

**FIVE-MEMBERED HETEROCYCLIC COMPOUNDS
WITH NITROGEN AND SULFUR
OR NITROGEN, SULFUR, AND OXYGEN
(EXCEPT THIAZOLE)**

This is the fourth volume published in the series
THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

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A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER, *Consulting Editor*



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L. L. BAMBAS

Parke, Davis and Company, Detroit, Michigan

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INTRODUCTION TO THE SERIES

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.

*Research Laboratories
Eastman Kodak Company
Rochester, New York*

ARNOLD WEISSBERGER

Preface

The purpose of this book is the presentation of a complete and critical review of the literature on five-membered heterocyclic compounds containing nitrogen and sulfur, or nitrogen, sulfur and oxygen, as members of the ring. Spot checks and cross references to related substances have revealed that occasionally compounds have been omitted; the latter, however, comprise a very small percentage of the whole work.

While a reviewer should be an authority on the subject which he treats, this criterion can hardly be satisfied in a field as broad as that of this book. Therefore, the author has described the historical development of the chemistry of these compounds and usually followed this presentation by a discussion giving his own point of view, a résumé, or his evaluation of the subject. Thus, it behooves the reader to be critical rather than passive in accepting the interpretation of the facts.

In such a treatise, the question of nomenclature arises to plague both author and reader. In general, the systems employed by *Chemical Abstracts* and *Ring Index* are used, with occasional modifications for the sake of consistency. Unfortunately, such modifications add confusion to chaos. To assist the reader, structural formulas are given whenever feasible. In general, the index follows *Chemical Abstracts* as regards nomenclature, irrespective of the manner in which the chemical name appears in the text; an attempt has also been made to cross index the minor variations from the *Chemical Abstracts* nomenclature.

The contents of this book are divided into three unrelated sections: (1) the thiadiazoles; (2) the five-membered rings containing nitrogen, sulfur and oxygen; and (3) the isothiazoles. Each section is then subdivided into small closely related classes of compounds. For instance, the 2-amino-1,3,4-thiadiazoles constitute such a small class of compounds while the 2,5-diamino-1,3,4-thiadiazoles are included in another class. This type of grouping assists in the understanding of these compounds and also in the location of a particular compound.

The author wishes to acknowledge with sincere thanks the cooperation and assistance of the following members of the staff at Parke, Davis and Company: Dr. L. A. Sweet, Director of Research and Development;

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Detroit, Michigan
April, 1952

L. L. BAMBAS

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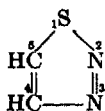
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PART I

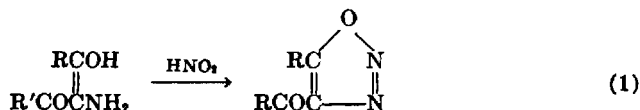
Thiadiazoles, Their Derivatives and Selenium Analogs

Derivatives of the 1,2,3-Thiadiazoles and Their Selenium Analogs

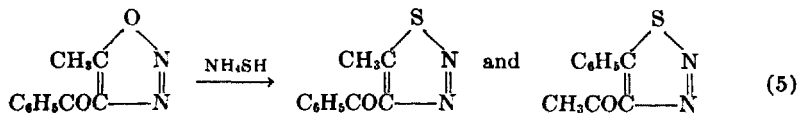
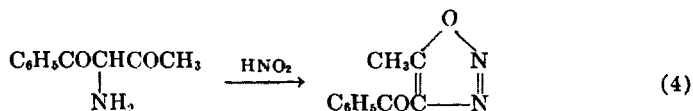
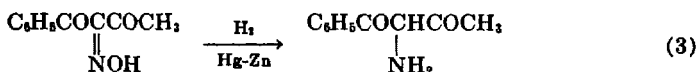
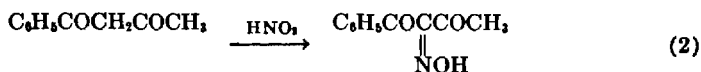
1,2,3-Thiadiazoles (Ring Index No. 70)



Wolff and his co-workers¹ studied the reactions of aliphatic diazoanhydrides, or 1,2,3-oxadiazoles. The diazoanhydrides, prepared by diazotizing α -aminoketones (1), when reacted with ammonium hydrosulfide



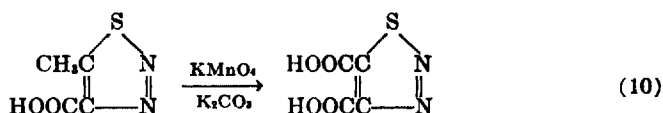
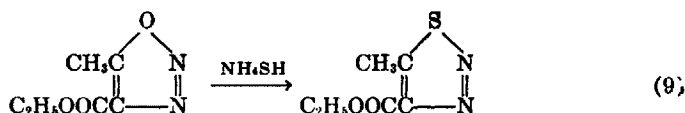
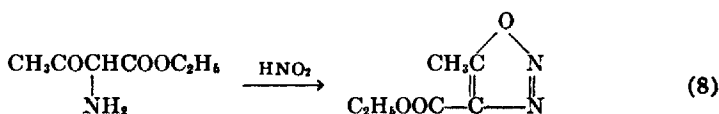
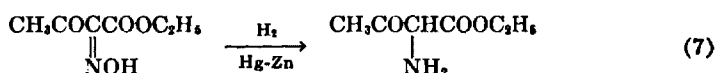
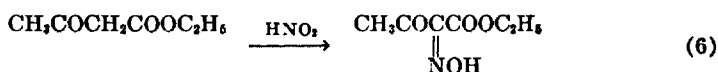
gave disubstituted 1,2,3-thiadiazoles. Wolff's synthesis proceeded as shown by equations (2-5). The two isomeric 1,2,3-thiadiazoles were readily separated, since 4-benzoyl-5-methyl-1,2,3-thiadiazole formed a mercuric chloride double salt while the other isomer did not form this complex.



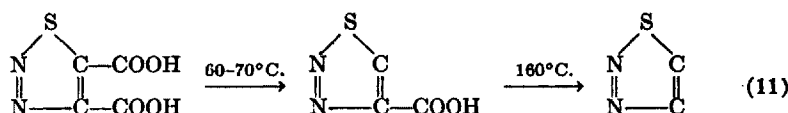
¹ Wolff, *Ann.*, **325**, 129 (1902).

Dimroth² and Staudinger³ felt that the formation of the two isomers cast some doubt as to the structure of the diazoanhydride. They believed that the diazoanhydrides were true aliphatic diazo compounds which were more stable than the usual aliphatic diazo compounds.

Wolff⁴ continued his studies with the preparation of a number of derivatives of 1,2,3-thiadiazole. Ethyl acetoacetate was the starting material in a number of these syntheses (6-9). Oxidation of 4-carboxy-5-methyl-1,2,3-thiadiazole gave 4,5-dicarboxy-1,2,3-thiadiazole (10). This compound was



also prepared by starting with ethyl oxalacetate. The carboxyl group in the 5-position readily ruptured from the 1,2,3-thiadiazole nucleus at 60 to 70°C. The carboxyl group in the 4-position split off when the temperature was raised to 160°C. or higher (11). The 5-methyl and 5-phenyl-1,2,3-thiadiazoles also were prepared by this synthesis.



² Dimroth, *Ann.*, **373**, 339 (1910).

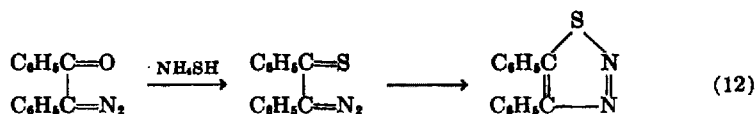
³ Staudinger, *Helv. Chim. Acta*, **4**, 239 (1921).

⁴ Wolff, *Ann.*, **333**, 1 (1904).

The 1,2,3-thiadiazoles were much more stable than the 1,2,3-oxadiazoles. Strong mineral acids caused very little decomposition and hot sodium hydroxide and alcoholic potassium hydroxide decomposed these compounds very slowly with the formation of hydrogen sulfide. 1,2,3-Thiadiazole decomposed in sodium hydroxide at 90–95°C. with the brisk evolution of a gas, while the homologs and the carboxy acids decomposed to a very slight extent.

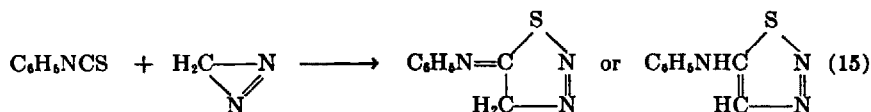
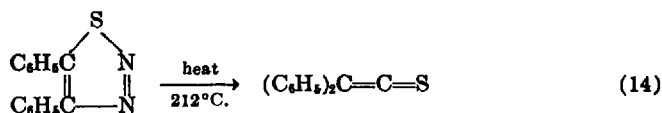
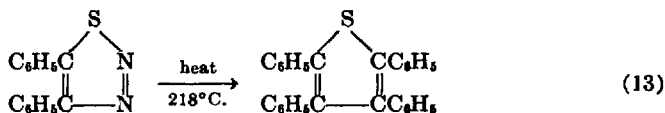
1,2,3-Thiadiazole and its homologs are very weak bases. They form hydrochlorides with concentrated hydrochloric acid which are hydrolyzed in water. They react with methyl iodide at elevated temperatures to give quaternary salts.

Staudinger and Seigwart⁵ found that phenylbenzoyldiazomethane and ammonium hydrosulfide give 4,5-diphenyl-1,2,3-thiadiazole (12), which



when heated in naphthalene at 218°C. produces tetraphenylthiophene. At a slightly lower temperature (212°C.) an intermediate, believed to be diphenyl methylene thioketone, was obtained (13,14).

Pechmann and Nold⁶ allowed diazomethane to react with phenyl isothiocyanate and obtained 5-anilino-1,2,3-thiadiazole (15). This compound reacted with nitrous acid, acetic anhydride, and benzoyl chloride to give the monosubstituted products.

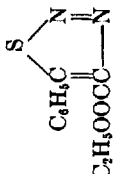
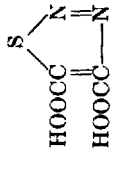
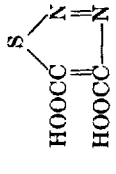
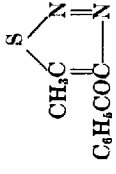
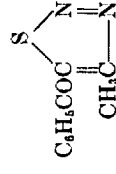
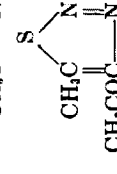


⁵ Staudinger and Siegwart, *Ber.*, **49**, 1918 (1916).

⁶ Pechmann and Nold, *Ber.*, **29**, 2588 (1896).

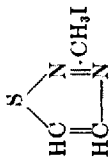
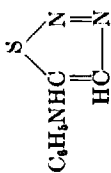
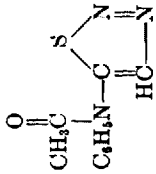
TABLE I. Preparation of the 1,2,3-Thiadiazoles

No.	Name	Ref.	Preparation	Structure	Solubility	M.p., °C.
1	1,2,3-Thiadiazole	1			very sol. in alc. and ether, sol. in water	liquid, boils 83-5 at 60 mm. Hg
2	5-Methyl-1,2,3-thiadiazole	1			very sol. in alc. and ether, sol. in water	liquid 91 at 38 mm. Hg
3	5-Phenyl-1,2,3-thiadiazole	1			sol. in ether, alc., and chloroform	53-3.5
4	4,5-Diphenyl-1,2,3-thiadiazole	2			sol. in ether	93-4
5	4-Carboxy-1,2,3-thiadiazole	1			sol. in alc. and hot water	228 dec.
6	4-Carboxy-5-methyl-1,2,3-thiadiazole	1			sol. in alc.	35
7	4-Carboxy-5-methyl-1,2,3-thiadiazole	1	saponification of 6 with 20% NaOH		sol. in water	113

No.	Name	Ref.	Preparation	Structure	Solubility	M.p., °C.
8	4-Carboxy-5-phenyl-1,2,3-thiadiazole	1	diazoanhydride of ethyl benzoylacetate →		sol. in alc. and ether	42
9	4-Carboxy-5-phenyl-1,2,3-thiadiazole	1	saponification of 8 with alkali	—	sol. in water	157 dec.
10	4,5-Dicarboxy-1,2,3-thiadiazole	1	 diazoanhydride of ethyl oxalacetate + NH ₄ SH $\xrightarrow[\text{K}_2\text{CO}_3]{\text{KMnO}_4}$		sol. in alc.	98 dec.
11	4-Benzoyl-5-methyl-1,2,3-thiadiazole	3	diazoanhydride of benzoylacetone + NH ₄ SH →		sol. in hot alc., forms HgCl ₂ complex	43
12	4-Methyl-5-benzoyl-1,2,3-thiadiazole	3	same as 11		sol. in hot alc., does not form HgCl ₂ complex	70
13	5-Methyl-4-acetyl-1,2,3-thiadiazole	3	diazoanhydride of acetylacetone NH ₄ SH →		sol. in alc. and oil ether	

(Table continued)

TABLE I. Preparation of the 1,2,3-Thiadiazoles (Continued)

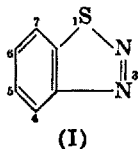
No.	Name	Ref.	Preparation	Structure	Solubility	M.p., °C.
14	1,2,3-Thiadiazolium methyl iodide	1	compound 1 + CH ₃ I $\xrightarrow{110-120^{\circ}\text{C.}}$	 exact structure unknown	sol. in 6-7 parts water, difficultly sol. in alc.	220-2 dec.
15	5-Methyl-1,2,3-thiadiazolium methyl iodide	1	compound 2 + CH ₃ I $\xrightarrow{\text{reflux in methanol}}$	see 14	very sol. in water	76-7
16	5-Phenyl-1,2,3-thiadiazolium methyl iodide	1	compound 3 + CH ₃ I $\xrightarrow{110-120^{\circ}\text{C.}}$	see 14	sol. in water	158
17	5-Anilino-1,2,3-thiadiazole	4	C ₆ H ₅ NCS $\xrightarrow{\text{H}_3\text{C}-\text{N}=\text{N}}$	 structure unknown	sol. in warm alc., insol. in water	173
18	Trinitro derivative of 17	4	compound 17 + HNO ₃ + H ₂ SO ₄	—	—	221
19	5-Acetanilido-1,2,3-thiadiazole	4	compound 17 + acetic anhydride $\longrightarrow$	 see 19	sol. in dil. alc.	162
20	5-Benzamido-1,2,3-thiadiazole	4	compound 17 + benzoyl chloride $\longrightarrow$	see 19	sol. in dil. alc.	157
21	5-N-Nitrosoanilino-1,2,3-thiadiazole	4	compound 17 $\xrightarrow{+\text{HNO}_2}$	see 19	sol. in dil. alc.	98

¹ Wolff, *Ann.*, 333, 1 (1904).² Staudinger and Siegwart, *Ber.*, 49, 1918 (1916).³ Wolff, *Ann.*, 325, 129 (1902).⁴ Pechmann and Nold, *Ber.*, 29, 2588 (1896).

TABLE II. Preparation of 2-Phenyl-4-methyl- Δ^1 -1,2,3-thiadiazoline-S-dioxide and Its Derivatives

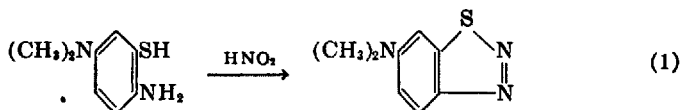
Compound	Solubility	M.p., °C.
2-Phenyl-4-methyl- Δ^1 -1,2,3-thiadiazoline-S-dioxide	alc., benzene	84-5
5-Bromo-2-phenyl-4-methyl- Δ^1 -1,2,3-thiadiazoline-S-dioxide	benzene, ligroin	123
5,5-Dibromo-2-phenyl-4-methyl- Δ^1 -1,2,3-thiadiazoline-S-dioxide	benzene, chloroform	95-6
5-Nitro-2-phenyl-4-methyl- Δ^1 -1,2,3-thiadiazoline-S-dioxide	alc.	170-2

1,2,3-Benzothiadiazoles



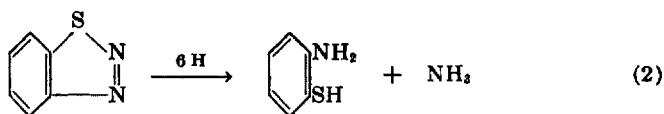
(Ring Index No. 693)

Bernthsen¹ allowed 4-amino-3-mercaptodimethylaniline to react with nitrous acid and obtained 6-dimethylaminobenzothiadiazole (Eq. 1).



Jacobson² prepared benzothiadiazole in the same manner and determined its molecular weight in order to prove that it was not a more complex structure.

Jacobson and his co-workers, Janssen, Kwaysser, Ney, and Schwartz,³ used this reaction in preparing a number of derivatives and homologs of benzothiadiazole. These benzothiadiazoles exhibited very weak basic characteristics. Reduction in ammonia gave the parent aminomercaptide

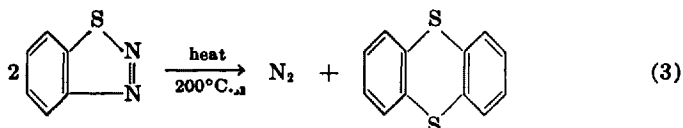


¹ Bernthsen, *Chem.-Ztg.*, **12**, 1318 (1888); *Ann.*, **251**, 1 (1888).

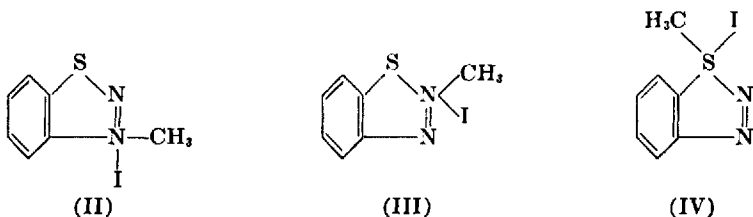
² Jacobson, *Ber.*, **21**, 3104 (1888).

³ Jacobson, *Ann.*, **277**, 209 (1893).

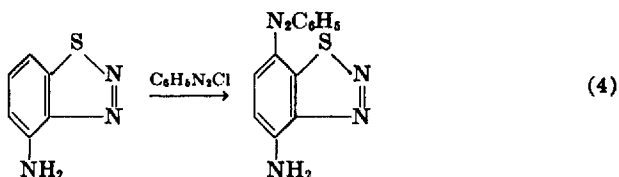
(2). Heating the benzothiadiazoles over 200°C. produced the thianthrenes (3). Alkyl iodides reacted with the benzothiadiazoles to give



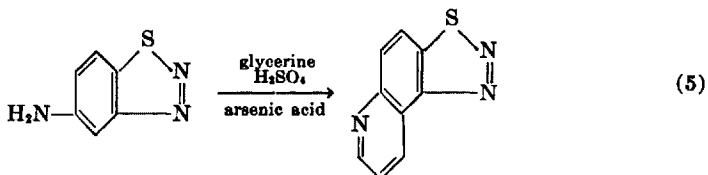
quaternary iodides whose exact structure has not been determined. Their structures may have been any one of compounds II-IV.



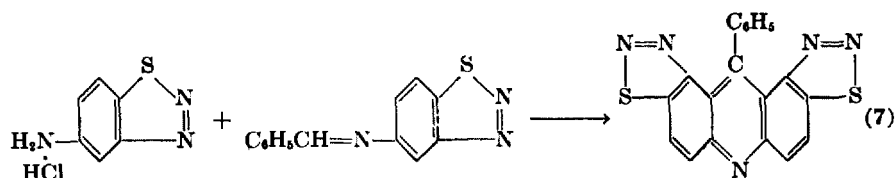
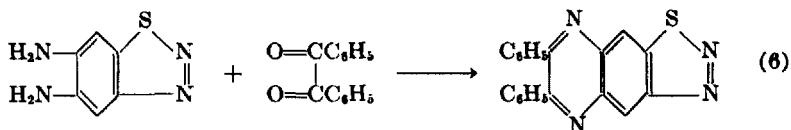
Fries *et al.* showed that benzothiadiazole possessed much the same chemical qualities as naphthalene. Phenyldiazonium chloride and 5-aminobenzothiadiazole produced 4-phenylazo-5-aminobenzothiadiazole, a red dyestuff. Reduction of this colored compound yielded 4,5-diaminobenzothiadiazole. Phenyldiazonium chloride would not react with 4-chloro-5-aminobenzothiadiazole, but did react with 4-aminobenzothiadiazole to give 4-amino-7-phenylazobenzothiadiazole (4).



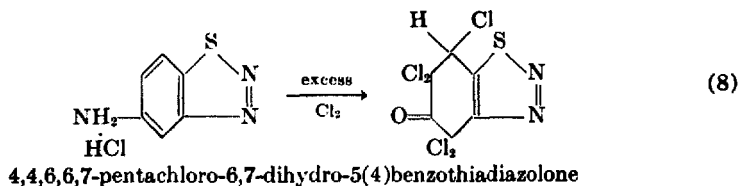
A number of condensed systems containing 1,2,3-thiadiazole rings were prepared from these aminobenzothiadiazoles. Skraup reactions with the 4- and 5-aminobenzothiadiazoles produced [1.2.3]thiadiazolo[4.5]-quinolines (5). Benzil and 4,5-diaminobenzothiadiazole gave a [1.2.3]-



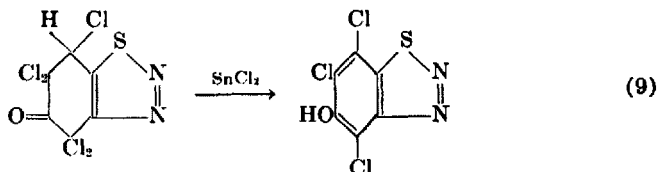
thiadiazolo[4.5-*f*]quinoxaline derivative (6). The 5-benzalaminobenzothiadiazole, on refluxing in an alcoholic solution of 5-aminobenzothiadiazole hydrochloride, yielded a substituted acridine (7).



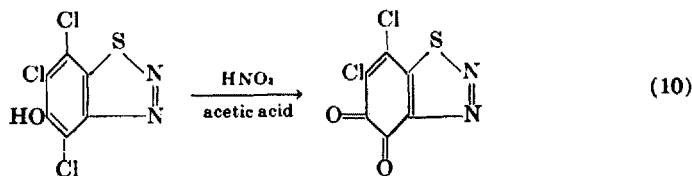
An excess of chlorine and 5-aminobenzothiadiazole hydrochloride produces a pentachloro ketochloride derivative (8). Reduction of this keto-



chloride with stannous chloride yields 5-hydroxy-4,6,7-trichlorobenzothiadiazole (9). The 6,7-dichloro-4,5-benzothiadiazolone is synthesized

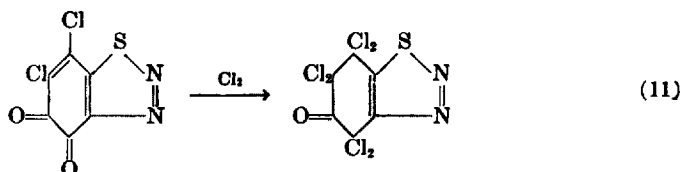


by oxidizing 5-hydroxy-4,6,7-trichlorobenzothiadiazole with concentrated nitric acid (10). Reduction of this quinone gives 4,5-dihydroxy-6,7-

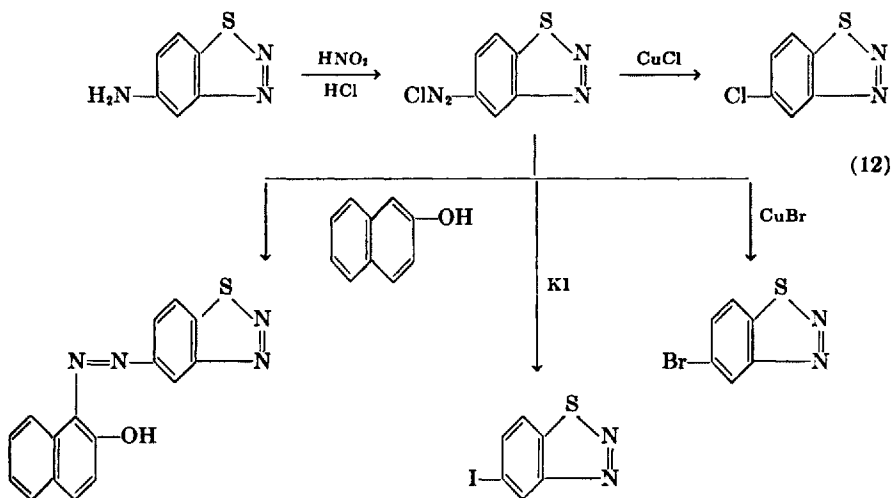


dichlorobenzothiadiazole. Chlorination of 6,7-dichloro-4,5-benzothiadiazolone produces a synthesis of 4,4,6,6,7,7-hexachloro-6,7-dihydro-5(4)-

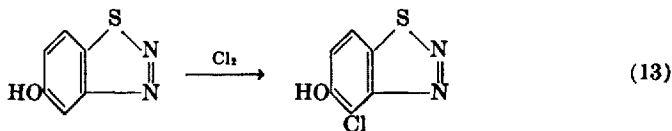
benzothiadiazolone (11). These reactions are analogous to those using 2-naphthylamine to prepare the same type of naphthalene compounds.



The 5-nitrobenzothiadiazole is prepared from the 2-mercapto-5-nitro aniline.⁴⁻⁶ Hodgson and Dodgson⁶ found that the amine formed by reducing the nitro group could be diazotized, with the usual reactions of the aryl diazonium compounds taking place (12).



The 5-hydroxybenzothiadiazole, an analog of 2-naphthol, is prepared by diazotizing 5-aminobenzothiadiazole in dilute sulfuric acid. These compounds halogenate in the 4-position (13). 4-Bromo-5-hydroxybenzothiadi-

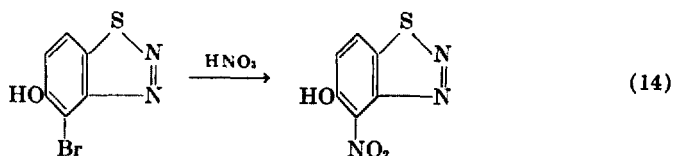


⁴ Fries, Vorbordt, and Siebert, *Ann.*, **454**, 172 (1927).

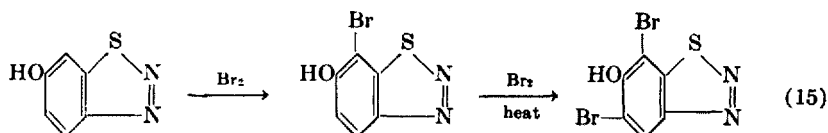
⁵ Fries and Reitz, *Ann.*, **527**, 38 (1937).

⁶ Hodgson and Dodgson, *J. Chem. Soc.*, 1948, 870.

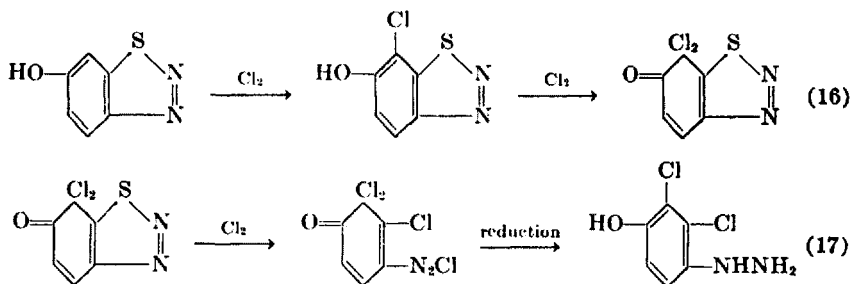
azole and nitric acid in chloroform give 4-nitro-5-hydroxybenzothiadiazole. This compound is identical to the compound prepared by the nitration of 5-hydroxybenzothiadiazole (14).



6-Hydroxybenzothiadiazole is prepared by demethylating 6-methoxybenzothiadiazole and forms the 7-bromo compound readily, but the second bromine does not enter in the 5-position very easily (15). 6-Hydroxy-7-



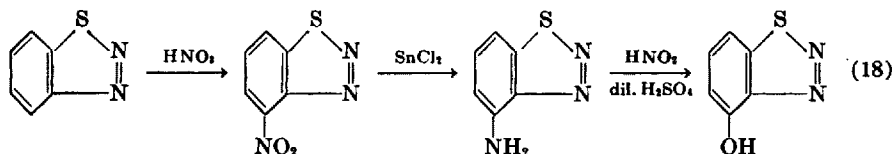
bromobenzothiadiazole and nitric acid give 6-hydroxy-7-nitrobenzothiadiazole. Chlorination of 6-hydroxybenzothiadiazole with an equivalent amount of chlorine gives 7-chloro-6-hydroxybenzothiadiazole. Further chlorination produces the 7,7-dichloro-6(7)-benzothiadiazolone (16). A fourfold addition of chlorine produces a 2,3,3-trichloro-4(3) benzenone diazonium chloride (17), which couples with R salt to give a red dyestuff. It is reduced to 2,3-dichloro-4-hydrazinophenol.



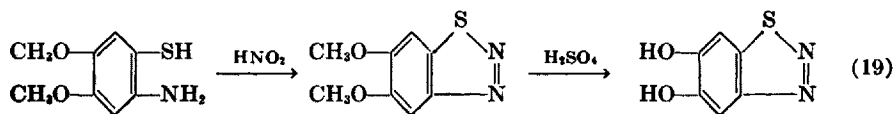
The 6-hydroxybenzothiadiazole decomposes to 2,3,4,6-tetrachlorophenol by chlorinating with an excess of chlorine, freeing the solution of chlorine, and reducing with stannous chloride.

Benzothiadiazole cannot be brominated with bromine in hot acetic acid, but the addition of iron as a catalyst produced a perbromide having the empirical formula $(\text{C}_6\text{H}_5\text{N}_2\text{S}_2)_2 \cdot 2\text{HBr} \cdot \text{Br}_2$. All the bromine was removed by reduction with stannous chloride.

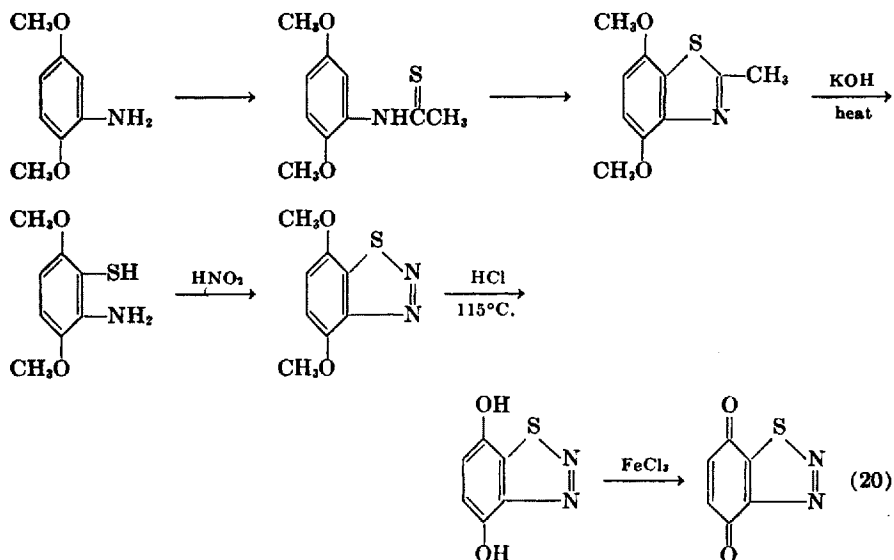
Nitration of benzothiadiazole with potassium nitrate and sulfuric acid yields 4-nitrobenzothiadiazole with some 7-nitro compound. 4-Hydroxybenzothiadiazole is then prepared in the usual manner (18) which can be brominated to 5,7-dibromo-4-hydroxybenzothiadiazole.



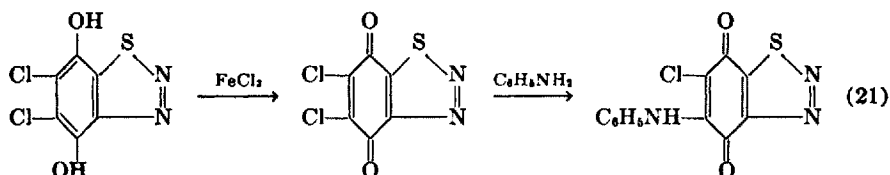
The 5,6-dihydroxybenzothiadiazole was synthesized according to scheme (19): oxidation of this 5,6-dihydroxybenzothiadiazole with nitric acid or lead peroxide in order to produce an orthoquinone met with very little success.



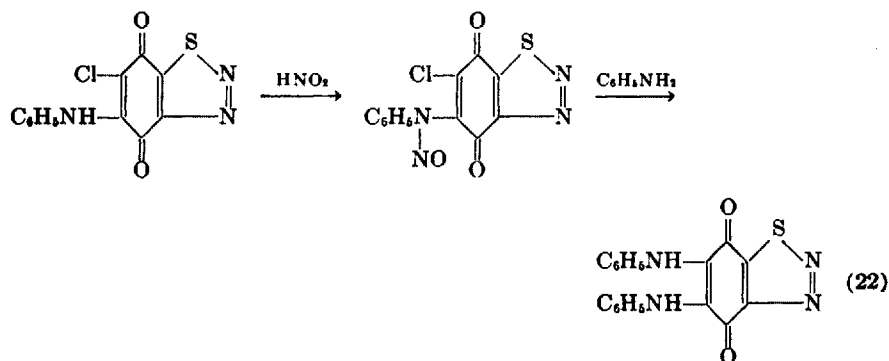
The synthesis of 4,7-benzothiadiazole-1,2-dione followed a similar set of procedures (20): this 4,7-benzothiadiazole-1,2-dione oxidized in the presence of calcium hypochlorite with elimination of hydrogen. Chlorination of this quinone yielded 4,7-dihydroxy-5,6-dichlorobenzothiadiazole.



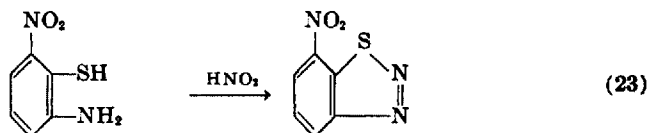
The 5,6-dichloro-4,7-benzothiadiazole-1,2-dione was prepared by oxidizing the parent hydroquinone with ferric chloride. This compound reacted with aniline and gave 6-chloro-5-anilino-4,7-benzothiadiazole-1,2-dione (21).



Nitrosating this compound and then allowing the nitroso compound to react with aniline produced 5,6-dianilino-4,7-benzothiadiazole-1,2-dione (22).



Hodgson and Dodgson⁷ prepared the 7-nitro and 7-nitro-5-methylbenzothiadiazoles from the parent thiophenols (23). Their synthesis



of the 7-nitrobenzothiadiazoles ascertained that the principle product of the nitration of benzothiadiazole is 4-nitrobenzothiadiazole along with some 7-nitrobenzothiadiazole.

Discussion

Fries and co-workers^{8,9} have established conclusively that the benzothiadiazoles are naphthalenelike rather than benzenoid in character. The

⁷ Hodgson and Dodgson, *J. Chem. Soc.*, 1948, 1006.

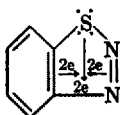
⁸ Fries, *Ann.*, 454, 121 (1927).

⁹ Fries and Reitz, *Ann.*, 527, 38 (1937).

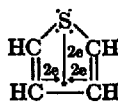
4- and 5-positions on the benzothiadiazole ring appear to be more naphthalenelike in character than do the 6- and 7-positions. For instance the nitration of benzothiadiazole gave 4-nitrobenzothiadiazole in predominance with a small fraction of 7-nitrobenzothiadiazole.

The 5,7-dibromo-6-hydroxybenzothiadiazole could be prepared by brominating the 6-hydroxybenzothiadiazole, but the analogous 4,6-dibromo-5-hydroxy-benzothiadiazole could not be prepared. Chlorination of the 5-aminobenzothiadiazole with an excess of chlorine produced 4,4,6,6,7-pentachloro-6,7-dihydro-5-(4) benzothiadiazolone, while chlorination of 6-hydroxybenzothiadiazole ruptured the thiadiazole ring and gave a chlorinated benzenediazonium compound. Benzothiadiazole does not appear to brominate as readily as does naphthalene.

Hodgson and Dodgson¹⁰ in an excellent review on the subject of benzothiadiazoles called attention to the similarity of the thiadiazole ring (V) to the thiophene nucleus (VI) which they depicted as follows:



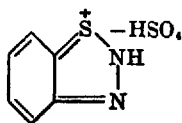
(V)



(VI)

They showed that benzothiadiazole is remarkably stable to iron and dilute acid.

Hodgson and Dodgson found that benzothiadiazole in concentrated sulfuric acid gave an intense blue color. Naphthalene gives no such color. They suggest that this color formation is due to salt formation and hence the presence of a methylene blue-like chromophore (VII).



(VII)

In all other respects the benzothiadiazoles behaved in the same manner as the naphthalenes. These characteristics are summarized as follows:

1. The 4- and 5-aminobenzothiadiazoles formed phenylazo compounds in the 7- and 4-positions, respectively, with phenyldiazonium chloride rather than the aminoazo compounds. The 4-chloro-5-aminobenzothiadiazole gave no reaction with phenyldiazonium chloride and a very small amount of dyestuff with *p*-nitrophenyl diazonium chloride. In this respect it resembled 1-chloro-2-aminonaphthalene.

¹⁰ Hodgson and Dodgson, *J. Soc. Dyers and Colourists*, 64, 65 (1948).

2. The 4- and 5-aminobenzothiadiazoles underwent the Skraup reaction to give the thiadiazoloquinolines, while 4-chloro-5-aminobenzothiadiazole would not react in this manner.

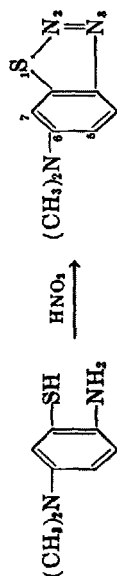
3. Oxidation of the 4,7- and the 4,5-dihydroxybenzothiadiazoles gave benzothiadiazolediones analogous to the 1,4- and 1,2-naphthoquinones. The 5,6-dihydroxybenzothiadiazole could not be oxidized to a quinone. The derivatives of these benzothiadiazolediones possessed the same chemical characteristics as the derivatives of the naphthoquinones.

4. Nitration of 4-bromo-5-hydroxy- and 7-bromo-6-hydroxybenzothiadiazoles replaced the bromo group with a nitro group.

5. Nitration occurred in the 4- and 7-positions of benzothiadiazole which is equivalent to the 1-position in the naphthalene structure.

TABLE IIIA. Preparation of Benzothiadiazoles (Compounds Prepared by the General Method)

The general method for the preparation of the benzothiadiazoles is the same as the first preparation given by Berntsen¹ for 6-dimethylaminobenzothiadiazole.



No.	Substituted benzothiadiazoles	Ref.	Solubility	M.p., °C.
1	Benzothiadiazole	2	organic solvents	36-7
2	4-Methyl	3	—	35
3	6-Methyl	4	—	Oil at 0°
4	4,6-Dimethyl	5	alc., ether	42-3
5	4,6,7-Trimethyl	5	alc., ether	37
6	5-Nitro	5	alc.	85
		6	benzene, acetone, acetic acid, chloroform	144
7	6-Nitro	7	—	143-5
8	6-Dimethylamino	5	alc., benzene	136-7
9	6-Diethylamino	1	alc., benzene	78
10	5-Chloro	1	alc., benzene	106-7
11	6-Methoxy	8	—	107
12	7-Chloro-6-methoxy	9	benzene, alc., acetic acid	72
13	5,6-Dimethoxy	6	alc.	114 dec.
14	4,7-Dimethoxy	10	—	138
15	6-Carboxy	11	alc., benzene, acetic acid	120
16	6-Carbomethoxy	5	hot water, alc.	138-9
17	7-Nitro-5-methyl	5	alc., benzene	150-1
		3	—	149

¹ Berntsen, *Ann.*, 251, 1 (1888).

² Jacobson, *Ber.*, 21, 3104 (1888).

³ Hodgson and Dodgson, *J. Chem. Soc.*, 1948, 1006.

⁴ Hodgson and Francoe, *J. Chem. Soc.*, 1933, 296.

⁵ Jacobson *et al.*, *Ann.*, 277, 209 (1893).

⁶ Fries, Vorbordt, Siebert, *Ann.*, 454, 172 (1927).

⁷ Hodgson and Dodgson, *J. Chem. Soc.*, 1948, 870.

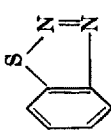
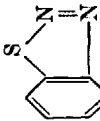
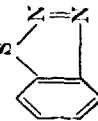
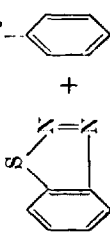
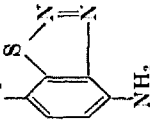
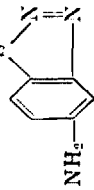
⁸ Pollak, Riesz, and Kahane, *Monatsh.*, 49, 213 (1928).

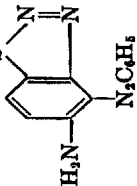
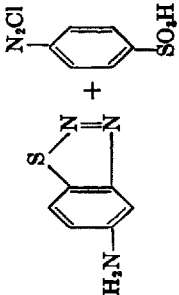
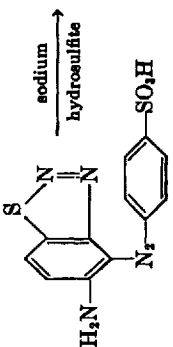
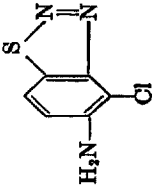
⁹ Fries and Engelberts, *Ann.*, 407, 194 (1915).

¹⁰ Fries, Koch, and Stukenbrock, *Ann.*, 468, 112 (1929).

¹¹ Fries and Reitz, *Ann.*, 527, 38 (1937).

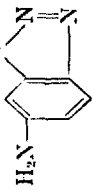
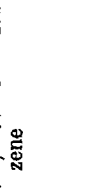
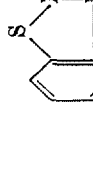
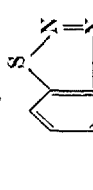
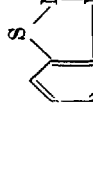
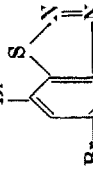
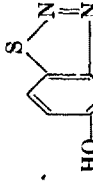
TABLE IIIB. Preparation of 1,2,3-Benzothiadiazoles (Compounds Prepared from Substituted Benzothiadiazoles)

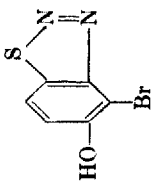
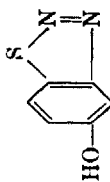
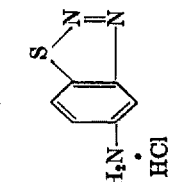
No.	Substituted benzothiadiazoles	Ref	Method of preparation	Structure	Solubility	M.p., °C.
1	4-Nitro	1,2	 $\xrightarrow[\text{H}_2\text{SO}_4]{\text{KNO}_3}$		benzene, alc.	95
2	4-Amino	1	reduction of compound 1 $\longrightarrow$		alc., acetic acid, benzene	136.5
3	4-Acetylamino	1	compound 2 + acetic anhydride	—	acetic acid	193
4	4-Amino-7-phenylazo	1	 + N_2Cl 		acetic acid nitrobenzene	over 300
5	5-Amino	3	reduction of 5-nitrobenzothiadiazole		alc., acetic acid	94
6	5-Acetylamino	4	—	—	—	95
7	5-Benzalalmino	3	compound 5 + acetic anhydride	—	acetic acid	161
		3	compound 5 + benzaldehyde	—	alc., hot benzene	90

No.	Substituted benzothiadiazoles	Ref.	Method of preparation	Structure	Solubility	M.p., °C.
8	5-Amino-4-phenylazo	3	compound 5 + phenyl-diazonium chloride →		hot alc.	222 dec.
9	4,5-Diamino	1			alc.	158
10	4-Chloro-5-amino	1			alc., acetic acid	169

(Table continued)

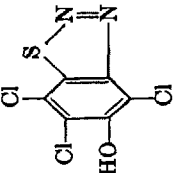
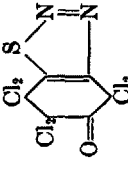
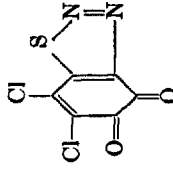
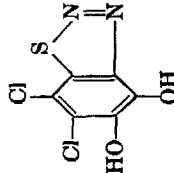
TABLE IIIB (Continued)

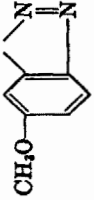
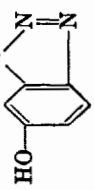
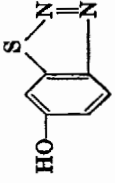
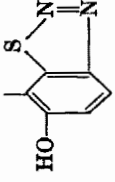
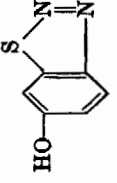
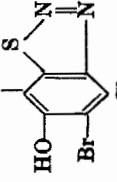
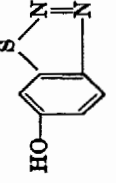
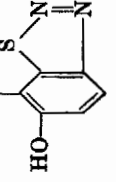
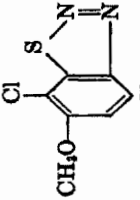
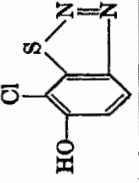
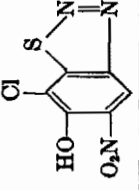
No.	Substituted benzothiadiazoles	Ref.	Method of preparation	Structure	Solubility	M.p., °C.
11	4-Chloro-5 acetylamino	1	compound 10 + acetic anhydride—		acetic acid	216
12	6-Amino	5	reduction of 6-nitrobenzothiadiazole		alc., hot benzene	112
13	4-Hydroxy	1	 $\xrightarrow[\text{dil. H}_2\text{SO}_4]{\text{HNO}_3}$		water, alc.	235
14	4-Acetoxy	1	compound 13 + acetic anhydride	—	water	52
15	5,7-Dibromo-4- hydroxy	1	 $\xrightarrow{\text{Br}_2}$		acetic acid	173 dec.
16	5,7-Dibromo-4- acetoxy	1	compound 15 + acetic anhydride	—	alc.	157
17	5-Hydroxy	3, 4	compound 5 $\xrightarrow[\text{dil. H}_2\text{SO}_4]{\text{HNO}_3}$		water	161
18	5-Acetoxy	3	compound 17 + acetic anhydride	—	alc.	122

No.	Substituted benzothiadiazoles	Ref.	Method of preparation	Structure	Solubility	M.p., °C.
19	4-Bromo-5-hydroxy	3	compound 17 + 1 equiv. Br ₂ →		alc., acetic acid	196
20	4-Chloro-5-hydroxy	3	compound 17 + 1 equiv. Cl ₂ →		acetic acid, alc.	197
21	4-Nitro-5-hydroxy	3	 $\xrightarrow[\text{chloroform}]{\text{HNO}_3}$		benzene, alc.	206 dec.
22	4,4,6,6,7-penta-chloro-6,7-dihydro-5(4)-benzothiadiazolone	3	 + HNO ₃ → 	acetic acid, alc.	149 dec.	

(Table continued)

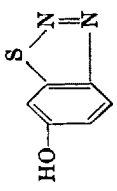
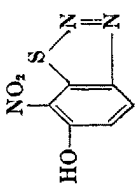
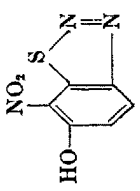
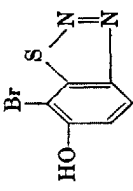
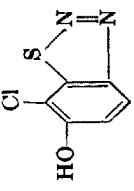
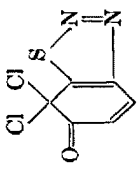
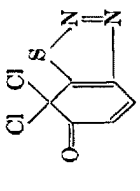
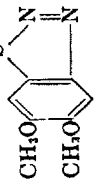
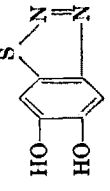
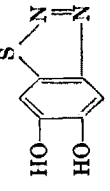
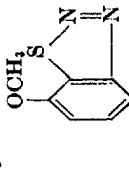
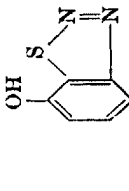
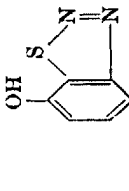
TABLE IIIB (Continued)

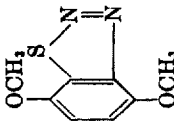
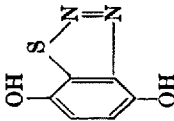
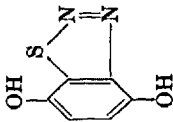
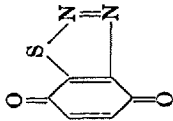
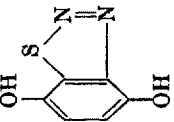
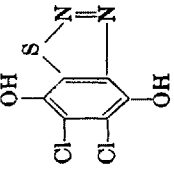
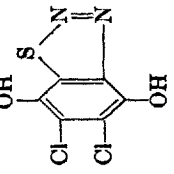
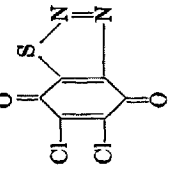
No.	Substituted benzothiadiazoles	Ref.	Method of preparation	Structure	Solubility	M.p., °C.
23	4,6,7-Trichloro-5-hydroxy	3	reduction of compound 22 with stannous chloride →		acetic acid, alc.	187
24	4,4,6,6,7,7-Hexachloro-6,7-dihydro-5(4)-benzothia-diazolone	3	compound 23 + chlorine →		acetic acid, benzene	151
25	6,7-Dichloro-4,5-benzothia-diazole-dione	3	oxidation of compound 23 with nitric acid →		benzene, CHCl ₃	164
26	6,7-Dichloro-4,5-dihydroxy	3	reduction of compound 25 with stannous chloride →		acetic acid, alc.	219
27	6,7-Dichloro-4,5-diacetoxy	3	compound 26 + acetic anhydride	—	alc.	137

No.	Substituted benzothiadiazoles	Ref.	Method of preparation	Structure	Solubility	M.p., °C.
28	6-Hydroxy	3	 $\xrightarrow[\text{heat}]{\text{HBr}}$		acetic acid, alc., aq. al- kali	211
29	7-Bromo-6- hydroxy	3	 $\xrightarrow{\text{Br}_2}$		acetic acid, dil. alkali	210
30	5,7-Dibromo-6- hydroxy	3	 $\xrightarrow[\text{heat}]{\text{Br}_2}$		acetic acid, alc.	228 dec.
31	7-Chloro-6- hydroxy	3	 $\xrightarrow{1 \text{ Cl}_2}$		acetic acid	200
32	5-Nitro-7-chloro-6- hydroxy	3	 $+ \text{HBr and heat}$  $\xrightarrow[\text{acetic acid}]{\text{HNO}_3}$		acetic acid, alc.	170

(Table continued)

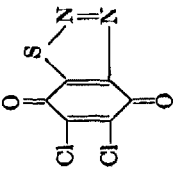
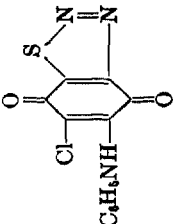
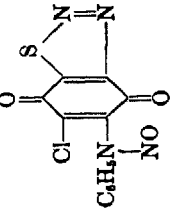
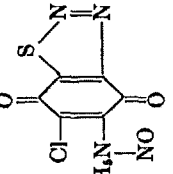
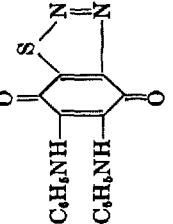
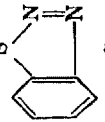
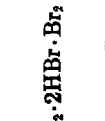
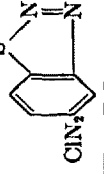
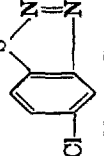
TABLE IIIB (Continued)

No.	Substituted benzothiadiazoles	Ref.	Method of preparation	Structure	Solubility	M.p., °C.
33	7-Nitro-6-hydroxy	3	 $\xrightarrow{\text{HNO}_3}$ 		acetic acid, alc., ben- zene	180
34	7,7-Dichloro-6(7)- benzothia- diazolone	3	 + $\text{HNO}_3 + \text{CHCl}_3$  $\xrightarrow{\text{Cl}_2}$ 		—	200 dec.
35	5,6-Dihydroxy	1	 $\xrightarrow[\text{heat}]{\text{dil. H}_2\text{SO}_4}$ 		water	249 dec.
36	5,6-Diacetoxy	1	compound 35 + acetic anhydride	—	water	120
37	4-Methoxy-7- hydroxy	1	 $\xrightarrow[\text{reflux}]{\text{HCl}}$ 		alc., benzene	101

No.	Substituted benzothiadiazoles	Ref.	Method of preparation	Structure	Solubility	M.p., °C.
38	4,7-Dihydroxy	1	 $\xrightarrow[115^{\circ}\text{C.}]{\text{HCl}}$		water, ether, alc., acetic acid	208, darkens m.p. 233
39	4,7-Diacetoxy	1	compound 38 + acetic anhydride	—		114
40	4,7-Benzothia- diazole-dione	1	 $\xrightarrow{\text{FeCl}_3}$		alc. alc., acetic acid, ben- zene	132
41	4,7-Dihydroxy- 5,6-dichloro	1	 $\xrightarrow{3 \text{ Cl}_2}$		benzene	205 dec.
42	5,6-Dichloro-4,7- benzothia- diazole-dione	1	 $\xrightarrow{\text{FeCl}_3}$		acetic acid, alc., ben- zene	237 dec.

(Table continued)

TABLE IIIB (Continued)

No.	Substituted benzothiadiazoles	Ref.	Method of preparation	Structure	Solubility	M.p., °C.
43	6-Chloro-5-anilino-4,7-benzothia-diazole	1	 $\xrightarrow{\text{C}_6\text{H}_5\text{NH}_2}$	 $\text{C}_6\text{H}_5\text{NH}$	toluene, alc., acetic acid	216
44	6-Chloro-5-(N-nitrosoanilino)-4,7-benzothia-diazole	1	compound 43 + nitrous acid $\longrightarrow$	 $\text{C}_6\text{H}_4\text{N}$ NO	alc.	228 dec.
45	5,6-Dianilino-4,7-benzothia-diazole	1	 $\xrightarrow{\text{C}_6\text{H}_5\text{NH}_2}$	 $\text{C}_6\text{H}_5\text{NH}$ $\text{C}_6\text{H}_5\text{NH}$	benzene	130-5
46	Perbromide of 1,2,3-benzothia-diazole	1	 $\xrightarrow{\text{Br}_2}$	 $(\text{C}_6\text{H}_3\text{N}_2\text{S})_2 \cdot 2\text{HBr} \cdot \text{Br}_2$	acetic acid	Sinters 80°, m.p., 110
47	5-Chlorobenzothiadiazole	4	 $\xrightarrow{\text{CuCl}}$	 Cl	ethanol	165

No.	Substituted benzothiadiazoles	Ref.	Method of preparation	Structure	Solubility	M.p., °C.
48	5-Bromobenzo- thiadiazole	4	same as 47 →		—	106
49	5-Iodobenzo- thiadiazole	4	 KI →		—	103
50	5-β-Naphtholazo- benzothiadiazole	4	 + →		—	209

¹ Fries and Reitz, *Ann.*, 527, 38 (1937).

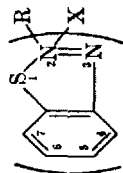
² Hodgson and Dodgson, *J. Chem. Soc.*, 1948, 1006.

³ Fries, Vorbordt, and Siebert, *Ann.*, 454, 172 (1927).

⁴ Hodgson and Dodgson, *J. Chem. Soc.*, 1948, 810.

⁵ Jacobson and Kwayssen, *Ann.*, 277, 209 (1893).

TABLE IIIC. Preparation of the Benzothiadiazolium Alkyl Halides.¹ Quaternary Salts Prepared from the Benzothiadiazoles Having the General Structure:

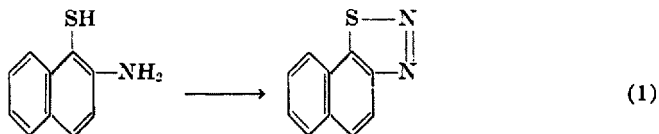


No.	Substituted benzothiadiazole	Constituent R	Constituent X	M.p., °C.
1	Benzothiadiazole	methyl	iodide	—
2	Benzothiadiazole	methyl	chloride	—
3	Benzothiadiazole	ethyl	iodide	—
4	Benzothiadiazole	ethyl	chloride	70–80
5	Benzothiadiazole	methyl	picrate	—
6	Benzothiadiazole	ethyl	picrate	—
7	6-Methyl	methyl	iodide	—
8	4,6-Dimethyl	methyl	iodide	—

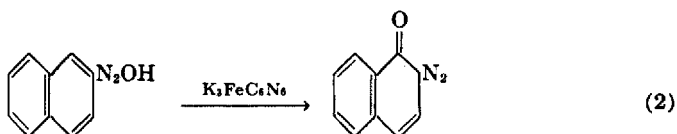
¹ Jacobson *et al.*, *Ann.*, 277, 209 (1893).

Naphthothiadiazoles

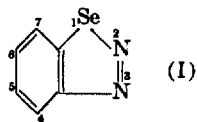
Jacobson and Schwartz¹ prepared naphtho[2.1]-1,2,3-thiadiazole with 1-mercapto-2-aminonaphthalene and nitrous acid. He was not successful in preparing the other isomer from 2-mercapto-1-aminonaphthalene (1).



Bamberger, Böcking, and Kraus² oxidized 2-naphthyldiazonium hydroxide with potassium ferricyanide and obtained 2-diazo-1(2) naphthalenone (2). This compound reacted with phosphorous pentasulfide to give the naphtho[2.1]-1,2,3-thiadiazole of Jacobson and Schwartz. Bamberger, Baum, and Schlein³ used the same method and prepared the other isomer from 1-diazo-2(1) naphthalenone.



Benzoselenadiazoles



(Ring Index No. 697)

Keimatsu and Satoda^{4,5} diazotized *o*-selenylaniline in a current of hydrogen at 0°C. and obtained benzoselenadiazole (1). The 4- and 6-methyl- and the 4,5-dimethylbenzoselenadiazoles were prepared in the same manner.

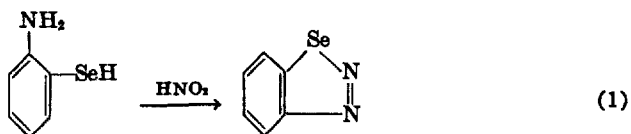
¹ Jacobson and Schwartz, *Ann.*, **277**, 221 (1893).

² Bamberger, Böcking, and Kraus, *J. prakt. Chem.*, **105**, 251 (1923).

³ Bamberger, Baum, and Schlein, *J. prakt. Chem.*, **105**, 266 (1923).

⁴ Keimatsu and Satoda, *Chem. Abstr.*, **31**, 6661 (1937); *Chem. Zentr.*, **I**, 2745 (1936); *J. Pharm. Soc. Japan*, **55**, 233 (1935).

⁵ Keimatsu, Satoda, and Tigono, *Chem. Abstr.*, **33**, 155 (1939); *J. Pharm. Soc. Japan*, **56**, 869 (1936).



Heating these compounds, preferably in solution such as refluxing glacial acetic acid or amyl alcohol, produced selenanthrenes (2).

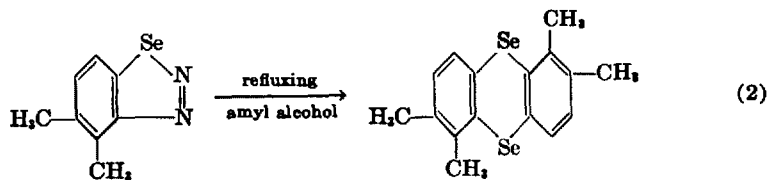
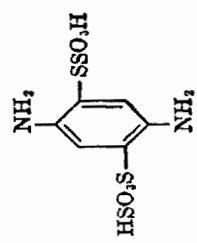
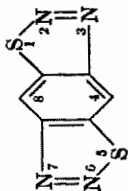
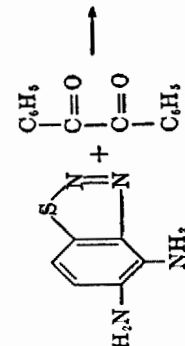
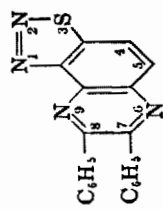
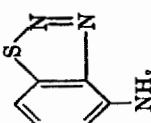
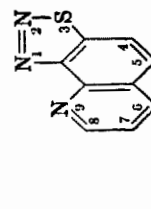
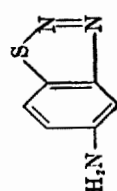
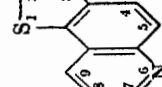


TABLE IV. Benzoselenadiazole and Its Derivatives

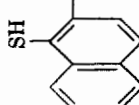
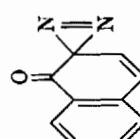
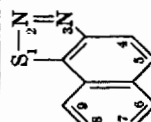
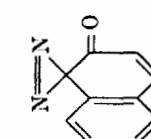
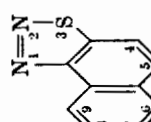
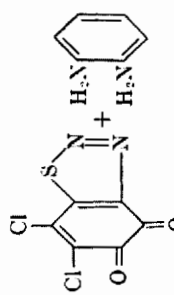
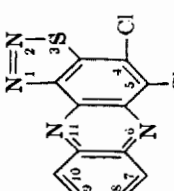
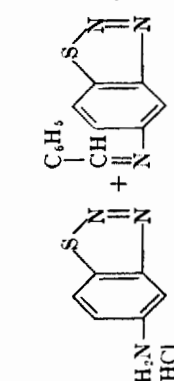
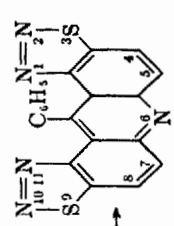
No.	Name	Ref. (see p. 31)	Solubility	M.p., °C.
1	Benzoselenadiazole	4	methanol	34
2	4-Methylbenzoselenadiazole	4	methanol	40.5-41
3	6-Methylbenzoselenadiazole	4	methanol	29
4	4,5-Dimethylbenzoselenadiazole	5	—	90

TABLE V. Preparation of 1,2,3-Thiadiazoles in Condensed Systems Other Than Benzothiadiazole

Ring Index No.	Compound	Ref.	Method of preparation	Structure and numbering according to Ring Index	M.p., °
1317	Benzo [1.2.4.5]bis-1,2,3-thiadiazole	1			224-6
1489	7,8-Diphenyl [1.2.3]thiadiazolo [4.5-f]quinoxaline	2			226 dec.
1491	[1.2.3]Thiadiazolo [5.4-b]quinoline	2			141
1490	[1.2.3]Thiadiazolo [4.5-f]quinoline	2			115

(Table continued)

TABLE V (Continued)

1492	Naphtho[2.1-1,2,3-thiadiazole	3	 $\xrightarrow{\text{HNO}_3}$ 	89		91-91.5
1494	Naphtho[1.2]-[1.2.3]thiadiazole	5	 $\xrightarrow{\text{P}_2\text{S}_5}$ 	68.5		
2342	4,5-Dichloro [1.2.3]thiadiazolo [4.5-a]phenazine	6	 $\xrightarrow{\text{H}_2\text{N}-\text{C}_6\text{H}_5, \text{H}_2\text{N}-\text{C}_6\text{H}_5}$ 	287		
2919	12-Phenyl-bis[1.2.3]thiadiazolo [a,f]acridine	6	 $\xrightarrow{\text{C}_6\text{H}_5}$ 	216		

¹ Green and Perkin, *J. Chem. Soc.*, **83**, 1201 (1903).² Fries and Reitz, *Ann.*, **527**, 38 (1937).³ Jacobson and Schwartz, *Ann.*, **277**, 221 (1893).⁴ Bamberger, Böcking, and Kraus, *J. prakt. Chem.*, **105**,

251 (1923).

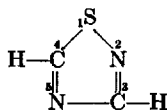
⁵ Bamberger, Baum, and Schlein, *J. prakt. Chem.*, **105**,

266 (1923).

⁶ Fries, Vorbordt, and Siebert, *Ann.*, **454**, 172 (1927).

Derivatives of the 1,2,4-Thiadiazoles and Their Selenium Analogs

1,2,4-Thiadiazoles

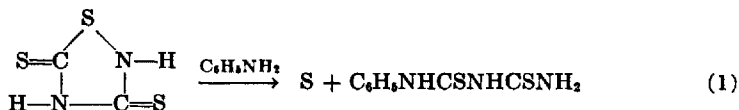
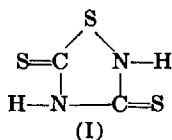


(Ring Index No. 71)

I. Derivatives of Perthiocyanic and Isoperthiocyanic Acids

There is considerable literature on variously substituted perthiocyanic acid derivatives having structures designated as 1,2,4-thiadiazoles. These perthiocyanic acids are closely related to the derivatives of isoperthiocyanic acid (*xanthanwasserstoff*), usually designated as 1,2,4-dithiazoles. The literature is confused and full of controversy, since these latter compounds may be explained as derivatives of 1,2,4-thiadiazole. Only further experimental work will solve the problem.

The controversy takes its origin in the beginnings of organic chemistry when Wöhler¹ found that a concentrated solution of thiocyanic acid decomposed to give a new structure having the empirical formula $C_2H_2N_2S_3$. Glutz² investigated this compound and found that the reduction of the perthiocyanic acid gave carbon disulfide and thiourea, so he assigned the following structure to the compound (I). This compound reacted with aniline to give sulfur and phenyl dithiobiuret (1).



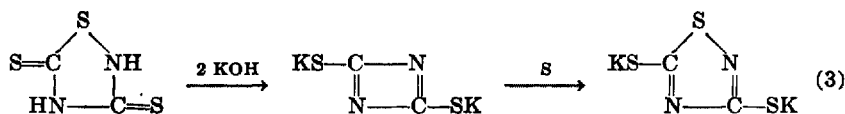
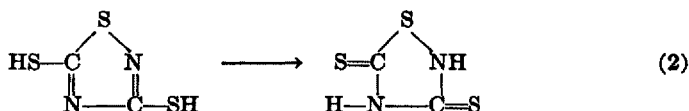
Klason³ investigated perthiocyanic acid, including the preparation of some of the ethers. He was convinced that the real structure for perthio-

¹ Wöhler, *Ann. Physik*, **69**, 273 (1821).

² Glutz, *Ber.*, **3**, 346 (1870).

³ Klason, *J. prakt. Chem.*, [2] **38**, 366 (1888).

cyanic acid (which could be changed to isoperthiocyanic acid) was as given in equation (2). He postulated that the transformation took part in two steps (3).



The preparation of the "labile or real" perthiocyanic acid consisted of digesting isoperthiocyanic acid with barium hydroxide. Sulfur at first precipitated and then largely redissolved. A barium salt of perthiocyanic acid was isolated. This salt in a dilute solution when precipitated with hydrochloric acid gave isoperthiocyanic acid. If the decomposition of the salt with hydrochloric acid took place at 0°C. and the solution was extracted with cold ether (0°C.), the free perthiocyanic acid was isolated. This acid, which was colorless and easily soluble in water and ether, readily changed to isoperthiocyanic acid, which was yellow and difficultly soluble in water and ether.

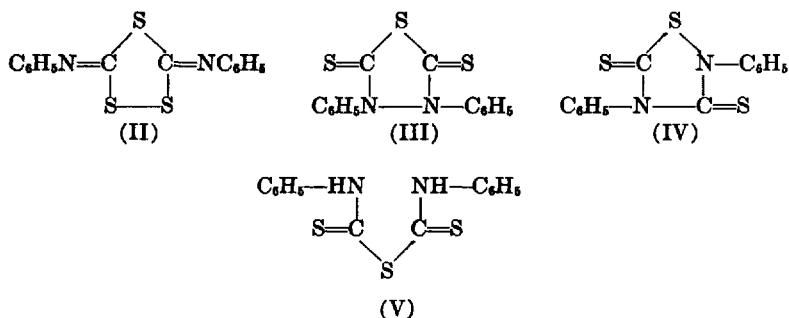
Klason³ prepared the diethyl ester of perthiocyanic acid by digesting isoperthiocyanic acid with potassium hydroxide and then treating with ethyl iodide. The diethyl perthiocyanate would not form an amide when treated with ammonia. When this ester was treated with concentrated hydrochloric acid at high temperatures, ammonia, carbon dioxide, hydrogen sulfide, ethyl mercaptan, and ethyl polysulfide were formed, showing that the ethyl groups were probably attached to the sulfur atoms in the molecule.

Sell⁴ found that by treating ethyl isothiocyanate with chlorine an addition product was obtained which on treatment with alkali gave a compound having the empirical formula $(\text{C}_2\text{H}_5\text{NCS})_2\text{O}$. Proskauer and Sell⁵ produced the compound $\text{C}_{14}\text{H}_{10}\text{N}_2\text{S}_2\text{Br}_2$ by allowing bromine to react with phenyl isothiocyanate in chloroform. On digesting this compound in alcohol a product having the melting point of 152°C. was obtained. They suggested that the structure might be any of formulas II-IV. They

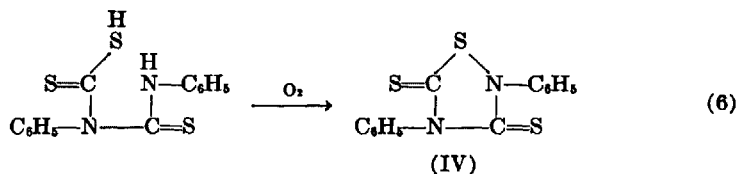
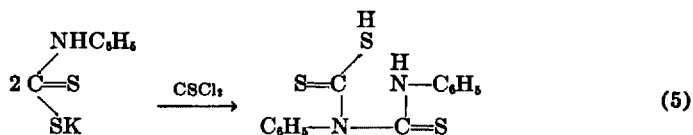
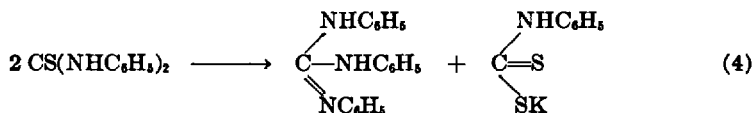
⁴ Sell, *Ber.*, 6, 323 (1873).

⁵ Proskauer and Sell, *Ber.*, 9, 1262 (1876).

felt that they had compound V which on the loss of two hydrogen atoms gave compound III.



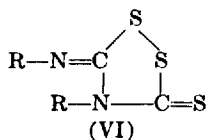
Freund and Wolf⁶ obtained the same product when digesting diphenyl thiourea with thiophosgene. They reasoned that the reaction took place in three steps (Eqs. 4-6).



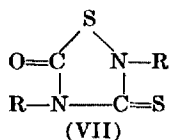
Freund and co-workers⁷ allowed bromine to react with methyl, ethyl, and phenyl isothiocyanates. In the presence of dry chloroform the following compounds are obtained: $(\text{RNCS})_2\text{SBr}_3$, where R is a methyl, ethyl, or phenyl group. On digestion with water and alcohol these compounds give products having the empirical formula, $(\text{RNCS})_2\text{S}$, and are designated by the structural formula (VI). If wet chloroform or alcohol

⁶ Freund and Wolf, *Ber.*, 25, 1456 (1892).

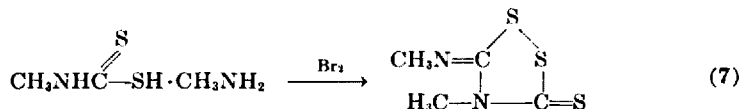
⁷ Freund, *Ann.*, 285, 154 (1895).



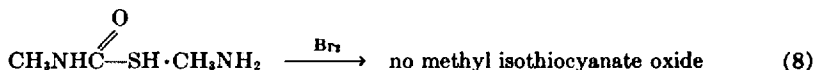
is added before the reaction between bromine and the alkyl isothiocyanate takes place, then compounds having the empirical formula $(\text{RNCS})_2\text{O}$ are obtained. These alkyl isothiocyanate oxides are thought to have structure (VII).



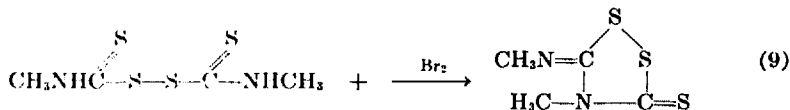
The difference in the assigned structures is due to the fact that the so-called alkyl isothiocyanate sulfides can be prepared by the reaction of alkylamine alkyldithiocarbamates and bromine (7), while alkylamine



alkylthiocarbamates and bromine give no so-called alkyl isothiocyanate oxides (8). Reaction (7) probably took place in two phases, since bis-



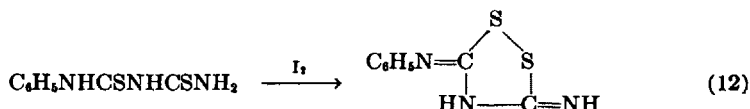
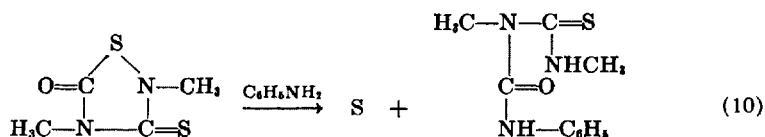
(methyl thiocarbamosulfide) and bromine also give the methyl isothiocyanate sulfide (9).



Reduction of the "isothiocyanate oxides" and the "isothiocyanate sulfides" give dialkyl thioureas. Aniline and the "isothiocyanate oxides" yield substituted thiobiurets (10,11).

Fromm⁸ found that he could obtain phenyl thiuret by oxidizing phenyl dithiobiuret with mild oxidizing agents such as iodine, ferric chloride, ammonical potassium ferricyanide, and dilute hydrogen peroxide (12). Dilute alkali splits free sulfur from the molecule.

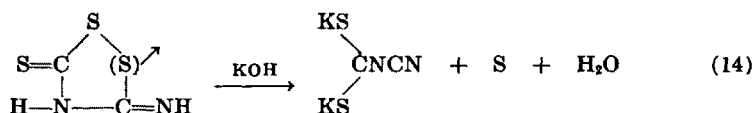
⁸ Fromm, *Ann.*, **275**, 20 (1893).



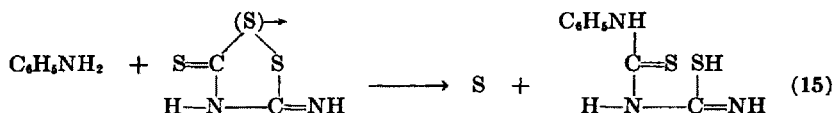
Hantzsch and Wolvekamp⁹ reviewed the previous work and added additional experimental work toward the proof of structure of these compounds. They took issue with Klason's formula for isoperthiocyanic acid and the potassium dithiocyanate. They proved that the potassium dithiocyanate of Klason was really potassium cyanodithiocarbamate by synthesis with carbon disulfide and cyanamide (13). They obtained the



same compound by the degradation of isoperthiocyanic acid with potassium hydroxide and interpreted the reaction as shown in equation (14).

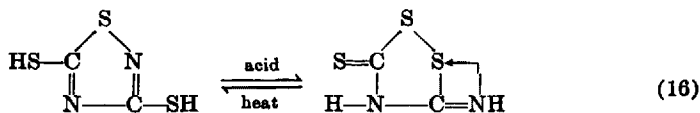


The reaction between aniline and isoperthiocyanic acid was then given as (15). They also took issue with Freund's formula for the so-



called isothiocyanate oxides which they believed to have the same ring structure as the so-called isothiocyanate sulfides. These two classes of compounds gave the same products on reduction, i.e., dialkyl thioureas. The so-called isothiocyanate oxides gave phenyl thiobiurets, the same as isoperthiocyanic acid.

⁹ Hantzsch and Wolvekamp, *Ann.*, **331**, 265 (1904).



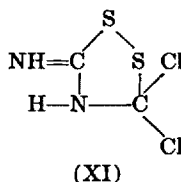
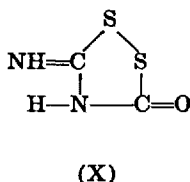
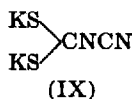
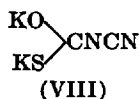
Hantzsch and Wolvekamp's conception of the transformation of a perthiocyanate derivative to an isoperthiocyanic acid derivative is summarized briefly by equation (16). Their reasons are:

(1) The 1,2,4-dithiazoles on reduction give thiourea derivatives. *Examples:* isoperthiocyanic acid, thiuret, so-called isothiocyanate oxides and sulfides. The 1,2,4-thiadiazoles form only a small amount of thioureas. *Examples:* dimethylperthiocyanates.

(2) The 1,2,4-dithiazoles and aniline (except the so-called isothiocyanate sulfides) react with the splitting off of sulfur from the molecule. *Examples:* isoperthiocyanic acid, biuret (?), so-called isothiocyanate oxides. The 1,2,4-thiadiazoles do not react analogously with aniline.

(3) The 1,2,4-dithiazoles in the presence of alkali split into sulfur and cyanamide derivatives. *Examples:* isoperthiocyanic acid, thiuret.

Söderbäck¹⁰ prepared thiocyanogen by allowing a halogen (preferably bromine) to react with a suspension of a heavy metal thiocyanate. Thiocyanogen in an anhydrous solvent on being mixed with cold hydrochloric acid gives two compounds, $(\text{SCN})_2 \cdot 2\text{HCl}$ and $(\text{SCN})_2 \cdot \text{HCl}$. The compound $(\text{SCN})_2 \cdot 2\text{HCl}$ hydrolyzes in water to give $(\text{SCN})_2 \cdot \text{H}_2\text{O}$, which, in the presence of concentrated potassium hydroxide, splits off sulfur to yield potassium cyanothiocarbamate (VIII)—analogous to Hantzsch and Wolvekamp's potassium cyanodithiocarbamate (IX).¹¹ Aniline and

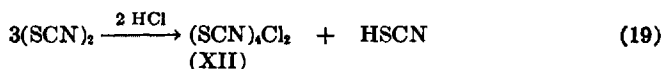
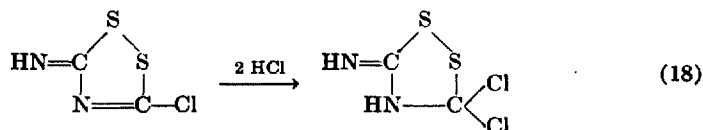
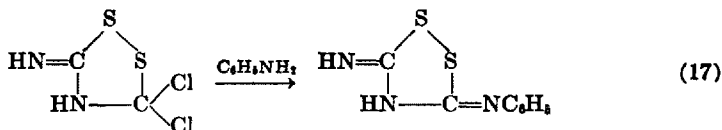


$(\text{SCN})_2 \cdot 2\text{HCl}$ give the so-called thiuret of Fromm (17).¹² On the basis of these reactions, Söderbäck¹⁰ assigned structures (X) and (XI) to $(\text{SCN})_2 \cdot \text{H}_2\text{O}$ and $(\text{SCN})_2 \cdot 2\text{HCl}$, respectively. Söderbäck theorized that the hydrochloric acid added across the triple bonds in thiocyanogen to form the

¹⁰ Söderbäck, *Ann.*, **419**, 217 (1919).

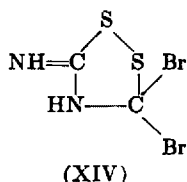
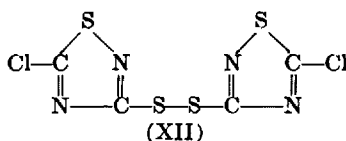
¹¹ Hantzsch and Wolvekamp, *Ann.*, **331**, 265 (1904).

¹² Fromm, *Ann.*, **275**, 20 (1893).

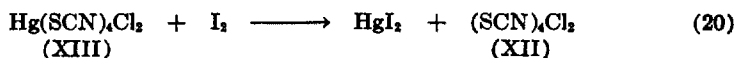


compound, $\text{HN}=\text{CCl}-\text{S}-\text{S}-\text{CCl}=\text{NH}$, which in turn formed a substituted ring (18).

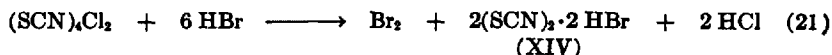
Söderbäck¹³ also examined the structure $(\text{SCN})_4\text{Cl}_2$ (XII) and gave the over-all equation (19) for the preparation of this compound. The addition of mercury gave $\text{Hg}(\text{SCN})_4\text{Cl}_2$ (XIII). Halogens such as bro-



mine, iodine, and free thiocyanic acid reacted with the mercurial to give the original compound (XII) (20). Mercury would react with aliphatic



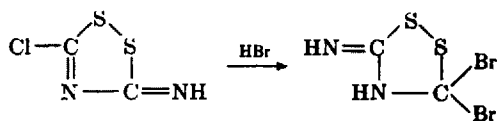
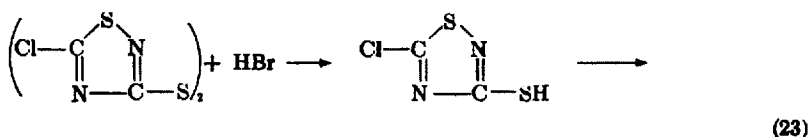
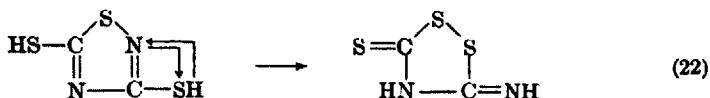
disulfides to form mercury mercaptides. On addition of a halogen to a mercury mercaptide, the original disulfide and the mercury halide would be recovered. On the basis of this reasoning, Söderbäck believed that the compound (XII) had this structure. Hydrobromic acid and compound (XII) gave a bromine compound analogous to the chlorine compound (XI) (21). Compound (XIII) hydrolyzed to give $(\text{SCN})_2 \cdot \text{H}_2\text{O}$ and



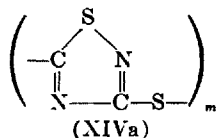
¹³ Söderbäck, *Ann.*, **465**, 184 (1928).

hydrobromic acid. Aniline reacted with this compound to give phenyl thiuret, thereby identifying its structure as 3,3-dibromo-5-imino-1,2,4-dithiazoline (XIV).

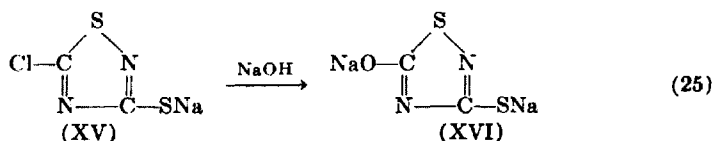
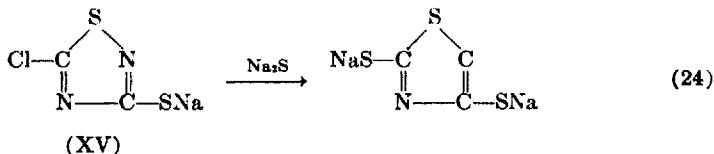
Söderbäck concluded that the mechanism of the transformation of the chlorine compound to the bromide was analogous to the transformation of perthiocyanic acid to isoperthiocyanic acid (22 and 23).

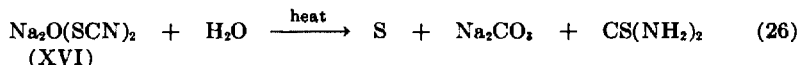


The reaction between sodium sulfide and the mercurial gave the sodium mercaptide and a polymer having the possible structure (SCN)_m (XIVa). The sodium mercaptide was isolated and had the empirical formula

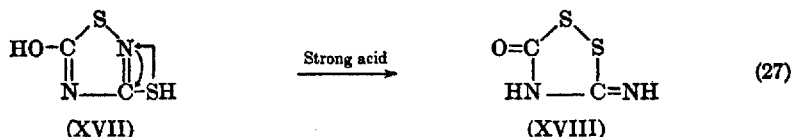


Na(SCN)₂Cl₂·2H₂O (XV). Sodium sulfide and this compound gave the sodium perthiocyanate (24). The labile chlorine also reacted with sodium hydroxide (25). Heating disodium 3-mercapto-5-hydroxy-1,2,4-thiadiazole (XVI) in water formed thiourea, sulfur, and sodium carbonate (26).

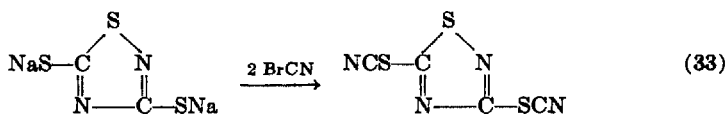
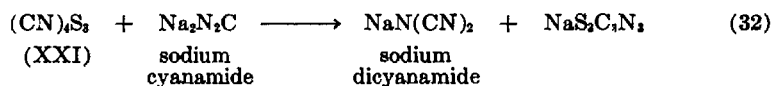
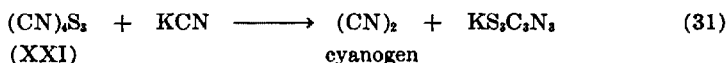
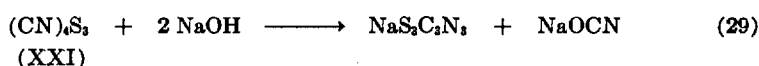
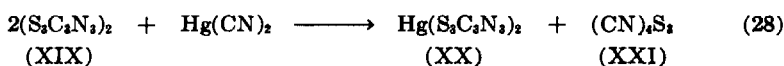




In strong acid the 3-mercapto-5-hydroxy-1,2,4-thiadiazole (XVII) was not stable and the isomer 3-imino-1,2,4-dithiazol-5-one (XVIII) was formed. Söderbäck represented the transformation by equation (27).



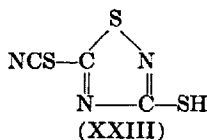
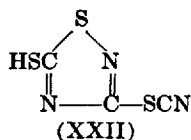
Söderbäck¹⁴ also investigated the polymers obtained by the polymerization of thiocyanic acid. A red polymer was obtained from the spontaneous decomposition of free thiocyanic acid, and a white polymer by the spontaneous decomposition of sodium 3-mercapto-5-chloro-1,2,4-thiadiazole in water, acetone, and alcohol. This polymer had the empirical formula $(\text{S}_3\text{C}_3\text{N}_3)_2$ and was designated by Söderbäck as hexathiocyanate (XIX). This compound was probably a disulfide, since it reacted with mercury to give a mercurial from which the original compound was obtained by treating it with a halogen. The hexathiocyanate (XIX) reacted with mercury cyanide (28) and gave a mercurial (XX) and 3,5-dithiocyano-1,2,4-thiadiazole (XXI). Proof of the structure (XXI) was accomplished as shown in equations (29–33).



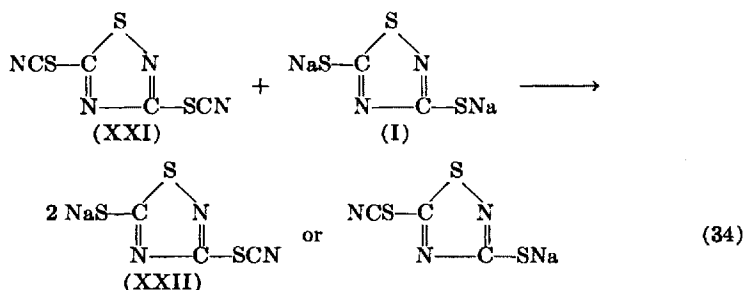
The other product from the decomposition of the hexathiocyanate was believed to be either 3-thiocyano-5-mercapto-1,2,4-thiadiazole (XXII)

¹⁴ Söderbäck, *Svensk Kem. Tid.*, 56, 207 (1944).

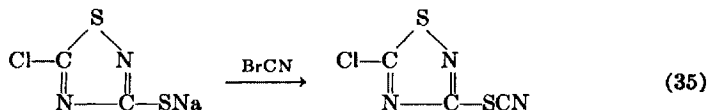
or 5-thiocyano-3-mercapto-1,2,4-thiadiazole (XXIII). The free base was



very unstable and decomposed with the evolution of hydrocyanic acid and thiocyanic acid. The barium salt reacted with dimethyl sulfate to give a monomethyl ester in practically theoretical yields. The 3,5-dithiocyano-1,2,4-thiadiazole (XXI) dissolved in an alkaline solution of perthiocyanate (I) in molecular proportions to give the salt of XXII or XXIII (34).



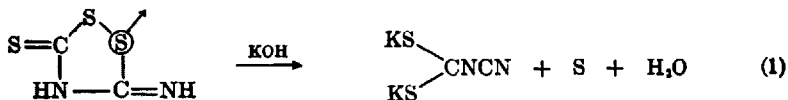
Söderbäck, using the reaction between cyanogen bromide and a sodium mercaptide, prepared a number of 2-thiocyano derivatives of 1,2,4-thiadiazole (35).



Discussion

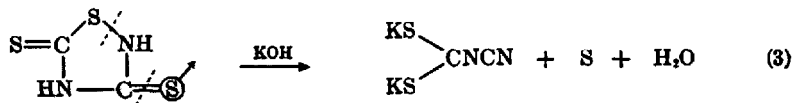
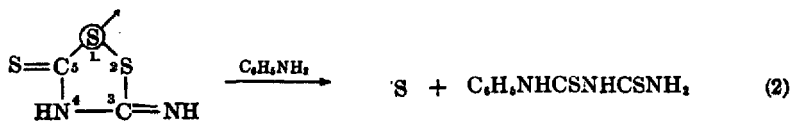
A careful analysis of the data presented in the literature will show that the formula (I) suggested by Klason¹ for isoperthiocyanic acid indicates a closer relationship to the actual facts than does the formula sponsored by Hantzsch and Wolvekamp (II).²

Consider Hantzsch and Wolvekamp's equations for the reaction between potassium hydroxide and isoperthiocyanic acid (1) and aniline and isoperthiocyanic acid (2). In this theoretical reaction, sulfur number 2 is eliminated from the molecule by the splitting of a sulfur-to-

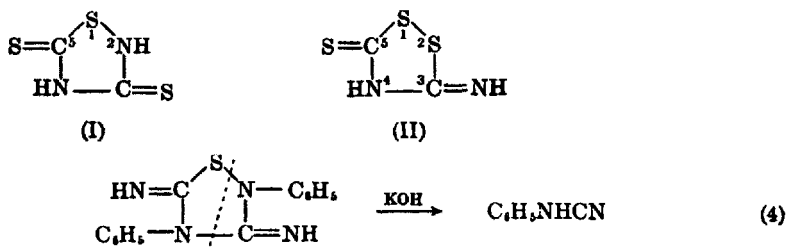


¹ Klason, *J. prakt. Chem.*, [2] **38**, 366 (1888).

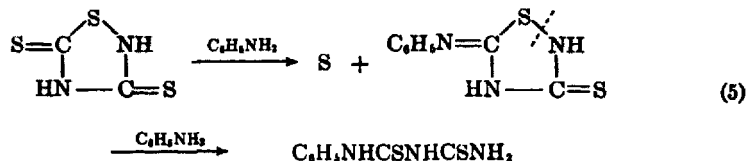
² Hantzsch and Wolvekamp, *Ann.*, **331**, 265 (1904).



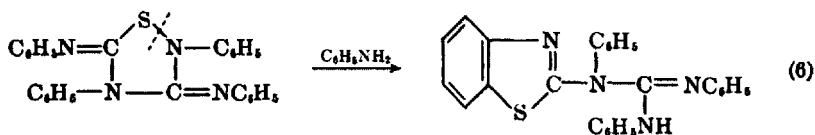
sulfur bond with alkali which usually requires a rather rigorous treatment. Klason's structure can also be used to explain this reaction (3). Here the reaction takes place by splitting of a nitrogen-to-sulfur bond. Hector³ has reported an analogous splitting of 2,4-diphenyl-3,5-diimino-1,2,4-thiadiazolidine to give phenyl cyanamide (4).



The reaction with aniline may be explained by either structure (2,5) In the Hantzsch and Wolvekamp equation (2) aniline must split to sulfur-to-sulfur linkage and form an amide from the dithiocarbamic acid between carbon 3 and sulfur 2. In considering Klason's structure, aniline would react with the 1,2,4-thiadiazolidine-3,5-dithione (5) in much the same way



as Barbos⁴ found that aniline would react with 3-phenyl-5-mercapto-1,2,4-thiadiazole. Then the nitrogen-to-sulfur bond would rupture in much the same manner as it does under treatment with alkali. Fromm and

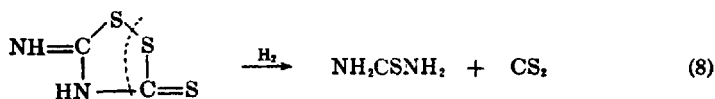
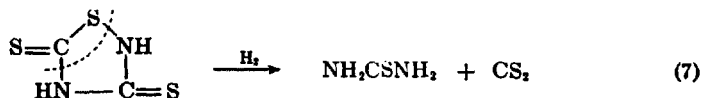


³ Hector, *Ber.*, 25, Ref. 799 (1892). *Oefvers. Kongl. Vet. Acad.*, 1892, 79.

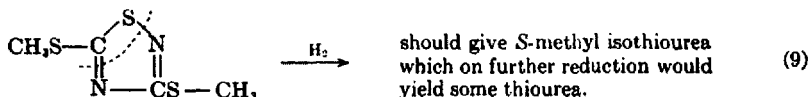
⁴ Barbos, *Ann. sci. univ. Jassy*, 126, 526 (1940).

Bitterich⁵ reported the same rupture of the nitrogen to sulfur bond with aniline in 2,4-diphenyl-3,5-bis(phenylimino)-1,2,4-thiadiazolidine (6).

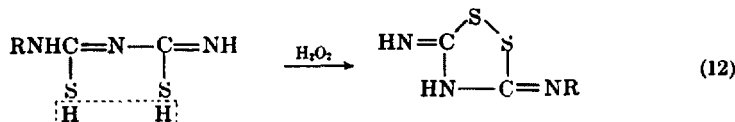
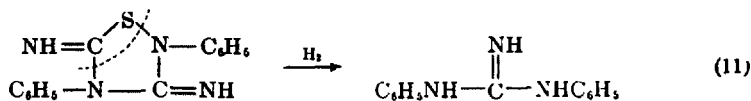
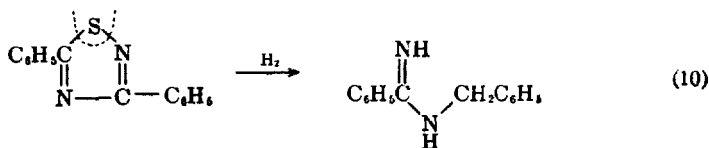
The reduction of this isoperthiocyanic acid and its derivative to give thiourea or *N*-substituted thioureas was one of the reasons which Hantzsch and Wolvekamp⁶ chose for assigning the 1,2,4-dithiazoline structures to these compounds. The complicating factor is that both structures theoretically will give thioureas (7,8). Hantzsch and Wolvekamp's



reasoning that the 1,2,4-thiadiazoles gave only a small amount of thiourea was based on the reduction of dimethyl perthiocyanate. The reduction of dimethyl perthiocyanate should not give much thiourea (9). Ishikawa⁷



reduced 3,5-diphenyl-1,2,4-thiadiazole and obtained benzyl benzamidine (10). Hector³ reduced 2,4-diphenyl-3,5-diimino-1,2,4-thiadiazolidine and obtained *N,N'*-diphenylguanidine (11).

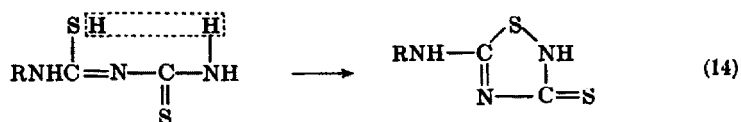
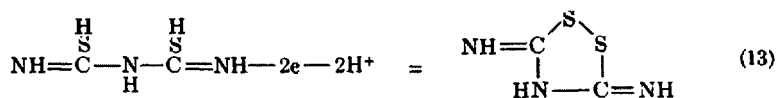


⁵ Fromm and Bitterich, *Ann.*, 394, 284 (1912).

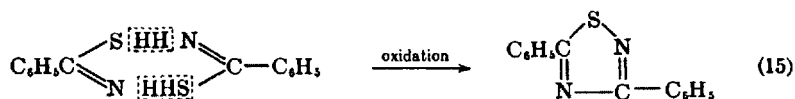
⁶ Hantzsch and Wolvekamp, *Ann.*, 331, 265 (1904).

⁷ Ishikawa, *Chem. Abstr.*, 19, 3087 (1925); *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, 3, 147 (1925).

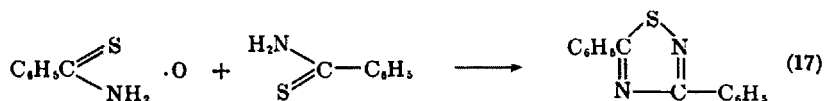
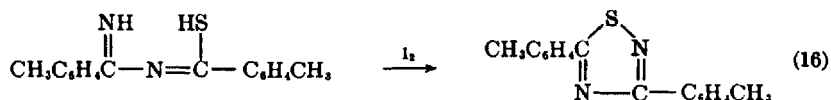
The proof of the structure of these compounds was inferred from their syntheses with substituted dithiobiurets. Fromm⁸ oxidized a number of phenyl dithiobiurets (12) and assumed that the two thio groups were oxidized to form the disulfide linkage. Preisler and Bateman⁹ measured the oxidation-reduction potential of dithiobiuret and its oxidation product, and assumed that the reaction took place (13). The assumptions of these workers are not wholly valid since these reactions might proceed along a different route (14).



Hoffmann and Gabriel's¹⁰ and Walther's¹¹ oxidation of thiobenzamide (15) to produce 3,5-diphenyl-1,2,4-thiadiazole is evidence that the reaction



probably occurs (14). Ishikawa¹² presented a similar reaction with the oxidation of *p*-toluimido-*p*-isothiotoluamide to produce 3,5-di-*p*-tolyl-1,2,4-thiadiazole (16). Kitamura and Suzuki's¹³ oxidation of thiobenz-



⁸ Fromm, *Ann.*, **275**, 20 (1893).

⁹ Preisler and Bateman, *J. Am. Chem. Soc.*, **69**, 2632 (1947).

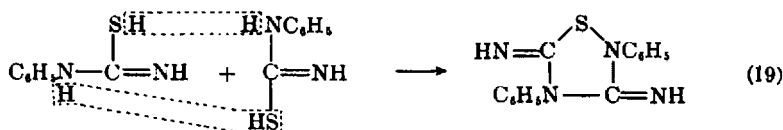
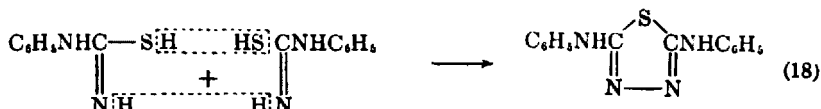
¹⁰ Hoffmann and Gabriel, *Ber.*, **25**, 1578 (1892).

¹¹ Walther, *J. prakt. Chem.*, **69**, 44 (1904).

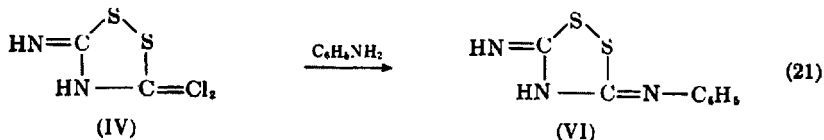
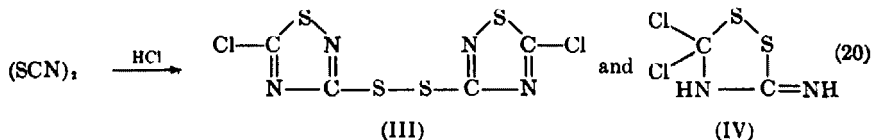
¹² Ishikawa, *Chem. Abstr.*, **22**, 1581 (1928); *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **7**, 237 (1928).

¹³ Kitamura and Suzuki, *Chem. Abstr.*, **33**, 1726 (1939); *J. Pharm. Soc.*, **57**, 246 (1937).

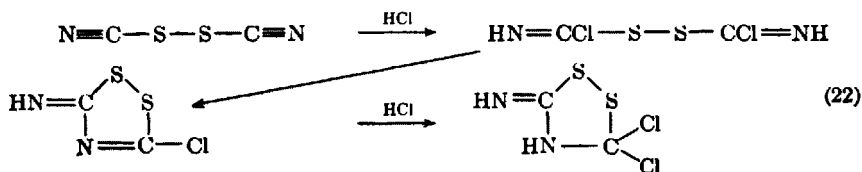
amide, and the subsequent reaction of this oxidation product with thio-benzamide to form 3,5-diphenyl-1,2,4-thiadiazole (17) probably falls in the same category of reactions. When Hector¹⁴ oxidized phenyl thiourea, he assumed that the sulfhydryl radicals were the first to be affected (18). Later in his proof of structure,¹⁵ he could find no evidence for such a reaction. The reaction probably follows this course (19).



Söderbäck¹⁶ obtained phenyl thiuret in another manner. He found that the addition of hydrochloric acid to thiocyanogen (20) gave two products (III and IV). Compound (IV) reacted with aniline (21) to



give the phenyl thiuret of Fromm, hence the above structure was assigned to it. Söderbäck reasoned that the hydrochloric acid added across the triple bonds in the thiocyanogen and then cyclization took place (22).



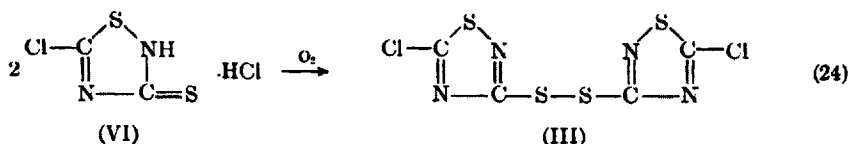
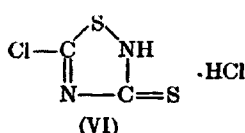
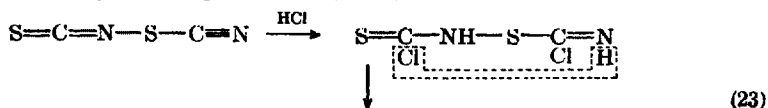
If $\text{N}=\text{C}-\text{S}-\text{S}-\text{C}=\text{N}$ is the structure of thiocyanogen then it is difficult to deduce any other structure for compound (IV). However, this mecha-

¹⁴ Hector, *Ber.*, 22, 1176 (1889).

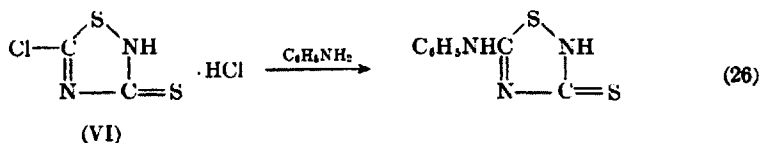
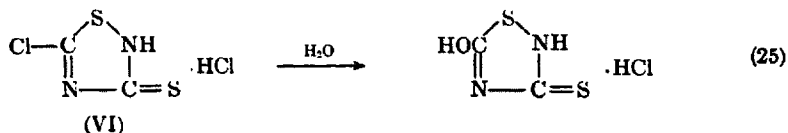
¹⁵ Hector, *Ber.*, 25, Ref. 799 (1892); *Oefvers. Kongl. Vet. Acad.*, 1892, 79.

¹⁶ Söderbäck, *Ann.*, 419, 217 (1919); 465, 184 (1928).

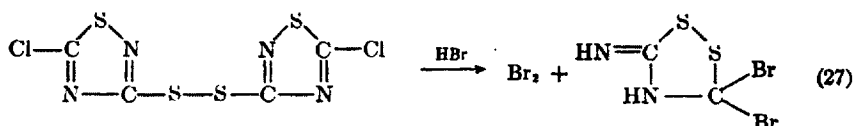
nism does not explain the formation of compound (III). Supposing the structure of thiocyanogen is assumed to be $\text{S}=\text{C}=\text{N}-\text{S}-\text{C}\equiv\text{N}$, then the following set of reactions (23) would take place. Oxidation of this structure (VI) would give compound (III) (24). Structure (VI) is a hydro-



chloride which would explain (III) the activation of the halogen attached to the carbon atom. The mechanism for this activation has been reported by Banks¹⁷ for a number of halonitrogen heterocycles and by Tomisek¹⁸ and Christensen for 4-chloroquinazoline. Structure (VI) would react with water (25) and aniline (26) as reported by Söderbäck. The last structure is Fromm's phenyl thiuret as postulated earlier in this discussion.



Söderbäck¹⁹ allowed hydrobromic acid to react with bis[5-chloro-3-(1,2,4-thiadiazolyl)] disulfide and obtained the dibromo analog of the so-called 5-imino-3,3-dichloro-1,2,4-dithiazoline (27). The bromo compound



¹⁷ Banks, *J. Am. Chem. Soc.*, **66**, 1127 (1944).

¹⁸ Tomisek and Christensen, *J. Am. Chem. Soc.*, **67**, 2112 (1945).

¹⁹ Söderbäck, *Ann.*, **465**, 184 (1928).

²² Söderbäck, *Svensk. Kem. Tid.*, **57**, 62 (1944).

discussion, the 1,2,4-thiadiazolidine structure may be used to describe the isoperthiocyanate derivatives with a considerable degree of accuracy.

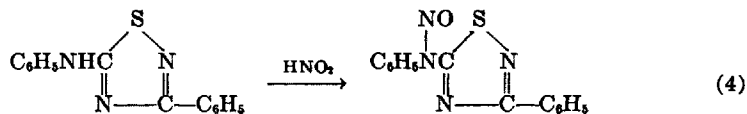
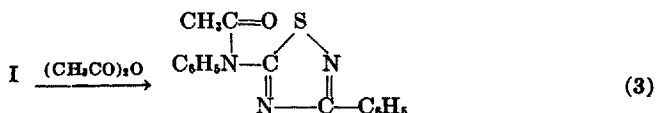
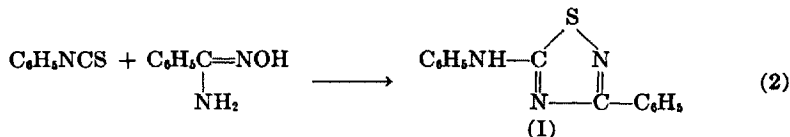
II. 3- and 5-Aryl Substituted 1,2,4-Thiadiazoles

The history of these 1,2,4-thiadiazoles is taken up separately because that is the way they occur in the literature. An analysis will show that these compounds have many of the characteristics in common with the perthiocyanic acid derivatives but only a few cross references are extant.

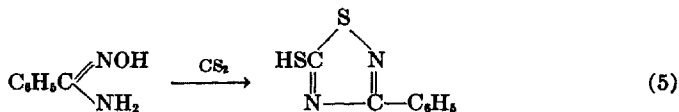
Kruger¹ found that phenyl isothiocyanate and benzhydroxamine in the cold gave benzenylphenylthiouramidoxime (1). Koch,² working



in Tiemann's³ laboratory, found that by condensing phenyl isothiocyanate and benzhydroxamine in refluxing chloroform 3-phenyl-5-anilino-1,2,4-thiadiazole (I) was formed (2). Heating (I) in concentrated hydrochloric acid gave hydrogen sulfide, sulfur, benzoic acid, aniline, and ammonium chloride. This compound (I) gave a monoacetyl derivative with acetic anhydride (3) and a mononitroso derivative with nitrous acid (4).



Crayen,⁴ also in Tiemann's laboratory, obtained 3-phenyl-5-mercapto-1,2,4-thiadiazole by allowing carbon disulfide to react with an alkaline solution of benzhydroxamine (5). Hydrolysis of this compound with



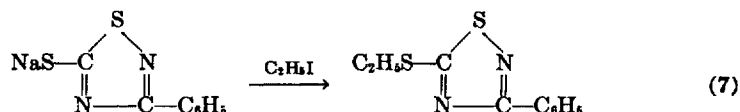
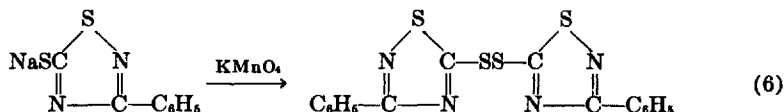
¹ Kruger, *Ber.*, 17, 1060 (1884).

² Koch, *Ber.*, 24, 394 (1891).

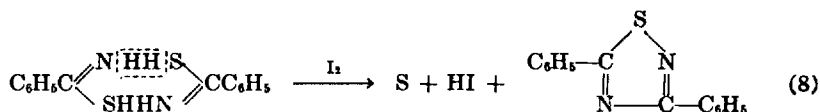
³ Tiemann, *Ber.*, 24, 369 (1891).

⁴ Crayen, *Ber.*, 24, 385 (1891).

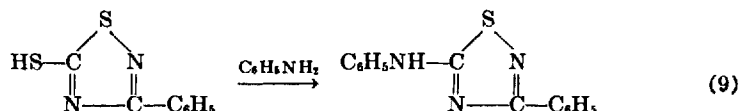
concentrated hydrochloric acid at 150°C. gave hydrogen sulfide, benzoic acid, carbon dioxide, ammonium chloride, and sulfur. It formed metallic salts and the mercury salt was characterized. Oxidation gave the disulfide (6) and ethyl iodide in alkaline solution gave the sulfide (7).



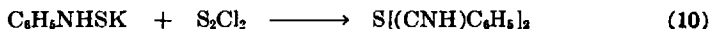
Hoffmann and Gabriel⁵ oxidized thiobenzamide and obtained 3,5-diphenyl-1,2,4-thiadiazole (8). In their proof of structure they reduced



this compound and obtained benzylbenzamidine. Walther⁶ repeated this oxidation with ammonium persulfate. Gheorghui and Barbos^{7,8} found that they could prepare the 3-phenyl-5-anilino-1,2,4-thiadiazole of Koch⁹ in two ways: first, by allowing phenyl isothiocyanate to react with benzhydroxamidine in an alcoholic solution; second, by gently heating 3-phenyl-5-mercapto-1,2,4-thiadiazole with aniline (9).



Chakravarti¹⁰ reported that potassium isothiobenzamide reacted with sulfur chloride to give an iminosulfide (10). Ishikawa¹¹ took issue with



⁵ Hoffmann and Gabriel, *Ber.*, **25**, 1578 (1892).

⁶ Walther, *J. prakt. Chem.*, **69**, 44 (1904).

⁷ Gheorghui and Barbos, *Ann. sci. univ. Jassy*, **126**, 271 (1940); *Chem. Abstr.*, **34**, 4388 (1940).

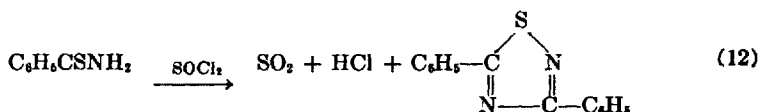
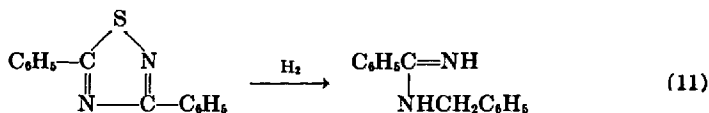
⁸ Barbos, *ibid.*, **26**, 526 (1940); *Chem. Abstr.*, **35**, 3254 (1941).

⁹ Koch, *Ber.*, **24**, 394 (1891).

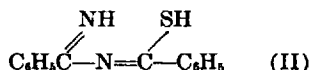
¹⁰ Chakravarti, *J. Chem. Soc.*, **123**, 964 (1923).

¹¹ Ishikawa, *Chem. Abstr.*, **19**, 3087 (1925); *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **3**, 147 (1925).

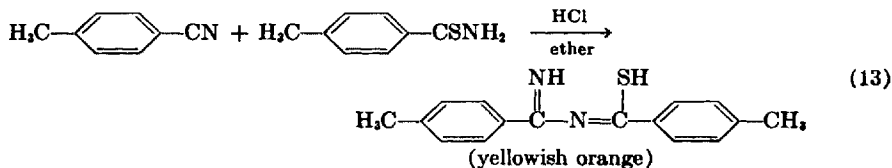
this conclusion and deduced that the product was 3,5-diphenyl-1,2,4-thiadiazole. This compound on reduction gave benzyl benzamidine (11). Ishikawa also prepared this thiadiazole using thiobenzamide and thionyl chloride (12).



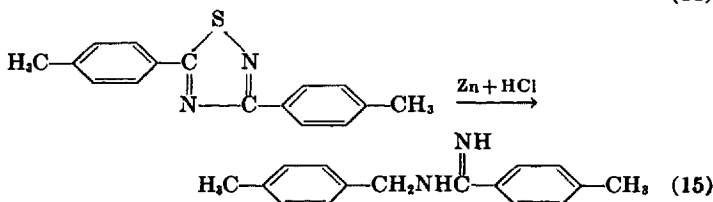
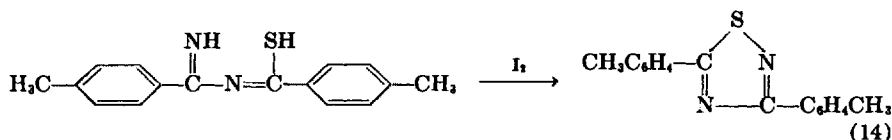
In the reactions which use sulfur chloride and thionyl chloride, a small amount of a red unstable intermediate was formed. This compound was believed to be benziminoisothiobenzamide (II). Ishikawa¹² prepared the



toluene homologs of this compound using toluinitrile and thiotoluidine in ether saturated with hydrochloride (13). Oxidation of this compound

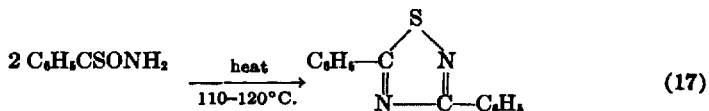


with iodine gave the disubstituted 1,2,4-thiadiazole. Ethyl iodide and *p*-toluimido-*p*-isothiitoluamide gave *S*-ethyl-*p*-toluimido-*p*-isothiitoluamide. Reduction of 3,5-di-*p*-tolyl-1,2,4-thiadiazole gave an amidine (15).

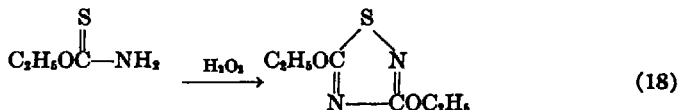


¹² Ishikawa, *Chem. Abstr.*, 22, 1581 (1928); *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, 7, 237 (1928).

Kitamura and Suzuki¹³ oxidized thiobenzamide with hydrogen peroxide (16). This oxidation product on heating gave 3,5-diphenyl-1,2,4-thiadiazole (17).



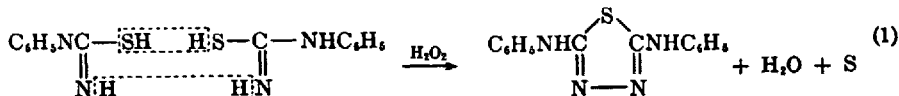
Holmberg¹⁴ prepared xanthamide. Oxidation of this compound with hydrogen peroxide gave a compound having the empirical formula $\text{C}_6\text{H}_{10}\text{O}_2\text{N}_2\text{S}$ (18). He assigned the structure 3,5-diethoxy-1,2,4-thiadiazole to this compound.



Dubsky and Trtilek¹⁵ believed the red color formed by the addition of cupric chloride to xanthamide could be explained by the formation of compounds having the general formula $\text{CuCl}_2(\text{C}_2\text{H}_5\text{OCSNH}_2)_2$ followed by the separation of cuprous chloride and the simultaneous formation of $\text{C}_6\text{H}_{10}\text{N}_2\text{O}_2\text{S}$. This 3,5-diethoxy-1,2,4-thiadiazole was also prepared by the oxidation of xanthamide by hydrogen peroxide or alcoholic iodine.

III. 1,2,4-Thiadiazolidines (Especially the 3,5-Bis(imino) Derivatives)

Hector^{1,2} oxidized a number of phenyl and diphenyl thioureas with hydrogen peroxide, dilute nitric acid, ferric chloride, and alcoholic iodine. He believed that the reaction proceeded along course (1). Later, when he worked on the constitution he could find no evidence for a hydrazine group.⁴



¹³ Kitamura and Suzuki, *Chem. Abstr.*, 33, 1726 (1939); *J. Pharm. Soc. Japan*, 57, 809, in English, 246 (1937).

¹⁴ Holmberg, *Svensk. Kem. Tid.*, 41, 249 (1929).

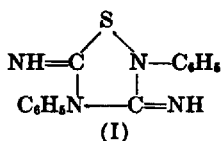
¹⁵ Dubsky and Trtilek, *Chem. Abstr.*, 27, 2137 (1933); *Chem. Obzor*, 8, 1 (1933).

¹ Hector, *Ber.*, 22, 1176 (1889).

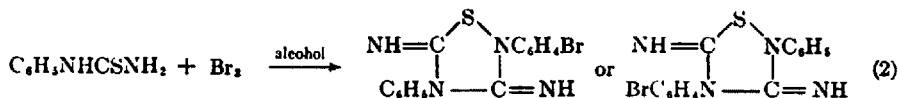
² Hector, *Ber.*, 23, 357 (1890).

⁴ Hector, *Ber.*, 25, Ref. 799 (1892); *Oefvers. Kongl. Vet. Akad.*, 1892, 79.

Treating the oxidation product with concentrated hydrochloric acid or with Zn and hydrochloric acid gave *N,N'*-diphenylguanidine. The oxidation product and sodium hydroxide produced phenyl cyanamide. Ethyl iodide reacted with the thiadiazolidine and gave the *N*-ethyl derivative, which on reduction with zinc and hydrochloric acid produced *N,N'*-diphenylguanidine, ethylamine, hydrogen sulfide, and carbon dioxide. As the result of this work, Hector assigned the 1,2,4-thiadiazolidine structure (I) to these compounds rather than the 1,3,4-thiadiazolidine structure.



Hugershoff⁴ brominated the phenylthiourea in alcohol (2) and obtained the bromo derivatives of this compound. Dost⁵ oxidized phenyl-



thiourea and obtained the 2,4-diphenyl-3,5-diimino-1,2,4-thiadiazolidine having the melting point of approximately 181°C. On heating this compound in alcoholic ammonia for 2.5 hours at 140 to 150°C., an isomer melting at 198° was obtained. Fromm and Heyder⁶ synthesized the same compound with the same melting point (198°C.) by allowing *p*-toluenesulfonyl chloride to react with phenylthiourea. Acetylation of this compound gave the same compound which Hector obtained by acetylating 2,4-diphenyl-3,5-diimino-1,2,4-thiadiazolidine. Haager and Dohrt⁷ produced this thiadiazolidine by the action of nitrous acid on phenyl isothiocyanate.

Dost⁵ obtained 2,4-diphenyl-3-imino-1,2,4-thiadiazolidine-5-one by heating the 2,4-diphenyl-3,5-diimino-1,2,4-thiadiazolidine in concentrated hydrochloric acid (3). Reduction of this compound gave *N,N'*-diphenylguanidine.



⁴ Hugershoff, *Ber.*, 34, 3130 (1901).

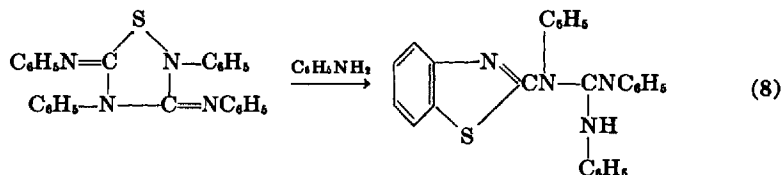
⁵ Dost, *Ber.*, 39, 863 (1906).

⁶ Fromm and Heyder, *Ber.*, 42, 3804 (1909).

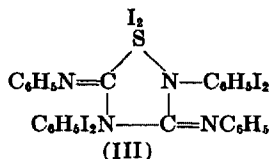
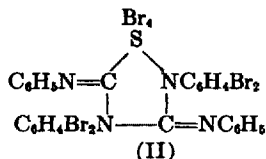
⁷ Haager and Dohrt, *Monatsh.*, 27, 277 (1906).

⁸ Dost, *Ber.*, 39, 863 (1906).

compound which Hugershoff¹² obtained by brominating diphenylthiourea in chloroform. 2,4-Diphenyl-3,5-bis(phenylimino)-1,2,4-thiadiazolidine heated in the presence of aniline produced 2-triphenylguanidinobenzo-thiazole (8).



Hunter¹³ studied the bromination and iodination of 2,4-diphenyl-3,5-bis(phenylimino)-1,2,4-thiadiazolidine. An octabromide was isolated which gradually lost bromine on exposure to the atmosphere and was reduced to the original thiadiazolidine by sulfurous acid. Iodination produced only the hexaiodide. The structure of these halogen compounds was believed to be (II) and (III).

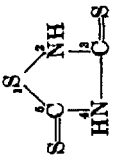
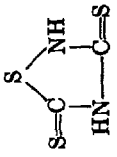
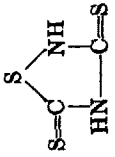
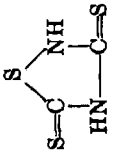
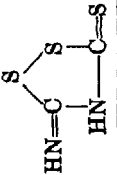


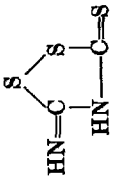
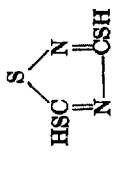
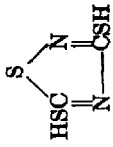
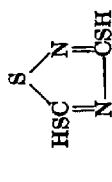
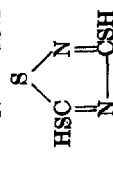
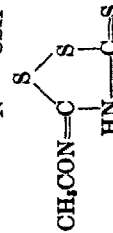
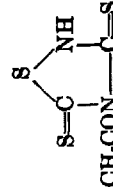
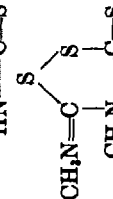
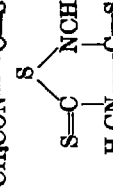
¹² Hugershoff, *Ber.*, **36**, 3121 (1903).

¹³ Hunter, *J. Chem. Soc.*, **129**, 533 (1926).

Tables VI-IX follow on pages 58-79.

TABLE VI. Controvertible Names and Structures of Some 1,2,4-Thiadiazoles Occurring in the Literature

No.	Name in literature	Ref.	Structure assigned in literature	Probable structure (see discussion)	Name assigned to compound
1	Perthiocyanic acid	1	$C_4H_2N_2S_3$		Isopertthiocyanic acid, 1,2,4-thiadiazolidine-3,5-dithione
1	Perthiocyanic acid	2		—	—
1	Pseudopertthiocyanic acid. Isopertthiocyanic acid (Xanthanwasserstoff)	3		—	—
1	Perthiocyanic acid	4		—	—
1	Isopertthiocyanic acid	5		—	—

No.	Name in literature	Ref.	Structure assigned in literature	Probable structure (see discussion)	Name assigned to compound
1	Isoperthiocyanic acid	6		—	—
2	Perthiocyanic acid	3			Perthiocyanic acid, 3,5-dimer-capto-1,2,4-thiadiazole
2	Perthiocyanic acid	5		—	—
2	Perthiocyanic acid	6		—	—
3	Acetyl perthiocyanic acid	5			(1) Acetyl isoperthiocyanic acid. (2) 4-Acetyl-1,2,4-thiadiazolidine-3,5-dithione
4	Methyl isothiocyanate sulfide. 1-Methyl-2-methylimido-5-thio-3,4-disulfazolidin	5, 7			2,4-Dimethyl-1,2,4-thiadiazolidine-3,5-dithione

(Table continued)

TABLE VI (Continued)

No.	Name in literature	Ref.	Structure assigned in literature	Probable structure (see discussion)	Name assigned to compound
5	Ethyl isothiocyanate sulfide. 1-Ethyl-2-ethylimido-5-thio-3,4-disulfazolidin	8	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{C}_2\text{H}_5\text{N}=\text{C} \quad \text{S} \\ \\ \text{C}_2\text{H}_5\text{N}-\text{C}=\text{S} \end{array}$	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{S}=\text{C} \quad \text{NC}_2\text{H}_5 \\ \\ \text{C}_2\text{H}_5\text{N}-\text{C}=\text{S} \end{array}$	2,4-Diethyl-1,2,4-thiadiazolidine-3,5-dithione
	Phenyl isothiocyanate sulfide. 1-Phenyl-2-phenylimido-5-thio-3,4-disulfazolidin	9	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{S}=\text{C} \quad \text{C}=\text{S} \\ \\ \text{C}_6\text{H}_5\text{N}-\text{NC}_6\text{H}_5 \end{array}$	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{S}=\text{C} \quad \text{NC}_6\text{H}_5 \\ \\ \text{C}_6\text{H}_5\text{N}-\text{C}=\text{S} \end{array}$	2,4-Diphenyl-1,2,4-thiadiazolidine-3,5-dithione
6	—	8	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_5\text{N}=\text{C} \quad \text{S} \\ \\ \text{C}_6\text{H}_5\text{N}-\text{C}=\text{S} \end{array}$	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{S}=\text{C} \quad \text{NC}_6\text{H}_5 \\ \\ \text{C}_6\text{H}_5\text{N}-\text{C}=\text{S} \end{array}$	—
7	Methyl isothiocyanate oxide. 3-Thio-2,4-dimethylbiazulfolid-5-on	7	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{O}=\text{C} \quad \text{NCH}_3 \\ \\ \text{CH}_3\text{N}-\text{C}=\text{S} \end{array}$	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{O}=\text{C} \quad \text{NCH}_3 \\ \\ \text{H}_3\text{CN}-\text{C}=\text{S} \end{array}$	2,4-Dimethyl-1,2,4-thiadiazolidine-3-thione-5-one
7	—	5	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{CH}_3\text{N}=\text{C} \quad \text{S} \\ \\ \text{H}_3\text{CN}-\text{C}=\text{O} \end{array}$	—	—
8	Ethyl isothiocyanate oxide. 3-Thio-2,4-diethylbiazulfolid-5-on	8	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{O}=\text{C} \quad \text{NC}_2\text{H}_5 \\ \\ \text{C}_2\text{H}_5\text{N}-\text{C}=\text{S} \end{array}$	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{O}=\text{C} \quad \text{NC}_2\text{H}_5 \\ \\ \text{C}_2\text{H}_5\text{N}-\text{C}=\text{S} \end{array}$	2,4-Diethyl-1,2,4-thiadiazolidine-3-thione-5-one

No.	Name in literature	Ref.	Structure assigned in literature	Probable structure (see discussion)	Name assigned to compound
8	—	5	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_5\text{N}=\text{C} \quad \text{S} \\ \quad \quad \\ \text{C}_6\text{H}_5\text{N}-\text{C}=\text{O} \end{array}$	—	—
9	Phenyl isothiocyanate oxide. 3-Thiophenyl-2,4-biazsulfolid-5-on	8	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{O}=\text{C} \quad \text{NC}_6\text{H}_5 \\ \quad \quad \\ \text{C}_6\text{H}_5\text{N}-\text{C}=\text{S} \end{array}$	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{O}=\text{C} \quad \text{NC}_6\text{H}_5 \\ \quad \quad \\ \text{C}_6\text{H}_5\text{N}-\text{C}=\text{S} \end{array}$	2,4-Diphenyl-1,2,4-thiadiazolidine-3-thione-5-one
9	—	5	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_5\text{N}=\text{C} \quad \text{S} \\ \quad \quad \\ \text{C}_6\text{H}_5\text{N}-\text{C}=\text{S} \end{array}$	—	—
10	3-Imino-1,2,4-dithiazolin-5-one	6	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{NH}=\text{C} \quad \text{S} \\ \quad \quad \\ \text{HN}-\text{C}=\text{O} \end{array}$	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{O}=\text{C} \quad \text{NH} \\ \quad \quad \\ \text{HN}-\text{C}=\text{S} \end{array}$	1,2,4-Thiadiazolidine-3-thione-5-one
11	3,3-Dichloro-5-imino-1,2,4-dithiazoline	6	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{HN}=\text{C} \quad \text{S} \\ \quad \quad \\ \text{HN}-\text{C}=\text{Cl}_2 \end{array}$	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{Cl}-\text{C} \quad \text{NH} \\ \quad \quad \\ \text{N}=\text{C}=\text{S} \end{array} \cdot \text{HCl}$	5-Chloro-1,2,4-thiadiazoline-3-thione hydrochloride
12	3,3-Dibromo-5-imino-1,2,4-dithiazoline	6	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{HN}=\text{C} \quad \text{S} \\ \quad \quad \\ \text{HN}-\text{C}=\text{Br}_2 \end{array}$	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{Br}-\text{C} \quad \text{NH} \\ \quad \quad \\ \text{N}=\text{C}=\text{S} \end{array} \cdot \text{HBr}$	5-Bromo-1,2,4-thiadiazoline-3-thione hydrobromide

(Table continued)

TABLE VI (Concluded)

No.	Name in literature	Ref.	Structure assigned in literature	Probable structure (see discussion)	Name assigned to compound
13	3,5-Diimino-1,2,4-dithiazoline	10			5-Imino-1,2,4-thiadiazolidine-3-thione
14	Phenyl thiuret	11			5-Phenylimino-1,2,4-thiadiazolidine-3-thione
14	Thiuret	5		—	—
14	Thiuret	6		—	—
15	The other substituted thiurets prepared by Fromm and co-workers may be treated in a manner similar to compound 14.				

¹ Wohler, *Ann. Physik.*, **69**, 273 (1821).² Glutz, *Ber.*, **3**, 346 (1870).³ Klason, *J. prakt. Chem.*, [2] **38**, 366 (1888).⁴ Freund, *Ann.*, **285**, 154 (1895).⁵ Hantsch and Wolvelkamp, *Ann.*, **331**, 265 (1904).⁶ Soderbäck, *Ann.*, **419**, 217 (1919); *Ann.*, **465**, 184 (1928);*Svensk. Chem. Tid.*, **56**, 207 (1944).⁷ Freund and Asbrand, *Ann.*, **285**, 166 (1895).⁸ Freund and Bachrach, *Ann.*, **285**, 184 (1895).⁹ Proskauer and Sell, *Ber.*, **9**, 1262 (1876).¹⁰ Preisler and Bateman, *J. Am. Chem. Soc.*, **69**, 2632 (1947).¹¹ Fromm, *Ann.*, **275**, 20 (1893).

TABLE VII. Preparation of the 1,2,4-Thiadiazoles

No.	Name of compound	Ref.	Method of preparation	Structure	Solubility	M.p., °C.
1	Perthiocyanic acid, 3,5-Dimercapto-1,2,4-thiadiazole	3,5-1,2	$\text{NH}_2\text{NH}_2\text{HSC}=\text{N}-\text{C}(\text{SH})=\text{N}-\text{NH}_2$	$\xrightarrow{\text{HCl}}$ 	very sol. in water	167-8
2	Barium perthiocyanate trihydrate, tetrahydrate, pentahydrate	2	$\text{Ba}(\text{OH})_2$		sol. in water, difficultly sol. in alc.	—
3	3,5-Bis(methylmercapto)-1,2,4-thiadiazole	3	CH_3I		sol. in alc.	42
4	3,5-Bis(ethyl mercapto)-1,2,4-thiadiazole	4	$\text{C}_2\text{H}_5\text{I}$		—	oil dec. at 190°
5	3,5-Bis(benzyl mercapto)-1,2,4-thiadiazole	5	$\text{C}_6\text{H}_5\text{I}$		—	52
6	3,5-Bis(mercaptoacetic acid)-1,2,4-thiadiazole	4	$\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$		—	oil dec. at 177°
7	Bis(5-chloro-3-(1,2,4-thiadiazolyl)) disulfide	5	ClCH_2COOH		sol. in ether, alc., CS_2 , CCl_4 , CHCl_3 , benzene	69-70

(Table continued)

TABLE VII (Continued)

No.	Name of compound	Ref.	Method of preparation	Structure	Solubility	M.p., °C.
8	Mercury 3-mercapto-5-chloro-1,2,4-thiadiazole	5			sol. in hot benzene	168-9
9	Sodium 3-mercapto-5-chloro-1,2,4-thiadiazole	6			sol. in acetone	—
10	Sodium 3-mercapto-5-hydroxy-1,2,4-thiadiazole	6			sol. in water	—
11	Disodium bis[(5-hydroxy-3-(1,2,4-thiadiazolyl)]disulfide	6			difficultly sol. in abs. alc.	—
12	Disodium 5-hydroxy-3-(1,2,4-thiadiazolyl)-3'-mercapto-5'-(1',2',4'-thiadiazolyl) sulfide	6			sol. in alc.	—

No.	Name of compound	Ref.	Method of preparation	Structure	Solubility	M.p., °C.
13	3-Thiocyano-5-chloro-1,2,4-thiadiazole	7			sol. in ether	75-6
14	3-Thiocyano-5-hydroxy-1,2,4-thiadiazole	7			insol. in water	—
15	5,3'-Dithiocyano-3-(1,2,4-thiadiazolyl)-5'-(1',2',4'-thiadiazolyl) sulfide	7			sol. in warm benzene, warm acetone	—
16	3,5-Dithiocyano-1,2,4-thiadiazole	7			sol. in ether	100
17	Mercury 3-mercapto-5-thiocyano-1,2,4-thiadiazole	7			sol. in hot amyl alc.	200 dec.
	or Mercury-3-thiocyano-5-mercapto-1,2,4-thiadiazole					

(Table continued)

TABLE VII (Continued)

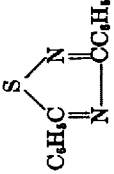
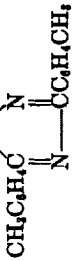
No.	Name of compound	Ref.	Method of preparation	Structure	Solubility	M.p., °C.
18	Methyl derivative of No. 17	7	barium salt of 17	$\begin{array}{c} \text{NCSC} \begin{array}{c} \diagup \text{N} \\ \diagdown \text{N} \end{array} \text{C} \text{SCH}_3 \\ \text{or} \\ \text{CH}_3\text{SC} \begin{array}{c} \diagup \text{N} \\ \diagdown \text{N} \end{array} \text{C} \text{SCN} \end{array}$	sol. in benzene, difficultly sol. in ether	108-12
19	Barium 5-mercapto-3-(1,2,4-thiadiazolyl)-3'-thiocyano-5'-c-(1',2,4'-thiadiazolyl) sulfide	7	$2\text{BaSC} \begin{array}{c} \diagup \text{N} \\ \diagdown \text{N} \end{array} \text{C} \text{SCN}$	$\begin{array}{c} \text{S} \\ \diagup \text{N} \\ \diagdown \text{N} \end{array} \text{C} \text{SCH}_3 \text{ or } \text{CH}_3\text{SC} \begin{array}{c} \diagup \text{N} \\ \diagdown \text{N} \end{array} \text{C} \text{SCN}$	insol. in cold water	—
20	Hexathiocyanate	7	compound 17	$\begin{array}{c} \text{NCSC} \begin{array}{c} \diagup \text{N} \\ \diagdown \text{N} \end{array} \text{C} \text{SCH}_3 \\ \text{or} \\ \text{CH}_3\text{SC} \begin{array}{c} \diagup \text{N} \\ \diagdown \text{N} \end{array} \text{C} \text{SCN} \end{array}$	difficultly sol. in ether, sol. in acetone	138-42
21	3-Phenyl-5-mercapto-1,2,4-thiadiazole	8	$\begin{array}{c} \text{NOK} \\ \text{C}_6\text{H}_5\text{C}=\text{N} \\ \text{NH}_2 \end{array}$	$\begin{array}{c} \text{S} \\ \diagup \text{N} \\ \diagdown \text{N} \end{array} \text{C} \text{SCH}_3$	insol. in water, sol. in hot alc., glacial acetic acid	162
[22	Bis(3-phenyl-5-(1,2,4-thiadiazolyl)) disulfide	8	oxidation of 21	$\left(\begin{array}{c} \text{S} \\ \diagup \text{N} \\ \diagdown \text{N} \end{array} \text{C} \text{SCH}_3 \right)_2$	insol. in water and alc.	120

No.	Name of compound	Ref.	Method of preparation	Structure	Solubility	M.p., °C.
23	3-Phenyl-5-ethylmercapto-1,2,4-thiadiazole	8	$\text{KSC} \begin{array}{c} \diagup \text{N} \\ \diagdown \text{N} \end{array} \begin{array}{c} \diagup \text{C}_6\text{H}_5 \\ \diagdown \text{C}_2\text{H}_5 \end{array} \xrightarrow{\text{C}_2\text{H}_5\text{I}} \text{S} \begin{array}{c} \diagup \text{N} \\ \diagdown \text{N} \end{array} \begin{array}{c} \diagup \text{C}_6\text{H}_5\text{SC} \\ \diagdown \text{C}_2\text{H}_5 \end{array}$	$\text{S} \begin{array}{c} \diagup \text{N} \\ \diagdown \text{N} \end{array} \begin{array}{c} \diagup \text{C}_6\text{H}_5\text{SC} \\ \diagdown \text{C}_2\text{H}_5 \end{array}$	sol. in dil. alc. and alc., ether, acetone and benzene	49
24	3-Phenyl-5-benzylmercapto-1,2,4-thiadiazole	8	$\text{KSC} \begin{array}{c} \diagup \text{N} \\ \diagdown \text{N} \end{array} \begin{array}{c} \diagup \text{C}_6\text{H}_5 \\ \diagdown \text{C}_6\text{H}_5 \end{array} \xrightarrow{\text{C}_6\text{H}_5\text{CH}_2\text{Cl}} \text{S} \begin{array}{c} \diagup \text{N} \\ \diagdown \text{N} \end{array} \begin{array}{c} \diagup \text{C}_6\text{H}_5\text{CH}_2\text{SC} \\ \diagdown \text{C}_6\text{H}_5 \end{array}$	$\text{S} \begin{array}{c} \diagup \text{N} \\ \diagdown \text{N} \end{array} \begin{array}{c} \diagup \text{C}_6\text{H}_5\text{CH}_2\text{SC} \\ \diagdown \text{C}_6\text{H}_5 \end{array}$	sol. in alc.	79
25	3- <i>p</i> -Tolyl-5-mercapto-1,2,4-thiadiazole	8	$\text{CH}_3\text{C}_6\text{H}_4\text{C} \begin{array}{c} \diagup \text{NOH} \\ \diagdown \text{NH}_2 \end{array} \xrightarrow{\text{CS}_2} \text{HSC} \begin{array}{c} \diagup \text{N} \\ \diagdown \text{N} \end{array} \begin{array}{c} \diagup \text{C}_6\text{H}_4\text{CH}_3 \\ \diagdown \text{C}_6\text{H}_4\text{CH}_3 \end{array}$	$\text{HSC} \begin{array}{c} \diagup \text{N} \\ \diagdown \text{N} \end{array} \begin{array}{c} \diagup \text{C}_6\text{H}_4\text{CH}_3 \\ \diagdown \text{C}_6\text{H}_4\text{CH}_3 \end{array}$	sol. in alc. and acetic acid	166
26	Bis[3- <i>p</i> -tolyl-5-(1,2,4-thiadiazolyl)]disulfide	8	oxidation of 25	$\left(\text{SC} \begin{array}{c} \diagup \text{N} \\ \diagdown \text{N} \end{array} \begin{array}{c} \diagup \text{C}_6\text{H}_4\text{CH}_3 \\ \diagdown \text{C}_6\text{H}_4\text{CH}_3 \end{array} \right)_2$	insol. in water and alc.	169
27	3- <i>p</i> -Tolyl-5-ethylmercapto-1,2,4-thiadiazole	8	ethyl iodide + 25	$\text{C}_2\text{H}_5\text{SC} \begin{array}{c} \diagup \text{N} \\ \diagdown \text{N} \end{array} \begin{array}{c} \diagup \text{C}_6\text{H}_4\text{CH}_3 \\ \diagdown \text{C}_6\text{H}_4\text{CH}_3 \end{array}$	sol. in ether, alc., and acetone	37
28	3-Phenyl-5-anilino-1,2,4-thiadiazole	9	$\text{C}_6\text{H}_5\text{C} \begin{array}{c} \diagup \text{NOH} \\ \diagdown \text{NH}_2 \end{array} \xrightarrow{\text{C}_6\text{H}_5\text{NCS}} \text{C}_6\text{H}_5\text{NHC} \begin{array}{c} \diagup \text{N} \\ \diagdown \text{N} \end{array} \begin{array}{c} \diagup \text{C}_6\text{H}_5 \\ \diagdown \text{C}_6\text{H}_5 \end{array}$	$\text{S} \begin{array}{c} \diagup \text{N} \\ \diagdown \text{N} \end{array} \begin{array}{c} \diagup \text{C}_6\text{H}_5\text{NHC} \\ \diagdown \text{C}_6\text{H}_5 \end{array}$	sol. in benzene, CHCl_3 , alc., and ether	174

(Table continued)

TABLE VII (Continued)

No.	Name of compound	Ref.	Method of preparation	Structure	Solubility	M.p., C.°
28	(<i>contd.</i>)	10 11	— $\begin{array}{c} \text{HSC} \diagup \text{N} \\ \diagdown \text{S} \diagup \text{N} \\ \text{N}=\text{C}_6\text{H}_5 \end{array}$	— —	— —	174 175-6
29	3-Phenyl-5-acetanilido-1,2,4-thiadiazole	9	acetic anhydride + 28 $\xrightarrow{\text{C}_6\text{H}_5\text{NH}_2}$	$\begin{array}{c} \text{CH}_3\text{CO} \text{ S} \\ \quad \diagup \text{N} \\ \text{C}_6\text{H}_5\text{N} \text{C} \quad \diagdown \text{N} \\ \quad \quad \quad \text{N}=\text{C}_6\text{H}_5 \end{array}$	sol. in alc., benzene, ether, and CHCl_3	196
30	3-Phenyl-5-nitrosoanilino-1,2,4-thiadiazole	9	nitrous acid + 28 $\longrightarrow$	$\begin{array}{c} \text{NO} \text{ S} \\ \quad \diagup \text{N} \\ \text{C}_6\text{H}_5\text{N} \text{C} \quad \diagdown \text{N} \\ \quad \quad \quad \text{N}=\text{C}_6\text{H}_5 \end{array}$	sol. in acetic acid	119 with dec.
31	3-Phenyl-5- <i>p</i> -bromoanilino-1,2,4-thiadiazole	9	Br_2 + 28 $\longrightarrow$	$\begin{array}{c} \text{S} \\ \quad \diagup \text{N} \\ \text{C}_6\text{H}_4\text{Br} \text{N} \text{C} \quad \diagdown \text{N} \\ \quad \quad \quad \text{N}=\text{C}_6\text{H}_5 \end{array}$	sol. in alc., CHCl_3 , ether, and benzene	—
32	3-Phenyl-5- <i>p</i> -toluidino-1,2,4-thiadiazole	9	$\begin{array}{c} \text{NOH} \\ \diagup \text{C} \diagdown \\ \text{C}_6\text{H}_5 \text{C} \quad \text{NH}_2 \end{array}$ $\xrightarrow{\text{CH}_3\text{C}_6\text{H}_4\text{NCS}}$	$\begin{array}{c} \text{S} \\ \quad \diagup \text{N} \\ \text{CH}_3\text{C}_6\text{H}_4 \text{N} \text{C} \quad \diagdown \text{N} \\ \quad \quad \quad \text{N}=\text{C}_6\text{H}_5 \end{array}$	sol. in alc., benzene, ether, CHCl_3 , and acetone	135

No.	Name of compound	Ref.	Method of preparation	Structure	Solubility	M.p., °C.
33	3,5-Diphenyl-1,2,4-thiadiazole	12	$\text{C}_6\text{H}_5\text{C}(\text{NH}_2)=\text{S} \xrightarrow{\text{I}_2}$		—	90-1
13			$\text{C}_6\text{H}_5\text{C}(\text{NH})=\text{SK} \xrightarrow{\text{S}_2\text{Cl}_2}$			
14			$\text{C}_6\text{H}_5\text{C}(\text{NH})=\text{SK} \xrightarrow{\text{S}_2\text{Cl}_2}$			
15			$\text{C}_6\text{H}_5\text{C}(\text{NH})=\text{SK} \xrightarrow{\text{SOCl}_2}$			
16			$\text{C}_6\text{H}_5\text{C}(\text{NH})=\text{SK} \xrightarrow{\text{H}_2\text{O}_2}$			
			$\text{C}_6\text{H}_5\text{CSONH}_2 \xrightarrow[\Delta]{110-20}$			
			$\text{C}_6\text{H}_5\text{CSONH}_2 \xrightarrow{\text{C}_6\text{H}_5\text{CSNH}_2}$			
34	3,5-Di- <i>p</i> -tolyl-1,2,4-thiadiazole	14, 15	$\text{CH}_3\text{C}_6\text{H}_4\text{CNH}_2 \xrightarrow{\text{S}_2\text{Cl}_2}$		—	129
			$\text{CH}_3\text{C}_6\text{H}_4\text{CSNH}_2 \xrightarrow{\text{CH}_3\text{C}_6\text{H}_4\text{CN}}$			
			$\text{CH}_3\text{C}_6\text{H}_4\text{C}(\text{NH})=\text{N}-\text{CC}_6\text{H}_4\text{CH}_3 \xrightarrow{\text{I}_2}$			
35	3,5-Di- <i>m</i> -tolyl-1,2,4-thiadiazole	14, 15	see 34		—	49.5

(Table continued)

TABLE VII (Concluded)

No.	Name of compound	Ref.	Method of preparation	Structure	Solubility	M.p., °C.
36	3-Phenyl-5- <i>p</i> -tolyl-1,2,4-thiadiazole	14, 15	see 34, second series of equations		—	56
37	3-Phenyl-5- <i>m</i> -tolyl-1,2,4-thiadiazole	13, 14	see 36	—	—	88
38	3,5-Di- α -naphthyl-1,2,4-thiadiazole	14			—	129
39	3,5-Diethoxy-1,2,4-thiadiazole	17	$\text{C}_{10}\text{H}_7\text{CNHSHK} \xrightarrow{\text{SeCl}_2}$ $\text{OC}_2\text{H}_5 \quad \text{C}=\text{S} \quad \text{NH}_2$	—	—	53
18			$\text{OC}_2\text{H}_5 \quad \text{C}=\text{S} \quad \text{NH}_2$		—	49-50

- ¹ Busch, *Ber.*, 27, 2518 (1899).
² Söderbäck, *Svensk. Kem. Tid.*, 57, 62 (1944).
³ Hantzsch and Wolkecamp, *Ann.*, 331, 265 (1904).
⁴ Klasen, *J. prakt. Chem.*, [2] 38, 366 (1888).
⁵ Rosenheim, Levy, Greenbaum, *Ber.*, 42, 2823 (1909).
⁶ Söderbäck, *Ann.*, 465, 184 (1928).
⁷ Söderbäck, *Svensk. Kem. Tid.*, 56, 207 (1944).
⁸ Crayen, *Ber.*, 24, 385 (1891).
⁹ Koch, *Ber.*, 24, 385 (1891).
¹⁰ Gheorghiu and Barbosa, *Ann. sci. univ. Jassy*, 126, 271 (1940); *Chem. Abstr.*, 34, 4388 (1940).
¹¹ Barbosa, *Ann. Sci. univ. Jassy*, 126, 271 (1940); *Chem. Abstr.*, 35, 3254 (1941).
¹² Hoffmann and Gabriel, *Ber.*, 25, 1578 (1892).
¹³ Chakravarti, *J. Chem. Soc.*, 123, 964 (1923).
¹⁴ Ishikawa, *Chem. Abstr.*, 19, 3087 (1925); *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, 3, 147 (1925).
¹⁵ Ishikawa, *Chem. Abstr.*, 22, 1581 (1928); *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, 7, 237 (1927).
¹⁶ Kitamura and Suzuki, *Chem. Abstr.*, 33, 1726 (1939); *J. Pharm. Soc. Japan*, 57, 809, 246 (1937).
¹⁷ Holmberg, *Svensk. Kem. Tid.*, 41, 249 (1929).
¹⁸ Dubsky and Trillek, *Chem. Abstr.*, 27, 2137 (1933); *Chem. Obozr.*, 8, 1 (1933).

TABLE VIII. Preparation of the 1,2,4-Thiadiazolines*

No.	Name of compound	Ref.	Method of preparation	Structure	Solubility	M.p., °C.
1	5-Chloro-1,2,4-thiadiazoline-3-thione hydrochloride	1, 2	$(\text{SCN})_2 \xrightarrow{\text{HCl}}$		Sol. in water with dec.; insol. in benzene	—
2	5-Bromo-1,2,4-thiadiazoline-3-thione hydrobromide	2	$\xrightarrow{\text{HBr}}$		—	—
3	5-Phenylmethylamino-1,2,4-thiadiazoline-3-thione	3	$\xrightarrow{\text{I}_2}$		Sol. in hot alc.	193

* These structures are in dispute. See Table VI for alternate structures.

1 Söderbäck, *Ann.*, 419, 217 (1919); 465, 184 (1928).2 Söderbäck, *Ann.*, 465, 184 (1928).3 Fromm and Junius, *Ber.*, 28, 1096 (1895).

TABLE IX. Preparation of the 1,2,4-Thiadiazolidines

No.*	Name of compound	Ref.	Method of preparation	Structure	Solubility	M.p., °C.
1	Isopertthiocyanic acid	1	$\text{NH}_4\text{SCN} + \text{HCl}$	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{C} \quad \text{NH} \\ \quad \\ \text{HN} \quad \text{C}=\text{S} \end{array}$	difficultly sol. in hot water	—
2	1,2,4-Thiadiazolidine-3,5-dithione	2	$\text{KSCN} + \text{HCl}$	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{C} \quad \text{NH} \\ \quad \\ \text{HN} \quad \text{C}=\text{S} \end{array}$	—	—
2	Acetyl isopertthiocyanate	3,4	$\text{CH}_3\text{COOH} + \text{NH}_4\text{SCN}$ $(\text{CH}_3\text{CO})_2\text{O} + \text{NH}_4\text{SCN}$	structure unknown	sol. in hot alc.	—
3	2,4-Dimethyl-1,2,4-thiadiazolidine-3,5-dithione tribromide	5	$\text{CH}_3\text{NCS} + \text{Br}_2$	structure unknown	sol. in nitrobenzene unstable	248
4	2,4-Dimethyl-1,2,4-thiadiazolidine-3,5-dithione	5	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{C} \quad \text{NCH}_3 \\ \quad \\ \text{CH}_3\text{N} \quad \text{C}=\text{S} \end{array} + \text{Br}_2$ $\text{CH}_3\text{NHCSSNH}_2\text{CH}_3 + \text{Br}_2$ $\text{CH}_3\text{NHCSSSCNHCH}_3 + \text{Br}_2$	—	—	—
5	2,4-Diethyl-1,2,4-thiadiazolidine-3,5-dithione	6	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{C} \quad \text{NCH}_3 \\ \quad \\ \text{H}_3\text{CN} \quad \text{C}=\text{S} \end{array} \cdot \text{Br}_2$ $\xrightarrow{\text{H}_2\text{S}}$	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{C} \quad \text{NCH}_3 \\ \quad \\ \text{H}_3\text{CN} \quad \text{C}=\text{S} \end{array}$	sol. in alc., ether, benzene, and CHCl_3	86
5	2,4-Diethyl-1,2,4-thiadiazolidine-3,5-dithione tribromide	6	$\text{C}_2\text{H}_5\text{NCS}$	structure unknown	sol. in nitrobenzene	—
6	2,4-Diethyl-1,2,4-thiadiazolidine-3,5-dithione	6	$\text{C}_2\text{H}_5\text{NHCSSH} \cdot \text{NH}_2\text{C}_2\text{H}_5 + \text{Br}_2$	—	—	—
6	2,4-Diethyl-1,2,4-thiadiazolidine-3,5-dithione	6	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{C} \quad \text{NCH}_3 \\ \quad \\ \text{H}_3\text{CN} \quad \text{C}=\text{S} \end{array}$ $\xrightarrow{\text{Br}_2}$	—	—	—

No.*	Name of compound	Ref.	Method of preparation	Structure	Solubility	M.p., °C.	
6	2,4-Diethyl-1,2,4-thiadiazolidine-3,5-dithione	6	compound 5 + H ₂ O 5 + NaHCO ₃		sol. in methanol, ethanol, ether, benzene, acetic acid, and CHCl ₃	—	
7	2,4-Diphenyl-1,2,4-thiadiazolidine-3,5-dithione	7	 C ₆ H ₅ NHC(=S)NHC ₆ H ₅	CSCl ₂	insol. in water; sol. in alc., ether, benzene, toluene, CS ₂ , and acetic acid	156	
8		8	C ₆ H ₅ NCS	 (C ₆ H ₅ NCS) ₂ SBr ₂	Br ₂ alc.	—	152
6		6	 C ₆ H ₅ NHC(=S)SNH ₂	Br ₂	Bromide	—	154-6
9	2,4-Dimethyl-1,2,4-thiadiazolidine-3-thione-5-one	9	C ₆ H ₅ NCS + AlCl ₃		alc.	—	154
10		10	C ₆ H ₅ N ₃ + AlCl ₃ + CS ₂		—	—	154-6
11		11	 NaOC(=S)N	strong acid	—	—	—
5	2,4-Dimethyl-1,2,4-thiadiazolidine-3-thione-5-one tribromide	5	CH ₃ NCS (alc. and CHCl ₃)	 structure unknown	Br ₂	sol. in nitrobenzene	158

(Table continued)

(Table continued)

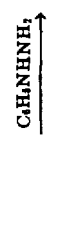
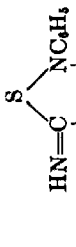
TABLE IX (Continued)

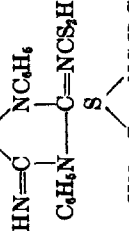
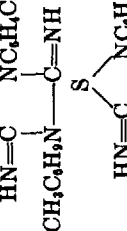
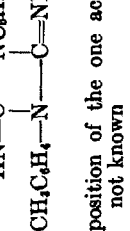
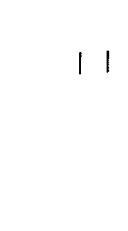
No.*	Name of compound	Ref.	Method of preparation	Structure	Solubility	M.p., °C.
10	2,4-Dimethyl-1,2,4-thiadiazolidine-3-thione-5-one	5	compound 9 $\xrightarrow{\text{Na}_2\text{CO}_3}$	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{O}=\text{C} \quad \text{NCH}_3 \\ \quad \quad \\ \text{H}_2\text{CN} \quad \text{C}=\text{S} \end{array}$	sol. in alc., ether, and CHCl_3	108
11	2,4-Diethyl-1,2,4-thiadiazolidine-3-thione-5-one di-chloride	12	$\text{C}_2\text{H}_5\text{NCS} \xrightarrow{\text{Cl}_2}$	structure unknown	—	—
12	2,4-Diethyl-1,2,4-thiadiazolidine-3-thione-5-one tri-bromide	6	$\text{C}_2\text{H}_5\text{NCS}$ (alc. in chloroform) $\xrightarrow{\text{Br}_2}$	structure unknown	sol. in nitrobenzene	180-1 with dec.
13	2,4-Diethyl-1,2,4-thiadiazolidine-3-thione-5-one	12, 6	hydrolysis of compounds 11 or 12 with aqueous Na_2CO_3	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{O}=\text{C} \quad \text{NC}_2\text{H}_5 \\ \quad \quad \\ \text{C}_2\text{H}_5\text{N} \quad \text{C}=\text{S} \end{array}$	sol. in alc., ether, ligroin, nitrobenzene, and CHCl_3	45
14	2,4-Diphenyl-1,2,4-thiadiazolidine-3-thione-5-one · X bromide	13, 6	$\text{C}_6\text{H}_5\text{NCS}$ (alc. and CHCl_3) $\xrightarrow{\text{Br}_2}$	structure unknown	sol. in nitrobenzene	189-92
15	2,4-Diphenyl-1,2,4-thiadiazolidine-3-thione-5-one	13, 6	hydrolysis of compound No. 14 with alc. and Na_2CO_3	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{O}=\text{C} \quad \text{NC}_6\text{H}_5 \\ \quad \quad \\ \text{C}_6\text{H}_5\text{N} \quad \text{C}=\text{S} \end{array}$	sol. in benzene, CHCl_3 , and ether	117-8

No.*	Name of compound	Ref.	Method of preparation	Structure	Solubility	M.p., °C.
16	5-Imino-1,2,4-thiadiazolidine-3-thione	14	$\text{NH}_4\text{CSNHCSNH}_2 \xrightarrow{\text{H}_2\text{O}_2}$		—	—
17	5-Phenylimino-1,2,4-thiadiazolidine-3-thione	15	$\text{C}_6\text{H}_5\text{NHCSNHCSNH}_2$ + oxidizing agent such as FeCl_3 , H_2O_2 , I_2		sol. in alc.	110 with 1 mole methanol
Derivatives of 5-phenylimino-1,2,4-thiadiazolidine-3-thione						
18	<i>o</i> -Methyl	16	oxidation of the dithiobiuret with H_2O_2 or FeCl_3 , oxidation of the dithiobiuret		sol. in alc.	87
19	<i>p</i> -Methyl	16	"		—	101
20	2',4'-Dimethyl	16	"		—	99
21	β -Naphthyl	16	"		—	over 300
22	2-Ethoxy	17	"		—	181-2
23	4-Ethoxy	17	"		—	137
24	4-Dimethylamino	17	"		—	dec. 175

(Table continued)

TABLE IX (Continued)

No.*	Name of compound	Ref.	Method of preparation	Structure	Solubility	M.p., °C.
25	1,2,4-Thiadiazolidine-3-thione-5-one, phenylhydrazone	16	$\text{C}_6\text{H}_5\text{NHNH}_2 \xrightarrow{\text{H}_2\text{O}_2}$		—	224-7
26	2,4-Diphenyl-3,5-diimino-1,2,4-thiadiazolidine	18, 19	$\text{C}_6\text{H}_5\text{NHC(S)NH}_2 \xrightarrow{\text{H}_2\text{O}_2}$		sol. in hot alc. and acetic acid	181
19			$\text{C}_6\text{H}_5\text{NHC(S)NH}_2 + \text{NH}_3 + \text{alc.}$		—	198
20			(low melting form) $\text{C}_6\text{H}_5\text{NCS} + \text{HNO}_2$	—	—	190
21			$\text{C}_6\text{H}_5\text{NHC(S)NH}_2 + \text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{Cl}$	—	—	198
27	Acetyl-2,4-diphenyl-3,5-diimino-1,2,4-thiadiazolidine	18, 21	$\text{C}_6\text{H}_5\text{NHC(S)NH}_2 + (\text{Ac})_2\text{O}$	position of the one acetyl group unknown	sol. in hot alc.	233
28	Benzoyl derivative of 26	18	see 26 and 27, benzoyl chloride + 26	—	—	—
29	Nitroso derivative of 26	18	see 26 and 27, HNO ₂ + 26	—	insol. in water and alc.	179 with dec.
30	Cyanogen derivative of 26	18	cyanogen + 26	structure unknown	sol. in hot alc.	—

No.*	Name of compound	Ref.	Method of preparation	Structure	Solubility	M.p., °C.
31	Dithiocarboxy derivative of 26	22	26 + CS ₂		difficultly sol. in alc.	162
32	2,4-Di- <i>p</i> -tolyl-3,5-bis(imino)-1,2,4-thiadiazolidine	23	CH ₃ C ₆ H ₄ NHCSNH ₂ $\xrightarrow{\text{H}_2\text{O}_2}$		sol. in alc.	127
19			$\xrightarrow[140-150^\circ]{\text{NH}_3}$ $\xrightarrow{\text{alcohol}}$		—	203
33	Acetyl-2,4-di- <i>p</i> -tolyl-3,5-bis(imino)-1,2,4-thiadiazolidine	23	 CH ₃ C ₆ H ₄ N—C(=NH)—C(=NH)—C(=O)CH ₃ + (Ac) ₂ O	position of the one acetyl group not known	sol. in alc.	166
34	Benzoyl deriv. of 32	23	see 32 and 33.	—	—	186
35	Nitroso deriv. of 32	23	see 32 and 33.	—	difficultly sol. in alc.	247 dec.
36	Cyanogen deriv. of 32	23	see 32 and 33.	structure unknown	sol. in alc.	190
37	2,4-Di- <i>o</i> -tolyl-3,5-dimino-1,2,4-thiadiazolidine	23	see 32.	see 32.	sol. in alc., acetone and benzene	135
38	Acetyl deriv. of 37	23	see 37 and 33.	—	—	221
39	Benzoyl deriv. of 37	23	see 37 and 34.	—	sol. in alc.	214
40	Nitroso deriv. of 37	23	see 37 and 35.	—	sol. in alc.	135 dec.
41	Cyanogen deriv. of 37	23	see 37 and 36.	—	sol. in alc.	89

(Table continued)

(Table continued)

TABLE IX (Continued)

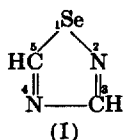
No.*	Name of compound	Ref.	Method of preparation	Structure	Solubility	M.p., °C.
42	2,4-Di-2',4'-xylyl-3,5-dimino-1,2,4-thiadiazolidine	23	$(\text{CH}_3)_2\text{C}_6\text{H}_4\text{NHCNHNH}_2$	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{HN}=\text{C} \quad \text{N} \text{C}_6\text{H}_4(\text{CH}_3)_2 \\ \quad \quad \\ \text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{N} \quad \text{C}=\text{NH} \end{array}$	sol. in alc.	79
43	Acetyl deriv. of 42	23	42 + acetic anhydride	$\xrightarrow{\text{H}_2\text{O}_2}$ see 33	sol. in alc.	—
44	Benzoyl deriv. of 42	23	42 + benzoyl chloride	see 33	sol. in alc.	211–2
45	Cyanogen deriv. of 42	23	42 + cyanogen	see 36	sol. in alc. and benzene	103
46	Nitroso deriv. of 42	23	42 + HNO_2	see 35	sol. in alc.	146
47	2,4-Di- α -naphthyl-3,5-dimino-1,2,4-thiadiazolidine	23	$\text{C}_{10}\text{H}_7\text{NHCNHNH}_2$	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{HN}=\text{C} \quad \text{N} \text{C}_{10}\text{H}_7 \\ \quad \quad \\ \text{H}_2\text{N}-\text{C}_{10}\text{H}_7-\text{N} \quad \text{C}=\text{NH} \end{array}$	sol. in alc.	136
48	Acetyl deriv. of 47	23	47 + acetic anhydride	$\xrightarrow{\text{H}_2\text{O}_2}$ see 33	sol. in alc.	263
49	Benzoyl deriv. of 47	23	47 + benzoyl chloride	see 34	difficultly sol. in alc.	270
50	Cyanogen deriv. of 47	23	47 + cyanogen	unknown	sol. in alc.	203
51	2,4-Di- β -naphthyl-3,5-dimino-1,2,4-thiadiazolidine	23	see 47	see 47	sol. in alc.	110–117
52	Acetyl deriv. of 51	23	51 + acetic anhydride	see 48	sol. in alc.	203
53	Benzoyl deriv. of 51	23	51 + benzoyl chloride	see 49	difficultly sol. in alc.	247 with dec.
54	Cyanogen deriv. of 51	23	51 + cyanogen	see 50	sol. in alc.	200
55	2,4-Diphenyl-3,4-bis-(phenylimino)-1,2,4-thiadiazolidine	24	$(\text{C}_6\text{H}_5\text{NH})_2\text{CS} + \text{Br}_2$	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{HN}=\text{C} \quad \text{N} \text{C}_6\text{H}_5 \\ \quad \quad \\ \text{C}_6\text{H}_5\text{N}-\text{C}_6\text{H}_5-\text{N} \quad \text{C}=\text{NC}_6\text{H}_5 \end{array}$	sol. in alc., acetic acid, and benzene	131, 135–6

No.*	Name of compound	Ref.	Method of preparation	Structure	Solubility	M.p., °C.
56	Octabromide deriv. of 55	25	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_4\text{N}=\text{C} \quad \text{NC}_6\text{H}_5 \\ \\ \text{C}_6\text{H}_4\text{N}-\text{C}=\text{NC}_6\text{H}_5 \end{array} \longrightarrow$	$\begin{array}{c} \text{Br}_4 \\ \\ \text{S} \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_4\text{N}=\text{C} \quad \text{NC}_6\text{H}_5\text{Br}_3 \\ \\ \text{Br}_3\text{C}_6\text{H}_4\text{N}-\text{C}=\text{NC}_6\text{H}_5 \end{array}$	sol. in CHCl_3	sinters at 110, 200 with dec.
57	Hexaiodide deriv. of 55	25	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_4\text{N}=\text{C} \quad \text{NC}_6\text{H}_5 \\ \\ \text{C}_6\text{H}_4\text{N}-\text{C}=\text{NC}_6\text{H}_5 \end{array} \xrightarrow{55 + \text{I}_2}$	$\begin{array}{c} \text{I}_2 \\ \\ \text{S} \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_4\text{N}=\text{C} \quad \text{NC}_6\text{H}_5\text{I}_3 \\ \\ \text{C}_6\text{H}_4\text{I}_2\text{N}-\text{C}=\text{NC}_6\text{H}_5 \end{array}$	sol. in acetic acid, ether, ethyl acetate, and alc.	122 with dec.
58	2,4-Di- <i>p</i> -tolyl-3,5-bis(<i>p</i> -tolylimino)-1,2,4-thiadiazolidine	24	$(\text{CH}_3\text{C}_6\text{H}_4\text{NH})_2\text{S} + \text{Br}_3$ $\xrightarrow{\text{alc.}}$	$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{CH}_3\text{C}_6\text{H}_4\text{N}=\text{C} \quad \text{NC}_6\text{H}_4\text{CH}_3 \\ \\ \text{CH}_3\text{C}_6\text{H}_4\text{N}-\text{C}=\text{NC}_6\text{H}_4\text{CH}_3 \end{array}$	difficultly sol. in hot alc.; sol. in benzene and acetic acid	138

* Structures of compounds Nos. 1-25 are in dispute. See Table VI for alternate structures.

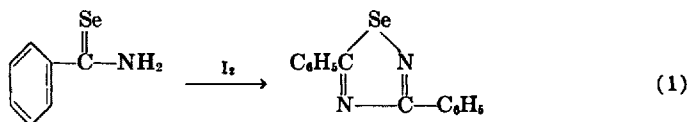
- ¹ Klason, *J. prakt. Chem.*, [2] **38**, 366 (1898).
- ² Chattaway and Stevens, *J. Chem. Soc.*, **71**, 607 (1897).
- ³ Nemicki and Leppart, *Ber.*, **6**, 902 (1873).
- ⁴ de Clermont, *Bull. soc. chim. France*, **1**, 25 (1876).
- ⁵ Freund and Asbrand, *Ann.*, **285**, 166 (1895).
- ⁶ Freund and Bachrach, *Ann.*, **285**, 184 (1895).
- ⁷ Freund and Wolf, *Ber.*, **25**, 1456 (1892).
- ⁸ Proskauer and Sell, *Ber.*, **9**, 1262 (1876).
- ⁹ Friedmann and Gatterman, *Ber.*, **25**, 3525 (1892).
- ¹⁰ Borsche, *Ber.*, **B75**, 1312 (1942).
- ¹¹ Söderback, *Ann.*, **465**, 184 (1928).
- ¹² Sell, *Ber.*, **6**, 323 (1873).
- ¹³ Helmers, *Ber.*, **20**, 789 (1887).
- ¹⁴ Preisler and Bateman, *J. Am. Chem. Soc.*, **69**, 2632 (1947).
- ¹⁵ Fromm, *Ann.*, **275**, 20 (1893).
- ¹⁶ Fromm and Schneider, *Ann.*, **348**, 161 (1906).
- ¹⁷ Fromm and Vetter, *Ann.*, **356**, 178 (1907).
- ¹⁸ Hector, *Ber.*, **22**, 1176 (1889).
- ¹⁹ Dost, *Ber.*, **39**, 863 (1906).
- ²⁰ Haager and Dohrt, *Monatsh.*, **27**, 277 (1906).
- ²¹ Fromm and Heyder, *Ber.*, **42**, 3804 (1909).
- ²² Hector, *Ber.*, **25**, 799 (1892); *Oefvers. Kongl. Vet. Acad.* 1892, 79.
- ²³ Hector, *Ber.*, **23**, 357 (1890).
- ²⁴ Hugerahoff, *Ber.*, **36**, 3121 (1903).
- ²⁵ Hunter, *J. Chem. Soc.*, **129**, 533 (1926).

1,2,4-Selenadiazoles (I)



(Ring Index No. 74)

Becker and Meyer¹ oxidized selenobenzamide with iodine and obtained the 3,5-diphenyl-1,2,4-selenadiazole (1). The compounds formed platinum



salts. Reduction with sodium and alcohol gave benzylamine. The *p*-tolyl analog on reduction with zinc and alcoholic hydrochloric acid yielded the methylbenzyltolamidine (2).

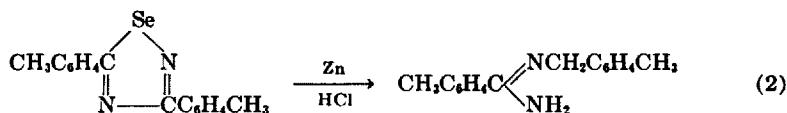


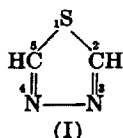
TABLE X

No.	Substituents on the 1,2,4-selenadiazole	Solubility	M.p., °C.
1	3,5-Diphenyl	alc.	85
2	3,5-Di- <i>p</i> -tolyl	alc.	116

¹ Becker and Meyer, *Ber.*, **37**, 2550 (1904).

Derivatives of the 1,3,4-Thiadiazoles and Their Selenium Analogs

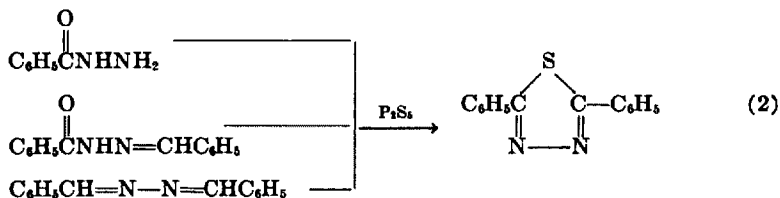
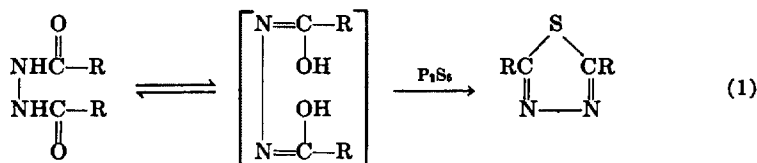
1,3,4-Thiadiazoles (I)



(Ring Index No. 73)

2,5-Dialkyl- and the 2,5-Diaryl-1,3,4-thiadiazoles

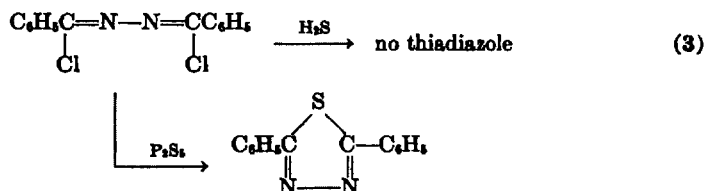
Stolle¹ found that the diacylhydrazides reacted with phosphorus pentasulfide to give 2,5-dialkyl-1,3,4-thiadiazoles. He postulated that the reaction probably proceeded in this manner (1). Using this method, Stolle and his co-workers²⁻¹⁰ prepared a large number of 2,5-dialkyl- and 2,5-diaryl-1,3,4-thiadiazoles.



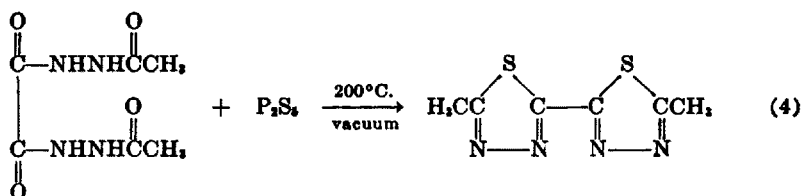
- ¹ Stolle, *Ber.*, **32**, 797 (1899).
- ² Stolle, *J. prakt. Chem.*, **69**, 145 (1904).
- ³ Stolle and Stevens, *J. prakt. Chem.*, **69**, 366 (1904).
- ⁴ Stolle and Foerster, *J. prakt. Chem.*, **69**, 382 (1904).
- ⁵ Stolle and Johannissen, *J. prakt. Chem.*, **69**, 474 (1904).
- ⁶ Stolle and Hille, *J. prakt. Chem.*, **69**, 481 (1904).
- ⁷ Stolle and Zinsser, *J. prakt. Chem.*, **69**, 486 (1904).
- ⁸ Stolle and Gutmann, *J. prakt. Chem.*, **69**, 497 (1904).
- ⁹ Stolle and Schatzlein, *J. prakt. Chem.*, **69**, 503 (1904).
- ¹⁰ Stolle and Dellschaft, *J. prakt. Chem.*, **69**, 506 (1904).

Stolle and Kind¹¹ examined several modifications of this method. They found that benzhydrazide, benzalbenzhydrazide, and benzalazine could be used in the preparation of 2,5-diphenyl-1,3,4-thiadiazole (2).

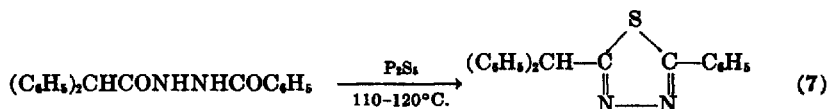
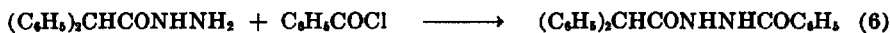
Stolle *et al.*^{12,13} found that dichlorobenzalazine and hydrogen sulfide in an alcoholic solution gave no 2,5-diphenyl-1,3,4-thiadiazole. However, the dichlorobenzalazine and phosphorus pentasulfide yielded 2,5-diphenyl-1,3,4-thiadiazole (3).



Stolle and Kind¹¹ synthesized the bis-2-(1,3,4-thiadiazoles) from diacyloxalylhydrazides (4).



Aspelund¹⁴ in an attempt to prepare the diphenyl-2-phenyl-5-thiadiazolymethyl free radical explored the chemistry of 2-benzhydryl-5-methyl-1,3,4-thiadiazole. Diphenylacetylhydrazide was prepared from ethyl diphenylacetate and hydrazine hydrate. The asymmetrical diphenylacetylbenzoylhydrazide was then obtained by allowing benzoyl chloride to react with the hydrazide. The thiadiazole was prepared after the method of Stolle with phosphorus pentasulfide (5-7). Bromination of



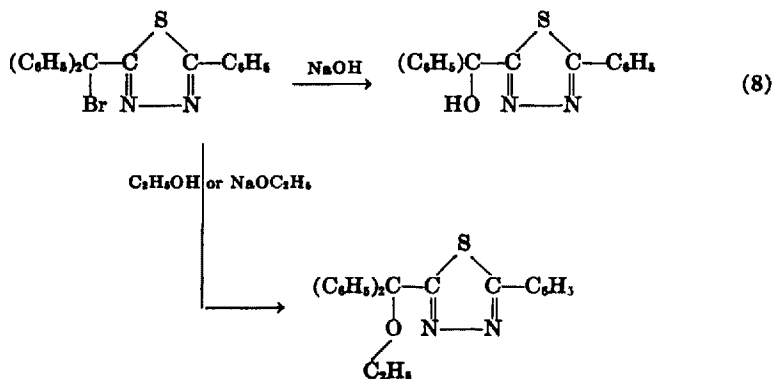
¹¹ Stolle and Kind, *J. prakt. Chem.*, **70**, 423 (1904).

¹² Stolle, *J. prakt. Chem.*, **73**, 277 (1906).

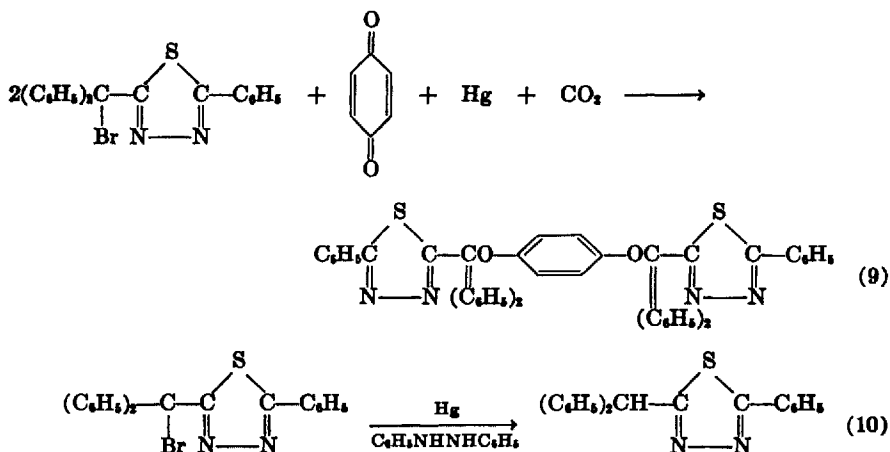
¹³ Stolle and Thoma, *J. prakt. Chem.*, **73**, 289 (1906).

¹⁴ Aspelund, *Chem. Zentr.*, **1100**, 2414 (1929); *Acta Acad. Aboensis, Math. et Phys.*, **5**, No. 1, 1 (1929).

this compound with an equivalent of bromine in carbon tetrachloride produced 2-diphenylbromomethyl-5-phenyl-1,3,4-thiadiazole. An excess of bromine in acetic acid produced a reddish perbromide. Treating the bromide with a dilute alkali afforded the carbinol. The ethoxy compound was synthesized either by refluxing the bromide in ethyl alcohol or by allowing the bromide to react with sodium ethoxide (8).

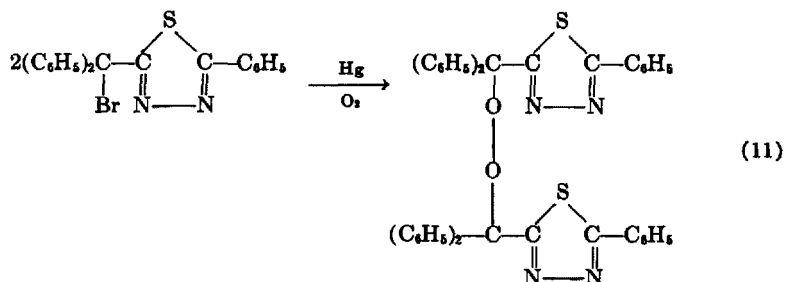


Stirring the bromide in benzene with mercury and quinone in the presence of carbon dioxide produced the substituted 1,4-dimethoxybenzene (9). Mercury and hydrazobenzene replaced the bromine with hydrogen (10).

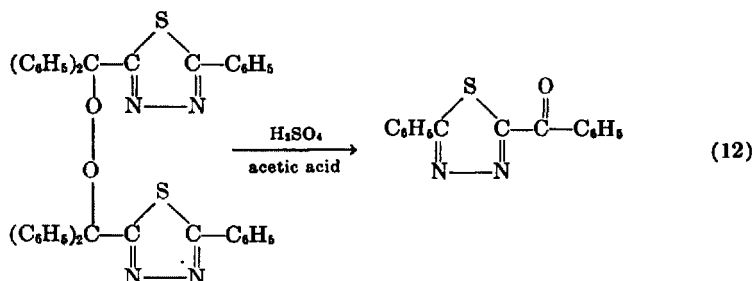


The diphenyl-2-phenyl-5-thiadiazolymethyl radical could not be obtained by shaking the bromide with mercury in the presence of carbon dioxide; however, shaking the bromide with mercury in the presence of

oxygen produced the peroxide (11). Refluxing this peroxide in amyl alcohol yielded the carbinol. The peroxide was reduced to the methane



derivative with phosphorus and hydrogen iodide in acetic acid. Aspelund¹⁵ found that the peroxide, on dissolving in acetic and sulfuric acids, produced 3-phenyl-5-thiadiazolylphenyl ketone (12).

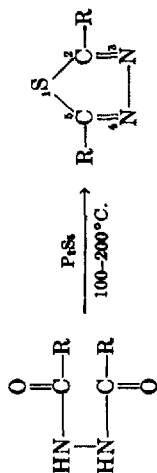


2-Benzhydryl-5-methyl-1,3,4-thiadiazole exhibited the same chemical characteristics as 2-benzhydryl-5-phenyl-1,3,4-thiadiazole.

¹⁵ Aspelund, *Ber.*, **63**, 1325 (1930).

TABLE XI

The 2,5-dialkyl and diaryl substituted 1,3,4-thiadiazoles prepared by the general method. This method consists of preparing the diacylhydrazide and then heating this compound with about three parts of phosphorus pentasulfide in a vacuum at 100 to 200°C.



1,3,4-Thiadiazoles					Solubility	M.p., °C.	B.p., °C.
No.	2-	5-	Ref.				
1	Methyl	methyl	1	water, alc.	—	64	89 at 14 mm.
2	Ethyl	ethyl	2	—	—	64	202-4
3	Isobutyl	isobutyl	3	water, alc.	—	—	105 at 14 mm.
4	Propyl	propyl	3	alc., ether	—	—	130-2 at 25 mm.
5	Isopropyl	isopropyl	4	—	—	—	127 at 13 mm.
6	Undecyl	undecyl	5	alc., ether	—	—	126 at 27 mm.
7	Pentadecyl	pentadecyl	6	hot alc., ether	—	49	—
8	Phenyl	phenyl	7	hot alc., ether	—	60	—
9	p-Tolyl	p-tolyl	1,8	alc., hot CHCl ₃ , benzene	—	141-2	259 at 17 mm.
10	Benzyl	benzyl	9	alc., ether, CHCl ₃	—	156-8	—
11	m-Chlorophenyl	m-chlorophenyl	9	hot water, alc., ether	—	98	—
12	o-Bromophenyl	o-bromophenyl	10	hot alc., acetone, CHCl ₃	—	151	—
13	m-Bromophenyl	m-bromophenyl	11	ether, hot alc.	—	117	—
14	p-Bromophenyl	p-bromophenyl	11	alc.	—	175	—
15	Benzhydryl	phenyl	11	ether, hot alc.	—	237	—
16	Benzhydryl	methyl	12	—	—	137	—
17	Bis-2(5-methylthiadiazolyl) (complete name)	—	12	—	—	145	—
18	Bis-2(5-phenylthiadiazolyl) (complete name)	—	13	—	—	238	—
			13	—	—	245-52	—

¹ Stolle, *Ber.*, 32, 797 (1899).

² Stolle, *J. prakt. Chem.*, 69, 145 (1904).

³ Stolle and Hille, *J. prakt. Chem.*, 69, 481 (1904).

⁴ Stolle and Zinsser, *J. prakt. Chem.*, 69, 486 (1904).

⁵ Stolle and Gutmann, *J. prakt. Chem.*, 69, 497 (1904).

⁶ Stolle and Schatzlein, *J. prakt. Chem.*, 69, 503 (1904).

⁷ Stolle and Dellschaft, *J. prakt. Chem.*, 69, 506 (1904).

⁸ Stolle, *J. prakt. Chem.*, 69, 365 (1904).

⁹ Stolle and Stevens, *J. prakt. Chem.*, 69, 366 (1904).

¹⁰ Stolle and Foerster, *J. prakt. Chem.*, 69, 382 (1904).

¹¹ Stolle and Johannissen, *J. prakt. Chem.*, 69, 474 (1904).

¹² Aspelund, *Chem. Zentr.*, 1100, 2414 (1929); *Acta Acad. Aboensis, Math. et Phys.*, 5, No. 1, 1 (1929).

¹³ Stolle and Kind, *J. prakt. Chem.*, 70, 423 (1904).

TABLE XII. 2,5-Dialkyl and 2,5-Alkylaryl-1,3,4-thiadiazoles Prepared by Methods Other Than the General Method

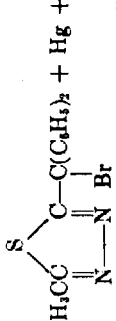
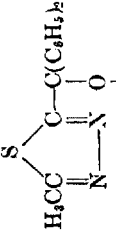
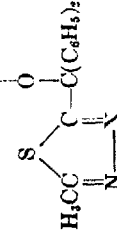
No.	Substituents on 1,3,4-thiadiazole			Ref.	Methods of preparation	Solubility	M.p., °C.
	2-Position	5-Position					
1	Phenyl	α -bromobenzo- hydryl		1	$\text{C}_6\text{H}_5\text{C}(\text{C}_6\text{H}_4)_2 + \text{Br}_2 + \text{CCl}_4$	petroleum ether	124, HBr 196-7
2	Pertinoridine structure un- known	—		1	$\text{C}_6\text{H}_5\text{C}(\text{C}_6\text{H}_4)_2 + \text{excess Br}_2 + \text{acetic acid}$	—	145-6 dec.
3	Methyl	α -bromobenzo- hydryl		1	$\text{H}_3\text{C}-\text{C}(\text{C}_6\text{H}_4)_2 + \text{Br}_2 + \text{CCl}_4$	petroleum ether	138, HBr 182-3
4	Phenyl	α -hydroxy- benzohydryl			$\text{C}_6\text{H}_5\text{C}(\text{C}_6\text{H}_4)_2 + \text{dil. alkali}$	alc., petroleum ether	168
5	Phenyl	α -acetoxy- benzohydryl		1	compound 4 + acetic anhydride	—	152
6	Methyl	α -hydroxy- benzohydryl		1	$\text{H}_3\text{CC}(\text{C}_6\text{H}_4)_2 + \text{dil. alkali}$	petroleum ether	151
7	Phenyl	α -ethoxy- benzohydryl		1	$\text{C}_6\text{H}_5\text{C}(\text{C}_6\text{H}_4)_2 + \text{NaOC}_2\text{H}_5 \text{ or } \text{HOC}_2\text{H}_5 \text{ and reflux}$	—	111
8	Methyl	α -ethoxy- benzohydryl		1	compound 3 + KOC_2H_5	alc.	99

Substituents on 1,3,4-thiadiazole					M.p., °C.	
No.	2-Position	5-Position	Ref.	Methods of preparation		
9	1,4-Bis[diphenyl-5-(2-phenyl-1,3,4-thiadiazolyl)methoxy]benzene		1	$ \begin{array}{c} \text{C}_6\text{H}_5-\text{C} \begin{array}{l} \diagup \text{S} \diagdown \\ \diagdown \text{N} \diagup \end{array} -\text{C}(\text{C}_6\text{H}_5)_2-\text{Br} + \text{Hg} + \text{CO}_2 \xrightarrow{\text{benzene}} \\ \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{C}_6\text{H}_4 \end{array} $ $ \begin{array}{c} \text{C}_6\text{H}_5-\text{C} \begin{array}{l} \diagup \text{S} \diagdown \\ \diagdown \text{N} \diagup \end{array} -\text{C}(\text{C}_6\text{H}_5)_2-\text{O}-\text{C}_6\text{H}_4-\text{O}-\text{C}(\text{C}_6\text{H}_5)_2-\text{C} \begin{array}{l} \diagup \text{S} \diagdown \\ \diagdown \text{N} \diagup \end{array} -\text{C}(\text{C}_6\text{H}_5)_2 \end{array} $	—	202-3
10	Bis[α -(2-phenyl-1,3,4-thiadiazol-5-yl)benzohydryl]peroxide		1	$ \begin{array}{c} \text{C}_6\text{H}_5-\text{C} \begin{array}{l} \diagup \text{S} \diagdown \\ \diagdown \text{N} \diagup \end{array} -\text{C}(\text{C}_6\text{H}_5)_2-\text{Br} + \text{Hg} + \text{O}_2 \xrightarrow{\text{benzene}} \\ \text{C}_6\text{H}_5-\text{C} \begin{array}{l} \diagup \text{S} \diagdown \\ \diagdown \text{N} \diagup \end{array} -\text{C}(\text{C}_6\text{H}_5)_2-\text{O}-\text{O}-\text{C}(\text{C}_6\text{H}_5)_2-\text{C} \begin{array}{l} \diagup \text{S} \diagdown \\ \diagdown \text{N} \diagup \end{array} -\text{C}(\text{C}_6\text{H}_5)_2 \end{array} $	benzene	187 dec.

(Table continued)

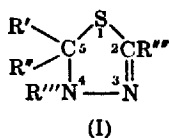
(Table continued)

TABLE XII (Concluded)

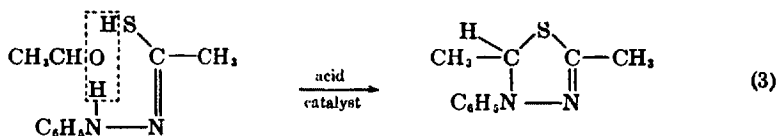
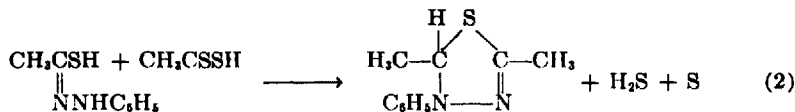
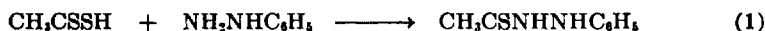
11	Bis[α -(2-methyl-1,3,4-thiadiazol-5-yl)benzohydril]peroxide	1		—	183 dec.
12	2-Phenyl-5-benzoyl-1,3,4-thiadiazole	2		compound 10 + H ₂ SO ₄ + acetic acid	ether, benzene, 129 acetic acid, hot alc.
13	2-Phenyl-5-benzoyl-1,3,4-thiadiazole oxime	2		compound 12 + hydroxylamine	alc. 238 dec.

¹ Aspelund, *Chem. Zentr.*, 1100, 2414 (1929); *Acta Acad. Aboensis, Phys. et Math.*, 5, No. 1, 1 (1929).

² Aspelund, *Ber.*, 63, 1352 (1930).

Δ^2 -1,3,4-Thiadiazolines (I)

The chemistry of these Δ^2 -1,3,4-thiadiazolines has been developed by Wuyts and his co-workers over a period of years. Wuyts and Lacourt,¹ in studying the action of dithiocarboxylic acids on substituted hydrazines, obtained a product from dithioacetic acid and phenylhydrazine in presence of pyridine which they believed to be 2,5-dimethyl-4-phenyl- Δ^2 -1,3,4-thiadiazoline. They postulated that the reaction proceeded as shown in equations (1) and (2).² Acetaldehyde and 2-thioaceto-1-phenylhydrazide produced an identical compound (3). Other aldehydes and ketones were



used in this reaction to make a large series of compounds. The reaction proceeded so readily and the products were recrystallized so easily that Wuyts and Wachsmuth³ suggested that this reaction be used to characterize aldehydes.

The intermediates and products were prepared according to schemes (4-8). Hydrochloric acid was usually employed as the catalyst.

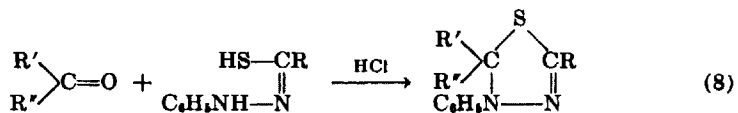
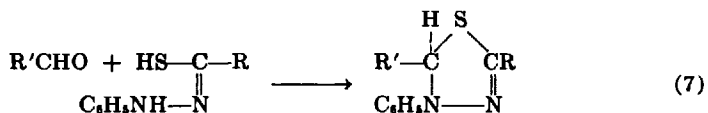
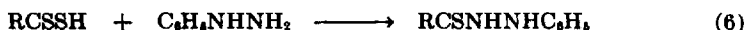
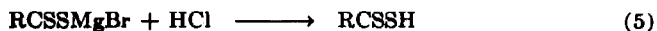
The compounds were poorly soluble in hydrochloric acid. Continued heating in concentrated hydrochloric acid hydrolyzed these compounds only slightly.⁴ Silver nitrate and these compounds formed stable white

¹ Wuyts and Lacourt, *Bull. soc. chim. Belges*, **42**, 1 (1933); *Chem. Abstr.*, **27**, 3916 (1933).

² Wuyts and Lacourt, *Bull. soc. roy. belge ing. et ind.*, **19**, 543 (1933); *Bull. soc. chim. Belges*, **42**, 376 (1933) (identical); *Chem. Abstr.*, **27**, 5075 (1933).

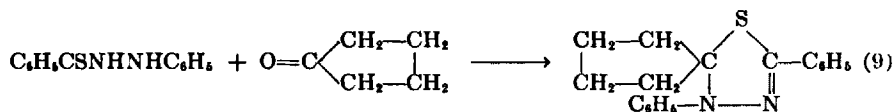
³ Wuyts and Wachsmuth, *J. pharm. chim.*, **22**, 289 (1935); *Chem. Abstr.*, **30**, 289 (1935).

⁴ Wuyts and Lacourt, *Bull. soc. roy. belge ing. et ind.*, **20**, 156 (1934); *Bull. soc. chim. Belges*, **43**, 261 (1934) (identical); *Chem. Abstr.*, **28**, 3407 (1934).



precipitates which contained a mole of silver nitrate per mole of thiadiazoline. These Δ^2 -1,3,4-thiadiazolines, in the presence of concentrated sulfuric acid and oxidizing agents, produced colors generally toward the greens, blues, and violets.

Lacourt^{5,6} attempted to isolate isomers in the crude 2-(α -naphthyl)-4-phenyl-5-(β -naphthyl)- Δ^2 -1,3,4-thiadiazoline with no success. She found that cyclic ketones also condensed readily (9).



The thiadiazolines formed by formaldehyde with a 2-thiobenz-1-phenylhydrazide contained a labile hydrogen as determined with Zerevitinow's method.^{7,8} These compounds would not react with Grignard reagents.

The 2,4-disubstituted- Δ^2 -1,3,4-thiadiazolines easily formed crystalline pentiodides in chloroform with an excess of iodine, one mole of hydriodic acid being liberated. Two of the iodine atoms were so labile that they could be eliminated by washing the pentiodide with solvents, especially carbon disulfide and the relatively stable triiodide remained. The pentiodide could also be prepared by dissolving the triiodide in a chloroform

⁵ Lacourt, *Bull. soc. chim. Belges*, **43**, 193 (1934); *Chem. Abstr.*, **28**, 4418 (1934).

⁶ Lacourt, *Bull. soc. chim. Belges*, **43**, 206 (1934); *Chem. Abstr.*, **28**, 4057 (1934).

⁷ Wuyts and Lacourt, *Bull. soc. chim. Belges*, **45**, 445 (1936); *Chem. Abstr.*, **30**, 8212 (1936).

⁸ Wuyts and Deshommes, *Bull. soc. chim. Belges*, **46**, 231 (1937); *Chem. Abstr.*, **32**, 557 (1938).

solution of iodine. A heptiodide was obtained with 2-tolyl-4-phenyl- Δ^2 -1,3,4-thiadiazoline.

In addition to the 2,4-disubstituted- Δ^2 -1,3,4-thiadiazolines which were formed from formaldehyde and 2-thiobenz-1-phenylhydrazide, some slightly soluble compounds having approximately twice the molecular weight of the Δ^2 -1,3,4-thiadiazolines were obtained; their structure is unknown.

TABLE XIII. Iodine Derivatives of the Δ^2 -1,3,4-Thiadiazolines¹

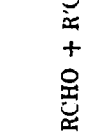
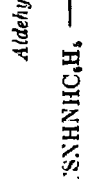
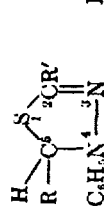
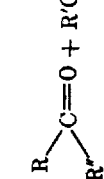
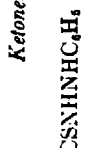
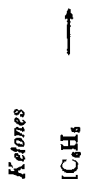
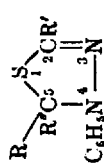
Parent, Δ^2 -1,3,4-thiadiazoline	Iodine derivative	M.p., °C.
2-Naphthyl-4-phenyl	pentaiodide	118
2-Naphthyl-4-phenyl	triiodide	145.5
2,4-Diphenyl	pentaiodide	98
2,4-Diphenyl	triiodide	151.5
2- <i>p</i> -Tolyl-4-phenyl	heptaiodide	116
2- <i>p</i> -Tolyl-4-phenyl	pentaiodide	109
2- <i>p</i> -Tolyl-4-phenyl	triiodide	106 (108)
2-Benzyl-4-phenyl	pentaiodide	55 (57)
2-Benzyl-4-phenyl	triiodide	85

¹ Wuyts and Deshommes, *Bull. soc. chim. Belges*, **46**, 231 (1937); *Chem. Abstr.*, **32**, 557 (1938).

Tables XIV and XV follow on pages 92-96.

TABLE XIV. $\Delta^2,1,3,4$ -Thiadiazolines Prepared by Wuyts and Co-workers from Aldehydes or Ketones and 1-Thioacyl-2-phenylhydrazines

Substituents on the ring and compound name							
No.	2-Position	4-Position	5-Position*	Ref.	Aldehyde or ketone used	Solubility	M.p., °C.
1	Methyl	phenyl	methyl	1	acetaldehyde or paraldehyde	alc.	80
2	2,5-Dimethyl-4-phenyl-	$\Delta^2,1,3,4$ -thiadiazoline	—	1	formaldehyde	alc.	75
3	2-Methyl-4-phenyl-	$\Delta^2,1,3,4$ -thiadiazoline	—	1	formaldehyde	alc.	68
4	2-Benzyl-4-phenyl-	$\Delta^2,1,3,4$ -thiadiazoline	—	1	formaldehyde	alc.	97
5	1-Naphthyl	phenyl	methyl	1	paraldehyde	alc.	102
6	2- α -naphthyl-4-phenyl-	5-methyl- $\Delta^2,1,3,4$ -thiadiazoline	phenyl	1	benzaldehyde	hot alc.	92
7	2-Benzyl-4,5-diphenyl-	$\Delta^2,1,3,4$ -thiadiazoline	phenyl	1	benzaldehyde	alc.	97
8	2,4,5-Triphenyl-	$\Delta^2,1,3,4$ -thiadiazoline	phenyl	1	benzaldehyde	alc.	147
9	1-Naphthyl	phenyl	phenyl	1	acetone	—	oil, b.p. 108-9, 1 mm. Hg
10	2,5,5-Trimethyl-4-phenyl-	$\Delta^2,1,3,4$ -thiadiazoline	dimethyl	1	acetone	alc.	74



No.	Substituents on the ring and compound name			Ref.	Aldehyde or ketone used	Solubility	M.p., °C.
	2-Position	4-Position	5-Position*				
11	Phenyl 3-Phenyl-1- <i>p</i> -bromophenyl-4-thia-1,2-diazaspiro-[4.5]dec-2-ene (<i>Ring Index</i> No. 695)	<i>p</i> -bromophenyl	spirocyclohexano	1	cyclohexanone	alc.	97
12	Phenyl 2,4-Diphenyl-5- <i>o</i> -nitrophenyl- Δ^2 -1,3,4-thiadiazoline	phenyl	<i>o</i> -nitrophenyl	2	<i>o</i> -nitrobenzaldehyde	alc.	120
13	Phenyl 2,4-Diphenyl-5- <i>m</i> -nitrophenyl- Δ^2 -1,3,4-thiadiazoline	phenyl	<i>m</i> -nitrophenyl	2	<i>m</i> -nitrobenzaldehyde	benzene	139
14	Phenyl 2,4-Diphenyl-5- <i>p</i> -nitrophenyl- Δ^2 -1,3,4-thiadiazoline	phenyl	<i>p</i> -nitrophenyl	2	<i>p</i> -nitrobenzaldehyde	alc.	129
15	Phenyl 2,4-Diphenyl-5- <i>p</i> -dimethylaminophenyl- Δ^2 -1,3,4-thiadiazoline	phenyl	<i>p</i> -dimethylaminophenyl	2	<i>p</i> -dimethylaminobenzaldehyde	alc.	144
16	1-Naphthyl 2- α -Naphthyl-4-phenyl-5- <i>p</i> -methoxyphenyl- Δ^2 -1,3,4-thiadiazoline	phenyl	<i>p</i> -methoxyphenyl	2	<i>p</i> -methoxybenzaldehyde	alc.	101
17	1-Naphthyl 2- α -Naphthyl-4-phenyl-5-(1,3-benzodioxolyl)- Δ^2 -1,3,4-thiadiazoline	phenyl	5-(1,3-benzodioxolyl)	2	piperonal	alc.	131
18	Phenyl 2-Phenyl-4- <i>p</i> -bromophenyl-5-(2-furyl)- Δ^2 -1,3,4-thiadiazoline	<i>p</i> -bromophenyl	2-furyl	2	furfural	alc.	128
19	1-Naphthyl 2- α -Naphthyl-4-phenyl-5-(2-furyl)- Δ^2 -1,3,4-thiadiazoline	phenyl	2-furyl	2	furfural	benzene, methanol	118
20	1-Naphthyl 2- α -Naphthyl-4-phenyl-5- <i>o</i> -tolyl- Δ^2 -1,3,4-thiadiazoline	phenyl	<i>o</i> -tolyl	2	<i>o</i> -tolaldehyde	benzene	150
21	1-Naphthyl 2,5-Dinaphthyl-4-phenyl- Δ^2 -1,3,4-thiadiazoline	phenyl	1-naphthyl	2	1-naphthaldehyde	benzene	196
22	1-Naphthyl 2- α -Naphthyl-4-phenyl-5- β -naphthyl- Δ -1,3,4-thiadiazoline	phenyl	2-naphthyl	2	2-naphthaldehyde	methanol	197
23	Phenyl 2,4-Diphenyl-5-styryl- Δ^2 -1,3,4-thiadiazoline	phenyl	styryl	3	cinnamaldehyde	acetone	127.5-8

(Table continued)

TABLE XIV (Continued)

No.	Substituents on the ring and compound name			Ref.	Aldehyde or ketone used	Solubility	M.p., °C.
	2-Position	4-Position	5-Position*				
24	Phenyl	phenyl	<i>p</i> -methoxyphenyl	3	<i>p</i> -anisaldehyde	acetone	130.5-31
	2,4-Diphenyl-5- <i>p</i> -methoxyphenyl- Δ^2 ,1,3,4-thiadiazoline						
25	Phenyl	phenyl	5-(1,3-benzodioxolyl)	3	piperonal	acetone	154.5-155
	2,4-Diphenyl-5-(1,3-benzodioxolyl)- Δ^2 ,1,3,4-thiadiazoline						
26	Phenyl	phenyl	2-furyl	3	furfural	acetone	111-1.5
	2,4-Diphenyl-5-(2-furyl)- Δ^2 ,1,3,4-thiadiazoline						
27	Phenyl	<i>p</i> -bromophenyl	—	3	formaldehyde	alc.	112.5-3.5
	2-Phenyl-4- <i>p</i> -bromophenyl- Δ^2 ,1,3,4-thiadiazoline						
28	Phenyl	<i>p</i> -bromophenyl methyl		3	acetaldehyde	alc.	93.5-4
	2-Phenyl-4- <i>p</i> -bromophenyl-5-methyl- Δ^2 ,1,3,4-thiadiazoline						
29	Phenyl	<i>p</i> -bromophenyl phenyl		3	benzaldehyde	acetone	142.5-3.5
	2,5-Diphenyl-4- <i>p</i> -bromophenyl- Δ^2 ,1,3,4-thiadiazoline						
30	Phenyl	<i>p</i> -bromophenyl styryl		3	cinnamaldehyde	alc., acetone	114-4.5
	2-Phenyl-4- <i>p</i> -bromophenyl-5-styryl- Δ^2 ,1,3,4-thiadiazoline						
31	Phenyl	<i>p</i> -bromophenyl <i>p</i> -methoxyphenyl		3	<i>p</i> -anisaldehyde	acetone	132.5-3
	2-Phenyl-4- <i>p</i> -bromophenyl-5-methoxyphenyl- Δ^2 ,1,3,4-thiadiazoline						
32	Phenyl	<i>p</i> -bromophenyl 5-(1,3-benzodioxolyl)		3	piperonal	alc., acetone	138-9
	2-Phenyl-4- <i>p</i> -bromophenyl-5-(1,3-benzodioxolyl)- Δ^2 ,1,3,4-thiadiazoline						
33	1-Naphthyl phenyl	—		3	formaldehyde	acetone	71-1.5
	2- α -Naphthyl-4-phenyl- Δ^2 ,1,3,4-thiadiazoline						
34	1-Naphthyl phenyl	styryl		3	cinnamaldehyde	methanol, alc.	52-3.5
	2- α -Naphthyl-4-phenyl-5-styryl- Δ^2 ,1,3,4-thiadiazoline						
35	Phenyl	phenyl	<i>o</i> -hydroxyphenyl	3	salicylaldehyde	alkali, alc.	51-2.5
	2,4-Diphenyl-5- <i>o</i> -hydroxyphenyl- Δ^2 ,1,3,4-thiadiazoline						
36	Phenyl	phenyl	3-methoxy-4-hydroxyphenyl	3	vanillin	acetone, alc.	132.5-3
	2,4-Diphenyl-5-(3-methoxy-4-hydroxyphenyl)- Δ^2 ,1,3,4-thiadiazoline						

Substituents on the ring and compound name					Aldehyde or ketone used	Solubility	M.p., °C.
No.	2-Position	4-Position	5-Position*	Ref.			
37	Phenyl 2-Phenyl-4- <i>p</i> -bromophenyl-5- <i>o</i> -hydroxyphenyl- Δ^2 -1,3,4-thiadiazoline	<i>p</i> -bromophenyl 2-Phenyl-4- <i>p</i> -bromophenyl-5- <i>o</i> -hydroxyphenyl- Δ^2 -1,3,4-thiadiazoline	<i>o</i> -hydroxyphenyl	3	salicylaldehyde	alc.	159.5-60
38	Phenyl 2-Phenyl-4- <i>p</i> -bromophenyl-5- Δ^2 -1,3,4-thiadiazoline	<i>p</i> -bromophenyl 2-Phenyl-4- <i>p</i> -bromophenyl-5-(3-methoxy-4-hydroxyphenyl)- Δ^2 -1,3,4-thiadiazoline	3-methoxy-4-hydroxyphenyl	3	vanillin	acetone, alc.	152.5-3
39	1-Naphthyl 2- α -Naphthyl-4-phenyl-5- <i>o</i> -hydroxyphenyl- Δ^2 -1,3,4-thiadiazoline	phenyl 2- α -Naphthyl-4-phenyl-5- <i>o</i> -hydroxyphenyl- Δ^2 -1,3,4-thiadiazoline	<i>o</i> -hydroxyphenyl	3	salicylaldehyde	acetone	72-3.5
40	1-Naphthyl 2- α -Naphthyl-4-phenyl-5-(3-methoxy-4-hydroxyphenyl)- Δ^2 -1,3,4-thiadiazoline	phenyl 2- α -Naphthyl-4-phenyl-5-(3-methoxy-4-hydroxyphenyl)- Δ^2 -1,3,4-thiadiazoline	3-methoxy-4-hydroxyphenyl	3	vanillin	acetone, methanol	156.5-7
41	1-Naphthyl 2- α -Naphthyl-4-phenyl-5,5-dimethyl- Δ^2 -1,3,4-thiadiazoline	phenyl 2- α -Naphthyl-4-phenyl-5,5-dimethyl- Δ^2 -1,3,4-thiadiazoline	dimethyl	4	acetone	methanol	68
42	Benzyl 2-Benzyl-4,5-diphenyl-5-methyl- Δ^2 -1,3,4-thiadiazoline	phenyl 2-Benzyl-4,5-diphenyl-5-methyl- Δ^2 -1,3,4-thiadiazoline	methyl phenyl	4	acetophenone	methanol	120
43	1-Naphthyl 2- α -Naphthyl-4,5-diphenyl-5-methyl- Δ^2 -1,3,4-thiadiazoline	phenyl 2- α -Naphthyl-4,5-diphenyl-5-methyl- Δ^2 -1,3,4-thiadiazoline	methyl phenyl	4	acetophenone	benzene, methanol	110
44	Phenyl 2,4-diphenyl-1-thia-3,4-diazaspiro-4,4-non-2-ene (Ring Index No. 579)	phenyl 2,4-diphenyl-1-thia-3,4-diazaspiro-4,4-non-2-ene	spirocyclopentano	4	cyclopentanone	methanol	94
45	Phenyl 2-Phenyl-4- <i>p</i> -bromophenyl-1-thia-3,4-diazaspiro-4,4'-non-2-ene	<i>p</i> -bromophenyl 2-Phenyl-4- <i>p</i> -bromophenyl-1-thia-3,4-diazaspiro-4,4'-non-2-ene	spirocyclopentano	4	cyclopentanone	methanol	79
46	1-Naphthyl 2- α -Naphthyl-4-phenyl-1-thia-3,4-diazaspiro-4,4'-non-2-ene	phenyl 2- α -Naphthyl-4-phenyl-1-thia-3,4-diazaspiro-4,4'-non-2-ene	spirocyclopentano	4	cyclopentanone	alc.	98

* Other than hydrogen.

1 Wuyts and Lacourt, *Bull. soc. roy. belge ing. et ind.*, 19, 543 (1933); *Chem. Abstr.*, 27, 5075 (1933).2 Wuyts and Wachsmuth, *J. pharm. chim.*, 22, 289 (1935); *Chem. Abstr.*, 30, 3745 (1936).3 Wuyts and Lacourt, *Bull. soc. roy. belge ing. et ind.*, 20, 156 (1934); *Chem. Abstr.*, 28, 3407 (1934).4 Lacourt, *Bull. soc. chim. Belges*, 43, 206 (1934); *Chem. Abstr.*, 28, 4057 (1934).

TABLE XV. Optical Activity of the 2,4-Diphenyl-5-glyco- Δ^2 -1,3,4-thiadiazolines

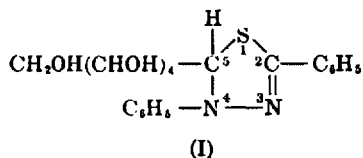
No.	Name	Parent sugar	Spec. rotatory power ($[\alpha]^{20}$)			Mol. rotatory power		
			Sol. isomer	SI. sol. isomer	Difference	Sol. isomer	SI. sol. isomer	Difference
1	2,4-Diphenyl-5-glucos- Δ^2 -1,3,4-thiadiazoline	glucose	-406.6°	+290.5°	697°	-1586°	+1132°	2718°
2	2,4-Diphenyl-5-manno- Δ^2 -1,3,4-thiadiazoline	mannose	-233.6	+970	1203	-911	+3783	4694
3	2,4-Diphenyl-5-galacto- Δ^2 -1,3,4-thiadiazoline	galactose	-568.2	+1406	1974	-2215	+5483	7698
4	2,4-Diphenyl-5-xylo- Δ^2 -1,3,4-thiadiazoline	xylose	-1153	+1651	2804	-4153	+5943	10096
5	2,4-Diphenyl-5-arabino- Δ^2 -1,3,4-thiadiazoline	arabinose	+763.5	+228	535.5	+2747	+821	1926
6	2,4-Diphenyl-5-rhamno- Δ^2 -1,3,4-thiadiazoline	rhamnose	+991	-1022	2013	+3705	-3821	7528
7	2,4-Diphenyl-5-fuco- Δ^2 -1,3,4-thiadiazoline	fucose	-1030	-70.5	959.5	-3853	-263.7	3589.3

TABLE XVI. Optical Properties of 2-Benzyl-4-phenyl-5-arabino- Δ^2 -1,3,4-thiadiazolines¹

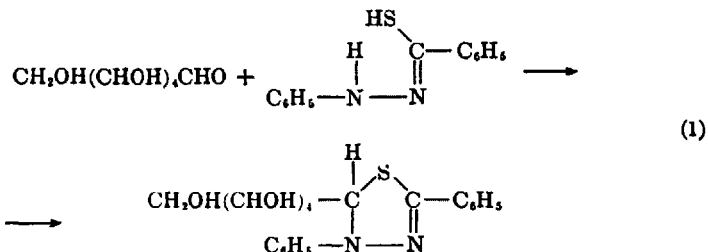
No.	Parent sugar	Isomer	[α] ²⁰		[α] ²⁵	
			[α] ²⁰	[α] ²⁵	[α] ²⁰	[α] ²⁵
1	L-Arabinose	least sol.	+650.1	+784.0	+1900	
2	D-Arabinose	least sol.	-708.0	-839.5	-2008	
3	L-Arabinose	sol.	+57.5	+70.1	+164.9	
4	D-Arabinose	sol.	-87.6	-94.8	-226.1	

¹ Wuyts and Verstraeten, *Bull. soc. chim. Belges*, 45, 65 (1936); *Chem. Abstr.*, 30, 7572 (1936).

Glycothiadiazolines or the 2,4-Diphenyl-5-polyhydroxyalkyl- Δ^2 -1,3,4-thiadiazolines (I)



Wuyts¹ reported that the reducing sugars, especially glucose, mannose, galactose, and arabinose reacted with 2-thiobenz-1-phenylhydrazide to give 5-substituted-2,4-diphenyl- Δ^2 -1,3,4-thiadiazolines. Wuyts called these compounds glycothiadiazolines (see the discussion on nomenclature). Evidently the sugars reacted as aldehydes (1). These compounds had



well-defined melting points and were optically active. No compound could be isolated from fructose and 2-thiobenz-1-phenylhydrazide. There was an indication that lactose might have given a glycothiadiazoline, but no data were given.

Wuyts and Verstraeten^{2,3} continued this study with a number of reducing sugars. They found that by fractionally separating the crude product with methanol and benzene two fractions were obtained; this was true in each of the seven sugars studied. The only possible exception occurred with fucose, where a third component or an impurity was noted.

Both fractions had the same empirical composition; they differed in their solubility and in their optical rotation. Wuyts and Verstraeten believed that in Wuyts's original work the more soluble fraction had been lost during recrystallization procedures.

The most striking feature of these isomers was their optical rotatory power; they possessed greater optical rotatory power than any other organic substance known. A comparison between the glycothiadiazoline

¹ Wuyts, *Compt. rend.*, 196, 1678 (1933).

² Wuyts and Verstraeten, *Bull. soc. roy. belge ing. et ind.*, 20, 168 (1934); *Bull. soc. chim. Belges*, 43, 261 (1934) (identical); *Chem. Abstr.*, 28, 3407 (1934).

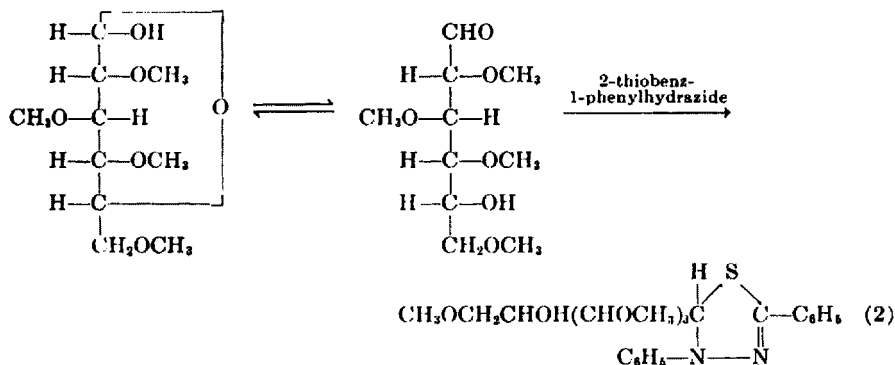
³ Wuyts and Verstraeten, *Bull. soc. roy. belge ing. et ind.*, 21, 415 (1935); *Chem. Abstr.*, 29, 5112 (1935).

and the parent sugar was complicated by the mutarotation of the sugars which the glycothiadiazoline did not possess (see Discussion). When the optical rotation due to the mutarotation was taken into account, it was noted that the optical rotation of the sugar was greatly augmented when it became a portion of the glycothiadiazoline.

They examined the condensation products of D- and L-arabinose with 2-phenylthioacetyl-1-phenylhydrazide.⁴ Each sugar gave two products which resembled the products obtained from the other. The slightly soluble compounds from the D- and L-arabinose have the same melting point, 194.8 to 197.2°C. The soluble compounds have practically the same melting points; from L-arabinose 198°C. and from D-arabinose 197.6°C. The optical rotatory power of each compound was similar.

In general, the two optical isomers possessed different solubilities and large differences in optical activity. Only the derivatives of arabinose showed a relatively slight difference in optical activity between the two isomers.

Wuyts and Vandervelden⁵ investigated the two glycothiadiazolines obtained from 2,3,4,6-tetramethylglucose and 2-thiobenz-1-phenylhydrazide (2). Whereas the soluble glycothiadiazoline from glucose was levo-



rotatory, $[\alpha]_{20}^{5780} = -406$, and the least soluble was dextrorotatory, $[\alpha]_{20}^{5780} = +645$, tetramethylation inverted the rotatory power and augmented it. The most soluble tetramethyl derivative was dextrorotatory, $[\alpha]_{20}^{5461} = +1154$, and the least soluble was levorotatory, $[\alpha]_{20}^{5461} = -905$.

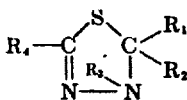
Lifschitz and Froentjes⁶ found that the ultraviolet absorption was identical for the two isomers. They believed that the isomers were the

⁴ Wuyts and Verstraeten, *Bull. soc. chim. Belges*, **45**, 65 (1936); *Chem. Abstr.*, **30**, 7572 (1936).

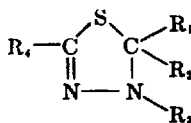
⁵ Wuyts and Vandervelden, *Bull. soc. chim. Belges*, **47**, 506 (1938); *Chem. Abstr.*, **33**, 1727 (1939).

⁶ Lifschitz and Froentjes, *Rec. trav. chim.*, **55**, 573 (1936).

result of *cis-trans* isomerism and that there was a possibility of eighteen isomers (II, III). Experimentally, Wuyts and his co-workers⁷⁻⁹ did not

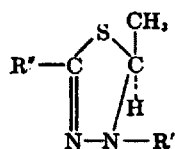


(II)

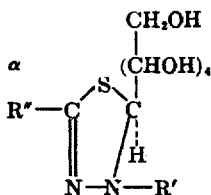
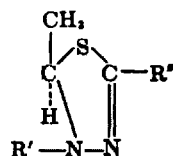


(III)

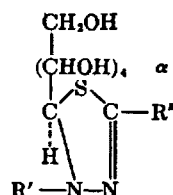
agree with this postulate. Lacourt¹⁰ could isolate only one compound when R_1 and R_2 were unlike. Only in the glycothiadiazolines were two isomers found. Wuyts believed that when the Δ^2 -1,3,4-thiadiazolines were synthesized a mixture of two unresolvable forms was obtained (3). In the case of the glycothiadiazolines four isomers are possible since the D- and L-sugars can be used.



Antipodes



Non-antipodes



(3)

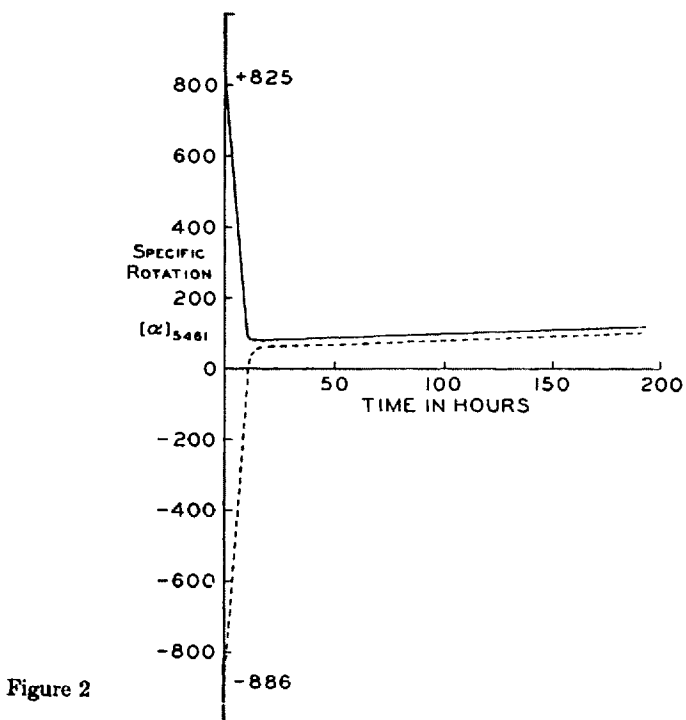
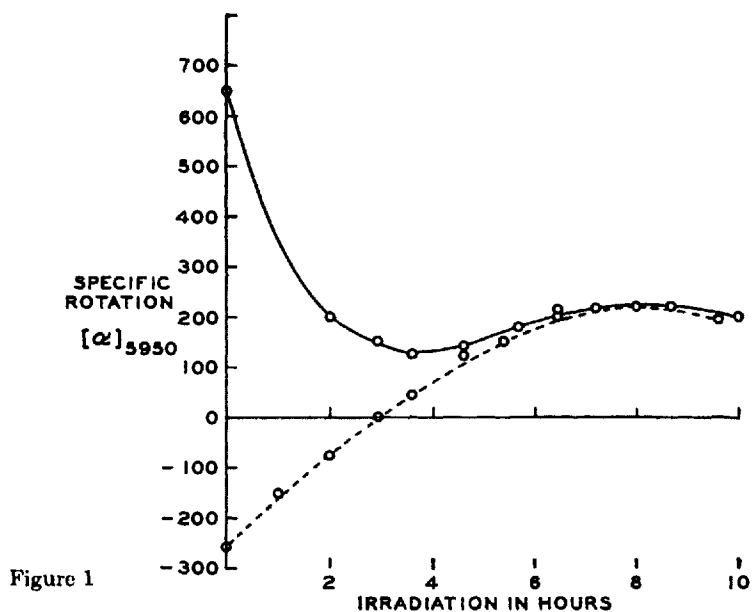
Lifschitz *et al.*⁶ found that the methanol solutions of the dextro and levo forms lost their activity on exposure to ultraviolet irradiation. The dextro form (see Figure 1) rapidly lost its activity and then slowly increased in activity and finally there was some loss in optical rotatory power. The levo form lost its activity and then became dextrorotatory approaching the same activity as the dextro form. They believed that initial change was due to racemization of the compounds. The final slight loss in activity was probably due to oxidation of the carbohydrate moiety, since reducing substances were noted in the solution (4). Wuyts and Verstraeten⁸ confirmed the fall of the rotatory powers even in the absence of light. How-

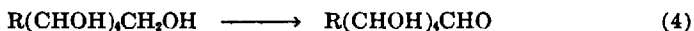
⁷ Wuyts, *Bull. soc. chim. Belges*, **46**, 27 (1937); *Chem. Abstr.*, **31**, 4978 (1937).

⁸ Wuyts and Verstraeten, *Bull. soc. chim. Belges*, **45**, 65 (1936); *Chem. Abstr.*, **30**, 7572 (1936).

⁹ Wuyts and Vandervelden, *Bull. soc. chim. Belges*, **47**, 506 (1938); *Chem. Abstr.*, **33**, 1727 (1939).

¹⁰ Lacourt, *Bull. soc. chim. Belges*, **43**, 193 (1934); *Chem. Abstr.*, **28**, 4418 (1934).





ever, this loss of optical activity was slight compared to that shown by Lifschitz and Froentjes and it was evident only after a period of several weeks.

Wuyts and Vandervelden⁹ explored the optical activity of the tetramethylglucothiadiazolines at 78°C. During the first twelve hours, the dextro compound and the levo compound lost optical rotating power to a point where they had approximately the same dextrorotatory power (see Figure 2). From 12 to 200 hours a slight rise in dextrorotating power

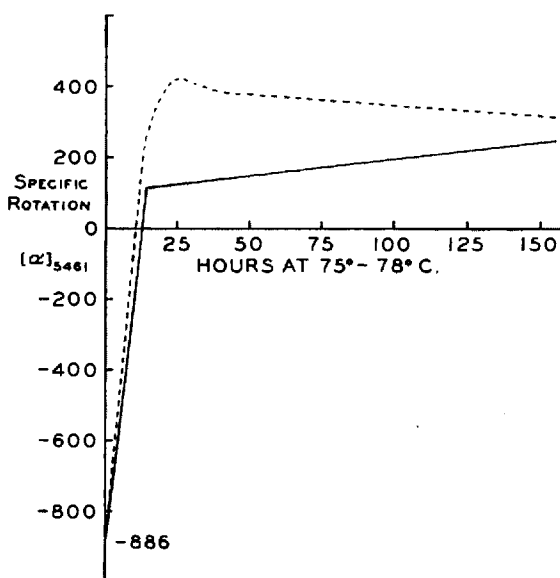


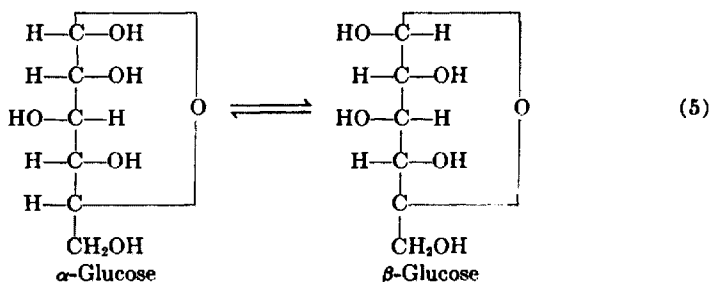
Figure 3

was noted. The levo form was studied extensively (see Figure 3). In the absence of air the levo form rapidly became dextrorotatory and this rotatory power slowly increased between the 30th and 155th hours. When heated in the presence of an excess of air, the levo form rapidly became dextrorotatory and then gradually lost some of its dextrorotatory power which was reminiscent of Lifschitz and Froentjes' experience with the galactothiadiazolines. The presence of light did not influence the rotation to any great degree. Wuyts believed that the initial change in rotatory power was due to racemization and possibly transposition in stereoisomerism. They could find no evidence of oxidation.

Discussion

Wuyts¹¹ has named these compounds as glycothiadiazolines, indicating their carbohydrate origin. While his use of the prefixes *gluco*, *manno*, *galacto*, etc. may be misleading to those expecting a six carbon chain, any attempt to name the side chain on the basis of the alcohol presents a number of difficulties. The position of the hydroxy group on the 1-carbon atom in the alcohol will be left in doubt unless one uses the designation α and β , which might entail more confusion. In addition, there is no name for the alcohol side chain formed when rhamnose and fucose are used to produce glycothiadiazolines. The use of the prefix such as *manno* is in accord with the custom of naming the sugars as *mannose*, the sugar acids as *mannonic*, *mannuronic*, and *mannosaccharic* acids, the alcohols as *mannitol*, and the seven carbon sugars as *mannoheptoses*.

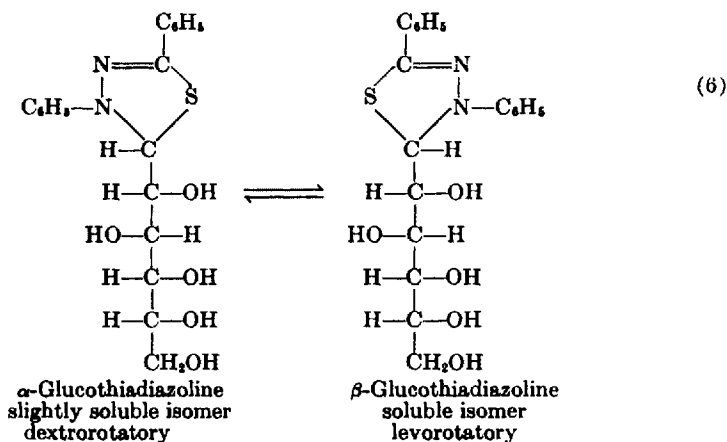
The optical rotation of these compounds has been explained by Lifschitz on the basis of *cis-trans* isomerism and by Wuyts on the basis of the stereoisomerism of the 5-carbon atom in the Δ^2 -1,3,4-thiadiazoline. There is an additional explanation in that glycothiadiazolines resemble the α and β forms of the monosaccharides. The α and β forms of the monosaccharide differ in melting points, solubility, and particularly in optical properties. Thus, for α -glucose $[\alpha]$ is $+109.6^\circ$, and for β -glucose $+20.5^\circ$. If α -glucose is dissolved in water, the rotation gradually decreases to 52.3° and remains constant at that figure. The rotation of a solution of β -glucose increases until it reaches 52.3° . This final value corresponds to an equilibrium state between α - and β -sugars, which in solution are reversibly converted into one another. Glucose is pictured in this manner (5). The similarity of the two forms of 5-glyco- Δ^2 -1,3,4-thiadiazolines



to the α and β forms of the monosaccharides appears to be more than coincidence. The melting points and solubilities of the two glycothiadiazolines are different. The optical activity of the two forms is different, but in solution the activities change, albeit slowly, until apparently an

¹¹ Wuyts, *Compt. rend.*, 196, 1678 (1933).

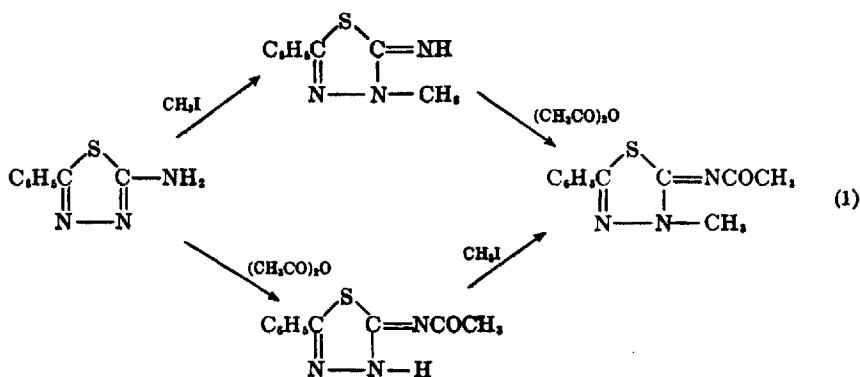
equilibrium is reached (see Figures 1 and 2). Additional research may show that the two forms of the glycothiadiazolines can be designated as follows. Such a hypothesis would involve the splitting of the Δ^2 -1,3,4-thiadiazoline ring and then its regeneration about the other bond.



2-Amino-1,3,4-thiadiazoles and the 5-Imino- Δ^2 -1,3,4-thiadiazolines (I)



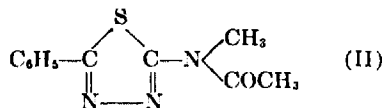
These two classes of compounds are grouped together because Young and Eyre¹ presented evidence that the 2-amino-1,3,4-thiadiazoles behaved in the same manner as did the 2-aminothiazoles² and the 2-iminothiazolo-



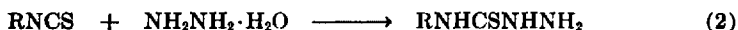
¹ Young and Eyre, *J. Chem. Soc.*, 79, 54 (1901).

² Traumann, *Ann.*, 249, 53 (1893).

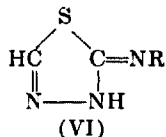
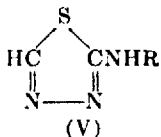
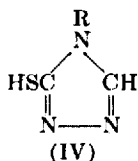
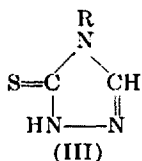
lines.³ Methylation of 2-amino-5-phenyl-1,3,4-thiadiazole produced 2-imino-3-methyl-5-phenyl-1,3,4-thiadiazoline. Acetylation of this compound produced the same compound as was obtained from the methylation of 2-acetylamino-5-phenyl-1,3,4-thiadiazole (1). Young and Eyre postulated that the acetyl derivative of 2-methylamino-5-phenyl-1,3,4-thiadiazole had this constitution (II).



Pulvermacher⁴ synthesized some substituted 2-amino-1,3,4-thiadiazoles by the following steps. 4-Alkyl thiosemicarbazides were prepared from alkyl isothiocyanate and hydrazine hydrate in the cold which on heating with formic acid yielded the 2-alkylamino-1,3,4-thiadiazole (2,3).



There was some doubt as to the structure of these compounds, since the four structures (III-VI) could have been obtained. The formation



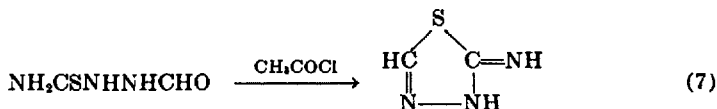
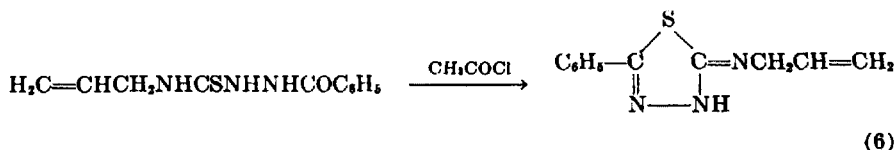
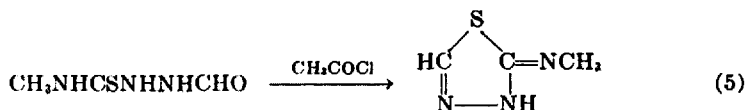
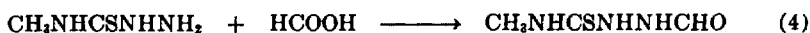
of mononitroso and monoacetyl derivatives showed the presence of the imino or amino group. Methylation and then decomposition with concentrated mineral acids at a high temperature produced methylamine and the alkyl amine rather than methyl mercaptan. Heating the compound with freshly precipitated mercuric oxide formed only a small trace of mercuric sulfide. Oxidation with hydrogen peroxide or nitric acid did not split the sulfur from the ring. Reduction with zinc and hydrochloric acid did not lead to a substituted thiourea. In view of this evidence, structure (VI) would be the correct one.

Pulvermacher⁴ heated 4-methylthiosemicarbazide with formic acid and obtained 1-formyl-4-methylthiosemicarbazide. Heating this compound with acetyl chloride yielded 2-methylamino-1,3,4-thiadiazole instead

³ Gabriel, *Ber.*, **22**, 1144 (1899).

⁴ Pulvermacher, *Ber.*, **27**, 613 (1894).

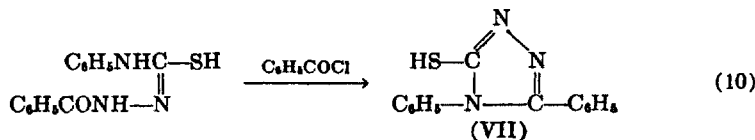
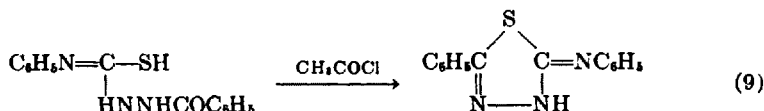
of the acetyl derivative (4,5). The same type of reaction was obtained with benzoylallylthiosemicarbazide (6). Freund and Meinecke⁵ also used this reaction to prepare 2-amino-1,3,4-thiadiazole and 2-amino-5-methyl-1,3,4-thiadiazole (7). They found that 2-amino-1,3,4-thiadiazole reduced Fehling solution.



Marckwald⁶ was interested in the stereoisomerism of phenylthiosemicarbazide, which he believed to exist in two forms (8). Marckwald and



Bott⁷ found that the benzoylphenylthiosemicarbazide and acetyl chloride gave 2-phenylamino-5-phenyl-1,3,4-thiadiazole of Pulvermacher, but the substitution of benzoyl chloride for acetyl chloride produced 5-mercapto-3,4-diphenyl-4,1,2-triazole (9,10). The proof of the structure of the



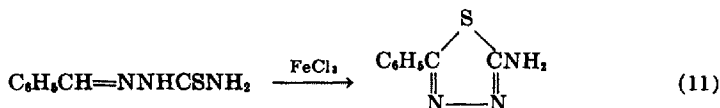
⁵ Freund and Meinecke, *Ber.*, 29, 2511 (1896).

⁶ Marckwald, *Ber.*, 25, 3098 (1892); *Ber.*, 32, 1081 (1899).

⁷ Marckwald and Bott, *Ber.*, 29, 2914 (1896).

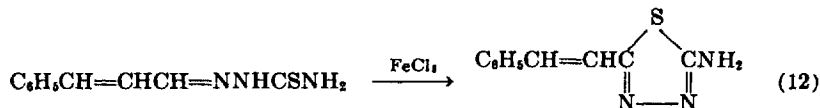
product (VII) was based on methylation and oxidation, methanesulfonic acid being obtained.

Young and Eyre⁸ found that they could oxidize benzalthiosemicarbazone with ferric chloride and obtain 2-amino-5-phenyl-1,3,4-thiadiazole (11). No triazole corresponding to Marckwald's compound was obtained,

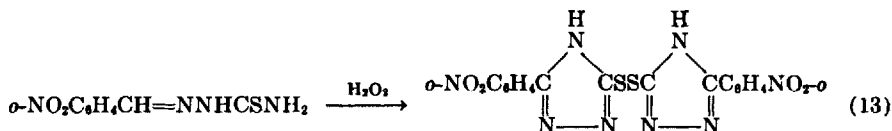


although in some experiments a very small fraction which was soluble in alkali was observed. Using benzal-4-phenylthiosemicarbazone they obtained the same compound which Marckwald and Bott had synthesized from benzoylphenylthiosemicarbazide and acetyl chloride.

De and Roy-Choudhury⁹ repeated Young and Eyre's work on the oxidation of benzalthiosemicarbazone with ferric chloride and isolated 2-amino-5-phenyl-1,3,4-thiadiazole. Using this reaction a large number of 5-substituted 2-amino-1,3,4-thiadiazoles, such as 2-amino-5-styryl-1,3,4-thiadiazoles, were prepared (12). They found no trace of a higher



melting material as described by Young and Eyre. When, however, the benzalthiosemicarbazones were oxidized with hydrogen peroxide, the 4,1,2-triazoles such as Marckwald and Bott described were obtained (13).



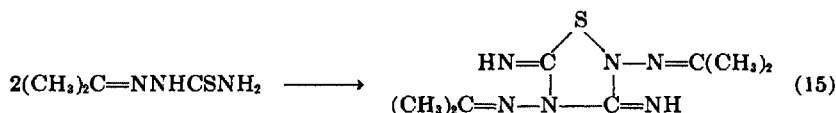
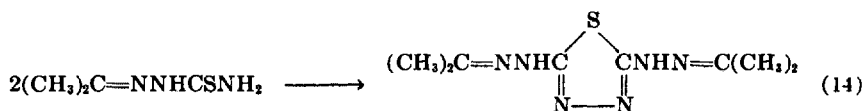
Oxidation with hydrogen peroxide of acetone thiosemicarbazone presented a special case, as there is no methylene hydrogen and the compound behaved as a substituted thiourea. In view of Hector's early work¹⁰ De and Roy-Choudhury believed that they had obtained a 2,5-dihydrazino-1,3,4-thiadiazole. They neglected Hector's later work¹¹ in which he showed that these compounds were probably 1,2,4-thiadiazoles. (See the discussion on 1,2,4-thiadiazoles.) [De and Roy-Choudhury's reaction (14). Probable reaction (15).]

⁸ Young and Eyre, *J. Chem. Soc.*, 79, 54 (1901).

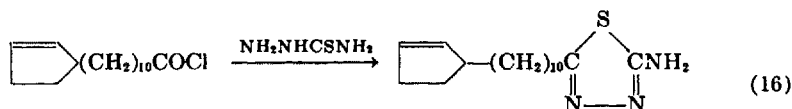
⁹ De and Roy-Choudhury, *J. Indian Chem. Soc.*, 5, 269 (1928); *Chem. Abstr.*, 22, 4123 (1928).

¹⁰ Hector, *Ber.*, 22, 1177 (1889); *Ber.*, 25, 1578 (1892).

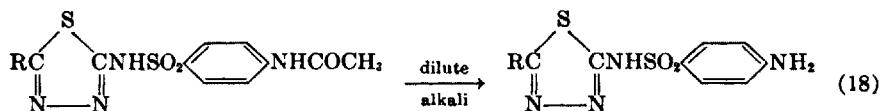
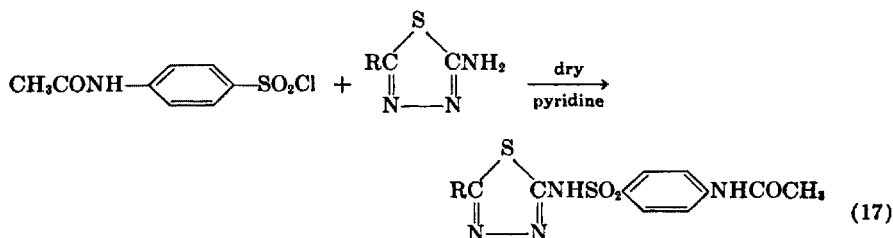
¹¹ Hector, *Ber.*, 25, Ref. 799 (1892); *Oefvers. Kongl. Vet. Akad.*, 1892, 79.



Arnold¹² used a modification of Pulvermacher's method¹³ in preparing 2-amino-5-norhydrocarpyl-1,3,4-thiadiazole and other thiadiazoles with long chains in the 5-position. The acyl chloride was heated with the thiosemicarbazide to give the 2-amino-5-alkyl-1,3,4-thiadiazole directly (16). Steahly¹⁴ used two equivalents of the acyl chloride and obtained yields as high as 96%.



With the discovery of the antibacterial activity of the sulfanilamido-heterocycles, particularly sulfathiazole, it was natural that the antibacterial activity of the various 2-sulfanilamido-1,3,4-thiadiazoles should be examined. Northey¹⁵ has summarized the antibacterial activities of these compounds in his excellent review on the sulfonamides. The most interesting compounds of this group were 2-sulfanilamido-5-methyl-1,3,4-thiadiazole ("Sulfamethyl-thiadiazole," "Lucosil," or "Tetracid") and 2-sulfanilamido-5-ethyl-1,3,4-thiadiazole ("Sulfaethylthiadiazole," or "Glo-



¹² Arnold, *Ber.*, **75**, 87 (1942).

¹³ Pulvermacher, *Ber.*, **27**, 613 (1894).

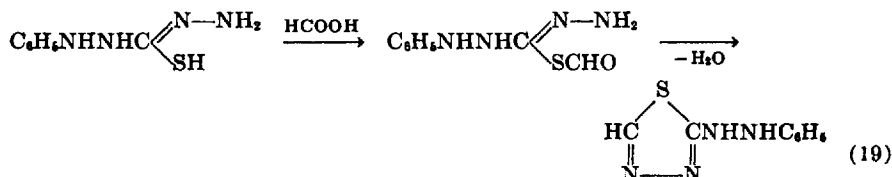
¹⁴ Steahly, U. S. Pat. 2,422,050 (1947).

¹⁵ Northey, *The Sulfonamides and Allied Compounds*. Reinhold, New York, 1948, pp. 35-36, 92-93, 408.

bucid"). These compounds were extensively studied and were found to be less potent than sulfathiazole for streptococcal and pneumococcal infections. Their activity approximated that of sulfapyridine.

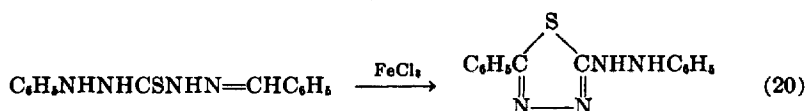
The general method for the preparation of these compounds consisted of allowing *N*-acetylsulfanilyl chloride to react with the aminoheterocycle in the presence of dry pyridine, and then deacetylating (17,18). The alternate method used *p*-nitrobenzenesulfonyl chloride instead of the *N*-acetylsulfanilyl chloride and then the nitro group was reduced.

Guha and Roy-Choudhury^{16,17} found that formic acid reacted with 1-phenylthiocarbohydrazide to yield 2-phenylhydrazino-1,3,4-thiadiazole (19). This compound was insoluble in dilute alkali and gave no mercuric

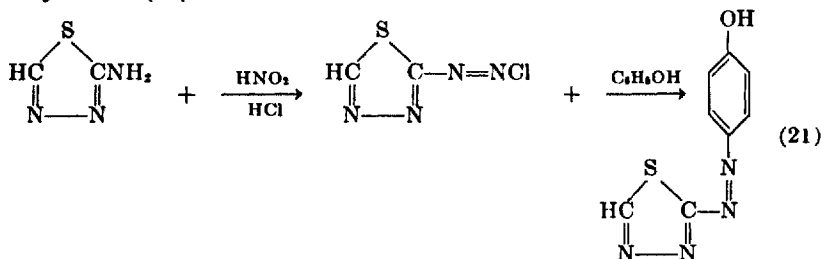


sulfide when treated with freshly precipitated mercuric oxide; acetic anhydride and thiocarbohydrazide did not cyclize.

Oxidation of benzal-1-phenylthiocarbohydrazide with ferric chloride gave 2-phenylhydrazino-5-phenyl-1,3,4-thiadiazole (20).



Stolle and Fehrenbach¹⁸ found that 2-amino-1,3,4-thiadiazole and 2-amino-5-methyl-1,3,4-thiadiazole could be diazotized in concentrated hydrochloric acid to form diazonium chlorides which coupled with phenol to give dyestuffs (21).



¹⁶ Guha and Roy-Choudhury, *J. Indian Chem. Soc.*, **5**, 163 (1928); *Chem. Abstr.*, **23**, 1397 (1929).

¹⁷ Guha and Roy-Choudhury, *J. Indian Chem. Soc.*, **5**, 149 (1928); *Chem. Abstr.*, **23**, 139 (1929).

¹⁸ Stolle and Fehrenbach, *J. prakt. Chem.*, [2] **122**, 289 (1929).

TABLE XVII. Preparation of the 2-Amino-1,3,4-thiadiazoles or 2-Imino-1,3,4-thiadiazolines Including the 3- and 5-Alkyl and Aryl Derivatives

Substituents on 2-amino-1,3,4-thiadiazole					
No.	Groups on the 2-amino	3-Position	5-Position	Preparation method	Ref.
1	Phenyl	H	H	$C_6H_5NHCSNHNH_2 + HCOOH$	1
2	Phenyl nitroso	—	H	compound 1 + HNO_2	1
3	Phenyl acetyl	—	H	compound 1 + acetic anhydride	1
4	Phenyl	methyl	H	compound 1 + methyl iodide	1
5	Phenyl	H	methyl	$C_6H_5NHCSNHNH_2 + CH_3COCl$	1
6	Phenyl nitroso	—	methyl	compound 5 + HNO_2	1
7	Phenyl acetyl	—	methyl	compound 5 + acetic anhydride	1
8	Phenyl	methyl	methyl	compound 6 + methyl iodide	1
9	Methyl	H	H	$CH_3NHCSNHNHCHO + CH_3COCl$	1
10	Methyl	methyl	H	compound 9 + methyl iodide	1
11	Methyl	H	methyl	$CH_3NHCSNHNH_2 + CH_3COCl$	1
12	Methyl	methyl	methyl	compound 11 + methyl iodide	1
13	Allyl	H	H	$CH_2=CHCH_2NHCSNHNHCHO + CH_3COCl$	1
14	Allyl acetyl	—	H	compound 13 + acetic anhydride	1
15	Allyl	methyl	H	compound 13 + methyl iodide	1
16	Allyl	H	methyl	$CH_2=CHCH_2NHCSNHNH_2 + CH_3COCl$	1
17	Allyl acetyl	—	methyl	compound 16 + acetic anhydride	1

(Table continued)

TABLE XVII (Continued)

Substituents on 2-amino-1,3,4-thiadiazole					Preparation method	Solubility	M.p., °C.	Ref.
No.	Groups on the 2-amino	3-Position	5-Position					
18	Allyl	methyl	methyl	compound 16 + methyl iodide	—	(HI, 115-6)	1	
19	Allyl	H	phenyl	$\text{CH}_2=\text{CHCH}_2\text{NHCSNHNHOCOC}_6\text{H}_5 + \text{CH}_3\text{COCl}$ $\text{CH}_2=\text{CHCH}_2\text{NHCSNHNH}=\text{CHC}_6\text{H}_5 + \text{FeCl}_3$	alc.	115 (HCl, 115) 114-5	2	
20	Allyl acetyl	—	phenyl	compound 19 + acetic anhydride	—	123-4 120	1	
21	Allyl nitroso	—	phenyl	compound 19 + HNO_2	acetic acid benzene, CHCl_3	95	2	
22	—	H	H	$\text{NH}_2\text{CSNHNHNHCHO} + \text{CH}_3\text{COCl}$	water, alc.	191	1	
23	Nitroso	H	H	compound 22 + HNO_2	—	220 (dec.)	3	
24	Acetyl	H	H	compound 22 + acetic anhydride	dil. alc.	268	3	
25	—	methyl	H	compound 22 + methyl iodide	—	oil (HI, sinters, 215; dec.) 243	3	
26	—	H	methyl	$\text{NH}_2\text{CSNHNH}_2 + \text{CH}_3\text{COCl}$	water, alc.	235 (HCl, 110)	3	
27	Nitroso	H	methyl	compound 26 + HNO_2	—	227 (dec.)	3	
28	Acetyl	H	methyl	compound 26 + acetyl chloride	water	292	3	
29	—	methyl	methyl	compound 26 + methyl iodide	—	oil (HI, 215); (HCl, 285)	3	
30	Phenyl	H	phenyl	$\text{C}_6\text{H}_5\text{NHCSNHNHOCOC}_6\text{H}_5 + \text{CH}_3\text{COCl}$ $\text{C}_6\text{H}_5\text{NHCSNHNH}=\text{CHC}_6\text{H}_5 + \text{FeCl}_3$	alc.	200 199-200	4	
31	Phenyl acetyl	—	phenyl	compound 30 + acetyl chloride	alc.	140	5	
32	Phenyl nitroso	—	phenyl	compound 30 + HNO_2	—	—	4	
33	—	—	phenyl	$\text{NH}_2\text{CSNHNH}=\text{CHC}_6\text{H}_5 + \text{FeCl}_3$	alc.	222-3	5	
34	Acetyl	H	phenyl	compound 33 + acetic anhydride	alc.	276	5	
35	Acetyl	methyl	phenyl	silver salt of compound 34 + methyl iodide	alc.	144	5	

Substituents on 2-amino-1,3,4-thiadiazole					Preparation method	Solubility	M.p., °C.	Ref.
No.	Groups on the 2-amino	3-Position	5-Position					
36	—	methyl	phenyl		compound 33 + methyl iodide	—	(HI, 245-6) (HCl, 218-9)	5
37	Methyl	H	phenyl		$\text{CH}_3\text{NHCSNHNH}=\text{CHC}_6\text{H}_5 + \text{FeCl}_3$	alc., benzene	183-4	5
38	Methyl acetyl	—	phenyl		compound 37 + acetic anhydride	alc.	195	5
39	—	H	ethyl		$\text{NH}_2\text{CSNHNH}_2 + \text{CH}_3\text{CH}_2\text{COCl}$	—	188-93	6
40	—	H	vinyl		$\text{NH}_2\text{CSNHNH}_2 + \text{ClCH}_2\text{CH}_2\text{COCl} \xrightarrow{\text{NaOH}}$	—	—	6
41	—	H	cyclopropyl		$\text{NH}_2\text{CSNHNH}_2 + \text{H}_2\text{C}-\underset{\text{CH}_3}{\text{CH}}-\text{COCl}$	—	210-11	6
42	—	H	propenyl		$\text{NH}_2\text{CSNHNH}_2 + \text{CH}_2=\text{CHCH}_2\text{COCl}$	—	—	6
43	—	H	styryl		$\text{NH}_2\text{CSNHNH}=\text{CHCH}=\text{CHC}_6\text{H}_5 + \text{FeCl}_3$ $\text{NH}_2\text{CSNHNH}_2 + \text{C}_6\text{H}_5\text{CH}=\text{CHCOCl}$	alc.	261 233-5	2 7
44	Phenyl	H	<i>o</i> -hydroxy-phenyl		$\text{C}_6\text{H}_4\text{NHCSNHNH}=\text{CH}-\text{C}_6\text{H}_4-\text{OH} + \text{FeCl}_3$	benzene	190-1	2
45	Phenyl	H	<i>m</i> -nitrophenyl		$\text{C}_6\text{H}_4\text{NHCSNHNH}=\text{CH}-\text{C}_6\text{H}_4-\text{NO}_2 + \text{FeCl}_3$	acetic acid	249-50	2
46	Phenyl acetyl	—	<i>m</i> -nitrophenyl		compound 45 + acetic anhydride	acetic acid	246	2
47	<i>p</i> -Tolyl	H	phenyl		$p\text{-CH}_3\text{C}_6\text{H}_4\text{NHCSNHNH}=\text{CHC}_6\text{H}_5 + \text{FeCl}_3$	alc.	198-9	2
48	<i>p</i> -Tolyl acetyl	—	phenyl		compound 47 + acetic anhydride	alc.	155	2
49	<i>p</i> -Tolyl	H	<i>p</i> -nitrophenyl		$p\text{-CH}_3\text{C}_6\text{H}_4\text{NHCSNHNH}=\text{CH}-\text{C}_6\text{H}_4-\text{NO}_2 + \text{FeCl}_3$	acetic acid	197-8	2
50	<i>p</i> -Tolyl acetyl	—	<i>p</i> -nitrophenyl		compound 49 + acetic anhydride	alc.	243	2

(Table continued)

TABLE XVII (Continued)

Substituents on 2-amino-1,3,4-thiadiazole					Preparation method	Solubility	M.p., °C.	Ref.
No.	Groups on the 2-amino	3-Position	5-Position					
51	<i>p</i> -Tolyl	—	styryl	$p\text{-CH}_3\text{C}_6\text{H}_4\text{NHCSNHN}=\text{CHCH}=\text{CHC}_6\text{H}_5 + \text{FeCl}_3$	acetic acid	184	2	
52	Allyl	—	<i>m</i> -nitrophenyl	$\text{CH}_2=\text{CHCH}_2\text{NHCSNHN}=\text{CH}-\text{C}_6\text{H}_4\text{NO}_2 + \text{FeCl}_3$	alc.	170-1	2	
53	<i>m</i> -Tolyl	—	<i>p</i> -nitrophenyl	$m\text{-CH}_3\text{C}_6\text{H}_4\text{NHCSNHN}=\text{CHC}_6\text{H}_4\text{NO}_2 + \text{FeCl}_3$	acetic acid	257	2	
54	<i>m</i> -Tolyl	H	phenyl	$m\text{-CH}_3\text{C}_6\text{H}_4\text{NHCSNHN}=\text{CHC}_6\text{H}_5 + \text{FeCl}_3$	benzene	176	2	
55	<i>o</i> -Tolyl	H	<i>m</i> -nitrophenyl	$o\text{-CH}_3\text{C}_6\text{H}_4\text{NHCSNHN}=\text{CHC}_6\text{H}_4\text{NO}_2 + \text{FeCl}_3$	pyridine	247-8	2	
56	Methyl	H	<i>m</i> -nitrophenyl	$\text{CH}_3\text{NHCSNHN}=\text{CHC}_6\text{H}_4\text{NO}_2 + \text{FeCl}_3$	alc.	201	2	
57	Methyl acetyl	—	<i>m</i> -nitrophenyl	compound 56 + acetic anhydride	pyridine	225-6	2	
58	Methyl	methyl	<i>m</i> -nitrophenyl	compound 56 + methyl iodide	acetic acid	209	2	
59	Methyl	H	<i>p</i> -nitrophenyl	same as compound 56	pyridine	262	2	
60	Methyl acetyl	—	<i>p</i> -nitrophenyl	compound 59 + acetic anhydride	pyridine	279	2	
61	Methyl	methyl	<i>p</i> -nitrophenyl	compound 59 + methyl iodide	acetic acid	203	2	
62	<i>m</i> -Xylyl	H	<i>o</i> -nitrophenyl	$(\text{CH}_3)_2\text{C}_6\text{H}_3\text{NHCSNHN}=\text{CHC}_6\text{H}_4\text{NO}_2 + \text{FeCl}_3$	acetic acid	229	2	
63	<i>m</i> -Xylyl	H	<i>m</i> -nitrophenyl	same as compound 62	acetic acid	205	2	
64	<i>m</i> -Xylyl acetyl	—	<i>m</i> -nitrophenyl	compound 63 + acetic anhydride	alc.	197-8	2	
65	2-Naphthyl	H	<i>o</i> -nitrophenyl	$2\text{-C}_{10}\text{H}_7\text{NHCSNHN}=\text{CHC}_6\text{H}_4\text{NO}_2 + \text{FeCl}_3$	acetic acid	202	2	
66	Ethyl	H	phenyl	$\text{C}_2\text{H}_5\text{NHCSNHN}=\text{CHC}_6\text{H}_5 + \text{FeCl}_3$	acetic acid	238-40	2	
67	—	H	10-cyclopent-1-yl-decyl	 $(\text{CH}_2)_9\text{COCl} + \text{NH}_2\text{CSNHNH}_2$	methanol	150-2 (HCl, 112-4)	7	
68	—	H	8-hepta-decyl	oleoyl chloride + $\text{NH}_2\text{CSNHNH}_2$	methanol	110 (HCl, 85-90)	7	

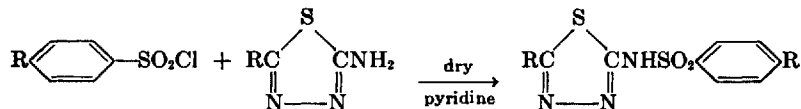
Substituents on 2-amino-1,3,4-thiadiazole					Preparation method	Solubility	M.p., °C.	Ref.
No.	Groups on the 2-amino	3-Position	5-Position					
69	—	tri-phenyl-methyl	ethyl		$(C_6H_5)_3CCl + C_2H_5-C \begin{array}{c} \diagup S \\ \diagdown C-NH_2 \\ N=N \end{array}$	—	207-8	8
70	—	H	carbethoxymethyl		$COCl + NH_2CSNHNH_2$ $ $ CH_3	water	158-60	9
71	—	H	carbethoxypropyl		$COOC_2H_5$ $ $ $COCl$ $(CH_2)_3 + NH_2CSNHNH_2$ $ $ $COOC_2H_5$	water	153-4	9
72	Anilino (phenylhydrazino)	H	phenyl		$C_6H_5NHNHCSNHN=CHC_6H_5 + FeCl_3$	alc.	172	10
73	Anilino	H	styryl		$C_6H_5NHNHCSNHN=CHCH=CHC_6H_5 + FeCl_3$	alc.	173	10
74	Anilino	H	p-nitrophenyl		$C_6H_5NHNHCSNHN=CHC_6H_4NO_2-p + FeCl_3$	acetic acid	263-4	10
75	Anilino	H	H		$C_6H_5NHNHCSNHNH_2 + HCOOH$	alc.	220	10

¹ Pulvermacher, *Ber.*, 27, 613 (1894).² De and Roy-Choudhury, *J. Indian Chem. Soc.*, 5, 269 (1928); *Chem. Abstr.*, 22, 4123 (1928).³ Freund and Meinecke, *Ber.*, 29, 2511 (1896).⁴ Marekwald and Bott, *Ber.*, 29, 2914 (1896).⁵ Young and Eyre, *J. Chem. Soc.*, 79, 54 (1901).⁶ Steahly, U. S. Pat. 2,422,050 (1947).⁷ Arnold, *Ber.*, 75, 87 (1942).⁸ Dahlbom and Ekstrand, *Svensk. Kem. Tid.*, 56, 304 (1944); *Chem. Abstr.*, 40, 3415 (1946).⁹ Clark, English, Winnek, Marson, Cole, and Clapp, *J. Am. Chem. Soc.*, 68, 96 (1946).¹⁰ Guha and Roy-Choudhury, *J. Indian Chem. Soc.*, 5, 149 (1928).

TABLE XVIII. Derivatives of 2-Benzenesulfonamido-1,3,4-thiadiazole, Especially the 2-Sulfanilamido-1,3,4-thiadiazoles

This table does not contain the complete references concerning the 2-sulfanilamido-1,3,4-thiadiazoles. The activity of these compounds against microorganisms and some of the melting points may be found in Northey, *The Sulfonamides and Allied Compounds*, Reinhold, New York, 1948, pp. 92-93, 408.

The general method for the preparation of these compounds is as follows:



The amino group in the *para*-position was obtained by deacetylating an acetylamino group or reducing a nitro group.

Substituents on the 1,3,4-thiadiazole ring					
No.	On 2-phenyl sulfonamido group	On the 5-position	Solubility	M.p., °C.	Ref.
1	—	H	—	188-9	1
2	—	ethyl	—	128-30	2
3	<i>p</i> -Methyl	ethyl	—	132-2.5	2
4	<i>p</i> -Acetylamino	H	—	183 dec.	3
5	<i>p</i> -Amino	H	—	216-8 dec.	4
6	<i>p</i> -Amino	methyl	—	190-2	5
7	<i>p</i> -Amino	ethyl	—	185-6	6
8	<i>p</i> -Amino	<i>n</i> -propyl	—	165-6	6
9	<i>p</i> -Amino	isopropyl	—	195-7	6
10	<i>p</i> -Amino	isobutyl	—	223.5-5	6
11	<i>p</i> -Acetylamino	10-(cyclopenten-1-yl) decyl	dil. ethanol	117-9	7
12	<i>p</i> -Amino	10-(cyclopenten-1-yl) decyl	hot CHCl ₃	117-8	7
13	<i>p</i> -Acetylamino	8-heptadecenyl	acetone, methanol	104-6	7
14	<i>p</i> -Amino	8-heptadecenyl	dil. methanol	109-11	7
15	<i>p</i> -Acetylamino	styryl	methanol, ethanol	202-4	7
16	<i>p</i> -Amino	styryl	methanol, acetone	285-6	7
17	3-Bromo-4-amino	ethyl	—	163	8
18	3,5-Dibromo-4-amino	ethyl	—	197	8
19	<i>m</i> -Nitro	H	alc.	192-5	9
20	<i>m</i> -Amino	H	—	60 as 1 H ₂ O	9
21	<i>p</i> -Amino	carboxymethyl	—	209-10	10
22	<i>p</i> -Amino	carboxypropyl	—	185.5-6.5	10
23*	<i>p</i> -Sulfamylphenyl- azoamino	methyl	—	126 dec.	3
24*	<i>p</i> -Sulfamylphenyl- azoamino	H	—	215	3

* Substituents in the 2-position rather than on the 2-phenylsulfonamido group.

¹ English, Chappel, Bell, and Roblin, *J. Am. Chem. Soc.*, **64**, 2516 (1942).

² Dahlbom and Ekstrand, *Svensk. Kem. Tid.*, **55**, 1228 (1943); *Chem. Abstr.*, **38**, 5208 (1944).

³ Tappi and Migliardi, *Ricerca sci.*, **12**, 1056 (1942); *Chem. Abstr.*, **36**, 1023 (1942).

⁴ Roblin, Williams, Winnek, and English, *J. Am. Chem. Soc.*, **62**, 2002 (1940).

⁵ Ganapathi, *Proc. Ind. Acad. Sci.*, **A13**, 386 (1941); *Chem. Abstr.*, **36**, 1022 (1942).

⁶ Frisk, *Acta Med. Scand. Suppl.*, **142**, 1 (1943); *Chem. Abstr.*, **38**, 4692 (1944).

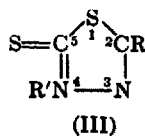
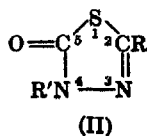
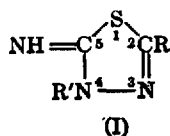
⁷ Arnold, *Ber.*, **75**, 87 (1942).

⁸ Wojahn, *Arch. Pharm.*, **281**, 193 (1943); *Chem. Abstr.*, **38**, 4919 (1944).

⁹ English, Clark, Shepherd, Marson, Krapcho, and Roblin, *J. A. C. S.*, **68**, 1039 (1946).

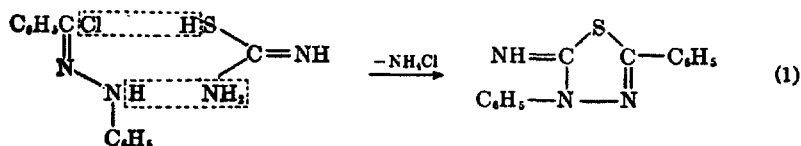
¹⁰ Clark, English, Winnek, Marson, Cole, and Clapp, *ibid.*, **68**, 96 (1946).

5-Imino- Δ^2 -1,3,4-thiadiazolines (I), 1,3,4-Thiadiazol-5 (4)-ones (II) and 1,3,4-Thiadiazol-5(4)-thiones (III)

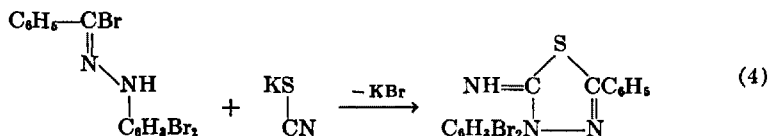
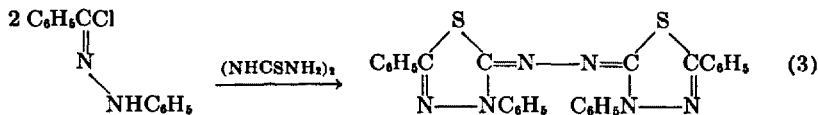
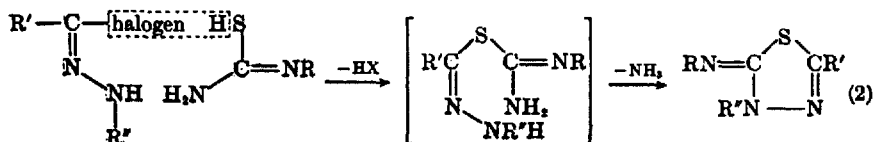


Fusco *et al.*¹⁻⁵ developed a novel method of preparing the 1,3,4-thiadiazolines and, in addition, prepared some isoxazoles and triazoles with this general method.

For example, 2,4-diphenyl-5-imino- Δ^2 -1,3,4-thiadiazoline was prepared from α -chlorobenzalphenylhydrazone and thiourea (1).



Substituted thioureas of the general formula $RNHCSNH_2$ give 1,3,4-thiadiazolines with substituted imino groups. The reaction proceeds as shown in equation (2). The reaction is independent of the R radical or the N substituent on the thiourea. The following thioureas, in addition to others, are used in this reaction: *N*-acetylthiourea, *N*-phenylthiourea,



¹ Fusco and Justoni, *Gazz. chim. ital.*, **67**, 3 (1937); *Chem. Abstr.*, **31**, 6230 (1937).

² Justoni and Fusco, *Gazz. chim. ital.*, **68**, 59 (1938).

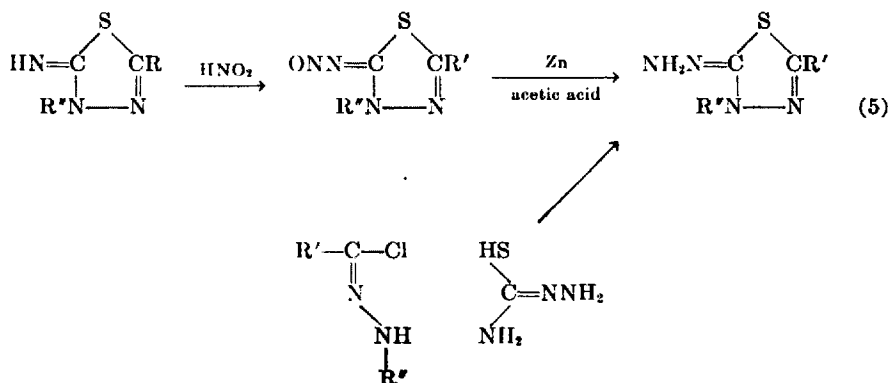
³ Fusco and Musante, *Gazz. chim. ital.*, **68**, 147 (1938); *Chem. Abstr.*, **32**, 7456 (1938).

⁴ Fusco and Musante, *Gazz. chim. ital.*, **68**, 665 (1938); *Chem. Abstr.*, **33**, 2518 (1939).

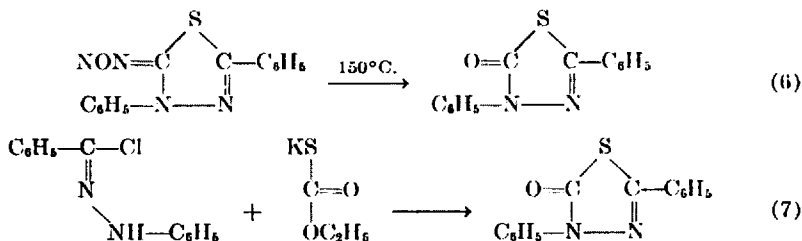
⁵ Fusco, *Rend. ist. lombardo sci.*, **71**, 425 (1938); *Chem. Abstr.*, **34**, 3267 (1940).

thiosemicarbazide, benzalthiosemicarbazone, and bithiourea. Bithiourea gave disubstitution (3). Potassium thiocyanate also reacted with the α -halobenzalphenylhydrazones (4).

The imino group was readily acylated with an acyl halide in pyridine. The compounds were resistant to alkalis and desulfurizing agents. Nitrous acid reacted with the imino group to give the 5-nitrosoimino derivatives. Reduction of these 5-nitrosoimino compounds gave the hydrazones which were identical to those obtained from thiosemicarbazide (5).



These nitroso compounds on refluxing in xylene yielded the 1,3,4-thiadiazol-5(4)-ones (6). The reaction between α -chlorobenzalphenylhydrazone and ethyl potassium thiocarbonate also produced 2,4-diphenyl-1,3,4-thiadiazol-5(4)-one (7).



The 1,3,4-thiadiazol-5(4)-thiones were prepared in a similar manner from potassium xanthate and α -halobenzalphenylhydrazones (8).

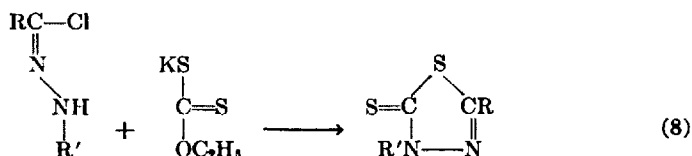
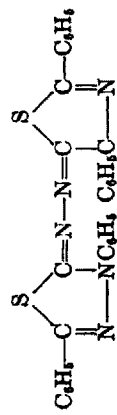


TABLE XIX. Preparation of 5-Imino- Δ^2 -1,3,4-thiadiazolines, 1,3,4-Thiadiazol-5(4)-ones and 1,3,4-Thiadiazol-5(4)-thiones

Substituents on the Δ^2 -1,3,4-thiadiazoline				
No.	2	4	5	
1	Phenyl	phenyl	imino	1 $\text{C}_6\text{H}_5\text{C}=\text{NNHC}_6\text{H}_5 + \text{NH}_4\text{CSNH}_2$ $\text{C}_6\text{H}_5\text{C}=\text{NNHC}_6\text{H}_5 + \text{KSCN}$
2	Phenyl	phenyl	acetylimino	1 compound 1 + acetyl chloride + pyridine 2 $\text{C}_6\text{H}_5\text{C}=\text{NNHC}_6\text{H}_5 + \text{CH}_3\text{CONHCSNH}_2$
3	Phenyl	phenyl	benzoylimino	1 compound 1 + benzoyl chloride + pyridine
4	Phenyl	phenyl	nitroacetylimino	1 compound 1 + nitrous acid
5	Phenyl	phenyl	phenylimino	2 $\text{C}_6\text{H}_5\text{C}=\text{NNHC}_6\text{H}_5 + \text{C}_6\text{H}_5\text{NHCSNH}_2$
6	 2,2'-Diphenyl-5,5'-azino-bis-(Δ^2-1,3,4-thiadiazoline)			2 $2\text{C}_6\text{H}_5\text{C}=\text{NNHC}_6\text{H}_5 + (\text{NH}_4\text{CSNH}_2)_2$
7	Phenyl	2,4-dibromophenyl	imino	1 $\text{C}_6\text{H}_5\text{C}=\text{NNHC}_6\text{H}_3\text{Br}_2 + \text{NH}_4\text{CSNH}_2$ $\text{C}_6\text{H}_5\text{C}=\text{NNHC}_6\text{H}_3\text{Br}_2 + \text{KSCN}$
8	Phenyl	2,4-dibromophenyl	acetylimino	1 compound 7 + acetic anhydride 2 $\text{C}_6\text{H}_5\text{C}=\text{NNHC}_6\text{H}_3\text{Br}_2 + \text{CH}_3\text{CONHCSNH}_2$

(Table continued)

Solubility M.p., °C.

— 97

alc. — 157
157

alc. 166
alc. 144 dec.
122

pyridine 273 dec.

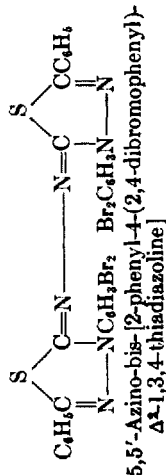
alc. 246

— —

alc., benzene, 175-6
acetone —

TABLE XIX (Continued)

Substituents on the $\Delta^1,1,3,4$ -thiadiazoline					Ref.	Method of preparation	Solubility	M.p., °C.
No.	2	4	5					
9	Phenyl	2,4-dibromo-phenyl	benzoylimino		1	compound 7 + benzoyl chloride + pyridine	xylene	198
10	Phenyl	2,4-dibromo-phenyl	nitrosoimino		1	compound 7 + nitrous acid	—	144 dec.
11	Phenyl	2,4-dibromo-phenyl	phenylimino		2	$C_6H_5C=NNHC_6H_4Br_{2,4} + C_6H_5NHCSNH_2$	benzene, $CHCl_3$	116
12	Phenyl	2,4-dibromo-phenyl	hydrazono		2	$C_6H_5C=NNHC_6H_4Br_{2,4} + NH_2CSNHNH_2$	alc.	153-4
13	Phenyl	2,4-dibromo-phenyl	isopropylideneazino		2	compound 10 + acetone $C_6H_5C=NNHC_6H_4Br_{2,4} + NH_2CSNHN=C(CH_3)_2$	benzene, acetone, alc.	165-6
14	Phenyl	2,4-dibromo-phenyl	benzylideneazino		2	compound 10 + benzaldehyde $C_6H_5C=NNHC_6H_4Br_{2,4} + NH_2CSNHN=CHC_6H_5$	alc., CCl_4 , benzene	173
15	Phenyl	2,4-dibromo-phenyl	anisylideneazino		2	Compound 10 + anisaldehyde $C_6H_5C=NNHC_6H_4Br_{2,4} + NH_2CSNHN=CHC_6H_4OCH_3, p$	benzene, CCl_4	164
16	Phenyl	2,4-dibromo-phenyl	p-nitrobenzylideneazino		2	compound 10 + p-nitrobenzaldehyde $C_6H_5C=NNHC_6H_4Br_{2,4} + NH_2CSNHN=CHC_6H_4NO_2, p$	benzene	246-7
17					2	$C_6H_5C=N-NHC_6H_4Br_{2,4} + (NH_2CSNH)_2$	pyridine	285-6

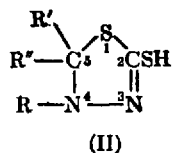
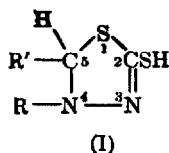


Substituents on the Δ^2 -1,3,4-thiadiazoline							
No.	2	4	5	Ref.			
Method of preparation							
Solubility							
M.p., °C.							
18	Carbethoxy	<i>p</i> -nitrophenyl	imino	3	$C_2H_5OOC-C(=NNHC_6H_4NO_2-p + KSCN$	alc., acetone, benzene	175
19	Carbethoxy	<i>p</i> -nitrophenyl	nitrosoimino	3	$C_2H_5OOC-C(=NNHC_6H_4NO_2-p + KSCN$	alc.	—
20	Phenyl	phenyl	oxo	1	compound 18 + nitrous acid compound 4 + heat (<i>i.e.</i> , 150 °C.)	alc.	85-6 92-3
21	Phenyl	2,4-dibromo-phenyl	oxo	3	$C_6H_5OOC-C(=NNHC_6H_4Br_2-2,4 + KSCOCOC_2H_5$	alc.	148-50
22	Carbethoxy	2-nitrophenyl	oxo	3	reflux compound 19 in xylene $C_2H_5OOC-C(=NNHC_6H_4NO_2-p + KSCOCOC_2H_5$	alc.	91
23	Phenyl	phenyl	thioxo	3	$C_6H_5OOC-C(=NNHC_6H_4 + NaSSCOC_2H_5$	alc., benzene	151-2
24	Phenyl	2,4-dibromo-phenyl	thioxo	3	$C_6H_5OOC-C(=NNHC_6H_4Br_2 + NaSSCOC_2H_5$	alc.	129
25	Carbethoxy	<i>p</i> -nitrophenyl	thioxo	3	$C_2H_5OOC-C(=NNHC_6H_4NO_2-p + NaSSCOC_2H_5$	alc., benzene, $CHCl_3$, acetic acid	151

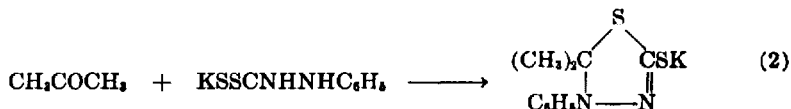
¹ Fusco and Musante, *Gazz. chim. ital.*, **68**, 147 (1938); *Chem. Abstr.*, **32**, 7456 (1938).

² Fusco, *Rend. ist. lombardo sci.*, **71**, 425 (1938); *Chem. Abstr.*, **34**, 3257 (1940).

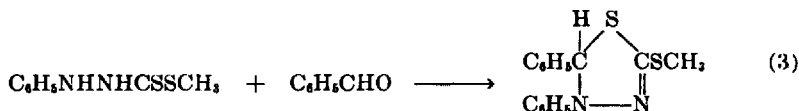
³ Fusco and Musante, *Gazz. chim. ital.*, **68**, 665 (1938); *Chem. Abstr.*, **33**, 2518 (1939).

2-Mercapto- Δ^2 -1,3,4,-thiadiazolines (I, II)

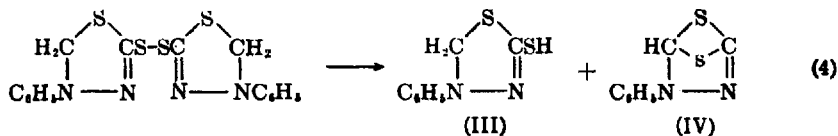
Busch¹ found that aldehydes reacted with 2-substituted dithiocarbazic acids to give 2-mercapto-4- and 5-substituted Δ^2 -1,3,4-thiadiazolines (1). Formaldehyde, acetaldehyde, and benzaldehyde were used in this reaction. Busch and Best² also made 5,5-dialkyl- Δ^2 -1,3,4-thiadiazolines by allowing ketones such as acetone and methylethyl ketone to react with 2-phenyl-dithiocarbazic acid (2). Acetophenone did not react with either the acid or the ester.



The 2-thioethers were prepared by alkylating the 2-mercapto group or by forming the ring with an ester of a dithiocarbazic acid and an aldehyde (3).



The 2-mercapto- Δ^2 -1,3,4-thiadiazolines were readily oxidized to the disulfides with oxidizing agents such as ferric chloride. The disulfides, on heating in chloroform, produced two products: the original sulfide (III) and a compound (IV), which Busch believed to have a bridged ring (4). (See the discussion of the 5,6-dithia-2,3-diazabicyclo[2.1.1]-3-hexenes.)



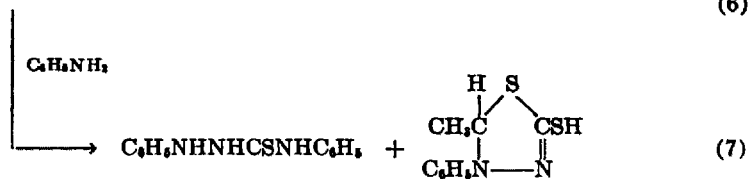
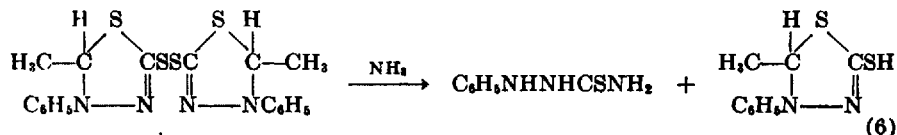
¹ Busch, *Ber.*, **28**, 2635 (1895).

² Busch and Best, *J. prakt. Chem.*, [2] **60**, 225 (1899).

The compound IV (1-phenyl-5,6-dithia-2,3-diazabicyclo[2.1.1]-3-hexene) formed a quaternary salt with methyl iodide. In the presence of alkali this compound degraded into the original 2-phenyldithiocarbazic acid (5).



Busch and Munker³ found that ammonia and aniline opened one ring in the disulfides to form thiosemicarbazides (6,7).



³ Busch and Munker, *J. prakt. Chem.*, [2] 60, 212 (1899).

Table XX follows on page 122.

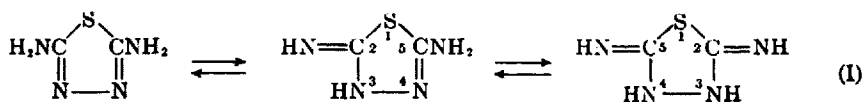
TABLE XX. Preparation of 2-Mercapto- Δ^2 -1,3,4-thiadiazolines

No.	Name	Ref.	Preparation	Solubility	M.p., °C.
1	2-Mercapto-4-phenyl- Δ^2 -1,3,4-thiadiazoline	1, 2	$\text{C}_6\text{H}_5\text{NHNHCSSK} + \text{CH}_2\text{O}$ 2,5-dimercapto-1,3,4-thiadiazole + sodium amalgam + an alcohol	alc., benzene, CHCl_3	112
2	2,2'-Dithiobis(4-phenyl- Δ^2 -1,3,4-thiadiazoline)	1	oxidation of compound 1	CHCl_3 , alc.	135
3	2-Mercapto-4-phenyl-5-methyl- Δ^2 -1,3,4-thiadiazoline	1	$\text{C}_6\text{H}_5\text{NHNHCSSK} + \text{CH}_3\text{CHO}$	alc., ether, CHCl_3	132
4	2,2'-Dithiobis(4-phenyl-5-methyl- Δ^2 -1,3,4-thiadiazoline)	1	oxidation of compound 3	benzene, CHCl_3 , alc.	140
5	2-Mercapto-4,5-diphenyl- Δ^2 -1,3,4-thiadiazoline	1	$\text{C}_6\text{H}_5\text{NHNHCSSK} + \text{C}_6\text{H}_5\text{CHO}$	benzene	156.5
6	2-Methylmercapto-4,5-diphenyl- Δ^2 -1,3,4-thiadiazoline	1	$\text{C}_6\text{H}_5\text{NHNHCSSCH}_3 + \text{C}_6\text{H}_5\text{CHO}$ compound 5 + CH_3I	alc.	93-4
7	2,2'-Dithiobis(4,5-diphenyl- Δ^2 -1,3,4-thiadiazoline)	1	oxidation of compound 5	ether, benzene, CHCl_3	138
8	2-Methylmercapto-4-phenyl- Δ^2 -1,3,4-thiadiazoline	1	$\text{C}_6\text{H}_5\text{NHNHCSSCH}_3 + \text{CH}_3\text{O}$	alc.	34-5
9	2-Mercapto-4- <i>p</i> -tolyl- Δ^2 -1,3,4-thiadiazoline	3	$p\text{-CH}_3\text{C}_6\text{H}_4\text{NHNHCSSK} + \text{CH}_2\text{O}$	alc.	80, 103-5
10	2,2'-Dithiobis(4- <i>p</i> -tolyl- Δ^2 -1,3,4-thiadiazoline)	3	oxidation of compound 9	CHCl_3 , alc.	102
11	2-Mercapto-4- <i>p</i> -tolyl-5-methyl- Δ^2 -1,3,4-thiadiazoline	3	$p\text{-CH}_3\text{C}_6\text{H}_4\text{NHNHCSSK} + \text{CH}_3\text{CHO}$	CHCl_3 , benzene	143
12	2,2'-Dithiobis(4- <i>p</i> -tolyl-5-methyl- Δ^2 -1,3,4-thiadiazoline)	3	oxidation of compound 11	CHCl_3 , benzene	123

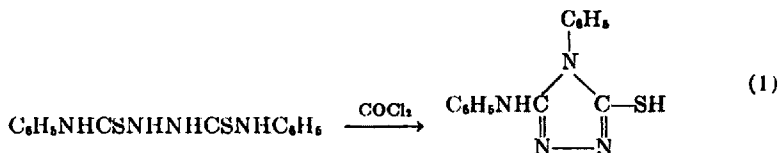
No.	Name	Ref.	Preparation	Solubility	M.p., °C.
13	2-Methylmercapto-4- <i>p</i> -tolyl-5-methyl- Δ^2 -1,3,4-thiadiazoline	3	compound 11 + CH_3I	alc.	50
14	2-Methylmercapto-4- <i>p</i> -tolyl-5-phenyl- Δ^2 -1,3,4-thiadiazoline	3	$p\text{-CH}_3\text{C}_6\text{H}_4\text{NHNHCSSCH}_3 + \text{C}_6\text{H}_5\text{CHO}$	alc.	99
15	2-Ethylmercapto-4- <i>p</i> -tolyl-5-phenyl- Δ^2 -1,3,4-thiadiazoline	3	$p\text{-CH}_3\text{C}_6\text{H}_4\text{NHNHCSSC}_2\text{H}_5 + \text{C}_6\text{H}_5\text{CHO}$	alc.	89
16	2-Benzylmercapto-4- <i>p</i> -tolyl-5-phenyl- Δ^2 -1,3,4-thiadiazoline	3	$p\text{-CH}_3\text{C}_6\text{H}_4\text{NHNHCSSCH}_2\text{C}_6\text{H}_5 + \text{C}_6\text{H}_5\text{CHO}$	alc.	105
17	2-Mercapto-4- <i>o</i> -anisyl-5-methyl- Δ^2 -1,3,4-thiadiazoline	4	$o\text{-CH}_3\text{OC}_6\text{H}_4\text{NHNHCSSK} + \text{CH}_3\text{CHO}$	alc., benzene	149
18	2-Mercapto-4- α -naphthyl-5-methyl- Δ^2 -1,3,4-thiadiazoline	4	$\alpha\text{-C}_{10}\text{H}_7\text{NHNHCSSK} + \text{CH}_3\text{CHO}$	alc., benzene, CHCl_3	104
19	2-Methylmercapto-4- α -naphthyl-5-methyl- Δ^2 -1,3,4-thiadiazoline	4	$\alpha\text{-C}_{10}\text{H}_7\text{NHNHCSSCH}_3 + \text{CH}_3\text{CHO}$ compound 18 + methyl iodide	alc., ether, benzene	108
20	2-Mercapto-4- β -naphthyl- Δ^2 -1,3,4-thiadiazoline	4	$\beta\text{-C}_{10}\text{H}_7\text{NHNHCSSK} + \text{CH}_2\text{O}$	ether, benzene	115
21	2-Mercapto-4- β -naphthyl-5-methyl- Δ^2 -1,3,4-thiadiazoline	4	$\beta\text{-C}_{10}\text{H}_7\text{NHNHCSSK} + \text{CH}_3\text{CHO}$	benzene	164-5
22	2-Mercapto-4-phenyl-5,5-dimethyl- Δ^2 -1,3,4-thiadiazoline	4	$\text{C}_6\text{H}_5\text{NHNHCSSK} + \text{CH}_3\text{COCH}_3$	benzene	135-6
23	2-Mercapto-4-phenyl-5-methyl-5-ethyl- Δ^2 -1,3,4-thiadiazoline	4	$\text{C}_6\text{H}_5\text{NHNHCSSK} + \text{CH}_3\text{COC}_2\text{H}_5$	benzene	158
24	2-Methylmercapto-4-phenyl-5-tetradecyl- Δ^2 -1,3,4-thiadiazoline	5	$\text{C}_6\text{H}_5\text{NHNHCSSCH}_3 + \text{CH}_3(\text{CH}_2)_{12}\text{CHO}$	—	—

¹ Busch, *Ber.*, 28, 2635 (1895).² Busch and Stramer, *J. prakt. Chem.*, [2] 60, 189 (1899).³ Busch, *J. prakt. Chem.*, [2] 60, 219 (1899).⁴ Busch and Best, *J. prakt. Chem.*, [2] 60, 225 (1899).⁵ St. Landa, *Chem. Abstr.*, 19, 3251 (1925); *Chem. Listy*, 19, 264 (1924).

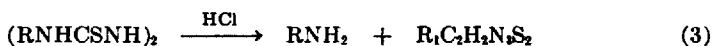
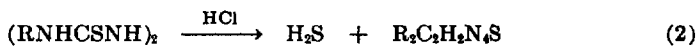
2,5-Diamino-1,3,4-thiadiazoles and Their Derivatives (I)



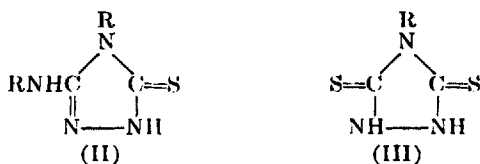
Freund and Wischewiansky¹ allowed 1,6-diphenylbithiourea to react with phosgene and obtained a product which they believed to be 3-anilino-4-phenyl-5-mercapto-4,1,2-triazole (1). Freund and Imgart² found that



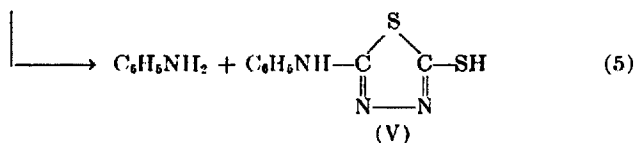
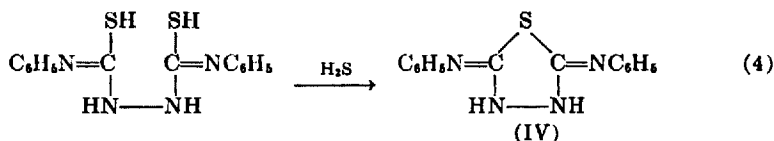
the bithioureas on heating with concentrated hydrochloric acid produced two products (2,3). They postulated the product of reaction (2):



to be a mercapto-4,1,2-triazole (II), and the product of reaction (3) to be a 3,5-dimercapto-4,1,2-triazole (III). The product of reaction (2) formed



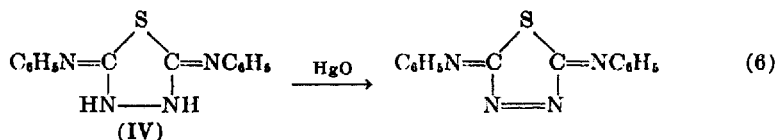
diacetyl, mononitroso, and monomethyl derivatives. Freund and Imgart believed that the oxidation of this product gave a disulfide. The product



¹ Freund and Wischewiansky, *Ber.*, **26**, 2877 (1893).

² Freund and Imgart, *Ber.*, **28**, 946 (1895).

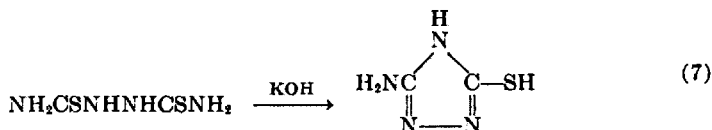
of reaction (3) formed a monoacetyl derivative. Busch and Schmidt³ took issue with the structures which Freund and his co-workers had set forth. They demonstrated that the reaction probably took place as shown in reactions (4) and (5). The oxidation of product (IV) with mercuric oxide gave a colored compound rather than the disulfide as postulated by Freund (6). A molecular weight determination supported Busch and



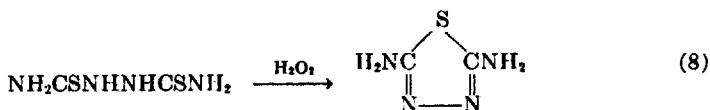
Schmidt's stand. Walther⁴ probably obtained (IV), since the product which he obtained in two separate ways had the same melting point as (IV). This compound was obtained by refluxing 1,6-diphenylbithiourea in alcohol and by heating 1,6-diphenylthiourea with hydrazine in acetic acid.

Busch and Lotz⁵ continued their work with bithiourea and 1,6-dimethylbithiourea. Oxidation of 2,5-diimino-1,3,4-thiadiazolidine with amyl nitrite, which they said formed a colored compound, has been discredited by later workers⁶ who have shown that a nitroso compound is probably formed.

Arndt and Milde⁷ disputed Freund's structure for the 3-mercapto-5-amino-4,1,2-triazole and then synthesized this structure from bithiourea and strong alkali in alcohol (7).



Fromm and co-workers⁸ obtained the 2,5-diamino-1,3,4-thiadiazole by oxidizing bithiourea with 3% hydrogen peroxide (8). This compound



³ Busch and Schmidt, *Ber.*, **46**, 2240 (1913).

⁴ Walther, *J. prakt. Chem.*, **74**, 222 (1906).

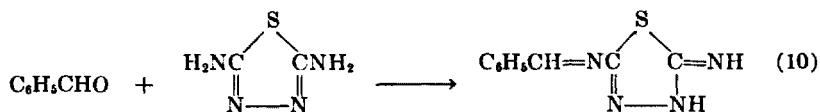
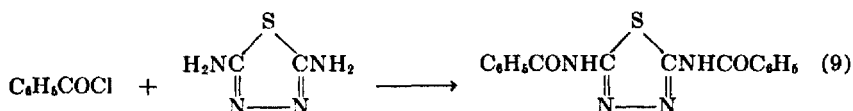
⁵ Busch and Lotz, *J. prakt. Chem.*, **90**, 257 (1914).

⁶ Stolle and Fehrenbach, *J. prakt. Chem.*, **122**, 289 (1929).

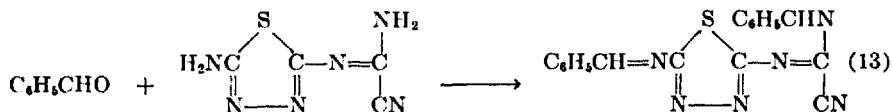
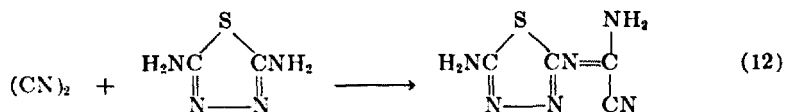
⁷ Arndt and Milde, *Ber.*, **54**, 2089 (1921); *Ber.*, **55**, 341 (1922).

⁸ Fromm, Layer, and Nerz, *Ann.*, **433**, 1 (1923).

formed dibenzoyl and diacetyl derivatives, but only a monobenzal derivative (9,10). Treating 2,5-diamino-1,3,4-thiadiazole with phenyl isothiocyanate produced substitution on only one of the amine groups (11). Heating this thiourea with acetic anhydride gave 2,5-diacetylamino-1,3,4-thiadiazole.



The 2,5-diamino-1,3,4-thiadiazole and cyanogen yielded only a mono-substituted product (12). Benzaldehyde and this cyanoamidine afforded the dibenzal derivative (13).



Fromm *et al.*⁹ synthesized 2,5-dianilino-1,3,4-thiadiazole by oxidizing 1,6-diphenylbithiourea with either ferric chloride, iodine, or hydrogen peroxide. This compound formed a dibenzoyl derivative through the use of the Schotten-Baumann reaction.

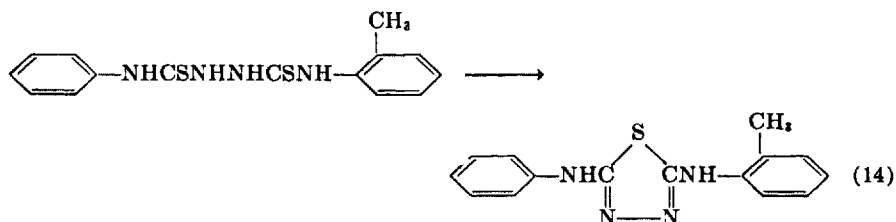
Fromm and Jokl¹⁰ obtained 2-amino-5-anilino-1,3,4-thiadiazole by oxidizing 1-phenylbithiourea. This compound formed monobenzal, monobenzoyl, and diacetyl derivatives. Patel and Chakravarti¹¹ prepared a

⁹ Fromm *et al.*, *Ann.*, **433**, 1 (1923).

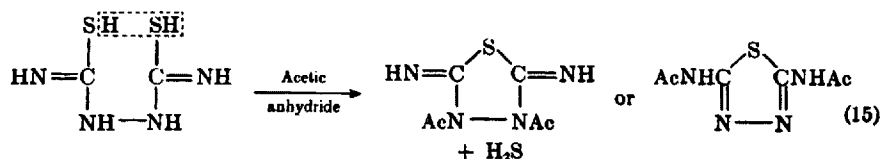
¹⁰ Fromm and Jokl, *Monatsh.*, **44**, 297 (1923).

¹¹ Patel and Chakravarti, *J. Indian Inst. Sci.*, **A13**, 85 (1930); *Chem. Abstr.*, **24**, 4770 (1930).

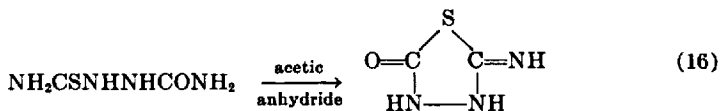
number of unsymmetrically substituted 2,5-diamino-1,3,4-thiadiazoles by oxidizing the corresponding 1,6-substituted bithioureas (14).



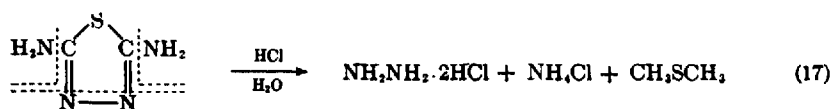
Guha¹² investigated the action of acetic anhydride on various substituted alkyl and aryl bithioureas. He found that ring closure occurred with the elimination of hydrogen sulfide (15). Hydrolysis with hydro-



chloric acid gave the diamine or diimine. This method was used to prepare a large number of 2,5-diamino-1,3,4-thiadiazoles. The monothiobiurea gave the 2-amino-5-thiadiazolone instead of the expected 2,5-diamino-1,3,4-thiadiazole or the 2,5-diamino-1,3,4-oxadiazole (16). In his proof



of structure Guha showed that the compound formed was not a mercapto-4,1,2-triazole. It was insoluble in alkali; it could not be desulfurized with mercuric oxide, nor would it form a disulfide or a thioether. The decomposition of 2,5-diamino-1,3,4-thiadiazole with concentrated hydrochloric acid at high temperatures and pressures gave hydrazine hydrochloride, ammonium chloride, and dimethyl sulfide (17).



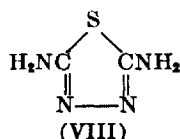
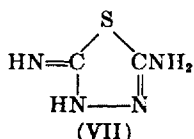
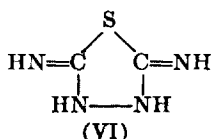
¹² Guha, *J. Am. Chem. Soc.*, **45**, 1036 (1923).

unused phenylthiosemicarbazide (20,21). The 1,4-diarylthiosemicarbazides and sulfur chloride produced amorphous polymers.

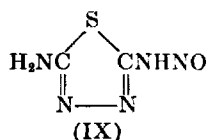
Guha and Mehta¹⁵ found that heat alone would give the same type of ring closure of 1,6-diarylthioureas as would hydrochloric acid. Heating the 1-aryl bithioureas gave 4-aryl-2-mercapto-5-amino-4,1,2-triazoles.

According to Patel and Chakravarti,¹⁶ refluxing 1,6-diphenylbithiourea in pyridine formed 2,5-dianilino-1,3,4-thiadiazole.

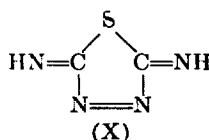
Stolle and Fehrenbach,¹⁷ in reviewing the literature, came to the conclusion that 2,5-diamino-1,3,4-thiadiazole existed in three forms (VI, 2,5-diimino-1,3,4-thiadiazolidine; VII, 2-amino-5-imino-1,3,4-thiadiazoline; VIII, 2,5-diamino-1,3,4-thiadiazole).



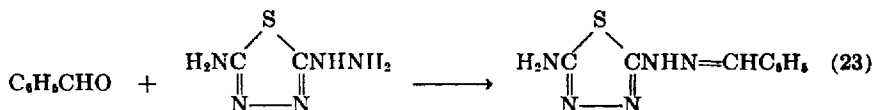
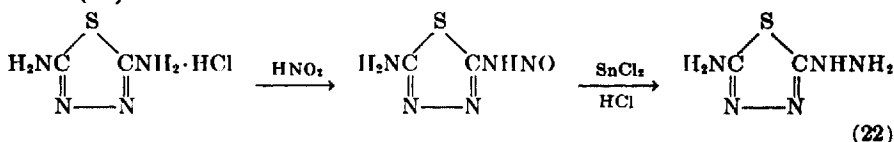
Stolle and Fehrenbach found that the addition of nitrous acid to this thiadiazole in concentrated hydrochloric acid or acetic acid gave 2-nitroso-amino-5-amino-1,3,4-thiadiazole (IX) rather than the azo compound of Busch and Lotz¹⁸ (X). Reduction of IX with stannous chloride gave 2-



rather than



hydrazino-5-amino-1,3,4-thiadiazole (22). This hydrazine with a large excess of benzaldehyde yielded 2-benzalhydrazino-5-amino-1,3,4-thiadiazole (23).



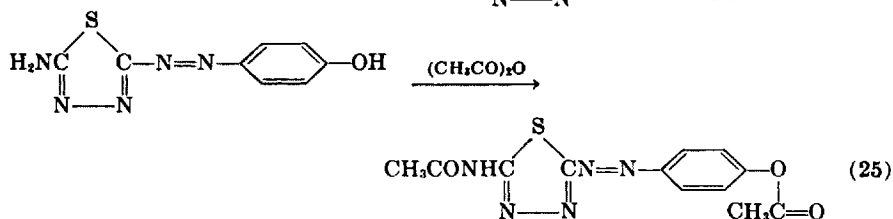
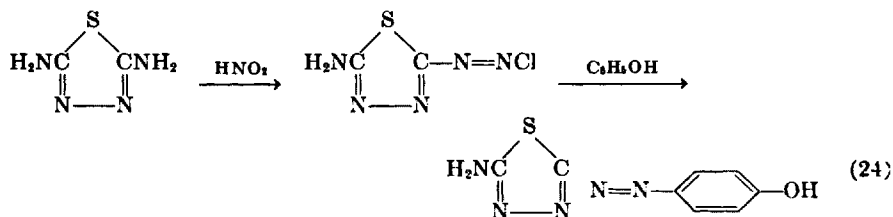
¹⁵ Guha and Mehta, *J. Indian Inst. Sci.*, A21, 41 (1938); *Chem. Abstr.*, 33, 598 (1939).

¹⁶ Patel and Chakravarti, *J. Indian Inst. Sci.*, A13, 85 (1930); *Chem. Abstr.*, 24, 4770 (1930).

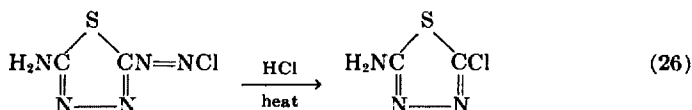
¹⁷ Stolle and Fehrenbach, *J. prakt. Chem.*, 122, 289 (1929).

¹⁸ Busch and Lotz, *J. prakt. Chem.*, 90, 257 (1914).

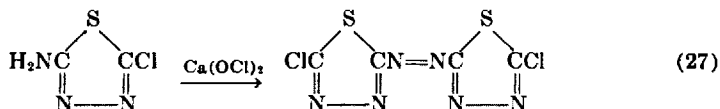
Diazotization in a cold concentrated hydrochloric acid solution gave 5-amino-2-(1,3,4-thiadiazolyl) diazonium chloride which will couple with phenol (24). Acetylation of this compound with acetic anhydride furnished the diacetyl derivative (25).



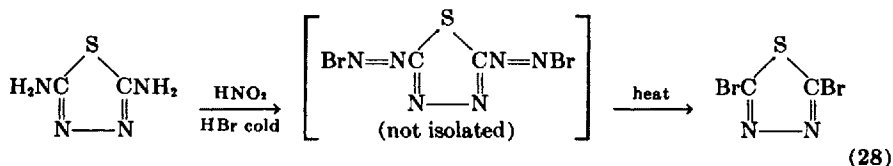
Heating 5-amino-2-(1,3,4-thiadiazolyl) diazonium chloride in a concentrated hydrochloric acid gave 2-chloro-5-amino-1,3,4-thiadiazole (26).



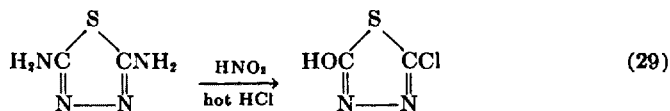
Calcium hypochlorite oxidized 2-chloro-5-amino-1,3,4-thiadiazole to 2,2'-dichloro-5,5'-azo-1,3,4-thiadiazole and a small amount of 2,5-dichloro-1,3,4-thiadiazole (27). Stolle and Fehrenbach obtained 2,5-dichloro-1,3,4-



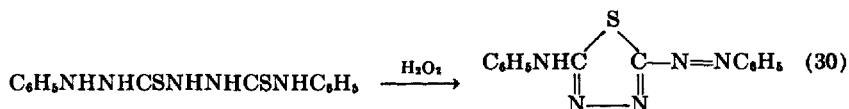
thiadiazole by diazotizing either 2-chloro-5-amino-1,3,4-thiadiazole or 2,5-diamino-1,3,4-thiadiazole in concentrated hydrochloric acid and then warming the solution. 2,5-Dibromo-1,3,4-thiadiazole was synthesized in a like manner (28). Passing nitrous acid through a hot solution of 2,5-



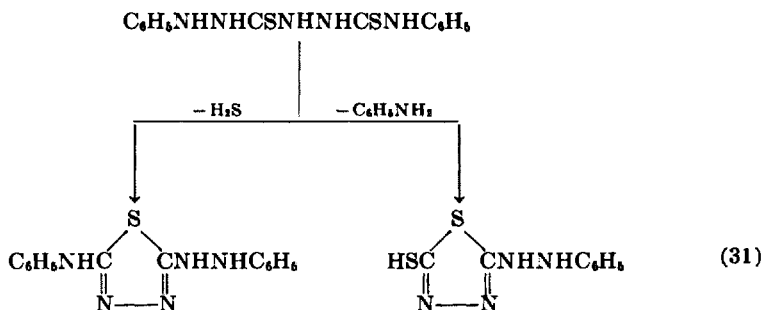
diamino-1,3,4-thiadiazole in hydrochloric acid produced 2-hydroxy-5-chloro-1,3,4-thiadiazole (29).



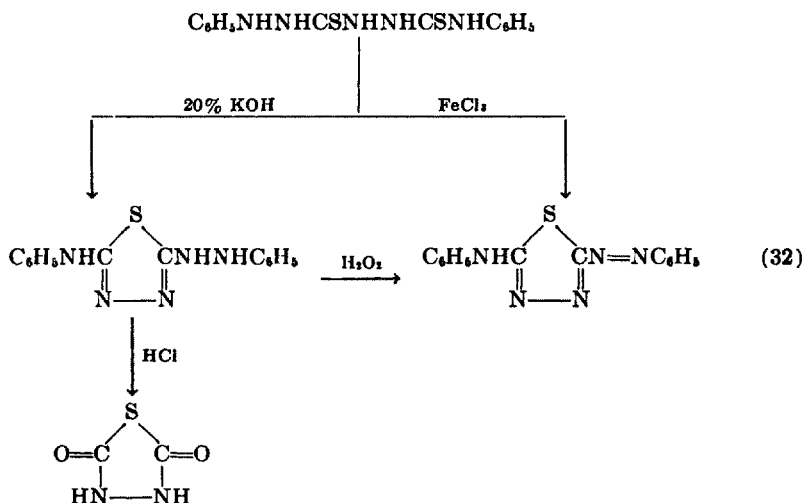
Guha and Roy-Choudhury¹⁹ studied the preparation of 2-phenylhydrazino-5-anilino-1,3,4-thiadiazole. Oxidation of 1-anilino-6-phenylbithiourea with hydrogen peroxide gave 2-phenylazo-5-anilino-1,3,4-thia-



diazole instead of the expected 2-phenylhydrazino-5-anilino-1,3,4-thiadiazole (30).



Digestion of 1-anilino-6-phenylbithiourea with alcoholic potassium hydroxide yielded two 1,3,4-thiadiazoles (31). Oxidation of 2-phenyl-

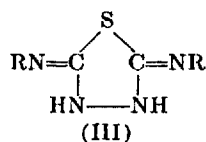
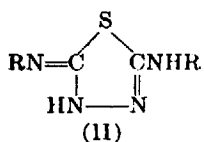
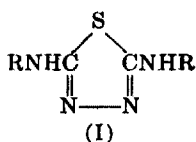


¹⁹ Guha and Roy-Choudhury, *J. Indian Chem. Soc.*, **5**, 163 (1928); *Chem. Abstr.*, **23**, 1397 (1929).

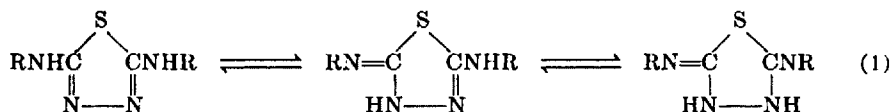
hydrazino-5-anilino-1,3,4-thiadiazole gave 2-phenylazo-5-anilino-1,3,4-thiadiazole and hydrolysis with concentrated hydrochloric acid produced 1,3,4-thiadiazolidine-2,5-dione (32).

Discussion of the Chemistry of the 2,5-Diamino-1,3,4-thiadiazoles

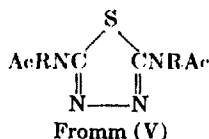
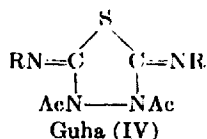
It will be noted that structures (I, II, and III) have been used loosely and interchangeably in discussing the history and the chemistry of these



compounds. Stolle and Fehrenbach¹ have postulated that these three forms exist in tautomeric equilibrium, which although not definitely proved is highly probable (1).



The proof of structures has been incomplete and these structures are largely the result of assumptions. For instance, the position of the acyl groups on the molecule after acylation is a matter of conjecture rather than positive proof. Guha *et al.*^{2,3} show them on the 3 and 4 positions (IV) while Fromm and others^{4,5} show the acetyl group on the amino groups (V).



The oxidation of substituted thiocarbamides, especially the substituted thioureas, involves a complex mechanism. Consider equations (2) and (3).

Hector in the first two papers referred to his products as 2,5-diaryl-amino-1,3,4-thiadiazoles, but in his later proof of structure (see discussion of 1,2,4-thiadiazolidines) he assigned the 2,4-diaryl-3,5-diimino-1,2,4-

¹ Stolle and Fehrenbach, *J. prakt. Chem.*, **122**, 289 (1929).

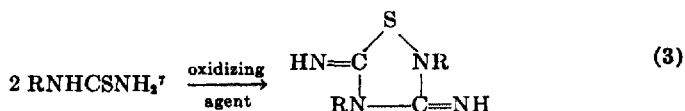
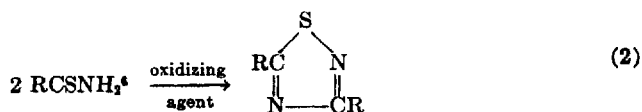
² Guha, *J. Am. Chem. Soc.*, **45**, 1036 (1923).

³ Guha and Mehta, *J. Indian Inst. Sci.*, **A21**, 41 (1938); *Chem. Abstr.*, **33**, 598, 599 (1939).

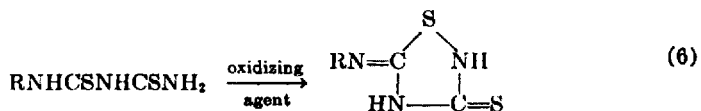
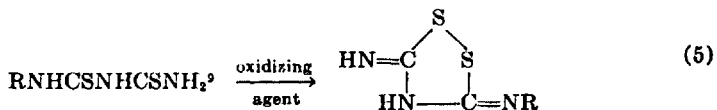
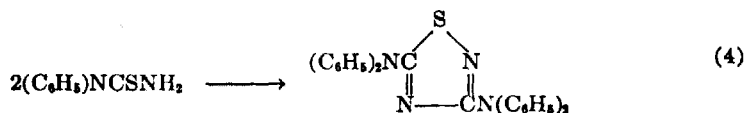
⁴ Fromm, Layer, and Nerz, *Ann.*, **433**, 1 (1923).

⁵ Stolle and Fehrenbach, *J. prakt. Chem.*, **122**, 289 (1929).

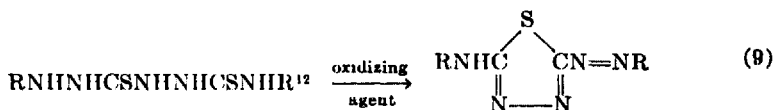
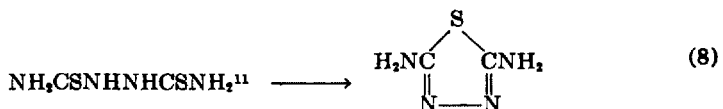
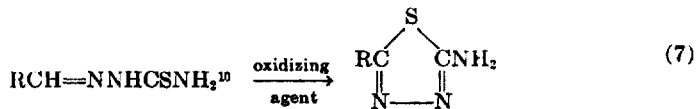
⁶ Hoffman and Gabriel, *Ber.*, **25**, 1578 (1892).



thiadiazolidine structure to these compounds. Chakravarti and De⁸ noted Hector's earlier work,⁷ but neglected his proof of structure. They oxidized a number of symmetrical and unsymmetrical dialkyl and diaryl thioureas and reported the products as 2,5-diarylimino-3,4-diaryl-1,3,4-thiadiazolidines. On the basis of Hector's work these compounds are probably 3,5-diarylimino-2,4-diaryl-1,2,4-thiadiazolidines (see Table XXII). In Chakravarti and De's work on the oxidation of *N,N*-diphenylthiourea⁸ the probable product is 3,5-di-(diphenylamino)-1,2,4-thiadiazole (4-6). For probable reaction see discussion on 1,2,4-thiadiazoles.



Probable reaction (see discussion on 1,2,4-thiadiazoles)



⁷ Hector, *Ber.*, 22, 1176 (1889); *Ber.*, 23, 357 (1890); *Ber.*, 25, Ref. 799 (1893); *Oeffers. Kongl. Vet. Akad.*, 1893, 79.

⁸ Chakravarti and De, *J. Indian Chem. Soc.*, 5, 661 (1928); *Chem. Abstr.*, 23, 1899 (1929).

An examination of these five oxidations shows that the mercapto group of the thiocarbamide is always affected. If an active methylene group is present, then the sulfur becomes attached to this carbon (7). If no active methylene group is present then another sulfur or a nitrogen atom is affected. In any case a stable five member ring analogous to benzene is formed. The 2-amino and 2,5-diamino-1,3,4-thiadiazoles resemble aniline in that the amines are diazotizable and can be replaced by halogens. The halogens are firmly bound as are the bromine atoms in 2,5-dibromo-1,3,4-thiadiazoles.

The action of hydrochloric acid, heat, alkali, acetic anhydride, or pyridine on bithiourea results in a number of products. Evidently a number of competing reactions take place. The mechanism of these reactions has not been wholly elucidated.

⁹ Fromm, *Ann.*, **275**, 20 (1893).

¹⁰ Young and Eyre, *J. Chem. Soc.*, **79**, 54 (1901).

¹¹ Fromm, Layer, and Nerz, *Ann.*, **433**, 1 (1923).

¹² Guha and Roy-Choudhury, *J. Indian Chem. Soc.*, **5**, 163 (1928); *Chem. Abstr.*, **23**, 1397 (1929).

TABLE XXI. Preparation of the 2,5-Diamino-1,3,4-thiadiazoles and Their Derivatives

No.	Substituent		Ref.	Method of preparation	Solubility	M.p., °C.
	2-Position	5-Position				
1	Amino	amino	1 2 3 4	$(\text{NH}_2\text{CSNH})_2 + \text{HCl}$ $(\text{NH}_2\text{CSNH})_2 + \text{HCl}$ $(\text{NH}_2\text{CSNH})_2 + \text{H}_2\text{O}_2$ $(\text{NH}_2\text{CSNH})_2 + \text{acetic anhydride}$ $\longrightarrow$	— water water —	— 221–3 210 — 210–11
2	Acetamido	acetamido	3 2	$\text{AcNHC} \begin{array}{c} \diagup \text{CNHAc} \\ \text{N} \text{---} \text{N} \end{array} + \text{dil. HCl}$ compound 1 + acetic anhydride	water, alc.	280 (darkens 291), over 315
3	Benzamido	benzamido	4	$(\text{NH}_2\text{CSNH})_2 + \text{acetic anhydride}$	glacial acetic acid	over 315
4	Amino	benzylideneimino	3	compound 1 + benzoyl chloride + alkali	alc.	280
5	Amino	$\text{C}_6\text{H}_5\text{NHCSNH}$	3	compound 1 + benzaldehyde	alc., benzene	218
			3	compound 1 + $\text{C}_6\text{H}_5\text{NCS}$	alc.	(discolors 210), over 280
6	Amino	NH_2 $\mid$ —N=C— $\mid$ CN	3	compound 1 + $(\text{CN})_2$	alc.	(discolors 200), over 280
7	Benzylideneimino	$\text{N=CHC}_6\text{H}_5$ $\mid$ —N=C— $\mid$ CN	3	compound 6 + benzaldehyde	—	—

(Table continued)

TABLE XXI (Continued)

Substituent			Ref.	Method of preparation	Solubility	M.p., °C.
No.	2-Position	5-Position				
8	Amino	nitroscamino	5	compound 1 + HNO ₂ + acetic acid	alc.	explodes 160
9	Amino	hydrazino	5	compound 8 + SnCl ₄ + HCl	water as the HCl	207 (dec.)
10	Amino	benzylidene hydra-zino	5	compound 9 + benzaldehyde	alc.	232 (dec.)
11	Amino	<i>p</i> -hydroxyphenylazo	5	compound 1 + HNO ₂ + phenol + conc. HCl	alc.	260 (dec.)
12	Acetamido	<i>p</i> -acetoxyphehylazo	5	compound 11 + acetic anhydride	acetic acid	315 (dec.)
13	Amino	chloro	5	compound 1 + cold HCl + 1 HNO ₂ + heat	hot water	(HCl, H ₂ O, 111); 192 (dec.)
14	Chloro	chloro	5	compound 1 + cold HCl + 2 HNO ₂ + heat	alc.	7
15	Chloro	hydroxy	5	compound 1 + hot HCl + HNO ₂	ether, alc., benzene	107
16	Bromo	bromo	5	compound 1 + HBr + HNO ₂ + cold + heat	alc., ether	111
17	—N=	chloro	5	compound 1 + Ca(OCi) ₂	acetic acid	247 (dec.)
18	Amino	2,2'-Dichloro-5,5'-azo-1,3,4-thiadiazole sulfanilamido	6	compound 1 + <i>p</i> -acetylsulfanilyl chloride + hydrolysis	alkali	259
19	Acetylsulfanilamido	acetylsulfanilamido	7	compound 1 + pyridine + <i>p</i> -acetylsulfanilyl chloride	acetic acid	252-4
20	Sulfanilamido	sulfanilamido	7	anilyl chloride	alc.	223
21	Amino	anilino	8	hydrolysis of compound 20	water, alc.	205
22	Acetamido	acetanilido	4	NH ₂ CSNHNHCSNHCH ₃ + H ₂ O ₂	alc.	215
23	Benzylideneimino	anilino	8	hydrolysis of compound 22	alc.	—
24	Benzamido	anilino	8	NH ₂ CSNHNHCSNHCH ₃ + acetic anhydride	alc.	264
25	Acetamido	acetyl- <i>o</i> -toluidino	9	compound 21 + acetic anhydride	—	264
26	Amino	<i>o</i> -toluidino	9	compound 21 + benzaldehyde	alc.	264
27	Acetamido	acetyl- <i>p</i> -toluidino	9	compound 21 + benzoyl chloride + alkali	alc.	278
28	Amino	<i>p</i> -toluidino	9	<i>o</i> -CH ₃ C ₆ H ₄ NHCSNHNHCSNH ₂ + acetic anhydride	alc.	264
			9	hydrolysis of compound 25	alc.	206-7
			9	<i>p</i> -CH ₃ C ₆ H ₄ NHCSNHNHCSNH ₂ + acetic anhydride	—	298
			9	hydrolysis of compound 27	alc.	203

Substituent		Ref.	Method of preparation	Solubility	M.p., °C.
No.	2-Position				
29	Methylamino	1	$(\text{CH}_3\text{NHCSNH})_2 + \text{HCl}$	water, alc., benzene	1 H ₂ O, 175-6
		4	hydrolysis of compound 30		180, (HCl, 235)
30	Acetylmethylamino	4	$(\text{CH}_3\text{NHCSNH})_2 + \text{acetic anhydride}$	water	219
31	Methylamino	4	compound 29 + HNO_3	alc.	151 (picrate, 205)
32	Ethylamino	1	—	alc.	136
33	Acetylmethylamino	2	$(\text{C}_2\text{H}_5\text{NHCSNH})_2 + \text{HCl}$	water, alc., ether	173
34	Ethylamino	2	compound 32 + acetic anhydride	alc.	165
		2	compound 32 + HNO_3	alc.	sinters 135-45
35	Ethylamino	2	compound 32 + methyl iodide + 100°C.	water, alc.	HI, 181
36	Acetylmethylamino	4	$(\text{CH}_3=\text{CHCH}_2\text{NHCSNH})_2 + \text{acetic anhydride}$	water	113
37	Allylamino	4	hydrolysis of compound 36	alc.	151
38	Anilino	10	$(\text{C}_6\text{H}_5\text{NHCSNH})_2 + \text{COCl}_2$	alc.	239-40
		11	$(\text{C}_6\text{H}_5\text{NHCSNH})_2 + 200^\circ\text{C.}$	—	240
		3	$(\text{C}_6\text{H}_5\text{NHCSNH})_2 + \text{oxidizing agent}$	acetic acid	243
		4	hydrolysis of compound 39	benzene	247
		9	$(\text{C}_6\text{H}_5\text{NHCSNH})_2 + \text{heat}$	—	248
		12	$\text{C}_6\text{H}_5\text{NHCSNHNH}_2 + \text{S}_2\text{O}_3$	alc., acetone	247
		12	$(\text{C}_6\text{H}_5\text{NHCSNH})_2 + \text{boiling pyridine}$	—	247
		13	$(\text{C}_6\text{H}_5\text{NHCSNH})_2 + \text{HCl}$	—	249
39	Acetylanilino	4	$(\text{C}_6\text{H}_5\text{NHCSNH})_2 + \text{acetic anhydride}$	alc., benzene	224
		13	compound 38 + acetic anhydride	—	224
		9	—	—	224
		12	—	—	225

(Table continued)

TABLE XXI (Continued)

No.	Substituent		Ref.	Method of preparation	Solubility	M.p., °C.
	2-Position	5-Position				
40	$\text{C}_6\text{H}_5\text{N}=\text{C}$ S N=N 2,5-diphenylimino- $\Delta^4,1,3,4$ -thiadiazoline	$\text{C}=\text{NC}_6\text{H}_5$ N=N	11	compound 38 + HgO	—	113
41	<i>p</i> -Toluidino	<i>p</i> -toluidino	4 9	hydrolysis of compound 42 (<i>p</i> - $\text{CH}_3\text{C}_6\text{H}_4\text{NHCSNH}_2$) ₂ + heat (185°C.) (<i>p</i> - $\text{CH}_3\text{C}_6\text{H}_4\text{NHCSNH}_2$) ₂ + HCl	alc.	249-50 246-7 246-7
42	Acetyl- <i>p</i> -toluidino	acetyl- <i>p</i> -toluidino	12 4 9 12 9	<i>p</i> - $\text{CH}_3\text{C}_6\text{H}_4\text{NHCSNH}_2$ + S_2Cl_2 (<i>p</i> - $\text{CH}_3\text{C}_6\text{H}_4\text{NHCSNH}_2$) ₂ + acetic anhydride alc. — compound 41 + acetic anhydride —	— — — — —	248 235 166-7 172 166-7
43	$\text{p-CH}_3\text{C}_6\text{H}_4\text{N}=\text{C}$ S N=N 2,5-Di- <i>p</i> -toluidino- $\Delta^4,1,3,4$ -thiadiazoline	$\text{C}=\text{NC}_6\text{H}_4\text{CH}_3$ - <i>p</i> N=N	9	compound 41 + KMnO_4	alc.	167
44	<i>o</i> -Toluidino	<i>o</i> -toluidino	9	hydrolysis of compound 45 (<i>o</i> - $\text{CH}_3\text{C}_6\text{H}_4\text{NHCSNH}_2$) ₂ + heat (<i>o</i> - $\text{CH}_3\text{C}_6\text{H}_4\text{NHCSNH}_2$) ₂ + HCl	alc.	217
45	Acetyl- <i>o</i> -toluidino	acetyl- <i>o</i> -toluidino	13 12 12 9, 13	<i>o</i> - $\text{CH}_3\text{C}_6\text{H}_4\text{NHCSNH}_2$ + S_2Cl_2 compound 44 + acetic anhydride (<i>o</i> - $\text{CH}_3\text{C}_6\text{H}_4\text{NHCSNH}_2$) ₂ + acetic anhydride	— — alc.	217 (dec.) 222 257 262 (dec.)
46	<i>p</i> -Bromoanilino	<i>p</i> -bromoanilino	4	hydrolysis of compound 47 ride	alc., benzene	251 241

Substituent		Ref.	Method of preparation	Solubility	M.p., °C.
No.	2-Position				
47	Acetyl- <i>p</i> -bromo-anilino	4	(<i>p</i> -BrC ₆ H ₄ NHCSNH) ₂ + acetic anhydride	alc.	229
48	<i>m</i> -Chloroanilino	4	hydrolysis of compound 49	alc.	170
49	Acetyl- <i>m</i> -chloro-anilino	4	(<i>m</i> -ClC ₆ H ₄ NHCSNH) ₂ + acetic anhydride	—	—
50	2,5-Dichloroanilino	4	same as compound 48	methanol	186-7
51	α -Naphthylamino	4	hydrolysis of compound 52	pyridine	275-6
52	Acetyl- α -naphthyl-amino	4	(α -C ₁₀ H ₇ NHCSNH) ₂ + acetic anhydride	ether	270
53	Anilino	12	<i>o</i> -CH ₃ C ₆ H ₄ NHCSNHNHCSNHCH ₃ + I ₂	alc.	200
54	Acetylanilino	12	compound 53 + acetic anhydride	alc.	223
55	Anilino	12	same as compound 53	alc.	216
56	Acetylanilino	12	compound 55 + acetic anhydride	alc.	177
57	<i>o</i> -Toluidino	12	same as compound 53	alc.	190
58	Acetyl- <i>o</i> -toluidino	12	compound 57 + acetic anhydride	—	231
59	2,4-Xylydino	12	same as compound 53	—	190
60	Acetyl-2,4-xylydino	12	compound 60 + acetic anhydride	—	263
61	2,4-Xylydino	12	same as compound 53	alc.	205
62	Acetyl-2,4-xylydino	12	compound 61 + acetic anhydride	—	224
63	Anilino	12	same as compound 53	alc.	189
64	Acetylanilino	12	compound 63 + acetic anhydride	alc.	120

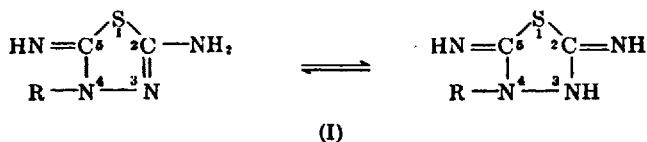
¹ Busch and Lotz, *J. prakt. Chem.*, 90, 257 (1914).² Freund and Imgart, *Ber.*, 28, 946 (1895).³ Fromm, Layer, and Nerz, *Ann.*, 433, 1 (1923).⁴ Guha, *J. Am. Chem. Soc.*, 45, 1036 (1923).⁵ Stolle and Fehrenbach, *J. prakt. Chem.*, 122, 289 (1929).⁶ Anderson, Faith, Marson, Winnek, and Roblin, *J. Am. Chem. Soc.*, 64, 2902 (1942).⁷ Guha and Das Gupta, *J. Indian Chem. Soc.*, 22, 79 (1945);*Chem. Abstr.*, 40, 1152 (1946).⁸ Fromm and Joki, *Monatsh.*, 44, 297 (1923).⁹ Guha and Mehta, *J. Indian Inst. Sci.*, A21, 41 (1938);*Chem. Abstr.*, 33, 598 (1939).¹⁰ Freund and Wischewiansky, *Ber.*, 26, 2877 (1893).¹¹ Busch and Schmidt, *Ber.*, 46, 2240 (1913).¹² Patel and Chakravarti, *J. Indian Inst. Sci.*, A13, 85 (1930);*Chem. Abstr.*, 24, 4770 (1930).¹³ Janniah and Guha, *J. Indian Inst. Sci.*, A16, 11 (1933);*Chem. Abstr.*, 27, 3711 (1933).

TABLE XXII. Compounds Erroneously Called 2,5-Diimino-1,3,4-thiadiazolidines (Hector's Compounds Are Not Included)

No.	Structures called 1,3,4-thiadiazolidines in the literature		Probable structures of the 1,2,4-thiadiazolidines (see discussion)		M.p., °C.	Ref.
	Groups on the 2- and 5-positions	Groups on the 3- and 4-positions	Groups on the 3- and 5-positions	Groups on the 2- and 4-positions		
1	Phenylimino	phenyl	phenylimino	phenyl	228-30	1
2	<i>p</i> -Tolylimino	<i>p</i> -tolyl	<i>p</i> -tolylimino	<i>p</i> -tolyl	261	1
3	<i>o</i> -Tolylimino	<i>o</i> -tolyl	<i>o</i> -tolylimino	<i>o</i> -tolyl	249	1
4	<i>m</i> -Xylylimino	<i>m</i> -xylyl	<i>m</i> -xylylimino	<i>m</i> -xylyl	247	1
5	1-Naphthylimino	1-naphthyl	1-naphthylimino	1-naphthyl	285	1
6	2-Naphthylimino	2-naphthyl	2-naphthylimino	2-naphthyl	288	1
7	Benzylimino	H	imino	benzyl	94	1
8	Phenylethylimino	H	imino	phenylethyl	107-9	1
9	Diphenylamino, oxo	H	diphenylamino, oxo	H	155	1

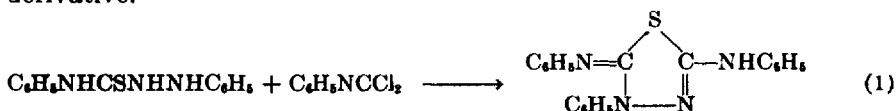
¹ Chakravarti and De, *J. Indian Chem. Soc.*, **5**, 661 (1928); *Chem. Abstr.*, **23**, 1899 (1929).

2-Amino-5-imino- Δ^2 -1,3,4-thiadiazolines and Their Derivatives (I)



This group of compounds is closely related to 2,5-diamino-1,3,4-thiadiazoles, the only difference being that the alkyl or aryl group in the 4-position does not migrate between the 5-imino group and the 4-nitrogen.

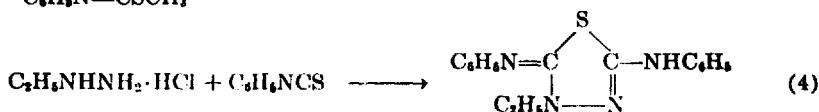
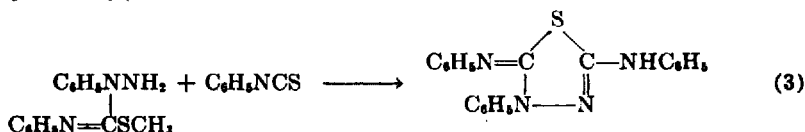
Freund and König¹ allowed phenyl isocyanodichloride to react with 1,4-diphenyl thiosemicarbazide and obtained 2-anilino-4-phenyl-5-phenylimino- Δ^2 -1,3,4-thiadiazoline (1). This compound formed a mononitroso derivative.



Marckwald and Sedlaczek² heated phenyl isothiocyanate with 2-methyl-4-phenyl thiosemicarbazide. The resultant product was probably 2-anilino-4-methyl-5-phenylimino- Δ^2 -1,3,4-thiadiazoline (2). Busch and



Holzmann³ found that phenyl isothiocyanate would also react with the α -S-methyl-1,4-diphenyl isothiosemicarbazide to form 2-anilino-4-phenyl-5-phenylimino- Δ^2 -1,3,4-thiadiazoline (3). Methylation took place on the nitrogen of the anilino group. Busch and Schmidt⁴ devised a modification of this method in that they used a substituted hydrazine and phenyl isothiocyanate (4).



¹ Freund and König, *Ber.*, 26, 2869 (1893).

² Marckwald and Sedlaczek, *Ber.*, 29, 2921 (1896).

³ Busch and Holzmann, *Ber.*, 34, 320 (1901).

⁴ Busch and Schmidt, *J. prakt. Chem.*, 130, 342 (1931).

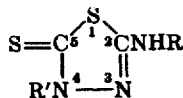
TABLE XXIII. Preparation of 2-Amino-5-imino-1,3,4-thiadiazolines

No.	Substituents			Ref.	Method of preparation		Solubility	M.p., °C.
	2-Position	4-Position	5-Position					
1	Anilino	methyl	phenylimino	1	$\text{C}_6\text{H}_5\text{NCS} + \text{NH}_2\text{NCH}_2\text{CSNHC}_6\text{H}_5 +$ heat (100°C.)	alc.		175
2	Anilino	ethyl	phenylimino	2	$\text{C}_6\text{H}_5\text{NCS} + \text{C}_2\text{H}_5\text{NHNH} \cdot \text{HCl}_2$	alc., benzene		147
3	Anilino	benzyl	phenylimino	2	same as 2	alc.		128 (HCl, 295 dec.)
4	Anilino	phenyl	phenylimino	3 4	$\text{C}_6\text{H}_5\text{NCCl}_2 + \text{C}_6\text{H}_5\text{NHNHCSNHC}_6\text{H}_5$ $\text{C}_6\text{H}_5\text{N}-\text{NH}_2 + \text{C}_6\text{H}_5\text{NCS}$	ether, benzene, CHCl_3 , alc.		154 155-6
5	N-Methylamilino	phenyl	phenylimino	4	$\text{C}_6\text{H}_5\text{N}=\text{C}-\text{SCH}_3$ methyl iodide + compound 4	ether, alc., benzene		143-4
6	N-Nitrosoamilino	phenyl	phenylimino	3	nitrous acid + compound 4	alc., ether, CHCl_3 , benzene		110 dec.
7	Phenylazo	phenyl	phenylimino	3	$\text{C}_6\text{H}_5\text{N}=\text{NCSNHNHC}_6\text{H}_5 + \text{C}_6\text{H}_5\text{NCCl}_2$	benzene, CHCl_3 , gl. acetic acid, alc.		180-1
8	Phenylhydrazo	phenyl	phenylimino	3	reduction of compound 7	alc.		150

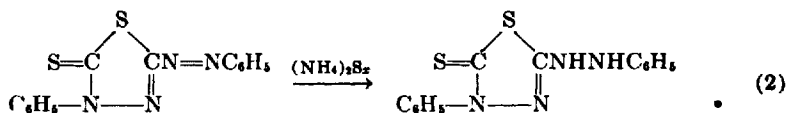
¹ Marckwald and Sedlaczek, *Ber.*, 29, 2920 (1896).³ Freund and König, *Ber.*, 26, 2869 (1893).² Busch and Schmidt, *J. prakt. Chem.*, 130, 342 (1931).⁴ Busch and Holzmann, *Ber.*, 34, 320 (1901).

$$\begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{HSC}^5 \quad \text{CNHR}^2 \\ \parallel \quad \parallel \\ \text{N}^4 \text{---} \text{N}^3 \end{array}$$

(I)



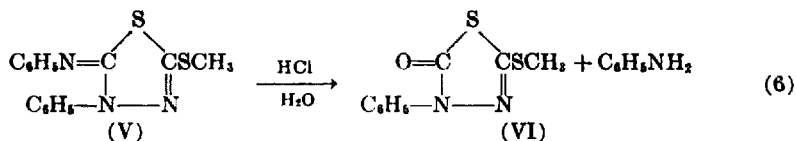
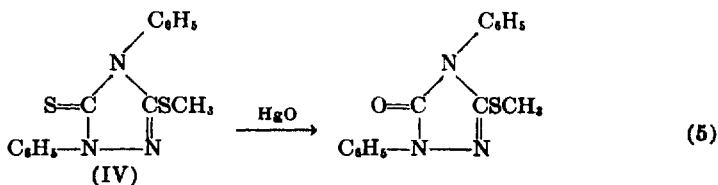
(II)

$$\text{C}_6\text{H}_5\text{N}=\text{NCSNHHC}_6\text{H}_5 \xrightarrow{\text{CSCl}_2} \begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{S}=\text{C} \quad \text{CN}=\text{NC}_6\text{H}_5 \\ | \quad \quad | \\ \text{C}_6\text{H}_5-\text{N} \quad \text{N} \\ \text{(III)} \end{array} \quad (1)$$

$$\begin{array}{ccc}
 \begin{array}{c} \text{C}_6\text{H}_5 \\ | \\ \text{N} \text{---} \text{H} \text{---} \text{S} \\ | \quad | \\ \text{S}=\text{C} \quad \text{C}=\text{S} \\ | \quad | \\ \text{C}_6\text{H}_5 \text{---} \text{N} \text{---} \text{N} \\ || \\ \text{N} \end{array} & \longrightarrow & \begin{array}{c} \text{C}_6\text{H}_5 \\ | \\ \text{N} \\ | \quad | \\ \text{S}=\text{C} \quad \text{C}=\text{S} \\ | \quad | \\ \text{C}_6\text{H}_5 \text{---} \text{N} \text{---} \text{N} \\ || \\ \text{N} \end{array}
 \end{array} \quad (3)$$

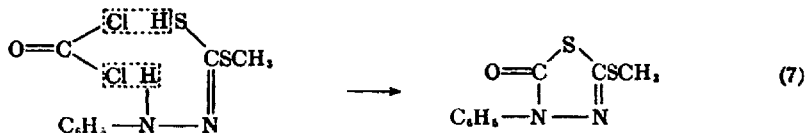

¹ Freund and Kuh, *Ber.*, 23, 2831 (1890).

* Freund, *Ber.*, 24, 4178 (1891).

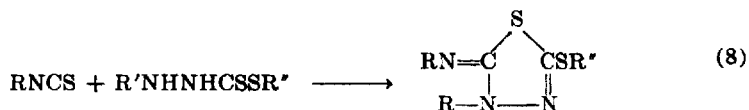
³ Busch and Wolpert, *Ber.*, **34**, 304 (1901).



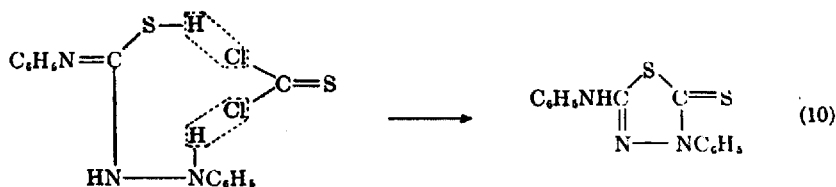
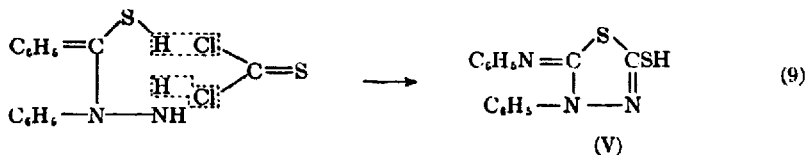
one, was also prepared from phosgene and methyl 2-phenyldithiocarbazate (7).



The thioethers could be synthesized in two ways: (a) from the mercaptan with an alkyl halide, and (b) from an aryl isothiocyanate and an ester of 2-aryldithiocarbazate (8). Busch and Holzmann⁴ obtained the

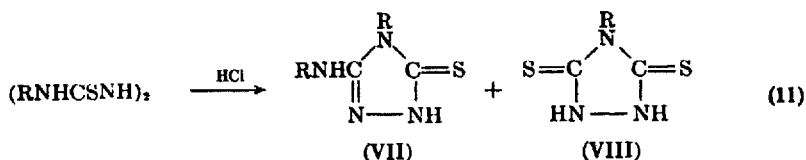


same compound (V) with thiophosgene and 2,4-diphenylthiosemicarbazide (9). 1,4-Diphenylthiosemicarbazide and thiophosgene yielded the other isomer (10).

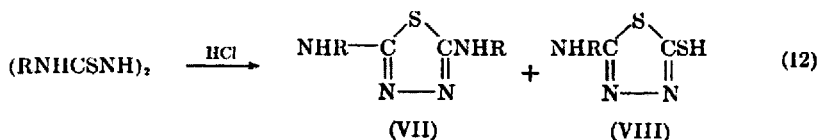


⁴ Busch and Holzmann, *Ber.*, **34**, 320 (1901).

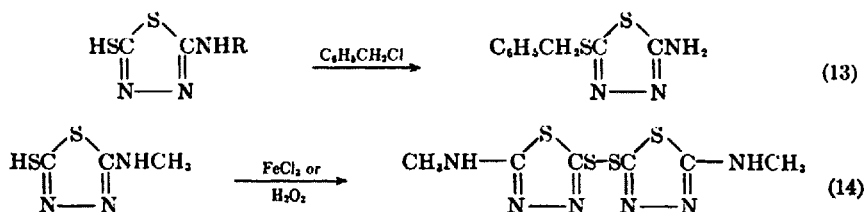
Freund and Imgart⁵ obtained two products when they treated bi-thioureas with hydrochloric acid. One of these was called dithiourazole (11). (For a more complete discussion see the section on 2,5-diamino-



1,3,4-thiadiazoles.) Busch and co-workers^{6,7} disagreed and showed that equation (12) applied and that compounds VII and VIII were 2,5-diamino-



1,3,4-thiadiazole and 2-amino-5-mercaptothiadiazole, respectively (12). Compound VIII showed the characteristics of a single mercapto group; it was soluble in alkali and a single alkyl or aralkyl group was added by alkylation (13). The disulfide was obtained by oxidation with hydrogen peroxide or ferric chloride (14). Guha⁸ completed the proof of structure



of these compounds. Only the monosodium and monosilver salts were formed. Titration with iodine showed that only one mercaptan group was present. Decomposition by heating in hydrochloric acid at 190–200°C. yielded hydrazine, ammonium chloride, carbon disulfide, and carbon dioxide.

Guha and Mehta⁹ found that heat as well as concentrated hydrochloric acid would cyclize some of the bi-thioureas (15).

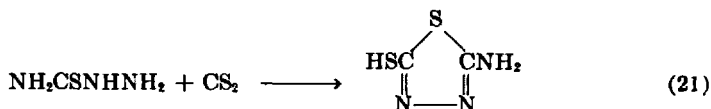
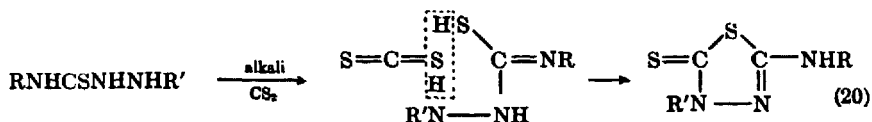
⁵ Freund and Imgart, *Ber.*, 28, 948 (1895).

⁶ Busch and Schmidt, *Ber.*, 46, 2240 (1913).

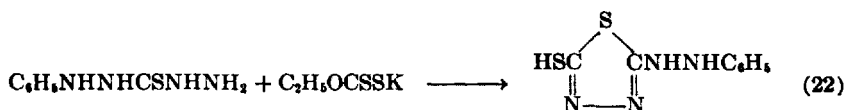
⁷ Busch and Lotz, *J. prakt. Chem.*, [2] 90, 257 (1914).

⁸ Guha, *J. Am. Chem. Soc.*, 44, 1502 (1922).

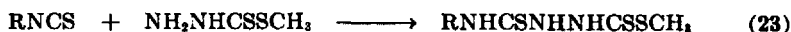
⁹ Guha and Mehta, *J. Indian Inst. Sci.*, A21, 41 (1938); *Chem. Abstr.*, 33, 598, 599 (1939).



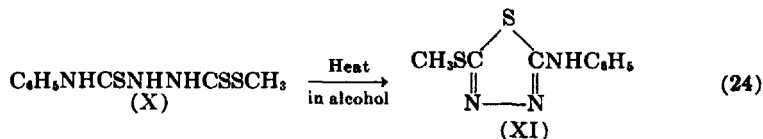
with carbon disulfide, while 4-phenylthiosemicarbazide gave 2-anilino-5-mercapto-1,3,4-thiadiazole. Guha and Roy-Choudhury¹⁰ used the reaction between potassium xanthate and 1-phenylthiocarbonylhydrazide to prepare 2-β-phenylhydrazino-5-mercapto-1,3,4-thiadiazole (22).



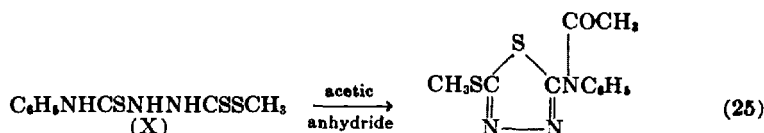
Guha and Guha¹² reported on the reactions between methyl dithiocarbazates and phenyl, tolyl, xylyl, and allyl isothiocyanates. The products of these reactions were substituted methyl 2-thiocarbamylthiocarbazates (23). Methyl phenylthiocarbamylthiocarbazate (X) was



cyclized by heating in alcohol and the resultant compound was 2-anilino-5-methylmercapto-1,3,4-thiadiazole (XI) (24). The action of acetic

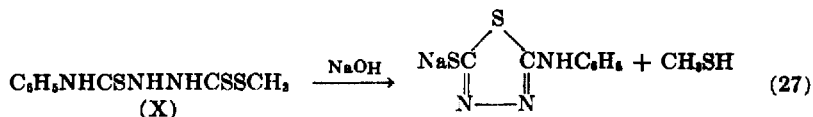
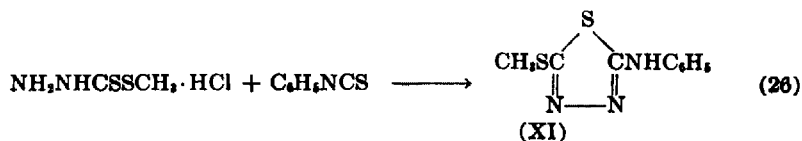


anhydride on compound X formed the acetyl derivative of compound XI (25). Compound XI was also obtained when an aqueous solution of

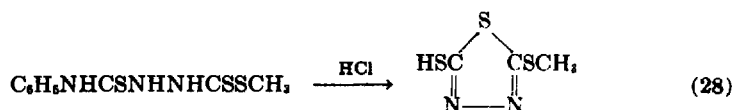


methyl dithiocarbazate hydrochloride was refluxed with phenyl isothiocyanate (26). Ring closure of compound X was also achieved with sodium

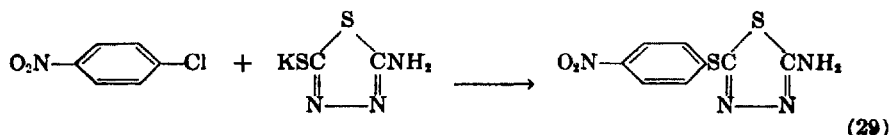
¹² Guha and Guha, *Quart. J. Indian Chem. Soc.*, **4**, 161 (1927); *Chem. Abstr.*, **21**, 3199 (1927).



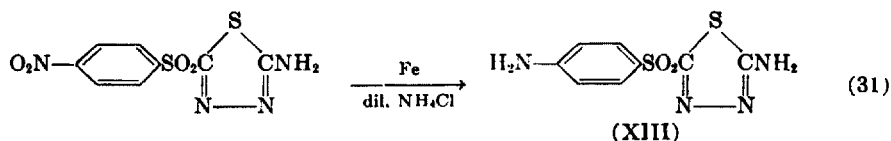
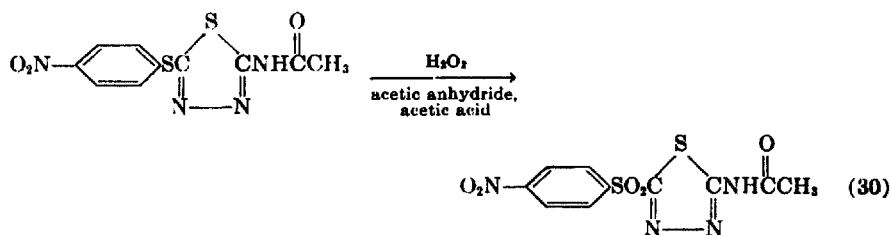
hydroxide. In this instance methyl mercaptan was eliminated (27). Hydrochloric acid effected ring closure with the elimination of aniline and the formation of 2-methylmercapto-5-mercapto-1,3,4-thiadiazole (28).



Bambas,¹³ in his synthesis of isosters of 4,4'-diaminodiphenylsulfone, allowed *p*-nitrochlorobenzene to react with the potassium salt of 2-amino-5-mercapto-1,3,4-thiadiazole (29). The resultant 2-amino-5-*p*-nitrophen-



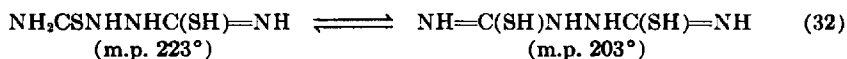
ylmercapto-1,3,4-thiadiazole was acetylated and oxidized to the sulfone with hydrogen peroxide and acetic anhydride (30). Deacetylation and reduction of compound XII yielded 2-amino-5-sulfanilyl-1,3,4-thiadiazole



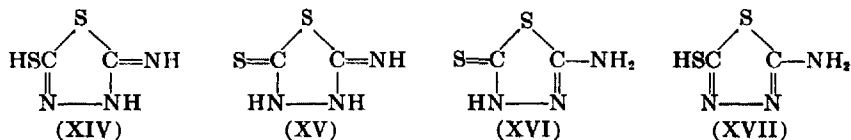
¹³ Bambas, *J. Am. Chem. Soc.*, **67**, 668 (1945).

(31). This compound (XIII) possessed antistreptococcal activity but very slight activity in pneumococcal and tuberculosis infections.

Guha¹⁴ reported three forms of the 2-amino-5-mercapto-1,3,4-thiadiazole; the first (as reported by Freund and Imgart¹⁵) melted at 245°C., yellowish prismatic needles; the second melted at 232°C., transparent white cubes; and the third melted at 224°C., brownish-yellow rectangular plates. All of these compounds had the same analyses and chemical properties. Janniah and Guha¹⁶ attempted to explain the discrepancies in the various melting points. They found that bithiourea exists in two forms (m.p. 203°C. and m.p. 223°C.). Bithiourea (m.p. 233°C.) was converted to the lower melting form by digestion with dilute hydrochloric acid for a short period of time. The chemical reactions of both forms were identical. The physical data, such as the melting points and ultraviolet absorption data, were different. The two forms were thought to be tautomeric (32). Both bithioureas, on being heated with dilute hydrochloric acid



for a long period of time or with concentrated hydrochloric acid for a short period of time, yielded a ring structure having the empirical structure $C_2H_3N_3S_2$, melting at $234^\circ C$. All the chemical properties of this compound were identical to Freund's compound, melting at $244-5^\circ C$.¹⁶ The acetyl derivatives of both compounds were indistinguishable. Hydrolysis of the acetyl derivatives of either form gave the higher melting form ($245^\circ C$.) possessing the same empirical composition ($C_2H_3N_3S_2$). Heating either bithiourea with concentrated hydrochloric acid for about a half hour yielded the higher melting form. It was also observed that, on standing for several weeks, the higher melting variety reverted to the lower melting form. The higher melting form did not respond to tests for an amino group (the identity of these tests was not disclosed). The question arose as to whether it was possible to explain the two isomers by any of the tautomers (XIV-XVII). Structures XVI and XVII were discarded because of the presence of an amine. Structures XIV and XV were not considered, since Janniah and Guha were doubtful that such tautomeric

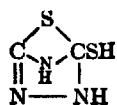


¹⁴ Guha, *J. Am. Chem. Soc.*, **44**, 1510 (1922).

¹⁵ Freund and Imgart, *Ber.*, 28, 948 (1895).

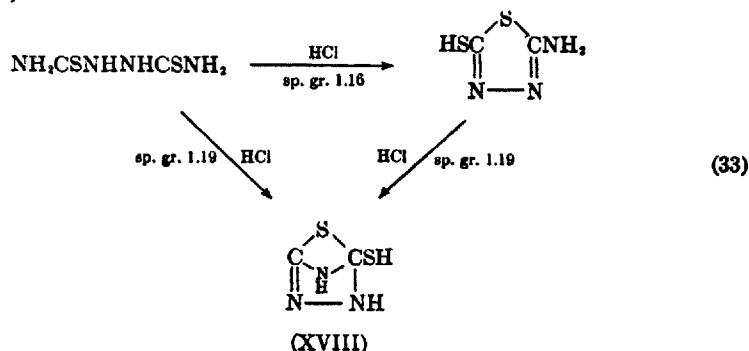
¹⁶ Janniah and Guha, *J. Am. Chem. Soc.*, **52**, 4860 (1930).

compounds could exist alone. Since the two forms had different ultra-violet absorption curves, Janniah and Guha proposed a bridged structure for the higher melting form (XVIII).^{16,17} They found that dilute hydro-



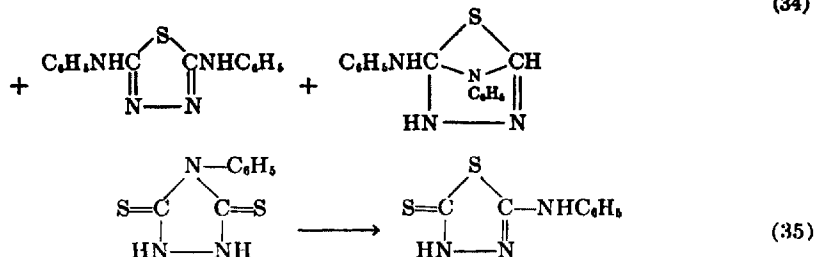
(XVIII)

chloric acid (sp.gr. 1.16) caused the formation of 2-amino-5-mercapto-1,3,4-thiadiazole, while concentrated hydrochloric (sp.gr. 1.19) promoted the formation of 1-mercapto-5-thia-2,3,6-triazobicyclo[2.1.1]-3-hexene (XVIII) (33).¹⁷



(XVIII)

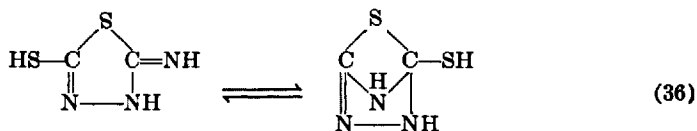
1-Phenylbithiourea gave the same products as bithiourea with the two concentrations of hydrochloric acid. The 1,6-diarylbithioureas gave three types of compounds (34). Janniah and Guha¹⁷ also showed that a di-thiourazole could be changed to a 2-amino-5-mercapto-1,3,4-thiadiazole (35).



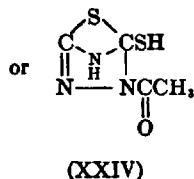
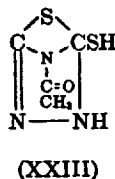
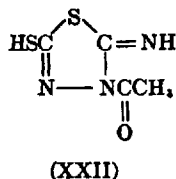
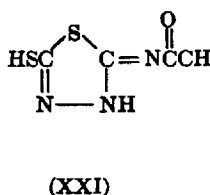
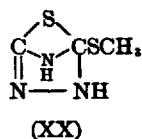
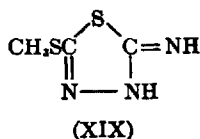
¹⁷ Janniah and Guha, *J. Indian Inst. Sci.*, **A16**, 11 (1933); *Chem. Abstr.*, **27**, 3711 (1933).

Discussion

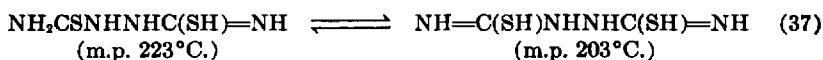
The variance in melting points and ultraviolet absorption spectra shown by Janniah and Guha^{16,17} for the various forms of the 2-amino-5-mercapto-1,3,4-thiadiazole poses a considerable problem. If their postulate is correct that one of the forms is a bridged nucleus, then some sort of equilibrium between the two forms should be evident. From their experimental work it would appear probable, especially in solution, that equation (36) would define this equilibrium. The change from one form to the



other would involve the formation of a bridged nucleus or a rupturing of the ring. Both forms gave the same methyl sulfide and acetylated compound, as would be expected if the equilibrium condition (36) existed. The structure of these compounds is in doubt. The methyl sulfide would have either structure (XIX) or (XX). A similar situation would exist as to the structure of the acetylated compound (XXI-XXIV).

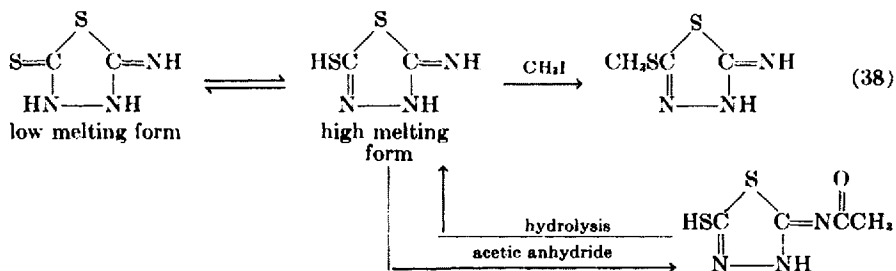


Janniah and Guha¹⁶ have discarded the possibility that the high and low melting forms are tautomers because they felt that such tautomers could not exist individually; yet, in the same paper they presented two stable tautomers of bithiourea (37). While the existence of stable tauto-

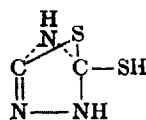


mers of acyclic compounds is admittedly a different problem than stable tautomers of heterocyclic compounds, there is no reason why such stable tautomers should not exist. The word stable is used in a relative sense. Furthermore, stable tautomers might exist in the crystalline state where their configuration would be relatively fixed. If these two different forms

are stable tautomers then their chemical reactions in solution may be explained by the following set of reactions (38).



If structure (XXV) does occur then it is not a planar molecule. Although the valence angles and stresses have not been calculated, it appears that such a molecule would be very unstable.



(XXV)

In Figure 4 the ultraviolet absorption curves were determined with a sample of 2-amino-5-mercapto-1,3,4-thiadiazole which had stood on the

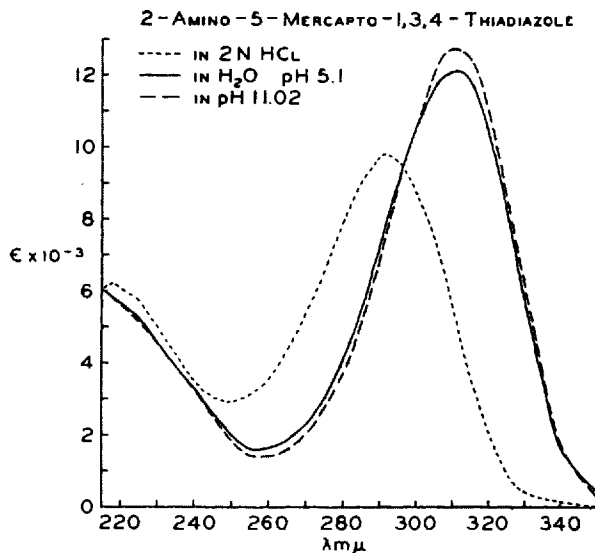


Figure 4

shelf for two years.¹⁸ The melting point of this substance was 232–3°C., while at the time of preparation the melting point was 242–3°C.

The difference in the curves in water at *pH* 5.1 and in 2 *N* hydrochloric acid indicates the presence of either a very strong amine or a very weak one. In this case, the supposition is made that the amine or imine is very weak. The change in absorption at *pH* 5.1 to the values at *pH* 11.02 may be due to the formation of the sodium mercaptide.

In any event the structures of the high and low melting forms have not been fully elucidated. Solution of the problem awaits more physical and chemical data. See the discussion of ψ -1,3,4-thiadiazoles.

¹⁸ Dr. J. M. Vandenberg of Parke, Davis and Co. prepared this curve.

Table XXIV follows on page 154.

TABLE XXIV. Preparation of the 2-Amino-5-mercapto-1,3,4-thiadiazoles, the 2-Mercapto-5-imino-Δ²-1,3,4-thiadiazolines and Related Compounds

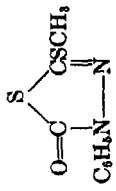
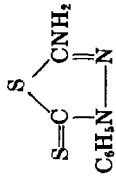
No.	Name	Ref.	Method of preparation	M.p., °C.
Part 1. The 2-Amino-5-mercapto-1,3,4-thiadiazoles				
1	2-Amino-5-mercapto-1,3,4-thiadiazole	1	$(\text{NH}_4\text{CSNH})_2 \xrightarrow{\text{HCl}} \text{HSC} \begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{CNH}_2 \\ \parallel \\ \text{N}=\text{N} \end{array}$	245
2	2-Acetyl-amino-5-mercapto-1,3,4-thiadiazole	2	$\text{NH}_4\text{CSNHHCSSK} + \text{heat}$	245
3	5,5'-Dithiobis(2-amino-1,3,4-thiadiazole)	3	$\text{NH}_4\text{CSNHNH}_2 + \text{CS}_2 + \text{heat}$	245
4	2-Amino-5-benzylmercapto-1,3,4-thiadiazole	3	reduction of the disulfide	—
5	2-Acetyl-amino-5-methylmercapto-1,3,4-thiadiazole	3	low melting isomer	232
6	2-Acetyl-amino-5-ethylmercapto-1,3,4-thiadiazole	3	low melting isomer	224
7	5,5'-Dithiobis(2-acetyl-amino-1,3,4-thiadiazole)	1	acetylation of compound 1	300 dec.
8	2-Methyl-amino-5-mercapto-1,3,4-thiadiazole	1,3	oxidation of compound 1	244-5
9	5,5'-Dithiobis(2-methyl-amino-1,3,4-thiadiazole)	2	compound 1 + benzyl chloride + NaOH	157-8
10	2-Ethyl-amino-5-mercapto-1,3,4-thiadiazole	4	compound 2 + methyl iodide	208-9
11	2-Ethyl-nitrosoamino-5-mercapto-1,3,4-thiadiazole	4	compound 2 + ethyl iodide	193
12	2-Ethyl-amino-5-methylmercapto-1,3,4-thiadiazole	4	acetylation of compound 3	275
13	2-Allyl-amino-5-mercapto-1,3,4-thiadiazole	4	oxidation of compound 2	275
		2	$(\text{CH}_3\text{NHCSNH})_2 + \text{HCl}$	190
		2	oxidation of compound 8	202
		1	$(\text{C}_2\text{H}_5\text{NHCSNH})_2 + \text{HCl}$	140
		1	compound 10 + nitrous acid	118-20
		1	compound 10 + methyl iodide	88
		2,5	$(\text{C}_2\text{H}_5\text{NHCSNH})_2$	—
			$(\text{C}_2\text{H}_5\text{NHCSNH})_2 \xrightarrow{\text{HCl}} \text{HSC} \begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{CNHC}_2\text{H}_5 \\ \parallel \\ \text{N}=\text{N} \end{array}$	

No.	Name	Ref.	Method of preparation	M.p., °C.
14	5,5'-Dithiobis(2-allylamino-1,3,4-thiadiazole)	2, 5	oxidation of compound 13	174
15	2-Allylamino-5-methylmercapto-1,3,4-thiadiazole	6	$C_6H_4NHCSNHNHCSCH_3$ was allowed to stand in alcohol for several days	77-8
16	2-Acetyllallylamino-5-methylmercapto-1,3,4-thiadiazole	6	compound 15 + acetic anhydride $C_6H_4NHCSNHNHCSCH_3$ + acetic anhydride	93-4
17	2-Amino-5- <i>p</i> -nitrophenylmercapto-1,3,4-thiadiazole	7	compound 1 + <i>p</i> -nitrochlorobenzene + alkali	—
18	2-Acetylamino-5- <i>p</i> -nitrophenylsulfonyl-1,3,4-thiadiazole	7	acetylation and oxidation of compound 17	196-200
19	2-Amino-5- <i>p</i> -nitrophenylsulfonyl-1,3,4-thiadiazole	7	deacetylation of compound 18	250-4
20	2-Amino-5-sulfanyll-1,3,4-thiadiazole	7	reduction of compound 19	228-32
21	2-Anilino-5-mercapto-1,3,4-thiadiazole	1	$(C_6H_4NHCSNH)_2 \xrightarrow{HCl} HSC \begin{array}{c} \diagup \quad \diagdown \\ S \quad N=N \\ \diagdown \quad \diagup \\ CNHC_6H_5 \end{array}$	211-4 219
22	2-Acetanilido-5-mercapto-1,3,4-thiadiazole	1 3 3	$C_6H_4NHCSNHNHCSCH_3$ + NaOH $C_6H_4NHCSNHNH_2$ + CS_2 + KOH $(C_6H_4NHCSNH)_2$ + heat acetic anhydride + compound 21 — 244 °C. form on heating or standing	215-6 208 219 205 244 236
23	2-Acetanilido-5-acetylmercapto-1,3,4-thiadiazole	1	acetic anhydride + sodium acetate + compound 21	176
24	2-Anilino-5-methylmercapto-1,3,4-thiadiazole	6 4	$C_6H_4NHCSNHNHCSCH_3$ + heat deacetylation of compound 25	132-3 139
25	2-Acetanilido-5-methylmercapto-1,3,4-thiadiazole	6 4 4	$C_6H_4NHCSNHNHCSCH_3$ + acetic anhydride compound 24 + acetic anhydride —	153-4 150 76
26	2-Acetanilido-5-ethylmercapto-1,3,4-thiadiazole	4	—	208
27	5,5'-Dithiobis(2-acetanilido-1,3,4-thiadiazole)	1	oxidation of compound 22	208
28	2- <i>o</i> -Toluidino-5-mercapto-1,3,4-thiadiazole	8	$(o-CH_3C_6H_4NHCSNH)_2$ + heat (170° for 45 min.)	213-4
29	5,5'-Dithiobis(2- <i>o</i> -toluidino-1,3,4-thiadiazole)	8	oxidation of compound 28	200
30	2- <i>o</i> -Toluidino-5-methylmercapto-1,3,4-thiadiazole	8	compound 28 + methyl iodide + NaOH	158
31	2- <i>o</i> -Toluidino-5-benzylmercapto-1,3,4-thiadiazole	8	compound 28 + benzyl chloride + alkali	112-3

(Table continued)

TABLE XXIV (Continued)

No.	Name	Ref.	Method of preparation	M.p., °C.
32	2-Acetyl- <i>o</i> -toluidino-5-methylmercapto-1,3,4-thiadiazole	8	compound 30 + acetic anhydride	123
33	2-Acetyl- <i>o</i> -toluidino-5-acetylmercapto-1,3,4-thiadiazole	8	compound 28 + acetic anhydride with reflux	145
34	2-Acetyl- <i>o</i> -toluidino-5-mercapto-1,3,4-thiadiazole	8	recrystallize 33 from dilute alcohol	249
35	2-Acetyl- <i>o</i> -toluidino-5-benzylmercapto-1,3,4-thiadiazole	8	compound 33 + dilute acetic acid + heat	—
			acetylating compound 31	—
36	2- <i>p</i> -Toluidino-5-mercapto-1,3,4-thiadiazole	6	compound 34 + benzyl chloride	93
37	2- <i>p</i> -Toluidino-5-methylmercapto-1,3,4-thiadiazole	6	$p\text{-CH}_3\text{C}_6\text{H}_4\text{NHCsNHHCsCH}_3 + \text{NaOH}$	215-6
		6	$p\text{-CH}_3\text{C}_6\text{H}_4\text{NHCsNHHCsCH}_3 + \text{warming}$	137-8
38	2-Acetyl- <i>p</i> -toluidino-5-methylmercapto-1,3,4-thiadiazole	6	compound 36 + methyl iodide	—
39	5,5'-Dithiobis(2- <i>p</i> -toluidino-1,3,4-thiadiazole)	6	acetylation of compound 37	94-5
40	2-Xylylamino-5-methylmercapto-1,3,4-thiadiazole	6	oxidation of compound 36	210-2
41	2-Acetylxilylamino-5-methylmercapto-1,3,4-thiadiazole	6	$(\text{CH}_3)_2\text{C}_6\text{H}_3\text{NHCsNHHCsCH}_3 + \text{warming}$	135-6
42	2- β -Phenylhydrazino-5-mercapto-1,3,4-thiadiazole	9	acetylation of 40	128-9
			$(\text{CH}_3)_2\text{C}_6\text{H}_3\text{NHCsNHHCsCH}_3 + \text{acetic anhydride}$	—
43	5,5'-Dithiobis(2- β -phenylhydrazino-1,3,4-thiadiazole)	9	$\text{C}_6\text{H}_5\text{NHNHCsNHHCsNH}_2 + \text{C}_2\text{H}_5\text{OCSSK}$	258-9
44	Triacetyl-2- β -phenylhydrazino-5-mercapto	9	$\text{C}_6\text{H}_5\text{NHNHCsNHHCsNHC}_6\text{H}_5 + \text{NaOH}$	—
			oxidation of compound 42 with ferric chloride	205
		9	acetylation of compound 42	206-7
Part 2. The 5-Imino-2-mercapto- Δ^2 -1,3,4-thiadiazolines and the 2-Mercapto-1,3,4-thiadiazol-5(4)-ones				
45	2-Mercapto-4-phenyl-5-phenylimino- Δ^2 -1,3,4-thiadiazoline	10	$\text{C}_6\text{H}_5\text{NCS} + \text{C}_6\text{H}_5\text{NHNHCSSK} \longrightarrow \text{S} \begin{array}{c} \text{C}_6\text{H}_5\text{N}=\text{C} \\ \text{C}_6\text{H}_5\text{N}=\text{N} \end{array} \begin{array}{c} \text{C}_6\text{H}_5 \\ \text{C}_6\text{H}_5 \end{array}$	171-2
46	2-Methylmercapto-4-phenyl-5-phenylimino- Δ^2 -1,3,4-thiadiazoline	11	$\text{C}_6\text{H}_5\text{NHCsN}(\text{C}_6\text{H}_5)_2\text{NH}_2 + \text{CSCl}_2$	169-70
		10	compound 45 + methyl iodide	67
47	2-Mercapto-4- <i>p</i> -tolyl-5-phenylimino- Δ^2 -1,3,4-thiadiazoline	10	$\text{C}_6\text{H}_5\text{NCS} + \text{C}_6\text{H}_5\text{NHNHCSSCH}_3$	—
			$\text{C}_6\text{H}_5\text{NCS} + p\text{-CH}_3\text{C}_6\text{H}_4\text{NHNHCSSK}$	162-3

No.	Name	Ref.	Method of preparation	M.p., °C.
48	2,2'-Dithiobis(4- <i>p</i> -tolyl-5-phenylimino- Δ^2 -1,3,4-thiadiazoline)	10	oxidation of compound 47	130
49	2-Methylmercapto-4- <i>p</i> -tolyl-5-phenylimino- Δ^2 -1,3,4-thiadiazoline	10	compound 47 + methyl iodide	68
50	2-Methylmercapto-4-phenyl-5- <i>p</i> -tolylimino- Δ^2 -1,3,4-thiadiazoline	10	p -CH ₃ C ₆ H ₄ NCS + C ₆ H ₅ NHNHCSSCH ₃	101
51	2-Methylmercapto-4-phenyl-5-allylimino- Δ^2 -1,3,4-thiadiazoline	10	C ₆ H ₅ NCS + C ₆ H ₅ NHNHCSSCH ₃	183
52	2-Methylmercapto-4-phenyl-1,3,4-thiadiazol-5(4)-one	10	C ₆ H ₅ NHNHCSSCH ₃ + COCl ₂ $\longrightarrow$ 	40-1
53	2-Methylmercapto-4- <i>p</i> -tolyl-1,3,4-thiadiazol-5(4)-one	10	compound 46 + dilute hydrochloric acid hydrolysis of compound 47 CH ₃ C ₆ H ₄ NHNHCSSCH ₃ + COCl ₂	— 52 —
54	2-Mercapto-4-phenyl-5-methylimino- Δ^2 -1,3,4-thiadiazoline	3	CH ₃ NHCSNC ₆ H ₅ NH ₂ + CS ₂ + KOH	142-3
55	2-Mercapto-4-tolyl-5-methylimino- Δ^2 -1,3,4-thiadiazoline	3	CH ₃ NHCSNC ₆ H ₄ CH ₃ NH ₂ + CS ₂ + KOH	174-5
Part 3. The 2-Amino-5-thioxo- Δ^2 -1,3,4-thiadiazolines				
56	2-Amino-4-phenyl-5-thioxo- Δ^2 -1,3,4-thiadiazoline	3	NH ₂ CSNHNHC ₆ H ₅ + KOH + CS ₂ $\longrightarrow$ 	183
57	2-Anilino-4-phenyl-5-thioxo- Δ^2 -1,3,4-thiadiazoline	3	C ₆ H ₅ NHCSNHNHC ₆ H ₅ + KOH + CS ₂	202
		11	C ₆ H ₅ NHCSNHNHC ₆ H ₅ + CSeCl ₂	188-9

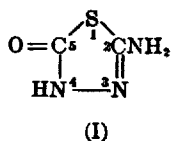
(Table continued)

TABLE XXIV (Concluded)

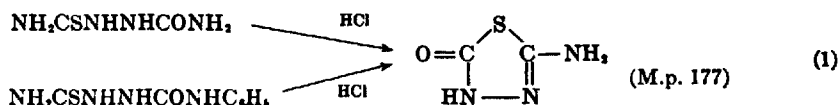
No.	Name	Ref.	Method of preparation	M.p., °C.
58	2-Allylamino-4-phenyl-5-thioxo- Δ^2 -1,3,4-thiadiazoline	3	$C_6H_5NHC_3H_5NHNHC_6H_5 + CS_2 + KOH$	145
59	2-Allylamino-4-tolyl-5-thioxo- Δ^2 -1,3,4-thiadiazoline	3	$C_6H_5NHC_3H_5NHNHC_6H_4CH_3 + CS_2 + KOH$	125-6
60	2-Anilino-4-tolyl-5-thioxo- Δ^2 -1,3,4-thiadiazoline	3	$C_6H_5NHC_3H_5NHNHC_6H_4CH_3 + CS_2 + KOH$	222
61	2-Anilino-4-naphthyl-5-thioxo- Δ^2 -1,3,4-thiadiazoline	12	$C_6H_5NHC_3H_5NHNHC_{10}H_7 + CCl_4$	255
		3	$C_6H_5NHC_3H_5NHNHC_{10}H_7 + CS_2 + KOH$	217
62	2-Toluidino-4-naphthyl-5-thioxo- Δ^2 -1,3,4-thiadiazoline	3	$CH_3C_6H_4NHC_3H_5NHNHC_{10}H_7 + KOH + CS_2$	268
63	2-Toluidino-4-phenyl-5-thioxo- Δ^2 -1,3,4-thiadiazoline	3	$CH_3C_6H_4NHC_3H_5NHNHC_6H_5 + KOH + CS_2$	188-9
64	2-p-Toluidino-4-tolyl-5-thioxo- Δ^2 -1,3,4-thiadiazoline	3	$p-CH_3C_6H_4NHC_3H_5NHNHC_6H_4CH_3 + KOH + CS_2$	205
65	2-Naphthylamino-4-phenyl-5-thioxo- Δ^2 -1,3,4-thiadiazoline	3	$C_{10}H_7NHC_3H_5NHNHC_6H_5 + CS_2 + KOH$	219
66	2-Naphthylamino-4-tolyl-5-thioxo- Δ^2 -1,3,4-thiadiazoline	3	$C_{10}H_7NHC_3H_5NHNHC_6H_4CH_3 + CS_2 + KOH$	217
67	2-Naphthylamino-4-naphthyl-5-thioxo- Δ^2 -1,3,4-thiadiazoline	3	$C_{10}H_7NHC_3H_5NHNHC_{10}H_7 + CS_2 + KOH$	218
68	2-Methylimino-3,4-dinaphthyl-5-thioxo- Δ^2 -1,3,4-thiadiazoline	3	$CH_3NHC_3H_5NHC_{10}H_7NHC_{10}H_7 + CS_2 + KOH$	183, 175
69	2-Phenylazo-4-phenyl-5-thioxo- Δ^2 -1,3,4-thiadiazoline	13	$C_6H_5N=N-C_3H_5NHNHC_6H_5 + CCl_4$	160-5
70	2- β -Phenylhydrazino-4-phenyl-5-thioxo- Δ^2 -1,3,4-thiadiazoline	13	reduction of compound 69 with ammonium sulfide	142
71	2-p-Tolylazo-4-phenyl-5-thioxo- Δ^2 -1,3,4-thiadiazoline	12	$p-CH_3C_6H_4N=N-C_3H_5NHNHC_6H_5 + CCl_4$	237-8
72	2- β -p-Tolylhydrazino-4-phenyl-5-thioxo- Δ^2 -1,3,4-thiadiazoline	12	reduction of compound 71 with ammonium sulfide	155
73	2-o-Tolylazo-4-phenyl-5-thioxo- Δ^2 -1,3,4-thiadiazoline	12	$o-CH_3C_6H_4N=N-C_3H_5NHNHC_6H_5 + CCl_4$	155
74	2- β -o-Tolylhydrazino-4-phenyl-5-thioxo- Δ^2 -1,3,4-thiadiazoline	12	reduction of compound 73 with ammonium sulfide	156

¹ Freund and Ingart, *Ber.*, 28, 948 (1895).² Busch and Lotz, *J. prakt. Chem.*, [2] 90, 257 (1914).³ Guha, *J. Am. Chem. Soc.*, 44, 1510 (1922). Guha does not always give the position on the tolyl or naphthyl groups.⁴ Guha, *J. Am. Chem. Soc.*, 44, 1502 (1922).⁵ Freund and Heilbrun, *Ber.*, 29, 859 (1896).⁶ Guha and Guha, *Quart. J. Indian Chem. Soc.*, 4, 161 (1927); *Chem. Abstr.*, 21, 3199 (1927).⁷ Bambas, *J. Am. Chem. Soc.*, 67, 668 (1945).⁸ Guha and Mehta, *J. Indian. Inst. Sci.*, A21, 41 (1938); *Chem. Abstr.*, 33, 598, 599 (1939).⁹ Guha and Roy-Choudhury, *J. Indian Chem. Soc.*, 5, 163 (1928); *Chem. Abstr.*, 23, 1397 (1929).¹⁰ Busch and Wolpert, *Ber.*, 34, 304 (1901).¹¹ Busch and Holzmann, *Ber.*, 34, 320 (1901).¹² Freund, *Ber.*, 24, 4178 (1891).¹³ Freund and Kuh, *Ber.*, 23, 2821 (1890).

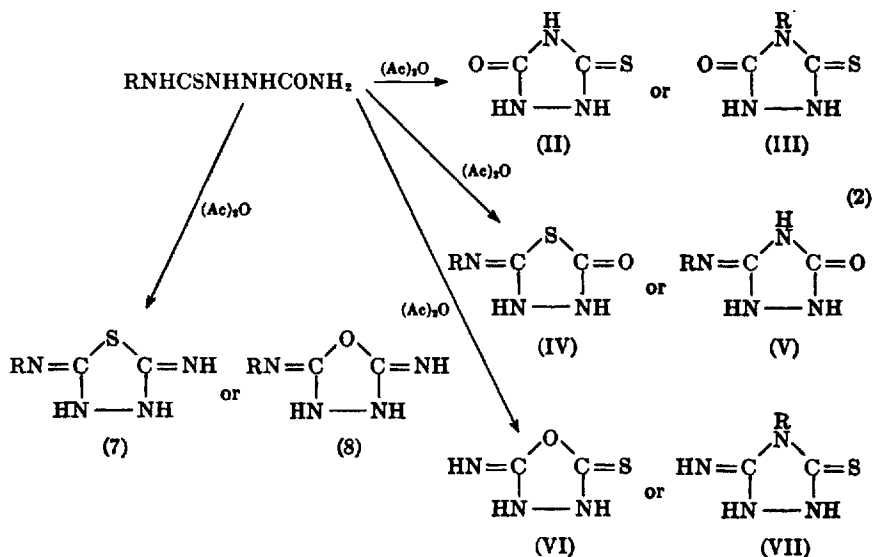
2-Amino- Δ^2 -1,3,4-thiadiazol-5(4)-ones (I)



Freund and Schander¹ heated 2-thiobiurea with concentrated hydrochloric acid and obtained a compound which they designated as 4,1,2-triazolid-3-one-5-thione. Heating 6-phenyl-2-thiobiurea with concentrated hydrochloric acid produced the same compound. Busch and Lotz² believed this compound to be 2-amino-1,3,4-thiadiazol-5(4)-one. Arndt *et al.*³ synthesized 4,1,2-triazolid-3-one-5-thione and proved that it was not identical to Freund and Schander's product (1).



Guha⁴ allowed 2-thiobiurea to react with acetic anhydride and obtained a compound which had the same chemical composition as Freund's



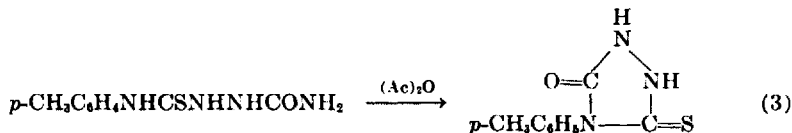
¹ Freund and Schander, *Ber.*, 29, 2506 (1896).

³ Busch and Lotz, *J. prakt. Chem.*, 90, 257 (1914).

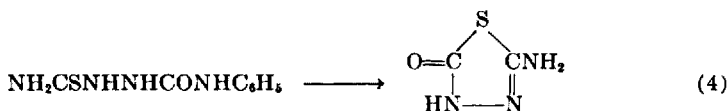
* Arndt, Milde, and Teschner, *Ber.*, **55**, 341 (1922).

⁴ Guha, *J. Am. Chem. Soc.*, **45**, 1036 (1923).

compound but had a different melting point (m.p. 235°C.). Guha and Chakraborty⁵ studied the ring closure of the 1- and 6-substituted 2-thiobiureas with acetic anhydride. 2-Thiobiureas substituted in the 1-position might react in any of the ways shown in reaction (2). The products actually isolated corresponded to the general formula $C_2H_2RON_3S$, which eliminated all the structures except (III) and (IV). The compounds possessed no mercaptan group so that structure (IV) was accepted as the formula of the compounds produced by closure with acetic anhydride. The compounds were isolated as acetyl derivatives which on hydrolysis gave the 2-alkylamino or 2-arylamino-1,3,4-thiadiazol-5(4)-ones. 1-Allyl, 1-phenyl, and 1-*p*-tolyl-2-thiobiureas upon reacting with acetic anhydride produced additional products. Using 1-*p*-tolyl-2-thiobiurea and acetic anhydride, 4-*p*-tolyl-3-imino-5-thio-4,1,2-triazolidine was isolated (3).



The 1-(β -naphthyl)-2-bithiourea decomposes to β -naphthylisothiocyanate. Gently heating 6-phenyl-2-thiobiurea with acetic anhydride gives the mono and diacetyl 2-amino-1,3,4-thiadiazol-5(4)-one (4).



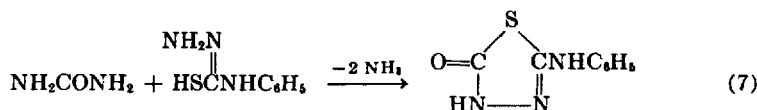
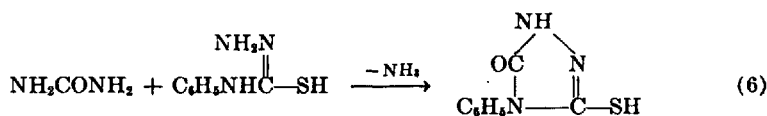
The 1,6-diphenyl-2-thiobiurea and acetic anhydride produced 4-phenyl-3-anilino-5-mercapto-4,1,2-triazole (5). Biurea was unaffected by acetic anhydride.



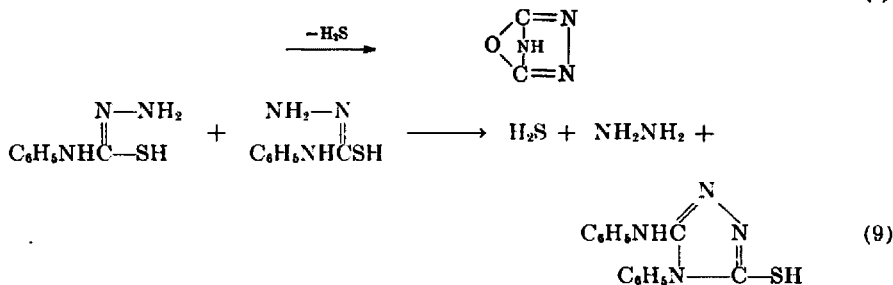
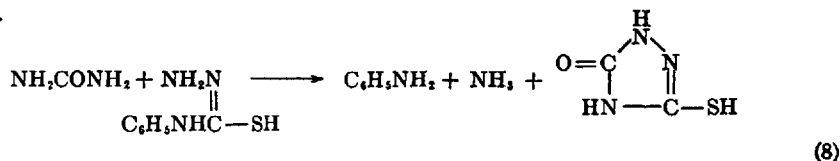
Guha and Sen⁶ found that when 4-substituted thiosemicarbazides are heated with urea four compounds are formed. This phenomenon may be explained by existence of *syn* and *anti* forms. The *anti* form of 4-phenyl thiosemicarbazide and urea yielded 3-mercapto-4-phenyl-4,1,2-triazol-5(1)-one (6). The presence of 2-anilino-1,3,4-thiadiazol-5(4)-one necessitated the presence of *syn* form (7). The formation of 5-oxa-2,3,6-

⁵ Guha and Chakraborty, *J. Indian Chem. Soc.*, **6**, 99 (1929); *Chem. Abstr.*, **23**, 2974 (1929).

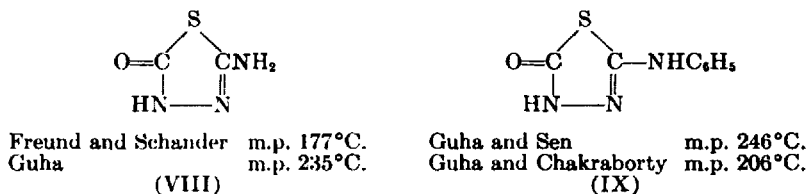
⁶ Guha and Sen, *J. Indian Chem. Soc.*, **4**, 43 (1927); *Chem. Abstr.*, **21**, 2900 (1927).



triazabicyclo[2.1.1]-1,3-hexadiene was attributed to the *anti* form (8). Guha and Sen⁶ believed that the *syn* and *anti* forms reacted with one another (9).



Janniah and Guha^{7,8} investigated the apparent discrepancy in the melting points reported for 2-amino-1,3,4-thiadiazol-5(4)-one (VIII) and 2-anilino-1,3,4-thiadiazol-5(4)-one (IX). They prepared 2-amino-1,3,4-

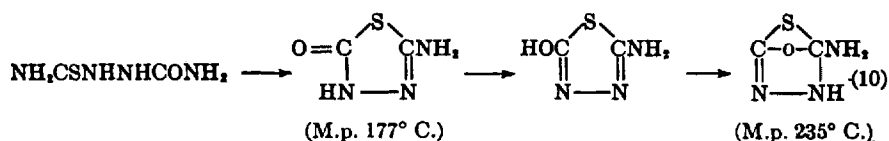


thiadiazol-5(4)-one by gently heating 2-thiobiurea in concentrated hydrochloric acid. The product had a melting point of 177°C. An acetyl

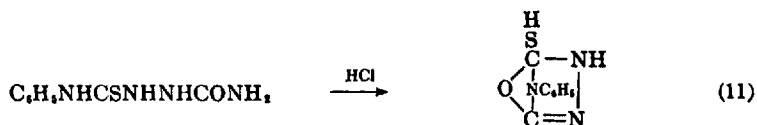
⁷ Janniah and Guha, *J. Indian Inst. Sci.*, **A16**, 19 (1933); *Chem. Abstr.*, **27**, 3712 (1933).

⁸ Janniah and Guha, *J. Am. Chem. Soc.*, **52**, 4860 (1930).

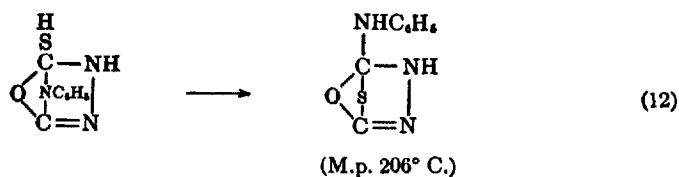
derivative (m.p. 254°C.) was obtained which on hydrolysis with concentrated hydrochloric acid gave a hydrochloride whose melting point was 107–8°C. The free base melted at 235°C. and had the same composition ($C_2H_3ON_3S$) as the starting material. It was insoluble in alkali, remained unchanged with mercuric chloride, and formed compounds with phenyl isocyanate, phenyl thiocyanate, and benzaldehyde. It was apparent that the sulfur was in the ring and that an amino group was present. Janniah and Guha believed that this compound, 1-amino-5-oxa-6-thia-2,3-diazobicyclo[2.1.1]-3-hexene, was formed as shown in reaction (10).



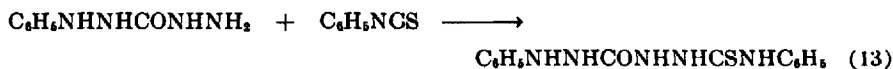
Guha and Janniah believed that the action of concentrated hydrochloric acid on 1-phenyl-2-thiobiurea probably gave 1-mercapto-6-phenyl-5-oxa-2,3,6-triazabicyclo[2.1.1]-3-hexene (11). This compound on acetyl-



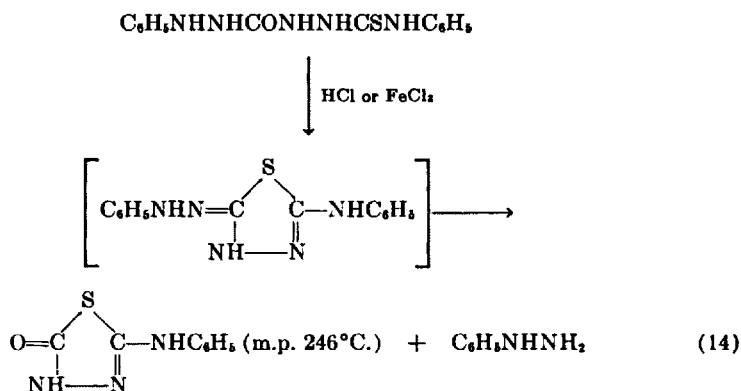
ation and then hydrolysis gave a compound which had no mercapto group but which had a melting point of 206°C., the same as Guha and Chakraborty's compound. It was believed to be 1-anilino-5-oxa-6-thia-2,3-diazabicyclo[2.1.1]-3-hexene (12).



Guha and Hye⁹ prepared 1-phenyl-2-thio-6-anilinobiurea from 1-phenyl carbohydrazide and phenyl isothiocyanate (13). Heating this compound with concentrated hydrochloric acid or ferric chloride produced



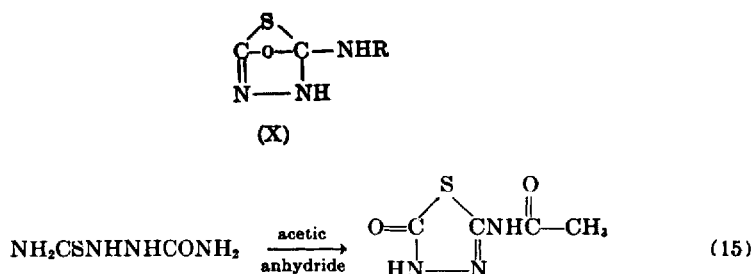
⁹ Guha and Hye, *J. Indian Chem. Soc.*, **7**, 933 (1930); *Chem. Abstr.*, **25**, 3633 (1931).



2-anilino-1,3,4-thiadiazol-5(4)-one. With hydrochloric acid, phenylhydrazine hydrochloride was obtained as a by-product (14).

Discussion

From Janniah and Guha's work^{10,11} it appears that Guha's¹² and Guha and Chakraborty's¹³ structures are open to question. If the 2-amino-1,3,4-thiadiazol-5(4)-one structure does not describe the compound obtained by the acetylation and hydrolysis of 2-thiobiurea, then the other compounds prepared in the same manner from 1-substituted-2-thiobiurea also must be questioned. According to Janniah and Guha's postulate that the oxygen formed a bridge between the carbon atoms, these compounds may be classified as 1-alkylamino (or arylamino) 5-oxa-6-thia-2,3-diazabicyclo[2.1.1]-3-hexenes (X).



¹⁰ Janniah and Guha, *J. Indian Inst. Sci.*, **A16**, 19 (1933); *Chem. Abstr.*, **27**, 3712 (1933).

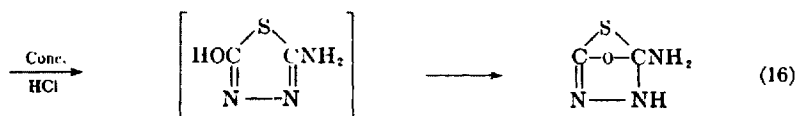
¹¹ Janniah and Guha, *J. Am. Chem. Soc.*, **52**, 4860 (1930).

¹² Guha, *J. Am. Chem. Soc.*, **45**, 1036 (1923).

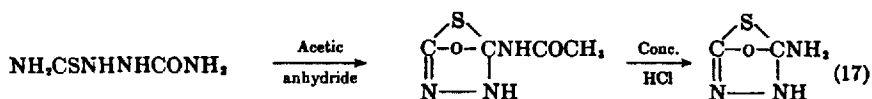
¹³ Guha and Chakraborty, *J. Indian Chem. Soc.*, **6**, 99 (1929); *Chem. Abstr.*, **23**, 2974 (1929).

Janniah and Guha theorized that this bridging occurred during the hydrolysis of the acetyl derivatives. From their experimental procedures one could predicate that the bridging took place during the acetylation reaction (15).

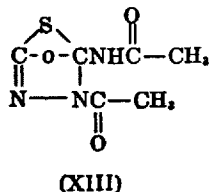
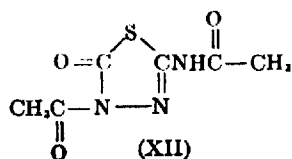
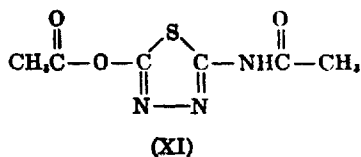
In any instance the concept of an epoxy or bridged nucleus is open to question. (See the discussion on this type of compound.) Freund and Schander¹⁴ and Janniah and Guha¹⁰ heated 2-thiobiurea with concentrated hydrochloric acid with no apparent bridging of the two carbon atoms with the oxygen atom. Possibly prolonged heating with hydrochloric acid might give the same effect as acetic anhydride (17). In every instance where bridging apparently occurred, acetic anhydride was used.



Janniah's and Guha's Postulate



Guha and Chakraborty¹⁵ reported diacetyl derivatives of these compounds. These are probably one of structures (XI), (XII), or (XIII). It



¹⁴ Freund and Schander, *Ber.*, **29**, 2506 (1896).

¹⁵ Guha and Chakraborty, *J. Indian Chem. Soc.*, **6**, 99 (1929); *Chem. Abstr.*, **23**, 2974 (1929).

appears that regardless of the condensing agent in ring closure the carbonyl group is involved (18).

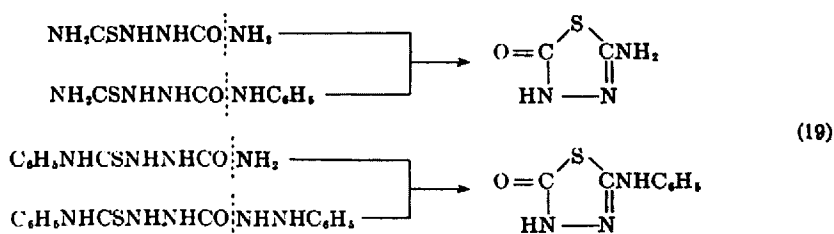
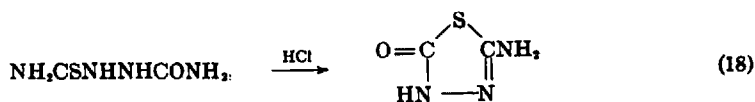


TABLE XXV. Preparation of 2-Amino-1,3,4-thiadiazol-5(4)-ones (See Table XXVI for Compounds Having Other Possible Structures)

No.	Substituents on the amine	Ref.	Methods of preparation	Solubility	M.p. °C.
1	H	1	$\text{NH}_2\text{CSNHNHCONH}_2 + \text{HCl}$	water, methanol, ethanol, acetic acid	177
		2	—	—	177
		1	$\text{NH}_2\text{CSNHNHCONHC}_6\text{H}_5 + \text{HCl}$	—	177
2	Phenyl	3	$\text{C}_6\text{H}_5\text{NHCSNHNH}_2 + \text{NH}_2\text{CONH}_2 + \text{heat}$	acetone	246
		4	$\text{C}_6\text{H}_5\text{NHCSNHNH}_2 + \text{NH}_2\text{CONH}_2 + \text{amyl alcohol (reflux)}$	—	246
		5	$\text{C}_6\text{H}_5\text{NHCSNHNHCONHNHC}_6\text{H}_5 + \text{FeCl}_3 \text{ or HCl}$	acetone	246
3	<i>o</i> -Tolyl	5	$\text{o-CH}_3\text{C}_6\text{H}_4\text{NHCSNHNHCONH-NHC}_6\text{H}_5 + \text{HCl or FeCl}_3$	alc.	220–1
4	<i>p</i> -Tolyl	3	$\text{p-CH}_3\text{C}_6\text{H}_4\text{NHCSNHNH}_2 + \text{NH}_2\text{CONH}_2 + \text{heat}$	alc.	227
5	2,4-Xylyl	3	$2,4\text{-(CH}_3)_2\text{C}_6\text{H}_3\text{NHCSNHNH}_2 + \text{NH}_2\text{CONH}_2$	acetone	218–9

¹ Freund and Schauder, *Ber.*, 29, 2506 (1896).

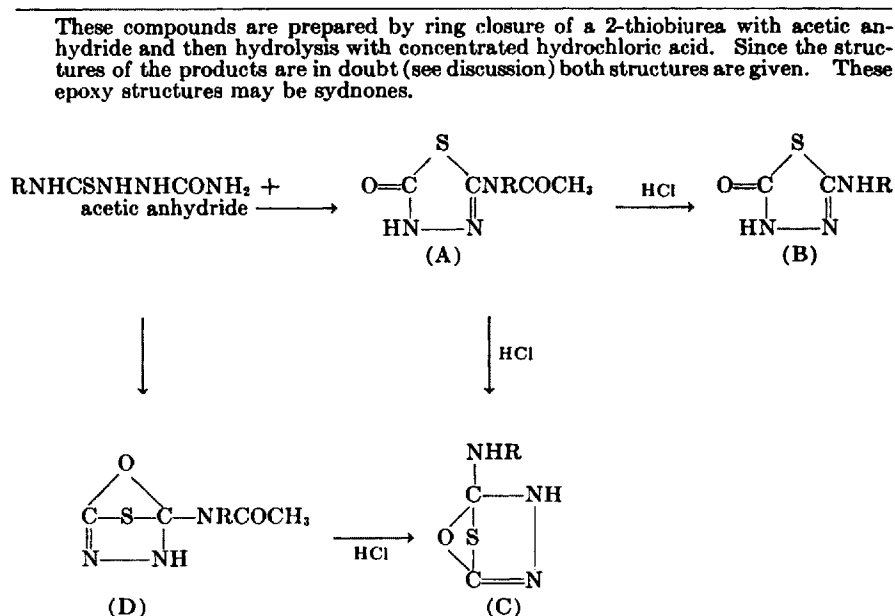
² Janniah and Guha, *J. Indian Inst. Sci.*, A16, 19 (1933); *Chem. Abstr.*, 27, 3712 (1933).

³ Guha and Sen, *J. Indian Chem. Soc.*, 4, 43 (1927); *Chem. Abstr.*, 21, 2900 (1927).

⁴ Mistry and Guha, *J. Indian Chem. Soc.*, 7, 793 (1930); *Chem. Abstr.*, 25, 1503 (1931).

⁵ Guha and Hye, *J. Indian Chem. Soc.*, 7, 933 (1930); *Chem. Abstr.*, 25, 3633 (1931).

TABLE XXVI. Preparation of 2-Amino-1,3,4-thiadiazol-5(4)-ones



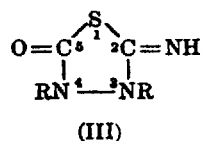
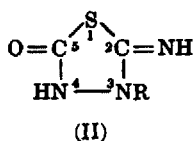
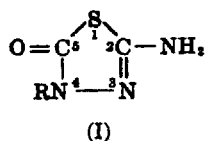
No.	Structure				M.p., °C.	Ref.
	In Literature (A)	In Literature (B)	Janniah and Guha's (C)	Possible alternate (D)		
	Where R equals					
1	H	—	—	H	275, 296	1
2	H	—	—	H	295	2, 3
3	—	H	H	—	235	2, 3
4	Methyl	—	—	methyl	197	1
5	—	methyl	methyl	—	232	1
6	Allyl	—	—	allyl	171	1
7	—	allyl	allyl	—	210	1
8	Phenyl	—	—	phenyl	173	1
9	—	phenyl	phenyl	—	206	1
10	<i>o</i> -Tolyl	—	—	<i>o</i> -tolyl	183	1
11	—	<i>o</i> -tolyl	<i>o</i> -tolyl	—	210	1
12	—	<i>p</i> -tolyl	<i>p</i> -tolyl	—	247	1
13	2,4-Xylyl	—	—	2,4-xylyl	218	1
14	—	2,4-xylyl	2,4-xylyl	—	232	1

¹ Guha and Chakraborty, *J. Indian Chem. Soc.*, **6**, 99 (1929); *Chem. Abstr.*, **23**, 2974 (1929).

² Guha, *J. Am. Chem. Soc.*, **45**, 1036 (1923).

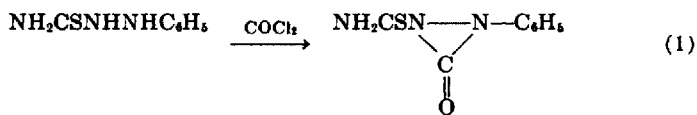
³ Janniah and Guha, *J. Indian Inst. Sci.*, **A16**, 19 (1933); *Chem. Abstr.*, **27**, 3712 (1933).

**2-Amino-3- and -4-Substituted-1,3,4-thiadiazol-5(4)-ones
and Related Compounds (I), (II), and (III)**

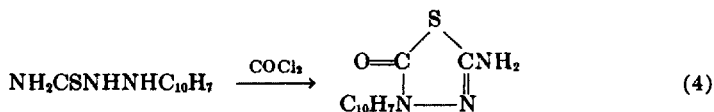
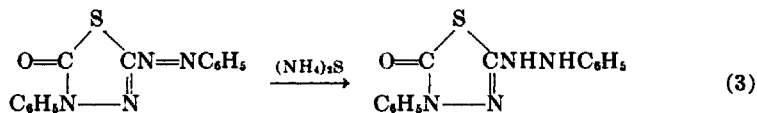
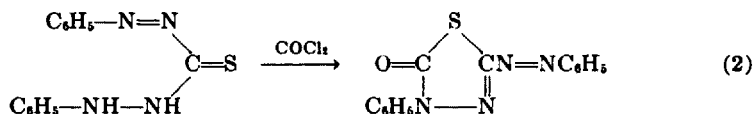


Inasmuch as these 2-amino-1,3,4-thiadiazol-5(4)-ones have been described by a number of structures, the literature concerning these compounds is somewhat confusing. In addition, the reaction between phosgene and substituted thiosemicarbazides used to produce these compounds yields other products.

Freund and Goldsmith¹ allowed phosgene to react with 4-phenylthiosemicarbazide and pictured the resultant product as a three-membered ring (1).



Freund and Kuh² studied the reaction products of phosgene and thio-phosgene with a number of hydrazine derivatives. They believed that five-membered rings were formed. For instance, 1,5-diphenylthiocarbazone and phosgene gave 2-phenylazo-4-phenyl-1,3,4-thiadiazol-5(4)-one (2). Reduction of this compound with ammonium sulfide yielded 2-

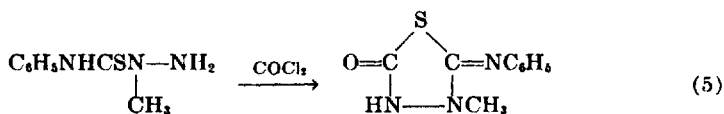


¹ Freund and Goldsmith, *Ber.*, 21, 2456 (1888).

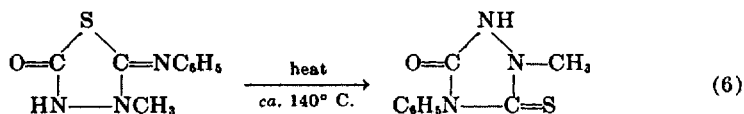
² Freund and Kuh, *Ber.*, 23, 2821 (1890).

phenylhydrazo-4-phenyl-1,3,4-thiadiazol-5(4)-one (3). Freund *et al.*³ repeated this work with 5-di-*p*-tolylthiocarbazono and phosgene. The naphthyl compounds were also prepared (4).

Marckwald and Sedlacek⁴ allowed 2-methyl-4-phenyl thiosemicarbazide (this compound was given as 1-methyl-4-phenyl thiosemicarbazide in the original report, but was later proved to be 2-methyl-4-phenyl thiosemicarbazide) to react with phosgene and obtained 2-phenylimino-3-methyl-1,3,4-thiadiazolid-5-one (5). Heating this compound over a



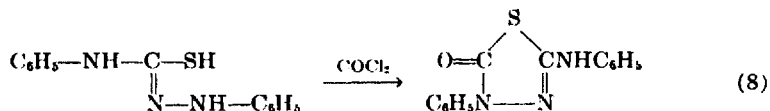
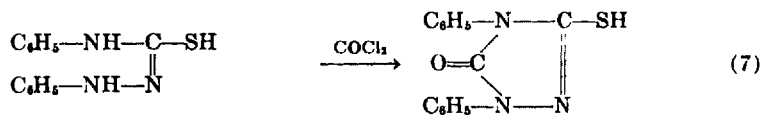
prolonged period of time produced 2-methyl-3-mercapto-4-phenyl-4,1,2-triazolid-5(4)-one (6).



Marckwald⁵ believed that the thiosemicarbazide molecule existed in two forms: the labile or *anti* form (IV) and the stable or *syn* form (V).



Phosgene and the labile form yielded the 4,1,2-triazol-5(4)-one (7), while the stable form produced the 1,3,4-thiadiazol-5(4)-one (8). Using this



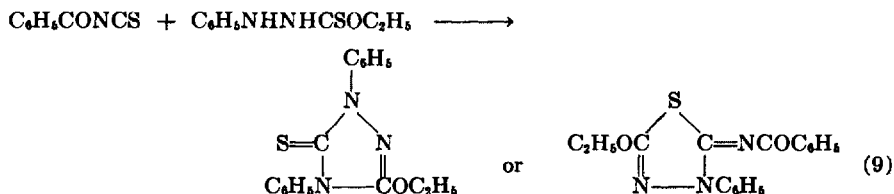
reaction as a criterion, Marckwald prepared a large number of disubstituted thiosemicarbazides. The reaction of these thiosemicarbazides with phosgene was then used to determine if they occurred as the *syn* or *anti* forms.

³ Freund, *Ber.*, **24**, 4178 (1891).

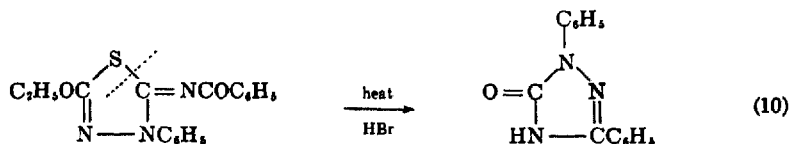
⁴ Marckwald and Sedlacek, *Ber.*, **29**, 2920 (1896).

⁵ Marckwald, *Ber.*, **32**, 1081 (1899).

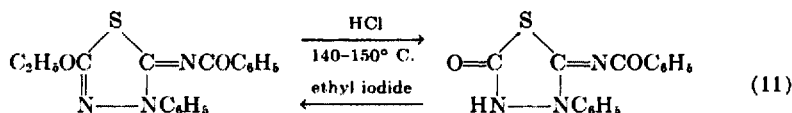
Wheeler and Dustin⁶ found that the action of benzoyl isothiocyanate on ethyl 2-phenylthiocarbazate produced a compound which was either a triazole or a thiadiazole (9). Wheeler and Statiropoulos⁷ obtained the



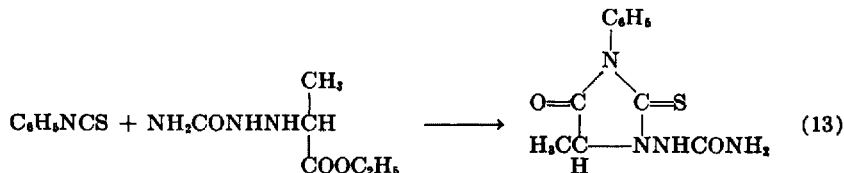
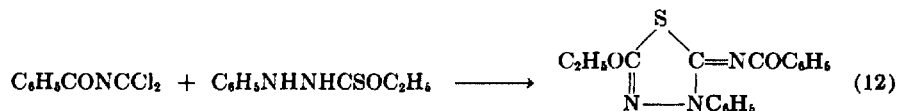
same product with benzoyl isothiocyanate and ethyl 2-phenylthiocarbazate. Heating this product with hydrobromic acid formed a triazolone. They suggested that the thiadiazole split as shown in equation (10). A



stream of dry hydrogen chloride at 140–145°C. gave ethyl chloride and the resultant thiadiazolid-5-one. Ethyl iodide regenerated the starting material (11). This compound was also prepared from benzoyl isocyanato-



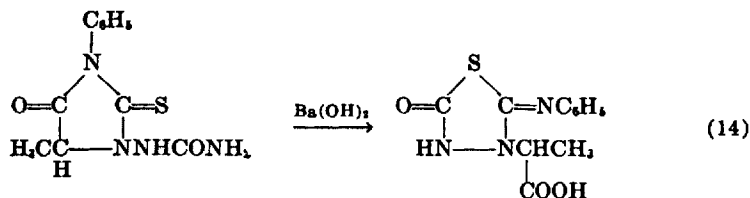
chloride and the ethyl 2-phenylthiocarbazate (12). Silver nitrate did not desulfurize this compound.



⁶ Wheeler and Dustin, *Am. Chem. J.*, **24**, 424 (1900).

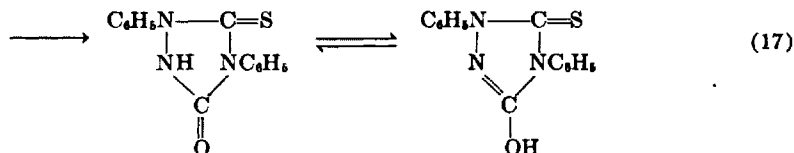
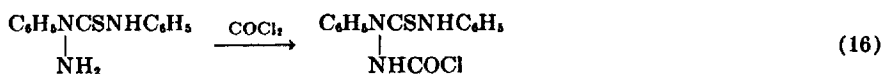
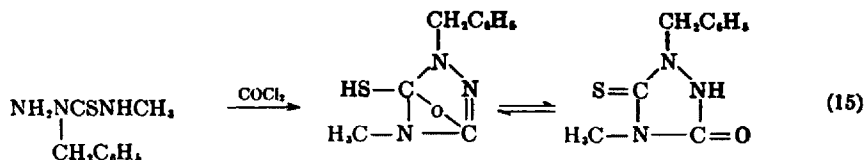
⁷ Wheeler and Statiropoulos, *Am. Chem. J.*, **34**, 117 (1905).

Bailey⁸ found that the phenyl isothiocyanate and α -(4-semicarbazino)-propionic acid produced 5-methyl-1-ureido-3-phenyl-2-thiohydantoin (13). Heating this thiohydantoin with barium hydroxide formed 3- α -propionic acid-2-phenylimino-1,3,4-thiadiazolid-5-one (14). The ethyl ester and



amide of this acid were prepared. A benzoyl derivative of the ester was synthesized. This compound did not give a color reaction with ferric chloride (unlike the amide and the ester, which gave blue solutions with this reagent). On heating an ammoniacal solution of mercuric oxide and this thiadiazolidone, mercuric sulfide was precipitated. The acid titrated as a dibasic acid.

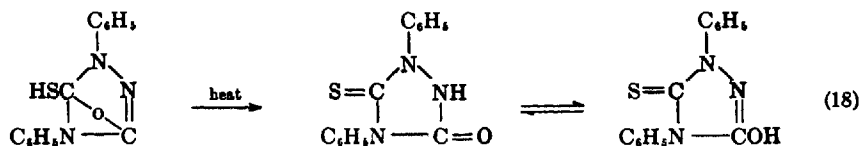
Busch and Opfermann⁹ reacted phosgene with 2,4-dialkyl thiosemicarbazides and obtained two series of compounds: a labile form, which was readily transformed to the high melting or stable form; at that time Busch believed the low melting form to be a bridged triazole ring, while the higher melting compounds were supposed to be 4,1,2-triazolid-3-one-5-thiones (15).



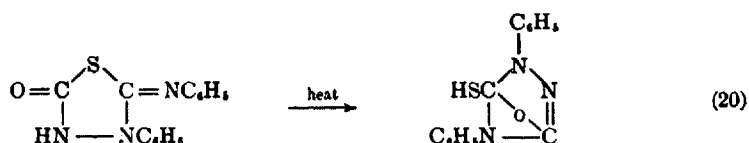
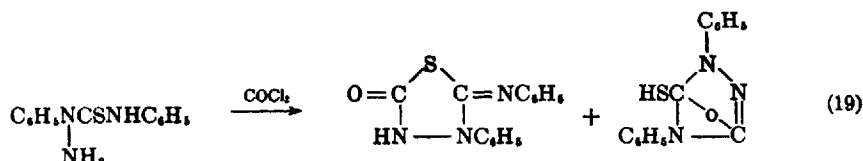
⁸ Bailey, *J. Am. Chem. Soc.*, **26**, 1006 (1904).

⁹ Busch and Opfermann, *Ber.*, **37**, 2333 (1904).

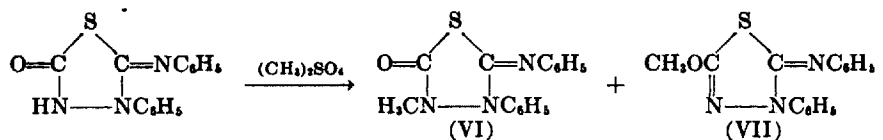
Nirdlinger and Acree¹⁰ sought to prove that the opposite was true. They postulated that reactions (16) and (17) took place. Heating the high melting form gave the low melting form (18).



Busch and Limpach¹¹ examined the products formed in the reaction between phosgene and 1- and 2-substituted 4-phenylthiosemicarbazides. These compounds consisted of 2-phenylimino-3-phenyl-1,3,4-thiadiazolid-5-one and a small amount of 1-mercapto-3,6-diphenyl-5-oxa-2,3,6-triazabicyclo[2.1.1]-3-hexene (19). The first compound was converted into the second by heating (20).



Warming 2-phenylimino-3-phenyl-1,3,4-thiadiazolid-5-one with aniline produced 1,4-diphenylsemicarbazide and 1,3-diphenylthiourea (21). With

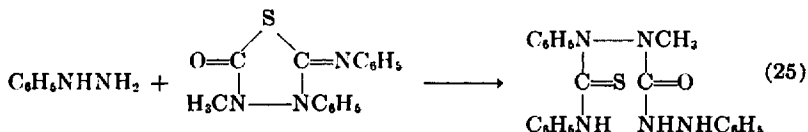
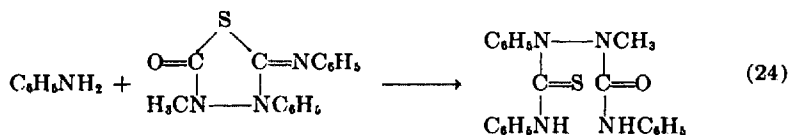
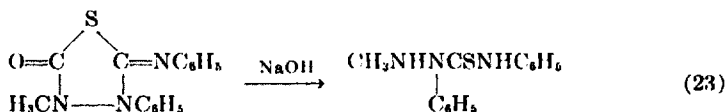


¹⁰ Nirdlinger and Acree, *Am. Chem. J.*, **44**, 1219 (1910).

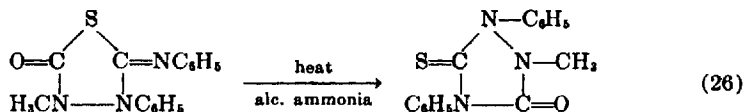
¹¹ Busch and Limpach, *Ber.*, **44**, 560 (1911).

benzylamine, 1,3-phenylbenzylthiourea was isolated and 2-phenyl-4-benzylsemicarbazide was probably formed. Phenylhydrazine and the 1,3,4-thiadiazolid-5-one yielded 1,4-diphenylthiosemicarbazide and diphenylcarbazine.

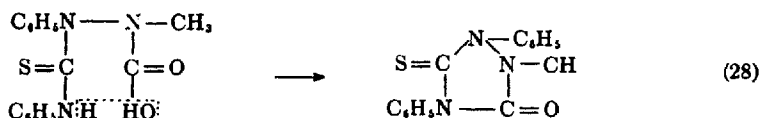
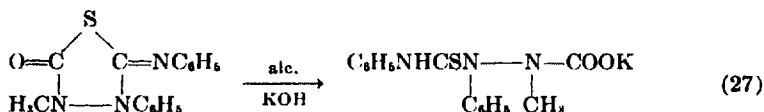
Methylation of 2-phenylimino-3-phenyl-1,3,4-thiadiazolid-5-one with dimethyl sulfate gave two compounds (see 22). Methyl-2,4-diphenylthiosemicarbazide and phosgene also gave 2-phenylimino-3-phenyl-4-methyl-1,3,4-thiadiazolid-5-one (VI). This compound decomposed with alkali, while the methyl ether (VII) was unaffected (23-25).



Refluxing 2-phenylimino-3-phenyl-4-methyl-1,3,4-thiadiazolid-2(3)-one in alcoholic ammonia produced 1-methyl-2,4-diphenyl-4,1,2-triazolid-5-thione-3-one (26). Gently heating 2-phenylimino-3-phenyl-4-methyl-

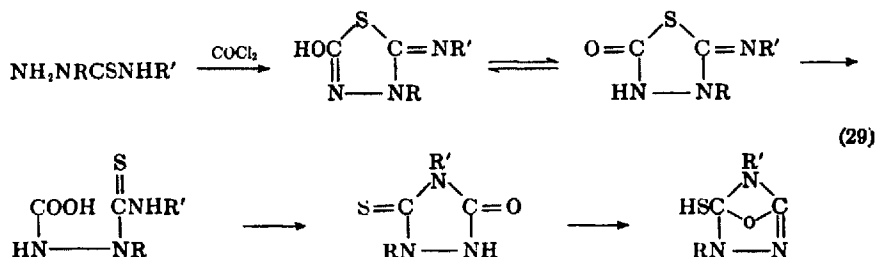


1,3,4-thiadiazolid-5-one with alcoholic potassium hydroxide yielded potassium 1-methyl-2-phenyl-2-thiocarbanilidocarbazate (27). This acid readily condensed to the 4,1,2-triazolidine ring (28).



The 2-phenylimino-3-methyl-4-phenyl-1,3,4-thiadiazolid-5-one underwent a similar series of reactions.

The formation of the triazolidines from phosgene and substituted thiosemicarbazides was then explained as shown in equation (29).



Discussion

On examining the chemistry of the 2-amino-3 and 4-substituted-1,3,4-thiadiazolid-5-ones it becomes evident that these compounds are very labile. They are sensitive to heat, alkalis, and amines. Because of this relative instability it is difficult to evaluate the compounds produced by the reaction between phosgene and a substituted thiosemicarbazide. It has been assumed that the primary reaction product is a 2-amino-1,3,4-thiadiazolid-5-one or one of its tautomers. This may not be completely valid, since the operation of recrystallization from a hot solvent may have altered the substituted 2-amino-1,3,4-thiadiazolid-5-one to one of the sequelae in the series of reactions. This lability has confused the proof of the structure of these compounds.

Tables XXVII and XXVIII follow on pages 174-176.

No.	Substituents on the 1,3,4-thiazolid-5-ones				Ref.	Solubility	M.p., °C.
	2-Position	3-Position	4-Position				
18	p-Chlorophenylimino	H	p-tolyl	5	—	—	229-30
19	p-Chlorophenylimino	H	p-chlorophenyl	5	—	—	155
20	2,4-Xylylimino	H	phenyl	5	—	—	126
21	1-Naphthylimino	H	phenyl	5	—	—	160
22	2-Naphthylimino	H	p-tolyl	5	—	—	210
23	2-Naphthylimino	H	p-bromophenyl	5	—	—	254
24	2-Naphthylimino	H	1-naphthyl	5	—	—	233
25	Phenylimino	methyl	H	8	—	isoamyl alc.	163
26	Methylimino	benzyl	H	9	—	alc.	117
27	Allylimino	benzyl	H	9	—	alc.	108
28	Phenylimino	benzyl	H	9	—	—	147
29	Phenylimino	phenyl	H	10-13	—	alc., benzene	139-40
30	Phenylimino	m-tolyl	H	10	—	—	125
31	Phenylimino	p-tolyl	H	10	—	—	144
32	Phenylimino	m-chlorophenyl	H	10	—	—	108-11
33	Phenylimino	m-bromophenyl	H	10	—	—	118-9
34	Phenylimino	p-bromophenyl	H	10	—	—	169-70
35	Phenylimino	2-naphthyl	H	10	—	—	133-4
36	Phenylimino	phenyl	methyl	12	—	alc., ether, benzene	92
37	Phenylimino	methyl	phenyl	12	—	alc.	102
38	Phenylazo	—	phenyl	2	—	alc., benzene, CHCl ₃ , ether	140
39	o-Tolylazo	—	o-tolyl	3	—	alc.	144
40	p-Tolylazo	—	p-tolyl	3	—	alc.	174

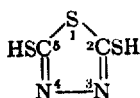
¹ Freund and Goldsmith, *Ber.*, 21, 2456 (1888).² Freund and Kuh, *Ber.*, 23, 2821 (1890).³ Freund, *Ber.*, 24, 4178 (1891).⁴ König, *Ber.*, 26, 2876 (1893).⁵ Marckwald, *Ber.*, 32, 1081 (1899).⁶ Mangini and Deliddo, *Gazz. chim. ital.*, 65, 214 (1935);*Chem. Abstr.*, 29, 5423 (1935).⁷ Freund and Hilringhaus, *Ber.*, 24, 4178 (1891).⁸ Marckwald and Sedlacek, *Ber.*, 29, 2920 (1896).⁹ Busch and Opfermann, *Ber.*, 37, 2333 (1904).¹⁰ Busch, *Ber.*, 42, 4763 (1909).¹¹ Busch and Holmann, *Ber.*, 34, 320 (1901).¹² Busch and Limpach, *Ber.*, 44, 560 (1911).¹³ Nirdlinger and Acree, *Am. Chem. J.*, 44, 1219 (1910).

TABLE XXVIII. Substituted 2-Imino-1,3,4-thiadiazolid-5-ones or Their Tautomers Prepared by Other Methods

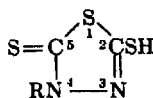
No.	Substituents on the 1,3,4-thiadiazolidine ring					Method of preparation	M.p., °C.
	2	3	4	5	Ref.		
1	Benzimidio	phenyl	—	ethoxy	1 2	$\begin{array}{c} \text{C}_6\text{H}_5\text{NHNHC(SOC}_2\text{H}_5)_2 + \text{C}_6\text{H}_5\text{CONCS} \\ \text{C}_6\text{H}_5\text{NHNHC(SOC}_2\text{H}_5)_2 + \text{C}_6\text{H}_5\text{CONCCl}_2 \end{array}$ $\begin{array}{c} \text{C}_6\text{H}_5\text{CON}=\text{C} \begin{array}{c} \diagup \text{S} \diagdown \\ \text{C}=\text{O} \quad \text{NH} \\ \\ \text{C}_6\text{H}_5\text{N}-\text{NH} \end{array} \\ + \text{ethyl iodide} \end{array}$	136-8 —
2	Benzimidio	phenyl	H	oxo	1	heat compound 1 with HCl at 140°C.	240 dec.
3	Phenylhydrazo	—	phenyl	oxo	3	reduce compound 38, XXVII, with ammonium sulfide	124
4	<i>o</i> -Tolylhydrazo	—	<i>o</i> -tolyl	oxo	4	reduce compound 39, XXVII, with ammonium sulfide	159-60
5	<i>p</i> -Tolylhydrazo	—	<i>p</i> -tolyl	oxo	4	same as above	168
6	Phenylimino	β -propionic acid	H	oxo	5	warm 1-ureido-3-phenyl-5-methyl-2-thiohydantoic with Ba(OH) ₂	220
7	Phenylimino	ethyl β -propionate	H	oxo	5	compound 6 + ethanol + HCl	171
8	Phenylimino	ethyl β -propionate	—	benzoxy	5	compound 7 + benzoyl chloride	110
9	Phenylimino	β -propionamide	H	oxo	5	compound 7 + ammonia	228 dec.
10	Phenylimino	phenyl	—	benzoxy	6	$\begin{array}{c} \text{C}_6\text{H}_5\text{N}=\text{C} \begin{array}{c} \diagup \text{S} \diagdown \\ \text{C}=\text{O} \quad \text{NH} \\ \\ \text{C}_6\text{H}_5\text{N}-\text{NH} \end{array} \\ + \text{benzoyl chloride} + \text{pyridine} \end{array}$	146

¹ Wheeler and Stathiropoulos, *Am. Chem. J.*, **34**, 117 (1905).² Wheeler and Dustin, *Am. Chem. J.*, **24**, 424 (1900).³ Freund and Kuh, *Ber.*, **23**, 2821 (1890).⁴ Freund and Wolfe, *Ber.*, **24**, 4178 (1891).⁵ Bailey, *J. Am. Chem. Soc.*, **26**, 1006 (1904).⁶ Busch, *Ber.*, **42**, 4763 (1909).

2,5-Dimercapto-1,3,4-thiadiazole (I), 2-Mercapto-1,3,4-thiadiazol-5(4)-thiones (II) and Related Compounds

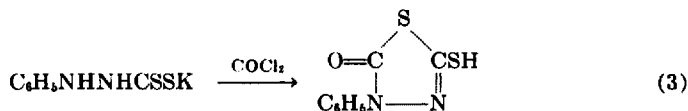
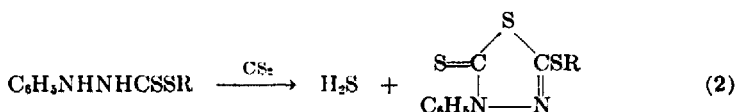
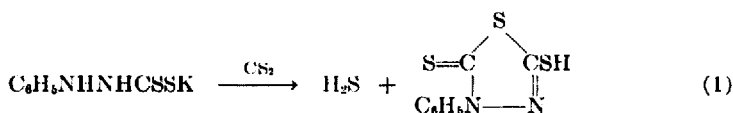


(I)

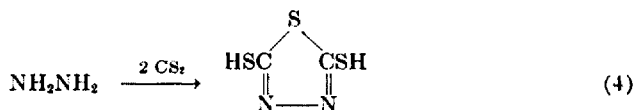


(II)

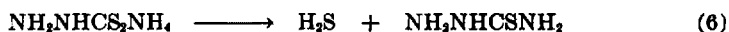
Busch¹ found that carbon disulfide reacted with 2-substituted dithiocarbazates and their esters to form 2-mercapto-1,3,4-thiadiazol-5(4)-thiones (1,2). Phosgene reacted with the dithiocarbazates in a similar manner (3).



2,5-Dimercapto-1,3,4-thiadiazole was synthesized from hydrazine and carbon disulfide (4). Busch and Biehler² used a modification of this method to produce 2-methylmercapto-5-mercapto-1,3,4-thiadiazole (5).



Losanitch³ investigated the formation of 2,5-dimercapto-1,3,4-thiadiazole from ammonium dithiocarbamate. The first step in the reaction was the formation of thiosemicarbazide (6). This thiosemicarbazide reacted

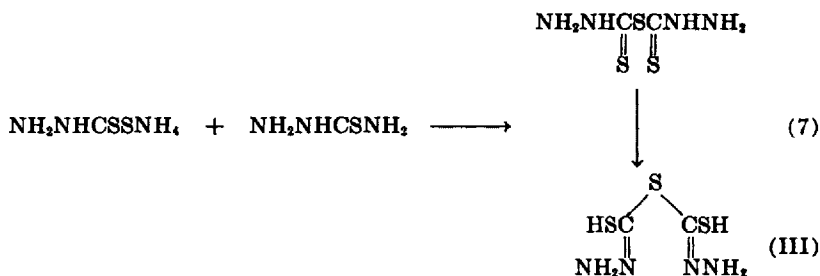


¹ Busch, *Ber.*, 27, 2507 (1894).

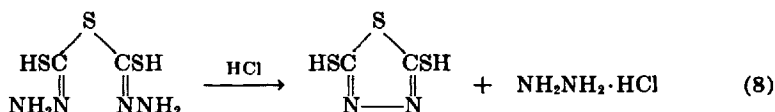
² Busch and Biehler, *J. prakt. Chem.*, [2] 93, 339 (1916).

³ Losanitch, *J. Chem. Soc.*, 121, 2542 (1922).

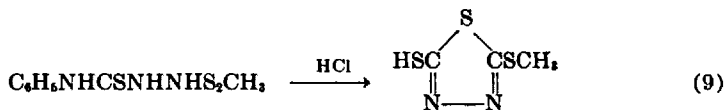
with the ammonium dithiocarbazate to form thiocarbazic thioanhydride which readily tautomerized (7). Busch¹ was inclined to regard compound



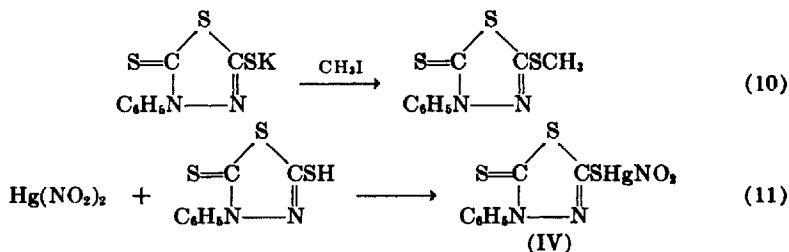
III as the monohydrazine salt of 2,5-dimercapto-1,3,4-thiadiazole, although only strong acid would liberate the free mercaptan. Losanitch² believed that the hydrochloric acid cyclized the thiocarbazic thioanhydride (8).



Methyl iodide and the thiocarbazic thioanhydride gave 2,5-dimethyl-mercapto-1,3,4-thiadiazole which was also obtained from 2,5-dimercapto-1,3,4-thiadiazole. Guha and Guha³ found that reaction (9) took place.



The mercaptans readily formed thioethers with alkyl iodides (10).⁴ Ray *et al.*⁵⁻⁷ found that mercuric nitrite and 2-mercapto-4-phenyl-1,3,4-thiadiazol-5(4)-thione formed a mercuric nitrite salt (11). In the instance

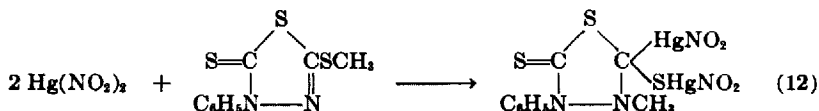


⁴ Guha and Guha, *Chem. Abstr.*, 21, 3199 (1927); *J. Indian Chem. Soc.*, 4, 161 (1927).

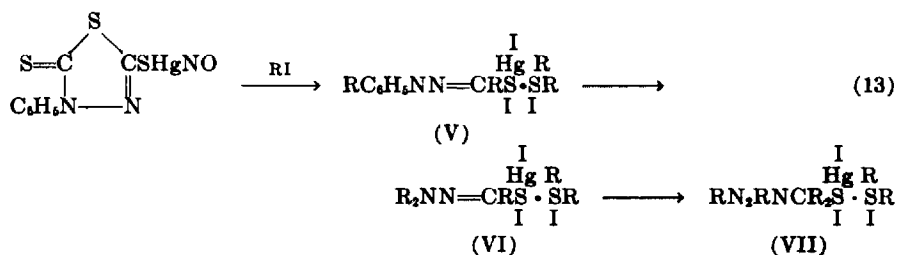
⁵ Ray and Guha, *J. Chem. Soc.*, 115, 261 (1919).

⁶ Ray, Guha, and Das, *J. Chem. Soc.*, 115, 1308 (1919).

⁷ Ray and Das, *J. Chem. Soc.*, 121, 323 (1922).

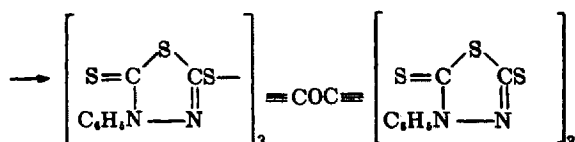
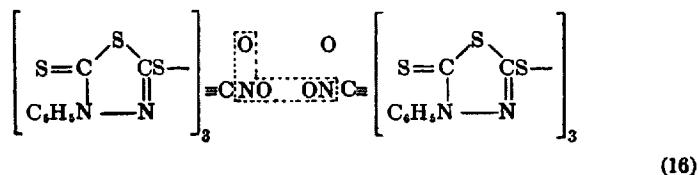
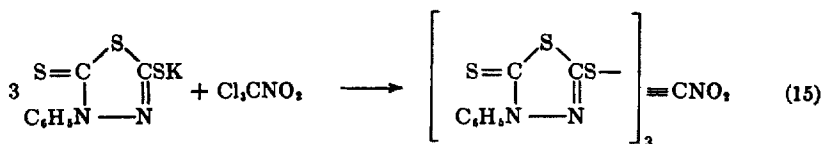
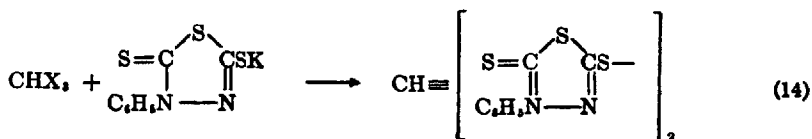


of 2-methylmercapto-4-phenyl-1,3,4-thiadiazol-5(4)-thione the methyl group migrated (12). When compound IV was digested with methyl or ethyl iodides, the ring ruptured and three sulfonium compounds were isolated (13). Compounds V and VII were found when methyl iodide was

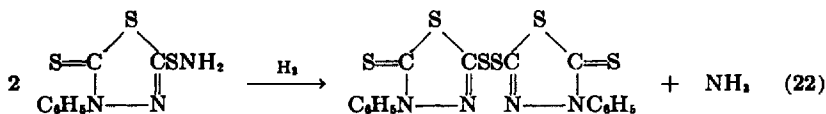


used and VI when ethyl iodide was used. Only analyses were offered as a proof of structure for these compounds.

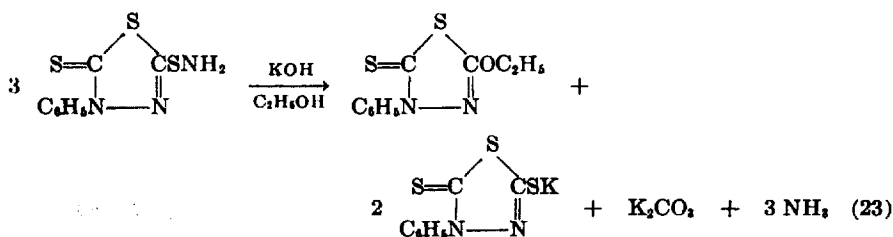
2,5-Dimercapto-1,3,4-thiadiazole and 2-mercapto-4-phenyl-1,3,4-thiadiazol-5(4)-thione reacted with chloroform, bromoform, and iodoform to give trisubstituted methanes (14). Chloropicrin in the cold (30–50°C.) reacted in a typical manner (15). Higher temperatures decomposed the



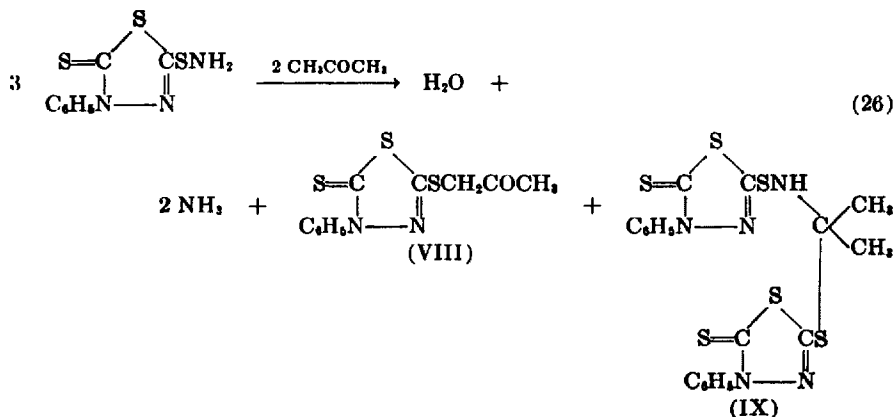
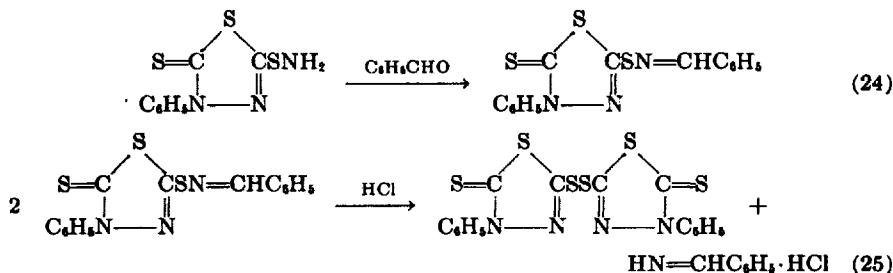
sulfenamides in the presence of a reducing substance gave ammonia and the parent disulfide (22). On treating the sulfenamide with an alcoholic



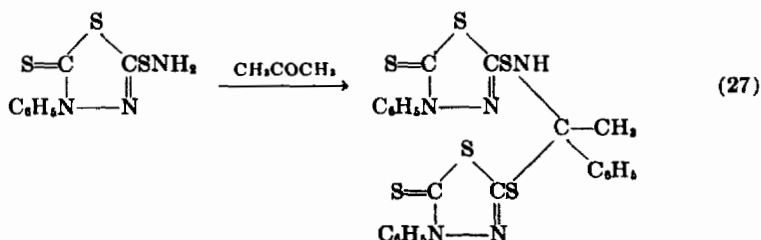
potassium hydroxide solution, 2-ethoxy-1,3,4-thiadiazol-5(4)-thione was formed along with 2-mercapto-4-phenyl-1,3,4-thiadiazol-5(4)-thione (23).



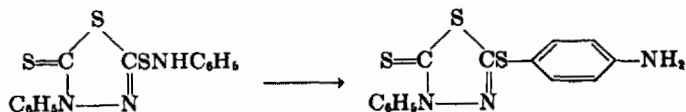
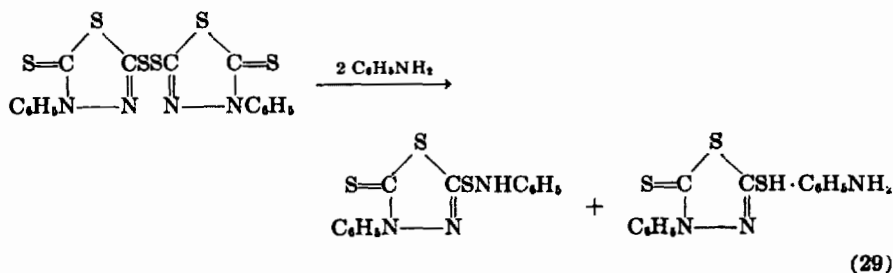
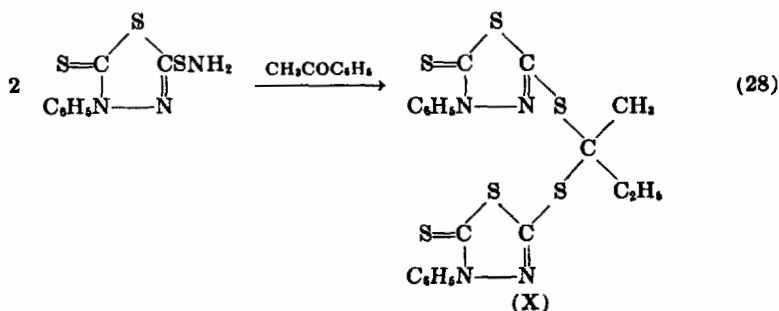
The primary sulfenamides reacted with aldehydes such as benzaldehyde, cinnamaldehyde, etc. (24). Heating these benzylidene-type compounds with hydrochloric acid yielded the parent disulfide (25).



Acetone and the sulfenamides gave two products¹³: 2-acetylmercapto-4-aryl-1,3,4-thiadiazol-5(4)-thione (VIII) and 4-phenyl-*N*-[1-(4-phenyl-5-thioxo- Δ^2 -1,3,4-thiadiazol-2-yl)mercapto]isopropyl]-5-thioxo- Δ^2 -1,3,4-thiadiazoline-2-sulfenamide (IX) (26). Acetophenone yielded a compound similar to (IX) (27). Methyl ethyl ketone and the sulfenamides



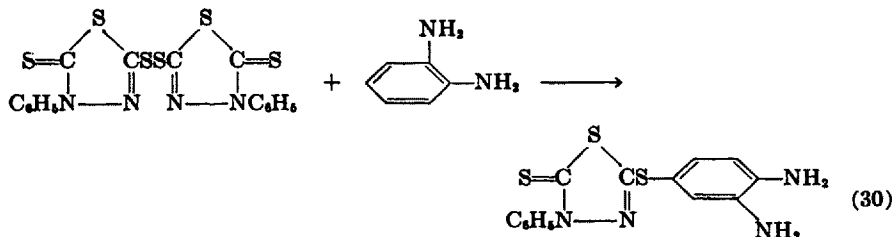
produced still another type of compound (28), 2,2'-(*sec*-butylidenedithio) bis(4-phenyl-1,3,4-thiadiazol-5(4)-thione) (X).



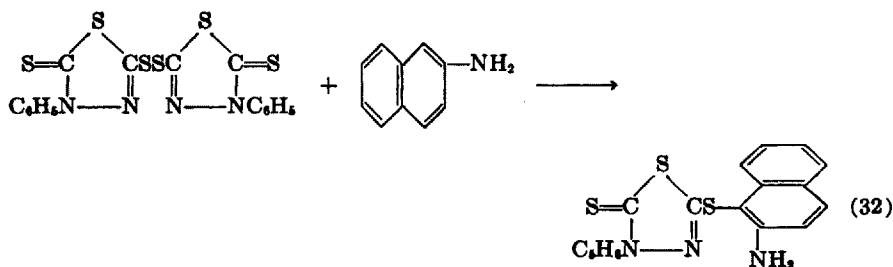
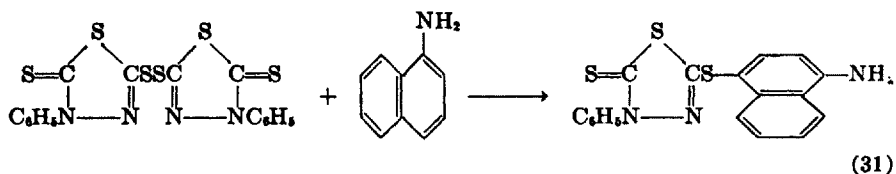
¹³ Busch and Wolf, *J. prakt. Chem.*, [2] 60, 197 (1899).

¹⁴ Busch, *Ber.*, 29, 2127 (1896).

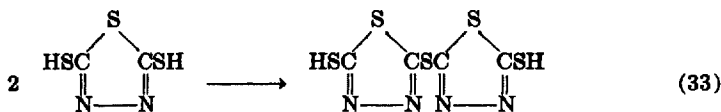
Busch¹⁴ found that the disulfides reacted with aryl amines (primary and secondary, but not tertiary) to form the sulfenamides, which immediately rearranged to the sulfides (29).



The *ortho*- and *meta*-phenylenediamines gave similar reactions (30).¹⁵ The α - and β -naphthylamines underwent like rearrangements (31,32). These amines on the aryl or naphthyl nuclei exhibited all the properties of aromatic amines.



Losanitch¹⁶ found that refluxing an aqueous solution of 2,5-dimercapto-1,3,4-thiadiazole for several days produced 2,2'-bis(5-mercapto-1,3,4-thiadiazoly) sulfide (33). Guha and Janniah¹⁷ obtained the same com-



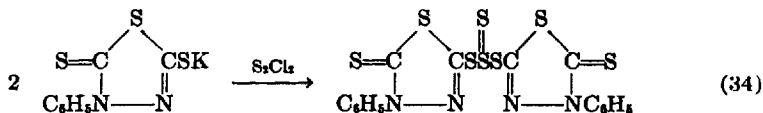
¹⁴ Busch and Wolf, *J. prakt. Chem.*, [2] 60, 192 (1899).

¹⁵ Losanitch, *J. Chem. Soc.*, 121, 2542 (1922).

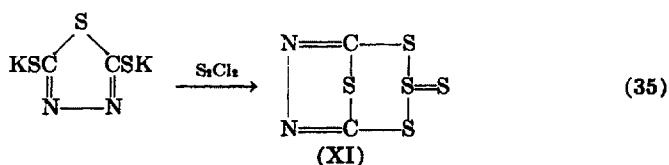
¹⁷ Guha and Janniah, *J. Indian Inst. Sci.*, A21, 60 (1938); *Chem. Abstr.*, 33, 599 (1939).

pound from 2,5-dimercapto-1,3,4-thiadiazole and acetic anhydride. This compound formed the bis(thioether) with methyl iodide.

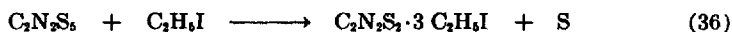
Chakravarti¹⁸ investigated the reactions of sulfur monochloride with the mercaptans of this series. Sulfur monochloride and 2-mercapto-4-phenyl-1,3,4-thiadiazol-5(4)-thione produced a tetrasulfide or, more correctly, 2,2'-tetrathiobis(4-phenyl-5-thioxo- Δ^2 -1,3,4-thiadiazoline) (34).



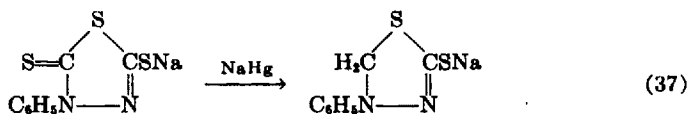
Methyl and ethyl iodides formed complexes in which seven alkyl halides add to the molecule ($\text{C}_{16}\text{H}_{10}\text{S}_8\text{N}_4 \cdot 7 \text{CH}_3\text{I}$ and $\text{C}_{16}\text{H}_{10}\text{S}_8\text{N}_4 \cdot 7 \text{C}_2\text{H}_5\text{I}$). The 2,5-dimercapto-1,3,4-thiadiazole apparently reacted with only one molecule of sulfur chloride which yielded a structure (35) designated as 3-



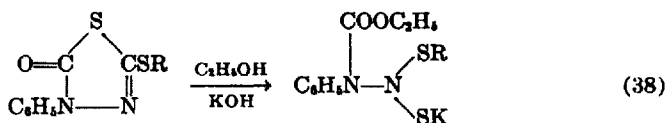
thio-2,3,4,8-tetrathia-6,7-diazabicyclo[3.2.1]octa-5,7-diene (XI). Only analyses substantiated this structure (XI). Refluxing compound XI with ethyl iodide yielded sulfur and a compound containing three molecules of ethyl iodide (36).



Reduction of 2-mercapto-1,3,4-thiadiazol-5(4)-thiones with sodium amalgam yielded 2-mercapto- Δ^2 -1,3,4-thiadiazoline (37).¹⁹



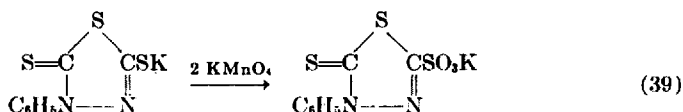
2-Alkylmercapto-4-phenyl-1,3,4-thiadiazol-5(4)-ones²⁰ were decomposed by warm alcoholic potassium hydroxide (38). Oxidation¹⁹ of these 2-mercapto-1,3,4-thiadiazol-5(4)-thiones with potassium permanganate



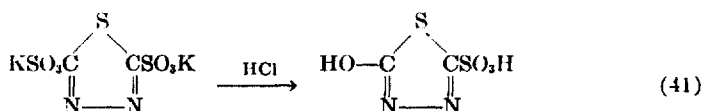
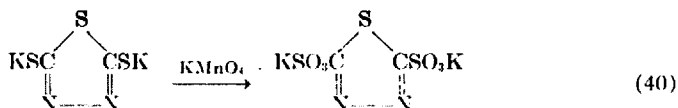
¹⁸ Chakravarti, *J. Chem. Soc.*, 123, 964 (1923).

¹⁹ Busch and Stramer, *J. prakt. Chem.*, [2] 60, 189 (1899).

²⁰ Busch, *Ber.*, 27, 2507 (1894).



produced sulfonic acids (39). A disulfonic acid was also synthesized from 2,5-dimercapto-1,3,4-thiadiazole (40).²¹ Refluxing the sulfonic acid in concentrated hydrochloric acid gave 2-sulfo-5-hydroxy-1,3,4-thiadiazole (41).

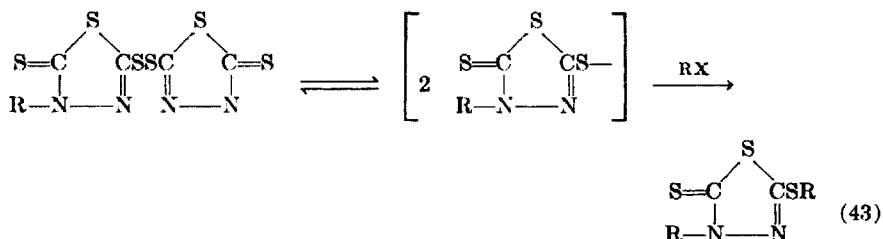
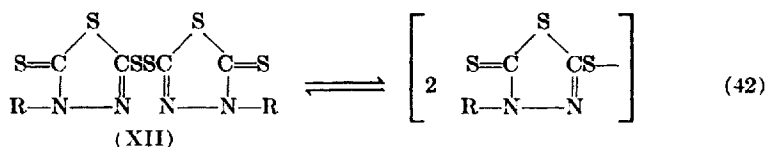


Potassium 1,3,4-thiadiazole-2,5-disulfonate was heated at 200°C. in hydrochloric acid and the decomposition products were hydrogen sulfide, sulfur dioxide, sulfur, and potassium sulfate.

Discussion

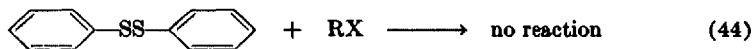
These compounds exhibited all the properties of mercaptans, *i.e.*, formation of thioethers, oxidation to the disulfides and sulfonic acids, and the formation of sulfenamides. The fact that these mercaptides can be oxidized to the sulfonic acid without rupturing the ring is an indication of the stability of the 1,3,4-thiadiazole nucleus.

The reactions of the 2,2'-dithiobis(1,3,4-thiadiazol-5(4)-thione)s (XII) suggest the presence of a 2-thio-1,3,4-thiadiazol-5-thione radical (42).

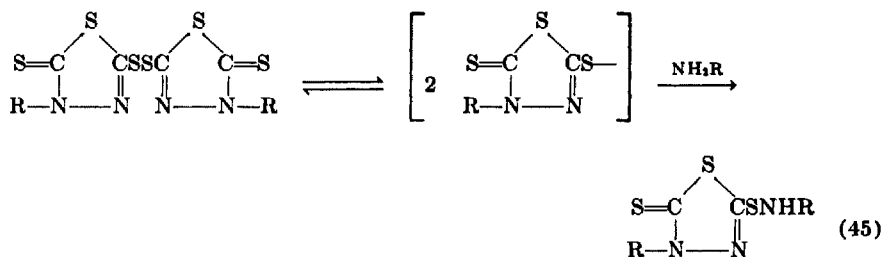


²¹ Busch and Ziegele, *J. prakt. Chem.*, [2] 60, 40 (1899).

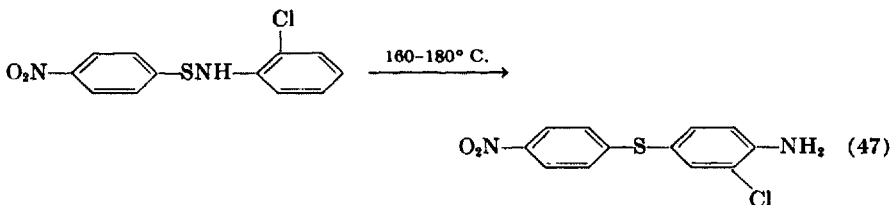
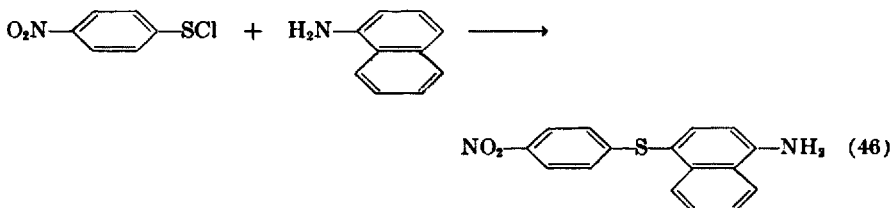
Alkylation of XII with an alkyl halide yields the thioether (43). Aryl or alkyl disulfides do not react with alkylhalides (44). Structure XII reacts



with amines to give sulfenamides, while aliphatic and aryl disulfides do not give a comparable reaction (45).



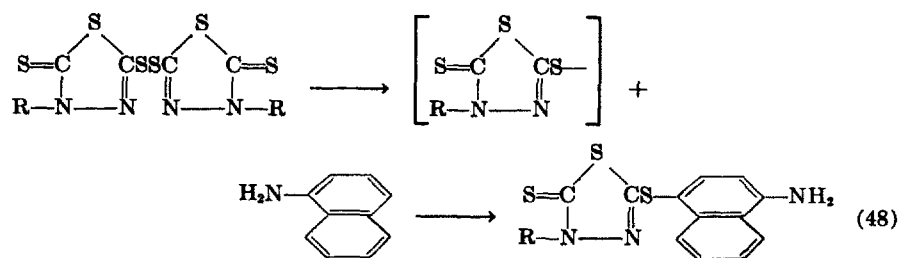
Zincke²² found that *p*-nitrophenylsulfenyl chloride, on reacting with some aromatic amines, gave the sulfenamide which rearranged to the sulfide (46).



Moore and Johnson²³ found that rather severe conditions were required to rearrange some of the sulfenamides (47). Structure XII reacted readily with naphthylamine to give the sulfide (48).

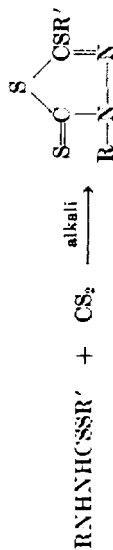
²² Zincke, *Ann.*, **400**, 2 (1913).

²³ Moore and Johnson, *J. Am. Chem. Soc.*, **58**, 1091 (1936).



Tables XXIX-XXXVII follow on pages 188-198.

TABLE XXIX. 2,5-Dimercapto-1,3,4-thiadiazoles and 2-Mercapto-1,3,4-thiadiazol-5(4)-thiones Prepared by Ring Closure Employing a Dithiocarbamic Acid or Ester and Carbon Disulfide



No.	Name	Ref.	Solubility	M.p., °C.
1	2,5-Dimercapto-1,3,4-thiadiazole	1, 2	ether	167-8
2	2-Mercapto-4-methyl-1,3,4-thiadiazol-5(4)-thione	3	ether	69
3	2-Mercapto-4-phenyl-1,3,4-thiadiazol-5(4)-thione	1	—	90-1
4	2-Mercapto-4- <i>p</i> -tolyl-1,3,4-thiadiazol-5(4)-thione	4	ether	155
5	2-Mercapto-4- <i>o</i> -tolyl-1,3,4-thiadiazol-5(4)-thione	5	alc., ether, benzene, CHCl_3	—
6	2-Mercapto-4- α -naphthyl-1,3,4-thiadiazol-5(4)-thione	5	ether	127
7	2-Mercapto-4- β -naphthyl-1,3,4-thiadiazol-5(4)-thione	5	alc., benzene	160
8	2-Mercapto-4- <i>o</i> -anisyl-1,3,4-thiadiazol-5(4)-thione	5	benzene	119-20

¹ Busch, *Ber.*, 27, 2507 (1894).

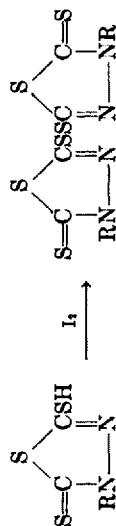
² Losanitch, *J. Chem. Soc.*, 121, 2542 (1922).

³ Busch and Ziegele, *J. prakt. Chem.*, [2] 60, 40 (1899).

⁴ Busch and Baur-Breitenfeld, *J. prakt. Chem.*, [2] 60, 206 (1899).

⁵ Busch and Munkner, *J. prakt. Chem.*, [2] 60, 212 (1899).

TABLE XXXI. Preparation of the 2,2'-Dithiobis(5-mercapto-1,3,4-thiadiazoles), the 2,2'-Dithiobis(1,3,4-thiadiazol-5(4)-thione)s and the Related Compounds. (These compounds were produced by the oxidation of the mercaptans by iodine or ferric chloride. The only exception is 2,5-dimercaptothiadiazole, which was oxidized with ferric chloride, and a polymer resulted)



No.	Name	Ref.	Solubility	M.p., °C.
1	2,2'-Dithiobis(5-mercapto-1,3,4-thiadiazole)	1	methanol, alc.	175
2	Poly-[2,2'-dithio-5,5'-dithio-1,3,4-thiadiazole]	1	alc.	207
3	2,2'-Dithiobis(4-methyl-1,3,4-thiadiazol-5(4)-thione)	1	alc.	138-41
4	2,2'-Dithiobis(4-phenyl-1,3,4-thiadiazol-5(4)-thione)	2	ethyl acetate, CHCl_3	124-5
5	2,2'-Dithiobis(4- <i>p</i> -tolyl-1,3,4-thiadiazol-5(4)-thione)	3	alc.	139-40
6	2,2'-Dithiobis(4- <i>o</i> -tolyl-1,3,4-thiadiazol-5(4)-thione)	4	—	—
7	2,2'-Dithiobis(4- α -naphthyl-1,3,4-thiadiazol-5(4)-thione)	4	CHCl_3 , alc.	228
8	2,2'-Dithiobis(4- β -naphthyl-1,3,4-thiadiazol-5(4)-thione)	4	—	188
9	2,2'-Dithiobis(4- <i>o</i> -anisyl-1,3,4-thiadiazol-5(4)-thione)	4	—	174-5
10	2,2'-Dithiobis(5-methylmercapto-1,3,4-thiadiazole)	5	—	70-8

¹ Busch and Ziegler, *J. prakt. Chem.*, [2] 60, 40 (1899).

² Busch, *Ber.* 27, 2507 (1894).

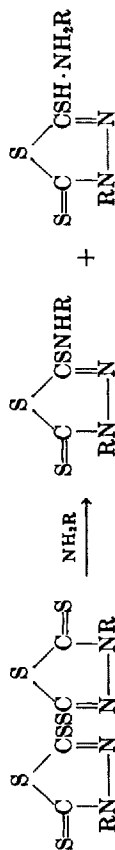
³ Busch and Baur-Breitenfeld, *J. prakt. Chem.*, [2] 60, 206 (1899).

⁴ Busch and Mumker, *J. prakt. Chem.*, [2] 60, 212 (1899).

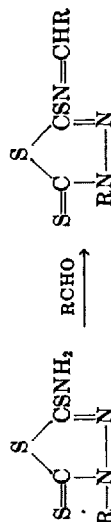
⁵ Busch and Biehler, *J. prakt. Chem.*, [2] 93, 339 (1916).

TABLE XXXII. Preparation of the 5-Mercapto-1,3,4-thiadiazole-2-sulfenamides, the 5-Thioxo-1,3,4-thiadiazole-2-sulfenamides and Related Compounds

The sulfenamides were prepared by the action of ammonia or alkylamines on the 2,2'-dithiobis(5-thioxo- Δ^1 ,3,4-thiadiazoline).



The *N*-benzylidene type of sulfenamides were prepared by allowing the sulfenamides to react with aryl aldehydes.



No.	Name	Ref.	Solubility	M.p., °C.
1	4-Phenyl-5-thioxo- Δ^1 ,3,4-thiadiazoline-2-sulfenamide	1	benzene, ligroin	130-6
2	4-Phenyl-5-thioxo- Δ^1 ,3,4-thiadiazoline-2-sulfenmethylanilide	1	alc.	85
3	4-Phenyl-5-thioxo- Δ^1 ,3,4-thiadiazoline-2-sulfenethylanilide	1	benzene	95-6
4	4-Phenyl-5-thioxo- Δ^1 ,3,4-thiadiazoline-2-sulfendimethylanilide	1	alc.	117-8
5	4-Phenyl-5-thioxo- Δ^1 ,3,4-thiadiazoline-2-sulfenamide, <i>N</i> -benzylidene	1	—	153-4
6	4-Phenyl-5-thioxo- Δ^1 ,3,4-thiadiazoline-2-sulfenamide, <i>N</i> -cinnamylidene	1	benzene, alc., CHCl_3	172-3
7	4-Phenyl-5-thioxo- Δ^1 ,3,4-thiadiazoline-2-sulfenamide, <i>N</i> -furfurylidene	2	benzene, CHCl_3	152
8	4-Phenyl-5-thioxo- Δ^1 ,3,4-thiadiazoline-2-sulfenamide, <i>N</i> - <i>p</i> -nitrobenzylidene	2	benzene, CHCl_3	173-4
9	4-Phenyl-5-thioxo- Δ^1 ,3,4-thiadiazoline-2-sulfenamide, <i>N</i> - <i>p</i> -anisylidene	2	alc., benzene, CHCl_3	145-6
10	4-Phenyl-5-thioxo- Δ^1 ,3,4-thiadiazoline-2-sulfenamide, <i>N</i> -piperonylidene	2	benzene, alc., CHCl_3	186-7
11	4- <i>p</i> -Tolyl-5-thioxo- Δ^1 ,3,4-thiadiazoline-2-sulfenamide	3	CHCl_3 , ether, alc., benzene	150
12	4- <i>p</i> -Tolyl-5-thioxo- Δ^1 ,3,4-thiadiazoline-2-sulfenethylanilide	3	alc., benzene	118-9
13	4- <i>p</i> -Tolyl-5-thioxo- Δ^1 ,3,4-thiadiazoline-2-sulfendimethylanilide	3	alc.	85
14	4-Phenyl-5-thioxo- Δ^1 ,3,4-thiadiazoline-2-sulfen- <i>p</i> -sulfonamidoanilide	4	—	155

¹ Busch, *Ber.*, 29, 2127 (1896).

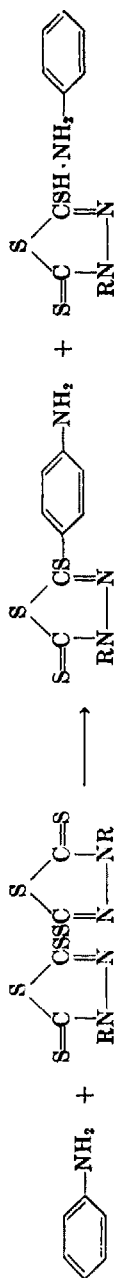
² Busch and Wolf, *J. prakt. Chem.*, [2] 60, 192 (1899).

³ Busch and Baur-Breitenfeld, *J. prakt. Chem.*, [2] 60, 206 (1899).

⁴ Guha and Dopia, *Chem. Abstr.*, 38, 6278 (1943); *Current Sci. (India)*, 12, 120 (1943).

TABLE XXXIII. Preparation of the 2-*p*-Aminophenylmercapto- $\Delta^2,1,3,4$ -thiadiazol-5(4)-thiones and 2-Aminonaphthylmercapto- $\Delta^2,1,3,4$ -thiadiazol-5(4)-thiones and Their Derivatives

These compound were prepared by allowing the arylamine to react with the 2,2'-dithiobis(5-thioxo- $\Delta^2,1,3,4$ -thiadiazoline).



No	Name	Ref.	Solubility	M.p., °C.
1	2- <i>p</i> -Aminophenylmercapto-5-mercapto-1,3,4-thiadiazole	1	hot water, alc., ether	187 (HCl, 206)
2	2-(2'-Hydroxy-1'-naphthylazophenylmercapto)-5-mercapto-1,3,4-thiadiazole (from compound 1)	1	CHCl ₃ , alc.	223
3	2- <i>p</i> -Aminophenylmercapto-4-phenyl-5-thioxo- $\Delta^2,1,3,4$ -thiadiazoline	2	alc., ether, benzene, CHCl ₃	163-4
4	2-Phenylmercapto-4-phenyl-5-thioxo- $\Delta^2,1,3,4$ -thiadiazoline (from compound 3)	2	alc.	—
5	2-(4'-Amino-3'-methylphenylmercapto)-4-phenyl-5-thioxo- $\Delta^2,1,3,4$ -thiadiazoline	2	ether	128
6	2-(4'-Ethylaminophenylmercapto)-4-phenyl-5-thioxo- $\Delta^2,1,3,4$ -thiadiazoline	2	alc., ether, benzene	165
7	2-(4'-Nitrosoethylaminophenylmercapto)-4-phenyl-5-thioxo- $\Delta^2,1,3,4$ -thiadiazoline (from compound 6)	2	alc.	136-8
8	2-(3'-4'-Diaminophenylmercapto)-4-phenyl-5-thioxo- $\Delta^2,1,3,4$ -thiadiazoline	3	—	—
9	2-(6'-Benzotriazolylmercapto)-4-phenyl-5-thioxo- $\Delta^2,1,3,4$ -thiadiazoline (from compound 8)	3	alc.	186-7
10	2-(2'-4'-Diaminophenylmercapto)-4-phenyl-5-thioxo- $\Delta^2,1,3,4$ -thiadiazoline	3	alc.	164-5
11	2-(1'-Amino-4'-naphthylmercapto)-4-phenyl-5-thioxo- $\Delta^2,1,3,4$ -thiadiazoline	3	acetone, alc., CHCl ₃	132-3
12	2-(2'-Amino-1'-naphthylmercapto)-4-phenyl-5-thioxo- $\Delta^2,1,3,4$ -thiadiazoline	3	alc.	152
13	2- <i>p</i> -Aminophenylmercapto-4- <i>p</i> -tolyl-5-thioxo- $\Delta^2,1,3,4$ -thiadiazoline	4	benzene, CHCl ₃	173
14	2- <i>p</i> -Methylaminophenylmercapto-4- <i>p</i> -tolyl-5-thioxo- $\Delta^2,1,3,4$ -thiadiazoline	4	alc., benzene, CHCl ₃ , acetic acid	184
15	2- <i>p</i> -Aminophenylmercapto-4- <i>o</i> -tolyl-5-thioxo- $\Delta^2,1,3,4$ -thiadiazoline	4	—	128

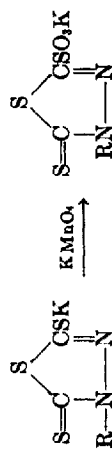
¹ Busch and Ziegele, *J. prakt. Chem.*, [2] 60, 40 (1899).

² Busch and Wolff, *J. prakt. Chem.*, [2] 60, 192 (1899).

³ Busch and Baur-Breitenfeld, *J. prakt. Chem.*, [2] 60, 206 (1899).

TABLE XXXIV. Preparation of the 1,3,4-Thiadiazolesulfonic Acids and the 5-Thioxo- Δ^2 -1,3,4-thiadiazolinesulfonic Acids

These sulfonic acids were prepared by oxidizing the mercaptans with potassium permanganate.



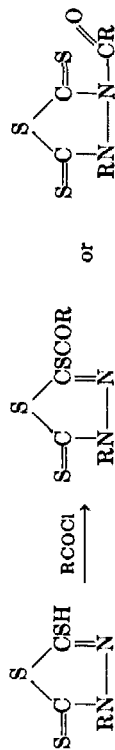
No.	Name	Ref.	Solubility	M.p., °C.
1	1,3,4-Thiadiazole-2,5-disulfonic acid	1	water	—
2	2-Hydroxy-1,3,4-thiadiazole-5-sulfonic acid (from compound 1)	1	—	—
3	4-Methyl-5-thioxo- Δ^2 -1,3,4-thiadiazoline-2-sulfonic acid	1	water	—
4	4-Phenyl-5-thioxo- Δ^2 -1,3,4-thiadiazoline-2-sulfonic acid	2	water	268
5	4- <i>p</i> -Tolyl-5-thioxo- Δ^2 -1,3,4-thiadiazoline-2-sulfonic acid	3	alc., water	—
6	4- β -Naphthyl-5-thioxo- Δ^2 -1,3,4-thiadiazoline-2-sulfonic acid	4	water	—

¹ Busch and Ziegele, *J. prakt. Chem.*, [2] 60, 40 (1899).

² Busch and Baur-Breitenfeld, *J. prakt. Chem.*, [2] 60, 206 (1899).

⁴ Busch and Mumker, *J. prakt. Chem.*, [2] 60, 212 (1899).

TABLE XXXV. Preparation of Acyl Derivatives of 2-Mercapto-1,3,4-thiadiazol-5(4)-thiones Which Are Probably 2-Acylmercapto-1,3,4-thiadiazol-5(4)-thiones



No.	Name	Ref.	Solubility	M.p., °C.
1	2-Acetylmercapto-4-phenyl-1,3,4-thiadiazol-5(4)-thione	1	alc.	121-2
2	2-Benzylmercapto-5-mercapto-1,3,4-thiadiazole	1	alc.	220 dec.
3	2-5-Bis(benzoylmercapto)-1,3,4-thiadiazole	1	alc., ethyl acetate	184-5
4	2-Benzylmercapto-4-phenyl-1,3,4-thiadiazol-5(4)-thione	2	benzene, CHCl ₃	154
5	2-Benzylmercapto-4- <i>p</i> -tolyl-Δ ² -1,3,4-thiadiazol-5(4)-thione	3	—	100
6	2-Acetylmercapto-4- <i>p</i> -tolyl-Δ ² -1,3,4-thiadiazol-5(4)-thione	3	—	158
7	2-Benzylmercapto-4-α-naphthyl-Δ ² -1,3,4-thiadiazol-5(4)-thione	4	alc.	146

¹ Busch, *Ber.*, 27, 2507 (1894).

² Busch and Stramer, *J. prakt. Chem.*, [2] 60, 187 (1899).

³ Busch and Baur-Breitenfeld, *J. prakt. Chem.*, [2] 60, 206 (1899).

⁴ Busch and Mumker, *J. prakt. Chem.*, [2] 60, 212 (1899).

TABLE XXXVI. Halogen Addition Compounds of the 2-Mercapto-5-thioxo-1,3,4-thiadiazolines Prepared by the Addition of Halogens to the Compounds. Their Structure Is Not Known.

No.	Name	Ref.	Solubility	M.p., °C.
1	2-Methylmercapto-4-methyl-5-thioxo-Δ ² -1,3,4-thiadiazoline dibromide	1	benzene	124
2	2-Ethylmercapto-4-phenyl-5-thioxo-Δ ² -1,3,4-thiadiazoline dibromide	2	benzene	131
3	2-Ethylmercapto-4-phenyl-5-thioxo-Δ ² -1,3,4-thiadiazoline diiodide	2	benzene	123

¹ Busch and Ziegele, *J. prakt. Chem.*, [2] 60, 40 (1899).

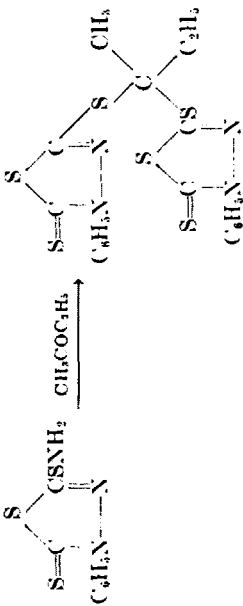
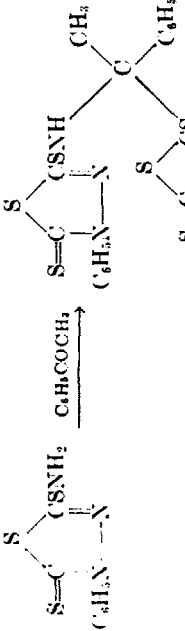
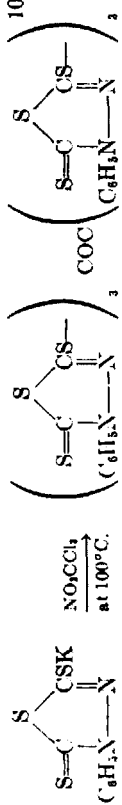
² Busch and Stramer, *J. prakt. Chem.*, [2] 60, 187 (1899).

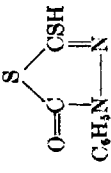
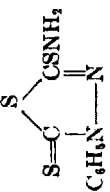
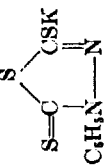
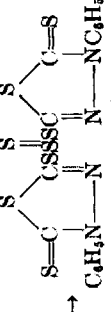
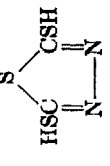
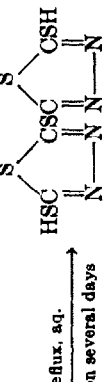
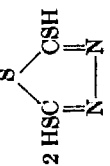
TABLE XXXVII. Preparation of 2,5-Mercapto-1,3,4-thiadiazoles, 2-Mercapto-1,3,4-thiadiazol-5(4)-thiones and Related Compounds by Methods Other Than Those Given in Tables XXIX-XXXVI

No.	Name	Ref.	Method of preparation	M.p., °C.
1	2-Benzylmercapto-5-mercapto-1,3,4-thiadiazole	1	$ \begin{array}{c} \text{S} \quad \text{S} \\ \diagup \quad \diagdown \\ \text{C} \quad \text{C} \\ \diagdown \quad \diagup \\ \text{N} \quad \text{N} \\ \text{C}_6\text{H}_5\text{CH}_2\text{SC} \quad \text{CSCH}_2\text{C}_6\text{H}_5 + \text{alc. ammonia} \end{array} $	131
2	2-Phenylazomercapto-4-phenyl- Δ^2 -1,3,4-thiadiazol-5(4)-thione	2	$ \begin{array}{c} \text{S} \quad \text{S} \\ \diagup \quad \diagdown \\ \text{C} \quad \text{C} \\ \diagdown \quad \diagup \\ \text{N} \quad \text{N} \\ \text{CSH} \quad \text{CSN}_2\text{C}_6\text{H}_5 \\ \text{C}_6\text{H}_5\text{N} \quad \text{C}_6\text{H}_5\text{N} \end{array} \xrightarrow{\text{C}_6\text{H}_5\text{N}_2\text{Cl}} \begin{array}{c} \text{S} \quad \text{S} \\ \diagup \quad \diagdown \\ \text{C} \quad \text{C} \\ \diagdown \quad \diagup \\ \text{N} \quad \text{N} \\ \text{CSN}_2\text{C}_6\text{H}_5 \quad \text{CSN}_2\text{C}_6\text{H}_5 \end{array} $	—
3	2-Acetylmercapto-4-phenyl-1,3,4-thiadiazol-5(4)-thione	3	$ \begin{array}{c} \text{S} \quad \text{S} \\ \diagup \quad \diagdown \\ \text{C} \quad \text{C} \\ \diagdown \quad \diagup \\ \text{N} \quad \text{N} \\ \text{CSNH}_2 \quad \text{CSCH}_2\text{COCH}_3 \\ \text{C}_6\text{H}_5\text{N} \quad \text{C}_6\text{H}_5\text{N} \end{array} \xrightarrow{\text{CH}_3\text{COCH}_3} \begin{array}{c} \text{S} \quad \text{S} \\ \diagup \quad \diagdown \\ \text{C} \quad \text{C} \\ \diagdown \quad \diagup \\ \text{N} \quad \text{N} \\ \text{CSCH}_2\text{COCH}_3 \quad \text{CSCH}_2\text{COCH}_3 \end{array} $	98-9
4	4-Phenyl-N-[1-(4-phenyl-5-thioxo- Δ^2 -1,3,4-thiadiazolinyl)-2-mercapto]isopropyl]-5-thioxo- Δ^2 -1,3,4-thiadiazoline-2-sulfenamide	3	$ \begin{array}{c} \text{S} \quad \text{S} \\ \diagup \quad \diagdown \\ \text{C} \quad \text{C} \\ \diagdown \quad \diagup \\ \text{N} \quad \text{N} \\ \text{CSNH} \quad \text{CSCH}_2\text{COCH}_3 \\ \text{C}_6\text{H}_5\text{N} \quad \text{C}_6\text{H}_5\text{N} \end{array} \xrightarrow{\text{CH}_3\text{COCH}_3} \begin{array}{c} \text{S} \quad \text{S} \\ \diagup \quad \diagdown \\ \text{C} \quad \text{C} \\ \diagdown \quad \diagup \\ \text{N} \quad \text{N} \\ \text{CSNH} \quad \text{CSCH}_2\text{COCH}_3 \\ \text{C}_6\text{H}_5\text{N} \quad \text{C}_6\text{H}_5\text{N} \end{array} $	186

(Table continued)

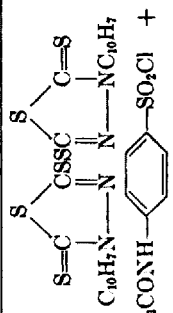
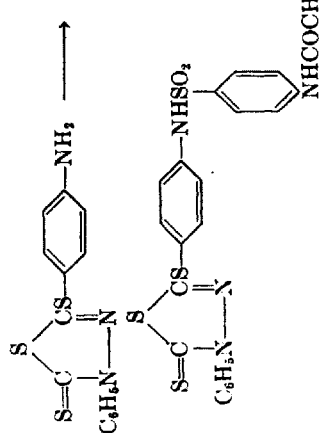
TABLE XXXVII (Continued)

No.	Name	Ref.	Method of preparation	M.P., °C.
5	2,2'-(<i>sec</i> -isobutyldiene)-bis(4-phenyl-1,3,4-thiadiazol-5(4)-thione)	3		oil
6	4-Phenyl-N-[1-(4-phenyl-5-thioxo-Δ ² -1,3,4-thiadiazolyl)-2-mercapto]-α-methylbenzyl-5-thioxo-Δ ² -1,3,4-thiadiazoline-2-sulfenamide	3		158-9
7	Hexakis(4-phenyl-5-thioxo-Δ ² -1,3,4-thiadiazolyl)mercapto)-dimethylether	4		106-7
8	2-Ethoxy-4-phenyl-1,3,4-thiadiazol-5(4)-thione	5		87-8

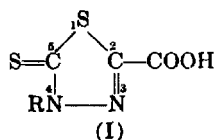
No.	Name	Ref.	Method of preparation	M.p., °C.
9	2-Mercapto-4-phenyl-1,3,4-thiadiazol-5-(4)-one	6	$C_6H_5NHNHCSSK \xrightarrow{COCl_2}$ 	86-7
10	2,2'-Dithiobis(4-phenyl-1,3,4-thiadiazol-5-(4)-one)	6	oxidation of compound 9	78-9
11	2,2'-Tetrathiobis(4-phenyl-1,3,4-thiadiazol-5-(4)-thione)	5	 $\xrightarrow{\text{heat to m.p.}}$ exact structure unknown	131-2
12	2,2'-Tetrathiobis(4-phenyl-1,3,4-thiadiazol-5-(4)-thione)	7	 $\xrightarrow{S_2Cl_2}$ 	131-2
13	2,2'-Thiobis(5-mercapto-1,3,4-thiadiazole)	8	 $\xrightarrow{\text{reflux. aq.}}$  $\xrightarrow{\text{solution several days}}$	178
14	2-Methylmercapto-5-mercapto-1,3,4-thiadiazole	12	 $\xrightarrow{\text{acetic anhydride}}$ 	180
14	2-Methylmercapto-5-mercapto-1,3,4-thiadiazole	9	$NH_4NHCSSCH_3 + KSCN$	136

(Table continued)

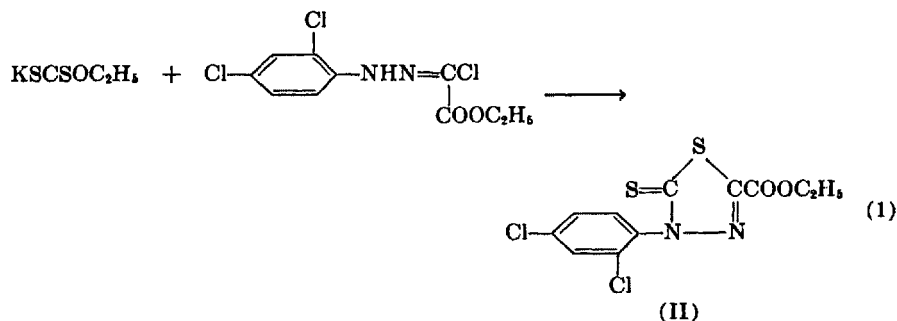
TABLE XXXVII (Concluded)

No.	Name	Ref.	Method of preparation	M.p., °C.
15	2-Methylmercapto-4- β -naphthyl-1,3,4-thiadiazol-5(4)-thione	10	 $\text{C}_{10}\text{H}_7\text{N}=\text{N}=\text{N}=\text{C}(\text{S})\text{SC}(\text{S})\text{C}(\text{S})\text{C}_6\text{H}_4\text{SO}_2\text{Cl} + \text{CHI}_3$	112
16	2-(Acetylsulfanylanilido- <i>p</i> -mercapto)-4-phenyl-1,3,4-thiadiazolid-5(4)-thione	11	 $\text{CH}_3\text{CONH}-\text{C}_6\text{H}_4-\text{SO}_2\text{Cl} + \text{C}_6\text{H}_5\text{N}=\text{N}=\text{N}=\text{C}(\text{S})\text{SC}(\text{S})\text{C}(\text{S})\text{C}_6\text{H}_4\text{NH}_2 \longrightarrow$	222
17	2(Sulfanylanilido- <i>p</i> -mercapto)-4-phenyl-1,3,4-thiadiazolid-5(4)-thione	11	hydrolysis of compound 16	173

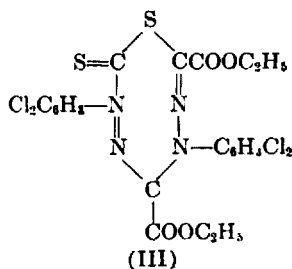
¹ Busch and Ziegele, *J. prakt. Chem.*, [2] 60, 40 (1899).² Busch and Stramer, *J. prakt. Chem.*, [2] 60, 187 (1899).³ Busch and Wolff, *J. prakt. Chem.*, [2] 60, 192 (1899).⁴ Ray and Das, *J. Chem. Soc.*, 121, 323 (1922).⁵ Busch, *Ber.*, 29, 2127 (1896).⁶ Busch, *Ber.*, 27, 2507 (1894).⁷ Chakravarti, *J. Chem. Soc.*, 123, 964 (1923).⁸ Losanitch, *J. Chem. Soc.*, 121, 2542 (1922).⁹ Busch and Biehler, *J. prakt. Chem.*, [2] 93, 339 (1916).¹⁰ Busch and Mumker, *J. prakt. Chem.*, [2] 60, 212 (1899).¹¹ Guha and Dopia, *Chem. Abstr.*, 38, 6278 (1944); *Current Sci. (India)*, 12, 120 (1943).¹² Guha and Janniah, *J. Indian Inst. of Sci.*, A21, 60 (1938); *Chem. Abstr.*, 33, 599 (1939).

2-Carboxy-5-thioxo- Δ^2 -1,3,4-thiadiazolines (I)

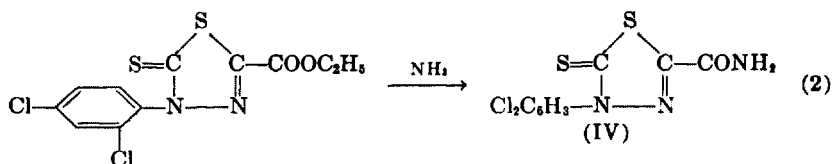
Bulow and Seidel¹ reported the synthesis of 2-carbethoxy-4-(2,4-dichlorophenyl)-5-thioxo- Δ^2 -1,3,4-thiadiazoline from potassium xanthate and



ethyl α -chloro- α -[2,4-dichlorophenylhydrazono]-glyoxylate (1). A by-product of this reaction was thought to be an eight-membered ring (III).

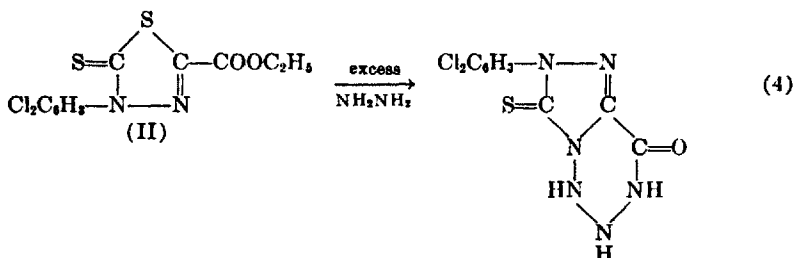
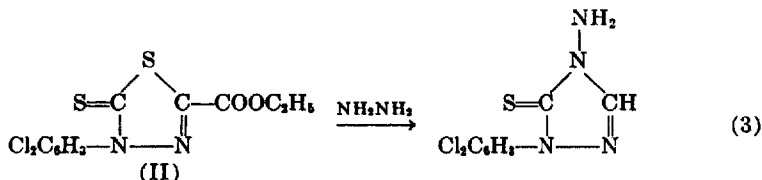


The amide (IV) was prepared from the ester (II) with alcoholic ammonia (2). The ester (II) and an equivalent amount of hydrazine hydrate gave a



¹ Bulow and Seidel, *Ber.*, **57**, 357 (1924).

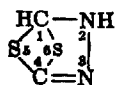
1-amino-4-(2,4-dichlorophenyl)-5-thioxo- Δ^2 -1,3,4-triazoline (3). The ester (II) and an excess of hydrazine yielded a condensed structure (4).



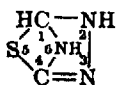
a. 2-Carboethoxy-4-(2,4-dichlorophenyl)-5-thioxo- Δ^2 -1,3,4-thiadiazoline is soluble in alcohol, acetic acid, ether, and acetone; m.p. 122°C.

b. 2-Carbamyl-4-(2,4-dichlorophenyl)-5-thioxo- Δ^2 -1,3,4-thiadiazoline is soluble in alcohol and acetic acid; m.p. 235°C.

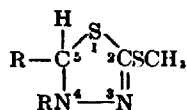
**5,6-Dithia-2,3-diazabicyclo[2.1.1]hex-3-enes (I),
5-Thia-2,3,6-triazabicyclo[2.1.1]hex-3-enes (II),
and Related Δ^2 -1,3,4-Thiadiazolines (III)
or ψ -1,3,4-Thiadiazoles**



(I) *Ring Index* No. 518

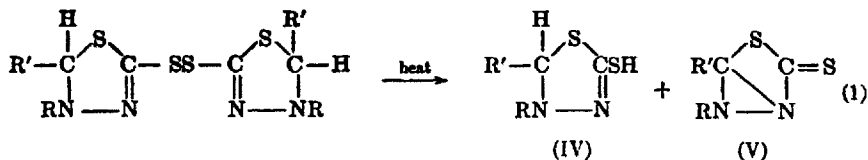


(II) *Ring Index* No. 512



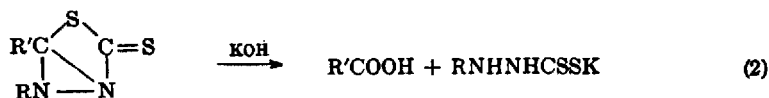
(III)

Busch^{1,2} found that the heating of 2,2'-dithiobis(Δ^2 -1,3,4-thiadiazoline) gave two products: the parent mercaptan (IV) and a compound (V) which he believed contained a bridged nucleus (1). Compound V and alkali



¹ Busch, *Ber.*, 28, 2635 (1895).

² Busch *et al.*, *J. prakt. Chem.*, [2] 60, 25, 187 (1899).



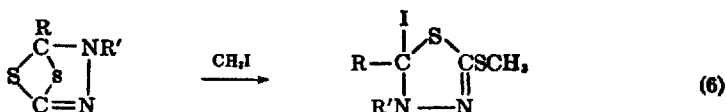
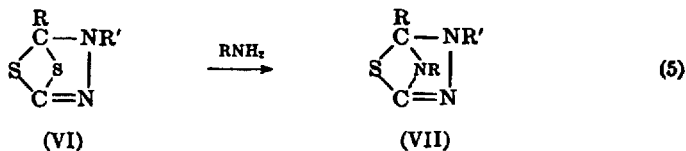
yielded the 2-aryldithiocarbazate (2). The same substance was synthesized with an acyl chloride and a 2-substituted dithiocarbazate, so he assigned the 5,6-dithia-2,3-diazabicyclo[2.1.1]hexene structure to this series of compounds (3). Oxidation³ of the diphenyl derivative with mercuric oxide



yielded some α,β -dibenzhydrazide. A similar oxidation with nitric acid produced benzanilide. Ammonia and aliphatic amines reacted with VI and gave substituted thiosemicarbazides (4). In the instance of benzylamine



and aniline a second compound was obtained which he designated as a 5-thia-2,3,6-triazabicyclo[2.1.1]hex-3-ene (5). Methyl iodide and compound VI produced a 2-methylmercapto-5-iodo- Δ^2 -1,3,4-thiadiazoline (6).

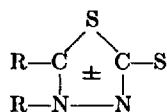


The structure of these compounds is in doubt. They violate Bredt's rule, which says that a double bond may not occur at a bridgehead. While Bredt's rule applied originally to terpenes, it has been shown that in a molecule of the type $\text{X}=\text{C} \begin{array}{l} \diagup \text{Y} \\ \diagdown \text{Z} \end{array}$ all four atoms should be in a plane unless

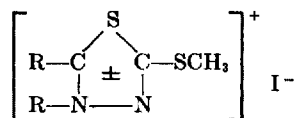
³ Busch *et al.*, *J. prakt. Chem.*, [2] 67, 201 (1903).

extraordinary forces are in operation.⁴ It would seem unlikely that the atoms in structures VI and VII would be in a single plane. Thus, these structures are probably in error.

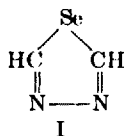
Schonberg⁵ has represented these compounds as monocyclic five membered rings as shown in the following structure:



These views have been supported by Jensen and Friediger,⁶ and Edgerley and Sutton,⁷ who have found that these compounds possess high dipole moments. Baker, Ollis, *et al.*⁸ have studied these sydnones and have used the term meso-ionic to describe these compounds. They differ from Schonberg in that they believe that a resonance structure is not satisfactory to explain their properties. They name such compounds as derivatives of ψ -1,3,4-thiadiazoles. These compounds form methiodides which are probably best represented by this structure:



1,3,4-Selenadiazoles (I)



(Ring Index No. 75)

Stolle¹ prepared the 2,5-dimethyl and the 2,5-diphenyl-1,3,4-selenadiazoles by heating the diacylhydrazide with phosphorus pentaselenide

⁴ Remick, *Electronic Interpretations of Organic Chemistry*. Wiley, New York, 1949, p. 126.

⁵ Schönberg, *J. Chem. Soc.*, 1938, 824.

⁶ Jensen and Friediger, *Kgl. Danske Videnskab. Selskab.*, 20, 1 (1943).

⁷ Edgerley and Sutton, in press; see also footnote 8c.

⁸ (a) Baker, Ollis, and Poole *et al.*, *J. Chem. Soc.*, 1542 (1950); (b) *ibid.*, 311 (1949); (c) *ibid.*, 289 (1951).

¹ Stolle, *J. prakt. Chem.*, [2] 69, 509 (1904).

under reduced pressure. A 10% yield was obtained with a considerable by-product consisting of 2,5-disubstituted 1,3,4-oxadiazole (1). These selenadiazoles formed complexes with silver nitrate.

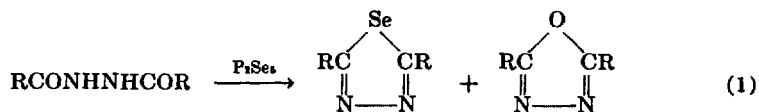
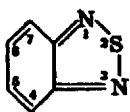


TABLE XXXVIII. 1,3,4-Selenadiazole Derivatives

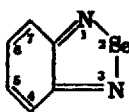
No.	Name	Solubility	M.p., °C.
1	2,5-Dimethyl	alc., ether, water	77
2	2,5-Diphenyl	alc., ether	156

Derivatives of the 2,1,3-Thiadiazoles and Their Selenium Analogs

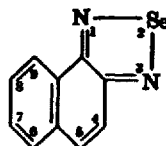
2,1,3-Benzothiadiazoles (I), 2,1,3-Benzoselenadiazoles (II), and Related Compounds (III), (IV), and (V)



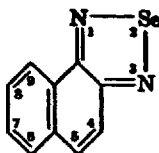
(I) *Ring Index* No. 694



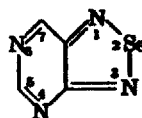
(II) *Ring Index* No. 698



(III) *Ring Index* No. 1493

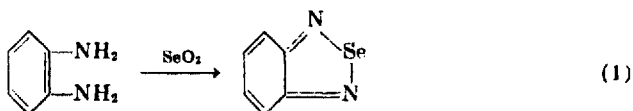


(IV) *Ring Index* No. 1495

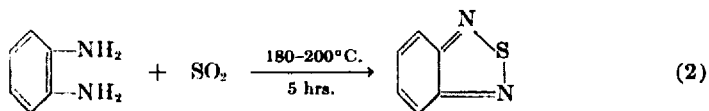


(V) *Ring Index* No. 696

Hinsberg¹ found that selenium dioxide reacted with *o*-phenylenediamine to give 2,1,3-benzoselenadiazoles (1). He then published a series of



papers²⁻⁵ on the preparation and characteristics of these 2,1,3-benzoselenadiazoles and 2,1,3-benzothiadiazoles. While selenium dioxide reacted with



¹ Hinsberg, *Ber.*, 22, 862 (1889).

² Hinsberg, *Ber.*, 22, 2895 (1889).

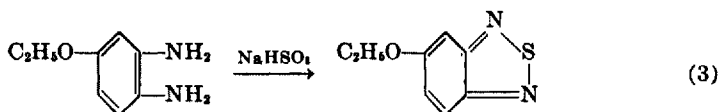
³ Hinsberg, *Ber.*, 23, 1393 (1890).

⁴ Autenreith and Hinsberg, *Ber.*, 25, 492 (1892).

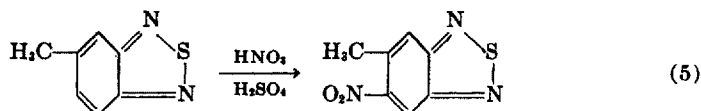
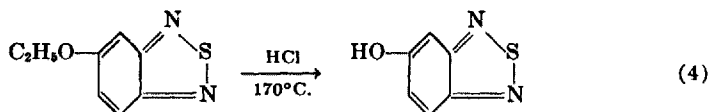
⁵ Hinsberg, *Ber.*, 48, 1611 (1915).

o-phenylenediamine at room temperature, sulfur dioxide required heating at 180–200°C. for a considerable period of time (2). Sodium bisulfite was also used instead of sulfur dioxide.^{2,6} Michaelis⁷ found that refluxing either thionyl chloride or thionylaniline with *o*-phenylenediamine in benzene yielded 2,1,3-benzothiadiazole.

The substituted 2,1,3-benzothiadiazoles and 2,1,3-benzoselenadiazoles were prepared in two ways: from the substituted *o*-phenylenediamine and sulfur dioxide or selenium dioxide (3) and from the parent 2,1,3-benzo-

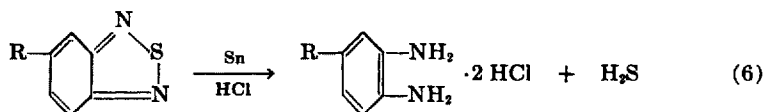


thiadiazole or 2,1,3-benzoselenadiazole (4). The 5-methyl-2,1,3-benzothiadiazole nitrated probably in the 6 position (5).² Bromine and 5-



methyl-2,1,3-benzoselenadiazole in chloroform yielded a perbromide. Bromination of 5-methyl-2,1,3-benzothiadiazole in hot acetic acid formed a bromo compound which was probably 6-bromo-5-methyl-2,1,3-benzothiadiazole. A quaternary was prepared by heating at 100°C. 5-methyl-2,1,3-benzoselenadiazole with methyl iodide.

Reduction of these compounds with tin or stannous chloride in the presence of hydrochloric acid gave the parent *o*-phenylenediamine and sulfur or selenium. Vigorous reduction produced hydrogen sulfide or hydrogen selenide (6). The products which resulted from a vigorous

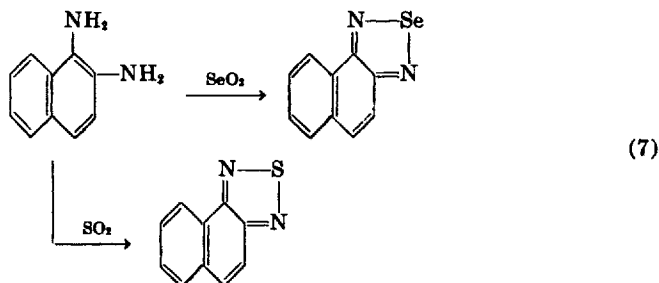


oxidation were not determined. Hinsberg⁵ attempted to oxidize 2,1,3-benzothiadiazole with hydrogen peroxide and acetic anhydride but he was unsuccessful.

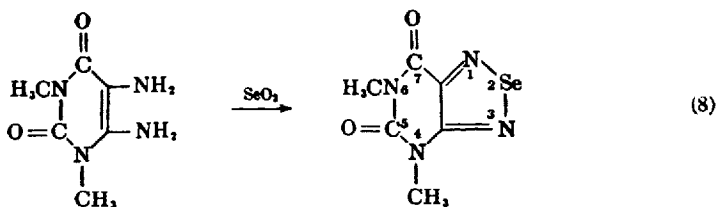
⁶ Bayer and Co., *Friedländer*, 2, 534 (1891).

⁷ Michaelis, *Ann.*, 274, 200 (1893).

1,2-Diaminonaphthalene reacted with selenium dioxide and sulfur dioxide and gave naphtho[1.2][1.2.5]selenadiazole and naphtho[1.2]-[1.2.5]thiadiazole (7). The naphtho[1.2][1.2.5]selenadiazole exhibited an intense yellow color in a concentrated sulfuric acid solution.



Sachs and Meyerheim⁸ found that selenium dioxide reacted with 1,3-dimethyl-5,6-diaminouracil and gave 4,6-dimethylpyrimido[4.5-c][1.2.5]-selenadiazole-5,7-dione (8).



Ring Index No. 696

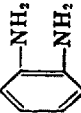
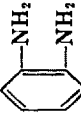
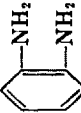
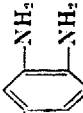
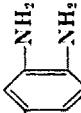
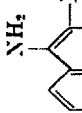
Discussion

The nature of the 2,1,3-benzothiadiazole and 2,1,3-benzoselenadiazole structure is in doubt. Hinsberg⁹ proposed several structures for these compounds. He felt that 2,1,3-thiadiazole ring exhibited thiophene-like properties.⁶ In view of this conclusion the structure with double bonds between the nitrogens and the carbon atoms is used in this review (I).

⁸ Sachs and Meyerheim, *Ber.*, 41, 3957 (1908).

⁹ Hinsberg, *Ann.*, 260, 40 (1890).

TABLE XXXIX. Preparation of the 2,1,3-Benzothiadiazoles and Naphtho[2,1][1,2,5]thiadiazole

No.	Name	Ref.	Method of preparation	Solubility	M.P., °C.	B.P., °C.
1	2,1,3-Benzothiadiazole	1	 + SO ₂ and heat 5 hours at 180–200°C.	sl. sol. in hot water	44	206
2	5-Methyl-2,1,3-benzothiadiazole	2	 + NaHSO ₃ and heat at 180–200°C.	—	44	206
5		5	 + SOCl ₂ and heat at 80°C.	—	44	—
2	5-Methyl-2,1,3-benzothiadiazole	1,2	 + SO ₂ (or NaHSO ₃) and heat at 180°C.	alc., ether	34	233–4
3	6-Nitro-5-methyl-2,1,3-benzothiadiazole	1	compound 2 + nitric acid in sulfuric acid	acetic acid, alc.	154–6	—
4	6-Bromo-5-methyl-2,1,3-benzothiadiazole	1	compound 2 + bromine in hot acetic acid	alc.	98	—
5	5-Ethoxy-2,1,3-benzothiadiazole	3	 + NaHSO ₃ and heat	alc., ether	76–7	—
6	5-Hydroxy-2,1,3-benzothiadiazole	3	compound 5 + HCl and heat at 170°C.	hot water	157–8	—
7	Naphtho[1,2][1,2,5]thiadiazole	4	 + NaHSO ₃ and heat	methanol	81	—

¹ Hinsberg, *Ber.*, 22, 2895 (1899).² Bayer and Co., *Friedländer*, 2, 534 (1891).³ Autenreith and Hinsberg, *Ber.*, 25, 492 (1892).⁴ Hinsberg, *Ber.*, 23, 1393 (1890).⁵ Michaelis, *Ann.*, 274, 200 (1893).

TABLE XL. Preparation of 2,1,3-Benzoselenadiazoles, Naphtho[1,2][1,2,5]selenadiazoles and Related Compounds

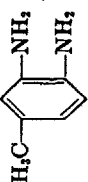
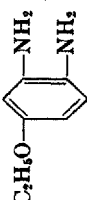
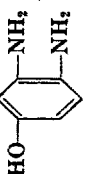
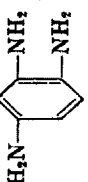
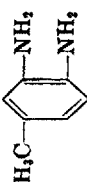
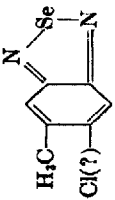
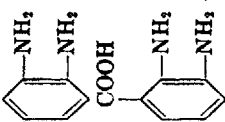
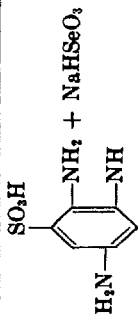
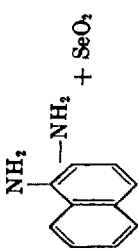
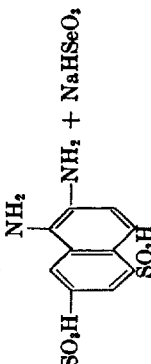
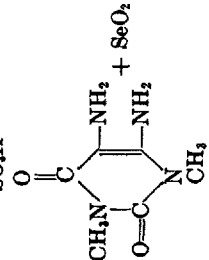
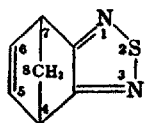
No.	Name	Ref.	Method of preparation	Solubility	M.P., °C.	B.P., °C.
1	2,1,3-Benzoselenadiazole	1	 + SeO ₂	alc., ether, benzene	76	—
2	5-Methyl-2,1,3-benzoselenadiazole	2	 + SeO ₂	water, alc., ether	72-3	267
3	5-Methyl-2,1,3-benzoselenadiazolium methiodide	2	compound 2 + methyl iodide and heat at 100°C.	water	—	—
4	5-Ethoxy-2,1,3-benzoselenadiazole	1	 + SeO ₂	dil. alc.	103-4	—
5	5-Hydroxy-2,1,3-benzoselenadiazole	3	 + NaHSeO ₃	alkali	200-9	—
6	5-Amino-2,1,3-benzoselenadiazole	1	 + SeO ₂	ether, alc., benzene	149-50	—
7	5-Methyl-2-chloro-2,1,3-benzoselenadiazole	4	 $\xrightarrow[\text{HCl}]{\text{SeO}_2}$ 	—	149-50	—
8	4-Carboxy-2,1,3-benzoselenadiazole	3	 + NaHSeO ₃	hot water, alc.	222-3	—

TABLE XL (Concluded)

No.	Name	Ref.	Method of preparation	Solubility	M.P., °C.	B.P., °C.
9	6-Amino-4-sulfo-2,1,3-benzoselenadiazole	3		cold water	—	—
10	Naphtho [1.2] [1.2.5] selenadiazole	4		methanol	81	—
11	6,8-Disulfonaphtho [1.2] [1.2.5] selenadiazole	3		water	—	—
12	4,6-Dimethylpyrimido [4.5-c] [1.2.5] selenadiazole	5		hot water	227-8	—

¹ Hinsberg, *Ber.*, 22, 2895 (1899).² Hinsberg, *Ber.*, 22, 862 (1899).³ Heineman, *Friedländer*, 11, 1126 (1915).⁴ Hinsberg, *Ber.*, 23, 1393 (1890).⁵ Sachs and Meyerheim, *Ber.*, 41, 3957 (1908).

4,7-Methanobenzisothiadiazoles (I)



(I)

(Ring Index No. 1274)

Sen,¹ in the investigation of the sulfur analogs of camphor, found that hydroxylamine on *dl*-isonitrosothiocamphor yielded three compounds: (a) α -camphorquinone dioxime, (b) β -camphordioxime, and (c) *dl*-7,8,8-trimethyl-5,6-dihydro-4,7-methanobenzisothiadiazole (II). The formation of II evidently took place with the hydrogen sulfide liberated in the first step. This reaction was confirmed by the action of hydrogen sulfide on β -camphorquinonedioxime (1).

Reduction of II produced bornylenediamine (2).

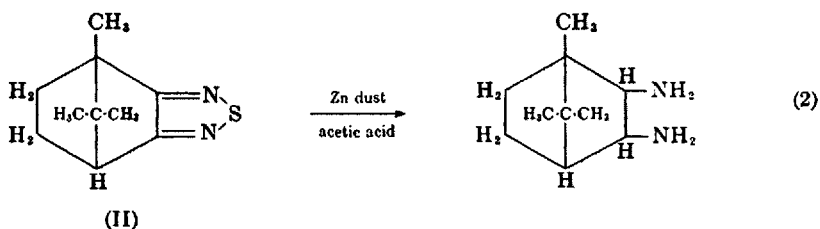
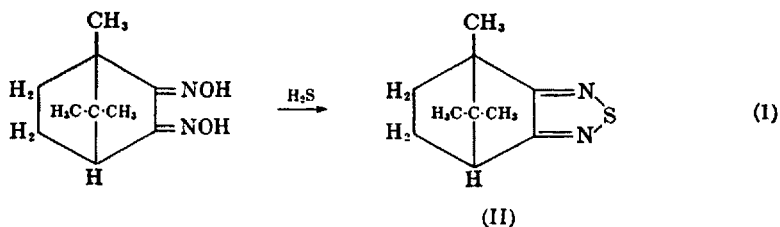


TABLE XLI

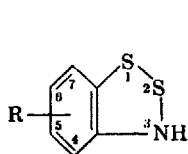
No.	Name	Solubility	M.p., °C
1	<i>dl</i> -7,8,8-Trimethyl-5,6-dihydro-4,7-methanobenzisothiadiazole (<i>dl</i> -bornylene isothiadiazole)	alc.	218
2	<i>l</i> -7,8,8-Trimethyl-5,6-dihydro-4,7-methanobenzisothiadiazole (<i>l</i> -bornylene isothiadiazole)	ether, benzene	221

¹ Sen, *J. Indian Chem. Soc.*, **15**, 537 (1938); *Chem. Abstr.*, **33**, 2506 (1939).

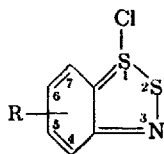
PART II

Five-Membered Rings Containing Nitrogen, Sulfur, Selenium, or Oxygen Atoms in Addition to One Sulfur and One Nitrogen

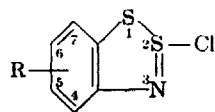
1,2,3-Benzodithiazoles (I), Benzo-2,3-thiaza-1-thionium Chlorides (II), and Benzo-1,3-thiaza-2-thionium Chlorides (III)



(I) Ring Index No. 680

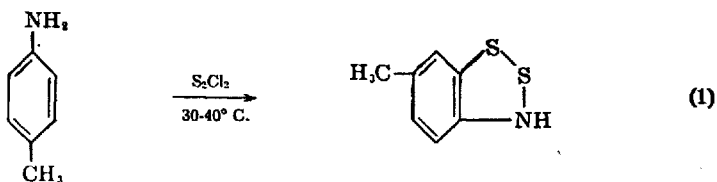


(II) Ring Index No. 681

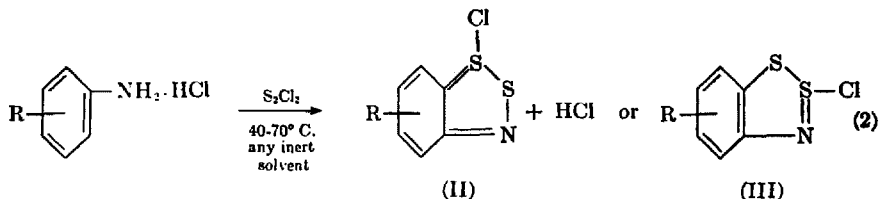


(III) Ring Index No. 682

These compounds are known in the literature as the Herz compounds since they were first described by him in a series of German patents assigned to Cassella and Co.¹ Type I was claimed by Herz² and was prepared by allowing *p*-toluidine to react with sulfur chloride in nitrobenzene at 30–40°C. for several days (1). Types II and III are used interchangeably in



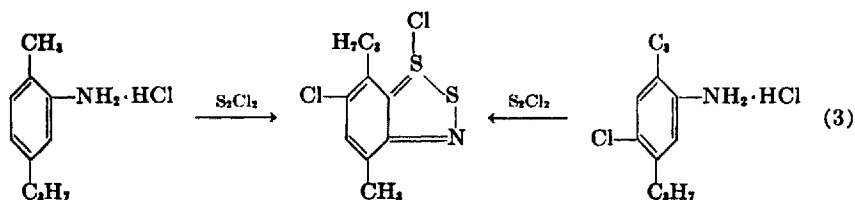
the literature to represent the compounds obtained in the reaction between an arylamine hydrochloride and sulfur chloride (2). If the arylamine hydrochloride was not substituted in the *para* position, chlorination was



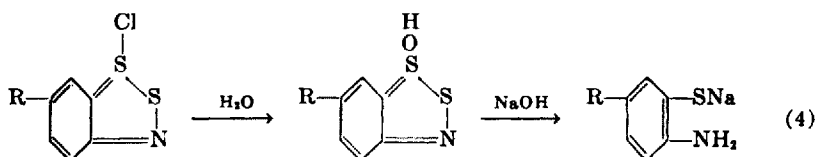
¹ Herz, *Friedländer*, 14, 908, 908–923 (1926); Germ. Pats. 360,690, 367,344, 367,345, 367,346, 367,493, and 367,822.

² Herz, *Friedländer*, 14, 915 (1926); Germ. Pat. 370,854.

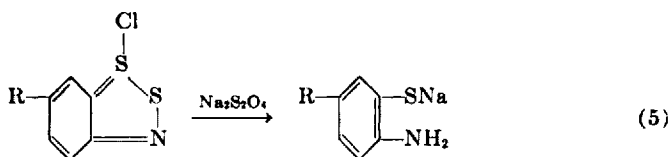
apt to take place.³ This was shown to be the case in the instance of aminocymene hydrochloride (3).⁴



These compounds are unstable to diffused light and air⁵; soluble in aromatic hydrocarbons; and char on heating. They were hydrolyzed by cold water to an unstable hydroxide which was soluble in alkali which further decomposed the compound to an *o*-aminothiophenol (4).⁴⁻⁸ So-



dium hydrosulfite also reduced these compounds to substituted *o*-aminothiophenols (5).^{9,10} Reactions 4 and 5 have afforded a convenient syn-



thesis of *o*-aminothiophenols needed for the preparation of substituted benzothiazoles.^{4,6-10}

³ Cassella and Co., *Chem. Abstr.*, 16, 500 (1922); Brit. Pat. 17,417.

⁴ Hixson and Cauwenberg, *J. Am. Chem. Soc.*, 52, 2118 (1930).

⁵ Bezzubets and Ignatyak-Maistrenk, *Chem. Abstr.*, 34, 3269 (1940); *J. Applied Chem. (U. S. S. R.)*, 12, 1137 (1939); *Chem. Abstr.*, 35, 7403 (1941); *Org. Chem. Ind. (U. S. S. R.)*, 7, 377 (1940).

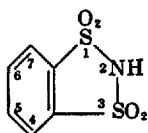
⁶ Leaper, *J. Am. Chem. Soc.*, 53, 1891 (1931).

⁷ Fox and Bogert, *J. Am. Chem. Soc.*, 61, 2013 (1939).

⁸ Fox and Bogert, *J. Am. Chem. Soc.*, 63, 2996 (1941).

⁹ Ast and Bogert, *Rec. trav. chim.*, 54, 917 (1935).

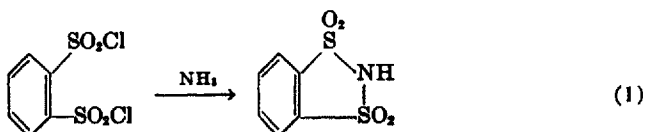
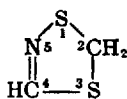
¹⁰ Fierz-David, *Helv. Chim. Acta*, 27, 1 (1944).

1,3,2-Benzodisulfonazole (I)

(I)

(Ring Index No. 683)

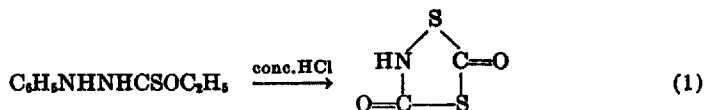
Holleman¹ prepared 1,3,2-benzodisulfonazole with *o*-phenyldisulfonyl chloride and ammonia in benzene (1). The compound was very sweet, with some bitterness. Salts were formed on the hydrogen of the nitrogen atom.

**1,3,4-Dithiazoles (I)**

(I)

(Ring Index No. 64)

Guha and Dutta² found that the action of concentrated acid on ethyl-2-phenylthiocarbazate produced a compound to which he assigned the structure 4,5-dihydro-1,3,4-dithiazole-2,4-dione (1). The proof of structure in-

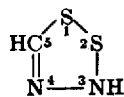


cluded the facts that the compound could not be desulfurized with mercuric oxide and did not form a disulfide with iodine.

No.	Name	Solubility	M.p., °C.
1	4,5-Dihydro-1,3,4-dithiazole-2,4-dione	water	135

¹ Holleman, *Rec. trav. chim.*, **40**, 446 (1921).

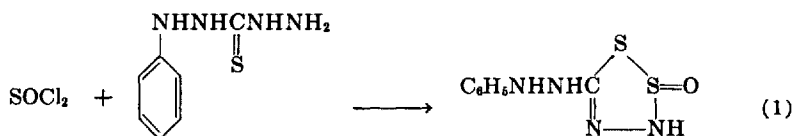
² Guha and Dutta, *J. Indian Chem. Soc.*, **6**, 65 (1929); *Chem. Abstr.*, **23**, 2952 (1929).

1,2,3,4-Dithiadiazoles (I)

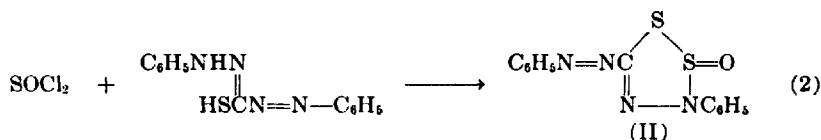
(I)

(Ring Index No. 49)

The dithiadiazoles described in the literature occur as the 2-oxide form. A typical reaction such as described by Guha and Roy-Choudhury¹ was the basis for the formation of 5-phenylhydrazino-1,2,3,4-dithiadiazole-2-oxide (1). Freund and Wischewiansky² gave the preparation of 3-phenyl-5-



phenylazo-1,2,3,4-dithiadiazole-2 oxide and 3-phenyl-5-hydrazino-1,2,3,4-dithiadiazole-2 oxide (2). Reduction of II with ammonium sulfide yielded



the 5-phenylhydrazino derivative. This compound was moderately stable in aqueous alkali and was not easily split by heating with alcoholic potassium hydroxide.

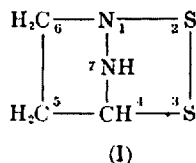
TABLE XLII. 1,2,3-Dithiadiazole-2-oxides

No.	Substituents on 1,2,3,4-dithiadiazole-2-oxide	Ref.	M. p., °C.
1	5-Phenylhydrazino	1	220
2	3-Phenyl-5-phenylazo	2	144-5
3	3-Phenyl-5-phenylhydrazino	2	162

¹ Guha and Roy-Choudhury, *J. Indian Chem. Soc.*, **5**, 163 (1928); *Chem. Abstr.*, **23**, 1398 (1929).

² Freund and Wischewiansky, *Ber.*, **26**, 2494 (1893).

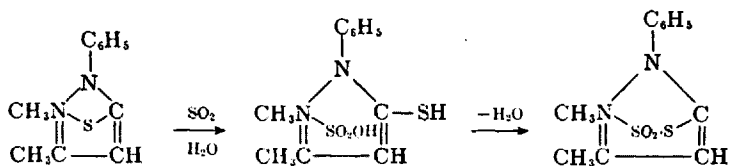
Condensed Systems Containing 1,2,3,4-Dithiadiazoles (I)



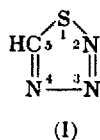
(I)

(Ring Index No. 572)

Michaelis¹ gave the only example of a condensed system containing a 1,2,3,4-dithiadiazole ring. He condensed thiopyrrole with sulfur dioxide according to the following equations:

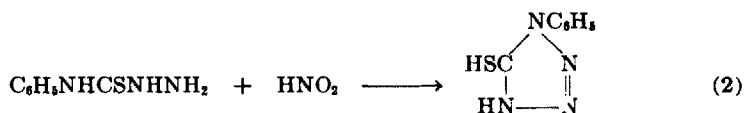


1,2,3,4-Thiatriazoles (I)



(I)

Freund and co-workers^{2,3} reported the preparation of a number of 5-aminothiatriazoles. The preparation of these compounds is given by gen-

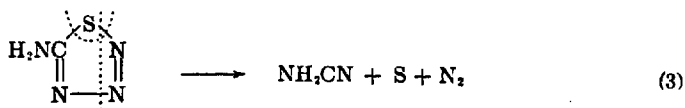


¹ Michaelis, *Ann.*, **320**, 1 (1901).

² Freund and Schwarz, *Ber.*, **29**, 2491 (1896).

³ Freund and Schander, *Ber.*, **29**, 2500 (1896).

eral reaction (1). Where R is an aryl group, the reaction then followed course (2).⁴ Heating 5-amino-1,2,3,4-thiatriazole in water gave sulfur, nitrogen, and dicyandiamide (3). Heating the 5-alkylaminothiatriazoles



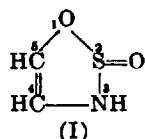
yielded sulfur, nitrogen, and trialkyl isomelamine.² Cold hydrochloric acid produced the hydrochloride of the aminothiatriazole. Heating 5-aminothiatriazole in hydrochloric acid yielded nitrogen and thiocyanamide, $\text{NH}=\text{C}-\text{NH}$ or $\text{NH}_2\text{C}=\text{N}$. The decomposition products of 5-amino-

thiatriazole obtained by heating an alkaline solution and then neutralizing were sulfur and hydrazoic acid.

TABLE XLIII. 1,2,3,4-Thiatriazoles

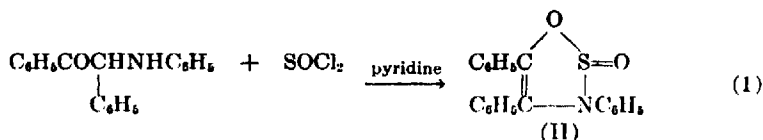
No.	Substituents on the 1,2,3,4-thiatriazole ring	Refs. on p. 219	M.p., °C.
1	5-Amino	2	128-30
2	5-Methylamino	3	96
3	5-Ethylamino	3	66-67
4	5-Allylamino	3	54

1,2,3-Oxathiazole-S-oxides or 1,2,3-Oxasulfinazoles (I)



(Ring Index No. 59)

McCombie and Parkes¹ found that thionyl chloride reacted with α -phenyl- α -anilinoacetophenone in presence of pyridine to form 3,4,5-tri-



⁴ Freund and Hempel, *Ber.*, 28, 74 (1895).

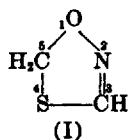
¹ McCombie and Parkes, *J. Chem. Soc.*, 101, 1991 (1912).

phenyl-1,2,3-oxasulfinazole (1). Phosgene gave the analogous 2,3-dihydro-oxazole. The reaction with sulfonyl chloride was not successful. Heating compound II with concentrated aqueous potassium hydroxide regenerated the ketone. With a drop of concentrated sulfuric acid the 1,2,3-oxasulfinazole gave a dark emerald green color.

TABLE XLIV

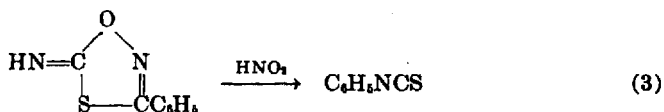
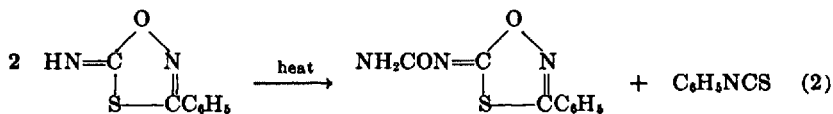
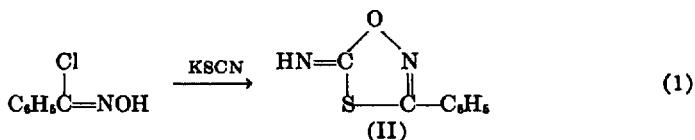
No.	Substituents on the 1,2,3-oxasulfinazole	Solubility	M.p., °C.
1	3,4,5-Triphenyl	petroleum, alc.	128
2	3- <i>m</i> -Tolyl-4,5-diphenyl	alc.	102
3	3- <i>p</i> -Tolyl-4,5-diphenyl	alc.	134

1,4,2-Oxathiazoles (I)



(Ring Index No. 60)

Musante¹ in continuing his work on the synthesis of heterocycles, used α -chlorobenzaldehyde oxime and potassium thiocyanate to prepare 3-phenyl-5-imino-1,4,2-oxathiazole (I). Heating compound II gave 3-

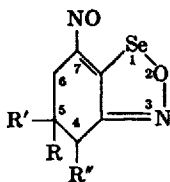


phenyl-1,4,2-oxathiazol-5-yl urea and phenyl isothiocyanate (2). Nitrous acid and compound II yielded phenyl isothiocyanate (3).

¹ Musante, *Gazz. chim. ital.*, **68**, 331 (1938).

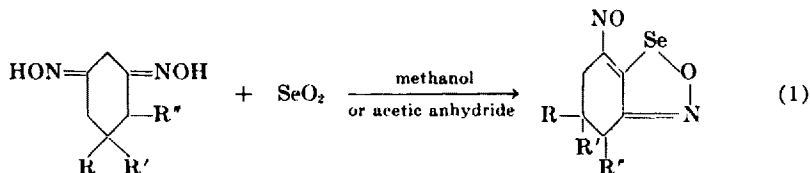
TABLE XLV

No.	Name	Solubility	M.p., °C.
1	3-Phenyl-5-imino-1,4,2-oxathiazole	alc.	82-4
2	3-Phenyl-5-ureido-1,4,2-oxathiazole	alc.	165-6 dec.

7-Nitroso- $\Delta^{3,7}$ -dihydrobenz-2,1,3-oxaselenazoles (I)

(I)

King and Felton¹ found that when the dioxime of a cyclohexane-1,3-dione was treated with powdered selenium dioxide a vigorous reaction ensued and a red compound was obtained. From analytical data, spectroscopic data, and polarographic studies it was proposed to name them as derivatives of 7-nitroso- $\Delta^{3,7}$ -dihydrobenz-2,1,3-oxaselenazole (1). These



red compounds are very stable toward acids from which they may be recrystallized. They decomposed in alkali with deposition of selenium. A Zerewitinoff determination gave no active hydrogen.

TABLE XLVI

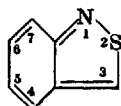
No.	Substituent on the 7-nitroso- $\Delta^{3,7}$ -dihydrobenz- 2,1,3-oxaselenazole	Solubility	M.p., °C.
1	None	methanol	106
2	5-Methyl	methanol	91
3	5,5-Dimethyl	methanol	109
4	5-Phenyl	methanol	165
5	4,5-Diphenyl	methanol	180-1 dec.
6	4-Phenyl-5,5-dimethyl	methanol	137

¹ King and Felton, *J. Chem. Soc.*, 1949, 274.

PART III

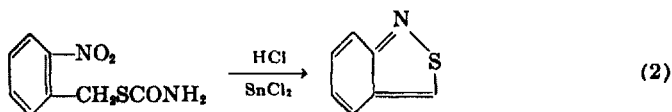
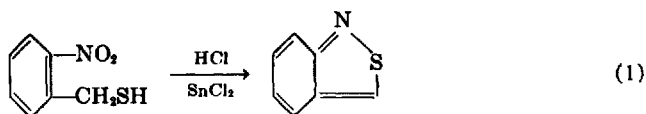
Isothiazoles, Their Derivatives and Selenium Analogs

The 2,1-Benzisothiazoles

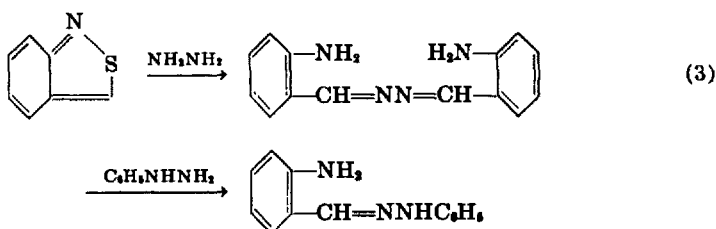


(Ring Index No. 737)

Gabriel and co-workers^{1,2} found that the reduction of *o*-nitrobenzyl-mercaptan (1) and *o*-nitrobenzyl thiolcarbamate (2) yielded 2,1-benziso-



thiazole. This compound was a yellowish oil which was soluble in strong acids and formed complexes with picric acid, platinum, gold, and lead salts. Gabriel and Leupold³ showed that hydrazine and phenylhydrazine split the nucleus with the formation of hydrazones (3). Auwers and Ernst⁴



¹ Gabriel and Posner, *Ber.*, 28, 1025 (1895).

² Gabriel and Stelzner, *Ber.*, 29, 160 (1896).

³ Gabriel and Leupold, *Ber.*, 31, 2185 (1898).

⁴ Auwers and Ernst, *Z. physik. Chem.*, 122, 231 (1926).

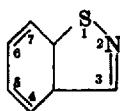
investigated the molecular refraction of 2,1-benzisothiazole and found that this compound resembled 2,1-benzisooxazole.

TABLE XLVII

No.	Name	Ref.	B.p. or M.p., °C.
1	2,1-Benzisothiazole	1	b.p. 242–242.5 (748 mm.)
2	Picrate of 1	1	m.p. 123–4°

The 1,2-Benzisothiazoles, Their Homologs and Selenium Analogs

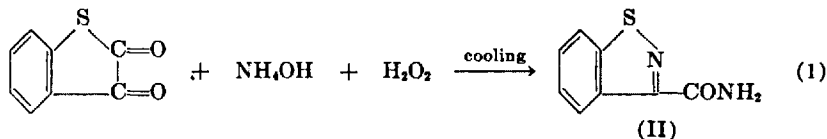
The 1,2-Benzisothiazoles (I)



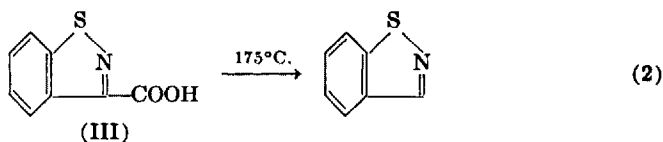
(I)

(Ring Index No. 736)

Stolle and co-workers^{1,2} reported the synthesis of a number of 3-substituted 1,2-benzisothiazoles. They found that thianaphthalene-2,3-dione in the presence of ammonia and perhydrol yielded 3-carbamyl-1,2-benzisothiazole (1). The acid was obtained by hydrolysis. This acid (III) lost



carbon dioxide when heated at 175°C. under diminished pressure to form 1,2-benzisothiazole (2). 1,2-Benzisothiazole was a low melting solid (m.p.



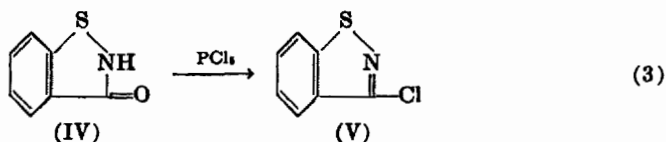
37°C.) which had a bitter almond-like odor. It was slightly soluble in water but very soluble in concentrated acids. In concentrated sulfuric acid this compound exhibited a yellow color. 1,2-Benzisothiazole formed a complex with one mole of silver nitrate. Reissert³ attempted to prepare this compound from 3(2)-benzisothiazolone (IV). Compound IV was heated with

¹ Stolle and Geisel, *Angew. Chem.*, **36**, 159 (1923).

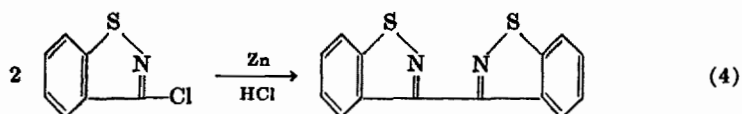
² Stolle, Geisel, and Badstubner, *Ber.*, **58**, 2095 (1925)

³ Reissert, *Ber.*, **61**, 1680 (1928).

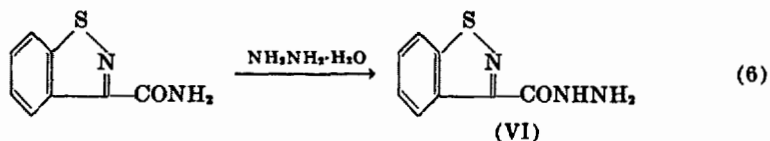
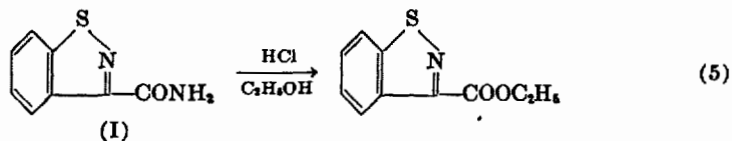
phosphorus pentachloride and the resultant 3-chlorobenzisothiazole was obtained (3). Reduction of compound V with zinc dust in concentrated



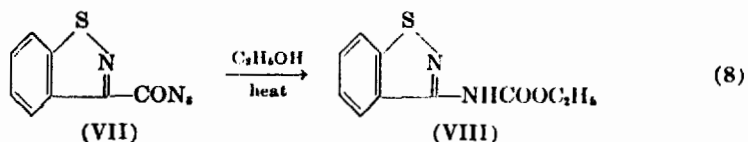
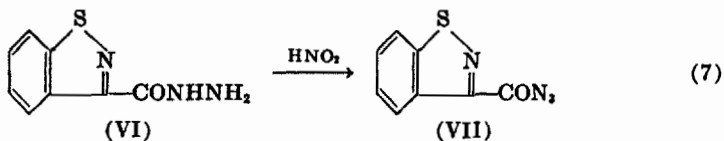
hydrochloric acid yielded 3,3'-bibenzisothiazolyl (4). Reduction of compound V with hydroiodic acid decomposed the compound.



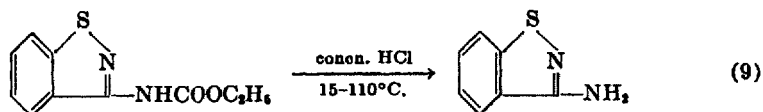
Stolle *et al.*² prepared 3-carbethoxybenzisothiazole with compound I and alcoholic hydrochloric acid (5). The hydrazide was obtained by heating the amide with hydrazine hydrate (6). Compound VI reduced an ammoni-



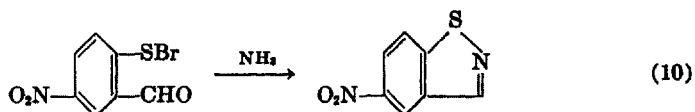
acal solution of silver nitrate, especially when warmed. 3-Benzisothiazolyl carboxazide (VII) was synthesized from compound VI with sodium nitrite and acid (7). Compound VI and aniline gave 3-benzisothiazolyl carboxanilide. Heating VII with absolute alcohol yielded ethyl 3-benzisothiazolyl



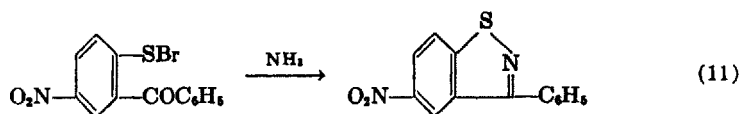
carbamate (8). 3-Aminobenzisothiazole was obtained by the hydrolysis of the urethan (VIII) (9).



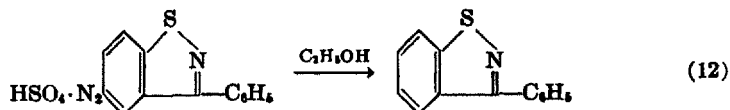
Fries and Brothuhn⁴ found that 2-formyl-4-nitrophenylsulfenyl bromide and ammonia produced 5-nitro-1,2-benzisothiazole (10). Fries, Eis-



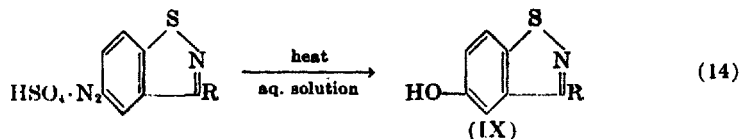
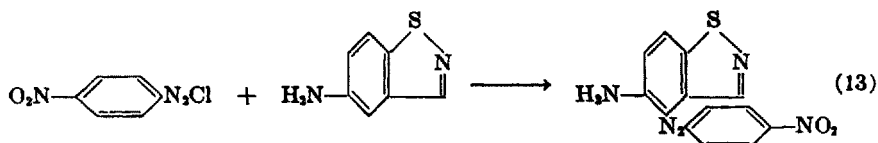
hold, and Vahlberg⁵ prepared the 5-nitro-3-phenyl-1,2-benzisothiazole in the same manner (11). The 5-amino-1,2-benzisothiazoles were prepared



by reducing the nitro compounds. 3-Phenyl-1,2-benzisothiazole was synthesized by decomposing 5-(3-phenyl-1,2-benzisothiazolyl)diazonium sulfate in absolute ethanol (12). *p*-Nitrophenyl diazonium chloride formed an



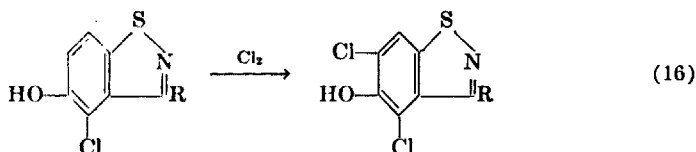
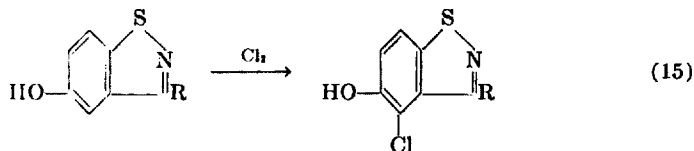
azoamino compound with 5-amino-1,2-benzisothiazole. This diazonium salt coupled in the 4 position on the 1,2-benzisothiazole (13). The 3-phenyl compound yielded an azoamino derivative.



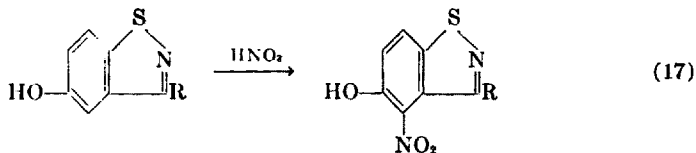
⁴ Fries and Brothuhn, *Ber.*, **56**, 1630 (1923).

⁵ Fries, Eishold, and Vahlberg, *Ann.*, **454**, 264 (1927).

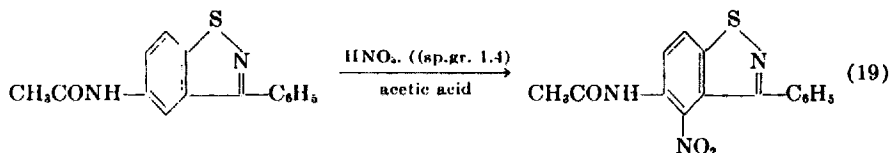
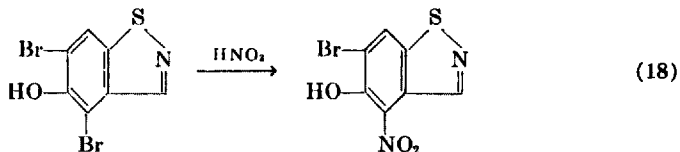
The 5-hydroxy-1,2-benzisothiazoles⁵ were obtained by diazotizing the amine and decomposing by heating (14). Chlorination of IX with two equivalents of chlorine yielded the 4-chloro-5-hydroxy-1,2-benzisothiazoles (15).⁵ Chlorine added to the 5-hydroxy-1,2-benzisothiazoles produced 4,6-dichloro-5-hydroxy-1,2-benzisothiazoles (16).*



Nitration of the 5-hydroxy-1,2-benzisothiazoles yielded the 4-nitro-5-hydroxy-1,2-benzisothiazoles (17).^{*} Nitration of 4,6-dibromo-5-hydroxy-

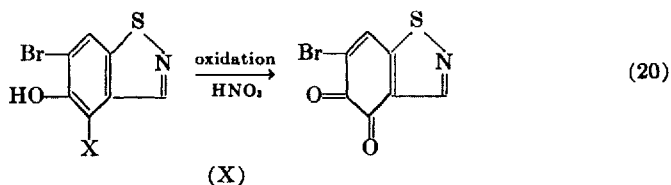


1,2-benzisothiazole produced 4-nitro-5-hydroxy-6-bromo-1,2-benzisothiazole (18). 5-Acetylamino-3-phenyl-1,2-benzisothiazole was nitrated to yield 5-acetylamino-4-nitro-3-phenyl-1,2-benzisothiazole (19).

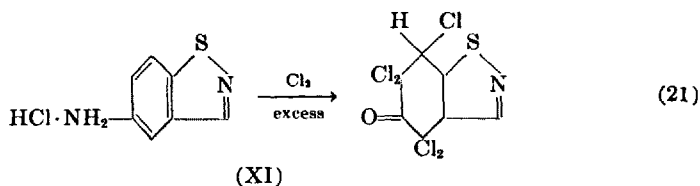


Oxidation of 4,6-dibromo-5-hydroxy-1,2-benzisothiazole with dilute nitric acid yielded 6-bromo-1,2-benzisothiazole-4,5-dione (20). Aniline formed crystalline derivatives with this compound X.

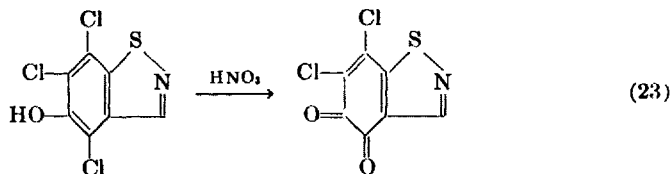
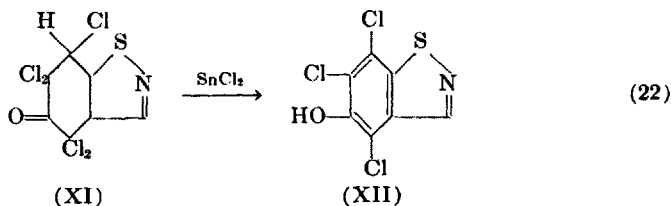
* The R in these compounds represents either a hydrogen or phenyl group.



Chlorination of 5-amino-1,2-benzisothiazole hydrochloride produced 4,4,6,6,7-pentachloro-6,7-dihydro-1,2-benzisothiazole-5(4)-one (21). Reduc-



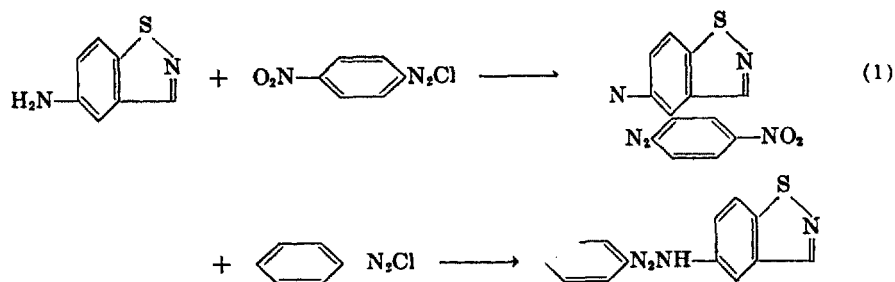
tion of compound XI with stannous chloride afforded the 2-hydroxy-4,6,7-trichloro-1,2-benzisothiazole (22). Oxidation of this compound (XII) yielded the 6,7-dichloro-1,2-benzisothiazole-4,5-dione (23).



Discussion

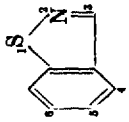
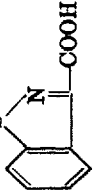
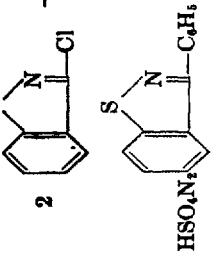
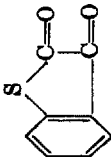
Fries¹ compared the 1,2-benzisothiazoles with naphthalene and other condensed systems such as the 1,2,3-benzothiadiazoles. The 5-amino-1,2-benzisothiazoles only partially resembled β -aminonaphthalene since *p*-nitrophenyl diazonium chloride formed an azo linkage in the 4 position of the 1,2-benzisothiazole, while phenyl diazonium chloride formed an azo-

¹ Fries, Eishold, and Vahlberg, *Ann.*, **454**, 264 (1927).



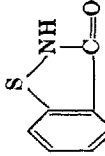
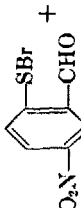
amino linkage (1). The 5-hydroxy-1,2-benzisothiazoles resembled β -naphthol in a number of ways. Chlorination and bromination of the 5-hydroxy compound occurred in the same manner as β -naphthol. The halogen (4 position) adjacent to the hydroxy group was replaced by a nitro group. The 1,2-benzisothiazole ring is apparently stable to mild oxidation and reduction procedures.

TABLE XLVIII. Preparation of the 1,2-Benzisothiazoles

No.	Name	Ref.	Method of preparation	Solubility	M.p., °C.
1	1,2-Benzisothiazole	1		ether, alc.	37 (b.p. 220)
2	3,3'-Bis(1,2-benzisothiazolyl)	4	 with heat at 175°C.	alc.	100
3	3-Phenyl-1,2-benzisothiazole	3	 + Zn dust + HCl + abs. alc.	acetic acid, alc., benzene	71
4	3-(1,2-Benzisothiazolyl) carboxamide	1	 + NH4OH + H2O2	water, alc.	134

(Table continued)

TABLE XLVIII (Continued)

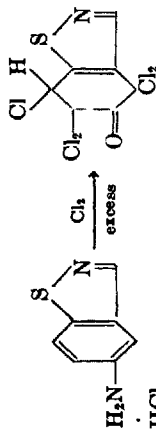
No.	Name	Ref.	Method of preparation	Solubility	M.P., °C.
5	3-(1,2-Benzisothiazolyl)carboxylic acid	1	hydrolysis of compound 4	water	143
6	Ethyl 3-(1,2-benzisothiazolyl) carboxylate	1	compound 4 + alc. + HCl and reflux	ether, alc.	44
7	3-(1,2-Benzisothiazolyl) carboxy- hydrazide	1	compound 4 + $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ and reflux in alcohol	alc.	138
8	3-(1,2-Benzisothiazolyl) carboxazide	1	compound 7 + HNO_2	ether	102 dec.
9	Ethyl 3-(1,2-benzisothiazolyl) carbamate	1	compound 8 + alc. with heat	alc.	107
10	3-Amino-1,2-benzisothiazole	1	hydrolysis of compound 9 with conc. HCl and heated at 105–109°	hot water, alc., ether	115
11	3-Chloro-1,2-benzisothiazole	4	 + PCl_5 with heat	alc.	40
12	5-Nitro-1,2-benzisothiazole	2	 + NH_3	alc., benzene, acetic acid	149
13	5-Nitro-3-phenyl-1,2-benzisothiazole	3	 + NH_3	acetic acid, acetone, alc.	124
14	5-Amino-1,2-benzisothiazole	3	reduction of compound 12 with ammonia and ferrous sulfate	alc., acetic acid, benzene	130
15	5-Amino-3-phenyl-1,2-benzisothiazole	3	reduction of compound 13 + SnCl_2 + HCl	alc., benzene, acetone	131
16	5-Acetylamino-1,2-benzisothiazole	3	acetylation of compound 14	dil. acetic acid	172
17	5-Acetylamino-3-phenyl-1,2-benzisothiazole	3	acetylation of compound 15	alc., acetic acid	109–10

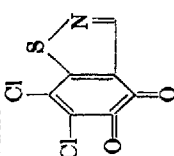
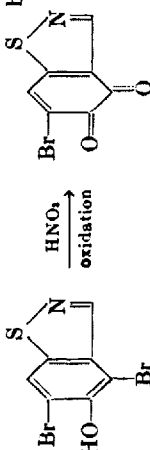
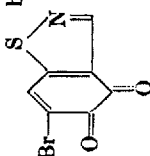
No.	Name	Ref.	Method of Preparation	Solubility	M.p., °C.
18	5-Amino-1,2-benzisothiazole, <i>N</i> -benzylidene	3	compound 14 + benzaldehyde	alc.	101
19	4- <i>p</i> -Nitrophenylazo-5-amino-1,2-benzisothiazole	3	<i>p</i> -nitrophenyl diazonium chloride + compound 14	nitrobenzene, xylene	225 dec.
20	5-Phenylazoamino-1,2-benzisothiazole	3	phenyl diazonium chloride + compound 14	—	—
21	5-Phenylazocetyl-amino-1,2-benzisothiazole	3	compound 20 + acetic anhydride + sodium acetate	—	—
22	5-Acetyl-amino-4-nitro-3-phenyl-1,2-benzisothiazole	3	compound 17 + nitric acid (sp.gr. 1.4) + acetic acid	alc.	270 dec.
23	5-Amino-4-nitro-3-phenyl-1,2-benzisothiazole	3	hydrolysis of compound 22	alc.	208
24	5-Phenylazoamino-3-phenyl-1,2-benzisothiazole	3	compound 15 + phenyl diazonium chloride	petroleum ether	140-3 dec.
25	5-Hydroxy-1,2-benzisothiazole	3	compound 14 + HNO ₃ + dil. H ₂ SO ₄ with heat	water, alc., benzene	156
26	5-Hydroxy-3-phenyl-1,2-benzisothiazole	3	compound 15 + HNO ₃ + dil. H ₂ SO ₄ with heat 5(3-phenyl-1,2-benzisothiazolyl) diazonium sulfate + acetic acid with heat	alc., dil. acetic acid	159-60
27	5-Benzoxo-1,2-benzisothiazole	3	compound 25 + benzoyl chloride + alkali	alc.	125
28	5-Acetoxy-3-phenyl-1,2-benzisothiazole	3	compound 26 + acetic anhydride + anhydr. sodium acetate	dil. alc., acetic acid	109-10
29	5-Methoxy-3-phenyl-1,2-benzisothiazole	3	compound 26 + alkali + dimethyl sulfate	dil. alc.	80
30	4-Chloro-5-hydroxy-1,2-benzisothiazole	3	compound 25 + Cl ₂	alc., acetic acid, benzene	195
31	4-Chloro-3-phenyl-5-hydroxy-1,2-benzisothiazole	3	compound 26 + Cl ₂	acetic acid, alc., acetone	206
32	4-Chloro-3-phenyl-5-acetoxy-1,2-benzisothiazole	3	compound 31 + acetic anhydride + conc. H ₂ SO ₄	alc.	81
33	4,6-Dichloro-5-hydroxy-1,2-benzisothiazole	3	compound 30 + Cl ₂	alc., acetic acid	176

(Table continued)

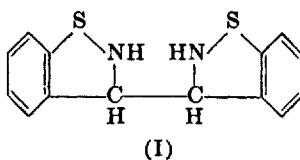
TABLE XLVIII (Continued)

No.	Name	Ref.	Method of preparation	Solubility	M.p., °C.
34	4,6-Dichloro-3-phenyl-5-hydroxy-1,2-benzisothiazole	3	compound 31 + Cl ₂	acetic acid	216
35	4,6-Dichloro-3-phenyl-5-acetoxy-1,2-benzisothiazole	3	compound 34 + acetic anhydride + sodium acetate	alc.	170
36	4-Bromo-5-hydroxy-1,2-benzisothiazole	3	compound 25 + Br ₂	alc., acetic acid	200 dec.
37	4-Bromo-5-hydroxy-3-phenyl-1,2-benzisothiazole	3	compound 26 + Br ₂	acetone, alc.	216
38	4-Bromo-5-acetoxy-3-phenyl-1,2-benzisothiazole	3	compound 37 + acetic anhydride + sodium acetate	alc.	89
39	4,6-Dibromo-5-hydroxy-1,2-benzisothiazole	3	compound 25 + Br ₂ + sodium acetate	alc., acetic acid	171
40	4,6-Dibromo-5-hydroxy-3-phenyl-1,2-benzisothiazole	3	compound 26 + Br ₂ + sodium acetate	acetic acid	201
41	4,6-Dibromo-5-acetoxy-3-phenyl-1,2-benzisothiazole	3	acetylation of compound 40	alc.	162
42	4,4,6,6,7-Pentachloro-6,7-dihydro-1,2-benzisothiazole-5(4)-one	3		alc.	183
43	4,6,7-Trichloro-5-hydroxy-1,2-benzisothiazole	3	compound 42 + SnCl ₂	alc., acetic acid, benzene	234



No.	Name	Ref.	Method of preparation	Solubility	M.p., °C.
44	6,7-Dichloro-1,2-benzisothiazole-4,5-dione	3	compound 43 + nitric acid oxidation 	acetic acid, benzene, CHCl_3	145
45	6-Bromo-1,2-benzisothiazole-4,5-dione	3	 $\xrightarrow[\text{oxidation}]{\text{HNO}_3}$  oxidation of compound 46	benzene, CHCl_3	131 dec.
46	6-Bromo-5-hydroxy-4-chloro-1,2-benzisothiazole	3	compound 30 + Br_2 + sodium acetate	alc., acetic acid	186
47	4-Nitro-5-hydroxy-1,2-benzisothiazole	3	nitration of compound 25	acetic acid	145
48	4-Nitro-5-hydroxy-3-phenyl-1,2-benzisothiazole	3	nitration of compound 26	acetone, alc., acetic acid	220 dec.
49	4-Nitro-5-hydroxy-6-bromo-1,2-benzisothiazole	3	nitration of compound 39	benzene, CHCl_3 , benzine	131

¹ Stolle, Geisel, and Badstubner, *Ber.*, 58, 2095 (1925).² Fries and Brothuhn, *Ber.*, 56, 1630 (1923).³ Fries, Eishold, and Vahlberg, *Ann.*, 454, 264 (1927).⁴ Reissert, *Ber.*, 61, 168 (1928).

3,3'-Bis(1,2-benzisothiazoline) (I)

Stolle and Merkle¹ found that 3-amino-1,2-benzisothiazole and nitrous acid yielded compound I. This compound formed a silver salt with ammoniacal silver oxide. Oxidation with nitric acid gave 2,2'-disulfobenzil (1).

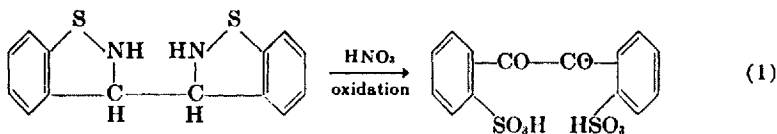
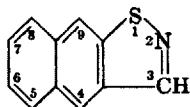
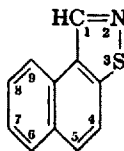
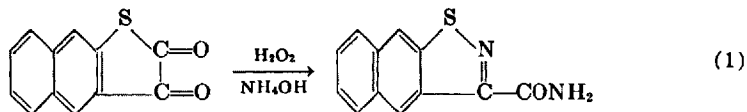


TABLE XLIX

No.	Name	Solubility	M.p., °C.
1	3,3'-Bis(1,2-benzisothiazoline)	alc.	104

Naphth[2.3-*d*]isothiazoles (I) and Naphth[1.2-*d*]isothiazoles (II)(I) *Ring Index* No. 1539(II) *Ring Index* No. 1544

Stolle and Badstubner² prepared 3-carbamyl-naphth[2.3-*d*]isothiazole from 2,3-dihydrothiophanthren-2,3-dione, ammonia, and hydrogen peroxide (1). Hydrolysis gave the acid.



¹ Stolle and Merkle, *J. prakt. Chem.*, [2] 138, 221 (1933).

² Stolle and Badstubner, *J. prakt. Chem.*, [2] 121, 266 (1929).

The 1-carbamyl-naphth[1.2-*d*]isothiazole was synthesized in a similar manner from 2,3-dihydro-naphtho[2.1-*b*]thiophen-2,3-dione (2).

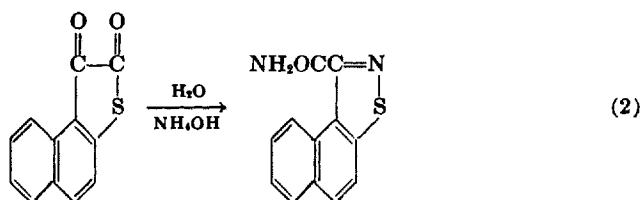
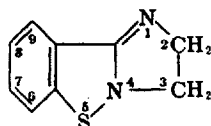


TABLE L

No.	Name	Solubility	M.p., °C.
1	3-Carbamyl-naphth[2.3- <i>d</i>]isothiazole	alc.	208
2	3-Carboxynaphth[2.3- <i>d</i>]isothiazole	alc.	197 dec.
3	1-Carbamyl-naphth[1.2- <i>d</i>]isothiazole	alc.	225 dec.

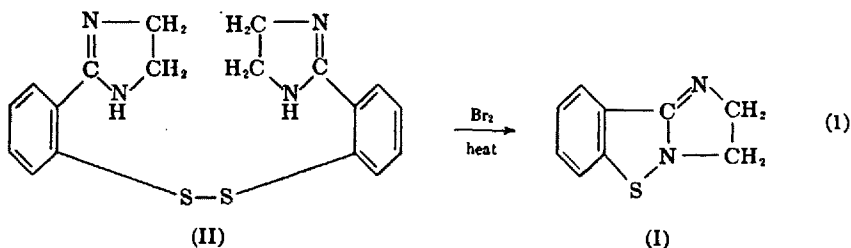
2,3-Dihydrobenz[*d*]imidazo[1.2-*b*]isothiazole (I)



(I)

(Ring Index No. 1348)

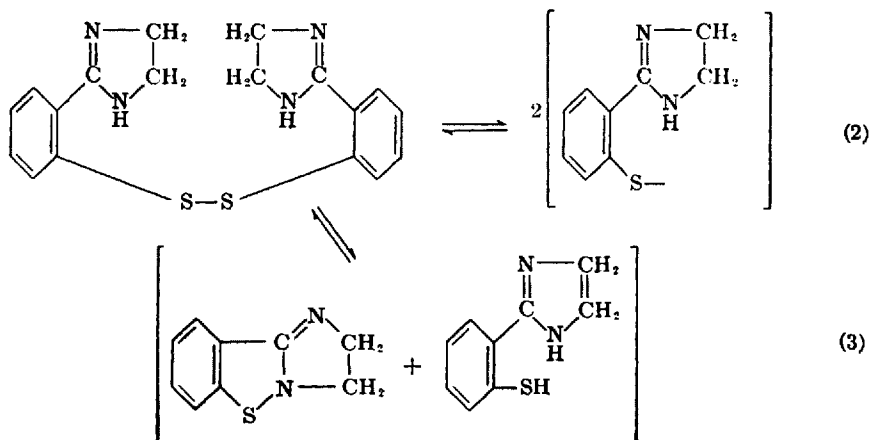
McClelland and Warren¹ attempted to prepare compound I from 1,2,3-benzodithiol-3-thione and ethylenediamine but were unsuccessful. Compound I was synthesized by brominating 2,2'-(dithiodi-*o*-phenylene)di- Δ^2 -imidazoline and then heating the resultant bromide (1). Excess bromine



formed a perbromide of unknown structure. The same compound was obtained when bromine was added to compound I.

¹ McClelland and Warren, *J. Chem. Soc.*, 1929, 2621.

They studied 2,2'-(dithiodi-*o*-phenylene)di- Δ^2 -imidazoline (II) in order to lend proof that the disulfides undergo dismutation.² Molecular weight determinations of material II in alcohol and benzene by the ebullioscopic method gave low values which diminished with dilution. The low values could not be ascribed to a reaction with the solvent since the unaltered product was recovered. The apparent molecular weight of the disulfide at a given concentration was constant even on prolonged heating, so it was evident that the anomalous results were not due to decomposition but in accord with a reversible dissociation of the disulfide. Solutions of the disulfide (II) were thermochromic; the intensity of color increased with the rise in temperature and decreased on cooling. This property was previously observed by Lecher³ in certain disulfides and was attributed to a weakening of the S—S linkage. Compound II, unlike the disulfides investigated by Lecher, showed a marked divergence from Beer's law. McClelland and Warren² felt that the unusual properties of the disulfide (II) might be accounted for by the dissociation in solution of free radicals (2) or by a reversible change of type (3) which they termed a reversible dismutation.



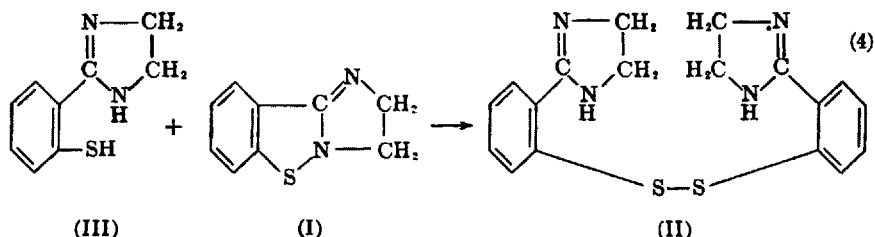
They dismissed the probability of reaction (2), although they admitted that any proof of reaction (3) did not exclude the formation of free radicals as the initial stage of the dismutation. Their reasons for doubting the existence of free radicals beyond a transitory existence were the facts that the solutions of 2,2'-(dithiodi-*o*-phenylene)di- Δ^2 -imidazoline did not react with oxygen and no evidence of abnormal reactivity could be obtained.

The addition of 2-*o*-mercaptophenyl- Δ^2 -imidazoline to a solution of compound II in alcohol increased the apparent molecular weight of com-

² McClelland and Warren, *J. Chem. Soc.*, 1930, 1095.

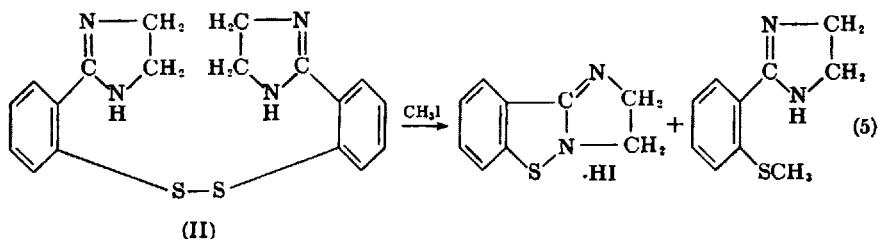
³ Lecher, *Ber.*, 48, 524 (1915).

pound II. Compound II was formed when 2-*o*-mercaptophenyl- Δ^2 -imidazoline was added to compound I (4). Direct proof that the reaction

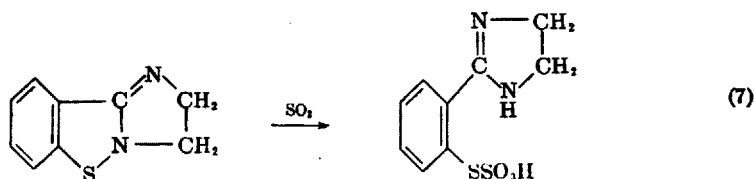
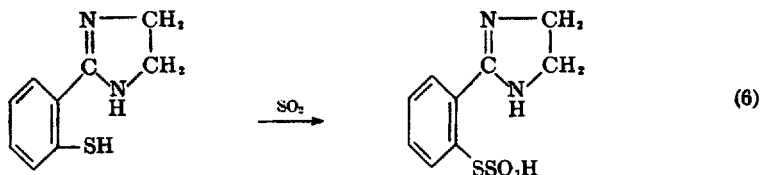


(4) was identical to the equilibrium reaction (3) was lacking, since compound (I) could not be isolated from the reaction mixture.

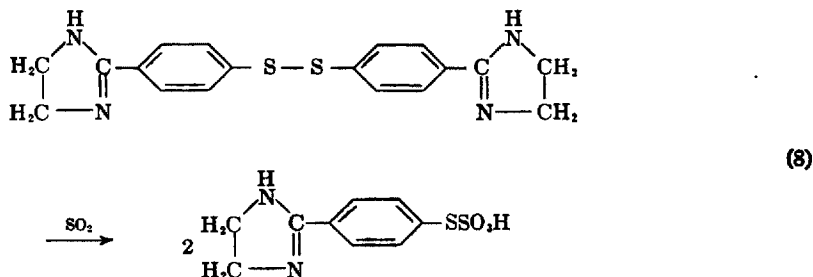
Methyl iodide and compound II yielded compound I and 2-*o*-methylmercapto- Δ^2 -imidazoline (5).



McClelland and Warren⁴ found that the following compounds reacted with sulfur dioxide to form thiosulfonic acids: 2-mercaptophenyl- Δ^2 -imidazoline, 2,3-dihydrobenz[d]imidazo[1,2-*b*]isothiazole (I), 2,2'-(dithiodi-*o*-phenylene)di- Δ^2 -imidazoline (11), 2,2'-(dithiodi-*m*-phenylene)di- Δ^2 -imidazoline, and 2,2'-(dithiodi-*p*-phenylene)di- Δ^2 -imidazoline (6-8). A

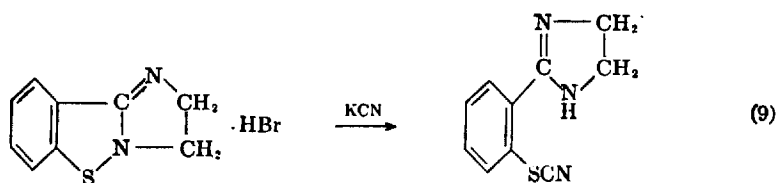


⁴McClelland and Warren, *J. Chem. Soc.*, 1930, 2690.



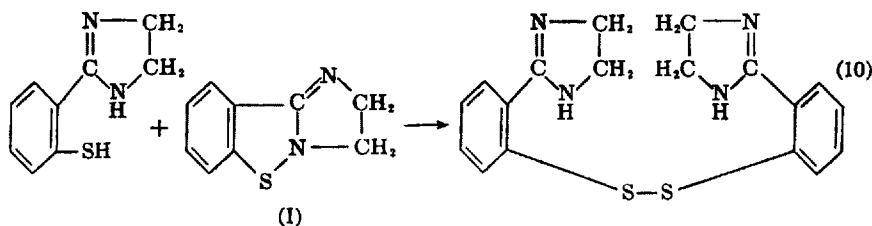
number of other phenyl and naphthyl disulfides with substituents other than an imidazoline ring did not react with sulfur dioxide. McClelland and Warren⁴ felt that this reaction was an anomaly. The dismutation phenomenon did not occur since the *para* and *meta* disulfide could not dismute.

A similar reaction occurred between potassium cyanide and the hydrobromide of compound I (9).



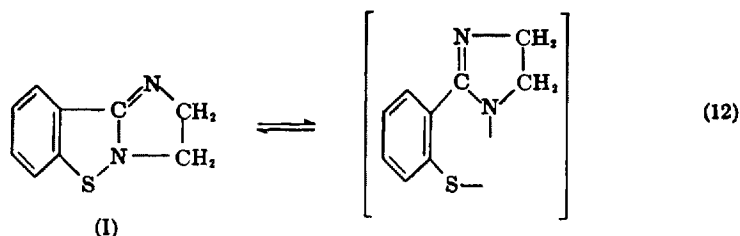
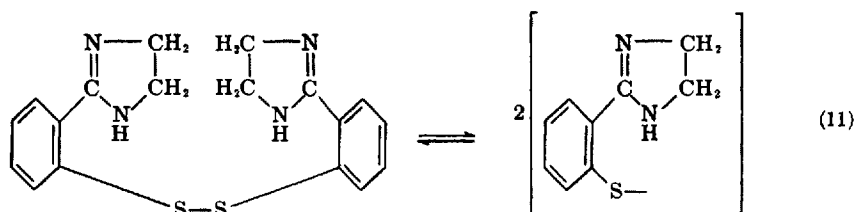
Discussion

The main fault with the dismutation theory is that the conditions of an equilibrium are not met. Consider the reaction between 2-*o*-mercapto-phenyl- Δ^2 -imidazoline and compound I (10). In this reaction, compound

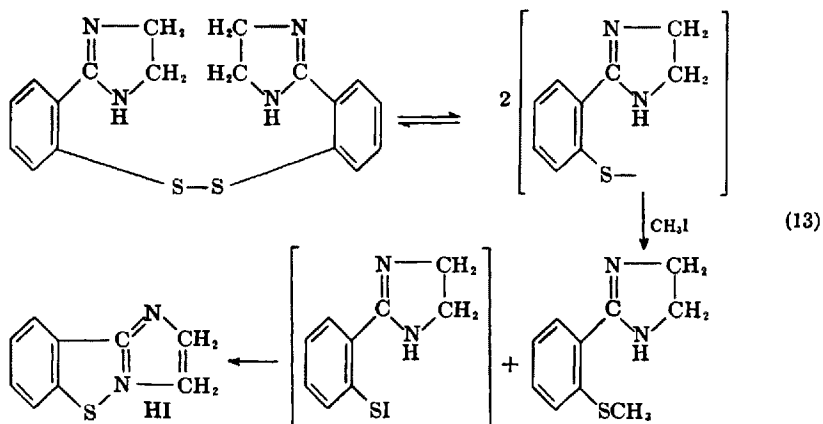


I apparently disappears from the reaction. A possible argument might be that the equilibrium is shifted toward the disulfide so that no detectable amounts of compound I can be isolated.

A more plausible explanation is the presence of similar types of free radicals in the 2,2'-(dithiodi-*o*-phenylene)di- Δ^2 -imidazoline and 2,3-di-



hydrobenz[d]imidazol[1.2-b]isothiazole (11,12). The reactions of both compounds could be explained on this basis. Thus, methyl iodide would react in this manner with compound II (13). Furthermore, the reaction of



sulfur dioxide may be explained in the same manner. It is doubtful that sulfur dioxide can reduce a disulfide. In this series of reactions sulfur dioxide reacts as sulfurous acid (14). If such a hypothesis is correct, then sulfur dioxide would not react with the 2-*o*-mercaptophenyl- Δ^2 -imidazoline to form these compounds. McClelland and Warren⁴ reported that this reaction took place during refluxing for 24 hours. In this time, oxidation to the disulfide may have taken place.

The reactions of compound I may follow a similar pattern (15).

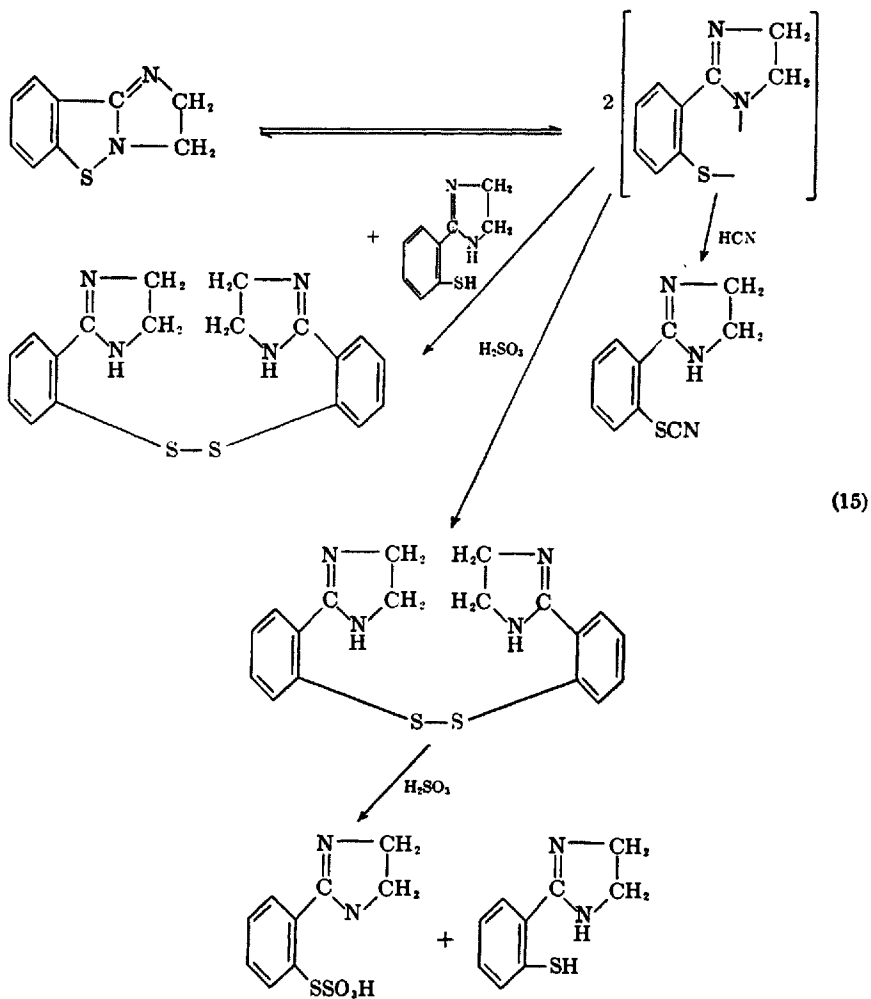
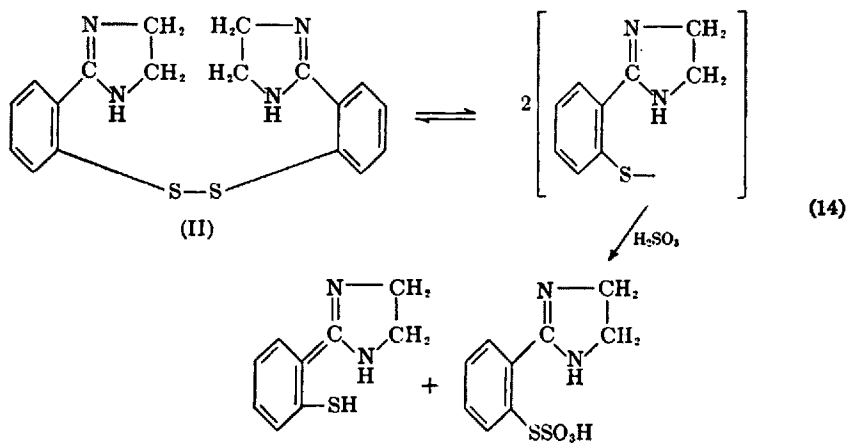
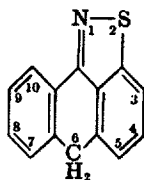


TABLE LI

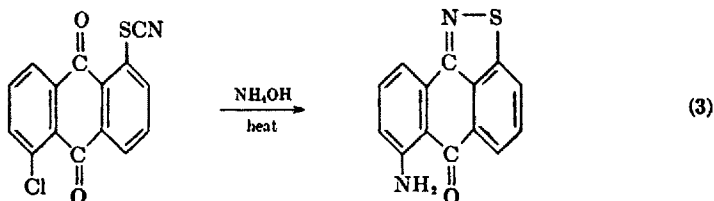
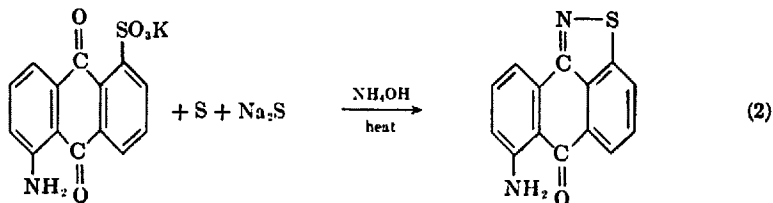
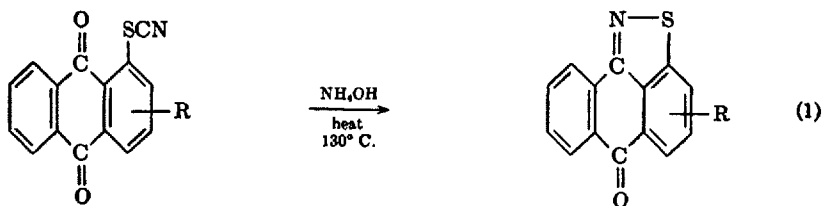
No.	Name	Solubility	M.p., °C. ¹
1	2,3-Dihydrobenz[d]imidazol[1.2-b]isothiazole hydrobromide	alc.	259
2	2,3-Dihydrobenz[d]imidazol[1.2-b]isothiazole picrate	—	241-2
3	2,3-Dihydrobenz[d]imidazol[1.2-b]isothiazole perbromide	acetic acid	139-40

¹ McClelland and Warren, *J. Chem. Soc.*, 1929, 2621.**6-Anthr[9.1]isothiazoles (I) and Related Compounds**

(I)

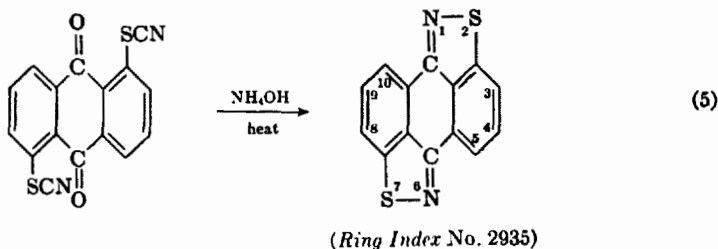
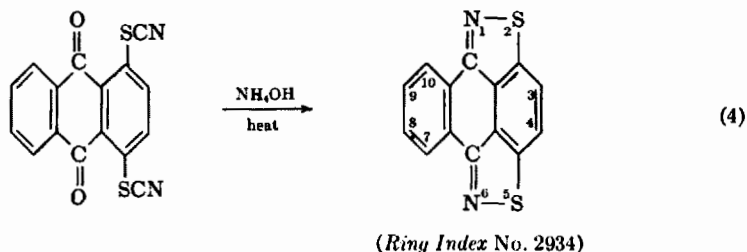
(Ring Index No. 2375)

Gatterman¹ prepared the 1-thiocyananthraquinones. Heating these compounds with ammonia in a bomb at about 130°C. yielded isothiazoles

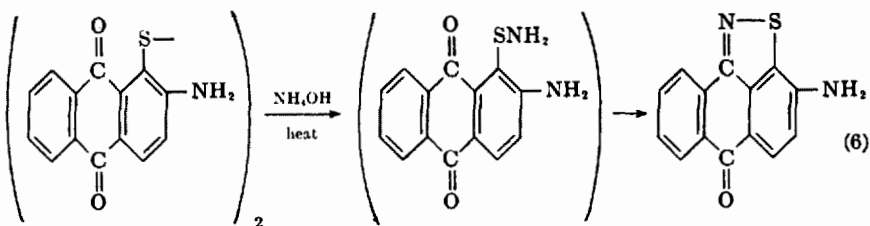
¹ Gatterman, *Ann.*, 393, 113 (1912).

(1). He synthesized the 7-amino-6-anthr[9.1]isothiazol-6-one in two additional ways (2,3).

Anthra[9.1-*cd*, 10.4-*c'd'*]diisothiazole and anthra[9.1-*cd*, 10.5-*c'd'*]diisothiazole were prepared from 1,4-dithiocyananthraquinone and 1,5-dithiocyananthraquinone, respectively (4,5).



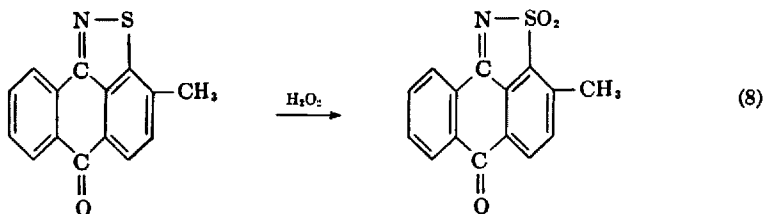
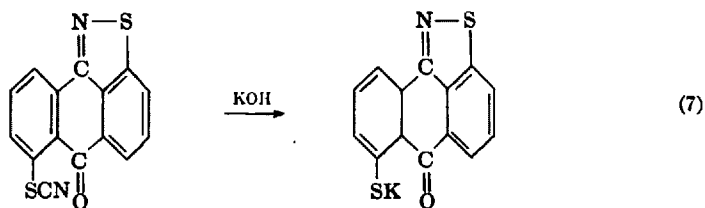
Kopetschni and Wiesler² believed that an intermediate sulfenamide was formed. Heating 1,1-dithiobis(2-aminoanthraquinone) with ammonia yielded 3-amino-6-anthr[9.1]isothiazol-6-one (6). 1-Mercapto-2-aminoanthraquinone and ammonia gave the same compound.



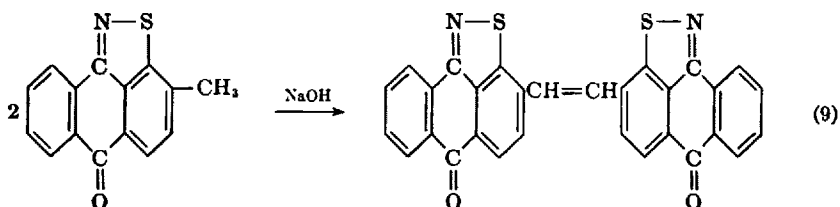
The 5- and 7-amino groups were diazotized and replaced by thiocyanate groups.² Splitting the thiocyanate group with alcoholic potassium hydroxide formed the mercaptans (7).

These compounds possess yellow to blue dyeing properties. As a result, a great many of their chemical characteristics have been described in the patent literature. The 6-anthr[9.1]isothiazol-6-ones may be oxidized to 6-anthr[9.1]isothiazol-6-one-*S*-dioxides with hydrogen peroxide or chromic oxide in an acid medium (8).³⁻⁵

² Kopetschni and Wiesler, *Monatsh.*, **43**, 81 (1922).



Treatment of 3-methyl-6-anthr[9.1]isothiazol-6-one with alkali produced an ethylene with the α and β carbon atoms attached to 6-anthr[9.1]isothiazol-6-one (9).^{6,7} The methyl group may be brominated to the di-



bromo compound with bromine in trichlorobenzene.⁸ Mild oxidation gave the 3-aldehyde.⁸ Nitrobenzene and barium hydroxide yielded the 3-carboxy compound.⁹

Reduction with sulfur dioxide in the presence of pyridine and metallic copper produced the leuco lases.¹⁰

Grossman and Bonner¹¹ prepared a cotton fast yellow dye by heating 5-amino-6-anthr[9.1]isothiazol-6-one with 2-chlorocarbonylanthraquinone in nitrobenzene at 175°C. Buxbaum¹² obtained green and blue shades in synthesizing 7-amino-9- and 10-substituted 6-anthr[9.1]isothiazol-6-ones.

³ Friedländer, 18, 1370 (1933); *Chem. Abstr.*, 26, 1620 (1932); Ger. Pat. 538,451.

⁴ *Chem. Abstr.*, 25, 5178 (1931); Fr. Pat. 705,215.

⁵ *Chem. Abstr.*, 26, 2875 (1932); Br. Pat. 348,241.

⁶ *Chem. Abstr.*, 25, 215 (1931); Br. Pat. 331,269.

⁷ *Chem. Abstr.*, 24, 1988 (1930); Fr. Pat. 669,706.

⁸ *Chem. Abstr.*, 26, 1944 (1932); Br. Pat. 346,373.

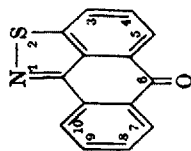
⁹ *Chem. Abstr.*, 25, 5177 (1931); Fr. Pat. 705,387.

¹⁰ *Chem. Abstr.*, 31, 2616 (1937); Fr. Pat. 803,304.

¹¹ Grossman and Bonner, *Chem. Abstr.*, 33, 4435 (1939); U. S. Pat. 2,149,433; *Chem. Abstr.*, 31, 8212 (1937); Br. Pat. 467,183.

¹² Buxbaum, U. S. Pat. 2,363,042; *Chem. Abstr.*, 39, 3164 (1945).

TABLE LII. Preparation of the 6-Anthr[9.1]isothiazol-6-ones and Related Compounds



No.	Substituents on the 6-anthr[9.1]isothiazol-6-one other than hydrogen	Ref.	Method of preparation	Solubility	M.p., °C.
1	None	1	1-thiocyananthraquinone + NH_4OH with heat at 130°C , 3-4 hours	acetic acid	221
2	3-Methyl	2	1,1'-dithiobis(anthraquinone) + NH_4OH with heat at 100°	nitrobenzene	221
3	3-Aldehyde or 3-formyl	1	1-thiocyano-2-methylanthraquinone + NH_4OH with heat	alc.	218
4	3-Dibromomethyl	3	mild oxidation of compound 2	—	—
5	3-Carboxy	3	bromination of compound 2	—	—
		4	oxidation of compound 2 with nitrobenzene and $\text{Ba}(\text{OH})_2$	—	—
6	3-Chlorocarbonyl	3,5	1-chloro-2-carboxyanthraquinone + Na_2S_2 + NH_4OH	—	—
7	α,β -Di(3-(6-anthr[9.1]isothiazol-6-one)ethylene (complete name)	3	SOCl_2 + compound 5	—	—
		6	compound 2 + alkali	—	—
8	3-Benzoyl	7	1-thiocyano-2-benzoylanthraquinone + NH_4OH with heat	nitrobenzene	258
9	3- α -Naphthoyl	7	1-thiocyano-2- α -naphthoylanthraquinone + NH_4OH with heat	nitrobenzene	272
10	5-Carboxy	1	1-thiocyano-4-carboxy anthraquinone + NH_4OH with heat	—	260
11	3-Amino	2	1-mercaptop-2-aminoanthraquinone + NH_4OH with heat	acetone	285
		2	1,1'-dithio-bis(2-aminoanthraquinone) + NH_4OH with heat	—	—
12	3-Acetyl amino	2	acetylation of compound 11	nitrobenzene	294
13	3-Amino-4-chloro	2	1,1'-dithiobis(2-amino-3-chloroanthraquinone) + alc. NH_3 with heat	—	322-4
14	5-Amino	1	1-thiocyano-4-aminoanthraquinone + NH_4OH with heat	acetic acid	251
15	5-Methyl amino	1	1-thiocyano-4-methylaminoanthraquinone + NH_4OH with heat	acetic acid	219
16	5-Dimethyl amino	1	1-thiocyano-4-dimethylaminoanthraquinone + NH_4OH with heat	benzene	212

TABLE LII (Continued)

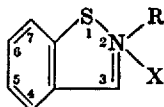
No.	Substituents on the 6-anthr[9.1]isothiazol-6-one other than hydrogen	Ref.	Method of preparation	Solubility	M.p., °C.
17	7-Amino	1	1-thiocyano-5-aminoanthraquinone + NH ₄ OH with heat	acetic acid	250
			1-sulfo-5-aminoanthraquinone + S + Na ₂ S + NH ₄ OH with heat	—	—
18	7-Methylamino	1	1-thiocyano-5-chloroanthraquinone + NH ₄ OH with heat	—	—
			1-sulfo-5-methylaminoanthraquinone + S + Na ₂ S + NH ₄ OH with heat	acetic acid	185
19	7-Dimethylamino	1	1-sulfo-5-dimethylaminoanthraquinone + S + Na ₂ S + NH ₄ OH	pyridine	152
20	5- <i>p</i> -Tolylmercapto	1	1-thiocyano-4- <i>p</i> -tolylmercaptoanthraquinone + NH ₄ OH with heat	pyridine	210
21	7-Thiocyano	1	diazotization of compound 17 and coupling with KSCN	nitrobenzene	276
22	7-Methylmercapto	1	decomposition of compound 21 and then methylation	nitrobenzene	245
23	3(2-Anthraquinonecarboxamido)	8	2-chlorocarbonyl anthraquinone + 7-amino-6-anthr[9.1]isothiazol-6-one, heat 175°C. in nitrobenzene	—	375
24	7-Amino-8,10-dibromo	9	compound 17 + Br ₂ + SO ₂ Cl	—	273
25	7-Amino-8-bromo-10- <i>p</i> -toluidino	9	compound 24 + toluidine + potassium acetate + copper acetate 140–5°C.	benzene, gasoline	226.5
26	7-Benzamido-10-anilino	9	7-benzamido-8-chloro-6-anthr[9.1]isothiazol-6-one + aniline + potassium acetate + basic copper	benzene, gasoline	248
27	7-Amino-10-bromo	9	7-benzamido-6-anthr[9.1]isothiazol-6-one + bromine hydrolysis	—	255
28	7-Benzamido-10-amino	9	hydrolysis of 7-benzamido-10- <i>p</i> -tolylsulfonamidoanthr[9.1]isothiazol-6-one	—	313
29	Anthra[9.1- <i>c,d</i> ,10.4- <i>c'd'</i>]disothiazole	1	1,4-dithiocyanosanthraquinone + NH ₄ OH with heat	acetic acid	226
30	Anthra[9.1- <i>c,d</i> ,10.5- <i>c'd'</i>]disothiazole	1	1,5-dithiocyanosanthraquinone + NH ₄ OH with heat	nitrobenzene	287

¹ Gatterman, *Ann.*, 303, 113 (1912).² Kopetschni and Wiesler, *Monatsh.*, 43, 81 (1922).³ *Chem. Abstr.*, 26, 1944 (1932); Br. Pat. 346,373.⁴ *Chem. Abstr.*, 25, 5177 (1931); Fr. Pat. 705,387.⁵ *Chem. Abstr.*, 24, 4941 (1930); Br. Pat. 326,487.⁶ *Chem. Abstr.*, 25, 215 (1931); Br. Pat. 331,269.*Chem. Abstr.*, 24, 1988 (1930); Fr. Pat. 669,706.⁷ Friedländer, 18, 1371 (1933); *Chem. Abstr.*, 26, 2472 (1932); Ger. Pat. 541,716.⁸ Grossman and Bonner, *Chem. Abstr.*, 31, 8212 (1937); U. S. Pat. 2,149,433.⁹ Buxbaum, U. S. Pat. 2,363,042; *Chem. Abstr.*, 39, 3164 (1939).

6-Anthr[9.1]isoselenazoles

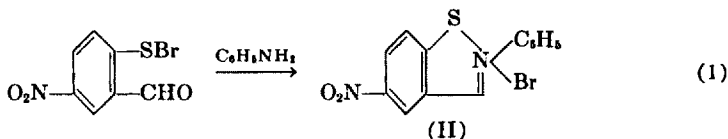
The 6-anthr[9.1]isoselenazol-6-ones were prepared in much the same manner as the 6-anthr[9.1]isothiazol-6-ones with 1-chloroanthraquinones, ammonia, and sodium selenide.¹⁻³

1,2-Benzisothiazolium Compounds (I)



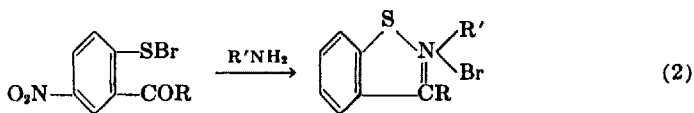
(I)

Fries and Brothuhn⁴ found that 2-formyl-4-nitrophenylsulfenyl bromide reacted with aniline to yield 5-nitro-1,2-benzisothiazolium phenylbromide (1). The chloride was prepared by heating the bromide (II) in concentrated hydrochloric acid.

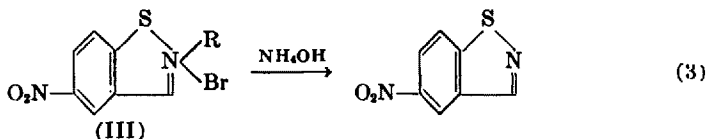


(II)

Fries, Eishold, and Vahlberg⁵ investigated the preparation and the properties of these compounds. 2-Benzoyl-4-nitrophenylsulfenyl bromide also reacted with primary aliphatic or aromatic amines to give 5-nitro-1,2-benzisothiazolium compounds (2).



(2)



(III)

¹ Lulek, *Chem. Abstr.*, **30**, 6577 (1936); U. S. Pat. 2,049,212.

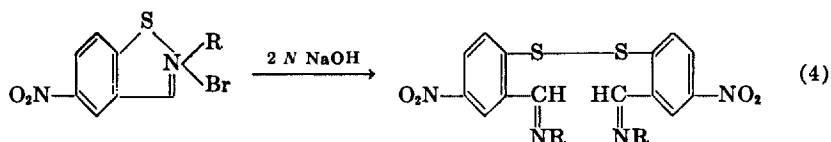
² Lulek, *Chem. Abstr.*, **30**, 6578 (1936); U. S. Pat. 2,049,213.

³ I. G. Farbenindustrie, *Chem. Abstr.*, **31**, 2616 (1937); Fr. Pat. 803,304.

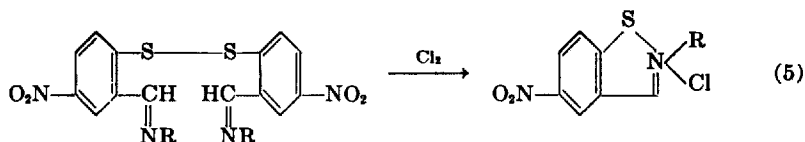
⁴ Fries and Brothuhn, *Ber.*, **56**, 1630 (1923).

⁵ Fries, Eishold, and Vahlberg, *Ann.*, **454**, 264 (1927)

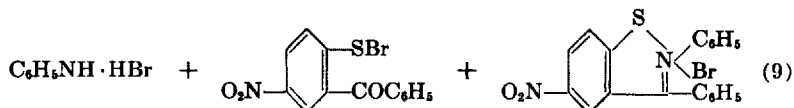
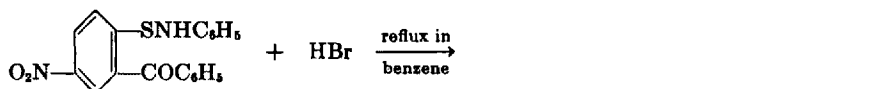
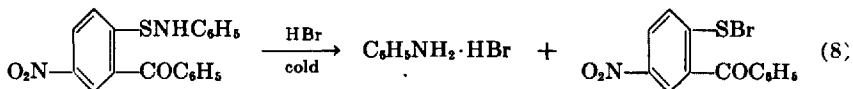
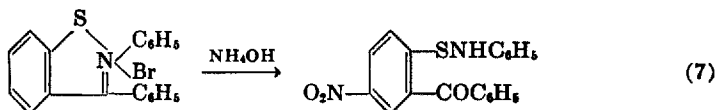
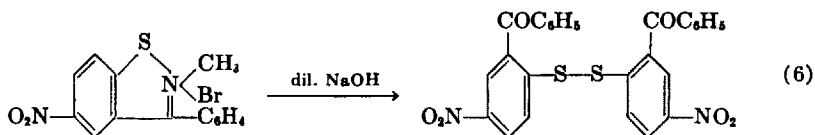
The 5-nitro-1,2-benzisothiazolium alkyl or aryl halides were decomposed by ammonia to 5-nitro-1,2-benzisothiazole (3). The R in structure III was a methyl, phenyl, or tolyl group. Dilute alkali (2 N sodium hydroxide, sodium acetate, and sodium carbonate) split compounds of the type III into the 2,2'-dithiobis(5-nitrobenzylidenimines) (4). Chlorination of



these disulfides yielded the 5-nitro-1,2-benzisothiazolium alkyl (or aryl) chlorides (5).



5-Nitro-3-phenyl-1,2-benzisothiazolium methyl bromide behaved in the same manner with ammonia but yielded the 2,2'-dithiobis(5-nitrobenzophenone) when treated with alkali (6).



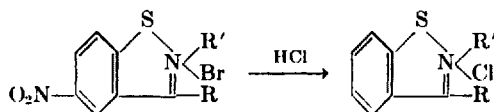
The 5-nitro-3-phenyl-1,2-benzisothiazolium phenyl (and tolyl) bromides with ammonia and alkali formed 2-benzoyl-4-nitrophenyl sulfen-anilides (7). These sulfen-anilides on treatment with dry hydrogen bromide in the cold gave aniline hydrobromide and 2-benzoyl-4-nitrophenylsulfenyl bromide (8). Heating this reaction yielded a mixture of aniline hydrobromide, 2-benzoyl-4-nitrophenylsulfenylbromide, and 5-nitro-3-phenyl-1,2-benzisothiazolium phenylbromide (9).

TABLE LIII. Preparation of 1,2-Benzisothiazolium Alkyl (or Aryl) Bromides and Chlorides

The bromides were prepared as follows:



The chlorides were prepared by ion interchange:

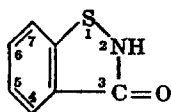


No.	Name	Ref.	Solubility	M.p., °C.
1	5-Nitro-1,2-benzisothiazolium phenylbromide	1	benzene, alc., acetic acid	149
2	5-Nitro-1,2-benzisothiazolium phenylchloride	1	alc., acetic acid	240
3	5-Nitro-1,2-benzisothiazolium <i>p</i> -tolylbromide	2	hydrobromic acid, alc.	darkens 200 (240 dec.)
4	5-Nitro-1,2-benzisothiazolium <i>p</i> -tolylchloride	2	hydrochloric acid	240 dec.
5	5-Nitro-1,2-benzisothiazolium methylbromide	2	water	212 dec.
6	5-Nitro-3-phenyl-1,2-isothiazolium phenylbromide	2	hydrobromic acid, acetic acid	303-6 dec.
7	5-Nitro-3-phenyl-1,2-isothiazolium <i>p</i> -tolylbromide	2	acetic acid, hydrobromic acid	319-20 dec.
8	5-Nitro-3-phenyl-1,2-isothiazolium methylbromide	2	alc., acetic acid	201 dec.

¹ Fries and Brothuhn, *Ber.*, **56**, 1630 (1923).

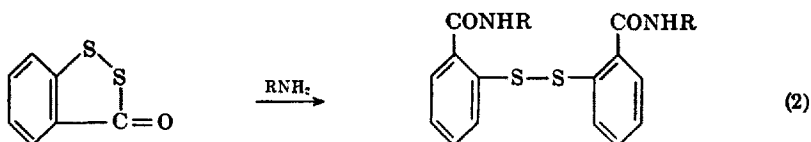
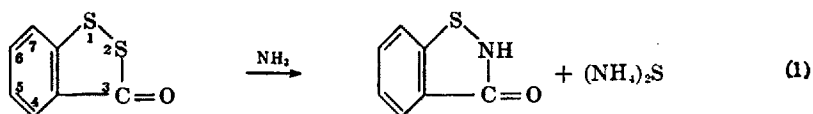
² Fries, Eishold, and Vahlberg, *Ann.*, **454** 264 (1927).

1,2-Benzisothiazol-3(2)-ones (I)

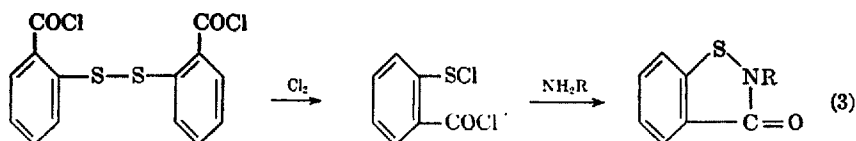


The elucidation of this structure, its derivatives, and its reactions which has continued over a period of twenty-four years is largely the work of McClelland and collaborators.

McKibben and McClelland¹ examined the chemistry of 1,2,3-benzodithiol-3-one (II) (2-dithiobenzoyl) and found that ammonia ruptured the ring with the formation of 1,2-benzisothiazol-3(2)-one and ammonium sulfide (1). Under the same conditions primary aryl and alkyl amines and compound II formed 2,2'-dithiobis(benzamides) (2).^{1,2} However, McClelland



land and Gait³ showed that the 2-alkyl and 2-aryl-1,2-benzisothiazol-3(2)-ones could be prepared with 2-chlorocarbonylphenylsulfenyl chlorides and primary amines (3). Several modifications of this method were used by



Reissert and Manns⁴ and McClelland *et al.*⁵⁻⁷ in preparing these substituted 1,2-benzisothiazol-3(2)-ones. Reissert and Manns⁴ brominated the *N*-

¹ McKibben and McClelland, *J. Chem. Soc.*, 123, 170 (1923).

² McClelland and Longwell, *J. Chem. Soc.*, 123, 3310 (1923).

³ McClelland and Gait, *J. Chem. Soc.*, 1926, 921.

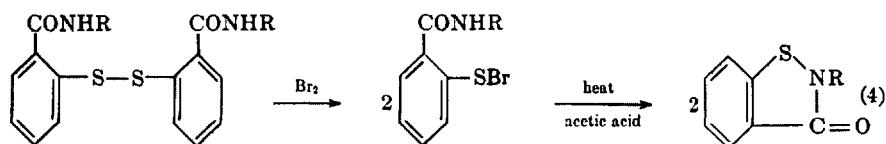
⁴ Reissert and Manns, *Ber.*, 61, 1308 (1928).

⁵ Bartlett and McClelland, *J. Chem. Soc.*, 1934, 818.

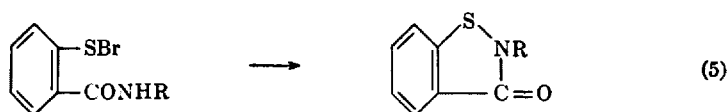
⁶ Hart, McClelland, and Fowkes, *J. Chem. Soc.*, 1938, 2114.

⁷ Bartlett, Hart, and McClelland, *J. Chem. Soc.*, 1939, 760.

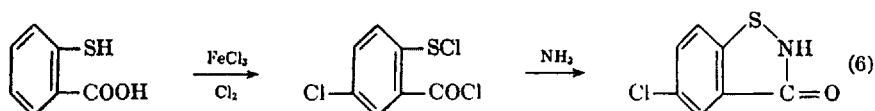
substituted 2,2'-dithiobis(benzamides) and then heated the resultant 2-aryl- or alkylcarbamyphenylsulfenyl bromide in acetic acid (4).



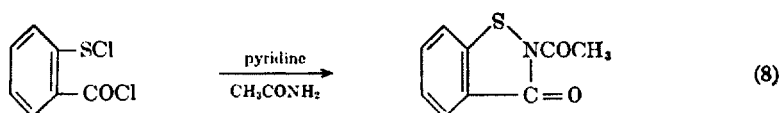
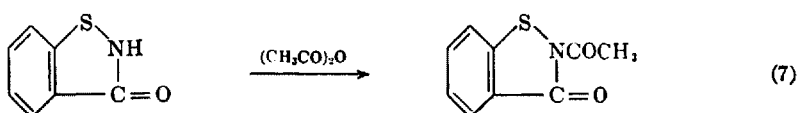
Bartlett and McClelland⁵ brominated the 2,2'-dithiobis(benzamides) in carbon tetrachloride (5).



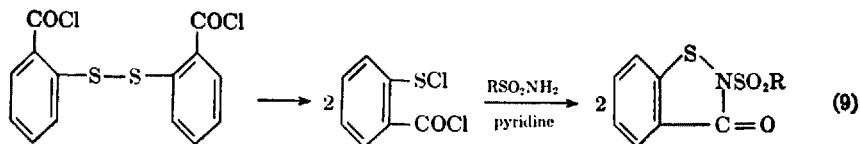
5-Chloro-1,2-benzisothiazol-3(2)-one was prepared by chlorinating 2-mercaptobenzoic acid (thiosalicylic acid) in the presence of ferric chloride and then adding ammonia (6).⁶



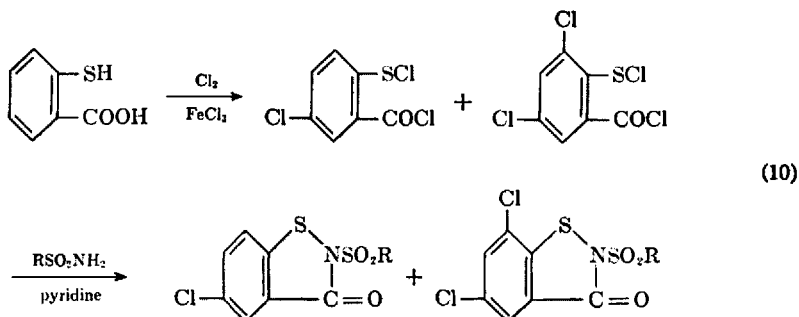
2-Acetyl-1,2-benzisothiazol-3(2)-one^{1,6} was synthesized in two ways: with acetic anhydride and 1,2-benzisothiazol-3(2)-one (7) and with 2-chlorocarbonylphenylsulfenyl chloride and acetamide in pyridine (8).



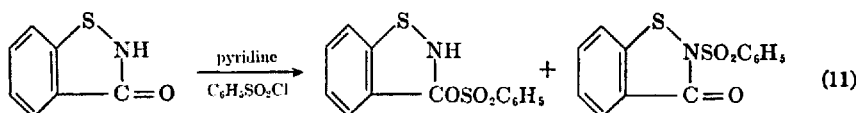
Reissert and Manns⁴ prepared the 2-benzoyl derivative by benzoylating the sodium salt of 1,2-benzisothiazol-3(2)-one.



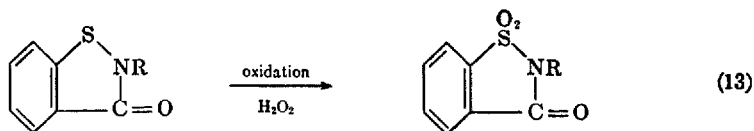
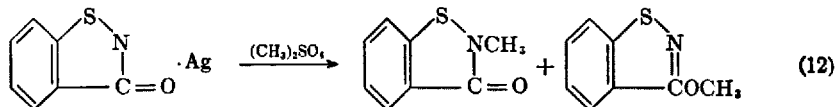
Bartlett, Hart, and McClelland⁷ found that the 2-arylsulfonyl-1,2-benzisothiazol-3(2)-ones could be prepared by chlorinating 2,2'-dithiobis(benzoyl chloride) and then condensing the resultant 2-chlorocarbonyl phenylsulfonyl chloride with an aryl sulfonamide in the presence of pyridine (9). Chlorination of 2-mercaptobenzoic acid in the presence of anhydrous ferric chloride produced a mixture of 4-chloro- and 4,6-dichloro-2-chlorocarbonylphenylsulfonyl chlorides. Condensation of this mixture with aryl sulfonamides yielded a mixture of 5-chloro- and 5,7-dichloro-2-arylsulfonyl-1,2-benzisothiazol-3(2)-ones (10). 1,2-Benzisothiazol-3(2)-one



and benzenesulfonyl chloride in the presence of pyridine gave a mixture consisting principally of 3-phenylsulfonyloxy-1,2-benzisothiazole and some 2-phenylsulfonyl-1,2-benzisothiazol-3(2)-one (11). This reaction was



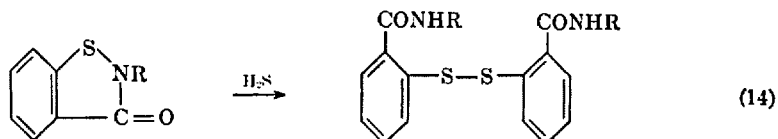
analogous to Reissert and Manns' treatment of the silver salt of 1,2-benzisothiazol-3(2)-one with dimethyl sulfate from which they obtained 3-methoxy-1,2-benzisothiazole and 2-methyl-1,2-benzisothiazol-3(2)-one (12).⁸



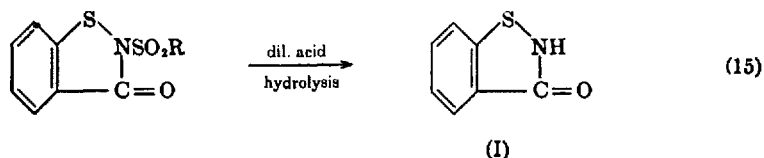
⁸ Reissert and Manns, *Ber.*, **61**, 1308 (1928).

Oxidation of these 1,2-benzisothiazol-3(2)-ones with potassium permanganate⁹ or hydrogen peroxide^{8,10,11} produced saccharin or 2-substituted benzosulfonazoles (13), where R is a hydrogen, an acyl, an alkyl, an aryl, or an aryl sulfonyl group.

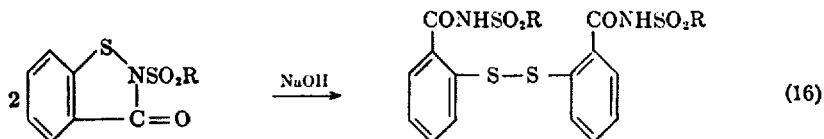
Hydrogen sulfide and sulfur dioxide reduced the 2-substituted 1,2-benzisothiazol-3(2)-ones to the 2,2'-dithiobis(benzamides) (14).^{9,11,12}



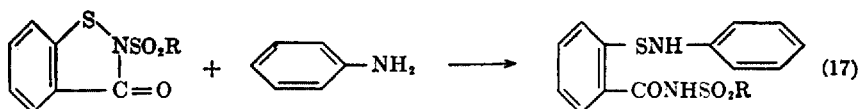
Acid hydrolysis¹¹ of the 2-arylsulfonyl-1,2-benzisothiazol-3(2)-ones eliminated the arylsulfonyl group (15). 1,2-Benzisothiazol-3(2)-one (I) gave a purple color with alcoholic ferric chloride.



This compound (I) formed a sodium salt which was soluble in water.⁹ The 2-arylsulfonyl-1,2-benzisothiazol-3(2)-ones¹¹ were less stable to alkali than the 2-aryl or alkyl derivatives; they underwent hydrolytic splitting to form the disulfides (16).



Bartlett, Hart, and McClelland¹¹ found that aniline reacted with 2-arylsulfonyl-1,2-benzisothiazol-3(2)-ones to give 2-N-arylsulfonyl carbamyl-phenyl sulfenylanilides (17). McClelland and Peters¹³ studied this reaction



⁹ McKibben and McClelland, *J. Chem. Soc.*, 123, 170 (1923).

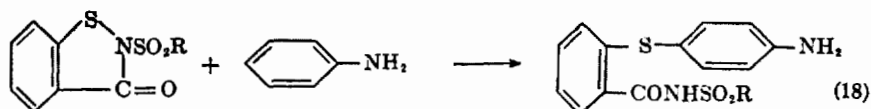
¹⁰ McClelland and Gait, *J. Chem. Soc.*, 1926, 921.

¹¹ Bartlett, Hart, and McClelland, *J. Chem. Soc.*, 1939, 760.

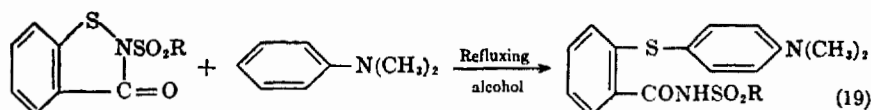
¹² McClelland, Warren, and Jackson, *J. Chem. Soc.*, 1929, 1582.

¹³ McClelland and Peters, *J. Chem. Soc.*, 1947, 1229.

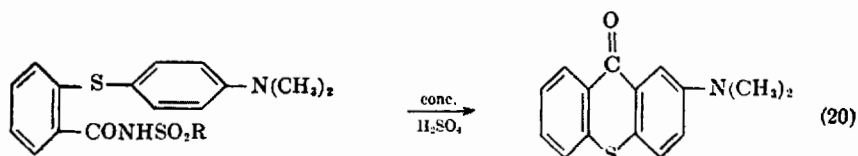
with a number of substituted anilines. After considerable work they concluded that reaction (17) proceeded as shown in equation (18). When



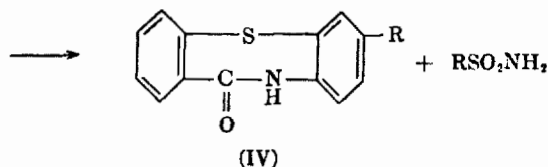
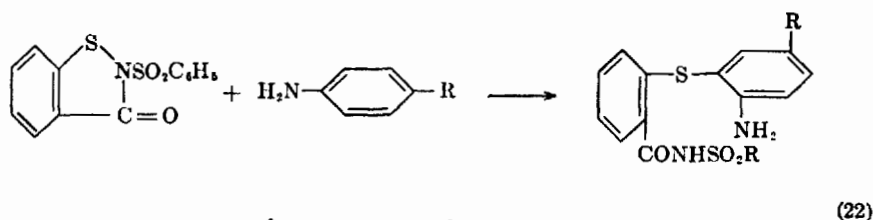
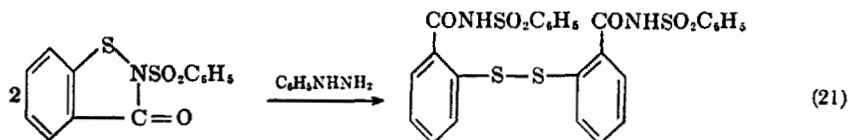
dimethylaniline was used in place of aniline in reaction (17), the resultant was 2-*N*-arylsulfonylcarbonyl-4'-dimethylaminodiphenyl sulfide (19).



Compound III was converted to 2-dimethylaminothioxanthone when heated with concentrated sulfuric acid (20). Similar results were obtained

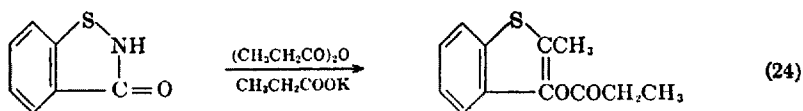
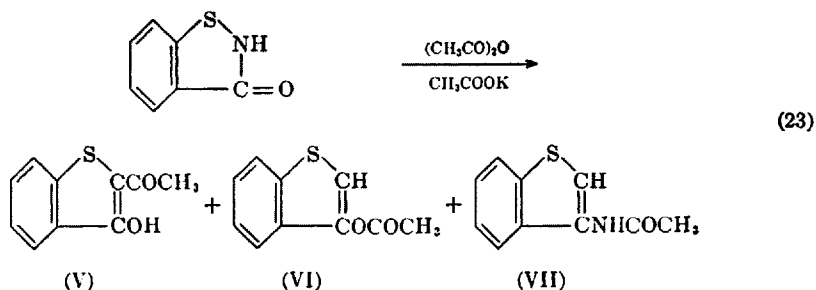


with methylethylaniline, benzylmethylaniline, methylaniline, and *o*-toluidine. Benzylamine and phenylhydrazine did not condense with the 2-arylsulfonyl-1,2-benzisothiazol-3(2)-ones, but they ruptured the ring (21). The 2-arylsulfonyl-1,2-benzisothiazol-3(2)-ones reacted with *para*-



substituted anilines such as *p*-toluidine, *p*-anisidine, and *p*-chloroaniline to give still another type of compound and aryl sulfonamide (22). Compound IV, containing a seven-membered ring, was prepared by another synthesis. Weak amines such as *p*-nitroaniline did not enter into reaction (22). Attempts to bring about a reaction between dimethylaniline and 2-methyl, 2-phenyl, 2-*p*-tolyl, 2-*p*-nitrophenyl or 2-benzoyl-1,2-benzisothiazol-3(2)-one were unsuccessful. McClelland and Peters¹³ concluded that this type of reaction of 2-arylsulfonyl-1,2-benzisothiazol-3(2)-one depended on the joint action of the SO₂ and CO groups attached to the same nitrogen atom, the simultaneous presence of which facilitated the rupture of the heterocyclic ring.

McClelland and his collaborators¹⁴⁻¹⁹ have extensively investigated the reaction between acetic anhydride, anhydrous potassium acetate and the 2-substituted 1,2-benzisothiazol-3(2)-ones. McClelland¹⁴ found that acetic anhydride and 1,2-benzisothiazol-3(2)-one yielded 2-acetyl-1,2-benzisothiazol-3(2)-one, but on the addition of potassium acetate other products were obtained. Further studies^{15,16} showed that these products were 3-hydroxy-2-acetyl-1-thianaphthene (V), 3-acetoxy-1-thianaphthene (VI), and 3-acetamido-1-thianaphthene (VII) (23). Propionic anhydride¹⁵ and potassium propionate gave the same type of reaction (24). 2,2'-



Dithiobis(benzamide),¹⁶ acetic anhydride, and potassium acetate gave the same compounds (V, VI, VII) as those obtained in reaction (23). This led

¹⁴ McClelland, *J. Chem. Soc.*, 1929, 1588.

¹⁵ McClelland and D'Silva, *J. Chem. Soc.*, 1931, 2972.

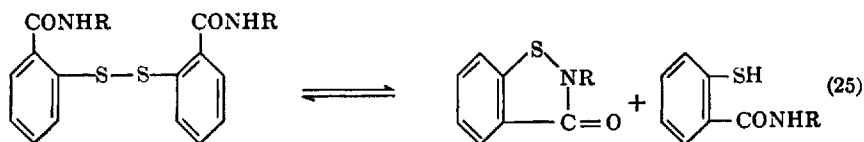
¹⁶ McClelland and D'Silva, *J. Chem. Soc.*, 1932, 2883.

¹⁷ Bartlett and McClelland, *J. Chem. Soc.*, 1934, 818.

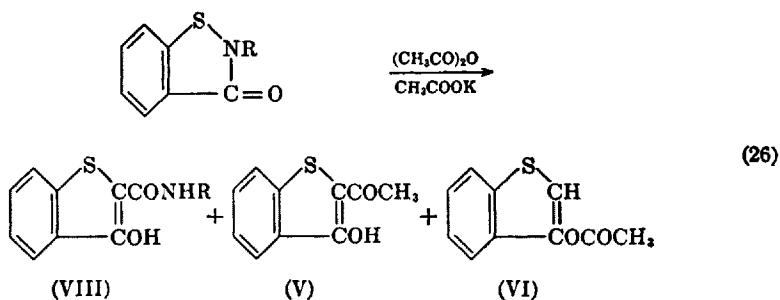
¹⁸ McClelland, Rose, and Bartlett, *J. Chem. Soc.*, 1940, 323.

¹⁹ Fowkes and McClelland, *J. Chem. Soc.*, 1945, 405.

to the belief that an equilibrium existed between the 2,2'-dithiobis(benzamides) and the 2-substituted 1,2-benzisothiazol-3(2)-ones (25).

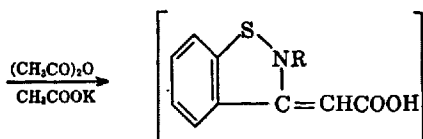
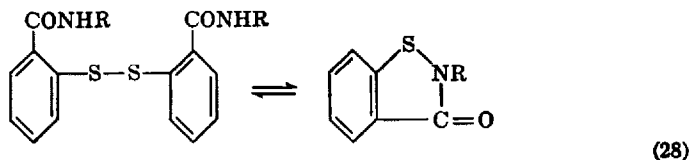
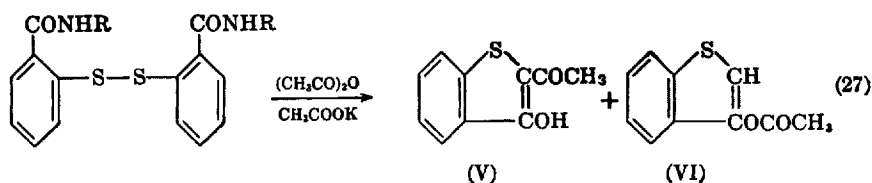


Bartlett and McClelland¹⁷ examined the reaction when 2-alkyl or 2-aryl-1,2-benzisothiazol-3(2)-ones were used. Instead of the expected *N*-substituted 3-amino-1-thianaphthenes, 3-hydroxy-2-alkyl (or aryl) carbamyl-1-thianaphthenes, 3-hydroxy-2-alkyl (or aryl) carbamyl-1-thianaphthenes were obtained (26). The 2,2'-dithiobis(benzamides) with acetic

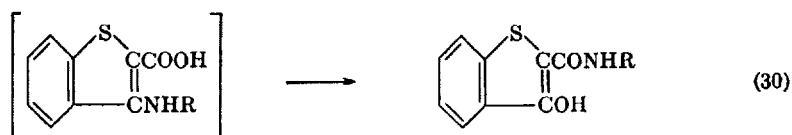
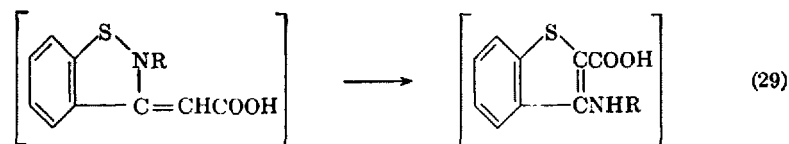


where R is an alkyl or aryl group

anhydride and potassium acetate yielded compounds V and VI with only traces of compound VIII (27). McClelland *et al.*^{14,17} believed that acetyla-



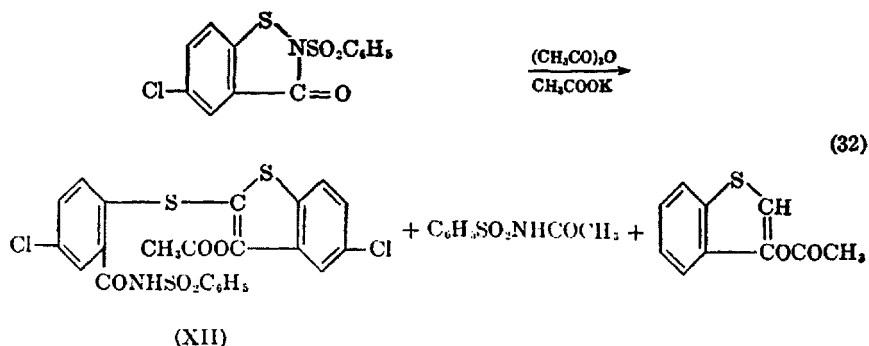
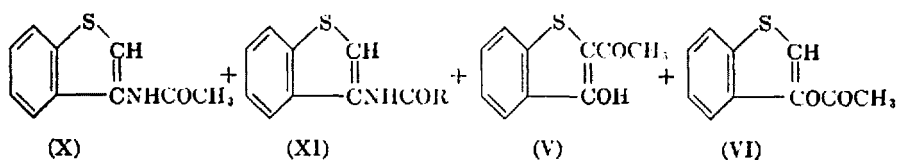
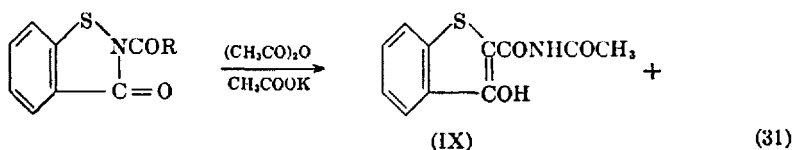
tion occurred at the 3-carbon atom and two rearrangements followed according to reactions (28, 29, 30). Reaction (29) was thought to be analo-



gous to the rearrangement of the alkylidenephthalides to the diketohydrindenes. Intramolecular rearrangements analogous to reaction (30) are unknown, although a reverse reaction was cited.

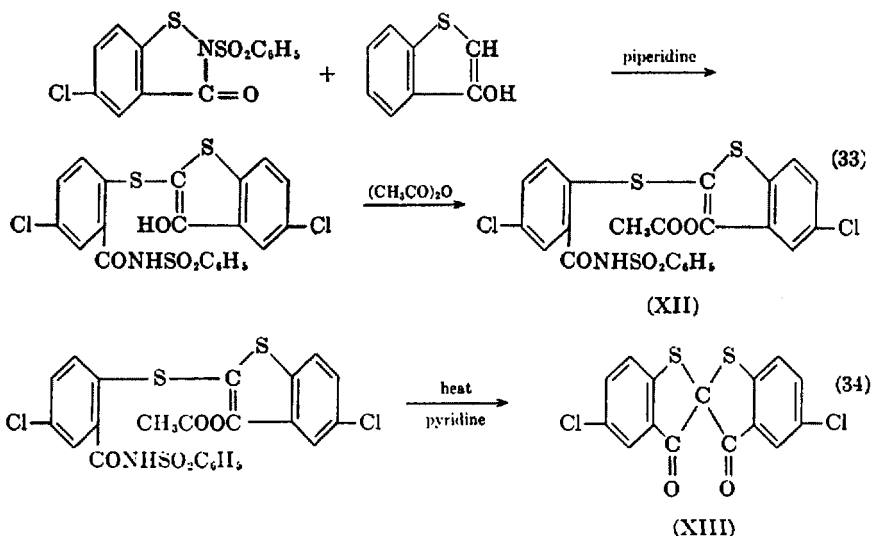
The formation of 3-hydroxy-2-acetyl-1-thianaphthene (V) was reasoned to be an example of direct carbon acetylation.

McClelland, Rose, and Bartlett¹⁸ studied the reaction between the 2-acyl-1,2-benzisothiazol-3(2)-ones and acetic anhydride in the presence of potassium acetate (31). The displacement of the parent acyl group by the

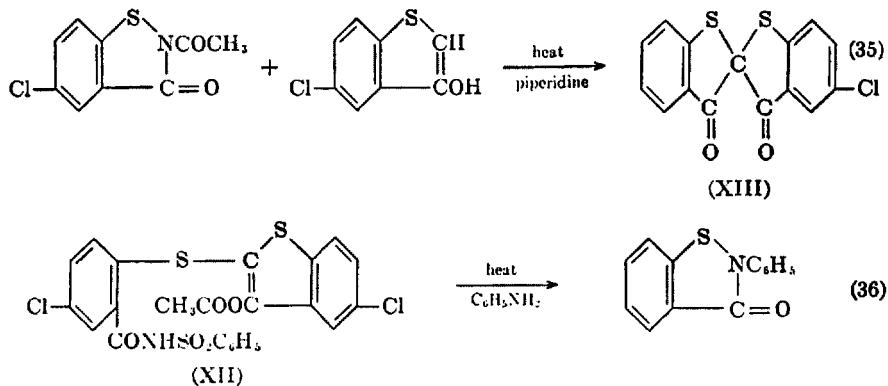


acetyl group took place in the initial step. If the reaction (31) took place at 70°C., the main product was 3-hydroxy-2-acetylcarbonyl-1-thianaphthene (IX), whereas at 110°C. 3-acetamido-1-thianaphthene (X) was the major resultant.

Fowkes and McClelland¹⁹ examined the course of 5-chloro-2-phenylsulfonyl-1,2-benzisothiazol-3(2)-one in this reaction (32). Compound XII was also prepared by condensing 5-chloro-2-phenylsulfonyl-1,2-benzisothiazol-3(2)-one with 5-chloro-3-hydroxy-1-thianaphthene in the presence of piperidine and acetylating the resultant product (33). Heating compound XII with pyridine gave a nitrogen-free substance (XIII) (34)

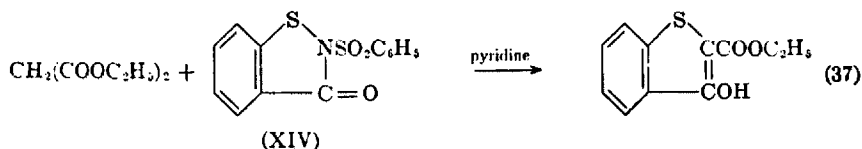


Condensing 5-chloro-2-acetyl-1,2-benzisothiazol-3(2)-one with 5-chloro-3-hydroxy-1-thianaphthene by refluxing in toluene with piperidine also

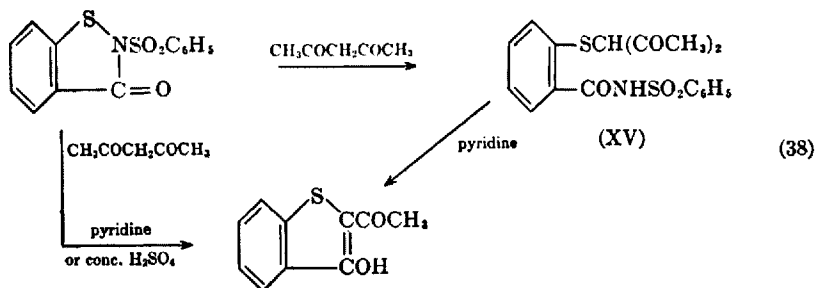


yielded compound XIII (35). Aniline and compound XII yielded 2-phenyl-5-chloro-1,2-benzisothiazol-3(2)-one (36). The nonchlorinated 2-phenylsulfonyl-1,2-benzisothiazol-3(2)-ones gave the same type of reactions. Fowkes and McClelland¹⁹ concluded that the arylsulfonyl group in the 2-position weakened the S—N bond in the nucleus. Some weakening was due to the chlorine in the *para* position to the sulfur, but the maximum effect was noted when both groups were present.

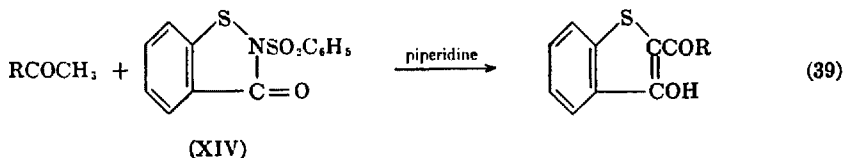
Barton and McClelland²⁰ found that 2-phenylsulfonyl-1,2-benzisothiazol-3(2)-one (XIV) reacted in the presence of pyridine or piperidine with substances containing an active methylene group to give 2-substituted 3-hydroxy-1-thianaphthenes. The reaction with ethyl malonate, ethyl acetoacetate, or ethyl acetonedicarboxylate in the presence of pyridine or piperidine gave 2-carbethoxy-3-hydroxy-1-thianaphthene (37). When



compound XIV was heated with acetylacetone in alcohol without any catalyst an intermediate (XV) resulted. Heating this intermediate with pyridine yielded the same compound as if pyridine were used in the condensation of XIV and acetylacetone (38). Benzoylacetone and aceto-

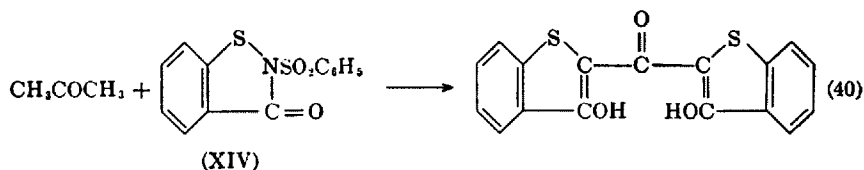


phenone formed 2-benzoyl-3-hydroxy-1-thianaphthene. A reaction of the same kind took place with ketones in general, but only in the presence of

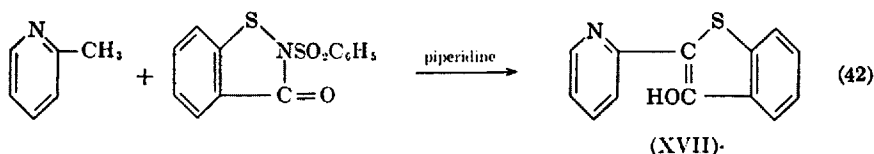
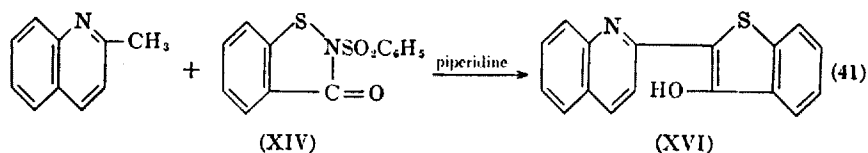


²⁰ Barton and McClelland, *J. Chem. Soc.*, 1947, 1574.

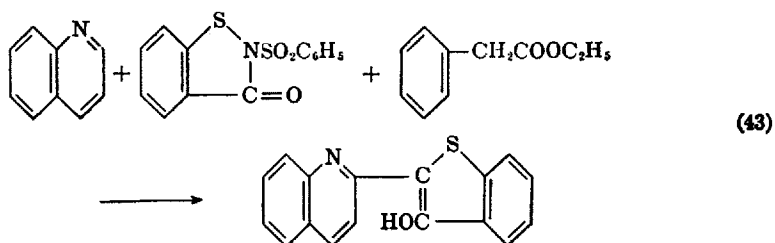
piperidine (39). With acetone both methylene groups entered the reaction (40).



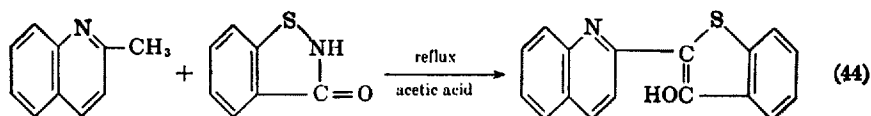
Quinaldine and 2-picoline also condensed with compound XIV to form 3-hydroxy-2,2'-quinolyl-1-thianaphthene (XVI) and 3-hydroxy-2,2'-pyridyl-1-thianaphthene (XVII), (41, 42). No reaction was detected with



ethyl phenylacetate and compound XIV in the presence of piperidine. When pure quinoline or pyridine was added to this reaction mixture compound XVI or XVII was obtained (43). No 3-hydroxy-2-phenyl-1-thianaphthene could be found in this reaction mixture.

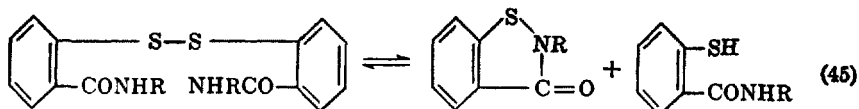


1,2-Benzisothiazol-3(2)-one did not react with boiling acetone but it reacted slowly with methyl ethyl ketone and quinaldine (44).



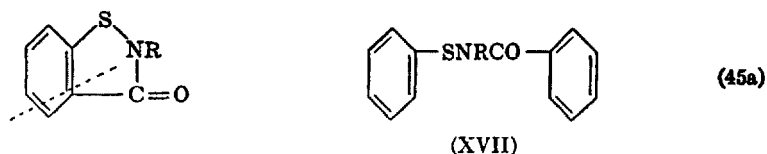
Discussion

According to McClelland's dismutation theory, the reactions of these compounds may be explained by the equilibrium between the disulfides and the 1,2-benzisothiazol-3(2)-ones depicted in reaction (45). A complete

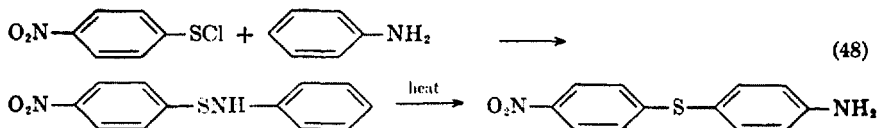
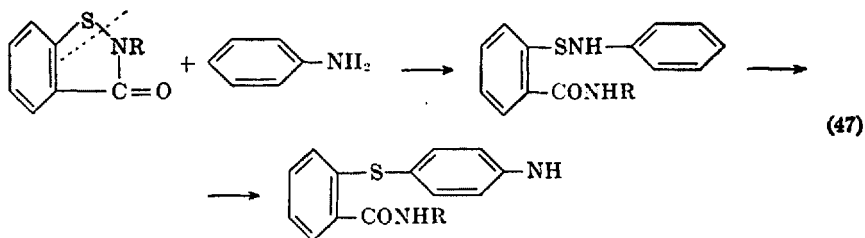
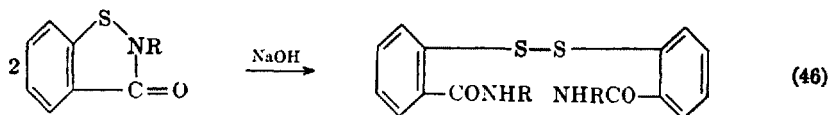


discussion of this theory and his rejection of the probability of phenylthio free radicals may be found under the reactions of 2,3-dihydrobenz[d]imidazo[1,2-b]isothiazole.

Another possible explanation exists for the reactions of these compounds. The properties of these 1,2-benzisothiazol-3(2)-ones resemble *N*-phenylsulfenylbenzamides (XVII) (45a). Such sulfenamides would be

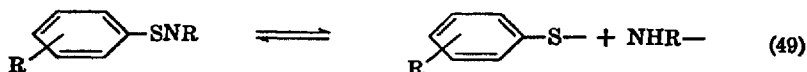


sensitive to alkali and strong amines with the formation of the 2,2'-dithio-bis(benzamides) (46). Arylamines such as aniline, dimethylaniline, etc.,

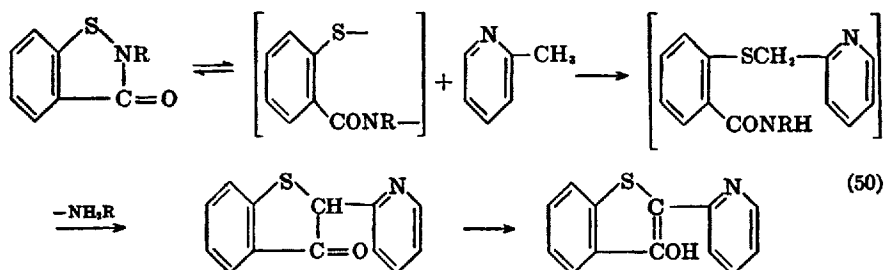


which are stronger bases than benzamide, would rupture the N—S bond to form the sulfenamide if possible, and then rearrange to form the sulfide (47). Compare this reaction with Zincke's²¹ and Moore and Johnson's²² experiments with the *p*-nitrophenylsulfenamides (48).

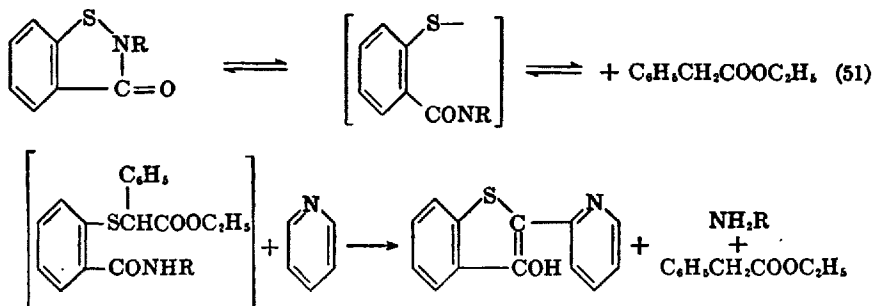
To account for these rearrangements the fleeting presence of a phenylthio free radical must be postulated (49). The existence of such a radical



would explain the reaction of the 1,2-benzisothiazol-3(2)-one with compounds having active methylene groups (50). The reaction between pyri-



dine or quinoline and the 2-arylsulfonyl-1,2-benzisothiazol-3(2)-ones in the presence of ethyl phenylacetate would require the formation of an unstable intermediate or a hydrogen donor, since only one hydrogen is available from the pyridine or quinoline (51).

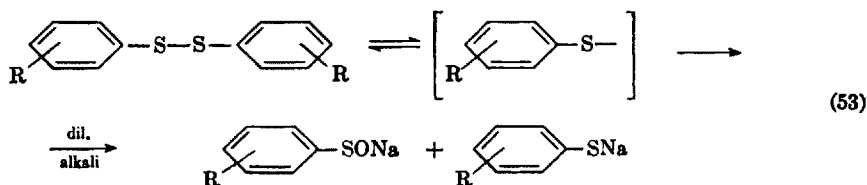
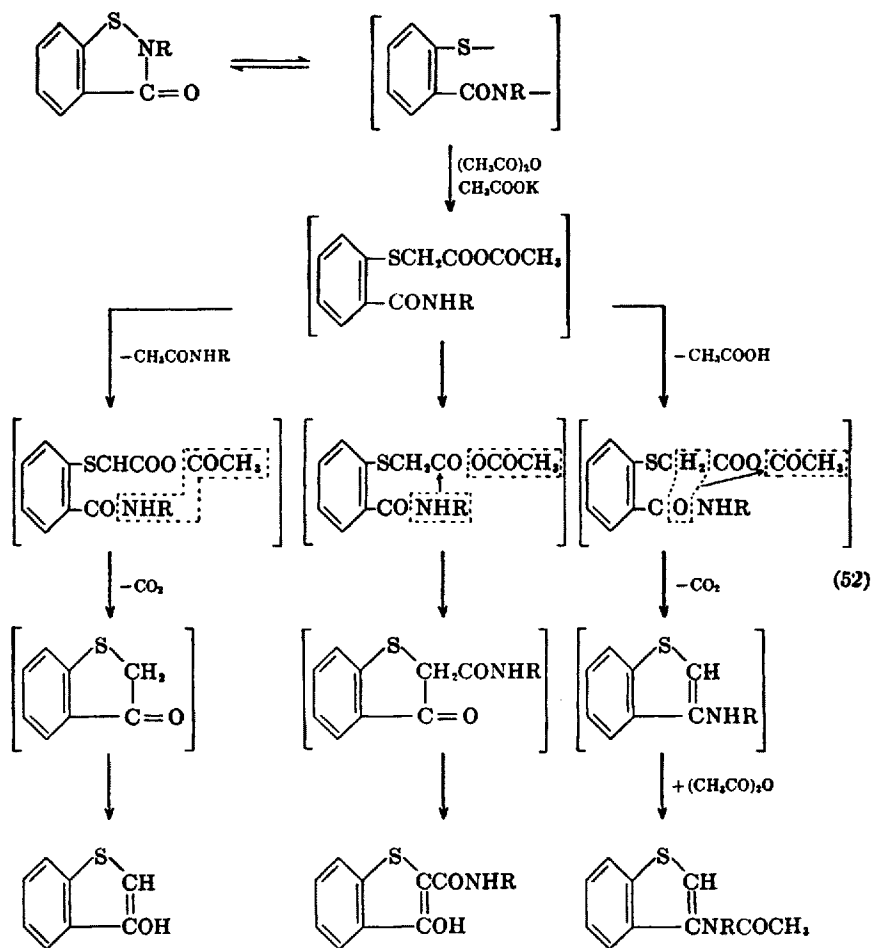


The multitude of products obtained by the action of acetic anhydride and potassium acetate is probably due to the number of active centers involved. The following possible reactions would explain the formation

²¹ Zincke and Linhart, *Ann.*, **400**, 2 (1913).

²² Moore and Johnson, *J. Am. Chem. Soc.*, **58**, 1091 (1936).

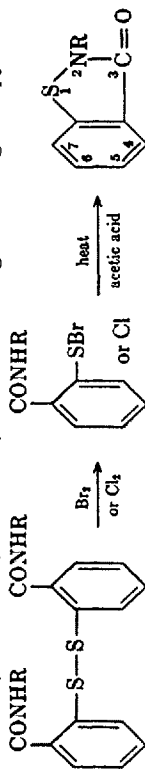
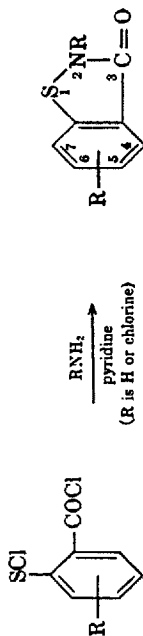
of these compounds (52). Such a series of reactions may not be the true course of the reaction, but it is a possible explanation for the many products formed.



The formation of these compounds from the 2,2'-dithiobis-(benzamides) can be readily shown, since the disulfides probably form the phenylthio free radical (53). The existence of a phenylthio free-radical may be open to question, but it is the best explanation for the reactivity of the disulfides, the lability of the phenylsulfenamides, and the rearrangements of the phenylthio group from a nitrogen atom to a carbon atom. (Additional discussions of the properties of the disulfides occur under the chemistry of 2,3-dihydrobenz[*d*]imidazo[1.2-*b*]isothiazole, and the 2-mercapto-4-substituted-1,3,4-thiadiazol-5(4)-thiones.)

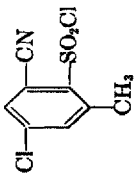
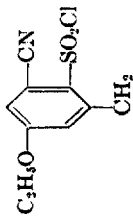
Table LIV follows on pages 268-270.

TABLE LIV. Preparation of the 1,2-Benzisothiazol-3(2)-ones

Method 1: Acylation of 1,2-benzisothiazol-3(2)-one.*Method 2:* Halogenation of the 2,2'-dithiobis(benzamides) and then heating or treating with pyridine.*Method 3:* Preparation of 2-chlorocarbonyl[phenylsulfenyl] chloride and then the addition of the amine or amide with pyridine.

No.	Substituents on the 1,2-benzisothiazol-3(2)-one other than hydrogen	Ref.	Method	Solubility	M.p., °C.
1	None	1		alc., water	158
2	5-Chloro	2	method 3	—	155-6
		3	method 2	—	157-8
		4	method 3	alc.	259-61

TABLE LIV (Continued)

No.	Substituents on the 1,2-benzisothiazol-3(2)-one other than hydrogen	Ref.	Method	Solubility	M.p., °C.
3	4-Methyl-6-chloro	5	 + mild reducing agent	—	220
4	6-Ethoxy	5	 + mild reducing agent	—	225
5	2-Methyl	2 3	method 3 method 2	ether benzene	51-2 54
6	2-Ethyl	6	method 2 method 3	alc.	118-20
7	2-n-Propyl	2	method 3	—	—
8	2-Benzyl	6	method 2 method 3	methanol	oil 89
9	2-Phenyl	3 2	method 2 method 3	methanol	143-4 140
10	2-o-Tolyl	2	method 2	methanol	122-3
11	2-p-Tolyl	7	method 3	methanol	135
12	2-p-Nitrophenyl	7	method 3	acetic acid	238
13	5-Chloro-2-phenyl	9	method 3	—	179

(Table continued)

No.	Substituents on the 1,2-benzothiazol-3(2)-one other than hydrogen	Ref.	Method	Solubility	M.p., °C.
14	2-Acetyl	8	method 1	acetic acid	138
		10	method 3	—	139
15	2-Propionyl	11	method 1	alc.	144
			method 3	—	—
16	2-Chloracetyl	11	method 1	alc.	171
17	2-Phenylacetyl	11	method 1	alc.	137
18	2-Benzoyl	11	method 3	alc.	170
19	2-Acetyl-5-chloro	4	method 1	alc.	176
			method 3	—	—
20	2-Phenylsulfonyl	10	method 3	acetic acid	218
21	5-Chloro-2-phenylsulfonyl	10	method 3	acetic acid	205
22	5,7-Dichloro-2-phenylsulfonyl	10	method 3	acetic acid	162
23	2- <i>p</i> -Tolylsulfonyl	10	method 3	acetic acid, pyridine	207
24	5-Chloro-2- <i>p</i> -tolylsulfonyl	10	method 3	acetic acid	203

¹ McKibben and McClelland, *J. Chem. Soc.*, 123, 170 (1932).

² McClelland and Galt, *J. Chem. Soc.*, 1926, 921.

³ Reissert and Mannas, *Ber.*, 61, 1308 (1928).

⁴ Hart, McClelland, and Fowkes, *J. Chem. Soc.*, 1938, 2114.

⁵ Steger and Schulte, *Chem. Abstr.*, 27, 5339 (1933); *Fr. Pat.* 748,516; *Chem. Abstr.*, 30, 1392 (1936); *U. S. Pat.* 2,020,622.

⁶ Bartlett and McClelland, *J. Chem. Soc.*, 1934, 818.

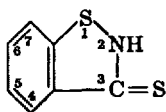
⁷ McClelland and Peters, *J. Chem. Soc.*, 1947, 1239.

⁸ McClelland and Longwell, *J. Chem. Soc.*, 123, 3310 (1923).

⁹ Fowkes and McClelland, *J. Chem. Soc.*, 1945, 405.

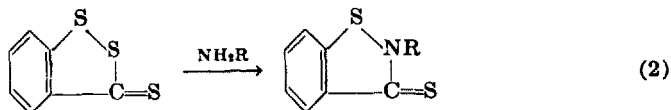
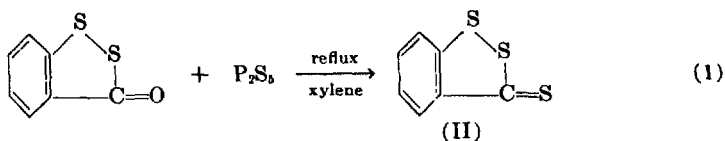
¹⁰ Bartlett, Hart, and McClelland, *J. Chem. Soc.*, 1939, 760.

¹¹ McClelland, Rose, and Bartlett, *J. Chem. Soc.*, 1940, 323.

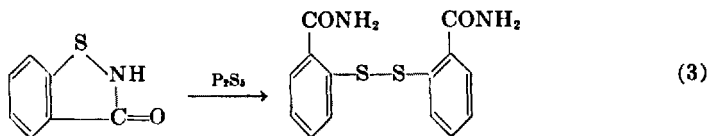
1,2-Benzisothiazol-3(2)-thiones (I)

(I)

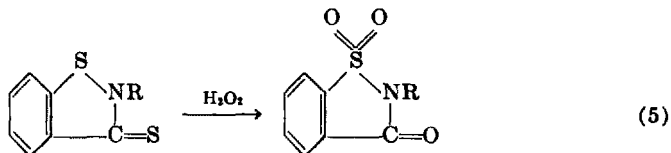
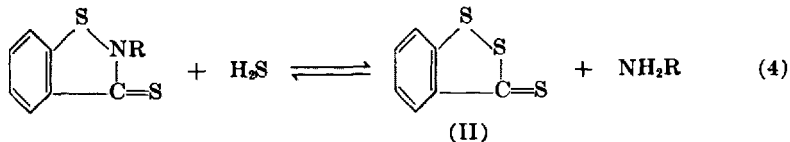
McClelland, Warren, and Jackson¹ studied the preparation and characteristics of some 2-substituted 1,2-benzisothiazol-3(2)-thiones. 1,2,3-Benzodithiol-3-thione was prepared with phosphorus pentasulfide and 1,2,3-benzodithiol-3-one (1). Compound II reacted with primary amines to give the 2-substituted 1,2-benzisothiazol-3(2)-thiones (2). Ammonia resulted



in the production of a tarry product consisting largely of starting material. An attempt to produce these compounds from 1,2-benzisothiazol-3(2)-one and phosphorus pentasulfide resulted in 2,2'-dithiobis(benzamide) (3).



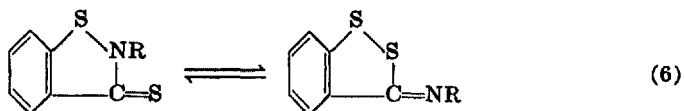
Sulfur dioxide did not reduce the 1,2-benzisothiazol-3(2)-thiones. Hydrogen sulfide and the 1,2-benzisothiazol-3(2)-thiones yielded compound II indicating that the reaction was reversible (4).



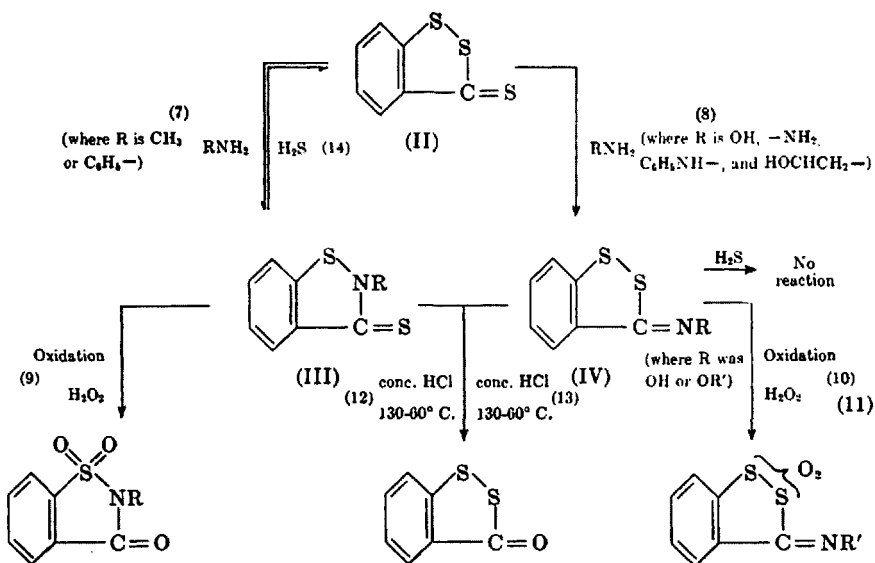
¹ McClelland, Warren, and Jackson, *J. Chem. Soc.*, 1929, 1582.

Oxidation of the 1,2-benzisothiazol-3(2)-thiones yielded 2-substituted saccharin derivatives (5).

McClelland and Salkeld² investigated the possibility of an equilibrium between the 1,2-benzisothiazol-3(2)-thiones and the 3-imino-1,2,3-benzodithioles (6). Alkyl and aryl amines reacted with 1,2,3-benzodithiol-3-



thione to yield the 2-alkyl or aryl-1,2-benzisothiazol-3(2)-thiones (7), while hydroxylamine, hydrazine, phenylhydrazine, and β -ethanolamine formed the 3-substituted imino-1,2,3-benzodithioles (8). Oxidation of compound III produced the 2-substituted saccharins or 2-substituted-1,2-benzosulfonazol-3(2)-ones (9). Oxidation of IV yielded a sulfone without the elimina-



tion of a sulfur atom (10). Hydrolysis of either type III or IV with concentrated hydrochloric acid at 130–160°C. for two hours formed 1,2,3-benzodithiol-3-one (12,13). Hydrogen sulfide reacted with the 2-substituted 1,2-benzisothiazol-3(2)-ones to give compound II. No reaction was observed between the 3-imino-1,2,3-benzodithioles (11).

² McClelland and Salkeld, *J. Chem. Soc.*, 1936, 1143.

Hydrogen selenide and 2-methyl-1,2-benzisothiazol-3(2)-thione did not form the expected selenium analog of 1,2,3-benzodithiol-3-thione but produced the 2-mercaptothiobenzmethylamide by reduction (15).

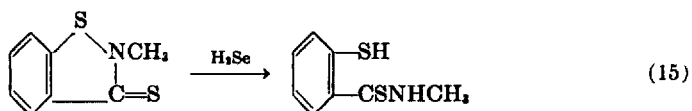
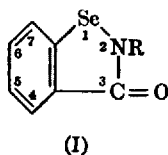


TABLE LV.¹ 1,2-Benzisothiazol-3(2)-thiones

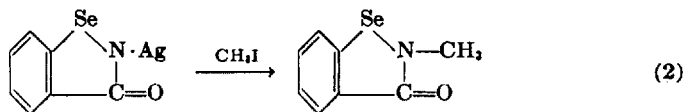
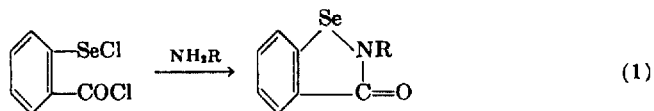
No.	Name	Solubility	M.p., °C.
1	2-Methyl-1,2-benzisothiazol-3(2)-thione	acetic acid, benzene	138-9
2	2-Ethyl-1,2-benzisothiazol-3(2)-thione	benzene, ligroin	63-4
3	2-Benzyl-1,2-benzisothiazol-3(2)-thione	alc.	122-3
4	2-Phenyl-1,2-benzisothiazol-3(2)-thione	alc.	77

¹ McClelland *et al.*, *J. Chem. Soc.*, 1929, 1582.

1,2-Benzisoselenazol-3(2)-ones (I)



Lesser and Weiss¹ synthesized 2-alkyl- and 2-aryl-1,2-benzisoselenazol-3(2)-ones from primary amines and 2-chlorocarbonylphenylselenyl chloride (1).



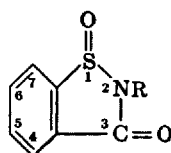
¹ Lesser and Weiss, *Ber.*, 57, 1077 (1924).

1,2-Benzisoselenazol-3(2)-one formed difficultly soluble alkaline salts. Oxidation of 1,2-benzisoselenazol-3(2)-one did not give the selenosaccharin. Acetylation gave the 2-acetyl-1,2-benzisoselenazol-3(2)-one. Methylation yielded 2-methyl-1,2-benzisoselenazol-3(2)-one (2), which was identical to that obtained from methylamine and 2-chlorocarbonylphenylselenyl chloride.

TABLE LVI

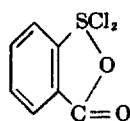
No.	Name	Solubility	M. p., °C.
1	1,2-Benzisoselenazol-3(2)-one	water	234-5
2	2-Acetyl-1,2-benzisoselenazol-3(2)-one	acetic acid	172-4
3	2-Methyl-1,2-benzisoselenazol-3(2)-one	benzene	159-60
4	2-Ethyl-1,2-benzisoselenazol-3(2)-one	petroleum ether	102-3
5	2-Phenyl-1,2-benzisoselenazol-3(2)-one	alc.	182-3
6	2- <i>o</i> -Tolyl-1,2-benzisoselenazol-3(2)-one	alc.	187-8

1,2-Benzisothiazol-3(2)-one *S*-oxides (I)



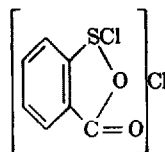
(I)

Hart, McClelland, and Fowkes¹ found that the chlorination of 2-mercaptobenzoic acid gave a dichloro product which may be represented by formulas X or XI². Acetamide and arylsulfonamides condensed with



(X)

or



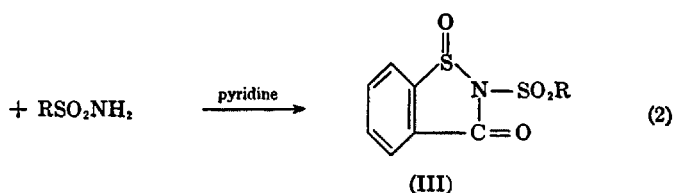
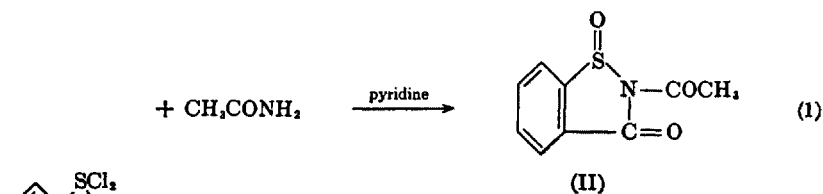
(XI)

compound X in the presence of pyridine to give 2-acetyl and the 2-arylsulfonyl-1,2-benzisothiazol-3(2)-one *S*-oxides (1,2).

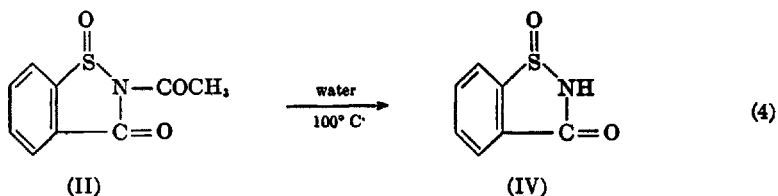
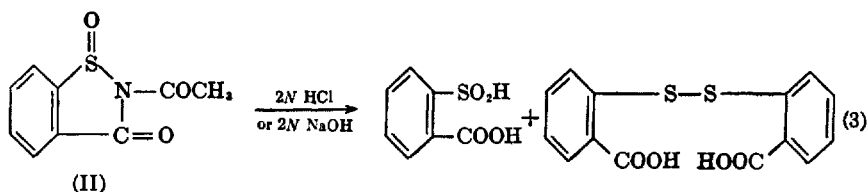
Hydrolysis of 2-acetyl-1,2-benzisothiazol-3(2)-one *S*-oxide (II) with dilute alkali or dilute acid gave a mixture of 2-carboxyphenylsulfonic acid

¹ Hart, McClelland, and Fowkes, *J. Chem. Soc.*, 1938, 2114.

² The structure of this compound may also be represented as .



and 2,2'-dithiobis(benzoic acid) (3). Heating II with water at 100°C. gave 1,2-benzisothiazol-3(2)-one *S*-oxide (4). Oxidation of II with hydro-



gen peroxide yielded *o*-benzoicsulfinide (5). Reduction of 1,2-benzisothiazol-3(2)-one *S*-oxide formed 2,2'-dithiobis(benzamide) (6).

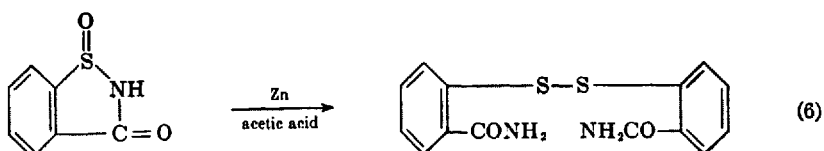
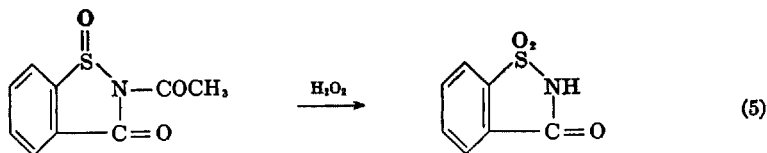
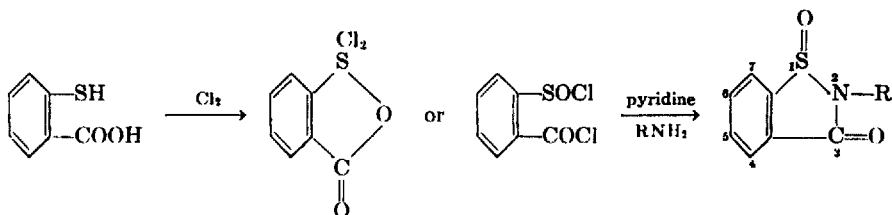


TABLE LVII. Preparation of the 1,2-Benzisothiazol-3(2)-one *S*-oxides

The compounds were prepared by chlorinating 2-mercaptobenzoic acid and then allowing the reaction product to react with an amide in the presence of pyridine,

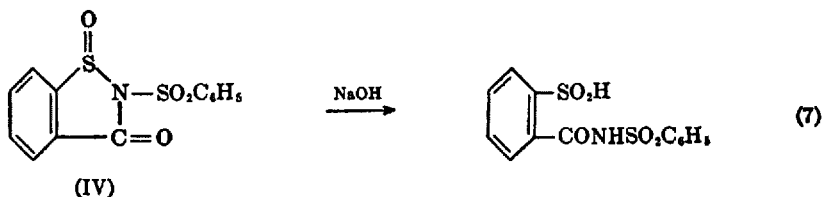


where R is an acyl or a phenyl sulfonyl group.

The exception was 1,2-benzisothiazol-3(2)-one *S*-oxide, which was obtained by the hydrolysis of 2-acetyl-1,2-benzisothiazol-3(2)-one *S*-oxide.

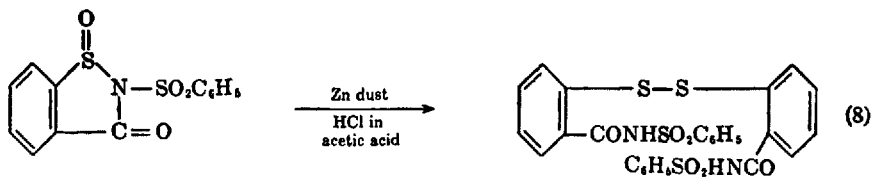
No.	Name	Ref.	Solubility	M.p., °C
1	1,2-Benzisothiazol-3(2)-one <i>S</i> -oxide	1	water	159
2	2-Acetyl-1,2-benzisothiazol-3(2)-one <i>S</i> -oxide	1	alc.	150
3	2-Propionyl-1,2-benzisothiazol-3(2)-one <i>S</i> -oxide	2	alc.	136
4	2-Phenylacetyl-1,2-benzisothiazol-3(2)-one <i>S</i> -oxide	2	alc.	162
5	2-Benzoyl-1,2-benzisothiazol-3(2)-one <i>S</i> -oxide	2	benzene	150
6	2-Phenylsulfonyl-1,2-benzisothiazol-3(2)-one <i>S</i> -oxide	1	acetic acid	182
7	2-Tolylsulfonyl-1,2-benzisothiazol-3(2)-one <i>S</i> -oxide	1	acetic acid	179

Hydrolysis of 2-phenylsulfonyl-1,2-benzisothiazol-3(2)-one *S*-oxide (IV) yielded a 2-*N*-benzenesulfonylcarbamylphenylsulfonic acid (7). Oxidation



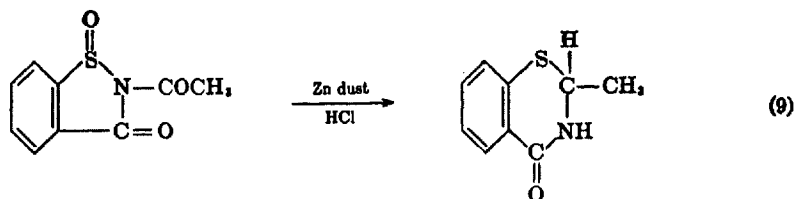
of IV with hydrogen peroxide gave a small quantity of *N*-benzenesulfonyl-*o*-benzoisulfonide and benzenesulfonamide.

Ingram and McClelland² studied the reduction of the 2-acyl derivatives. Reduction of the 2-phenylsulfonyl or the benzoyl compounds gave the corresponding disulfides (8).



¹ Hart, McClelland, and Fowkes, *J. Chem. Soc.*, 1938, 2114.

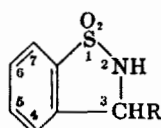
² Ingram and McClelland, *J. Chem. Soc.*, 1947, 763.



When the 2-substituent was an acyl group such as acetyl, propionyl, or phenylacetyl, then 2-alkyl-2,3-dihydro-1,3-benzothiazin-4-ones were formed (9).

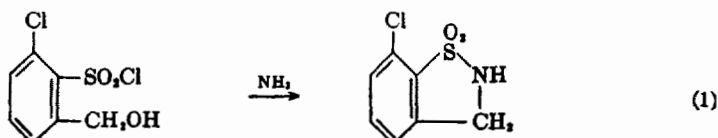
The 1,2-Benzisosulfonazoles, Their Homologs and Derivatives

2,3-Dihydro-1,2-benzisosulfonazoles (I) or 2,3-Dihydro-1,2-benzisothiazole *S*-dioxides

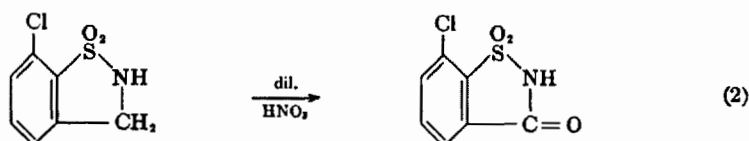


(I)

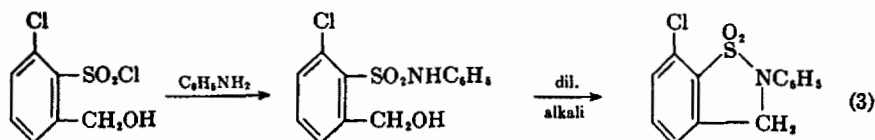
Reissert and Cramer¹ synthesized 7-chloro-2,3-dihydro-1,2-benzisosulfonazole from 2-hydroxymethyl-6-chlorophenylsulfonyl chloride and ammonia (1).



Oxidation of this compound with dilute nitric acid or potassium dichromate yielded 7-chlorosaccharin (2). Methylation gave 2-methyl-7-

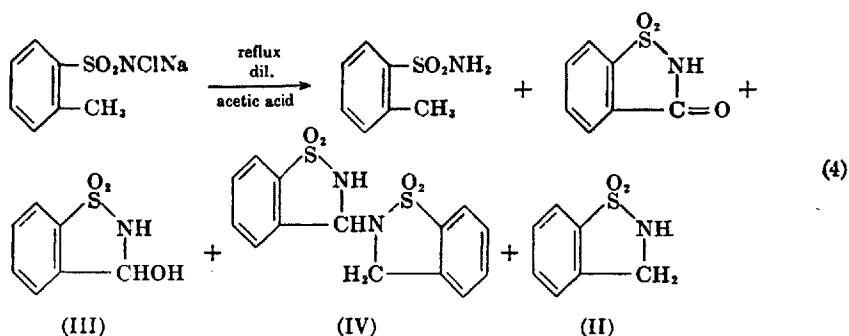


chloro-2,3-dihydro-1,2-benzisosulfonazole. Aniline and 2-hydroxymethyl-6-chlorophenylsulfonyl chloride formed the sulfonanilide. Warming this anilide with dilute alkali produced 2-phenyl-7-chloro-2,3-dihydro-1,2-benzisosulfonazole (3).

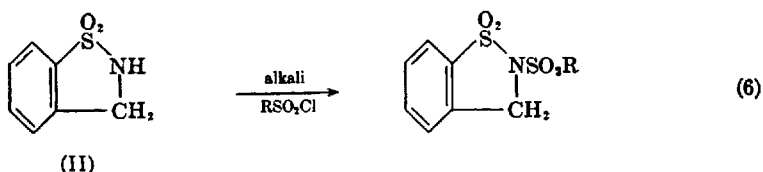
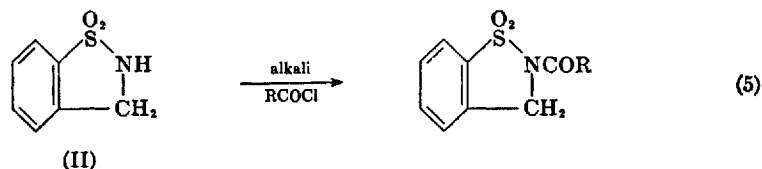


¹ Reissert and Cramer, *Ber.*, 61, 2555 (1928).

In studying the oxidizing powers of chloramine TO, chloramine B, and halozone, Koetschet and Koetschet^{2,3} found that these compounds oxidized *o*-tolylsulfonamides with the formation of saccharin (or its derivatives) and a number of 2,3-dihydro-1,2-benzisosulfonazoles. Hydrolysis of chloramine TO with hot dilute acetic acid yielded saccharin, *o*-tolylsulfonamide, 2,3-dihydro-1,2-benzisosulfonazole (II), 3-hydroxy-2,3-dihydro-1,2-benzisosulfonazole (III), and 2-(2,3-dihydro-1,2-benzisosulfonazol-3-yl)-2,3-dihydro-1,2-benzisosulfonazole (IV) (4).



Matsui *et al.*⁴ investigated the electrolytic reduction of saccharin in an acid medium. With lead, zinc, mercury, or zinc in mercury cathodes at 30°C. or less and 5 amperes per 70 cm.², compound IV was formed. At 50°C. 2,3-dihydro-1,2-benzisosulfonazole (II) was obtained. When phenylhydrazine was added before the reduction took place, 3- β -phenylhydrazino-2,3-dihydro-1,2-benzisosulfonazole could be isolated.

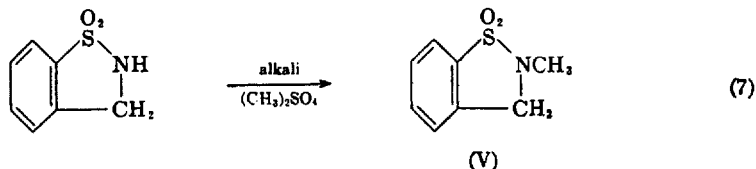


² Koetschet and Koetschet, *Helv. Chim. Acta*, **12**, 669 (1929).

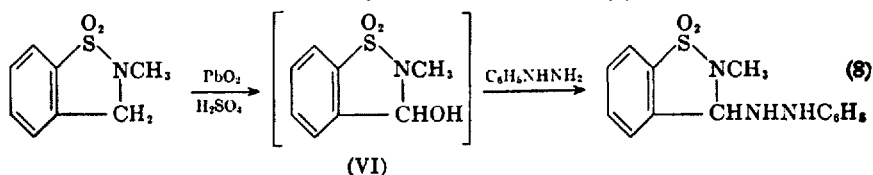
³ Koetschet, Koetschet, and Viaud, *Helv. Chim. Acta*, **13**, 587 (1930).

⁴ Matsui, Sawamura, and Adachi, *Chem. Abstr.*, **26**, 5264 (1932); *Brit. Chem. Abstr.*, **1932**, 1046; *Mem. Coll. Sci. Kyoto, Imp. Univ.*, **A15**, 151 (1932).

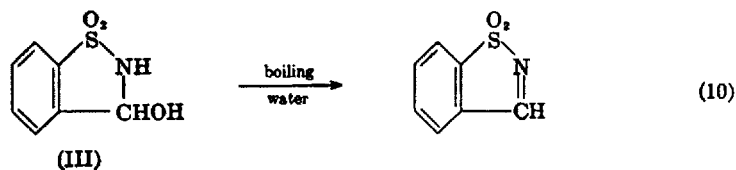
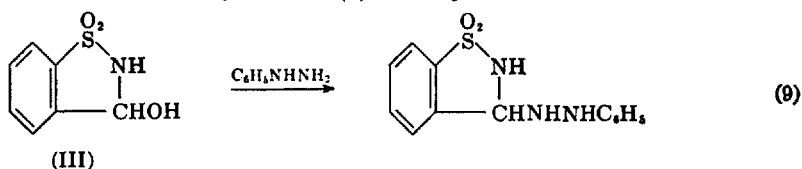
Acylation³ of compound II in the presence of alkali gave the 2-acyl-2,3-dihydro-1,2-benzisulfonazoles (5). The 2-arylsulfonyl derivatives were prepared in a similar manner (6). Methylation with dimethyl sulfate in the presence of alkali yielded 2-methyl-2,3-dihydro-1,2-benzisulfonazole (7). Oxidation of compound V with lead dioxide and dilute sulfuric acid



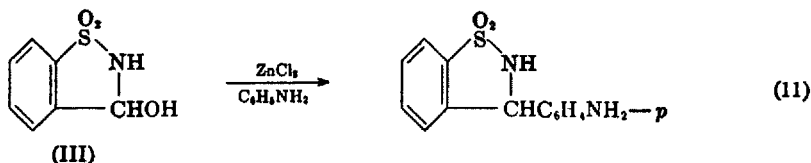
formed 2-methyl-3-hydroxy-2,3-dihydro-1,2-benzisulfonazole (VI). Compound VI was isolated as the hydrazine derivative (8).



3-Hydroxy-2,3-dihydro-1,2-benzisulfonazole (III) was too unstable to isolate *per se*. It had a great many properties of an aldehyde and was referred to as the pseudo aldehyde by Koetschet and Koetschet.^{2,3} It was usually isolated as the hydrazine (9). Dehydration occurred when com-

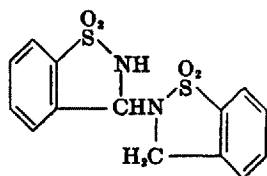


compound III was boiled in water to form 1,2-benzisulfonazole (10). Compound III reacted with aniline in the presence of anhydrous zinc chloride to give 3-*p*-aminophenyl-2,3-dihydro-1,2-benzisulfonazole (11). This

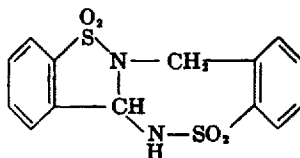


compound had all the properties of an aromatic primary amine. It did not react with phenylhydrazine. Dimethylaniline gave a similar reaction with compound III. Sodium hydroxide and calcium hydroxide decomposed compound III only when heated.

Compound IV or 2-(2,3-dihydro-1,2-benzisosulfonazol-3-yl)-2,3-dihydro-1,2-benzisosulfonazole could be represented by another possible structure (VII), although Koetschet and Koetschet^{2,3} preferred structure (IV).

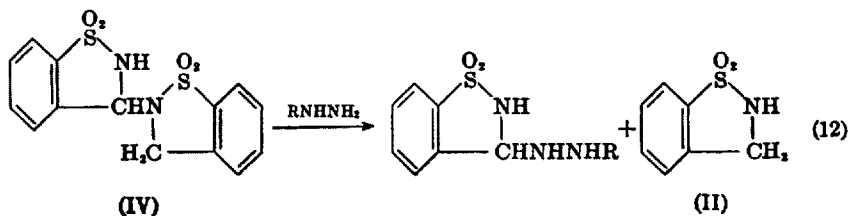


(IV)



(VII)

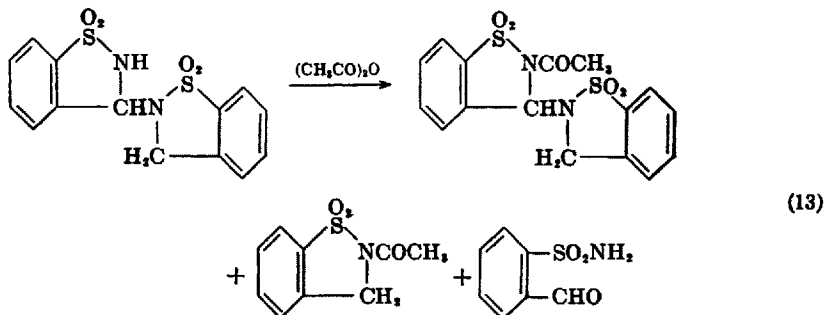
This compound was soluble in dilute alkali from which it could be precipitated by dilute acids such as carbonic acid. Hot hydrochloric acid caused no decomposition. Aryl hydrazine reacted with compound IV to give the 3- β -arylhydrazino-2,3-dihydro-1,2-benzisosulfonazoles and 2,3-dihydro-1,2-benzisosulfonazole (II) (12).



(IV)

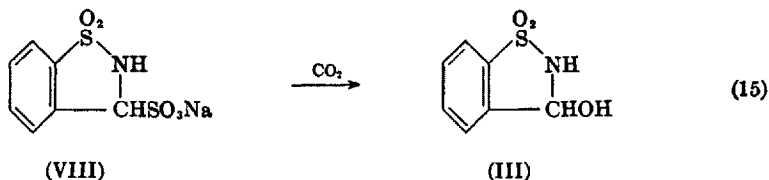
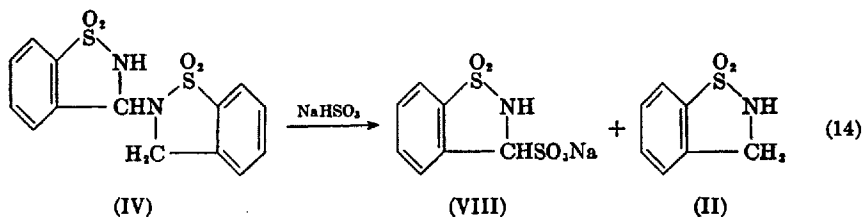
(II)

Acetylation of IV gave a mixture consisting of a monoacetyl derivative of IV, 2-acetyl-2,3-dihydro-1,2-benzisosulfonazole, and 2-sulfamylbenzaldehyde (13).

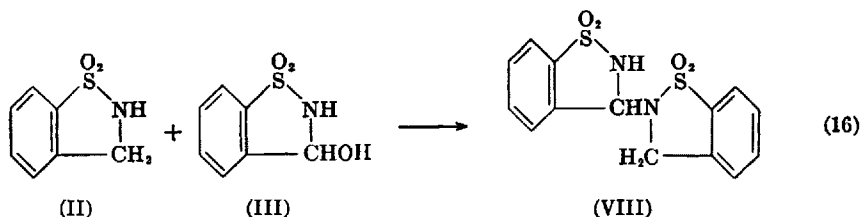


(13)

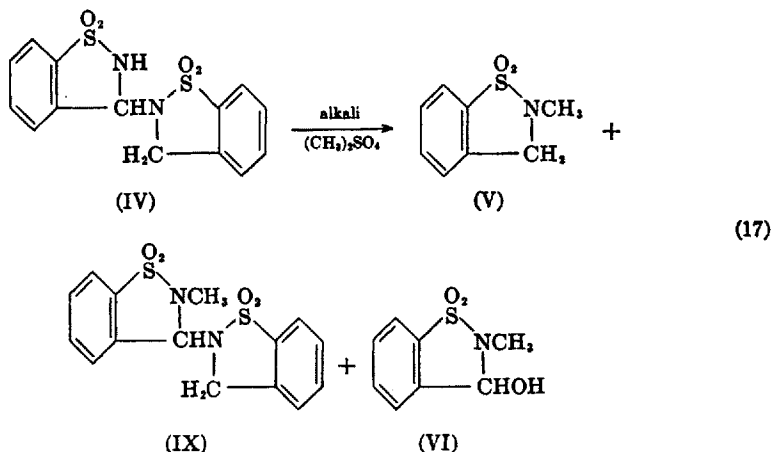
Sulfur dioxide, sodium bisulfite, and sodium sulfite split compound IV to form 2,3-dihydro-1,2-benzisosulfonazole (II) and 3-hydroxy-2,3-dihydro-1,2-benzisosulfonazole (III), the latter probably existing as the sodium sulfonate (14). Compound III was prepared by passing a stream of carbon dioxide through the solution containing compound VIII (15). Compound



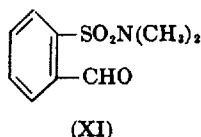
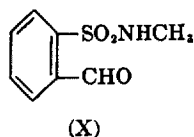
VIII readily reacted with arylhydrazines to give the 3- β -arylhydrazino-2,3-dihydro-1,2-benzisosulfonazoles. Compound IV was reconstituted by warming a solution containing compounds II and III (16).



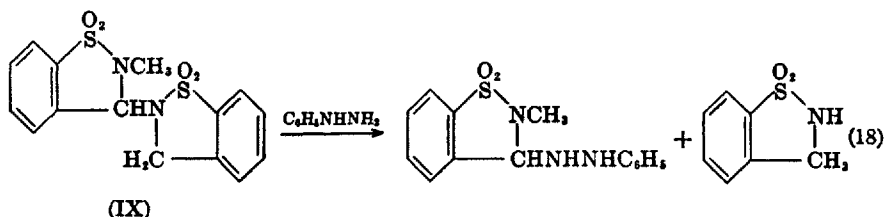
Methylation of compound IV gave three compounds: 2-methyl-2,3-dihydro-1,2-benzisosulfonazole (V), 3-hydroxy-2-methyl-2,3-dihydro-1,2-benzisosulfonazole (VI) which was isolated as the 3-phenylhydrazino compound, and 2-(2-methyl-2,3-dihydro-1,2-benzisosulfonazol-3-yl)-2,3-dihydro-1,2-benzisosulfonazole (IX) (17). Compound V was identical to that obtained by methylating 2,3-dihydro-1,2-benzisosulfonazole. Compound VI possessed the same characteristics as the oxidation product of 2-methyl-2,3-dihydro-1,2-benzisosulfonazole. This compound was no longer soluble in dilute alkali. This property led Koetschet and Koetschet to assign the 3-hydroxy-2,3-dihydro-1,2-benzisosulfonazole structures to this series of compounds rather than 2-formylphenylsulfonamide. Compound VI could



be neither X or XI, since their analyses and properties did not agree. Compound X would be soluble in alkali and the calculated analyses of XI were not in agreement with compound VI.

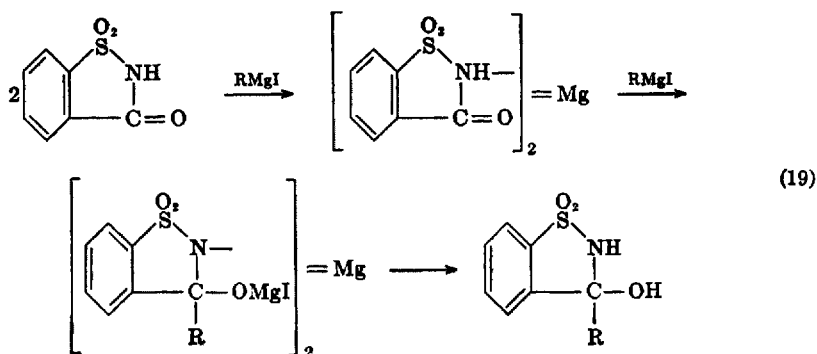


Compound IX was insoluble in dilute alkalis. It did not react with phenylhydrazine at the usual temperatures. However, when it was heated in a glycerine solution of phenylhydrazine at 160–170°C., compound IX yielded 2-methyl-3-β-phenylhydrazino-2,3-dihydro-1,2-benzisosulfonazole (18).



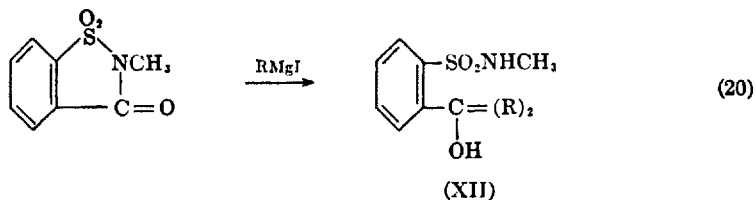
Oddo and Mingoa⁵ prepared the 3-alkyl and 3-aryl-3-hydroxy-2,3-dihydro-1,2-benzisosulfonazoles using the Grignard reaction with saccharin. The first step was the formation of the magnesium salt. Further addition of the Grignard reagent formed the magnesium iodide salt of the tertiary alcohol (19). These compounds were insoluble in alkali. They formed

⁵ Oddo and Mingoa, *Gazz. chim. ital.*, **57**, 465 (1927); *Chem. Abstr.*, **21**, 3202 (1927).

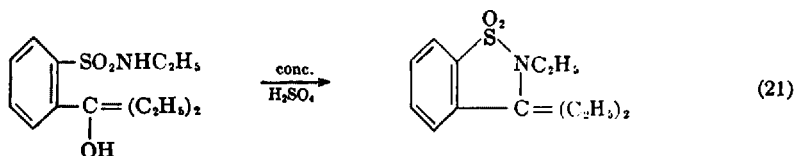


crystalline precipitates with Deniges reagent (mercuric sulfate plus sulfuric acid) which is characteristic of tertiary alcohols. Dibenzoyl and diacetyl derivatives were obtained by treating either a pyridine solution of these compounds or the magnesium complex with acylating agents.

Sachs *et al.*^{6,7} found that the 2-methyl and 2-ethylsaccharins reacted with Grignard reagents to give 2-methyl and 2-ethylsulfamylphenyldialkyl carbinols (20). Compounds of type XII were soluble in alkali, a fact which



was in contradistinction to the compounds obtained by Oddo and Mingoia.⁵ These compounds also gave precipitates with Deniges reagent showing that they were tertiary alcohols. Dehydration of these compounds by dissolving in concentrated sulfuric acid formed the 2,3,3-trisubstituted 2,3-dihydro-1,2-benzisulfonazoles designated in the earlier literature as sultams. This reaction was applicable to the methyl and ethyl numbers of the series (21).

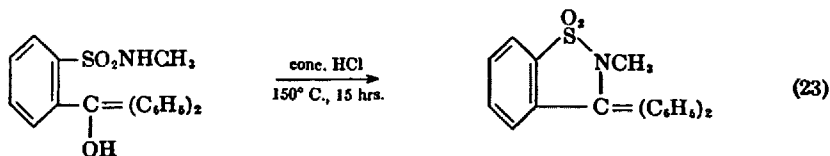
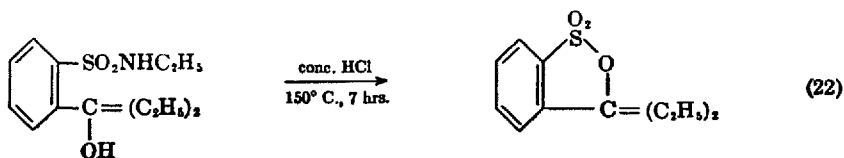


Heating compounds of type XII in concentrated hydrochloric acid for seven hours at 150°C. gave "sultones" (22). Cobb and Fuller⁸ showed that this concentrated hydrochloric acid treatment produced the 2,3-dihydro-

⁶ Sachs and Ludwig, *Ber.*, **37**, 385 (1904).

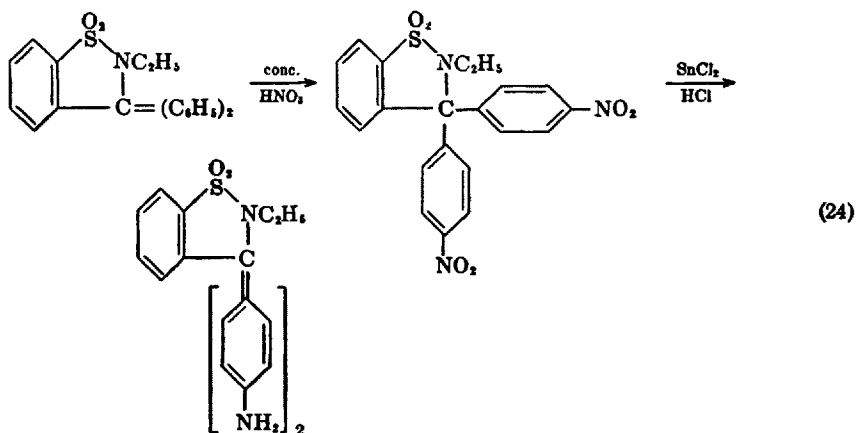
⁷ Sachs, Wolff, and Ludwig, *Ber.*, **37**, 3252 (1904).

⁸ Cobb and Fuller, *Am. Chem. J.*, **45**, 605 (1911).

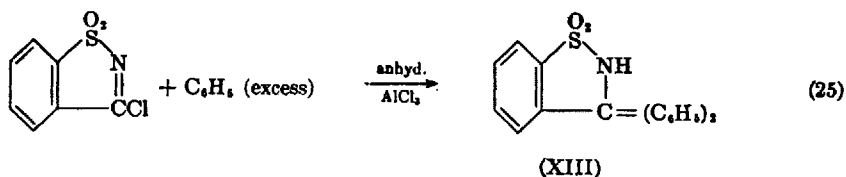


1,2-benzisosulfonazole in the instance of 2-methylsulfamyltriphenyl carbinol (23). 2-Methylsulfamylphenyl-di(*p*-tolyl) carbinol did not undergo ring closure with either sulfuric acid or concentrated hydrochloric acid.

Nitration⁷ of 2-ethyl-3,3-diphenyl-2,3-dihydro-1,2-benzisosulfonazole yielded the dinitro derivative with the nitro groups probably in the *para* position of the phenyl rings. Reduction gave the corresponding diamine (24).

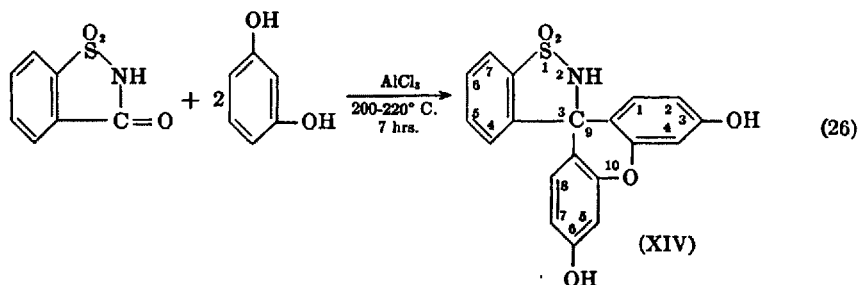


Fritsch⁸ prepared the 3,3-diphenyl-2,3-dihydro-1,2-benzisosulfonazole from 3-chloro-1,2-benzisosulfonazole and benzene with anhydrous aluminum chloride (25).

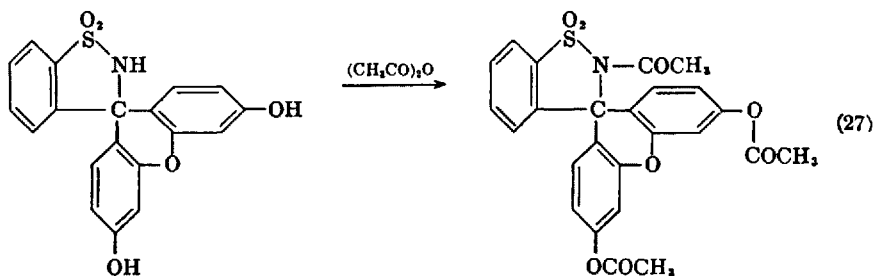


⁸ Fritsch, *Ber.*, 29, 2290 (1896).

Monnet and Koetschet¹¹ condensed saccharin with resorcinol in the presence of anhydrous aluminum chloride to obtain a dyestuff (3',6'-dihydroxyspiro[1,2-benzisulfonazole-3(2)9'-xanthene]) (*Ring Index* No. 3036) which resembled fluorescein (26). Compound XIV was soluble in

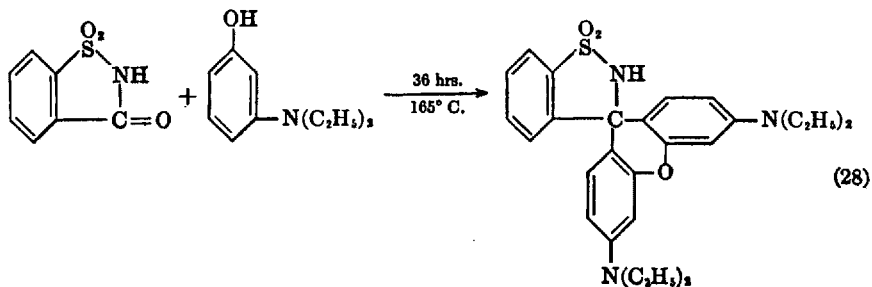


dilute alkalis with a yellowish orange color. In dilute solution it exhibited a strong greenish fluorescence. Acetylation gave a triacetyl derivative (27).



Compound XIV was readily brominated and iodinated. Monnet and Koetschet¹¹ also prepared the diethylamino analog with *m*-diethylaminophenol and saccharin (28). Acetylation produced only a monoacetyl derivative. An additional ethyl group was added by alkylation with ethyl iodide.

Monnet and Koetschet¹¹ described the color reactions of the 3,3-di-*p*-

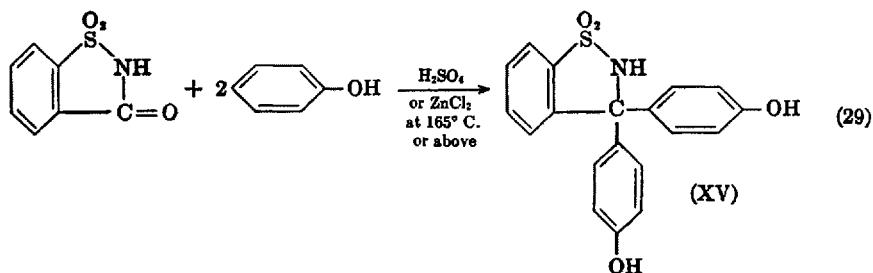


¹¹ Monnet and Koetschet, *Bull. soc. chim. France*, [3] 17, 690 (1897).

¹² Dutt, *J. Chem. Soc.*, 121, 2389 (1922).

¹³ Kaufman and Zobel, *Ber.*, 55, 1499 (1922).

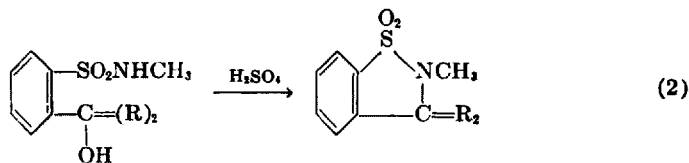
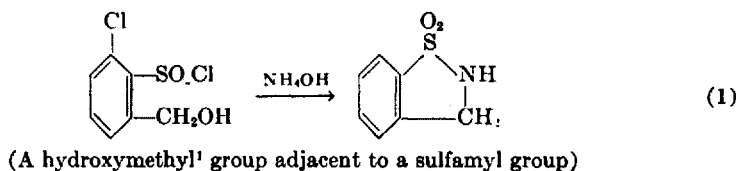
hydroxyphenyl-2,3-dihydro-1,2-benzisosulfonazole but did not give the preparation or other characteristics. Dutt¹² synthesized this compound with phenol and saccharin in the presence of anhydrous zinc chloride or concentrated sulfuric acid (29). Compound XV existed in two chromoisomeric



forms: yellow and red. It dissolved in dilute alkali to give a bright pink solution. Compound XV gave trimethyl, diacetyl, and dibenzoyl derivatives. Dutt¹² named these compounds sulfamphthaleins. The naphthalene analog has also been prepared.¹³

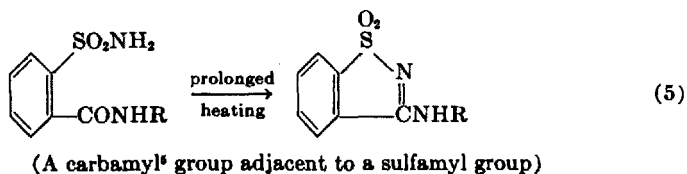
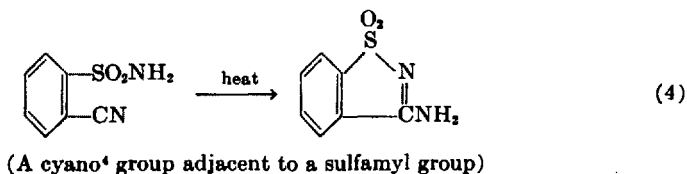
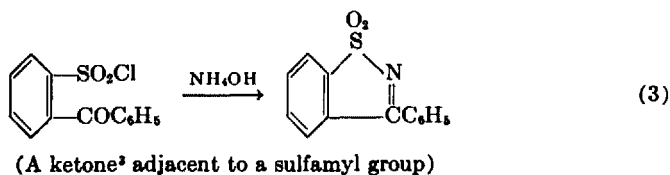
Discussion

The substituents on the 3-carbon atom of the 2,3-dihydro-1,2-benzisosulfonazole are apparently quite labile. Mild oxidation of the parent compound yielded saccharin. A hydroxy group in this position is even more labile than hydrogen. Koetschet and Koetschet's compound would be suspected of being 2-formylphenylsulfonamide rather than 3-hydroxy-2,3-dihydro-1,2-benzisosulfonazole if it were not for a number of factors. First, a hydroxymethyl, a formyl, or a carboxy group adjacent to a sulfonamide group on a benzene ring predisposes the arylsulfonamide toward cyclization (1-5). It is doubtful that 2-formylphenylsulfonamide would exist as

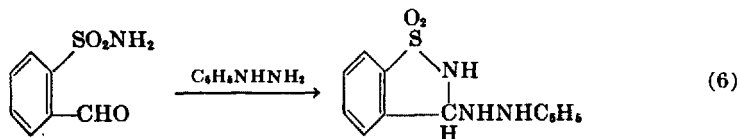


¹ Reissert and Cramer, *Ber.*, **61**, 2555 (1928).

² Sachs, Wolff, and Ludwig, *Ber.*, **37**, 3252 (1904).



such except under carefully controlled conditions. Second, the properties of the derivatives are inconsistent with the possible derivatives of 2-formylphenylsulfonamide. The monomethyl compound is no longer soluble in alkali. Phenylhydrazine gave a phenylhydrazo compound rather than a phenylhydrazone. A possibility exists that phenylhydrazine may cyclize 2-formylphenylsulfonamide (6).



The discrepancy between the work of Oddo and Mingoia⁶ and the work of Sachs *et al.*⁷ on the reaction of Grignard compounds may be real, the result of different chemical techniques, or may be due to the fact that 2-alkylsaccharins behave differently with the Grignard compounds. It should be remembered that Cobb and Fuller⁸ found that 2-*N*-methylsulfamyl-

³ Remsen and Saunders, *Am. Chem. J.*, **17**, 347 (1895).

⁴ Jesurum, *Ber.*, **26**, 2286 (1893).

⁵ Mannesier-Mameli, *Gazz. chim. ital.*, **65**, 51 (1935); *Chem. Abstr.*, **29**, 3997 (1935).

⁶ Oddo and Mingoia, *Gazz. chim. ital.*, **57**, 465 (1927); *Chem. Abstr.*, **21**, 3202 (1927).

⁷ Sachs *et al.*, *Ber.*, **37**, 385 (1904); *ibid.*, **37**, 3252 (1908).

⁸ Cobb and Fuller, *Am. Chem. J.*, **45**, 605 (1911).

phenyldi-*p*-tolylcarbinol did not undergo ring closure, while the phenyl analog did under mild conditions. The reaction in this instance may occur as shown in equation (7).

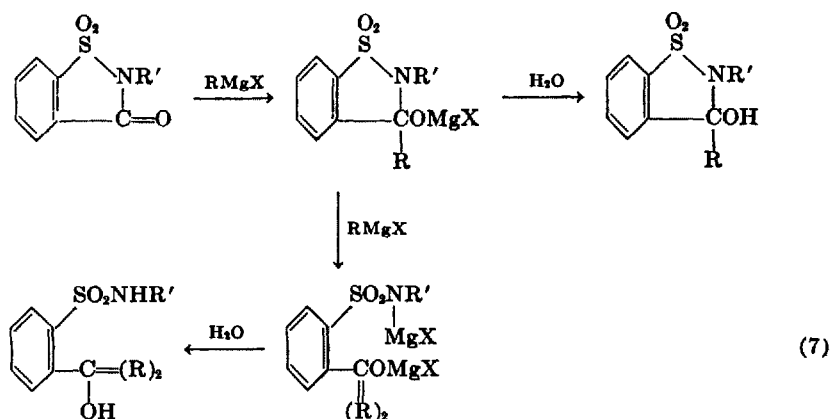
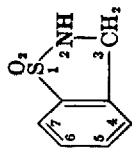
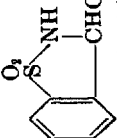
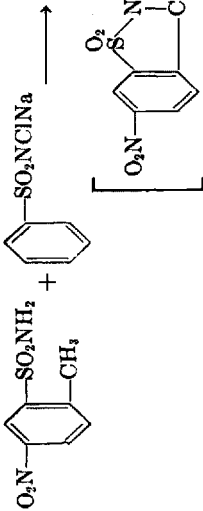


Table LVIII follows on page 290.

TABLE LVIII. Preparation of the 2,3-Dihydro-1,2-benzisosulfonazoles



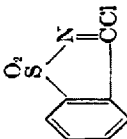
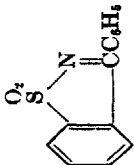
No.	Substituents on 2,3-dihydro-1,2-benzisosulfonazole other than hydrogen	Ref.	Method of preparation	Solubility	M.p., °C.
1	None	1	 CH_3 SO_2NClNa + dil. acetic acid reflux $\longrightarrow$ compounds 1 + 9 + 19 compound 19 + R-hydrazine or SO_2 electrolytic reduction of saccharin in acid medium	water	112.5-3
1a	7-Chloro	2 4 9	 Cl SO_2Cl CH_2OH + NH_3	— — water, alc.	— — 158
2	2-Acetyl	2	compound 1 + sodium acetate + acetic anhydride (see 20)	benzene, alc., acetone	108-9
3	2-Benzoyl	2	compound 1 + benzoyl chloride + alkali	alc.	117-117.5
4	2-Phenylsulfonyl	2	compound 1 + phenylsulfonyl chloride + alkali	alc.	174-5
5	2-β-Naphthylsulfonyl	2	compound 1 + β-naphthylsulfonyl chloride + alkali	alc.	214
6	2-Methyl	2	compound 1 + dimethyl sulfate alkali (see 21)	water	127
6a	7-Chloro-2-methyl	9	compound 1a + dimethyl sulfate	benzene	127
6b	7-Chloro-2-phenyl	9	 Cl SO_2Cl CHOH + $\text{C}_6\text{H}_5\text{NH}_2$ $\longrightarrow$ $\text{SO}_2\text{NHC}_6\text{H}_5$ CH_2OH + Dil. alkali	benzene, alc., ether	151

No.	Substituents on 2,3-dihydro-1,2-benzisulfonazole other than hydrogen	Ref.	Method of preparation	Solubility	M.p., °C.
7	3- <i>p</i> -Aminophenyl	2	 + C ₆ H ₄ NH ₂ + anhydr. ZnCl ₂ same as 7 with dimethylamine	alc.	236-7
8	3- <i>p</i> -Dimethylamino-phenyl	2	same as 7 with dimethylamine	benzene	152-4
9	3-Hydroxy	2	compound 19 $\xrightarrow[\text{or Na}_2\text{SO}_4]{\text{SO}_3, \text{NaHSO}_4}$ as the sulfonate	—	—
10	3-Hydroxy-2-methyl	2	sulfonate + CO ₂ $\xrightarrow{\text{unstable}}$ (see 1 and 19) compound 19 + dimethyl sulfate $\xrightarrow{\text{oxidation of 6 with lead dioxide + dilute sulfuric acid}}$ 10 + 21 + 6 (unstable)	—	—
11	3- β -Phenylhydrazino	1	compound 9 + C ₆ H ₅ NHNH ₂	alc.	198
12	3- β - <i>p</i> -Tolylhydrazino	2	compound 19 + C ₆ H ₅ NHNH ₂	alc.	207-9
13	3- β , β -Methylphenyl-hydrazino	2	compound 9 + <i>p</i> -tolylhydrazine	alc.	165
14	3- β , <i>p</i> -Nitrophenyl-hydrazino	1	compound 9 + 1,1-methylphenyl hydrazine	alc.	250 dec.
15	3- α -Naphthylhydrazino	1	compound 19 + phenylhydrazine	alc.	206-8
16	2-Methyl-3- β -phenyl-hydrazino	1,2	compound 10 + phenylhydrazine compound 21 + phenylhydrazine at 160-70°C.	alc.	153-4
17	6-Nitro-3- β -phenyl-hydrazino	2		alc.	228 dec.

(Table continued)

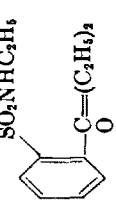
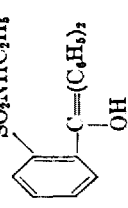
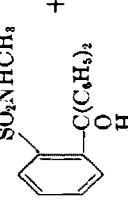
TABLE LVIII (Continued)

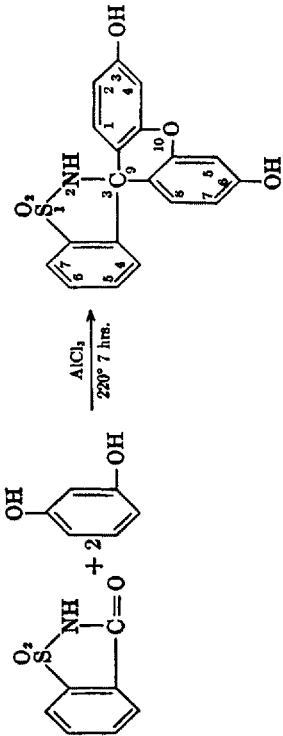
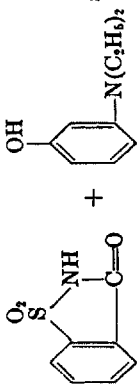
No.	Substituents on 2,3-dihydro-1,2-benzisothiazole other than hydrogen	Ref.	Method of preparation	Solubility	M.p., °C.
18	6-Sulfamyl-3- β -phenylhydrazino	2	$ \begin{array}{c} \text{NH}_2\text{SO}_2 \\ \\ \text{C}_6\text{H}_4 \\ \\ \text{SO}_2\text{NH}_2 \\ \\ \text{CH}_3 \end{array} + \begin{array}{c} \text{SO}_2\text{NCINa} \\ \\ \text{C}_6\text{H}_4 \\ \\ \text{COOH} \end{array} \longrightarrow \begin{array}{c} \text{NH}_2\text{SO}_2 \\ \\ \text{C}_6\text{H}_3 \\ \\ \text{SO}_2\text{NH} \\ \\ \text{CHOH} \end{array} + \text{C}_6\text{H}_5\text{NHNH}_2 $	alc.	241-2
19	2-(2,3-Dihydro-1,2-benzisulfonazol-3-yl)-	1, 2	$ \begin{array}{c} \text{CH}_3 \\ \\ \text{C}_6\text{H}_4 \\ \\ \text{SO}_2\text{NCINa} \end{array} \xrightarrow[\text{saccharin}]{\text{dil. acetic acid}} 19 + 1 + 9 $	water, benzene	141-2
20	2-(2-Acetyl-2,3-dihydro-1,2-benzisulfonazol-3-yl)-	4	$ 1 + 9 \longrightarrow \text{electrolytic reduction of saccharin in acid medium} $	acetic anhydride	250-4
21	2-(2-Methyl-2,3-dihydro-1,2-benzisulfonazol-3-yl)-	1, 2	$ \text{compound 19} + \text{dimethylsulfate} \longrightarrow 21 + 6 + 10 $	alc.	263-4
22	3-Methyl-3-hydroxy	3	saccharin + CH_3MgI	alc.	110-1
23	2-Benzoyl-3-methyl-3-benzoy	3	compound 22 + benzoyl chloride + pyridine	alc.	183-4
24	3-Ethyl-3-hydroxy	3	saccharin + $\text{C}_2\text{H}_5\text{MgBr}$	alc., methanol	119-20
25	2-Acetyl-3-ethyl-3-acetoxy	3	compound 24 as magnesium salt + acetyl chloride	—	138

No.	Substituents on 2,3-dihydro-1,2-benzisosulfonazole other than hydrogen	Ref.	Method of preparation	Solubility	M.p., °C.
26	3-Propyl-3-hydroxy	3	saccharin + $n\text{-C}_3\text{H}_7\text{MgI}$	alc.	124
27	2-Benzoyl-3-propyl-3-benzoy	3	compound 26 + benzoyl chloride	—	—
28	3-Phenyl-3-hydroxy	3	saccharin + $\text{C}_6\text{H}_5\text{MgBr}$	alc., ether, benzene	185
29	3-Benzyl-3-hydroxy	3	saccharin + $\text{C}_6\text{H}_5\text{CH}_2\text{MgCl}$	alc.	134
30	3,3-Diphenyl	5	 + $\text{C}_6\text{H}_5 + \text{AlCl}_3$	alc.	210
31	3,3-Di- <i>p</i> -hydroxyphenyl	6	 + $\text{C}_6\text{H}_5 + \text{AlCl}_3$ + phenol + ZnCl_2 or H_2SO_4	water, acetic acid, alc.	—
32	3,3-Di- <i>p</i> -acetoxyphenyl	6	compound 31 + acetic anhydride	—	112
33	3,3-Di- <i>p</i> -benzoxyphenyl	6	compound 31 + benzoyl chloride	—	127
34	2-Methyl-3,3-dimethoxyphenyl	6	compound 31 + dimethyl sulfate + alkali	—	142

(Table continued)

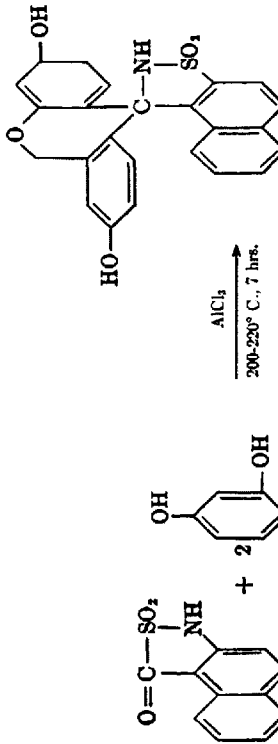
TABLE LVIII (Continued)

No.	Substituents on 2,3-dihydro-1,2-benzisulfonazole other than hydrogen	Ref.	Method of preparation	Solubility	M.p., °C.
35	2-Ethyl-3,3-dimethyl	7	 + H ₂ SO ₄	water	40
36	2,3,3-Triethyl	7	 + H ₂ SO ₄	—	140-50
37	2-Ethyl-3,3-diphenyl	7	 + H ₂ SO ₄	—	155-65
38	2-Ethyl-3,3-di- <i>p</i> -nitrophenyl	7	nitration of compound 37	—	220-30
39	2-Ethyl-3,3-di- <i>p</i> -amino-phenyl	7	reduction of compound 38	—	250 dec.
40	2-Methyl-3,3-diphenyl	8	 + H ₂ SO ₄ or HCl at 150°C. for 15 hrs.	alc.	211-12

No.	Substituents on 2,3-dihydro-1,2-benzisulfonazole other than hydrogen	Ref.	Method of preparation	Solubility	M.p., °C.
41	3',6'-DihydroxySpiro[2,3-dihydro-1,2-benzisulfonazole-3(2),9'-xanthene] (Ring Index No. 3036)	10, 11		alc.	265-7
42	2-Acetyl-3',6'-diacetoxySpiro[2,3-dihydro-1,2-benzisulfonazole-3(2),9'-xanthene]	10, 11	acetylation of compound 41	acetic acid	286 dec.
43	3',6'-Di(diethylamino)-Spiro[2,3-dihydro-1,2-benzisulfonazole-3(2),9'-xanthene]	10		chloroform, benzene, toluene	243
44	2-Acetyl-3',6'-di(diethylamino)-Spiro[2,3-dihydro-1,2-benzisulfonazole-3(2),9'-xanthene]	10, 11	acetylation of compound 43	alc., chloroform, ether	230-2

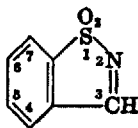
(Table continued)

TABLE LVIII (Concluded)

45	2-Ethyl-3',6'-di(diethylamino)-spiro[2,3-dihydro-1,2-benzisulfonazole-3(2),9'-xanthene]	10	compound 43 + ethyl iodide	benzene, alc.	220-2
46	Naphthalene analog of 41	12		alc.	—

¹ Koetschet and Koetschet, *Helv. Chim. Acta*, **12**, 669 (1929).² Koetschet, Koetschet, and Viaud, *Helv. Chim. Acta*, **13**, 587 (1930).³ Oddo and Mingoa, *Gazz. chim. ital.*, **57**, 465 (1927); *Chem. Abstr.*, **21**, 3202 (1927).⁴ Matsui, Sawamura, and Adachi, *Chem. Abstr.*, **26**, 5264 (1932); *Brit. Chem. Abstr.*, 1046 (1932); *Mem. Coll. Sci. Kyoto Imp. Univ.*, **A15**, 151 (1932).⁵ Fritsch, *Ber.*, **29**, 2290 (1896).⁶ Dutt, *J. Chem. Soc.*, 121, 2389 (1922). (Dutt describes other sulfamphthaleins principally by color.)⁷ Sachs, Wolff, and Ludwig, *Ber.*, **37**, 3252 (1904).⁸ Cobb and Fuller, *Am. Chem. J.*, **45**, 605 (1911).⁹ Reissert and Cramer, *Ber.*, **61**, 255 (1928).¹⁰ Monnet and Koetschet, *Bull. soc. chim. France*, [3] **17**, 690 (1897).¹¹ Gilliard, Monnet, and Carlier, *Friedl. d. 5*, 233, 235 (1901); *Ger. Pat.* 100,779.¹² Kaufmann and Zobel, *Ber.*, **55**, 1499 (1922).

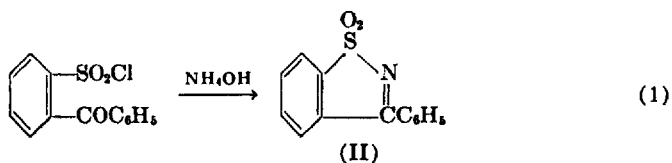
1,2-Benzisosulfonazoles (I)



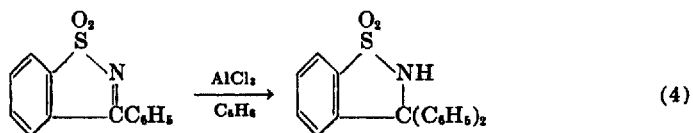
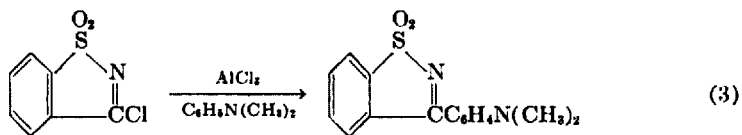
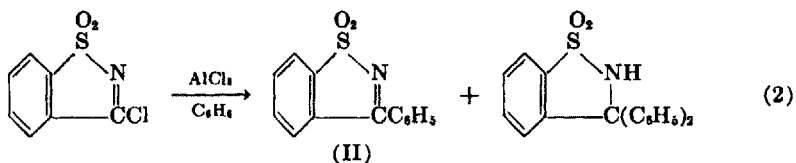
(I)

1,2-Benzisosulfonazole (I)¹ was prepared by the dehydration of 3-hydroxy-2,3-dihydro-1,2-benzisosulfonazole (see complete discussion under the 2,3-dihydro-1,2-benzisosulfonazoles).

Remsen and Saunders² found that ammonium hydroxide reacted with 2-benzoylphenyl sulfonyl chloride to give 3-phenyl-1,2-benzisosulfonazole (II) (1). 5-Nitro-3-phenyl-1,2-benzisosulfonazole was synthesized in a



similar manner by Hollis.³ Fritsch⁴ showed that 3-chloro-1,2-benzisosulfonazole underwent the Friedel-Crafts reaction with benzene and dimethylaniline (2,3). The second product of reaction 2 was believed to be 3,3-diphenyl-2,3-dihydro-1,2-benzisosulfonazole. This compound was also



¹ Koetschet, Koetschet, and Viaud, *Helv. Chim. Acta*, **13**, 587 (1930).

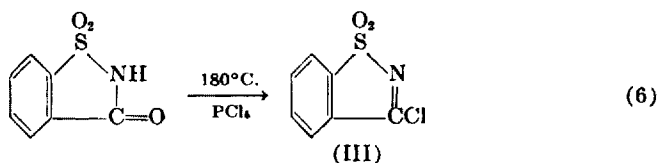
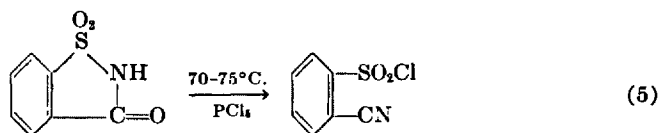
² Remsen and Saunders, *Am. Chem. J.*, **17**, 347 (1895).

³ Hollis, *Am. Chem. J.*, **23**, 233 (1900).

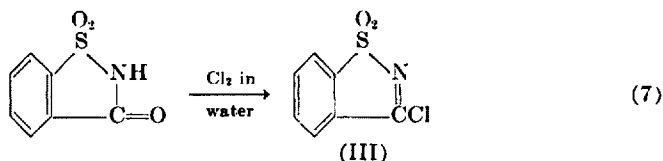
⁴ Fritsch, *Ber.*, **29**, 2290 (1896).

prepared by heating compound II in benzene in the presence of anhydrous aluminum chloride (4).

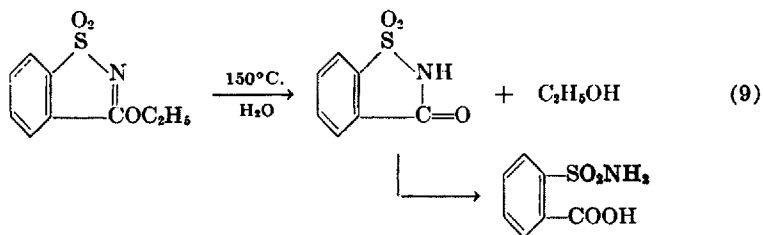
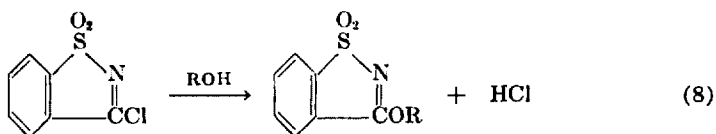
Jesurum⁵ investigated the reaction between phosphorus pentachloride and saccharin. At 70–75°C. *o*-cyanophenylsulfonyl chloride was formed (5). At 180°C., 3-chloro-1,2-benzisulfonazole was obtained (6).^{5,7}



Maselli⁶ prepared compound III by allowing saccharin to stand in saturated solution of chlorine in water (7).



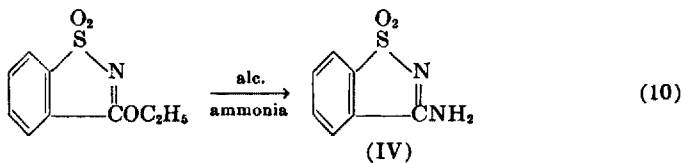
Heating compound III with alcohols⁵⁻⁷ yielded the 3-alkoxy-1,2-benzisulfonazoles. Phenols gave the 3-phenoxy-1,2-benzisulfonazoles



⁵ Jesurum, *Ber.*, 26, 2286 (1893).

⁶ Maselli, *Gazz. chim. ital.*, 30, 529 (1900).

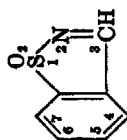
⁷ Meadon and Reid, *J. Am. Chem. Soc.*, 65, 457 (1943).



(8).⁷ Since these alkoxy derivatives give sharp, well-defined melting points, Mead and Reid⁷ have suggested that 3-chloro-1,2-benzisosulfonazole be used as a reagent to identify primary and secondary alcohols. These ethers decompose when heated with water at 150°C. to saccharin and some *o*-carboxyphenylsulfonamide (9).⁵ 3-Ethoxy-1,2-benzisosulfonazole⁶ and ammonia gave 3-amino-1,2-benzisosulfonazole (10).

Tables LIX and LX follow on pages 300-301.

TABLE LIX. Preparation of the 1,2-Benzisulfonazoles



No.	Substituents on 1,2-benzisulfonazole other than hydrogen	Ref.	Method of preparation	Solubility	M.p., °C.
1	None	1	 and dehydration	nitrobenzene, nitrotoluene	257-8
2	3-Phenyl	2	 + NH ₃	alc., benzene	163
3	5-Nitro-3-phenyl	3	compound 5 + C ₆ H ₆ + AlCl ₃	—	164
4		4	 + NH ₃	—	234
5	3- <i>p</i> -Dimethylaminophenyl	3	compound 5 + dimethylaniline + anhydr. AlCl ₃	toluene, acetone	221
6	3-Chloro	5	saccharin + PCl ₅ at 180° C.	benzene, CHCl ₃	143-5
7	3-Chloro-4-chlorocarbonyl	6	saccharin + aq. sol. of Cl ₂	CCl ₄ , xylene	155
		7	 + PCl ₅ at 150-160°C.	acetic acid, benzene, CHCl ₃	156

¹ Koetschet, Koetschet, and Viaud, *Helv. Chim. Acta*, **13**, 587 (1930).

² Remsen and Saunders, *Am. Chem. J.*, **17**, 347 (1895).

³ Frisch, *Ber.*, **29**, 2290 (1896).

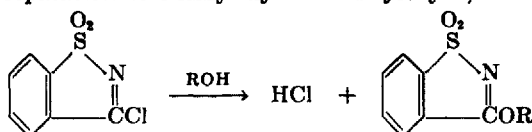
⁴ Hollis, *Am. Chem. J.*, **23**, 233 (1900).

⁵ Jesurum, *Ber.*, **26**, 2286 (1893).

⁶ Maselli, *Gazz. chim. ital.*, **30**, 529 (1900).

⁷ Zincke and Greune, *Ann.*, **427**, 221 (1922).

TABLE LX. Preparation of 3-Alkyloxy and 3-Aryloxy 1,2-Benzisoxulfonazole.*

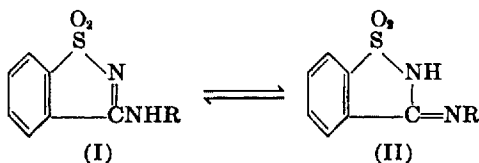


No.	Substituents on the 1,2-benzisoxulfonazole ring other than hydrogen	Ref.	Solubility	M.p., °C.
1	3-Methoxy	1, 2	methanol	182-3
2	3-Methoxy-4-carbomethoxy	3	acetic acid	163
3	3-Ethoxy	1	ether	217-8
		2	—	219
		4	—	225
4	3-Ethoxy-4-carbethoxy	3	benzene	142-3
5	3-Propoxy	2	—	124.5
6	3-Isopropoxy	2	—	137
7	3-Butoxy	2	—	96
8	3-Isobutoxy	2	—	100
9	3-sec-Butoxy	2	—	65.5
10	3-Amoxy	2	—	62
11	3-Isoamoxy	2	—	64
12	3-sec-Amoxy	2	—	38
13	3-Hexyloxy	2	—	60
14	3-Heptyloxy	2	—	55
15	3-Octyloxy	2	—	46
16	3-(2-Ethylhexyloxy)	2	—	53.5
17	3-(3-Methylheptyloxy)	2	—	24
18	3-(4-Methylheptyloxy)	2	—	34
19	3-(5-Methylheptyloxy)	2	—	53
20	3-(1-Propylamoxy)	2	—	10
21	3-Nonyloxy	2	—	49
22	3-Decyloxy	2	—	47.5
23	3-Undecyloxy	2	—	58.5
24	3-Dodecyloxy	2	—	54
25	3-Tridecyloxy	2	—	66
26	3-Tetradecyloxy	2	—	62
27	3-Pentadecyloxy	2	—	72
28	3-Hexadecyloxy	2	—	69.5
29	3-Heptadecyloxy	2	—	76
30	3-Octadecyloxy	2	—	74.5
31	3-Nonadecyloxy	2	—	80.5
32	3-(10-Oxoctadecyloxy)	2	—	77
33	3-Benzyloxy	2	—	30
34	3-Phenoxy	2	—	182
35	3-o-Toloxo	2	—	163
36	3-m-Toloxo	2	—	146
37	3-p-Toloxo	2	—	171.5
38	3-Thymyloxy	2	—	147
39	3-o-Nitrophenoxy	2	—	236
40	3-p-Nitrophenoxy	2	—	192
41	6-Bromo-3-ethoxy	5	—	199-9.5

* Prepared by heating 3-chloro-1,2-benzisoxulfonazole in the parent alcohol.

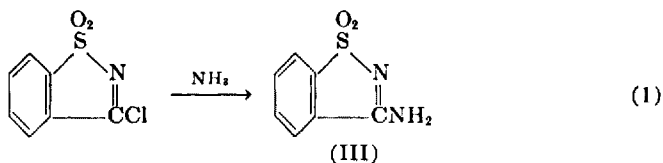
¹ Jesurum, *Ber.*, 26, 2286 (1893). ² Meadoc and Reid, *J. Am. Chem. Soc.*, 65, 457 (1943). ³ Zincke and Greune, *Ann.*, 427, 221 (1922). ⁴ Maselli, *Gazz. chim. ital.*, 30, 529 (1900). ⁵ Remsen and Bayley, *Am. Chem. J.*, 8, 233 (1886).

3-Amino-1,2-benzisosulfonazoles (I) or 3-Imino-2,3-dihydro-1,2-benzisosulfonazoles (II)

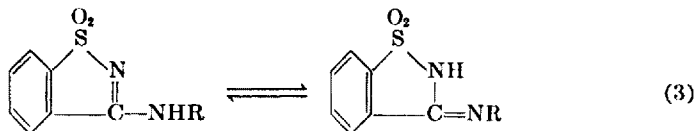
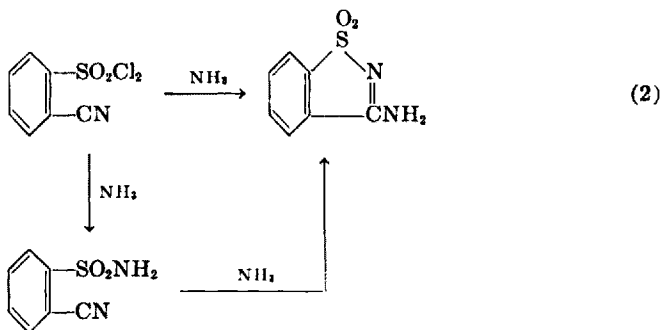


While it is undoubtedly true that these compounds exist in form II, the simpler form (I) will be used to arrive at a name for these compounds. This is in accordance with the accepted usage of naming such compounds as 2-aminopyridine, 2-aminothiazole, etc. as the parent heterocycle rather than the dihydro form.

Jesurum¹ found that 3-amino-1,2-benzisosulfonazole could be prepared from 3-chloro-1,2-benzisosulfonazole (1). Compound III^{1,2} was also syn-



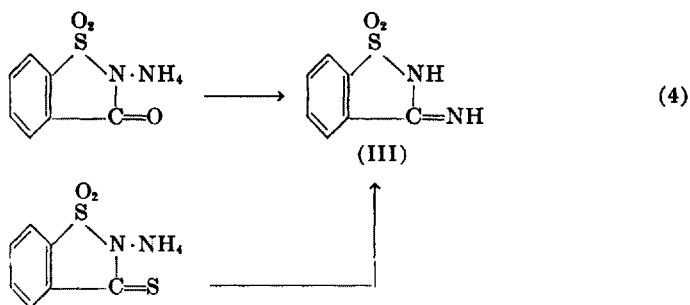
thesized from either *o*-cyanophenylsulfonyl chloride or *o*-cyanophenylsulfonamide (2). Mannessier-Mameli studied extensively the preparation



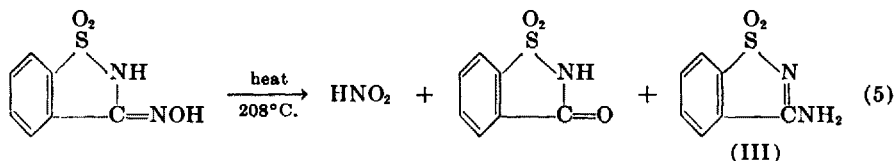
¹ Jesurum, *Ber.*, **26**, 2286 (1893).

² Bradshaw, *Am. Chem. J.*, **35**, 335 (1906).

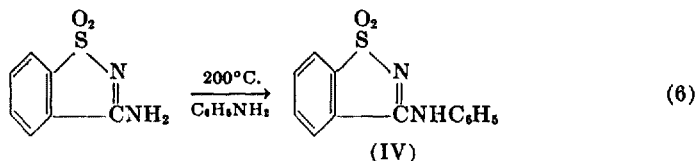
of the various 3-substituted amino-1,2-benzisulfonazoles. She came to the conclusion that they were tautomeric with the imino form, in which form they existed in the greatest concentration (3). She obtained 3-amino-1,2-benzisulfonazole from saccharin and thiosaccharin in a number of ways.^{3,4} Saccharin and thiosaccharin with aqueous ammonium hydroxide in the cold yielded the ammonium salts. While saccharin and boiling ammonium hydroxide gave the salt, thiosaccharin and boiling ammonium hydroxide gave some 3-amino-1,2-benzisulfonazole. When ammonium carbonate was used, salts were obtained at 110°C. and the amine was obtained at 250 to 300°C. With alcoholic urea, thiosaccharin formed the amine at 150°C., whereas saccharin yielded the amine at 250°C. Pyrolysis of the ammonium salts at 250–300° produced compound III (4). Mannessier-



Mameli⁵ heated the oxime of saccharin and obtained nitrous acid, saccharin, and 3-aminobenzisulfonazole (5). Sodium hydroxide⁵ decomposed com-



pound III to saccharin. Acetylation of compound III with acetic anhydride and sodium acetate produced 3-acetamido-1,2-benzisulfonazole.⁵

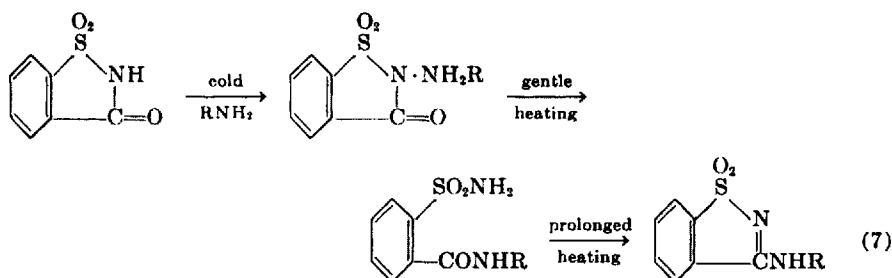


³ Mameli and Mannessier-Mameli, *Gazz. chim. ital.*, **70**, 855 (1940); *Chem. Abstr.*, **36**, 1026 (1942).

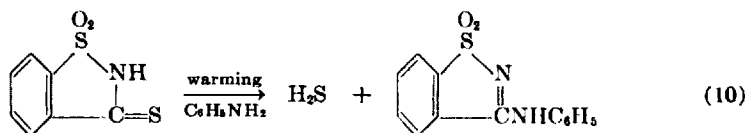
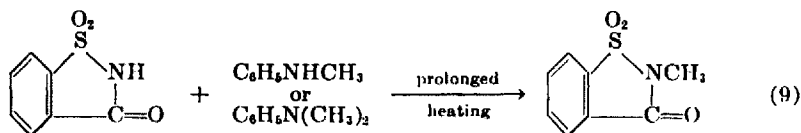
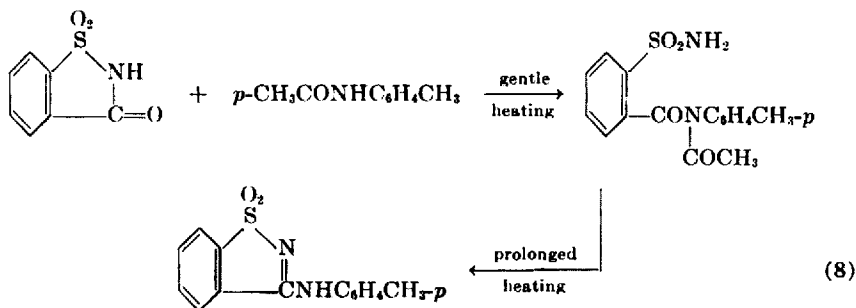
⁴ Mannessier-Mameli, *Gazz. chim. ital.*, **71**, 3 (1941); *Chem. Abstr.*, **36**, 1028 (1942).

⁵ Mannessier-Mameli, *Gazz. chim. ital.*, **65**, 77 (1935); *Chem. Abstr.*, **29**, 3999 (1935).

Heating compound III with aniline yielded 3-anilino-1,2-benzisosulfonazole (IV) (6).⁶ Refluxing saccharin with aniline produced compound IV.⁷⁻⁹ Mannessier-Mameli⁹ studied this reaction and found that in the cold, primary aromatic amines formed salts with saccharin. Gentle warming ruptured the ring to form the 2-carbamylphenylsulfonanilides. Prolonged heating yielded the 3-arylamino-1,2-benzisosulfonazoles (7). *p*-



Acetyltoluide produced 3-*p*-toluidino-1,2-benzisosulfonazole (8). Methyl-aniline and dimethylaniline formed 2-methylsaccharin (9).



⁶ Jesurum, *Ber.*, 26, 2286 (1893).

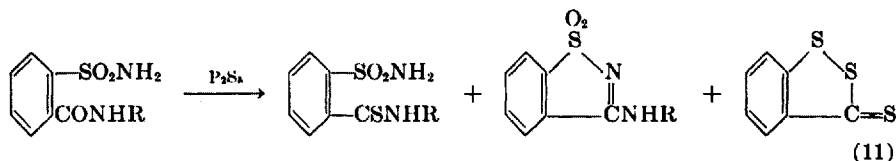
⁷ Remsen and Dohme, *Am. Chem. J.*, 11, 34 (1889).

⁸ Koetschet and Koetschet, *Helv. Chim. Acta*, 12, 669 (1929).

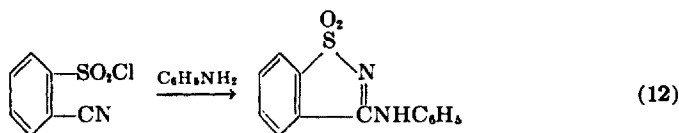
⁹ Mannessier-Mameli, *Gazz. chim. ital.*, 65, 51 (1935); *Chem. Abstr.*, 29, 3997 (1935).

Thiosaccharin reacted readily with aniline and the three isomeric toluidines to give the corresponding 3-anilino- and 3-toluidino-1,2-benzisosulfonazoles (10).

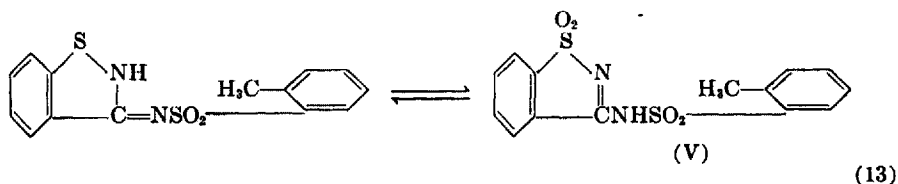
Mannessier-Mameli¹⁰ found that phosphorus pentasulfide and the 2-carbanilinophenylsulfonamides gave a mixture of 2-thiocarbanilinophenylsulfonamides, 3-anilino-1,2-benzisosulfonazoles, and 1,2-benzodithiol-3-thione (11).



Jesurum¹¹ also synthesized 3-anilino-1,2-benzisosulfonazole from *o*-cyanophenylsulfonyl chloride and aniline (12).



Herzog¹² described a bitter principle that occurred in commercial saccharin. Klages¹³ and Herzog¹⁴ isolated this compound and showed that its structure was probably 3-*o*-tolylsulfonamido-1,2-benzisosulfonazole (V) (13). Compound V was prepared by oxidizing *o*-tolylsulfonamide with



potassium permanganate in alkaline solution and then fractionally precipitating the reaction products. The yield was approximately 3%. Koetschet and Koetschet¹⁵ obtained a better yield (5–14%) on oxidizing *o*-tolylsulfonamide in a hydrochloric acid solution. They proposed that the reaction

¹⁰ Mannessier-Mameli, *Gazz. chim. ital.*, **65**, 69 (1935); *Chem. Abstr.*, **29**, 3999 (1935).

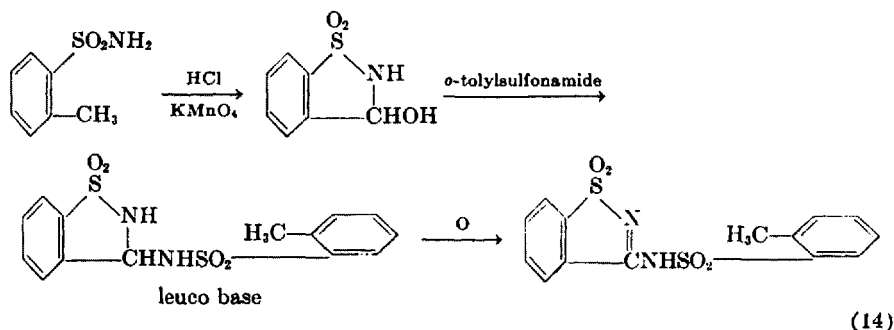
¹¹ Jesurum, *Ber.*, **26**, 2286 (1893).

¹² Herzog, *Chem. Technologie* (1912) (a pamphlet).

¹³ Klages, *Angew. Chem.*, **39**, 671 (1926).

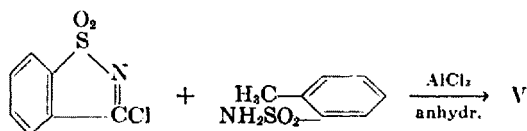
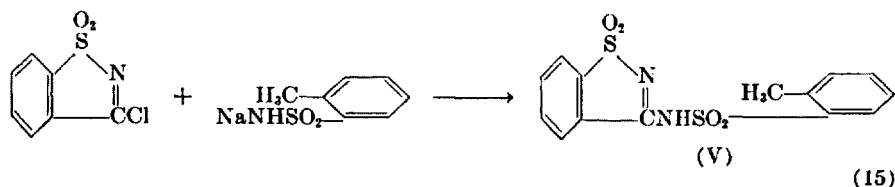
¹⁴ Herzog, *Angew. Chem.*, **39**, 728 (1926).

¹⁵ Koetschet and Koetschet, *Helv. Chim. Acta*, **12**, 669 (1929).

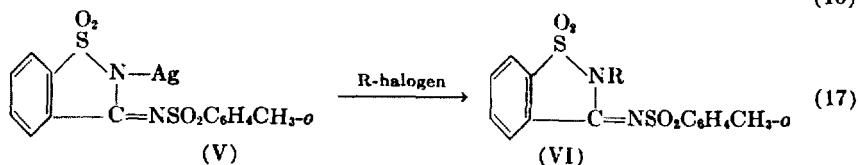
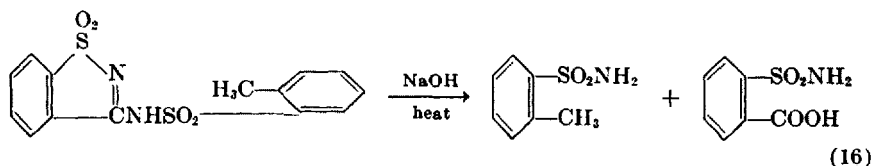


proceeded as shown in equation (14). (For a more complete discussion of the work of Koetschet and Koetschet, see the chemistry of the 2,3-dihydro-1,2-benzisothiazoles.)

Klages *et al.*^{13,16} synthesized compound V from 3-chloro-1,2-benzisulfonazole and *o*-tolylsulfonamide (15). The phenyl and *p*-tolyl analogs were also prepared using anhydrous aluminum chloride as the catalyst.

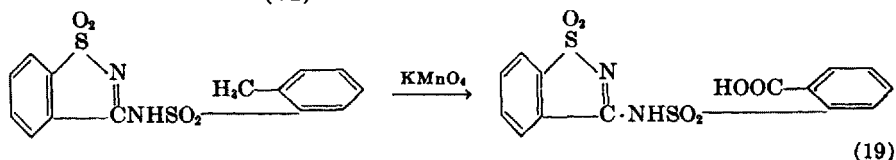
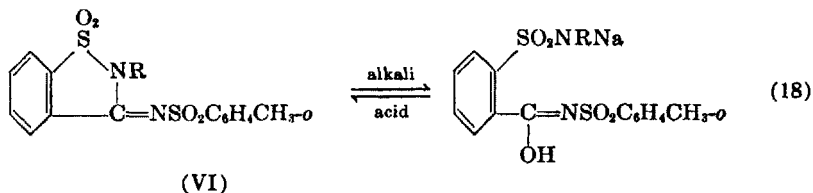


Compound V¹⁶ formed a sodium salt with sodium carbonate. Heating this compound with sodium hydroxide caused decomposition with the formation of *o*-tolylsulfonamide and *o*-carboxyphenylsulfonamide (16).



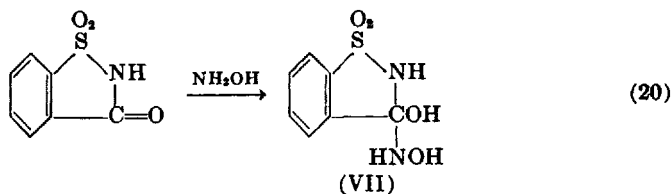
¹⁶ Klages, Strum, and Weniger, *J. prakt. Chem.*, [2] 116, 163 (1927).

Acid did not affect this compound. Alkylation of the silver salt gave 2-substituted products (17). Dilute alkali split these compounds (type VI), while dilute acid reformed the ring (18). Oxidation of compound V yielded 3-(*o*-carboxyphenylsulfonamido)-1,2-benzisulfonazole (19). Compound



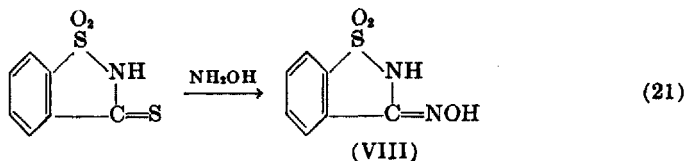
V was approximately twice as bitter as quinine and half as bitter as strychnine.

Hydroxylamine¹⁷ reacted with saccharin to form 3-hydroxy-3-hydroxylamino-2,3-dihydro-1,2-benzisulfonazole (20). Compound VII was soluble



in alkali and reduced Fehling's solution. Ferric chloride gave a red precipitate. Heat and concentrated sulfuric acid decomposed compound VII to saccharin. Acetic anhydride and compound VII yielded acetylsaccharin. 2-Methylsaccharin and 2-acetylsaccharin gave very little evidence of reacting with hydroxylamine.

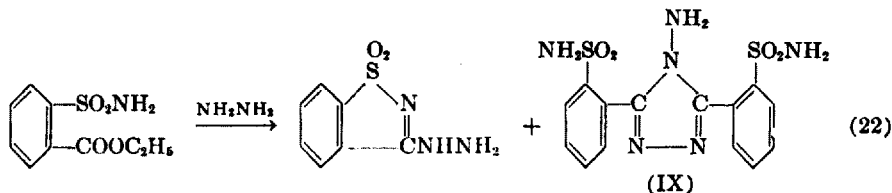
Thiosaccharin¹⁷ and hydroxylamine produced a 3-hydroxylamino-1,2-benzisulfonazole (21). Ferric chloride gave a violet color with compound VIII and gradually decomposed it to saccharin. It was soluble in alkalis



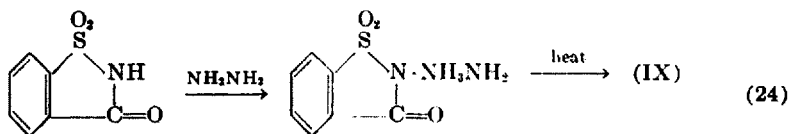
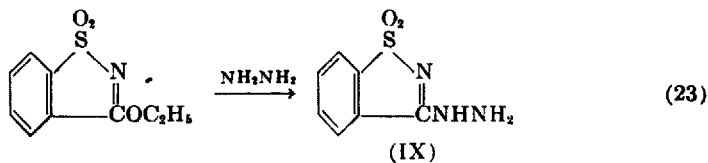
¹⁷ Mannessier-Mameli, *Gazz. chim. ital.*, 62, 1067 (1932); *Chem. Abstr.*, 27, 2682 (1933).

and alkaline carbonates. Compound VIII formed an acetyl compound which was decomposed to the parent compound with boiling water.

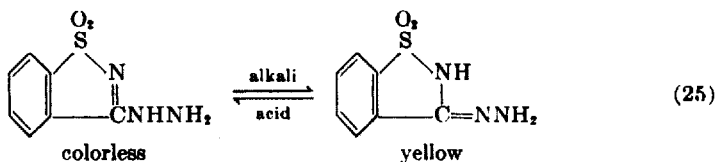
Schrader¹⁸ prepared 3-hydrazino-1,2-benzisulfonazole in three ways: from *o*-carbethoxyphenylsulfonamide and hydrazine (22), from 3-ethoxy-



1,2-benzisulfonazole and hydrazine (23), and from saccharin and hydrazine (24). Mannessier-Mameli¹⁹ investigated reaction (24) and found that



in the cold, hydrazine formed salts with saccharin and thiosaccharin. When these salts were heated, compound IX was formed. 3-Hydrazino-1,2-benzisulfonazole^{18,19} gave the typical reactions of a hydrazino compound; it was readily acylated, it reacted with aldehydes, and it reduced ammoniacal silver nitrate and Fehling's solution. This compound, on dissolving in alkali, gave an intense yellow solution. Acidic solutions were colorless. Schrader¹⁸ believed that the tautomers of equation (25) existed.



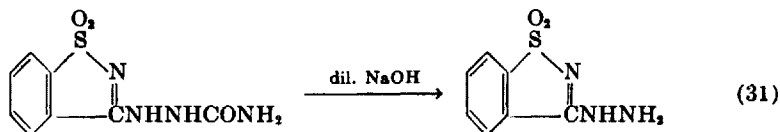
Phenylhydrazine did not react with saccharin in a glacial acetic acid solution.²⁰ Phenylhydrazine and saccharin at 160–180°C. produced 3-β-

¹⁸ Schrader, *J. prakt. Chem.*, [2] 95, 312 (1917).

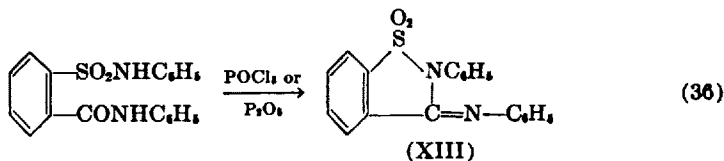
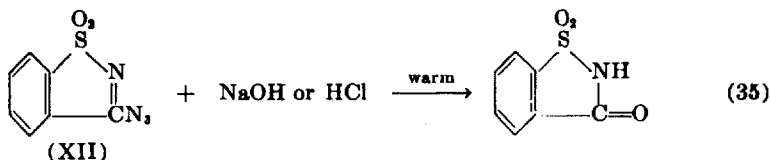
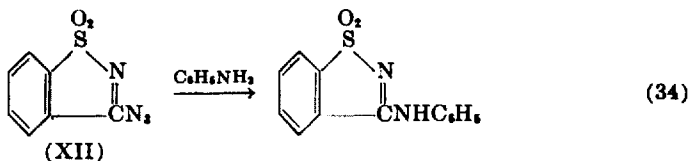
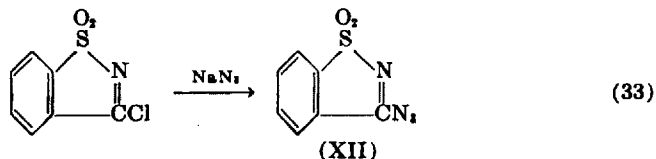
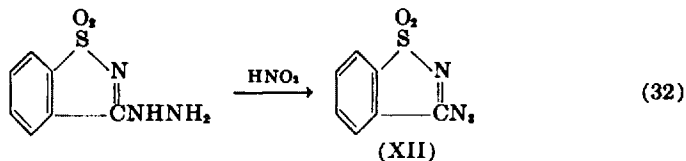
¹⁹ Mannessier-Mameli, *Gazz. chim. ital.*, 71, 18 (1941); *Chem. Abstr.*, 36, 1029 (1942).

²⁰ Mannessier-Mameli, *Gazz. chim. ital.*, 71, 596 (1941); *Chem. Abstr.*, 37, 100 (1943).

with thiosaccharin and semicarbazide (30). Acetylation of XI with sodium acetate and acetic anhydride formed the triacetyl derivative. Dilute alkali and compound XI gave 3-hydrazino-1,2-benzisulfonazole (31).

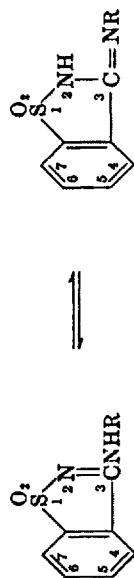


The 3-azido-1,2-benzisulfonazole (XII) was prepared either from compound IX and sodium nitrite (32) or from 3-chloro-1,2-benzisulfonazole and sodium azide (33).²² Compound XII and aniline formed 3-

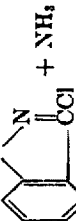
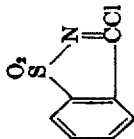
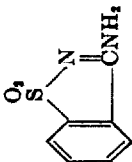
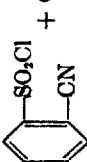
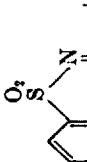
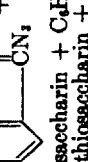


²² Schrader, *J. prakt. Chem.*, [2] 95, 312 (1917).

TABLE LXI. Preparation of the 3-Amino-1,2-benzisothiazolones or the 3-Imino-2,3-dihydro-1,2-benzisothiazolones

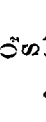
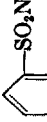
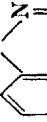


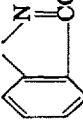
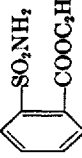
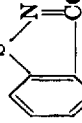
No.	Substituents on the 1,2-benzisothiazole ring	Ref.	Method of preparation	Solubility	M.p., °C.
1	3-Amino			water, alc.	over 300
1		1		—	315
2		2		—	—
1		1		—	—
1		1		—	—
1,3		1,3		—	297
4		4	boiling solution of ammonium thio-saccharinate	—	315
4		4	pyrolysis of ammonium saccharinate	—	315
4		4	pyrolysis of ammonium thiosaccharinate	—	315
4		4	saccharin + (NH ₄) ₂ CO ₃ at 250°C.	—	—
4		4	thiosaccharin + (NH ₄) ₂ CO ₃ at 300°C.	—	—
4		4	saccharin + urea at 250°C.	—	—
2		2	thiosaccharin + urea at 150°C.	—	—
2		2	pyrolysis of 3-hydroxyamino-1,2-benzisulfonazole	—	—

No.	Substituents on the 1,2-benzisulfonazole ring	Ref.	Method of Preparation	Solubility	M.p., °C.
2	3-Acetamido	2	compound 1 + sodium acetate + acetic anhydride	alc.	256 sublimes
3	4-Carbamyl-3-amino	5	 + NH ₃	water	over 280
4	3-Anilino	1	 + C ₆ H ₅ NH ₂	alc.	over 300
		1	 + C ₆ H ₅ NH ₂	—	—
		1	 + C ₆ H ₅ NH ₂	—	—
		1	 + C ₆ H ₅ NH ₂ , at 150°C.	—	—
		6	 + C ₆ H ₅ NH ₂	aniline	over 300
		7,8	saccharin + C ₆ H ₅ NH ₂ , with reflux	—	313-5
		9	thiosaccharin + C ₆ H ₅ NH ₂ , with gentle heating	acetic acid	315-7
		10	 + P ₂ S ₅	—	—

(Table continued)

TABLE LXI (Continued)

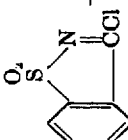
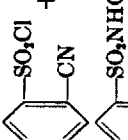
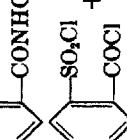
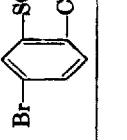
No.	Substituents on the 1,2-benzisulfonazole ring	Ref.	Method of preparation	Solubility	M.p., °C.
5	3- <i>o</i> -Toluidino	10	saccharin + α -CH ₃ C ₆ H ₄ NH ₂	acetic acid	276
6	3- <i>m</i> -Toluidino	10	thiosaccharin + α -CH ₃ C ₆ H ₄ NH ₂	acetic acid, nitrobenzene	296-7
7	3- <i>p</i> -Toluidino	10	same as compound 5	acetic acid	285
8	3-Phenylsulfonamido	11	 $+ \text{C}_6\text{H}_5\text{SO}_2\text{NH}_2 + \text{AlCl}_3$	acetic acid, acetone	213
9	3-Phenylsulfonimido-2-benzyl-2,3-dihydro	11	Ag salt of compound 8 + benzyl chloride	alc.	112
10	3- <i>o</i> -Tolylsulfonamido	11	 $+ \text{KMnO}_4 + \text{NaOH}$	water, acetic acid, acetone	255
11	3- <i>o</i> -Tolylsulfonimido-2-methyl-2,3-dihydro	11	 $+ \text{AlCl}_3$	—	—
12	3- <i>o</i> -Tolylsulfonimido-2-ethyl-2,3-dihydro	11	Ag salt of compound 10 + CH ₃ I	alc.	128
13	3- <i>o</i> -Tolylsulfonimido-2-benzyl-2,3-dihydro	11	Ag salt of compound 10 + C ₆ H ₅ I	alc., ether	155
14	3- <i>o</i> -Tolylsulfonimido-2-carbophenoxy-2,3-dihydro	11	Ag salt of compound 10 + benzyl chloride	alc.	165
		11	Na salt of compound 10 + C ₆ H ₅ OCOCl	alc.	225

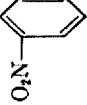
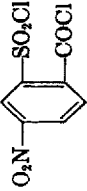
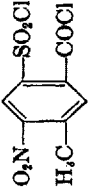
No.	Substituents on the 1,2-benzisotoulonazole	Ref.	Method of preparation	Solubility	M.p., °C.
15	3- <i>p</i> -Tolylsulfonamido	11	 + <i>p</i> -CH ₃ C ₆ H ₄ SO ₂ NH ₂ Ag salt of compound 15 + benzyl chloride water	265	
16	3- <i>p</i> -Tolylsulfonimido-2-benzyl-2,3-dihydro	11	Ag salt of compound 15 + benzyl chloride alc.	112	
17	3- <i>o</i> -Carboxyphenylsulfonamido	11	oxidation of compound 10 + KMnO ₄ water, alc.	190-230	
18	3- <i>o</i> -Carboxyphenylsulfonimido-2-benzyl-2,3-dihydro	11	sodium salt of compound 17 + benzyl chloride ether, acetone, benzene	115	
19	3-Hydroxy-3-hydroxylamino-2,3-dihydro	12	saccharin + hydroxylamine alc., benzene	157	
20	3-Hydroxylamino	12	thiosaccharin + hydroxylamine benzene	208-10	
21	3-Acetoxyamino	12	compound 20 + acetic anhydride alkali	225 dec.	
22	3-Benzoylamino	12	compound 20 + benzoyl chloride alc.	250	
23	3-Hydrazino	6	 + NH ₂ NH ₂ at 125°C. water	257	
		6	 + NH ₂ NH ₂ at 125°C.	—	
24	3-Benzhydrazo	6, 13	saccharin + NH ₂ NH ₂ at 125°C. thiosaccharin + NH ₂ NH ₂ —	257-60	
25	3-Benzylidenehydrazino	13	compound 23 + benzoyl chloride alc.	276	
26	3- <i>p</i> -Anisylidenehydrazino	6	compound 23 + benzaldehyde alc., water	287	
27	3- <i>β</i> -Phenylhydrazino	6	compound 23 + anisylaldehyde alc., nitrobenzene	270	
		14	saccharin + phenylhydrazine at 160-80°C. thiosaccharin + phenylhydrazine —	225	

(Table continued)

(Table continued)

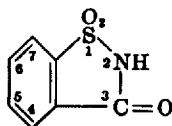
TABLE LXI (Continued)

No.	Substituents on the 1,2-benzisothiazole ring	Ref.	Method of Preparation	Solubility	M.p., °C.
28	3-(Benzoyl- β -phenylhydrazino)	14	compound 27 + benzoyl chloride	alc.	330-5
29	3- β -Carbamylhydrazino	15	thiosaccharin + semicarbazide	water, methanol, alc.	230-5
30	2-Acetyl-3-(β -acetylcarbamyl- β -acetylhydrazino)-2,3-dihydro	15	compound 29 + acetic anhydride + sodium acetate	water	205-10
31	3-Azido	6	compound 23 + HNO ₃	alc., benzene	153 dec.
		—		—	—
32	2-Phenyl-3-phenylimino-2,3-dihydro	1	 + NaN ₃	—	—
		1	 + C ₆ H ₅ NH ₂ with heat	—	—
16		16	 + SO ₂ NHC ₆ H ₅ + P ₂ O ₅ or POCl ₃	acetic acid	189.5
17		17	 + SO ₂ Cl + C ₆ H ₅ NH ₂	—	—
18		18	+ SO ₂ NHC ₆ H ₅ + POCl ₃ or P ₂ O ₅	—	200
33	6-Bromo-2-phenyl-3-phenylimino-2,3-dihydro			—	

No.	Substituents on the 1,2-benzisulfonazole ring	Ref.	Method of preparation	Solubility	M.p., °C.
34	6-Nitro-2-phenyl-3-phenylimino-2,3-dihydro	19	 $\text{SO}_2\text{NHC}_6\text{H}_5$ + POCl_3	acetone, benzene	208
35	5-Methyl-6-nitro-3-phenylimino-2,3-dihydro	20	 SO_2Cl + $3 \text{ C}_6\text{H}_5\text{NH}_2$	acetic acid	—
			 SO_2Cl + $3 \text{ C}_6\text{H}_5\text{NH}_2$	alc., benzene	188

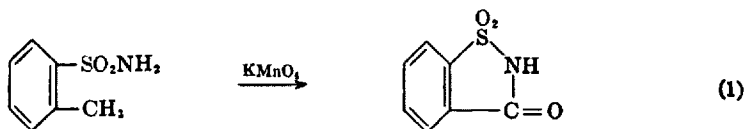
- ¹ Jesurun, *Ber.*, 25, 2286 (1893).
² Mannessier-Mameli, *Gazz. chim. ital.*, 65, 77 (1935); *Chem. Abstr.*, 29, 3999 (1935).
³ Bradshaw, *Am. Chem. J.*, 35, 335 (1906).
⁴ Mannessier-Mameli, *Gazz. chim. ital.*, 71, 3 (1941); *Chem. Abstr.*, 36, 1028 (1942); Mameli and Mannessier-Mameli, *Gazz. chim. ital.*, 70, 855 (1940); *Chem. Abstr.*, 36, 1026 (1942).
⁵ Zincke and Greune, *Ann.*, 427, 221 (1922).
⁶ Schrader, *J. prakt. Chem.*, [2] 95, 312 (1917).
⁷ Remsen and Dohne, *Am. Chem. J.*, 11, 34 (1889).
⁸ Koetschet and Koetschet, *Heb. Chim. Acta*, 12, 669 (1929).
⁹ Mannessier-Mameli, *Gazz. chim. ital.*, 65, 51 (1935); *Chem. Abstr.*, 29, 3997 (1935).
¹⁰ Mannessier-Mameli, *Gazz. chim. ital.*, 65, 69 (1935); *Chem. Abstr.*, 29, 3999 (1935).
¹¹ Klages, Strum, and Weniger, *J. prakt. Chem.*, [2] 116, 163 (1927).
¹² Mannessier-Mameli, *Gazz. chim. ital.*, 62, 1067 (1932); *Chem. Abstr.*, 27, 2682 (1933).
¹³ Mannessier-Mameli, *Gazz. chim. ital.*, 71, 18 (1941); *Chem. Abstr.*, 36, 1029 (1942).
¹⁴ Mannessier-Mameli, *Gazz. chim. ital.*, 71, 596 (1941); *Chem. Abstr.*, 37, 100 (1943).
¹⁵ Mannessier-Mameli, *Gazz. chim. ital.*, 71, 25 (1941); *Chem. Abstr.*, 36, 1030 (1942).
¹⁶ Remsen and Hunter, *Am. Chem. J.*, 18, 809 (1896).
¹⁷ Remsen and Clark, *Am. Chem. J.*, 30, 278 (1903).
¹⁸ Blanchard, *Am. Chem. J.*, 30, 485 (1903).
¹⁹ Henderson, *Am. Chem. J.*, 25, 1 (1901).
²⁰ Karslake and Bond, *J. Am. Chem. Soc.*, 38, 1338 (1916).

Saccharin, Benzoic Sulfinide, or 2,3-Dihydro-1,2-benzisosulfonazol-3-one (I)

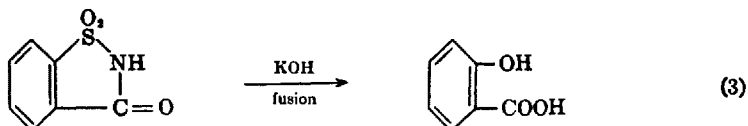
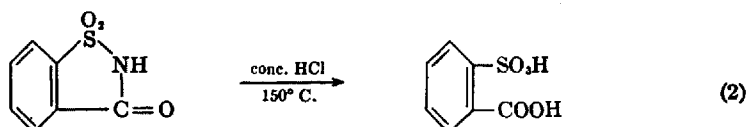


(I)

Remsen and Fahlberg,^{1,2} during a study of the tolylsulfonic acids, oxidized *o*-tolylsulfonamide with potassium permanganate and obtained 2,3-dihydro-1,2-benzisosulfonazol-3-one which they named benzoic sulfinide (1). In the filtrate from the reaction mixture a second compound



was isolated and found to be 2-carboxyphenylsulfonic acid. Hydrolysis of compound I with concentrated hydrochloric acid also yielded this compound (2). Fusion with potassium hydroxide formed salicylic acid (3).

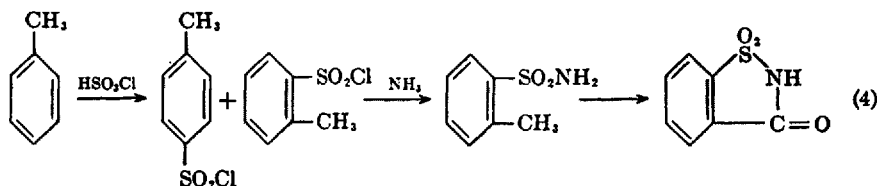


The announcement that saccharin possessed a very marked sweet taste¹ set off a tremendous amount of research in the field of saccharin-like compounds on the preparation of saccharin itself as well as that of analogs, homologs, and derivatives; on pharmacological properties of saccharin; on its detection in food and drink; on the analysis of the finished commercial product; and on the utilization of the by-products of its manufacture. The question of why such a structure as saccharin should stimulate the same nerve impulses in human beings as the sugars has not yet been adequately explained. Nonetheless, saccharin has evolved as a substitute for sugar during a scarcity of sugar production or in cases where sugar must be omitted from the diet.

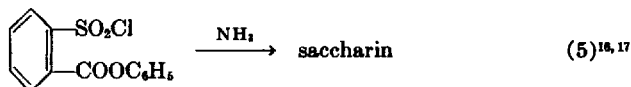
¹ Remsen and Fahlberg, *Am. Chem. J.*, 1, 426 (1879-80).

² Remsen and Fahlberg, *Ber.*, 12, 469 (1879).

The principal methods of manufacture closely follow the original work of Remsen and Fahlberg (4). Toluene is sulfonated at 0°C. to produce a



maximum yield of the *ortho* isomer. The isomers are separated on the basis of their solubility in 60% sulfuric acid or on the basis of the solubility of their sodium, zinc, and magnesium salts. A preferred method consists of chlorosulfonating toluene with chlorosulfonic acid and then freezing the *para* isomer from the reaction product. The amide is formed with ammonium hydroxide or ammonium carbonate. The oxidation can be brought about by any number of oxidizing agents; potassium permanganate,^{1,2} chromic acid and sulfuric acid,³⁻¹⁰ and by electrolysis.¹¹⁻¹⁵ In addition, saccharin has been prepared on a laboratory scale by a number of methods. These methods fall into two groups. One group consists of the cyclization



¹ Monnets and Cartier, *Chem. Abstr.*, 15, 2374 (1921); Brit. Pat. 153,520.

⁴ Monnets and Cartier, *Chem. Abstr.*, 16, 428 (1922); Brit. Pat. 165,428.

⁵ Bebie, *Chem. Abstr.*, 15, 1030 (1921); U. S. Pat. 1,366,349.

⁶ Altwegg and Collardeau, *Chem. Abstr.*, 18, 3386 (1924); U. S. Pat. 1,507,565.

⁷ Orelup, *Chem. Abstr.*, 20, 3696 (1926); U. S. Pat. 1,601,505.

⁸ Zaikov and Sokolov, *Chem. Abstr.*, 22, 2933 (1928); *J. Chem. Ind. (U. S. S. R.)*, 3, 1304 (1926).

⁹ Zil'berg, *Chem. Abstr.*, 29, 1794 (1935); *Khim. Farm. Prom.*, No. 4, 22 (1934).

¹⁰ Matveev, *Chem. Abstr.*, 41, 4812 (1947); U. S. S. R. Pat. 66,878.

¹¹ Klages, *Chem. Abstr.*, 13, 2374 (1919); Swiss Pat. 78,277.

¹² Lowe, *Chem. Abstr.*, 16, 1710 (1922); Brit. Pat. 174,193.

¹³ Fichter and Lowe, *Helv. Chim. Acta*, 5, 60 (1922).

¹⁴ Halla, *Chem. Abstr.*, 24, 2060 (1930); *Z. Electrochem.*, 36, 96 (1930).

¹⁵ Heyden, *Friedländer*, 4, 1263 (1899); Ger. Pat. 85,491.

¹⁶ Remsen and Humphreys, *Am. Chem. J.*, 30, 292 (1903).

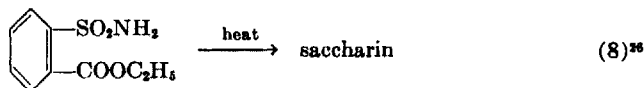
¹⁷ Borzhim, *Chem. Abstr.*, 40, 7233 (1946); U. S. S. R. Pat. 65,065.

¹⁸ Remsen and Saunders, *Am. Chem. J.*, 17, 347 (1895).

¹⁹ Remsen and McKee, *Am. Chem. J.*, 18, 791 (1896).

²⁰ List and Stein, *Ber.*, 31, 1648 (1898).

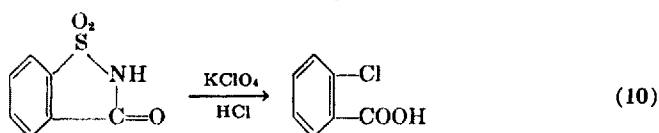
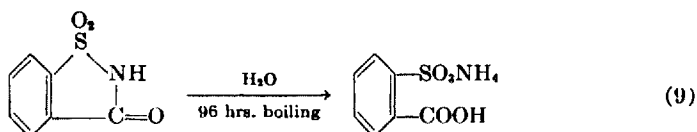
²¹ Remsen and Bird, *Am. Chem. J.*, 30, 245 (1903).



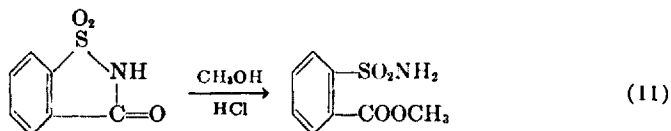
of an *o*-carboxy-, an *o*-chlorocarbonyl-, or an *o*-carbethoxyphenylsulfonamide or -phenylsulfonyl chloride (5-8). The other class consists of oxidizing 1,2-benzisothiazol-3(2)-one or hydrolysis of one of the 3-substituted 1,2-benzisulfonazoles. (These reactions are discussed under the parent compounds.)

The reactions of saccharin are classified into four divisions: the rupture of the sulfonazole ring, substitution on the 2-nitrogen, reaction of the 3-keto group, and substitution on the ring.

Heating an aqueous or an acidulated aqueous solution resulted in the hydrolysis of saccharin (9)^{27, 28} Saccharin, on being heated with potassium chlorate and dilute hydrochloric acid, gave *o*-chlorobenzoic acid (10).²⁹



Alcoholysis occurred with hydrogen chloride in methanol and with methanol alone at 170°C. (11)^{30, 31} Heating saccharin at low temperatures with.



²² Noyes, *Am. Chem. J.*, **8**, 179 (1886).

²³ Chem. Farb. vorm Sandoz, *Friedländer*, **6**, 1209 (1904); Ger. Pat. 113,720.

²⁴ Bradshaw, *Am. Chem. J.*, **35**, 335 (1906).

²⁵ Wilson, *Am. Chem. J.*, **30**, 347 (1903).

²⁶ Fahlberg and List, *Ber.*, **20**, 1596 (1887).

²⁷ Remsen and Fahlberg, *Ber.*, **12**, 469 (1879).

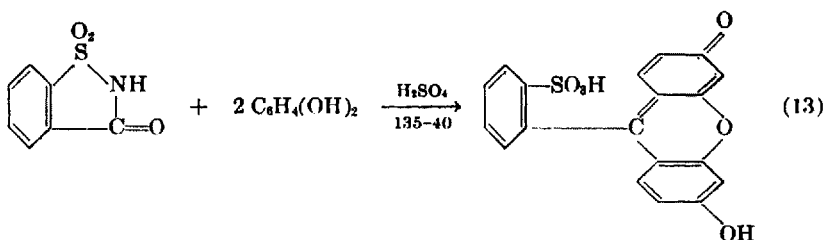
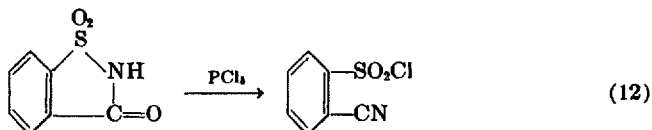
²⁸ Richmond and Hill, *Chem. Abstr.*, **12**, 2215 (1918); *J. Soc. Chem. Ind.*, **37**, 246 (1918); *Chem. Abstr.*, **13**, 979 (1919); *J. Soc. Chem. Ind.*, **38**, 8T (1919).

²⁹ Bertolo and Bertolo, *Chem. Abstr.*, **27**, 73 (1933); *Gazz. chim. ital.*, **62**, 487 (1932).

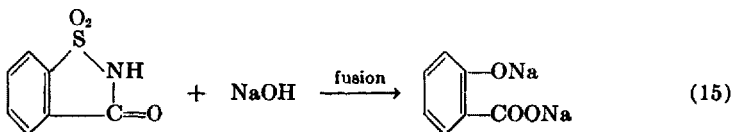
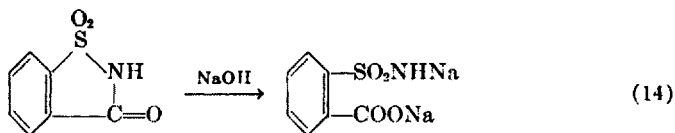
³⁰ Hoogerwerff and Van Dorp, *Rec. trav. chim.*, **18**, 358 (1899).

³¹ Jesurum, *Ber.*, **26**, 2286 (1893).

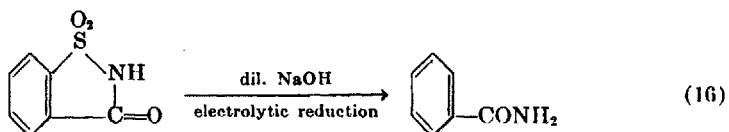
phosphorus pentachloride yielded *o*-cyanophenylsulfonyl chloride (12).^{31,32} Resorcinol and saccharin in sulfuric acid at 135–140°C. resulted in the formation of sulfone fluorescein (13).^{33,34}



Alkaline hydrolysis produced 2-carboxyphenylsulfonamide (14).³⁵ Fusion of saccharin with alkali gave salicylic acid (15).³⁶ Reduction in



alkali by sodium in amyl alcohol or electrolytic reduction in dilute alkali resulted in the formation of derivatives of benzoic acid (16).^{37,38} Mannessier-



³¹ Walker and Smith, *J. Chem. Soc.*, 89, 350 (1906).

³² Sisley, *Bull. soc. chim. France*, [3] 17, 822 (1897).

³³ Orndorff and Vose, *J. Am. Chem. Soc.*, 46, 1896 (1924).

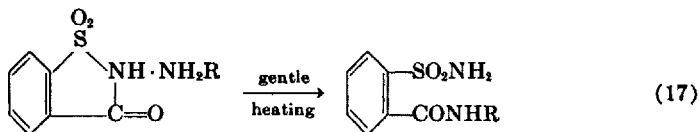
³⁴ Fahlberg and List, *Ber.*, 21, 242 (1888).

³⁵ Remsen and Fahlberg, *Ber.*, 12, 469 (1879).

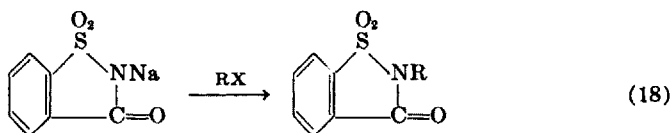
³⁶ Gianformaggio, *Chem. Abstr.*, 15, 520 (1921); *Gazz. chim. ital.*, 50, 327 (1920).

³⁷ Matsui, Sawamura, and Adachi, *Chem. Abstr.*, 26, 5264 (1932); *Mem. Coll. Sci. Kyoto Imp. Univ.*, A15, 151 (1932).

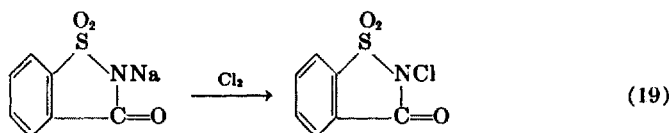
Mameli³⁹ found that arylamines formed salts with saccharin. Gentle heating of these salts caused cleavage with the formation of *o*-arylcarbamyphenylsulfonamides (17). (Additional information on this reaction is given



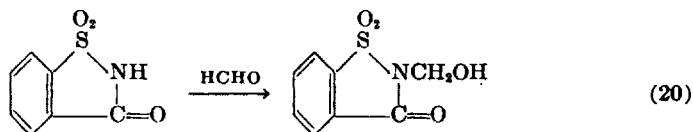
under the 3-amino-1,2-benzisothiazoles.) Saccharin acquires 2-substituents readily. Numerous salts of saccharin have been prepared, the hydrogen on the nitrogen being acidic in character. Alkylation in the 2-position has been achieved by direct alkylation of a salt with an alkyl halide or other alkylating agents (these compounds are discussed under the 2-substituted saccharins)(18). When the silver salt was used, both *N*- and



O-alkyl derivatives were formed.⁴⁰ The 2-chlorosaccharin was synthesized in good yield with the sodium salt and chlorine (19).⁴¹ An impure 2-iodo-



saccharin was obtained with the silver salt and iodine.^{42,43} The 2-acyl derivatives were prepared by the action of the acid chloride or anhydride upon saccharin or its sodium salt. Saccharin readily condensed with formaldehyde to give the 2-hydroxymethylsaccharin (20).^{44,45} In 70% sul-



³⁹ Mannessier-Mameli, *Gazz. chim. ital.*, **65**, 51 (1935); *Chem. Abstr.*, **29**, 3997 (1935).

⁴⁰ Heller, Buchwald, Fuchs, Kleinke, and Kloss, *J. prakt. Chem.*, [2] **111**, 1 (1925).

⁴¹ Chattaway, *J. Chem. Soc.*, **87**, 1882 (1905).

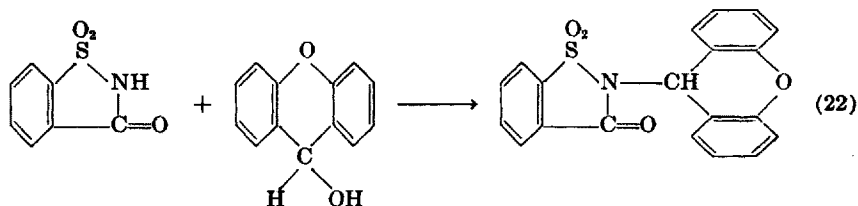
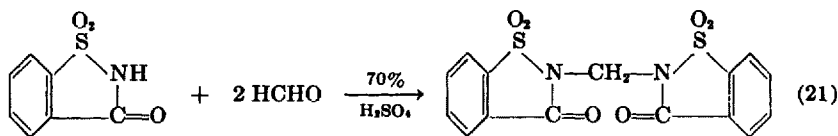
⁴² Feigl and Charga, *Monatsh.*, **49**, 417 (1928).

⁴³ Feigl and Bondi, *Monatsh.*, **53** and **54**, 508 (1929).

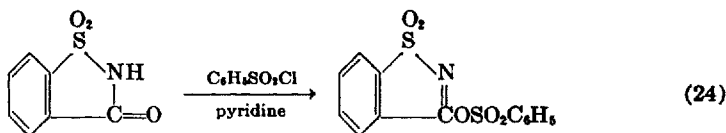
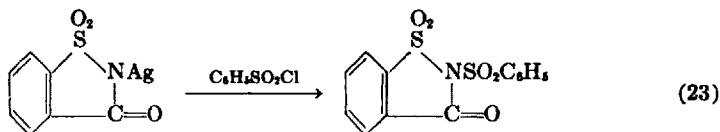
⁴⁴ Masselli, *Chem. Zentr.*, **71**, II, 629 (1900); *Gazz. chim. ital.*, **30**, 31 (1900).

⁴⁵ Parmeggiani, *Chem. Zentr.*, **79**, I, 1389 (1908); *Boll. chim. farm.*, **47**, 37 (1908).

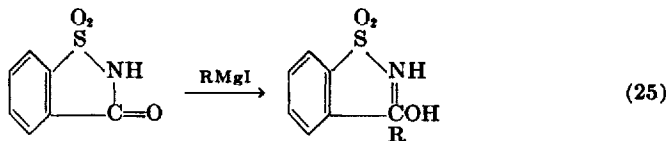
furic acid, disubstitution occurred (21).⁴⁶ Xanthidrol condenses with a number of amides as exemplified by its reaction with saccharin (22).⁴⁷



Hart, McClelland, and Fowkes⁴⁸ obtained the 2-phenylsulfonyl derivatives when the silver saccharinate and phenylsulfonyl chloride were used, and the 3-phenylsulfonyloxy-1,2-benzisulfonazoles when saccharin and pyridine were employed (23,24).



Substitution in the 3-position occurred when saccharin reacted with phosphorus pentachloride and phosphorus pentasulfide to yield the 3-chloro-1,2-benzisulfonazole and thiosaccharin, respectively. (These reactions are discussed under the 1,2-benzisulfonazoles and thiosaccharin.) Grignard reagents supposedly formed the tertiary alcohols:⁴⁹



(See the discussion of the 2,3-dihydro-1,2-benzisulfonazoles.)

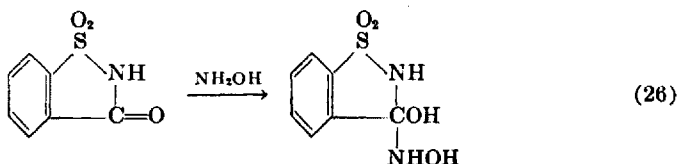
⁴⁶ Eckenroth and Koerppen, *Ber.*, **30**, 1265 (1897).

⁴⁷ Fabre, *Chem. Abstr.*, **18**, 83 (1924); *Bull. soc. chim. France*, **33**, 791 (1923).

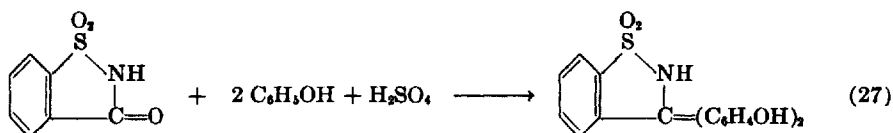
⁴⁸ Hart, McClelland, and Fowkes, *J. Chem. Soc.*, 2114 (1938).

⁴⁹ Oddo and Mingoia, *Gazz. chim. ital.*, **57**, 465 (1927); *Chem. Abstr.*, **21**, 3202 (1927).

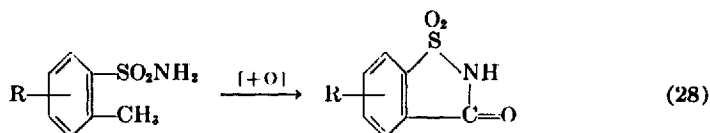
Hydroxylamine⁶⁰ and saccharin formed a substituted 2,3-dihydro-1,2-benzisosulfonazole instead of an oxime (26). Saccharin readily substituted



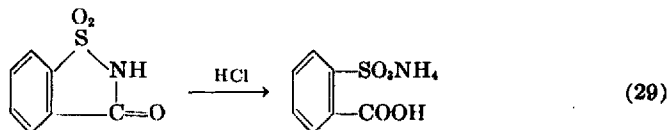
in the 3-position with the phenols in the presence of concentrated sulfuric acid, anhydrous aluminum chloride, or anhydrous zinc chloride and gave the so-called sulfamphthaleins. (These compounds are discussed under the 2,3-dihydro-1,2-benzisosulfonazoles.)



There is no literature on the direct substitution of any group on the phenyl ring in saccharin. Such substituted saccharin derivatives which have been prepared are the result of cyclizing a substituted phenyl derivative. (These compounds are discussed under the benzene ring-substituted saccharins.)



The analyses and detection of saccharin in various foods and beverages is present in an enormous amount of literature which cannot be given here in entirety. In general, these methods consist of extracting the saccharin from the product with ether. The most general analysis takes advantage of the acid hydrolysis of saccharin (29). Krantz⁶¹ in the recent literature



⁶⁰ Mannessier-Mameli, *Gazz. chim. ital.*, **62**, 1067 (1932); *Chem. Abstr.*, **27**, 2682 (1933).

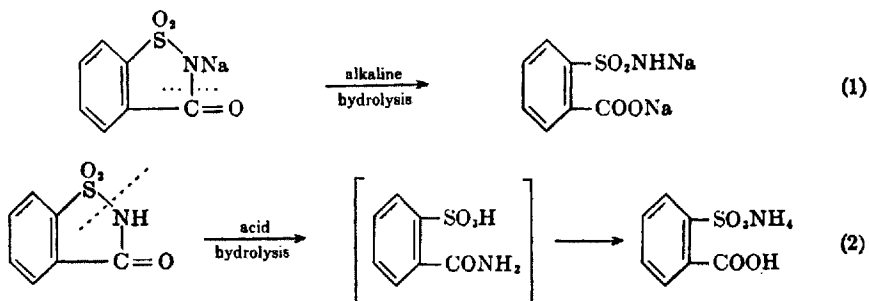
⁶¹ Krantz, *Chem. Abstr.*, **27**, 5118 (1933); *J. Assoc. Official Agr. Chemists*, **16**, 316 (1933); *Chem. Abstr.*, **28**, 4493 (1934); *J. Assoc. Official Agr. Chemists*, **17**, 193 (1934); *Chem. Abstr.*, **29**, 6966 (1935); *J. Assoc. Official Agr. Chemists*, **18**, 372 (1935).

has devised a number of methods of determining the amount of saccharin by using the quantity of ammonia liberated as an index of the saccharin present. Such methods are not new⁵² and others are continually supplying modifications of this method. Titration of the *o*-carboxyphenylsulfonic acid has also been suggested.^{53,54} In addition, a number of other methods have been used to determine the amount of saccharin present. These include sublimation,⁵⁵ heavy metal salts of saccharin⁵⁶ in the presence of ammonia, organic amines or pyridine, formation of sulfamphthaleins,⁵⁷ etc.

The physiological effects of saccharin are described in a considerable literature. It is believed to be a relatively nontoxic compound, though toxic manifestations have been observed on long and continued use of large quantities. A 0.2-gram dose is about $1/500$ of the tolerated dose per day.⁵⁸

Discussion

The products of the acid and the alkaline hydrolyses of saccharin are indications of its reactivity. In the acid hydrolysis, rupture occurs between the sulfur and the nitrogen, while in an alkaline hydrolysis ring cleavage occurs between the nitrogen and the 3-keto group (1,2). An acid hydrolysis



⁵² Richmond and Hill, *Chem. Abstr.*, **12**, 2215 (1918); *J. Soc. Chem. Ind.*, **37**, 246 (1918); *Chem. Abstr.*, **13**, 979 (1919); *J. Soc. Chem. Ind.*, **38**, 8T (1919).

⁵³ Illing, Dalley, and Stephenson, *Chem. Abstr.*, **41**, 4589 (1947); *Food*, **16**, 140 (1947); Solon, *Chem. Abstr.*, **41**, 7311 (1947); *Food*, **16**, 268 (1947).

⁵⁴ Rosenblum and Mildivorn, *Chem. Abstr.*, **41**, 4891 (1947); *J. Am. Pharm. Assoc.*, **35**, 336 (1946).

⁵⁵ Margarethe Oakley, *Chem. Abstr.*, **39**, 3854 (1945); *J. Assoc. Official Agr. Chemists*, **28**, 298 (1945).

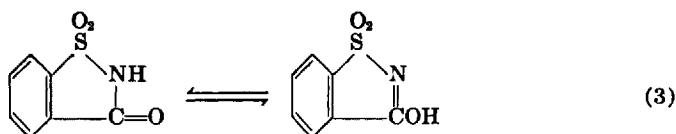
⁵⁶ Hernandez and Font, *Chem. Abstr.*, **42**, 1530 (1948); *Mon. farm. y terap. (Madrid)*, **53**, 359 (1947). Gutierrez and Altaba, *Chem. Abstr.*, **42**, 724 (1948); *Anales fis. y quim. (Madrid)*, **43**, 47 (1947).

⁵⁷ Krantz, *Chem. Abstr.*, **30**, 4935 (1936); *J. Assoc. Official Agr. Chemists*, **19**, 205 (1936).

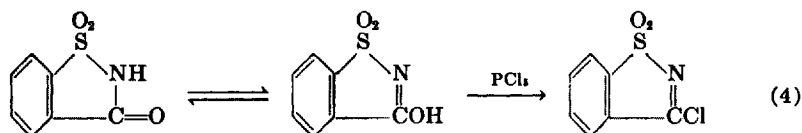
⁵⁸ Staub, *Chem. Abstr.*, **41**, 212 (1947); *Mitt. Lebensm. Hyg.*, **36**, 7 (1945).

of a sulfamyl group to a sulfonic acid and a strong amine such as ammonia is very difficult. However, hydrolysis of a sulfamyl group containing a weak amine such as an amide takes place readily.

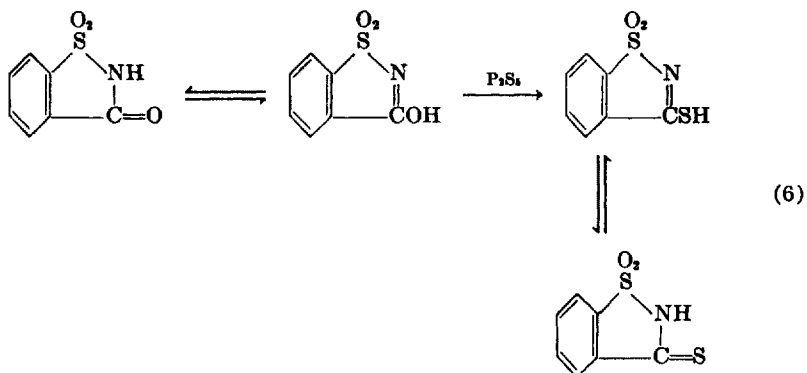
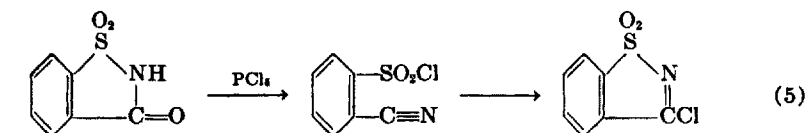
The structure of saccharin is usually given in the keto form, although there is a possibility that the other tautomer may exist (3). While the



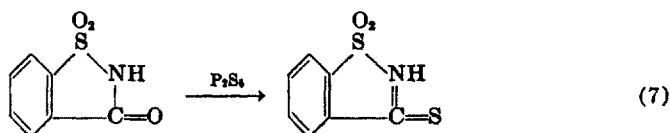
Na salt is undoubtedly in the keto form, the Ag salt exists in both forms since alkylation of the silver salt gave both the *N*- and *O*-substituted compounds. The reaction between phosphorus pentachloride and saccharin may be an indication of the existence of some of the hydroxy form (4).



However, the mechanism may be entirely different, since Jesurum⁵⁹ has shown that at low temperatures *o*-cyanophenylsulfonyl chloride is formed. Perhaps the sulfonyl chloride adds across the triple bond (5). The reaction

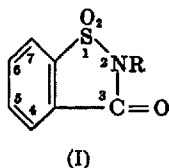


⁵⁹ Jesurum, *Ber.*, 26, 2286 (1893).

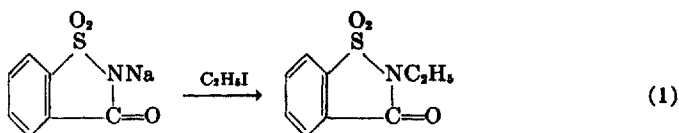


of saccharin with phosphorus pentasulfide falls in the same category; the course of the reaction may follow any one of three routes. Two are postulated in equations (6) and (7). The third may involve some cleavage of the ring as in the reaction between phosphorus pentachloride and saccharin.

2-Substituted Saccharins (I)



Fahlberg and List¹ heated sodium saccharinate with ethyl iodide to obtain the 2-ethylsaccharin (1). This method is a general one in which



the alkaline and silver salts were used by a number of authors to prepare numerous 2-alkyl derivatives. The alkyl iodides or bromides were usually employed, although methyl-*p*-toluenesulfonate was an excellent alkylating agent.² This reaction has been suggested as a method of identifying alkyl iodides and bromides, since the technique is simple and sharp melting points were obtained.³ 2-*n*-Propylsaccharin and 2-isobutylsaccharin have melting points differing by only 1°C., but a mixture showed an 8–10° depression. No derivatives could be obtained with methyl, ethyl, isopropyl, *sec*-butyl chlorides or ethylene dichloride.

The 2-substituted alkyl derivatives were synthesized in a similar manner. Ethylene dibromide^{3,4} and sodium saccharinate at low temperatures

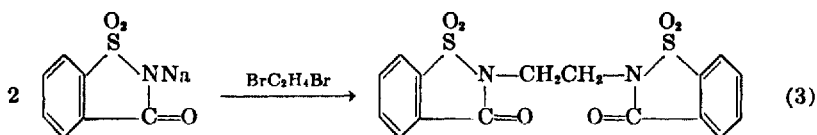
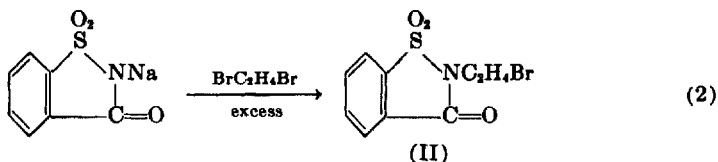
¹ Fahlberg and List, *Ber.*, 20, 1596 (1885).

² Magidson and Gorbatschow, *Ber.*, 56, 1810 (1923).

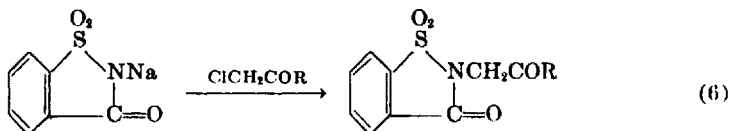
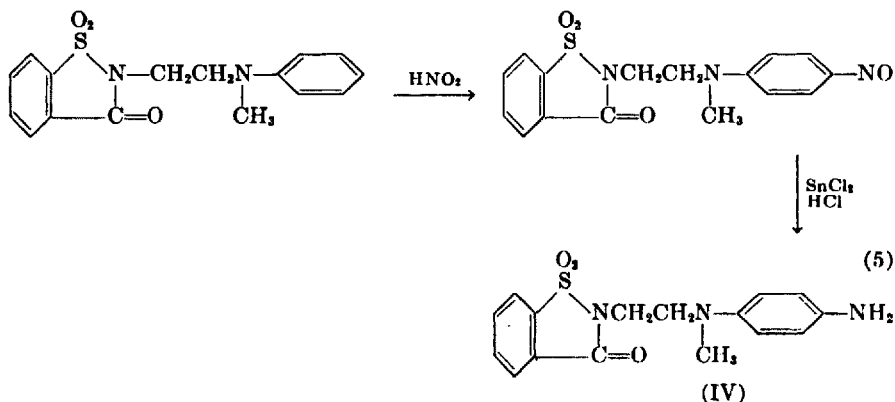
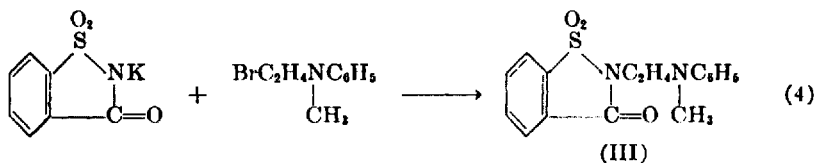
³ Merritt, Levey, and Cutler, *J. Am. Chem. Soc.*, 61, 15 (1939).

⁴ Eckenroth and Koerppen, *Ber.*, 29, 1048 (1896).

yielded 2- β -bromoethylsaccharin. At high temperatures with two equivalents of sodium saccharin, ethylene bissaccharin was produced (2,3).⁵



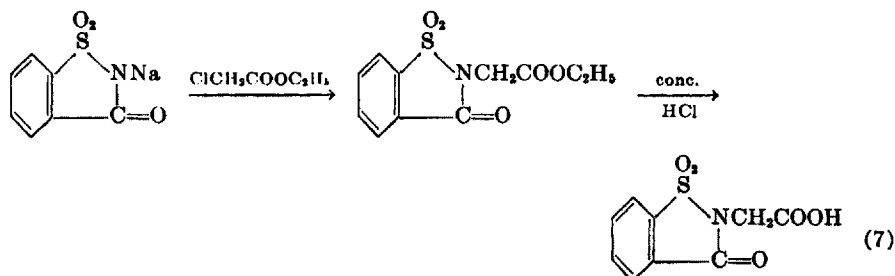
Titration of a boiling aqueous solution of II with dilute alkali formed 2- β -hydroxyethylsaccharin.⁵ 2-(β -*N*-methylanilinoethyl)saccharin⁶ (III) was synthesized with bromoethylmethylaniline and the potassium salt of saccharin (4). Methyl iodide and III yielded a quaternary. Nitrosation gave



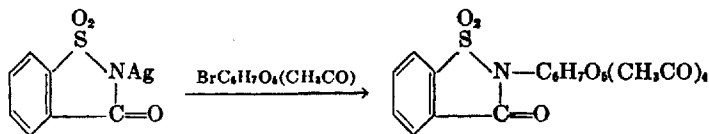
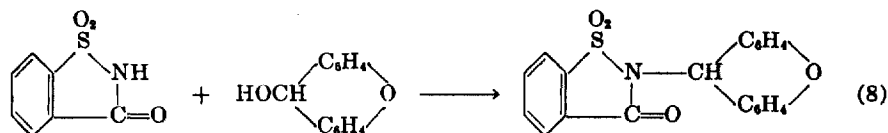
⁵ Eckenroth and Koerppen, *Ber.*, **30**, 1265 (1897).

⁶ Braun, Herder, and Muller, *Ber.*, **51**, 273 (1918).

the *p*-nitroso derivative which was reduced to the amine (5). Formaldehyde and IV produced a high molecular weight diphenylmethane derivative. Eckenroth and Klein⁷ allowed chloroacetone and phenacylbromide to react with sodium saccharinate to obtain the corresponding ketones (6). These ketones formed phenylhydrazones; only the ketone in the side chain reacted. The 2-carbethoxymethyl^{6,8} and 2-carbomethoxymethyl⁵ derivatives were prepared in a similar manner. Hydrolysis with concentrated hydrochloric acid yielded the acid (7).⁸ Saccharin readily condensed with



formaldehyde to give the 2-hydroxymethyl derivative.⁹ To obtain disubstitution, formaldehyde was added to a cold 70% sulfuric acid solution of saccharin.⁵ The methylene bissaccharin precipitated in a small yield, the principal products being *o*-carboxyphenylsulfonic acid and ammonium sulfate. Xanthidrol condensed readily with saccharin in a glacial acetic acid solution to form 2-xanthylsaccharin (8).¹⁰ Josephson^{10a} synthesized



⁷ Eckenroth and Klein, *Ber.*, 29, 329 (1896).

⁸ Magidson and Gorbatschow, *Ber.*, 56, 1810 (1928).

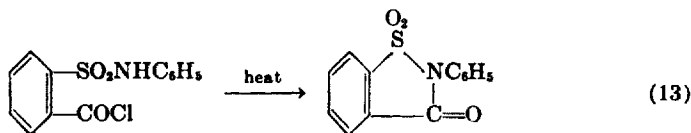
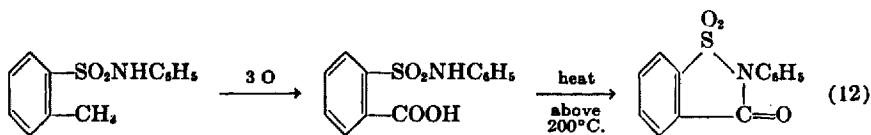
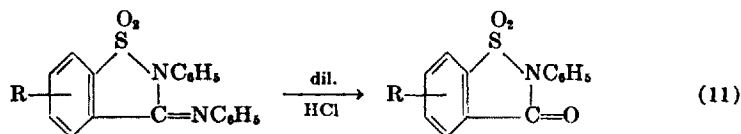
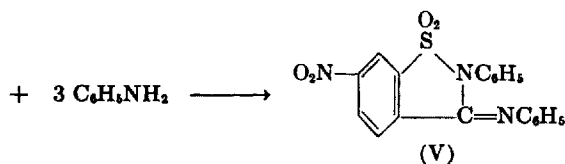
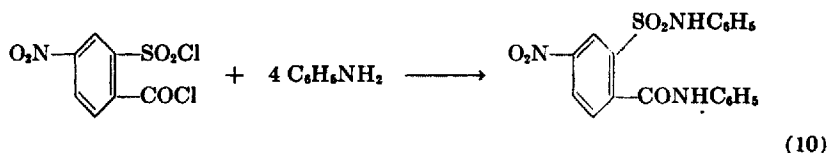
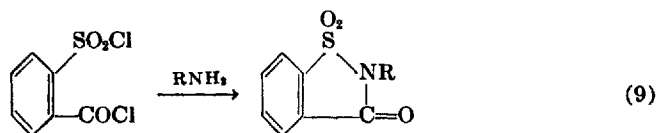
⁹ Masselli, *Chem. Zentr.*, 71, II, 629 (1900); *Gazz. chim. ital.*, 30, 31 (1900).

¹⁰ Fabre, *Bull. soc. chim. France*, 33, 791 (1923).

^{10a} Josephson, *Ber.*, 60, 1822 (1927).

2-(tetraacetylglycosido)saccharin from silver saccharinate and α -bromotetraacetylglucose. Hydrolysis with dilute barium hydroxide or alcoholic ammonia led to 2-*N*-glucosidosulfamylbenzoic acid (8a). 2-Picrylsaccharin⁵ was the only 2-arylsaccharin prepared in this manner.

Remsen and co-workers¹¹⁻¹³ found that 2-alkyl and 2-arylsaccharins could be synthesized with the *o*-chlorocarbonylbenzenesulfonyl chlorides and alkylamines or arylamines (9). This reaction involved a complex mechanism and led to a number of products (10).^{14, 15} In addition, a third



¹¹ Remsen and Coates, *Am. Chem. J.*, **17**, 309 (1895).

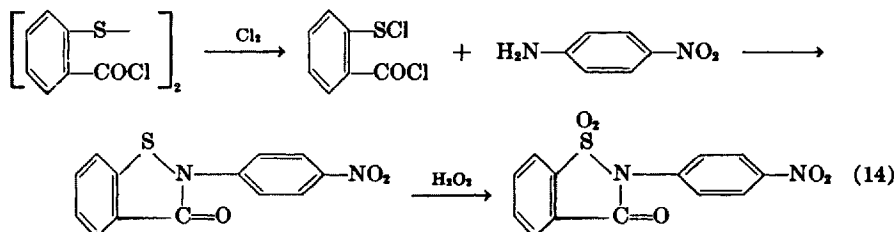
¹² Remsen and Kohler, *Am. Chem. J.*, **17**, 330 (1895).

¹³ Remsen and Clark, *Am. Chem. J.*, **30**, 278 (1903).

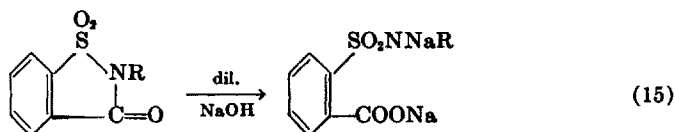
¹⁴ Henderson, *Am. Chem. J.*, **25**, 1 (1901).

¹⁵ Blanchard, *Am. Chem. J.*, **30**, 485 (1903).

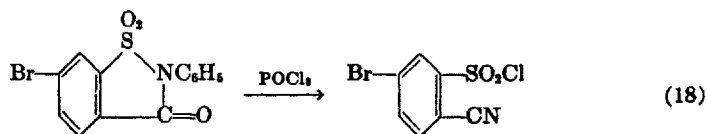
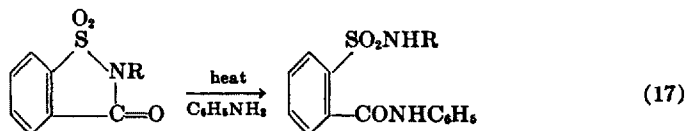
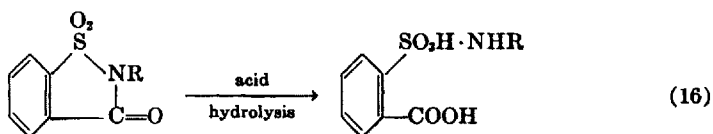
amide of undetermined structure was reported. Hydrolysis of the analogs of compound V yielded 2-arylsaccharins (11). Oxidation of 2-methylphenylsulfonanilide produced 2-carboxyphenylsulfonanilide. Heating this compound induced cyclization, although not quite so readily as saccharin (12).¹² 2-Chlorocarbonylphenylsulfonanilide cyclized easily (13). McClelland and Peters¹⁶ oxidized the 2-substituted 1,2-benzisothiazol-3(2)-one with hydrogen peroxide to obtain the 2-substituted saccharin (14).



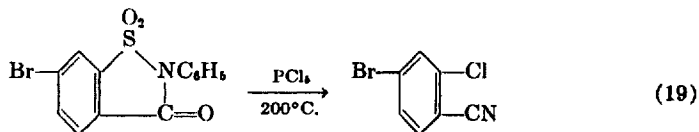
The reactions of 2-alkyl and 2-arylsaccharins were in general analogous to those of saccharin. Alkaline hydrolysis produced the sulfonamide (15).



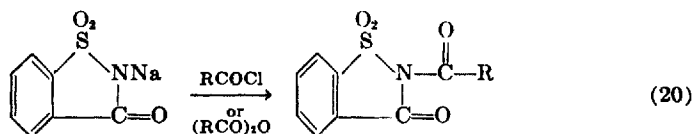
Acid hydrolysis gave the same product as that obtained by similar action on saccharin (16). Treatment with aniline resulted in formation of the diamide (17). Heating 6-bromo-2-phenylsaccharin with phosphorus oxy-



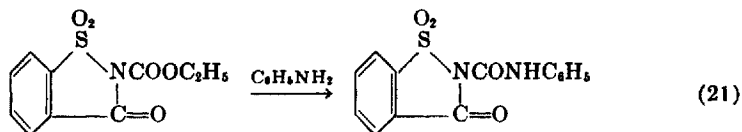
¹⁶ McClelland and Peters, *J. Chem. Soc.*, 1229 (1947).



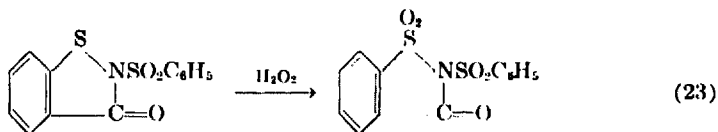
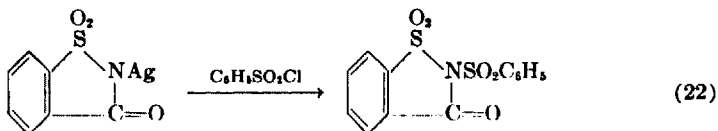
chloride yielded 2-cyano-5-bromophenylsulfonyl chloride,¹⁷ while phosphorus pentachloride gave 4-bromo-2-chlorobenzonitrile (18,19). Hydrolysis of 2-xanthrylsaccharin yielded saccharin.¹⁸ The 2-acyl and 2-aracyl saccharins were prepared with the sodium salt of saccharin and the acyl and aracyl chlorides or the corresponding anhydrides (20). 2-Carbethoxysac-



charin^{19,20} was synthesized with sodium saccharinate and ethyl chloroformate, although some difficulty attended this preparation.²¹ The 2-phenyl-carbamyl derivatives were obtained by heating aniline and *p*-ethoxyaniline (dulcin) in a solvent with 2-carbethoxysaccharin (21).²⁰ A number of long



chain fatty acid derivatives have been synthesized.^{21,22} Acid and alkaline hydrolysis of the 2-acyl saccharins produced saccharin.



¹⁷ Blanchard, *Am. Chem. J.*, **30**, 485 (1903).

¹⁸ Fabre, *Bull. soc. chim. France*, **33**, 791 (1923).

¹⁹ Eckenroth and Koerppen, *Ber.*, **29**, 1048 (1896).

²⁰ Finzi and Colonna, *Gazz. chim. ital.*, **68**, 132 (1938); *Chem. Abstr.*, **32**, 6638 (1938).

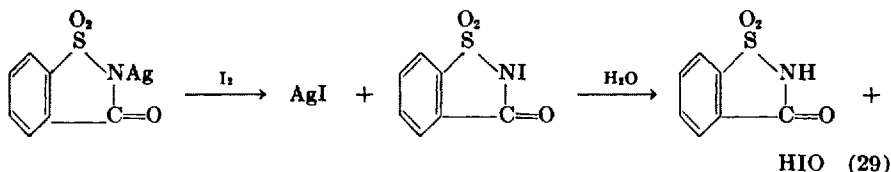
²¹ Magidson and Gorbatschow, *Ber.*, **56**, 1810 (1923).

²² Ford, *Chem. Abstr.*, **32**, 4943 (1938); *Iowa State Coll. J. Sci.*, **12**, 121 (1937).

to give benzyl chloride (27). 2-Chlorosaccharin reacted energetically with cyclohexene²⁷ to give a mixture of saccharin, chlorocyclohexane, 2-(2-chlorocyclohexyl)saccharin and some cyclohexane chlorohydrin (28).

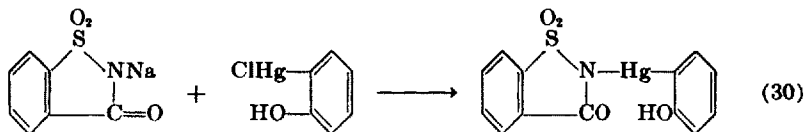
2-Bromosaccharin²⁷ could not be prepared from sodium saccharinate, but it was synthesized from the silver salt in carbon tetrachloride. With cyclohexene it yielded the bromo analogs of the compounds obtained in reaction 28.

Feigl and Chargaff²⁸ attempted to prepare 2-iodosaccharin from silver saccharinate and iodine. A quantitative yield of silver iodide was obtained along with saccharin. They felt that the reaction proceeded as shown in equation (29). Feigl and Bondi,²⁹ in continuing this study, found that a



number of the sulfides such as dibenzylsulfide activated or catalyzed the reaction between silver saccharinate and iodine. 2-Iodosaccharin was prepared in an impure form with powdered silver saccharinate and iodine in absolute ether. It would not react with silver saccharinate to give a bisaccharin. In a benzene solution free iodine and saccharin were gradually liberated.

The phenylmercuric chlorides reacted with sodium saccharinate to yield mercury derivatives (30).^{30,31}



In general, saccharin which was substituted in the 2-position lost its sweet taste. The 2-chloro derivative had a hypochlorite taste.

²⁸ Feigl and Chargaff, *Monatsh.*, **49**, 417 (1928).

²⁹ Feigl and Bondi, *Monatsh.*, **53** and **54**, 498 (1929).

³⁰ Anderson and Hart, *J. Am. Chem. Soc.*, **59**, 1115 (1937).

³¹ Anderson, *Chem. Abstr.*, **31**, 6877 (1937); U. S. Pat. 2,087,959.

TABLE LXII. Preparation of the 2-Substituted Saccharins Without Substituents in the Benzene Ring. (Compounds included in this table were prepared using saccharin or its salts and an alkylating agent, an acylating agent, a halogen, etc. Simple derivatives of these compounds are designated with a small letter.)

No.	Substituents on the 2-position of saccharin	Ref.	Solubility	M.p., °C.
1	Methyl	1	alc.	128-9
		2	—	129
		—	—	129
		4	—	130
		5	—	132
2	Hydroxymethyl	6, 7	alc.	225
3	Methylenebis	8	—	290
4	Ethyl	2	alc.	94
		3	acetone	94
		9	benzene	94
		5	—	94
5	Bromoethyl	10	alc.	96
		5	—	99
5a	Hydroxyethyl	8	alc.	183
6	Phenoxyethyl	8	alc., benzene	81-2
7	<i>N</i> -Methylanilinoethyl	11	alc.	115
7a	<i>N</i> -Methylanilinoethyl methyl iodide	11	alc.	150
7b	<i>p</i> -Nitroso- <i>N</i> -methylanilinoethyl	11	—	190
7c	<i>p</i> -Amino- <i>N</i> -methylanilinoethyl	11	—	111-2
8	Ethylene α, β -bissaccharin	8	acetic acid	245-6
9	Carbomethoxymethyl	8	—	118
10	Carbethoxymethyl	8	—	104
		4	—	107
10a	Carboxymethyl	4	water	212-5
11	<i>n</i> -Propyl	5	alc.	74
12	Isopropyl	5	alc.	134
13	Allyl	5	alc.	98
14	Dihydroxypropyl	12	water	—
15	Tetracetylglucosido	23	methanol, ethanol	154
16	Acetonyl	13	water, alc., benzene	143
16a	Acetonyl, phenylhydrazone	13	alc., benzene	166
16b	α -Bromoacetonyl ?	13	alc.	168
17	Phenacyl	13	alc., acetic acid, ether	194-5
17a	Phenacyl, phenylhydrazone	13	alc., acetic acid	168
18	<i>n</i> -Butyl	5	alc.	38-9.5
19	Isobutyl	5	alc.	75
20	<i>sec</i> -Butyl	5	alc.	81
21	<i>n</i> -Amyl	5	alc.	58
22	Benzyl	10	alc.	118
		5	—	110-1
23	<i>p</i> -Nitrobenzyl	10	alc., acetic acid	175.5-176
		5	benzene	175.5
24	Picryl	8	acetic acid	262
25	Xanthrydryl	14	benzene, toluene	199-200
26	Carbethoxy	8	alc., ether	136
26a	Phenylcarbamy	15	alc.	190-5 dec.
26b	<i>p</i> -Ethoxyphenylcarbamy	15	alc.	156
27	Acetyl	10	alc., water	193
28	Lauroyl	16	CHCl ₃	88-9
29	Myristoyl	16	CHCl ₃	90-1
30	Palmitoyl	16	CHCl ₃	90
31	Stearoyl	16	CHCl ₃	95

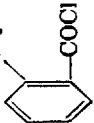
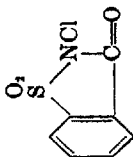
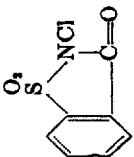
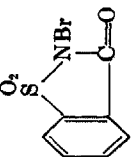
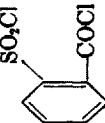
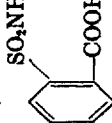
(Table continued)

TABLE LXII (Concluded)

No.	Substituents on the 2-position of saccharin	Ref.	Solubility	M. p., °C.
32	Oleoyl	16	CHCl ₃	oil
33	Benzoyl	8	alc.	165
34	Phenylsulfonyl	17	alc.	202
35	Chloro	18	acetic acid, CHCl ₃	152
		4	—	—
		19	—	—
36	Bromo	19	—	—
37	Iodo	20	—	—
38	Phenylmercuri	21	—	212
39	<i>o</i> -Hydroxyphenylmercuri	22	alc.	242-3

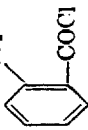
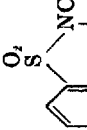
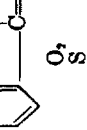
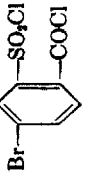
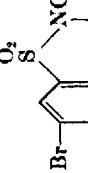
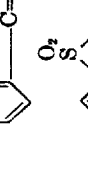
¹ Remsen and Palmer, *Am. Chem. J.*, **8**, 226 (1886).² Remsen and Clark, *Am. Chem. J.*, **30**, 278 (1903).³ Brackett, *Am. Chem. J.*, **9**, 496 (1887).⁴ Magidson and Gorbatschow, *Ber.*, **56**, 1810 (1923).⁵ Merritt, Levey, and Cutter, *J. Am. Chem. Soc.*, **61**, 15 (1939).⁶ Masselli, *Chem. Zentr.*, **71**, II, 629 (1900); *Gazz. chim. ital.*, **30**, 31 (1900).⁷ Parmeggiani, *Chem. Zentr.*, **79**, I, 1389 (1908); *Boll. chim. farm.*, **47**, 37 (1908).⁸ Eckenroth and Koerppen, *Ber.*, **30**, 1265 (1897).⁹ Fahlberg and List, *Ber.*, **20**, 1596 (1887).¹⁰ Eckenroth and Koerppen, *Ber.*, **29**, 1048 (1896).¹¹ Braun, Heider, and Muller, *Ber.*, **51**, 273 (1918).¹² Jones and Halpern, *J. Am. Pharm. Assoc. Sci.*, **36**, 376 (1947).¹³ Eckenroth and Klein, *Ber.*, **29**, 329 (1885).¹⁴ Fabre, *Bull. soc. chim. France*, **33**, 791 (1923).¹⁵ Finzi and Colonna, *Gazz. chim. ital.*, **68**, 132 (1938); *Chem. Abstr.*, **32**, 6638 (1938).¹⁶ Ford, *Chem. Abstr.*, **32**, 4943 (1938); *Iowa State Coll. J. Sci.*, **12**, 121 (1937).¹⁷ Hart, McClelland, and Fowkes, *J. Chem. Soc.*, **1938**, 2114.¹⁸ Chattaway, *J. Chem. Soc.*, **87**, 1882 (1905).¹⁹ Zeigler, Späth, Schaaf, Schuman, and Winkelmann, *Ann.*, **551**, 80 (1942).²⁰ Feigl and Bondi, *Monatsh.*, **53** and **54**, 498 (1929).²¹ Anderson, *Chem. Abstr.*, **31**, 6827 (1937); U. S. Pat. 2,087,959.²² Anderson and Hart, *J. Am. Chem. Soc.*, **59**, 1115 (1937).²³ Josephson, *Ber.*, **60**, 1822 (1927).

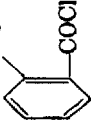
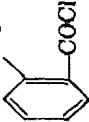
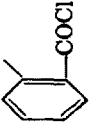
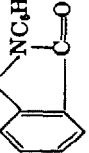
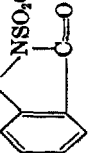
TABLE LXIII. Preparation of the 2-Substituted Saccharins by Methods Other Than That Given in Table LXII

No.	Substituents in the saccharin ring	Ref.	Method of preparation	Solubility	M.p., °C.
1	2-Methyl	1	 $+ \text{CH}_3\text{NH}_2$	alc.	129
2	2-(2-Chlorocyclohexyl)	2	 $+ \text{CH}_3\text{OH}$	—	130
3	2-(2-Chlorocyclohexyl)	3	 $+ \text{C}_6\text{H}_{11}$	acetic acid	169
3	2-(2-Bromocyclohexyl)	3	 $+ \text{C}_6\text{H}_{11}$	acetic acid	128
4	2-Phenyl	4	 $+ \text{C}_6\text{H}_5\text{NH}_2$	alc., ether	190.5
5		5	 with heat	—	190

(Table continued)

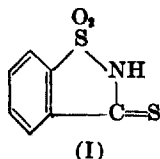
TABLE LXIII. (Continued)

No.	Substituents in the saccharin ring	Ref.	Method of preparation	Solubility	M.p., °C.
4	2-Phenyl (continued)				
5		5	 $\text{SO}_2\text{NHC}_6\text{H}_5$ with heat	—	—
6		6	 $\text{SO}_2\text{NHC}_6\text{H}_5$ + dil. HCl	—	—
7		7	 $\text{SO}_2\text{NHC}_6\text{H}_5$ + dil. HCl	—	189-90
8		3	 $\text{SO}_2\text{NHC}_6\text{H}_5$ + $\text{C}_6\text{H}_5\text{COCl}$	—	—
5	6-Bromo-2-phenyl	8	 $\text{SO}_2\text{NHC}_6\text{H}_5$ + $\text{C}_6\text{H}_5\text{NH}_2$ alc., acetone, benzene	alc., acetone, benzene	184.5
8		8	 $\text{SO}_2\text{NHC}_6\text{H}_5$ + dil. HCl	—	—
6	6-Nitro-2-phenyl	9	 $\text{SO}_2\text{NHC}_6\text{H}_5$ + HCl	alc., acetic acid	183

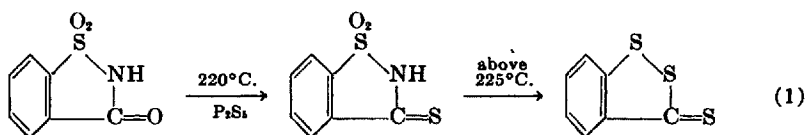
No.	Substituent in the saccharin ring	Ref.	Method of preparation	Solubility	M.p., °C.
7	2- <i>o</i> -Tolyl	4	 SO_2Cl $+ o\text{-CH}_3\text{C}_6\text{H}_4\text{NH}_2$	alc.	172-4
8	2- <i>m</i> -Tolyl	4	 SO_2Cl $+ m\text{-CH}_3\text{C}_6\text{H}_4\text{NH}_2$	alc.	147.5
9	2- <i>p</i> -Tolyl	4	 SO_2Cl $+ p\text{-CH}_3\text{C}_6\text{H}_4\text{NH}_2$	alc.	195.5
10	2- <i>p</i> -Nitrophenyl	10	 SO_2Cl $+ p\text{-CH}_3\text{C}_6\text{H}_4\text{NH}_2$	acetic acid	229
11	2-Phenylsulfonyl	11	 SO_2Cl $+ \text{H}_2\text{O}_2$	alc.	202
12	2- <i>p</i> -Tolylsulfonyl	11	 SO_2Cl $+ \text{H}_2\text{O}_2$	alc.	214

¹ Remsen and Clark, *Am. Chem. J.*, 30, 278 (1903).² Magidson and Gorbatschow, *Ber.*, 56, 1810 (1923).³ Zeigler, Späth, Schaal, Schuman, and Winkelman, *Ann.*, 551, 80 (1942).⁴ Remsen and Coates, *Am. Chem. J.*, 17, 309 (1895).⁵ Remsen and Kohler, *Am. Chem. J.*, 17, 330 (1895).⁶ Remsen and Hunter, *Am. Chem. J.*, 18, 809 (1896).⁷ List and Stein, *Ber.*, 31, 1648 (1898).⁸ Blanchard, *Am. Chem. J.*, 30, 485 (1903).⁹ Henderson, *Am. Chem. J.*, 25, 1 (1901).¹⁰ McClelland and Peters, *J. Chem. Soc.*, 1947, 1229.¹¹ Bartlett, Hart, and McClelland, *J. Chem. Soc.*, 1939, 760.

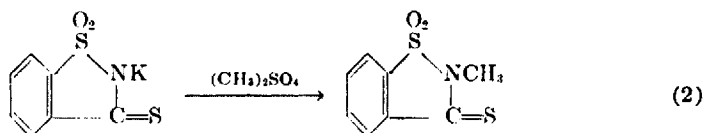
Thiosaccharin or 2,3-Dihydro-1,2-benzisulfonazol-3(2)-thione (I)



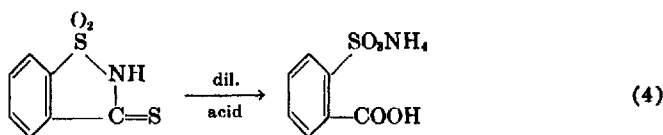
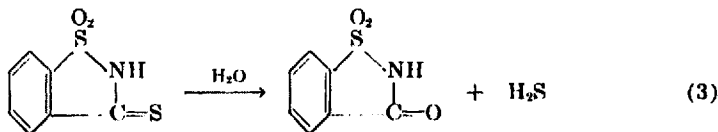
Mannessier¹ prepared thiosaccharin by heating saccharin with phosphorus pentasulfide. Heating at slightly higher temperatures converted the saccharin to 1,2-benzodithiol-3-thione (1).² 2-Methyl thiosaccharin



was synthesized with dimethyl sulfate and thiosaccharin in the presence of alkali (2).



Thiosaccharin is a comparatively unstable compound. It was hydrolyzed by water to saccharin and by dilute acid to the ammonium salt of *o*-carboxyphenylsulfonic acid (3,4). Dilute alkaline carbonates caused hydrolysis to saccharin, while dilute alkali produced *o*-carboxyphenyl-



¹ Mannessier, *Gazz. chim. ital.*, **45**, 540 (1915).

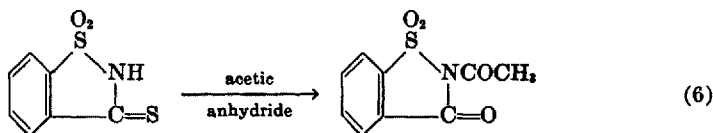
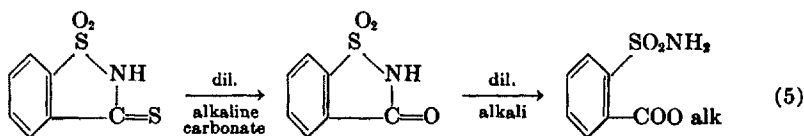
² Mannessier, *Gazz. chim. ital.*, **46**, 231 (1916).

TABLE LXIV. Preparation of the Thiosaccharins

No.	Name	Ref.	Solubility	M.p., °C.
1	Thiosaccharin	1	cold pyridine	180 dec.
2	2-Methylthiosaccharin	1	alc., benzene	221

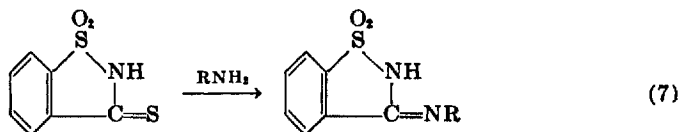
¹ Mannessier, *Gazz. chim. ital.*, **45**, 540 (1915).

phenylsulfonamide (5). An alcoholic solution of potassium iodide also yielded saccharin from thiosaccharin. Acetylation gave 2-acetylsaccharin (6). Nitric acid produced a nitro compound of unknown structure.



Meadow and Cavagnol¹⁰ prepared the *S*-methyl- and *S*-ethyl- as well as the 2-methyl- and 2-ethylthiosaccharins.

In a series of papers, Mannessier-Mameli found that various amines would react readily with thiosaccharin to give the 3-amino-1,2-benzisulfonazoles (7). These amines included ammonia,^{3,4} hydroxylamine,⁵



hydrazine,⁶ phenylhydrazines,⁷ semicarbazide,⁸ and arylamines.⁹ (These reactions are discussed fully under the 3-amino-1,2-benzisulfonazoles.)

³ Mameli and Mannessier-Mameli, *Gazz. chim. ital.*, **70**, 855 (1940); *Chem. Abstr.*, **36**, 1026 (1942).

⁴ Mannessier-Mameli, *Gazz. chim. ital.*, **71**, 3 (1941); *Chem. Abstr.*, **36**, 1028 (1942).

⁵ Mannessier-Mameli, *Gazz. chim. ital.*, **62**, 1067 (1932); *Chem. Abstr.*, **27**, 2682 (1933).

⁶ Mannessier-Mameli, *Gazz. chim. ital.*, **71**, 18 (1941); *Chem. Abstr.*, **36**, 1029 (1942).

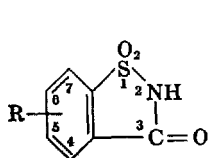
⁷ Mannessier-Mameli, *Gazz. chim. ital.*, **71**, 596 (1941); *Chem. Abstr.*, **37**, 100 (1943).

⁸ Mannessier-Mameli, *Gazz. chim. ital.*, **71**, 25 (1941); *Chem. Abstr.*, **36**, 1030 (1942).

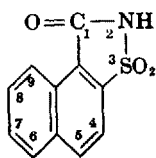
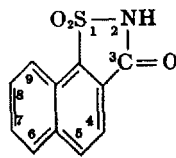
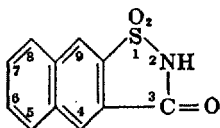
⁹ Mannessier-Mameli, *Gazz. chim. ital.*, **65**, 69 (1935); *Chem. Abstr.*, **29**, 3999 (1935).

¹⁰ Meadow and Cavagnol, *J. Org. Chem.*, **16**, 1582 (1951).

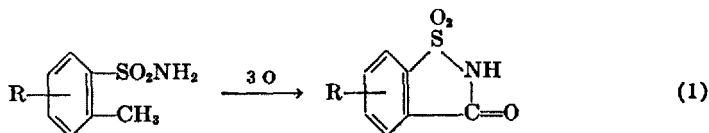
**Saccharin Derivatives Substituted in the Benzene Ring
or the 2,3-Dihydro-1,2-Benzisotiazol-3(2)-ones (I)
and Condensed Systems (II, III, and IV)**



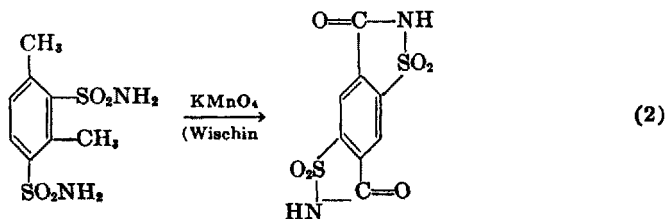
(I)

(II *Ring Index* No. 1544)(III *Ring Index* No. 1541)(IV *Ring Index* No. 1539)

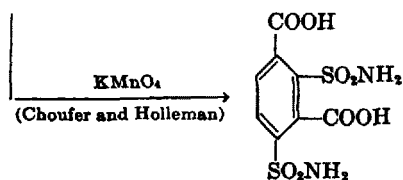
In general, the methods used for the preparation of saccharin were utilized for the synthesis of these derivatives. The oxidation of an *o*-methylphenylsulfonamide was employed to prepare a number of compounds which included alkyl, aryl, carboxy, halogen, nitro, sulfamyl, sulfonyl, methoxy, and acetamido saccharins and disaccharin (1). In some instances oxidation does not appear to give the isosulfonazole ring. Wischin¹ oxidized the 1,3-xylyl-2,4-disulfonamide and obtained a compound which he



(1)



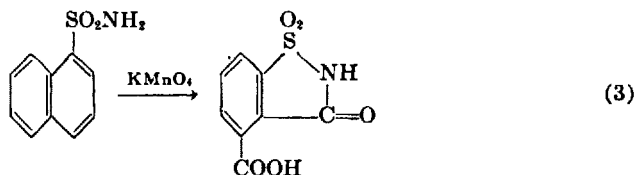
(2)



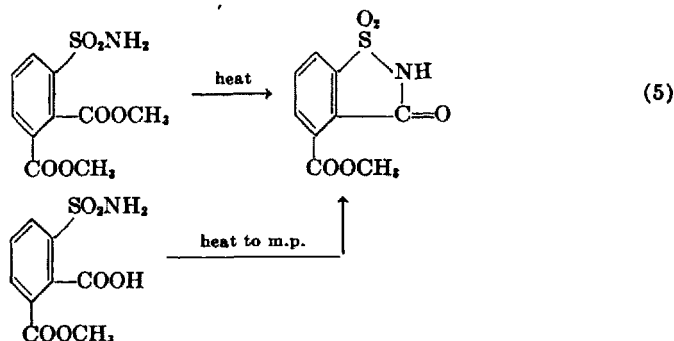
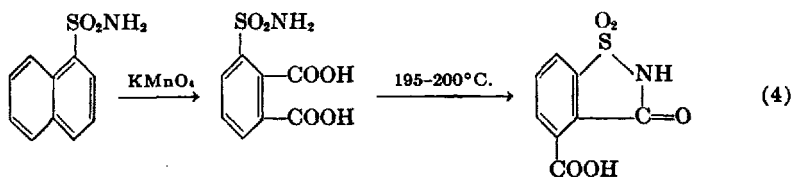
¹ Wischin, *Ber.*, 23, 3113 (1890).

believed to be benzo[1.2-*d*, 3.4-*d'*]benzisosulfonazole. Choufer² and Holleman³ in attempting to repeat this work, obtained only the 2,4-disulfamyl-1,3-toluic acid (2). Choufer's proof of structure consisted of titrating the compound using methyl red as an indicator.² Holleman³ was unable to obtain any saccharin derivative from 1,3-xylyl-2,4-disulfonamide, 1,4-xylyl-2,5-disulfonamide, and 1,4-xylyl-2,6-disulfonamide.

4-Carboxysaccharin appeared to be a special case. Oxidation of α -naphthylsulfonamide with potassium permanganate yielded 4-carboxysaccharin along with some phthalic, oxalic, and sulfuric acids (3).^{4,5} Zincke



and Schürmann,⁶ on oxidizing α -naphthylsulfonamide, obtained the 3-sulfamylphthalic acid, which on heating to 195–200°C. produced 4-carboxysaccharin (4). The methyl and ethyl esters⁶ were prepared in a similar manner (5). A novel method of synthesis of 4-carboxysaccharin was the



² Choufer, *Chem. Abstr.*, 19, 2195 (1925); *Verslag Gewone Vergader. Afdeel. Natuurk. Nederland. Akad. Wetenschap.*, 33, 999 (1924).

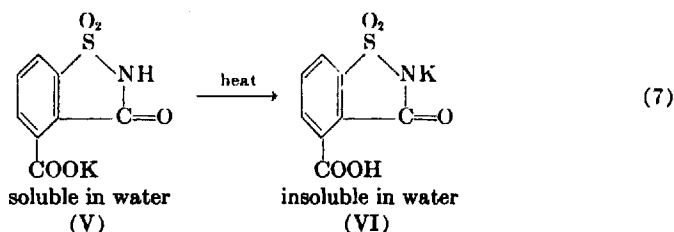
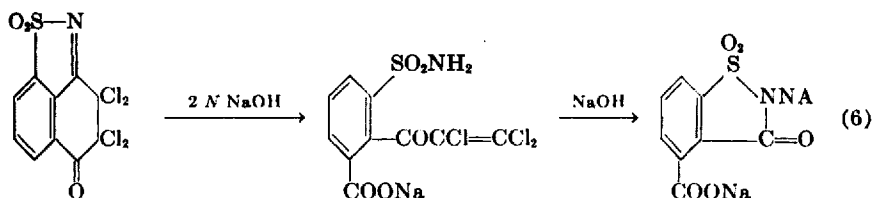
³ Holleman, *Chem. Abstr.*, 24, 85 (1930); *Anales soc. españ. fis. y quim.*, 27, 473 (1929).

⁴ Remsen and Comstock, *Am. Chem. J.*, 5, 106 (1883–4).

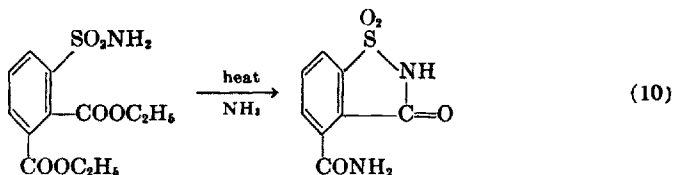
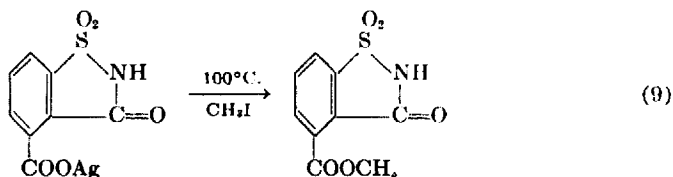
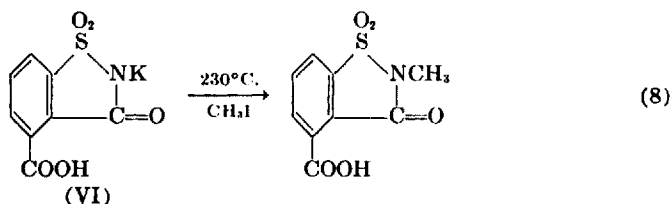
⁵ Remsen and Stokes, *Am. Chem. J.*, 6, 260 (1884–5).

⁶ Zincke and Schurmann, *Ann.*, 416, 65 (1913).

alkaline hydrolysis of 2,2,3,3-tetrachloro-1,8-naphthasultam-4-quinone, which took place as shown in equation (6).⁷ It was claimed that 4-carboxy-saccharin had two different potassium salts.^{6,7} Heating one of them gave the other salt (7). Heating VI with methyl iodide yielded the 2-methyl



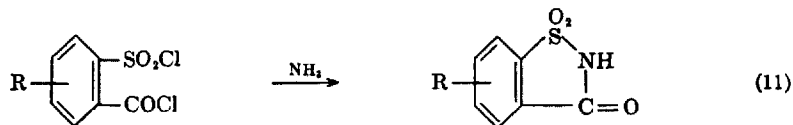
derivative. The neutral silver salt and methyl iodide formed the methyl ester (8,9). Moulton⁸ prepared the 4-carbamyl derivative by heating diethyl 3-sulfamylphthalate with ammonia (10).



⁷ Zincke and Greune, *Ann.*, **427**, 221 (1925).

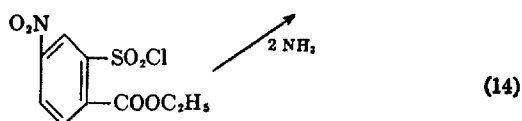
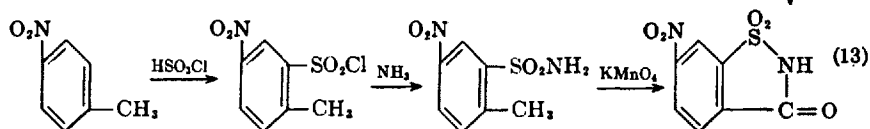
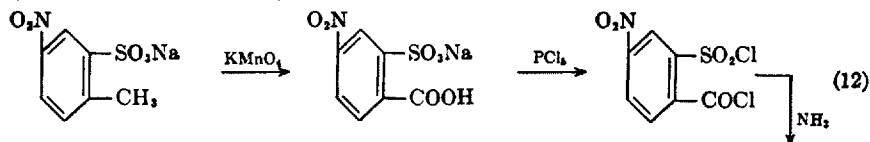
⁸ Moulton, *Am. Chem. J.*, **13**, 193 (1891).

A second method of synthesizing the benzene ring substituted saccharins consisted of ring closure of the *o*-chlorocarbonylphenylsulfonyl chloride with ammonia or primary amines (11). This synthesis has been



used to prepare 5,7-dimethyl, 5- and 6-nitro, 6-bromo-2-phenyl, 6-nitro-2-phenyl, 5-methyl-6-nitro, 5-methyl-6-nitro-2-phenyl, and 6-carbamyl-saccharins.

Sometimes a number of methods were employed to obtain the same compound. For example, 6-nitrosaccharin⁹⁻¹² has been synthesized according to the following diagrams (12-14).



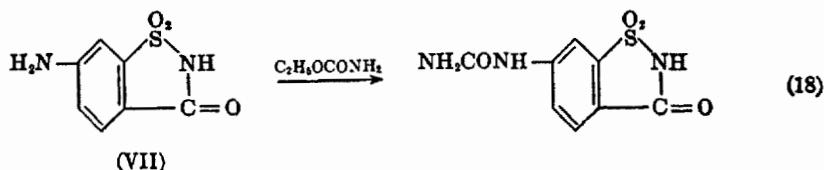
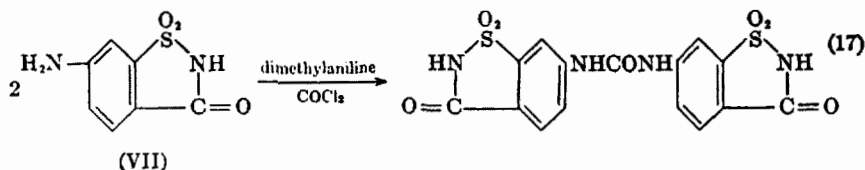
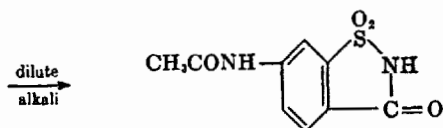
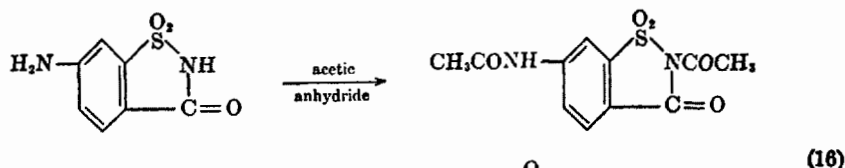
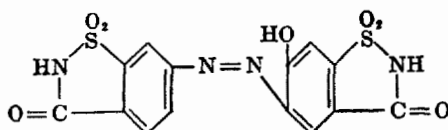
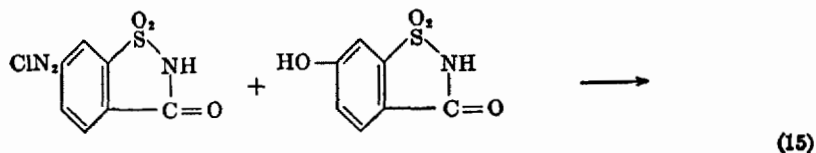
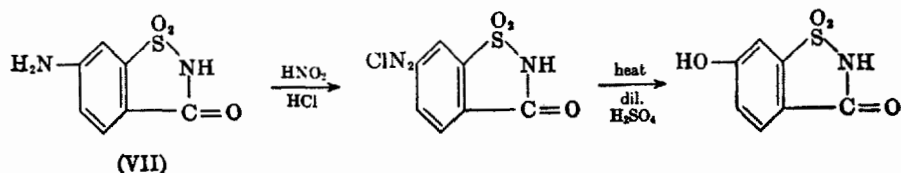
6-Nitrosaccharin was the starting material for a number of derivatives of 6-aminosaccharin.¹² Reduction with ammonium polysulfide yielded 6-aminosaccharin, which compound gave the typical reactions of an aromatic amine. Diazotization gave rise to the diazonium salt, which was readily decomposed to the 6-hydroxysaccharin. This diazonium compound was coupled to a molecule of 6-hydroxysaccharin (15). Acetylation of VII produced 2-acetyl-6-acetamidosaccharin. Mild alkaline hydrolysis formed 6-acetamidosaccharin (16). The 6,6'-ureylendisaccharin was synthesized from 6-aminosaccharin and phosgene in the presence of dimethylaniline (17). Compound VII and ethylurethan formed 6-ureidosaccharin (18). One equivalent of ethyl chloroformate and 6-aminosaccharin produced the urethan in the 6-position. An excess gave the 2-carbethoxy-6-carbethoxy-

⁹ Noyes, *Am. Chem. J.*, 8, 169 (1886).

¹⁰ Kastle, *Am. Chem. J.*, 11, 181 (1889).

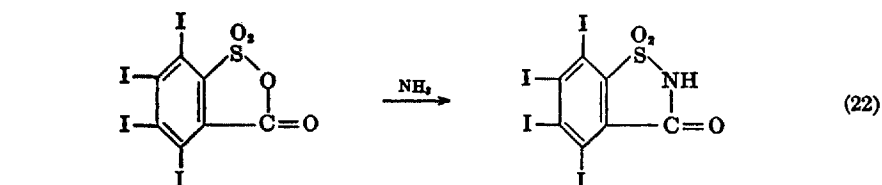
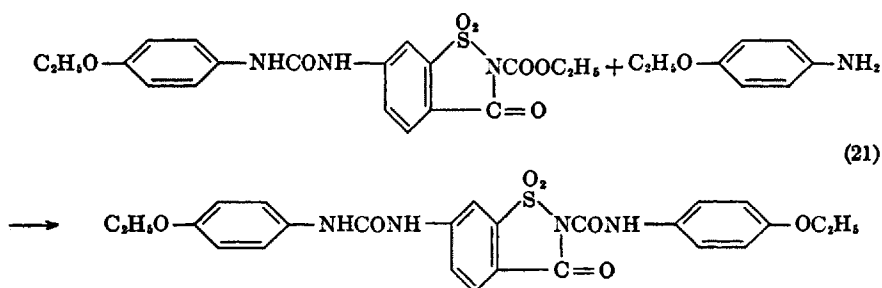
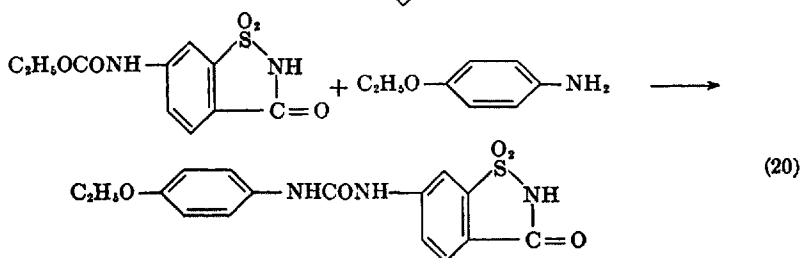
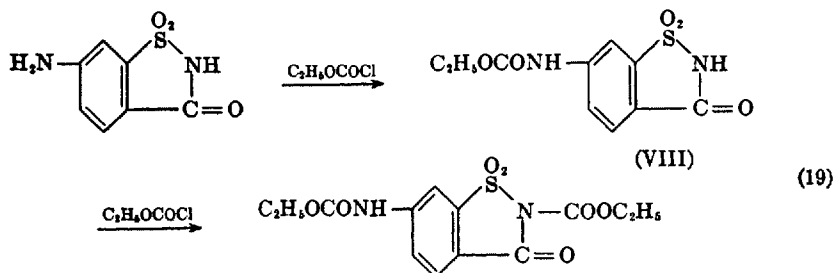
¹¹ Remsen and Gray, *Am. Chem. J.*, 19, 496 (1897).

¹² Finzi and Colonna, *Gazz. chim. ital.*, 68, 132 (1938); *Chem. Abstr.*, 32, 6638 (1938).



aminosaccharin (19). Compound VIII and *p*-phenetidine yielded 6-*p*-ethoxyphenylureylenesaccharin (20). 2-*p*-Ethoxyphenylcarbonyl-6-*p*-ethoxyphenylureylenesaccharin was prepared as shown in equation (21).

A number of the variations of the closure of *o*-sulfobenzoic acids have been used to prepare saccharin derivatives. Tetraiodosaccharin was syn-



thesized from tetraiodosulfobenzoic anhydride and ammonia.¹³ This compound was insoluble in alkali (22). 6-Bromosaccharin¹⁴ and the naphthalene analogs^{15,16} have been prepared from the *o*-cyanosulfonyl chloride derivatives and ammonia, giving the *o*-cyanosulfonamides or 3-aminoisotriazole derivatives (23). 6-Bromo-2-phenylsaccharin,¹⁷ 6-*o*-biphenyl-

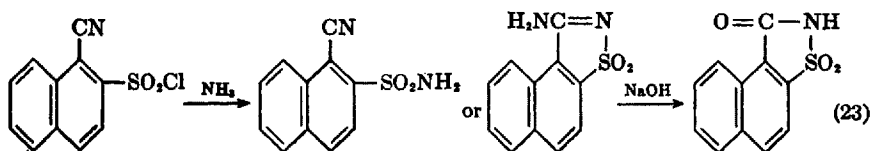
¹³ Boyd and Row, *J. Am. Chem. Soc.*, **52**, 4954 (1930).

¹⁴ Kreis, *Ann.*, **286**, 377 (1895).

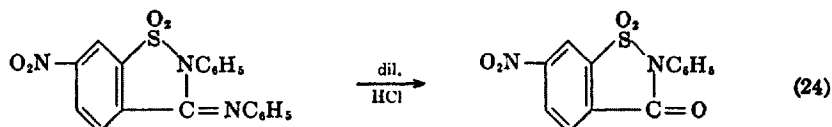
¹⁵ Kalcher, *Ann.*, **414**, 244 (1918).

¹⁶ Kaufmann and Zobel, *Ber.*, **55**, 1499 (1922).

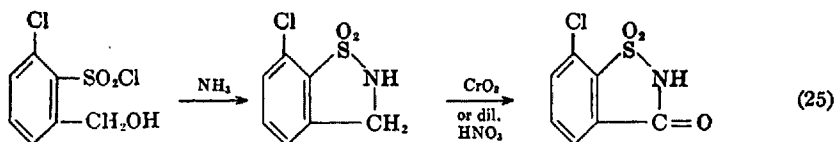
¹⁷ Blanchard, *Am. Chem. J.*, **30**, 485 (1903).



saccharin,¹⁸ and 6-nitro-2-phenylsaccharin¹⁹ have also been synthesized by hydrolysis of the corresponding phenylimine or imine (24). Reissert and



Cramer²⁰ allowed ammonia to react with 2-chloro-6-hydroxymethylphenylsulfonyl chloride. The 7-chloro-2,3-dihydro-1,2-benzisosulfonazole was then oxidized to 7-chlorosaccharin with dilute HNO_3 or H_2CrO_4 (25).



A great many of these substituted saccharins possess some sweet taste, although the predominant taste is bitter. None of them have a greater sweetness than saccharin. Saccharin with a low molecular weight substituent such as a hydroxy, a methyl, or a fluoro group on the benzene ring retains the greatest amount of sweetness. DeRoode²¹ showed that as the atomic weight of halogen in the 6-position increased sweetness decreased:

saccharin		very sweet, no bitterness.
6-fluorosaccharin		very sweet, slightly bitter.
6-chlorosaccharin		sweet, very bitter.
6-bromosaccharin		sweet, bitter.
6-iodosaccharin		no sweetness, slightly bitter.

Sweetness also varies as to the position of the group in the benzene ring. 5-, 6-, and 7-chlorosaccharins are sweet, while 4-chlorosaccharin is about one-half as sweet as saccharin, with a somewhat astringent taste. The substitution of another group having a sweet taste (dulcin²²) in the saccharin molecule decreased the sweetness. Since there is no way to measure taste physically these data must remain inconclusive.

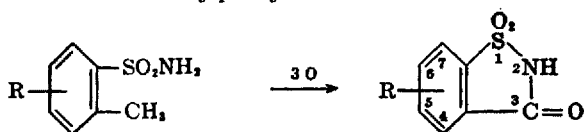
¹⁸ Allen and Burness, *J. Org. Chem.*, **14**, 163 (1949).

¹⁹ Henderson, *Am. Chem. J.*, **25**, 1 (1901).

²⁰ Reissert and Cramer, *Ber.*, **61**, 2555 (1938).

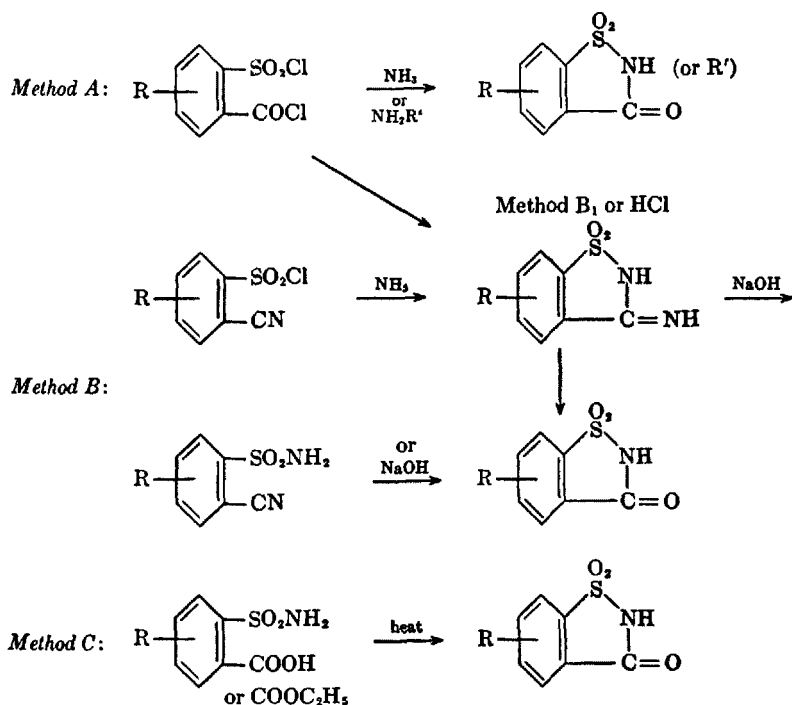
²¹ De Roode, *Am. Chem. J.*, **13**, 217 (1891).

²² Finzi and Colonna, *Gazz. chim. ital.*, **68**, 132 (1938); *Chem. Abstr.*, **32**, 6638 (1938).

TABLE LXV. Saccharins Substituted in the Benzene Ring and Prepared by the Oxidation of an *o*-Methylphenylsulfonamide

No.	Substituent on saccharin molecule	Ref.	Taste (degree of sweetness is not given)	Solubility	M.p., °C.
1	6-Methyl	1	sweet	water, acetic acid	249-50
		2	—	alc., benzene	246
2	5,7-Dimethyl	8	—	water, alc.	255-62
3	6-Fluoro	3	sweet, sl. bitter	water	—
4	4-Chloro	4	sweet, astringent	acetone	210-2
5	5-Chloro	5/6	sweet, bitter	—	—
6	6-Chloro	3	sweet, very bitter	water	—
7	6-Bromo	3,7	sweet, bitter	water	217
8	6-Iodo	3	no sweetness, sl. bitter	water	—
9	5-Methoxy	9	bitter	acetone	242
10	7-Methoxy	9	bitter	alc.	227-8 dec.
11	5,6-Dimethoxy	10	acid, bitter	acetic acid	290
12	5-Acetamido	11	—	alc.	299
13	6-Nitro	12	very bitter	alc.	209
14	4-Carboxy (from α -naphthylsulfonamide)	13, 14	—	water	2 H ₂ O, 155-60
15	5-Carboxy	15, 16	—	—	—
		17, 18	—	water	289
16	6-Carboxy	19, 20	—	water	—
		21	—	—	297-9
		22	—	—	284
17	7-Carboxy-5-methyl	23	—	—	279
18	5-Carboxy-7-methyl	24	—	—	—
19	6-Sulfamyl	25	—	water, alc.	285
20	6,6'-Sulfonyl	26	—	alc.	—
21	6,6'-Disaccharin	27	tasteless	—	—

¹ Randall, *Am. Chem. J.*, **13**, 256 (1891). ² Weber, *Ber.*, **25**, 1737 (1892). ³ De Roode, *Am. Chem. J.*, **13**, 217 (1891). ⁴ Davies, *J. Chem. Soc.*, **119**, 876 (1921). ^{5/6} Gerver, *Chem. Abstr.*, **16**, 1572 (1922); *Verslag. Gewone Vergader. Afdel. Natuurk. Nederland Akad. Wetenschap.*, **30**, 236 (1922). ⁷ Remsen and Bayley, *Am. Chem. J.*, **9**, 229 (1887). ⁸ Hall and Remsen, *Am. Chem. J.*, **2**, 130 (1880-1). ⁹ Haworth and Lapworth, *J. Chem. Soc.*, **125**, 1299 (1924). ¹⁰ Brown and Robinson, *J. Chem. Soc.*, **111**, 952 (1917). ¹¹ Backeberg and Marais, *J. Chem. Soc.*, **1943**, 78. ¹² Noyes, *Am. Chem. J.*, **8**, 169 (1886). ¹³ Remsen and Comstock, *Am. Chem. J.*, **5**, 106 (1883-4). ¹⁴ Remsen and Stokes, *Am. Chem. J.*, **6**, 260 (1884-5). ¹⁵ Iles and Remsen, *Ber.*, **11**, 462, 888 (1878). ¹⁶ Remsen and Coale, *Am. Chem. J.*, **3**, 209 (1881). ¹⁷ Jacobsen, *Ber.*, **11**, 17 (1878). ¹⁸ Jacobsen, *Ber.*, **13**, 1554 (1880). ¹⁹ Remsen and Hall, *Am. Chem. J.*, **2**, 50 (1880-1). ²⁰ Hall and Remsen, *Ber.*, **12**, 1434 (1879). ²¹ Noyes and Walker, *Am. Chem. J.*, **9**, 97 (1887). ²² Weber, *Ber.*, **25**, 1737 (1892). ²³ Hall and Remsen, *Am. Chem. J.*, **2**, 130 (1880-1). ²⁴ Jacobsen, *Ann.*, **206**, 180 (1881). ²⁵ Fahlberg, *Am. Chem. J.*, **2**, 181 (1880-1). ²⁶ Pollak *et al.*, *Monatsh.*, **55**, 358 (1930). ²⁷ Harding, *J. Soc. Chem. Ind.*, **44**, 138T (1925).

TABLE LXVI. Saccharin Substituted in the Benzene Ring and Prepared by Ring Closure of an *o*-Sulfamylbenzoic Acid or a Derivative of This Acid

No.	Name or substituent on the saccharin molecule	Ref.	Method of preparation	Taste	Solubility	M.p., °C.
1	5,7-Dimethyl	1	A	—	water	287–8
2	6-Bromo	2	A	sweet, bitter	—	—
		3	B	—	—	227.5
3	4,5,6,7-Tetraiodo	4	A (from anhydride)	faint, bitter	acetone	above 345
4	6-Bromo-2-phenyl	2	A	—	alc., benzene	184.5
		2	B ₁	—	—	—
5	5-Nitro	5	A	intense bitter sweet after-taste	water, alc.	—
6	6-Nitro	6	A	bitter	alc.	—
		7	modification of C	—	alc.	209
7	6-Nitro-2-phenyl	9	A-B	—	alc., acetic acid	183

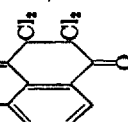
TABLE LXVI (Continued)

No.	Name or substituent on the saccharin molecules	Ref.	Method of preparation	Taste	Solubility	M.p., °C.
8	5-Methyl-6-nitro	8	A	—	alc.	213.5
9	5-Methyl-6-nitro-2-phenyl	8	A	—	alc.	203-5
10	5-Methoxy	10	A	bitter	acetone	242
11	4-Carboxy	11	C	—	alc., acetic acid	slow 240-5; fast 275-6
12	4-Carbomethoxy	12	C	—	benzene	184-5
13	4-Carbethoxy	12	C	—	—	—
14	4-Carbamyl	13	C	—	—	275
15	6-Carbamyl	14	A	—	water	—
16	6- <i>o</i> -Biphenyl	15	B	—	methanol	244.5-247.5
17	Naphth[1.2- <i>d</i>]isosulfonylazole (complete name)	16	B	—	alc.	sinters 240-4
18	Naphth[2.1- <i>d</i>]isosulfonylazole (complete name)	17	B	bitter	alc.	294
		17	B	bitter	alc., acetone	267 dec.
19	Naphth[2.3- <i>d</i>]isosulfonylazole (complete name)	17	A	bitter	—	288

¹ Remsen and Brown, *Am. Chem. J.*, **3**, 216 (1881-2).² Blanchard, *Am. Chem. J.*, **30**, 485 (1903).³ Kreis, *Ann.*, **286**, 377 (1895).⁴ Boyd and Rowe, *J. Am. Chem. Soc.*, **52**, 4954 (1930).⁵ Stubbs, *Am. Chem. J.*, **50**, 193 (1913).⁶ Finzi and Colonna, *Gazz. chim. ital.*, **68**, 132 (1938); *Chem. Abstr.*, **32**, 6638 (1938).⁷ Remsen and Gray, *Am. Chem. J.*, **19**, 496 (1897).⁸ Karslake and Bond, *J. Am. Chem. Soc.*, **38**, 1338 (1916).⁹ Henderson, *Am. Chem. J.*, **25**, 1 (1901).¹⁰ Haworth and Lapworth, *J. Chem. Soc.*, **125**, 1299 (1924).¹¹ Zincke and Schürmann, *Ann.*, **416**, 65 (1918).¹² Zincke and Greune, *Ann.*, **427**, 221 (1922).¹³ Moulton, *Am. Chem. J.*, **13**, 193 (1891).¹⁴ Remsen and Burney, *Am. Chem. J.*, **2**, 405 (1880-1).¹⁵ Allen and Burness, *J. Org. Chem.*, **14**, 163 (1949).¹⁶ Kalcher, *Ann.*, **414**, 244 (1918).¹⁷ Kaufmann and Zobel, *Ber.*, **55**, 1499 (1922).

Table XLVII follows on page 352.

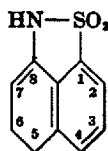
TABLE LXVII. Saccharins Substituted in the Benzene Ring Prepared by Methods Other Than Given in Tables LXV and LXVI

No.	Name or substituent on the saccharin molecule	Ref.	Method of preparation	Taste	Solubility	M.p., °C.
1	6-Amino	1	6-nitrosaccharin + (NH ₄) ₂ S ₂	sweet	alc.	285
2	2-Acetyl-6-acetamido	2	compound 1 + acetic anhydride	tasteless	acetic acid	278
3	6-Acetamido	2	compound 2 + dil. KOH	—	—	261
4	6-Amino, salicylidene	2	compound 1 + salicylaldehyde	—	—	284 dec.
5	6-Hydroxy	2	compound 1 + diazotization and hydrolysis	sweet	alc.	276-7
6	6-Ethoxyformamido	2	compound 1 + C ₂ H ₅ OCOC	—	alc.	264 dec.
7	2-Carbethoxy-6-ethoxyformamido	2	compound 1 + 2 C ₂ H ₅ OCOC	—	alc.	265 dec.
8	6-Ureido	2	compound 6 + NH ₃	—	alkali	203 dec.
9	6,6'-Ureylenebis	2	compound 1 + COCl ₂ + dimethyl-aniline	—	dil. Na ₂ CO ₃	over 305
10	6-(<i>p</i> -Ethoxyphenylureylene)	2	compound 6 + <i>p</i> -ethoxyaniline (<i>p</i> -phenetidine)	no sweetness	alc.	over 300
11	2-(<i>p</i> -Ethoxyphenylcarbamyloxy)-6-(<i>p</i> -ethoxyphenylureylene)	2	compound 7 + phenetidine at 150-160°C.	—	alc.	227-8
12	4-Carboxy	9	O ₂ S-N  + 2 N NaOH	—	alc., acetic acid	228-9
						slow 240-5; fast 275-6

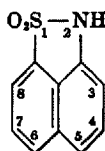
No.	Name or substituent on the saccharin molecule	Ref.	Method of preparation	Taste	Solubility	M.p., °C.
13	4-Carboxy-2-methyl	3	silver (or K) 4-carboxysaccharin + methyl iodide at 100°C.	—	alc., water, methanol	190.7–191.7
		4	at 230°C.	—	—	189
14	4-Carbomethoxy-2-methyl	3	silver 4-carboxysaccharin + excess methyl iodide	—	methanol, alc.	176
		4	—	—	acetic acid	176
15	4-Carbomethoxy	4	silver 4-carboxysaccharin + methyl iodide at 100°C.	—	methanol, benzene	184–5
16	5,6-Dimethoxy-2-methyl	5	5,6-dimethoxysaccharin + alkali + dimethyl sulfate	bitter	alc.	227
17	5-Nitro-2-methyl	6	5-nitrosaccharin + methyl iodide	—	alc.	179
18	5-Nitro-2-ethyl	6	5-nitrosaccharin + ethyl iodide	—	alc.	172
19	7-Chloro	7	oxidation with dil. nitric acid or chromic acid of 7-chloro-2,3-dihydro-1,2-benzisulfonazole	very sweet, bitter	water, alc.	153.5
20	2-Methylnaphth [1,2-d]iso-sulfonazole	8	+ dimethyl sulfate	—	alc.	220–1

¹ Noyes, *Am. Chem. J.*, **8**, 169 (1886).² Finzi and Colonna, *Gazz. chim. ital.*, **68**, 132 (1938); *Chem. Abstr.*, **32**, 6638 (1938).³ Remsen and Stokes, *Am. Chem. J.*, **6**, 260 (1884–5).⁴ Zincke and Greune, *Ann.*, **427**, 221 (1922).⁵ Brown and Robinson, *J. Chem. Soc.*, **111**, 952 (1917).⁶ Remsen and Gray, *Am. Chem. J.*, **19**, 496 (1897).⁷ Reissert and Cramer, *Ber.*, **61**, 2555 (1938).⁸ Kalcher, *Ann.*, **414**, 244 (1918).⁹ Zincke and Schürmann, *Ann.*, **416**, 65 (1918).

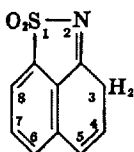
1,8-Naphthosultams or the 2-, 3-, and 5-Naphth-[1.8-*cd*]isosulfonazoles (I)¹



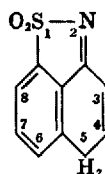
1,8-Naphthosultams
(*Chemical Abstracts* numbering)
(I)



(*Ring Index* No. 1546 numbering)

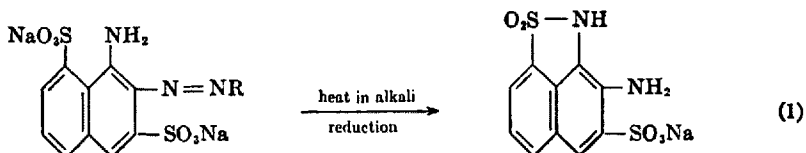


3-Naphth [1.8-*cd*] isosulfonazole
(*Ring Index* No. 1547)

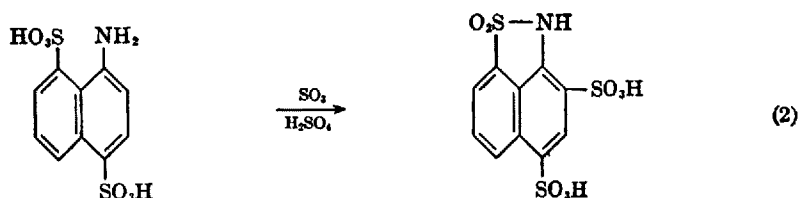


5-Naphth [1.8-*cd*] isosulfonazole
(*Ring Index* No. 1548)

Bernthsen² believed that he had obtained a 2-naphth[1.8-*cd*]isosulfonazole sulfonic acid by heating a dye with alkali and then reducing (1).



Dressel and Kothe,³ in their work on the 1,8-naphthylaminesulfonic acids, produced 2-naphth[1.8-*cd*]isosulfonazole sulfonic acids (2). (These com-

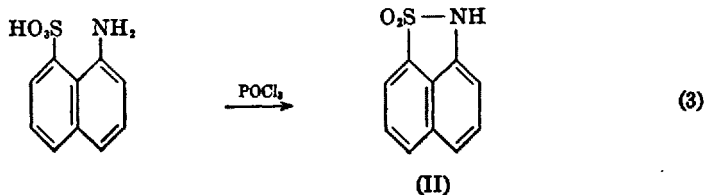


¹ The names and numbering used in this discussion are derived from the *Ring Index* nomenclature in order to differentiate between the 2,3- and 5-naphth[1.8-*cd*]isotiazoles. The term isosulfonazole instead of isothiazole-*S*-dioxide is used for consistency and conciseness.

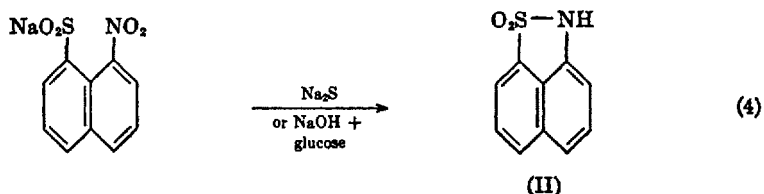
² Bernthsen, *Ber.*, **23**, 3088 (1890).

³ Dressel and Kothe, *Ber.*, **27**, 2137 (1894).

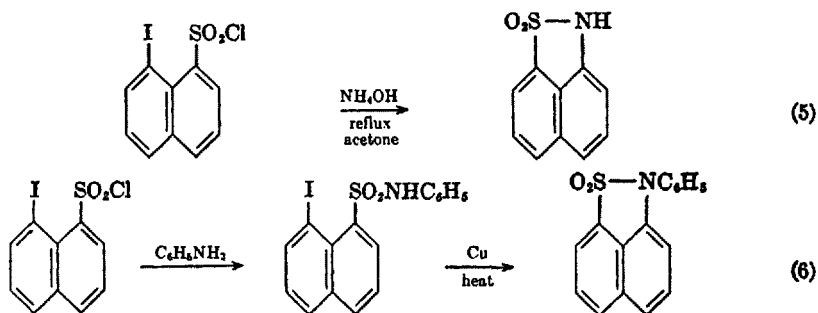
pounds will be discussed in more detail under the 2-naphth[1.8-*cd*]-isosulfonazole sulfonic acids.) Dannerth⁴ found that ring closure could be effected by phosphorus oxychloride (3). This method is a general method



and has been used to prepare 2-phenyl⁵ and other 2-naphth[1.8-*cd*]iso-sulfonazoles. Reduction of 1-nitro-8-naphthylsulfonic acid with either sodium sulfide or glucose and alkali yielded 2-naphth[1.8-*cd*]isosulfonazole (4).⁶ This compound has been synthesized from 8-iodo-1-naphthylsul-



fonylchloride and ammonia (5).⁷ A modification of this method was used to synthesize 2-phenyl-2-naphth[1.8-*cd*]isosulfonazole (6). 2-Naphth-



[1.8-*cd*]isosulfonazole is very stable. The isosulfonazole ring was ruptured by alkaline fusion to yield 1,8-aminonaphthol or 1,8-dihydroxynaphthalene.⁴ It has been hydrolyzed by an excess of 60% sulfuric acid.⁸ Com-

⁴ Dannerth, *J. Am. Chem. Soc.*, **29**, 1319 (1907).

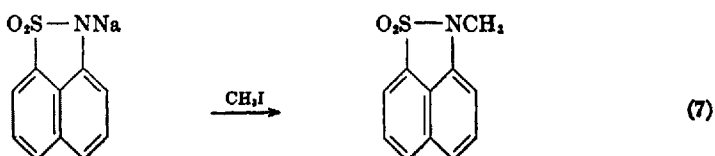
⁵ König and Wagner, *Ber.*, **57**, 1058 (1924).

⁶ Woroshtzow and Koslow, *Ber.*, **69**, 416 (1936).

⁷ Cumming and Muir, *J. Roy. Tech. Coll. (Glasgow)*, **3**, 562 (1936); *Chem. Abstr.*, **30**, 4491 (1936).

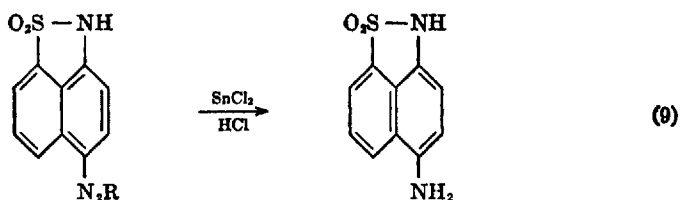
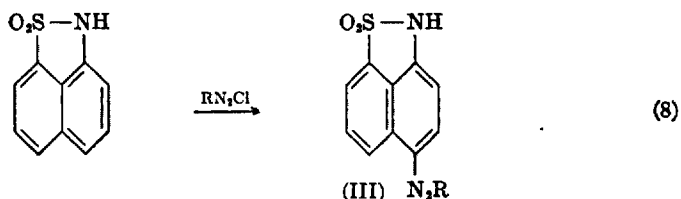
⁸ Volodarski and Kolosova, *Chem. Abstr.*, **30**, 4492 (1936); *Anilinokrasochnaya Prom.*, **5**, 260 (1935).

pound II formed soluble sodium salts on the 2-position. 2-Alkylmercuri compounds have been disclosed.⁹ Alkylation of the sodium salt yielded 2-alkyl derivatives (7).^{10,11} These compounds are not soluble in alkali.



Dannerth¹¹ felt that acetylation gave an isonaphthosultam, but Zincke¹² proved that 2-acetyl-2-naphth[1.8-*cd*]isosulfonazole was formed. This compound is not soluble in cold alkali. Mild hydrolysis with either alkali or dilute acid yields the parent 2-naphth[1.8-*cd*]isosulfonazole.

Phenyldiazonium salts^{10,11,13} couple with II in the 5-position, since König¹⁰ showed that the 2-methyl derivatives also coupled in the 5-position (8). Compound III was reduced with stannous chloride to synthesize 5-amino-2-naphth[1.8-*cd*]isosulfonazole (9).¹³ Acetylation of IV gave



2-acetyl-5-acetamido-2-naphth[1.8-*cd*]isosulfonazole, which on mild hydrolysis with dilute alkali yielded a monacetyl derivative whose exact structure is uncertain.¹³

Dannerth¹¹ thought that he had the mononitro derivative when he used dilute nitric acid (sp.gr. 1.2) with 2-naphth[1.8-*cd*]isosulfonazole. Zincke¹³ showed that this compound was probably 3,5-dinitro-2-naphth[1.8-*cd*]isosulfonazole (V). Dannerth¹¹ also prepared compound V by the

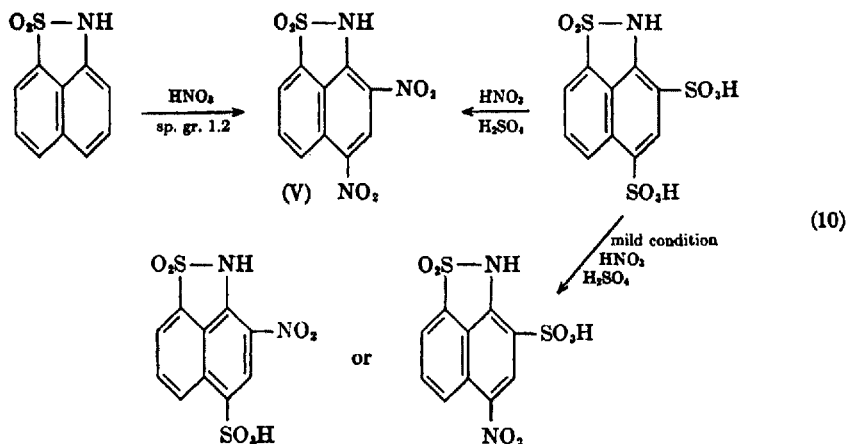
⁹ Kloss, *Chem. Abstr.*, **36**, 3906 (1942); U. S. Pat. 2,273,443.

¹⁰ König and Köhler, *Ber.*, **55**, 2138 (1922).

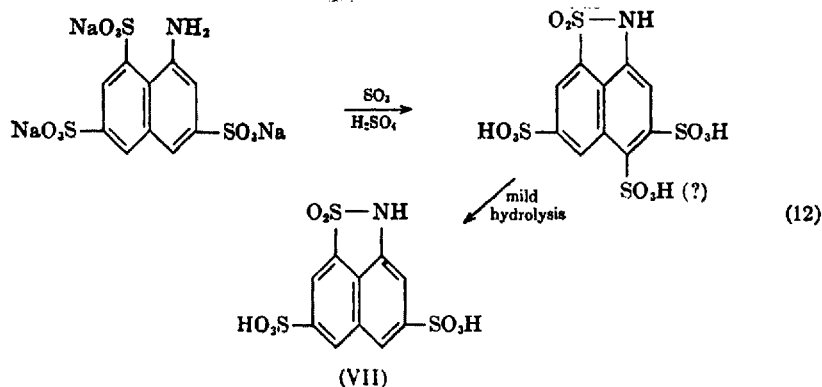
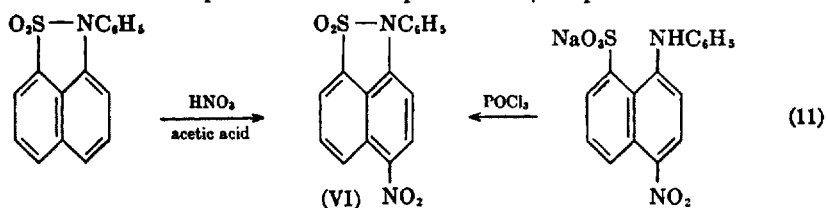
¹¹ Dannerth, *J. Am. Chem. Soc.*, **29**, 1319 (1907).

¹² Zincke and Julicher, *Ann.*, **411**, 195 (1916).

¹³ Zincke and Schürmann, *Ann.*, **412**, 78 (1916).



method of Dressel and Kothe¹⁵ which consisted of heating the disulfonic acid in nitric acid and sulfuric acid (10). Mild conditions in this replacement reaction produced a mononitro derivative.¹⁶ König and Wagner¹⁷ were able to nitrate 2-phenyl-2-naphth[1.8-*cd*]isosulfonazole with nitric acid in acetic acid and obtained 5-nitro-2-phenyl-2-naphth[1.8-*cd*]isosulfonazole (11). Compound VI was readily reduced to the amine, which could be diazotized and coupled to such compounds as β -naphthol and R salt.

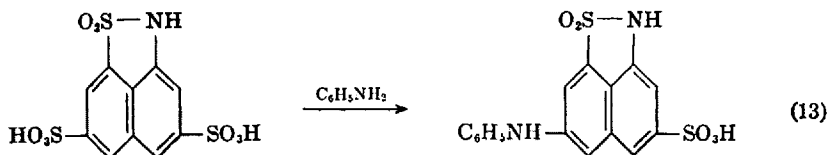


¹⁵ Dressel and Kothe, *Ber.*, **27**, 2137 (1894).

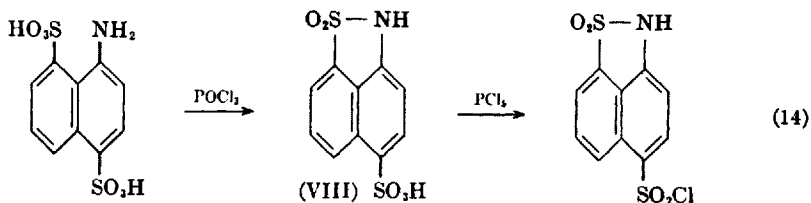
¹⁶ Bayer and Co., *Friedländer*, **9**, 178 (1911); Ger. Pat. 210,222

¹⁷ König and Wagner, *Ber.*, **57**, 1058 (1924).

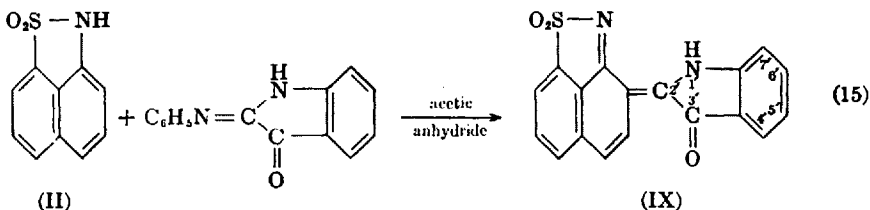
The preparation of the di- and trisulfonic acids was accomplished with fuming sulfuric acid (12).¹⁵ The 3-sulfonic,¹⁸ 3,5-disulfonic^{15,18} and 3,5,7-trisulfonic acids¹⁹ prepared in the same manner have been described. The sulfo group in compound VII has been replaced by aryl amines²⁰⁻²² on heating VII in an excess of the amine (13). König and Keil²³ prepared the 2-



naphth[1.8-*cd*]isosulfonazole-5-sulfonic acid with 1-amino-4,8-naphthyl-disulfonic acid and phosphorus oxychloride. The action of phosphorus pentachloride on compound VIII yielded the sulfonylchlorides from which the sulfonamides were produced (14). Compound VIII coupled in the 3-position with phenyldiazonium salts.



In the presence of acetic anhydride, 2-naphth[1.8-*cd*]isosulfonazole reacted with α -isatinanilide to give a dark violet blue dye (3-naphth[1.8-*cd*]isosulfonazole-2'-indole indigo) (IX) along with some 2-acetyl-2-naphth[1.8-*cd*]isosulfonazole (15).^{24,25} 5,7-Dibromoisatin chloride, on being



¹⁸ Bayer and Co., *Friedländer*, **4**, 530 (1899); Ger. Pat. 79,566.

¹⁹ Bayer and Co., *Friedländer*, **4**, 534 (1899); Ger. Pat. 84,140.

²⁰ Neelmeier and Nocken, *Chem. Abstr.*, **24**, 5767 (1930); U. S. Pat. 1,777,931.

²¹ I. G. Farbenindustrie, *Chem. Abstr.*, **23**, 613 (1929); Swiss Pat. 126,340.

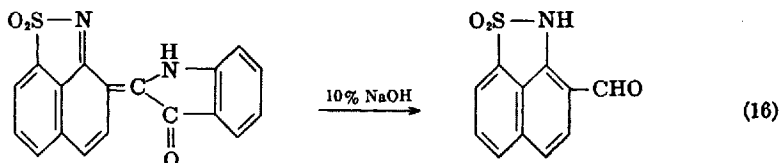
²² I. G. Farbenindustrie, *Chem. Abstr.*, **23**, 609 (1929); Swiss Pat. 126,338 and 126,339.

²³ König and Keil, *Ber.*, **55**, 2149 (1922).

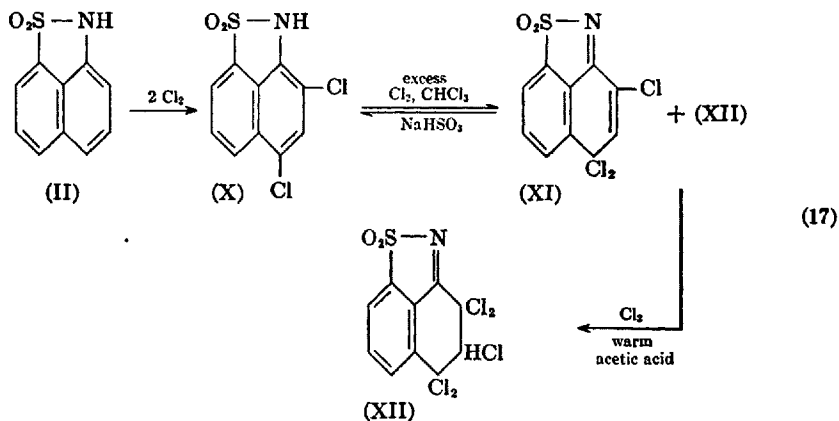
²⁴ Friedländer and Sander, *Ber.*, **57**, 637 (1924).

²⁵ König and Wagner, *Ber.*, **57**, 1058 (1924).

warmed with compound II, yielded the 5',7'-dibromo analog of compound IX.²⁵ A *para* isomer may have been obtained. Hydrolysis of IX with 10% sodium hydroxide produced 3-formyl-2-naphth[1.8-*cd*]isosulfonazole (16).



Bromination of II resulted in the formation of 3,5-dibromo-2-naphth[1.8-*cd*]isosulfonazole.²⁶ The chlorination of II and its derivatives has been studied extensively by Zincke.²⁷⁻²⁹ Chlorination of 2-naphtho[1.8-*cd*]isosulfonazole proceeded in stages yielding results in accordance with the amount of chlorine and other conditions: a twofold equivalent amount, 3,5-dichloro-2-naphth[1.8-*cd*]isosulfonazole; an excess of chlorine in chloroform, 3,5,5-trichloro-5-naphth[1.8-*cd*]isosulfonazole; and an excess of chlorine in warm acetic acid, 3,3,4,5,5-pentachloro-4,5-dihydro-3-naphth[1.8-*cd*]isosulfonazole (17). The 2-acetyl derivative of X was synthesized.



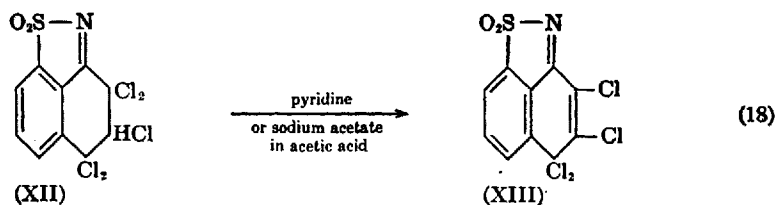
Compound XI exists in two forms; a yellow unstable form which on heating gives a white stable form. Both forms undergo the same chemical reactions. An acetic acid solution of XI liberates iodine from potassium iodide. Compound XI is reduced by either sodium bisulfite or stannous chloride to compound X (see 17). Compound XII liberates iodine from potassium iodide and is slowly attacked by aqueous alkali. Compound XII reacts with either pyridine or sodium acetate in acetic acid to form 3,4,5,5-tetra-

²⁵ Dannerth, *J. Am. Chem. Soc.*, **29**, 1319 (1907).

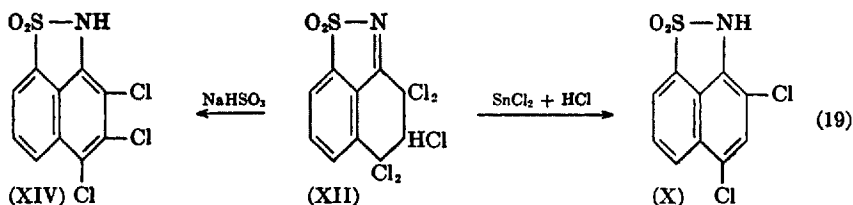
²⁷ Zincke and Julicher, *Ann.*, **411**, 195 (1916).

²⁸ Zincke and Schürmann, *Ann.*, **412**, 78 (1916).

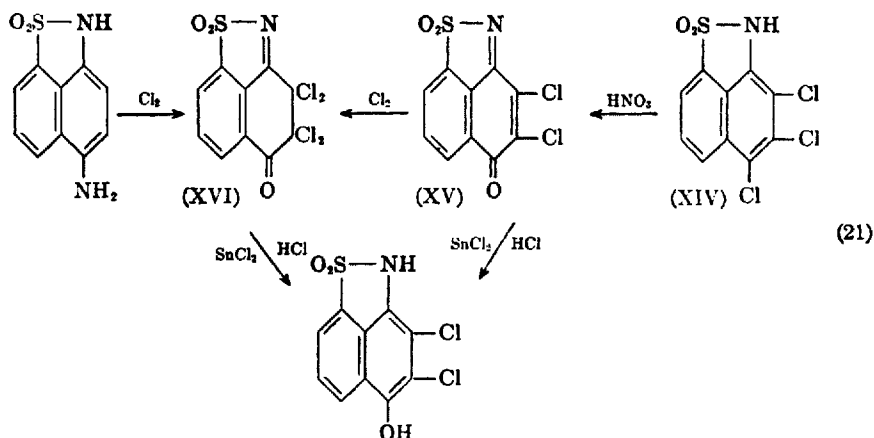
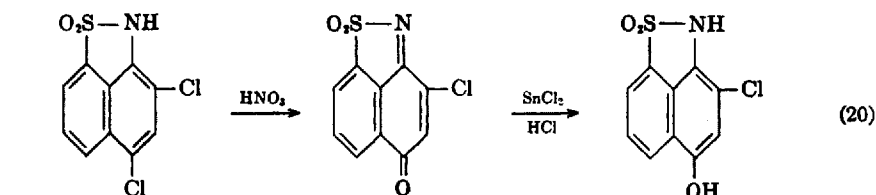
²⁹ Zincke and Schürmann, *Ann.*, **416**, 65 (1918).



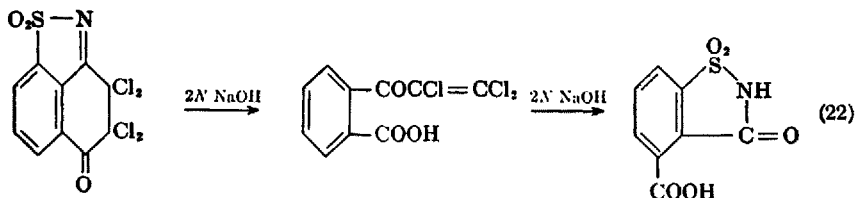
chloro-5-naphth[1.8-*cd*]isulfonazole (18). Stannous chloride in hydrochloric acid reduces compound XII to 3,5-dichloro-2-naphth[1.8-*cd*]isulfonazole, while sodium bisulfite reduces it to 3,4,5-trichloro-2-naphth[1.8-*cd*]isulfonazole (19).



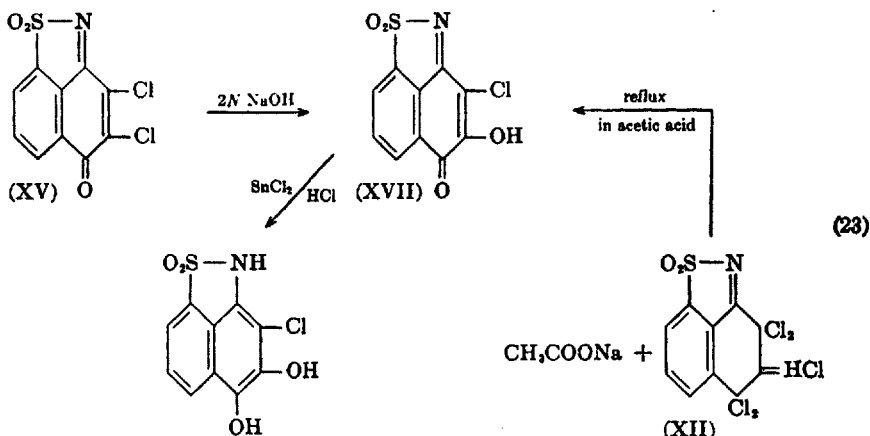
Compounds X and XIV were oxidized with nitric acid to their respective ketones, 3-chloro-5-naphth[1.8-*cd*]isulfonazol-5-one and 3,5-dichloro-5-naphth[1.8-*cd*]isulfonazol-5-one. Reduction yielded the corresponding 5-hydroxy derivative (20). Chlorination of 5-amino-2-naphth-



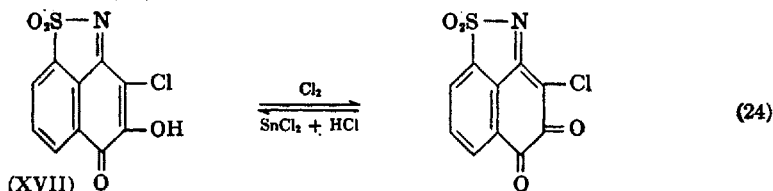
[1.8-*cd*]isosulfonazole afforded 3,3,4,4-tetrachloro-3,4-dihydro-5-naphth-[1.8-*cd*]isosulfonazol-5-one which was reduced to the 3,4-dichloro-5-hydroxy-2-naphth[1.8-*cd*]isosulfonazole (21). Compound XVI was decomposed stepwise by dilute alkali to 4-carboxysaccharin (22). 3-Chloro-4-



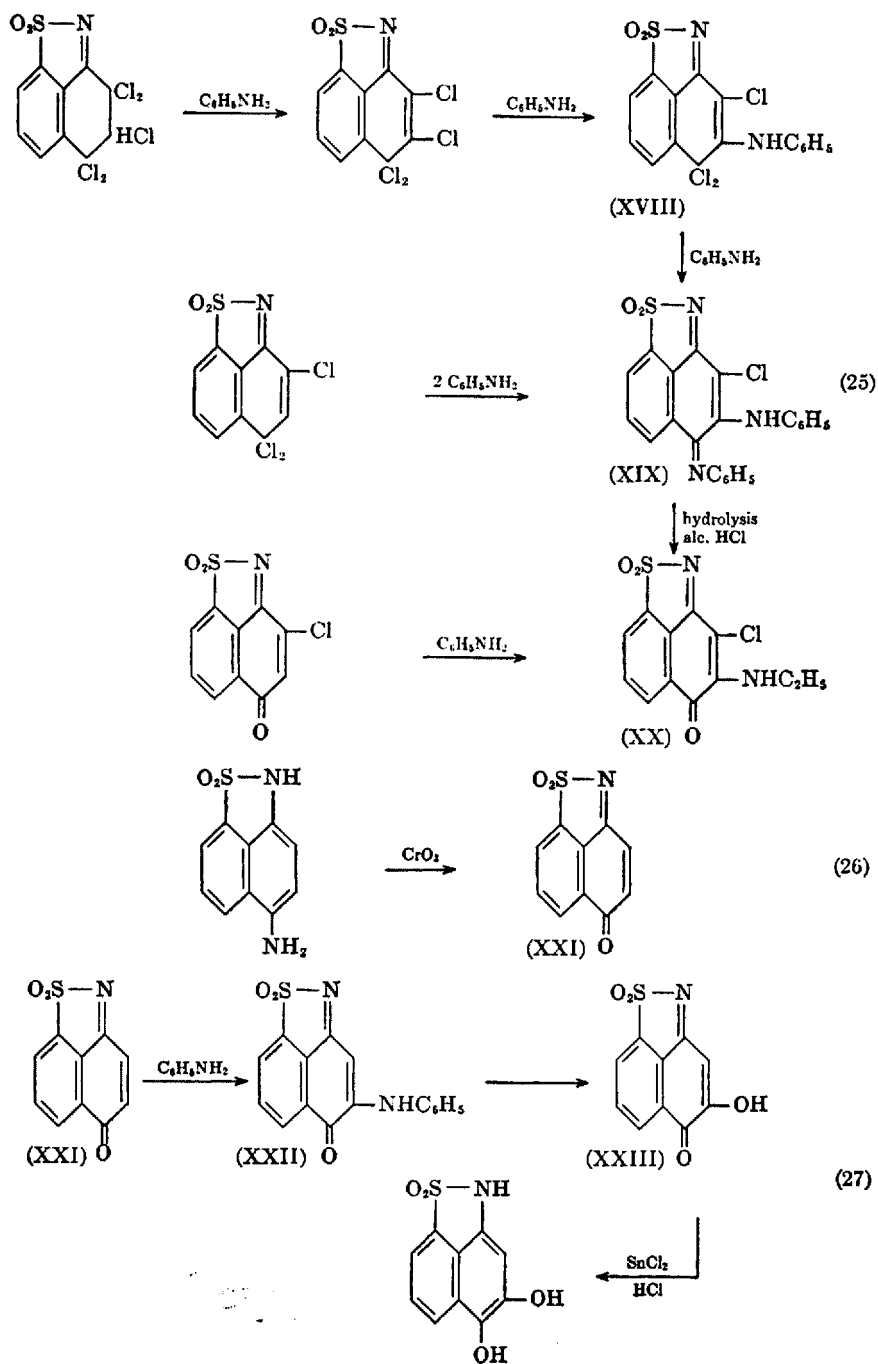
hydroxy-5-naphth[1.8-*cd*]isosulfonazol-5-one (XVII) was synthesized from compound XV with 2 N sodium hydroxide and from compound XII with sodium acetate in acetic acid (23). Reduction of XVII yielded 3-



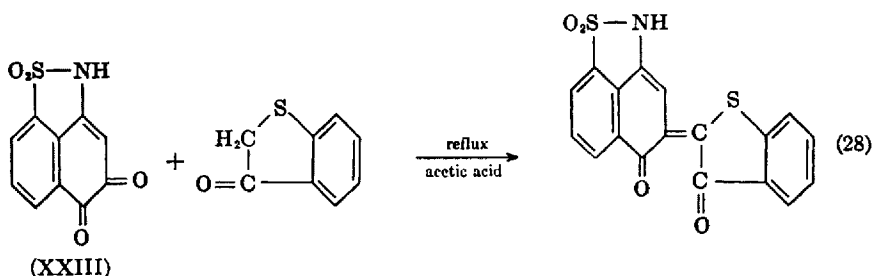
chloro-4,5-dihydroxy-2-naphth[1.8-*cd*]isosulfonazole. Chlorine oxidized compound XVII to 3,3-dichloro-3,4-dihydro-5-naphth[1.8-*cd*]isosulfonazol-4,5-dione. This compound was reduced to the starting material with stannous chloride (24).



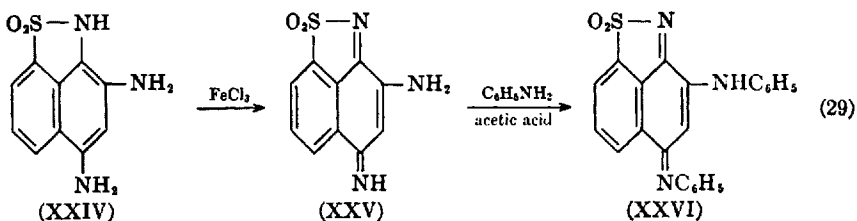
Aniline reacted with these derivatives to give 4-anilino-3,5,5-trichloro-5-naphth[1.8-*cd*]isosulfonazole (XVIII), 4-anilino-3-chloro-5-phenylimino-5-naphth[1.8-*cd*]isosulfonazole (XIX), and 4-anilino-3-chloro-5-naphth[1.8-*cd*]isosulfonazol-5-one (XX) (25).



Oxidation of 5-amino-2-naphth[1.8-*cd*]isosulfonazole with chromic acid produced 5-naphth[1.8-*cd*]isosulfonazol-5-one (XXI) (26). Aniline reacted with XXI to form 4-anilino-5-naphth[1.8-*cd*]isosulfonazol-5-one (XXII). Hydrolysis of XXII with dilute alkali gave 4-hydroxy-5-naphth[1.8-*cd*]isosulfonazol-5-one which was reduced to 4,5-dihydroxy-2-naphth[1.8-*cd*]isosulfonazole (27). Compound XXIII condensed with 2,3-dihydrothianaphthen-3-one in the presence of hot acetic acid to form a violet dye (28).³⁰

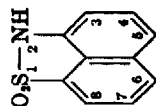


Zincke *et al.*³¹ reduced 3,5-dinitro-2-naphth[1.8-*cd*]isosulfonazole to the diamine (XXIV). Oxidation of this amine with ferric chloride yielded 3-amino-5-imino-5-naphth[1.8-*cd*]isosulfonazole (XXV). Heating XXV with aniline in acetic acid and alcohol produced 3-anilino-5-phenylimino-5-naphth[1.8-*cd*]isosulfonazole (29).

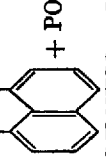
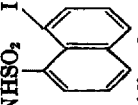
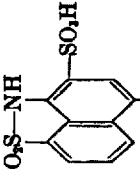


³⁰ Friedlander and Sander, *Ber.*, **57**, 637 (1924).

³¹ Zincke and Schürmann, *Ann.*, **416**, 65 (1918).

TABLE LXVIII. Preparation of the 2-Naphth[1,8-*cd*]isosulfonazoles

No.	Substituents on the 2-naphth[1,8- <i>cd</i>]sulfonazole	Ref.	Method of preparation	Solubility	M.p., °C.
1	None	1	 + POCl ₃ at 130°C.	water, ether, benzene, CHCl ₃	177-8
2	 + NH ₄ OH and reflux in acetone	2	 + POCl ₃ at 130°C.	alc.	176
3	 + Na ₂ S or NaOH + glucose	3	 + NH ₄ OH and reflux in acetone	—	175.5-176
2	2-Acetyl	4	acetic anhydride + 1	acetic acid	188-9
3	2-Methyl	1	compound 1 + methyl iodide or dimethyl sulfate + alkali	—	188
4	2-Ethyl	5	—	—	125
		1	compound 1 + ethyl iodide + alkali	alc.	125
					85

No.	Substituents on the 2-naphth[1.8- <i>cd</i>]isulfonazole	Ref.	Method of preparation	Solubility	M.p., °C.
5	2-Phenyl	6	HO_2S  + POCl_3 $\text{C}_6\text{H}_4\text{NHSO}_2$ I  + Cu powder	alc.	158
2				acetic acid	165
6	2- <i>p</i> -Tolyl	6	1- <i>p</i> -toluidino-8-naphthylsulfonic acid + POCl_3	alc.	152
7	2-Methylmercuri	7	compound 1 + methylmercuri chloride	—	256-7
8	6-Methyl	8	same as preparation of 1	benzene	221-2
9	3,5-Dibromo	1	compound 1 + Br_2	CHCl_3	239
10	3,5-Dichloro	4	compound 1 + 2 Cl_2	acetic acid, benzene	195
		4	reduction of 3,5,5-trichloro-5-naphth[1.8- <i>cd</i>]isulfonazole (Table LXX) with SnCl_4 in HCl or NaHSO_3	—	—
		4	reduction of 3,3,4,5,5-pentachloro-4,5-dihydro-3-naphth[1.8- <i>cd</i>]isulfonazole (Table LXIX) with SnCl_4 + HCl	—	—
11	2-Acetyl-3,5-dichloro	4	compound 10 + acetic anhydride	acetic acid	170
12	3,4,5-Trichloro	4	reduction of either 3,4,5,5-tetrachloro-5-naphth[1.8- <i>cd</i>]isulfonazole (Table LXX) or 3,3,4,5,5-pentachloro-4,5-dihydro-3-naphth[1.8- <i>cd</i>]isulfonazole with SnCl_4 + HCl	acetic acid	235
13	3,5-Dinitro	1	compound 1 + HNO_3 , sp. gr. 1.2-1.4	alc.	259
		9	—	—	258 dec.
		1	$\text{O}_2\text{S}-\text{NH}$  + HNO_3 + H_2SO_4	—	—

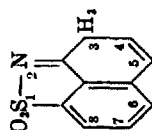
(Table continued)

TABLE LXVIII (Continued)

No.	Substituents on the 2-naphthyl[1,8- <i>cd</i>]isoulsulfonazole	Ref.	Method of preparation	Solubility	M.p., °C.
14	2-Phenyl-5-nitro	6	compound 5 + HNO ₃ + acetic acid, also same as compound 1	alc.	200
15	5-Amino	10	reduction of 5-(<i>p</i> -sulphophenylazo)-2-naphthyl[1,8- <i>cd</i>]isoulsulfonazole with SnCl ₂ + HCl	—	—
16	2-Acetyl-5-acetamido	10	compound 15 + acetic anhydride + sodium acetate	acetic acid	over 260
17	5-Acetamido	10	compound 16 + dilute alkali	acetic acid	sint. 276
18	2-Phenyl-5-amino	6	reduction of 14 with SnCl ₂ + HCl	alc.	185
19	3,5-Diamino	1,9	compound 13 + Sn + HCl	—	—
20	3,5-Diacetamido	1	compound 19 + acetic anhydride + sodium acetate	nitrobenzene	290
21	2-Acetyl-3,5-diacetamido	9	compound 21 + dilute alkali	acetic acid	over 270
22	5-(<i>p</i> -Sulphophenylazo)	1,10	compound 19 + acetic anhydride + sodium acetate	nitrobenzene	over 270
23	5-(4-Sulfo-1-naphthylazo)	5	<i>p</i> -sulphophenyl diazonium chloride + compound 7	—	—
24	5-(<i>p</i> -Nitrophenylazo)	5	4-sulfo-1-naphthyl diazonium + compound 1	—	chars 320
25	5-(2,4-Dinitrophenylazo)	5	<i>p</i> -nitrophenyl diazonium sulfate + compound 1	alc., nitrobenzene	288-9
26	2-Methyl-5-(<i>p</i> -nitrophenylazo)	5	2,4-dinitrophenyl diazonium sulfate + compound 3	nitrobenzene	over 355
27	2-Methyl-5-(2,4-dinitrophenylazo)	5	<i>p</i> -nitrophenyl diazonium sulfate + compound 3	acetic acid	236-7
28	2-Phenyl-5-(2,4-dinitrophenylazo)	6	2,4-dinitrophenyl diazonium sulfate + compound 5	acetic acid	263
29	5-Hydroxy	10	reduction of 5-naphthyl[1,8- <i>cd</i>]isoulsulfonazol-5-one with SnCl ₂	alc.	240
30	2-Acetyl-5-acetoxy	10	compound 29 + acetic anhydride + sodium acetate	alc., acetic acid	120
31	3-Chloro-5-hydroxy	10	compound 29 + acetic anhydride + sodium acetate	acetic acid	199
32	2-Acetyl-5-acetoxy-3-chloro	10	reduction of 3-chloro-5-naphthyl[1,8- <i>cd</i>]isoulsulfonazol-5-one with SnCl ₂ + HCl	acetic acid, alc.	217-8
33	3,4-Dichloro-5-hydroxy	10	compound 31 + acetic anhydride + H ₂ SO ₄	acetic acid	186
34	2-Acetyl-5-acetoxy-3,4-dichloro	10	reduction of 3,4-dichloro-5-naphthyl[1,8- <i>cd</i>]isoulsulfonazol-5-one with SnCl ₂ + HCl	acetic acid, alc.	254 dec.
35	4,5-Dihydroxy	10	compound 33 + acetic anhydride + H ₂ SO ₄	acetic acid, alc.	205-6
		10	reduction of 4-hydroxy-5-naphthyl[1,8- <i>cd</i>]isoulsulfonazol-5-one with SnCl ₂ + HCl	acetic acid, alc., water	230 dec.

No.	Substituents on the 2-naphth[1.8- <i>cd</i>]isulfonazole	Ref.	Method of preparation	Solubility	M.p., °C.
36	2-Acetyl-4,5-diacetoxy	10	compound 35 + acetic anhydride + H ₂ SO ₄	acetic acid	222
37	3-Formyl	6	10% NaOH + 3-naphth[1.8- <i>cd</i>]isulfonazole-2'-indole indigo	—	200 dec.
38	5-Sulfo	11	1-naphthylamine-4,8-disulfonic acid + POCl ₃	K salt sol. in water	300 dec.
		—	2-naphth[1.8- <i>cd</i>]isulfonazole + H ₂ SO ₄ + acetic acid at 50°C.	—	—
39	5-Chlorosulfonyl	11	compound 38 + PCl ₅	benzene, toluene	185 dec.
40	5-Phenylsulfonyl	11	compound 39 + C ₆ H ₅ NH ₂	alc.	230 dec.
41	5- α -Naphthylsulfonyl	11	compound 39 + α -C ₁₀ H ₇ NH ₂	alc.	240 dec.
42	5-Sulfo-3- <i>p</i> -nitrophenylazo	11	compound 38 + <i>p</i> -nitrophenyldiazonium sulfate	alc.	280 dec.
43	5-Sulfo-3- <i>o</i> -methoxyphenylazo	11	compound 38 + <i>o</i> -methoxyphenyldiazonium sulfate	water, alc.	—
44	3,5-Disulfo	12	1-amino-4,8-naphthyldisulfonic acid + H ₂ SO ₄ + SO ₃	—	—
45	3-Nitro-5-sulfo or 5-nitro-3-sulfo	13	compound 44 + HNO ₃ (mild cond.) (sp. gr. 1.2)	—	—
46	4,5(?)7-Trisulfo	12	1-amino-3,6,8-naphthyldisulfonic acid + H ₂ SO ₄ + SO ₃ alc.	—	—
47	4,7-Disulfo	12	hydrolysis of 46 with hydrochloric acid	—	—
48	7-Anilino-4-sulfo	14	compound 47 + C ₆ H ₅ NH ₂ + HCl	—	165-170
49	7- <i>p</i> -Toluidino-4-sulfo	14	compound 47 + <i>p</i> -CH ₃ C ₆ H ₄ NH ₂	—	—
50	7- <i>p</i> -Methoxyanilino-4-sulfo	14	compound 47 + <i>p</i> -CH ₃ OC ₆ H ₄ NH ₂	—	—
51	3-Sulfo	15	1-amino-2,8-naphthyldisulfonic acid + H ₂ SO ₄ + SO ₃	—	—
52	3,5,7-Trisulfo	16	1-amino-2,4,6,8-naphthyltetrasulfonic acid	—	—

¹ Dannenrath, *J. Am. Chem. Soc.*, **29**, 1319 (1907).² Cumming and Muir, *J. Roy. Tech. Coll. (Glasgow)*, **3**, 562 (1936); *Chem. Abstr.*, **30**, 4491 (1936).³ Woroshtzow and Koslow, *Ber.*, **69**, 416 (1936).⁴ Zincke and Julicher, *Ann.*, **411**, 195 (1916).⁵ König and Kohler, *Ber.*, **55**, 2139 (1922).⁶ König and Wagner, *Ber.*, **57**, 1058 (1924).⁷ Kloss, *Chem. Abstr.*, **36**, 3906 (1942); U. S. Pat. 2,273,443.⁸ Vesely and Bubenik, *Chem. Abstr.*, **34**, 6890 (1940); *Collection Czechoslov. Chem. Commun.*, **11**, 412 (1939).⁹ Zincke and Schürmann, *Ann.*, **416**, 65 (1918).¹⁰ Zincke and Schürmann, *Ann.*, **412**, 78 (1916).¹¹ König and Keil, *Ber.*, **55**, 2149 (1922).¹² Dressel and Kothé, *Ber.*, **27**, 2137 (1894).¹³ Bayer and Co., *Friedländer*, **9**, 178 (1911); Ger. Pat. 210,222.¹⁴ I. G. Farbenindustrie, *Chem. Abstr.*, **23**, 613 (1929); Swiss Pat. 126,340; *Chem. Abstr.*, **23**, 609 (1929); Swiss Pats. 126,338 and 126,339; Neelmeier and Nocken, *Chem. Abstr.*, **24**, 5764 (1930); U. S. Pat. 1,777,931.¹⁵ Bayer and Co., *Friedländer*, **4**, 530 (1899); Ger. Pat. 79,566.¹⁶ Bayer and Co., *Friedländer*, **4**, 534 (1899); Ger. Pat. 84,140.

TABLE LXIX. Preparation of the 3-Naphth[1.8-*cd*]isotulfonazoles

No.	Substituents on the 3-naphth[1.8- <i>cd</i>]isotulfonazole	Ref.	Method of preparation	Solubility	M.p., °C.
1	3-(2-Indole indigo)-	1	2-naphth[1.8- <i>cd</i>]isotulfonazole + α -isatinanilide + acetic anhydride	nitrobenzene	—
2	3(5,7-Dibromoindole indigo)-	2	2-naphth[1.8- <i>cd</i>]isotulfonazole + 5,7-dibromo-2-chloroisatin	nitrobenzene	over 360 sublimes 200

¹ Friedländer and Sander, *Ber.*, 57, 637 (1924).

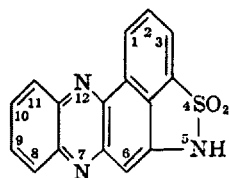
² König and Wagner, *Ber.*, 57, 1058 (1924).

TABLE LXX. Preparation of the 5-Naphth[1.8-*cd*]isosulfonazoles

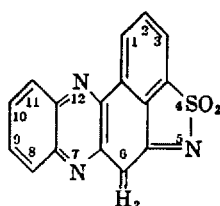
No.	Substituents on the 5-naphth[1.8- <i>cd</i>]isosulfonazole	Ref.	Method of preparation	Solubility	M.p., °C.
1	3,5,5-Trichloro	1	2-naphth[1.8- <i>cd</i>]isosulfonazole + excess chlorine + chloroform	alc. acetic acid	labile 195 stable 252 dec.
2	3,4,5,5-Tetrachloro	1	compound 3 + pyridine or sodium acetate	acetic acid	254
3	3,3,4,5,5-Pentachloro-3,4-dihydro	1	2-naphth[1.8- <i>cd</i>]isosulfonazole + excess chlorine in warm acetic acid	benzene, acetic acid	211
4	3,5,5-Trichloro-4-anilino	1	compound 2 + C ₆ H ₅ NH ₂	alc.	200
5	3-Amino-5-imino	—	compound 3 + C ₆ H ₅ NH ₂	acetic acid	—
6	3-Anilino-5-phenylimino-	2	3,5-diamino-2-naphth[1.8- <i>cd</i>]isosulfonazole + FeCl ₃	alc.	230-5
7	3-Chloro-4-anilino-5-phenylimino	2	compound 5 + C ₆ H ₅ NH ₂	alc., benzene	235-6
8	5-Oxo	1	compound 2 + C ₆ H ₅ NH ₂	alc., acetic acid	215
9	4-Anilino-5-oxo-	3	5-amino-2-naphth[1.8- <i>cd</i>]isosulfonazole + chromic acid	acetic acid, alc.	195 dec.
10	3-Chloro-5-oxo	3	compound 8 + C ₆ H ₅ NH ₂	acetic acid, alc.	257-60
11	3,4-Dichloro-5-oxo	3	3,5-dichloro-2-naphth[1.8- <i>cd</i>]isosulfonazole + HNO ₃	acetic acid, alc.	217-8
12	3-Chloro-4-anilino-5-oxo	3	3,4,5-trichloro-2-naphth[1.8- <i>cd</i>]isosulfonazole + HNO ₃	acetic acid, alc.	216-7 dec.
13	4-Hydroxy-5-oxo	1	compound 7 + alc. HCl	alc.	265 dec.
14	3-Chloro-4-hydroxy-5-oxo	3	compound 10 + C ₆ H ₅ NH ₂	acetic acid	265
15	3,3,4-Tetrachloro-3,4-dihydro-5-oxo-	3	compound 9 + 0.25 N NaOH	acetic acid	sinters 230
16	3,3-Dichloro-4,5-dioxo-	3	compound 3 + sodium acetate	benzene, xylene	—
17	4,4-[2,2,3-Dihydrothianaphth-3-one)]	3	5-amino-2-naphth[1.8- <i>cd</i>]isosulfonazole + hydrochloride + excess Cl ₂	acetic acid	(H ₂ O) 175
		3	compound 14 + Cl ₂ excess	acetic acid	(2H ₂ O) 195-6
		4	compound 13 + 2,3-dihydrothianaphthen-3-one heat in acetic acid	nitrobenzene	—

* Zincke and Schürmann, *Ann.*, 412, 78 (1916).* Zincke and Schürmann, *Ann.*, 411, 195 (1916).* Zincke and Schürmann, *Ann.*, 416, 65 (1918).* Friedländer and Sander, *Ber.*, 57, 637 (1924).

4-[1.2]Benzisosulfonazolo[4.3-*ab*]phenazines (I) and the 6-[1.2]Benzisosulfonazolo[4.3-*ab*]phenazines (II)

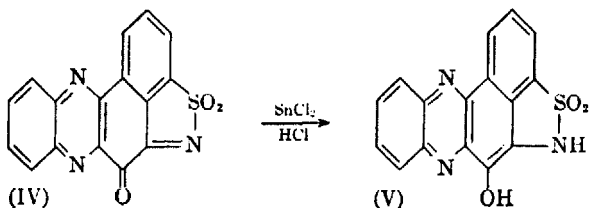
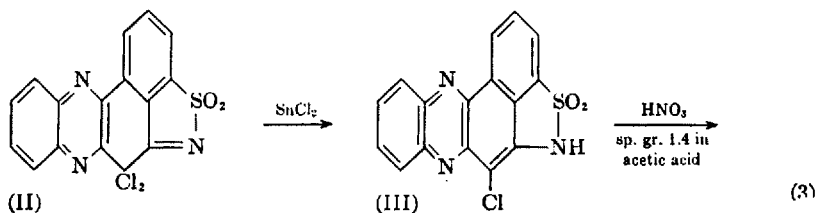
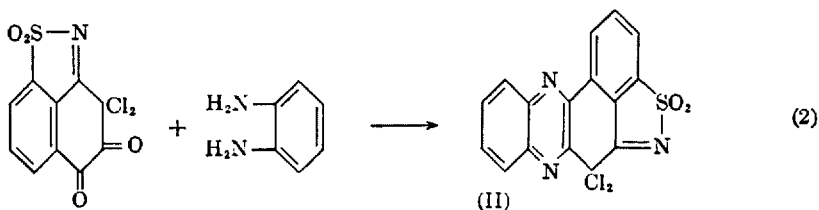
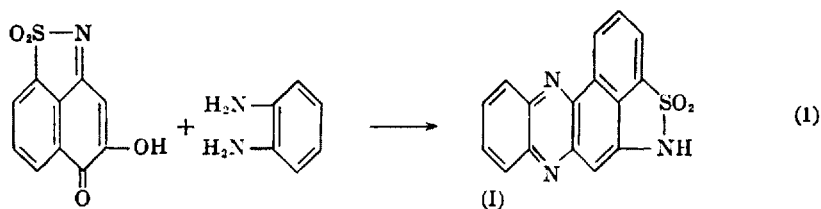


(I Ring Index No. 3033)



(II Ring Index No. 3034)

Zincke and Schürmann¹ synthesized 5-[1.2]benzisulfonazolo[4.3-*ab*]-phenazine with *o*-phenylenediamine and 4-hydroxy-5-naphth[1.8-*cd*]iso-

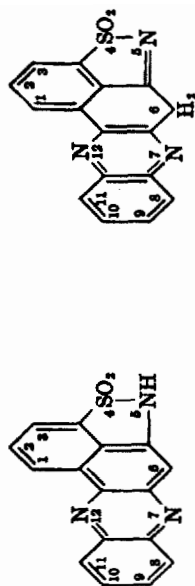


¹ Zincke and Schürmann, *Ann.*, **412**, 78 (1916).

sulfonazol-5-one (1). Compound I was soluble in acid and alkali. On acetylation, it gave a monoacetyl derivative. The 6,6-dichloro-6-[1.2]-benzisosulfonazolo[4.3-*ab*]phenazine (II) was prepared with *o*-phenylenediamine and 3,3-dichloro-3,4-dihydro-5-naphth[1.8-*cd*]isosulfonazol-4,5-dione (2). Reduction of II with stannous chloride gave 6-chloro-5-[1.2]benzisosulfonazolo[4.3-*ab*]phenazine (III) which compound was oxidized with nitric acid to 6-[1.2]benzisosulfonazolo[4.3-*ab*]phenaz-6-one (IV) (3). Compound IV was reduced to 6-hydroxy-5-[1.2]benzisosulfonazolo[4.3-*ab*]phenazine (V).

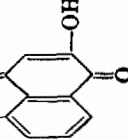
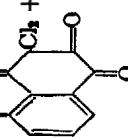
Table LXXI follows on page 372.

TABLE LXXI. Preparation of the 5-[1.2]Benzisotiazolo[4.3-ab]phenazine (I) and the 6-[1.2]Benzisotiazolo[4.3-ab]phenazines (II)



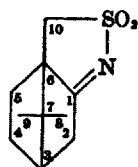
(I)

(II)

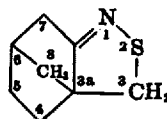
No.	Name	Ref.	Method of preparation	Solubility	M.p., °C.
1	5-[1.2]Benzisotiazolo[4.3-ab]phenazine	1	O_2S-N  + phenylenediamine	acetic acid	over 260
2	5-Acetyl-5-[1.2]benzisotiazolo[4.3-ab]phenazine	1	compound 1 + acetic anhydride	acetic acid	270
3	6-Chloro-5-[1.2]benzisotiazolo[4.3-ab]phenazine	1	reduction of compound 6 with $SnCl_2$ in ^{acetic} nitrobenzene	acetic acid in nitrobenzene	over 290
4	6-Hydroxy-5-[1.2]benzisotiazolo[4.3-ab]phenazine	1	reduction of compound 7 with $SnCl_2$	acetic acid	over 270
5	5-Acetyl-6-acetoxy-5-[1.2]benzisotiazolo[4.3-ab]phenazine	1	compound 5 + acetic anhydride + H_2SO_4	acetic acid	sinters 245-6
6	6,6-Dichloro-6-[1.2]benzisotiazolo[4.3-ab]phenazine	1	O_2S-N  + o-phenylenediamine	nitrobenzene	265-6 dec.
7	6-Oxo-6-[1.2]benzisotiazolo[4.3-ab]phenazine	1	oxidation of compound 3 with HNO_3 sp-gr. 1.4	acetic acid	over 280 dec.

¹ Zincke and Schürmann, *Ann.*, 412, 78 (1916).

10-Camphorsulfonanhydramide (I) and Related Compounds

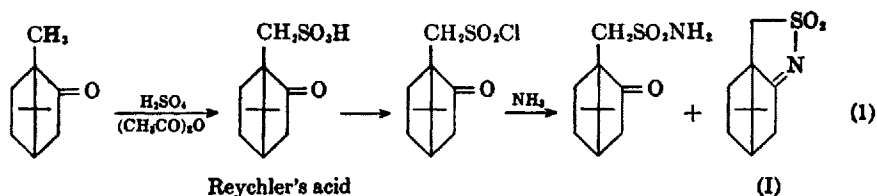


(I)

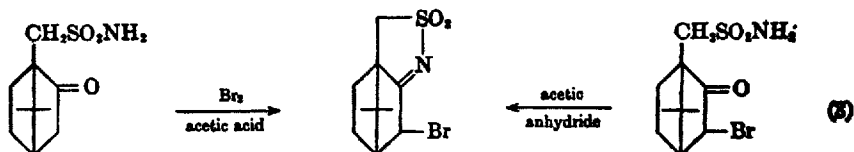
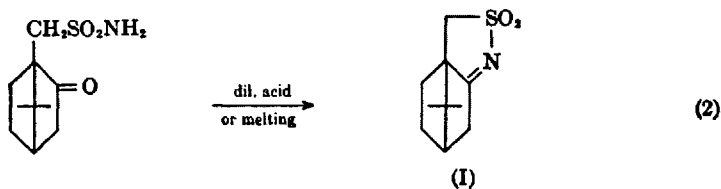


(Ring Index No. 1280)

Reychler¹ sulfonated camphor in acetic anhydride with concentrated sulfuric acid at room temperature. A single sulfonic acid was obtained. Derivatives of this sulfonic acid included one sulfonyl chloride and two sulfonamides. Reychler felt that these sulfonamides were stereoisomers. Armstrong and Lowry² showed that one of the isomers was the sultam of 1-iminocamphane-10-sulfonic acid or 10-camphorsulfonanhydramide (I).



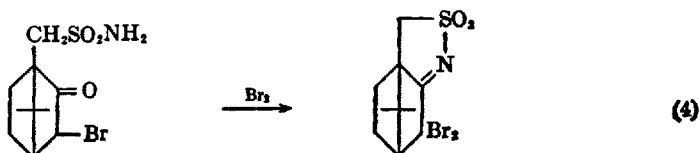
10-Camphorsulfonamide² was readily changed to 10-camphorsulfonanhydramide by boiling with dilute acids and heating at 170–200°C. (2). Apparently this reaction did not occur with the sulfonanilide and sulfonpiperide.



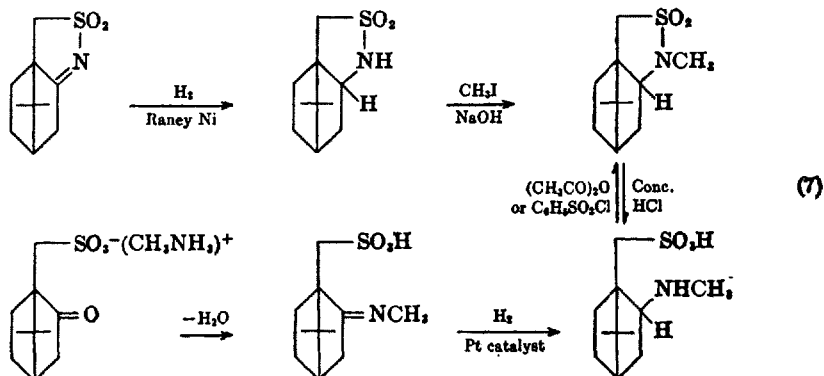
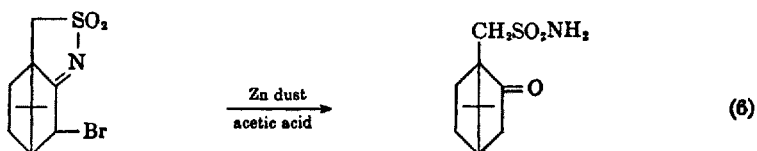
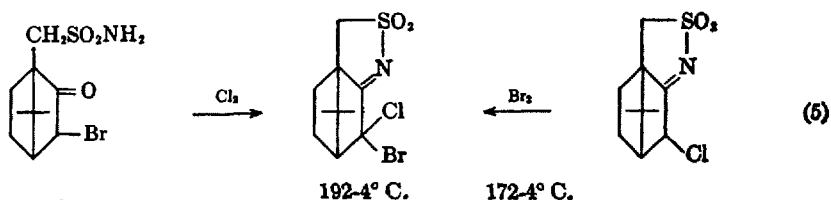
¹ Reychler, *Bull. soc. chim.*, 19, 120 (1898).

² Armstrong and Lowry, *J. Am. Chem. Soc.*, 81, 1441 (1902).

The α -bromo-10-camphorsulfonanhydramide² was prepared in two ways: the bromination of 10-camphorsulfonamide in acetic acid and the cyclization of α -bromocamphor-10-sulfonamide (3). Bromination of α -bromocamphor-10-sulfonamide yielded the α, α -dibromo-10-camphorsulfonanhydramide (4). The α -chloro derivatives were synthesized in a similar



manner. The α, α -bromochloro compound was made by either chlorinating α -bromocamphor-10-sulfonamide or brominating α -chlorocamphor-10-sulfonamide. However, different melting points were noted for the compounds obtained by the different syntheses (5). Reduction of α -bromo-10-



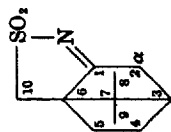
camphorsulfonanhydramide with zinc dust and acetic acid gave 10-camphorsulfonamide (6). Shriner *et al.*^{3,4} found 10-camphorsulfonanhydramide could be hydrogenated with Raney nickel in the presence of hydrogen. The resultant sultam of 1-amino-10-camphanesulfonic acid was methylated with methyl iodide in the presence of alkali and then hydrolyzed with concentrated hydrochloric acid. This furnished a clue as to the compounds obtained by the dehydration of the amine salts of Reychler's acid (7).

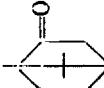
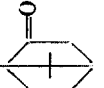
³ Shriner, Shotton, and Sutherland, *J. Am. Chem. Soc.*, **60**, 2794 (1938).

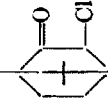
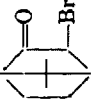
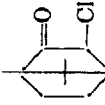
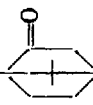
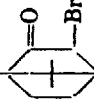
⁴ Schreiber and Shriner, *J. Am. Chem. Soc.*, **57**, 1896 (1933).

Table LXXII follows on page 376.

TABLE LXXII. Preparation of 10-Camphorsulfonanhydramide and Related Compounds

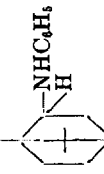
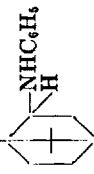


No.	Name	Ref.	Method of preparation	Solubility	Optical properties in degrees	M.p., °C.
1	10-Camphorsulfonanhydramide	1	 + NH_4OH $\text{CH}_3\text{SO}_2\text{Cl}$	alc.	$[\alpha]_D^{25} = -33.5$	220
2		2	 + $\text{CH}_3\text{SO}_2\text{NH}_2$ + dil. acid or heat	—	—	223
3		3	—	—	$[\alpha]_D^{25} = -32$	224 (corr.)
2	2-Bromo-10-camphorsulfonanhydramide	2	 + Br_2 $\text{CH}_3\text{SO}_2\text{NH}_2$	acetic acid, acetone	$[\alpha]_D^{25} = +99.3$	186
2		2	 + $(\text{CH}_3\text{CO})_2\text{O}$ $\text{CH}_3\text{SO}_2\text{NH}_2$	—	$[\alpha]_D^{25} = +40.5$	166

No.	Name	Ref.	Method of preparation	Solubility	Optical properties in degrees	M.p., °C.
3	2-Chloro-10-camphorsulfonanhydramide	2	 $\text{CH}_3\text{SO}_2\text{NH}_2$ + acid or $(\text{CH}_3\text{CO})_2\text{O}$	alc., acetic acid	$[\alpha]_D^{25} = +59.5$	167
4	2-Bromo-2-chloro-10-camphorsulfon-anhydramide	2	 $\text{CH}_3\text{SO}_2\text{NH}_2$ + Cl_2	acetic acid	$[\alpha]_D^{25} = -38.3$	192.4
		2	 $\text{CH}_3\text{SO}_2\text{NH}_2$ + Br_2	acetic acid	$[\alpha]_D^{25} = +7.8$ to $+2.4$	172-4
5	2,2-Dibromo-10-camphorsulfonanhydramide	2	 $\text{CH}_3\text{SO}_2\text{NH}_2$ + Br_2	acetic acid, alc.	$[\alpha]_D^{25} = -7.2$	195
			 $\text{CH}_3\text{SO}_2\text{NH}_2$ + Br_2	—	—	—

(Table continued)

TABLE LXXII (Concluded)

No.	Name	Ref.	Method of preparation	Solubility	Optical properties in degrees	M.p., °C
6	2,2-Dichloro-10-camphorsulfonamide	2	same as 5 with Cl ₂	alc., acetic acid	[α] _D = +16	172-6
7	2-Amino- <i>d</i> -camphane-10-sulfonic acid	3	reduction of compound 1 with Raney nickel	alc.	[α] _D ²⁵ = -33.0	181-2
8	2-Methylamino- <i>d</i> -camphane-10-sulfonic acid sultam	3	methylation of compound 7 dehydration of 2-methylamino-10-camphane sulfonic acid	water	[α] _D ²⁵ = 59.6 CHCl ₃	80
9	α-form: 2-anilino- <i>d</i> -camphane-10-sulfonic acid sultam	4	CH ₃ SO ₃ H 	methanol	[α] _D ²⁵ = -110	172-3
10	β-form: 2-anilino- <i>d</i> -camphane-10-sulfonic acid sultam	4	CH ₃ SO ₃ H 	methanol	[α] _D ²⁵ = 140.5	137-8

¹ Reyckler, *Bull. soc. chim.*, 19, 120 (1898).² Armstrong and Lowry, *J. Chem. Soc.*, 81, 1441 (1902).³ Shriner, Shotton, and Sutherland, *J. Am. Chem. Soc.*, 60, 2794 (1938).⁴ Schreiber and Shriner, *J. Am. Chem. Soc.*, 57, 1896 (1933).

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