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The Chemical Properties of Thioamides

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The principal chemical properties of thioamides are surveyed—hydrolysis, reduction and oxidation, and reactions with inorganic and organic amines, acid chlorides, aldehydes and ketones, alkyl halides, and halogenated amines, ketones, and acids. A list of 274 references is included.

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I. INTRODUCTION

Thioamides are reactive compounds, and have been well studied. The changes they undergo on oxidation, reduction, reaction with inorganic and organic amines, and addition to halogenated amines, ketones, acids, and esters are widely used in obtaining derivatives of pyrimidine, purine, and uracil, thiazoles, vitamin B_1, etc. [1-16].

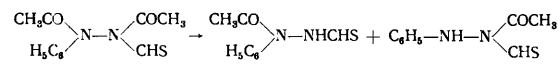
There is a vast literature on the chemical properties of thioamides, which has not yet been systematised. Existing reviews [17-23] are concerned mainly with the preparation of thioamides; the chemical properties are not dealt with adequately [17,18,21-23]. The Soviet literature contains no reviews on the chemical properties of thioamides. This is the reason for publishing the present Review.

II. HYDROLYSIS OF THIOAMIDES

Like amides of carboxylic acids, thioamides can be hydrolysed by water, better in the presence of acids or alkalis. The products are usually carboxylic acids, but sometimes amides and nitriles. Unsubstituted thioamides are relatively easily hydrolysed with the formation in acid medium mainly of carboxylic acids, but in the presence of alkalis aromatic thioamides yield carboxylic acids, nitriles, and amides. Thus thioacetamide is hydrolysed by bases and acids to acetic acid, hydrogen sulphide, and ammonia [24]. With boiling water or hot 1 *N* hydrochloric acid thiobenzamide yields benzoic acid, hydrogen sulphide, and ammonia; but with caustic potash it forms benzonitrile and hydrogen sulphide (ammonia also is formed on heating with 1 *N* caustic potash). [25] Phenylthioacetamide behaves similarly: with dilute hydrochloric acid it gives phenylacetic acid, hydrogen sulphide, and ammonia; but on heating with caustic potash phenylacetonitrile and hydrogen sulphide are obtained [26].

Thioamides are more difficult to hydrolyse than are the corresponding amides [27]. *N*-Thiobenzoylmorpholine is hydrolysed in 10 *N* caustic potash at only one-tenth the rate of *N*-benzoylmorpholine [28].

N-Substituted thioamides are considerably more difficult to hydrolyse than are the unsubstituted compounds. Thus *N*-benzylthiobenzamide hydrolyses very slowly even when boiled in 50% sulphuric acid, whereas thiobenzamide is hydrolysed with the formation of benzoic acid even by boiling water. Phenyl *N*-phenyl-*N*-thiobenzoylthiocarbamate $C_6H_5.CS.N(C_6H_5).CSOC_6H_5$ is hydrolysed slowly by sulphuric acid, one of the products being thiobenzanilide [29]. The hydrolysis of *N*-phenyl-*N'*-thioformyldiacetohydrazide in 10% caustic soda does not affect the thioformyl group, the product being *N'*-phenyl-*N*-thioformylacetohydrazide contaminated with other substances [30]:



The great stability of the thioanilide group in comparison with thiocarbamoyl [31] is evident also in the hydrolysis of *N*-phenyldithio-oxamide: it has proved possible to choose conditions under which only the thiocarbamoyl group is hydrolysed. In the hydrolysis of thioamides of oxalic and oxamic acids the carbon–carbon bond is not broken if a thioanilide group is present, but it is broken in the presence of unsubstituted thiocarbamoyl groups [31].

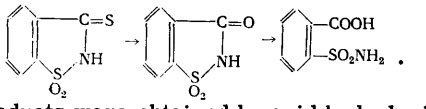
An ester group present in an *N*-substituent can be hydrolysed without decomposition of the thioamide molecule. Thiobenzoylglycine $C_6H_5CS.NH.CH_2.COOH$, which resists the action of alkali in the cold, can be obtained by hydrolysing its ethyl ester with alcoholic caustic potash in the cold [32], but when thiobenzoylglycine is boiled in acid or alkali, sulphur is split off [33], with the formation of hippuric acid, thiobenzoic acid, glycine, and hydrogen sulphide [34].

The hydrolysis of thioamides is substantially influenced also by the nature of the radical attached to the carbon of the thiocarbamoyl group. Thus *N*-β-benzylidynethiopropionylmorpholine $C_6H_5.C\vdots C.CH_2.CS.NC_4H_8O$ is not hydrolysed by boiling for 10 h with 20% alcoholic caustic potash or in concentrated hydrochloric acid; *N*-β-benzylidenethiopropionylmorpholine $C_6H_5.CH:CH.CH_2.CS.NC_4H_8O$, however, is not hydrolysed by alkali under similar conditions, but is hydrolysed by acids [35,36].

Cyclic thioamides are relatively stable to hydrolysis [37].

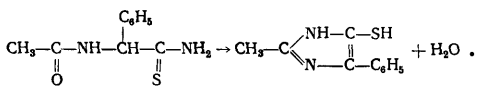
Hydrolysis does not occur when thiosaccharin is treated with sodium carbonate solution in the cold, but the soluble sodium salt of thiosaccharin is formed. The same effect was observed by the action of aqueous ammonia in the cold and on heating, and also with caustic soda solution in the

cold. Boiling with caustic soda hydrolyses thiosaccharin to saccharin, after which cleavage of the ring occurs [38]:



The same products were obtained by acid hydrolysis. Hydrolysis of *o*-sulphamoylthiobenzanilide with hot dilute alkali also gives *o*-sulphamoylbenzoic acid.

Several thioamides undergo cyclisation during alkaline or acid hydrolysis. For example, α-acetamido-α-phenylthioacetamide is rapidly cyclised when heated with a 10% solution of caustic potash [33]:

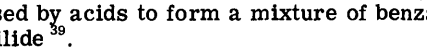


When α-phenyl-α-acetamidothiopropionamide is heated with 20% hydrochloric acid or with dilute caustic potash (with subsequent acidification), it also undergoes cyclisation, to 2,4-dimethyl-4-phenylimidazoline-5-thione [33].

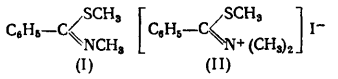
Isothioamides are relatively stable to alkaline hydrolysis, but are easily hydrolysed in the presence of acids†.

Bis-*N*-phenylbenzimidoyl sulphide $C_6H_5.C(:N.C_6H_5).S.C(:N.C_6H_5).C_6H_5$ is stable to hot concentrated alkali, but is easily hydrolysed by acids to form a mixture of benzanilide and thiobenzanilide [39].

Immonium salts of isothioamides are considerably more easily hydrolysed, usually with the formation of good yields of thiolic esters:

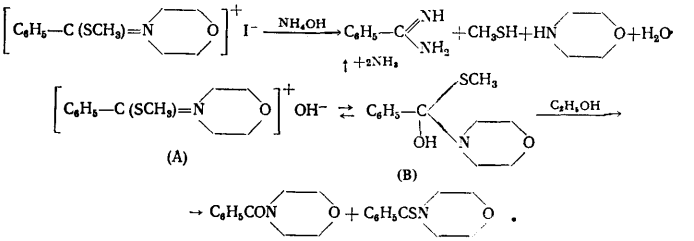


This reaction is used for the hydrolysis of stable thioamides [40]. Thus *N*-phenylthioacetylmorpholine is hydrolysed with difficulty. If, however, it is treated with methyl iodide in acetone, the product‡ is easily hydrolysed by hot water to methyl phenylthioacetate, which is then converted into phenylacetic acid. When ammonia is used instead of hot water, the final product of hydrolysis is phenylthioacetamide.



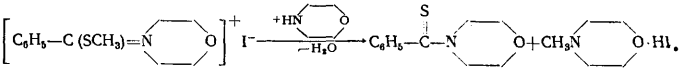
The difference in stability to hydrolysis between isothioamides and their alkylated products—salts of quaternary ammonium bases—can be illustrated by other examples. *S*-Methyl *N*-methylthiobenzimidate (I) is stable in concentrated potassium hydroxide solution, but its quaternary salt (II) is not stable [43]. When (II) is treated with strong alkalis, the methylthio-group is split off and *NN*-dimethylbenzamide is formed. The cation $C_6H_5.C(OH):N(CH_3)_2^+$ is assumed to be formed as an intermediate. A methylthio-group combined with a carbon atom attached to a quaternary nitrogen atom is found to be extremely reactive [42]. Homologues of (I) and (II) behave similarly towards alkaline hydrolysis [42].

The quaternary salt, formed by addition of methyl iodide to *N*-thiobenzoylmorpholine $[C_6H_5.C(S.CH_3):NC_4H_8O]^+I^-$, dissolves in aqueous ammonia (21°Bé) [44] with the formation of benzamidine. A probable intermediate is the pseudo-base (B) corresponding to the hypothetical hydroxide of the quaternary base (A):

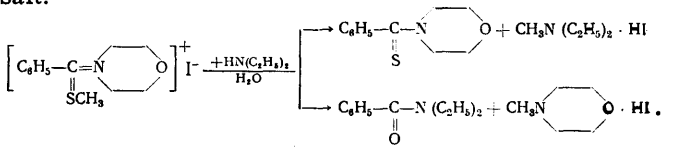


The pseudo-base (B) was isolated [44], but could be not be analysed, although there is other, indirect evidence of its structure. When boiled in alcohol, it is converted into a mixture of *N*-benzoylmorpholine and *N*-thiobenzoylmorpholine with the liberation of methanethiol or methanol. A quaternary salt was obtained with hydrogen iodide. On treatment with aqueous ammonia the pseudo-base (B) gives benzamidine [44].

The quaternary salt reacts similarly with primary amines [44]. *NN'*-Dimethylbenzamidine has been obtained by the action of methylamine. However, hydrolysis with an aqueous solution of a secondary amine follows a different path, the quaternary salt now acting as a methylating agent. Reaction with morpholine gave *N*-thiobenzoylmorpholine and *N*-methylmorpholine:



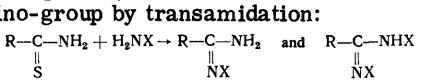
With diethylamine the main product *N*-thiobenzoylmorpholine was accompanied by a small quantity of *NN*-diethylbenzamide, the normal hydrolysis product of the quaternary salt:



NN-Diethylbenzamide is formed also by the reaction of ethyl thiobenzoate with diethylamine. In the presence of tertiary amines hydrolysis of the salt yields only thiolic esters [44]. Other examples are known of the hydrolysis of unsubstituted and substituted thioamides and isothioamides [45-47].

III. REACTIONS OF THIOAMIDES WITH INORGANIC AND ORGANIC AMINES AND SODIUM AZIDE

The reaction of thioamides with inorganic amines (hydroxylamine and hydrazine) is accompanied by replacement of sulphur by the amine residue and sometimes by the amino-group by transamidation:

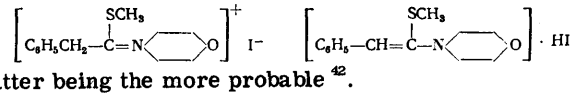


where X = OH, NH_2, NHR^1, NR^1R^2.

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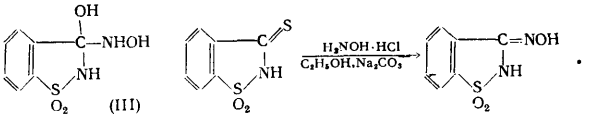
†Isothioamides, being strong bases, give salts with strong mineral acids, but excess of acid hydrolyses them to thiolic esters and ammonium chloride. In this respect the dibenzoyl derivative of thiobenzoxamic acid $C_6H_5.C(S.CO.C_6H_5):N.CO.CO.C_6H_5$ is exceptional: it is stable to hydrolysis in boiling dilute hydrochloric acid, but is hydrolysed by alcoholic caustic potash. The hydrolysis products are benzoxamic and thiobenzoic acids contaminated by thiobenzoxamic and benzoic acids [41].

‡Two structures are possible for the addition product of methyl iodide and *N*-phenylthioacetylmorpholine



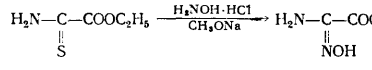
the latter being the more probable [42].

Thiobenzamide when boiled with an alcoholic solution of hydroxylamine gives hydroxyiminobenzamide [48,49]. When *NN'*-diphenyldithio-oxamide $C_6H_5.NH.CS.CS.NH.C_6H_5$ is treated with hydroxylamine, dihydroxyimino-*NN'*-dithio-oxamide $C_6H_5.NH.C(:N.OH).C(:N.OH).NH.C_6H_5$ is formed [49]. Rubeanic acid reacts with hydroxylamine hydrochloride in alcoholic sodium carbonate solution for form dihydroxy-imino-oxamide [50]. Under the same conditions saccharin yields the stable addition product (III), and thiosaccharin yields a hydroxyiminoamide [51]:

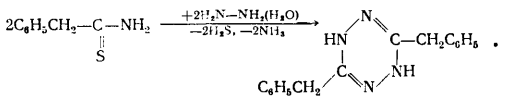


It is assumed that an addition product is formed initially with thiosaccharin also, from which hydrogen sulphide splits off [51].

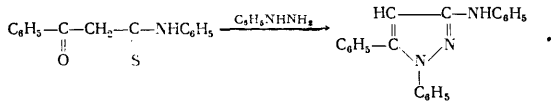
Ethyl thio-oxamate reacts with hydroxylamine hydrochloride in alcoholic sodium methoxide solution to give ethyl hydroxyimino-oxamate [52]:



The reaction between thioamides and aqueous solutions of hydrazine involves replacement of sulphur and trans-amidation with the formation of 3,6-disubstituted 1,4-di-hydro-1,2,4,5-tetrazines [53]:

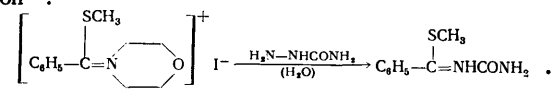


β-Carbonylthioamides (or addition products of enamines and isothiocyanates) react with hydrazine or phenyl-hydrazine to form aminopyrazoles [54]:

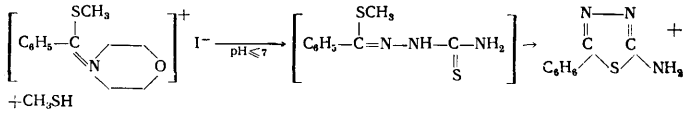


3-Anilino-1,5-diphenylpyrazole

3-Anilino-4-ethylpyrazole and 3-anilino-5-phenylpyrazole have been obtained in this way (by boiling the corresponding thioamides with ethanolic hydrazine for 1½–2 h). Hydrazine reacts similarly with other thioamides [55]. With mono- and di-thio-oxamides sulphur is replaced by the hydrazine residue [56–58]. The isothioamide, *N*-*α*-methylthiobenzyli-denemorpholinium iodide $[C_6H_5.C(S.CH_3):NC_4H_8O]^+I^-$, reacts with excess of hydrazine to give a good yield of 1,4-dihydro-3,6-diphenyl-1,2,4,5-tetrazine [44]. The same compound is formed by the action of hydrazine on thio-benzamide [53]. The above morpholinium iodide does not give a cyclic product with semicarbazide in aqueous solution [59]:



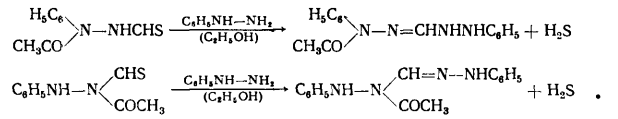
But cyclisation occurs with thiosemicarbazide in acid or neutral medium to form 2-amino 5-phenyl-1,3,4-thiadia-zole. It is supposed that even here the primary product is analogous to that obtained with semicarbazide, but methanethiol is then eliminated to give the thiadiazole [60]:



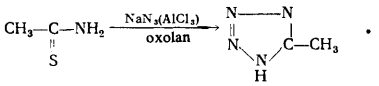
+CH_3SH

If these reagents interact in the presence of weak or strong bases in aqueous solution or in non-aqueous solvents, cyclisation does not occur, but 1-*α*-morpholino-benzylidenethiosemicarbazide is formed. In dilute acids this compound is cyclised to 1,3,4-thiadiazole [60].

The reaction of acylated phenylthioformylhydrazides with phenylhydrazine involves replacement of sulphur by the phenylhydrazine residue:



With sodium azide thioamides form tetrazoles. Thio-acetamide reacts with excess of sodium azide in the presence of aluminium chloride in oxolan to give 5-methyl-tetrazole (yield 55%):[61]



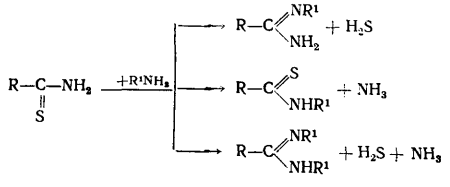
Similarly pentamethylenetetrazole (Cardiazole) has been obtained from *ε*-caprolactam. Since nitriles also give tetrazoles with sodium azide, it is assumed that nitriles are formed as intermediates in these reactions.

Thioamides and isothioamides react differently with primary, secondary, and tertiary amines.

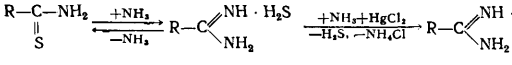
Tertiary amines, being acceptors of hydrogen sulphide, decompose thioamides to the nitrile and hydrogen sulphide. Boiling thioacetamide or thiobenzamide in pyridine yields the corresponding nitrile and hydrogen sulphide [62]. Pyri-dine initiates this reaction by forming the pyridinium salt of the thioamide.

Secondary amines usually transamidate thioamides: in ethereal solution thioacetamide and piperidine yield *N*-thioacetylpiperidine [63]; and diethylamine and thioform-amide give *NN*-diethylthioformamide [94].

Primary amines, like inorganic amines, replace the sulphur by the amine residue and effect transamidation with the formation of *N*-substituted amidines, *N*-substituted thioamides, or mixtures of these products:

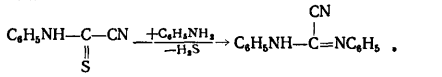


The formation of salts of amidines by the reaction of aliphatic and aromatic thioamides with concentrated solu-tions of ammonium hydroxide was established as long ago as the nineteenth century [65,66]. The yield of amidines was increased by adding mercury(II) chloride, which shifted the equilibrium by forming mercury sulphide:



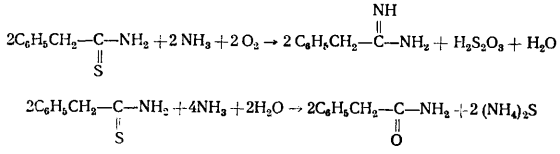
The action of primary amines under similar conditions yields *N*-substituted amidines. Aniline hydrochloride reacts with phenylthioacetamide in absolute ethanol to form *N*-phenylacetamidine [67], and with thiobenzamide to give *N*-phenyl- and *NN'*-diphenyl-benzamidines [68]. *NN'*-Diphen-ylbenzamidine has been obtained by the reaction of thio-benzanilide with molten aniline hydrochloride [69].

The reaction of thio-oxanilonitrile with aniline in boiling benzene gives the amidine in 40% yield, the nitrile group being unaffected [70]:



With change in the conditions the amidine undergoes hydrolysis with formation of the corresponding amide.

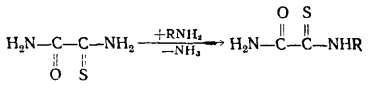
Phenylthioacetamide reacts with ammonium hydroxide solution at room temperature to form phenylacetamidine and a thiosulphate:



and on boiling to give phenylacetamide and ammonium sulphide [95].

With *NN'*-disubstituted thioamides (e.g. dimethylthioformamide) primary amines form *NNN'*-trisubstituted amidines. Thus *NN'*-dimethyl-*N*-naphth-1-ylformamidine has been isolated as its complex with trinitrobenzene by boiling a mixture of dimethylthioformamide, 1-naphthylamine, and sodium methoxide [71].

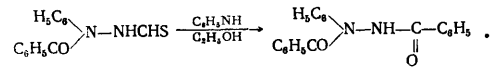
Thioamides undergo transamidation on being heated with amines. Ammonia is evolved when thioacetamide is boiled in butylamine, with the formation of *N*-butylthioacetamide, the yield being almost theoretical [70]. This reaction has been used to obtain several *N*-alkyl- and *N*-aryl-thioamides and *NN'*-dialkyl- and *NN'*-diaralkyldithio-oxamides [70,72-74]. It should be noted that only the thiocarbamoyl group is involved in this reaction, the carbamoyl group being unaffected. The interaction of monothio-oxamide with various amines yields *N*-alkylmonothio-oxamides [75]:



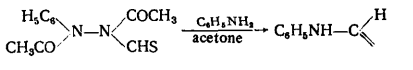
where R = CH_3, C_4H_9, $C_{12}H_{25}$.

A mixture of a thioamide and an amine can be replaced by a mixture of the amide, phosphorus pentasulphide, and the amine: the thioamide obtained initially reacts with the amine to form *N*-substituted derivatives. Aliphatic, aromatic, aliphatic–aromatic, and heterocyclic amines and diamines have been used in this reaction [64,76].

N-Benzoyl-*N*-phenyl-*N'*-thioformylhydrazide reacts differently with aniline when boiled in aqueous–alcoholic solution [77]:

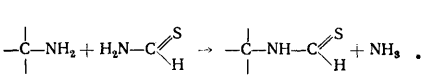


Diacetylphenylthioformylhydrazide reacts with aniline in acetone as follows [30]:

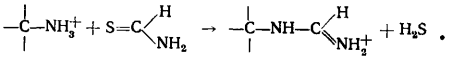


The reaction between thioamides and amines has been studied also in the case of thioformamide and amino-acids [63]. The carbonates of arginine and L-lysine, and also the ethyl ester of glycine, react with thioformamide in methanol at room temperature to give crystalline products. Glycine, L-leucine, DL-alanine, and histidine with excess of thioformamide yield similar products only on being heated to 60°C.

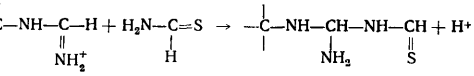
Only amino-acids containing free amino-groups react easily with thioformamide, the products being thioformyl derivatives:



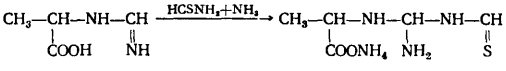
The amino-groups of monoamino-acids (glycine, DL-alanine, L-leucine), the terminal amino-group of L-lysine, and the NH group in the imidazole ring of histidine, which are present as amphoteric ammonium ions, react with thioformamide at 60°C with the elimination of hydrogen sulphide and the formation of formamidine derivatives:



In the cases of L-leucine, DL-alanine, and L-lysine the latter react with a second thioformamide molecule:



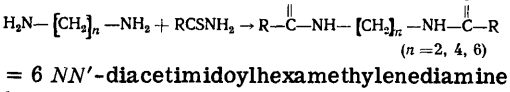
N-Formimidoyl-alanine and -leucine react with molten thioformamide and with ammonia to give products identical with those obtained from the amino-acids and thioformamide at 60°C:[78]



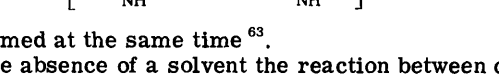
Thioformamide reacts in the cold also with proteins. The products, "thioproteins", are probably analogous to those obtained with amino-acids [63,79,80].

Sometimes thioamides do not react with ammonia and primary amines. For example, the ester group in ethyl monothio-oxamate $N_2N.CS.COOC_2H_5$ is probably converted into a carbamoyl group, while the thiocarbamoyl group plays no part in the reaction [81]. Alcoholic solutions of ammonia or the primary amine have been used. Treatment of ethyl thio-oxamate or ethyl thio-oxanilate $C_6H_5.NH.CS.COOC_2H_5$ with aniline at 140°C gives monothio-oxanilide $C_6H_5.NH.CS.CO.NH.C_6H_5$. [82,83]

Diamines (ethylene-, tetramethylene, hexamethylene-) react with monothioamides in ethereal solution to form *NN'*-dithioacyl derivatives [63]:

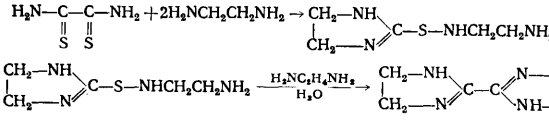


When *n* = 6 *NN'*-diacetimidoylhexamethylenediamine thiosulphate

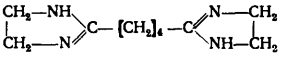


was formed at the same time [63].

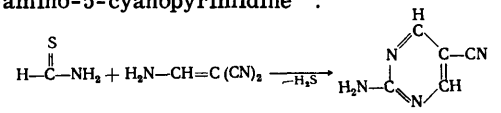
In the absence of a solvent the reaction between dithio-oxamide and ethylenediamine hydrate involves transamidation and replacement of sulphur by an imido-group to give 2,2'-bi-imidazolinyl [84]. In hot alcoholic solution (molar ratio of dithio-oxamide to diamine = 1 : 2) 2-2'-aminoethylaminothio-Δ^2-imidazoline was isolated as an intermediate product. [85] On being heated with ethylenediamine hydrate this compound is converted into 2,2'-bi-imidazolinyl:



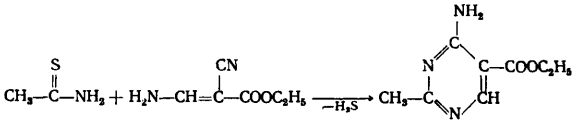
Ethylenediamine hydrate reacts with dithioadipamide, both in the absence of solvent and in alcohol, also with the formation of a cyclic product—tetramethylene-2,2′-bis-imidazoline



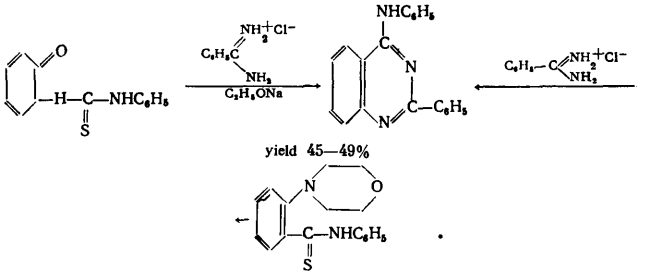
The reactions between thioamides and amines are widely used for synthesising pyrimidine and purine derivatives. Thioformamide reacts with aminomethylene-malononitrile on boiling with alcoholic sodium ethoxide to form 2-amino-5-cyanopyrimidine [86]:



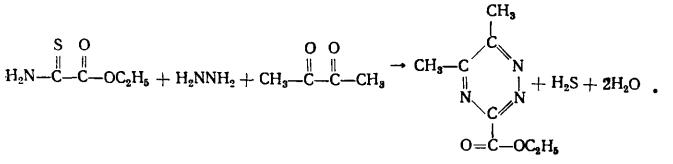
Under similar conditions thioacetamide reacts with ethyl β-amino-α-cyanoacrylate $H_2N.CH:C(CN).COOC_2H_5$ to give ethyl 4-amino-2-methylpyrimidine-5-carboxylate [87]:



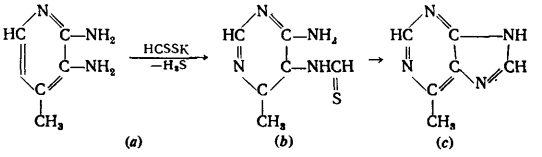
Pyrimidine derivatives are obtained also by the reaction of β-carbonylthioamides with benzamidine in the presence of sodium ethoxide [54]:



The action of ethyl monothio-oxamate on hydrazine and butane-2,3-dione gives a good yield of ethyl 5,6-dimethyl-1,2,4-triazine-3-carboxylate [88]:

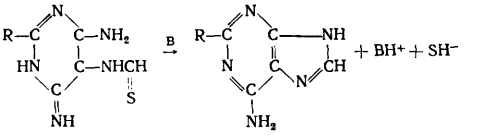


The reaction of 4,5-diamino-6-methylpyrimidine (*a*) with a salt of dithioformic acid gives 4-amino-6-methyl-5-thioformamidopyrimidine (*b*), which cyclises into a purine derivative (*c*) by interaction of the amino- and thioamido-groups:



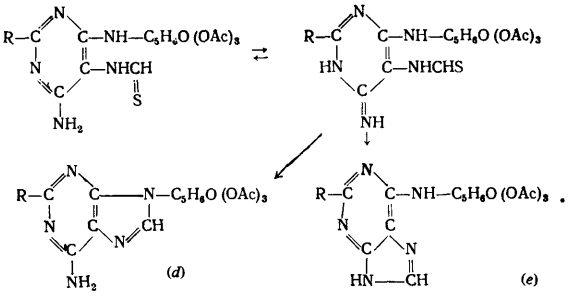
The reaction is conducted in hot pyridine or quinoline solution or in a solution of sodium ethoxide in anhydrous alcohol. In aqueous solution the yield is often diminished by hydrolysis of the thioformamide. The best media for this reaction are alcoholic solutions of sodium ethoxide, although the reaction is then slower than in excess of pyridine or quinoline, but the yields are considerably higher. The molar ratio of the pyrimidine derivative to the alkoxide is 1 : 1. [89]

Pyrimidine derivatives containing a 2-methylthio-group (e.g. 4,6-diamino-2-methylthio-5-thioformamido-pyrimidine) are the easiest to cyclise [89]. It is assumed that ring closure is effected by the action of the base on a tautomeric form of the pyrimidine [83,89]:

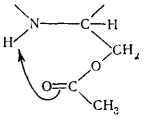


where R = H, CH_3, CH_3S.

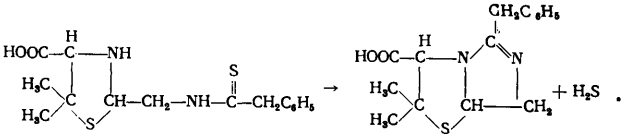
The cyclisation of 4-amino-6-glucosidoamino-5-thio-formamidopyrimidine, its triacetyl derivative, and many other compounds has also been accomplished [89]:



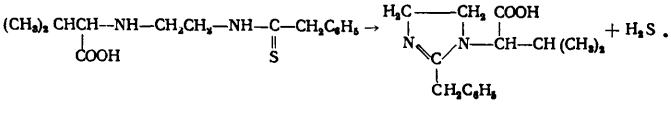
Cyclisation in alcoholic sodium ethoxide yielded in all cases only the 9-glucosidoaminopurines (*d*): the isomeric 6-glucosidoaminopurines (*e*) were not formed. Since the 6-triacetylglucosidoaminopyrimidine is easily deacetylated, it is cyclised in pyridine or in a solution of potassium acetate and acetic acid in anhydrous acetonitrile. In these cases not only the 9-triacetylglucosidoaminopurine but also a considerable yield of the 6-triacetylglucosido-aminopurine (*e*) are formed [90]. Cyclisation is assumed to involve formation of an intermediate product by hydrogen bonding between the 2′-acetyl group of the sugar residue and the hydrogen of the glucosidic NH group. Such ring closure induces a negative charge on the glucosidic nitrogen and thereby enhances the reactivity of the 6-amino-group:



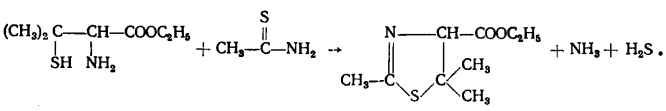
Heterocyclic systems other than purine derivatives have been obtained in a similar manner. Thus boiling 5,5-dimethyl-2-phenylthioacetamidomethylthiazolidine-4-carboxylic acid in quinoline yields benzylpenillamine [91,92]:



The ethyl ester of this acid could not be made to react [93]. The next example of the preparation of heterocycles is the synthesis of imidazoline derivatives [94]:



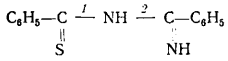
The ethyl ester of penicillamine with thioacetamide forms ethyl 2,5,5-trimethyl-Δ^2-thiazoline-4-carboxylate [95]:



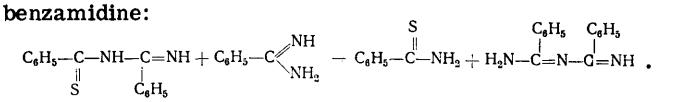
Investigation of the reactions of *N*-benzimidoylthiobenzamide $C_6H_5.CS.N:C(NH_2).C_6H_5$ with ammonia, amines, and amidines [81] indicated that this thioamide is stable in an alcoholic solution of aniline for several days. On addition of mercuric oxide, however, *N'*-*N''*-phenylbenzimidoylbenzamidine $C_6H_5.N:C(C_6H_5).N:C(C_6H_5).NH_2$ was formed rapidly [96]. In alcoholic ammonia and in the absence of a desulphurising agent, *N*-benzimidoylthiobenzamide is rapidly split into benzamidine, thiobenzamide, triphenyltriazine, 3,5-diphenyl-1,2,4-thiadiazole, and nitrogen- and sulphur-containing compounds of basic character, whose structure has not been established [96]. The disubstituted 1,2,4-thiadiazole is probably formed by oxidation of thiobenzamide [97] and *N*-benzimidoylthiobenzamide [98].

The reaction between *N*-benzimidoylthiobenzamide and benzylamine at room temperature gave thiobenzamide (58.5%), *N*-benzylbenzamidine (78%, as the picrate), *N*-benzylthiobenzamide (3.5%), and benzamidine (1.2%, as the picrate). *N*-Benzylbenzamidine and *N*-benzylthiobenzamide were probably formed by secondary reactions of benzylamine with benzamidine and thiobenzamide respectively.

It is assumed that *N*-benzimidoylthiobenzamide

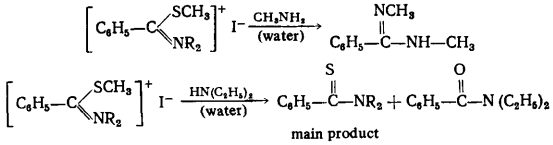


is cleaved both by ammonia and by benzylamine mainly at bond *2*. This occurs also with benzamidine, when the main products are thiobenzamide and *N'*-benzimidoylbenzamidine:

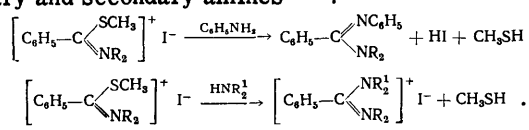


In contrast to benzamidine, substituted amidines—*N*-phenylbenzamidine and *N*-benzylbenzamidine—do not react with *N*-benzimidoylthiobenzamide at room temperature. In boiling benzene, however, *N*-phenylbenzamidine forms small amounts of triphenyltriazine and *N*-phenyl-*N'*-*N''*-phenylbenzimidoylbenzamidine $C_6H_5.N:C(C_6H_5).N:C(C_6H_5).NH.C_6H_5$. The latter product results either from disproportionation of the triphenyldiamine or from a secondary reaction with benzamidine.

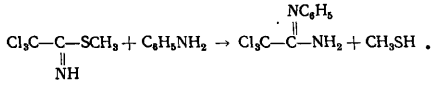
S- and *N*-Substituted thioamides and their salts react with primary, secondary, and tertiary amines in aqueous solution as follows [60]:



In non-aqueous media these salts react differently with primary and secondary amines [40,48]:



The action of alkylthioamides on aniline is a general method for obtaining *N*-phenylamidines [46,99,100]:



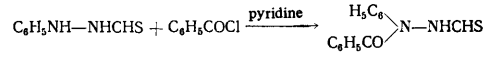
The thermal stability of alkyl thioimidate hydrochlorides increases as the alkyl group becomes larger.

IV. REACTIONS OF THIOAMIDES WITH ACID CHLORIDES

The reactions of thioamides with chlorides of carboxylic acids, imidoyl chlorides, sulphur monochloride and dichloride, thionyl chloride, sulphuryl chloride, and benzenesulphonyl chloride have been studied. With chlorides of carboxylic acids the main reaction is acylation of the thioamides, *N*-substituted thioamides are formed with imidoyl chlorides, and with the other reagents *N*-imidoylthioamides and their oxidation products are formed.

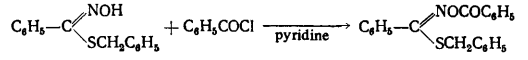
Thioacetamide reacts with acetyl chloride to give an extremely unstable crystalline product [101].

A few cases of benzoylation have been reported. The action of benzoyl chloride on a warm solution of thiocamphorimide, ethyl iodide, and magnesium produces benzoylation of the imido-group of thiocamphorimide [102]. The acylation of 2-phenyl-1-thioformylhydrazide by benzoyl chloride in pyridine leads to the formation of 2-benzoyl-2-phenyl-1-thioformylhydrazide:



the product being soluble in alkalis. If two equivalents of benzoyl chloride are used, the product is insoluble in alkalis. A similar reaction occurs with acetyl chloride.

Benzoyl chloride reacts also with *S*-benzyl thiobenzohydroximate in pyridine [41]:

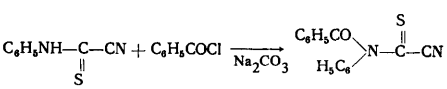


Salts of *N*-benzylthioacetamide and *N*-benzylthiobenzamide are easily acylated by acetyl and benzoyl chlorides [103]:



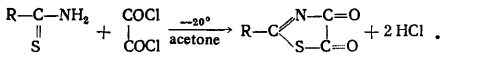
where $R^1 = CH_3$, C_6H_5.

The benzoylation of thio-oxanilonitrile in aqueous sodium carbonate solution yields benzoylthio-oxanilonitrile [104]:



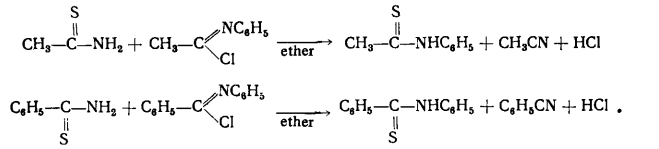
but in caustic soda solution the amide $C_6H_5.CO.N(C_6H_5).CS.CO.NH_2$ is obtained.

The action of thioamides on oxalyl chloride (either in the absence of a base or in the presence of e.g. pyridine) produces derivatives of thiazoline-4,5-dione [105]:

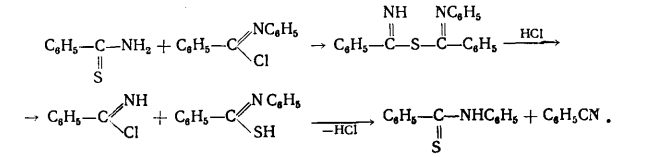


With cyclohexylthioamide in the absence of a base the acid-catalysed elimination of cyclohexene takes place [105].

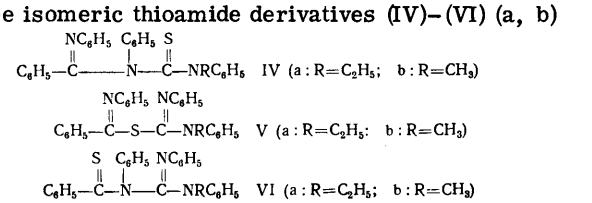
Unsubstituted thiobenzamide and thioacetamide react with *N*-phenylimidoyl chlorides in ethereal solution to form thioanilides [106]:



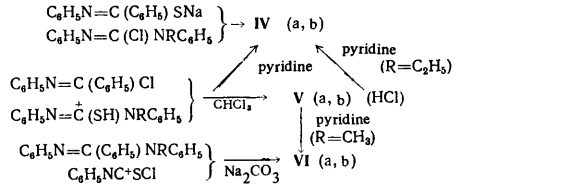
This reaction, like that of nitriles with thioamides, involves the intermediate formation of a product which is cleaved by hydrogen chloride into thiobenzanilide and benzonitrile:



Three isomeric thioamide derivatives (IV)–(VI) (a, b)

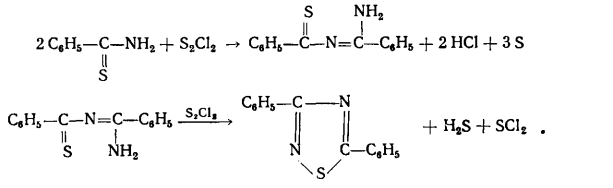


have been obtained by the reaction of thioamides with an imidoyl chloride [107] (scheme cited in Ref. 18):



Reaction of the sodium salt of thiobenzanilide with the imidoyl chloride $C_6H_5.N:CCl.NR.C_6H_5$ (R = C_2H_5, CH_3) did not yield the expected product (V), but (IV) was formed. Treatment of the hydrochlorides of (Va) and (Vb) with pyridine results in (IVa) and (VIb) respectively, the main product being the free base (V) in both cases. When (VIa) is heated it is converted into (IVa), and (IVb) into (VIb). In these cases also (V) is an intermediate product.

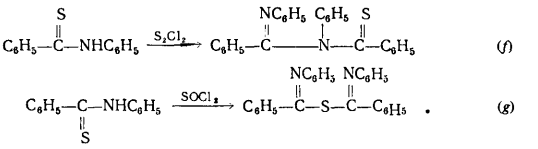
On the slow addition of sulphur monochloride to a solution of thiobenzamide in ether in the cold [104,108] *N*-benzimidoylthiobenzamide and 3,5-diphenyl-1,2,4-thiadiazole are formed, the latter being an oxidation product of the former [109]:



N-Benzimidoylthiobenzamide separates also when the reaction is conducted in alcoholic potassium carbonate solution. The same products are obtained by the interaction of thiobenzamide and thionyl chloride in ether in the cold, when sulphur, sulphur dioxide, and hydrogen chloride are also liberated [39]. Thiobenzamide and other thioamides react similarly with sulphuryl and benzenesulphonyl chlorides: in the latter case the main products are 3,5-diphenyl-1,2,4-thiadiazole and sulphur [39], and in the former case *N*-benzimidoylthiobenzamide.

On reaction of thioacetamide with thionyl chloride, thioacetamide, sulphur, sulphur dioxide, and hydrogen chloride separate. The same result is obtained by the action of thionyl chloride on thioacetanilide.

Sulphur monochloride and thionyl chloride give different products with the same thioamide. With thiobenzanilide the former yields *N*-*N'*-phenylbenzimidoylthiobenzanilide (*f*) and the latter the isomeric product di-*N*-phenylbenzimidoyl sulphide (*g*):[39]



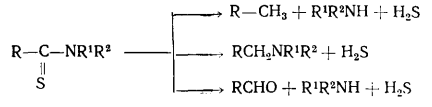
However, the structures of products (*f*) and (*g*) have not been proved. In both cases sulphur, aniline hydrochloride, and benzanilide were isolated§.

Thiobenzanilide forms with benzenesulphonyl chloride a small quantity of *N*-*N'*-phenylbenzimidoylthiobenzanilide, the yield of which is increased by using the sodium salt of thiobenzanilide. Another product of the reaction is benzenethiosulphonic acid $C_6H_5.SO_2SH$. [39]

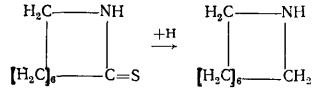
Substituted thioformamides $HCS.NR_2$ react with sulphur monochloride, sulphur dichloride, and thionyl chloride in the presence of pyridine in dichloromethane to form the chlorothioformamides $ClCS.NR_2$ (i.e. they are chlorinated. [111]

V. REDUCTION OF THIOAMIDES

Thioamides are reduced in the presence of Raney nickel in neutral solvents, by the action of metals in acid medium and of metal amalgams, and electrolytically [112,113]. Depending on the method of reduction the products are hydrocarbons, amines, aldehydes, and other substances:



The methods of reduction differ substantially in their effectiveness. For example, the lactam of the thioamide of ω-amino-octanoic acid (perhydroazonine-2-thione) is not reduced by magnesium amalgam in moist ether, by aluminium amalgam in aqueous alcohol, or by zinc dust in acetic acid [38], whereas sodium in glacial acetic acid yields a small quantity of perhydroazonine, and electrolytic reduction in 55% sulphuric acid with a lead cathode at 30°C gives an 85% yield of perhydroazonine [38]:



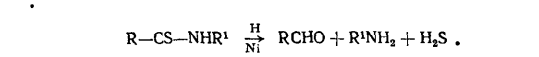
We shall examine below all the above methods for reducing thioamides.

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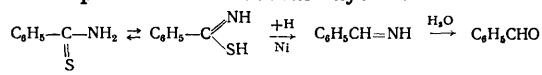
§Benzanilide is probably formed by decomposition of the sulphide $C_6H_5.N:C(C_6H_5).S.C(C_6H_5):N.C_6H_5$ (or its isomer). If this sulphide is treated initially with hydrogen chloride in absolute ether, and then with dilute sodium hydroxide solution, it is split into benzanilide and thiobenzanilide [110].

1. Reduction of Thioamides in the Presence of Raney Nickel [114]

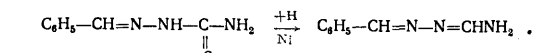
The course of the reduction of thioamides may vary with the nature of the Raney nickel. In the presence of Raney nickel which has been partly deactivated in boiling acetone the thioamide is reduced to the aldehyde in good yield [115]:



Thus the corresponding aldehydes were obtained when thiobenzamide and thio-*p*-toluamide were reduced in ethanol at room temperature for several days [116]:

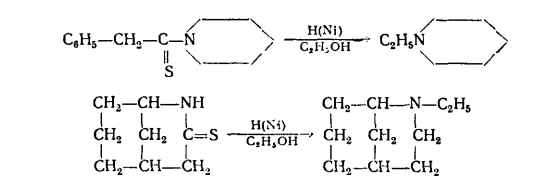


Desulphurisation of the thioamide and formation of a carbon–nitrogen bond are observed also in other cases. Thiourea and its derivatives are reduced to formamidines [117,118]. Thiosemicarbazones are reduced similarly [119]:

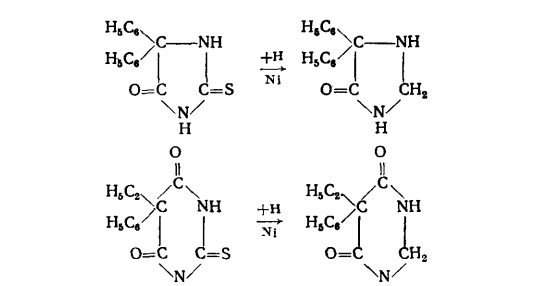


Reduction on Raney nickel prepared in the usual way converts thiocarbonyl into methylene groups [120].

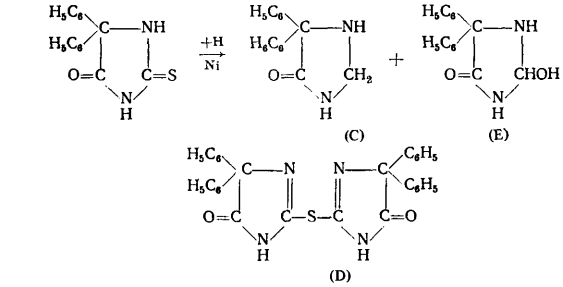
The solvent has a substantial influence on the reduction. With *N*-phenylthioacetylmorpholine in 8% alcohol ethylmorpholine and ethylbenzene are formed in quantitative yield as a result of *N*-ethylation, but in dioxan phenethylmorpholine is obtained [120]. *N*-Ethylation occurs on reduction in ethanol in other cases. For example, the thiopiperidide of phenylacetic acid gives a 44% yield of *N*-ethylpiperidine [120,121], and the thiolactam of 3′-aminocyclohexylacetic acid a 76% yield of 2-ethyl-2-azabicyclo-[3,3,1]nonane [122]:



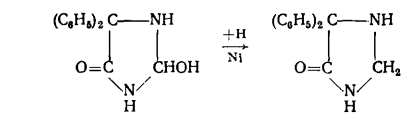
The reduction of heterocyclic thioamides has been studied in detail on thiohydantoins and thiobarbituric acids. The reduction of these compounds in ethanolic solution (boiling for 2–5 h) leads to replacement of sulphur by hydrogen and formation of the normal reduction products. Examples are the reduction of 5,5-diphenyl-2-thiohydantoin [123,124], and of 5-ethyl-5-phenyl-2-thiobarbituric acid [125–128]:



When the thiohydantoin is reduced under milder conditions (ratio of thiohydantoin to Raney nickel 1 : 5 by weight, boiled for 30 min), approximately equal quantities of 4-oxo-5,5-diphenylimidazolidine (C) and bis-5-oxo-4,4-diphenyl-Δ^2-imidazolin-2-yl sulphide (D) are formed together with a small quantity of 2-hydroxy-4-oxo-5,5-diphenylimidazolidine (E): [129]

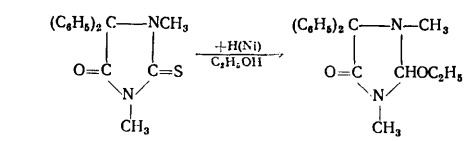


Further reduction in the presence of Raney nickel in boiling ethanol for 2 h converts (E) into a good yield of the imidazolidone [129]:



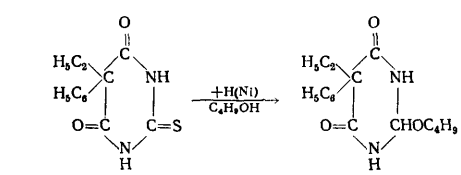
2-Hydroxy-derivatives analogous to (E) are formed also by the reduction of other thiohydantoin derivatives [123].

Tetra-substituted thiohydantoins on reduction in ethanolic solution are ethoxylated (cf. *N*-alkylation) with the formation of 2-ethoxy-derivatives [129]:



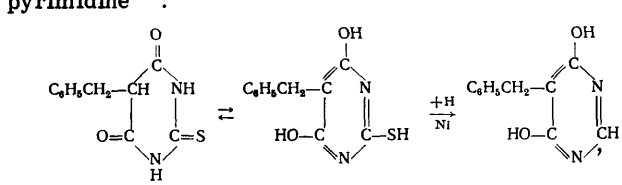
Replacement of ethanol by methanol, propan-1-ol, and cyclohexanol yields the corresponding 4-oxoimidazolidines [129].

The reduction of derivatives of thiobarbituric acid yields initially the 2-alkoxy-derivatives [129]:



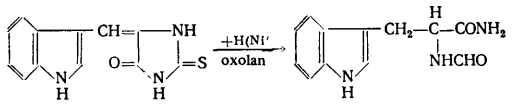
On further treatment with hydrogen both alkoxy- and hydroxy-derivatives are converted with quantitative yields into the normal reduction products [129].

5-Mono-substituted 2-thiobarbituric acids react on reduction in the tautomeric pyrimidine-2-thiol form, since the product of the reaction is always a 4,6-dihydroxypyrimidine [129]:

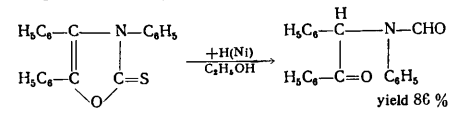


When 5-alkylidene- and 5-benzylidene-2-thiohydantoins are reduced in moist oxolan solution, the thiohydantoin

ring undergoes fission with the formation of amides of α-formylamino-acids:



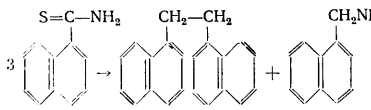
This reaction is used for the preparation of α-amino-acids [124]. 3,4,5-Triphenyl-Δ^3-oxazoline-2-thione in ethanol undergoes analogous reduction [130]:



Other examples of reduction with Raney nickel will be found in Refs. 131–142.

2. Reduction of Thioamides by Metals in Acid Medium and by Metal Hydrides

The reduction of thioamides by this method often yields hydrocarbons, amines [143], and aldehydes. 1,2-Di-1'-naphthylethane and 1-naphthylmethylamine have been obtained on reduction of the thioamide of 1-naphthoic acid:



Thiobenzamide on reduction gives stilbene, benzylamine, and 1,2-diphenylethane. The action of zinc and hydrochloric acid on *N*-benzimidoylthiobenzamide $C_6H_5.CS.NH.C(:NH).C_6H_5$ gives only *N*-benzylbenzamidine $C_6H_5.CH_2.NH.C(C_6H_5):NH$, [144] and *m*-ethoxythiobenzamide gives *m*-ethoxybenzylamine [145]. When iron powder is heated with thiobenzamide in 50% acid for 4 days a 60% yield of benzaldehyde is obtained [146]¶. Tin in hydrochloric acid converts *N*-benzyl-*p*-nitrothiobenzamide into *N*-benzyl-*p*-aminothiobenzamide (yield 95%): the thiocarbamoyl group is not reduced [148].

Reduction of thiobenzamide with lithium hydride in ether at −60°C for 15 min gave benzonitrile (30%) and benzylamine (8%); [114] and from 2-thiohomophthalimide and 5-methyl-2-thiohomophthalimide have been obtained 1,2,3,4-tetrahydroisoquinoline (40%, as the picrate) and 1,2,3,4-tetrahydro-6-methylisoquinoline (40%, as the picrate) respectively [37].

3. Electrolytic Reduction of Thioamides

Solutions in hydrochloric and sulphuric acids are used for the electrolytic reduction of thioamides. With relatively dilute acids amines are usually formed, but in concentrated acids (80% sulphuric acid) predominant formation of aldehydes occurs.

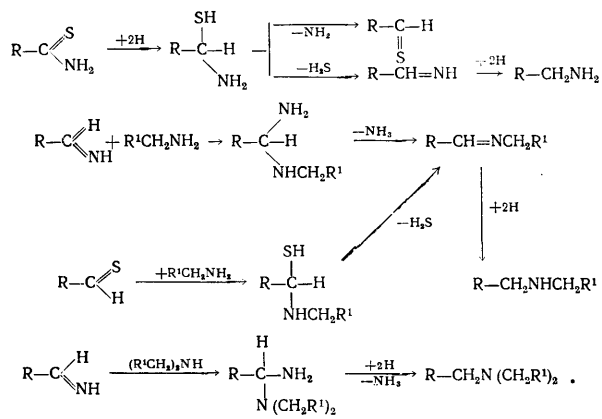
Phenylthioacetamide is reduced in solution in alcohol and hydrochloric acid to phenethylamine; *NN*-dimethylthiobenzamide in 60% sulphuric acid gives the corresponding tertiary amine in 75–100% yield; and *N*-alkylthioamides are reduced to secondary amines [146]. When, however, *NN*-dimethylthiobenzamide was reduced in 80% sulphuric acid, benzaldehyde (40%) was obtained together with small quantities of dimethylamine and benzyldimethylamine [112,113,149].

¶Thiobenzamide is converted into benzaldehyde also by the action of zinc and caustic potash (yield 42%). [147]

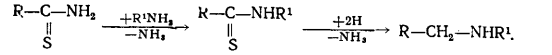
4. Reduction of Thioamides with Metal Amalgams

Aluminium and sodium amalgams are used for the reduction of thioamides, with ether and ethanol as solvents. The amalgams are added to the reaction mixture slowly and in slight excess. The reduction products are primary and secondary amines [146], their relative proportions depending on the thioamide. The reduction of thiobenzamide with an amalgam in moist ether yields benzylamine (85%) and dibenzylamine (8%); but when phenylthioacetamide was reduced under these conditions the products were phenethylamine and diphenethylamine in yields of 26% and 66% respectively [149].

Different products are formed if reduction takes place in the presence of an amine [146]. In the presence of ethylamine, for example, phenylthioacetamide yields a mixture of phenethylamine, diphenethylamine, and *N*-ethylphenethylamine. The thioamide is probably reduced initially to an α-amino-thiol, from which hydrogen sulphide splits off to form an aldimine. The latter is either reduced further to a primary amine or added to a primary or a secondary amine to form a secondary or a tertiary amine respectively. Formation of the various products can be represented by the schemes

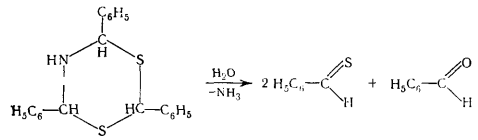


The formation of secondary amines can be explained by transamidation of the thioamide and reduction of the *N*-substituted thioamide:



Sodium amalgam has been used to reduce phenylthioacetamide and thiobenzamide in alcoholic solution [26,150]. Phenylthioacetamide gave a small quantity of 2-phenethylamine, but the main product was a solid, probably 2,4,6-tribenzyl-5,6-dihydro-1,3,5-dithiazine. The principal reduction product of thiobenzamide was thiobenzaldehyde; small quantities of benzylamine, benzonitrile, and benzaldehyde were also isolated. In this case it is assumed that 5,6-dihydro-2,4,6-triphenyl-1,3,5-dithiazine is an intermediate reduction product, hydrolysis of which

yields benzaldehyde and thiobenzaldehyde [150]:



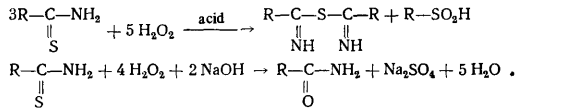
N-Substituted thioamides are reduced by sodium amalgam initially to the corresponding amines, after which other products are formed as a result of secondary reactions, as has been shown above [146].

VI. OXIDATION OF THIOAMIDES

The great variety of oxidising agents—hydrogen peroxide, acid hydroperoxides, nitrous, nitric, and sulphuric acids, halogens, hexacyanoferrates(III), potassium permanganate, ozone, metal oxides, alkene oxides, and other oxidants—have been used for oxidising thioamides.

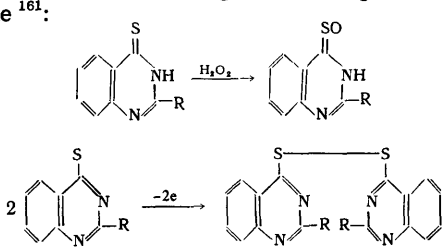
1. Oxidation of Thioamides by Hydrogen Peroxide and Hydroperoxides of Acids

The reaction between thioamides and hydrogen peroxide is conducted under acid, neutral, or alkaline conditions. In acid and neutral media disulphides, sulphinic acids, and other products depending on structure of the thioamides, but in alkaline medium the corresponding oxo-compound is always formed [37,151-155]:



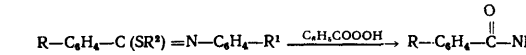
For example, thiobenzamide is oxidised by hydrogen peroxide in aqueous alkali to benzamide [151]; disulphides are not formed by this method of oxidation [153]. The oxidation of thioamides in alkaline medium takes place at low temperatures, its rate depending on the concentration of hydroxide ions. The reaction is used for the quantitative determination of sulphur in thioamides [151,156,157]. The oxidation of thioamides has been studied in detail [12,97,151-160].

Dihydroquinazoline-4-thione on oxidation with hydrogen peroxide in neutral medium gives the sulphoxide and the disulphide [161]:

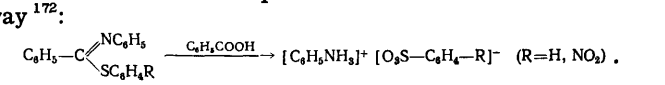


The oxidation of unsubstituted and mono- and di-*N*-substituted thioamides by hydrogen peroxide in neutral and weakly alkaline media (water, methanol to which pyridine has been added, or pyridine itself) often gives rise to *S*-oxides of thioamides [155,162-171] which are more stable than the thioamides themselves [162].

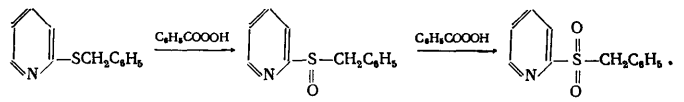
When isothioamides are oxidised with perbenzoic acid in chloroform, anilides are obtained [172]:



Sometimes anilinium sulphonates are obtained in this way [172]:

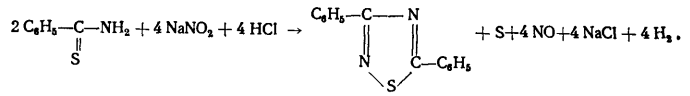


Sulphoxides [and sulphones] are other possible products [172]:



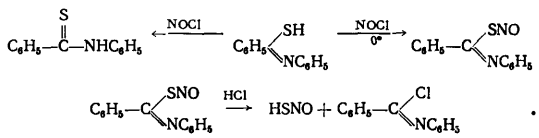
2. Oxidation of Thioamides by Nitrogen Compounds

Various compounds of nitrogen (nitric and nitrous acids, nitrosyl chloride, nitrogen dioxide, pentyl nitrite, etc.) are used, the nature of the products depending on the oxidant and the thioamide. If a solution of sodium nitrite is added to a solution of thiobenzamide in a mixture of ethanol and hydrochloric acid, the thiobenzamide is oxidised to 3,5-diphenyl-1,2,4-thiadiazole [45]:

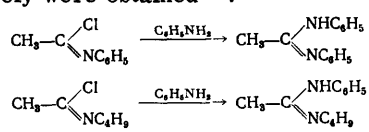


The same product is formed (in 75% yield) by the oxidation of thiobenzamide with nitric acid in acidic aqueous and non-aqueous media [173].

The oxidation of thiobenzanilide by nitrosyl chloride in ethereal solution in an atmosphere of nitrogen in the cold gives *N*-phenylbenzimidoyl chloride (yield 44%) and benzanilide [174]. It is assumed that an *S*-nitroso-derivative is formed as an intermediate:



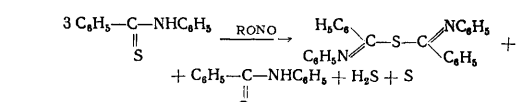
When thioacetanilide and *N*-butylthioacetamide were subjected to the same treatment with nitrosyl chloride, the imidoyl chlorides could not be isolated owing to their instability. However, their formation was proved by the action of excess of aniline on the reaction mixture, when *NN'*-diphenylacetamidine and *N'*-butyl-*N*-phenylacetamidine respectively were obtained [174]:



In pyridine oxidation of thiobenzanilide by nitrosyl chloride takes a different course: the oxidation products are di-*N*-phenylbenzimidoyl sulphide $C_6H_5.C(:N.C_6H_5).S.C(:N.C_6H_5).C_6H_5$ and an oily product; the latter decomposes slowly into sulphur and a sulphide [174].

With nitric oxide in ether in the cold *N*-butylthioacetamide gives *N*-butyl-*N*-nitrosoacetamide [174].

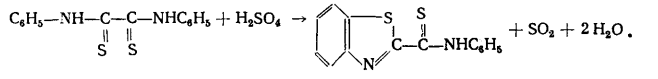
The reaction of thiobenzanilide with pentyl nitrite and ethyl nitrite at 0°C yielded after 2 days benzanilide and di-*N*-phenylbenzimidoyl sulphide [174]:



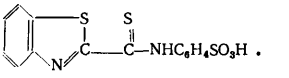
where $R = C_5H_{11}$, C_2H_5.

3. Oxidation of Thioamides by Sulphuric Acid

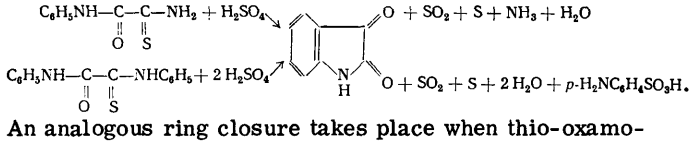
The oxidation of thioamides by sulphuric acid is used to obtain benzothiazole, isatin, and indole derivatives. The action of oleum or concentrated sulphuric acid on dithiooxanilide at room temperature gives a quantitative yield of benzothiazole-2-carbothioanilide [31]:



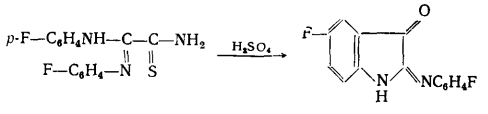
On being warmed with sulphuric acid this product is sulphonated to give



When oxanilothioamide or monothio-oxanilide is heated with 95% sulphuric acid until sulphur dioxide ceases to be evolved, isatin is obtained in 25% yield [31]:

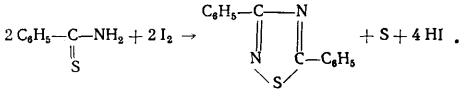


An analogous ring closure takes place when thio-oxamo-*NN'*-di-*p*-fluorophenylamidine is oxidised with sulphuric acid to give an indole derivative [175]:



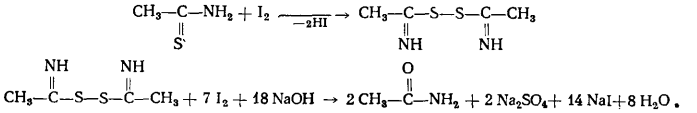
4. Oxidation of Thioamides by Halogens

On treatment with excess of iodine in alcoholic solution thiobenzamide undergoes condensation with elimination of a sulphur atom and formation of 3,5-diphenyl-1,2,4-thiadiazole [176]:



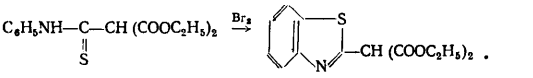
This product has previously been regarded as the isomeric 2,5-diphenyl-1,3,4-thiadiazole [26]. The reaction is probably common to thioamides in which the nitrogen atom is unsubstituted. According to the early results thiobenzamide is not oxidised by iodine [69,174].

In alkaline solution thioamides are oxidised by iodine to amides [157]. This reaction is used for the quantitative determination of thioamides. With thioacetamide the reaction can be expressed by the equations [157]

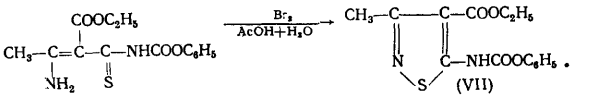


The intermediate disulphide has been isolated only when the thioamide is oxidised by iodine in a mineral acid. Bromine or a mixture of potassium bromide and bromite can be used instead of iodine in acid medium. Dithiooxamides are oxidised by iodine in acid medium better than is thioacetamide.

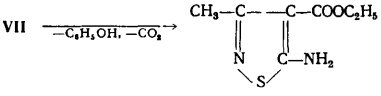
The oxidation of thioanilides by bromine in formic or acetic acid yields benzothiazoles [8,177,178]:



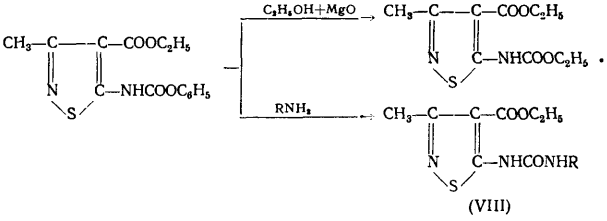
Phenyl 4-ethoxycarbonyl-3-methylisothiazol-5-ylcarbamate (VII) has been obtained in this way [179]:



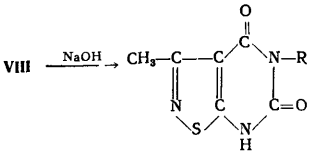
When (VII) is treated with a weak base, or when it is boiled in aqueous dimethylformamide for a long time, phenol and carbon dioxide are split off with formation of the amine:



Other nucleophilic reagents will remove only the phenoxy-group from (VII):



The latter compound can be cyclised on heating to form isothiazolo[5,4-*d*]pyrimidines:



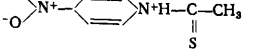
where R = H, CH_3, C_6H_5, OH, NH_2.

Isothiazoles are products of the oxidation of thioamides by bromine in acetic acid and in other cases [8,180-183].

5. Oxidation of Thioamides by Hexacyanoferrates(III)

The oxidation of thioacetanilide and thiobenzanilide derivatives by means of potassium hexacyanoferrate(III) in alkaline aqueous solution involves cyclisation with the formation of benzothiazole derivatives (Jacobson's method) [184]. Thioacetanilide derivatives yield 2-methylbenzothiazole derivatives, ease of cyclisation being affected by the nature of the substituent (methoxyl, methyl, chloro, nitro), its position in the anilide ring, and the solubility of the thioacetanilide derivative in the alkaline solution [185-187]†. Thus the yield of 2-methylbenzothiazole

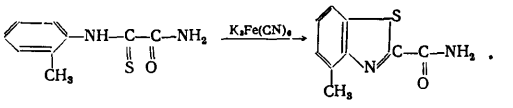
†*p*-Nitrothioacetanilides are unable to form 2-methyl-6-nitrobenzothiazole. This is explained by the existence of the isomeric structure



in which thiol–enolisation [sic], and hence also ring closure, are difficult. In this case oxidation results in the formation of a 50% yield of *p*-nitroacetanilide [186].

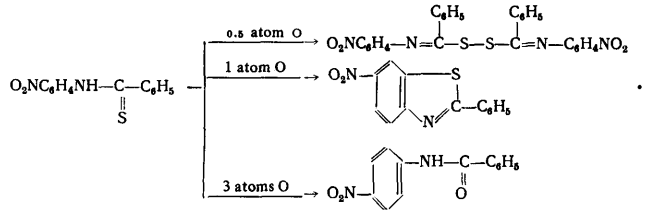
increases as the solubility of thioacetanilide increases with rise in the sodium hydroxide concentration to 2 *N*, after which it falls appreciably [186].

Various derivatives of thio-oxanilic acid are easily cyclised to benzothiazoles under the influence of potassium hexacyanoferrate(III):



If a large excess of the ferricyanide is taken, the reaction is complete in 10 min [82].

Sometimes cyclisation does not occur on the oxidation of thioanilides by potassium hexacyanoferrate(III) in alkaline solution, other products being formed [188]:

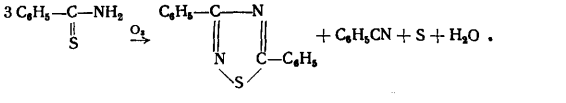


The main product of the oxidation of *p'*-nitrothiobenzanilide in cold alkaline solution was a derivative of dibenzimidoyl disulphide [189], and in hot alkali the main product was *p'*-nitrobenzanilide. In both cases the yield of 6-nitro-2-phenylbenzothiazole was small [186,189,190].

The action of potassium hexacyanoferrate(III) in alkaline solution sometimes converts a thioamide into a nitrile and an oxamide [82]. Thio-oxanilonitrile $C_6H_5.NH.CS.CN$ and thio-oxanilamide $C_6H_5.NH.CS.CO.NH_2$ have been obtained by treating *N*-phenyldithio-oxamide with a quantity of the oxidant corresponding to 1 atom of oxygen, when 75% of the thioamide is converted into the nitrile, and 25% into the oxamide. Although thio-oxanilamide can be obtained by heating thio-oxanilonitrile in alkaline solution, it is more probably directly from the phenyldithio-oxamide [82].

6. Other Methods for the Oxidation of Thioamides

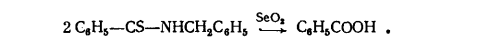
Thioamides are oxidised by ozone in inert anhydrous solvents, e.g. benzene and carbon tetrachloride. Thiobenzamide is converted into *N*-benzimidoylthiobenzamide $C_6H_5.C(:NH).NH.CS.C_6H_5$, which is then cyclised to 3,5-diphenyl-1,2,4-thiadiazole [191]:



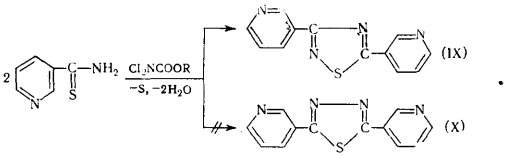
Other products of the reaction are benzonitrile and sulphur [192]. Thio-*p*-toluamide behaves similarly, but thioacetanilide is converted into acetanilide and resinous products. The corresponding amides and nitriles have been obtained also by the action of ozone on unsubstituted thiobenzamide in aqueous medium. The reaction between thioacetamide and ozone in benzene or water, on the other hand, yields acetic and sulphuric acids, ammonia, and sulphur.

Dithiocamphorimide is oxidised by potassium permanganate to camphorimide [102].

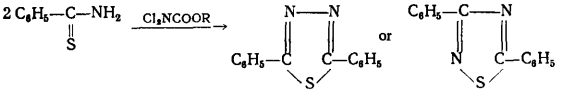
The oxidation of thioamides by selenium dioxide (in alcoholic solution) yields the corresponding amides and selenium trisulphide [159,193-195]. The oxidation of *N*-benzylthiobenzamide gives the amide only when more than 2 moles of the thioamide are taken per mole of selenium dioxide. With equimolecular proportions of the reactants oxidation is accompanied by cleavage of the carbon–nitrogen bond [194]:



NN-Dichlorocarbamates Cl_2NCOOR resemble iodine in their oxidising action on thioamides [17,196,197]. Oxidation is usually conducted in an aqueous suspension of the reactants containing a slight excess of the dichlorocarbamate. Nicotinothioamide is oxidised to 3,5-dipyrid-3'-yl-1,2,4-thiadiazole (IX), not the isomeric 1,3,4-thiadiazole (X):[195]



In the case of thiobenzamide it has not been established whether the oxidation product is a 2,5-disubstituted 1,3,4-thiadiazole or a 3,5-disubstituted 1,2,4-thiadiazole [195]:

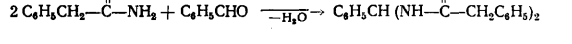


Thioamides can be oxidised also by alkene oxides and certain esters. Thus boiling a solution of thioacetamide in methanol with cyclohexene oxide for 5 h gave acetamide (85%) and a sulphur-containing residue [198]. When thiobenzamide was oxidised by the ethyl ester of phenylglycine $C_6H_5.NH.CH_2.COOC_2H_5$, the products were benzamide, ethyl cinnamate, and sulphur.

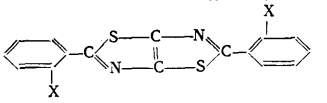
The oxidation of thioamides by sodium *o*-hydroxymercuribenzoate $HOHgC_6H_4COONa$ is used for the analytical determination of thioamides [199,200]. Certain *N*-monoarylthioamides are not determined by this method [200].

VII. REACTIONS OF THIOAMIDES WITH ALDEHYDES AND KETONES

Phenylthioacetamide reacts with benzaldehyde to form an oily product:

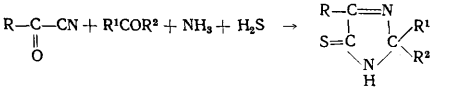


which gives a solid salt with platinum(II) chloride [150]. The reaction of dithio-oxamide with benzaldehyde and salicylaldehyde [201] is accompanied by dehydrogenation and the formation of thiazolothiazole derivatives [202]:

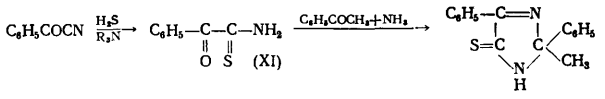


where X = H, OH. *o*-Nitrobenzaldehyde does not react [202].

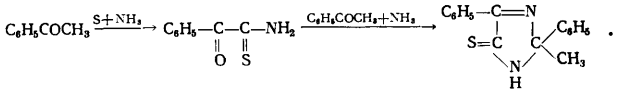
Nor could individual products be isolated from the reaction of thioamides with aliphatic aldehydes and aryl methyl ketones. Acyl cyanides (aromatic and aliphatic) react with ketones in the presence of hydrogen sulphide and ammonia to form substituted Δ^3-imidazoline-5-thiones [203,204]:



α-oxo-thioamides being formed from the acyl cyanide as intermediate products. The action of hydrogen sulphide on benzoyl cyanide in the presence of a tertiary amine in an aprotic solvent gives an excellent yield of the thioamide of phenylglyoxylic acid (XI), which on reaction with acetophenone and ammonia for a few minutes is converted quantitatively into 2-methyl-2,4-diphenyl-Δ^3-imidazoline-5-thione:

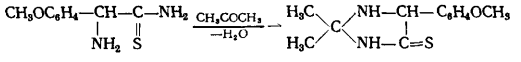


Imidazoline-5-thione derivatives are formed also by the action of elementary sulphur and ammonia on ketones [205]. Reaction between a thioamide and a ketone is assumed to underlie the synthesis of a Δ^3-imidazoline-5-thione by the action of excess of ammonia and sulphur on acetophenone [204,206]:

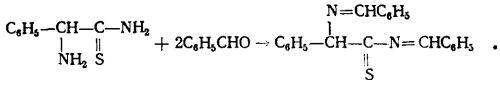


Other Δ^3-imidazoline-5-thiones have been obtained similarly.

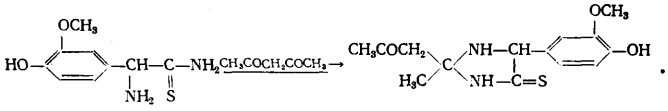
When α-amino-thioamides are boiled in absolute alcohol with equimolecular quantities of aliphatic [207] or aromatic [208] aldehydes, ketones [209], and αγ-dioxo-compounds [210], 2,2-disubstituted imidazolidine-4-thiones are formed in good yield:



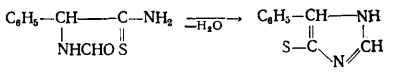
If two equivalents of the oxo-compound are used, heterocycles are not formed [207]:



It is probable that only one oxo-group is involved in the interaction of equimolecular quantities of a thioamide and pentane-2,4-dione, since imidazolidine-4-thiones—not methylenebis-2-imidazolidine-4-thiones—are formed [211]:

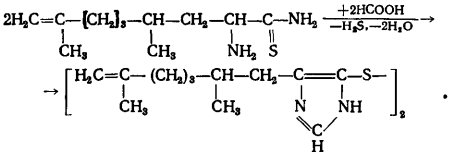


Imidazoline-4-thiones are obtained also by the cyclisation of α-amido-thioamides‡ when boiled in alcoholic solution in the presence of an acid or a base [212-214]:



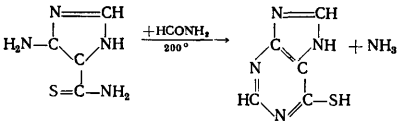
‡The intermediate α-amido-thioamides were obtained by treating α-amino-thioamides with formic acid in the absence of a solvent [207], or by the action of acetic anhydride (1–2 equivalent) or benzoyl chloride on the α-amino-thioamide [33,208]. In this way α-formamide, α-acetamide, or α-benzamide derivatives were obtained; the yields of the latter compounds were low.

When 2-amino-4,8-dimethylnon-8-enothioamide is heated with formic acid the resulting imidazolinethione is oxidised to the disulphide [213]:



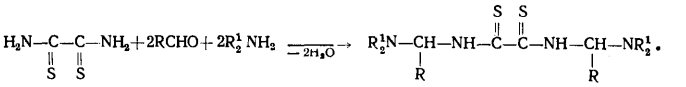
Disulphides are formed also by the oxidation of imidazolinethiones by hydrogen peroxide or iodine.

Cyclic amino-thioamides also react with aldehydes. Thus 4-amino-Δ^2-imidazoline-5-carbothiamide and formamide yield purine-6-thiol [215]:



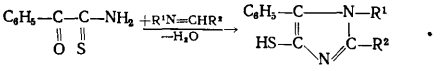
Phenanthraquinone also undergoes this reaction.

The reaction of dithio-oxamide (or an *NN'*-dialkyldithio-oxamide) with a solution of an aldehyde and a secondary amine in chloroform involves condensation of the three reactants [216]:



Benzaldehyde and several aliphatic aldehydes have been used together with dialkylamines, piperidine, and alkylarylamines in this reaction.

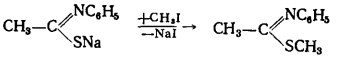
Phenylglyoxylothioamide reacts with aldimines (in benzene at 45°C for 2 h) to form 4-mercapto-5-phenylimidazoles [6]:



Primary amines do not undergo this reaction, since the addition product of a primary amine and an aldehyde immediately eliminates water, and the resulting Schiff base does not react with dithio-oxamide. Nor do dithio-oxanilides undergo this reaction; tetra-substituted dithio-oxamides form unstable compounds, which decompose into their components [216]. These products are oils in the case of the reaction of tetra-substituted dithio-oxamides with formamide and the lower dialkylamines, and crystalline solids in other cases.

VIII. REACTIONS OF THIOAMIDES WITH ALKYL HALIDES AND HALOGENATED AMINES, KETONES, and ACIDS

Alkyl and aralkyl halides act on the sodium salts of thioamides to form isothioamides, which are usually prepared in this way. Thus methylated *N*-phenylthioacetamide was first obtained by the action of methyl iodide on the sodium salt of thioacetanilide [217]:



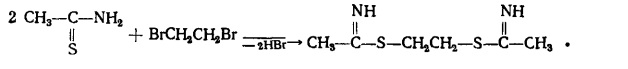
the solvent being ethanol. Heating *N*-benzylthioacetamide in methyl iodide gives a quantitative yield of the hydriodide of S-methyl *N*-benzylthioacetimidate [218]; on treatment with

caustic potash the free base $CH_3.C(:N.CH_2.C_6H_5).S.CH_3$ was isolated in 64% yield§.

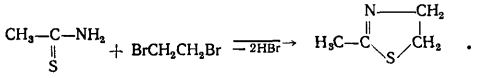
Unsubstituted thioamides also react with the lower alkyl halides to form salts of isothioamides [219]. Equimolecular quantities of the alkyl halide and the thioamide are usually taken, and the reaction is conducted in dry acetone. Propyl and butyl iodides hardly react even when boiled for 2 h.

The sodium and potassium salts of *N*-benzylthioamides react with alkyl halides in xylene solution to form products $C_6H_5.C(SR):N.CH_2.C_6H_5$ in 45–65% yields [159]. The action of alkyl halides on *NN'*-disubstituted thioamides gives salts to which the structure $[R.S.CR^2:NR_2^1]^+X^-$ is assigned [60].

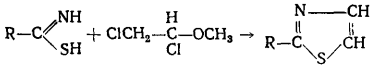
Reaction between dibromoethane and thioamides involves cyclisation with the formation of 2-thiazoles [184], and *N*-arylthioamides yield *N*-aryl-2-thiazole salts. Cyclisation is accompanied by bis-*S*-alkylation. Temperature has a substantial effect on the course of the reaction. Thus thioacetamide reacts with dibromoethane at 100°C to form ethylene diacetimidothioate [47]:



But at the boiling point of dibromoethane (131°C) 2-methyl-Δ^2-thiazoline is formed in low yield [220]:

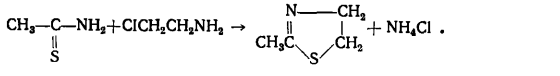


Thiazole and 2-methylthiazole have been obtained in good yield by treating thioformamide and thioacetamide respectively with an aqueous solution of 1,2-dichloroethyl methyl ether at 60°C:



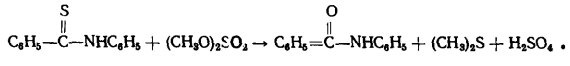
where R = H, CH_3.

Another general method for obtaining Δ^2-thiazolines is the reaction between thioamides and β-halogenated amines. When, for example, thioacetamide is boiled with 2-chloroethylamine for 2 h, at 32.3% yield of 2-methyl-Δ^2-thiazoline is obtained [222]:

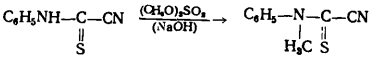


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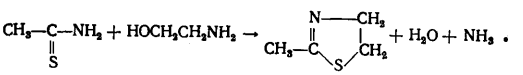
§ Dialkyl sulphates react differently with thioamides. In dry inert solvents dimethyl sulphate does not react with thioamides. In the presence of small quantities of water the process goes as follows [103]:



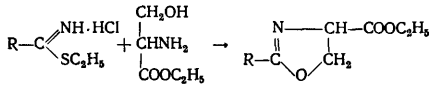
However, alkylation in aqueous alkali yields *N*-alkylated thioamides. For example, thio-oxanilonitrile reacts with dimethyl sulphate in 20% aqueous alkali to form the *N*-methylated product [104]:



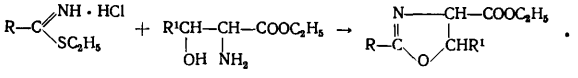
2-Aminoethanol reacts similarly:



Esters of β-hydroxy-α-amino-acids react with salts of isothioamides to form oxazolines. Thus ethyl 2-alkyl- and 2-aryl-oxazoline-4-carboxylates are easily obtained from the ethyl ester of serine:

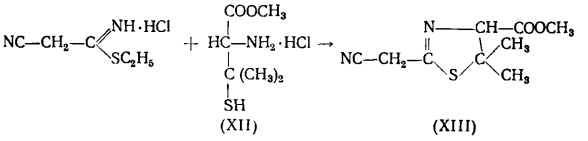


Application of this reaction to derivatives of serine gives 5-substituted oxazoline derivatives [223,224]:

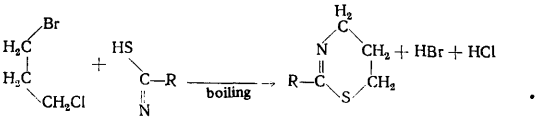


The yield of oxazolines improves substantially as the molecular weight of the ester group in the serine increases from methyl to propyl [223].

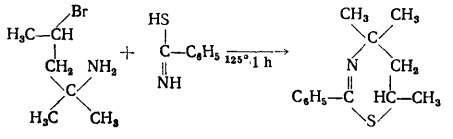
Esters of β-mercapto-α-amino-acids, in contrast to β-hydroxy-α-amino-carboxylic esters, react with thioamides [225,226] to form thiazoles. Thus the ester of penicillamine (XII) and the hydrochloride of ethyl cyanothioacetimidate react in dry chloroform to produce the 2-cyanomethyl-5,5-dimethylthiazoline-4-carboxylic ester (XIII):[227,228]



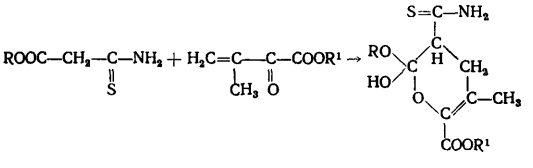
1-Bromo-3-chloropropane reacts with thioamides to form the 2-substituted 5,6-dihydro-1,3-thiazines:



The yields are often theoretical, but only 10% in the case of thioacetamide. 5,6-Dihydro-1,3-thiazines are obtained also by the reaction of thioamides with γ-halogeno-amines:



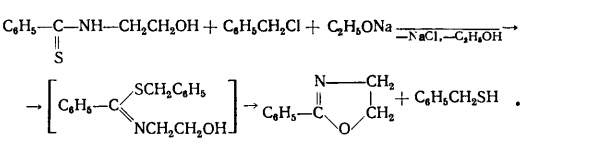
Another method of obtaining Δ^2-dihydrothiazines is the reaction between α-thiocarbamoylacetic esters and vinylglyoxylic esters:



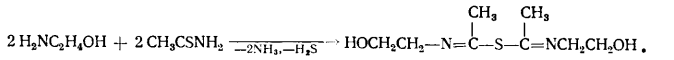
where R = CH_3, $C_6H_5CH_2$, $(CH_3)_3C$. The reaction goes smoothly in neutral medium at room temperature [229].

Reviews have been published [184,230,231] on the synthesis of thiazoles, Δ^2-thiazolines, and 5,6-dihydro-1,3(or 4)thiazines, which include this method. A modification of the method is the preparation of Δ^2-thiazolines by treating *N*-2-hydroxyalkyl-amides with phosphorus pentasulphide [184,232]. Thus *N*-2-hydroxyethylbenzamide gives a 68% yield of 2-phenyl-Δ^2-thiazoline [233-237]. Thioamides are assumed to be formed as intermediates [238].

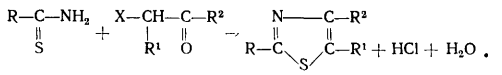
When *N*-2-hydroxyethylbenzothioamide is boiled with sodium ethoxide and benzyl chloride in ethanol (these conditions are usual for the *S*-alkylation of thioamides), 2-phenyloxazoline [111] and phenylmethanethiol [59] are obtained:



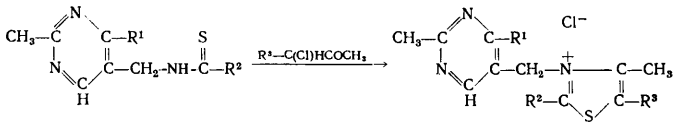
It is assumed that *S*-benzyl *N*-2-hydroxyethylthiobenzimidate is formed initially, and then undergoes cyclisation. Aminoethanol is able also to react differently with thioamides from the way mentioned above [70]. When an equimolecular mixture of this amine and thioacetamide is heated at 75°C, two molecules of each reactant undergo condensation with the evolution of two molecules of ammonia and one molecule of hydrogen sulphide, a sulphide being formed:



Thiazoles can be obtained also by the reaction of thioamides with α-halogeno-ketones and -aldehydes [9,184,239,240]:

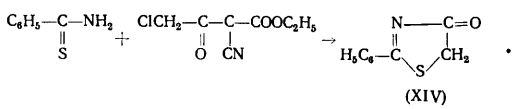


N-Substituted thioamides, e.g. 4-amino-5-thioformamidomethylpyrimidine [241], are converted into the corresponding *N*-substituted thiazoles [76,242-251]:



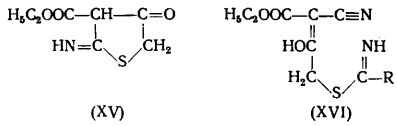
where $R^1 = NH_2$ and $R^2 = R^3 = H$.

When thiobenzamide is heated with γ-chloro-α-cyanoacetoacetic ester in aqueous ethanol for several days, 4-oxo-2-phenyl-Δ^2-thiazoline (XIV) is formed in 75% yield [252]:



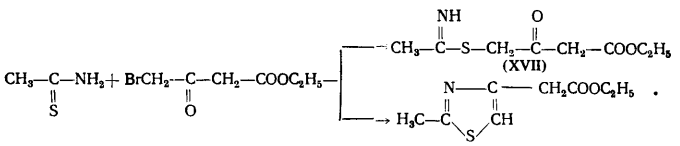
(XIV)

Under these conditions thioacetamide yielded two products



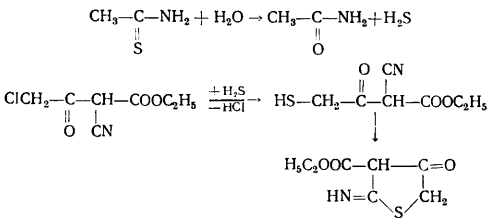
(XV) (XVI)

ethyl 2-imino-4-oxothiolan-3-carboxylate (XV) and a small quantity of a compound $C_7H_7NO_2S$, whose structure was not established. It is assumed that (XV) is formed by cyclisation of the intermediate product (XVI: R = C_6H_5). This hypothesis is based on the formation of ethyl 2-methylthiazol-4-ylacetate when thioacetamide is boiled with ethyl γ-bromoacetoacetate for 30 min and allowed to stand for a long time [253]:

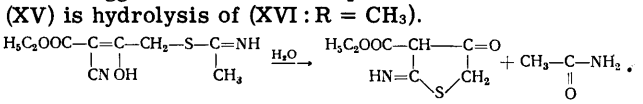


(XVII)

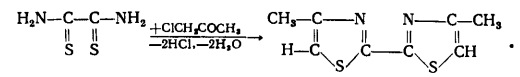
If the reaction is halted and rapid crystallisation is effected, ethyl γ-acetimidoylthioacetoacetate (XVII) is formed [253]. After isolation the latter does not give thiazole derivatives under various reaction conditions. If R = C_6H_5 in (XVI), the mobility of the imino-proton is increased, and favourable conditions are created for ring closure and the formation of (XIV). [252] If, however, R = CH_3, the nitrogen-hydrogen bond becomes more stable, and cyclisation does not occur. Since this hypothesis does not explain the formation of (XV), the reaction scheme



has been suggested. Another explanation of the formation of (XV) is hydrolysis of (XVI: R = CH_3).

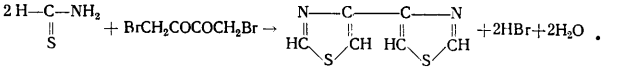


Dithio-oxamides react with α-halogeno-ketones to form bithiazolyls. Thus 4,4′-dimethyl-2,2′-bithiazolyl is readily formed from dithio-oxamide and chloroacetone in alcoholic solution [254]:

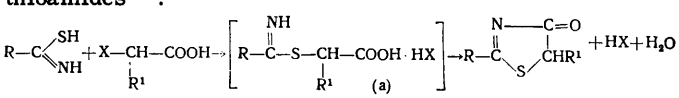


The action of dithio-oxamide on 1,4-dibromobutane-2,3-dione results in the rapid formation of brown polymeric products of high melting point (probably polythiazolines [254]), which are practically insoluble in almost all solvents. Polymeric products are obtained also by the reaction of 1,4-dibromobutane-2,3-dione with dithioterephthalamide and dithiomalonamide [255,256].

Thioformamide gives 4,4′-bithiazolyl when warmed with 1,4-dibromobutane-2,3-dione in alcohol [257]:

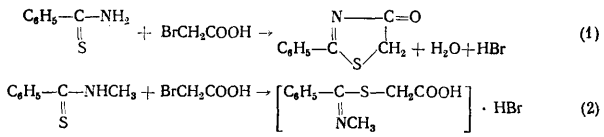


α-Halogeno-carboxylic acids react with thioamides to form 4-oxothiazolines [184,258]. 2-Alkylated and 2-arylated derivatives are obtained from aliphatic and aromatic thioamides [196]:



where R = Alk or Ar. Equimolecular quantities of the reactants are usually boiled in water or in toluene. Reaction is slow. An isothioamide salt (a) is formed as the first stage [196]. In some cases (e.g. with α-bromoisobutyric acid) the intermediate isothioamides do not undergo cyclisation.

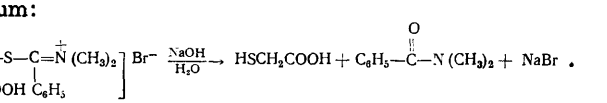
Thioamides in which the nitrogen atom is not substituted react with bromoacetic acid to form 4-oxothiazolines, whereas *N*-substituted thioamides yield acyclic "isothioamides":[77]



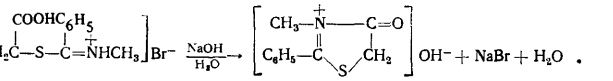
(1)

(2)

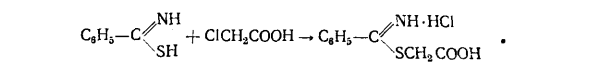
N-Methylthiobenzamide gives the hydrobromide of α-*N*-methylbenzimidoylthioacetic acid (Eqn. (2). Several other *N*-substituted and *NN*-disubstituted thioamides react similarly. *N*-α-Carboxymethylthiobenzylidene-*NN*-dimethylammonium bromide is hydrolysed in alkaline medium:



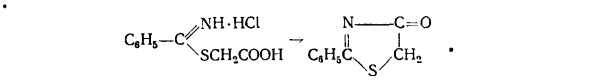
But if the imino-group is incompletely substituted, cyclisation occurs:



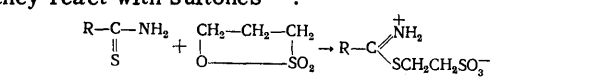
In acid media *N*-monosubstituted thiobenzimidates also give 4-oxothiazolines, whereas *NN*-disubstituted thiobenzimidates yield isothioamides. With chloroacetic acid thiobenzamide forms initially an alkylation product[197,259]:



When heated to 100°C or in the presence of a condensing agent, e.g. acetic anhydride, this gives a 4-oxothiazoline[258]:

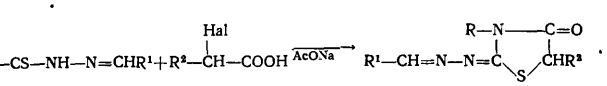


This reaction usually occurs more rapidly and under more moderate conditions with derivatives of aliphatic thioamides. *S*-Alkylation of thioamides is observed also when they react with sultones[259]:

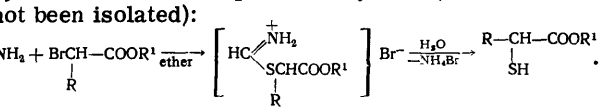


where R = CH_3, C_6H_5, *o*- and *p*-$CH_3C_6H_4$. The reaction is accomplished by boiling in benzene for 1 h. With aromatic thioamides the yield reached ~ 80%.

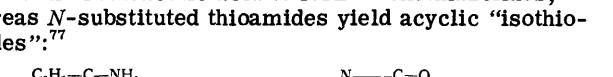
α-Halogenated carboxylic acids react also with thiosemicarbazones in the presence of fused sodium acetate. Cyclisation takes place with the formation of 5-alkyl(or aryl)-2-alkylidenehydrazono-3-aryl-4-oxothiazolidines[260-262]:



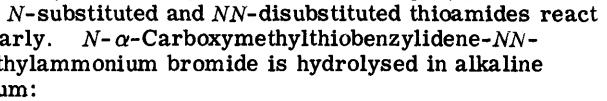
Thioformamide differs from other thioamides in its reaction with α-halogenated carboxylic acids[263]. Thus with α-halogeno-carboxylic esters 50–80% yields of α-mercapto-carboxylic esters are obtained. When the reaction is conducted in ether, salts of α-formimidoylthioalkanoic esters are formed initially, and are easily hydrolysed to the α-mercapto-carboxylates (thiazolones have not been isolated):



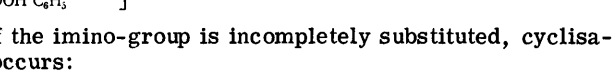
Diethyl dibromomalonate oxidises thioformamide under these conditions:



N-Carboxymethylthioamides R.CS.NH.CH_2.COOH, either as such or as intermediate products at the instant of isolation, are used to obtain thiazole and oxazole derivatives. For example, the action of acetic anhydride and phosphorus tribromide on *N*-α-mercaptophenethylideneaminoacetic acid yields 2-benzyl-5-hydroxythiazole[264]:



When acetic anhydride and pyridine are used, 2-benzylthiazol-5-yl acetate is formed:

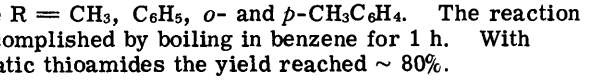


Similarly, 5-ethoxy-2-methylthiazole is obtained by heating the ethyl ester of *N*-acetylglycine with phosphorus pentasulphide[265].

2-Benzyl-4-benzylidene-5-oxothiazoline is formed when thiophenaceturic acid [phenylthioacetylglycine] is treated with acetic anhydride in the presence of benzaldehyde[266]:

When benzaldehyde is replaced by ethyl orthoformate, intermolecular condensation takes place[266]:

5-Oxazolones are formed by the treatment of an *N*-carboxymethylthioamide with a silver salt or oxide[267]. In dry ether thiophenaceturic acid is cyclised by silver oxide to 2-benzyl-5-oxo-oxazoline[264,267,268]:

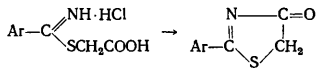


2-Benzyl-5-ethoxyoxazole is formed by treating ethyl thiophenaceturate with silver benzenesulphonate in cold pyridine[269]:

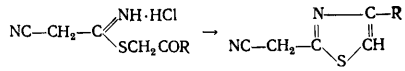
The free acid reacts similarly[61,270].

Thioamides in which the nitrogen atom is unsubstituted react with silver salts or the oxide, usually with formation of the corresponding nitrile and precipitation of silver sulphide. When equimolecular quantities of the thioamide of hippuric acid and mercury(II) acetate are mixed, mercury(II) sulphide is precipitated, and hippuronitrile remains in solution[270]:

Aromatic imidate derivatives of thioglycollic acid [271] and its esters [272] form 2-substituted 4-oxothiazolines when boiled in toluene:

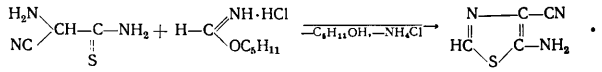


4-Methyl- and 4-phenyl-thiazoles are formed similarly [272]:



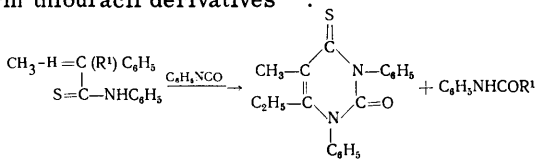
where R = CH_3, C_6H_5.

The thioamide of α-cyanoglycine reacts with isopentyl formimidate to give aminothiazole:



Other formimidates and salts of thioformimidates, however, do not yield definite products [273].

Aminoalkenothioanilides react with phenyl isocyanates to form thiouracil derivatives [274]:



Oxidation of these products by hydrogen peroxide replaces the sulphur by oxygen.

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