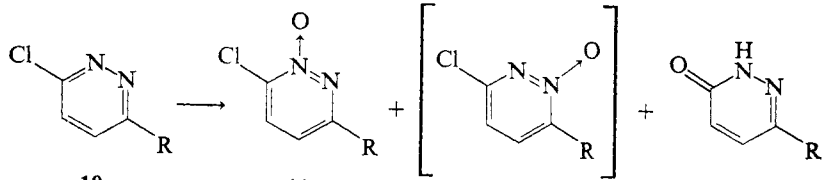
5 Method	**6**	**7**	References
2	9.1% (recov. 54%)		16
3	44.6%		19
	By-product	Main product	24

When large quantities of **6** are needed, it is best prepared by diazotization of 3-chloro-6-aminopyridazine 1-oxide (**8**) followed by the Gattermann reaction (24) (see Section VI.G.1).



8 **9** **6**

N-Oxides are not easily produced, as stated in Section I.B.1, when alkoxy and chloro substituents are located at the 3,6-positions. Actually, yields of the *N*-oxides are low, and much of the starting material is recovered. Even though the alkoxy group is a methoxy group, oxygen combines with the ring nitrogen next to the chlorine atom (16, 19). By method 1 hydrolysis of the chlorine atom gave rise to a hydroxy group.



10 **11** **12** **13**

R = MeO, EtO, *n*-PrO

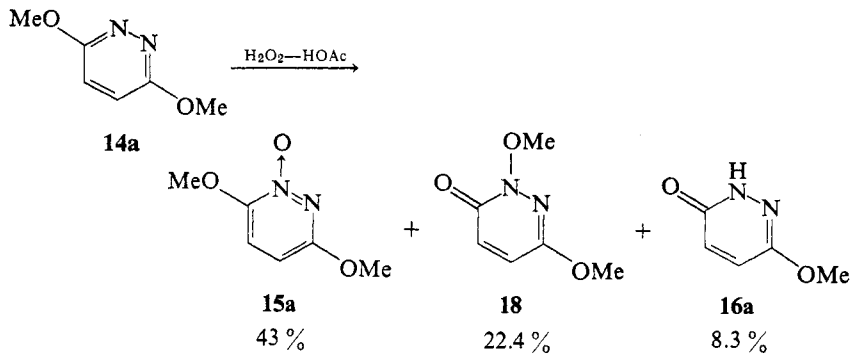
As stated before, the 3-methoxy group of 3-methoxypyridazine results in some hindrance to an adjacent ring nitrogen in the *N*-oxidation, and the remote nitrogen (at 1-position) is oxidized. However, *N*-oxidation of 3,6-dialkoxypyridazines (methoxy, ethoxy-, *n*-propoxy- and *n*-butoxy-) (**14a–d**) give monoxides in average yields of 50%. (See Table II for *N*-oxidation of 3,6-dialkoxylpyridazines.)

3,6-Di-*tert*-butoxy- (**16e**) and 3,6-dibenzyloxypyridazine (**16f**) did not produce the corresponding *N*-oxides but gave 3-hydroxy-6-(1*H*)pyridazinone (**17**) (maleic hydrazide) and 3-benzyloxy-6(1*H*)pyridazinone (**16f**) in high yields. These two compounds are obtained by merely warming the dialkoxypyridazines with glacial acetic acid and arise by hydrolysis (37).

In 1965, Yanai and Kinoshita (23) reexamined this reaction and determined that not only dealkylation from the 6-methoxy group of **16a** but also methyl migration from the methoxy group to the oxygen of the *N*-oxide group occurred to produce **18** (23).

If the *N*-oxidation of **14a** is carried out with hydrogen peroxide–maleic acid in dichloromethane, no hydrolysis is observed, rather methyl migration is the side reaction, that is, **15a** and **18** are produced in a ratio of 5:3 from **14a**.

Combinations of an amino group and either an alkoxy group or a chlorine atom at the 3,6-positions, regardless of whether the amino group is free or acetylated, oxygen always combines with the ring nitrogen next to the



amino group (33, 34, 38). Upon oxidation of 3-amino-6-chloropyridazine by method 1, crystals of high purity precipitate out from the solution (33, 34).

N-Oxidation of 3,6-disubstituted pyridazines is summarized in Table III.

3. *4-Mono- and Trisubstituted Pyridazines*

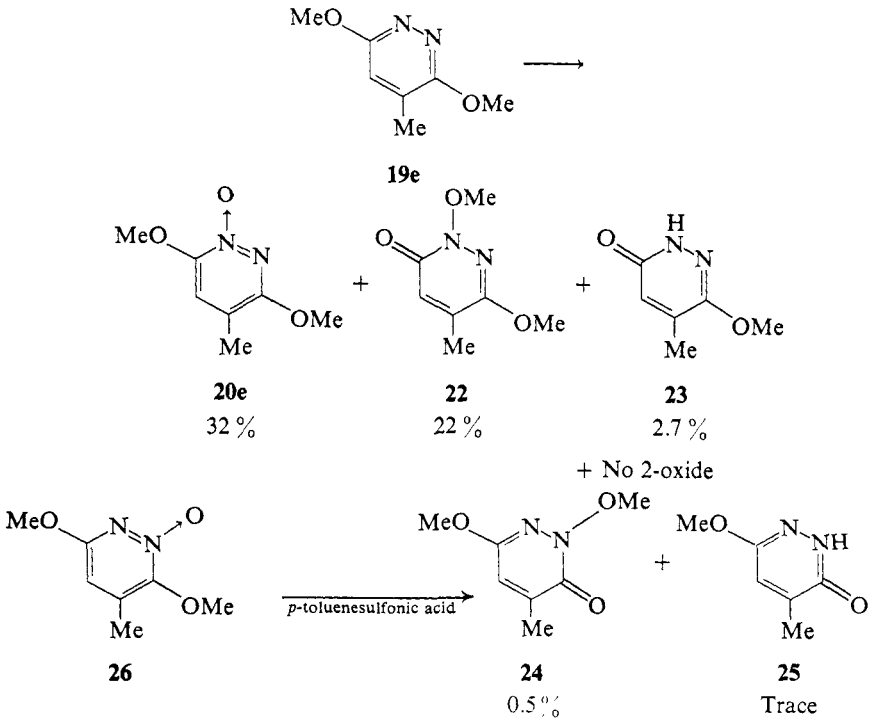
Among 4-substituted pyridazines, 4-methyl- (**19a**) (39) and 4-methoxypyridazines (**19b**) (40, 41) were the only compounds studied, and the *N*-oxidation products were obtained in low yields. It is difficult to predict which isomer is preferentially produced because of the limited number of examples.

As examples of *N*-oxidation of pyridazines substituted by the same groups in the 3,6-positions and another group in the 4-position, 3,6-dimethyl-4-chloro- (**19c**) (42), 3,6-dichloro-4-methyl- (**19d**) (8), 3,6-dimethoxy-4-methyl- (**19e**) (43), 3,6-diethoxy-4-methyl- (**19f**) (43), and 3,6-dimethoxy-4-azidopyridazines (**19g**) (44) are described in the literature. *N*-Oxidation of the above compounds affords more 1-oxide than 2-oxide, regardless of the nature of the 4-substituent, that is, a methyl and a methoxy group are electron donors, and a chlorine atom is an electron-withdrawing group. Substituents at the 3,6-positions have much influence on the yields. These data are summarized in Table IV.

N-Oxidation of 3,6-dimethoxy-4-methylpyridazine (**19e**) is reported in detail here; **19e** affords the 1-oxide (**20e**) but no 2-oxide (**21e**) as indicated.

However, a close examination of the products revealed that the existence of 1,3-dimethoxy-5-methyl-6(1*H*)pyridazinone (**24**) suggested a transient production of 3,6-dimethoxy-5-methylpyridazine 1-oxide (**26**). This fact was proved by heating **26** in the presence of a trace amount of *p*-toluenesulfonic acid to obtain **24**. From 3,6-diethoxy-4-methylpyridazine (**19f**), the corresponding 1- and 2-oxides were obtained in 58.7 and 5.1 % yields, respectively, by method 1 (23).

Unsymmetrical 3,4,6-trisubstituted pyridazines (**27**), such as 3,4-dimethoxy-6-chloro- (**27a**) (40) and 3-methoxy-4-methyl-6-chloropyridazines (**27c**)



(43) afford the 1-oxides (**28**), however, 3-chloro-4-methyl-6-methoxy- (**27b**) (43) and 3,4-dimethyl-6-chloropyridazines (**27d**) (46) give the 2-oxides predominantly. The factor influencing the position of *N*-oxidation is mainly the substituents at the 3,6-positions. This fact has already been pointed out in Section I.B.2. It appears that the 3- and 4-methyl groups seem to increase the yields. These data are summarized in Table V.

Furthermore, 3,4,5-trisubstituted pyridazines (**30**), such as 3,4-dichloro-5-amino- (**30a**) (45), 3,5-dichloro-4-amino- (**30b**) (45) 3,4-dichloro-5-methoxy- (**30c**) (13), and 3,4-dimethylpyridazine (**30d**) (46), have been *N*-oxidized at the 1-position because of the vacancy at the 6-position. Under these circumstances the influence of substituents at the 4- and/or 5-position seems unimportant. 3,4,5-Trisubstituted pyridazine 1- and 2-oxides are summarized in Table VI.

II. Deoxygenation

A. Catalytic Reduction

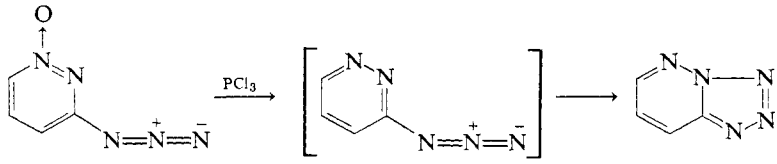
In an earlier stage of the studies on pyridine and quinoline 1-oxides, catalytic reduction with palladium–carbon was used for removal of oxygen from the *N*-oxide group, but the reaction was slow and difficult (49). In 1959,

Hayashi (50) and his collaborators found that pyridine *N*-oxides were reduced very quickly and preferentially with Raney nickel as the catalyst; double bonds, chlorine atoms, or benzyloxy groups often remained intact (50). The *N*-oxide in the pyridazine series is often reduced easily with palladium–carbon as the catalyst in neutral solution and, needless to say, in acidic media such as acetic or hydrochloric acid solutions. Therefore it may be concluded that *N*-oxides of the pyridazine series are reduced more easily than those of the pyridine series. There are reports on catalytic hydrogenation with palladium-carbon in the presence of acetic anhydride (59, 60). The deoxygenation of substituted pyridazine 1-oxides are reported in Table VII.

B. Deoxygenation with Phosphorus Trichloride

When nitropyridine 1-oxide is reduced catalytically, the nitro group is first reduced to the aminopyridine 1-oxide; then the *N*-oxide is reduced to the tertiary nitrogen atom (see Section VI.C.1). In 1951, Hamana (66, 67) found that a reaction of nitropyridine or -quinoline 1-oxide with phosphorus trichloride caused deoxygenation without affecting the nitro or other reducible groups. In the pyridazine 1-oxide series, there are only a few instances and these are summarized in Table VIII.

3-Azidopyridazine 1-oxide (**33**) produces tetrazolo[5,1-*b*]pyridazine (**35**) on deoxygenation via 3-azidopyridazine (**34**).

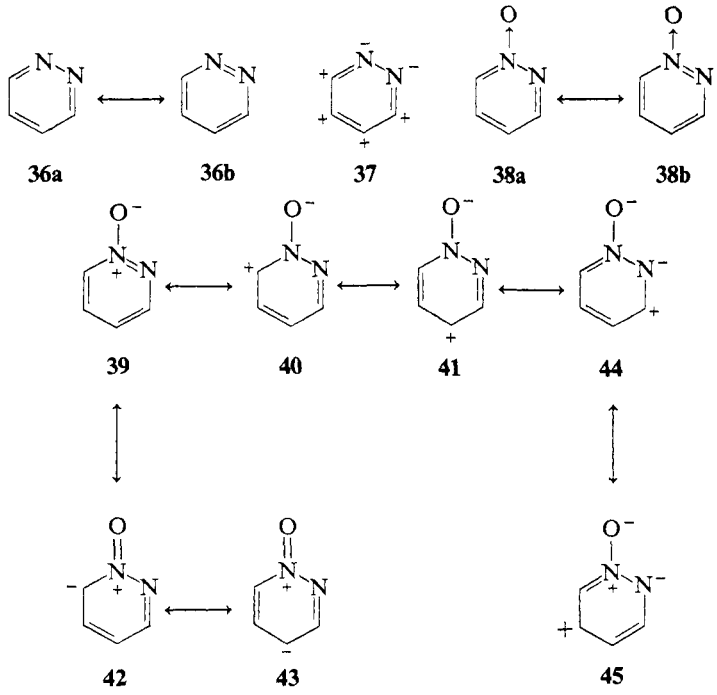


33 **34** **35**

III. Electrophilic Substitution

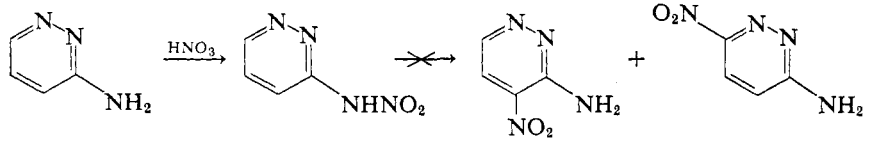
A. General

The 3-, 4-, 5-, and 6-positions of pyridazine are ordinarily electron-deficient by virtue of the negative mesomeric effect of the ring nitrogen atoms, as shown in **37**. For pyridazine 1-oxide the following variety of resonance structures can be considered by virtue of the negative mesomeric and inductive effects of the *N*-oxide function and the negative mesomeric effect of the tertiary ring nitrogen atom, as shown in **39–45**.



Thus pyridazine is presumed active to nucleophilic reagents and inactive to electrophilic reagents (72). As a matter of fact, electrophilic substitution in pyridazines is in general difficult even in the presence of one or two electron-releasing substituents on the ring. The nitration of 3-aminopyridazine (**46**) gives only 3-nitraminopyridazine (**47**) but no 4- or 6-nitro-3-aminopyridazine (**48** or **49**) (73), and the bromination of 3,6-dihydroxypyridazine (maleic hydrazide) is also unsuccessful (74). 3,6-Dimethoxy-4-aminopyridazine is nitrated to 3,6-dimethoxy-4-amino-5-nitropyridazine (75), that is, the nitration of the pyridazine is feasible for the first time with the introduction of three electron-releasing groups.

In 1955 it was reported by Itai and Igeta (77) that 3,6-dimethoxy-4-nitropyridazine 1-oxide was obtained with a mixture of nitric acid and sulfuric acid, as in pyridine *N*-oxides (76). Subsequently, this group also succeeded in the nitration of pyridazine 1-oxide with acyl nitrate, giving 3- or



5-nitropyridazine 1-oxide (78, 79). Since then the nitration of substituted pyridazine 1-oxides has been extensively studied in Japan (see Table IX and Section III.B.2). Although 3- and 5-pyridazinol 1-oxides undergo the Mannich reaction (80–82), and bromination (83) fairly readily, they do not react with diazonium compounds (84). The deuteration reaction of pyridazine 1-oxide derivatives seems to be more difficult than for pyridine and quinoline *N*-oxides (102, 85).

B. Nitration

1. *Nitration with Nitric Acid and Sulfuric Acid*

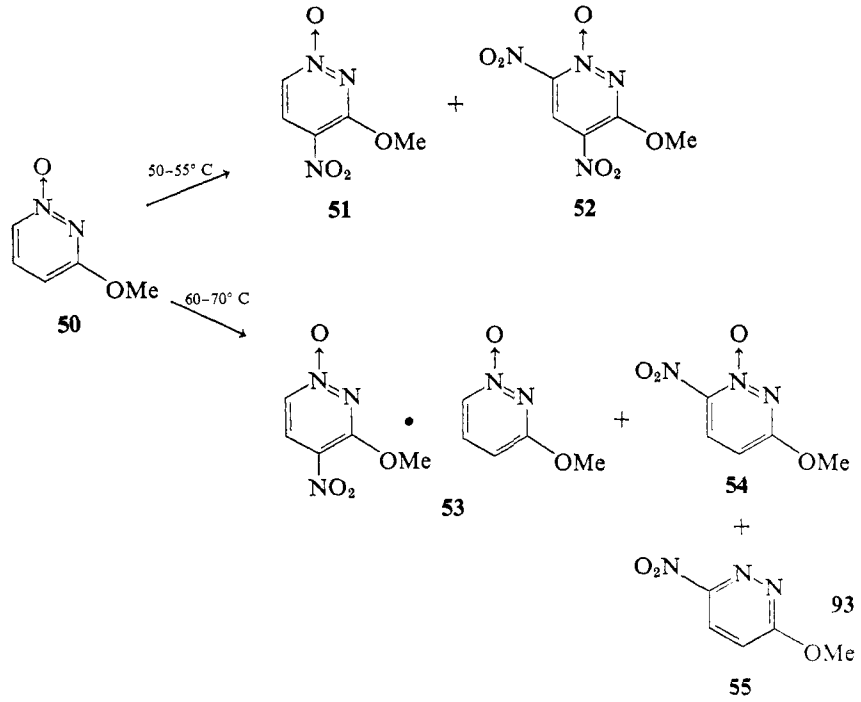
Pyridazine 1-oxide was nitrated with a mixture of nitric acid and sulfuric acid at 105–110° C to give 4-nitropyridazine 1-oxide in 8% yield (86). However, by elevating the reaction temperature to 130–140° C and using an excess of nitric acid in concentrated sulfuric acid, the same product was obtained in 22% yield (91).

It was reported by Ogata and Kano (87, 89) that 3- and 4-methylpyridazine 1-oxides were not converted to the corresponding nitro compounds (3-methyl-4-nitro- and 4-methyl-6-nitropyridazine 1-oxides), however, 5- and 6-methylpyridazine 1-oxides afforded the corresponding 4-nitropyridazine 1-oxides under the conditions mentioned above (87, 89). In 1963 the synthesis of 3-methyl-4-nitropyridazine 1-oxide was reported by Nakagome (88) although in a poor yield.

As shown in Table IX, dimethylpyridazine *N*-oxides yield the 4-nitropyridazine 1-oxides when the 4-position is vacant, and the 6-nitro-substituted compounds when the 4-position is occupied (86–88). This formation of 6-nitropyridazine 1-oxides is in contrast with the nitration of pyridine 1-oxide, that is, 4-nitropyridine 1-oxide is a major product together with a small amount of 2-nitropyridine, and no 2-nitropyridine 1-oxide is obtained (76). The introduction of methyl groups into the pyridazine 1-oxide ring makes the nitration easy, however, the yields are not necessarily high. When a methyl group or certain other groups are present at the 6-position, nitration becomes easier and the yields are high.

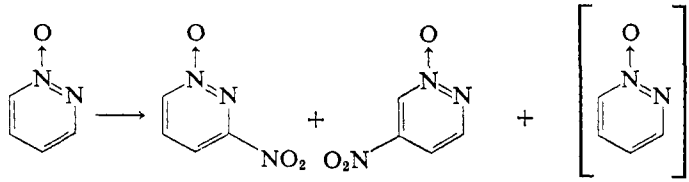
The nitration of 3-methoxypyridazine 1-oxide (**51**) was first reported by Igeta (92) and then by Nakagome (93). Their results are somewhat different.

A pyridazine 1-oxide derivative having two or more substituents, such as alkyl-alkoxy, dialkoxy, alkyl-acetamino, alkoxy-acetamino groups, is easily nitrated at a temperature below 10° C. The results are summarized in Table X which shows that nitration occurs first at the 4-position and then at the 6-position.



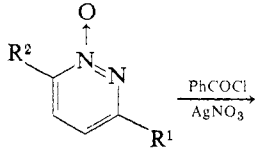
2. *Nitration with Acyl Nitrate*

Ochiai and Kaneko (98) reported a new nitration method for quinoline 1-oxide with silver nitrate and acyl chloride, which resulted in the production of 3-nitroquinoline 1-oxide, and so on. Using acetyl chloride as the acyl chloride in this method, Itai and Natsume (99) obtained 3-nitropyridazine 1-oxide (**57**) as the major product and 5-nitropyridazine 1-oxide (**58**) as the minor product from pyridazine 1-oxide (**56**). Benzoyl chloride gives a little better yield of **57** as indicated (99).

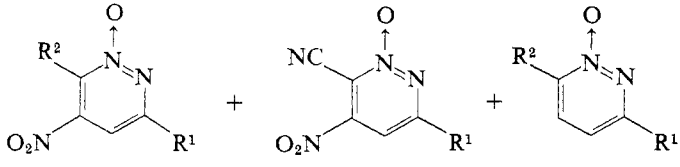


	56	**57**	**58**	**56**
PhCOCl + $AgNO_3$		33 %	0.8 %	28 %
AcCOCl + $AgNO_3$		17	0.8	35

The same reaction of the pyridazine 1-oxides substituted at the 3- and also at the 3,6-positions (**59**) affords the corresponding 5-nitro isomers (**60**) shown. In this reaction the 6-methyl group is primarily converted to a cyano group (61) (99).

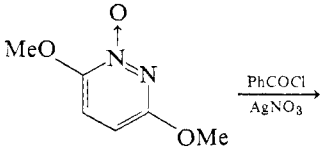


59

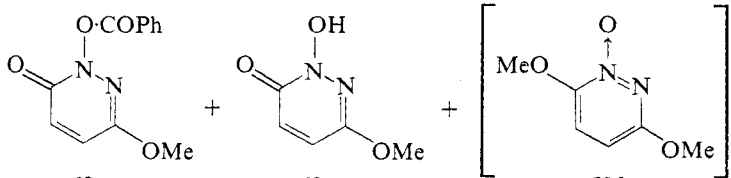


	60	**61**	**59**
a: R^1 = Me; R^2 = H	12%		43%
b: R^1 = R^2 = Me	25%	31%	31%
c: R^1 = OMe; R^2 = H	11%		21%
d: R^1 = R^2 = OMe			

Furthermore, the 6-methoxy group of **59d** is demethylated by benzoyl chloride to 1-benzoyloxy-3-methoxy-6(1*H*)pyridazinone (**62**) and 1-hydroxy-3-methoxy-6(1*H*)pyridazinone (**63**) (99).



59d



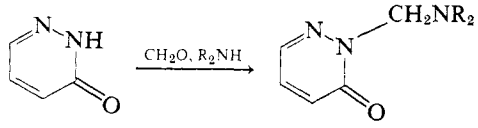
62 56%

63 26%

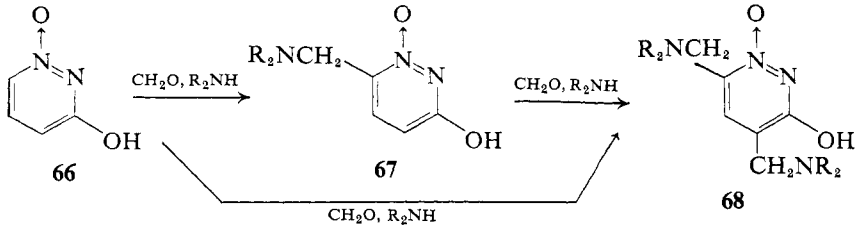
59d 11%

C. Mannich Reaction

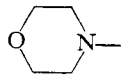
3(2*H*)Pyridazinone derivatives (**64**) are known to produce 2-dialkylaminomethyl-3(2*H*)pyridazinone derivatives (**65**) in good yield when **64** is allowed to react with formaldehyde and dialkylamines (80). In this case no *C*-substituted derivative is obtained.

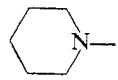


64 65



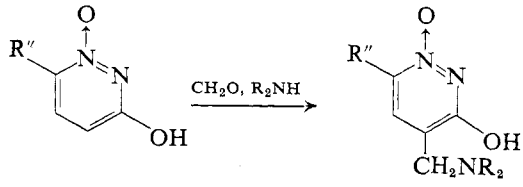
66 67 68

a: R_2N- =  49 % 71 %

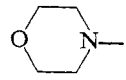
b: R_2N- =  50 %

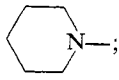
c: R_2N- = $(Me)_2N-$ 53 %

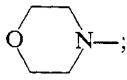
d: R_2N- = $(ClCH_2CH_2)_2N-$ 29 %

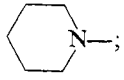


69 70

a: R'_2N- =  ; R″ = Cl 54 %

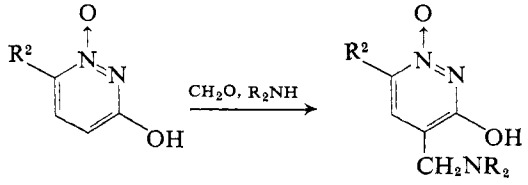
b: R'_2N- =  ; R″ = Cl 32 %

c: R'_2N- =  ; R″ = Me

d: R'_2N- =  ; R″ = Me

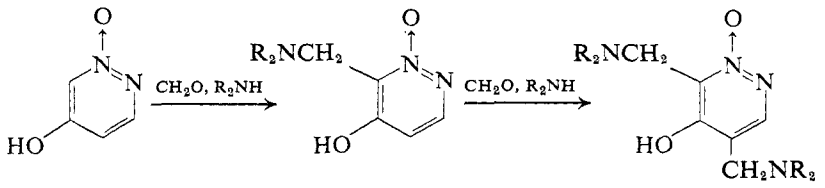
3-Pyridazinol 1-oxide (**66**) gives the corresponding 6-substituted 3-hydroxypyridazine 1-oxide (**67**), when subjected to the Mannich reaction using secondary amines such as piperidine, morpholine, dimethylamine, or bis(2-chloroethyl)amine and formaldehyde. No 4-substituted *C*-Mannich base is found in these cases, however, if excess amounts of reagents are added, 4,6-bis(dialkylaminomethyl)-3-pyridazinol 1-oxides (**68**) are obtained as indicated (80, 81).

When the 6-position of 3-pyridazinol 1-oxide is blocked with a chloro or a methyl group (**69**), a dialkylamino methyl group enters into the 4-position (**70**) (81).

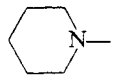


69

5-Pyridazinol 1-oxide (**71**) also reacts with an equimolar mixture of 37% formalin and piperidine or dimethylamine to give 6-piperidinomethyl- or dimethylaminomethyl-5-pyridazinol 1-oxide (**72a** and **b**) together with small amounts of disubstituted *C*-Mannich bases (82). Further treatment of 5-pyridazinol 1-oxide or this monopiperidinomethyl-Mannich base (**72a**) with an excess of the reagents yields a 4,6-disubstituted product (**73a**) in 42% yield.



71 **72** **73**

a: R_2N- =  56% 42%

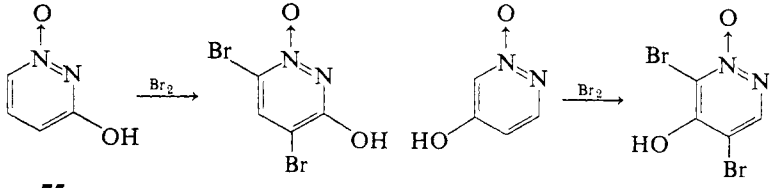
b: R_2N- = Me_2N- 36%

D. Acid-Catalyzed Hydrogen Exchange Reaction

Deuteration in acidic solution is considered electrophilic. This reaction of 3-pyridazinol 1-oxide does not proceed even in 98% D_2SO_4 at 200° C, and decomposition takes place in 10% D_2SO_4 at above 120° C (102) (see Section IV.E).

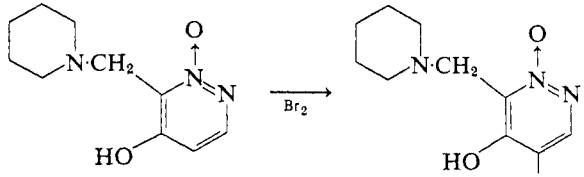
E. Halogenation

The bromination of 3- and 5-pyridazinol 1-oxides (**74** and **76**) under several conditions gives the corresponding 4,6-dibromo compounds (**75** and **77**) and the monobromo compound could not be isolated in either case (83).



75 **76** **77** **78**

When the 6-position of 5-pyridazinol 1-oxide is blocked with a piperidinomethyl group (**79**), the product is 4-bromo-6-piperidinomethyl-5-pyridazinol 1-oxide (**80**) (83).



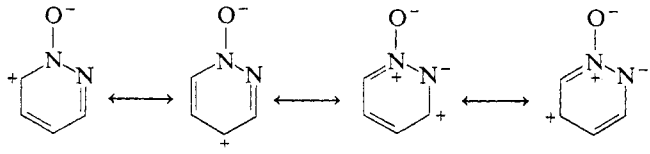
79 **80**

Later, Igeta also examined chlorination and bromination of 3-pyridazinol 1-oxide and its monomethyl homologs and obtained halogenated products substituted at the 4- and/or 6-position(s) (103).

IV. Nucleophilic Substitution

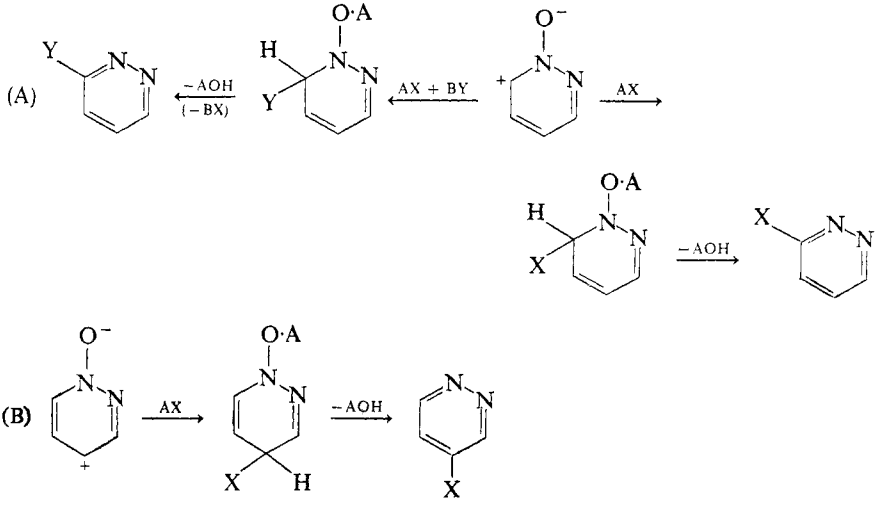
A. General

As seen from the resonance structures of pyridazine 1-oxide (**81–84**) described below nucleophilic substitution seems to take place at all the carbon atoms of the ring.



81 **82** **83** **84**

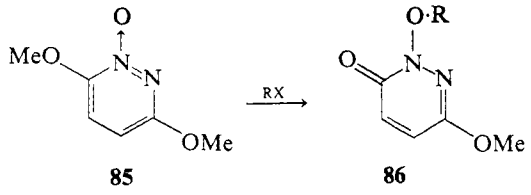
It is known that reactive halides and acid anhydrides undergo nucleophilic reactions in the pyridine and quinoline 1-oxides series (104). This reaction was first reported by Meisenheimer (105), by Bobranski (106), and by Henze (107). Ochiai, Hamana, and their co-workers extended the scope widely (104). Using these studies as models, the nucleophilic displacement reaction has been examined in the pyridazine 1-oxide series by many researchers. The reaction proceeds through route A and/or B, as shown below. Usually, the reaction proceeds through route A when the 6-position is vacant, and no 4-substituted compound is produced. In both cases, when the second nucleophilic reagent BY is added after a nucleophilic reagent AX has been reacted, a compound having a substituent Y is obtained as shown.



The sole exception to this description is the reaction of 3- or 5-nitropyridazine 1-oxide with acyl chloride (see Section V.C.2.a).

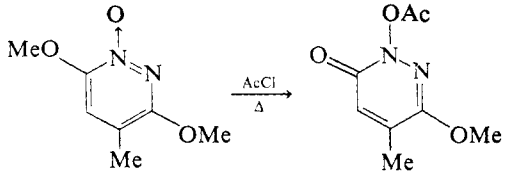
In the pyridazine 1-oxide series, alkyl halides, inorganic and organic acid halides, and an acid anhydride are used as RX. As BY, there is only an example using potassium cyanide (the Reissert reaction).

When a methyl or an alkoxy group (**85**, **87**, and **89**) is located on a pyridazine 1-oxide ring, these RXs react with the group in certain cases as shown.

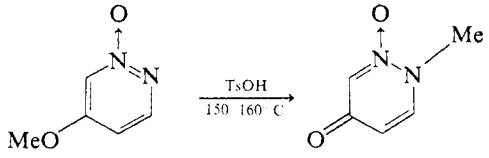


85 **86**

RX = MeI, EtI, $PhCH_2Cl$



87 **88**



89 **90**

However, these reactions are explored in detail in Section VI.E.3. In addition, exchange reactions of halogeno, nitro, alkoxy groups, and so on, are described in Section VI.

B. Reaction with Inorganic Acid Halides

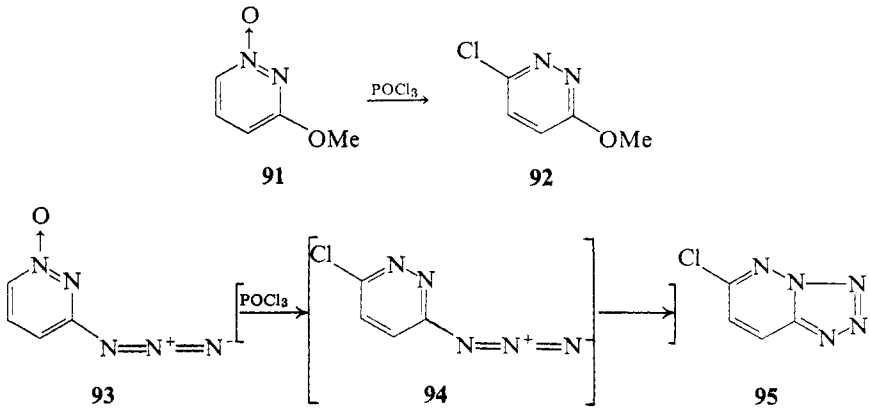
On reacting with phosphorus oxychloride at room temperature, 3-methoxypyridazine 1-oxide (**91**) is converted to 3-methoxy-6-chloropyridazine (**92**) (108). Similarly, 3-azidopyridazine 1-oxide (**93**) is converted into 5-chloropyridazino[2,3-*d*]tetrazole (**95**) on refluxing with phosphorus oxychloride through 3-azido-6-chloropyridazine (**94**) (109).

When the 6-position is blocked as in 3,6-dimethyl- (**96a**) (110) or 3,6-dimethoxypyridazine 1-oxide (**96b**) (112), the reaction yields the corresponding 4-chloro derivatives (**97**).

It was reported that 3-methylpyridazine 1- and 2-oxides, and also 3-chloro-6-methylpyridazine 1-oxide, were either recovered or resinified in the reaction with phosphorus oxychloride (111). These data are summarized in Table XI.

C. Reaction with Organic Acid Halides

When quinoline is allowed to react with an acid chloride in the presence of potassium cyanide, a cyano group is introduced into the 2-position of the



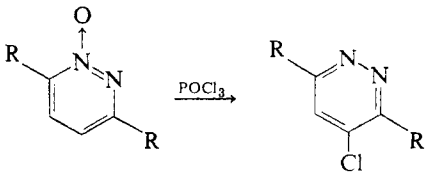
91 **92**

93 **94** **95**

quinoline ring (the Reissert reaction) (114). However, either pyridine or quinoline *N*-oxides are converted mainly to the 4-cyanopyridine or the 4-cyanoquinoline. This occurs when the *N*-oxide had been allowed to react with dimethyl sulfate to form the corresponding methosulfate, followed by reaction with potassium cyanide (115).

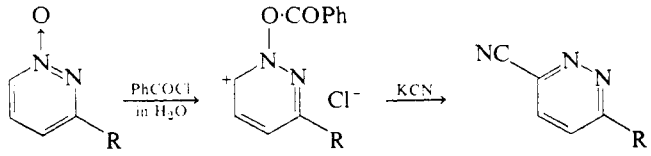
In the pyridazine 1-oxide series, these reactions were examined by Igeta (116) and by Ogata (117) independently. Pyridazine 1-oxide (**98a**) and 3-chloropyridazine 1-oxide (**98d**) did not give cyano compounds by the Reissert reaction. However, other 3-substituted pyridazine 1-oxides (**98b, c, e, f**) could be converted to the corresponding 6-cyano compounds, although the yields were poor.

In spite of the above results, these cyano compounds are obtained from all the starting materials except pyridazine 1-oxide by Okamoto and Tani's method in higher yields than those by the Reissert reaction. The position of the entering cyano group is usually the 6-position of 3-substituted pyridazine 1-oxides (**102**), that is, in the position alpha to the *N*-oxide function. This differs slightly from the pyridine *N*-oxides, which produce 2- and 4-cyano compounds, and the ratio of yields of the isomers depends upon the reaction conditions.



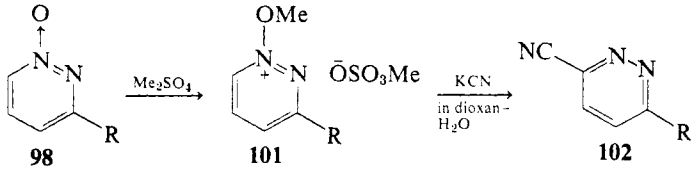
96 **97**

a: R = Me
b: R = MeO



98 **99** **100**

a: R = H **d**: R = Cl
b: R = Me **e**: R = OMe
c: R = Ph **f**: R = OCH_2Ph

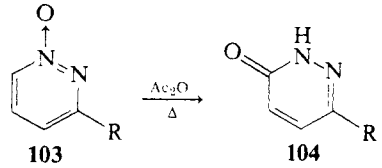


98 **101** **102**

These results are summarized in Table XII.

D. Reaction with Acid Anhydrides

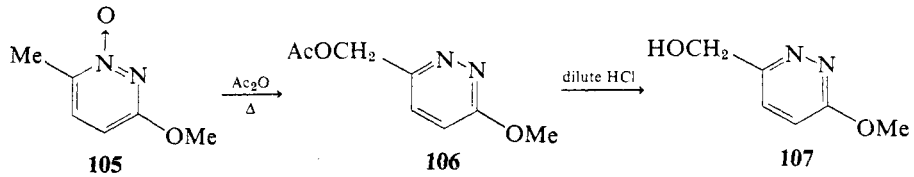
3-Pyridazinol 1-oxide (**103a**) reacts with boiling acetic anhydride to form 3-hydroxy-6(1*H*)pyridazinone (**104a**) (108). Similarly, 3-aminopyridazine 1-oxide (**103b**) is converted to 3-amino-6(1*H*)pyridazinone (**104b**) by boiling with the same reagent and later with water (118). The oxygen of the *N*-oxide rearranges to the α-position in boiling acetic anhydride. However, when a methyl group, an alkoxy group, or a chlorine atom is located on the pyridazine 1-oxide ring, it is attacked by the reagent in some cases. This is illustrated below.



103 **104**

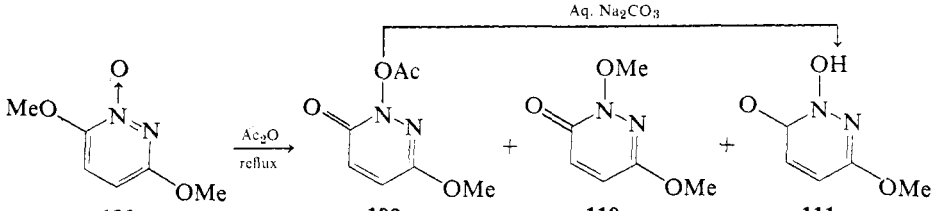
a: R = OH; **b**: R = NH_2

The same reaction of 3-methoxy-6-methylpyridazine 1-oxide (**105**) yields 3-methoxy-6-acetoxymethylpyridazine (**106**), from which 3-methoxypyridazine-6-methanol (**107**) is produced by hydrolysis with hydrochloric acid (113, 119, 120).



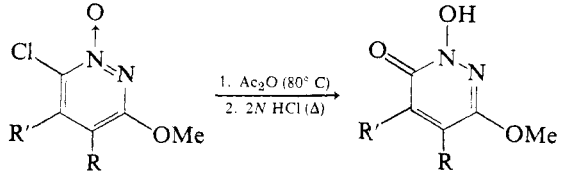
105 **106** **107**

When 3,6-dimethoxypyridazine 1-oxide (**108**) is refluxed with acetic anhydride, 1-acetoxy-3-methoxy-6(1*H*)pyridazinone (**109**), 1,3-dimethoxy-6(1*H*)pyridazinone (**110**), and 1-hydroxy-3-methoxy-6(1*H*)pyridazinone (**111**) are produced (122).



108 **109** 68 % **110** 23 % **111** 9 %

6-Chloropyridazine 1-oxide derivatives (**112**) are converted to 1-hydroxy-6(1*H*)pyridazinones (**113**) by warming with acetic anhydride at about 80° C followed by treatment with 2 *N* hydrochloric acid (121).

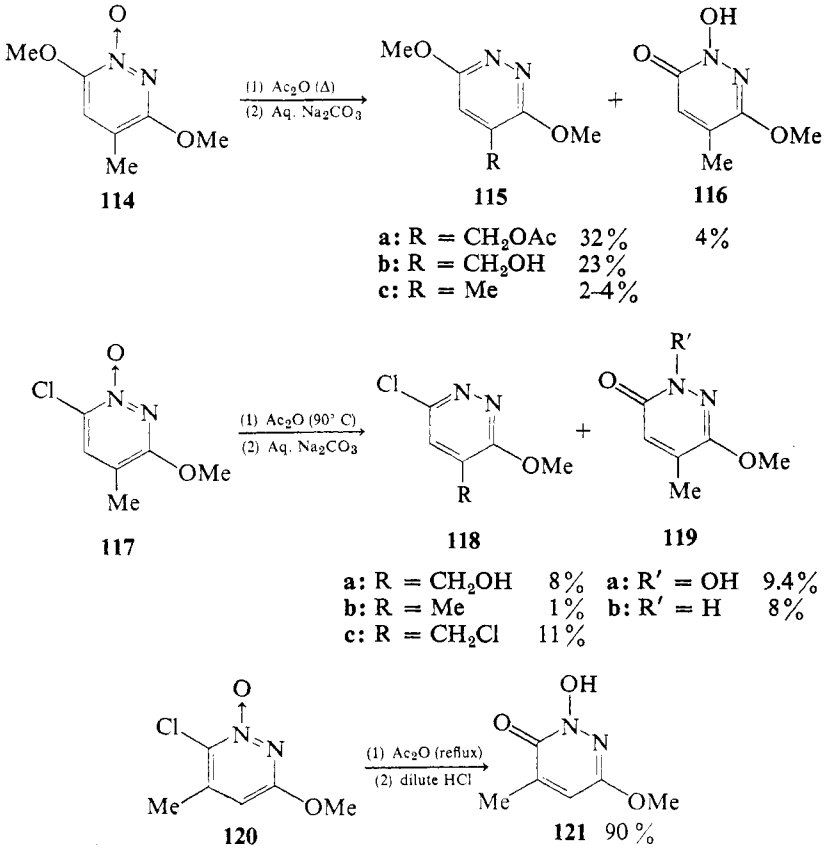


112 **113**

a: R = ME, R′ = H 64%
b: R = H, R′ = ME 90%
c: R = R′ = H 68%

Furthermore, the combination of 4-methyl and 6-chloro or 6-methoxy groups on the pyridazine 1-oxide ring is mentioned below. The 4-methyl group of 3,6-dimethoxy-4-methylpyridazine 1-oxide (**114**) is converted by acetic anhydride to the acetoxymethyl compound (**115a**) and to the carbinol (**115b**), while the methoxy group is removed to give the 6(1*H*)pyridazinone (**116**) (122). 3-Methoxy-4-methyl-6-chloropyridazine 1-oxide (**117**) is converted with the same reagent at methyl and chloro groups as follows (122).

In contrast, 3-methoxy-5-methyl-6-chloropyridazine 1-oxide (**120**) is attacked at the 6-chloro atom only, the 5-methyl group remaining intact (122).

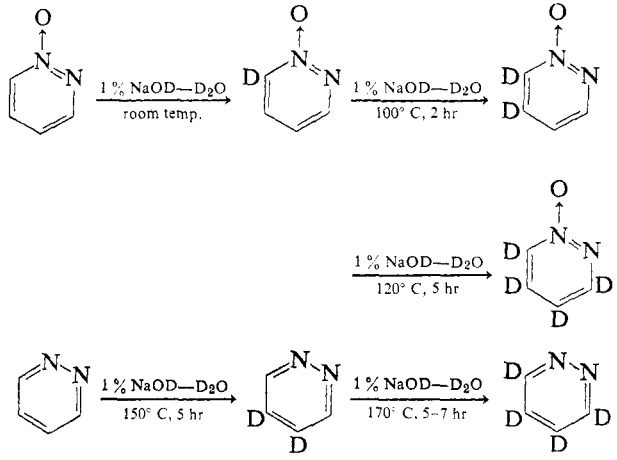


E. Base-Catalyzed Hydrogen Exchange Reaction

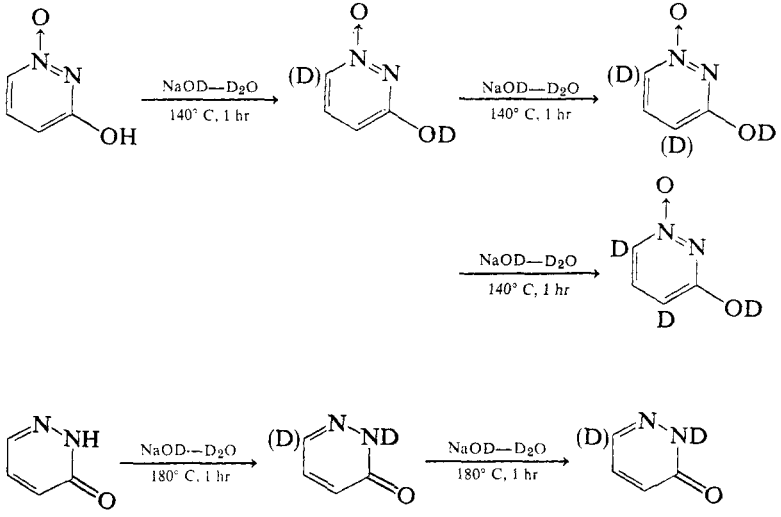
The deuteration of pyridazine 1-oxide with a 1% NaOD–D_2O solution occurs stepwise at the 6-, 5- and then 4- and 3-positions. In this case deuteration at the 5-position is a little faster than that at the 4-position (123). However, in pyridazine, the 4- and 5-hydrogens are more easily deuterated than the 3- and 6-hydrogens which are located adjacent to the ring nitrogens (123).

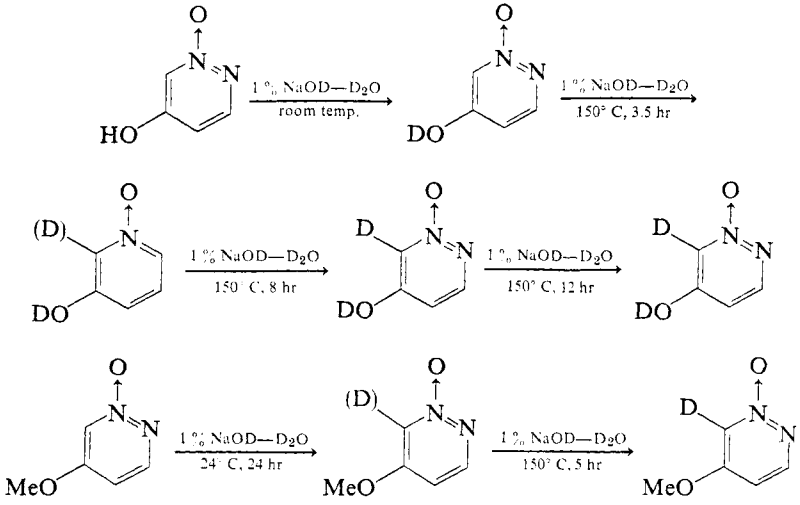
Deuteration at the 4- and 5-positions was a little faster than that at the 3- and 6-positions.

However, the deuteration of 3-pyridazinol 1-oxide and its deoxygenated product, 3(2*H*)pyridazinone, in a NaOD–D_2O medium proceeds as shown below (124).



Later, 5-hydroxy- and 5-methoxypyridazine 1-oxides were subjected to deuteration with 0.5 and 1% NaOD–D_2O solutions by Okusa et al (125). The results are shown below. As seen from the reaction scheme, the 6-hydrogen of 5-methoxypyridazine 1-oxide is partly changed by deuterium at room temperature, but no other ring hydrogen is reacted even by heating at 150° C for 12 hr. However, 5-hydroxypyridazine 1-oxide is displaced by deuterium, that is, the hydroxy group at room temperature, then the 6- and 4-positions at 150° C.



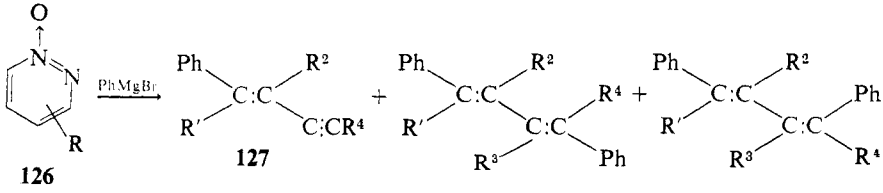


F. Grignard Reaction

Grignard reactions with aromatic amine oxides have been reported abundantly (126). The main reaction is nucleophilic substitution by alkyl or aryl groups at the α-carbon of the *N*-oxide with deoxygenation of the *N*-oxide group; in some cases this occurs without deoxygenation, giving substituted 1-hydroxy-1,2-dihydro derivatives (127).

In 1969, Okusa's (128) group reported that the reaction of pyridazine 1-oxide with phenylmagnesium bromide in ether gave 1,4-diphenyl-1,3-butadiene (**123**) as the main product and 1-phenyl-1-butene-3-yne (**124**) and 3,6-diphenylpyridazine (**125**) as by-products. When tetrahydrofuran was used as solvent, compound **124** was the sole product and the others were scarcely found. These investigators extended the study using substituted phenylmagnesium bromides. The yields of these crude products were high, but they dropped after vacuum distillation. These reaction products are recorded in Table XIII.

In 1969 Igeta, Tsuchiya, and Nakai (129) also examined the reaction of pyridazine 1-oxide and its methyl homologs (**126**) with organometallic compounds using phenylmagnesium bromide and phenyllithium. They separated the products by absorption chromatography and obtained further a cis-trans isomer (**129**), as described below. These data are summarized in Table XIV.



126 **127** **128** **129**

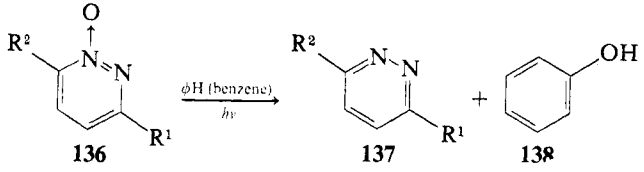
+ Substituted pyridazines **130**

V. Photochemical Reaction

Recently, photochemical reactions seem to be of great interest in the field of organic chemistry. In the pyridazine *N*-oxide series, two studies were performed, and hydroxymethylation, ring contraction, and hydroxylation of hydrocarbons with oxygen in pyridazine *N*-oxides were observed.

In 1967, Ogata and Kano (130) reported that irradiation of a methanol solution of pyridazine *N*-oxide derivatives (**131**) through Pyrex glass with a high-pressure mercury arc lamp under an argon atmosphere at room temperature gave the corresponding deoxygenated (**132**) and hydroxymethyl (**133**) derivatives as main products and, in a few cases, the corresponding ring-contracted products (**134**) as by-products (see Table XV).

In 1968, Igeta (131) and his group found that the corresponding deoxygenated pyridazines and hydroxylated hydrocarbons in 30–40% yields were produced when pyridazine *N*-oxide derivatives with hydrocarbon, such as benzene, or naphthalene, were irradiated with a high-pressure mercury lamp in dichloromethane solution under a nitrogen atmosphere. When irradiation was continued until all the *N*-oxides were consumed, the yields of phenols were 30–40%.



136 **137** **138**

a: $R^1 = R^2 = H$
b: $R^1 = Me$, $R^2 = H$

Further, his group extended the study to the reaction of pyridazine *N*-oxide derivatives with an ethylenic bond, leading to formation of epoxides, ketones, or 1,2-diols. Indane, tetralin, cyclohexenylbenzene, styrene, cholesterol, and so on were examined (132).

VI. Reactions of Substituents on Pyridazine 1-Oxide

A. General

Pyridazine 1-oxide polarizes into the forms described in Section III.A, that is, in which the 3-, 4-, 5-, and 6-positions of the ring are all electron-deficient with the 4- and 6-positions being in a relatively electron-rich state in some cases. These suggestions are borne out by the facts presented in Sections III and IV. However, it is also well known that the electron-withdrawing effect of the *N*-oxide group is stronger than that of a ring tertiary nitrogen when pyridine is compared with its *N*-oxide series (133–136). Since pyridazine 1-oxide has both an *N*-oxide group and tertiary ring nitrogen within a single molecule, it is presumed that nucleophilic activity at the positions alpha and gamma to the *N*-oxide group, that is, the 4- and 6-positions, is higher than that of positions alpha and gamma to tertiary ring nitrogen, that is, the 5- and 3-positions. Among various nucleophilic reactions of the pyridazine 1-oxide series, ionic substitution reactions of the halogeno group has been most widely investigated, and the activity of halogens is shown to be in the order $5 > 3 > 6 > 4$ from kinetic studies reported by Sako (137) in 1966. This result is inconsistent with above-mentioned experimental facts. He explained this phenomenon by considering that the nucleophilic reactivity of the 4- and 6-positions is smaller than that of the 3- and 5-positions because the electron-donating effect of the *N*-oxide partially minimizes the electron-withdrawing effect of the same group toward the 4- and 6-positions (138).

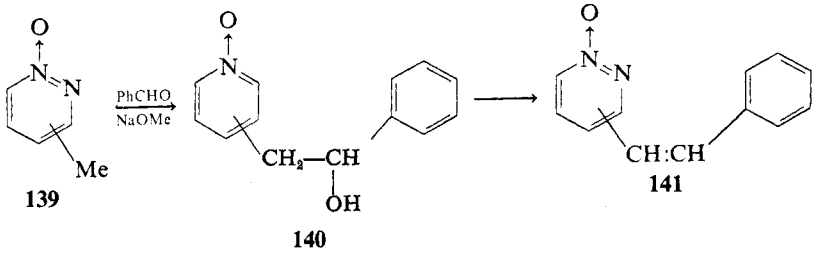
Other nucleophilic substitution reactions were not investigated kinetically, therefore it is impossible to compare precisely the activity of each position. When the nucleophilic acitivity of each position was postulated by comparing yields of products under similar reaction conditions, the orders of reactivity differ in individual reactions. Further studies are necessary to clarify these results.

Furthermore, since reactions of various substituents on pyridazine oxide were investigated, these results are reviewed in this section.

B. Methyl Group

1. *Reaction with Benzaldehyde*

When methylpyridazine 1-oxides (**139**) were allowed to react with benzaldehyde in the presence of sodium methoxide at room temperature or by



139 **140** **141**

a: 3-; **b**: 4-; **c**: 5-; **d**: 6-

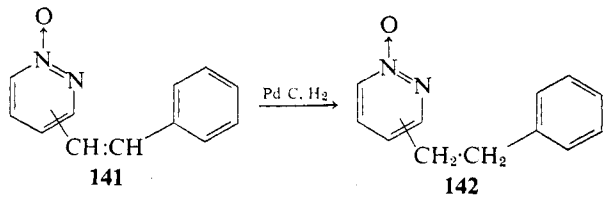
warming, styrylpyridazine 1-oxides (**141**) were produced through (2-phenyl-2-hydroxyethyl)pyridazine *N*-oxides (**140**) (139).

When sodium methoxide was replaced by piperidine, the starting materials were recovered.

In order to obtain a more detailed knowledge of the reactivity of each position, the reaction was examined at three different reaction temperatures, while maintaining the same reaction time and comparing yields of the products. The results are summarized in Table XVI.

From this table it can be seen that the reaction of 3-methylpyridazine 1-oxide (**139a**) at 45° C is marginal, while the starting material is almost entirely recovered at 40° C. 4- and 5-Methylpyridazine 1-oxides (**139b** and **c**) are not recovered even at 40° C, and the addition products (**140b** and **c**) are produced together with styryl derivatives (**141b** and **c**). The reactivity of 6-methylpyridazine 1-oxide (**139d**) is almost the same as that of **139b** and **c**, however, the 6-styryl compounds (**141d**) cannot be obtained at 40° C.

In the reaction of 3,6-dimethylpyridazine 1-oxide with benzaldehyde, 3,6-distyrylpyridazine 1-oxide is always produced even with 1.1 mole of benzaldehyde, without production of the monostyryl derivative. The same results were obtained even with 4-methoxy- or 4-dimethylaminobenzaldehyde, which are presumed to have a less reactive aldehyde group owing to the electron-donating effect of the 4-substituent. Consequently, it seems likely that the reactivity of the methyl group is in the order $5 > 4 > 6 > 3$, and this is different from the reactivity of halogens (see Section VI.D) on pyridazine 1-oxide.



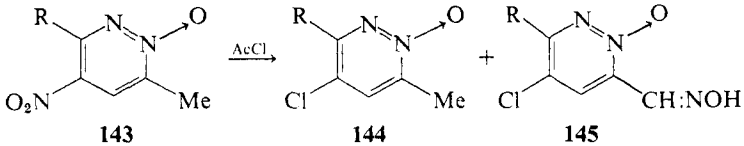
141 **142**

When these styrylpyridazine 1-oxides (**141**) are reduced catalytically with palladium–carbon in neutral solutions, they are converted into phenethylpyridazine 1-oxides (**142**) in good yield.

2. *Reaction with Acetyl or Amyl Nitrite*

When 4-nitro-6-methylpyridazine 1-oxide (**143a**) was allowed to react with acetyl chloride, 4-chloro-6-methylpyridazine 1-oxide (**144a**) and a high-melting product (**145a**) were produced, and the yield of **145a** was far more than **144a** (140). Compound **145a** was proven to be 4-chloro-6-formylpyridazine 1-oxide oxime by Ogata (141) in 1963.

Other 6-methyl-substituted 4-nitropyridazine 1-oxides, such as 3,6-dimethyl-4-nitro- (**143b**), 3-chloro-4-nitro-6-methyl- (**143c**), and 3-methoxy-4-nitro-6-methylpyridazine 1-oxide (**143d**) also gave the corresponding 6-formylpyridazine 1-oxide oximes (**145b–d**) in considerable yields.

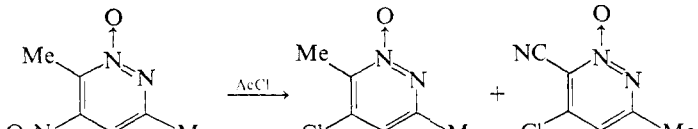


143 **144** **145**

a: R = H	0.7%	27%
b: R = Me	11.9%	38%
c: R = Cl	15.7%	49%
d: R = MeO	15%	29%
R = MeO	21.4%	26.4%

However, 3- or 5-methyl-4-nitropyridazine 1-oxide was never converted to the formyl *N*-oxide derivative.

Similar reactions were observed in the methylpyridine 1-oxide series by Kato (142), and in the methylquinoline 1-oxide series by Hamana (143); and 3,6-dimethyl-5-nitropyridazine 1-oxide (**146**) with acetyl chloride gave 3-methyl-5-chloro-6-cyanopyridazine 1-oxide (**148**) (144).

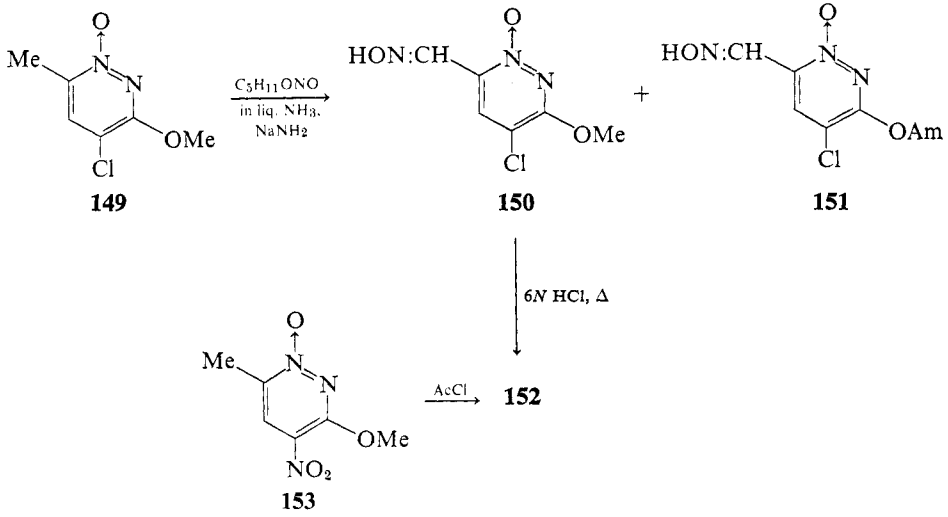


146 **147** **148**

To summarize these facts, chloroformylpyridazine 1-oxide oximes were all derived from compounds with a methyl group adjacent to the *N*-oxide group. However, no special relationship to the position of a nitro group was

found, that is, both 5- and 4-nitro groups participated in the reaction. When concentrated hydrochloric acid was substituted for acetyl chloride, no high-melting substance was obtained. From these facts it is very likely acetyl nitrite produced in the first step of the reaction participated in the reaction, however, the mechanism has not yet been elucidated (145).

3-Methoxy-4-chloro-6-methylpyridazine 1-oxide (**149**) reacted readily with amyl nitrite in liquid ammonia in the presence of sodium amide at −50 to −60° C to give 3-methoxy-4-chloro-6-formylpyridazine 1-oxide oxime (**150**) and 3-amyloxy-4-chloro-6-formylpyridazine 1-oxide oxime (**151**) (145). Compound **150** was not identical with the oxime (**152**) derived from 3-methoxy-4-nitro-6-methylpyridazine 1-oxide (**153**) with acetyl chloride, however, **150** was isomerized to the latter oxime (**152**) by warming with 6*N* hydrochloric acid.



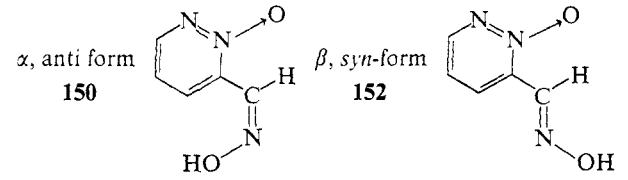
149 **150** **151**

152

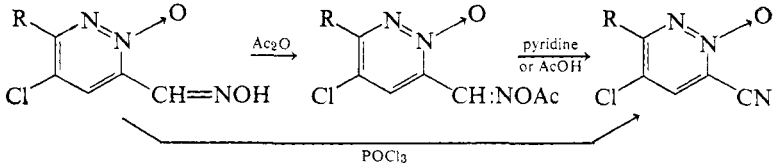
153

Subsequently, 3-, 4-, 5-, and 6-methylpyridazine 1-oxides were subjected to the same reaction; crystals separated out from the reaction mixtures were identical with the crystals from the mother liquors after the former was isomerized by warming with the acid. The unstable isomers were called α-aldoximes and the stable ones β-aldoximes. These structures were examined by infrared (ir) and nuclear magnetic resonance (nmr) spectroscopy, and it was indicated that the α-aldoximes were *anti* isomers (**150**) and the β-aldoximes were *syn* isomers (**152**), as illustrated below. 3,4-Dichloro-6-methylpyridazine 1-oxide did not give its aldoxime by this reaction (see Table XVII).

Substituted 6-formylpyridazine 1-oxide oximes (**150** and **152**) so obtained are converted to the corresponding 6-cyanopyridazine 1-oxides (**156**) either (1) by refluxing with phosphorus oxychloride in chloroform solution, or (2)



by heating with pyridine or glacial acetic acid after acetylating the aldoximes with acetic anhydride to formylpyridazine 1-oxide oxime acetates (**155**) (141). Both are valuable synthetic methods for 6-cyanopyridazine 1-oxides together with Okamoto and Tani's method (see Section IV.C).

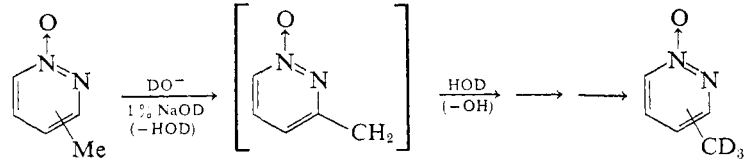


a: R = H
b: R = Me
c: R = MeO
d: R = Cl

3. *Base-Catalyzed Hydrogen Exchange Reaction*

When methylpyridazines and their *N*-oxides were allowed to react with alkaline deuterium oxide, hydrogen atoms of the methyl group were exchanged stepwise with deuterium atoms (146) (see Table XVIII).

As mentioned in Table XVII, the reactivity of the methyl groups on the pyridazine ring was compared judging from the yields and the reaction temperature of the reaction. It is easily established that the reactivity of the methyl group in pyridazine 1-oxide is higher that of pyridazine, and it decreases in the order 6- > 5- > 4- > 3-position. This reaction of pyridine 1-oxide has been investigated by Kawazoe, Ohnishi, and Yoshioka (147).

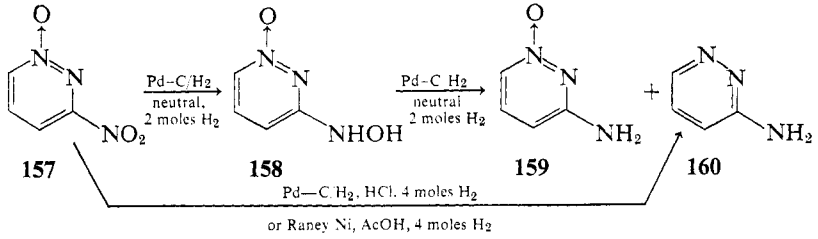


C. Nitro Group

1. *Reduction*

The nitro group in pyridine and quinoline 1-oxides is reduced with certain reducing agents a little differently from nitrobenzene, that is, the reaction proceeds bimolecularly through azoxy, azo, and hydrazo groups to the amino group even in acid solution, and ultimately the *N*-oxide is reduced (148). In the nitropyridazine 1-oxide series, catalytic reduction with palladium–carbon or Raney nickel is most frequently used. There are very few reports of reductions with other reducing agents.

3-Nitropyridazine 1-oxide (**157**) is reduced over palladium–carbon and with 2 moles of hydrogen in a neutral solution. 3-Hydroxylaminopyridazine 1-oxide (**158**) is isolated in good yield. Compound **158** is reduced mainly to 3-aminopyridazine 1-oxide (**159**) with a smaller quantity of accompanying 3-aminopyridazine (**160**) (149). However, reduction with 4 moles of hydrogen and the same catalyst provided **160** (149).

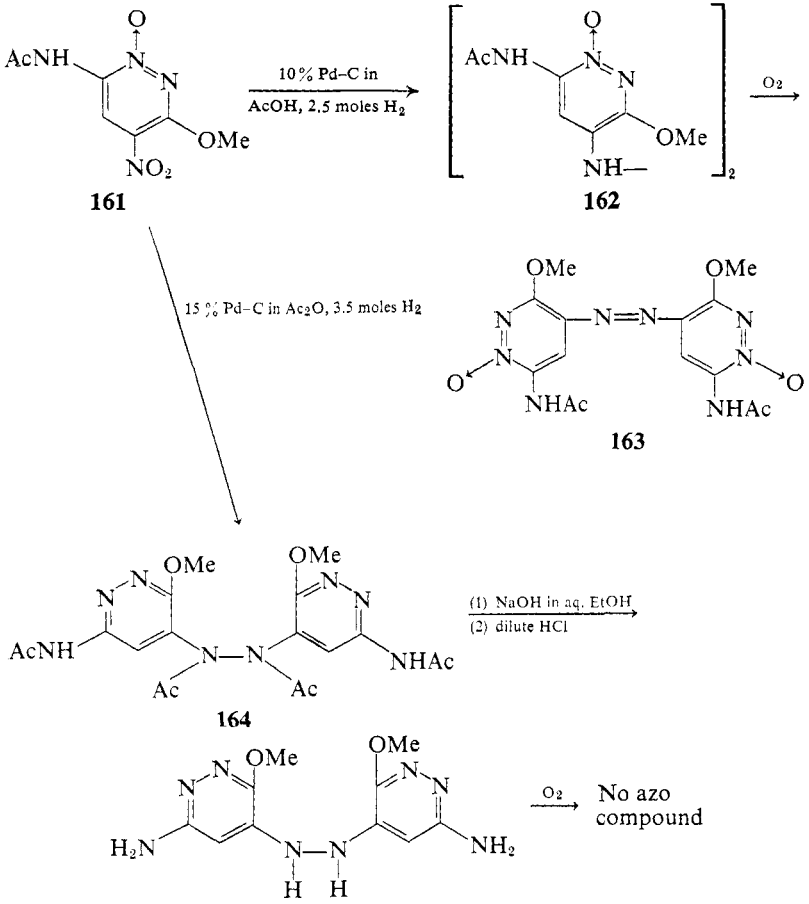


4-Nitropyridazine 1-oxide is reduced with the same catalyst in neutral solution directly to 4-aminopyridazine 1-oxide, absorbing three moles of hydrogen (150, 151, 140).

The catalytic reduction of 3-methoxy-4-nitro-6-aminopyridazine 1-oxide with palladium–carbon in hydrochloric acid solution gave a result similar to that mentioned above (152).

3-Methoxy-4-nitro-6-acetaminopyridazine 1-oxide (**161**) was reduced with 10% palladium–carbon as the catalyst in acetic acid solution, producing the products shown below (152).

Phenylhydrazine is known to reduce a nitro group specifically to a hydroxylamino group (153). This method was applied to 3-methoxy- and 3-methyl-4-nitro-6-methylpyridazine 1-oxides by Nishimura et al. (154) to produce the corresponding 3-substituted 4-hydroxylamino-6-methylpyridazine 1-oxides. These data are summarized in Table XIX.

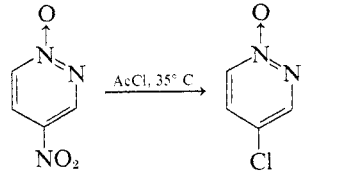


2. *Activity toward Nucleophilic Reagents*

a. HALOGEN SUBSTITUTION. When 4-nitropyridine or 4-nitroquinoline 1-oxide is allowed to react with an acyl chloride, a nitro group is replaced by a chlorine atom and the oxide function is retained (155, 156). The acyl chloride, phosphorus oxychloride, sulfuryl chloride, acetyl chloride, and benzoyl chloride were examined. Acetyl chloride was reported to be the most suitable one for the preparation of 4-chloro 1-oxide derivatives. Concentrated hydrochloric and hydrobromic acids were studied as substitutes of acid halides by Okamoto (157) and by den Hertog (158).

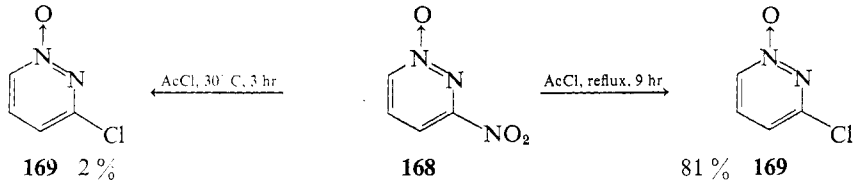
In the pyridazine 1-oxide series, acetyl chloride has been used most frequently, with phosphorus oxychloride, benzoyl chloride, and hydrogen halides being used less frequently.

4-Nitropyridazine 1-oxide (**166**) is converted to 4-chloropyridazine 1-oxide (**167**) with acyl chloride at 35° C in good yield (150).

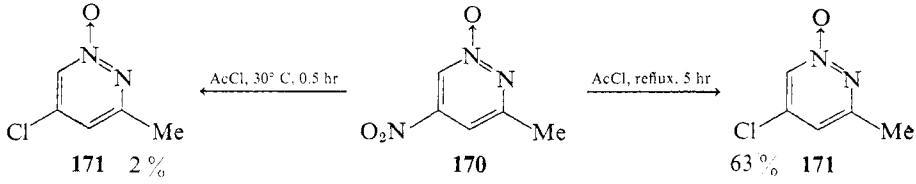


166 **167** 76%

3- and 5-Nitropyridazine 1-oxides (**168** and **170**) react with acetyl chloride in a similar manner. The yields at room temperature are much lower than with **166**. However, when the reaction mixture is heated, the yields are increased considerably (149).



169 2% **168** 81% **169**

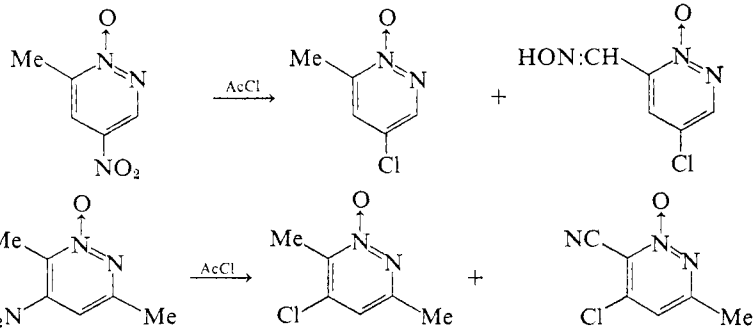


171 2% **170** 63% **171**

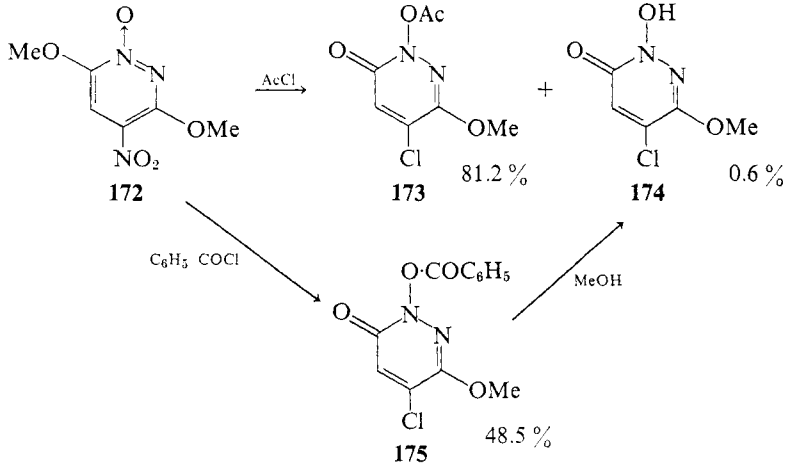
Compound **168** does not react with phosphorus oxychloride even at 70° C, but **166** is converted to **167** at 55° C in 20% yield with 36% of **166** remaining and at 100° C and on refluxing in 65 and 33% yields, respectively.

When the methyl group is located at the α-position (6-position) of the *N*-oxide, this methyl group is very liable to convert to an aldoxime or a cyano group. The yields of the desired chloromethyl compounds are very low, as indicated in Section VI.B 2 The two cases are shown below (141, 144) (see Table XX).

When a hydrogen halide is allowed to react with warming in place of the usual acetyl chloride, the above side reaction does not take place and the yield of methylchloropyridazine 1-oxides is rather high. 4-Bromopyridazine 1-oxide was obtained by Sako (167) by warming the mixture of 4-nitropyridazine 1-oxide with 47% hydrobromic acid. In 1969 these instances were added by Igeta et al (159) (see Table XXI).

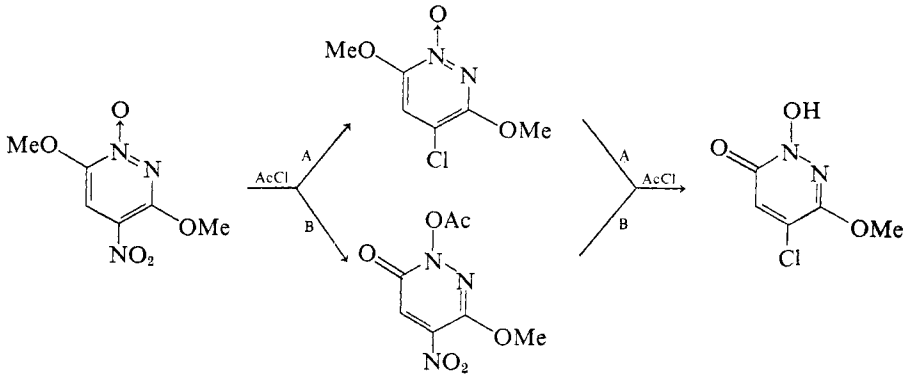


When a methoxy or another alkoxy group is located at the 6-position of a pyridazine 1-oxide, the alkyl group cleaves and a cyclic hydroxamic acid structure is formed. In 1955, Itai and his colleague reported that 3,6-dimethoxy-4-chloropyridazine 1-oxide (**173**) could be obtained by the action of acetyl chloride on 3,6-dimethoxy-4-nitropyridazine 1-oxide (**172**) (160, 193). Yanai and Kinoshita (162) reexamined this reaction and reported the product was 1-acetoxy-3-methoxy-4-chloro-6(1*H*)pyridazinone (**173**) as described below



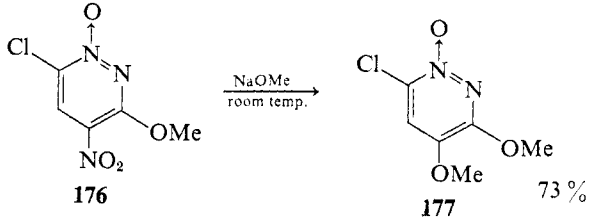
Assuming two possible routes and examining the reaction products by thin-layer chromatography, it was determined that the reaction followed route A, that is,

b. SUBSTITUTION WITH ALKOXIDE AND PHENOXIDE. Similar to nitropyridine 1-oxide, a nitro group in the pyridazine 1-oxide series is easily exchanged with alkoxide anion to the alkoxypyridazine 1-oxides. The exchange reaction of 3-nitropyridazine 1-oxides (**168**) (150) and of 4-nitropyridazine 1-oxides (144) was examined under the same reaction conditions.

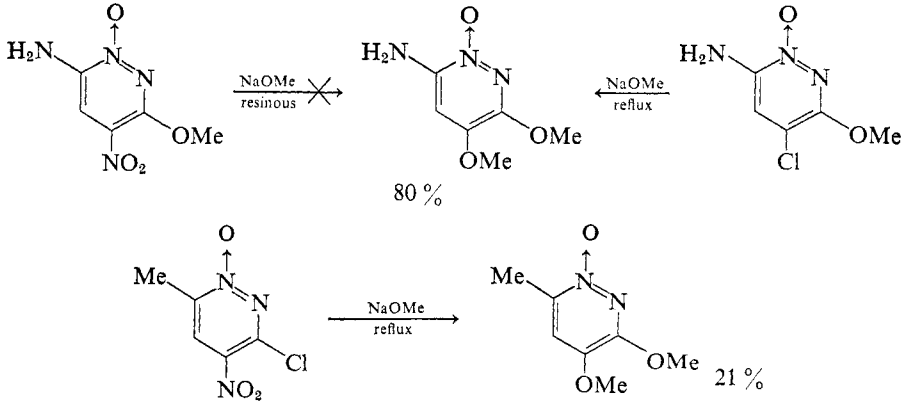


When the reactivity of these nitro groups was determined based on the yields, the order was 5- > 4- > 3-position.

In the reaction of 3-methoxy-4-nitro-6-chloropyridazine 1-oxide (**176**) at room temperature, only the 4-nitro group reacted with methoxide anion to produce 3,4-dimethoxy-6-chloropyridazine 1-oxide (**177**) (166), similar to 2-chloro-4-nitropyridine 1-oxide (164).

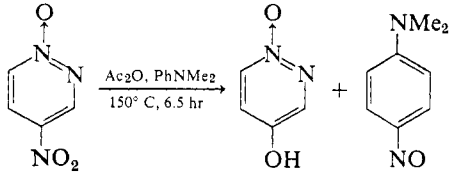


However, the following reactions were also reported, therefore further studies are necessary to compare the reactivity of both groups (163, 140).



Sodium phenoxide also reacts with 3-nitropyridazine 1-oxide to give 3-phenoxypyridazine 1-oxide in 50% yield (149) (see Table XXII).

c. MISCELLANEOUS. 4-Nitropyridazine 1-oxide (**178**) is converted to 4-hydroxypyridazine 1-oxide (**179**) on treatment with acetic anhydride. In this case dimethylaniline is usually used as the nitrous acid acceptor (168, 169).



178 **179**

D. Halogens

Halogenopyridazine 1-oxide or its derivatives are synthesized mainly by one of the following methods.

(1) *N*-Oxidation of halopyridazines (see Section I).
(2) Reaction of nitropyridazine 1-oxide or its derivatives with a hydrogen halide or an acid halide (see Section VI.C).
(3) Diazotization of aminopyridazine *N*-oxide or its derivatives followed by a Gattermann reaction (see Section VI.G).

1. *Dehalogenation*

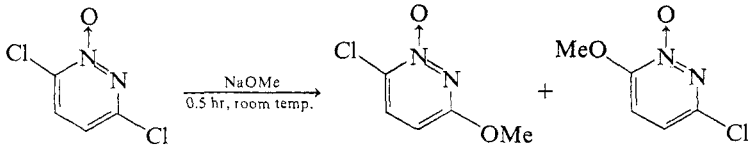
Although hydrogen was rapidly absorbed in catalytic hydrogenation of 3,6-dichloropyridazine in an alcoholic solution with a palladium–carbon catalyst, the solution was colored red-brown and the yield was low. When an excess of ammonia was added to the solution, the reduction proceeded smoothly. Dehalogenation of halopyridazine 1-oxide is usually performed in an ammonia–alkaline solution, and the *N*-oxide group is retained in these cases (see Table XXIII).

2. *Activity toward Nucleophilic Reagents*

a. SUBSTITUTION WITH AN ALKOXY OR AN AMINO GROUP. As described in Sections III.A and VI.A, the ring carbons of pyridazine 1-oxide are all electron-deficient by polarization, consequently, all chlorine atoms attached

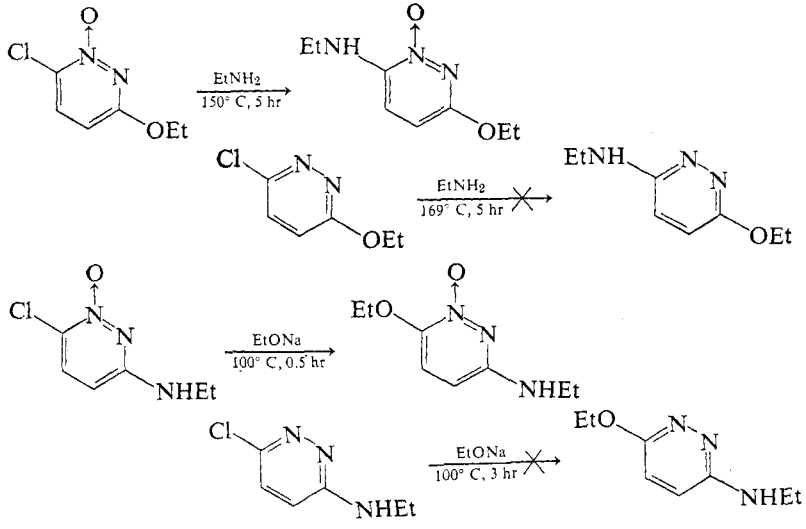
to these carbon atoms are reactive to nucleophilic substitution. Furthermore as the 4-chlorine atom of pyridine 1-oxide is reported to be more reactive than the 4-chlorine atom of pyridine, it is presumed that the 4- and 6-chlorine atoms are more reactive than the 3- and 5-chlorine atoms in pyridazine 1-oxides.

3-Chloropyridazine 1-oxide was converted to 3-pyridazinol 1-oxide by heating on a water bath with 5% sodium hydroxide solution (175), and 3,6-dichloropyridazine 1-oxide (**180**) was converted to 3-methoxy-6-chloropyridazine 1-oxide (**181**) by the reaction of sodium methoxide (176). In 1962, Sako (177) examined the same reaction and found that **180** gave the 3-methoxy (**181**) and the 6-methoxy compounds (**182**) in a ratio of 10:1.



180 **181** 80 % **182** 7.5 %

On account of this unexpected result, the reaction was studied with three different sodium alkoxides and two different amines as the nucleophilic reagent, under different reaction temperatures and with different solvents. However, the 3-substituted product was always obtained in higher yield than the 6-substituted product. Subsequently, 3-, 4-, 5-, and 6-monochloropyridazine 1-oxides were examined. The difference in the reactivity of the



3- and 6-chlorine atoms was not established (178), but the 5-chlorine atom is certainly more reactive than the 4-chlorine atom (179) (see Table XXIV).

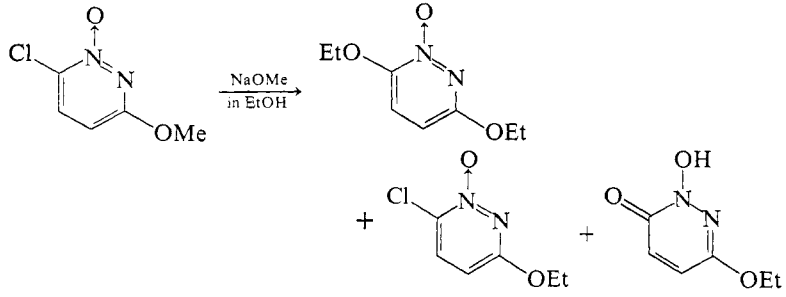
Participation of the *N*-oxide function in this nucleophilic activity is apparent from the reactions shown below (177).

In order to ascertain the differences in activity of these chlorine atoms in detail, Sako (180) studied this reaction kinetically, and it was found that the order was 5- > 3- > 6- > 4-position, and the ratio of the rate was 41:18:5.6:1.

Pyridazine 1-oxide	$K_2^{50} \times 10^5$ (mole^{-1} sec^{-1})	Pyridazine 1-oxide	$K_2^{50} \times 10^5$ (mole^{-1} sec^{-1})
5-Cl	288	3-Br	187
3-Cl	126	4-Br	7.34
6-Cl	39.4	5-Cl, 3,6-$(Me)_2$	3.15
4-Cl	7.08	4-Cl, 3,6-$(Me)_2$	0.0694

When these kinetic data are compared with nmr data (181, 182) which is in the order 3-, 6-, 5-, and 4-position from low to high magnetic field, the results are not inconsistent except for the 5-position which is the most reactive in the kinetic study and it has a high magnetic field in the nmr study. This special order of activity of the halogen on the ring has not yet been elucidated completely (see Section VI.A).

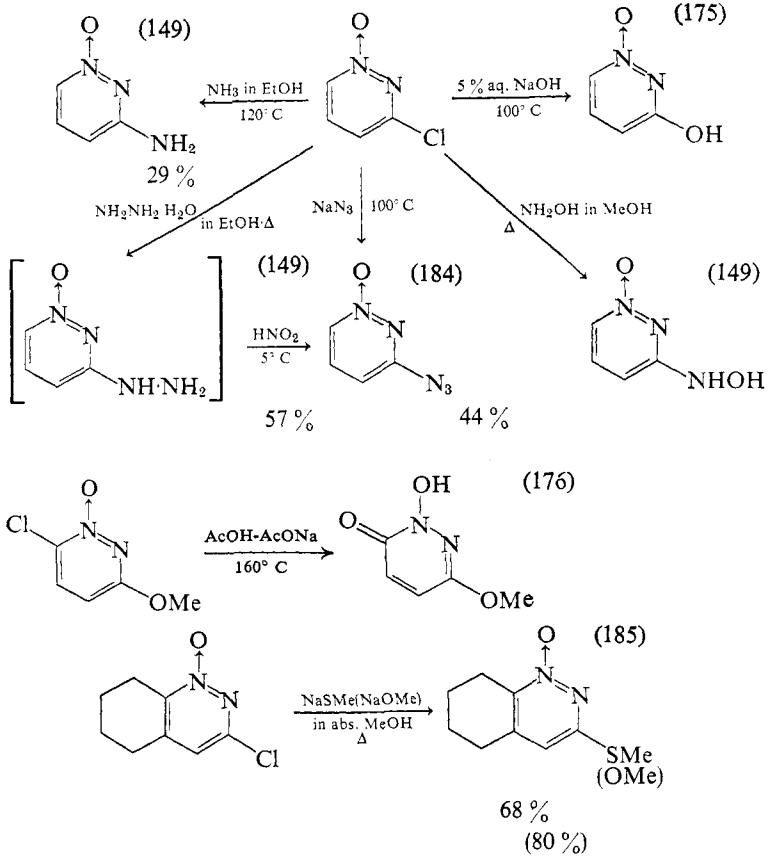
The 4-nitro- or 4-chloro substituent on 3-methyl-6-chloropyridazine 1-oxide (166) reacts first with sodium methoxide. However, the reaction of 3-methoxy-6-chloropyridazine 1-oxide is rather complicated, including only exchange of the chlorine atom by alkoxide but also exchange of the alkoxy group. An example is shown below (183). (See Section VI.E.1.b.)



Reflux, 90 min	82.5%		3.3%
70° C, 30 min	34.8%	10.9%	
50° C, 20 min	23.3%		

The reaction of halopyridazine 1-oxides with amines is summarized in Table XXV.

b. SUBSTITUTION WITH NUCLEOPHILIC REAGENTS OTHER THAN ALKOXIDES AND AMINES. A chlorine atom on the pyridazine 1-oxide ring reacts with ammonia, hydrazine, hydroxylamine, sodium azide, sodium hydroxide, acetic acid–sodium acetate, or methyl mercaptan to produce the corresponding amino, hydrazino, hydroxylamino, azido, hydroxy, or methylthio compound, respectively, as indicated below and are summarized in Table XXVI.



E. Alkoxy Group

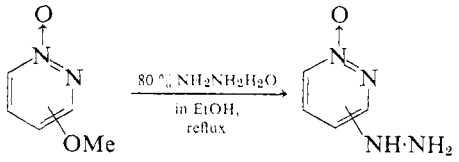
Synthetic methods of alkoxypyridazine 1-oxides are:

(1) *N*-Oxidation of alkoxypyridazine. Especially, 5-alkoxypyridazine 1-oxides are prepared by the *N*-oxidation of 3,4-dichloro-5-alkoxypyridazine followed by catalytic dehalogenation.

(2) Exchange reaction of nitro- or halogenopyridazine 1-oxide with sodium alkoxide (see Sections VI.C.2.b and D.2).

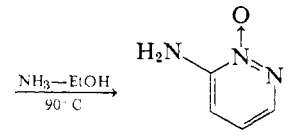
1. *Activity toward Nucleophilic Reagents*

a. SUBSTITUTION WITH HYDRAZINE OR AMMONIA. Refluxing methoxypyridazine 1-oxides (**183**) and 80% hydrazine hydrate in an ethanolic solution results in the production of hydrazinopyridazine 1-oxides (**184**) (184, 186). Similarly, the reaction of 6-ethoxypyridazine 1-oxide (**185**) with ammonia in a sealed tube heating in a water bath gave 6-aminopyridazine 1-oxide (**186**) (184). The synthesis with chloropyridazine 1-oxide as the starting material gave ammonium chloride which was very difficult to separate. Then the methoxy group on pyridazine 1-oxide seems to be far more active than that on pyridine 1-oxide.



183 **184** **185**

3-: 26%, 5-: 55%
4-: 43%, 6-: 43% (from EtO)

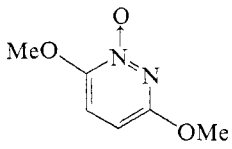


186

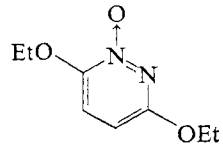
b. EXCHANGE WITH ANOTHER ALKOXY GROUP. As mentioned in Section VI.D., when 6-chloro-3-alkoxypyridazine 1-oxide was warmed with an alcoholic solution of a sodium alkoxide in which the alkoxy group is derived from a higher alcohol than the alkoxy group on the ring, exchange of the alkoxy group took place as a side reaction. Yanai and Kinoshita (183) reported complicated reactions of 3,6-dimethoxy- (**187a**) and 3,6-diethoxypyridazine 1-oxide (**187b**).

In these reactions group A is 3,6-di-exchanged dialkoxy compounds (**187a** and **b**), group B 3- or 6-mono-exchanged dialkoxy compounds (**188** and **191**), group C 3-exchanged 6-dealkylated 1-hydroxy-3-alkoxy-6(1*H*)-pyridazinone (**189a** and **b**), and group D 3-unchanged 6-dealkylated 3-alkoxy-1-hydroxy-6(1*H*)pyridazinone (**189a**). It is not clear whether the 6-position is dealkylated before or after the exchange reaction.

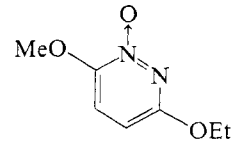
Reaction 1:



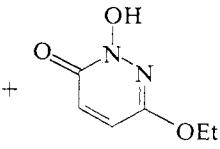
187a



187b



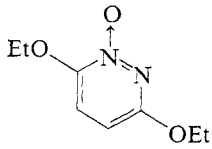
188



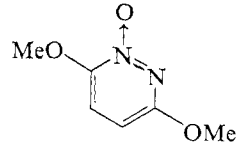
189b

Reflux, 90 min			25%
80° C, 60 min	Little		15%
40° C, 40 min	50%	32%	1.5%
15–16° C, 135 min	40.6%		12%

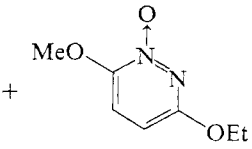
Reaction 2:



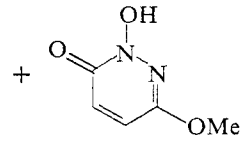
187b



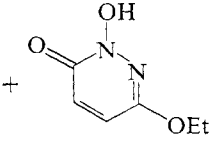
187a



188



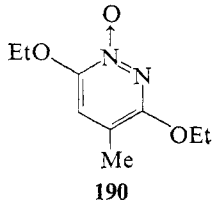
189a



189b

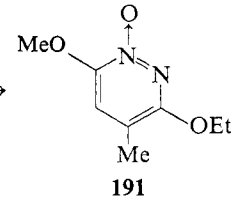
Reflux, 60 min	8.5%		9%	42%
50° C, 40 min	2.2%	49%		Little
40° C, 40 min	1.2%	36%		
20° C, 120 min		Rec. 85%		
16–19° C, 900 min	17%			2.4%

Reaction 3:



190

MeONa 55° C, 40 min



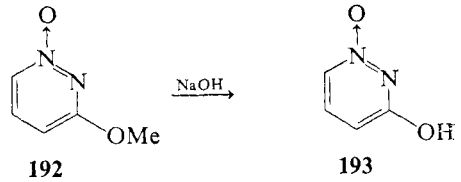
191

61%

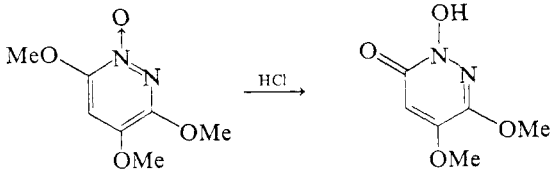
2. *Dealkylation with Acid or Alkali*

3-, 4-, 5-, and 6-methoxy groups on pyridazine 1-oxide are easily demethylated with 5% sodium hydroxide solution by warming, for example, 3-methoxypyridazine 1-oxide (**192**) gives 3-pyridazinol 1-oxide (**193**) (187). Furthermore, dealkylation also takes place with bases such as pyridine (141) and methanolic sodium hydroxide solution (150) (see Section VI.F.1.a). Among these, the 6-methoxy group is most easily dealkylated.

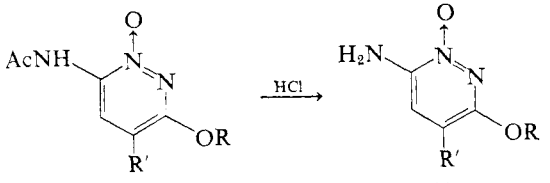
When 3,4,6-trimethoxypyridazine 1-oxide (**194**) is heated with diluted hydrochloric acid, the 6-methoxy group is only cleaved. As seen from the cases mentioned below, alkoxy groups other than in the 6-position do not cleave by acid, and other groups, such as the acetamino (**196**) or the cyano group (**198**), are liable to be hydrolyzed (144, 152). These reactions are summarized in Table XXVII.



192 **193**

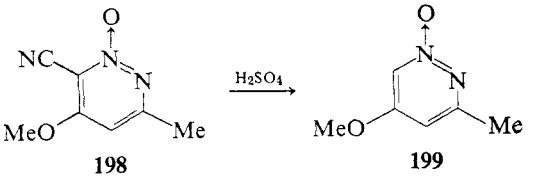


194 **195**



196 **197**

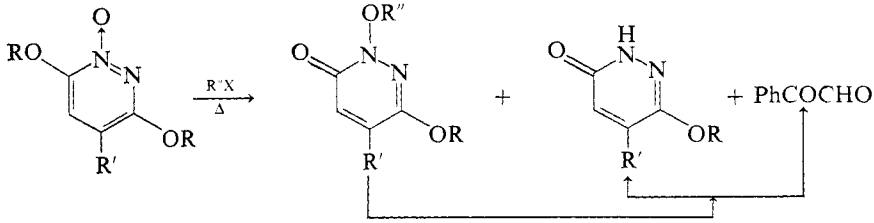
R = Me—Bu; R′ = NO_2 or Cl



198 **199**

3. *Reaction with Alkyl Halides or Halo Ketones*

In 1966, Yanai, Kinoshita, and Yamaguchi (189) presumed that rearrangement of 3,6-dimethoxypyridazine 1-oxide (**200**) to 1,3-dimethoxy-6(1*H*)-pyridazinone (**201**) might be initiated by carbonium ion (see Section VI.E.5) and performed an experiment with an alkyl halide or a halo ketone as the carbonium ion source (189).



200 **201** **202** **203**

a: R = Me, R′ = H
b: R = Me, R′ = H, R″X = $PhCOCH_2Br$

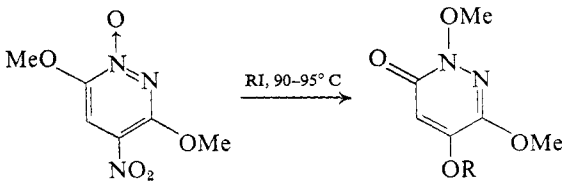
Reaction of 4-substituted 3,6-dimethoxypyridazine 1-oxide (**200**) with phenacyl bromide gives 1-phenacyloxy-3-alkoxy-6(1*H*)pyridazinone (**201**) as the main product and 3-alkoxy-6(1*H*)pyridazinone (**202**) and phenyl glyoxal (**203**) as the by-products. These compounds are also produced by heating the main product (**201**) (189).

Many instances of this reaction are summarized in Table XXVIII.

The reactivity of alkyl halides is in the following order: EtI ≋ MeI > $PhCH_2Cl$.

The reaction of 4-nitro-3,6-dimethoxypyridazine 1-oxide (**204**) with methyl or ethyl iodide gave 1,3-dimethoxy-4-alkoxy-6(1*H*)pyridazinone (**205**) (189).

Compounds, that cannot be easily changed to a cyclic hydroxamic acid structure, that is, ones that have no methoxy group in the 6-position, such as



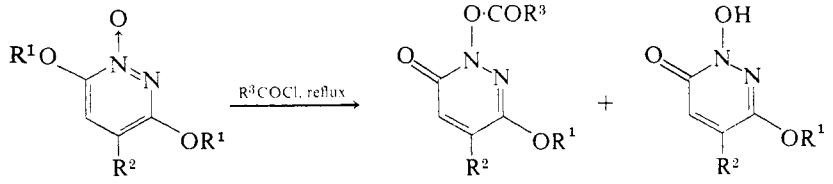
204 **205**

a: R = Me 65%
b: R = Et 69.5%

4-nitro- or 3-methoxy-4-nitro-6-chloropyridazine 1-oxide, are not subjected to this reaction, and the starting materials are recovered.

4. *Reaction with Organic Acyl Chlorides or Acid Anhydride*

On refluxing with acetic anhydride, 3,6-dimethoxy-4-methylpyridazine 1-oxide (**206**) gave 1-acetoxy-3-methoxy-4-methyl-6(1*H*)pyridazinone (**207**) in 90% yield (**190**), and also the nitration of 3,6-dimethoxypyridazine 1-oxide (**206a**) with silver nitrate and benzoyl chloride resulted in the formation of 1-benzoyloxy-3-methoxy-6(1*H*)pyridazinone (**207**) (R^3 = Ph) (188).



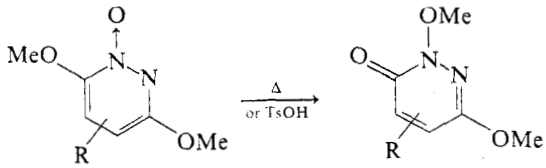
206 **207** **208**

a: R^1 = Me; R^2 = H
b: R^1 = Et; R^2 = H; R = Ac or Bz
c: R^1 = Me; R^2 = Me
d: R^1 = Et; R^2 = Me

The similar reaction with acetyl chloride was examined later by Yanai and Kinoshita (162), and compounds of type **207** were obtained with acetyl or benzoyl chloride in good yield even at room temperature. This acetoxy group is easily hydrolyzed, for example, when the compound is heated in water or alcohol and is chromatographed through an alumina column, it is liable to produce 1-hydroxy-3-alkoxy-6(1*H*)pyridazinones (**208**). Stretching vibrations of the carbonyl groups in 1-acetoxy-6(1*H*)pyridazinone show characteristic absorptions in the ir spectrum, and 1-hydroxy-6(1*H*)pyridazinone as a cyclic hydroxamic acid develops a deep-red coloration with ferric ion (144). These transformations are summarized in Table XXIX.

5. *Rearrangement of an Alkyl Group to the N-Oxide from an Alkoxy Group*

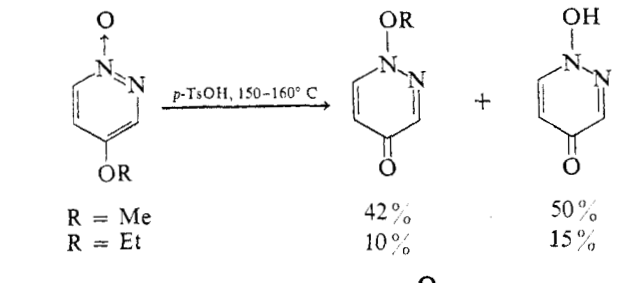
When 3,6-dimethoxy- or 3,4,6-trimethoxypyridazine 1-oxide (**209a** and **b**) is fused, the methyl group from the 6-methoxy group migrated to the *N*-oxide group forming 1,3-dimethoxy- or 1,3,4-trimethoxy-6(1*H*)pyridazinone (**210a** and **b**) in good yields (193).



209 210

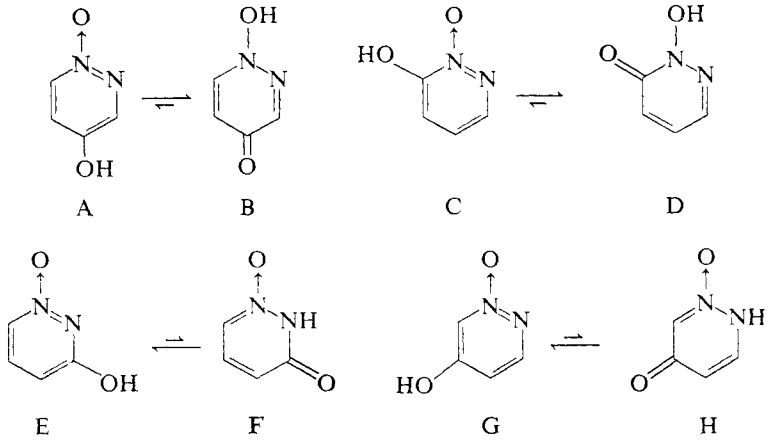
			Yield (%)	References
a:	R = H	150–160° C	81	190
b:	R = 4-MeO	150–160° C, TsOH	87	168
c:	R = H	150–160° C, TsOH	40	168
d:	R = 4-Me	130–140° C, TsOH	31	168
	R = 4-Me	150–160° C, TsOH	66	168
e:	R = 5-Me	150–160° C, TsOH	48	168

As stated in Section I.B.2 regarding *N*-oxidation of 3,6-dimethoxypyridazine, the same alkyl migration was observed in one of the products. Since this migration took place solely with acetic acid or by heating in the absence of hydrogen peroxide, **209a** was heated with a small quantity of a strong acidic substance such as *p*-toluenesulfonic acid. Compound **210a** was produced in medium yield as presumed. By heating with the acid, not only the 6-alkoxy group but also the 4- or 5-alkoxy group rearranges in the following manner, however, the yields are usually not high, except for the 4-methoxy compound (**191**).



F. Hydroxy Group

Tautomerism of hydroxypyridazine 1-oxides has been investigated by several methods. Roughly speaking, it may be said types B and D predominate in 4- and 6-hydroxypyridazine 1-oxides, and types E and G predominate in 3- and 5-hydroxypyridazine 1-oxides, respectively (171, 173, 179, 186, 187).



Apart from the physicochemical studies, some reactions such as alkylation and acylation are noted here.

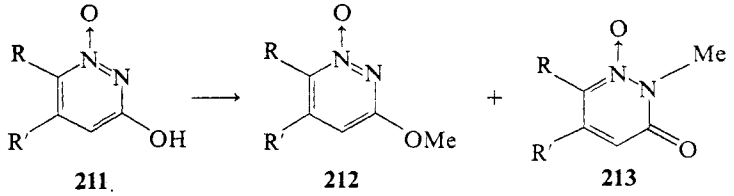
Alkylation and Acylation

By using methyl iodide and silver oxide, 3- or 5-hydroxypyridazine 1-oxides (**211** and **214**) are easily alkylated to the corresponding 3- or 5-methoxypyridazine 1-oxides (**212**) (171, 179, 187, 192, 193).

In contrast, 4- or 6-hydroxypyridazine 1-oxides (**215** and **218**) are methylated to produce 1-methoxy-4(1*H*)- or -6(1*H*)pyridazinones (**217** and **218**). The yields of compounds are fairly good (165, 176, 179).

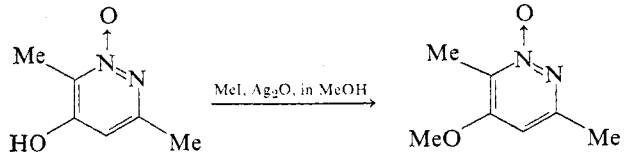
When dimethyl sulfate in the presence of alkali is used as the alkylating agent, 3-hydroxy-6-methylpyridazine 1-oxide (**211b**) produces 2,6-dimethyl-3(2*H*)pyridazinone 1-oxide (**213b**) and (**212b**). In these cases the ratios of the products are different depending upon the type of alkali used, such as an aqueous solution of sodium hydroxide or methanolic sodium methoxide solution, as shown in Table XXX.

4- or 6-Hydroxypyridazine 1-oxides (**216** and **218**) always produce solely 1-alkoxypyridazinones (**217** and **219**) regardless of the alkylating agents,



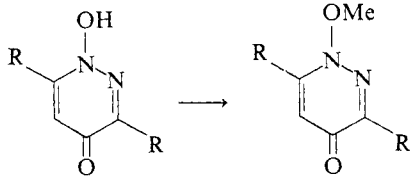
211 212 213

				Ref.
a: R = H; R′ = H	MeI, Ag_2O, 100° C			186
b: R = Me, R′ = H	MeI, Ag_2O, in MeOH	70%		171
	Me_2SO_4, NaOH aq. soln.	5.4%	25% (1:5)	192
	Me_2SO_4, NaOMe in MeOH	6%	8.5% (5:7)	192
c: R = R′ = Me	Me_2SO_4, 2 *N* NaOH	4.5%	19.5% (1:4)	194



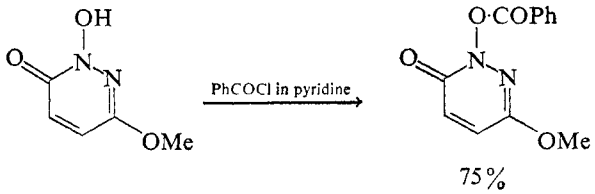
214 215

26% 179



216 217

a: R = Me	MeI, Ag_2O, in MeOH	31%
b: R = H	MeOTs, NaOH in MeOH	47%



75%

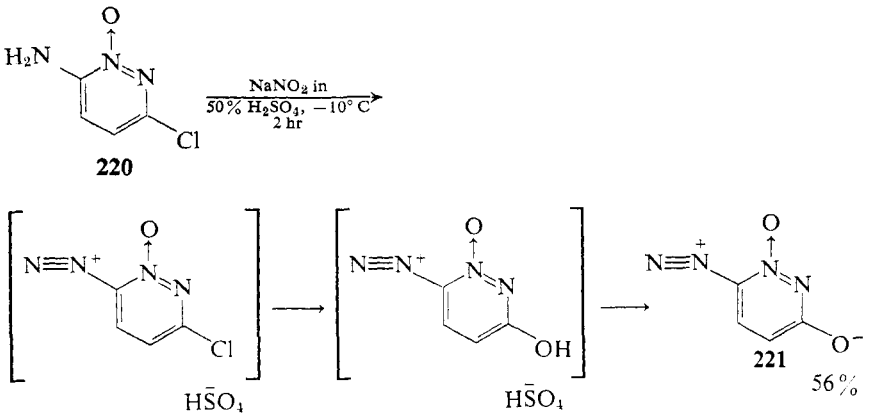
that is, when alkylation is with one of the following compounds such as dimethyl sulfate, diethyl sulfate, methyl tosylate or benzyl chloride in sodium hydroxide or methanolic sodium methoxide solution (144, 150, 176, 192).

Acylation of a hydroxy group of 1-hydroxy-3-methoxy-6(1*H*)pyridazinone is shown as an example of this kind of reaction (144).

G. Amino Group

Diazotization and Related Reactions

3,6-Dimethoxy-4-aminopyridazine 1-oxide was diazotized and coupled with β-naphthol, giving a red coloration; 4- and 5-aminopyridazine 1-oxides showed a similar coloration. However, it was observed that the former reacted more rapidly than the latter (194). 4-Amino, 4-amino-6-methyl-, 3,6-dimethyl-4-amino-, and 3-methoxy-4-amino-6-methylpyridazine 1-oxides were reported to give a positive diazo coupling reaction, but no detailed description was given (151). When 3-chloro-6-aminopyridazine 1-oxide (**220**) was diazotized in 50% sulfuric acid and left for a few hours, a crystalline substance separated out. This was shown to be dehydrated 6-hydroxy-3-pyridazine diazonium hydroxide 2-oxide (inner salt) (**221**) (172).



The reaction of **221** with β-naphthol gave a purple precipitate which was isolated and found to be consistent with the azo compound. On boiling in dehydrated methanol, **221** was converted to 3-pyridazinol 1-oxide (172).

Amino groups of pyridazine 1-oxides can be diazotized and the diazonium salts can be replaced by halogens, hydroxy groups, or hydrogen. Not all aminopyridazine 1-oxides are diazotized with equal ease. After diazotizing 3,6-dimethyl-4-aminopyridazine 1-oxide and adding copper powder, Sako obtained 3,6-dimethyl-4-chloropyridazine 1-oxide in 55% yield (179). 4-Amino-3,5-dichloro-, 5-amino-3,4-dichloro-, 5-amino-, and 6-aminopyridazine 1-oxides were similarly diazotized in hydrochloric acid and warmed with or without copper powder to the corresponding chloro compounds (167, 178). However, in hydrobromic acid, 3-amino-, 4-amino-, and 5-aminopyridazine 1-oxides reacted similarly to give the corresponding bromopyridazine 1-oxides (167). 3,6-Dichloropyridazine 1-oxide was synthesized by Yoneda and Nitta from 3-chloro-6-aminopyridazine 1-oxide (196). Although some yields are low, this method is a very important one for the preparation of some starting materials that otherwise can not be obtained (see Table XXXI).

H. Azido Group

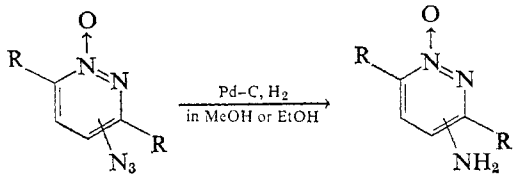
Azidopyridazine 1-oxides can be synthesized by one of the three following methods.

(1) Reaction of methoxypyridazine 1-oxides with hydrazine hydrate to hydrazinopyridazine 1-oxides (see Section VI.E.1.a) followed by treating with sodium nitrite in mineral acid solution.
(2) Substitution reaction of chloropyridazine 1-oxides with sodium azide (see Section VI.D.2.b).
(3) *N*-Oxidation of azidopyridazines (see Section I.B).

Azido compounds synthesized by one of the above-mentioned procedures are listed in Table XXXII together with their characteristics.

1. *Reduction*

When a methanol or ethanol solution of an isomer of azidopyridazine 1-oxides (**222**) is reduced catalytically in the presence of palladium–carbon as a catalyst, the corresponding amino compound (**223**) is produced in good yield, releasing 1 molar equivalent of nitrogen gas. In this case the *N*-oxide grouping remains intact.



222 **223**

a: 3-, R = H 28%
b: 6-, R = H 65%
c: 4-, R = MeO 84%

2. *Substitution with Sodium Alkoxides*

Each azido group in the 3-, 4-, 5-, or 6-position of pyridazine 1-oxide is easily replaced with sodium alkoxide. As reaction conditions reported were not the same, varying from room temperature to 100° C, the replacement reactivity of these azido groups can not be compared (184, 186, 193) (see Table XXXIII).

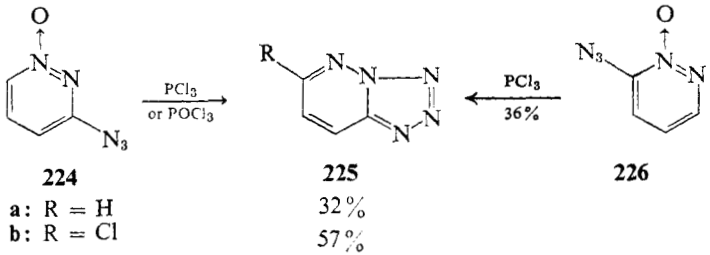
3. *Reaction with Phosphorus Trichloride or Phosphorus Oxychloride*

3- or 6-Azidopyridazine 1-oxide (**224** and **229**) is converted with phosphorus trichloride into 3- or 6-azidopyridazine, which immediately cyclyzes to tetrazolo[1,5-*b*]pyridazine (**225a**). Similarly, when **224a** or **229** is allowed to react with phosphorus oxychloride, 6-chlorotetrazolo[1,5-*b*]pyridazine (**225b**) is produced through 3-azido-6-chloropyridazine (184). However, the 4-azido group (**227**) remains unchanged after deoxygenation (186).

4. *Thermal Decomposition*

In thermal decomposition studies of 4-azidoquinoline 1-oxide by Itai and Kamiya, two main reactions were observed; after releasing nitrogen gas from the azido group, a diradical was produced which either dimerized to 4,4′-azoquinoline 1,1′-dioxide or abstracted hydrogen from the solvent to produce 4-aminoquinoline 1-oxide (197).

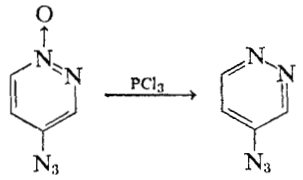
When 3-azidopyridazine 1-oxide (**224**) was refluxed in xylene solution, precipitation occurred. Analytical data for the product were consistent with



224
a: R = H
b: R = Cl

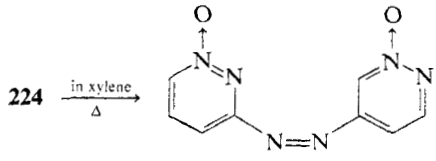
225
32%
57%

226



227 **228**

3,3′-azopyridazine 1,1′-dioxide (**230**). The reaction did not take place on refluxing in benzene or toluene (184). However, the same reaction of 4- or 6-azidopyridazine 1-oxides (**227** and **229**) proceeded in boiling benzene (186).



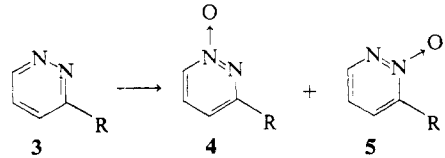
230

5. *Photolysis*

Whenever azidopyridazine 1-oxide is handled in the laboratory, differences in stability toward light are noticed, that is, the 3- or 5-isomers are stable, but the 4- or the 6-isomers usually turn blackish-brown in color. When 3,6-dimethoxy-4-azidopyridazine 1-oxide in benzene solution was exposed to sunlight, the azo dye precipitated (193).

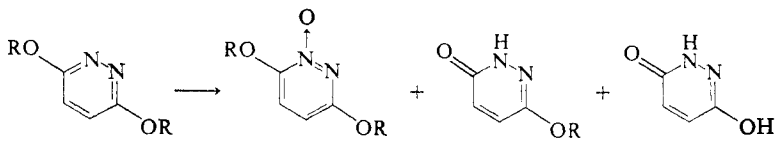
From the above results the differences in ionic activity of the 3-, 4-, 5-, and 6-azido groups could not be delineated, however, it seemed likely that the reactivity in thermal and photochemical reactions is higher in the 4- and 6-positions than in the 3- and 5-positions.

TABLE I. *N*-Oxidation of 3-Substituted Pyridazines



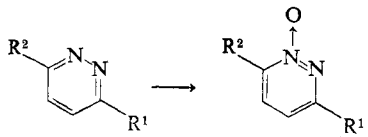
	3	4	5	
	Method	Yield (%)	Yield (%)	References
a: R = Me	1			29
	1	8.2	22.4	26, 27
	1	46	45	28, 48a
				48b
b: R = Ph	1	72.5	9.7	20
c: R = MeO	1	70		30
	1	75		31
d: R = $PhCH_2O$	3			19
e: R = Cl	3			32
f: R = NH_2	1		43	33, 34
g: R = NHAc	2	2	82	33, 34
	1	10	33	33, 34
	1		28	38
h: R = NHEt	1		20	47
i: R = NO_2	1			48b

TABLE II. *N*-Oxidation of 3,6-Dialkoxypyridazines



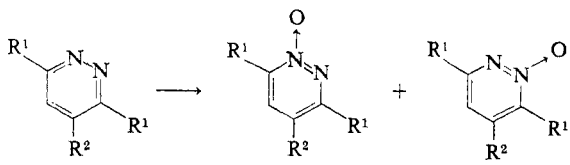
	14	15	16	17	
	Method	Yield (%)	Yield (%)	Yield (%)	References
a: R = Me	1	73			37
b: R = Et	1	40			37
c: R = *n*-Pr	1	30			37
d: R = *n*-Bu	1	47			37
e: R = *t*-Bu	1			100	37
f: R = $PhCH_2$	1		65		37

TABLE III. *N*-Oxidation of 3,6-Disubstituted Pyridazines



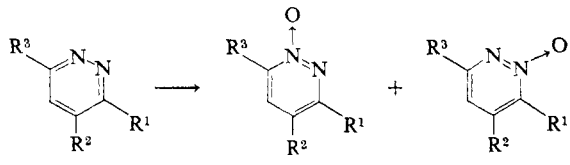
R^1	R^2	Method	Yield (%)	Yield (%)	References
H	H				48b, 48c
Me	Me	1	52		37
Me	Me				48a
Ph	Me	1			29
Me	Cl	1		63	27
		3		86	28
Me	MeO	1		74	26, 27
Ph	Cl	3	17	5	20
Me	EtO	1		83	28
Me	OH	1			29
Cl	Cl	2	9.4 (recov. 54)		16
		1	44.6		19
		4	40		24
MeO	Cl	2	32		16
		1	14		16
		1	18		19
EtO	Cl	2	16 (recov. 65)		16
		1	13 (recov. 30)		16
n-PrO	Cl	2	26		16
NH_2	Cl	1		91	33, 34
		1			38
EtNH	Cl	1		32	48
$NHCO_2Et$	Cl	1		88	33, 34
		1			38
NHAc	Cl	1		50	38
NH_2	MeO	1			38
NHAc	EtO	1			38
NHAc	*n*-PrO	1			38
NHAc	i-PrO	1			38
NHAc	*n*-BuO	1			38
NHAc	*n*-AmO	1			38
NHAc	i-AmO	1			38
NHAc	$C_6H_{13}O$	1			38
NHAc	$C_8H_{17}O$	1			38
NHAc	$C_{10}H_{21}O$	1			38
$NHCO_2Et$	MeO	1			38
Cl	NO_2				48b

TABLE IV. *N*-Oxidation of 3,4,6-Trisubstituted Pyridazines



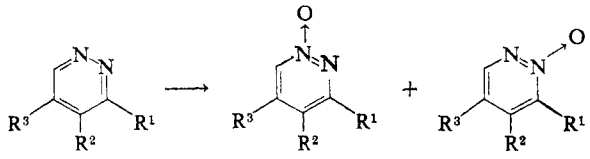
	19 R^1	R^2	Method	**20** Yield (%)	**21** Yield (%)	References
a	H	Me	1	36.6	7.7	39
b	H	MeO	1	7	13	40, 41
c	Me	Cl	2	23	11	42
d	Cl	MeO	2	12	4.5	8
e	MeO	Me	1	70		43
f	EtO	Me		58.7	5.1	43
g	MeO	N_3	1		(recov. 12)	44

TABLE V. *N*-Oxidation of 3,4,6-Trisubstituted Pyridazines



	27 R^1	R^2	R^3	Method	**28** Yield (%)	**29** Yield (%)	References
a	MeO	MeO	Cl	2	50		40
b	Cl	Me	MeO	3		95	43
c	MeO	Me	Cl	3	91		43
d	Me	Me	Cl	3	0.6	83	46
e	Me	Me	MeO	1			46
	Cl	NH_2	CH_3				48d

TABLE VI. *N*-Oxidation of 3,4,5-Trisubstituted Pyridazines



30 31 32

	R^1	R^2	R^3	Method	Yield (%)	Yield (%)	References
a	Cl	Cl	NH_2	2	77		45
b	Cl	NH_2	Cl	2	43		45
c	Cl	Cl	MeO	1	35		13
d	Me	Me	H	1	35.5	16	48

TABLE VII. Deoxygenation of Substituted Pyridazine 1-Oxides

Product pyridazine	Starting material pyridazine 1-oxide	Reagents		Yield (%)	References
		Catalyst	Adjuvant		
3-Me	3-Me	Pd–C	MeOH	70	51
6-Me	6-Me	Pd–C	MeOH	80	51
3-OH	3-OCH_2Ph	Pd–C	MeOH		52
4-MeO	4-MeO	Pd–C	MeOH–HCl		53
3-MeO-4-Me-6-OH	3-MeO-4-Me-6-OH	Raney Ni	MeOH–AcOH	75	54
3-MeO-5-Me-6-OH	3-MeO-5-Me-6-OH	Pd–C	MeOH–AcOH	73	54
3,6-$(Me)_2$-4-NH_2	3,6-$(Me)_2$-4-NO_2	Raney Ni	MeOH–AcOH	91	55
5,6-$(Me)_2$-4-NH_2	5,6-$(Me)_2$-4-NO_2	Raney Ni	MeOH–AcOH	82	56
3-MeO-4-NH_2	3-MeO-4-NO_2	Raney Ni	MeOH	61	57
		Raney Ni	EtOH–AcOH	83	58
3-MeO-4-NH_2-6-Me	3-MeO-4-NO_2-6-Me	Pd–C	Ac_2O	48	59
		Raney Ni	MeOH–AcOH	70	55
3,6-$(MeO)_2$-4-NHAc	3,6-$(MeO)_2$-4-NO_2	Pd–C	AcO_2	80	60
3,6-$(MeO)_2$-4-NH_2	3,6-$(MeO)_2$-4-NO_2	Raney Ni	AcOH	91	61
3-MeO-4,6-$(NH_2)_2$	3-MeO-4-NO_2-6-NH_2	Raney Ni	EtOH–AcOH	57	62
5-NH_2	5-NO_2	Pd–C	MeOH–HCl		63
3-MeO-6-NH_2	3-MeO-6-NO_2	Raney Ni	MeOH–AcOH	92	58
3-MeO-4-Me-6-NH_2	3-MeO-4-Me-6-NO_2	Raney Ni	MeOH–AcOH	72	54
3,4-$(Me)_2$-5-NH_2	3-Cl-4-NO_2-5,6-$(Me)_2$	Pd–C	MeOH	83.5	56
3,4-$(Me)_2$-6-NH_2	3,4-$(Me)_2$-6-NO_2	Pd–C	HCl	73	56
4-NH_2-6-Me	3-Cl-4-NO_2-6-Me	Pd–C, Raney–Ni	MeOH		55
3-OH-6-$CH_2NC_4H_8O$	3-OH-6-$CH_2NC_4H_8O$	Pd–C	MeOH	95	64
3-OH-6-CH_2NMe_2	3-OH-6-CH_2NMe_2	Pd–C	MeOH	94	64
3-OH-6-$CH_2NC_5H_{10}$	3-OH-6-$CH_2NC_5H_{10}$	Pd–C	MeOH	96	64
3-OH-4-$CH_2NC_4H_8O$	3-OH-4-$CH_2NC_4H_8O$-6-Cl	Pd–C	MeOH	95	64
3-OH-6-Me-4-$CH_2NC_5H_{10}$	3-OH-6-Me-4-$CH_2NC_5H_{10}$	Pd–C	MeOH	84	65
3-OH-4,6-$(CH_2NC_4H_8O)_2$	3-OH-4,6-$(CH_2NC_4H_8O)_2$	Pd–C	MeOH	95	65
3-OH-4-$CH_2NC_5H_{10}$	3-OH-4-$CH_2NC_5H_{10}$-6-Cl	Pd–C	MeOH	95	65
3-OH-4-$CH_2NC_4H_8O$-6-Me	3-OH-4-$CH_2NC_4H_8O$-6-Me	Pd–C	MeOH	80	65

TABLE VIII. Deoxygenation with Phosphorus Trichloride

Product pyridazine	Starting material pyridazine 1-oxide	Reagent	Reaction temperature	Yield (%)	References
3,4,6-$(MeO)_3$	3,4,6-$(MeO)_3$	PCl_3–$CHCl_3$	Room	60	60
3,6-$(Me)_2$-4-Cl	3,6-$(Me)_2$-4-Cl	PCl_3–$CHCl_3$	Room	59	68
3-MeO-4-Cl-6-Me	3-MeO-4-Cl-6-Me	PCl_3		41	59
3,6-$(MeO)_2$-4-Cl	3,6-$(MeO)_2$-4-Cl	PCl_3		55.8	69
3-MeO-?-Cl-6-OH		PCl_3		6	
3-MeO-4-Cl-6-AcNH	3-MeO-4-Cl-6-AcNH	PCl_3–$CHCl_3$	Reflux	48	62
Tetrazolo-[5,1-*b*]-pyridazine	3-N_3	PCl_3–$CHCl_3$	Reflux		70
4-N_3	4-N_3	PCl_3–$CHCl_3$	Reflux		71

TABLE IX. Nitration with Nitric Acid and Sulfuric Acid

Product pyridazine 1-oxide	Reagents[a]	Reaction temperature (°C)	Yield (%)	References
4-NO_2	HNO_3(1.5), H_2SO_4	130–140	22	91
	HNO_3(1.5), conc. fuming H_2SO_4	105–110	8	86
3-Me-4-NO_2	HNO_3(1.49), H_2SO_4	85–90	27	88 (cf. 87)
4-Me				(cf. 89)
5-Me-4-NO_2	Fuming HNO_3, H_2SO_4	100	18	89
6-Me-4-NO_2	Fuming HNO_3, H_2SO_4	100	86.7	87
	HNO_3(1.48), H_2SO_4	95–100	56	86
3,4-$(Me)_2$-6-NO_2	HNO_3(1.51), H_2SO_4	50	9	88
3,6-$(Me)_2$-4-NO_2	Fuming HNO_3, H_2SO_4	100	54	90
	HNO_3(1.5), H_2SO_4	100	80	86
5,6-$(Me)_2$-4-NO_2	HNO_3(1.5), H_2SO_4	70	78	88

[a] Concentration of nitric acid is shown in parentheses with its specific gravity. Unless otherwise stated, H_2SO_4 is concentrated sulfuric acid.

TABLE X. Nitration with Nitric Acid and Sulfuric Acid

Product pyridazine 1-oxide	Reagents	Reaction temperature (°C)	Yield (%)	References
3-MeO-4-NO_2	HNO_3(1.5), H_2SO_4	50–55	11.5	92
3-MeO-4,6-$(NO_2)_2$			6.5	
3-MeO-4-NO_2	HNO_3(1.5), H_2SO_4	45–70	29	93
3-MeO-6-NO_2			5	
3-MeO-6-NO_2 (no N → O)			0.5	
3-MeO-4,6-$(NO_2)_2$ from 3-MeO-4-NO_2	HNO_3(1.5), H_2SO_4	70–75		92
3-MeO-4-Me-6-NO_2	HNO_3(1.5), H_2SO_4	Room	64	94
	HNO_3(1.5), H_2SO_4	50–55	81	
3-MeO-4-NO_2-5-Me	HNO_3(1.5), H_2SO_4	70–80	30	103
3-MeO-5-Me-6-NO_2			13	
3-MeO-4,6-$(NO_2)_2$-5-Me			2.5	
3-MeO-4-NO_2-5,6-$(Me)_2$	HNO_3(1.48), H_2SO_4	Room	81	100
3,6-$(MeO)_2$-4-NO_2	Fuming HNO_3, 90% H_2SO_4	10–15	84	77
3,6-$(EtO)_2$-4-NO_2	HNO_3(1.38), 80% H_2SO_4	10	44	95
3,6-(*n*-PrO)$_2$-4-NO_2	HNO_3(1.38), 80% H_2SO_4	10	35	95
3,6-(*n*-BuO)$_2$-4-NO_2	HNO_3(1.38), H_2SO_4	10	54	95
3-Cl-6-Me-4-NO_2	HNO_3(1.5), H_2SO_4	85–90	46	86
	Fuming HNO_3, H_2SO_4	100	32	87
3-Cl-4-NO_2-5,6-$(Me)_2$	HNO_3(1.48), H_2SO_4	70	66	93
3-MeO-4-NO_2-6-Cl	HNO_3(1.38), H_2SO_4	50	65	96
3-OH-4-NO_2-6-Cl	HNO_3(1.38), H_2SO_4	50	53	96
3-MeO-4-NO_2-6-AcNH	HNO_3(1.5), H_2SO_4	10		97
3-EtO-4-NO_2-6-AcNH	HNO_3(1.5), H_2SO_4	10		97
3-PrO-4-NO_2-6-AcNH	HNO_3(1.5), H_2SO_4	10		97
3-BuO-4-NO_2-6-AcNH	HNO_3(1.5), H_2SO_4	10		97
3-AmO-4-NO_2-6-AcNH	HNO_3(1.5), H_2SO_4	10		97
3-iso-AmO-4-NO_2-6-AcNH	HNO_3(1.5), H_2SO_4	10		97
3-C_6H_{13}O-4-NO_2-6-NHAc	HNO_3(1.5), H_2SO_4	10		97
3-C_8H_{17}O-4-NO_2-6-NHAc	HNO_3(1.5), H_2SO_4	10		97
3-$C_{10}H_{21}$O-4-NO_2-6-AcNH	HNO_3(1.5), H_2SO_4	10		97
3-OH-4-NO_2	Fuming HNO_3, H_2SO_4	70	28	103
3-OH-4-NO_2-5-Me	Fuming HNO_3, H_2SO_4	70	15	103
3-OH-4-Me-6-NO_2	Fuming HNO_3, H_2SO_4	45–50	13	103
3-OH-4-NO_2-6-Me	Fuming HNO_3, H_2SO_4	Room	43	103

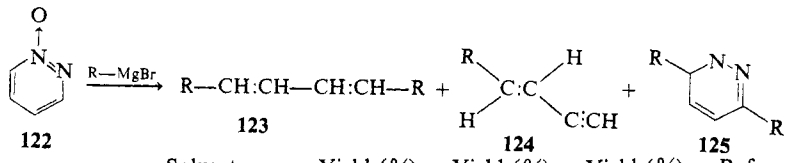
TABLE XI. Reaction with Inorganic Acid Halides

Prooduct pyridazine 1-oxide	Starting material pyridazine 1-oxide	Reagents	Reaction temperature	Yield (%)	References
3-MeO-6-Cl	3-MeO	$POCl_3$ in $CHCl_3$	Room	52	108
5-Cl-pyridazino [2,3-*d*]tetrazole	3-N_3	$POCl_3$ in $CHCl_3$	Reflux	57	109
3,6-Me_2-4-Cl	3,6-Me_2	$POCl_3$	60–70°C	28	110
3,6-$(MeO)_2$-4-Cl	3,6-$(MeO)_2$	$POCl_3$	Room	72	112
3-MeO-4-Cl-6-Me	3-MeO-6-Me	$POCl_3$ in $CHCl_3$	Reflux	58	111

TABLE XII. Introduction of the Cyano Group

Product 6-cyanopyridazine	Reissert reaction yield (%)	Okamoto–Tani method yield (%)	References
3-Me	0.6	35	117
3-Ph	41.6	57	117
3-Cl		35	
3-OMe	28.4	72	116, 117
3-OCH_2Ph	10	68.5	117

TABLE XIII. Products from Pyridazine 1-Oxide and Grignard Reagents



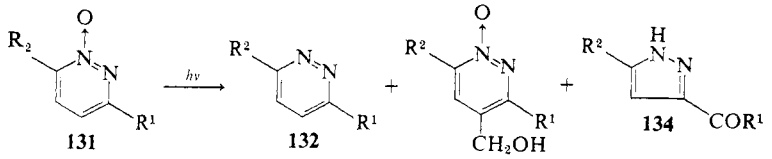
122 123 124 125

R	Solvent	Yield (%)	Yield (%)	Yield (%)	References
C_6H_5—	Ether THF	28	Little	Little	128
	THF		35 (81)		128
p-$CH_3OC_6H_4$—	THF		35 (82)		128
o-$CH_3C_6H_4$—	THF		41 (76)		128
m-$CH_3C_6H_4$—	THF		31 (62)		128
p-$CH_3C_6H_4$—	THF		8 (16)		128
o-$CH_3OC_6H_4$—	THF		22		128

TABLE XIV. Products from Methyl-substituted Pyridazine 1-Oxides and either Phenylmagnesium Bromide or Phenyllithium

Starting material	127			128				129				130	References
	R^1	R^2	R^4	R^1	R^2	R^3	R^4	R^1	R^2	R^3	R^4		
R = H	H	H	H	H	H	H	H	H	H	H	H	3,6-Diphenylpyridazine	129
3-Me	H	H	Me	H	H	H	Me	H	H	H	Me		129
4-Me	H	H	Me	H	H	Me	H	H	H	Me	H		129
5-Me	H	Me	H	H	H	Me	H	H	H	Me	H		129
6-Me	Me	H	H	H	H	H	Me	H	H	H	Me	3-Phenyl-6-methylpyridazine 1-oxide	129
Yield	40–50%			10–15%				15–20%				ca. 5%	

TABLE XV. Photochemical Reactions of Pyridazine Oxides



131 132 133 134

	Yield (%)	Yield (%)	Yield (%)
a: $R^1 = R^2 = H$	6.2 (recov. 21.3)		
b: $R^1 = H$; $R^2 = Me$	18.9	0.02	
c: $R^1 = R^2 = Me$	10.9	0.5	
d: $R^1 = Cl$; $R^2 = Me$	25.3	7.0	0.2
e: $R^1 = OMe$; $R^2 = Me$	9.0	1.1	0.2

TABLE XVI. Reaction with Benzaldehyde

Reaction temperature	100° C	65° C		40° C		
Product	**141**	**141**	**139**	**141**	**140**	**139**
Starting material pyridazine 1-oxide						
3-Me (**139a**)	36%	13.5%	68%			82%
4-Me (**139b**)	75%	51%		14.5%	58%	6%
5-Me (**139c**)	Resinous	58%		32%	28%	26%
6-Me (**139d**)	51%	53%			36%	50%

TABLE XVII. Reaction with Amyl Nitrite

Product pyridazine 1-oxide	Starting material pyridazine 1-oxide	Yield (%)	References
3-CH:NOH (α)	3-Me	34.9	145
3-CH:NOH (β)		16.3 } 51.2	
4-CH:NOH (α)	4-Me	31.0	145
4-CH:NOH (β)		36.4 } 67.4	
5-CH:NOH (α)	5-Me	69.8	145
5-CH:NOH (β)		7.2 } 76.0	
6-CH:NOH (α)	6-Me	48.9	145
6-CH:NOH (β)		11.5 } 60.4	
3,6-(CH:NOH)$_2$	3,6-(Me)$_2$	6.6	145
4-Cl-6-CH:NOH (β)	4-Cl-6-Me	37.8	145
	3,4-(Cl)$_2$-6-Me	Decomposed	145
3-MeO-4-Cl-6-CH:NOH (α)	3-MeO-4-Cl-6-Me	44.6	145
3-AmO-4-Cl-6-CH:NOH (α)		10.8 } 55.4	

TABLE XVIII. Relative Rate of Deuterium Exchange in 1% NaOD–D_2O

Pyridazine	20° C, 22 hr	50° C, 1 hr	100° C, 1 hr	125° C, 1 hr	140° C, 1 hr
3-Me			40%	90%	Completed
4-Me			90%	Completed	
3-Me-1-O	20%	40%	Completed		
4-Me-1-O	20%	40%	Completed		
5-Me-1-O	40%	70%	Completed		
6-Me-1-O	50%	90%	Completed		

TABLE XIX. Reduction

Starting material pyridazine 1-oxide	Reagents		H_2 (moles)	Product pyridazine	Yield (%)	References
	Catalyst	Adjuvant				
3-NO_2	Pd–C (20%)	MeOH, HCl	4	3-NH_2		149
	Pd–C (20%)	MeOH	2	3-NHOH-1-O	76	149
	Pd–C (20%)	MeOH	3	3-NHOH-1-O	21	149
				3-NH_2	10	
				3-NH_2-1-O	32	
3-NHOH	Pd–C (20%)	MeOH	1	3-NH_2	12	149
				3-NH_2-1-O	43	
4-NO_2	Pd–C (20%)	MeOH, 5% HCl	4	4-NH_2		150
	Pd–C (20%)	MeOH	3	4-NH_2-1-O	44	150
	Raney Ni	MeOH, AcOH	4	4-NH_2	59	150
	Pd–C (10%)	MeOH	3	4-NH_2-1-O	89	151
	Raney Ni	MeOH, AcOH	4	4-NH_2	75	151
4-NO_2-6-Me	Pd–C (10%)	MeOH	3	4-NH_2-6-Me-1-O	87	151
	Raney Ni	MeOH, AcOH	4	4-NH_2-6-Me	70	151
	Pd–C (10%)	MeOH	3	4-NH_2-6-Me-1-O	62	140
3-MeO-4-NO_2	Pd–C	MeOH	3	3-MeO-4-NH_2-1-O		161
	Raney Ni	MeOH	4	3-MeO-4-NH_2	61	161
3,6-$(Me)_2$-4-NO_2	Pd–C (10%)	MeOH	3	3,6-$(Me)_2$-4-NH_2-1-O	80	151
	Raney Ni	MeOH, AcOH	4	3,6-$(Me)_2$-4-NH_2	91	151
3-MeO-4-NO_2-6-Me	Pd–C (10%)	MeOH	3	3-MeO-4-NH_2-6-Me-1-O	90	151
	Raney Ni	MeOH	4	3-MeO-4-NH_2-6-Me	70	151
3,6-$(MeO)_2$-4-NO_2	Pd–C (10%)	EtOH	3	3,6-$(MeO)_2$-4-NH_2-1-O	95	160
3-MeO-4-NO_2-6-NH_2	Pd–C (20%)	5% HCl	2	3-MeO-4-NHOH-6-NH_2-1-O	39	163

TABLE XIX (*continued*)

Starting material pyridazine 1-oxide	Reagents		H_2 (moles)	Product pyridazine	Yield (%)	References
	Catalyst	Adjuvant				
	Pd–C (20%)	10% HCl	3	3-MeO-4,6-$(NH_2)_2$-1-O		163
	Raney Ni	90% EtOH, AcOH	4	3-MeO-4,6-NH_2	85	163
5-NO_2	Pd–C (20%)	50% MeOH, HCl	4	5-NH_2		149
3-MeO-6-NO_2	Pd–C	EtOH	3	3-MeO-6-NH_2-1-O		161
3-MeO-4-Me-6-NO_2	Raney Ni	EtOH, AcOH	4	3-MeO-6-NH_2	92	165
	Pd–C (5%)	MeOH	3	3-MeO-4-Me-6-NH_2-1-O		165
	Raney Ni	MeOH, AcOH		3-MeO-4-Me-6-NH_2		165
3-MeO-4-NO_2-6-Cl	Pd–C (9%)	EtOH	4	3-MeO-4-NH_2-1-O	54	166

TABLE XX. Reaction of Substituted Nitropyridazine 1-Oxide with Acetyl Chloride

Product pyridazine 1-oxide	Starting material pyridazine 1-oxide	Reaction conditions		Yield (%)	References
		Temperature	Time (hr)		
3-Cl	3-NO_2	35°C	3	2	149
		Reflux	9	81	149
4-Cl	4-NO_2	35°C	3	76	150
3-Me-4-Cl	3-Me-4-NO_2	Room	0.5	70	141
4-Cl-5-Me	4-NO_2-5-Me	Room	0.5	30	141
4-Cl-6-Me	4-NO_2-6-Me	Room	2	0.7	141, 140
4-Cl-6-CH:NOH				27	
3,6-$(Me)_2$-4-Cl	3,6-$(Me)_2$-4-NO_2	Room	0.15	41	179
3,6-$(Me)_2$-4-Cl	3,6-$(Me)_2$-4-NO_2	Room	2	11.9	141
3-Me-4-Cl-6-CH:NOH				38	
3-MeO-4-Cl-6-Me	3-MeO-4-NO_2-6-Me	Room	1	15, 21.4	141, 140
3-MeO-4-Cl-6-CH:NOH				29, 26.4	
3,4-$(Cl)_2$-6-Me	3-Cl-4-NO_2-6-Me	Reflux	0.5	15.7	141
3,4-$(Cl)_2$-6-CH:NOH				49	
3,6-$(MeO)_2$-4-Cl	3,6-$(MeO)_2$-4-NO_2	Room	1	66	160
3-MeO-4,6-$(Cl)_2$	3-MeO-4-NO_2-6-Cl	Reflux	0.5	18	166
3-MeO-4-Cl-6-AcNH	3-MeO-4-NO_2-6-AcNH	Reflux	1.5	74	163
3-Me-5-Cl	3-Me-5-NO_2	Reflux	5	63	144
3-Me-5-Cl	3-Me-5-NO_2	30°C	0.5	2	
3,6-$(Me)_2$-5-Cl	3,6-$(Me)_2$-5-NO_2	35°C	2.5	9	144
3-Me-5-Cl-6-CN				60	

TABLE XXI. Reaction of Substituted Pyridazine 1-Oxides with Hydrogen Halides

Product pyridazine 1-oxide	Starting material pyridazine 1-oxide	Reaction conditions		Yield (%)	References
		Temperature (°C)	Time (hr)		
4-Br	4-NO_2	100	4	52	167
4-Cl-6-Me	4-NO_2-6-Me	100	2	54	141
3-MeO-4-Cl-6-Me	3-MeO-4-NO_2-6-Me	100	2	48	140
3-MeO-4-Cl-6-NH_2	3-MeO-4-NO_2-6-NH_2	100	8	60–70	163
3-EtO-4-Cl-6-NH_2	3-EtO-4-NO_2-6-NH_2	100	8	60–70	163
3-PrO-4-Cl-6-NH_2	3-PrO-4-NO_2-6-NH_2	100	8	60–70	163
3-BuO-4-Cl-6-NH_2	3-BuO-4-NO_2-6-NH_2	100	8	60–70	163
3-Me-5-Cl	3-Me-5-NO_2	100	0.5	14	144
3,6-$(Me)_2$-5-Cl	3,6-$(Me)_2$-5-NO_2	35	2.5	9	144
3-Me-5-Cl-6-CN				60	
	3-MeO-5-NO_2	100	0.5	Rec. 76	144
3-MeO-4-Cl	3-MeO-4-NO_2			47	159
3-MeO-4-Cl-5-Me	3-MeO-4-NO_2-5-Me	90	2	59	159
3-OH-4-Cl	3-OH-4-NO_2	90	2.5	47	159
3-OH-4-Cl-5-Me	3-OH-4-NO_2-5-Me	90	2.5		159
3-OH-4-Cl-6-Me	3-OH-4-NO_2-6-Me	100	3	43	159
3-MeO-4,6-Cl_2	3-MeO-4,6-$(NO_2)_2$			68	159
3-MeO-4,6-Cl_2-5-Me	3-MeO-4,6-$(NO_2)_2$-5-Me	90	2.5	55	159
3-MeO-5-Me-6-Cl	3-MeO-5-Me-6-NO_2	90	2	77	159
3-OH-4-Me-6-Cl	3-OH-4-Me-6-NO_2	100	3	86	159

TABLE XXII. Substitution with Sodium Methoxide and Phenoxide

Product pyridazine 1-oxide	Position of reacted site	Reaction temperature	Yield (%)	References
3-MeO	3	30° C	15	149
3,4-$(MeO)_2$	4	Reflux	58	161
3,4-$(MeO)_2$-6-Me	4	Reflux	40	151
	4	Reflux	76	140
	4	Room	73	144
	3-Cl-4-NO_2	Reflux	28	140
3,4,6-$(MeO)_3$	4	Reflux	78	160
	4,6	Reflux		161
3,5-$(MeO)_2$	5	Room	87	144
3,5-$(MeO)_2$-4-Me	5	Reflux	70	144
3,6-$(MeO)_2$-4-Me	6	Reflux	70	165
4-MeO	4	Room	64.2	150
4-MeO-6-Me	4	Reflux	30	150
4-MeO-6-Me	4	Reflux	37	140
	4	Reflux	0.4	151
5-MeO-3-Me	5	Room	74	144
3,6-$(MeO)_2$-4-EtO	4	Room		169
3-PhO	3	100° C	50	149

TABLE XXIII. Dehalogenation

Product pyridazine 1-oxide	Position of reaction site	Catalyst	Adjuvant	H_2 (moles)	Yield (%)	References
3-MeO	6	Pd–C (6%)	EtOH–NH_4OH	1	38	174
3-EtO	6	Pd–C (6%)	EtOH–NH_4OH	1	64	174
3-PrO	6	Pd–C (6%)	EtOH–NH_4OH	1	37	174
3-OH	4	Pd–C (10%)	1% NaOH	1	54	141
3-OH-6-COOH	4	Pd–C (10%)	5% NaOH	1	49	141
4-Me	3	Pd–C (10%)	MeOH–NH_3	1	22	170
4-MeO	3,6	Pd–C (10%)	MeOH–NH_4OH	2	85	150
5-Me	3	Pd–C (10%)	MeOH–NH_3	1	37	170
5-MeO	3,4	Pd–C (7%)	MeOH–NH_4OH	2	85	173
5-NH_2	3,4	Pd–C (8.5%)	MeOH–NaOH	2	84	167
6-Me	3	Pd–C (10%)	NH_4OH	1	80	171
6-NH_2	3	Pd–C (13%)	EtOH–NaOH	1	78	172
6-$NHCO_2Et$	3	Pd–C (20%)	EtOH–NH_4OH	1	98	172

TABLE XXIV. Reaction with Sodium Alkoxides

Starting material pyridazine 1-oxide	Product pyridazine 1-oxide	Reagent	Reaction temperature	Yield (%)	References
3-Cl	3-MeO	NaOMe	Room	79	178
3-Cl-6-Me	3-MeO-6-Me	NaOMe	Reflux	70	171
3-Cl-4-NO_2-6-Me	3,4-$(MeO)_2$-6-Me	NaOMe	Reflux	28	140
3,6-$(Cl)_2$	3-MeO-6-Cl	NaOMe			176
3,6-$(Cl)_2$	3-MeO-6-Cl	NaOMe	17° C	80	174
	3-Cl-6-MeO			7.5	
3,6-$(Cl)_2$	3-EtO-6-Cl	NaOEt	16° C	72	174
	3-Cl-6-EtO			11	
3,6-$(Cl)_2$	3-PrO-6-Cl	NaOPr		57	174
3,6-Cl_2-4-MeO	3,4,6-$(MeO)_3$	NaOMe	Reflux	8	150
4-Cl	4-MeO	NaOMe	Reflux	96	150
4-Cl-6-Me	4-MeO-6-Me	NaOMe	Reflux	33	140
3,6-Me_2-4-Cl	3,6-Me_2-4-MeO	NaOMe	100° C	82	179
3-MeO-4-Cl-6-OH	3,4-$(MeO)_2$-6-OH	NaOMe	150–160° C	19	193
3-MeO-4-Cl-6-NH_2	3,4-$(MeO)_2$-6-NH_2	NaOMe	Reflux	73	163
3,6-$(MeO)_2$-4-Cl	3,4,6-$(MeO)_3$	NaOMe			162
3-MeO-4,6-Cl	3,4-$(MeO)_2$-6-Cl	NaOMe	Room	47	166
4,6-Br_2-5-OH	Recovered	NaOMe	100–120° C		201
3-Me-5-Cl-6-CN	3-Me-5-MeO-6-CN	NaOMe	Reflux	75	144
3,6-Me_2-5-Cl	3,6-Me_2-5-MeO	NaOMe	100° C	87	179
6-Cl	6-MeO	NaOMe	30° C	84	178
3-MeO-5-Me-6-Cl	3,6-$(MeO)_2$-5-Me	NaOMe	Reflux		168
	3-MeO-5-Me-6-OH				
3,4-$(MeO)_2$-6-Cl	3,4,6-$(MeO)_3$	NaOMe	Reflux		165
3-EtNH-6-Cl	3-EtNH-6-EtO	NaOEt	100° C		174

TABLE XXV. Reaction with Amines

Starting material pyridazine 1-oxide	Product pyridazine 1-oxide	Reagent	Reaction temperature	Yield (%)	References
3-Cl	3-EtNH	$EtNH_2$	100° C	72	178
3,6-Me_2-4-Cl	3,6-Me_2-4-EtNH	$EtNH_2$	120–130° C	10.5	179
3,6-Me_2-5-Cl	3,6-Me_2-5-EtNH	$EtNH_2$	120–130° C	85	179
6-Cl	6-EtNH	$EtNH_2$	100° C	79	178
3-EtO-6-Cl	3-EtO-6-EtNH	$EtNH_2$	150° C		174
3,6-Cl_2	3-EtNH-6-Cl	$EtNH_2$	100° C	54	174
	3-Cl-6-EtNH			14	
3,6-Cl_2	3-$C_5H_{10}N$-6-Cl	$C_5H_{10}NH$	100° C	65	174
	3,6-$(C_5H_{10}N)_2$				

TABLE XXVI. Reaction with Nucleophiles Other than Alkoxides and Amines

Product pyridazine 1-oxide	Starting material pyridazine 1-oxide	Reagent	Reaction temperature	Yield (%)	References
3-OH	3-Cl	NaOH	100° C		175
3-N_3		NaN_3	100° C	44	184
3-N_3		$(NH_2)_2$, HNO_2		57	149
3-NH_2		NH_3	120° C	29	149
3-NHOH		NH_2OH	Reflux		149
3-OH-6-Me	3-Cl-6-Me	NaOH	100° C	50	171
3-MeS-5,6-$(CH_2)_4$	3-Cl-5,6-$(CH_2)_4$	NaSMe	Reflux	68	185
4-OH	4-Cl	NaOH	100° C	24	150
4-N_3		NaN_3	100° C	51	186
3-Me-4-MeO-6-COOH	3-Me-4-Cl-6-CN	MeOH–NaOH	100° C		141
3-Me-4-Cl-6-COOH	3-Me-4-Cl-6-CN	Dilute NaOH	100° C		141
3-OH-4-Cl-6-COOH	3-MeO-4-Cl-6-CN	Dilute NaOH	100° C		141
3-MeO-6-OH	3-MeO-6-Cl	AcOH, AcONa	160° C	55	176
3-OH-4,6-$(SH)_2$	3-OH-4,6-Br_2	KSH in DMF	Reflux		159
3-OH-5-Me-4,6-$(SH)_2$	3-OH-5-Me-4,6-Br_2	KSH in DMF	Reflux	75	159
3-OH-4-Me-6-SH	3-OH-4-Me-6-Br	KSH in DMF	Reflux	33	159
3-OH-6-Me-4-SH	3-OH-4-Br-6-Me	KSH in DMF	Reflux	47	159

TABLE XXVII. Dealkylation with Acid or Alkali

Product pyridazine 1-oxide	Starting material pyridazine 1-oxide	Reagent	Reaction temperature	Yield (%)	References
3-OH	3-MeO	5% NaOH	100° C	74	187
3-OH-5-Me	3-MeO-5-Me	5% NaOH	80° C	74	159
3-OH-6-Me	3-MeO-6-Me	5% NaOH	100° C	77	171
3-OH-4-Me	3-MeO-4-Me	10% NaOH	100° C	60	165
3-OH-4-Cl-6-CN	3-MeO-4-Cl-6-CH:NOAc	Pyridine	Reflux		141
3-OH-4-Cl	3-MeO-4-Cl	5% NaOH	80° C	44	159
3-OH-4,6-Cl_2	3-MeO-4,6-Cl_2	5% NaOH	80° C	59	159
3-OH-4-Me-6-Cl	3-MeO-4-Me-6-Cl	5% NaOH	100° C	53	159
3-OH-4-Cl-5-Me	3-MeO-4-Cl-5-Me	5% NaOH	80° C	59	159
3-OH-5-Me-6-Cl	3-MeO-5-Me-6-Cl	5% NaOH	80° C	64	159
3-OH-4-Cl-6-Me	3-MeO-4-Cl-6-Me	5% NaOH	100° C	64	159
3-OH-5-Me-4,6-Cl_2	3-MeO-5-Me-4,6-Cl_2	5% NaOH	80° C		159
3-MeO-6-OH	3,6-$(MeO)_2$	$NH_2NH_2H_2O$ in MeOH	Reflux	100	193
3-MeO-4-Me-6-OH	3,6-$(MeO)_2$-4-Me	2 *N* HCl	80–90° C	64	165
3-MeO-4-Cl-6-OH	3,6-$(MeO)_2$-4-Cl	$NH_2NH_2H_2O$ in EtOH			193
3,4-$(MeO)_2$-6-OH	3,4,6-$(MeO)_3$	10% HCl	100° C	95	150
4-OH	4-MeO	5% NaOH in MeOH	Reflux	64	150
3,6-$(Me)_2$-4-OH	3,6-$(Me)_2$-4-MeO	5% NaOH	100° C	80	179
3,6-$(Me)_2$-5-OH	3,6-$(Me)_2$-5-MeO	5% NaOH	100° C	70	179

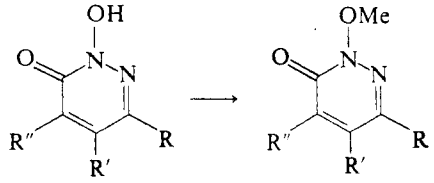
TABLE XXVIII. Reaction with Alkyl Halides or Haloketones

Product 6(1*H*)pyridazinone	Starting material pyridazine 1-oxide	Reagent	Reaction temperature	Yield (%)	References
1,3-$(MeO)_2$	3,6-$(MeO)_2$	MeI	100°C	70	189
1-MeO-3-EtO	3,6-$(EtO)_2$	MeI	Reflux	60	189
1,3-$(MeO)_2$-4-Me	3,6-$(MeO)_2$-4-Me	MeI	Reflux	75	189
1-MeO-3-EtO-4-Me	3,6-$(EtO)_2$-4-Me	MeI	Reflux	60	189
1-EtO-3-MeO	3,6-$(MeO)_2$	EtI	100°C	81	189
1,3-$(EtO)_2$	3,6-$(EtO)_2$	EtI	Reflux	72.5	189
1-EtO-3-MeO-4-Me	3,6-$(MeO)_2$-4-Me	EtI	100°C	84	189
1,3-$(EtO)_2$-4-Me	3,6-$(EtO)_2$-4-Me	EtI	Reflux	93	189
1-$PhCH_2O$-3-MeO	3,6-$(MeO)_2$	$PhCH_2Cl$	150–155° C	74	189
1-$PhCH_2O$-3-EtO	3,6-$(EtO)_2$	$PhCH_2Cl$	145–155° C	92	189
1-$PhCH_2O$-3-MeO-4-Me	3,6-$(MeO)_2$-4-Me	$PhCH_2Cl$	145–155° C	75	189
1-$PhCH_2O$-3-EtO-4-Me	3,6-$(EtO)_2$-4-Me	$PhCH_2Cl$	145–155° C	63	189
1-$PhCOCH_2O$-3-MeO	3,6-$(MeO)_2$	$PhCOCH_2Br$	95–100° C	83	189
1-$PhCOCH_2O$-3-EtO	3,6-$(EtO)_2$	$PhCOCH_2Br$-$CHCl_3$	Reflux	53	189
1-$PhCOCH_2O$-3-MeO-4-Me	3,6-$(MeO)_2$-4-Me	$PhCOCH_2Br$	95–100° C	35	189
1-$PhCOCH_2O$-3-EtO-4-Me	3,6-$(EtO)_2$-4-Me	$PhCOCH_2Br$	95–100° C	60	189

TABLE XXIX. Dealkylation with Organic Acyl Chlorides

Product 6(1*H*)pyridazinone	Starting material pyridazine 1-oxide	Reagent	Reaction temperature	Yield (%)	References
1-AcO-3-MeO	3,6-$(MeO)_2$	AcCl	Room	95.5	162
1-AcO-3-EtO	3,6-$(EtO)_2$	AcCl	Room	92	162
1-AcO-3-MeO-4-Me	3,6-$(MeO)_2$-4-Me	AcCl	Room	78	162
1-AcO-3-EtO-4-Me	3,6-$(EtO)_2$-4-Me	AcCl	Room	95	162
1-BzO-3-MeO	3,6-$(MeO)_2$	BzCl	Room	82.5	162
1-BzO-3-EtO	3,6-$(EtO)_2$	BzCl	Room	80	162
1-Bz-3-MeO-4-Me	3,6-$(MeO)_2$-4-Me	BzCl	Room	77	162
1-BzO-3-EtO-4-Me	3,6-$(EtO)_2$-4-Me	BzCl	Room	66	162
1-AcO-3-MeO-4-Cl	3,6-$(MeO)_2$-4-Cl	AcCl	Room	90	162

TABLE XXX. *O*-Methylation of 1-Hydroxy-6-pyridazinones



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	Reaction conditions	Yield (%)	References
a: R = MeO, R′ = H, R″ = H	MeI, Ag_2O in MeOH	100	176
b: R = MeO, R′ = Me, R″ = H	MeI, Ag_2O in MeOH	92	165
c: R = MeO, R′ = H, R″ = Me	MeI, Ag_2O in MeOH	57	165
d: R = R′ = MeO, R″ = H	R_2SO_4, 20% NaOH in MeOH	87	193
e: R = MeO, R′ = Cl, R″ = H	Me_2SO_4, 20% NaOH in MeOH	81	193
a: R = MeO, R′ = R″ = H,	$PhCH_2Cl$, NaOMe	52	176
a: R = MeO, R′ = R″ = H,	PhCOCl, pyridine	75	144

TABLE XXXI. Synthesis of Halopyridazine 1-Oxides through Diazonium Compounds

Product pyridazine 1-oxide	Starting material pyridazine 1-oxide	Reagents	Yield (%)	References
3-Br	3-NH_2	47% HBr, $NaNO_2$	8	167
4-Br	4-NH_2	24% HBr, $NaNO_2$, Cu	63	167
3,6-Me_2-4-Cl	3,6-Me_2-4-NH_2	18% HCl, $NaNO_2$, Cu	55	179
3,4,5-Cl_3	3,5-Cl_2-4-NH_2	35% HCl, $NaNO_2$	36	167
5-Cl	5-NH_2	27% HCl, $NaNO_2$	31	167
5-Br	5-NH_2	47% HBr, $NaNO_2$	40	167
3,4,5-Cl_3	5-NH_2-3,4-Cl_2	35% HCl, $NaNO_2$	37	167
6-Cl	6-NH_2	35 HCl, $NaNO_2$, Cu	61	178
3,6-Cl_2	6-NH_2-3-Cl	Conc. HCl, $NaNO_2$		196

TABLE XXXII. Azidopyridazine 1-Oxides

Product pyridazine 1-oxide	Method	Yield (%)	Characteristics	References
3-N_3	1			149
	1	60	Insensitive to sunlight	184
	2 (100° C)	44		184
3-N_3-6-Cl	2	19		184
4-N_3	1	48	Sensitive to sunlight	186
	2 (100° C)	51	4-NH_2-1-oxide (4%) as by-product	186
4-N_3-3,6-$(MeO)_2$	3		Very hygroscopic, explosive	193
5-N_3	1	70	Stable under light	186
6-N_3	1		Sensitive to sunlight	186

TABLE XXXIII. Substitution with Alkoxides

Starting material pyridazine 1-oxide	Reagent	Reaction	Product pyridazine 1-oxide	Yield (%)	References
3-N_3	NaOMe	100° C	3-MeO	80	184
	NaOEt	Room temp.	3-EtO	67	184
	$NaOCH_2Ph$	Room temp.	3-$PhCH_2O$	53	184
4-N_3	NaOMe	100° C	4-MeO	74	186
	$NaOCH_2Ph$	100° C	4-$PhCH_2O$	71	186
5-N_3	NaOMe	100° C	5-MeO	63	186
	$NaOCH_2Ph$	100° C	5-$PhCH_2O$	51	186
6-N_3	NaOMe	Room temp.	6-MeO	50	184
	NaOEt	Room temp.	6-EtO	40	184
	$NaOCH_2Ph$	Room temp.	6-$PhCH_2O$		184
4-N_3-3,6-$(MeO)_2$	NaOMe	Reflux	3,4,6-$(MeO)_3$	38	193
			1-OH-3,4-$(MeO)_2$-6-O	14	

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CHAPTER IX

Sulfur Compounds of Pyridazines

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I. Pyridazinethiones and Pyridazinethiols

A. Introduction

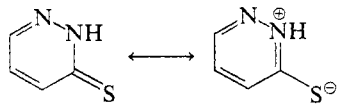
Pyridazines with one or more mercapto groups attached to the ring carbons of the pyridazine ring are usually referred to as mercaptopyridazines. This designation originates from earlier chemical evidence that azines with a mercapto group display reactions typical of thiols. Extensive investigations on the problem of prototropic tautomerism of heterocyclic compounds with potential mercapto groups have been reviewed by Katritzky and Lagowski (1). It is now firmly established that mercapto groups ortho or para to a ring nitrogen in pyridazines exist in the thioxo form. Details about structure investigations on such pyridazines are discussed later in this chapter (Section I.B). For mercaptopyridazines, thione structures are generally used in this chapter, and the compounds are referred to as pyridazinethiones. When additional mercapto groups are present, compounds are represented as mercaptopyridazinethiones, although in many cases compounds were simply designated polymercaptopyridazines.

B. Structure

The detailed structure of pyridazinethiones has been examined spectroscopically and by x-ray analysis.

An x-ray structure analysis of 3(2*H*)pyridazinethione revealed that the compound exists in the solid state in the thione form and that the planar molecules form dimers through N—H · · · S bonds (2).

Further evidence for the thione form in solution has been gained from spectroscopic data and ionization constants. Ultraviolet (uv) spectra of 3(2*H*)pyridazinethione and 4(1*H*)pyridazinethione were compared with those of their *N*- and *S*-methyl derivatives and with their anions and cations (3). The results were interpreted by Albert and Barlin in terms of the preponderance of the thione form. However, it should be pointed out that these forms are resonance hybrids and that contribution of the dipolar form is appreciable (**1**). It is well known that the nitrogen lone pair of electrons in thioamides is more delocalized than in the corresponding amides. Pyridazinethiones



1

represent a six π-electron aromatic system capable of sustaining an induced ring current (4). The ratio of the thione and thiol tautomers has been calculated for 4(1*H*)pyridazinethione (R = 10,000) (3).

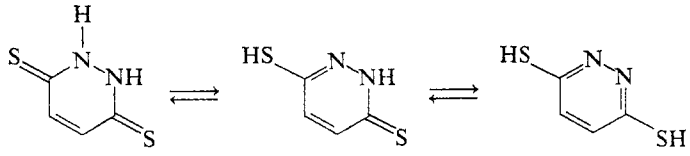
Ionization constants for 3(2*H*)pyridazinethione and 4(1*H*)pyridazinethione and their methyl derivatives, determined spectrophotometrically (3), are listed in Table I.

Pyridazinethiones are weaker bases than the corresponding pyridazinones and this is also observed for the *N*-methyl derivatives. There are only slight differences between the methylthio and methoxy derivatives, the methylthiopyridazines being slightly weaker bases (3). For pyridazine-3(2*H*)thione π-bond order bond length relations have been determined, and for this and other π systems with C—S bonds empirical resonance integral parameters were derived (174).

The structure of 3,6-disubstituted pyridazines that contain two equal or different potential tautomeric groups, such as mercapto, hydroxy, or amino, has been studied by spectrophotometric methods.

For 6-mercapto-3(2*H*)pyridazinethione three tautomeric forms (**2a–c**) can be written (the contribution of resonance forms is neglected).

Formerly, each of these forms had been proposed: dithione (5), dithiol (6), and thiol-thione (7). Compound **2** exhibits in its infrared (ir) spectrum

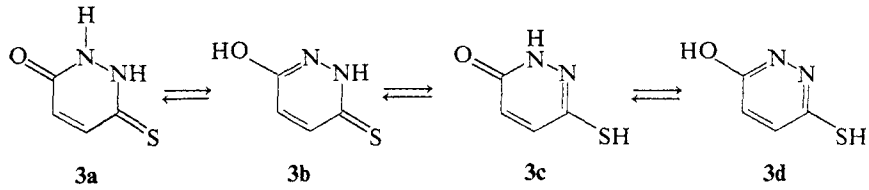


2a **2b** **2c**

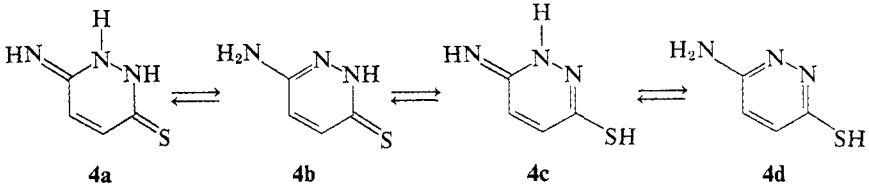
an intense band at 2350–2360 cm^{-1} (8–10), assignable to a mercapto group. Spectroscopic evidence from uv spectra of its cationic, neutral, and anionic form and comparison with some related model compounds in which the mobile proton had been substituted by an immobile methyl group indicated that the structure of **2** is thione-thiol (**2b**) rather than dithione or dithiol (8).

For the assignment of the preponderant form of 6-hydroxy-3(2*H*)pyridazinethione and 6-amino-3(2*H*)pyridazinethione, similar studies were performed by Fujisaka et al (11). Each of these compounds is capable of existing in four tautomeric forms (**3a–d** and **4a–d**). The results indicate that for the first compound the hydroxythione form (**3b**) predominates and that for the second one there is strong evidence for the preponderance of the aminothione form (**4b**).

Spectrophotometrically determined pK_a values for some of these 3,6-disubstituted pyridazines with potentially tautomeric groups and for some derivatives thereof are listed in Table II.



3a **3b** **3c** **3d**



4a **4b** **4c** **4d**

Structure investigations on pyridazines having more than two potential tautomeric mercapto or other groups are completely lacking. By analogy with the simpler analogs, the most probable preponderant forms for some polyfunctional sulfur-containing pyridazines can be represented with formulas **5–9**.

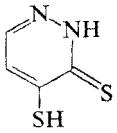
Reduced pyridazinethiols exist as true thiols. For hexahydropyridazine-4-thiols absorption frequencies typical of thiols were observed in their ir spectra (12).

C. Preparation

1. *Nuclear Synthesis*

Elaboration of the heterocyclic ring of pyridazinethiones from noncyclic precursors has been recorded in only one case.

N-Phenylthioacetyl benzilmonohydrazone (**12**), obtained in the reaction between benzilmonohydrazone (**10**) and carboxymethyl dithiophenylacetate (**11**), was transformed by heating its ethanolic solution in the presence of sodium ethoxide into 4,5,6-triphenyl-3(2*H*)pyridazinethione (**13**). The latter compound is also obtainable in almost the same yield directly from benzilmonohydrazone (**10**) and carboxymethyl dithiophenylacetate (**11**) when these compounds are heated in the presence of sodium ethoxide (13). It is interesting to note that thiation of 4,5,6-triphenyl-3(2*H*)pyridazinone with phosphorus pentasulfide in toluene gave an inferior yield of **13** (13).



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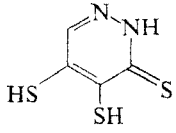

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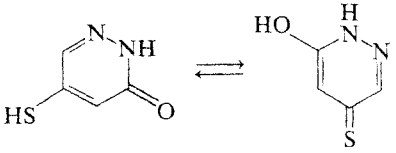

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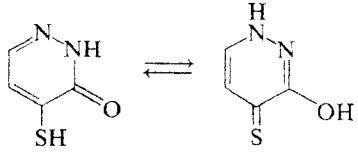

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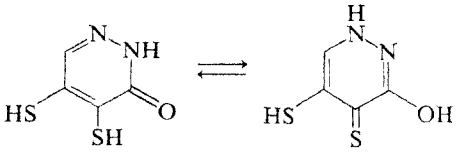

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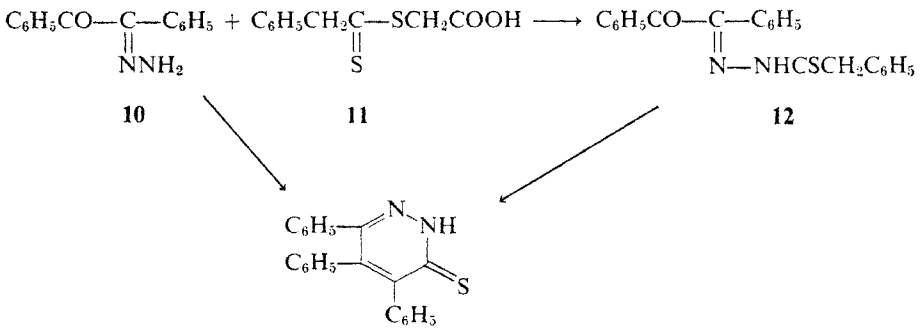


10 **11** **12**

13

2. *From Halopyridazines*

There are several methods that can be used for the displacement of halogen(s) from halopyridazines or halopyridazinones, which have found widespread application.

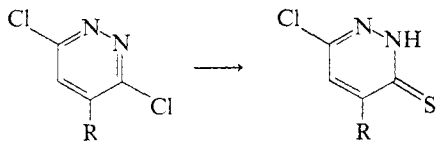
Frequently, the standard method of introducing a thiol group by heating a halopyridazine or halopyridazinone with an alcoholic solution of sodium or potassium hydrogen sulfide at elevated temperature (usually in a sealed tube) has been used to synthesize 3(2*H*)- or 4(1*H*)pyridazinethiones (8, 11, 14–30), or 6-mercapto-3(2*H*)pyridazinethiones (6, 21, 31, 32).

There are many factors that influence this nucleophilic displacement and which have been discussed in detail in a review by Shepherd and Fedrick (33). In addition, some peculiarities observed during syntheses of several pyridazinethiones should be mentioned here. That the displacement of the halogen is influenced by the quantity of potassium hydrogen sulfide used has been demonstrated in the synthesis of 6-methoxy-3(2*H*)pyridazinethione from 3-chloro-6-methoxypyridazine. Under like reaction conditions and with 1 equivalent of potassium hydrogen sulfide, the yield of the thione was low (15%) but could be raised to 40% when 2 equivalents of potassium hydrogen sulfide were used (21).

Polyhalopyridazines display pronounced differences in reactivities of halogens attached to different carbon atoms of the pyridazine nucleus, and this can be very helpful in the stepwise introduction of thiol or thione groups.

In order to replace both chlorine atoms in 3,6-dichloropyridazine, it is necessary to heat the reaction mixture for several hours at temperatures to 140–150° C (6, 34). When the reaction was conducted at room temperature for 2 hr (6) or 1–3 hr at reflux temperature (21), only 6-chloro-3(2*H*)pyridazinethione was obtained. Similar results were observed with 3,6-dibromopyridazine (18).

Asymmetrically substituted pyridazines are expected to afford different isomeric substitution products. Usually, only one isomer has been isolated, for example, **14** (R = Me (21, 23); R = NH_2 (18)). Although in the reaction between 3,6-dichloro-4-methylpyridazine and ethanolic potassium hydrogen



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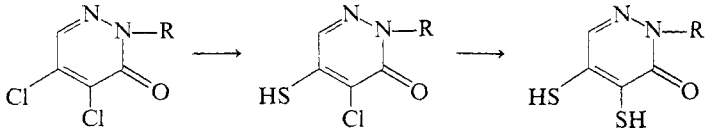
sulfide the position of the introduced thioxo group was not firmly established (21). Takahayashi later concluded that 6-chloro-4-methyl-3(2*H*)pyridazinethione is formed (23).

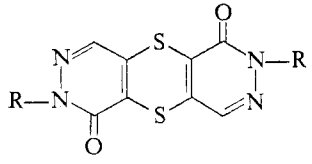
Treatment of 4,5-dichloro-3(2*H*)pyridazinones with alcoholic sodium or potassium hydrogen sulfide solution is reported to replace only the chlorine at position 5 (**15**) (20, 29, 35, 175–177). These monothiols, when heated for



15 **16**

10 hr at higher temperatures and under pressure with the same reagent, afforded the corresponding dithiols (**16**) (35, 175), and similar results were obtained with the 2-phenyl analogs (36, 37). This selectivity can be explained in terms of vinylogy, since a 5-halo-3(2*H*) pyridazinone can be regarded as an activated cyclic vinylog of an acid chloride.

In an attempt to prepare 4,5-dimercapto-3(2*H*)pyridazinone from the 4,5-dichloro compound by the sodium hydrogen sulfide method Castle, Kaji, and Wise (38) isolated the tricyclic dipyridazo[4,5-*b*:4,5-*e*]-1,4-dithiin-1,6-dione (**17**: R = H) in high yield, and similar behavior was observed with the 2-phenyl analog which yielded **17** (R = C_6H_5) (181).



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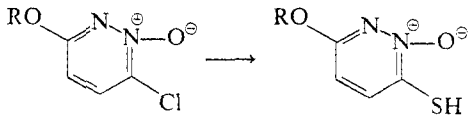
The displacement method with the aid of alkali hydrogen sulfides was also successfully applied to halopyridazine *N*-oxides (39–41, 179, 180). Some compounds reacted with remarkable ease, for example, in the synthesis of **18**, whereas other reactions, as the synthesis of **19**, required refluxing with a solution of potassium hydrogen sulfide in *N*,*N*-dimethylformamide (42, 179) in order to exchange both halogens. These reaction conditions are indicative of the inactivating effect of the oxo group since the starting compound also did not react with amines under the usual reaction conditions. For sulfur-containing pyridazine *N*-oxides, see Table XXXVIII.

It is claimed that 3-acetamido-5-chloro-6-methoxypyridazine is resistant to hot 30% sodium hydrogen sulfide solution, whereas the 3-amino analog



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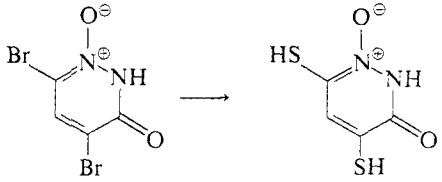

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can be converted to the corresponding thione with the same reagent (120–125° C, 6 hr) (17).

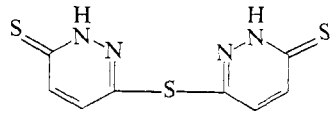
There are no reports that functional groups other than halogens, when present, undergo changes during displacement experiments. Thus alkoxy, amino, sulfonamido, or oxo groups remain unaltered and are not displaced.

The second approach in forming pyridazinethiones from halopyridazines is represented by the thiourea method. A halopyridazine is usually treated with thiourea in an alcoholic solution and the thiuronium salt is thereafter decomposed with base. For the formation of thiuronium salts, thiourea appears to have the required combination of considerable nucleophilicity and a weak basic strength. Thiuronium salts are usually decomposed with a strong base such as an alkali hydroxide. Aqueous sodium carbonate at room temperature has also been tried, but results were poor and often without success (43). The thiourea method was used successfully to prepare 3(2*H*)-pyridazinethiones (14, 43–50) or the corresponding 3,4- (51) and 3,6-thione-thiol analogs (45, 47, 49).

Although it was claimed that 6-amino-3-chloropyridazine does form a thiuronium salt (45), Kumagai and Bando (46) established later that this reaction does not occur, the reason probably being related to the strong resonance effect of the amino group. However, when the acylated analog was treated with thiourea, the corresponding pyridazinethione could be prepared (46).

In an attempt to prepare 6-mercapto-3(2*H*)pyridazinethione by the thiourea method from 3,6-dichloropyridazine, only the sulfide (**20**) was isolated and this most probably results from a two-step transformation (52).

A very useful approach in introducing a thioxo or a thiol group by means of phosphorus pentasulfide in boiling pyridine was introduced by Castle and Kaji (53) and then extended for the preparation of several pyridazinethiones.



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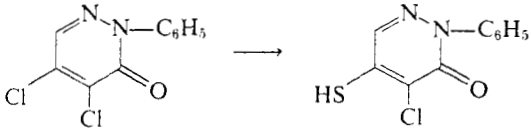
The reaction has been used to prepare different mono- or, particularly in combination with the thiation of oxo groups, polymercaptopyridazines (44, 51, 53, 176, 177). In this connection it should be mentioned that it was observed that commercial grade phosphorus pentasulfide gave 6-methyl-3(2*H*)pyridazinethione from 3-chloro-6-methylpyridazine in better yield than phosphorus pentasulfide previously purified by extraction with carbon disulfide (44).

A comparison of the utility of different methods has been made to evaluate them for the preparation of 4-mercapto-5-amino-3(2*H*)pyridazinethione. The best yield is reported from the reaction between 3,4-dichloro-5-amino-pyridazine and phosphorus pentasulfide in pyridine (64%), whereas the thiourea method or treatment of 4-chloro-5-amino-3(2*H*)pyridazinone with phosphorus pentasulfide in pyridine afforded the final product in low yields (16 and 20%, respectively) (51). Another comparison showed that 3-chloro-6-*n*-propoxypyridazine gave a 55% yield of the corresponding thione by the thiourea method, yet a yield of 87% could be attained by applying the phosphorus pentasulfide–pyridine method (44) Similar differences were observed in the preparation of 6-methyl-3(2*H*) pyridazinethione.

There are some less frequently used methods for the preparation of pyridazinethiones. A solution of sodium sulfide in water (26, 54–56), methanol (57), or pyridine (58) has been used. As with the hydrogen sulfide method, different reactivities were observed in the case of 4,5- or 4,6-dichloro-3(2*H*)pyridazinones. Thus compound **21** gave with sodium sulfide in pyridine at low temperature **22**, and at a higher temperature the remaining halogen could also be displaced (58). Similarly, **23**, when treated with a methanolic solution of sodium sulfide at 40–50° C for several hours, is claimed to afford **24** (57). However, structural proof is lacking.

A particular synthetic approach represents the transformation of 4-amino-3,6-dichloropyridazine. This, when treated with ammonia in a solution containing a mixture of organic solvents and thereafter for 1 hr with carbon disulfide, gave the corresponding 3(2*H*)pyridazinethione derivative in a better yield than the corresponding treatment with an alcoholic solution of potassium hydrogen sulfide (18).

A mercapto group also resulted from a free-radical addition of thioacetic acid to tetrahydropyridazines with subsequent hydrolysis of the thioacetoxy group with 1 *N* ethanolic hydrogen chloride. Few hexahydropyridazine-4-thiols were thus obtained (12).



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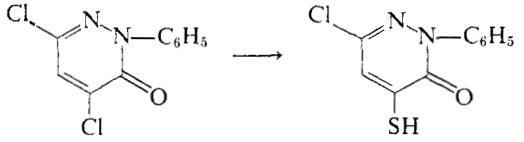

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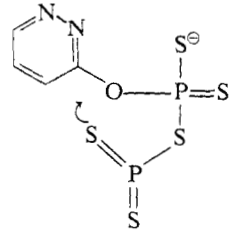
3. *From Pyridazinones*

One of the widely used methods in heterocyclic chemistry for the introduction of thioxo groups by direct displacement of oxygen with sulfur in oxoheterocycles by means of phosphorus pentasulfide has also been successfully applied to many pyridazinones. The most common procedure requires heating of the appropriate 3(2*H*)pyridazinone with phosphorus pentasulfide in a higher-boiling solvent such as toluene (13, 59), xylene (3, 15, 59), or preferentially pyridine (59–64, 178). For the synthesis of 4(1*H*)pyridazinones benzene or pyridine was used as solvent (3). In addition to the basicity and boiling point of the solvent, the solvation capacity is certainly an important factor in the selection of the solvent.

The oxo group is thiated presumably through nucleophilic substitution of a thiophosphoryloxy intermediate, involving an intramolecular mechanism as shown (**25**) (65).

Thiation of 4(1*H*)pyridazinone takes place very easily as judged from the reaction conditions. 4(1*H*)Pyridazinethione is obtained in 95% yield after 4 min of refluxing the pyridine solution of the oxo compound (3).



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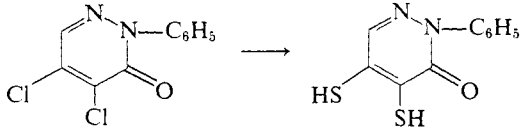
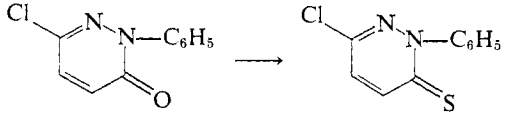
The direct thiation method also has some limitations, as can be concluded from the preparation of 6-methyl-3(2*H*)pyridazinethione (15). Here the synthetic method that utilizes phosphorus pentasulfide in xylene is inferior to the reaction that uses an alkali hydrogen sulfide.

With halopyridazinones simultaneous displacement of both halogen and oxo group generally takes place. Some exceptional cases should be mentioned. Only halogens are displaced when 4,5-dichloro-2-phenyl-3(2*H*)pyridazinone (**26**) is treated with phosphorus pentasulfide in boiling pyridine for 16 hr, and **27** is formed (14, 44). Contrary to this, the 2-unsubstituted analog of **26** undergoes a normal displacement of both halogens and oxygen.



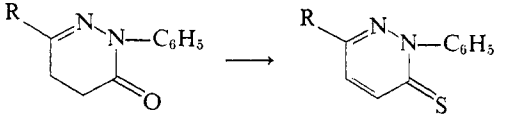
26 **27**

From several thiation experiments with phosphorus pentasulfide, it has been concluded (51) that in halopyridazinones the halogen is displaced more readily than oxygen in the oxo group. As an unverified exception to this observation, compound **28** is claimed to be converted into **29** without any halogen displacement (64).



28 **29**

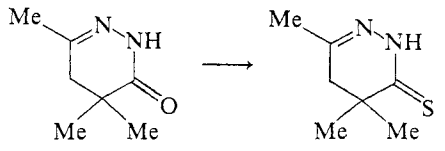
Treatment of some reduced pyridazinones with phosphorus pentasulfide, even under the mildest reaction conditions, can be followed by aromatization. This has been observed in the case of compounds of type **30** (R = Me or Ph) (59), which are transformed into **31**. No aromatization was observed with



30 **31**

the 2-unsubstituted analogs of **30** (66), although the product of another such experiment (28) has a melting point much closer to that of the corresponding aromatic 6-methyl-3(2*H*)pyridazinethione.

When aromatization is impossible, unless changes in structure would occur, only thiation of the oxo group takes place (**32**) (59, 66).



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There were some attempts to prepare pyridazinethiones by means of aluminium sulfide, but the desired products were generally obtained in low yields.

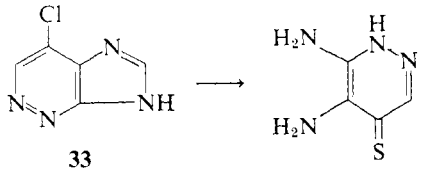
A comparative study with different thiation agents for the synthesis of 6-methyl-3(2*H*)pyridazinethione disclosed the following results. 3-Chloro-6-methylpyridazine, when treated with an alcoholic solution of sodium hydrogen sulfide (150° C, 3 hr), afforded the thione in 53% yield; treatment of 6-methyl-3(2*H*)pyridazinone with phosphorus pentasulfide in boiling xylene (3 hr) gave a 20% yield of the same product, whereas passage of the last-mentioned pyridazinone over heated aluminium sulfide *in vacuo* yielded the thione in less than 10% yield (15).

4. *Other Synthetic Approaches*

Because the methylsulfonyl group is known to be a good leaving group, some reactions have been performed in which this group was displaced with alkali hydrogen sulfide (100° C, 2 hr), and thus 3(2*H*)pyridazinethione was formed in good yield (67). In general, sulfonyl groups in alkyl- and arylsulfonyl heterocycles display high reactivity (68). It should be mentioned that methylsulfonylpyridazines are about 40 to 100 times more reactive toward methoxy ions than are the corresponding chloro compounds (69). The reactivity of such pyridazines is discussed in Section IV.

A *p*-toluenesulfonyl group, for example, in 3-amino-6-*p*-toluenesulfonylpyridazine, has been similarly displaced with an alcoholic solution of sodium hydrogen sulfide (150° C, 8 hr) to form 6-amino-3(2*H*)pyridazinethione (25). However, all these reactions are of limited practical value.

Several pyridazinethiones were obtained from polycyclic systems as a consequence of ring opening during thiation experiments. Thus, in an attempt to prepare the corresponding thione from 7-chloroimidazo[4,5-*c*]pyridazine (**33**) by the phosphorus pentasulfide method, the imidazole ring underwent rupture, and after replacement of the halogen 5,6-diamino-4(1*H*)pyridazinethione (**34**) was obtained in 17% yield (70). The 6-chloro analog of **33** (**35**) reacted similarly with sodium hydrogen sulfide, but here 5,6-diamino-3(2*H*)pyridazinethione (**37**) was obtained (140° C, 8 hr) together with the bicyclic thione (**36**) (71).



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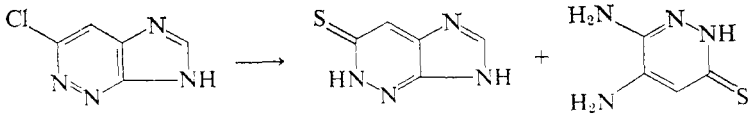
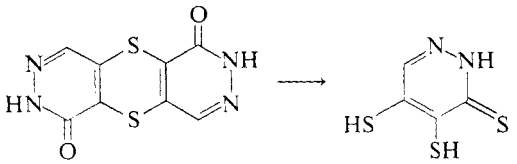


35 36 37

A further example is dipyridazo[4,5-*b*:4,5-*e*]-1,4-dithiin-1,6-dione (**38**), which when allowed to react with phosphorus pentasulfide in boiling pyridine (16 hr) did not afford the corresponding dithione, and 4,5-dimercapto-3(2*H*)pyridazinethione (**39**) was isolated as the sole product in 88% yield (38). The known pyridazinethiones are listed in Tables III–XII.



38 39

D. Reactions

Pyridazinethiones undergo reactions typical of thiols, which are more-or-less common to related heteroaromatic systems.

They are readily oxidized to the corresponding disulfides by means of iodine (45), aqueous ferric chloride (72), potassium permanganate in acetic acid at room temperature (72), or with hydrogen peroxide in acetic acid (7).

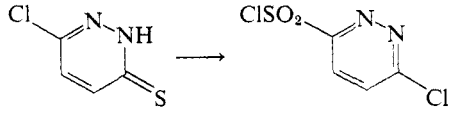
Whereas upon oxidation of 6-chloro-3(2*H*)pyridazinethione with potassium permanganate in acetic acid at room temperature the corresponding disulfide was formed, the same compound was decomposed with potassium permanganate in 5*N* sulfuric acid at room temperature or recovered unchanged with aqueous permanganate at 90° C (72). Similarly, the 4-methyl analog is reported to be recovered unchanged after treatment with potassium permanganate in 5*N* sulfuric acid at room temperature after 15 min (72).

Another report about disulfide formation concerns 6-methyl-3(2*H*)-pyridazinethione which when heated with iodobenzene at 150–160° C did

not form the expected arylthio derivatives, and a small amount of the corresponding disulfide was isolated (73). Here the formation of the disulfide is most probably due either to air oxidation or to iodine, if present, or both. The same disulfide was formed when the starting compound was left to stand for several days in a 5*N* solution of ammonia in ethanol (73). The reaction was certainly due to air oxidation.

The same oxidative action causes the formation of some disulfide obtained along with the expected 3,5,6-triphenyl-4(1*H*)pyridazinethione after treatment of the corresponding 4-bromo compound with an alcoholic potassium hydrogen sulfide solution (22). The thione itself, upon longer exposure to air, is also transformed into the disulfide.

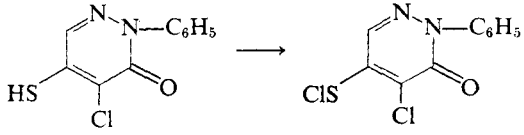
Oxidative chlorination of 6-chloro-3(2*H*)pyridazinethione (**40**) at 0° C in dilute acetic acid afforded a rather unstable sulfonyl chloride (**41**) which was



40 **41**

subsequently transformed into more stable sulfonamides (74). A similar experiment with 6-mercapto-3(2*H*)pyridazinethione failed, and the compound decomposed even at low temperatures.

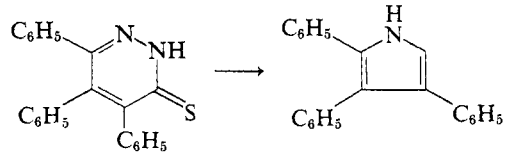
The action of chlorine on 2-phenyl-4-chloro-5-mercapto-3(2*H*)pyridazinone (**42**) is reported to give the corresponding sulfenic acid chloride (**43**) (58), but experimental details are lacking.



42 **43**

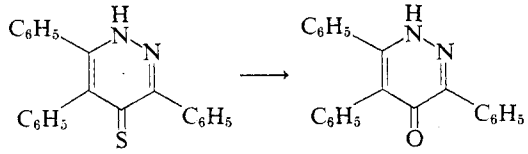
The well-elaborated method of substitution of a thiol or thioxo group with hydrogen by reductive desulfurization with Raney nickel has been successfully applied to pyridazines only in one case. 6-Phenyl-3(2*H*)pyridazinethione gave 3-phenylpyridazine after being treated with Raney nickel in aqueous ammonia solution (59).

In an attempt to desulfurize 4,5,6-triphenyl-3(2*H*)pyridazinethione (**44**) with Raney nickel W6 in boiling ammoniacal ethanol, instead of the expected pyridazine, triphenylpyrrole **45** was isolated (13). Evidently, the final product is formed through a rearrangement, and a mechanism that has been suggested for the ring contraction of related cinnolines into indoles (75) may be operative as well in this case.



44 45

6-Mercapto-3(2*H*)pyridazinethione is not desulfurized with mercuric oxide when heated for 2 hr as a suspension in alcohol or water (8). A replacement of the thioxo group by oxo was shown to be possible with selenium dioxide in acetic acid (10 hr) (**46**) (22).



46

There are only a few cases reported of the displacement of a thioxo group. Ammonolysis proceeded only with difficulty, as exemplified by 6-methyl-3(2*H*)pyridazinethione which, when treated with ammonia in a solution of methanol (100° C, 24 hr), yielded 3-amino-6-methylpyridazine in poor yield (15). Hydrazinolysis of 6-mercapto-3(2*H*)pyridazinethione in a solution of ethanol (reflux temperature, 6 hr) proceeds with greater ease (6, 31, 32, 48, 76), and this method of preparation of 3,6-dihydrazinopyridazine seems to be preferential to hydrazinolysis of 3,6-dichloropyridazine.

There are several other important reactions of pyridazinethiones, such as alkylations, acylations, and addition reactions, but they are considered in the following chapters.

II. Pyridazinyl Sulfides

Pyridazinyl sulfides are obtainable by several general methods, direct alkylation of pyridazinethiones or thiols or treatment of halopyridazines with thiols being the most used methods.

A. Preparation

1. *Nuclear Synthesis*

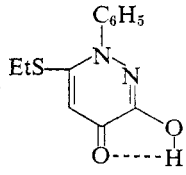
There are only a few examples in which pyridazinyl sulfides have been prepared by direct cyclization reactions.

$$(EtS)_2C{=}CHCOCOCl \longrightarrow (EtS)_2C{=}CHCOCOSEt \longrightarrow$$

47 **48**

$$(EtS)_2C{=}CHCOCONHNHC_6H_5 \longrightarrow$$

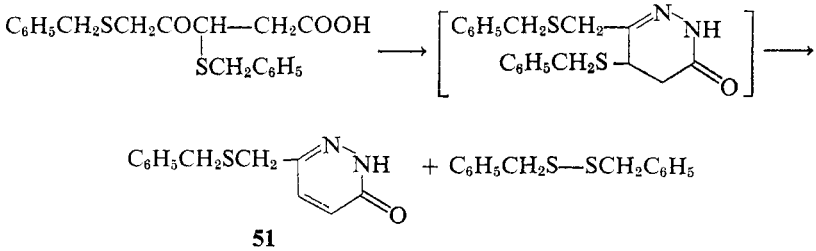
49



50

Compound **50** (or the tautomeric form) is claimed to result from treatment of ketene diethyl mercaptal with oxalyl chloride between −20 and −50° C, and the resulting chloride (**47**) was transformed into the thio ester (**48**) which upon treatment with phenylhydrazine and dilute acid gave **50** via **49**. The structure of the final product (**50**) has not been verified (77).

Another example of a nuclear synthesis is the Huang-Minlon reduction of 3,5-bis(benzylmercapto)levulinic acid, which is claimed to afford a mixture of a pyridazinone (**51**) and dibenzyl disulfide (78).



51

2. *From Halopyridazines*

A widely used method for the preparation of pyridazinyl sulfides involves treatment of halopyridazines with a thiol in the form of its alkali salt, or with a thiol in the presence of a base such as sodium alkoxides, sodium, sodium amide, or sodium hydroxide. The corresponding thiols can also be generated directly in the reaction mixture from thiuronium salts in the presence of alkali (44, 53, 79).

A great variety of thiols was used for these purposes, from simple aliphatic thiols (6, 11, 16, 17, 52, 54, 80–84), α-mercapto acids and derivatives thereof (26, 34, 54, 56, 85–87), *N*,*N*-dialkylaminoalkylthiols (88, 89), cycloalkylthiols (84), arylthiols (16, 52, 54, 83, 90–95, 183, 186, 188), arylalkylthiols (14, 44, 53, 96, 175, 176), heteroaromatic thiols (97, 98, 175),

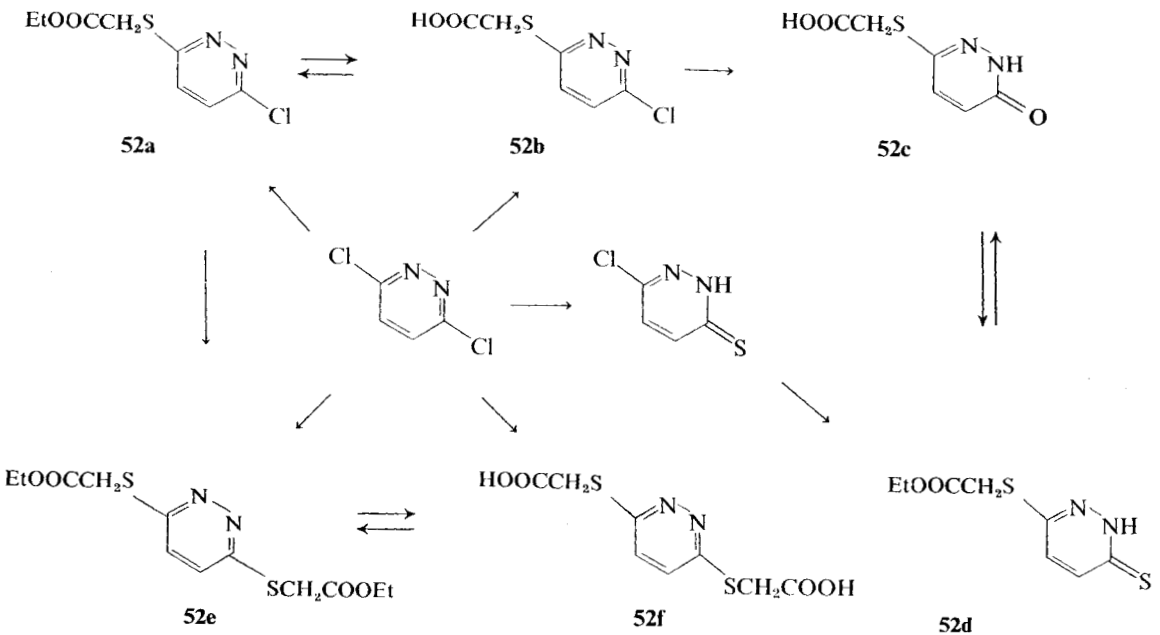
alkylheteroaromatic thiuronium salts (79), or thiols (97) to heterocycles with a thioamide group as a part of the ring (95, 99–101).

In this way many pyridazinyl sulfides were synthesized, those with the sulfide group attached at position 3 (11, 16, 26, 34, 52, 54, 56, 80–83, 86, 87, 95, 96, 98), at position 4 (17, 54, 91, 102, 188), at positions 3 and 6 (6, 52, 83, 86–89, 95, 99–101), at positions 4 and 5 (14, 54, 93), at positions 3, 4, and 5 (53, 54, 93), and at positions 3, 4, 5, and 6 (93). Sulfides of 3(2*H*)pyridazinones were similarly prepared with the sulfide group attached at position 4 (14, 175), at position 5 (92, 94, 175, 176, 186), at position 6 (34, 85, 96), or at positions 4 and 5 (14, 44, 53, 79, 84, 97, 175, 186), as were sulfides of 4(1*H*)pyridazinones with the sulfide group at position 3 (183), and sulfides of 3(2*H*)pyridazinethiones with the sulfide group attached at position 6 (34).

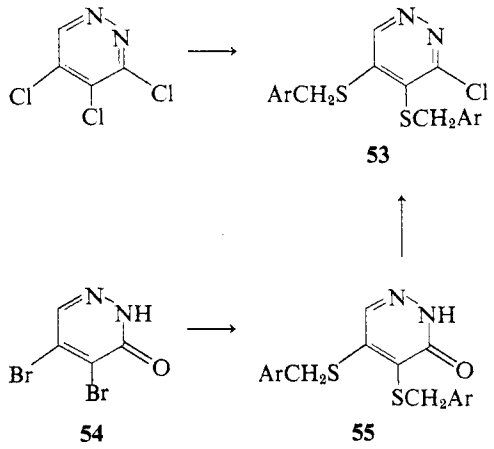
Unfortunately, there are no available data from kinetic measurements which would permit a more detailed discussion of the reactivity of halopyridazines in their reactions with thiols. It is known, mainly from synthetic work, that there are different reactivities of halopyridazines, that is, a halogen attached at position 4 or 5 is generally more susceptible to nucleophilic attack than if it is located at position 3 or 6. Di- and polyhalopyridazines exhibit enhanced reactivity and, for example, position 4 of 3,4,5- or 3,4,6-trichloropyridazines is the most reactive one toward nucleophiles. It has been calculated that the electron density at position 4 in 3,4,6-trichloropyridazine is the lowest and that superdelocalizability for the nucleophilic reaction is the greatest at this position (102). This proved to be in good accord with experimental findings. Thus the reaction with *o*-aminothiophenol (91, 102, 103), or with an equimolar quantity of an alkyl or arylthiol (54), afforded the corresponding 4-thio ethers. A similar situation is encountered with 3,4,5,6-tetrafluoropyridazine (93), which is discussed later, or with 3,4,5,6-tetrachloropyridazine which forms with sodium methyl or ethyl mercaptide the 4,5-bis(methylthio) or 4,5-bis(ethylthio) derivative (54).

Thus it is possible to replace one halogen selectively in 3,6-dichloropyridazine as exemplified by the preparation of 3-methylthio-6-chloropyridazine (80). In a similar manner, with thioglycollic acid or its ester, the mono (**52a–d**) or disubstitution products (**52e** and **f**) were obtained (34). In general, in the reaction between 3,6-dihalopyridazines and thiolates, the use of lower temperatures (50–100° C) and approximately equimolar quantities of a thiol favor monosubstitution, whereas use of higher temperatures (100–150° C), a longer heating period, and an excess of thiol favor the formation of 3,6-bisthio ethers (83, 89).

3,4,5-Trichloropyridazine, when treated with 2 moles of a sodium benzyl mercaptide in alkaline alcoholic solution, undergoes nucleophilic displacement at positions 4 and 5 (**53**) (14). Structural proof was presented by the following reaction sequence, starting from 4,5-dibromo-3(2*H*)pyridazinone



52a **52b** **52c** **52e** **52f** **52d**



(**54**), displacing the halogens with the thiol (**55**), and converting the oxo group by means of phosphorus oxychloride into the 3-chloro substituent (**53**).

A consecutive replacement of halogen atoms has also been observed with 3,4,5,6-tetrafluoropyridazine. This compound formed with sodium thiophenoxide in *N*-methylpyrrolidone at 0° C the 4,5-disubstituted product, although the thiol was used in one molecular proportion. With three molecular proportions and under the same reaction conditions, a mixture of di-, tri-, and tetrasubstituted products was obtained, whereas at −10° C only fluorine atoms at positions 4 and 5 were displaced (93). These results are explained in terms of an ortho-activating effect of an initial phenylthio group toward further substitution of fluorine. Furthermore, the orientation of substitution in tetrafluoropyridazine is primarily controlled by the ring nitrogen(s) (93).

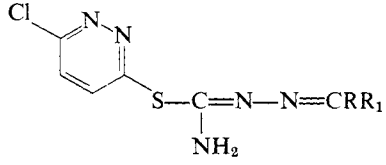
A different reactivity of halogens can also be observed with halopyridazinones. Thus 4,5-dichloro-3(2*H*)pyridazinone reacts with thiols and thiophenols under mild reaction conditions to exchange first the chlorine atom at position 5, whereas more rigorous reaction conditions favor the formation of 4,5-bis(alkyl or arylthio)-3(2*H*)pyridazinones (58, 94).

Kinetic studies of the reaction between 4,5-dichloro-2-(2′-carbethoxyethyl)-3(2*H*)pyridazinone and thiols were reported (104). Only a chlorine atom at position 5 was exchanged, and the remaining 4-chlorine remained unchanged under ordinary conditions (room temperature, sodium carbonate solution, threefold excess of thiol). The reaction has been extended to other 4,5-dibromopyridazinones and mercapto groups containing substrates such as cysteine or enzymes (189, 190).

A particular case represents the reaction between 1-methyl-2-phenyl-4-bromo-3,6-dioxo-1,2,3,6-tetrahydropyridazine and ethyl mercaptan in benzene solution and in the presence of triethylamine. The structure of 1-methyl-2-phenyl-5-ethylthio-3,6-dioxo-1,2,3,6-tetrahydropyridazine has been assigned to the product obtained (105), although no structural proof was presented. If the structure is correct, it is most likely that the displacement takes place via a hetaryne intermediate, by analogy with the known reaction with amines or methoxide ion (106).

Finally, it should be mentioned that sulfur nucleophiles, in particular the thiophenoxide ion, are among the most powerful nucleophilic reagents on account of the high polarizability of the sulfur and their ability to supply electrons for the formation of a new bond at relatively large separations (107).

In addition to true thiols some compounds that contain a thioamide group as part of the molecule are also sufficiently nucleophilic to react with halopyridazines. Such an example is the reaction between halopyridazines and thiourea which produces pyridazinethiones. In some cases the intermediate thiuronium salts have been isolated (45). A similar reaction also took place between 3,6-dichloropyridazine and thiosemicarbazones of aldehydes or ketones to give thioethers of type **56** (or the tautomeric form) (47).



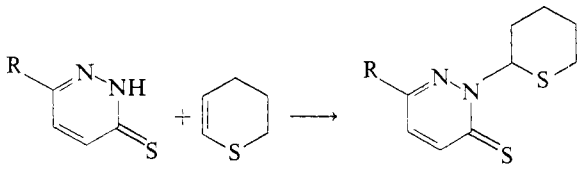
56

It should also be mentioned that analogous transformations convert 3-halopyridazine 1-oxides into the corresponding 3-pyridazinyl sulfides (108, 109).

3. *Addition of Pyridazinethiones or Pyridazinethiols to Unsaturated Compounds*

Pyridazinethiones, when treated with 2,3-(4*H*)dihydropyran, its sulfur analog, or with 2,3-dihydrofuran in the presence of an acid catalyst, form *N*-addition products.

In this manner 3(2*H*)pyridazinethione, when treated with 2,3-(4*H*)-dihydrothiopyran in anhydrous benzene and in the presence of *p*-toluenesulfonic acid, forms the N_2-tetrahydrothiopyranyl derivative (**57**: R = H) in low yield (110, 184). The 6-chloro derivative (**57**: R = Cl) decomposes at room temperature after standing a few months. The site of the reaction



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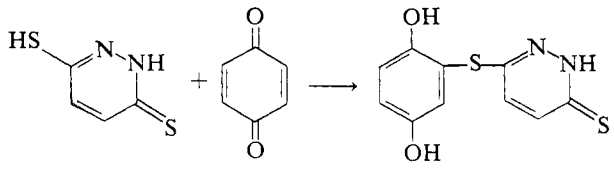
and thus the structure of the resulting addition products have been deduced from ir spectra.

N_2-Tetrahydropyranyl and N_2-tetrahydrofuranyl derivatives of 3(2*H*)-pyridazinethiones were prepared as model compounds to study the stability of the *N*-glycosidic linkage of π-deficient *N*-heteroaromatic glycosides (111, 184). N_2-Tetrahydropyranyl- or N_2-tetrahydrofuranyl-3(2*H*)pyridazinethiones are easily hydrolyzed back to pyridazinethiones. The hydrolytic cleavage takes place with 1*N* hydrogen chloride in ethanol and has been found to be a first-order reaction (111). Tetrahydrofuranyl derivatives are cleaved faster than the corresponding tetrahydropyranyl derivatives, and both react faster than the corresponding pyridazinone derivatives. In addition, substituents have been found to exert a stabilizing effect in the following order: 6-chloro < 6-bromo < 5,6-diphenyl < 6-phenyl (111, 185).

6-Mercapto-3(2*H*)pyridazinethione is capable of addition to compounds with activated double bonds, such as acrylonitrile or acrylic ester, to form the corresponding mono-*S*-alkylated products in good yield. Similarly, addition of cyclopentadiene or dicyclopentadiene is possible and in both cases an identical product, on analysis for the dicyclopentadiene adduct, was obtained (8).

Addition of thiols to quinones is a well-known reaction and can proceed in two directions. It is possible that under the oxidative influence of the quinone a disulfide is formed or that addition to the quinone takes place. Depending on the substance and quinone employed and on reaction conditions, the reaction may end at this stage, or it can proceed further with oxidative transformation of the hydroquinone–thio ether adduct into the quinone–thio ether adduct. An irreversible addition of 6-mercapto-3(2*H*)-pyridazinethione to quinones at room temperature has been observed (**58**),



58

and this can be best explained in terms of an acid-catalyzed addition reaction (112).

4. *Alkylations or Arylations of Pyridazinethiones or Pyridazinethiols*

Pyridazinethiones alkylate easily with alkyl halides or sulfates exclusively upon the sulfur atom, which is in contrast to pyridazinones which alkylate on the ring nitrogen.

A variety of compounds can be used as alkylating agents. In most cases, for the preparation of pyridazinyl methyl sulfides, methyl iodide in the presence of a base (with or without heating) has been used. In this manner different 3-methylthiopyridazines (7, 11, 21, 23, 43, 48, 59, 66, 113), 4-methylthiopyridazines (3), 3,6-bis(methylthio)pyridazines (6, 7), or 4,5-bis(methylthio)pyridazines (24) have been prepared.

Among other alkylating agents mention should be made of dimethyl or diethyl sulfate (7, 11, 25, 50), ethyl iodide (15, 22, 66) and other alkyl halides (21, 25, 54, 113), α-halo acids and esters (7, 18, 27, 34, 54, 114, 177) or amides (19, 26, 54, 56), β-halo acids and derivatives thereof (8, 26, 54, 56), α-halo ketones (54, 115, 187), dimethylamide of phenyliminocarbonic acid chloride (116), benzyl halides or substituted benzyl halides (14, 18, 175, 176, 37, 53, 112, 114), aryl halides (73), and heteroarylmethyl halides (29, 117).

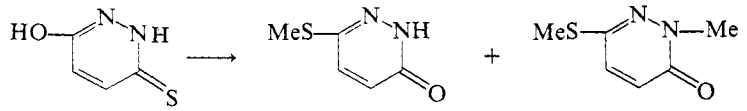
In this way thio ethers of pyridazines or pyridazinones were synthesized, such as 3-alkylthio- (7, 8, 15, 18, 19, 21, 25–27, 34, 50, 54, 56, 66, 113, 114, 178), 4-alkylthio- (22), 3,6-bis(substituted alkylthio)- (7, 27, 34, 116), 3-arylalkylthio- (14, 18, 112, 114, 187), 3,4,5-tris(arylalkylthio)- (14, 53), 3-arylthiopyridazines (73) and the following 3(2*H*)pyridazinones: 4,5-bis-(arylalkylthio)- (14, 53, 175, 176), 4-arylalkylthio- (14, 177), 5-arylmethylthio (37, 177), and 5- (29) or 4,5-bis(heteroarylmethylthio) derivates (29, 117).

6-Methyl-3(2*H*)pyridazinethione is reported to fail to react with iodobenzene in the attempted preparation of the corresponding sulfide, whereas an activated aryl halide such as *p*-nitrobromobenzene reacted in the presence of sodium methoxide and the corresponding sulfide was formed (73).

Pyridazinethiones with other functional groups capable of undergoing reactions with alkylating agents, such as hydroxy, mercapto, and amino groups, need some explanation.

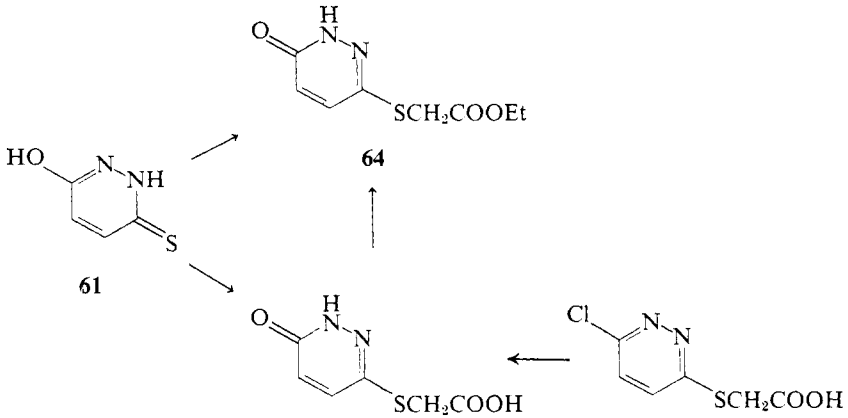
Methylation studies of 6-hydroxy-3(2*H*)pyridazinethione and 6-amino-3(2*H*)pyridazinethione with methyl iodide and dimethyl sulfate gave some insight into the different reactivity of the functional groups (11). In both cases the thioxo group is methylated more readily than the hydroxy or amino group. When 6-hydroxy-3(2*H*)pyridazinethione was methylated with

dimethyl sufate (100° C, 1 hr), besides the expected 6-methylthio-3(2*H*)-pyridazinone (**59**) a minor product was obtained and this was the sole product when higher temperatures (140° C, 3 hr) were applied. For this dimethylated compound the structure of 2-methyl-6-methylthio-3(2*H*)pyridazinone (**60**) has been established (11).



59 **60**

6-Hydroxy-3(2*H*)pyridazinethione forms the 3-methylthio derivative with methyl iodide (11) and reacts similarly with monochloroacetic acid or its ester (27, 34) The structures of the products obtained have been ascertained by the reaction sequence **61–64**.



61 **62** **63** **64**

The same that was said for the 6-hydroxy-3(2*H*)pyridazinethione holds for 6-amino-3(2*H*)pyridazinethione which is *S*-alkylated with dimethyl or diethyl sulfate or *n*-butyl bromide (25).

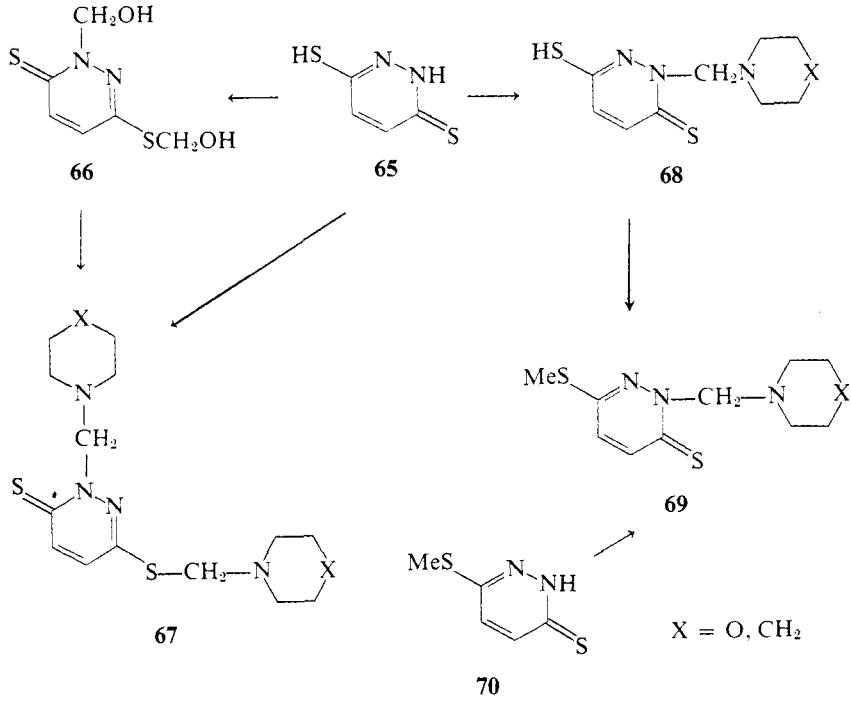
6-Mercapto-3(2*H*)pyridazinethione can react, according to reaction conditions, on one or both sulfur atoms. Thus, when treated with monochloroacetic acid, 6-carboxymethylthio-3(2*H*)pyridazinethione is formed at lower pH and when molal quantities of reactants are employed, whereas the 3,6-bis(carboxymethylthio) derivative is obtained at higher pH and with an excess of monochloroacetic acid (27, 34). In contrast to pyridazinones, pyridazinethiones do not form *N*-carboxymethyl derivatives.

In an analogous manner the reaction with benzyl chloride in the presence of alkali takes place, but in addition to the monosubstitution product, that is,

6-benzylthio-3(2*H*)pyridazinethione, some 3,6-bis(benzylthio)pyridazine was formed (114). The same holds for methylation with methyl iodide in the presence of alkali (7), but under strictly selected reaction conditions it is possible to obtain only 6-methylthio-3(2*H*)pyridazinethione or 3,6-bis-(methylthio)pyridazine (7).

With dimethyl sulfate alone 6-mercapto-3(2*H*)pyridazinethione yielded the 3,6-bis(methylthio) derivative, yet when the reaction is conducted in a methanol solution and in the presence of dilute sodium hydroxide, in addition to the disubstituted derivative some 2-methyl-6-methylthio-3(2*H*)pyridazine-thione is also obtained (7).

Hydroxymethylation and aminomethylation reactions have been investigated with 3(2*H*)pyridazinethiones and 6-mercapto-3(2*H*)pyridazinethione (118). Since the latter compound contains two reactive hydrogen atoms, mono- or disubstituted products would be expected. Hydroxymethylation of **65** afforded a bishydroxymethyl derivative assigned as an *N*,*S*-disubstituted product (**66**) on the basis of uv spectroscopic correlation. Compound **66** can be further transformed with amines into the bis-Mannich base (**67**), also obtained directly by applying the Mannich reaction to **65** and using an excess of reagents.



Aminomethylation of **65**, using a molar ratio of reactants, gave a mono-Mannich base (**68**). The structure was deduced from methylation of **68** to **69**, which could otherwise be prepared in a Mannich reaction with **70**.

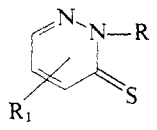
Monoaminoalkylation of **65** thus proceeds on the ring nitrogen and not on the exocyclic sulfur, which has been attributed to the involvement of the thiol group of **65** in salt formation with amines.

5. *Glycosides*

Pyridazinethiones react with halogenated sugars to form the corresponding *S*-glycosides.

For example, 3,5,6-triphenyl-4(1*H*)pyridazinethione forms with α-bromotetraacetyl glucose the corresponding *S*-tetraacetylglucoside in the presence of sodium ethoxide (22).

2-(Tetracetyl-1-β-D-glucosyl)-3(2*H*)pyridazinethiones (**71**) have been prepared from the corresponding 3(2*H*)pyridazinethiones and α-acetobromoglucose according to the Sabalitschka process (119), or by thiation of the corresponding 2-(tetraacetyl-1-β-D-glucosyl)-3(2*H*)pyridazinones (60). It was later shown (120, 121) that 3(2*H*)pyridazinethiones when treated with α-acetobromoglucose according to the Sabalitschka procedure afforded a mixture of 2-(tetraacetyl-1-β-D-glucosyl)-3(2*H*)pyridazinethiones (**71**: R = tetraacetyl-1-β-D-glucosyl) and 3-(tetraacetyl-1-β-D-glucosylthio)pyridazines (**72**: R = tetraacetyl-1-β-D-glucosyl). The separation of the acetylated



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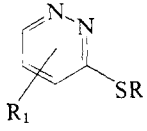
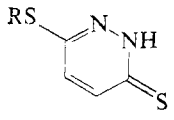


72

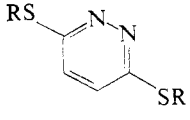
S- and *N*-glucosides was possible by fractional crystallization. Both kinds of glucosides possess a β configuration and a pyranoid structure.

Deacetylation of tetraacetyl *S*- and *N*-glucosides with catalytic amounts of sodium methylate gave the free *S*- or *N*-glucosides (**71** or **72**: R = 1-β-D-glucosyl) (60–62, 120–123).

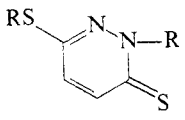
With the use of the above-mentioned synthetic approaches, several types (**73a–d** and **74a** and **b**) of glycosidated pyridazines were prepared (R = 1-β-D-glucosyl or tetraacetyl-1-β-D-glucosyl) (61, 62, 121–123). In some cases α anomers were also obtained (61, 62). When 3(2*H*)pyridazinethiones-in the form of their sodium salts, were treated with 3,5-di-*O*-*p*-tolyl-2, deoxy-α-D-ribofuranosyl chloride at room temperature, a mixture of tolylated



73a



73b



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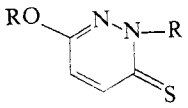

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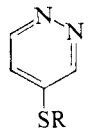
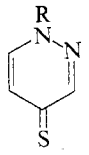


74a

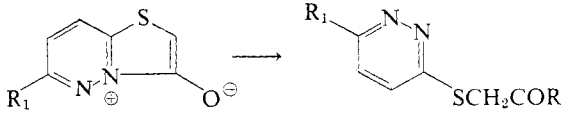


74b

S- and *N*-2′-deoxyribofuranosides resulted. The ratio of *S*-:*N*-glycosides varied from 0.9 to 11, and the β-anomers were formed preponderantly, suggesting that an S_N2 type of reaction occurs (191). Tables XXVI–XXX list the known glycosides of pyridazinethiones.

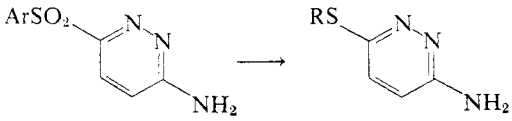
6. *Other Methods*

Mesoionic bicyclic pyridazine derivatives of type **75** are transformed upon heating with 50% sulfuric acid into the corresponding carboxymethylthiopyridazines (**76**: R = OH), or with a solution of phenylhydrazine in ethanol (into the corresponding hydrazide (**76**: R = C_6H_5NHNH) (114).



75 **76**

In addition to halogen displacement in halopyridazines, it is also possible to displace an arylsulfonyl group with an alkylthiol, benzylthiol, or thiophenol in the presence of sodium methoxide at 130–140° C for several hours (**77**: R = Me, Et, $C_6H_5CH_2$, C_6H_5) (25).



77

R = Me, Et, C_6H_5-, $C_6H_5CH_2$-

In the case of two adjacent thiol groups, as for example, 2-phenyl-4,5-dimercapto-3(2*H*)pyridazinethione, it is possible to form a cyclic thioacetal with benzaldehyde, or a cyclic thioketal with cyclohexanone (24).

The known pyridazinyl sulfides are given in Tables XIII–XXX.

B. Reactions

There are several types of important reactions of pyridazinyl sulfides which can be broadly divided into three groups: displacement reactions, quaternizations, and oxidations.

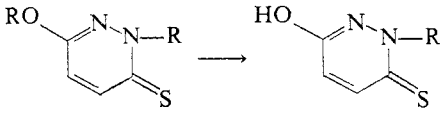
The sulfide linkage in pyridazinyl thioethers is not affected by many reagents employed in transformation reactions of other functional groups attached at the pyridazine ring. It is thus possible to acetylate an amino group (108) or acylate a hydroxy group (124), deacetylate an acetylamino group with hot alkali (17), and displace a halogen with aniline or sulfanilamide (48), methoxide (21), phenoxide (43), or alkali hydroxide (54). Furthermore, dehalogenation with zinc in a solution of ammonia in ethanol (113) or with sodium in liquid ammonia (196) can be performed, or carbethoxymethylthio groups can be saponified with dilute alkali (7, 34, 87), or converted with amines into the corresponding amides (125). Similarly a halogen can be displaced with alkali hydroxide without affecting the carboxymethylthio group, in contrast to the corresponding carboxymethyl ethers of the pyridazine series (34).

However, there are many examples of a more-or-less facile displacement of a thio ether group in pyridazines. Pyridazinyl sulfides react with ammonia or amines only under forced reaction conditions, at elevated temperatures, and under pressure. For example, 3-ethylthio-6-methylpyridazine gives, under vigorous reaction conditions (160° C, 3 days) with methanolic ammonia, the corresponding 3-amino compound in low yield (18%, together with 80% of unchanged material) (15). Similar drastic conditions are required for the reaction between 3-methylthiopyridazine and ethanolamine (180° C, 18 hr) (126), 4,5-bisbenzylthio-3(2*H*)pyridazinone and ammonia to give the 5-amino derivative (195), and 3- or 4-methylthiopyridazine and sodium methoxide (194). Complete elimination of the sulfide function has been accomplished in the case of benzylthio ethers by means of Raney nickel (175). Debenzylation of benzylthio ethers was also accomplished with the aid of aluminium trichloride to give the corresponding mercaptopyridazines (176).

There are some examples from which the stability of pyridazinyl sulfides toward the influence of acids or alkali can be judged. A relatively facile cleavage of the thioether linkage has been observed with products obtained

by addition of acrylonitrile or acrylic ester (the product from the latter is identical to that from an alkylation experiment with ethyl β-bromopropionate) to 6-mercapto-3(2*H*)pyridazinethione. These products, when heated with a 5% solution of potassium hydroxide in ethanol for 15 minutes, yielded the starting pyridazine derivative (8). This conversion can be regarded as an example of a "retro-Michael" reaction.

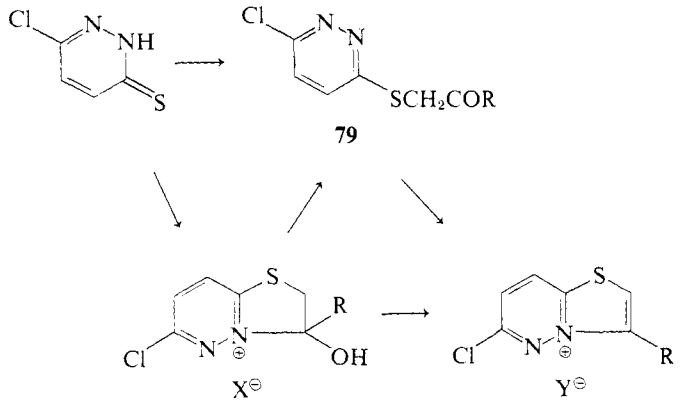
Glycosides of pyridazinethiones were investigated for their stability toward acid treatment. 2-(1-β-D-glucosyl)-3(2*H*)pyridazinethiones remain unchanged in a solution of 1*N* hydrochloric acid at 80° C after 24 hr (60). Such great stability is said to be characteristic of *N*-glycosides (127). Accordingly, with 0.01*N* hydrochloric acid a selective cleavage of an *O*-glucosidic linkage can be achieved (**78**: R = 1-β-D-glucosyl) (61, 62).



78

With some pyridazinethione glycosides an S → N transglycosidation has been observed. This rearrangement proceeds easily under the influence of mercuric bromide and had been observed earlier with the corresponding pyridazinones. In this way 3-(tetraacetyl-1-β-D-glucosylmercapto)pyridazines rearrange under the influence of mercuric salts (usually mercuric bromide is used) when heated for 10–30 min in a solution of toluene to 2-(tetraacetyl-1-β-D-glucosyl)-3(2*H*)pyridazinethiones (121, 128). The *N*-glucosides are reported to have a β configuration and a pyranoid structure. Yields are variable (5–95%) and are better for 6-substituted pyridazines, in particular for 6-phenyl and 5,6-diphenyl derivatives. A reaction mechanism for these transformations has been presented. Contrary to this rearrangement, transglycosidation of 4-(tetraacetyl-1-β-D-glucopyranosylmercapto)pyridazines into the corresponding *N*-glucosides is reported to have failed (122, 123). A similar S → N transglycosidation of tolylated *S*-2′-deoxy-β-D-ribofuranosides of 3(2*H*)pyridazinethiones afforded a mixture of α and β anomers of the *N*-glycosides with a slight preference for the formation of the β anomer (192). The orientation of the aglycone of acetylated tetra-*O*-acetyl-*N*-β-D-glucopyranosides of 3(2*H*)pyridazinethiones was determined on the basis of nmr spectra (193).

A detailed investigation of the reaction between α-haloketones and 3(2*H*)-pyridazinethiones revealed that, depending on reaction conditions, the reaction can take different courses. In the presence of sodium alkoxide, α-haloketones react to form the corresponding keto sulfides (**79**), whereas in the absence of this base and in the presence of an organic solvent such as

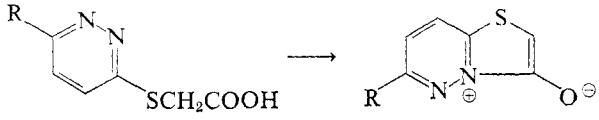


79

80 81

tetrahydrofuran the intermediate 3-hydroxy-6-chloro-2,3-dihydrothiazolo-[3,2-*b*]pyridazin-4-ium salt (**80**) is obtained (115). Compounds of type **80** are not too stable and are converted into **79** when crystallized from a mixture of ethanol and *N*,*N*-dimethylformamide. Both **79** and **80** are transformed in the presence of concentrated sulfuric acid into **81**.

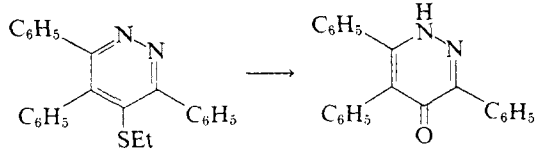
Another case involving the formation of bicyclic products is the treatment of 3-carboxymethylthiopyridazines with a mixture of acetic anhydride, pyridine, and triethylamine. A mesoionic structure has been assigned (**82**) to the compounds obtained (114).



82

Finally, displacement of the ethylthio group by an oxo group with the aid of selenium dioxide in acetic acid solution has been reported (**83**) (22).

Quaternizations of different pyridazinethiones and pyridazinyl sulfides have been studied by several investigators. A review on quaternization of



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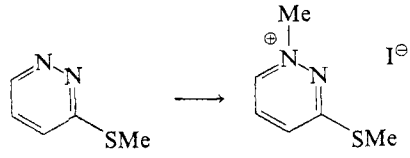
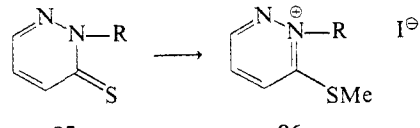


84

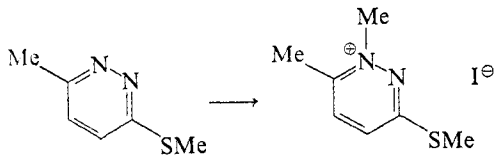
heterocycles which also includes mechanistic interpretations has been provided by Duffin (129).

Duffin and Kendall (59) observed that 3-methylmercaptopyridazine reacted fairly slowly with methyl iodide to form the quaternary salt (**84**), whereas the same reaction with 2-methyl-3(2*H*)pyridazinethione (**85**: R = Me) was very rapid toward the formation of **86**. A rapid quaternization could also be observed with other pyridazines of type **85**, and in all cases products of type **86** were obtained (59). The difference in reactivity is explained in terms of inductive effects because the alkylthio group deactivates the adjacent ring nitrogen. Support for this suggestion is given by quaternization of **87** into **88** and not into the other possible isomer (59). A similar case was recorded with the 4,5-dihydro analog (59, 66).

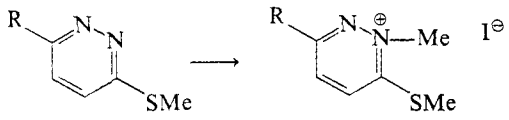
A substituent at position 6 may influence the site of quaternization of pyridazinyl sulfides. Thus compounds of type **89** (R = OMe, Ph) afford quaternary salts (**90**).



85 **86**



87 **88**



89 **90**

Duffin and Kendall (59) claimed that in no case was it possible to isolate two isomeric methiodides. However, during the preparation of monomethincyanine dyes, it became evident that the isomeric quaternary salt was also formed from 3-methylthio-6-methylpyridazine (59).

In a recent study, Lund (130) used nuclear magnetic resonance (nmr) spectroscopy to study the composition of reaction mixtures resulting from quaternization of pyridazines. Quaternization of 6-methylthio-3-methylpyridazine with methyl iodide was shown to afford a mixture of the N_1 (12%) and N_2 (88%) quaternized compounds. As general conclusion, Lund states that the composition of the mixture resulting from quaternization is determined mainly by inductive and pronounced steric effects, although other effects may also be operative. Another observation from these studies is that the composition of the reaction mixture seems to be kinetically controlled.

All quaternary salts are readily converted to the corresponding pyridazinethiones with boiling pyridine or aqueous sodium sulfide (59). They were used for the synthesis of cyanine dyes (59, 131, 132).

The known quaternized sulfur-containing pyridazines are listed in Table XXXI.

Oxidation of alkyl- or arylthiopyridazines can give, depending on the oxidizing agent involved and its amount and reaction conditions, different kinds of oxidation products, such as sulfoxides, sulfones, and sulfonic acid; in addition to sulfur oxidation, nuclear oxidation leading to *N*-oxides can take place.

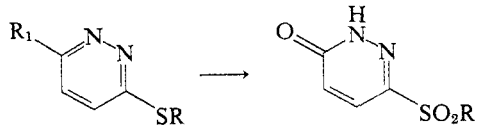
Gregory, Owens, and Wiggins (73) oxidized 3-ethylthio-6-methylpyridazine with permanganate in acid solution at 0° C and obtained the corresponding sulfone. Instead of permanganate, hydrogen peroxide in acetic acid (3 days, room temperature) was used for oxidation of the pyridazine derivative, although under the same reaction conditions the 3-(*p*-nitrophenylthio) analog was transformed into the corresponding sulfoxide (73). 3-(*p*-Nitrophenylthio)-6-methylpyridazine is oxidized with potassium permanganate to both the sulfoxide or sulfone, depending on the quantity of the oxidizing agent and on reaction conditions (73). Although it is well known, it is worthwhile to mention that oxidation of sulfides to sulfoxides is a faster reaction than oxidation of sulfoxides to sulfones (133).

There are several other examples of oxidative transformations of sulfur containing pyridazines. Thus a 3-methylthio group has been transformed either into the 3-methyl sulfoxide group by means of hydrogen peroxide in aqueous (134–136) or acetic acid solution (137) or with *m*-chloroperoxybenzoic acid (194), or into a 3-methylsulfonyl group with hydrogen peroxide in acetic acid (48), with potassium permanganate in acid solution (69), with chlorine at low temperature (69, 80), or with sulfur dioxide (69). Depending upon reaction conditions, the 4- or 5-methylthio group of methylthio

6-chloro-2-phenyl-3(2*H*)pyridazinones can be converted with hydrogen peroxide in acetic acid into the corresponding methyl sulfoxide or methylsulfone derivatives (177). 3-Methylsulfinylpyridazine was oxidized to the corresponding sulfone with potassium permanganate (197). Other examples involve formation of a 3-ethyl sulfoxide group from a 3-ethylthio group by means of hydrogen peroxide (134–136, 138), formation of a methylsulfonyl group from a 4- or 5-methylthio group with the aid of permanganate or hydrogen peroxide in acetic acid solution (69, 139), or a 3-benzylsulfonyl group from a 3-benzylthio group with hydrogen peroxide in formic acid (96). Moreover, a carboxymethylthio group has been oxidized to the carboxymethylsulfone with peroxyacetic acid in moderate yield (14 days, room temperature) (85), and a 3-benzylthio group was converted with chlorine to the corresponding pyridazinyl-3-sulfonyl chloride (140).

Takahayashi (72) submitted 6-chloro-3-alkylthiopyridazines and their 4- (or 5-) alkyl analogs to oxidation under various conditions and used different oxidizing agents such as permanganate, hydrogen peroxide in acetic acid, fuming nitric acid, or ferric chloride. He was not able to establish firmly the structure of several products and he designated compounds simply as monoxides or dioxides, although comparisons of uv spectra suggested that some oxidation products could be sulfoxides and some *N*-oxides. That in some instances *N*-oxides were indeed formed is evident from the observation that some monoxides could be converted with phosphorus trichloride to the starting alkylthiopyridazines. There is also another report by Horie (108) from which it appears most likely that in addition to oxidation of the thio ether group *N*-oxidation also takes place.

Furthermore, oxidation with peroxyacetic acid can occur concurrently with hydrolytic displacement of the halogen at position 6 and with the formation of the corresponding pyridazinones. In fact, this was observed when several 6-substituted 3-alkylthiopyridazines were oxidized with potassium permanganate in dilute sulfuric acid. Takahayashi (141) first assumed that mono- and dioxides of undetermined structure were formed. In a more detailed study he later determined the structure of several of these oxidation products which proved to be 6-alkylsulfonyl-3(2*H*)pyridazinones (142). In this manner 3-alkylthiopyridazines with a methoxy, phenoxy, or chloro substituent at position 6 yielded upon oxidation with peroxyacetic acid compounds of type **91**.



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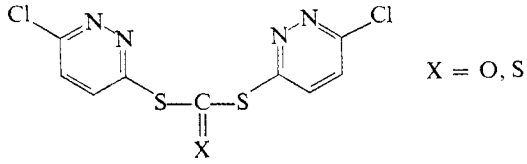
III. Acylthiopyridazines

Acylthiopyridazines have been prepared by direct acylation of pyridazinethiones or, in the case of reduced pyridazines, by free-radical additions of thioacetic acid.

Benzoylation of 6-chloro-3(2*H*)pyridazinethione is reported to give the 3-benzoylthio derivative (54), and several 3-alkoxycarbonylthio or phenoxycarbonylthio derivatives were similarly obtained from esters of chloroformic acid (18, 30). Acylated derivatives of 4- or 5-mercapto-6-chloro-2-phenyl-3(2*H*)pyridazinones have also been prepared (177). With phosgene or thiophosgene in the presence of alkali, a bispyridazinyl derivative of type **92** is formed (18).



92

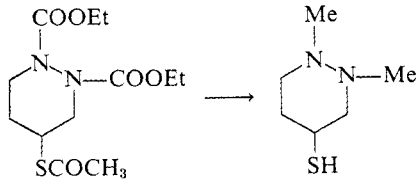
6-Mercapto-3(2*H*)pyridazinethione can be mono- or diacetylated with acetyl chloride, and the products have been designated *S*-acetyl compounds (6). Contrary to this, Kumagai (7) reported that the mentioned pyridazine is only monoacetylated, whereas benzoylation yielded a mixture of the monobenzoyl and dibenzoyl derivative. Acylation of a pyridazinethiol *N*-oxide has also been carried out (41).

1,2-Dicarbethoxy-4-acetylthiohexahydropyridazine and its 5-methyl analog have been prepared by free-radical addition of thioacetic acid to the corresponding 1,2,3,6-tetrahydropyridazine (12). In contrast to this facile addition, 1,2-dicarbethoxy-4,5-dimethyl- and -3,6-diphenyl-1,2,3,6-tetrahydropyridazine failed to react with thioacetic acid, and this is explained in terms of steric effects (12). The stereochemistry of the addition products was not stated.

Deacetylations of the *S*-acylated pyridazinethiones are easily carried out with dilute hydrochloric acid in ethanol (12) or, in the case of acetylated 6-mercapto-3(2*H*)pyridazinethione, upon short heating with sodium bicarbonate (6).

1,2-Dicarbethoxy-4-acetylthiohexahydropyridazine, when treated with lithium aluminium hydride at room temperature, is deacetylated to the free thiol and the carbethoxy groups are simultaneously reduced to methyl

groups (**93**) (12). For the known acylthiopyridazines, see Tables XXXII–XXXVII.



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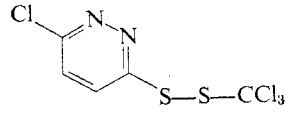
IV. Pyridazinyl Disulfides, Sulfoxides, Sulfones, and Sulfonic Acids

It has already been mentioned (Section I.D) that pyridazinethiones or pyridazinethiols are readily oxidized to disulfides. The reagents used for these purposes and examples of disulfide formation are noted under reactions of pyridazinethiones. Another approach to disulfide formation is the reaction of 6-chloro-3(2*H*)pyridazinethione with perchloromethylmercaptan, leading to compound **94** (143).



94

Oxidation of pyridazinyl sulfides to the corresponding sulfoxides or sulfones has also been discussed in detail (see Section II.B). An exception to the standard methods of synthesis of pyridazinylsulfones is the synthesis of the sulfone resulting from the reaction between 3-chloro-6-methoxypyridazine and the sodium salt of *p*-acetaminobenzenesulfinic acid (3 days, 120–125° C, under pressure) (198). More details are given here, in particular with regard to the reactivity of pyridazinylsulfones.

An outstanding characteristic of pyridazinylsulfones is their ability to undergo a facile displacement in reactions with nucleophilic reagents. Replacements of a 3- or 4-methylsulfonyl group from pyridazine by aqueous sodium hydroxide, aqueous methylamine, with *n*-propylamine, aqueous sodium hydrogen sulfide, aqueous ammonia, and aqueous ammoniacal ammonium chloride have been carried out by Barlin and Brown (67). 3-Methylsulfonylpyridazine gave with ammonium hydroxide at 100° C only a small amount of 3-aminopyridazine, but a substantial amount of

3(2*H*)pyridazinone was also isolated. When ammonium chloride was added to the reaction mixture, this reduced the proportion of the pyridazinones, and 3-aminopyridazine was obtained in an increased yield, up to 42% (67). Replacements of the arylsulfonyl group from 3-arylsulfonylpyridazines by alkoxides (144), by sodium hydrogen sulfide, and by alkali mercaptides (25) have been also carried out.

As judged from the preparative data, deactivated pyridazinylsulfones, such as 3-amino- or 3-sulfonylamido-6-(*p*-tolysulfonyl)pyridazine, display about the same reactivity toward alkoxide or hydrosulfide ion (25, 144) as their 6-chloro analogs (145). However, the methylsulfonyl group of 3-chloro-6-methylsulfonylpyridazine is not displaced with alkylamines, aniline, ethyleneimine, or *p*-aminobenzenesulfonamide (48, 80), and the reaction takes place preferentially with the chloro group.

Pyridazinylsulfones are apparently stable in acidic media, and the benzylsulfonyl group remains attached during demethylation of 3-methoxy-6-benzylsulfonylpyridazine with hot concentrated hydrochloric acid (20 hr) to the corresponding pyridazinone (96).

Recent kinetic studies by Barlin and Brown (69) gave a better insight into the reactivity of pyridazinylsulfones. Thus in the 3-substituted pyridazines the methylsulfonyl compound was about 90 times more reactive toward methoxide ion at 40.2° C than the corresponding chloropyridazine. This greater reactivity is attributed mainly to a lower energy of activation. Comparison of the reactivity of 3- and 4-methylsulfonylpyridazines toward methoxide ion confirmed the expected greater reactivity of the 4-isomer (69).

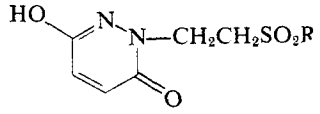
The ionization constants of 3- and 4-methylsulfonylpyridazine ($pK_a = -1.01$ and -1.06, respectively) reveal the strong electron-withdrawing nature of the methylsulfonyl group, and this was also concluded from a study of nmr spectra (69). These studies revealed downfield chemical shifts of all protons as compared with the parent compound. Nuclear magnetic resonance studies of protonated 4-methylsulfonylpyridazine and the corresponding 4-methylthio analog showed that protonation takes place on both nitrogens, on N-1 and N-2.

Recent kinetic studies on the reactivity of 3- and 4-methylsulfinylpyridazines and other azines with sodium methoxide revealed a high reactivity which is comparable to that of the analogous sulfonyl derivatives (194). Again a reactivity of 4-methylsulfinylpyridazine greater than that of the 3-isomer was observed, and the corresponding methylthio compounds were much less reactive. Moreover, 4-methylsulfinylpyridazine reacted anomalously and, in addition to the anticipated 4-methoxy compound (70.5%), the 4-methylthio compound (6.4%) was also obtained (194). Similar behavior was observed when 3- or 4-methylsulfinylpyridazines were treated with aqueous sodium hydroxide at 90° C. Besides the expected pyridazinones

(3-, 65%; and 4-, 31%), the corresponding methylthio compounds were isolated in significant quantity (3-, 6%; and 4-, 45%) (197), whereas spectroscopic analysis of the reaction mixture revealed an OH/SMe ratio of 88:12 for 3- and 55:45 for 4-substituted pyridazines (197). Displacement of 3- or 4-methylsulfinyl groups in pyridazine required temperatures over 100°C. There are only a few examples of the formation of pyridazinylsulfonic acids or their derivatives, and these have already been mentioned (Section I.D).

Moreover, some interesting reactions involving the synthesis of isomeric 4(or 5)-amino-2-methyl-3(2*H*)pyridazinone 5(or 4)-sulfonamides should be mentioned. 4-Amino-2-methyl-3(2*H*)pyridazinone-5-sulfonamide was prepared by oxidative chlorination of 5-benzylthio-4-chloro-2-methyl-3(2*H*)-pyridazinone and subsequent treatment with ammonia. For the synthesis of the other isomer, 4,5-dichloro-2-methyl-3(2*H*)pyridazinone was treated with potassium sulfite to give the labile 2-methyl-3(2*H*)pyridazinone-4,5-disulfonic acid which, after treatment with a mixture of phosphorus pentachloride and phosphorus oxychloride and subsequently with ammonia afforded 5-amino-2-methyl-3(2*H*)pyridazinone-4-sulfonamide in moderate yield (182).

Pyridazines with a sulfonic group in the side chain and derivatives thereof should be mentioned. They have been prepared by sulfoethylation of maleic hydrazide with esters or amides of ethenesulfonic acid in alkaline solution (**95**) (146). The acid itself does not add to maleic hydrazide, and with derivatives of ethenesulfonic acid no disulfoethylated products were isolated.



R = OR_1, NR_1R_2, Cl

95

Tables XXXIX and XL list the known disulfides; pyridazinyl sulfoxides are listed in Table XLI. Tables XLIII–XLVI contain sulfones, and Tables XLVII and XLVIII sulfonic acid and derivatives.

V. Thiocyanatopyridazines

Two main groups of thiocyanatopyridazines, according to the position of the attached functional group, can be distinguished: those with the thiocyanato group at the pyridazine nucleus and those with this group in a side chain. Nevertheless, common to both groups are synthetic methods for their preparation which in general involve halogen displacement.

There are several reports on halogen displacement at position 3 of the

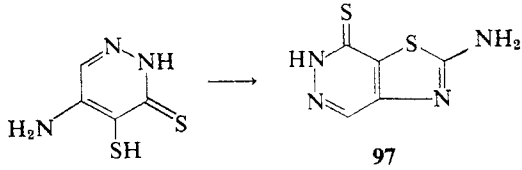
pyridazine ring by means of sodium thiocyanate (30) or ammonium thiocyanate (30, 147), at position 4 or on the pyridazine side chain with ammonium thiocyanate (54, 147), or at positions 4, 5, or 6 of chloro-2-phenyl-3(2*H*)-pyridazinones (177). Schönbeck (54) erroneously designated these compounds 1-isothiocyanatomethyl (or -ethyl) pyridazinones or 4-isothiocyanato-3,6-dichloropyridazine, although the compounds are represented by formulas as thiocyanatopyridazines.

A detailed study of halogen displacement with thiocyanates on 3,6-dichloropyridazine presented evidence that with ammonium thiocyanate in hot ethanol only one chlorine atom is displaced (65° C, 1.5 hr) even when 2 moles of the reagent are employed. Yields were moderate even in the case of the more reactive 3,6-dibromopyridazine. It seems therefore that the reaction between 6-bromo-3(2*H*)pyridazinethione and cyanogen bromide is a better method for preparing 3-thiocyanato-6-bromopyridazine than the direct displacement method (147).

As expected, 3,4,6-trichloropyridazine displays a greater reactivity of the chlorine atom at position 4 to give 3,6-dichloro-4-thiocyanatopyridazine (54, 147).

Another versatile method for the preparation of thiocyanatopyridazines involves treatment of pyridazinethiones or mercaptopyridazinones with a solution of cyanogen bromide in ethanol and/or acetone (15 min, cooling) (30, 147, 177). A similar reaction, but using cyanogen chloride, gave a low yield of 6-chloro-3-thiocyanatopyridazine (30). Whereas 6-chloro-3(2*H*)-pyridazinethiones react with cyanogen bromide to form 3-chloro-6-thiocyanatopyridazines in yields that are almost the same or even better as compared to the direct displacement method using thiocyanates as reagents, with the 6-bromo analog appreciably higher yields were obtained (30, 147).

Kuraishi and Castle (51), in an attempt to prepare the corresponding thiocyanatopyridazine from 5-amino-4-mercapto-3(2*H*)pyridazinethione (**96**) and cyanogen bromide, obtained a thiazolo[4,5-*d*]pyridazine derivative (**97**).



96 **97**

It is well known that thiocyanate is an ambident anion (148) and that it frequently depends upon reaction conditions whether in the displacement reaction of alkyl halides the corresponding thiocyanates or isomeric isothiocyanates (or a mixture of both) are formed. In nucleophilic aromatic

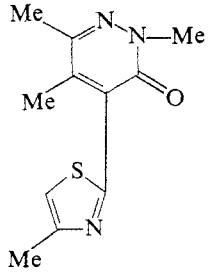
substitutions thiocyanates are usually formed first, and elevated temperatures then cause isomerization to the thermally stable isothiocyanates. These conversions have been reviewed (149).

There are no indications of such isomerizations in the case of thiocyanatopyridazines. It is most probable that the relatively low temperatures employed in synthetic experiments favor rather the formation of thiocyanates and that for their isomerization into the corresponding isothiocyanates more drastic conditions would be required. The known thiocyanatopyridazines are listed in Tables XLIX and L.

VI. Thiocarbamide Groups Containing Pyridazines

These compounds fall into two types and are consequently prepared in two different ways. Compounds of the first type contain a thiocarbamide group attached directly to one of the carbons of the pyridazine skeleton. They are obtainable by the action of hydrogen sulfide on cyanopyridazines, particularly in the presence of basic catalysts. In this way a few 3- or 4-pyridazinylthiocarbamides have been synthesized by Robba (150) and by Schmidt and Druey (151). It is well known that aromatic nitriles are readily converted to the corresponding thiocarbamides. Furthermore, 4-cyanopyridazine reacted with a saturated solution of hydrogen sulfide in ethanol at 0° C (150); 4-cyano-3(2*H*)pyridazinone requires the addition of a basic catalyst to accelerate the reaction (150), whereas 2,5,6-trimethyl-4-cyano-3(2*H*)pyridazinone requires heating (110° C) for several hours in order to accomplish the transformation (151).

4-Pyridazinylthiocarbamide was decomposed back into the 4-cyano compound on an attempted sublimation at 160° C/0.01 mm (150). Moreover, there is only one report concerning a transformation of pyridazinylthiocarbamides. By means of chloroacetone a thiazole ring was formed, a reaction that is otherwise common to thiocarbamides. The structure of the product is **98** (151).



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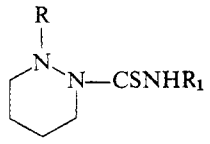

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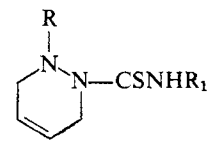

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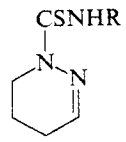

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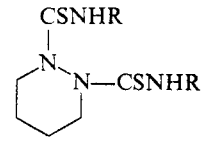


102

Another type of thiocarbamide group containing pyridazines is derived from reduced pyridazines containing NH groups. With isothiocyanates the corresponding thioureas can be formed, and the known compounds can be represented by four structural types: **99** (152), **100** (152, 153) **101** (153–155), and **102** (153).

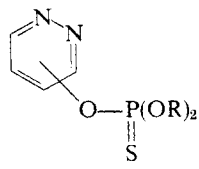
The known pyridazines containing thiocarbamide groups are listed in Tables LI and LII.

VII. Pyridazinylthio- and Dithiophosphates

Pyridazines of this type are covered exclusively by patent literature and their chemistry has been developed only recently. These compounds are claimed to be useful as insecticides.

Thiophosphonylpyridazines can be prepared by treating an appropriate chloropyridazine with an *O,O*-dialkylthiophosphate (as the potassium salt) and compounds of type **103** are thus obtained (156). From treatment of pyridazinones with thiophosphonyl chlorides, compounds of type **104** result (157, 158).

Dithiophosphonylpyridazines are similarly prepared from *O,O*-dialkyldithiophosphates and chloropyridazines (type **105**) (156).



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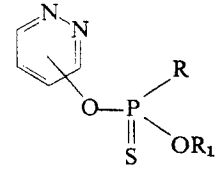
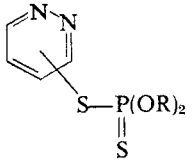


104

Finally, compounds with the structural formula **106** were prepared from 2-hydroxymethyl- or 2-chloromethyl-3(2*H*)pyridazinones with phosphorus pentasulfide in methanol and toluene (159, 160).



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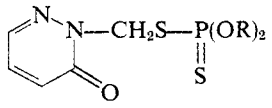


106

Only a few reactions of compounds of the above structural types are described, such as alkylation or acylation of the pyridazinone moiety (161, 162).

The known phosphorus-containing pyridazine derivatives are listed in Tables LIII and LIV.

VIII. Miscellaneous

Preparation of a few 3-substituted 6-methylmercurithiopyridazines was reported in connection with their testing for antifungal activity (163).

IX. Biological Activity and Other Applications

Although among sulfur-containing pyridazines one cannot find such biological important compounds as among sulfur-containing purines and pyrimidines, some pyridazine derivatives deserve to be mentioned for their possible applications as therapeutic agents. A short review on pyridazines with physiological and/or therapeutic activity, including sulfur-containing pyridazines, has been compiled (164).

4-Cyano-3(2*H*)pyridazinethiones or their methylthio analogs are reported to be analgesics (50). Sedative-narcotic activity is reported for 1-phenyl-2-lower alkyl 5-alkylthio-3,6-pyridazinediones, and 3,6-bis(substituted thio) pyridazines also possess sedative action (83). Quaternized 3,6-bis(dialkylaminoalkylthio)pyridazines are claimed to be useful curare-mimetic agents (89).

Amides of 3-halo- or 3-methoxy-6-carboxymethylthiopyridazines are reported to be active as choleretics (19, 26, 56, 165). The most powerful choleretic activity was found to reside in pyridazines that have the amide part of the molecule substituted with lower alkyl residues, in particular the

diethylamide group, such as 3-chloro-6-carboxymethylthiopyridazine diethylamide (19).

3(2*H*)Pyridazinethione has remarkable antithyroid activity which is 34 times the activity of 2-mercaptopyrazine but 1/10 that of 2-carbethoxythio-1-methylimidazole (carbimazole) (166).

Antibacterial and bactericidal activity has been found in several kinds of sulfur-containing pyridazines: 3-alkylthio-6-arylsulfonamido(or sulfamylyl)-pyridazines (16, 25), 4,5-diaryl(or heteroaryl)methylthio-1-phenyl-6(1*H*)-pyridazinones and their 4-monosubstituted analogs (117, 37), 6-alkoxy-3(2*H*)pyridazinethiones (39, 40), pyridazinones containing a methylsulfonyl group (139), and 2-phenyl-6-chloro-4-mercapto-3(2*H*)pyridazinones and their alkyl derivatives (57). 4,5-Bis[2′-furyl(or 2′-thienylmethylthio)] 3(2*H*)-pyridazinones are useful as bactericides, especially as anti-TBC drugs (29, 79). 2-Phenyl-5-mercapto-3(2*H*)pyridazinones are useful as antitubercular drugs as well as antiacetylcholinic drugs (36).

Antifungal activity is displayed by 3-halo-6-thiocyanatopyridazines and 4-thiocyanato-3,6-dichloropyridazines (147). Strong antifungal activity was found in 6-chloro(or bromo)-3(2*H*)pyridazinethiones, their 6-methoxy analogs, and other sulfur-containing pyridazines (18). Trichloromethyl-6-chloropyridazinyl-3-disulfide also belongs to this group (143).

Several bis- or trissubstituted benzylthiopyridazines were tested for antitumor activity and some compounds showed significant activity (14).

Some hexahydropyridazine-4-thiols were examined as potential anti-radiation agents (12).

Many sulfur-containing pyridazines were tested for their herbicidal activity. Different types of pyridazines comprise thio ethers (84, 167, 168) or carboxymethylthio derivatives (27, 86, 87). Several sulfur-containing pyridazines were tested for their herbicidal activity, and a relation between structure and herbicidal activity has been reported (169).

Other applications are as antimicrobial agents for agricultural use (30), antioxidants for rubber (100), vulcanization accelerators (28), and photographic desensitizing compounds (131, 132); pyridazines with thiophosphate or dithiophosphate groups are claimed to be useful insecticides (157, 158, 170).

Finally, some analytical procedures, such as determination of 3-amino-6-alkylsulfoxypyridazines (171) or paper chromatographic separation of benzylsulfonylpyridazines (96) and *S*- and *N*-glycosides (62, 121) have been described.

TABLE I. pK_a Values

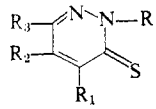
Compound	Proton gain	Proton loss
3(2*H*)Pyridazinethione	−2.68	8.30
2-Methyl-3(2*H*)pyridazinethione	−2.95	
3-Methylmercaptopyridazine	2.26	
4(1*H*)Pyridazinethione	−0.75	6.54
1-Methyl-4(1*H*)pyridazinethione	−0.83	
4-Methylmercaptopyridazine	3.26	

TABLE II. pK_a Values of 3,6-Disubstituted Sulfur-Containing Pyridazines

		Proton loss		
Compound	Proton gain	First	Second	References
6-Mercapto-3(2*H*)pyridazinethione	−0.5	2.1	10.4	8
3,6-Bis(methylmercapto)pyridazine	−6.0			8
6-Hydroxy-3(2*H*)pyridazinethione	−1.7	3.6	>12	8
	−1.39	3.32		11
6-Methylthio-3(2*H*)pyridazinone		10.11[a]		11
6-Methoxy-3(2*H*)pyridazinethione	−2.36	6.95[a]		11
	−2.3	8.5		8
3-Methoxy-6-methylthiopyridazine	1.84			11
6-Amino-3(2*H*)pyridazinethione	−0.14	9.05[a]		11
6-Amino-3-methylthiopyridazine	5.61			11
6-Methylamino-3(2*H*)pyridazinethione	−0.04	9.46[a]		11
3-Methylthio-6-methylaminopyridazine	5.94			11
6-Piperidino-3(2*H*)pyridazinethione	−0.06	9.31		11
3-Methylthio-6-piperidinopyridazine	5.13			11

[a] Value obtained by potentiometric titration.

TABLE III. 3(2*H*)Pyridazinethiones



R	R_1	R_2	R_3	MP (°C) or BP (°C/mm Hg)	References
None				169–170	3, 67
				170	59
				168–169.5	196
Methyl				110	59
				108–109	3
			Methyl	203	45, 49, 59
				205	8
				205–209 (dec)	44
				202–205	28
				203–205 (dec)	15
			Phenyl	160	45
			Methoxy	171–176 (dec)	19, 26
				191–193	11
				200	21
			n-Propoxy	159–161	44
				165	14
			Ethoxy	190	14
			Chloro	100	43
					55
				130–140	6
				136–138 (dec)	21
				140	45
				150	47
				136 (dec)	54
			Bromo	140–145	18, 30
				140–150 (dec)	19
			Amino	cca 250 (dec)	25
				cca 268	16
				281–282	44
				285 (dec)	46
			Methylamino	234–237 (dec)	11
			Diethylamino	147–149	11
			Acetylamino	>300	46
			Benzoylamino	225	46
			p-$CH_3C_6H_4SO_2NH$	209	46
			Anilino	184–185	48
			p-NH_2SO_2-C_6H_4-NH	229–230	48
Methyl			Methyl	91–93, 115–119/0.8 mm	59
Methyl			Methoxy	107	59
Methyl			Phenyl	151	59

TABLE III (*continued*)

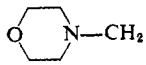
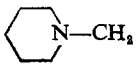
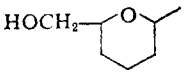
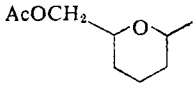
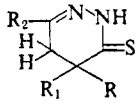
R	R_1	R_2	R_3	MP (°C) or BP (°C/mm Hg)	References
Phenyl			Methyl	109	59
Phenyl			Phenyl	158–159	59
Phenyl			Methoxy	109–110	64, 177
Phenyl			Chloro	128–129	64, 177
			Chloro	121–122	118
			Chloro	98–99	118
			Chloro	92–93.5	111, 184
			Phenyl	101–103	111, 184
			Chloro	88–92	111, 184
			Phenyl	133–136	111, 184
			Chloro	70–75	110, 184
	Amino		Chloro	185–195	18
		Phenyl	Phenyl	230–235	121
		Methyl	Methoxy	208 (dec)	23
		Amino	Amino	>270 (dec)	71
Phenyl	Amino		Chloro	205–206	64, 177
		Phenyl	Phenyl	152–154	111, 184
		Phenyl	Phenyl	198–200	111, 184
		Phenyl	Phenyl	172–175	110, 184
	Phenyl	Phenyl	Phenyl	303–304	13
	Methyl (or H)	H (or methyl)	Chloro	147 (dec)	21[a]
	Cyano	Methyl	Methyl	213–214	50
	Amino	Amino		241–243	178

TABLE III (*continued*)

R	R_1	R_2	R_3	MP (°C) or BP (°C/mm Hg)	References
Phenyl				119	177
				Oil	184
		Phenyl	Phenyl	Oil	184
		Phenyl	Phenyl	162–172	184

[a] Most probably R_1 = methyl.

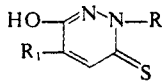
TABLE IV. Reduced 3(2*H*)Pyridazinethiones



R	R_1	R_2	MP (°C)	References
		Methyl	127	66
			182–185[a]	28
Methyl	Methyl	Methyl	90	66
			92	59

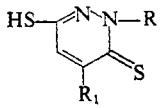
[a] Possibly aromatized.

TABLE V. 6-Hydroxy-3(2*H*)pyridazinethiones



R	R_1	MP (°C)	References
None		157–158	6
	Methyl	187 (dec)	23
Phenyl		235–245 (dec)	62, 177

TABLE VI. 6-Mercapto-3(2*H*)pyridazinethiones



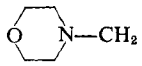
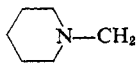
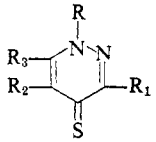
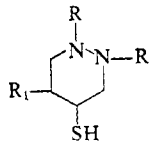
R	R_1	MP (°C)	References
None		220–240 (dec)	31, 32
		230–240 (dec)	6
		237 (dec)	21
		245–246 (dec)	44
		246 (dec)	8, 47
		~250	45
		255 (dec)	49
	Methyl	175–180 (dec)	6
		165–166	118
		152–153	118

TABLE VII. 4(1*H*)Pyridazinethiones



R	R_1	R_2	R_3	MP (°C)	References
None				206–210 (dec)	3
Methyl				164–165.5	3
	Methoxy		Amino	207–209 (dec)	17
	Amino		Methyl	188 (dec)	172
		Amino	Amino	300 (dec)	70
	Phenyl	Phenyl	Phenyl	279	22

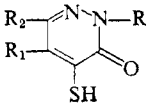
TABLE VIII. Reduced Pyridazine-4-thiols



R	R_1	MP (°C) or BP (°C/mm Hg)	References
None		60/0.15, HCl 108–110	12
	Methyl	113/7[a], HCl 140–142	12
Methyl		90/12, Picrate 155.5–157	12
Methyl	Methyl	104/15[a], Picrate 189 (dec) Picrate 167–168	12
COOEt		112/0.045	12
COOEt	Methyl	110–112/0.02	12

[a] Cis-trans mixture.

TABLE IX. 4-Mercaptopyridazin-3(2*H*)ones



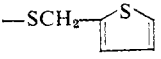
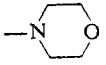
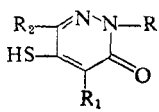
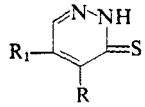
R	R_1	R_2	MP (°C) or BP (°C/mm)	References
Phenyl		Chloro	137–138, 133	57, 177
Phenyl	Methoxy		137–138	14
			150–151	29
			171	175
Benzyl	Chloro		61–62	176
			110/113	176
	Chloro		157	176
Methyl	Chloro		85	176

TABLE X. 5-Mercaptopyridazin-3(2*H*)ones



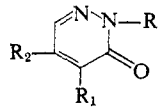
R	R_1	R_2	MP (°C)	References
Phenyl	Chloro		180 (dec)	36, 37
			178–179	20
	Chloro		—	35
			>300	29, 175
Phenyl	Bromo		150 (dec)	36
Phenyl		Chloro	152–156 (dec)	177
	Bromo		>300	175
Benzyl	Chloro		165	176
Methyl	Chloro		179	176
	Chloro		>300	176

TABLE XI. Polymercaptopyridazines



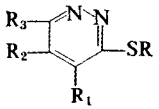
R	R_1	MP (°C)	References
Mercapto	Mercapto	>400	38, 44, 53
Mercapto	Amino	>350 (dec)	51

TABLE XII. Dimercaptopyridazin-3(2*H*)ones



R	R_1	R_2	MP (°C)	References
	Mercapto	Mercapto	>300	35, 175
Phenyl	Mercapto	Mercapto	122	36
			110	14, 44, 53
			125–126.5	24
Benzyl	Mercapto	Mercapto	97	176
Methyl	Mercapto	Mercapto	112	176

TABLE XIII. 3-Alkylthiopyridazines



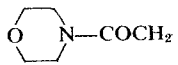
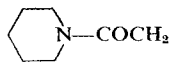
R	R_1	R_2	R_3	MP (°C) or BP (°C/mm)	References
Methyl				37–38, 138/15	59
				39–40, 73/0.1	3
				101, 118–120/3	113
				42	194
Methyl			Methyl	135–141/20	59
Methyl			Methoxy	84.5	21
				85–87	11
				87	59
Methyl			Chloro	101–102	43, 48
				102	21
				103–104	59, 80
Methyl			Amino	112, HCl 216	81
				117–118	25
				116	16
				116–117	11
Methyl			Methylamino	83–84	11
Methyl			Anilino	179–180	48
Methyl			Piperidino	77–79	11
Methyl			Acetylamino	228	108
Methyl			*p*-$NH_2SO_2C_6H_4NH$	193–195	48
Methyl			MeNHCOO—	160	124
Methyl			*p*-$MeC_6H_4SO_2NH$	129–130	82
Methyl			*o*-$MeOC_6H_4O$—	133	43
Methyl			Phenoxy	99	43
Methyl	Amino	Amino		193.5–194.5	178

TABLE XIII (*continued*)

R	R_1	R_2	R_3	MP (°C) or BP (°C/mm)	References
Ethyl			Methyl	41	15
Ethyl			Chloro	65	21
Ethyl			Amino	53–54	25
				92, 192/1	81
				HCl	81
				53	16
Ethyl			Me_2NCOO—	112	124
Ethyl			MeNHCOO—	89	124
Ethyl			*p*-$MeC_6H_4SO_2NH$	144	82
i-Propyl			Chloro	61	113
Allyl			Chloro	66	21
n-Butyl			Amino	84–85	25
				85	16
$HOOCCH_2$			Chloro	115–120	18
				136 (dec)	27, 34, 86, 87
$HOOCCH_2$			Methyl	138–139	114
$HOOCCH_2$			Phenyl	149–150	114
$EtOOC—CH_2$			Chloro	70–72	18
				73–74	34
$C_6H_5NHNHCOCH_2$			Methyl	138–139	114
$C_6H_5NHNHCOCH_2$			Phenyl	181–181.5	114
H_2NCOCH_2			Chloro	180–183 (dec)	19, 125
$HOCH_2CH_2$			Chloro	79–80	54
CH_3COCH_2			Chloro	108–109	19
				100–102	187
$Me_2CHCOCH$			Chloro	72–73	19
$C_6H_5COCH_2$			Chloro	115–116	19
				118–119	187
2,4-di-$MeOC_6H_3COCH_2$			Chloro	139–139.5	19
$(HOCH_2CH_2)_2NCOCH_2$			Chloro	110–112	19
				110–120	56, 125

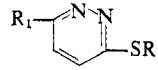
$CH_2CONHCOCH_3$	Chloro	168–170	54
CH_2CH_2COOH	Chloro	153–156	54
—CH(CH$_3$)—COOH	Chloro	115–118	54
—CH(CH$_3$)—CONH$_2$	Chloro	130	54
$EtNHCOCH_2$	Chloro	153–154	19, 26, 125, 165
$MeNHCOCH_2$	Chloro	148–150	19, 26, 125, 165
$C_6H_{11}NHCOCH_2$	Chloro	179–180	19, 125, 165
Me_2NCOCH_2	Chloro	139–140	19, 125
Et_2NCOCH_2		64–65	19
Et_2NCOCH_2	Methyl	36–37	19, 26
Et_2NCOCH_2	Methoxy	Oil	19, 125,
Et_2NCOCH_2	Chloro	95–97	26, 56, 125, 165
		97–98	19
Et_2NCOCH_2	Bromo	87–89	19, 26, 56, 125
$Et_2NCOCH(CH_3)$	Chloro	55–57	26, 54, 56, 125
$Et_2NCOCH_2CH_2$	Chloro	Oil	26, 54, 56, 125
(*n*-Propyl)$_2$NCOCH$_2$	Chloro	55–56	19, 26, 56, 125
(i Propyl)$_2$NCOCH$_2$	Chloro	91–92	19, 125
(*n*-Butyl)$_2$NCOCH$_2$	Chloro	Oil	19, 125
$HOCH_2NHCOCH_2$	Chloro	157	19
$(CH_2{=}CHCH_2)_2NCOCH_2$—	Chloro	56	19, 26, 56, 125
$C_6H_5NHCOCH_2$´	Chloro	147–149	19, 56, 125
$C_6H_5N(Et)COCH_2$	Chloro	87–90	19, 56, 125

TABLE XIII (*continued*)

R	R_1	R_2	R_3	MP (°C) or BP (°C/mm)	References
			Chloro	150–153	19, 26, 56, 125
			Chloro	125–127	19, 26, 56, 125
—CNHN=CMe_2 ‖ NH (or tautomer)			Chloro	121	47
—CNHN=CHC_6H_5 ‖ NH (or tautomer)			Chloro	159	47
Methyl		Methyl	Methoxy	58	23
Methyl	Methyl		Methoxy	100	23
Methyl	Methyl		Chloro		23
				98.5	21
Methyl	Methyl (or H)	H (or methyl)	Chloro	98.5	21
Ethyl	Methyl (or H)	H (or methyl)	Chloro	88	21[a]
Allyl	Methyl (or H)	H (or methyl)	Chloro	80–81.5	21[a]
CH_2COOH	Dimethylamino		Chloro	160	54
CH_2COOEt	Dimethylamino		Chloro	83–84	54
Methyl	Cyano	Methyl	Methyl	66–67	50, 151

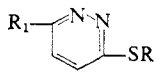
[a] Most probably R_1 = methyl.

TABLE XIV. 3-Arylalkylthiopyridazines



R	R_1	MP (°C)	References
Benzyl	Methyl	93	14
p-Cl-C_6H_4-CH_2	Methyl	97	14
o-Cl-C_6H_4-CH_2	Methyl	64	14
2,4-di-Cl-C_6H_3-CH_2	Methyl	89	14
3,4-di-Cl-C_6H_3-CH_2	Methyl	91	14
o-F-C_6H_4-CH_2	Methyl	80	14
m-F-C_6H_4-CH_2	Methyl	67	14
p-F-C_6H_4-CH_2	Methyl	107	14
Benzyl	Methoxy	80–82	96
Benzyl	Ethoxy	96–97	14
m-F-C_6H_4-CH_2	Ethoxy	88	14
o-F-C_6H_4-CH_2	Ethoxy	59	14
p-F-C_6H_4-CH_2	Ethoxy	116	14
p-Br-C_6H_4-CH_2	Ethoxy	117	14
Benzyl	*n*-Propoxy	70	14
p-F-C_6H_4-CH_2	*n*-Propoxy	90	14
m-F-C_6H_4-CH_2	*n*-Propoxy	56	14
Benzyl	Amino	105	25
		99–101	96
Benzyl	Acetylamino	190–191	96
Benzyl	*p*-$CH_3CONHC_6H_4SO_2NH$	182–183	96
Benzyl	*p*-$NH_2C_6H_4SO_2N(COCH_3)$—	203–204	96
Benzyl	*p*-$NH_2C_6H_4SO_2NH$	191–193	96
o-(OH)$C_6H_4COCH_2$	Chloro	134	54
p-(MeO)$C_6H_4COCH_2$	Chloro	120	54
2,4-di$MeOC_6H_3COCH_2$	Chloro	139	54

TABLE XV. 3-Arylthiopyridazines



R	R_1	MP (°C)	References
Phenyl	Chloro	107–108	18
		82	90
Phenyl	Amino	136	25
		138	16
Phenyl	$NHCHMe_2$	119.3–120.3	99, 95
		Picrate 172.2–177.2	99

TABLE XV (*continued*)

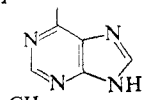
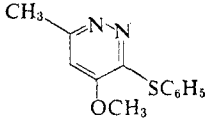
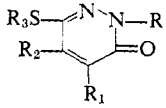
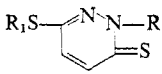
R	R_1	MP (°C)	References
p-ClC_6H_4-	Chloro	96.5–97.5	52, 83
p-MeC_6H_4-	Amino	149	16
p-$NO_2C_6H_4$-	Methyl	142	73
	Chloro		98
		208–209	183

TABLE XVI. 6-Alkyl(or aryl)thiopyridazin-3(2*H*)ones



R	R_1	R_2	R_3	MP (°C)	References
			Methyl	132	113
				132–133	11
			CH_2COOH	210 (dec)	34
				242	27
	Methyl		Methyl	104	23
		Methyl	Methyl		23
			Benzyl	159–161	96
			CH_2COOEt	132	34
			Et_2NCOCH_2	134–136	19
Phenyl			CH_2COOH	213–214	85
Phenyl			CH_2COOMe	114	85
Phenyl			CH_2COOEt	115	85

TABLE XVII. 6-Alkyl(or aryl)thiopyridazine-3(2*H*)thiones



R	R_1	MP (°C)	References
	Methyl	148	7
	CH_2COOH	180 (dec)	27, 34, 114
		184–185 (dec)	7
	CH_2COOEt	125–126	34
		126	7

TABLE XVII (*continued*)

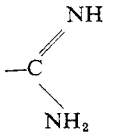
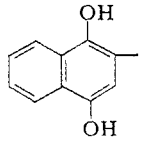
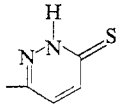
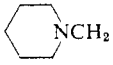
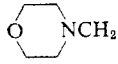
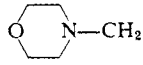
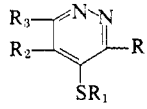
R	R_1	MP (°C)	References
	CH_2CONEt_2	145–147	19
	CH_2CH_2CN	176	8
	CH_2CH_2COOEt	110.5–111	8
		cca 255 (dec)	45
	Dicyclopentadienyl	218–220	8
	Benzyl	178–179	114
	2,5-di-OHC_6H_3—	225–226	112
		184–185	112
		250 (dec) 266–267 (immersed at 260°)	45 52
Methyl	Methyl	73–74	7
CH_2OH	CH_2OH	148–149	118
$(CH_2)_5NCH_2$—	Methyl	71–72	118
		86–87	118
	Methyl	143–144	118
		96–97	118

TABLE XVIII. 4-Alkyl- and Arylthiopyridazines

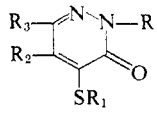


R	R_1	R_2	R_3	MP (°C)	References
	Methyl			44–45	194
				Picrate 155–157	194
				Picrate 149–150.5	3
				HCl 190–191	3
Methoxy	Methyl		Acetylamino	269–271 (dec)	17

TABLE XVIII (*continued*)

R	R_1	R_2	R_3	MP (°C)	References
Methoxy	Methyl		Amino	155–156	17
Chloro	*o*-Aminophenyl		Chloro	cca 150 (dec)	102
Methoxy	*o*-Aminophenyl		Chloro	133 (dec)	102
Chloro	*o*-Methylamino-phenyl		Chloro	cca 120 (dec)	102
Chloro	Methyl		Chloro	126–128	54
Chloro	Ethyl		Chloro	81–82	54
Chloro	CH_2COOH		Chloro	135–136	54
Chloro	$CH_2COOC_4H_9$		Chloro	90	54
Chloro	CH_2CONH_2		Chloro	197	54
Chloro	*p*-Chlorophenyl		Chloro	148–150	54
Phenyl	Ethyl	Phenyl	Phenyl	110	22
Chloro	*o*-$Me_2N(CH_2)_2$-NHC_6H_4—		Chloro	HCl 175–178 (dec)	188

TABLE XIX. 4-Alkyl (or aryl)thiopyridazin-3(2*H*)ones



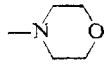
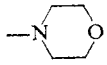
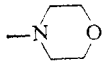
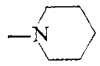
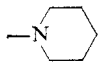
R	R_1	R_2	R_3	MP (°C) or BP (°C/mm Hg)	References
	Methyl		Chloro	190	54
	Benzyl			201	14
Phenyl	Benzyl			114	14
Phenyl	*p*-$ClC_6H_4CH_2$			125	14
Phenyl	Benzyl			138	14
Phenyl	*p*-$ClC_6H_4CH_2$			164	14
Phenyl	Methyl		Chloro	135–136	57
				132–133	177
Phenyl	Ethyl		Chloro	117–118	57
				127–128	177
Phenyl	*p*-$ClC_6H_4CH_2$	Methoxy		114–116	14

TABLE XIX (*continued*)

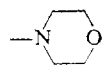
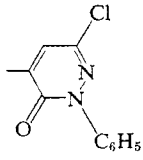
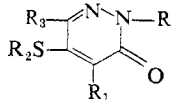
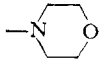
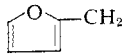
R	R_1	R_2	R_3	MP (°C) or BP (°C/mm Hg)	References
Phenyl	*p*-$ClC_6H_4CH_2$	Ethoxy		87	14
Phenyl	3,4-di-$ClC_6H_3CH_2$	Methoxy		118	14
Phenyl	3,4-di-$ClC_6H_3CH_2$	Ethoxy		92	14
Phenyl	Benzyl	Methoxy		115	14
Phenyl	Benzyl	Ethoxy		98	14
CH_2COOH	Methyl	Chloro		190 (dec)	54
Phenyl	CH_2COOMe		Chloro	121	177
Phenyl	CH_2COOEt		Chloro	101	177
Phenyl	CH_2CONH_2		Chloro	185–186	177
Phenyl	$CH_2CONHNH_2$		Chloro	213	177
Phenyl	$CH_2CONHOH$		Chloro	205–206	177
Phenyl	$CH_2CONHNHCOMe$		Chloro	245–246	177
Phenyl	$CH_2CONHNHCONH_2$		Chloro	234–235	177
Phenyl	$CH_2CONHNHCSNH_2$		Chloro	216–217	177
	Benzyl		Amino	248 (dec)	195
Phenyl	*n*-Propyl		Chloro	96	177
Phenyl	i-Propyl		Chloro	181	177
Phenyl	Allyl		Chloro	126–127	177
Phenyl	CH_2COMe		Chloro	134	177
Phenyl	CH_2OMe		Chloro	87–88	177
Phenyl	CH_2COOH		Chloro	203–204	177
Phenyl	COOEt		Chloro	82–83	177
Phenyl	Benzyl		Chloro	118	177
Phenyl	*p*-$ClC_6H_4CH_2$		Chloro	162	177
Phenyl	2,4-di-$ClC_6H_3CH_2$		Chloro	158	177
Phenyl	3,4-di-$ClC_6H_3CH_2$		Chloro	136–137	177
	Benzyl			201	175
Benzyl	Benzyl	Hydroxy		150	176
Methyl	Benzyl	Hydroxy		167	176
Benzyl	Benzyl	Chloro		96	176
Methyl	Benzyl	Chloro		186/4	176
Phenyl			Chloro	300	177

TABLE XX. 5-Alkyl (or aryl)thiopyridazin-3(2*H*)ones



R	R_1	R_2	R_3	MP (°C)	References
	Chloro	*o*-$NH_2C_6H_4$		198 (dec)	92
				260–261	92
	Bromo	*o*-$NH_2C_6H_4$		196	186
CH_2CH_2COOH	Chloro	CH_2CH_2OH		180–180.5[a]	104
CH_2CH_2COOH	Chloro	CH_2COOH		166	104
				179.5–180.5[b]	104
Phenyl	Chloro	CH_2CH_2OH		104–105	104
Phenyl	Chloro	*p*-$CH_3C_6H_4$—		145–146	104
Phenyl	Chloro	CH_2CONH-*β*-naphthyl		224–225	104,
	Chloro			170	29, 175
Phenyl	Chloro	*o*-$CH_3CONHC_6H_4$		209–210.5	34, 94
	Chloro	CH_2COOH		234–235	168
	Chloro	Ethyl		231–232	168
	Chloro	Phenyl		210–211	168
Phenyl	Chloro	Methyl		116–117	168, 177
Phenyl	Chloro	Phenyl		117–118	168
Phenyl	Chloro	CH_2COOH		157–158	168
				194–194.5[a]	104
Phenyl	Chloro	Benzyl		141	37
Phenyl	Chloro	*p*-$ClC_6H_4CH_2$		155–156	37
	Mercapto			150–151, 153	29, 175
Methyl	Chloro	Benzyl		112–113, 110	182, 176
Phenyl	Chloro	Ethyl		96–98	177
Phenyl	Chloro	Allyl		99–100	177
Phenyl		Methyl	Chloro	178–180	177
Phenyl		Ethyl	Chloro	153	177
Phenyl		*n*-Propyl	Chloro	141–142	177
Phenyl		Allyl	Chloro	131	177
	Bromo	*o*-CH_3CONH-C_6H_4—			
Methyl	Bromo	*o*-CH_3CONH-C_6H_4—		216–217	186
Methyl	Bromo	*o*-$(CH_3CO)_2N$-C_6H_4—		189–190	186
Methyl	Bromo	*o*-NH_2-C_6H_4—		171–172	186
		Benzyl		191	175
	Chloro	Benzyl		197	175
	Bromo	Benzyl		197	175
	Chloro			133	175
Benzyl	Chloro	Benzyl		175	176
Benzyl	Hydroxy	Benzyl		142	176
	Mercapto	Benzyl		186	175
	Mercapto			145	175

[a] Dicyclohexylammonium salt. [b] Bisdicyclohexylammonium salt.

TABLE XXI. 5-Arylthiopyridazin-4(1*H*)ones

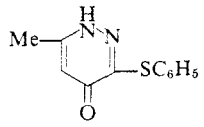
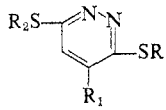
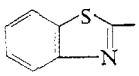
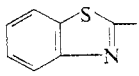
Compound	MP (°C)	References
	252–254	183

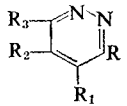
TABLE XXII. 3,6-Bis(substituted thio)pyridazines



R	R_1	R_2	MP (°C) or BP (°C/mm)	References
Methyl		Methyl	124.5–125.5	52, 83
			126–127	6, 7
			128–129	6
Methyl		CH_2CONEt_2	54–55	19
Methyl		$C_6H_4NHNHCOCH_2$	152–153	114
CH_2COOH		Methyl	183–184	114
CH_2COOH		Benzyl	108–109	114
CH_2COOH		CH_2COOH	130 (dec)	34, 86, 87
			155	27
			168 (dec)[a]	7
			H_2O 123–124	7
CH_2COOEt		CH_2COOEt	52–53	86, 87
			56–57	7
$CH_2CH_2NEt_2$		$CH_2CH_2NEt_2$	52–53	89
			165–167/0.07	89
			205–206 (dec)[b]	89
$(CH_2)_3NEt_2$		$(CH_2)_3NEt_2$	cca $140/2.6 \times 10^{-5}$	89
			184–184.5[b]	89
			205[c]	89
			$140/3.10^{-3}$ [c]	88
$(CH_2)_4NEt_2$		$(CH_2)_4NEt_2$	cca $175/10^{-4}$	89
			Dioxalate 181–183	89
$(CH_2)_4NEt_2$	Methyl	$(CH_2)_4NEt_2$	$170/10^{-3}$	88
Phenyl		Phenyl	78	90
p-ClC_6H_4		*p*-ClC_6H_4	150–150.5	52, 83
o-$COOHC_6H_4$		*o*-$COOHC_6H_4$	203–205.5[d]	52, 83
$C_6H_5N{=}C(NMe_2)-$		$C_6H_5N{=}C(NMe_2)-$	Viscous oil	116
Benzyl		Benzyl	121–122	114
Benzyl		2,5-di-OHC_6H_3	189–190	112
			180.5–182.5	95, 99–101

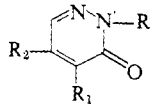
[a] Structure not verified. [b] Bismethobromide. [c] Bis(4-nitrobenzobromide) salt.
[d] Decomposition of part at 170° C, the residue then darkening at melting point indicated.

TABLE XXIII. Bis- and Polysubstituted Alkylthio-, Arylalkylthio-, or Arylthiopyridazines



R	R_1	R_2	R_3	MP (°C)	References
Chloro	Benzylthio	Benzylthio		113–114	14
Chloro	*p*-$ClC_6H_4CH_2S$	*p*-$ClC_6H_4CH_2S$		120–121	14
Chloro	*o*-$ClC_6H_4CH_2S$	*o*-$ClC_6H_4CH_2S$		135–136	14
Chloro	3,4-di-$ClC_6H_3CH_2S$	3,4-di-$ClC_6H_3CH_2S$		130–131	14
Benzylthio	Benzylthio	Benzylthio		151–152	44
				157	14, 53
p-$ClC_6H_4CH_2S$	*p*-$ClC_6H_4CH_2S$	*p*-$ClC_6H_4CH_2S$		164	14
o-$ClC_6H_4CH_2S$	*o*-$ClC_6H_4CH_2S$	*o*-$ClC_6H_4CH_2S$		123.5	14
2,4-di-$ClC_6H_3CH_2S$	2,4-di-$ClC_6H_3CH_2S$	2,4-di-$ClC_6H_3CH_2S$		167	14
3,4-di-$ClC_6H_3CH_2S$	3,4-di-$ClC_6H_3CH_2S$	3,4-di-$ClC_6H_3CH_2S$		173	14
p-$BrC_6H_4CH_2S$	*p*-$BrC_6H_4CH_2S$	*p*-$BrC_6H_4CH_2S$		170	14
p-$IC_6H_4CH_2S$	*p*-$IC_6H_4CH_2S$	*p*-$IC_6H_4CH_2S$		179.5	14
o-$FC_6H_4CH_2S$	*o*-$FC_6H_4CH_2S$	*o*-$FC_6H_4CH_2S$		124	14
m-$FC_6H_4CH_2S$	*m*-$FC_6H_4CH_2S$	*m*-$FC_6H_4CH_2S$		149.5	14
p-$FC_6H_4CH_2S$	*p*-$FC_6H_4CH_2S$	*p*-$FC_6H_4CH_2S$		153	14
Chloro	Methylthio	Methylthio	Methylthio	82–83	54
Chloro	Methylthio	Methylthio	Chloro	112–115	54
Chloro	Ethylthio	Ethylthio	Chloro	47–48	54
Fluoro	Phenylthio	Phenylthio	Fluoro	97–99	93
Fluoro	Phenylthio	Phenylthio	Phenylthio	140.5–143	93
Phenylthio	Phenylthio	Phenylthio	Phenylthio	208–210	93

TABLE XXIV. Di- and Polyalkyl (or aryl)thiopyridazin-3(2*H*)ones



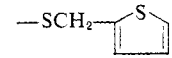
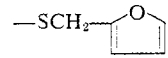
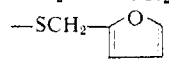
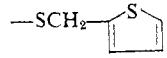
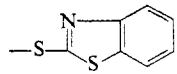
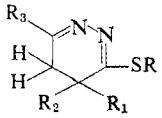
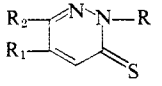
R	R_1	R_2	MP (°C)	References
	Benzylthio	Benzylthio	166–167	14
			160	175
	Phenylthio	Phenylthio	162–164	84
	Ethylthio	Ethylthio	151–152	84
			121	29, 79, 175
			97	79, 175
Methyl	Methylthio	Methylthio	123.5–124.8	24
			100–101.5	84
Phenyl	Methylthio	Methylthio	114–116	84
Phenyl	Ethylthio	Ethylthio	74–76	84
Cyclohexyl	Methylthio	Methylthio	103–104	84
3,4-di-ClC_6H_3	Methylthio	Methylthio	167–169	84
p-ClC_6H_4	Methylthio	Methylthio	150–152	84
m-MeC_6H_4	Methylthio	Methylthio	118–120	84
Cyclooctyl	Methylthio	Methylthio	62–64	84
p-BrC_6H_4	Methylthio	Methylthio	142–143	84
o-FC_6H_4	Methylthio	Methylthio	137–139	84
Phenyl	Phenylthio	Phenylthio	164–165	84
Phenyl	Benzylthio	Benzylthio	163	53, 54
			163–164	14
Phenyl	$—SCH_2COOH$	$—SCH_2COOH$	188–190	84
Phenyl	*p*-$MeOC_6H_4S—$	*p*-$MeOC_6H_4S—$	128–129	84
Phenyl	*p*-$ClC_6H_4S—$	*p*-$ClC_6H_4S—$	123–125	84
Phenyl	*p*-$BrC_6H_4CH_2S—$	*p*-$BrC_6H_4CH_2S—$	170	14
Phenyl	*o*-$ClC_6H_4CH_2S—$	*o*-$ClC_6H_4CH_2S—$	128–129	14
Phenyl	*p*-$ClC_6H_4CH_2S—$	*p*-$ClC_6H_4CH_2S—$	167–169	14
Phenyl	*o*-$FC_6H_4CH_2S—$	*o*-$FC_6H_4CH_2S—$	132	14
Phenyl	*m*-$FC_6H_4CH_2S—$	*m*-$FC_6H_4CH_2S—$	137	14
Phenyl	*p*-$FC_6H_4CH_2S—$	*p*-$FC_6H_4CH_2S—$	131	14
Phenyl	3,4-di-$ClC_6H_3CH_2S—$	3,4-di-$ClC_6H_3CH_2S—$	195–197	14
Phenyl	2,4-di-$ClC_6H_3CH_2S—$	2,4-di-$ClC_6H_3CH_2S—$	145	14
Phenyl	Cyclohexylthio	Cyclohexylthio	80–82	84
Phenyl	$SCH_2CCl{=}CCl_2$	$SCH_2CCl{=}CCl_2$	79–81	84
Phenyl			66	97, 117
Phenyl			112	97, 117
Phenyl			157–158	84
Benzyl	Benzylthio	Benzylthio	92	176
Methyl	Benzylthio	Benzylthio	91	176
	o-CH_3CONH-C_6H_4-S—	*o*-$CH_3CONHC_6H_4$-S—	245–246 (dec)	186
Methyl	*o*-CH_3CONH-C_6H_4-S—	*o*-CH_3CONH-C_6H_4-S—	201–202	186
Methyl	*o*-NH_2-C_6H_4-S—	*o*-NH_2-C_6H_4-S—	135–136	186

TABLE XXV. Reduced 3-Alkylthiopyridazines



R	R_1	R_2	R_3	MP (°C) or BP (°C/mm Hg)	References
Methyl	Methyl	Methyl	Methyl	118–120/15	66
				100–105/0.7	59
Methyl			Methyl	Oil	66
Ethyl	Methyl	Methyl	Methyl	125–130/20	66

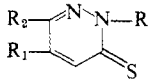
TABLE XXVI. N_2-Glycosides of Pyridazine-3(2*H*)thiones[a]



R	R_1	R_2	MP (°C)	References
		—*O*-β-Gl(Ac)$_4$	192–194	63
		—*S*-β-Gl(Ac)$_4$	154–156	121
Phenyl		—*O*-β-Gl(Ac)$_4$	134–135	62
β-Gl			150–160	60, 120, 121
β-Gl		Methyl	257–258	60, 120, 121
β-Gl		Chloro	192–194 (dec)	120, 121
β-Gl		Phenyl	145–150	120, 121
β-Gl		Methoxy	205–206	121
β-Gl		Hydroxy		61, 62
β-Gl	Phenyl	Phenyl	240–244	120, 121
β-Gl(Ac)$_4$			157–158	60, 120, 121
β-Gl(Ac)$_4$		Methyl	137–139	60, 120, 121
β-Gl(Ac)$_4$		Chloro	155–157	120, 121
β-Gl(Ac)$_4$		Methoxy	163–164	121
β-Gl(Ac)$_4$		CH_3COO	187–189	61, 62
			184–186	62
β-Gl(Ac)$_4$		Phenyl	145–146 and 160–165 (double mp)	120, 121
β-Gl(Ac)$_4$		—*O*-β-Gl(Ac)$_4$	194–195	61, 62
β-Gl(Ac)$_4$		—*O*-β-Gl(Ac)$_4$	120–125	61, 62
β-Gl(Ac)$_4$	Phenyl	Phenyl	184–186	120, 121

[a] β-Gl(Ac)$_4$ = tetraacetyl-1-β-D-glucosyl; α-Gl(Ac)$_4$ = tetraacetyl-1-α-D-glucosyl; β-Gl = 1-β-D-glucosyl.

TABLE XXVII. *N*-2′-Deoxy-D-ribofuranosylpyridazine-3(2*H*)thiones



R[a]	R_1	R_2	R_3	MP (°C)	References
α		Phenyl	*p*-Toluyl	118–122	191
β		Phenyl	*p*-Toluyl	162–163	191
α		Phenyl		154–155	191
β		Phenyl		163–165	191
α	Phenyl	Phenyl	*p*-Toluyl	160–162	191
β	Phenyl	Phenyl	*p*-Toluyl	207–209	191
α	Phenyl	Phenyl		195–196	191
β	Phenyl	Phenyl		216–219	191

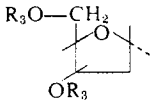
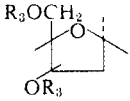
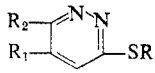
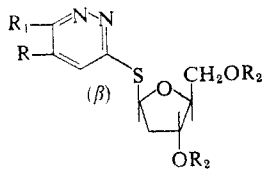
[a] α =  ; β = 

TABLE XXVIII. 3-Glycosylthiopyridazines



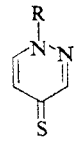
R[a]	R_1	R_2	MP (°C)	References
β-Gl			179–181	120, 121
β-Gl		Methyl	113–114	120, 121
β-Gl		Chloro	120–121 (dec)	120, 121
β-Gl		Methoxy	87–88	121
β-Gl		Phenyl	183–186	120, 121
β-Gl		—*S*-β-Gl	156–157	121
β-Gl	Phenyl	Phenyl	Amorphous	120, 121
β-Gl(Ac)$_4$			180–181	120, 121
β-Gl(Ac)$_4$		Methyl	185–186	120, 121
β-Gl(Ac)$_4$		Chloro	136–137	120, 121
β-Gl(Ac)$_4$		Methoxy	132–133	121
β-Gl(Ac)$_4$		Phenyl	199–200	120, 121
β-Gl(Ac)$_4$		—*S*-β-Gl(Ac)$_4$	186–187	121
β-Gl(Ac)$_4$	Phenyl	Phenyl	180–182	120, 121



R	R_1	R_2	MP (°C)	References
	Phenyl	*p*-Toluyl	105–110 (dec)	191
	Phenyl		125–130 (dec)	191
Phenyl	Phenyl	*p*-Toluyl	Syrup	191
Phenyl	Phenyl		87–90	191

[a] β-Gl = 1-β-D-glucosyl; β-Gl(Ac)$_4$ = tetraacetyl-1-β-D-glucosyl.

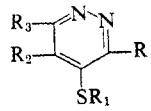
TABLE XXIX. N_1-Glycosides of Pyridazine-4(1*H*)thione



R[a]	MP (°C)	References
β-Gl	209–210	122, 123
β-Gl(Ac)$_4$	175–176	122, 123

[a] β-Gl = 1-β-D-glucosyl; β-Gl(Ac)$_4$ = tetraacetyl-1-β-D-glucosyl.

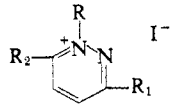
TABLE XXX. 4-Glycosylthiopyridazines



R	R_1[a]	R_2	R_3	MP (°C)	References
	β-Gl			155–157 (dec)	122, 123
	βGl(Ac)$_4$			186–187 and 190-191[b]	122,123
Phenyl	β-Gl(Ac)$_4$	Phenyl	Phenyl	182	22

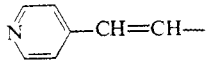
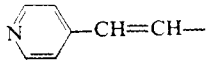
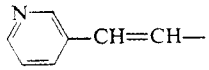
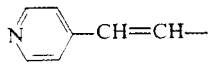
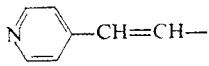
[a] β-Gl = 1-β-D-glucosyl; β-Gl(Ac)$_4$ = tetraacetyl-1-β-D-glucosyl.
[b] Double melting point.

TABLE XXXI. Quaternized Sulfur-Containing Pyridazines



R	R_1	R_2	MP (°C)	References
Methyl	Methylthio		147–148	59
Methyl		Methylthio	188	59
Methyl	Methylthio	Methylthio	160–162	59
Methyl	Methyl	Methylthio	159	59
Methyl	Methylthio	Methyl	132–134	59
Methyl	Methoxy	Methylthio	198	59

TABLE XXXI (*continued*)

R	R_1	R_2	MP (°C)	References
Methyl	Phenyl	Methylthio	177	59
Phenyl	Methyl	Methylthio	197–198	59
Phenyl	Phenyl	Methylthio	183	59
Methyl	Methyl		191–193	131
Methyl	Methylthio		192	131
Methyl	Methylthio		230 (dec)	132
Ethyl	Methyl		125–126	131
Ethyl	Methylthio		180–182	131

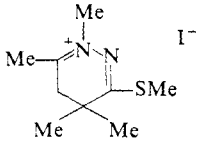
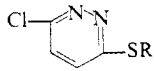
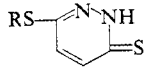
Compound	MP (°C)	References
	213–214 (dec)	59, 66

TABLE XXXII. 3-Acylthio-6-chloropyridazines



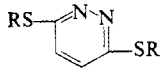
R	MP (°C)	References
COOEt	49.5–50.5	18
COOMe	88–89	18
n-PrCOO—	61–62	18
n-BuCOO—	29–30	18
n-C_5H_{11}COO—	32–33	18
n-C_6H_{13}COO—	45–46	18
n-C_7H_{15}COO—	45–46	18
n-C_8H_{17}COO—	59–60	18
$COOCH_2C_6H_5$	101–103	18
$COOC_6H_5$	122–124	18
C_6H_5CO—	112–114	54

TABLE XXXIII. 6-Acylthiopyridazine-3(2*H*)thiones



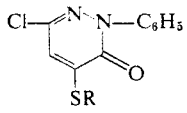
R	MP (°C)	References
Acetyl	152–153	6
	154–155	7
Benzoyl	207 (dec)	7

TABLE XXXIV. 3,6-Bis(acylthio)pyridazines



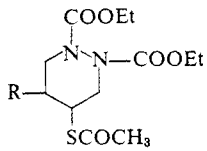
R	MP (°C)	References
CH_3CO—	123–124	6
C_6H_5CO—	180	7

TABLE XXXV. 4-Acylthio-3(2*H*)pyridazinones



R	MP (°C)	References
CH_3CO—	163–165	177
C_6H_5CO—	133	177
CH_2=$CH(CH_2)_8CO$—	48–49	177

TABLE XXXVI. Reduced 4-Acetylthiopyridazines



R	BP (°C/mm Hg)	References
None	140/0.02	12
Methyl	140/0.08[a]	12

[a] Probably a mixture of cis and trans isomers.

TABLE XXXVII.

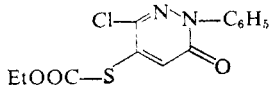
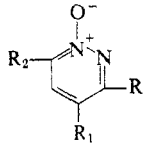
Compound	MP (°C)	References
	99–100	177

TABLE XXXVIII. Sulfur-Containing Pyridazine *N*-Oxides



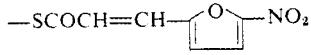
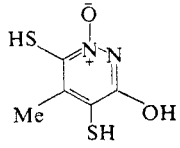
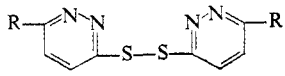
R	R_1	R_2	MP (°C)	References
Methoxy		Mercapto	140–141	39, 40, 41
Phenoxy		Mercapto	143–145	39, 40
Methoxy			167–168	41
Methylthio		Methyl	135–136	109
Methyl-sulfonyl		Methyl	162–163	109
Methylthio		Amino	155	108
Methylthio		Acetylamino	209	108
Hydroxy	Mercapto	Mercapto	242–247 (dec)	42, 179
Hydroxy	Mercapto	Methyl	233 (dec)	180
Hydroxy	Methyl	Mercapto	213 (dec)	180
			182	180

TABLE XXXIX. Disulfides



R	MP (°C)	References
Methylthio	182	7
Methyl	148	73
Phenyl	230–234	45
Chloro	157.5	72
	171	45

TABLE XXXIX (*continued*)

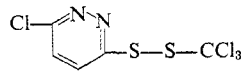
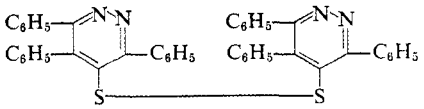
Compound	MP (°C)	References
	94–95	143
	236	22

TABLE XL. Disulfides of Pyridazin-3(2*H*)ones and -thiones

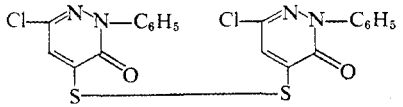
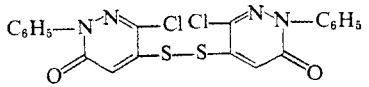
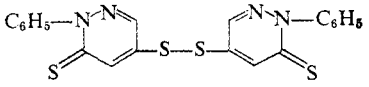
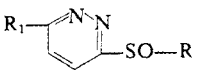
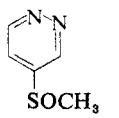
Compound	MP (°C)	References
	260–262	177
	213–214	177
	218–220	177

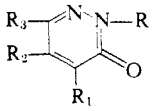
TABLE XLI. Pyridazinyl Sulfoxides



R	R_1	MP (°C)	References
Methyl	Chloro	110–112	137
Methyl	Amino	137.5 70[a]	134, 135, 136
Ethyl	Amino	143	134, 135, 136
Ethyl	*p*-$MeC_6H_5SO_2NH$—	198	138
p-$NO_2C_6H_4$—	Methyl	121–123	73
Methyl		65	194
		92–93	194

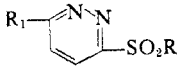
[a] Monohydrate.

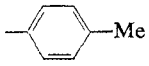
TABLE XLII. Pyridazinonyl Sulfoxides



R	R_1	R_2	R_3	MP (°C)	References
Phenyl	MeSO		Chloro	154–156	177
Phenyl		MeSO	Chloro	163–163.5	177
p-NO_2-C_6H_4—	MeSO		Chloro	176	177
2,4-di-NO_2-C_6H_3—	MeSO		Chloro	213.5–214.5	177
p-NO_2-C_6H_4—		MeSO	Chloro	205	177
2,4-di-NO_2-C_6H_3—		MeSO	Chloro	229–230	177

TABLE XLIII. 3-Pyridazinyl Sulfones

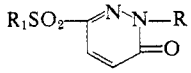


R	R_1	MP (°C)	References
Methyl		87–88	69, 194, 197
Methyl	Chloro	118–120	48, 80
Methyl		147–148	80
Methyl	Dimethylamino	116–118.5	80
Methyl	*n*-Butylamino	117–118	80
Methyl	Anilino	168–170	80
Methyl	Cyclohexylamino	160–162	80
Methyl	*p*-$NH_2SO_2C_6H_4NH$—	208–210	48
Ethyl	Methyl	107–108	73
Amino	Acetylamino	246–247	140
n-Butylamino	Chloro	65	74
n-Propylamino	Chloro	127–128	74
Morpholino	Chloro	210–211	74
	—$NHSO_2C_6H_4NH_2$-*p*	195	144
Hydrazino	Chloro	185–186	74
p-$MeCONHC_6H_4$—	Methoxy	239.5–240.5	198
p-$NO_2C_6H_4$—	Methyl	175	73
p-$NH_2C_6H_4$—	Methyl	120–121[a]	73
Benzyl	Methoxy	144–146	96
Benzyl	*p*-$CH_3CONHC_6H_4SO_2NH$—	229–231	96
Benzyl	*p*-$NH_2C_6H_4SO_2NH$—	216–217	96
C_6H_5CH— | CH_3	Chloro	173–174[b]	74

[a] H_2O.

[b] D,L—.

TABLE XLIV. Pyridazin-3(2*H*)onyl-6-sulfones



R	R_1	MP (°C) or BP (°C/mm)	References
	Methyl	202	142
	Ethyl	151	142
	i-Propyl	144	142
	Benzyl	210–211	96
Methyl	Methyl	159.5	142
Methyl	Ethyl	99.5	142
Methyl	i-Propyl	131.5	142
Ethyl	Methyl	91.5–92.5	142
Ethyl	Ethyl	55	142
Ethyl	i-Propyl	97–98.5	142
CH_2COOEt	Methyl	96–96.5	142
CH_2COOEt	Ethyl	51.5 118–123/0.02	142
CH_2COOEt	i-Propyl	88–89.5	142
Phenyl	CH_2COOH	175	85

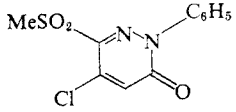
Compound	MP (°C)	References
	169–170	177

TABLE XLV. Pyridazinyl-4 (or 5)-sulfones

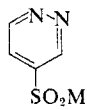
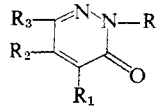
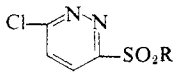
Compound	MP (°C)	References
	144	69

TABLE XLVI. Pyridazinonyl-4 (or -5)-Sulfones

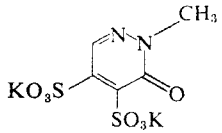


R	R_1	R_2	R_3	MP (°C)	References
Phenyl	$MeSO_2$		Chloro	175–176	177
Phenyl	$MeSO_2$	Chloro		174–175	139
Phenyl	Chloro	$MeSO_2$		160–162	139
Phenyl		$MeSO_2$	Chloro	189.5–191	177
p-NO_2-C_6H_4—	$MeSO_2$		Chloro	222–223	177
2,4-di-NO_2-C_6H_3—	$MeSO_2$		Chloro	213–214	177
p-$NO_2C_6H_4$—		$MeSO_2$	Chloro	247–248	177
2,4-di-NO_2-C_6H_3—		$MeSO_2$	Chloro	217–218	177
p-NO_2-C_6H_4	Chloro	$MeSO_2$		244.5–246.5	177
2,4-di-NO_2-C_6H_3—	Chloro	$MeSO_2$		200.5–202.5	177

TABLE XLVII. 6-Chlorpyridazinyl-3-sulfonic Acid and Sulfonyl Chloride



R	MP (°C)	References
Hydroxy	249 (dec)	72
Chloro	50–55 (dec)[a]	74

Compound	MP (°C)	References
	365–370 (dec)	182

[a] Crude product.

TABLE XLVIII. Sulfonamides of Pyridazin-3(2*H*)ones

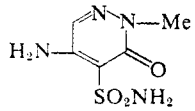
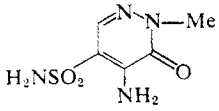
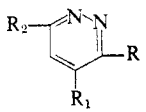
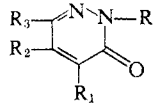
Compound	MP (°C)	References
	267–269	182
	222–223	182

TABLE XLIX. Thiocyanatopyridazines



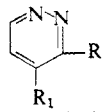
R	R_1	R_2	MP (°C)	References
Chloro		SCN	110–112 (dec)	147
			123–124 (dec)	30, 147
Bromo		SCN	113–115 (dec)	30, 147
Chloro	SCN	Chloro	115–117	54, 147

TABLE L. Thiocyanato-3(2*H*)pyridazinones

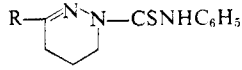


R	R_1	R_2	R_3	MP (°C)	References
CH_2SCN			Chloro	153–154	54
CH_2CH_2SCN			Chloro	104–105	54
CH_2SCN	Chloro		Chloro	112–113	54
CH_2SCN	Chloro	Chloro	Chloro	120–122	54
CH_2SCN		Chloro	Chloro	108–109	54
CH_2SCN	Chloro	Chloro		105–106	54
Phenyl	SCN		Chloro	147–149	177
Phenyl		SCN	Chloro	110.5–112	177
Phenyl		Chloro	SCN	99–100	177

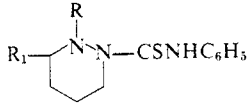
TABLE LI. Pyridazinylthioamides



R	R_1	MP (°C)	References
$CSNH_2$		168	150
	$CSNH_2$	214–215	150



R	MP (°C)	References
Methyl	106	153
Phenyl	106–108	154
o-Br-C_6H_4—	109–110	155



R	R_1	MP (°C)	References
COOEt	Methyl	119–120 (dec)	152
C_6H_5NHCS	Methyl	163–163.5	153

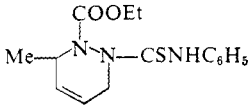
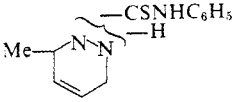
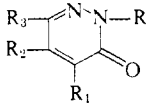
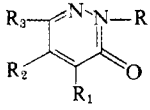
Compound	MP (°C)	References
	183	152
	112.5–113	153

TABLE LII. Pyridazin-3(2*H*)onyl Thioamides



R	R_1	R_2	R_3	MP (°C)	References
	$CSNH_2$			305	150
Methyl	$CSNH_2$	Methyl	Methyl	213–214	151

TABLE LIII. Pyridazin-3(2*H*)onyl Thiophosphates

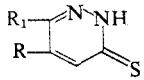


R	R_1	R_2	R_3	MP (°C)	References
CH_2CH_2CN			$O—P(OEt)_2$ ‖ S	51–53	158
			$OPS(OEt)C_6H_5$	121–123	157
	H (or chloro)	Chloro (or H)	$O—P(OEt)(C_6H_5)$ ‖ S	138–144	157
COOEt			$OPS(OEt)_2$	Oil	161
CH_2CH_2COOEt			$OPS(OEt)_2$	Oil	158
CH_2CH_2COOMe			$OPS(OEt)_2$	Oil	158
CH_2CH_2COO-*n*-Pr			$OPS(OEt)_2$	Oil	158
CH_2CH_2COO-*i*-Pr			$OPS(OEt)_2$	Oil	158
CH_2CH_2COO-*n*-Bu			$OPS(OEt)_2$	Oil	158
CH_2COOEt			$OPS(OEt)_2$	36–37	158
CH_2COOMe			$OPS(OEt)_2$	55–56	158
CH_2COO-*n*-Pr			$OPS(OEt)_2$	Oil	158
CH_2COO-*i*-Pr			$OPS(OEt)_2$	Oil	158
CH_2COO-*n*-Bu			$OPS(OEt)_2$	Oil	158
CH_2CH_2OH			$OPS(OEt)_2$	Oil	158
$CH_2CON(i\text{-}Pr)_2$			$OPS(OEt)_2$	88–89	158
CH_2CONMe_2			$OPS(OEt)_2$	Oil	158
CH_2CONEt_2			$OPS(OEt)_2$	Oil	158
$CH_2CON(n\text{-}Pr)_2$			$OPS(OEt)_2$	Oil	158
$CH_2CH_2CONMe_2$			$OPS(OEt)_2$	Oil	158
$CH_2CH_2CONEt_2$			$OPS(OEt)_2$	Oil	158
p-$NO_2C_6H_4$-CO—			$OPS(OEt)_2$	108–110	161
Benzoyl			$OPS(OEt)_2$	Oil	161
$C_{11}H_{23}CO$—			$OPS(OEt)_2$	40–47	161
$C_{15}H_{31}CO$			$OPS(OEt)_2$	50	161

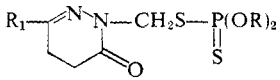
TABLE LIII (*continued*)

R	R_1	R_2	R_3	MP (°C)	References
C_6H_5SO—			$OPS(OEt)_2$	Oil	161
p-$MeC_6H_4SO_2$			$OPS(OEt)_2$	Oil	161
$MeSO_2$—			$OPS(OEt)_2$	Oil	161
Me_2NCO—			$OPS(OEt)_2$	Oil	161
Me_3CCO—			$OPS(OEt)_2$	Oil	161
	$OPS(OEt)_2$		Hydroxy		156
	$OPS(OMe)_2$		Methyl		156

TABLE LIV. Thio- and Dithiophosphates of Miscellaneous Pyridazines



R	R_1	References
—$OPO(O\text{-}n\text{-}Pr)_2$	Methyl	156
—$SPS(OEt)_2$	Mercapto	156



R	R_1	References
Methyl	Methyl	159, 160
Ethyl	Methyl	159, 160
Methyl	Phenyl	159, 160
Ethyl	Phenyl	159, 160
Methyl	*p*-ClC_6H_4	159, 160

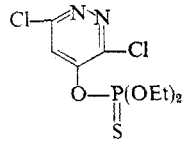
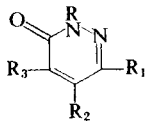
Compound	
	156

TABLE LV. Miscellaneous Sulfur-Containing Pyridazines



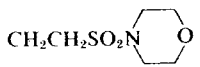
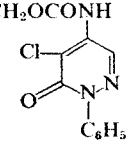
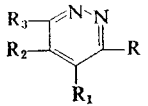
R	R_1	R_2	R_3	MP (°C)	References
	$CH_2SCH_2C_6H_5$			131.5–132	78
$CH_2CH_2SO_3H$	Hydroxy			295	146
$CH_2CH_2SO_3$-C_6H_5	Hydroxy			150	146
$CH_2CH_2SO_2NEt_2$	Hydroxy			216	146
	Hydroxy			180	146
Phenyl		NSO	Chloro	240–241	173
Phenyl		$NHCOSC_6H_5$	Chloro	143–145	173
Phenyl		*p*-ClC_6H_4SCONH	Chloro	159–160	173
Phenyl		*p*-BrC_6H_4SCONH	Chloro	165–168	173
Phenyl		$NHCOS{-}CH_2C{=}CCl_2$ (Cl)	Chloro	86–89	173
Phenyl		$NHCOSCH_2CH_2COOH$	Chloro	165 (dec)	173
Phenyl		$NHCOSCH_2CH_2NEt_2 \cdot HCl$	Chloro	175–177	173
Phenyl		$NHCOSCH_2CH_2OCONH$ 	Chloro	194–195	173
Cl_3CSO—			Chloro	156–157	143
Phenyl	NHCSOEt	Phenyl	Phenyl	186	22

TABLE LV (*continued*)



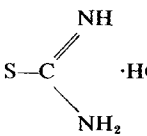
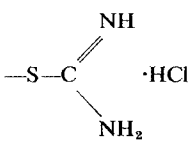
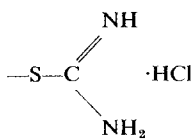
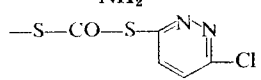
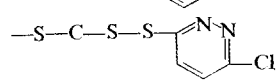
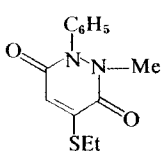
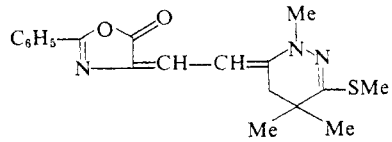
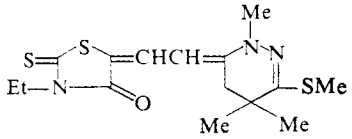
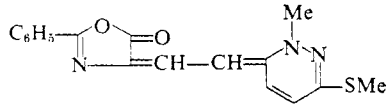
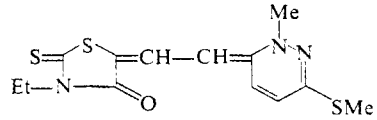
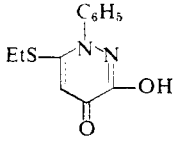
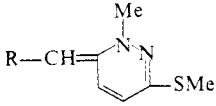
R	R_1	R_2	R_3	MP (°C)	References
			Chloro	158–159	45
CH_2—S—C(NH_2)=NH·2 HCl				187–188 (dec)	199
CH_2SH					199
CH_2S—C_6H_5				54–55.5	199
				Picrate 112–113	199
				132–135	45
			Chloro	136–138 (dec)	18
			Chloro	149–150 (dec)	18
MeHgS—			*p*-$NH_2C_6H_4SO_2NH$—	210 (dec)	163
MeHgS—			Chloro	196	163
MeHgS—			Ethoxy	103.5	163
				133–135	105

TABLE LV (*continued*)

Compound	MP (°C)	References
	194	59
	194	59
	235–237	59
	216–218	59
	225–227	77



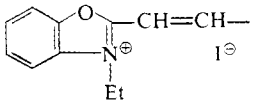
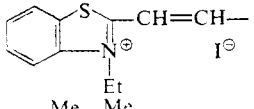
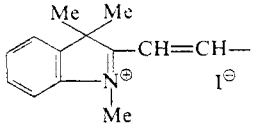
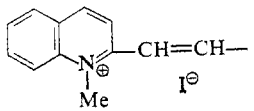
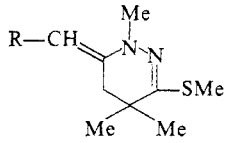
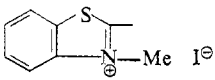
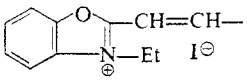
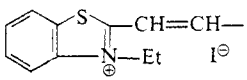
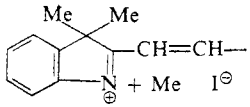
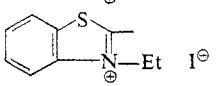
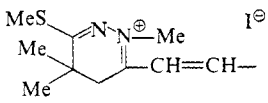
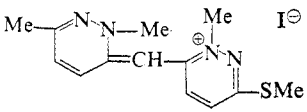
R	MP (°C)	References
	250	59
	238	59
	191	59

TABLE LV (*continued*)

R	MP (°C)	References
	267	59
	268–269	59



R	MP (°C)	References
	266	59
	251	59
	259	59
	254	59
	258	59
	282	59

Compound	MP (°C)	References
	247 (dec)	59

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Subject Index

Compounds which are referred to only in tables and which can be found by examining the tables listed under the appropriate general headings covering the types of compounds are not listed individually in the index.

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