THE PREPARATION AND CHEMICAL PROPERTIES OF THIONAMIDES

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I. Introduction

Although the history of the thionamides goes back to the first part of the 19th century it has only been in the last twenty years or so that these compounds have demonstrated much potential value as intermediates in the preparation of products of industrial and pharmaceutical value. The range of uses to which thionamides have been successfully applied in this short interval of time is very broad; it includes such widely diversified fields as metal deactivators in petroleum products and organic chemicals, vulcanization accelerators, pigments for plastics, and the synthesis of aliphatic, aromatic, and heterocyclic compounds of pharmacological interest.

These developments stimulated the preparation of this review of the literature through 1958 concerning the preparation and chemical properties of thionamides. This article is concerned with compounds that contain the groups —C(=S)NRR′ and —C(SR)=NR′, where R and R′ may represent hydrogen, a metal, and aliphatic, aromatic, or heterocyclic groups. As a practical limitation to the size of this review only those thionamides containing these groups bonded to either hydrogen or carbon are considered. Thus, a large body of literature on such classes of compounds as thioureas and thiocarbamates has been excluded. A further limitation is that the physical properties of the thionamides are not discussed as such.

II. Nomenclature

It has been common practice to name the sulfur analog of a carboxylic acid derivative by adding the prefix "thio" to the common name for the acid. This has led to some degree of ambiguity, in that use of the prefix "thio" does not sufficiently describe the manner in which the sulfur atom is bound in the organic compound. Thioglycolamide, for example, could be either $HSCH_2CONH_2$ or $HOCH_2CSNH_2$, although in common usage this name represents the former compound, mercaptoacetamide.

Since thionamides are derivatives of the corresponding thio acids, naming the latter necessarily sets the pattern for the former. I.U.C. Rules 1, 29, and 30 were used to define such nomenclature. Geneva names of acids were retained as I.U.C. systematic names (*cf.* I.U.C. Rule 29, J. Am. Chem. Soc. **55**, 3905 (1933)). Examples are hexanoic acid, $C_5H_{11}COOH$, and heptanedioic acid, $HOOC(CH_2)_5COOH$. I.U.C. Rule 30 states that for acids in which an atom of sulfur replaces an atom of oxygen of the carboxyl group, suffixes such as "thiolic" and "thionic" will be used. Examples are hexanethiolic acid, $C_5H_{11}COSH$, and heptanedithionic acid, $HOCS(CH_2)_5CSOH$.

These views were modified, however, by I.U.C. Rule 1, which says that "as few changes as possible will be made in terminology universally adopted." Thus, common names of acids, such as formic, acetic, propionic, oxalic, malonic, etc., belong not only to the common system but also to the I.U.C. system. This status was recognized by the I.U.P.A.C. at its 1949 and 1951 meetings, in that it recommended as official names for acyl radicals such common names as formyl, acetyl, propionyl, oxalyl, and malonyl to replace names not used in common practice such as methanoyl, ethanoyl, propanoyl, etc. By inference, then, the common names of the parent acids of these acyl radicals, such as formic, acetic, and propionic, are also recognized as official names in the I.U.P.A.C. system. Ethanethiolic acid, for example, which was the name for the structure CH_3COSH required by I.U.C. Rule 30, would now be modified to acetothiolic acid, and ethanethionic acid for the structure CH_3CSOH would be modified to acetothionic acid. Similarly, the hypothetical acid HOCSCSOH would be named oxalodithionic acid by this plan.

Amides are named by substituting the ending "-amide" for "-ic acid" or "-oic acid" of the name of the acid. By applying the I.U.C. and I.U.P.A.C. rules for amides to acids that have common names, thioacetamide becomes acetothionamide and dithiooxamide becomes oxalodithionamide.

An alternative method of naming sulfur derivatives of acids is to use the prefixes "thiol-" and "thion-" instead of "thio-." Thus, thioacetamide becomes thionacetamide and dithioöxamide becomes dithionoxamide.

The term thionamide represents a thio-keto form, $RCSNH_2$. The enolic form has been loosely referred to in the literature as an "isothioamide." In conformance with present rules of nomenclature the enolic forms should be named as derivatives of imidic acids. Thus, the compound $CH_3C(=NH)SH$ should be named acetimidothiolic acid or thiolacetimidic acid, just as its analog, $CH_3C(=NH)OH$, is called acetimidic acid.

Since hydroxamic acids, RCONHOH, are really *N*-hydroxyamides, it should be noted that they have always been named by use of the suffix (e.g., benzohydroxamic acid, not *N*-hydroxybenzamide). Here again, the term thio is not sufficiently descriptive, whether used as a prefix or as a suffix. The correct name for the hydroxamic acid $C_6H_5CH_2CSNHOH$, for example, is phenylacetothionhydroxamic acid.

Complex acids that require the additive carboxylic plan of nomenclature, such as 1,2,3-butanetricarboxylic acid, have no common names recognized by the I.U.P.A.C., and their thionamides should be named in accordance with I.U.C. Rule 30 (e.g., the above example becomes 1,2,3-butanetricarbothionamide, $CH_3CH(CSNH_2)CH(CSNH_2)CH_2CSNH_2$).

Throughout this review the thionamides have been named in accordance with the above discussion. In the case of thionamides of acids with common names,

the prefix "thion-" has generally been used unless for reasons of clarity it seemed best to employ the suffix "thionamide."

III. Preparation of Thionamides

A. Reaction of amides with phosphorus pentasulfide

This method, first reported in 1878 by A. W. Hofmann (141), has been widely utilized to prepare a variety of thionamides, examples of which are listed in table 1. The generalized reaction is represented

TABLE 1

Representative thionamides from phosphorus pentasulfide and amides

Thionamide	Yield	References
	per cent	
$HCSNH_2$	30–50	(47, 140, 243, 279, 325, 329)
CH_3CSNH_2	35–40	(127, 140, 184, 243)
$(CH_3)_2CHCSNH_2$	30–50	(47)
$C_6H_5CH_2CSNH_2$	—	(42, 180)
$C_6H_5CH_2CSNHCH_3$	—	(180)
$3,4\text{-}(CH_3O)_2C_6H_3NHCSCH_3$	55	(107)
$\overline{NH(CH_2)_7C{=}S}$	50–90	(269)
$4\text{-}ClC_6H_4NHCSCH_3$	54	(32)
$4\text{-}O_2NC_6H_4CSNH_2$	70–90	(47)
$4\text{-}H_2NC_6H_4CSNHC_6H_5$	5	(266)
$4\text{-}(CH_3)_2NC_6H_4CSNHC_6H_5$	—	(264)
Thionsaccharin	90	(210, 211, 213)
$C_6H_5NHCSCN$	—	(257)
$C_6H_5CH_2CSNHCH_2COOC_2H_5$	—	(130)
$(CH_3CSNH)_2CH_2$	—	(251)
$H_2NCSCOOC_2H_5$	—	(258)
Dithioncamphorimide	—	(239)
4-Aminoimidazole-5-carbothionamide	—	(132)

by the following equation:

$$5RCONR_2 + P_2S_5 \rightarrow 5RCSNR_2 + P_2O_5$$

Although Hofmann used inert diluents in many of his preparations, there were many contemporary reports of syntheses in which stoichiometric amounts of powdered phosphorus pentasulfide and amide were warmed or fused to a tarry mass from which the thionamide was isolated by extraction (42, 141, 290, 329). Thionformamide was so prepared in 50 per cent yield (329). This yield was much more dependent on the purity of the sulfide than on that of the formamide.

An improved procedure results from the use of dry, inert solvents. Although side products are also formed with this procedure, they are generally insoluble in the solvents used, whereas the thionamides are soluble. Hydrocarbons, such as benzene, xylene, or tetralin, and ethers, such as tetrahydrofuran and dioxane, have most commonly been used. The boiling points of these solvents are high enough so that the reaction is generally complete in less than 1 hr. at the reflux temperature.

Kindler found that increased yields were obtained by the use of an intimate, powdered mixture of phosphorus pentasulfide and potassium sulfide (180). The usual practice has been to use either equal weights of the components or a slight excess of potassium sulfide to form the mixture. However, hexahydro-1*H*-azonine-2(3*H*)-thione, $\overline{NH(CH_2)_7C{=}S}$, was formed in only 50 per cent yield by treatment of the corresponding lactam with this mixture in hot xylene, whereas a nearly quantitative yield was obtained by omitting the potassium sulfide and adding sodium hydroxide at the end of the reaction (269). *N*-Methylthionbenzanilide was prepared by warming a mixture of *N*-methylbenzanilide, phosphorus pentasulfide, and phosphorus trisulfide in the absence of a solvent (217).

In the case of *N*-unsubstituted thionamides, the yield may be reduced by a secondary reaction.

$$RCSNH_2 \xrightarrow{P_2O_5} RCN + H_2S$$

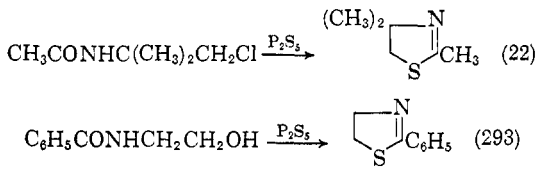
To minimize the effect of this reaction it is important to isolate the thionamide as soon as it has been formed. Certain nitriles have been prepared in good yield by this secondary reaction (128).

The phosphorus pentasulfide reaction cannot be used successfully with either heat-sensitive amides or thionamides. Thionformamidopyrimidines could not be made from the corresponding formamidopyrimidines (302, 303).

A systematic study of the effect of aromatic substituents upon the yields of thionbenzamide and thionbenzanilide derivatives has not been reported, but it is evident that this effect may be large. 3- and 4-Nitrobenzanilides or *N*-(3-nitrophenyl)- and *N*-(4-nitrophenyl)benzamides gave the corresponding thionamides in 70–90 per cent yields upon treatment for a short time with phosphorus pentasulfide in boiling xylene (266). The corresponding 3- and 4-amino analogs, however, could be obtained in only 5 per cent yields, even when a fused, powdered mixture of phosphorus pentasulfide and potassium sulfide was used. When boiling toluene was used as the medium for conversion of the 3- and 4-amino analogs, the reaction rate was very slow.

In contrast to the above, the reduction of the nitro groups of 4,4′-dinitroöxanilide was believed to occur when this dianilide was refluxed for 7 hr. in boiling xylene with phosphorus pentasulfide (250). Analysis of the product demonstrated that it was not the expected 4,4′-dinitrodithionoxanilide, and the analysis suggested that reduction of the nitro groups had occurred.

N-Substituted amides with functional groups in the *N*-substituent that are beta to the nitrogen may undergo cyclization upon treatment with phosphorus pentasulfide. The following examples are illustrative:



The second reaction, above, gave a cystamine derivative, $(C_6H_5CONHCH_2CH_2S—)_2$, in addition to 2-phenyl-2-thiazoline. This disulfide was believed to have arisen from the oxidation of *N*-(2-mercaptoethyl)-benzamide, formed by replacement of the hydroxyl group by a mercapto group. Mild treatment of methyl phenylacetamidoacetate with phosphorus pentasulfide and potassium sulfide gave $C_6H_5CH_2CSNHCH_2COOCH_3$ (130), whereas more drastic treatment of this ester with phosphorus pentasulfide led to 2-benzyl-5-methoxythiazole (229).

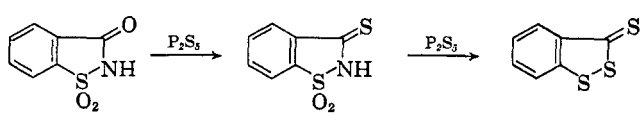
With diamides, both mono- and dithionamides are formed. A mixture of 2,4-diacetamidotoluene and phosphorus pentasulfide in ca. 2:1 molar ratio gave a mixture of mono- and dithionamides in 7:2 molar ratio (87). Similarly, *N*-phenyloxamide gave both oxanilothionamide, $C_6H_5NHCOCSNH_2$, and *N*-phenyldithionoxamide (257). The former product was transformed into the latter by further treatment with phosphorus pentasulfide. Oxanilide behaved similarly.

Ester groups are unaffected by the conditions of the reaction, as was shown by the preparation of ethyl thionoxanilate, $C_6H_5NHCSCOOC_2H_5$ (257).

Kindler (180) discovered that when a mixture of *N,N*-dimethylbenzamide and phosphorus pentasulfide was boiled in carbon disulfide, an oily addition compound was formed whose composition corresponded to one mole of phosphorus pentasulfide and two moles of the amide. This intermediate could be hydrolyzed to give amide, phosphoric acid, and hydrogen sulfide, or decomposed on warming in a higher boiling solvent to the corresponding thionamide.

The preparation of thionformamide and its subsequent conversion to *N*-substituted or *N,N*-disubstituted thionformamides by reaction with primary and secondary amines, respectively, has been combined into one step by the reaction of formamide and phosphorus pentasulfide in the presence of primary or secondary amines (326).

Thionsaccharin (II) was rapidly formed in 90 per cent yield upon heating saccharin (I) and phosphorus pentasulfide (III) to 225°C. (210, 211). In addition, a small amount of 1,2-benzodithiole-3-thione (IV) was isolated. II was shown to be an intermediate



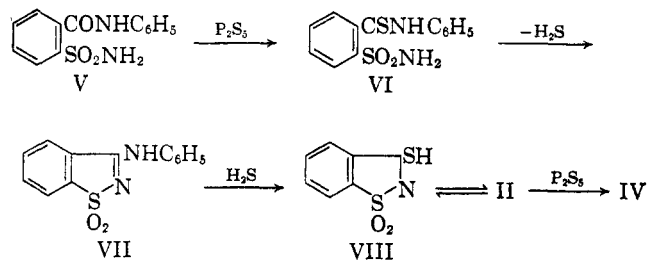
I
Saccharin

II
Thionsaccharin

IV

in the formation of IV, as further treatment of II with III gave IV in good yield.

When the anilide (V) was fused with III, the expected thionamide (VI) was formed, but in addition IV was again isolated. The following sequence of reactions was proposed to account for these transformations (213):



In support of this hypothesis was the observation that compound VI, upon being heated to 280°C., evolved hydrogen sulfide and formed VII and IV. The last step, though not proved, was supported by the fact that the yield of IV by treatment of II with phosphorus pentasulfide was greater than that from similar treatment of I. When equimolar amounts of V and III were heated to 180°C., hydrogen sulfide was evolved and three products were isolated: VI, VII, and an intensely violet substance also obtained in small yield upon prolonged heating of a mixture of saccharin and aniline.

B. REACTION OF AMIDES WITH ALUMINUM TRISULFIDE AND HYDRATES

A thionamide is formed by heating an amide, aluminum trisulfide, and a hydrated salt, such as sodium sulfate hexahydrate, in a sealed tube (185). Enough sulfide and hydrate are used to insure that there is an excess of hydrogen sulfide present in the reaction mixture. Thionbenzamide was thus prepared in a sealed tube heated to 250°C. for 90 min. (185). If, instead of an amide, the ammonium salt of the corresponding acid is used, the hydrate may be omitted from the reaction mixture. Kindler found that good yields were obtained with both aliphatic and aromatic thionamides (182).

C. THIONAMIDES FROM NITRILES AND CYANOGEN

There are several related routes to thionamides from nitriles, and when considered as a whole these routes make nitriles a most important source of thionamides.

One procedure is to saturate an ammoniacal, absolute alcoholic solution of the nitrile with hydrogen sulfide. The resulting solution may then be left to stand at room temperature, warmed, or heated under pressure to complete the reaction. This preparation is favored by exclusion of water and a high concentration of hydrogen sulfide (178). A number of examples are given in table 2.

TABLE 2

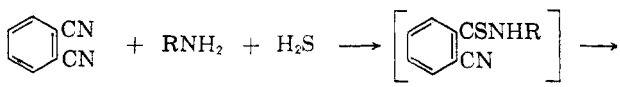
Thionamides from nitriles by reaction with ammonia and hydrogen sulfide in absolute alcohol

Thionamide	Yield	References
	per cent	
CH_3CSNH_2	—	(41)
$C_6H_5CH_2CSNH_2$	—	(34, 179)
$CH_3CCl_2CSNH_2$	—	(304)
$C_2H_5OCOCSNH_2$	—	(319)
4-FC_6H_4NH, $CCSNH_2$, 4-FC_6H_4N	—	(267)
1,4-$(CSNH_2)_2C_6H_4$	93	(93)
3-$C_2H_5OC_6H_4CSNH_2$	100	(323)
4-$CH_3SO_2C_6H_4CSNH_2$	100	(105)
4-$H_2NCSC_6H_4CHOHCH$, $NHCOCH_3$, CH_2OH	75	(234)

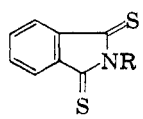
Hydrosulfides, such as ammonium hydrosulfide and potassium hydrosulfide, were found to be effective catalysts for this preparation, and dimethylammonium hydrosulfide was recommended to catalyze the reaction in dry benzene (178).

The effect of ring substituents upon reaction velocity has been measured for a series of benzonitrile derivatives (181). When the measured reactions were carried out in anhydrous alcohol with sodium ethoxide at 60°C. and under a slight pressure (1.75 atm.), no side reactions occurred. Velocities, relative to that of benzonitrile (100), were obtained for the following derivatives (ring substituents only named): *m*-bromo, 831; *p*-iodo, 518; *p*-chloro, 493; *p*-bromo, 451; *p*-methyl, 51.9; *p*-methoxy, 41.6.

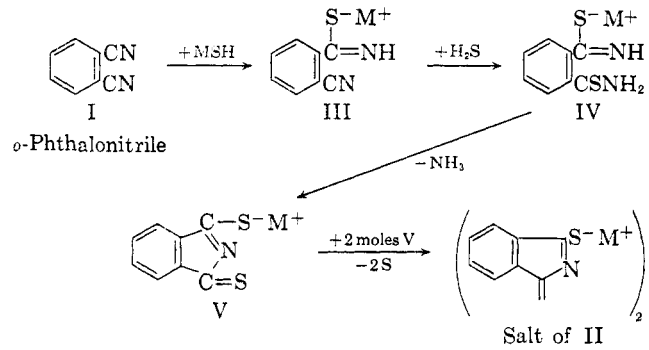
This procedure has been extended to the use of primary amines, in place of ammonia, for the preparation of *N*-substituted thionamides (126). A slight excess of amine and nitrile were dissolved in a solvent, such as an alcohol, an aromatic hydrocarbon, dioxane, or acetone, saturated at 0°C. with hydrogen sulfide, and then heated to 100–150°C. in a pressure vessel for 6–10 hr. Nitriles, such as *o*-phthalonitrile, in which nitrile groups are separated by only two carbon atoms, were found to form *N*-substituted dithionimides under these conditions.



o-Phthalonitrile



In contrast to the above reaction under pressure, Drew and Kelly (85) found that when *o*-phthalonitrile (I) was treated with hydrogen sulfide in the presence of aqueous or alcoholic ammonia or alkali at room pressure a good yield of dithion-β-isoindigo (II) was formed rather than the expected product, dithionphthalimide. They proposed the following mechanism:



M = NH_4^+ or Na^+.

The principal product of the reaction of I with aqueous alcoholic ammonium hydrosulfide (85) or sodium hydrosulfide (248) was the salt of *o*-cyanothionbenzamide (III). Ammonium hydrosulfide was observed to have no action upon I in dry benzene, even after long refluxing; in the presence of a small amount of alcohol, reaction quickly occurred (85). Compound I did not react with ammonia in either hydroxylic or nonhydroxylic solvents. Likewise, sodium sulfide did not react with I to form III, and neither did hydrogen sulfide in nonhydroxylic solvents. Thus, the formation of III required a hydroxylic solvent and was enhanced by the presence of a base (85).

Further evidence that III was an intermediate in the formation of II was shown by the quantitative conversion of III to II by treatment with hydrogen sulfide and aqueous or alcoholic ammonia. V could be isolated as an intermediate product by using a lesser proportion of ammonia in a benzene–alcohol system (85).

V was oxidized to II in a number of ways: heating with silver powder, treatment with alcoholic ammonia either in the presence of or without hydrogen sulfide, treatment with aqueous or alcoholic alkali, or heating the dry salt to 200°C. (85). All of these methods gave nearly quantitative yields of II. The sulfur formed in these reactions was obtained either as free sulfur or as a mixture of sulfur and polysulfides.

The fact that *o*-cyanobenzamide did not react with hydrogen sulfide and an aqueous or alcoholic ammonia solution means that there was no possibility that the first step in the above mechanism was due to addition of either water or alcohol to a cyano group of *o*-phthalonitrile. It was considered that since *o*-phthalonitrile (I) did not react with hydrogen sulfide and ammonia in a nonhydroxylic solvent, there was no possibility that the first step was addition of ammonia to a cyano group of I.

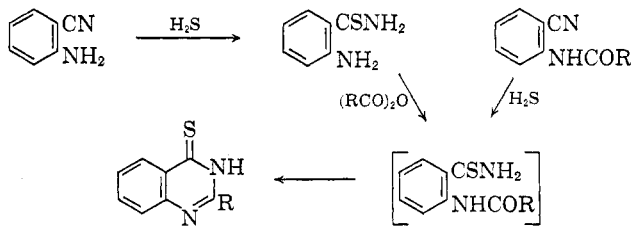
In contrast to *o*-phthalonitrile, malononitrile was found to form dithionmalonamide on reaction with hydrogen sulfide in cold alcoholic solution containing potassium ethoxide (199). In similar fashion, adiponitrile gave dithionadipamide (92).

Thionamides have been prepared by direct reaction of a nitrile with hydrogen sulfide without use of a base or an inert solvent. Thus, acetonitrile gave thionacetamide at 80°C. and 8500 atm. (56). Careful temperature control had to be observed, as hydrogen sulfide acts as a reducing agent at this pressure and a temperature of 125–150°C. Thionacetamide, for example, was reduced to a polysulfide, $(CH_3CH_2)_2S_3$.

Tertiary amines have been employed in place of ammonia to prepare unsubstituted thionamides in chloroform (241) and pyridine (96). Excellent yields were obtained by treating a solution of an aromatic cyanide in an equal weight of pyridine with dry hydrogen sulfide in the presence of triethylamine for 2 to 4 hr. The following products were reported: *p*-chlorothionbenzamide (100 per cent), *p*-ethanesulfonylthionbenzamide (70 per cent), and phenylazothionacetamide (75 per cent) (96). It was noted that this procedure offered no advantage for the preparation of aliphatic thionamides because of the slow rate of reaction.

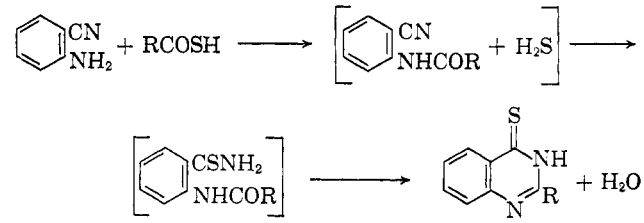
Aqueous conditions may also be utilized. Thionoxamide, $H_2NCOCSNH_2$, was isolated in 70 per cent yield from the reaction of 1-cyanoformamide and hydrogen sulfide in dilute, aqueous base at room temperature (321).

N-Acylanthranilonitriles, as well as the nitriles of alanine and glycine, undergo cyclization during attempts to convert them to thionamides. Anthranilonitrile, itself, could be converted to thionanthranilamide, which was then cyclized by reaction with an acid anhydride to a derivative of quinazolin-4(3*H*)-thione (45). The two reactions could be carried out simultaneously by treating the aminonitrile with an acid anhydride and sodium sulfide. This heterocycle was also prepared directly by the action of hydrogen sulfide upon *N*-acetylanthranilonitrile. The various reactions are shown below:



R = CH_3, C_2H_5, $(CH_3)_2CH$, or C_4H_9.

The thionamide derivatives of anthranilic acid used in the above study were prepared in sealed tubes by the reaction of nitriles with hydrogen sulfide in ammoniacal solution at 100°C. The yield of 2-methylquinazolin-4-(3*H*)-thione from the reaction of anthranilonitrile, acetic anhydride, and sodium sulfide in a sealed tube at 100° C. was excellent. Poor yields resulted from boiling thionanthranilamide with acetic anhydride or from heating *N*-acetylanthranilonitrile with hydrogen sulfide in ammoniacal, alcoholic solution at atmospheric pressure. The latter procedure gave a good yield when executed in a sealed tube. The same products were obtained upon heating anthranilonitrile and thiolic acids in sealed tubes. Thionamides were again presumed to be intermediates according to the following equation. 2-Methylquinazolin-4(3*H*)-thione was prepared in quan-



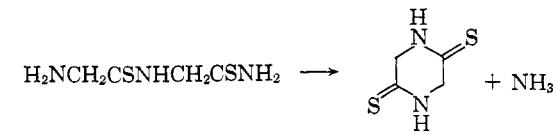
titative yield in this manner (45). It was later discovered that a small yield of *N*-acetylthionanthranilamide could be isolated from the reaction of *N*-acetylanthranilonitrile and hydrogen sulfide in the presence of tris(2-hydroxyethyl)amine in alcoholic solution (72). The main product, however, was the same heterocycle.

Normal thionamide formation occurred upon treatment of 2-(*N*-acetylsulfanilamido)benzonitrile with hydrogen sulfide in pyridine at 100°C. (73).

Aminoacetonitrile reacted with hydrogen sulfide in a cold, ammoniacal, alcoholic solution containing ammonium sulfate to give the heterocycle, 2,5-dithionpiperazine (116). Thionamides are known to condense with primary amines with the evolution of ammonia, so the ring closure may proceed as follows:

$$H_2NCH_2CN + H_2S \rightarrow H_2NCH_2CSNH_2$$

$$2H_2NCH_2CSNH_2 \rightarrow H_2NCH_2CSNHCH_2CSNH_2 + NH_3$$



2-Aminopropionitrile cyclized similarly to give 3,6-dimethyl-2,5-dithionpiperazine (207). Yields in both cases were small. In the latter instance the major product was the corresponding iminodipropionitrile. Because the yields of 2,5-dithionpiperazines in these two cases were small and these two α-aminonitriles were the only ones of many examined that gave dithionpiperazines, this reaction cannot be regarded as general. For example, α-aminoisobutyronitrile under the same reaction conditions gave a crystalline product, $C_7H_{14}N_2S$ (117). This product was shown not to be a dithionpiperazine, α-aminoisobutyrothionamide, or a thionpolypeptide. The structure 2,2,4,4-tetramethylimidazolidine-5-thione was tentatively assigned to the product. Since pure iminodiisobutyronitrile interacted with hydrogen sulfide to give the same product, the reaction of α-aminoisobutyronitrile was formulated as follows:

$$2(CH_3)_2C(NH_2)CN \rightarrow NH[C(CH_3)_2CN]_2 + NH_3$$

$$NH[C(CH_3)_2CN]_2 \xrightarrow{2H_2S} NH[C(CH_3)_2CSNH_2]_2$$

$$NH[C(CH_3)_2CSNH_2]_2 \longrightarrow \begin{matrix}(CH_3)_2 & \text{—} & NH \\ & & | \\ HN & & CS \\ & & (CH_3)_2\end{matrix}$$

In contrast, aminoacetonitrile and iminodiacetonitrile did not react with hydrogen sulfide to form the same product. Thus, several mechanisms must be operative in these transformations of α-amino acids. The synthesis of thionamides from aminonitriles is discussed further in Section III,D.

As noted already in the case of anthranilonitrile (*loc. cit.*), thionamides have been prepared by the interaction of *o*-aminonitriles and thiolic acids under acidic conditions and under pressure (45). Cold ethereal solutions of equimolar amounts of nitriles and thiolic acids, saturated with hydrogen chloride, also give rise to thionamides (158). The yields are dependent on the thiolic acid used: thionbenzamide was so formed from benzonitrile in yields of 75 per cent and 100 per cent by the use of acetothiolic acid and benzothiolic acid, respectively. Aromatic substitution of the benzonitrile derivatives also exerted an effect: acetothiolic acid gave rise to *p*-nitro- and *m*-nitrothionbenzamides in yields of 40 and 6 per cent, respectively, from the corresponding benzonitrile derivatives. *p*-Tolunitrile and 2-naphthonitrile gave very small yields of thionamides under these conditions. Several side products have been isolated from these preparations. Dibenzimidoyl sulfide, $(C_6H_5C{=}NH)_2S$, was isolated in small amounts from the above reactions in which benzonitrile was used. In the preparation of thionbenzamide much more of this contaminant appeared with the use of acetothiolic acid than with benzothiolic acid.

Any speculation on the formation of thionamides from nitriles under such acidic conditions must take into account that the thiolic acids do not, by themselves, react with hydrogen chloride in ether. Ishikawa stated that an imidochloride was first formed which then condensed with the thiolic acid (158).

$$RCN + HCl \xrightarrow{\text{ether}} RC(=NH)Cl$$

$$RC(=NH)Cl + R'COSH \rightarrow [RC(=NH)SCOR'] + HCl$$

$$\downarrow$$

$$RCSNH_2 + R'COCl$$

$$RCN + RCSNH_2 \rightarrow (RC{=}NH)_2S$$

When a nitrile in ether solution saturated with hydrogen chloride was treated with hydrogen sulfide or a sulfide, either a thionamide or a diimidyl sulfide was obtained as the major product.

The formation of dithionoxamide (rubeanic acid) from cyanogen and hydrogen sulfide has been the subject of much investigation (31, 83, 90, 104, 165, 256, 309, 311, 332, 334). Most procedures have dealt with the reaction of the gaseous starting materials in alcohol or the reaction of cyanogen in liquid hydrogen sulfide (31, 165, 309, 311, 332, 334). In either case, an excess of hydrogen sulfide is used. 1-Cyanothionformamide was identified as an intermediate product of the reaction in liquid hydrogen sulfide (165) and was prepared using an excess of cyanogen in alcohol (309). Several processes have been described in which potassium hydrosulfide (256) or sodium hydrosulfide (83, 90, 334) was used.

Rubeanic acid has been produced on a commercial scale by passing a mixture of cyanogen and hydrogen chloride into a stirred, aqueous solution (pH 7–9) of sodium hydrosulfide at temperatures below 50°C.

$$(CN)_2 + 2H^+ + 2HS^- \rightarrow H_2NCSCSNH_2$$

(83). The gaseous starting materials were prepared from the reaction of chlorine and hydrogen cyanide at high temperatures in a tube packed with charcoal. In this process, dark-colored side products that limited the utility of the reaction under acid conditions were avoided.

Dithionoxamide has also been made by the reaction of ethyl cyanoformimidate, $NCC(=NH)OC_2H_5$, or diethyl oxaldiimidate, $(—C(=NH)OC_2H_5)_2$, with hydrogen sulfide in the presence of base (307).

D. THIONAMIDES FROM ALDEHYDE AND KETONE CYANOHYDRINS

This method is an extension of the previous one in that hydrogen sulfide reacts with the nitrile group of a cyanohydrin to form an α-hydroxythionamide. Thus, α-hydroxythionisobutyramide was obtained in 58 per cent yield by the interaction of α-hydroxyisobutyronitrile and hydrogen sulfide under high pressure (8500 atm.) at 30°C. (56).

In comparison with the reactions of α-aminonitriles (158, 170, 294) (Section III,C), the cyanohydrins have not been found to give oxydinitriles (corresponding to iminodinitriles) or 2,5-dithiondioxane derivatives (corresponding to 2,5-dithionpiperazines).

Abe (8) treated ketones successively with hydrogen cyanide, ammonia, and hydrogen sulfide under mild conditions and observed that the type of product isolated was dependent upon the type of ketone from which the α-aminonitrile was formed. Aliphatic ketones gave derivatives of imidazolidine-4-thione, aliphatic aromatic ketones gave α-aminothionamides, and aromatic ketones gave derivatives of dibenzhydryl disulfide. Three examples are given below:

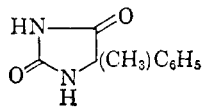
$$CH_3COC_2H_5 \longrightarrow \begin{matrix} & & HN & \text{—} & S \\ & & & & \\ C_2H_5(CH_3) & & & & (CH_3)C_2H_5 \\ & & N & & \\ & & H & & \end{matrix}$$

$$C_6H_5COCH_3 \rightarrow C_6H_5C(NH_2)(CH_3)CSNH_2$$

$$C_6H_5COC_6H_5 \rightarrow [(C_6H_5)_2CHS—]_2$$

The yields of the major product isolated were poor in

each case. For some reactions the side products were isolated and identified. In the case of acetophenone they were 5-methyl-5-phenylhydantoin and a minute amount of α-iminobis(α-phenylpropionitrile):



$NH[-C(CH_3)(C_6H_5)CN]_2$

α-Iminobis(α-methylthionbutyramide) was the structure tentatively assigned to an unstable by-product of the reaction with ethyl methyl ketone.

Aromatic aldehydes and α,β-unsaturated aliphatic ketones gave thionamides unaccompanied by heterocyclic side products when similarly treated with hydrogen cyanide, ammonia, and hydrogen sulfide. From vanillin was obtained in good yield, α-amino-α-(4-hydroxy-3-methoxyphenyl)thionacetamide (4); mesityl oxide gave a poor yield of 2-amino-2,4-dimethyl-3-pentenethionamide (9).

Thionamides were readily prepared by treatment of basic alcoholic solutions of acylated aldehyde cyanohydrins with hydrogen sulfide (240). Thus, α-phenyl-α-benzoyloxythionacetamide was prepared in good yield. The bases used included triethylamine, triethanolamine, pyridine, and potassium hydrosulfide. Pyridine, however, tended to exert a desulfurizing action.

E. THIONAMIDES FROM AMIDINES AND AMIDOXIMES

Hydrogen sulfide reacts with amidines and amidoximes in a manner closely related to its reaction with nitriles. Yields are variable. By saturating alcoholic

$$RC(=NH)NH_2 + H_2S \rightarrow RCSNH_2 + NH_3$$

solutions of oxamidine derivatives with hydrogen sulfide the following dithionoxamides were isolated (yields in parentheses): *N,N'*-dibutyl- (70 per cent); *N,N'*-diethyl- (45 per cent); *N,N'*-bis(3-methoxypropyl)- (60 per cent); and *N,N'*-bis(2-hydroxyethyl)- (8.5 per cent) (335). *N*-Substituted and *N,N'*-disubstituted amidines have been used to prepare the corresponding substituted thionamides (38, 310).

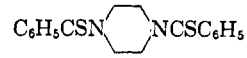
Similarly, the thionamide $(C_6H_5)_2NCOCSNH_2$ was prepared by the action of hydrogen sulfide on *N*-phenyloxanilamidoxime, $(C_6H_5)_2NCOC(=NOH)NH_2$, in ammoniacal solution (222).

The preparation of *N*-substituted thionamides by heating the corresponding *N*-substituted amidines with carbon disulfide to 100°C. has been reported (227).

F. THE WILLGERODT–KINDLER REACTION

Thionamides are isolated as the principal products of the Kindler modification of the Willgerodt reaction, in which ketones are heated with approximately equimolar amounts of sulfur and an amine under anhydrous conditions (180, 183). The literature on this subject has been thoroughly reviewed up to 1948 (58, 221). Carmack and Spielman, in their review (58), observed that the potentialities of this method as a source of thionamides and nitrogenous bases derived from them had only recently been appreciated. During the era of these reviews the mechanism of this reaction was extensively investigated (59, 187), and it was found that in addition to ketones many other types of compounds also gave thionamides under the same conditions (58, 221). These included aldehydes, the reduction products of ketones (secondary and tertiary alcohols), thiols, disulfides, imines, olefins, acetylenes, and α,β-unsaturated acids (which give the thionamide of the next lower homolog). For example, acetophenone, phenylacetylene, and styrene all gave *N*-(phenylthionacetyl)morpholine in about the same yield upon heating to 150°C. with morpholine and sulfur (59). The use of high-boiling amines, such as morpholine, in this procedure has made it possible to carry out the reaction in open vessels rather than autoclaves or sealed tubes.

Since these reviews, the application of this method has been extended. A general method for the preparation of *N,N*-disubstituted thionamides in good yields from aromatic aldehydes has been reported (66). Thus, *N*-(thionbenzoyl)morpholine was isolated in 85 per cent yield from the reaction of equimolecular amounts of benzaldehyde, sulfur, and morpholine in refluxing carbon disulfide solution. With piperazine, both nitrogens were thionacylated to form *N,N'*-bis-(thionbenzoyl)piperazine,



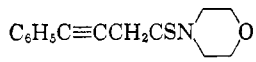
in two steps: (*1*) the water of hydration of piperazine was removed as an azeotrope in benzene and the di-Schiff base formed; (*2*) solvent was removed and the di-Schiff base heated (100–150°C.) with sulfur.

A failure of the Willgerodt–Kindler reaction conditions to produce a thionamide has been reported. 3,5-Diiodosalicylaldehyde did not react with sulfur and morpholine to form a thionamide; instead, morpholinium iodide was obtained (66). This behavior was in contrast to the easy reaction of 5-bromo- or 3,5-dibromosalicylaldehyde.

Both dithionoxalyl-*N,N'*-dimorpholine (53 per cent yield) and *N*-(thionacetyl)morpholine (45 per cent yield) were obtained upon the passage of acetylene through a refluxing mixture of sulfur and morpholine (204). After removal of excess morpholine the former product was isolated by heating the methanol-extracted, solid product with an aqueous solution of sodium sulfide. The latter product was obtained by distilling the methanolic extracts. Interestingly, *N*-(thionacetyl)-morpholine was converted into dithionoxalyl-*N,N'*-dimorpholine by refluxing with sulfur in morpholine for an extended time during which hydrogen sulfide

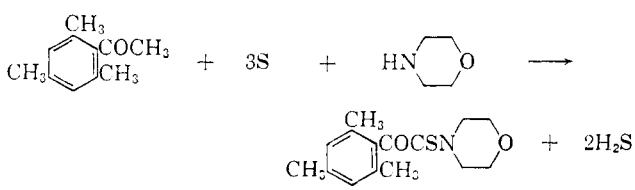
was evolved. Similar product mixtures were obtained with thiomorpholine, piperidine, and pyrrolidine. Ammonia could be used in place of secondary amines by operating in dioxane or pyridine at 100–150°C. (203).

N-(4-Phenyl-3-butynothionyl)morpholine,



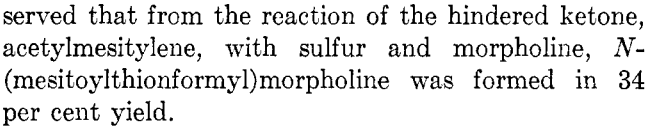
was prepared in 51 per cent yield by refluxing methyl phenylethynyl ketone with sulfur and morpholine for 3 hr. (238). When the conditions of the original Willgerodt reaction were applied to this acetylene derivative, by heating it with ammonium polysulfide to 190°C., an unstable product containing nitrogen and sulfur was obtained.

Neither of the above two reactions, with acetylene or methyl phenylethynyl ketone, could be completely explained by any of the mechanisms proposed up to the time of the aforementioned reviews (58, 221). Other limitations had already been suggested. Both of the mechanisms that appeared to come closest to fitting the experimental data (59, 187) required initial attack at the carbonyl group (either by addition of amine or by reduction to a hydroxyl or mercapto group). Dauben and Rogan have proposed that the reaction is initiated upon the activated α-methylene (or methyl) group in aliphatic aromatic ketones (81). They observed that from the reaction of the hindered ketone, acetylmesitylene, with sulfur and morpholine, *N*-(mesitoylthionformyl)morpholine was formed in 34 per cent yield.



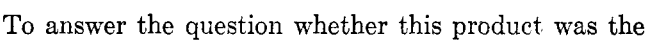
To answer the question whether this product was the result of a "normal" Willgerodt–Kindler reaction or whether it came from oxidation of the active methyl group by sulfur, propionylmesitylene was subjected to the same reaction conditions. The product was assigned the structure of *N*-(α-mesitoylthionacetyl)-morpholine. The question as to whether this product might have come from oxidation of the ω-carbon atom of the enol form of the ketone was answered in the negative by the similar synthesis of *N*-(β-mesitoylthionpropionyl)morpholine from butyrylmesitylene. These results were interpreted to mean that the ketone carbonyl group served to activate the α-carbon, and that the initial intermediate was an α,β-unsaturated ketone, rather than an olefin as proposed earlier (187). Dauben and Rogan suggested that this intermediate could be formed by attack of sulfur on the α-carbon atom, followed by loss of hydrogen sulfide. The double bond could then migrate to the terminal position by successive additions and eliminations of hydrogen sulfide or amines in the manner proposed by King and McMillan (187). The terminal double bond was then irreversibly oxidized. The ketonic carbonyl group was reduced to a methylene group at some undetermined point in the mechanism after attack at the α-carbon atom had occurred. In the case of methyl ketones, the Willgerodt–Kindler reaction would occur by oxidation of the methyl group followed by reduction of the carbonyl group.

When styrene was subjected to the Willgerodt–Kindler reaction in the presence of benzylamine, a small amount of *N*-benzylthionbenzamide was formed in addition to the major product, phenylacetic acid (219). No such side product was found when morpholine was substituted for benzylamine in this reaction. The formation of *N*-benzylthionbenzamide was explained by the observation that it could be prepared in 91 per cent yield when benzylamine and sulfur in equimolecular amounts were heated together in an open vessel. When this oxidation was carried out in a sealed tube, however, the product was thionbenzamide (314). In the open vessel ammonia was given off copiously. McMillan explained the difference by the following two reactions, which give rise to ammonia (219):



When morpholine was heated in the open with benzylamine and sulfur, *N*-(thionbenzoyl)morpholine was obtained, presumably by the reaction of the amine with intermediate thionbenzamide.

Closely related to the foregoing is the reaction of benzylamine, sulfur, and lead oxide in benzene at 20°C. to give bis(thionbenzamido) disulfide (206).



With ethylamine, only pitches and sulfur were obtained.

The above oxidations of amines by sulfur may proceed through the intermediate formation of Schiff bases. *N*-Benzylidenemethylamine was exothermically oxidized by sulfur at 200°C. to a good yield of *N*-methylthionbenzamide with concurrent evolution of hydrogen sulfide (46). Similarly, *N*-benzylideneëthylamine gave *N*-ethylthionbenzamide, but here a small amount of stilbene was also isolated. *N*-Benzylideneaniline, at 170–200°C., gave the expected thionbenzanilide; at 280°C. cyclization occurred with the formation of 2-phenylbenzothiazole.

N,N'-Dithiobis(dibenzylamine) gave dibenzylammonium hydrogen sulfide and *N*-benzylthionbenzamide upon thermal decomposition at 140°C. *in vacuo*

(273). Thionamides had previously been prepared from disulfides, in support of the mechanism of King and McMillan, who proposed that as one of the final intermediate steps in the Willgerodt–Kindler reaction disulfides are formed by the oxidation of terminal mercaptans (187). Saville suggested that upon thermal decomposition, an N—S bond of the disulfide ruptured and a Schiff base then formed (273).

$$(C_6H_5CH_2)_2\overset{\curvearrowleft}{N}—S—S—N(CH_2C_6H_5)_2 \rightarrow (C_6H_5CH_2)_2N^- + (C_6H_5CH_2)_2NS_2^+$$

$$(C_6H_5CH_2)_2N^- + H—CH(C_6H_5)N(CH_2C_6H_5)S_2^+ \rightarrow (C_6H_5CH_2)_2NH + C_6H_5CH{=}NCH_2C_6H_5 + S_2$$

A complex product mixture containing *N*-benzylthionbenzamide was obtained. The formation of several of the products in this mixture was attributed to Willgerodt reactions (273).

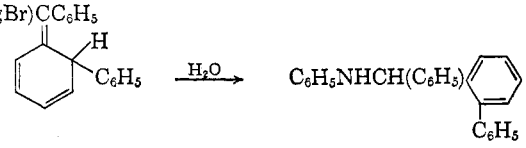
In support of the hypothesis that the Willgerodt reaction commences with attack by sulfur upon an activated methylene or methyl group (81), α- and γ-picoline produced *N*-(thionpicolinoyl)morpholine and *N*-(thionisonicotinoyl)morpholine in 40 and 22 per cent yields, respectively, by reaction with sulfur and morpholine at 150–170°C. (247). With aniline, α-picoline gave the corresponding thionanilide at 160°C. in 63 per cent yield; γ-picoline at 180°C. for twice as long a period gave 2-(4-pyridyl)benzothiazole by reaction with aniline. The relatively inactive methyl group of β-picoline, however, did not undergo these reactions. The reaction was extended to 4-ethylpyridine, which with morpholine gave the expected product, *N*-(4-pyridylthionacetyl)morpholine in 50 per cent yield.

G. THIONAMIDES FROM ISOTHIOCYANATES AND ISOCYANATES

Grignard reagents add to the thioncarbonyl bond of isothiocyanates to form adducts which, upon hydrolysis, give thionamides in excellent yield. Worrall has prepared a number of *N*-substituted thionvaleramides and thionvaleranilides, for example, in better than 90 per cent yields by using a 50 per cent excess of butylmagnesium bromide with various isothiocyanates (337). Thionbenzanilide was obtained in 88 per cent yield from the reaction of phenyl isothiocyanate and phenylmagnesium bromide (15).

When the intermediate Grignard adduct was treated with methyl sulfate, formation of an *S*-methyl isothionamide derivative occurred (122). If the Grignard reaction was executed at a much higher temperature for a longer period with a large excess of Grignard reagent a further reaction occurred. Thus, with phenyl isothiocyanate and phenylmagnesium bromide a 45 per cent yield of *o*-phenylbenzhydrylaniline was found (123). The proposed sequence is shown in the equations.

$$C_6H_5NCS + C_6H_5MgBr \rightarrow C_6H_5N{=}C(C_6H_5)SMgBr \xrightarrow{C_6H_5MgBr} (MgBr)_2S + C_6H_5N{=}C(C_6H_5)_2 \xrightarrow{C_6H_5MgBr}$$



Isothiocyanates yield thionamides by reaction with compounds containing active methylene groups. For example, diethyl sodiomalonate and methyl isothiocyanate formed a sodio adduct which gave an 80 per cent yield of *N*-(dicarbethoxymethyl)thionacetamide, $CH_3NHCSCH(COOC_2H_5)_2$, after hydrolysis (338).

Both the organodisodium compounds formed by 1,2-addition of sodium to olefins and those obtained by a dimerizing addition of sodium to olefins (120) react with isothiocyanates. There follows an example of each type (275):

$$2C_2H_5NCS + (C_6H_5)_2CNaCNa(C_6H_5)_2 \rightarrow C_2H_5N(Na)CSCSN(Na)C_2H_5 + (C_6H_5)_2C{=}C(C_6H_5)_2$$

$$2C_2H_5NCS + (C_6H_5)_2CNaCH_2CH_2CNa(C_6H_5)_2 \rightarrow (C_6H_5)_2CCH_2CH_2C(C_6H_5)_2CSN(Na)C_2H_5 \quad (\text{with } CSN(Na)C_2H_5 \text{ on the central carbon})$$

The dithionamides were obtained after hydrolysis of the disodio adducts.

Triphenylmethylsodium reacts with isothiocyanates like a Grignard reagent: with allyl isothiocyanate the product obtained was *N*-allyltriphenylthionacetamide (276).

Organolithium compounds have also been used with isothiocyanates to prepare thionamides. The olefin (or mixture of olefins) resulting from acid dehydration of 2-methyl-1,1-diphenylpropanol was treated with lithium for four weeks, after which reaction with phenyl isothiocyanate gave 3-methyl-2,2-diphenyl-3-butenethionanilide (275).

$$(CH_3)_2CHC(OH)(C_6H_5)_2 \xrightarrow{HCl} \left\{ (C_6H_5)_2C{=}C(CH_3)_2 \text{ and/or } (C_6H_5)_2CHC(CH_3){=}CH_2 \right\} \xrightarrow[(2)\ C_6H_5NCS]{(1)\ Li} CH_2{=}C(CH_3)C(C_6H_5)_2CSNHC_6H_5$$

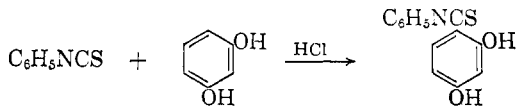
Phenyllithium and triphenylsilyl isothiocyanate underwent reaction in ether to give thionbenzamide in 57 per cent yield (121).

Phenyl isocyanate and phenyl isothiocyanate both react with dithioformic acid in toluene to give thionformanilide (303).

$$C_6H_5NCO + HCS_2H \rightarrow HCSNHC_6H_5 + COS$$

$$C_6H_5NCS + HCS_2H \rightarrow HCSNHC_6H_5 + CS_2$$

A variety of thionamides have been prepared by the condensation of phenyl isothiocyanate with phenols, polyhydric phenols (173, 261), phenyl ethers (305), and aromatic hydrocarbons (118) in the presence of acidic reagents such as aluminum chloride, zinc chloride, and hydrochloric acid.



When several isomers are possible the product that is isolated depends on the acidic reagent and the solvent used. The condensation of α-naphthol with phenyl isothiocyanate is illustrative: with aluminum chloride in carbon disulfide a 60 per cent yield of 1-hydroxy-*N*-phenyl-2-thionaphthamide was obtained (218); the same product was isolated with aluminum chloride in the absence of a solvent (261); in ether, aluminum chloride gave a mixture of this product and the 4-hydroxy isomer (218); and finally, by use of zinc chloride in ether the 4-hydroxy isomer was isolated in 50 per cent yield (218). Benzene, toluene, and anisole were condensed with aromatic isothiocyanates by warming with powdered aluminum chloride to give the expected *N*-arylthionbenzamide derivatives (118, 305).

H. THIONAMIDES FROM CARBODITHIOIC ACID DERIVATIVES

This route to thionamides has been put to much use in recent years in the preparation of thionamides that are intermediates in the syntheses of products of biochemical interest, such as thioacylated amino acids (76, 89, 144, 191, 192), purine derivatives (25), and vitamin B_1 derivatives (302). It is convenient to discuss this source of thionamides in two parts: (*1*) carbodithioic esters; (*2*) carbodithioic acids and their salts.

Carbodithioic esters are readily accessible. Holmberg (143) found that the highest yield (ca. 50 per cent) of carboxymethyl dithiobenzoate, $C_6H_5CS_2CH_2COOH$, was obtained by the reaction of chloroacetic acid with the product of interaction of benzotrichloride and potassium sulfide in alcoholic solution. On the other hand, Kjaer (191) reported that the most convenient large-scale preparation of this ester was by the reaction of phenylmagnesium bromide and carbon disulfide in ether, hydrolysis of the Grignard adduct, and immediate reaction of the intermediate dithioic acid with chloroacetic acid. Carboxymethyl phenyldithioacetate was similarly prepared from benzylmagnesium chloride in 70 per cent yield (192). These esters may be stored for long periods without deterioration (192).

Carbodithioic esters have a unique value in that there are no other generally satisfactory reagents for thionacylating amino acids. Both Kjaer (191) and McOmie (220) have reviewed this aspect of the literature on thionacylation. Thionbenzoylglycine was prepared in better than 90 per cent yield by the reaction at room temperature of equimolar amounts of glycine and carboxymethyl dithiobenzoate in aqueous base (144).

$$H_2NCH_2COOH + C_6H_5CS_2CH_2COOH \rightarrow C_6H_5CSNHCH_2COOH$$

Table 3 summarizes the results of thionacylation of some amino acids by carboxymethyl dithiobenzoate under mild basic conditions (191).

TABLE 3

Thionacyl amino acids

$C_6H_5CSNHCH(R)COR'$

R	R'	Yield
		per cent
H	OCH_3	68
CH_3*	OCH_3	78
H	NH_2	89
CH_3*	NH_2	82
C_6H_5*	NH_2	87
4-$HOC_6H_4CH_3$†	NH_2	89

* DL-racemate. † L-stereoisomer.

However, no reaction occurred with ethyl α-aminoisobutyrate (191). Failure was attributed to steric hindrance (191, 192). DL-Lysine gave a monothionacylated derivative upon reaction with carboxymethyl phenyldithioacetate (192). The product gave a positive ninhydrin test for an α-amino acid, and on this basis the following structure was assigned: $C_6H_5CH_2CSNH(CH_2)_4CH(NH_2)COOH$. Thionbenzoylation proceeded without racemization on L-alanine, L-valine, L-isoleucine, and L-leucine (192). Although thionbenzoylation of diethyl aminomalonate could be carried out in aqueous alkali, it was found to be more convenient to use pyridine containing triethylamine (76). Thionbenzoylanthranilic acid was formed in good yield by the reaction of anthranilic acid and carboxymethyl dithiobenzoate in aqueous alkali at room temperature (144). Thionbenzamides have also been prepared in good yields by the reaction of dithioic esters with amines such as morpholine and aniline (192). A standard procedure for the reaction of methyl phenyldithioacetate with amino acids has been described, in which a 10 per cent molar excess of the ester is added to an alcoholic solution of the sodium salt of the amino acid (75).

Thionamides have also been obtained directly from carbodithioic acids and their salts. The carbodithioic acids are readily available. Dithiobenzoic acid, 1-dithionaphthoic acid, and *p*-dithiotoluic acid were obtained in 48, 80, and 30 per cent yields, respectively, by reaction of the appropriate Grignard reagent with carbon disulfide (15). 2-Dithiofuroic acid was prepared in 50 per cent yield by reaction of furfural and sodium polysulfide (15). Potassium dithioformate was formed from the reaction of chloroform with potassium sulfide (205). Dithioic acids are unstable oils (15, 220); dithioformic and phenyldithioacetic acids are best kept as their potassium salts (220).

Water-soluble amines and potassium dithioformate react in aqueous solution at room temperature to

precipitate thionformamides. For easy isolation of a water-soluble product, it was suggested that the amine and dithioformic acid be shaken together in ether or dioxane until evolution of hydrogen sulfide is complete, and the solvent then removed. Water-insoluble amines react well with potassium dithioformate suspended in ether or chloroform (303). In this manner aniline and 6-aminoquinoline gave quantitative yields of their thionformyl derivatives. In general, the aliphatic thionformamides are liquids, with the exception of ethylenebis(thionformamide). A better yield (30 per cent) of thionformamide was obtained from the reaction of dithioformic acid and ammonia in ether than from the reaction of formamide and phosphorus pentasulfide (303).

In the case of certain diamines, unstable thionformyl compounds that readily cyclized were formed (303). Thus, *o*-phenylenediamine gave an unstable thionformyl derivative in aqueous solution at 0°C. which changed quickly into benzimidazole at room temperature. However, the formation and isolation of *N*-(2-aminophenyl)thionformamide from *o*-phenylenediamine under essentially the same reaction conditions has been reported (205). Monoacetyl-*o*-phenylenediamine gave a quantitative yield of stable *N*-(2-acetamidophenyl)-thionformamide (303). *o*-Aminobenzylamine also underwent cyclization on reaction with potassium dithioformate to give a dihydroquinazoline in quantitative yield (303). If the neighboring amino group is weakly basic, no cyclization occurs. Thus, no cyclization was observed during the thionformylation of the 5-amino group of 5,6-diamino-4-methylpyrimidine (302) and the 5-aminomethyl group of 4-amino-5-aminomethyl-2-methylpyrimidine (133, 134, 137).

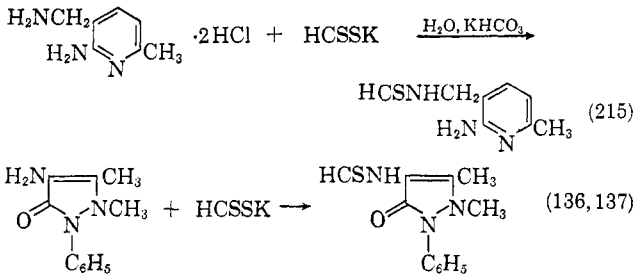
Potassium dithioformate did not react with indole, diphenylamine, or *N*-methylaniline (303).

3-Methylphenyldithioacetic acid reacted with 1-methyl-1-phenylhydrazine to form the corresponding hydrazide (341):

$$3\text{-}CH_3C_6H_4CH_2CSSH + H_2NN(CH_3)C_6H_5 \rightarrow 3\text{-}CH_3C_6H_4CH_2CSNHN(CH_3)C_6H_5$$

A great number of 2,4,6-trisubstituted 5-thionacylpyrimidines have been prepared from the corresponding 5-aminopyrimidines (18, 19, 25, 133, 134, 136, 137, 147, 150, 175, 196, 209, 215, 216, 221, 260, 298, 299, 302, 303). It was observed that only an amino group in the 5-position was readily acylated or thionacylated. These products were generally prepared under mild conditions, as described above, and in good—often quantitative—yields. If the hydrochlorides of 5-aminopyrimidines were used, as was often the case, a base such as potassium carbonate was added in sufficient amount for neutralization. 5-Thionacylpyrimidines could not be prepared by treatment of the corresponding 5-acylpyrimidines with phosphorus pentasulfide (302).

The thionacylation of other heterocycles has also been accomplished. Two examples are given in the following equations:



The salts of dithioic acids have been condensed with amines in the presence of an oxidizing agent such as iodine to give the same organic products obtained in the absence of the oxidizing agent. The technique used was to add an aqueous solution of iodine and potassium iodide slowly to a cold, basic, aqueous solution of the dithioic salt and the amine (15, 285). *p*-Thiontoluanilide (95 per cent yield) and 2-thionfuranilide (100 per cent yield) were prepared in this manner. It was suggested that unstable thionacylsulfenamides were the initial products of the oxidative condensations (15).

$$RCSSNa + H_2NC_6H_{13} \rightarrow [RCSSNHC_6H_{13}] \rightarrow RCSNHC_6H_{13}$$

This hypothesis was based upon the observation that *N*,*N*-dialkylthioncarbamoylsulfenamides were formed upon simultaneous addition of a solution of a dithiocarbamate and either iodine or a 10 per cent solution of sodium hypochlorite at about equimolar rates to an excess of concentrated ammonia (286).

$$RR'NCSSNa + NH_3 \xrightarrow{NaOCl} RR'NCSSNH_2 + NaOH$$

The thioncarbamoylsulfenamides were decomposed by heating or long standing into thioureas by loss of sulfur.

Related to the foregoing condensation is oxidation of the amines prior to condensation with a dithioic acid. *N*-(2-Thionfuroyl)piperidine and *N*-(thionbenzoyl)piperidine were obtained in quantitative yields by reaction of the corresponding dithioates with *N*-chloropiperidine (14, 15). Intermediate formation of sulfenamides was also proposed for these reactions (15).

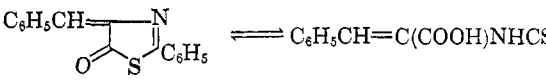
I. THIONAMIDES FROM THIONIC ESTERS

Thionic esters react with amines in a manner similar to dithio esters (*loc. cit.*) to yield thionamides. Esters of thionic acids, RCSOR′, are readily obtained by treatment of ether solutions of the corresponding imido esters with dry hydrogen sulfide (270). They should be prepared as used, since they are oxyluminescent (i.e., they oxidize spontaneously in air with emission of light) (84). These esters react with amines in ether solution to form thionamides; phenylthionhydrazides

are similarly formed from phenylhydrazine (271). Excess amine has also been used as solvent: *N*-(2-hydroxyethyl)thionbenzamide and *N*-isopropylthionbenzamide were formed in 53 and 63 per cent yields, respectively, by the reaction of ethyl thionbenzoate with excess 2-hydroxyethylamine and isopropylamine (124).

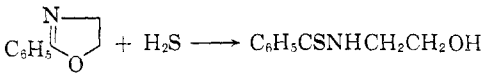
J. THIONAMIDES FROM THE CLEAVAGE OF HETEROCYCLIC RINGS

Thionamides result from basic attack at the carbonyl carbon of 5(4*H*)-thiazolones. Thus, α-(thionbenzamido)-cinnamic acid was formed by boiling 4-benzylidene-2-phenyl-5(4*H*)-thiazolone in normal sodium hydroxide solution (208). The reaction was reversed in 85 per cent yield by warming the cinnamic acid derivative in acetic anhydride.



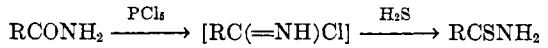
The same 5(4*H*)-thiazolone derivative gave the piperidide of α-(thionbenzamido)cinnamic acid in 60 per cent yield when warmed with piperidine. Similarly, *N* - [α - (thionbenzamido)dihydrocinnamoyl]piperidine was formed from 4-benzyl-2-phenyl-5(4*H*)-thiazolone.

2-Oxazolines are cleaved by hydrogen sulfide to yield thionamides. For example, treatment of a methanolic solution of 2-phenyl-2-oxazoline, ammonium sulfide, and ammonium hydroxide with hydrogen sulfide gave *N*-(2-hydroxyethyl)thionbenzamide in 77 per cent yield (124).



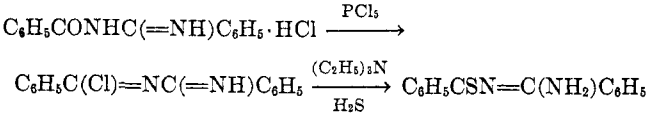
K. THIONAMIDES AND DITHIONIMIDES FROM ACID CHLORIDES

Thionamides have been obtained when the corresponding amides were treated with phosphorus pentachloride, then hydrogen sulfide, in an inert solvent (174). The intermediates, which were not isolated, were probably imidyl chlorides.

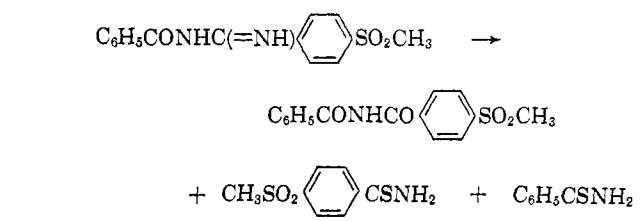


Hydroxyl and amino groups of polyfunctional amides were protected by reaction with toluenesulfonamides during this synthesis. Complex thionamides that have been prepared in this manner as precursors to cyanine dyes include thionphenacetin (4-$C_2H_5OC_6H_4NHCSCH_3$), *p*-thionacetanisidide (4-$CH_3OC_6H_4NHCSCH_3$), *N*,*N*′-*p*-phenylenebisthionacetamide [1,4-$(CH_3CSNH)_2C_6H_4$], and 5-thionacetamidotrimethylpyrogallol.

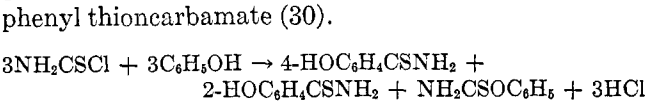
N-Thionbenzoylbenzamidine derivatives were obtained from the corresponding *N*-benzoylbenzamidines in a similar manner (241). For example, a 25 per cent yield of *N*-thionbenzoylbenzamidine was isolated by refluxing a chloroform solution of *N*-benzoylbenzamidine with phosphorus pentachloride, adding this reaction mixture dropwise to a solution of triethylamine in chloroform, chilling, and then saturating this mixture with hydrogen sulfide.



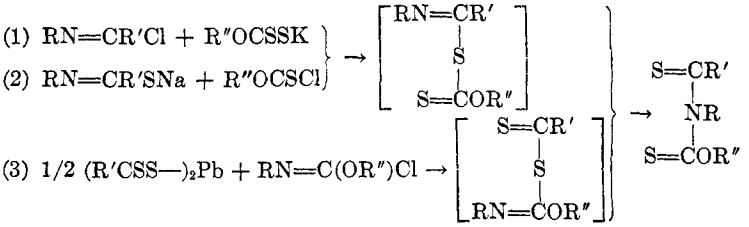
Similarly, *N*-thionbenzoylanisamidine and *N*-thionbenzoyl-*p*-chlorobenzamidine were made in 48 and 26 per cent yields, respectively (241). However, a like treatment of *N*-benzoyl-*p*-methanesulfonylbenzamidine gave three products arising from cleavage and hydrolysis (241):



Thioncarbamoyl chloride reacted with phenol to give thionsalicylamide, *p*-hydroxybenzthionamide, and phenyl thioncarbamate (30).



Rivier and Schalch (263) found three closely related routes to esters of *N*-(thionacyl)thioncarbanilic acids, generalized in the following three equations:



As an example of the first method ethyl *N*-(thionbenzoyl)thioncarbanilate, $C_6H_5CSN(C_6H_5)CSOC_2H_5$, was prepared by the reaction of *N*-phenylbenzimidoyl chloride and potassium *O*-ethylxanthate in boiling benzene. The *N*-(α-naphthyl) and *N*-(β-naphthyl) analogs were similarly prepared.

Ethyl chlorothioncarbonate was obtained for use in the second method shown above by the reaction of thionphosgene and sodium ethoxide in chloroform at room temperature. On warming the distilled ethyl ester with thionbenzanilide and sodium ethoxide in chloroform the same product, $C_6H_5CSN(C_6H_5)CSOC_2H_5$, was obtained. With variations in reaction temperatures,

the following carbamate and carbanilate esters were similarly prepared:

$4\text{-}(CH_3)_2NC_6H_4CSN(C_6H_5)CSOC_2H_5$
$C_6H_5CSN(\beta\text{-}C_{10}H_7)CSOC_6H_5$
$C_6H_5CSN(C_6H_5)CSO(\beta\text{-}C_{10}H_7)$
$C_6H_5CSN(\beta\text{-}C_{10}H_7)CSO(\beta\text{-}C_{10}H_7)$
$C_6H_5CSN(\alpha\text{-}C_{10}H_7)CSO(\beta\text{-}C_{10}H_7)$
$C_6H_5CSN(\beta\text{-}C_{10}H_7)CSO(\alpha\text{-}C_{10}H_7)$

Ethyl *N*-(thionbenzoyl)thioncarbanilate was also obtained according to equation 3 (above). The reaction took two or more months for completion at room temperature in benzene or chloroform; at higher temperatures decomposition occurred.

Analogous *N*-unsubstituted carbamates, RCSNHCSOR′, could not be made by any of these methods. Reaction of phenyl chlorothioncarbonate with thionbenzamide according to equation 2 (above) gave a mixture of products from which diphenyl thioncarbonate and benzonitrile were isolated.

Existence of the intermediate *S*-imidylxanthates of the above equations was not rigorously proved, but received support from other observations (164, 265).

Diimidyl sulfides, $[RN{=}C(C_6H_5){-}]_2S$, are compounds closely related to the foregoing esters of *N*-thionacylthioncarbanilates in methods of preparation and in structure. Of three methods that were tried, only one was found to be generally applicable for their preparation (265):

$$RN{=}C(C_6H_5)Cl + R'N{=}C(C_6H_5)SK \xrightarrow{C_2H_5OH} \begin{matrix} RN{=}CC_6H_5 \\ \diagdown \\ S \\ \diagup \\ R'N{=}CC_6H_5 \end{matrix} + HCl$$

R = C_6H_5, R′ = C_6H_5; R = α-$C_{10}H_7$, R′ = α-$C_{10}H_7$; R = C_6H_5, R′ = α-$C_{10}H_7$.

Another method was found to give small yields of the desired diimidyl sulfides and large yields of thionanilides. In this procedure an ethereal solution of an imidyl chloride was added to an alcoholic solution of potassium sulfide.

$$2RN{=}C(C_6H_5)Cl + K_2S \rightarrow [RN{=}C(C_6H_5)]_2S + 2KCl$$

A third method for the preparation of diimidyl sulfides was found in the interaction of thionbenzanilides and *N*-arylbenzimidyl chlorides. This reaction, however, was slow and gave poor yields in the presence or absence of solvents. The initially formed *N*-(*N*′-arylbenzimidyl)thionbenzanilide slowly rearranged to a diimidyl sulfide.

$$RN{=}C(C_6H_5)Cl + C_6H_5CSNHR' \rightarrow \begin{matrix} RN{=}CC_6H_5 \\ | \\ NR'\cdot HCl \\ | \\ S{=}CC_6H_5 \end{matrix} \rightarrow \begin{matrix} RN{=}CC_6H_5 \\ | \\ S \\ | \\ R'N{=}CC_6H_5 \end{matrix} + HCl$$

N-Thionbenzoylguanidines have been prepared by the reaction of thionbenzoyl chloride with 1-alkyl-1,2,3-triphenylguanidines in 75 per cent yield (262).

$$C_6H_5CSCl + C_6H_5NRC(NHC_6H_5){=}NC_6H_5 \rightarrow C_6H_5CSN(C_6H_5)C(NRC_6H_5){=}NC_6H_5$$

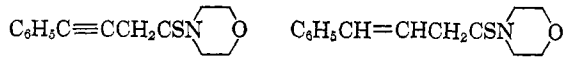
R = CH_3 or C_2H_5.

IV. Chemical Properties of Thionamides

A. Hydrolysis

Many thionamides and *N*-substituted thionamides are readily hydrolyzed by the action of acids or bases. Carboxylic acids are most frequently the end products, but nitriles and amides are also obtained in many cases. This discussion will be limited to hydrolysis in which neither oxidation nor heterocyclic ring formation occurs; such aspects of hydrolysis are discussed in either the section concerned with oxidation of thionamides or the sections dealing with the preparation of heterocyclic ring compounds from thionamides.

No report was encountered in the preparation of this review that dealt with a systematic study of the effects of other substituents in the thionamide derivatives upon the relative ease of either acidic or basic hydrolysis and on the nature of the hydrolysis products. It is apparent from a comparison of qualitative observations recorded in the literature that the nature of the substituent or functional group and its position in the molecule relative to the thionamide group exert considerable influence of this type. For example, thionhydrazides of the type $RCSNHNHC_6H_5$, where R may be an alkyl, aralkyl, or aryl hydrocarbon radical, were found to be easily hydrolyzed by both acids and alkalies (271). On the other hand, *N*-benzylthionbenzamide hydrolyzed very slowly in refluxing 50 per cent sulfuric acid (219). Another example is a comparison of *N*-(4-phenyl-3-butynthionoyl)morpholine and *N*-(thionstyrylacetyl)morpholine (238). The former was not hydrolyzed on refluxing for 10 hr. with either 20



per cent alcoholic potassium hydroxide reagent or a solution of concentrated hydrochloric acid in glacial acetic acid. The latter also was not hydrolyzed under similar basic conditions, but was hydrolyzed under the same conditions of acidic hydrolysis. The unidentified product of this hydrolysis was shown to be free of nitrogen and sulfur. It was not benzoic acid.

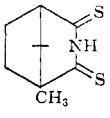
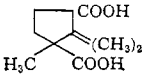
Thionamides may, under certain conditions, be more difficult to hydrolyze than the corresponding amides. Thus, *N*-(thionbenzoyl)morpholine was hydrolyzed in 10 *N* sodium hydroxide one-tenth as rapidly as *N*-benzoylmorpholine (62). *N*,*N*′-Bis(thionacyl)piperazine derivatives were similarly found to be quite resistant to hydrolysis (62).

Table 4 illustrates the types of products that have been obtained on acidic and basic hydrolysis of simple thionamides containing no other functional groups.

Nitrous acid in acidic or neutral media merely hydro-

TABLE 4

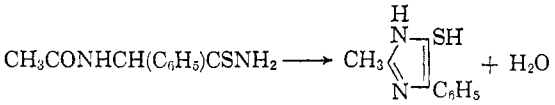
Hydrolysis of monofunctional thionamides

Thionamide	Acid or Base	Products	Reference
$HCSNH_2$	Boiling water	H_2S	(330)
	Cold NaOH	NH_3	(330)
	Concentrated H_2SO_4	H_2S, SO_2	(330)
CH_3CSNH_2	Acids or bases	CH_3COOH, NH_3, and H_2S	(127)
	$NaOC_2H_5$	Na_2S, CH_3CN	(170)
		C_2H_5SH, $Na_2S_2O_3$, NH_3, and CH_3COONa	
$CH_3CSNHC_2H_5$	Hot NaOH	$C_2H_5NH_2$	(271)
$(CH_3CSNH—)_2CH_2$	Acids or alkali	HCHO, CH_3COOH, NH_3, and H_2S	(251)
$C_6H_5CH_2CSNH_2$	Warm KOH	H_2S, $C_6H_5CH_2CN$	(34)
	Dilute HCl	H_2S, NH_3, and $C_6H_5CH_2COOH$	(34)
$C_6H_5CSNH_2$	Boiling water	C_6H_5COOH, H_2S	(197)
	Hot 1 *N* HCl	C_6H_5COOH, H_2S, and NH_3	(197)
	Cold KOH	C_6H_5CN; no NH_3	(197)
	Hot 1 *N* KOH	C_6H_5CN, H_2S, and NH_3	(197)
$CH_3CSNHC_6H_5$	Cold NaOH	No hydrolysis	(201)
	Hot NaOH		(239)

lyzes amides to carboxylic acids. In contrast, oxidation occurs with thionbenzamide, causing cyclization in 75 per cent yield to 3,5-diphenyl-1,2,4-thiadiazole (see the oxidation of thionamides by nitrous acid) (79). Likewise, oxidation occurs during the treatment of certain thionanilides with sulfuric acid, leading to the formation of benzothiazole derivatives (see the oxidation of thionamides by sulfuric acid, Section IV, E,10).

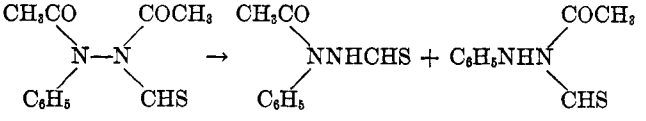
Thionbenzoylglycine, $C_6H_5CSNHCH_2COOH$, is stable in cold alkali, and can be prepared by saponification of its ethyl ester with cold, alcoholic potassium hydroxide (116). However, it was observed to lose sulfur on boiling in either acid or alkali (116). The products were identified as hippuric acid, thiolbenzoic acid, glycine, and hydrogen sulfide (191). When a carboxylic group is attached to the α-carbon atom of a thionamide, cleavage occurs. *N*-Methyl-α,α-dicarbethoxythionacetamide underwent hydrolysis in either dilute acid or base to give acetic acid, methylamine, ethyl alcohol, carbon dioxide, and hydrogen sulfide (338).

Cyclization occurred on warming α-acetamido-α-phenylthionacetamide with a 10 per cent potassium hydroxide solution for a short time (5).



2-Phenyl-2-acetamidothionpropionamide was cyclized by warming in 20 per cent hydrochloric acid or in dilute potassium hydroxide (followed by acidification) to give 2,4-dimethyl-4-phenyl-5(4*H*)-imidazolethione hydrochloride (5).

N,N'-Diacetyl-*N*-phenyl-*N'*-thionformylhydrazine on hydrolysis in 10 per cent sodium hydroxide solution gave a mixture of products, the major component of which was *N*-acetyl-*N*-phenyl-*N'*-thionformylhydrazine (272).



Phenyl *N*-(thionbenzoyl)thioncarbanilate, $C_6H_5CSN(C_6H_5)CSOC_6H_5$, slowly decomposed in sulfuric acid. Thionbenzanilide was one of the decomposition products (263).

The hydrolyses of thionamide derivatives of oxanilic acid and oxalic acid are summarized in table 5. One inference that may be drawn from table 5 is that a thionanilide group is much more resistant to hydrolysis than a thionamide group. Conditions may be adjusted so that only the latter group is hydrolyzed when the former is in an α-position in the same structure (257).

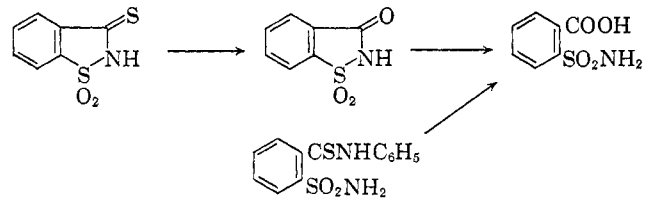
The carbon–carbon bonds of the thionamide derivatives of oxanilic and oxalic acids are not cleaved under hydrolytic conditions when a thionanilido group is present, but are broken when only an unsubstituted thioncarboxamide group is present.

The basic hydrolysis of thionsaccharin takes place in two steps (210).

TABLE 5

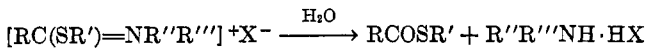
Hydrolysis of thionamide derivatives of oxanilic and oxalic acids

Thionamide	Conditions of Hydrolysis	Products	Reference
$H_2NCSCOOC_2H_5$	Boiling water	Sulfur	(319)
	Boiling alcoholic $Pb(OH)_2$	$HCOOC_2H_5$	(319)
H_2NCSCN	Dilute KOH	$K_2C_2O_4$, K_2S, and NH_3	(309)
	Concentrated KOH	KCN, K_2S, KCNS	(309)
$C_6H_5NHCSCOOC_2H_5$	Cold NaOH	$C_6H_5NHCSCOOH$	(257)
$C_6H_5NHCSCOOH$	Long boiling in water	$C_6H_5NHCOCOOH$, H_2S	(257)
$C_6H_5NHCOCSNH_2$	Hot NaOH	$C_6H_5NHCOCOOH$, Na_2S, and NH_3	(257)
$C_6H_5NHCSCSNH_2$	Boiling NaOH	$C_6H_5NHCSCOOH$, NH_3, and $C_6H_5NH_2$	(257)
	Cold 10 per cent NaOH	$C_6H_5NHCSCN$, Na_2S	(257)
$H_2NCSCSNH_2$	Boiling, concentrated KOH	K_2S, KCN, and KSCN	(309)
	Boiling, dilute KOH	K_2S, $K_2C_2O_4$, and NH_3	(309)
	Boiling, dilute HCl	NH_4Cl, $(COOH)_2$, and H_2S	(309)

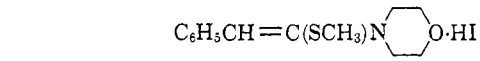


On prolonged boiling in water thionsaccharin was hydrolyzed to saccharin with evolution of hydrogen sulfide. On treatment with cold sodium carbonate solution, a soluble yellow sodium salt formed from which thionsaccharin precipitated on acidification. The same observations were made for either cold or hot ammonium hydroxide solutions. Under the more rigorous conditions of boiling sodium carbonate or cold sodium hydroxide solutions, thionsaccharin was hydrolyzed to saccharin. Finally, with boiling sodium hydroxide solution ring cleavage occurred, as shown in the above equation. The same products were found from acid hydrolysis. 2-(Sulfamoyl)thionbenzanilide was hydrolyzed by hot dilute alkali to the same product, 2-(sulfamoyl)-benzoic acid (213).

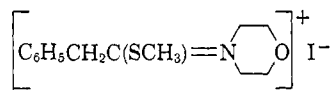
Esters of thiolimidic acids (also known as "isothioamides") are much more easily hydrolyzed than thionamides, although the initial products of hydrolysis are different. Thiolic esters are generally formed in good yield.



This reaction is the basis of a method for the hydrolysis of thionamides prepared by the Willgerodt–Kindler reaction, which is of value for thionamides that are resistant to direct hydrolysis or unstable under the conditions necessary for such hydrolysis (268). For example, *N*-(phenylthionacetyl)morpholine, prepared by the Willgerodt–Kindler reaction, was not readily hydrolyzed. However, it was treated with methyl iodide in acetone to yield a salt which was considered by Rogers to be the hydroiodide of β-methylthio-β-morpholinostyrene,



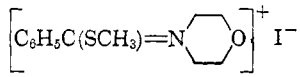
Treatment of this salt with warm, dry morpholine gave β,β-dimorpholinostyrene, a reaction which was interpreted as providing experimental support for assignment of the foregoing structure to the salt rather than that of the isomeric hydroiodide,



The methyl iodide adduct was readily hydrolyzed by hot water to methyl phenylthiolacetate, which could be further hydrolyzed to phenylacetic acid under mild conditions. When aqueous ammonia was used instead of hot water, the final product obtained was phenylacetamide.

"Isothionamides" are strong bases, giving salts with mineral acids. Excess mineral acid, however, hydrolyzes them to thiolic esters and ammonium chloride. They are more readily hydrolyzed in acidic than in alkaline media. In fact, bis(*N*-phenylbenzimidyl) sulfide, $[C_6H_5C(=NC_6H_5)—]_2S$, was found to be stable to hot concentrated alkali, although it was easily hydrolyzed by acid to a mixture of benzanilide and thionbenzanilide (157). Table 6 gives representative examples of the hydrolysis of thiolimidic esters.

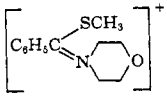
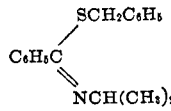
Chabrier and Renard observed that the product of reaction between methyl iodide and *N*-(thionbenzoyl)-morpholine,



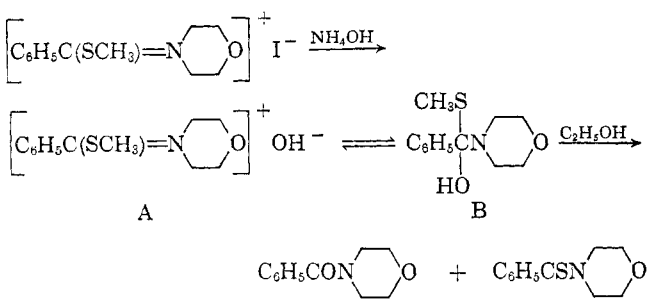
dissolved in a 21° Bé ammonia solution (63). From this solution an oily phase quickly appeared which solidified and then went into solution. Evaporation of this solution left a residue consisting chiefly of benzamidine. Peak and Stansfield were able to isolate and characterize the transitory solid. Its properties

TABLE 6

Hydrolysis of thiolimidic esters ("isothioamides")

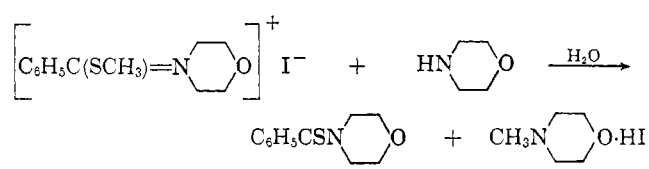
Ester	Conditions of Hydrolysis	Products	References
$CCl_3C(=NH)SCH_3 \cdot HCl$	Warm water	CCl_3COSCH_3	(288)
$(C_6H_5C(=NH)SCH_2—)_2 \cdot 2HBr$	Boiling water	$(C_6H_5COSCH_2—)_2$	(109)
	Warm water	$C_6H_5COSCH_3$, HN⟨⟩O, and HI	(62, 66)
	Refluxing 2 *N* HCl	$C_6H_5CH_2SH$ and $C_6H_5COSCH_2C_6H_5$	(124)
	Refluxing 0.5 *N* NaOH	No hydrolysis	(124)
	Refluxing 5 *N* NaOH and alcohol (1:3)	$C_6H_5COSCH_2C_6H_5$	(124)

were consistent with its formulation as a pseudo-base (B) corresponding to the hypothetical quaternary hydroxide (A) in the following equation (242). The pseudo-base was too unstable for a quantitative analysis. On boiling in alcohol it was converted to a



mixture of *N*-benzoylmorpholine and *N*-(thionbenzoyl)-morpholine formed by loss of either methyl mercaptan or methanol, respectively. With hydrogen iodide it gave back the quaternary iodide. The pseudo-base may have been an intermediate in the formation of benzamidine, since it gave benzamidine, along with *N*-(thionbenzoyl)morpholine, on further treatment with aqueous ammonia.

When the same quaternary salt, *N*-(α-methylthiobenzylidene)morpholinium iodide, was dissolved in an aqueous solution of a primary amine, an analogous reaction occurred (63). With methylamine the product obtained was *N*,*N*′-dimethylbenzamidine. With aqueous solutions of secondary amines the aminolysis took a different course. Thus, with morpholine the primary product of reaction with the same salt was *N*-(thionbenzoyl)morpholine, a reaction in which the quaternary salt acted as a methylating agent.



When diethylamine was used there was obtained in addition to the principal product, *N*-(thionbenzoyl)-morpholine, a minor amount of *N*,*N*-diethylbenzamide from the reaction of diethylamine with ethyl thiolbenzoate, the normal hydrolysis product of the quaternary salt. Tertiary amines gave only normal hydrolysis products, the thiolic esters (63).

For other reactions of thionamides and their *S*-substituted derivatives with amines in aqueous and nonaqueous media reference should be made to sections on the condensation of amines with thionamides and on the properties of the *S*-substituted derivatives.

The stability of thiolimidic esters to alkaline hydrolysis is dependent upon the degree of substitution of the imidic nitrogen. Thus, methyl *N*-methylthiolbenzimidate (I) is stable to concentrated potassium hydroxide solution, while the quaternary salt (II) is not stable (46).

$$\underset{\text{I}}{C_6H_5C(SCH_3)=NCH_3} \qquad \underset{\text{II}}{[C_6H_5C(SCH_3)=\overset{+}{N}(CH_3)_2]I^-}$$

Treatment of II with strong alkali eliminated the CH_3S— group with formation of *N*,*N*-dimethylbenzamide. It was suggested that this hydrolysis involved an intermediate cation, $C_6H_5C(OH)=\overset{+}{N}(CH_3)_2$ (46). Böttcher and Bauer noted that a CH_3S— group that is bonded to a carbon atom in an α-position to a quaternary nitrogen atom is very reactive and easily eliminated.

The above observations on the stability of thiolimidic esters to alkaline hydrolysis were extended to homologs of I and II (46). Further examples are shown in table 6 (124) and in the work of Chabrier and Renard (63) (*loc. cit.*).

The dibenzoyl derivative of thionbenzohydroxamic acid, $C_6H_5C(SCOC_6H_5)=NOCOC_6H_5$, behaved differently from esters of thiolimidic acids in that it was stable to hydrolysis in boiling dilute hydrochloric acid but was hydrolyzed by alcoholic potassium hydroxide solution to a mixture of products (57). The major components of this mixture were benzohydroxamic acid and thiolbenzoic acid; smaller quantities of thionbenzohydroxamic acid and benzoic acid were isolated.

B. REACTIONS WITH AMINES

Amines may react with thionamides and esters of thiolimidic acids in a number of ways. The discussion in this section will be concerned only with amines or diamines not containing another functional group that is primarily involved in the reaction.

Perhaps the simplest manner in which an amine may react with a thionamide is exemplified by the formation of acetonitrile on refluxing thionacetamide in pyridine (252). Thionbenzamide behaves similarly. Pyridine acts as a base in these reactions in neutralizing hydrogen sulfide. Two of the generally observed decomposition products of thionamides on heating are nitriles and hydrogen sulfide. It should be noted that pyridine may also initiate this reaction by forming a pyridinium salt of the thionamide.

Primary amines, however, act in a different manner on thionamides. Either amidines or *N*-substituted thionamides are formed, and there are several instances where a mixture of both types of products has been observed. Bernthsen first observed that amidine salts were formed from the reaction of aliphatic and aromatic thionamides with concentrated ammonium hydroxide solution (35, 40). Yields of amidines were improved by the addition of mercuric chloride to upset the following equilibrium by precipitation of mercuric sulfide.

$$RCSNH_2 + NH_3 \rightleftharpoons RC(=NH)NH_2 \cdot H_2S \xrightarrow{NH_3,\ HgCl_2} RC(=NH)NH_2 \cdot HCl + HgS + NH_4Cl$$

In similar fashion primary amines lead to *N*-substituted amidines. Aniline hydrochloride and phenylthionacetamide in absolute ethanol gave *N*,α-diphenylthionacetamidine (37). *N*-Substituted thionamides are a source of *N*,*N'*-disubstituted amidines, as shown by the reaction of thionbenzanilide with molten aniline hydrochloride to give *N*,*N'*-diphenylbenzamidine (201). An α-cyanothionformanilide was transformed into the corresponding amidine in 40 per cent yield without concurrent reaction of the cyano group by treatment with aniline in boiling benzene (259).

$$C_6H_5NHCSCN + C_6H_5NH_2 \rightarrow H_2S + C_6H_5NHC(=NC_6H_5)CN$$

By proper choice of reaction conditions the amidine may be hydrolyzed to the corresponding amide without isolation. Thus, the reaction of phenylthionacetamide and ammonium hydroxide solution at room temperature gave the thiosulfate salt of α-phenylacetamidine; however, at reflux temperature the products obtained were phenylacetamide and ammonium sulfide (35). Thiosulfuric acid in the former case was formed by air oxidation of ammonium sulfide (226).

Mixtures of *N*-substituted and *N*,*N'*-disubstituted amidines have been reported. Thionbenzamide and excess aniline hydrochloride, for example, were observed to give a mixture of *N*-phenyl- and *N*,*N'*-diphenylbenzamidines (36).

Under very similar reaction conditions thionamides react with primary aliphatic amines by replacement of their amido groups with substituted amino groups from the primary amines.

$$RCSNH_2 + R'NH_2 \rightarrow RCSNHR' + NH_3$$

Thus, *N*-butylthionacetamide was produced in nearly quantitative yield by refluxing thionacetamide in butylamine until evolution of ammonia ceased (274). This reaction, sometimes known as the Wallach reaction in honor of its discoverer, has been used to prepare a number of *N*-alkyl- or *N*-aralkylthionamides and *N*,*N'*-dialkyl- or *N*,*N'*-diaralkyldithionoxamides (125, 274, 315, 336). A difference between the amido and thionamido groups was clearly shown in the condensation of monothionoxamide and various alkylamines to form the corresponding *N*-alkylmonothionoxamides (321).

$$H_2NCOCSNH_2 + RNH_2 \rightarrow H_2NCOCSNHR + NH_3$$

R = CH_3, C_4H_9, and $C_{12}H_{25}$.

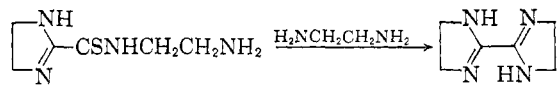
Several secondary amines have been reported to condense with a thionamide in a similar manner. Thionacetamide and piperidine in ether solution gave *N*-(thionacetyl)piperidine (226). It may be significant that this secondary amine, in which the two amino substituents offer a minimum of steric hindrance, is one of the only two secondary amines that have been observed to so react. Diethylamine and thionformamide gave the *N*,*N*-diethyl derivative (326).

Primary aromatic and heterocyclic amines have been condensed with thionformamide formed *in situ* in a mixture of the amine, formamide, and phosphorus pentasulfide (325, 326). The amines used included aliphatic amines and diamines, aralkyl amines, aromatic amines and diamines, and heterocyclic amines. Representative products obtained in this manner were *N*-ethylthionformamide, *N*-(2-hydroxyethyl)thionformamide, ethylene-*N*,*N'*-bis(thionformamide), 4-amino-2-methyl-5-thionformamidomethylpyrimidine, *N*-benzylthionformamide, *N*,*N'*-dithionformyl-*m*-phenylenediamine, and 6-thionformamidoquinoline.

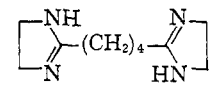
α,ω-Diamines, such as ethylenediamine, 1,4-diaminobutane, and 1,6-diaminohexane, form the expected *N*,*N'*-bis(thionacetyl) derivatives in ether solution (226). In the last-named case, the simultaneous formation of the thiosulfate of hexamethylene-1,6-bis(*N*-acetamidine) was observed, illustrating the competition that must exist between amidine and *N*-substituted thionamide formation.

2,2'-Bis(2-imidazoline) was obtained by the reaction of dithionoxamide and ethylenediamine hydrate in the absence of solvent (106). When this condensation was effected in hot alcoholic solution using a 1:2 molar ratio of dithionoxamide to diamine an intermediate product, 2-imidazoline-2-[*N*-(2'-aminoethyl)carbothionamide] was obtained (198). By warming with more ethylenediamine hydrate this intermediate was converted to 2,2'-bis(2-imidazoline).

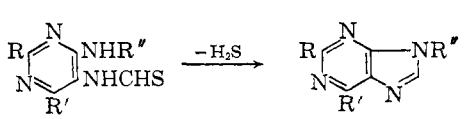
$$H_2NCSCSNH_2 + 2H_2NCH_2CH_2NH_2 \rightarrow$$



When dithionadipamide was warmed with ethylenediamine hydrate, either in the absence of solvent or in alcohol, the only product isolated was sulfur-free tetramethyl-2,2'-bis(2-imidazoline):



One of the most extensively studied applications to which thionamides have been put is the synthesis of purine derivatives, many of which are of pharmaceutical interest. This synthesis, with the exception noted below, commences with 4-amino-5-thionformamidopyrimidines:

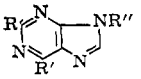


This ring closure is an extension of the reaction of thionamides with amines to form amidines. A large part of the work done in this field is by a group of

English chemists whose progress up to 1946 has been summarized by A. R. Todd (296). Table 7 lists some representative purine derivatives that have been prepared in this manner.

TABLE 7

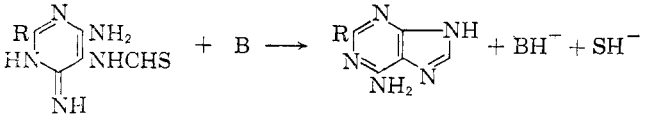
Purine derivatives from 4-amino-5-thionformamidopyrimidines



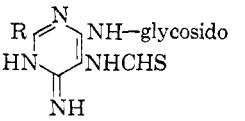
R	R′	R″	Reaction Conditions	Yield	Reference
				per cent	
H	H	H	Refluxing water	100	(26)
CH_3	NH_2	H	Refluxing quinoline	75	(25)
CH_3S	NH_2	H	Refluxing water	60	(25)
CH_3S	NH_2	CH_3	Refluxing water	94	(25)
CH_3S	NH_2	*d*-Xylopyranosido	Refluxing CH_3ONa/CH_3OH	63	(176)
CH_3	NH_2	*d*-Xylopyranosido	Refluxing CH_3ONa/CH_3OH	20	(176)

Cyclizations of 4-amino-5-thionformamidopyrimidines have been accomplished in hot basic solutions. Basic solvents used included pyridine, quinoline, and anhydrous alcoholic sodium alkoxides. In aqueous solution there was often a loss of yield due to hydrolysis of the thionformamido group. Of the alcoholic sodium alkoxide media, methanol and ethanol appeared to be best, and although reaction was slower than when an excess of base was used, the best yields with this solvent–base system were obtained with a 1:1 molar ratio of pyrimidine derivative to alkoxide (176).

Table 7 illustrates only two of a great many R substituents that were examined. Ring closure was most rapid in those pyrimidine derivatives containing a 2-methylthio group because of the increased basicity of the 4- and 6-amino groups, as shown by the increased ease of glycosidation of 4,6-diamino-2-methylthiopyrimidine (176). In the case of 4,6-diamino-5-thionformamidopyrimidines it was proposed that ring closure took place by action of base upon the following tautomer of the pyrimidine (176, 296):

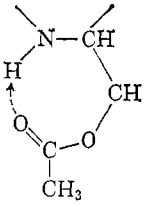


A number of the pyrimidines subjected to this cyclization were 4-glycosidoamino-5-thionformamido-6-aminopyrimidines or their 4-triacetylglycosidoamino derivatives (176). In every case when alcoholic sodium alkoxide was used to effect ring closure, only 9-glycosidoaminopurines were obtained; none of the isomeric 6-glycosidoaminopurines were observed. Under such conditions the 4-triacetylglycosidoaminopyrimidines were found to be deacetylated rapidly, before ring closure occurred. Ring closure was visualized as proceeding through an analogous tautomer of the pyrimidine:

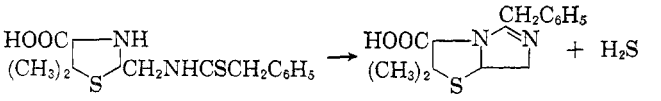


It should be noted that aniline and its derivatives do not condense with thionamides as do primary aliphatic amines with evolution of ammonia (*loc. cit.*). While this may seem incongruent with the condensation of the 5-thionformamido group with 4- and 6-amino groups of pyrimidines, these latter amino groups are more basic than those of aniline.

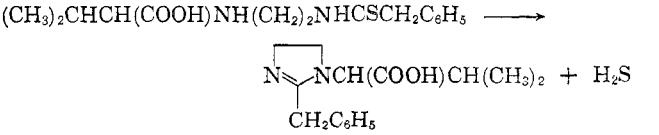
Under conditions where deacetylation of 4-triacetylglycosidoamino-5-thionformamido-6-aminopyrimidines did not occur, such as with the use of pyridine or an anhydrous acetonitrile solution of potassium acetate and acetic acid, considerable yields of 6-triacetylglycosidoaminopurines were obtained as well as the 9-isomers (27). To account for this, it was proposed that a quasi-ring was formed by a hydrogen bond between the 2-acetyl group of the sugar residue and the hydrogen of the glycosidic NH— group. Such chelation would induce a negative charge on the glycosidic nitrogen, increasing its basicity. Thus the 4-amino group would be rendered more reactive to such cyclization, and such was observed to be the case.



The amidine reaction has been utilized in the syntheses of other heterocyclic ring systems. In a manner analogous to purine ring formation, benzylpenillamine was prepared by refluxing 2-(phenylthionacetamidomethyl)-5,5-dimethylthiazolidine-4-carboxylic acid in quinoline (11, 71):



Attempts to similarly convert the ethyl ester were unsuccessful (23). Another example of heterocycle formation was the preparation of the following imidazoline derivative (306):

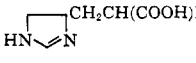


The condensation of thionamides, particularly thionformamide, with amino acids has been investigated (226). Only arginine and L-lysine (as their carbonate salts) and the ethyl ester of glycine reacted at room temperature with thionformamide in methanol to give crystalline products. Glycine, L-leucine, DL-alanine,

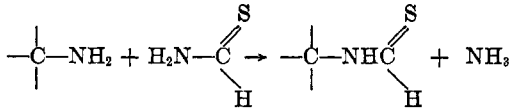
and histidine gave crystalline products, however, when warmed in thionformamide to 60°C. Structures of the products are given in table 8.

TABLE 8

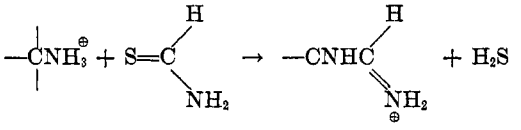
Condensation products of thionformamide and amino acids (226)

Amino Acid	Product
Arginine	$H_2NC(=NH)NH(CH_2)_3CH(COOH)NHCHS$
L-Lysine	$HCSNHCH(NH_2)NH(CH_2)_4CH(COOH)NHCHS$
Glycine	$NH=CHNHCH_2COOH$
L-Leucine	$(CH_3)_2CHCH_2CH(COOH)NHCH(NH_2)NHCHS$
DL-Alanine	$CH_3CH(COOH)NHCH(NH_2)NHCHS$
Histidine	

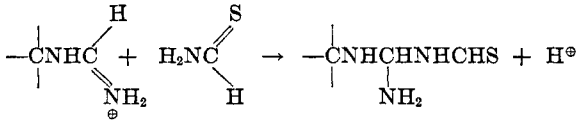
Only those amino acids that are basic (i.e., that have free amino groups) reacted easily with thionformamide. Thus, the free α-amino groups of arginine, lysine, and histidine condensed to form thionformyl derivatives:



All the amino acids studied were assumed to exist as zwitterions in thionformamide because of the high dielectric constant of this medium. Consequently, the amino groups of the monoamino acids glycine, DL-alanine, and L-leucine, the terminal amino groups of arginine and L-lysine, and the 1-nitrogen atom of the imidazoline ring of histidine were assumed to exist as ammonium zwitterions. These ammonium groups, with the exception of arginine, reacted at 60°C. with elimination of hydrogen sulfide and formation of the formamido derivatives:



In the case of L-leucine, DL-alanine, and L-lysine further condensation of the intermediate formimido group with an additional equivalent of thionformamide occurred:



The failure of glycine to undergo reaction with a second equivalent of thionformamide could not be explained. However, two closely related reactions are of interest in connection with reaction of the second equivalent of thionformamide. *N*-Formimidylalanine and *N*-formimidylleucine gave products on reaction with molten thionformamide and ammonia that were identical to the condensation products of alanine and leucine, respectively, with thionformamide at 60°C. (*cf.* table 8) (224).

$$CH_3CH(COOH)NHCH{=}NH + HCSNH_2 \xrightarrow{NH_3} CH_3CH(COOH)NHCH(NH_2)NHCHS$$

The reaction paths suggested above could not be regarded as conclusive, since at 60°C. thionformamide decomposed slowly to ammonia, hydrogen sulfide, and a slight amount of formamidine (226). Therefore, attempts were made to react the more stable thionacetamide with the same series of amino acids. Reaction occurred with the monobasic amino acids, but only at much higher temperatures, to give uncharacterized products. With lysine, a product was obtained that could not be purified, but which was believed to be N^{α}-thionacetyllysine.

Thionformamide reacted with proteins in the cold to give products that were probably analogous to those obtained with amino acids (223, 225, 226). The sulfur and nitrogen contents of the "thioproteins" could be correlated with the species of amino acids known to be in the proteins (226). Here again, dithioformic acid did not give the same "thioprotein" as thionformamide on reaction with a given protein.

There have been instances where the thionamide group has been observed not to react with ammonia or primary amines. For example, the carbethoxy group of ethyl oxalthionamidolate, $H_2NCSCOOC_2H_5$, could be converted into a carbamido group without the thionamido group also participating in the reaction (319). The reactions were executed in alcoholic solutions of ammonia or a primary amine. Treatment of either this ester or ethyl thionoxanilate, $C_6H_5NHCSCOOC_2H_5$, with aniline at 140°C. gave monothionoxanilide, $C_6H_5NHCSCONHC_6H_5$ (258).

The reactions of *N*-benzimidoylthionbenzamide, $C_6H_5CSN{=}C(NH_2)C_6H_5$, with ammonia, amines, and amidines have been investigated (241). It was found to be stable in an alcoholic solution of aniline for several days (241). When mercuric oxide was added to the solution, however, 1,2,4-triphenyl-1,3,5-triazapenta-1,3-diene, $H_2NC(C_6H_5){=}NC(C_6H_5){=}NC_6H_5$, was readily formed (241). In contrast, an alcoholic ammonia solution, without the added presence of a desulfurizing agent, quickly cleaved *N*-benzimidoylthionbenzamide (241). The resulting products were benzamidine, thionbenzamide, triphenyltriazine, 3,5-diphenyl-1,2,4-thiadiazole, and an unidentified base containing nitrogen and sulfur. The 1,2,4-thiadiazole derivative is a known oxidation product of both *N*-benzimidoylthionbenzamide (214) and thionbenzamide (139). To determine whether thionbenzamide and benzamidine arose through cleavage of bond *a* or bond *b*,

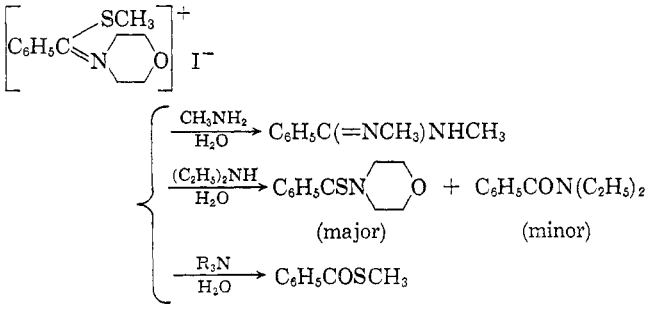
$$C_6H_5CS\overset{a}{-}NH\overset{b}{-}C(C_6H_5){=}NH$$

the reaction was repeated with an equivalent of benzylamine at room temperature (241). The products ob-

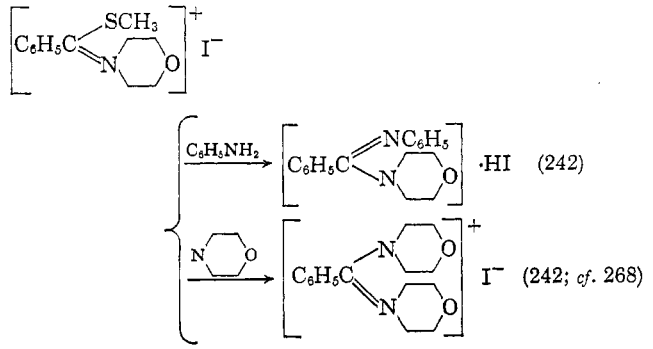
tained were thionbenzamide (58.5 per cent), *N*-benzylbenzamidine (78 per cent as the picrate), *N*-benzylthionbenzamide (3.5 per cent), and benzamidine (1.2 per cent as the picrate). It was not expected that under the prevailing mild reaction conditions a significant amount of *N*-benzylbenzamidine or *N*-benzylthionbenzamide was formed in a secondary reaction between benzylamine and benzamidine or thionbenzamide, respectively. Therefore, cleavage with benzylamine, and with ammonia by analogy, occurred mainly at bond *b*. Benzamidine gradually cleaved bond *b* of *N*-benzimidoylthionbenzamide also, the principal products being thionbenzamide and 2,4-diphenyl-1,3,5-triazapenta-1,3-diene, $H_2NC(C_6H_5)=NC(C_6H_5)=NH$.

On the other hand, the substituted amidines, *N*-phenylbenzamidine and *N*-benzylbenzamidine, did not react at room temperature with *N*-benzimidoylthionbenzamide. In refluxing benzene, however, *N*-phenylbenzamidine gave a small yield of triphenyltriazine and 1,2,4,5-tetraphenyl-1,3,5-triazapenta-1,3-diene, $NH(C_6H_5)C(C_6H_5)=NC(C_6H_5)=N(C_6H_5)$. The latter product was unexpected and could have been the result of either disproportionation of the expected triphenyldiamidine or a further reaction with benzamidine.

The hydrolysis or aminolysis of thiolbenzimidate esters, $RC(SR')=NR''$ (isothionamides), and their salts has previously been reviewed (*loc. cit.*, preceding section on hydrolysis) (63, 242). The following examples of such reactions for each class of amine are set forth for purposes of comparison.



The reaction of such salts with primary and secondary amines takes a different course under anhydrous conditions (242). For example:

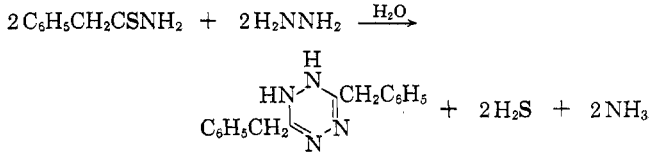


The reaction of alkyl thiolimidates with aniline is a general method for the preparation of *N*-phenylamidines (317, 318).

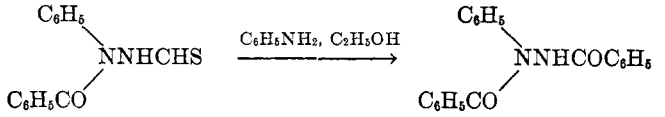
$$CCl_3C(=NH)SCH_3 + C_6H_5NH_2 \rightarrow CCl_3C(=NC_6H_5)NH_2 + CH_3SH \quad (288)$$

C. CONDENSATIONS WITH HYDRAZINE, SEMICARBAZIDE, AND THIOSEMICARBAZIDE

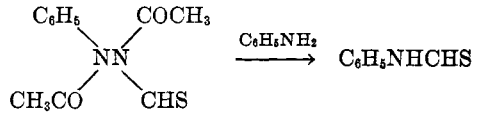
Thionamides react with aqueous solutions of hydrazine to form the corresponding 3,6-disubstituted-1,2-dihydro-1,2,4,5-tetrazines (171). Thus,



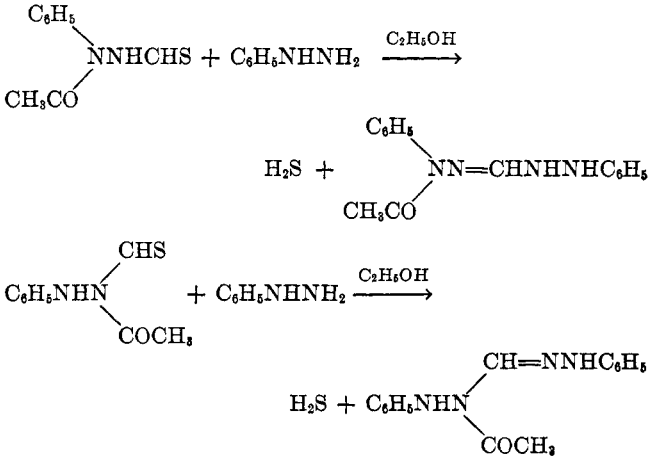
1-Thionformyl-2-phenylhydrazine derivatives have been studied under a variety of reaction conditions (272). *N*-Benzoyl-*N*-phenyl-*N'*-thionformylhydrazine was cleaved when refluxed with aniline in alcohol.



The mechanism of this reaction, which must involve two equivalents of the monoacylhydrazine derivative, was not ascertained. The point of cleavage was clearly shown, however, in the reaction of the related diacetylhydrazine derivative with aniline in acetone:



Both the 1-acetyl- and the 2-acetylthionformylhydrazine isomers shown below reacted in a similar manner with phenylhydrazine (272):



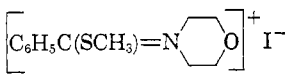
The reactions of mono- and dithionoxamide derivatives with hydrazine are summarized in table 9.

TABLE 9

Reactions of mono- and dithionoxamides with hydrazine

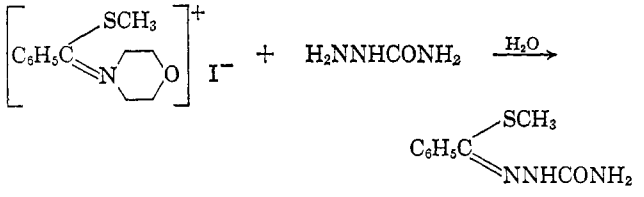
Oxamide Derivative	Reaction Conditions	Product	Reference
$C_2H_5OOCCSNH_2$	$N_2H_4 \cdot H_2O$ in alcohol	$C_2H_5OOCC(=NNH_2)NH_2$	(278)
$C_2H_5OOCCSNH_2$	$2N_2H_4 \cdot H_2O$ in alcohol	$H_2NNHCOC(=NNH_2)NH_2$	(278)
$H_2NCSCOOH$	N_2H_4, absolute alcohol	$(H_2NCSCOO)^-N_2H_5^+$	(253)
$H_2NCSCOOH$	$2N_2H_4$, absolute alcohol	$[H_2NC(=NNH_2)COO]^-N_2H_5^+$	(253)
$H_2NCSCSNH_2$	$2N_2H_4 \cdot H_2O$ in alcohol	$[H_2NC(=NNH_2)—]_2$	(82)

N-(α-Methylthiobenzylidene)morpholinium iodide,

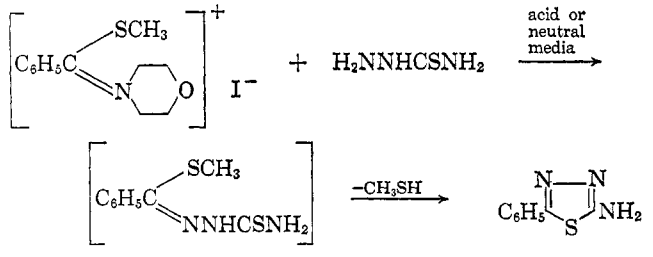


(an "isothioamide"), gave a very good yield of 3,6-diphenyl-1,2-dihydro-1,2,4,5-tetrazine upon reaction with excess hydrazine (63). This parallels the formation of the same product from the reaction of thionbenzamide with hydrazine (171).

Semicarbazide in aqueous solution, however, does not give a cyclic product with this morpholinium iodide derivative (124):



On the other hand, thiosemicarbazide leads to different products. Under acid or neutral conditions cyclization occurred to give 2-amino-5-phenyl-1,3,4-thiadiazole, presumably by way of an intermediate analogous to the product obtained with semicarbazide (242):



The thiomethyl group was eliminated with formation of 1-(α-morpholinobenzylidene)thionsemicarbazide when condensation of these reactants was executed under a variety of aqueous and nonaqueous, weakly basic and strongly basic conditions (242). This thionsemicarbazide derivative rapidly cyclized in dilute acid to the same 1,3,4-thiadiazole obtained from condensation under acidic conditions. The basic condensation was extended to a number of salts of the general formula $[RC(SCH_3)=NR'R'']^+I^-$ to readily obtain 1-(α-aminobenzylidene)thionsemicarbazones, $RC(NR'R'')=NNHCSNH_2$.

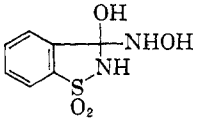
D. CONDENSATIONS WITH HYDROXYLAMINE

Thionamides, in general, condense with hydroxylamine to form amidoximes. Thionbenzamide yields benzohydroxamide on refluxing in an alcoholic solution of hydroxylamine (295).

$$C_6H_5CSNH_2 + H_2NOH \rightarrow C_6H_5C(=NOH)NH_2 + H_2S$$

Several other examples are recorded in table 10.

Thionsaccharin (table 10) gave a different product with hydroxylamine from that given by saccharin. Saccharin gave a stable addition compound:



It was presumed that an analogous addition compound was formed in the case of thionsaccharin, but that this intermediate was unstable and immediately evolved hydrogen sulfide (212).

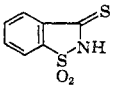
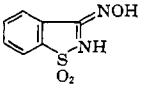
E. OXIDATION OF THIONAMIDES

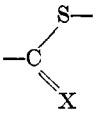
1. By hydrogen peroxide

Kitamura demonstrated that compounds containing the functional group

TABLE 10

Amidoximes from thionamides

Thionamide	Reaction Conditions	Product	Reference
$H_2NCSCOOC_2H_5$	$H_2NOH \cdot HCl$ in alcohol with $NaOCH_3$	$H_2NC(=NOH)COOC_2H_5$	(232)
	$H_2NOH \cdot HCl$ in alcohol with Na_2CO_3		(212)
$[H_2NCS—]_2$	$H_2NOH \cdot HCl$ in alcohol with Na_2CO_3	$[NH_2C(=NOH)—]_2$	(90)
$[C_6H_5NHCS—]_2$	H_2NOH	$[C_6H_5NHC(=NOH)—]_2$	(142)

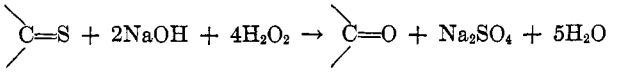


where X could be such atoms as nitrogen or oxygen, were invariably oxidized under alkaline conditions by hydrogen peroxide to the corresponding oxo compounds (189, 190). Thus, thionbenzamide was oxidized by hydrogen peroxide in aqueous alkaline solution to benzamide (188). Hydrogen sulfide formed in this reaction is oxidized to sulfuric acid. There are no disulfides produced as intermediates in this oxidation (190). The rate of oxidation is dependent on the hydroxyl-ion concentration. Kitamura arranged the various bases employed in this oxidation in the following order of decreasing rate of oxidation: (*a*) alkali metal hydroxides and carbonates; (*b*) ammonium hydroxide; (*c*) sodium tetraborate; (*d*) sodium bicarbonate and disodium phosphate. The stoichiometry of this oxidation was described as follows (129):

TABLE 11

Alkaline oxidation of thionamides by hydrogen peroxide

Thionamide	Product	Reference
$C_6H_5CSNH_2$	$C_6H_5CONH_2$	(188)
$C_6H_5CSNHC_6H_5$	$C_6H_5CONHC_6H_5$	(188)
$HCSNHC_6H_5$	$HCONHC_6H_5$	(188)
$CH_3CSNHC_6H_5$	$CH_3CONHC_6H_5$	(188)
$ArCSNHCH_2C_6H_5$	$ArCONHCH_2C_6H_5$	(48)
$C_6H_5CSNHCH_2COOH$	$C_6H_5CONHCH_2COOH$	(144)
$ArNHCSCN$	$ArNHCOCONH_2$	(139)



This reaction was utilized in the first method for quantitatively determining nonionizable sulfur in solution. It was claimed to be more accurate than the Carius method (188). Under the proper conditions oxidation is complete.

Warming of the alkaline oxidation mixtures is unnecessary.

In neutral or acidic media this oxidation may take a different course. Depending on the structure of the thionamide, sulfuric acid and disulfides may be formed. The corresponding amides are also formed, but by secondary reactions (189).

2. By ozonolysis

Thionamides may be ozonized in a number of ways (160). In inert anhydrous solvents, such as benzene or carbon tetrachloride, thionbenzamide was ozonized to *N*-benzimidoylthionbenzamide, $C_6H_5C(=NH)NHCSC_6H_5$, which then cyclized to 3,5-diphenyl-1,2,4-thiadiazole by further oxidation. Benzonitrile and sulfur were also formed (160). *p*-Toluthionamide behaved similarly. In contrast, the ozonolysis of thionacetanilide in benzene gave acetanilide and a tar.

Only the corresponding amides and nitriles were isolated from the aqueous ozonolysis of unsubstituted thionbenzamides. Thionacetamide differed in that acetic acid, sulfuric acid, ammonia, and sulfur were obtained on ozonolysis in either benzene or water.

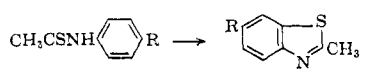
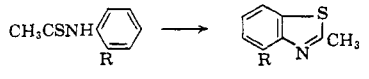
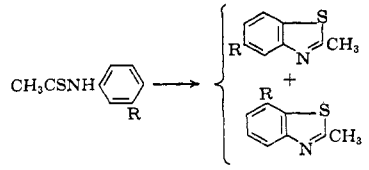
3. By ferricyanides

Oxidation of derivatives of thionacetanilide and thionbenzanilide by potassium ferricyanide in aqueous alkali has been an oft-used means of preparing benzothiazoles. This procedure, known as the Jacobsen synthesis, has been reviewed elsewhere (287).

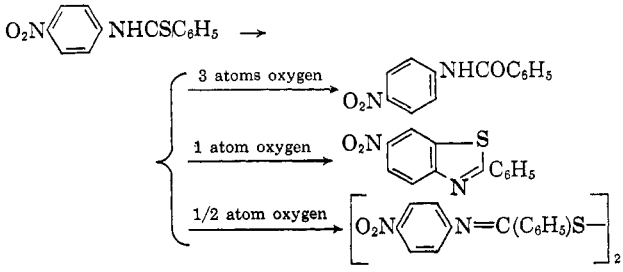
It has been possible in some cases to moderate the extent of oxidation of thionanilides so as to produce other oxidation products. Schematically (266):

TABLE 12

2-Methylbenzothiazoles from thionacetanilides by oxidation with potassium ferricyanide

	Yield where R is				
	OCH_3	CH_3	Cl	H	NO_2
	per cent	*per cent*	*per cent*	*per cent*	*per cent*
	76.3	73.1	72.0	67.5	0*
	42	52	45		
	11.2	6.4	42.6		
	48.3	64.0	28.4		

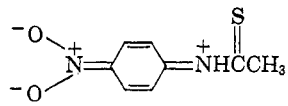
* In this case there was a 95 per cent conversion to *p*-nitroacetanilide.



Thus, thionbenzoyl-*p*-nitroaniline gave the corresponding dibenzimidoyl disulfide derivative as the major product upon oxidation in cold aqueous alkali (266). In hot alkali the major product was 4′-nitrobenzanilide. Under any conditions, the yield of 6-nitro-2-phenylbenzothiazole was very poor (108, 230, 266).

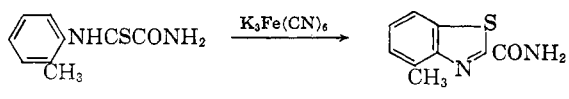
The influence of ring substituents of thionacetanilide derivatives on the ease of cyclization has been studied (230). The yields of substituted 2-methylbenzothiazoles obtained by potassium ferricyanide oxidation of the corresponding thionacetanilide derivatives in aqueous alkali are given in table 12 (230).

The failure of *p*-nitrothionacetanilide to form 2-methyl-6-nitrobenzothiazole was explained on the basis of resonance forms such as the following:



Such forms, which become more important with an electronegative group in the *p*-position, would inhibit thiol-enolization and, consequently, ring closure. However, oxidation of the thione group can still take place.

The transformation of a thionamide into a nitrile by potassium ferricyanide in alkaline solution has been observed (258). Thionoxanilonitrile, $C_6H_5NHCSCN$, along with thionoxanilamide, $C_6H_5NHCSCONH_2$, were formed upon treatment of *N*-phenyldithionoxamide with an amount of the oxidizing agent corresponding to one equivalent of oxygen. Although thionoxanilamide could be obtained by warming thionoxanilonitrile in alkaline solution, it is conceivable that it could also be formed directly from *N*-phenyldithionoxamide. Dithionoxanilide was transformed into monothionoxanilide under these conditions (258). Of the various derivatives of thionoxanilic acid, such as the foregoing, only the amides, $ArNHCSCONH_2$, were readily cyclized to benzothiazoles by potassium ferricyanide. The following reaction, for example, was complete in 10 min. when a large excess of oxidizing agent was used (258).



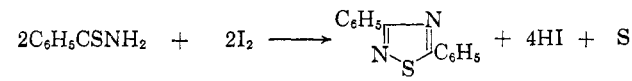
The solubility of thionacetanilide in alkaline solution was related to the yields of 2-methylbenzothiazole obained on oxidation of thionacetanilide by potassium ferricyanide in solutions of varying alkalinity (231). Thionacetanilide dissolved readily in sodium hydroxide solutions of up to 2 *N* concentration; at higher concentrations its solubility became much less. Similarly the yield of 2-methylbenzothiazole increased up to this point of maximum solubility and then decreased at higher concentration of alkali.

4. By olefin oxides

Thionacetamide gave an 85 per cent yield of acetamide and a sulfur-containing residue when refluxed in methanolic solution for 5 hr. with cyclohexene oxide (80). Thionbenzamide was oxidized by ethyl phenylglycidate; a 72 per cent yield of sulfur, in addition to benzamide and ethyl cinnamate, was recovered.

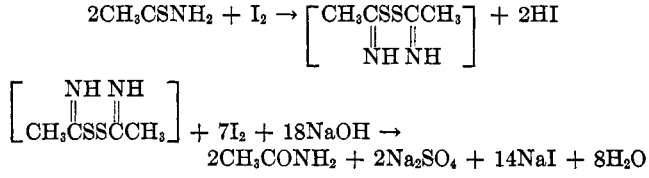
5. By halogens

Hofmann in 1867 observed that if thionbenzamide was treated in alcoholic solution with an excess of iodine a substance was obtained that appeared to be the result of condensation of two molecules of thionbenzamide with elimination of one atom of sulfur. Although the product was later considered to be 2,5-diphenyl-1,3,4-thiadiazole (34), Hofmann and Gabriel finally established the correct structure as 3,5-diphenyl-1,2,4-thiadiazole (141):



This reaction appears to be general for *N*-unsubstituted thionamides.

Thionamides are oxidized in alkaline solution to the corresponding amides (333). The reaction is quantitative and has been made the basis of a quantitative determination of thionamides. Four moles of iodine are consumed for each mole of thionamide. The following sequence was proposed for thionacetamide (333):



The intermediate disulfide has not been isolated. However, thionamides are oxidized only to the disulfides by iodine in mineral acid solution. In acid media, bromine or a mixture of potassium bromide and potassium bromate may be substituted for iodine. Although oxidation in acid solution by iodine is nearly quantitative in the case of dithionoxamide, it is incomplete for thionacetamide.

It is of interest to note that there are earlier reports in the literature that thionbenzamide is not oxidized by iodine (201, 202).

Thionanilides are oxidized by bromine to benzothiazoles (339, 340). The following is an example (340):

$$C_6H_5NHCSCH(COOC_2H_5)_2 \xrightarrow{Br_2} \text{2-}CH(COOC_2H_5)_2\text{-1,3,4-thiadiazole}$$

6. By N,N-dichlorocarbamates

N,N-Dichlorocarbamates of the general formula Cl_2NCOOR oxidize thionamides in a manner similar to that of iodine (60, 61, 65). Although it was claimed that the products were 2,5-disubstituted 1,3,4-thiadiazoles, proof of structure was by comparison of the products of oxidation of thionbenzamide by *N,N*-dichlorocarbamate and by iodine. The products were identical, and so the products of oxidation by an *N,N*-dichlorocarbamate must be regarded as 3,5-disubstituted 1,2,4-thiadiazoles. Thus, the oxidation product of nicotinthionamide was undoubtedly 3,5-(3′-pyridyl)-1,2,4-thiadiazole and not the 1,3,5-thiadiazole isomer reported (65). The usual procedure in this method of thionamide oxidation was to use a slight excess of the dichlorocarbamate in an aqueous suspension of the reactants.

7. By nitrous and nitric acids, nitrosyl chloride, nitrogen sesquioxide, and amyl nitrite

Nitrous acid oxidizes thionamides in a manner analogous to that of iodine. Thionbenzamide in an alcohol–hydrochloric acid solution was oxidized to 3,5-diphenyl-1,2,4-thiadiazole by the dropwise addition of sodium nitrite solution. The reaction was accompanied by the evolution of nitric oxide (197).

Oxidation of thionbenzanilide by nitrosyl chloride in cold ether solution under nitrogen gave a 44 per cent yield of *N*-phenylbenzimidoyl chloride (131). An *S*-nitroso intermediate was proposed for such oxidations.

$$C_6H_5N{=}C(SH)C_6H_5 \xrightarrow[0°C.]{NOCl} C_6H_5N{=}C(SNO)C_6H_5 \rightarrow C_6H_5N{=}C(Cl)C_6H_5$$

Benzanilide was also isolated from this reaction. Thionacetanilide and *N*-butylthionacetamide were similarly treated with nitrosyl chloride, but the resulting imidyl chlorides were too unstable for isolation and characterization. Their presence was demonstrated by reaction with excess aniline to yield *N*-phenyl-*N′*-phenylacetamidine and *N′*-butyl-*N*-phenylacetamidine, respectively (131).

In contrast, when thionbenzanilide was treated with nitrosyl chloride in the presence of pyridine, two products, an oil and a solid, were obtained (131). The latter was bis(*N*-phenylbenzimidoyl) sulfide, $(C_6H_5C{=}NC_6H_5)_2S$, and the former slowly decomposed into this sulfide and sulfur.

From the reaction of *N*-butylthionacetamide with nitrogen sesquioxide in cold ether, *N*-butyl-*N*-nitrosoacetamide was obtained (131).

Both benzanilide and bis(*N*-phenylbenzimidoyl) sulfide were isolated from a solution of thionbenzanilide in excess amyl nitrite kept at 0°C. for two days (131). Ethyl nitrite gave the same products under similar conditions. In neither case could any nitroso compound be detected.

Nitric acid in a number of acidic and neutral, aqueous and nonaqueous, solvents oxidized thionbenzamide to 3,5-diphenyl-1,2,4-thiadiazole in 75 per cent yield (79).

8. By selenium dioxide

Thionamides, particularly *N*-benzylthionamides, have been oxidized to the corresponding amides by treatment of their alcoholic solutions with selenium dioxide. Selenium trisulfide was also formed (48–50, 52). In the case of *N*-benzylthionbenzamide it was observed that the amide was formed only if at least two moles of thionamide were present per mole of selenium dioxide. If the reactants were present in 1:1 molar ratio, further oxidation took place with cleavage of the carbon–nitrogen bond (50):

$$2C_6H_5CSNHCH_2C_6H_5 \xrightarrow{SeO_2} C_6H_5CN + C_6H_5COOH$$

9. By potassium permanganate

Dithioncamphorimide has been oxidized to camphorimide by potassium permanganate (239).

10. By sulfuric acid

On standing in fuming or concentrated sulfuric acid, dithionoxanilide was quantitatively oxidized to benzothiazole-2-carbothionanilide (257):

$$C_6H_5NHCSCSNHC_6H_5 + H_2SO_4 \longrightarrow \text{2-}CSNHC_6H_5\text{-benzothiazole} + SO_2 + 2H_2O$$

If the reaction mixture containing fuming sulfuric acid was warmed, the sulfonated product, benzothiazole-2-carbothion(4′-sulfonanilide), was obtained instead (257). On boiling in dilute sulfuric acid, only simple hydrolysis to form oxalic acid took place (277).

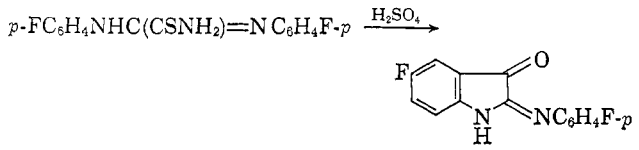
Reissert demonstrated that benzothiazole formation did not occur through the intermediate formation of a benzothiazine ring (257).

A 25 per cent yield of isatin was produced on warming either oxanilthionamide or monothionoxanilide with 95 per cent sulfuric acid until the evolution of sulfur dioxide ceased (257).

$$C_6H_5NHCOCSNH_2 + H_2SO_4 \longrightarrow \text{isatin} + SO_2 + S + NH_3 + H_2O$$

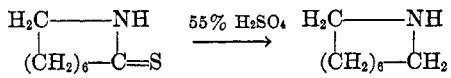
$$C_6H_5NHCOCSNHC_6H_5 + 2H_2SO_4 \longrightarrow \text{isatin} + SO_2 + S + 2H_2O + p\text{-}H_2NC_6H_4SO_3H$$

A similar ring closure to an indole derivative occurred on oxidation of *N,N'*-di-*p*-fluorophenylformamidine-1-carbothionamide by sulfuric acid (267):



F. REDUCTION OF THIONAMIDES

Four methods have been principally used to reduce thionamides: metal–acid combinations, amalgams, electrolytic reduction in acid solution, and desulfurization by Raney nickel in neutral solvents. Although the most common type of product obtained is the amine corresponding to the thionamide, it is not unusual to obtain other products such as aldehydes and secondary amines. Further, not all methods of reduction are equally successful with a given thionamide. The lactam of ω-aminocaprylthionamide (2-thionoctamethylenimine), for example, was not reduced by magnesium amalgam in moist ether, aluminum amalgam in aqueous alcohol, or zinc dust in acetic acid (269). It gave only a small yield of octamethylenimine on reduction with sodium in glacial acetic acid. However, electrolytic reduction at a lead cathode in 55 per cent sulfuric acid at 30°C. gave an 85 per cent yield of this amine.



1. By metal–acid combinations

The most frequently used combination is zinc and hydrochloric acid. Thus 3-ethoxybenzylamine was obtained from 3-ethoxythionbenzamide (323). Hydrocarbons are often obtained as side products, sometimes in larger yields than the amines (28). In the reduction of α-naphthionamide, for example, 1,2-di(α-naphthyl)-ethane was obtained as well as 1-naphthalenemethylamine. An unsaturated hydrocarbon (stilbene), benzylamine, and bibenzyl were isolated from the reduction of thionbenzamide. *N*-Benzimidoylthionbenzamide, $C_6H_5CSNHC(=NH)C_6H_5$, was reduced to *N*-benzylbenzamidine, $C_6H_5CH_2NHC(=NH)C_6H_5$, by zinc and hydrochloric acid (151).

Thionbenzamide was reduced only to benzaldehyde in about 60 per cent yield by the action of powdered iron in warm 50 per cent acetic acid (178). Nearly all of the unreduced thionbenzamide was recovered. This reduction was quite slow (four days).

2. By amalgams

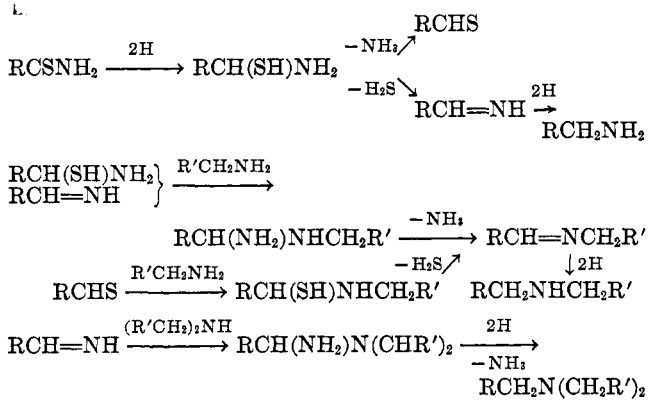
Aluminum amalgam has been most commonly reported for use in reducing thionamides. Kindler observed that the reduction of *N*-unsubstituted thionamides by this alloy proceeded with good yields in either ethanol or ether if the amalgam was added in small portions to the reaction mixture (178). The relative amounts of primary and secondary reduction products obtained by use of aluminum amalgam vary with the thionamide used. The following examples, in which reductions were carried out in moist ether, are illustrative (186):

$$C_6H_5CSNH_2 \rightarrow C_6H_5CH_2NH_2\ (85\%) + (C_6H_5CH_2)_2NH\ (8\%)$$

$$C_6H_5CH_2CSNH_2 \rightarrow C_6H_5CH_2CH_2NH_2\ (26\%) + (C_6H_5CH_2CH_2)_2NH\ (66\%)$$

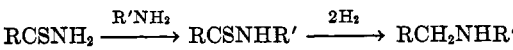
When reduction with aluminum amalgam was carried out in the presence of ethylamine or dimethylamine, these amines were found to participate in formation of the reduction product (178). Thus, α-phenylthionacetamide, in the presence of ethylamine, gave a mixture of 2-phenylethylamine, bis(2-phenylethyl)amine, and ethyl-2-phenylethylamine. It was suggested that the thionamides were first reduced to α-aminothiols, which cleaved hydrogen sulfide to form aldimines. These, in turn, were then either reduced further to primary amines or interacted by addition with the primary or secondary amines present to form secondary or tertiary amines, respectively.

This explanation was part of an overall scheme proposed by Kindler (178) to account for the various products observed on reduction of thionamides:



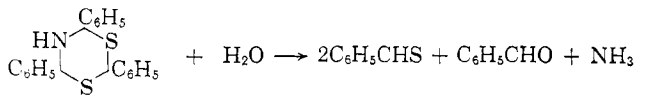
An analogous scheme was also suggested for the reduction of amides, differing from the above only in that oxygen replaced sulfur. It was noted that under hydrolytic conditions the thion compounds might be transformed into the corresponding oxo compounds.

An alternate mechanism to the above is based upon the reaction of thionamides and primary amines to give the corresponding *N*-substituted thionamides (*loc. cit.*). This mechanism, shown below, would also explain the formation of secondary amines.



The reduction of phenylthionacetamide and thionbenzamide by sodium amalgam has been studied in detail (34, 41). The experiments were executed in alcoholic solution with a slight excess of alloy. Reduction

of phenylthionacetamide gave a small amount of 2-phenylethylamine, but the principal product was a solid to which was assigned the structure 2,4,6-tribenzyl-5,6-dihydro-1,3,5-dithiazine, on the basis of complete elemental analysis. On the other hand, the major product isolated from the reduction of thionbenzamide was thionbenzaldehyde. Smaller amounts of benzylamine, benzonitrile, and benzaldehyde were also found. Bernthsen suggested that benzaldehyde and thionbenzaldehyde may have arisen from hydrolytic cleavage of transitory 2,4,6-triphenyl-5,6-dihydro-1,3,5-dithiazine (41).



$$+ \ H_2O \longrightarrow 2C_6H_5CHS + C_6H_5CHO + NH_3$$

N-Substituted thionamides are reduced primarily to the corresponding amines by sodium amalgam, but secondary reactions giving rise to other products have been observed (178).

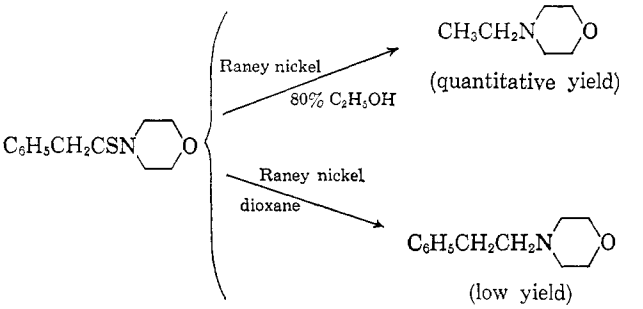
3. Electrolytic reduction

2-Phenylethylamine was obtained in 63 per cent yield by electrolytic reduction of α-phenylthionacetamide in a solution of alcohol and hydrochloric acid (178). *N,N*-Dialkylthionamides, such as *N,N*-dimethylthionbenzamide, were reduced to the corresponding tertiary amines in 75–100 per cent yields by using 60 per cent sulfuric acid and lead electrodes (178). *N*-Alkylthionamides were similarly reduced to the corresponding secondary amines.

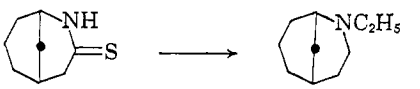
Aldehydes are preferentially formed by electrolytic reduction in stronger acid (80 per cent sulfuric acid). Thus, *N,N*-dimethylthionbenzamide gave a 40 per cent yield of benzaldehyde in addition to smaller amounts of benzyldimethylamine and dimethylamine (178).

4. By Raney nickel

Reductive desulfurization of thionamides with Raney nickel in the absence of hydrogen may give the corresponding amine or aldehyde, or secondary products, depending on the reaction conditions. One of the most important factors appears to be the solvent. The following example is illustrative (24):



It should be noted that reduction of *N,N*-disubstituted thionamides, such as the above morpholide, cannot be explained by Kindler's mechanism (*loc. cit.*). Another example of *N*-ethylation when reduction is carried out in ethanol is furnished by the formation of 2-ethyl-2-azabicyclo[3.3.1]nonane in 75 per cent yield upon treatment of the thionlactam of 3-aminocyclohexaneacetic acid in refluxing absolute ethanol with Raney nickel (77).



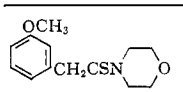
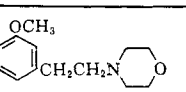
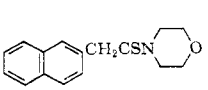
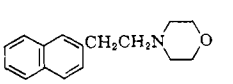
Thionbenzamide and thion-*p*-toluamide were reduced to the corresponding aldehydes by Raney nickel (55). Yields of 77 per cent and 40 per cent, respectively, were obtained by suspending the catalyst in an alcoholic solution of the thionamide at room temperature for a day. It was assumed that an intermediate Schiff base was formed that immediately hydrolyzed.

$$C_6H_5CSNH_2 \rightleftharpoons C_6H_5C(SH)=NH \xrightarrow{Ni(H)} C_6H_5CH=NH \xrightarrow{H_2O} C_6H_5CHO$$

The effect of the catalyst (manner of preparation, relative amount used) on the Raney nickel desulfurization of thionbenzamide in ethanol has been studied (78). The best yield of benzaldehyde (32 per cent) was obtained with nickel deactivated with acetone and

TABLE 13

Catalytic reduction of thionamides

Thionamide	Thionamide–Nickel Ratio in Grams Solvent Yield	Product
	3.1:1 80 per cent C_2H_5OH 69 per cent	
	1.8:1 80 per cent dioxane 56 per cent	
$C_6H_5CH_2CSNHC_4H_9$	2.2:1 80 per cent dioxane 49 per cent	$C_6H_5CH_2CH_2NHC_4H_9$

ammonium hydroxide at 25°C., although W-2 nickel, the commercial catalyst, and nickel deactivated with acetone at 25°C. or at the reflux temperature for an hour were also examined. Reaction was usually complete in 15 min. at a reaction temperature of 25°C.

When thionbenzanilide was reduced in refluxing benzene with the Adkins–Pavlic W-4 nickel catalyst an 86 per cent yield of benzylaniline was produced (148). About 11 per cent of the thionamide was recovered, and a trace of benzanilide was isolated.

Kornfeld successfully reduced many thionamides to the corresponding amine in either 80 per cent ethanol or 80 per cent dioxane using the Adkins–Pavlic catalyst (194). The three examples of Kornfeld's work given in table 13 were carried out in refluxing solvent and were completed in an hour or less.

5. Miscellaneous reductions

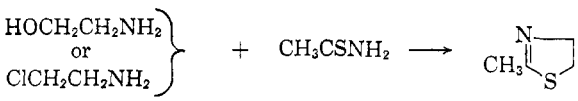
Thionbenzamide was reduced to benzylamine in 8 per cent yield by lithium hydride in ether after 15 min. of reaction at −60°C. (78). In addition, benzonitrile (30 per cent yield) was formed, and 33 per cent of the thionbenzamide was recovered unchanged.

Thionbenzamide has been reduced under basic conditions. By use of zinc and potassium hydroxide a 42 per cent yield of benzaldehyde was obtained (69).

N-Benzyl-*p*-nitrothionbenzamide was reduced in 95 per cent yield to *N*-benzyl-*p*-aminothionbenzamide by tin in hydrochloric acid without reduction of the thionamide group (51).

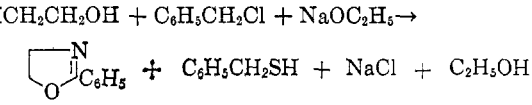
G. CONDENSATIONS WITH β-HALOAMINES, γ-HALOAMINES, AND β-HYDROXYAMINES

A general synthesis of 2-thiazolines results from the cyclization of thionamides with β-haloamines and β-hydroxyamines. For example, 2-methyl-2-thiazoline was obtained from thionacetamide by either heating it with β-hydroxyethylamine at 130°C. for 3 hr. or refluxing it with β-chloroethylamine for 2 hr. In the former case the yield was 10 per cent and in the latter case, 32.3 per cent (294).



In a similar manner, 5,6-dihydro-1,3,4-thiazines are formed by the reactions of thionamides with γ-haloamines. The synthesis of 2-thiazolines and 5,6-dihydro-1,3,4-thiazines by this method has been reviewed elsewhere (88, 287).

One of the most extensively applied ramifications of this 2-thiazoline synthesis has been the treatment of *N*-(2-hydroxyalkyl) amides with phosphorus pentasulfide (287). 2-Phenyl-2-thiazoline, for example, was produced in 68 per cent yield by such treatment of *N*-(2-hydroxyethyl)benzamide (280–282, 283, 322). Presumably the thionamide was an intermediate in this reaction. When this thionamide, $C_6H_5CSNHCH_2CH_2OH$, was subjected to conditions that normally bring about only *S*-alkylation in thionamides (i.e., refluxed in ethanol containing sodium ethoxide with benzyl chloride), the thiobenzyl group was eliminated and 2-phenyl-2-oxazoline and benzyl mercaptan were formed (124).



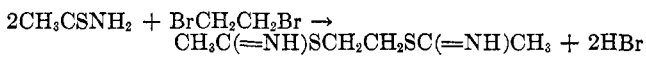
It was suggested that this reaction was an intramolecular cyclization of benzyl *N*-(2-hydroxyethyl)thiolbenzimidate, $C_6H_5C(SCH_2C_6H_5)=NCH_2CH_2OH$.

A variation from the usual reaction of β-hydroxyethylamine and thionamides was observed by Schlatter (274). He found that by warming an equimolar mixture of this amine and thionacetamide to 75°C. a product was obtained whose analysis indicated a reaction in which two moles of each reactant had combined with loss of two moles of ammonia and one of hydrogen sulfide. The product was formulated as $[HOCH_2CH_2N=C(CH_3)—]_2S$.

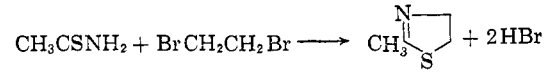
H. CONDENSATIONS WITH DIHALIDES

Cyclization of ethylene dibromide with a thionamide is another oft-used route to 2-thiazolines. When an *N*-arylthionamide is used, the product is an *N*-aryl-2-thiazolinium salt; this is the only method of synthesizing such quaternary salts. This preparative method for 2-thiazolines has been reviewed previously (287).

Cyclization competes with intermolecular bis(*S*-alkylation). This is to be expected, since the customary manner of preparing alkyl thiolbenzimidates ("isothioamides") is by the reaction of an alkyl halide with the salt of a thionamide. Reaction temperature appears to play an important role in the course of this reaction. Thionacetamide reacted with ethylene dibromide on the steam bath to give ethylene dithiolacetimidate (109):



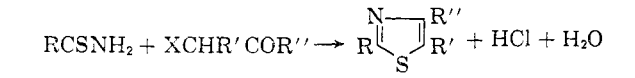
When thionacetamide was refluxed (at 131°C.) with ethylene dibromide, however, 2-methyl-2-thiazoline was obtained in small yield (245).



Thiazole and 2-methylthiazole were prepared in good yields from thionformamide and thionacetamide, respectively, by treatment of the thionamides in aqueous solution at 60°C. with 1,2-dichloroethyl methyl ether (237).

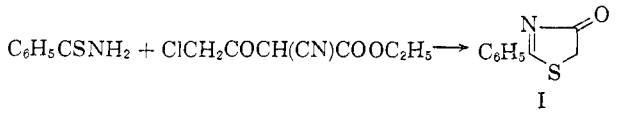
I. CYCLIZATIONS WITH α-HALO CARBONYL AND α-HALO CARBOXYLIC COMPOUNDS

Condensations of thionamides with α-halo ketones and aldehydes represent the most useful and versatile method of preparing thiazoles. This method has been extensively reviewed elsewhere (287, 328). A general equation expressing this synthesis is as follows:



A great amount of work has been published on this method, and the aforementioned reviews have discussed the basic features of this procedure that are necessary to an understanding or appreciation of it. *N*-Substituted thionamides, such as the 5-thionformamidopyrimidine derivatives (17, 33, 70, 147, 150, 249, 284, 297–301) give rise to the corresponding *N*-substituted thiazolium halides.

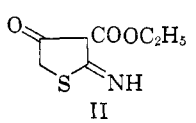
Ethyl γ-chloro-α-cyanoacetoacetate was found to undergo a similar condensation with thionbenzamide when warmed in aqueous ethanol for several days during which cleavage of the ester occurred. The product, 2-phenyl-4(5*H*)-thiazolone (I), was obtained in 75 per cent yield (43).



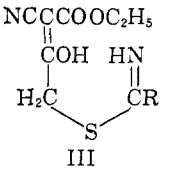
I

However, with thionacetamide a different reaction occurred. Two products were obtained: a small yield of a substance, $C_7H_7NO_2S$, that was not investigated further, and ethyl 4-oxo-2-iminotetrahydrothiophene-3-carboxylate (II).

Beyer and Lässig suggested that formation of I arose through cyclization of intermediate III (R = C_6H_5).

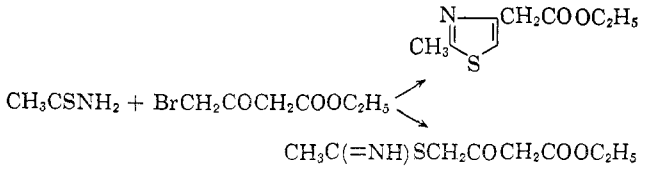


II



III

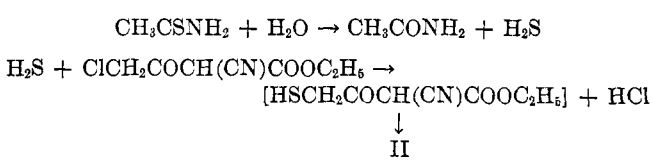
There is experimental justification for the proposal of III as the intermediate in the condensation of ethyl γ-chloro-α-cyanoacetoacetate with either thionacetamide or thionbenzamide. Stende had observed that the reaction of thionacetamide with the similar reagent, ethyl γ-bromoacetoacetate, after half an hour of boiling and long standing formed 2-methyl-4-carbethoxymethylthiazole (289). If, however, condensation was prematurely stopped and crystallization quickly brought about, a quantitative yield of ethyl γ-(acetimidylthio)acetoacetate was obtained (289). The latter product, after its isolation, could not be



cyclized into the thiazole derivative under various reaction conditions (289).

Beyer and Lässig proposed that when R (in III) was a phenyl group, sufficient proton mobility at the imino group was afforded to allow ring closure and formation of I (43). When R was a methyl group, however, the N—H bond in the imino group was stronger so that neither cleavage of water nor rearrangement of the olefinic bond occurred.

Although no hypothesis was advanced by Beyer and Lässig to explain the formation of II, a possible route to II is shown in the following equations:

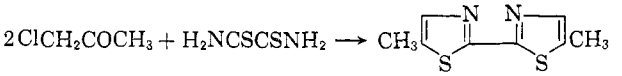


II

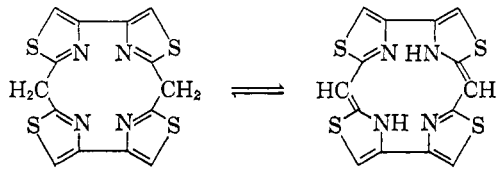
An alternate explanation of the formation of II can be imagined which involves hydrolysis of III (R = CH_3).

α-Halo acids react in a similar manner with thionamides to form 4-thiazolones. This synthesis has been reviewed (287). Both aliphatic and aromatic thionamides have been used to form 2-alkyl- and 2-aryl-4-thiazolones (60). Standard procedure is to reflux equivalent amounts of the reactants in water or toluene. The reactions are generally slow. It was demonstrated that the first step in this synthesis was the formation of a salt of a thiolimidic ester, R′C(=NH)SCHRCOOH·HX (60). In certain cases, such as with α-bromoisobutyric acid, the intermediate thiolic ester could not be cyclized.

Through the reactions of dithionoxamide with α-halo carbonyl compounds or thionamides with 1,4-dihalobutane-2,3-dione it has been possible to produce bithiazoles, polymers, and macro rings. For example, chloroacetone and dithionoxamide in alcoholic solution were found to condense readily to form 4,4′-dimethyl-2,2′-bithiazole (172):



With thionformamide and 1,4-dibromobutane-2,3-dione in warm alcohol, 4,4′-bithiazole was obtained (94). This dione gave high-melting polymers on condensation with either dithionoxamide (172) or dithioterephthalamide, 1,4-$(H_2NCS)_2C_6H_4$ (93). With dithionmalonamide, a highly colored product was obtained (199). It was suggested that this color might be due to chromophores in a structure such as the following:



Thionformamide behaves somewhat differently toward α-halo carboxylic acids than do its higher homologs (248). The reaction of thionformamide with esters of α-halo carboxylic acids can be used to obtain the corresponding esters of α-mercapto carboxylic acids in yields of 50–80 per cent. If this reaction is executed in ether, the salts of esters of α-(formidylthio)carboxylic acids are first isolated. These are readily hydrolyzed to the α-mercapto carboxylates. No thiazolones are found. The reaction sequence is as follows:

$$HCSNH_2 + RCHBrCOOR' \xrightarrow{\text{ether}} \left[\begin{array}{l} RCHCOOR' \\ | \\ S \\ | \\ CH{=}NH_2 \end{array}\right]^+ Br^- \xrightarrow{\text{water}} RCH(SH)COOR'$$

Diethyl bromomalonate was reported to act as an oxidizing agent toward thionformamide under these conditions.

J. SOME REACTIONS OF *N*-CARBOXYMETHYLTHIONAMIDES

N-Carboxymethylthionamides, either as stable starting materials or as intermediates prepared *in situ*, have been used as the source of many thiazole and oxazole derivatives. *N*-(Carboxymethyl)phenylacetothionamide, for example, was cyclized by the action of either acetic anhydride or phosphorus tribromide to 2-benzyl-5-hydroxythiazole (168). When pyridine was used with acetic anhydride the product was the 5-acetoxy analog.

$$C_6H_5CH_2CSNHCH_2COOH \xrightarrow[-H_2O]{(CH_3CO)_2O \text{ or } PBr_3} HO\text{-}\underset{S}{\overset{N}{\langle}}\rangle\text{-}CH_2C_6H_5$$

Similarly, 5-ethoxy-2-methylthiazole was obtained in 65 per cent yield by heating the ethyl ester of *N*-acetylglycine with phosphorus pentasulfide (292).

A number of ramifications of this 5-hydroxythiazole synthesis have been reported. 2-Benzyl-4-benzylidene-5-(4*H*)-thiazolinone was obtained on treating thionphenaceturic acid with acetic anhydride in the presence of benzaldehyde (12). When ethyl orthoformate was substituted for benzaldehyde the following intermolecular condensation took place (12):

$$C_6H_5CH_2CSNHCH_2COOH \xrightarrow[H(COOC_2H_5)_3]{(CH_3CO)_2O} C_6H_5CH_2\text{-}\underset{S}{\overset{N}{\langle}}\rangle\text{-}\underset{O}{\overset{CH}{\langle}}\rangle\text{-}\underset{O}{\overset{N}{\langle}}\rangle\text{-}\underset{S}{\rangle}\text{-}CH_2C_6H_5$$

Another type of cyclization is represented by the condensation of thionacetamide with the ethyl ester of penicillamine to give 4-carbethoxy-2,5,5-trimethyl-2-thiazoline (72):

$$(CH_3)_2C(SH)CH(NH_2)COOC_2H_5 + CH_3CSNH_2 \longrightarrow \underset{CH_3}{\overset{N}{\langle}}\rangle\text{-}\underset{S}{\rangle}\text{-}\underset{(CH_3)_2}{COOC_2H_5} + NH_3 + H_2S$$

5-Oxazolones are formed upon treatment of the *N*-carboxymethylthionamides with silver salts or silver oxide (13). Thionphenaceturic acid in dry ether was cyclized by silver oxide to 2-benzyl-5(4*H*)-oxazolone (10, 13, 168).

$$C_6H_5CH_2CSNHCH_2COOH \xrightarrow{Ag_2O} \underset{O}{\overset{N}{\langle}}\rangle\text{-}\underset{O}{\rangle}\text{-}CH_2C_6H_5$$

Ethyl thionphenaceturate gave 2-benzyl-5-ethoxyoxazole on treatment with silver benzenesulfonate in cold pyridine (54).

$$C_6H_5CH_2CSNHCH_2COOC_2H_5 \xrightarrow{C_6H_5SO_3Ag} C_2H_5O\text{-}\underset{O}{\overset{N}{\langle}}\rangle\text{-}CH_2C_6H_5$$

These cyclizations parallel those of the corresponding *N*-carboxymethylamides, such as phenaceturic acid (74). The usual reaction of an *N*-unsubstituted thionamide with a silver salt or silver oxide is to precipitate silver sulfide with the formation of a nitrile.

The corresponding *N*-carbamidomethylthionamides, such as thionhippuramide, react with mercuric salts in an entirely different manner (193). Equivalent amounts of thionhippuramide and mercuric acetate were mixed, and reaction instantly took place with precipitation of mercuric sulfide and formation in solution of hippuronitrile (193).

$$C_6H_5CSNHCH_2CONH_2 \xrightarrow{Hg(OCOCH_3)_2} C_6H_5CONHCH_2CN$$

In related fashion, *N*-benzylthionhippuramide ($C_6H_5CSNHCH_2CONHCH_2C_6H_5$) gave a small yield of *N*-benzylhippuramide on treatment with mercuric acetate.

K. CONDENSATIONS OF DITHIONOXAMIDES WITH SECONDARY AMINES AND ALDEHYDES

Wallach observed that when aldehydes and secondary amines were dissolved in chloroform, and the solution then treated with dithionoxamide, the following reaction occurred (316).

$$H_2NCSCSNH_2 + 2RCHO + 2R_2'NH \rightarrow R_2'NCHRNHCSCSNHCHRNR_2' + 2H_2O$$

A number of aliphatic aldehydes, as well as benzaldehyde, were successfully employed. The bases used included dialkylamines, piperidine, alkylarylamines, and diaralkylamines. In addition to dithionoxamide, *N*,*N*′-dialkyldithionoxamides participated in this reaction.

$$CH_3NHCSCSNHCH_3 + 2HCHO + 2C_6H_5NHCH_3 \rightarrow 2H_2O + CH_3N(C_6H_5)CH_2N(CH_3)CSCSN(CH_3)CH_2N(C_6H_5)CH_3$$

Primary amines could not be used. The adduct of a primary amine and an aldehyde immediately eliminates water, and the resulting Schiff base does not react with a dithionoxamide. Neither dithionoxanilides nor tetrasubstituted dithionoxamides undergo this reaction.

The *N,N'*-bis(disubstituted-aminomethyl)dithionoxamides produced in this reaction were generally unstable compounds that decomposed into their components (316). Those prepared from formaldehyde and dialkylamines of lower molecular weight were oils; the others were crystalline solids.

L. CONDENSATIONS WITH ALDEHYDES

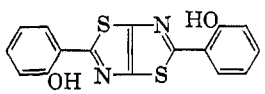
The condensation of a monothionamide with an aldehyde has been reported only once (41):

$$2C_6H_5CH_2CSNH_2 + C_6H_5CHO \rightarrow C_6H_5CH(NHCSCH_2C_6H_5)_2 + H_2O$$

The oily product was analyzed as its solid platinum chloride salt.

Condensation of dithionoxamide with benzaldehyde and salicylaldehyde was first reported long ago (91), but only recently have the structures of the products been established (177). It has been shown that this condensation is accompanied by dehydrogenation and that the products are aryl derivatives of thiazolo-[5,4-*d*]thiazole. Thus, for benzaldehyde the structure of the product is as follows:

With salicylaldehyde the symmetrical product was formed:



The condensation was extended to other aromatic aldehydes and appeared to be quite general. No condensation, however, was achieved with *o*-nitrobenzaldehyde (177). Aliphatic aldehydes and aryl methyl ketones also failed to give isolable products.

M. CONDENSATIONS WITH NITRILES

Matsui found that on passing dry hydrogen chloride into a cold ethereal solution of benzonitrile and thionbenzamide, condensation occurred (214). Ishikawa later demonstrated that the condensation product was *N*-benzimidoylthionbenzamide (152).

$$C_6H_5CSNH_2 + C_6H_5CN \xrightarrow{HCl} C_6H_5CSNHC(=NH)C_6H_5$$

The function of the hydrogen chloride is not to form benzimidoyl chloride, since both Matsui (214) and Ishikawa (155) demonstrated that imidyl chlorides react with thionamides to form products different from those given by the nitriles.

This reaction was extended to other nitrile–thionamide combinations (153, 154, 157). The principal product obtained from the condensation of acetonitrile and thionbenzamide was also *N*-benzimidoylthionbenzamide (153, 154). In order for this product to have formed, benzonitrile must have been produced as an intermediate. That the source of benzonitrile was not thionbenzamide was shown by the failure of thionbenzamide to react with dry hydrogen chloride in cold ether. Therefore, it was assumed that acetonitrile condensed with thionbenzamide in the same manner as benzonitrile, and that this condensate then decomposed to benzonitrile and thionacetamide. In support of this hypothesis thionacetamide was isolated from the reaction mixture.

$$CH_3CN + C_6H_5CSNH_2 \rightleftharpoons [CH_3C(=NH)N=C(SH)C_6H_5] \rightleftharpoons CH_3CSNH_2 + C_6H_5CN$$

When benzonitrile and thionbenzamide were condensed, the yield of *N*-benzimidoylthionbenzamide was nearly quantitative (152). This product was obtained in only 14 per cent yield, however, from the reaction of acetonitrile with thionbenzamide (153, 154). To account for this discrepancy Ishikawa studied the condensation of benzonitrile with thionacetamide; although *N*-benzimidoylthionbenzamide was obtained, a 71 per cent yield of thionbenzamide was also isolated (153, 154). It was suggested that the equilibria and the unisolated intermediate shown in brackets above existed. No mechanism was advanced to explain the decomposition of this intermediate into thionacetamide and benzonitrile.

Although Peak was able to reproduce the condensation of benzonitrile and thionbenzamide, he observed that the condensation was unsatisfactory in the case of benzonitrile and *N*-substituted thionbenzamides because of nearly complete precipitation of the hydrochloride of the thionamide (241).

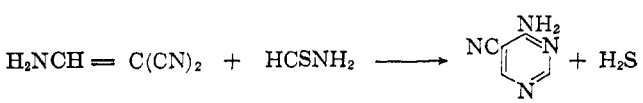
Primary thionamides react with cyanamide in warm alcoholic solution to give good yields of thiourea (64).

$$RCSNH_2 + NH_2CN \rightarrow RCN + NH_2CSNH_2$$

The same reactants gave excellent yields of the salts of thiodiformamidine, $[H_2NC(=NH)]_2S$, on reaction in cold alcoholic solution in the presence of mineral acids (64). Thiourea can be used in place of a thionamide in the latter reaction.

N. SYNTHESES OF PYRIMIDINES AND TRIAZINES

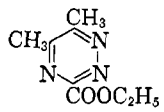
Thionformamide reacts with aminomethylenemalononitrile in refluxing alcoholic sodium ethoxide to give 4-amino-5-cyanopyrimidine (26).



A similar condensation between thionacetamide and the compound $H_2NCH{=}C(CN)COOC_2H_5$ gave 4-amino-5-carbethoxy-2-methylpyrimidine (138).

1-Carbethoxythionformamide gave a good yield of 3-carbethoxy-5,6-dimethyl-1,2,4-triazine on reaction with hydrazine and 2,3-butanedione (278).

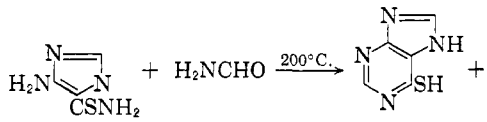
$$NH_2CSCOOC_2H_5 + NH_2NH_2 + CH_3COCOCH_3 \longrightarrow$$



$$+ H_2S + 2H_2O$$

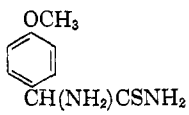
Phenanthrenequinone underwent a similar condensation.

6-Mercaptopurine was obtained by the reaction of formamide and 4-aminoimidazole-5-carbothionamide (132):

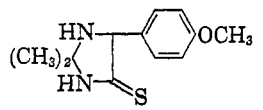


O. α-AMINOTHIONAMIDES: ACYLATION AND SYNTHESIS OF IMIDAZOLE DERIVATIVES

2,5-Disubstituted imidazolidine-4-thiones have been prepared by refluxing solutions in absolute alcohol of equimolar amounts of α-aminothionamides and various aldehydes or ketones (1–4).



$$+ CH_3COCH_3 \rightarrow$$

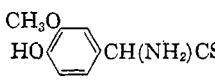


$$+ H_2O \quad (1)$$

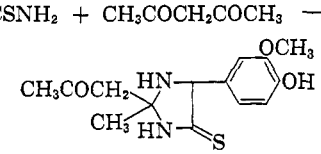
Aliphatic (3) and aromatic (2) aldehydes, ketones (1), and α,γ-dicarbonyl compounds (4) have been used to give imidazolidine-4-thiones in good yields. If two equivalents of carbonyl compound were used, condensation at both the amino and amido groups occurred and no heterocycle was obtained (3).

$$C_6H_5CH(NH_2)CSNH_2 + 2C_6H_5CHO \rightarrow C_6H_5CHCSN{=}CHC_6H_5$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad N{=}CHC_6H_5$$

α,γ-Dicarbonyl compounds gave imidazolidine-4-thiones on condensation with equimolar amounts of thionamides. Only one carbonyl group was involved, since no methylene-2,2′-bis(imidazolidine-4-thione) compounds were isolated (4).

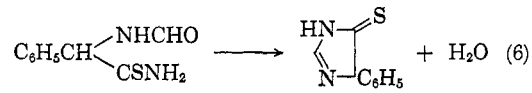


$$CH(NH_2)CSNH_2 + CH_3COCH_2COCH_3 \longrightarrow$$



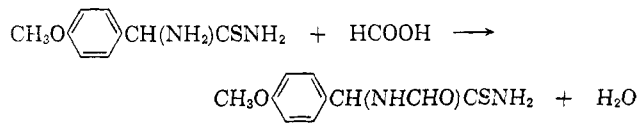
$$+ H_2O$$

Imidazoline-4-thiones were prepared by a similar procedure in which the α-amino groups of α-aminothionamides were first acylated, and the resulting α-amidothionamides were then cyclized (5–7).



$$+ H_2O \quad (6)$$

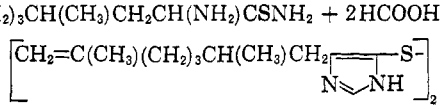
These cyclizations were effected in either acidic or basic, refluxing alcoholic solutions. The α-amidothionamides were prepared in three ways. First, treatment of an α-aminothionamide with formic acid in the absence of solvent gave α-formamido derivatives (3).



Secondly, α-aminothionamides when boiled with one or two equivalents of acetic anhydride gave the corresponding α-acetamido derivatives (5). And finally, α-benzamidothionamides were obtained in low yields by the reaction of α-aminothionamides with benzoyl chloride.

Oxidation of an imidazoline-4-thione formed *in situ* was observed when formic acid and 2-amino-4,8-dimethyl-8-nonene-1-carbothionamide were warmed (6).

$$2H_2C{=}C(CH_3)(CH_2)_3CH(CH_3)CH_2CH(NH_2)CSNH_2 + 2HCOOH$$
$$\rightarrow H_2S + 2H_2O +$$



It should be noted that imidazoline-4-thiones can, in general, be oxidized to the corresponding disulfides by either hydrogen peroxide or iodine.

P. REACTIONS WITH ACID CHLORIDES

Although a substantial amount of work has been published in this field, clarification of the results is needed. The reactions are characterized by rearrangements of one isomer into another. Absolute means of distinguishing one isomer from another, in general, have not been applied. The situation is complicated by the observation that structurally similar compounds are reported to undergo different rearrangements under the same reaction conditions. This section of the review should be read with these thoughts well in mind.

1. Acyl chlorides

Except for the acylation of α-aminothionamides discussed in the previous section there has been relatively little reported concerning the reactions of thionamides with acyl chlorides. Many years ago, the reaction of thionacetamide with acetyl chloride in ether solution was observed to give a very unstable, uncharacterized precipitate that appeared to be crystalline (170).

The relatively acidic imido group of dithioncamphorimide was benzoylated by addition of benzoyl chloride to a warm solution of thioncamphorimide, ethyl iodide, and magnesium (239).

Acylation of thionformylhydrazine derivatives has been observed (272). Equivalent amounts of 2-phenyl-1-thionformylhydrazine and benzoyl chloride reacted in pyridine to form 2-benzoyl-2-phenyl-1-thionformylhydrazine.

$$C_6H_5NHNHCHS + C_6H_5COCl \xrightarrow{\text{pyridine}} C_6H_5CON(C_6H_5)NHCHS$$

When two equivalents of benzoyl chloride were used, a different product was obtained. This product, unlike the former, was insoluble in dilute alkali. Acetyl chloride behaved similarly in these reactions.

S-Benzyl thiolbenzohydroxamate was benzoylated in pyridine by benzoyl chloride (57).

$$C_6H_5C(=NOH)SCH_2C_6H_5 + C_6H_5COCl \xrightarrow{\text{pyridine}} C_6H_5C(SCH_2C_6H_5)=NOCOC_6H_5$$

Acetyl chloride and benzoyl chloride reacted with the sodio derivatives of *N*-benzylthionacetamide and *N*-benzylthionbenzamide to form products that could not, in general, be purified, but whose properties were in accord with those expected for the product of the following generalized equation (48):

$$RC(SNa)=NCH_2C_6H_5 + R'COCl \rightarrow RC(NCH_2C_6H_5)(SCOR') + NaCl$$

The impure products were obtained in about 45 per cent yields.

Thionoxanilonitrile was benzoylated in aqueous sodium carbonate solution (259).

$$C_6H_5NHCSCN + C_6H_5COCl \xrightarrow{Na_2CO_3} C_6H_5CON(C_6H_5)CSCN$$

In sodium hydroxide solution, the product was the corresponding amide, $C_6H_5CON(C_6H_5)CSCONH_2$. This benzoylation was extended to other cyanothionanilides of the general formula ArNHCSCN.

2. Imidyl chlorides

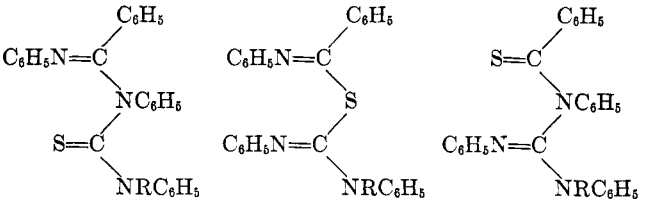
N-Phenylimidyl chlorides have been transformed into the corresponding thionanilides by reaction with unsubstituted thionamides (155).

$$C_6H_5CSNH_2 + CH_3C(=NC_6H_5)Cl \xrightarrow{\text{ether}} CH_3CSNHC_6H_5 \quad (46\%\ \text{yield})$$

$$CH_3CSNH_2 + C_6H_5C(=NC_6H_5)Cl \xrightarrow{\text{ether}} C_6H_5CSNHC_6H_5$$

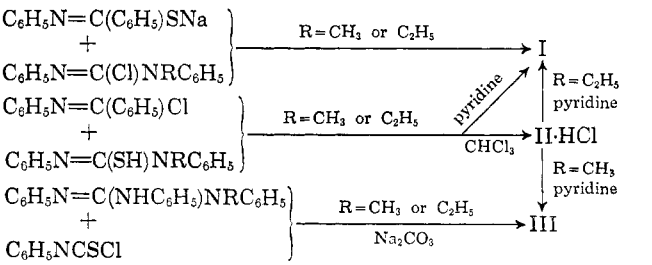
In the case of the reaction of thionbenzamide and *N*-phenylbenzimidoyl chloride, a 50 per cent yield of benzonitrile was obtained in addition to a 95 per cent yield of thionbenzanilide. These results should be compared with the condensations of thionamides and nitriles (*loc. cit.*).

Two homologous sets of three isomeric thionamide derivatives were obtained by Rivier and Langer in syntheses involving the reactions of thionamides with imidyl chlorides (262).



Ia: R = C_2H_5; Ib: R = CH_3 — IIa, IIb — IIIa, IIIb

The preparation of these compounds, the conversion of one isomer to another within each set, and the variation in type of rearrangement caused by homologous changes in the group R have been studied (262). This work is summarized in the following equations:



In the formation of I from condensation of the sodium salt of thionbenzanilide with the imidyl chloride, $C_6H_5N=C(Cl)NRC_6H_5$, none of the expected product, II, was isolated when R was either a methyl or an ethyl group. Treatment of the hydrochlorides of IIa and IIb with pyridine gave small yields of Ia and IIIb, respectively, the principal product in each case being the free base, II.

It was found that IIIa was converted to Ia, and Ib to IIIb, by heating (262). Rivier suggested that the common intermediate in these two rearrangements was II.

3. Sulfur monochloride

Although Chakravarti (67) first observed the reactions of thionamides with sulfur monochloride, it remained for Ishikawa (156) to characterize the products. Ishikawa found that on slow addition of an ethereal solution of sulfur monochloride to a cold ethereal solution of thionbenzamide two products were obtained: *N*-benzimidoylthionbenzamide and 3,5-diphenyl-1,2,4-thiadiazole. The latter was undoubtedly an oxidation product of the former. *N*-Benzimidoylthionbenzamide was also isolated when this reaction was executed in alcoholic potash solution.

The reaction was extended to other *N*-unsubstituted thionamides with similar results (156). With thion-

benzanilide, however, the reaction took a different course (156).

Addition of an ethereal solution of sulfur monochloride to one of thionbenzanilide caused separation of a yellow precipitate of sulfur, aniline hydrochloride, and a little benzanilide. From the mother liquor were obtained starting material and a solid believed to be *N*-(*N'*-phenylbenzimidoyl)thionbenzanilide, $C_6H_5C(=NC_6H_5)N(C_6H_5)CSC_6H_5$.

Ishikawa noted that benzanilide may have resulted from the decomposition of this sulfide, since it had been observed by others (265) that when this sulfide was treated with dry hydrogen chloride in absolute ether and the reaction mixture then taken up in dilute caustic soda, decomposition to benzanilide and thionbenzanilide occurred.

4. Thionyl chloride

Thionyl chloride was found to react with thionamides in a manner somewhat analogous to that of sulfur monochloride (157). Thionbenzamide, in cold ether solution, gave *N*-benzimidoylthionbenzamide, 3,5-diphenyl-1,2,4-thiadiazole, sulfur, sulfur dioxide, and hydrogen chloride. Thionbenzanilide yielded bis(*N*-phenylbenzimidoyl) sulfide, benzanilide, and aniline hydrochloride.

It should be noted that sulfur monochloride and thionyl chloride may react with the same thionamide to yield different products. Thus, with thionbenzanilide the former gave rise to *N*-(*N'*-phenylbenzimidoyl)-thionbenzanilide (156) and the latter yielded an isomeric product, bis(*N*-phenylbenzimidoyl) sulfide (157). The structure of neither product was rigorously demonstrated.

With thionacetamide no condensation products were found; only acetamide, sulfur, sulfur dioxide, and hydrogen chloride were isolated. The same absence of condensation product was experienced with thionacetanilide.

5. Sulfuryl chloride

The action of sulfuryl chloride upon thionamides is similar to that of thionyl chloride (157). The same products were obtained with the same thionamide. Sulfuryl chloride apparently gave relatively larger yields of condensation products [*N*-(benzimidoyl)thionbenzamide from thionbenzamide, for example] than did thionyl chloride.

6. Benzenesulfonyl chloride

Thionbenzamide and benzenesulfonyl chloride reacted to give principally 3,5-diphenyl-1,2,4-thiadiazole and sulfur (157). With thionbenzanilide a small yield of *N*-(*N'*-phenylbenzimidoyl)thionbenzanilide was isolated; the yield was greatly improved by use of the sodium salt of thionbenzanilide, in which case benzenethiosulfonic acid, $C_6H_5SO_2SH$, was also obtained (157).

Q. THIOLIMIDIC ESTERS (ISOTHIOAMIDES)

The organization of this review has been such as to include the syntheses and properties of the so-called "isothioamides" under the appropriate subject headings in the discussion of thionamides. In this section, therefore, only those synthetic methods and chemical properties not elsewhere described will be discussed.

The most general and widely used method of preparing a thiolimidic ester is to treat the sodium salt of a thionamide with an alkyl or aralkyl halide. In this manner, Wallach first made methyl *N*-phenylthiolacetimidate, $CH_3C(=NC_6H_5)SCH_3$, from methyl iodide and the sodium salt of thionacetanilide (313). A number of different media have been used as solvents for this reaction, the most usual being ethanol. When *N*-benzylthionacetamide was heated in methyl iodide a quantitative yield of the hydroiodide of methyl *N*-benzylthiolacetimidate was obtained (195). On treatment of this product with potassium hydroxide a 64 per cent yield of the free base, $CH_3C(=NCH_2C_6H_5)SCH_3$, was isolated.

Methyl sulfate can also be used as an alkylating agent. The reaction was observed to fail usually in inert organic solvents owing to the presence of small amounts of water that brought about the following hydrolysis (217):

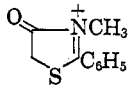
$$C_6H_5CSNHC_6H_5 + (CH_3)_2SO_4 + H_2O \rightarrow C_6H_5CONHC_6H_5 + (CH_3)_2S + H_2SO_4$$

If alkylation was executed in aqueous alkali, however, the "isothioamide" was formed. One exception to such basic alkylation has been noted. The reaction of thionoxanilonitrile with methyl sulfate in 20 per cent alkaline solution gave the *N*-methylated product (259):

$$C_6H_5NHCSCN + (CH_3)_2SO_4 \xrightarrow{20\%\ NaOH} C_6H_5N(CH_3)CSCN$$

Generally, *N*-unsubstituted thionamides react with bromoacetic acid to give 4(5*H*)-thiazolones (*loc. cit.*). *N*-Substituted thionamides, however, yield "isothioamides" upon reaction with bromoacetic acid in acetic anhydride (145). Thus, *N*-methylthionbenzamide gave the hydrobromide of carboxymethyl *N*-methylthiolbenzimidate, $HOOCCH_2SC(C_6H_5)=NCH_3\cdot HBr$. A number of other *N*-substituted and *N,N*-disubstituted thionamides were found to react similarly. The carboxymethyl thiolbenzimidates are hydrolyzed under alkaline conditions. If the imido group is not completely substituted, cyclization may occur instead of hydrolytic cleavage. Thus,

$$HOOCCH_2SC(C_6H_5)=\overset{+}{N}HCH_3Br^- + NaOH \xrightarrow{H_2O}$$



$$OH^- + NaBr + H_2O$$

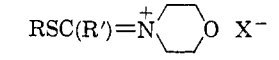
$$HOOCCH_2SC(C_6H_5)=\overset{+}{N}(CH_3)_2Br^- + NaOH \xrightarrow{H_2O}$$

$$HSCH_2COOH + C_6H_5CON(CH_3)_2 + NaBr$$

A similar difference prevailed under acidic conditions: the *N*-monosubstituted thiolbenzimidates gave 4(5*H*)-thiazolonium compounds and the *N*,*N*-disubstituted thiolbenzimidates yielded thiolic esters, $RCOSCH_2COOH$, in the usual manner of "isothioamide" hydrolyses (*loc. cit.*).

The sodium and potassium salts of *N*-benzylthionamides were found to react with alkyl halides to form products of the general formula $C_6H_5C(SR)=NCH_2C_6H_5$ in 45–65 per cent yields in xylene solutions (48).

N,*N*-Disubstituted thionamides, such as the *N*-thionacylmorpholines, form salts with alkyl halides. There has been some controversy as to the structure of these salts, but the majority opinion and greater part of the evidence seem to favor the following form (242):



Peak and Stansfield have reviewed the evidence bearing on this question (242).

A thiolimidic ester has been prepared in one other way, by a reaction analogous to the preparation of thionamides from acid chlorides (*loc. cit.*) (68).

$$C_6H_5C(Cl)=NC_6H_5 + C_6H_5SH \rightarrow C_6H_5C(=NC_6H_5)SC_6H_5$$

p-Tolyl *N*-(*p*-tolyl)thiolbenzimidate was similarly pre-

TABLE 14

*Use of thionamides for the detection and determination of metal cations**

Cation	Thionamide			
	$HCSNH_2$	CH_3CSNH_2	$C_6H_5CSNH_2$	$H_2NCSCSNH_2$ (97, 169, 320)
Ag	— —	— —	(110) —	(169)
As(III or IV)	— (112, 113, 236)	(44) (100)	— —	— —
Bi	— —	(44) —	— —	(169, 320) —
Cd	— —	(44) (102)	— —	— —
Co	— —	(44) —	— —	(169, 255, 320) (256)
Cu(II)	— (112, 113)	(44) (99)	(110) —	(169, 200, 255, 320, 324) (16, 244, 256, 291)
Fe	— —	— —	— —	(169, 320) —
Hg(I)	— —	— —	— —	(110, 169) —
Hg(II)	— —	(44) —	— —	(110, 111) —
Ir	— —	— —	— —	(110) —
Mn	— —	(44) —	— —	— —
Ni(II)	— —	(44) —	— —	(169, 255, 320) (256, 308)
Pd	— —	— —	— —	(110, 169) (20)
Pt	— (115)	— —	— —	(169) —
Ru(III or IV)	— —	— —	— —	(320) —
Sb(III)	— (236)	(44) (98, 325)	— —	— —
Sn(IV)	— (236)	(44) (103)	— —	— —
Zn	— —	(44) —	— —	— —

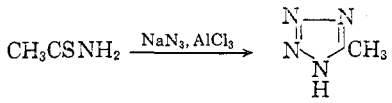
* References in the first line of each horizontal row refer to spot tests and qualitative detection of metals. References in the second line refer to the determination of metals.

pared from *p*-thiocresol and *N*-(*p*-tolyl)benzimidoyl chloride.

Many thiolimidic esters are syrupy, unstable liquids that decompose into nitriles and mercaptans (61).

R. REACTIONS WITH AZIDES

5-Methyltetrazole was obtained in 55 per cent yield by the addition of excess sodium azide to a tetrahydrofuran solution of thionacetamide and aluminum chloride (327).



Similarly, pentamethylenetetrazole ("Cardiazole") was prepared from ϵ-thioncaprolactam in 65 per cent yield. Tetrazoles also result from the reaction of aluminum azide with nitriles, suggesting that nitriles may be intermediates in the preceding reaction.

S. REACTIONS WITH METAL IONS

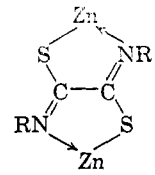
A number of metals that form water-insoluble sulfides react as their cations with thionamides in aqueous solution to precipitate metal sulfides while forming the corresponding amides. Analytical procedures have been developed for the substitution of thionacetamide for hydrogen sulfide in qualitative inorganic analyses (29, 233). Thionamides also form complexes with many metals, and such complex formation has been utilized for the detection and determination of these metals. The application of thionamides to the identification and determination of metals is summarized in table 14.

N-Benzylthionamides were found to react with finely powdered sodium or potassium in refluxing xylene or tetralin to precipitate the metal derivative of the thionamide (48). Alkyl and aryl halides reacted with these metallo compounds to form *S*-alkyl and *S*-aryl derivatives, respectively. Treatment of the metallo compounds with aqueous solutions of silver salts caused immediate decomposition to silver sulfide and *N*-benzylamides.

Dithionoxamide and its *N,N'*-disubstituted derivatives act as reagents for the detection and determination of the metals shown in table 14 by virtue of their ability to form highly colored complexes with them. For example, dithionoxamide will detect one part of copper in 1,000,000 parts of solution (169). Some of the complexes, such as those of the transition metals, are quite insoluble in water and most organic solvents; however, the blue ruthenium(III or IV) complex of dithionoxamide exhibits solubility in common media such as 1:1 hydrochloric acid–ethanol (21). The transition metal complexes of dithionoxamide are very stable. Complexes of other metals may be relatively unstable. Dithionoxamidolead(II), $PbC_2H_2N_2S_2$, decomposed in water with precipitation of lead sulfide (331). The dithionoxamide complexes of iron(II and III), rubidium, silver, cadmium, and mercury have been reported to be unstable and to rapidly decompose into the metal sulfides (256, 312). Gold and platinum were readily reduced from their dithionoxamide complexes to the metallic state (312).

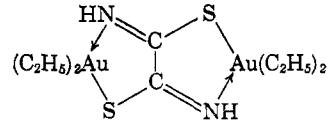
Rây and Rây found that the transition metal complexes of dithionoxamide were described by the general stoichiometric formula $MC_2H_2N_2S_2$ (256). They represented the complexes as being monomeric, nonionic, tetracoördinated metal complexes with S—M and N—M coördinate bonds (256). Jensen disagreed with this picture on the basis of magnetic susceptibility measurements and by analogy with the structure of nickel mercaptides (166). He suggested that the nickel complex is a polymer. Studies on the structure and properties of nickel complexes of *N,N'*-disubstituted dithionoxamides have been reported (149).

The zinc complexes of dithionoxamide and its *N,N'*-di-*sec*-butyl and *N,N'*-diallyl derivatives have been studied spectroscopically in buffered dipropylene glycol methyl ether solutions (228). From the relationships between maximum absorption and zinc concentration it appeared that these complexes consisted of a 2:1 molar ratio of zinc to dithionoxamide. The following structure was suggested:



It is of interest to note that under the same conditions *N,N'*-bis(2-hydroxyethyl)dithionoxamide did not form a complex with zinc.

Diethylgold(III) bromide was found to react with dithionoxamide in a solution of petroleum ether and alcohol made basic with potassium hydroxide, and a 77 per cent yield of a complex was obtained to which was assigned the following structure (95):



Monothionamides, of course, have a more limited role as complexing agents. The reactions of salicylthionamide and salicylamide with copper(II), cadmium, iron(III), nickel(II), and cobalt(II) have been studied and compared (86). Thionbenzamide formed a complex with mercuric chloride that contained two moles of thionamide for each mole of mercuric chloride (159). This complex, whose structure was not determined, decomposed in aqueous alkali according to the following equation:

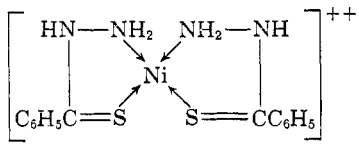
$$(C_6H_5CSNH_2)_2 \cdot HgCl_2 + 2KOH \rightarrow C_6H_5CSNH_2 + C_6H_5CN + HgS + 2KCl + 2H_2O$$

With mercuric chloride, *N*-benzimidoylthionamides formed 1:1 complexes that were oxidized in aqueous alkali to form 1,2,4-thiadiazoles.

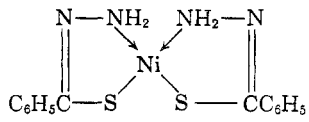
$$C_6H_5C(=NH)NHCSR \cdot HgCl_2 + 2KOH \longrightarrow \text{(1,2,4-thiadiazole)} + Hg + 2KCl + 2H_2O$$

Both of these types of mercuric chloride complexes were decomposed by aqueous solutions of hydrogen sulfide into their organic components and mercuric sulfide.

Thionbenzoylhydrazine and its *N'*-derivatives, $C_6H_5CSNHNHR$, were found to form three types of nickel complexes (167). Complex salt I was obtained in quantitative yield by the reaction of nickel salts and thionbenzoylhydrazine in acidified alcoholic solution. When this reaction was executed in ammoniacal alcoholic

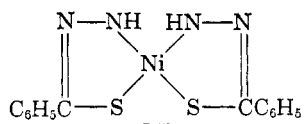


I



II

solution instead, a brown precipitate which quickly oxidized in air was observed. In the absence of air the brown complex (II) could be isolated. The oxidation product of II was blue and diamagnetic; its analyses supported structure III, a tetravalent nickel compound.



III

The N^2-derivatives of thionbenzoylhydrazine showed some deviations in behavior towards nickel salts under the same conditions. N^2-Phenyl and N^2-thioncarbamido derivatives formed only internal complexes, homologs of II, under either acidic or basic conditions. The N^2-methyl and N^2-carbamido derivatives underwent no visible reaction with nickel salts in acid solution, but in an ammoniacal medium the latter derivative gave a brown compound that was not further described. N^1-Thionbenzoyl-N^2-benzoylhydrazine underwent reaction with nickel nitrate, but analysis of the product indicated that complex formation was accompanied by decomposition of the organic portion.

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