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Synthesis of Thioamides

K.A.Petrov and L.N.Andreev

Exhaustive data are given on methods for the synthesis of thioamides, which have now found wide application in synthetic practice, in medicine, biology, and analytical chemistry, in the foodstuffs and metallurgical industries, and in other fields. Attention is paid mainly to methods for preparing thioamides from nitriles and amides and by the Willgerodt-Kindler reaction. This is the first review of the synthesis of thioamides to be published in the Soviet literature. The list of references contains 378 items.

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INTRODUCTION

Thioamides are reactive compounds which, because of the diversity of their chemical properties, find wide application in technology[1-6], in agriculture[7-12], and in synthetic practice and medicine. They are used as vulcanisation accelerators[13-15], additives to lubricating oils, corrosion-inhibitors for metals[16-19], flotation agents[1-6], insecticides and fungicides, preservatives[20-26], medicinals for the treatment of poisoning by salts of heavy metals, starting materials for the preparation of certain vitamins (e.g. B_1), and other pharmaceutical preparations[26-38].

Thioamides have been studied in detail: more than 400 representatives of this group have been synthesised, and about 500 papers and patents have been published. However, this information is scattered among many periodicals, and is difficultly accessible. The Soviet literature contains no review papers on the chemistry of thioamides, apart from a publication on the use of thioacetamide to replace hydrogen sulphide[39] in the analysis of metals. The foreign literature contains publications of a review character[40-45], but they are either out of date or incomplete. These are the reasons for the publication of the present review.

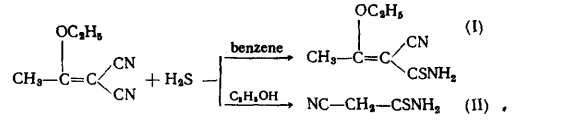
1. PREPARATION OF THIOAMIDES BY THE REACTION OF NITRILES WITH HYDROGEN SULPHIDE

Various method of preparation have been suggested for thioamides. The most convenient of them is based on the reaction of nitriles with hydrogen sulphide, since it uses readily available materials and there are practically no by-products[46-70]:

$$RCN + H_2S \rightarrow RCSNH_2$$

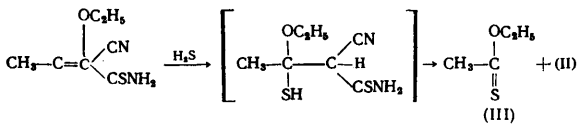
As early as 1841 the first member of the group—thiobenzamide—was obtained by this method[71]. The reaction between nitriles and hydrogen sulphide is usually conducted in various solvents and in the presence of amines, both of which influence the yield of thioamides. Among solvents which have been used are ethanol (aqueous or absolute)[72-79], aromatic hydrocarbons, dioxan, acetone[51-53,80], chloroform[81], pyridine[82,83], and in some cases water[80]. The nitrile solution was saturated with hydrogen sulphide usually at 0°C or room temperature (sometimes at 60°C[73]), a high concentration of hydrogen sulphide promoting better formation of thioamides[73]. After saturation the reaction mixture was either left at room temperature for a few days, or heated at 80–100°C,[84,85] sometimes at 100–150°C, for 6–10 h.

In isolated cases the solvent used has a substantial influence on the character of the products. Thus 1-ethoxyethylidenemalononitrile is able to give various reaction products with hydrogen sulphide depending on the solvent[86]: in benzene α-cyano-β-ethoxythiocrotonamide (I) is formed, whereas in ethanol cyanothioacetamide (II) is obtained:



The difference in the course of the reaction is explained by the differing solubility of the product (I) (formed initially

in both cases), which is insoluble in benzene and is precipitated, whereas it dissolves slightly in hot alcohol and reacts with hydrogen sulphide:



Ammonia, diethylamine, triethylamine, trishydroxyethylamine, and alkali-metal and ammonium hydrogen sulphides are used as catalysts[84,87,88]. When primary and secondary amines are used, mono- and di-substituted thioamides respectively are formed[49,50,89,90]. Hydrogen sulphide adds to nitriles especially readily in the presence of pyridine and of triethylamine[82,83].

Under otherwise similar conditions†, the yield of a thioamide depends on the nature of the nitrile: aliphatic nitriles usually add hydrogen sulphide with greater difficulty than do aromatic nitriles. The yields of aliphatic thioamides are increased by conducting the reaction at elevated temperatures and pressures. In the case of aromatic nitriles the yields are greatly affected by substituents in the aromatic ring: thus under identical conditions yields were obtained of 100% *o*-chlorothiobenzamide, 95% phenylthioacetamide, 94% thiobenzamide, 90% *p*-methoxythiobenzamide, 86% thionicotinamide, 81.5% *p*-aminothiobenzamide, 80% *p*-acetamidothiobenzamide, 70% *p*-ethylsulphonylthiobenzamide, 70% 3,4-dimethoxythiobenzamide, 65.5% thiopicolinamide, 60.5% dithioterephthalamide, and 48.5% *p*-chlorothiobenzamide[91].

The nature of the nitrile influences not only the yield of thioamide but also the reaction velocity. In the preparation of aromatic thioamides from benzonitriles containing various substituents in the ring, the following relative reaction velocities were obtained at 60°C and 1.75 atm (rate of addition of hydrogen sulphide to benzonitrile itself taken as 100): *m*-bromo 831, *p*-iodo 518, *p*-chloro 493, *p*-bromo 451, *p*-methyl 51.9, and *p*-methoxy 41.6.[92]

The action of hydrogen sulphide on dinitriles under the same conditions yields bisthioamides. Cyanogen reacts with hydrogen sulphide in the presence of bases to form dithio-oxamide (rubeanic acid $C_2H_4N_2S_2$)[58,92-100]. The reaction is conducted by saturating alcohol with the gaseous reactants or by mixing cyanogen with liquid hydrogen sulphide[27,58,92,100], the latter component being taken in excess in both cases. Cyanothioformamide is formed as an intermediate in the reaction[58], and has been isolated by carrying out the reaction in alcoholic solution with excess of cyanogen[97]. Sometimes potassium hydrogen sulphide[96] or the sodium compound[93,94,100] is used instead of hydrogen sulphide.

Dithio-oxamide has been obtained also by treating ethyl cyanoformimidate $NC.C(:NH).OC_2H_5$ or diethyl oxalyldiimidate $C_2H_5O.C(:NH).C(:NH).OC_2H_5$ with hydrogen sulphide in the presence of bases[101]. It has been proposed to obtain rubeanic acid on an industrial scale by passing a mixture of cyanogen and hydrogen chloride with stirring into an alkaline aqueous solution (pH 7–9) of sodium hydrogen sulphide at temperatures below 50°C:[93]

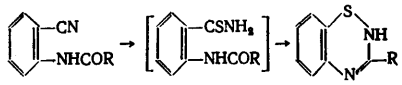
$$(CN)_2 + 2H^+ + HS^- \rightarrow H_2NCSCSNH_2.$$

No secondary products are formed in this case, unlike the process considered earlier. The initial mixture of cyanogen and hydrogen chloride is obtained by the interaction of chlorine and hydrogen cyanide at a high temperature in tubes filled with wood charcoal[93].

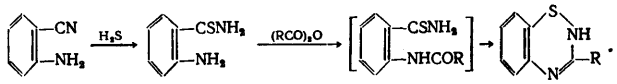
The reaction between a nitrile and hydrogen sulphide can be accomplished also in the absence of a solvent, by using the liquid reactants under pressure[85,102]. Hydrohalic acids[103] or an aluminosilicate[102] are used as catalyst in this case, besides amines. When liquid hydrogen sulphide and a liquid nitrile are used, the reaction is conducted at 50–60°C, a high yield of the thioamide being obtained. In the presence of an aluminosilicate catalyst the reaction between nitriles and hydrogen sulphide takes place under considerably more severe conditions (249–260°C)[102,104].

Under pressures of ~ 8500 atm hydrogen sulphide adds to nitriles at 80–100°C even in the absence of catalysts[85]. Thus acetonitrile and hydrogen sulphide at 80°C give thioacetamide (83%) and a certain quantity of by-products, mainly diethyl trisulphide. The temperature of the reaction must be carefully controlled, since hydrogen sulphide already acts as a reducing agent at 125–150°C.

Several nitriles, e.g. those of alanine, glycine, and *N*-acylanthranilic acids tend to cyclise when an attempt is made to prepare thioamides from them[105]. When an acylaminobenzonitrile is treated with hydrogen sulphide, ring closure occurs with the formation of thiadiazines[105]:

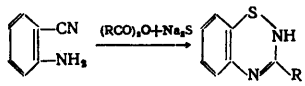


where R = CH_3, C_2H_5, $CH(CH_3)_2$, or C_4H_9. The same heterocycle can be obtained from the nitrile of unacylated anthranilic acid by treating with the anhydride of a carboxylic acid its reaction product with hydrogen sulphide (*o*-aminothiobenzamide):

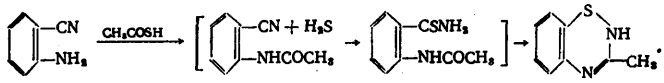


When the reaction is conducted in alcoholic–ammoniacal solution, too, cyclic products are formed. In the presence of an amine instead of ammonia an acyclic product can sometimes be isolated. Thus a small quantity of the non-cyclic thioamide of *N*-acetylanthranilic acid has been isolated from the reaction mass resulting from the interaction of *o*-acetamidobenzonitrile with hydrogen sulphide in the presence of trishydroxyethylamine; even in this case, however, the main product of the reaction was a cyclic thioamide.

The action of sodium sulphide and the anhydride of a carboxylic acid on an amino-nitrile gives a good yield also of the corresponding thiadiazine[105]:



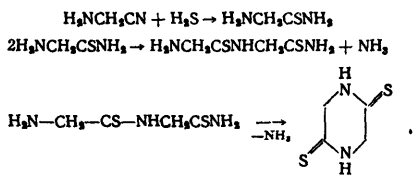
The reaction is conducted in sealed tubes at 100°C. Cyclic thioamides have been obtained also by interaction between *o*-amino-nitriles and thiolic acids in acid medium under pressure[105]:



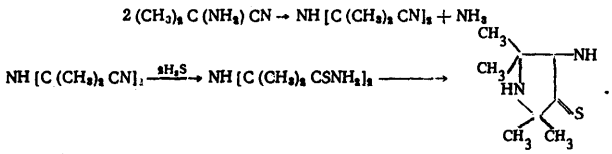
Cyclisation occurs also when hydrogen sulphide acts on aminoacetonitrile or α-aminopropionitrile in ammoniacal alcoholic solution containing ammonium sulphate, with the formation respectively of 2,5-dithionopiperazine and 3,6-dimethyl-2,5-dithionopiperazine respectively, but the

†The course of the reaction is greatly influenced by, for example, the degree of reagents and solvents.

yield is low in both cases. It is assumed that the normal thioamide is formed initially, and ammonia is eliminated from two molecules thereof with ring closure‡:

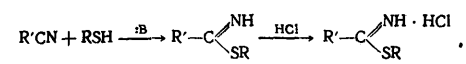


α-Aminopropionitrile reacts with hydrogen sulphide under the above conditions to form mainly aminobispropionitrile. Other α-amino-nitriles do not give dithionopiperazines at all on reaction with hydrogen sulphide. Thus α-aminoisobutyronitrile gives under the same conditions a crystalline product $C_7H_{14}N_2S$, for which the structure 2,2,4,4-tetramethyl-5-thionoimidazoline was proposed:

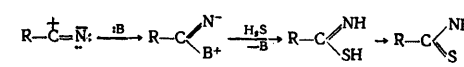


This scheme is supported by the fact that iminodi-isobutyronitrile on treatment with hydrogen sulphide yields the same cyclic product. 2-(*N*-Acetylsulphanilamido)benzonitrile on treatment with hydrogen sulphide in pyridine at 100°C gives the normal, acyclic thioamide[106].

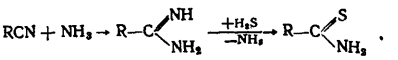
An interesting variant of the reaction of hydrogen sulphide with nitriles is that of perfluoroalkylnitriles with thiols and hydrogen sulphide. Perfluoronitriles add thiols in the presence of amines to form perfluorothioimides, from which perfluoroalkylthioamides and dithiocarboxylic esters are formed by the action of hydrogen sulphide[107]:



The mechanism of the reaction of nitriles with hydrogen sulphide has not been adequately studied. With a tertiary amine as catalyst this reaction is assumed to go according to the scheme[44]



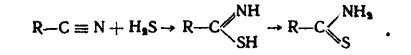
If the reaction is catalysed by a primary or a secondary amine or by ammonia, it is supposed that an amidine is formed initially, and interacts with the hydrogen sulphide to give the thioamide:



There is some indication that amidines could be isolated[89] and that they are converted into thioamides by the action of hydrogen sulphide (see below). However, these schemes probably represent only secondary reactions between hydrogen sulphide and nitriles in the presence of amines. Such reactions include also the formation of imidic esters when alcohols are used as solvent, especially as, like imides, these compounds are converted into thioamides by the action of hydrogen sulphide.

‡The interaction of thioamides with primary amines is known to liberate ammonia and involve ring closure. In the present case one thioamide molecule reacts as a primary amine, while the other acts as a thioamide.

It may be postulated that hydrogen sulphide adds directly to nitriles to form thiolomides, which then isomerise into thioamides:



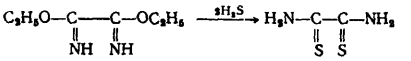
Such an assumption is supported by the fact that hydrogen sulphide reacts with nitriles at elevated temperatures and pressures to form thioamides even in the absence of amines. The role of amines as catalysts appears in the formation with hydrogen sulphide of hydrogen sulphides, which, because of the greater polarity of the bond, add to nitriles considerably more easily than does hydrogen sulphide itself.

2. PREPARATION OF THIOAMIDES BY THE REACTION OF AMIDINES, AMIDOXIMES, AND IMIDIC ESTERS WITH HYDROGEN SULPHIDE

As shown earlier, amidines and imidic esters§ are intermediates in the preparation of thioamides from nitriles and hydrogen sulphide. Therefore the reactions under consideration can be regarded as variants of the reaction of nitriles with hydrogen sulphide. They involve the intermediate addition of hydrogen sulphide at the multiple bond in the imino-compounds with formation of unstable products, which are then converted into the thioamides.

Both unsubstituted[117,118] and substituted[118-123] thioamides have been obtained by these methods. The following dithio-oxamides (percentage yields in parentheses)—*NN'*-dibutyl (70), *NN'*-diethyl (45), *NN'*-bis-3-methoxypropyl (60), and *NN'*-bis-2-hydroxyethyl (8.5)—have been isolated by saturating alcoholic solutions of the oxamidine derivatives with hydrogen sulphide[123]. *N*-Substituted thioamides are obtained also by heating *N*-substituted amidines with hydrogen sulphide at 100°C.[124] Hydrogen sulphide acts on *NN*-diphenyloxamidoxime $(C_6H_5)_2N.CO.C(:NOH).NH_2$ in ammoniacal solution to give the corresponding thioamide[125] $(C_6H_5)_2N.CO.CS.NH_2$

An interesting example of the use of imidic esters to obtain thioamides is the preparation of dithio-oxamide by the reaction of hydrogen sulphide with ethyl oximidate, which is readily formed from cyanogen chloride and ethanol, the yield of the thioamide being 90%:[101]

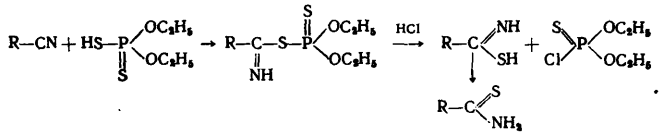


3. PREPARATION OF THIOAMIDES BY THE REACTION OF NITRILES WITH THIOPHOSPHORIC ACIDS AND THIOAMIDES

A variant of the reaction of nitriles with hydrogen sulphide is the addition of thiophosphoric acids and thioamides to nitriles. These two groups of reagents serve in such cases as sources of hydrogen sulphide. *OO'*-Diethyl hydrogen dithiophosphate has been used as the thio-

§Imidic esters are easily obtained by saturating a dry equimolecular mixture of the nitrile and the alcohol with dry hydrogen chloride[108-116].

phosphoric acid¶. The addition product is cleaved at the sulphur-phosphorus bond:



The yield of thioamides reaches 50–90%.[128]

Chlorothioacetamides, inaccessible by other methods, can be obtained[44,129]. In their synthesis, e.g. by the addition of hydrogen sulphide to chloroacetonitrile in the presence of ammonia, a sulphide is first formed, and is then converted into a bisthioamide[128]:

$$Cl{-}CH_2CN + H_2S + 2NH_3 \rightarrow S(CH_2CN)_2 + 2NH_4Cl$$

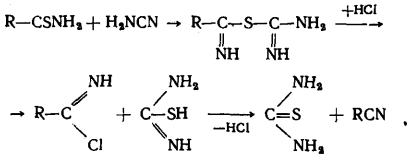
$$S(CH_2CN)_2 + 2H_2S \rightarrow H_2N{-}\underset{\underset{S}{\|}}{C}{-}CH_2{-}S{-}CH_2{-}\underset{\underset{S}{\|}}{C}{-}NH_2 .$$

The reaction of nitriles with thioacetamide involves an intermediate stage in which mixed anhydrides of thioimidic acids are formed[130–134]:

$$R{-}C{\equiv}N + CH_3CSNH_2 \rightleftarrows R{-}\underset{\underset{NH}{\|}}{C}{-}S{-}\underset{\underset{NH}{\|}}{C}{-}CH_3 \rightarrow RCSNH_2 + CH_3CN .$$

When the low-boiling acetonitrile is distilled off, the equilibrium is shifted to the right, and good yields (63–87%) are obtained of a thioamide containing more atoms than the original. Benzonitrile reacts less smoothly with *N*-substituted thiobenzamides.

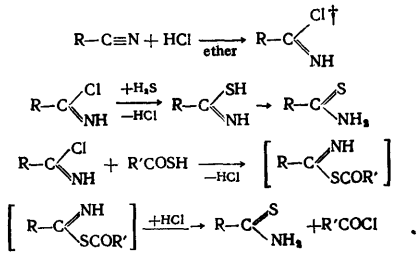
Unsubstituted thioamides react with cyanamide in warm alcoholic solution, giving a good yield of thiourea:



Interaction of these reactants in cold alcoholic solution in the presence of a mineral acid forms in good yield a salt of thiodiformamidine $NH_2C(:NH)SC(:NH)NH_2$. The same product can be obtained by the reaction of thiourea with cyanamide.

4. PREPARATION OF THIOAMIDES BY THE REACTION OF IMIDOYL CHLORIDES WITH HYDROGEN SULPHIDE AND THIO-ACIDS

Thioamides are formed[135] by the reaction of nitriles with hydrogen chloride and hydrogen sulphide or a thioacid:



¶ For the preparation of dithiophosphates see Refs. 126 and 127.

†Doubt has recently been cast on the formation of imidoyl chlorides in this way: formation of a complex of the nitrile with hydrogen chloride is regarded as more probable[136].

These reactions can likewise be regarded as a variant of the addition of hydrogen sulphide to nitriles, distinguished by the use of hydrogen chloride instead of ammonia as catalyst. Other hydrohalic acids also catalyse the interaction of hydrogen sulphide with nitriles: thuse use of hydriodic and hydrobromic acids as catalysts for the reaction conducted in sealed tubes at 32–50°C gave yields of thioamides of 51–93% with various nitriles[103].

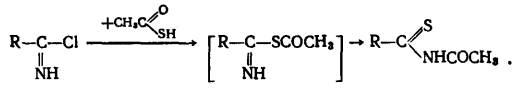
Another product of the reaction, besides those given in the scheme, is the di-imidoyl sulphide, probably formed by reaction between the nitrile and the thioamide:

$$R{-}CN + R{-}CSNH_2 \rightarrow [R{-}C(:NH)]_2S .$$

The relative proportions of thioamide and di-imidoyl sulphide depend on those of the reactants: the more nitrile is present, the higher the yield of the di-imidoyl sulphide.

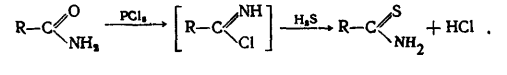
The yield of a thioamide depends on the nature of the thiolic acid and the nitrile, under otherwise similar conditions. The yield of thiobenzamide was 75% when thioacetic acid was used, 100% with thiobenzoic acid; on the other hand, interaction of *p*- and *m*-nitrobenzonitrile with acetothiolic acid gave 40% and 6% yields respectively of thiobenzamide derivatives. Some nitriles, e.g. *p*-tolunitrile and naphthonitrile, give hardly any thioamide under these conditions. A by-product in the preparation of thiobenzamide was dibenzimidoyl sulphide $C_6H_5C(:NH)SC(:NH)C_6H_5$, which is formed in good yield when benzonitrile is treated with thioacetic acid. Thiobenzoic acid gives less by-products than does thioacetic acid.

When thioacetic acid is used, an *N*-acetylthioamide may be formed as a by-product, probably by isomerisation of an intermediate product[137–139]:

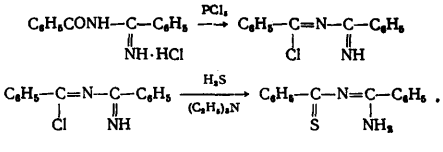


This rearrangement can be avoided by conducting the process at room temperature.

A somewhat similar method is the reaction of amides with phosphorus pentachloride and hydrogen sulphide in an inert solvent[81,140,141], in which thioamides are formed. Imidoyl chlorides are also formed as intermediates in this case:

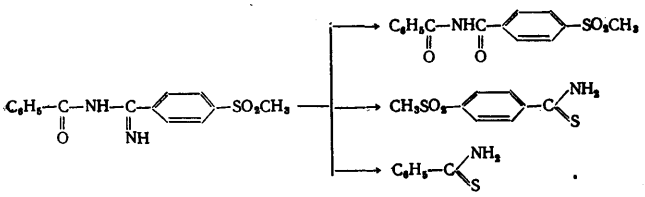


When amides containing hydroxy- and amino-groups are used, these groups are protected by treatment with toluenesulphonyl chloride. This method has been used for the preparation of thiophenacetin *p*-$C_2H_5OC_6H_4NHCSCH_3$, *p*-acetylthioacetanisidine *p*-$CH_3COC_6H_4NHCSCH_3$, *p*-phenylene-*NN'*-bisthioacetamide *p*-$CH_3CSNHC_6H_4NHCSCH_3$, and thioacetamide–trimethylpyrogallol. *N*-Thiobenzoylbenzamidine has been prepared from *N*-benzoylbenzamidine[81]:

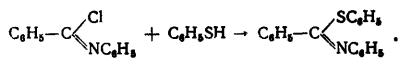


N-Thiobenzoylanisoylamidine and *N*-thiobenzoyl-*p*-chlorobenzamidine have been obtained in the same way, in yields of 48% and 26% respectively[81]. However, three products

were obtained from *N*-benzoyl-*p*-methylsulphonylbenzamidine, owing to cleavage and hydrolysis:

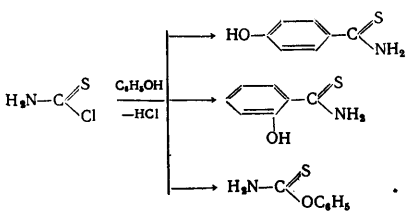


The action of arenethiols on imidoyl chlorides yields isothioamides (thiolimidic esters):



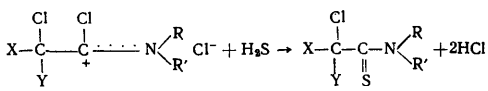
p-Tolyl *N*-*p*-tolylthiobenzimidate has been obtained from *N*-*p*-tolylbenzimidoyl chloride and toluene-*p*-thiol[141].

In several cases thiocarbamoyl chlorides are used for the synthesis of such compounds. Thus the reaction of thiocarbamoyl chloride with phenol has yielded thiosalicylamide, *p*-hydroxythiobenzamide, and phenyl thiocarbamate[141]:

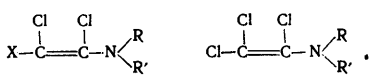


Analogous methods have been used to obtain *N*-thioacylthiocarbanilic esters[142], di-imidoyl sulphides[143,144], and several other derivatives[145].

The reaction of imidoyl chlorides with hydrogen sulphide in many cases enables thioamides to be obtained which are difficultly accessible by other methods. Thus α-chlorothioacetamides are obtained from α-chloroiminium chlorides and hydrogen sulphide[146]:

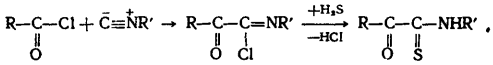


Iminium chlorides have been obtained by the addition of hydrogen chloride to 1,2-dichloro- and 1,2,2-trichlorovinylamines:



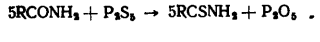
The iminium chlorides used for the preparation of trichlorothioacetamide were formed by the addition of chlorine to the above chlorovinylamines. Iminium chlorides are prepared also by the action of carbonyl chloride on *NN*-disubstituted amides of carboxylic acids.

Difficultly accessible *N*-substituted α-oxothioamides have also been prepared by the reaction of imidoyl chlorides[147,148]:



5. PREPARATION OF THIOAMIDES BY THE REACTION OF AMIDES WITH PHOSPHORUS PENTASULPHIDE

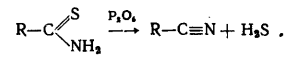
The interaction of amides of carboxylic acids with phosphorus pentasulphide involves exchange of oxygen for sulphur with formation of thioamides:



This method, first proposed in 1878, is among the most frequently used for obtaining unsubstituted and substituted thioamides[149,150]. In the latter case substituted amides must be taken:

where R, R′ = H, Alk, Ar.

When unsubstituted amides are used, nitriles are obtained as by-products, pr bably owing to decomposition of the resulting thioamide under the influence of phosphorus pentoxide[151,152]:

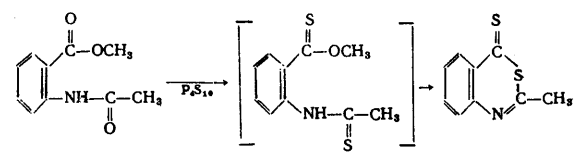


This side-reaction is sometimes so rapid that the amide is converted—not into the thioamide—but into a good yield of the nitrile[153]. Side-reactions go less vigorously with secondary[48,153-156] and tertiary[73] amides; aromatic amides react more smoothly than do aliphatic amides.

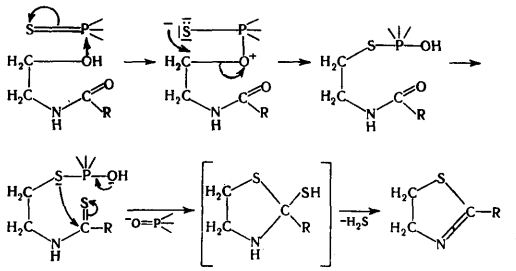
Various thioamides have been obtained by this method[157-179]. The process is conducted with heating, mostly in benzene, toluene, xylene, and tetralin; tetrahydrofuran, dioxan, and other ethers are also used as solvents. The reactions between phosphorus pentasulphide and amides are very rapid, being complete in a few minutes[150].

If the reaction between an amide and phosphorus pentasulphide is conducted in the presence of a primary or a secondary amine, *N*-mono- and *NN*-di-substituted thioamides can be obtained under suitable conditions. In this way *N*-substituted and *NN*-di-substituted thioformamides have been obtained by a one-stage process[180].

Depending on the amount of phosphorus pentasulphide taken, diamides can yield either mono- or bis-thioamides. For example, with a molar ratio of 2,4-diacetamidotoluene to phosphorus pentasulphide of ~ 2 : 1 a mixture of mono- and bis-thioamides (7 : 2) is formed[181]. Similarly, *N*-phenyloxamide yields the corresponding monothio- and dithio-compounds $C_6H_5NHCOCSNH_2$ and $C_6H_5NHCSCSNH_2$,[154] where further treatment of the former compound with phosphorus pentasulphide converts it into the latter, *N*-phenyldithio-oxamide. Oxanilides $C_6H_5NHCOCONHC_6H_5$ behave in the same way. The preparation of ethyl thio-oxanilate $C_6H_5NHCSCOOC_2H_5$ showed that the ester group does not influence the results of the reaction[154,182,183]. An exception to this rule is the reaction of methyl *N*-acetylanthranilate with phosphorus pentasulphide, accompanied by replacement of oxygen by sulphur in both amide and ester groups with cyclisation of the product to 3,4-dihydro-2-methylbenzo-3,1-thiazine-4-thione:

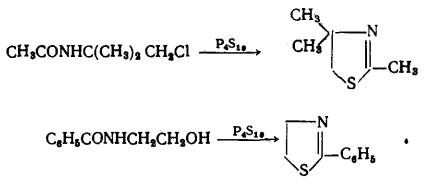


Formation of a thiazoline by the action of phosphorus pentasulphide of an *N*-2-hydroxyethylbenzamide is represented by the scheme[184,185]



The yield of thioamides obtained by treating substituted benzamides with phosphorus pentasulphide is greatly affected by the nature of the substituents. Thus treatment of *m*- and *p*-nitrobenzanilides with phosphorus pentasulphide in boiling xylene gives 70–90% yields of the corresponding thioamides; under the same conditions the aminobenzanilides form thioamides in only 5% yield[169]. Similar results were obtained in toluene, reaction being rapid with the nitro-derivatives and slow with the amino-derivatives. No thioamide is formed when *pp'*-dinitrooxanilide is treated with phosphorus pentasulphide in xylene for 7 h, the nitro-groups undergoing reduction to amino-groups[186]. However, no systematic study has yet been made of the influence of substituents on the yield of thioamides.

The reaction of phosphorus pentasulphide with certain *N*-substituted amides (containing a functional group in the β-position with respect to the nitrogen atom) is sometimes accompanied by cyclisation[184,187]:



In this example formation of 2-phenylthiazole is accompanied by that of a cystamine derivative $(C_6H_5CONHCH_2CH_2S)_2$.[184]

With hydantoins phosphorus pentasulphide yields thiohydantoins, whose specific action is weaker and less prolonged than that of the corresponding derivatives of barbituric acid[188].

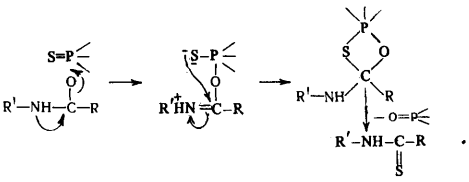
The yield of thioamides obtained from amides and phosphorus pentasulphide is appreciably increased by the presence of oxides or carbonates of alkaline-earth metals[189]; potassium sulphide also has a favourable effect[165]. In the latter case a suspension or a solution of the amide in xylene was treated with the carefully mixed finely ground phosphorus pentasulphide and potassium sulphide in amounts sufficient for the formation of potassium thiophosphate: $P_2S_5 + 3K_2S \rightarrow 2K_3PS_4$ (sometimes a slight excess of potassium sulphide is taken). This reaction goes especially well in pyridine[190].

In order to eliminate the inconvenience of working with a mixture of two solids (potassium sulphide and phosphorus pentasulphide), amides were treated with salts of thiophosphoric acid, this method giving yields of ~ 80% of thioacetamide[191,192]. An 80% yield of thioacetamide was also obtained by treating acetamide with a mixture of phosphorus pentasulphide and potassium sulphide (in the molar ratio: 1.5 : 5).[103]

The yield of thioamides depends on the nature of the initial amide. For example, treatment of acetamide in benzene with a mixture of phosphorus pentasulphide and potassium sulphide gave an 80% yield of thioacetamide, whereas the yield of isovaleramide was 0.4% (the main product being the nitrile).[103]

Thioamides can be obtained by the action of phosphorus pentasulphide on amides also in the absence of solvents[149,153–156,162–164]. In this case equimolecular quantities of the amide and phosphorus pentasulphide are melted together, and the thioamide is extracted from the resulting resinous mass with a suitable solvent. The yield of thioformamide prepared in this way is ~ 50%.[121]

The mechanism of the interaction of amides with phosphorus pentasulphide has not been established exactly. The reaction is presumably represented by the scheme[193]



6. PREPARATION OF THIOAMIDES BY REACTION WITH ALUMINIUM AND IRON SULPHIDES

Thioamides are formed by the action of aluminium sulphide on amides, nitriles, and ammonium salts[194–196], 1 or 2 moles of water being added to the mixture when an amide or a nitrile is used. This is usually added as water of crystallisation (e.g. $Na_2SO_4.6H_2O$). The process is conducted in a sealed tube or an autocalve at 200–250°C for ~ 90 min. When ammonium salts are used, water is not required.

Aromatic and aliphatic thioamides are obtained in good yields by this method[194].

Sulphides of other metals, e.g. iron, can be used instead of aluminium sulphide[195].

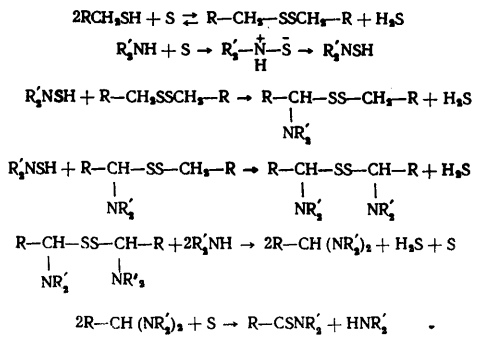
7. PREPARATION OF THIOAMIDES BY THE WILLGERODT–KINDLER REACTION

There exist several modifications of this method for obtaining thioamides—(*a*) reaction of sulphur with ketones or aldehydes in the presence of an equimolecular quantity of an amine[165,197–200], (*b*) direct oxidation of the amine by sulphur[201,202], and (*c*) interaction of sulphur with an alkyne and ammonia[203,206]—these three variants being included under the combined term the Willgerodt–Kindler reaction[207–227].

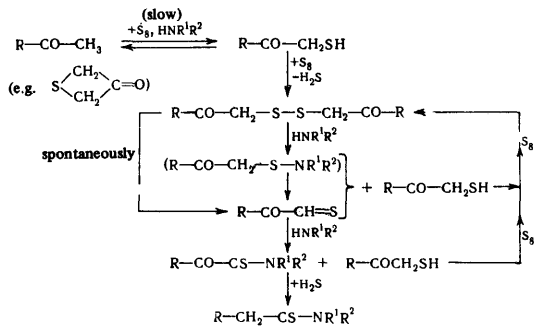
Several reviews have been devoted to this reaction[207–209,228,229], and special papers have been published on its mechanism[209,230–232]. However, the mechanism of the Willgerodt reaction is still not clear. Thiols are probably formed as intermediates, and are converted into thioamides[228]:

$$RCOCH_3 \rightarrow R{-}CH_2CH_2SH \rightarrow R{-}CH_2CSNR'_2 .$$

The conversion of thiols into thioamides takes place when both sulphur and an amine are present. The formation of thioamides is represented by the scheme



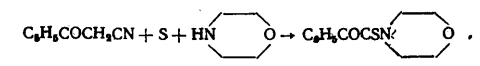
A rather different assessment of the mechanism of the Willgerodt–Kindler reaction has recently been expressed[224] in connection with an investigation of the formation of a thioamide from 3-oxothietan, a secondary amine, and sulphur:



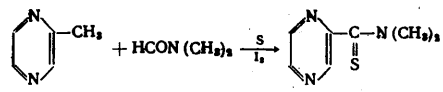
where R = CH_3. According to this scheme the reaction begins with formation of an α-mercapto-ketone, this being the rate-determining stage. The disulphide, which is formed very readily, passes via the oxosulphenamide into an oxo-thial. In the presence of an amine the oxo-thial undergoes disproportionation by the Cannizzaro reaction with formation of the α-mercapto-ketone and an α-oxo-thioamide, the latter then being reduced to the required thioamide.

There are also other interpretations of the mechanism of the Willgerodt–Kindler reaction. In this connection the view of several authors[165,182] must be accepted, that this reaction, which is characterised by a great variety of starting materials and process conditions, does not fit into a single mechanism.

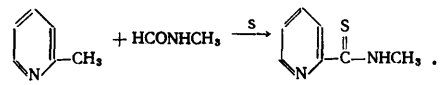
NN-Disubstituted thioamides can be obtained in good yield from aromatic aldehydes[212]. Under the conditions of this reaction diketones are reduced to monoketones, which then give thioamides[215]. α-Cyano-ketones form α-oxo-thioamides with loss of one carbon atom[216]:



Variants of the Willgerodt–Kindler reaction have been described in which certain heterocyclic compounds, dimethylformamide, and iodine are involved in the reaction[209,217,218]. Thus the *NN*-dimethylthioamide of pyrazine has been obtained from methylpyrazine, dimethylformamide, and sulphur in the presence of iodine[219]:

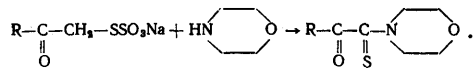


while the use of 2-methylpyridine and methylformamide yields *N'*-methylpyridine-2-thioamide[220]:



In this way quinaldine is converted into quinoline-2-thioamide. The reaction does not take place when anthranilic acid, *o*-aminophenol, sulphanilic acid, 2-aminothiazole, 2-amino-1,3,4-thiadiazole, or 2-aminopyridine is used as the amine component[221].

S-Acylmethyl thiosulphates form with amines good yields of *NN*-disubstituted α-oxo-thioamides[233,234]:



It has since proved possible to bring into reaction with sulphur secondary and tertiary alcohols, thiols, disulphides, imines, alkenes[206], diazo-ketones[200], Schiff bases[210], and also $\alpha\beta$-unsaturated acids[232] (in the last case thioamides are obtained having one carbon atom less than in the initial acid)[235–242].

Thioamides are formed when amines are heated with sulphur even in the absence of carbonyl compounds[210,243–253]. Heating benzylamine with sulphur in a sealed tube at 180°C gives a 91% yield of thiobenzamide:

$$C_6H_5CH_2NH_2 + S_2 \rightarrow C_6H_5CSNH_2 + H_2S\ .$$

Copious evolution of ammonia occurs when this reaction is conducted in an open vessel[207]:

$$2C_6H_5CH_2NH_2 \rightleftarrows C_6H_5CH_2NH{-}CH_2C_6H_5 + NH_3$$

$$C_6H_5CSNH_2 + C_6H_5CH_2NH_2 \rightleftarrows C_6H_5CSNHCH_2C_6H_5 + NH_3\ .$$

The interaction of benzylamine, sulphur, and lead monoxide in benzene at 20°C gives bisthiobenzamido-disulphide:

$$2C_6H_5CH_2NH_2 + 5S \rightarrow (C_6H_5CSNHS{-})_2 + 3H_2S\ .$$

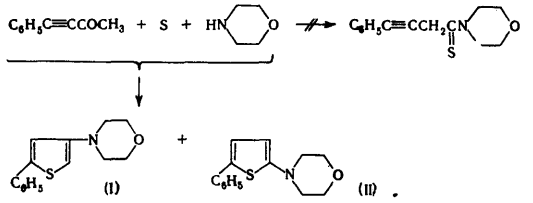
A modification of the Willgerodt–Kindler reaction in which an enamine is one of the components is of practical interest, the process being conducted in a polar solvent at room temperature. Thioamides in yields of ~ 75% are formed[222,223]:

$$R_1{-}C(NR_2){=}CH_2 \xrightarrow{S} R_1{-}CH_2{-}CSNR_2\ .$$

Thioamides are formed by the action of sulphur on unsaturated hydrocarbons in the presence of ammonia or an amine. The reactions are conducted in dry solvents at 50–300°C, gaseous ammonia or a low-boiling amine (e.g. methylamine) being used under pressure. In this way the interaction of acetylene, sulphur, and ammonia (or an amine) in dioxan or pyridine at 50–100°C has been applied to the preparation of thioacetamide[249], dithio-oxamides, and other thioamides[203,204,250–253].

The interaction of styrene and sulphur in the presence of morpholine gives a 52% yield of phenylthioacetomorpholide[190], whereas in the presence of benzylamine the main product is phenylacetic acid contaminated by *N*-benzylthiobenzamide. Phenylthioacetomorpholide is obtained in 20% yield also by the action of sulphur on phenylacetylene and morpholine[232,254].

It has recently been shown that acetylenic ketones do not yield thioamides—as has hitherto been supposed—but isomeric thiophen derivatives[211]:



The ratio of the isomers (I) and (II) thus obtained is 9 : 1.

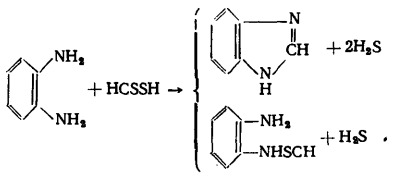
8. PREPARATION OF THIOAMIDES BY THE THIOACYLATION OF AMINES

The thioacylation—analogous to acylation—of amines often results in the formation of thioamides in very good yields. Carbodithioic acids[255-257], their salts[258-264], esters, and chlorides, as well as *O*-esters of carbothionic acids[261 265-268], are used as thioacylating agents. Depending on the reagent used, hydrogen sulphide, thiols, hydrogen chloride, and alcohols are also isolated in this reaction. The amines used are ammonia and primary and secondary amines.

An example of thioacylation by means of thiocarbonyl chlorides is the reaction of thiobenzoyl chloride with aniline to form thiobenzanilide[269]. This method is of no practical value because of the relative inaccessibility of thiocarbonyl chlorides[270]. Carbodithioic acids and their salts are used considerably more often‡. For example, sodium cyanodithioformate, obtained from carbon disulphide and sodium cyanide, gives with diethylamine and dimethylamine the *NN*-dialkylamides of cyanothioformic acid[273].

Potassium dithioformate‡ reacts with an aqueous solution of an amine at room temperature to form an *N*-substituted thioformamide; with water-insoluble amines the reaction is conducted in organic solvents (ether, chloroform, dioxan[262,274]). The yield of thioformamide obtained by the action of ammonia on dithioformic acid reached 30%, higher than in its preparation from formamide and phosphorus pentasulphide[262]. Aniline and 6-aminoquinoline give the corresponding substituted thioformamides in theoretical yields. The reaction does not take place with indole, diphenylamine, or *N*-methylaniline[262].

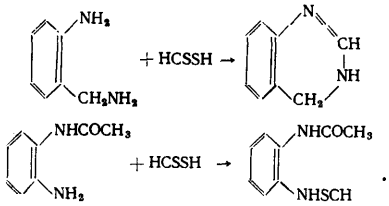
Diamines form with carbothioic acids unstable compounds, which readily undergo cyclisation. Thus *o*-phenylenediamine in aqueous solution at 10°C gives an unstable product, which at room temperature is rapidly converted into benzimidazole[262], though other results indicate that *N*-*o*-aminophenylthioformamide is produced in this case[271,272]:



‡The preparation of the initial carbodithioic acids and their derivatives has been studied in very great detail[228, 229,271,272].

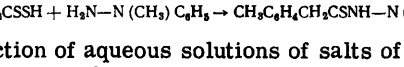
Cyclisation does not occur when dithioformic acids act on 4,5-diamino-6-methylpyrimidine[262] or on 4-amino-5-aminomethyl-2-methylpyrimidine[275-277], because of the feebly basic character of the amino-groups in the starting materials.

o-Aminobenzylamine and *o*-aminoacetanilide with dithioformic acid give quantitative yields of dihydrobenzopyrimidine and stable *N*-*o*-thioformamidoacetanilide[262]:

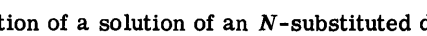


5-Thioacylpyrimidines, which are not formed from 5-acylpyrimidines and phosphorus pentasulphide, are easily obtained by this method[262,274-291].

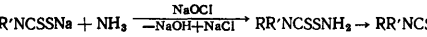
m-Tolyldithioacetic acid forms with 1-methyl-1-phenylhydrazine the corresponding hydrazide[292]:



By the action of aqueous solutions of salts of dithioacids on amines in the presence of an aqueous solution of iodine and potassium iodide *N*-substituted thioamides are formed in yields of 95–100%.[258,293] It is supposed that thioacylsulphenamides are formed initially, and split off sulphur to give the thioamides:



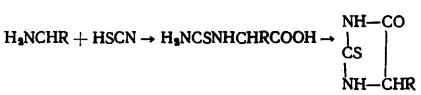
Thus addition of a solution of an *N*-substituted dithiocarbamate and iodine or 10% sodium hypochlorite solution (in equimolecular quantities) to excess of concentrated ammonia produces an *NN*-dialkylthioacylsulphenamide, which on prolonged standing or on heating passes into an *N*-substituted thiourea[294]:



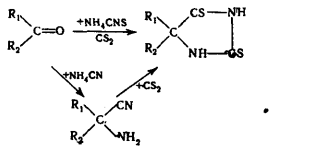
N-Chloropiperidine gives with salts of dithio-acids a quantitative yield of *N*-2′-thiofuroylpiperidine and *N*-thiobenzoylpiperidine. Here, too, sulphenamides are probably formed as intermediates[258,295].

Carbodithioic esters[255,256,296] are often used for the thioacylation of amino-acids[229,255,297-299]§ and the synthesis of purine derivatives[286], vitamin B_1,[274] and other biologically active substances. Equimolecular quantities of carboxymethyl dithiobenzoate and aminoacetic acid interact in

§Amino-acids are thioacylated also by the action of ammonium or potassium thiocyanate in acetic anhydride at 60–80°C, 1-acetyl-2-thiohydantoins being formed, from which the free 2-thiohydantoins can be isolated by the action of excess of concentrated hydrochloric acid[300]:



where R = H or CH_3. Ammonium thiocyanate acts on ketones in carbon disulphide to form dithiohydantoins[301,302]:



an aqueous solution of a base at room temperature to give a 90% yield of thiobenzoylglycine[299]:

$$C_6H_5CSSCH_2COOH + H_2NCH_2COOH \rightarrow C_6H_5CSNHCH_2COOH .$$

Similarly, the interaction of carboxymethyl dithiobenzoate and anthranilic acid gives a good yield of thiobenzoylanthranilic acid[299].

DL-Lysine interacts with carboxymethyl phenyldithioacetate to give a monoacylated derivative, probably $C_6H_5CH_2CSNH[CH_2]_4CH(NH_2)COOH$ (the product gives a positive ninhydrin reaction¶). No racemisation was observed in the thiobenzoylation of the L-stereoisomers of alanine, valine, isoleucine, and leucine[256]. Diethyl aminomalonate is more conveniently thiobenzoylated in pyridine to which triethylamine has been added[297]. The thiobenzylation of diamines gives good yields of polymethylenebisthiobenzamides $C_6H_5CSNH[CH_2]_xNHCSC_6H_5$ (x = 1–6). An α-aminoisobutyrate does not undergo thiobenzoylation, probably owing to steric hindrance[255,256].

Carboxymethyl dithioacetate as thioacylating agent is added in excess (10%) to a solution of the sodium salt of the amino-acid in alcohol[303-305]. N-2-Arylethylthioamides $RCSNHCH_2CH_2C_6H_5$ have been obtained by this method in yields of 86–99%.[306]

Thiobenzamides are formed in good yields by the reaction of dithioic esters with morpholine and with aniline[256]. Carbothionic esters RCSOR′ react similarly with amines[256,307,308]. In this way a phenylthiohydrazide has been obtained from phenylhydrazine and a carbothionic ester[263], the reaction being conducted in ether or excess of phenylhydrazine. The interaction of ethyl thiobenzoate with excess of 2-aminoethanol and isopropylamine respectively has given N-2-hydroxyethylthiobenzamide and N-isopropylthiobenzamide in yields of 53% and 63%.[261]

Good thioacylation results have been obtained by the interaction of carbothionic esters with substituted anilinomagnesium bromides[309,310]:

$$RO{-}C_6H_4{-}CS{-}OC_2H_5 + BrMgNHC_6H_4OR' \rightarrow RO{-}C_6H_4CS{-}NHC_6H_4OR' + C_2H_5OMgBr.$$

A convenient thioacylating reagent is a thioacylsuccimide, obtained in good yield by reaction of an aromatic unsubstituted thioamide with succinyl chloride[311]:

$$ArCSNH_2 + ClCOCH_2CH_2COCl \rightarrow ArCS{-}N\begin{matrix}CO{-}CH_2\\ |\\ CO{-}CH_2\end{matrix}$$

Unsubstituted thioamides are also thioacylating agents. Under mild conditions they undergo transamidation with primary aliphatic amines to form N-alkylated thioamides. This has been termed the Wallach reaction[312]. Several derivatives of dithio-oxamide have been obtained in this way, the two unsubstituted thiocarbamoyl groups being involved in the reaction[313]:

$$2R{-}CH_2{-}NH_2 + H_2N{-}CS{-}CS{-}NH_2 \rightarrow R{-}CH_2{-}NH{-}CS{-}CS{-}NH{-}CH_2{-}R + 2NH_3$$

where R = COOH, SO_3H. Only the thiocarbamoyl group is involved in the reaction of monothio-oxamide with aliphatic amines[143,312]. Morpholine reacts with dithio-oxamide to give N-morpholinodithio-oxamide[44,313], and other thio-oxamides have recently been obtained by this method[314]. Amino-acids also can be thioacylated with dithio-oxamide[315]. NN-Dimethylthioformamide gives amidines with amines[316].

Substituted thioformamides are obtained in good yield by the interaction of chloroform, an amine, and hydrogen sulphide in alkaline solution[317]. It is assumed that dichlorocarbene is formed initially from the chloroform (by α-elimination), and then reacts according to the equation

$$:CCl_2 + R'R''NH + 2SH^- \rightarrow R'R''N{-}CSH + H_2S + 2Cl^- .$$

¶ Boiling amino-acids with an aqueous solution of ninhydrin (indane-1,2,3-trione hydrate) produces a blue coloration.

9. PREPARATION OF THIOAMIDES BY THE REACTION OF ISOTHIOCYANATES WITH ORGANOMETALLIC COMPOUNDS, C–H ACIDS, AND ENAMINES

These reactions are employed considerably more rarely than those considered earlier for the preparation of thioamides. They are based on the addition of nucleophilic reagents at the multiple bond in an isothiocyanate, and in this respect show great similarity to the corresponding reactions of isocyanates:

$$R{-}\overset{\delta+}{N}{=}\overset{\delta-}{C}{=}\overset{\delta-}{S} + R'{-}\overset{\delta+}{X} \rightarrow R{-}N{=}\underset{R'}{\overset{|}{C}}{-}SX \xrightarrow[-OHX]{H_2O} R{-}NHC{=}\underset{R'}{\overset{|}{S}}$$

where X = M, H. The symbol X denotes a metal when an organometallic compound[318-333] or a C–H acid in the form of its sodium or lithium salt is used, and hydrogen in the case of an enamine.

The reaction between isothiocyanates and organometallic compounds was first studied by the use of Grignard reagents. Thioamides are obtained in good yield by the action of Grignard reagents on phenyl isothiocyanate followed by hydrolysis of the addition products[258,318-320]:

$$C_6H_5N{=}C{=}S + CH_3MgI \rightarrow C_6H_5N{=}C(CH_3){-}S{-}MgI \rightarrow C_6H_5NHCSCH_3 .$$

The action of dimethyl sulphate on the addition product of phenylmagnesium bromide and phenyl isothiocyanate gave an S-methyl derivative of an isothioamide[321]:

$$C_6H_5{-}N{=}C(C_6H_5){-}S{-}MgBr + (CH_3O)_2SO_2 \rightarrow C_6H_5N{=}C(C_6H_5)SCH_3 .$$

N-Substituted thioamides of valeric acid were obtained in 90% yield by the reaction of n-butylmagnesium bromide with isothiocyanates[322]. Phenylmagnesium bromide reacts with phenyl isothiocyanate to give thiobenzamide in 88% yield[288].

Isothiocyanates react with excess of a Grignard reagent at high temperatures to give other products. Thus a 45% yield of o-phenyldiphenylmethylaniline was obtained from phenyl isothiocyanate and phenylmagnesium bromide[323].

Bifunctional thioamides are formed by the interaction of sodium alkyls with phenyl isothiocyanate[325-328]:

$$\overset{\delta-\ \delta+}{RCH_2Na} + C_6H_5N{=}\overset{\delta+\ \delta-}{C{=}S} \rightarrow RCH_2\underset{NC_6H_5}{\overset{\|}{C}}SNa \xrightarrow[-H]{+Na}$$

$$\rightarrow \underset{\delta+\ \ \ \ \delta+}{\overset{\delta-}{RCH}}{-}\underset{Na\quad NC_6H_5}{\overset{\|}{C}}{-}SNa \xrightarrow{C_6H_5N=C=S} \underset{\ \ \ \ \

Organolithium compounds also can be used as the organometallic compounds. Thus 3-methyl-2,2-diphenylbut-3-enothioanilide was isolated after reaction with phenyl isothiocyanate of the organolithium compound obtained from the corresponding alkene and lithium[327], a 57% yield of thiobenzamide after reaction with triphenylsilyl isothiocyanate[329], and *N*-phenylthiobenzamide when phenyl isothiocyanate was used [with phenyl-lithium][330]:

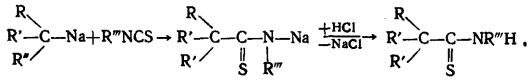
$$C_6H_5Li + C_6H_5NCS \rightarrow C_6H_5N(Li)CSC_6H_5 \xrightarrow{H_2O} C_6H_5NHCSC_6H_5 + LiOH .$$

Triethylaluminium (or a mixture of ethylaluminium dichloride and diethylaluminium chloride) gives with aliphatic and aromatic isothiocyanates a series of thioamides of propionic acid in yields of 58–96%.[331,332]

Phenyl isothiocyanate reacts with sodium tetrahydroborate to form thioformanilide[333,335]:

$$C_6H_5N{=}C{=}S + NaBH_4 \rightarrow [C_6H_5{-}NHCS{-}BH_3Na] \xrightarrow{H^+} C_6H_5NH{-}\underset{\underset{S}{\|}}{C}{-}H .$$

Isothiocyanates react with C–H acids in practically the same way as with organomagnesium compounds, since these acids are usually employed in the form of their alkali-metal salts[324,336–350]:



Triphenylmethylsodium reacts with isothiocyanates, e.g. with allyl isothiocyanate to form *N*-allyltriphenylthioacetamide[328].

Sodiomalonic ester gives with *p*-phenylene di-isothiocyanate in absolute alcohol the sodium salts of mono- and di-addition products, from which acidification yields diethyl *N*-*p*-isothiocyanatophenylthiocarbamoylmalonate (*a*) and tetraethyl *p*-phenylene-*NN'*-bisthiocarbamoylmalonate (*b*):[348]

$$S{=}C{=}N{-}C_6H_4{-}NH{-}CS{-}CH(COOC_2H_5)_2 \qquad (a)$$

$$(C_2H_5OCO)_2CH{-}CS{-}NHC_6H_4NH{-}CS{-}CH(COOC_2H_5)_2 . \qquad (b)$$

Sodioacetoacetic ester forms only the monoaddition product, which breaks down in alcoholic solution at room temperature into ethyl acetate and ethyl *N*-*p*-isothiocyanatophenylthiocarbamoylacetate[349,350]:

$$S{=}C{=}N{-}C_6H_4NHCS{-}\underset{\underset{COOC_2H_5}{\diagdown}}{\overset{\overset{COCH_3}{\diagup}}{C}}{-}H \rightarrow S{=}C{=}N{-}C_6H_4NHCS{-}CH_2COOC_2H_5 + CH_3COOC_2H_5 .$$

Sodium acetylacetonate reacts with aryl isothiocyanates in absolute alcohol to form *NN'*-diarylated bisthioamides of malonic acid[349].

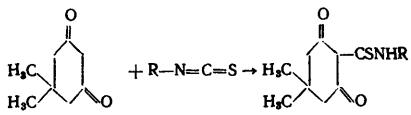
The sodium salt of acetylthioacetanilide reacts with phenyl isothiocyanate to give the dianilide of acetylmalonodithionic acid[350]:

$$CH_3{-}\underset{\underset{O}{\|}}{C}{-}\underset{\underset{Na}{|}}{\overset{\overset{-}{}}{CH}}{-}\underset{\underset{S}{\|}}{C}{-}NHC_6H_5 + C_6H_5N{=}C{=}S \rightarrow CH_3{-}\underset{\underset{O}{\|}}{C}{-}\underset{\underset{CSNHC_6H_5}{\diagdown}}{\overset{\overset{CSNHC_6H_5}{\diagup}}{C}}{-}H .$$

Other derivatives of malonodithionic acid have been obtained by using substituted phenyl isothiocyanates under the same conditions.

Cyclic C–H acids also react with isothiocyanates to form thioamides. In this way good yields of variously substituted anilides of pyrrolecarbothionic acid have been obtained by the use of pyrrole[351].

The addition of isothiocyanates to dimedone in acetonitrile in the presence of a small amount of alkali[352] leads to the formation of a thioamide in 60% yield:

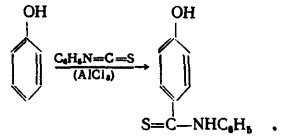


where R = C_6H_5, *p*-ClC_6H_4, *p*-$NO_2C_6H_4$, 1-naphthyl. The reaction does not take place in ethanol[353].

Alkali-metal cyanides give with isothiocyanates *N*-substituted cyanothioformamides, which react with hydrogen sulphide to produce *N*-substituted dithio-oxamides[354]. The best yields of thioamides are obtained with potassium cyanide:

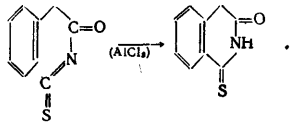
$$KCN + R{-}NHCS \rightarrow R{-}NHCSCN \xrightarrow{H_2S} R{-}NH{-}CS{-}CS{-}NH_2 .$$

Alkoxyphenyl isothiocyanates form with sodium cyanide alkoxylated cyanothioformamides, which are converted by hydrogen sulphide into alkoxyphenyldithio-oxanides[355]. Isothiocyanates react with phenols in the presence of aluminium chloride[356–359], with the formation not of thioneurethanes but of thioamides:



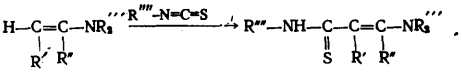
Thioamides are formed with phenyl ethers (and also ethyl phenyl sulphide) and phenyl isothiocyanate[360].

In the presence of aluminium chloride phenylacetyl isothiocyanate undergoes intramolecular rearrangement to give a 40–70% yield of homomonothiophthalamide[361]:

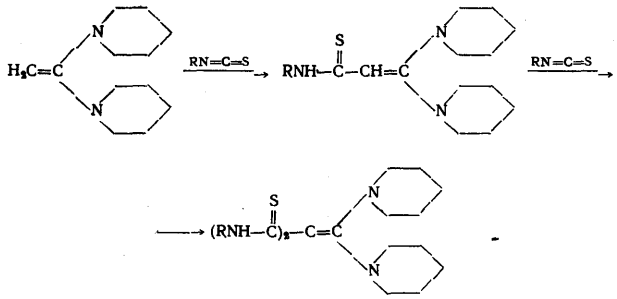


Isothiocyanates react in the presence of aluminium chloride also with aromatic hydrocarbons[362].

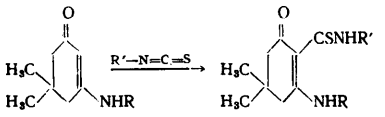
Enamines react with aryl isothiocyanates to form amides of β-aminocycloalkenecarbothioic acids, which are readily saponified to thioamides of β-oxo-carboxylic acids[363–365]:



The enamine of 1,1-dipiperid-1'-ylethylene adds two isothiocyanate molecules[366]:

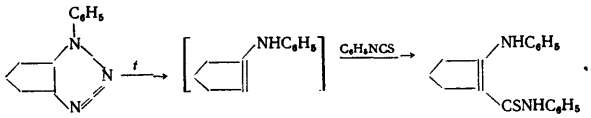


where R = Ar, Alk. Cyclic enamines also react with isothiocyanates[352]:



where R = H, CH_3 and R′ = C_6H_5, p-ClC_6H_4, p-$NO_2C_6H_4$.

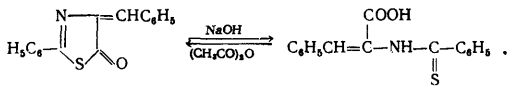
Substituted Δ^1-triazoles react with isothiocyanates to form thioamides (yield 50–99%):[367–370]



10. PREPARATION OF THIOAMIDES BY THE CLEAVAGE OF HETEROCYCLES

Certain heterocyclic compounds (derivatives of thiazole and oxazole) can undergo cleavage under the influence of alkaline reagents or hydrogen sulphide, thioamides being formed[371–374].

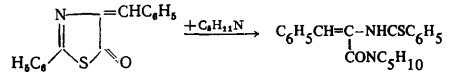
When 4-benzylidene-2-phenylthiazol-5-one is boiled with dilute caustic soda, α-thiobenzamidocinnamic acid $C_6H_5CH{:}C(NHCSC_6H_5)COOH$ is formed[371]. This reaction is reversible, heating the resulting substituted cinnamic acid with acetic anhydride giving an 85% yield of the original thiazolone[371]:



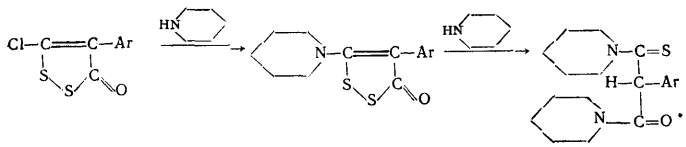
The original 4-benzylidene-2-phenylthiazol-5-one was prepared by the reaction of 4-benzylidene-2-phenyloxazol-5-one with thioacetic acid[371]:



Heating this thiazolone with piperidine gives an N-piperidyl derivative of α-thiobenzamidocinnamic acid in 60% yield:

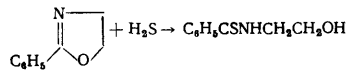


Mixed thioamide–amides of arylmalonic acids are obtained by the action of amines on 4-aryl-3-chloro-5-keto-1,2-dithioles[373]:

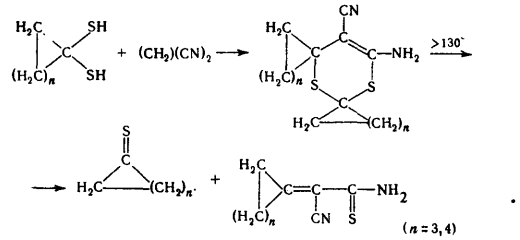


Similarly, N-α-thiobenzamidodihydrocinnamoylpiperidine is obtained from 4-benzyl-2-phenylthiazolone.

Thioamides are formed also by the cleavage of oxazolines by hydrogen sulphide. Treatment of a solution of 2-phenyloxazoline in methanol with ammonium sulphide (or ammonium hydroxide and hydrogen sulphide) gave N-2-hydroxyethylthiobenzamide (yield 77%):[261]

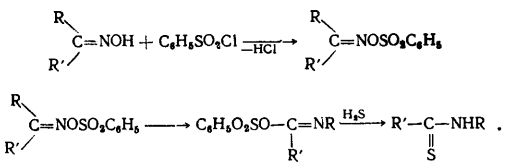


Substituted 1,3-dithi-ins, formed from *gem*-dithiols and malononitrile, when heated decompose into thioketones and thioamides[374]:



11. CONVERSION OF BENZENESULPHONATES OF KETOOXIMES INTO THIOAMIDES

Benzenesulphonates of ketoximes, formed by the action of benzenesulphonyl chloride on the ketoximes in pyridine, are converted in the presence of hydrogen sulphide, as a result of spontaneous Beckmann rearrangement into sulphonimidates, into good yields of N-substituted thioamides[375–378]:



A great variety of thioamides have been obtained by this method using aliphatic, cyclic, aromatic, and mixed ketoximes.

REFERENCES

1. J. Sübel, Erz, Kohle, Flotation, 26, 243, 938 (1956).
2. S. R. Zimmerley and M. W. Wilson, U. S. P. 2724500 (1955); Chem. Abs., 50, 3188 (1956).
3. Austrian P. 208 672 (1959); Chem. Zentr., 1962, 4711
4. A. W. Ralston, U. S. P. 2 168 848 (1939); Chem. Zentr., I, 1605 (1940).
5. French P. 1 235 348 (1960); Chem. Zentr., 6202 (1962).
6. French P. 1 232 597 (1960); Chem. Zentr., 6203 (1962).
7. J. F. L. Childs and E. A. Siegler, Science, 102, 68 (1945).
8. J. F. L. Childs and E. A. Siegler, Ind. Eng. Chem., 38, 82 (1946).
9. C. D. Cothran, U. S. P. 2 604 409 (1952); Chem. Abs., 46, 1503b (1952).
10. M. A. McCall, U. S. P. 3 068 274 (1962); Chem. Abs., 58, 8914 (1963).
11. B. P. 340 319 (1929); Chem. Zentr., II, 1372 (1931).
12. F. E. Denny, U. S. P. 2 093 865 (1937); Chem. Zentr., I, 209 (1938).
13. F. A. V. Sullivan and S. A. J. Westerback, U. S. P. 2 875 202 (1959); Chem. Abs., 53, 14122 (1959).
14. W. W. Wirth, U. S. P. 2 688 014 (1954); Chem. Abs., 50, 1076 (1956).
15. K. W. Powers and S. B. Robinson, U. S. P. 3 035 029 (1956); Chem. Abs., 57, 11358 (1962).

16. A. W. Lewis, U. S. P. 2 230 691 (1941); Chem. Abs., 35, 3810⁷ (1941).
17. A. W. Lewis and E. W. Cock, U. S. P. 2 139 086, 2 139 087, 2 139 088 (1936); 2 139 725, 2 139 725 [?], 2 139 758 (1937); Chem. Zentr., I, 4865 (1939).
18. F. E. Cislak, U. S. P. 2 891 958 (1959); Chem. Zentr., 10995 (1962).
19. R. A. Naplor and E. O. Hook, U. S. P. 2 723 969 (1955); Chem. Abs., 50, 4548 (1956).
20. Belgian P. 612 252 (1962); Chem. Abs., 58, 3362 (1963).
21. Belgian P. 626 788 (1963); Chem. Abs., 60, 6795 (1964).
22. J. Yates and S. E. Callander, U. S. P. 955 492 (1964); Chem. Abs., 61, 5566 (1964).
23. W. Schaefer, R. Wegler, L. Eue, and H. Hack, Belgian P. 639 645 (1964); Chem. Abs., 62, 15361 (1965).
24. W. M. Hoskins, H. P. Bloxham, and M. W. Van Ess, J. Econ. Entomol., 33, 878 (1940).
25. French P. 39 013 (1930); Chem. Zentr., II, 3175 (1931).
26. H. L. J. Haller and W. F. Barthel, U. S. P. 2 358 925 (1944); Chem. Abs., 39, 1948 (1945).
27. E. Kieser and H. Augustiny, Arzneimittel Forsch., 4, 423 (1954).
28. M. Edelmann and T. Lipice, Bull. Acad. polon. Sci., Classe II, 3, 95 (1955).
29. T. Lipice, Premysl. Chem., 11, 520 (1955).
30. P. Siegenthal, Praxis, 49, 633 (1960).
31. J. F. Thomson, J. Savit, and E. Goldwasser, J. Pharmacol., 89, 1 (1947).
32. N. Kreutzkamp, Deutsch. Apotheker-Ztg., 102, 1286 (1962).
33. D. Libermann, M. Moyeux, R. Rist, and F. Grumbach, Compt. rend., 242, 2409 (1956).
34. K. J. Markow and E. V. Colowinsky, Naturwiss., 47, 450 (1961).
35. T. P. Sycheva and I. V. Lebedeva, Zhur. Obshch. Khim., 29, 1135 (1959).
36. G. Hagelloch and K. Liebermeister, Z. Naturforsch., 5b, 79 (1950).
37. J. G. Miller, M. B. Chenoweth, and T. M. Brody, J. Pharmacol., 121, 32 (1957).
38. V. Becker and W. Walter, Acta hepato-splenologica, 12, 129 (1965).
39. P. Ya. Yakovlev and G. P. Razumova, "Tioatsetamid—Zamenitel' Serovodoroda v Analize Metallov" (Thioacetamide—Substitute for Hydrogen Sulphide in the Analysis of Metals), Metallurgizdat, Moscow, 1963.
40. P. Chabrier and S. H. Renard, Bull. Soc. chim. France, [5], 16, D-272 (1949).
41. R. N. Hurd and G. DelaMater, Chem. Rev., 61, 46 (1961).
42. E. E. Reid, "Organic Chemistry of Bivalent Sulfur", Chemical Publishing Co. N. Y., 1962, Vol. 4, p. 45–58.
43. A. Schöberl, in "Houben-Weyl Methoden der organischen Chemie", G. Thieme, Stuttgart, 4th Ed., 1955, Vol. 9, p. 741.
44. W. Walter and K. Bode, Angew. Chem., 78, 517 (1966).
45. E. Roger and D. G. Nelson, Chem. Rev., 61, 179 (1961).
46. E. N. Zil'derman, Uspekhi Khim., 31, 1309 (1962) [Russ. Chem. Rev., No. 11 (1962)].
47. M. Erne and H. Erlenmeyer, Helv. Chim. Acta., 31, 652 (1948).
48. K. Kindler, Annalen, 450, 1 (1926).
49. W. E. Hanford, U. S. P. 2 201 170 (1938); Chem. Abs., 34, 6388 (1940).
50. W. E. Hanford, U. S. P. 2 201 172 (1938); Chem. Abs., 34, 6389 (1940).
51. H. D. K. Drew and D. B. Kelly, J. Chem. Soc., 625 (1941).
52. H. Lehr, W. Grey, and H. Erlenmeyer, Helv. Chim. Acta, 27, 970 (1944).
53. J. C. Porter, R. Robinson, and W. Wyler, J. Chem. Soc., 620 (1941).
54. E. Erlenmeyer and G. Bischuff, Helv. Chim. Acta, 27, 412 (1944).
55. H. W. Lewis, J. Biol. Chem., 14, 255 (1913).
56. E. S. Gatewood and T. B. Johnson, J. Amer. Chem. Soc., 48, 2903 (1926).
57. A. H. Cook and I. M. Heilbron, "The Chemistry of Penicillin", N. Jersey, 194?, p. 921.
58. G. Jander and H. Schmidt, Wien Chem. Ztg., 46, 49 (1943); Chem. Abs., 38, 2870 (1944).
59. C. V. Jorgensen, J. prakt. Chem., [2], 66, 28 (1902).
60. W. Walter and J. Curts, Chem. Ber., 93, 1511 (1960).
61. E. C. Stump, M. M. Guy, H. Sutton, and G. Westmoreland, J. Chem. Eng. Data, 9, 249 (1964).
62. S. H. Eggers, V. V. Kane, and G. Lowe, J. Chem. Soc., 1263, (1965).
63. F. W. Stacey, U. S. P. 3 179 651 (1965); Chem. Abs., 63, 1734 (1965).
64. F. Eiden, Arch. Parmazie, 295, 516 (1962).
65. P. Reynard, R. C. Moreau, and V. J. Cohen, Bull. soc. chim France, 3155 (1964).
66. P. Reynard and R. C. Moreau, Bull. soc. chim France, 2314 (1965).
67. R. Reynard and R. C. Moreau, Bull. soc. chim France, 73 (1966).
68. D. Eilhauer, W. Moeffing, G. Reckling, and F. Andercas, Rumanian P. 34 198 (1965); Chem. Abs., 63, 13222 (1965).
69. B. P. 980 997 (1965); Chem. Abs., 63, 13221 (1965).
70. French P. 1 352 839 (1964); Chem. Abs., 61, 4324 (1964).
71. A. Cahours, Compt. rend., 27, 239 (1848).
72. A. Bernthsen, Annalen, 184, 290 (1876).
73. K. Kindler, Annalen, 431, 187 (1923).
74. J. Geordeler and H. Porrman, Chem. Ber., 95, 627 (1962).
75. A. Weddige, J. prakt. Chem., [2], 9, 133 (1874).
76. H. Erfenmeyer, W. Büchler, and H. Lehr, Helv. chim. Acta, 27, 969 (1944).
77. E. Wertheim, J. Amer. Chem. Soc., 57, 545 (1935).
78. H. S. Forrest and J. Walker, J. Chem. Soc., 1506 (1948).
79. D. S. Morris and S. D. Smith, J. Chem. Soc., 1608 (1954).
80. R. P. Welcher, M. E. Castellon, and V. P. Wystrach, J. Amer. Chem. Soc., 81, 2543 (1959).
81. D. A. Peak, J. Chem. Soc., 215 (1952).
82. J. F. Olin and T. B. Johnson, Rec. Trav. chim., 50, 72 (1931).
83. A. E. E. Fairfull, J. L. Lowe, and D. A. Peak, J. Chem. Soc., 742 (1952).
84. S. Gabriel and P. Neymann, Ber., 23, 137 (1890).
85. T. L. Cairas, A. W. Larchar, and B. C. McKusick, J. Org. Chem., 18, 748 (1953).
86. M. A. McCall, J. Org. Chem., 27, 2433 (1962).
87. A. Albert, Ber., 48, 470 (1915).
88. A. Roe and C. E. Teague, J. Amer. Chem. Soc., 71, 4019 (1949).
89. J. Troger, and E. Ewers, J. prakt. Chem., [2], 60, 520 (1899); 2, 7, 79 (1873).
90. F. Asinger, W. Schafer, and E. Ch. Witte, Angew. Chem., 76, 273 (1964).

91. R. W. Hurd and G. De La Mater, Chem. Rev., **61**, 50 (1961).
92. V. Ballista, Chem. Listy, **37**, 196 (1943).
93. G. De La Mater, U. S. P. 2 732 401 (1957); Chem. Abs., **51**, 1255 (1957).
94. F. Ephraim, Ber., **22**, 2305 (1899).
95. J. Formanek, Ber., **22**, 2655 (1889).
96. P. Räy and R. M. Räy, J. Indian. chem. Soc., **3**, 118 (1926); Chem. Abs., **20**, 3690 (1926).
97. C. Volckel, Annalen, **38**, 314 (1841).
98. D. Vorländer, F. Hoelkeskampf, and P. Günther, Ber,, **65B**, 359 (1932).
99. F. Wohler, Ann. Phys., **24**, 167 (1831).
100. R. Wollner, J. prakt. Chem., **29**, 129 (1884).
101. E. Urbschat, German P. 868 908 (1953); Chem. Abs., **50**, 2662 (1956).
102. J. E. Mahan, U. S. P. 2 421 031 (1947); Chem. Abs., **41**, 55451 (1947).
103. O. E. Schultz and U. Ranke, Arch. Pharm., **294/66**, N 2, 82 (1961).
104. P. V. McKinney, U. S. P. 2 142 324, 2 147 985; see Ref. 102.
105. M. T. Bogert, H. C. Breneman, and W. F. Hand, J. Amer. Chem. Soc., **25**, 372 (1903).
106. A. H. Cook, I. M. Heilbron, and K. J. Reed, J. Chem. Soc., 182 (1945).
107. H. C. Brown and R. Pater, J. Org. Chem., **27**, 2858 (1962).
108. A. Pinner, Imidoather und ihre Derivate, Berlin, 1892.
109. A. Pinner, Ber., **16**, 1654 (1883).
110. H. Reiter and G. Hess, Ber., 40, 3022 (1907).
111. T. Gutiyny, Bull. Soc. chim. France, 655 (1957).
112. A. J. Hill and I. Rabinovitz, J. Amer. Chem. Soc., 48, 732 (1926).
113. S. M. McElvan and J. W. Nelson, J. Amer. Chem. Soc., **64**, 1825 (1942).
114. F. C. Schaefer and J. A. Peters, J. Org. Chem., **26**, 2778 (1961).
115. A. I. Gravin, Zhur. Prikl. Khim., **16**, 105 (1943).
116. M. Matsui, Met. Coll. Gnf. Kyoto, 1, 285 (1908); Chem. Zentr., II, 423 (1909).
117. A. Bernthsen, Annalen, **192**, 39 (1878).
118. A. Bernthsen, Ber., 10, 1238 (1877).
119. A. Bernthsen, Annalen, **192**, 29 (1878).
120. A. Bernthsen, Ber., **10**, 36 (1877).
121. D. Vorlander, Ber,, **24**, 803 (1891).
122. A. W. Hofmann, Ber., **11**, 508 (1878).
123. H. M. Woodburn, W. Platek, and E. L. Graminski, J. Org. Chem., **23**, 319 (1958).
124. E. V. Meyer, J. prakt. Chem., **82**, 521 (1911).
125. V. Muigrdichian, "The Chemistry of Organic Cyanogen Compounds", Reinhold Publish, Corp., No. 9, 1947, p. 66.
126. T. W. Mastin, G. R. Norman, and E. A. Weilmuenster, J. Amer. Chem. Soc., **67**, 1662 (1945).
127. H. G. Schicke and G. Schrader, German P. 1 111 172 (1962); Chem. Zentr., 291 (1963).
128. N. A. Meinhardt, S. Z. Gardon, and P. W. Vogel, J. Org. Chem., **25**, 1991 (1960).
129. Belgian P. 612 252 (1962); Chem.Abs., 58, 3362 (1963).
130. J. Yates and S. E. Callander, B. P. 955 492 (1964); Chem. Abs., **61**, 5566 (1964).
131. W. Schaefer, R. Wegler, L. Eue, and H. Hack, Belgian P. 639 645 (1964); Chem. Abs., **62**, 15361 (1965).
132. E. C. Taylor and J. A. Zoltewicz, J. Amer. Chem. Soc., 82, 2656 (1960).
133. Jap. P. 6684/64 (1964); Chem. Abs., **61**, 13289 (1964).
134. A. M. von Esch and W. R. Sherman, U. S. P. 3 158 623 (1964); Chem. Abs., **62**, 4008 (1965).
135. S. Ishikawa, Scient Papers Inst. Phys. Chem. Research, Tokyo, 7, 293 (1927); Chem. Abs., 22, 1343 (1928).
136. J. W. Baker, "Electronic Theories of Organic Chemistry—an Introductory Treatment" (Translated into Russian), Mir, Moscow, 1965, p. 338.
137. H. Behringer, L. Hauser, and K. Kohl, Chem. Ber., **92**, 910 (1959).
138. H. Behringer and D. Weber, Annalen, **682**, 197 (1965).
139. H. Weidinger and H. Eilingsfeld, German P. 1168898 (1964); Chem. Abs., **61**, 6991 (1964).
140. J. Kendall, B. P. 408 638 (1933); Chem. Abs., 28, 5470 (1934).
141. M. Battegay and E. Hegazi, Helv. chim. Acta, **16**, 999 (1933).
142. H. Rivier and J. Schalch, Helv. chim. Acta, **6**, 605 (1923).
143. H. Rivier and G. Schneider, Helv. chim. Acta, 3, 115 (1920).
144. H. Rivier and M. Langer, Helv. chim. Acta, **26**, 1722 (1943).
145. G. S. Jamieson, J. Amer. Chem. Soc., **26**, 177 (1904).
146. A. J. Speziale and L. R. Smith, J. Org. Chem., 28, 3492 (1963).
147. W. Walter and K. D. Bode, Angew. Chem., **74**, 694 (1962).
148. F. Asinger, A. Saus, H. Offermans, and H. D. Hahn, Annalen, **691**, 92 (1966).
149. A. W. Hofmann and S. Gabriel, Ber., **25**, 1578 (1892).
150. A. W. Hofmann, Ber., **11**, 338 (1878).
151. L. Henry, Compt. rend., **68**, 1273 (1869).
152. L. Henry, Annalen, **152**, 148 (1869).
153. L. Henry, Ber., 2, 305 (1869).
154. A. Reissert, Ber., 37, 3708 (1904).
155. J. Stieglitz, Ber., 22, 3159 (1889)
156. G. M. Dyson, R. F. Hunter, J. W. T. Jones, and E. R. Styles, J. Indian chem. Soc., 8, 147 (1931).
157. K. Kindler, German P. 385 376 (1922); Chem. Zentr., I, 2633 (1924).
158. R. Boudet, Bull. soc. chim. France, 172 (1949).
159. A. G. Pesina, Zhur. Obshch. Khim., 9, 804 (1939).
160. W. R. Schmitz, U. S. P. 2 682 558 (1954); Chem. Abs., 48, 9029 (1955).
161. K. Westphal and H. Andersag, German P. 701 901 (1938); Chem. Zentr., I, 3005 (1941).
162. R. Willstätter and T. Wirth, Ber., **42**, 1908 (1909).
163. A. Hantsch, Annalen, **250**, 257 (1889).
164. A. Bernthsen, Ber., **11**, 503 (1878).
165. K. Kindler, Annalen, **431**, 207 (1923).
166. K. Fries, H. Koch, and H. Stuckenbrock, Annalen, **468**, 182 (1929).
167. L. Ruzicka, M. W. Golberg, H. Hürbin, and H. A. Boskenoegen, Helv. chim. Acta, **16**, 1323 (1933).
168. B. Beilenson and F. M. Hamer, J. Chem. Soc., 1225 (1936).
169. H. Rivier and J. Zeltner, Helv. chim. Acta, **20**, 691 (1937).
170. H. Rivier and C. Schneider, Helv. chim. Acta, **2**, 717 (1919).
171. A. Manessier, Gazz. chim. ital., **45**, 1, 546 (1915).
172. A. Manessier, Gazz. chim. ital., **46**, 1, 231 (1916).
173. A. Manessier-Mameli, Gazz. chim. ital., **65**, 69 (1935).

174. J. McOmie, Ann. Reports on Progr. Chem. (Chem. Soc. London), 45, 207 (1948).
175. Heyden Chemical Corporation: Report 574 to the Committee for Penicillin Synthesis of the Medical Research Coincil; see Ref. 41.
176. G. Pulvermacher, Ber., 25, 308 (1892).
177. A. Reissert, Ber., 37, 3721 (1904).
178. G. Oddo and A. Manessier, Gazz. chim. ital., 40, 1, 43 (1910).
179. G. H. Hitchings and G. B. Elion, U. S. P. 2 756 228 (1956); Chem. Abs., 51, 2887 (1957).
180. K. Westphal and H. Andersag, U. S. P. 2 265 212 (1941); Chem. Abs., 36, 1950 (1942).
181. E. R. Edge, J. Chem. Soc., 123, 153 (1923).
182. W. Walter and K. D. Bode, Annalen, 660, 74 (1962).
183. L. Legrand, Bull. soc. chim. France, 337 (1960).
184. S. Tatsuoka, S. Rin, and K. Hireta, Ann. Rep. Takeda Res. Lab., 9, 17 (1950); Chem. Abs., 46, 2489 (1952).
185. J. Roggero and J. Metiger, Bull. soc. chim. France, 2533 (1963).
186. C. C. Price and B. H. Welzen, J. Org. Chem., 12, 386 (1947).
187. S. H. Bablock and R. Adams, J. Amer. Chem. Soc., 59, 2260 (1937).
188. J. Stanek andJ. Sidlo, Chemické Listy, 47, 470 (1953).
189. W. Dieterie, German P. 741 109 (1943); Chem. Abs., 40, 1880 (1946).
190. E. Klingsberg and D. Papa, J. Amer. Chem. Soc., 73, 4988 (1951).
191. E. Glatzel, Z. anorg. allg. Chem., 44, 65 (1905).
192. R. Klement, Z. anorg. allg. Chem., 253, 237 (1947).
193. A. G. Long and T. Tulley, J. Chem. Soc., 1190 (1964).
194. K. Kindler, Annalen, 452, 90 (1927).
195. K. Kindler,and F. Finndorf, Ber., 54, 1079 (1921).
196. K. Kindler, German P. 370 973 (1923).
197. K. Kindler, Arch. Pharmaz., 265, 389 (1927).
198. K. Kindler, German P. 405 675 (1924); Chem. Zentr., 96, I, 1529 (1925).
199. R. Guepet, R. Piganivl, A. Carayon-Gentil, and P. Chabrier, Bull, soc. chim. France, 224 (1965).
200. G. Purello, Annalen, 51, 143 (1961).
201. T. G. Levi, Gazz. chim. ital., 61, 294 (1931).
202. W. J. Harton and J. van den Berghe, J. Amer. Chem. Soc., 70, 2425 (1948).
203. C. L. Levesque, U. S. P. 2 525 075 (1950); Chem. Abs., 45, 2499c (1951).
204. C. L. Levesque, U. S. P. 2 525 416 (1950); Chem. Abs., 45, 1623f (1951).
205. W. G. Toland, J. Org. Chem., 27, 869 (1962).
206. B. Brähler, J. Riese, and R. Zimmermann, Angew. Chem., 74, 468 (1962); Angew. chem. internat. Edit., 1, 401 (1962).
207. R. Wegler, E. Kühle, and W. Schäfer, Angew. Chem., 70, 351 (1958).
208. R. Wegler, E. Kühle, W. Schäfer, and W. Foerst, Neuere Methoden der preparativen organischen Chemie. Verlag Chemie Wienheim/Bergstr., 1961, t. III, cmp. 1.
209. F. Asinger, W. Schäfer, K. Haleour, A. Sans, and E. Friem, Angew. Chem., 75, 1050 (1963).
210. B. Böttcher and E. Bauer, Annalen, 568, 218 (1950).
211. T. Bacchetti, A. Alemagna, and B. Danieli, Tetrahedron Letters, 2001 (1965).
212. F. Asinger and A. Meyer, Angew. Chem., 77, 812 (1965); Angew. Chem. internat. Edit., 4, 788 (1965).
213. F. Asinger, W. Schäfer, G. Baumgarte, and P. F. Müting, Annalen, 661, 95 (1963).
214. F. Asinger, W. Schäfer, and A. Saus, Monatsh. Chem., 96, 1273, 1278 (1965).
215. F. Bottino and G. Purello, Gazz. chim. ital., 95, 1062 (1965).
216. G. Purrello, Gazz. chim. ital., 95, 1089 (1965).
217. A. Carayon:Gentil, M. Minot, and P. Charbrier, Bull. Soc. chim. France, 1420 (1964).
218. L. F. Fieser and G. W. Kilmer, J. Amer. Chem. Soc., 62, 1354 (1940).
219. T. Taguchi and K. Yoshira, Chem. pharmac. Bull. (Tokyo), 11, 1354 (1940); see Ref. 44.
220. W. Schaeffer and R. Wegler, German P. 1 149 356 (1963); Chem. Abs., 59, 11441 (1963).
221. O. N. Chupakhin, Z. V. Pushkareva, Z. I. Kokoshko, and M. I. Podgornaya, Zhur. Org. Khim., 1, 772 (1965).
222. E. Mayer and J. Wehl, Angew. Chem., 76, 861 (1964).
223. R. Mayer and J. Wehl, Angew. Chem., Internat. Edit., 3, 705 (1964).
224. K. F. Funk and R. Mayer, J. prakt. Chem., [4], 21, 65 (1963).
225. C. Willgerodt, Ber., 20, 2467 (1887).
226. K. Kindler and W. Peschke, Arch. Pharmaz., 270, 340 (1932).
227. K. Kindler and W. Peschke, Arch. Pharmaz., 272, 236 (1934).
228. M. Carmack and M. A. Spielmann, "Organic Reactions" (Translated into Russian), Inostr. Lit., Moscow, 1951, Vol. 3.
229. J. F. W. McOmie, Ann. Repts. on Progr. Chem., 45, 211 (1948).
230. J. A. King and F. McMillan, J. Amer. Chem. Soc., 68, 632, 2335 (1946).
231. J. A. King and F. McMillan, J. Amer. Chem. Soc., 70, 4143 (1948).
232. M. Caramack, De Tar, and F. De Los, J. Amer. Chem. Soc., 68, 2025, 2029, 2755 (1946).
233. B. Milligan and J. M. Swan, J. Chem. Soc., 2269 (1959).
234. B. Milligan and J. M. Swan, J. Chem. Soc., 1194 (1961).
235. P. Chabrier, S. H. Renard, and K. Smarzewski, Bull. soc. chim. France, 1167 (1950).
236. K. Kindler, Annalen, 431, 193, 222 (1923).
237. B. P. 558 774; Brit. Chem. Abs., B11, 102 (1944).
238. E. Schwenk and E. Bloch, J. Amer. Chem. Soc., 64, 3051 (1942).
239. H. L. J. Haller and W. F. Barthel, U. S. P. 2 358 925 (1943); Chem. Abs., 39, 1948 (1945).
240. E. Baumann and E. Fromm, Ber., 28, 891 (1895).
241. K. Kindler and T. Li, Ber., 74, 321 (1941).
242. R. T. Arnold, E. Schultz, and H. P. Klug, J. Amer. Chem. Soc., 66, 1606 (1944).
243. O. Wallach, Annalen, 259, 300 (1890).
244. F. H. McMillan, J. Amer. Chem. Soc., 70, 868 (1948).
245. H. D. Porter, J. Amer. Chem. Soc., 76, 127 (1954).
246. R. W. Saville, J. Chem. Soc., 2880 (1958).
247. B. Emmert and M. Groll, Chem. Ber., 86, 205, 208 (1953).
248. H. J. Thayer and B. B. Corson, J. Amer. Chem. Soc., 70, 2330 (1948).
249. C. L. Levesque, U. S. P. 2 116 182 (1938); Chem. Abs., 33, 2838 (1939).
250. C. L. Levesque, U. S. P. 2 489 094 (1949); Chem. Abs., 44, 6427 (1950).
251. C. L. Levesque, U. S. P. 2 514 300 (1950); Chem. Abs., 44, 8941 (1950).

252. C. L. Levesque, U. S. P. 2 531 283 (1950); Chem. Abs., **45**, 3412 (1951).
253. C. L. Levesque, U. S. P. 2 560 296 (1951); Chem. Abs., **46**, 3558 (1952).
254. M. Carmack, U. S. P. 2 495 567 (1950); Chem. Abs., 44, 8806 (1950).
255. A. Kjaer, Acta chem. scand., 4, 1347 (1950).
266. A. Kjaer, Acta chem. scand., **6**, 327 (1952).
257. H. Wuyts and L. Ch. Kuang, Bull. soc. chim. Belgique, **42**, 153 (1933).
258. G. Alliger, G. E. P. Smith, E. L. Carr, and H. P. Stevens, J. Org. Chem., **14**, 962 (1949).
259. G. E. P. Smith, U. S. P. 2 647 144 (1953); Chem. Abs., 48, 7637 (1954).
260. H. B. König, W. Sifken, and H. A. Offe, Chem. Ber., 87, 825 (1954).
261. G. A. Goldberg and W. Kelly, J. Chem. Soc., 1919 (1948).
262. A. R. Todd, F. Bergel, Karimullah, and R. Keller, J. Chem. Soc., 361 (1937).
263. Y. Sakurada, Bull. Chem. Soc. (Japan), **2**, 307 (1927); Chem. Zentr., I, 683 (1928).
264. M. Malawski, H. Mogilnicki, and W. Czerska, 48359 (1964); Chem. Abs., **62**, 7698 (1965).
265. P. Reynand and C. Moreau, Bull. soc. chim. France, 2999 (1964).
266. W. Ried and W. Von der Emden, Annalen, **642**, 128 (1961).
267. Jap. P. 30296/64 (1964); Chem. Abs., **62**, 11824 (1965).
268. O. Fuchs and A. Nemes, Hungarian P. 151 818 (1965); Chem. Abs., **62**, 13129 (1965).
269. H. Staudinger and J. Siegwart, Helv. chim. Acta, 3, 824 (1920).
270. K. Mayer and S. Scheithauer, Chem. Ber., 98, 829 (1965).
271. T. G. Levi, Gazz. chim. ital., **54**, 395 (1924).
272. T. G. Levi, Atti reale accad. Lincei, **32**, 569 (1923); see Ref. 41.
273. G. Bahr, Angew. Chem., **73**, 628 (1961).
274. A. R. Todd, F. Bergel, and Karimullah, J. Chem. Soc., 1557 (1936).
275. F. Hoffman-La Roche Co., French P. 822 533 (1937); Chem. Abs., **32**, 4175 (1938); German P. 675 851 (1939); Chem. Abs., **33**, 7046 (1939).
276. F. Hoffman-La Roche Co., Swiss P. 199 650 (1938); Chem. Abs., **33**, 5130 (1939).
277. M. Hoffer, U. S. P. 2 220 243 (1940); Chem. Abs., 35, 1423 (1941).
278. A. R. Todd and F. Bergel, J. Chem. Soc., 1504 (1937).
279. A. R. Todd and E. Bergel, J. Chem. Soc., 364 (1937).
280. R. H. Reitsema, J. Amer. Chem. Soc., **68**, 766 (1946).
281. T. Matsukawa and S. Yurugi, J. Pharm. Soc. Japan, **71**, 827 (1951).
282. T. Matsukawa and T. Matsuno, J. Pharm. Soc. Japan, **63**, 145 (1944).
283. B. Lythgoe and A. R. Todd, Symposia, Soc. Exptl. Biol. i Nucleic, Acid, 1947, p. 15; Chem. Abs., 42, 4142 (1948).
284. K. J. M. Andrews, N. Anand, A. R. Todd, and A. Topham, J. Chem. Soc., 2490 (1949).
285. K. J. M. Andrews, G. W. Kenner, and A. R. Todd, J. Chem. Soc., 2302 (1949).
286. J. Baddiley, B. Lythgoe, D. McNeil, and A. R. Todd, J. Chem. Soc., 383 (1943).
287. K. Kostic, Helv. chim. Acta, **33**, 1482 (1950).
288. G. W. Kenner, H. J. Rodda, and A. R. Todd, J. Chem. Soc., 1613 (1949).
289. T. Imai and K. Makino, Z. physiol. Chem., **252**, 76 (1938).
290. W. Huber, J. Amer. Chem. Soc., **65**, 2222 (1943).
291. F. Hoffman-La Roche, Co., Swiss P. 199 648 (1938); Chem. Abs., **33**, 5130 (1939).
292. H. Wuyst and A. Lagourt, Bull. sci. acad. roy. Belg., **21**, 736 (1935); Chem. Abs., **29**, 7952 (1935).
293. G. E. P. Smith, U. S. P. 2 647 144 (1948); Chem. Abs., 48, 7637 (1954).
294. G. E. P. Smith(Jnr), G. Alliger, E. L. Carr, and K. C. Yong, J. Org. Chem., **14**, 935 (**1949**).
295. G. Alliger, U. S. P. 2 560 046 (1951); Chem. Abs., **46**, 1587 (1952).
296. B. Holmberg, Arkiv. Kemi, Mineral. Geol., **17A**, N 23, 10 (1944); Chem. Abs., **39**, 4065 (1954).
297. J. C. Crawhall and D. F. Elliott, J. Chem. Soc., 2071 (1951).
298. D. F. Elliott, Nature, **162**, 658 (1948).
299. B. Holmberg, The Svedberg Memorial Volume, 1944, p. 299, see Ref. 41.
300. T. B. Johnson and B. N. Nicolet, J. Amer. Chem. Soc., **33**, 1973 (1911).
301. H. Carrington, J. Chem. Soc., 681 (1947).
302. H. T. Bucherer and W. Steiner, J. prakt. Chem., **140**, 291 (1934); **141**, 5 (1935).
303. Y. Sakurada, Bull. Chem. Japan, **2**, 307 (1927); Chem. Abs., **22**, 764 (1928).
304. W. Walter and J. Curts, Annalen, **649**, 88 (1961).
305. J. W. Corse, R. G. Jones, Q. E. Soper, C. W. Whitehead, and O. K. Behrens, J. Amer. Chem. Soc., 70, 2842 (1948).
306. S. Yamada, A. M. M. E. Omar, and F. Hino, Chem. pharmac. Bull (Japan), **12**, 244 (1964), Chem. Abs., **60**, 14426 (1964).
307. Y. Sakurada, Mem. coll, Sci. Kyoto Imp. Univ., **9**, 237 (1926); Chem. Abs., **21**, 2458 (1927).
308. M. Delépina, Compt. rend., **153**, 279 (1911).
309. P. Reynard, R. C. Moreau, and J. P. Samana, Bull. soc. chim. France, 3623 (1965).
310. P. Reynard, R. C. Moreau, and J. P. Samana, Bull. soc. chim. France, 3628 (1965).
311. J. Goerdeler and H. Horstmann, Chem. Ber., **93**, 671 (1960).
312. R. P. Welcher, M. E. Gastelloon, and V. P. Wystrach, J. Amer. Chem. Soc., **81**, 2541 (1959).
313. R. N. Hurd, G. De La Mater, G. C. McElheny, R. J. Turner, and V. H. Wallingford, J. Org. Chem., **26**, 3980 (1961).
314. B. Persson and J. Sandström, Acta Chem. scand., 18, 1059 (1964).
315. V. H. Wallingford, U. S. P. 3 023 232 (1962); Chem. Abs., **57**, 2082 (1962).
316. G. R. Pettit and L. R. Garson, Canad. J. Chem., **43**, 2640 (1965).
317. W. Walter and G. Maerten, Annalen, 669, 66 (1963).
318. F. Sachs and H. Loevy, Ber., **36**, 585 (1903).
319. F. Sachs and H. Loevy, Ber., 37, 874 (1904).
320. N. B. Metha and J. Z. Strelitz, J. Org. Chem., **27**, 4412 (1962).
321. H. Gilman and C. R. Kinney, J. Amer. Chem. Soc., **46**, 493 (1924).
322. D. E. Worrall, J. Amer. Chem. Soc., 47, 2974 (1925).
323. H. Gilman, J. E. Kirby, and C. R. Kinney, J. Amer. Chem. Soc., **51**, 2252 (1929).
324. D. E. Worrall, J. Amer. Chem. Soc., **50**, 1456 (1928).
325. H. E. Morley and W. J. Saint, J. Chem. Soc., 43, 400 (1883).

326. D. R. Morton, A. R. Olson, and J. W. Blattenberger, J. Amer. Chem. Soc., 63, 314 (1941).
327. W. Schlenk and E. Bergmann, Annalen, 463, 1 (1928).
328. W. Schlenk and E. Bergmann, Annalen, 464, 1 (1928).
329. H. Gilman, B. Hofferth, and H. W. Melvin, J. Amer. Chem. Soc., 72, 3045 (1950).
330. H. Gilman and F. W. Breuer, J. Amer. Chem. Soc., 55, 1262 (1933).
331. H. Reinheckel and D. Jahnke, Chem. Ber., 97, 2661 (1964).
332. H. Reinheckel, D. Jahnhe, and G. Kretzschmar, Chem. Ber., 99, 11 (1966).
333. S. E. Ellzey and C. H. Mack, J. Org. Chem., 28, 1600 (1963).
334. H. Gilman, "Organic Chemistry", 2nd Edit., N. Y., 1943, Vol. 1, p. 527.
335. S. E. Ellzey and C. H. Mack, U. S. P. 3 180 091 (1965); Chem. Abs., 63, 1730 (1965).
336. J. Goerdeler and U. Keuser, Chem. Ber., 97, 3106 (1964).
337. A. D. Grabenko, L. I. Kulaeva, and T. S. Pel'kis, Zhur. Obshch. Khim., 33, 2227 (1963).
338. A. Michael, J. prakt. Chem., [2], 35, 449 (1887).
339. J. Ross, J. Amer. Chem. Soc., 55, 3672 (1933).
340. S. Ruhemann, J. Chem. Soc., 93, 621 (1908).
341. A. N. Borisevich, A. D. Grabenko, and P. S. Pel'kis, Zhur. Obshch. Khim., 33, 2223 (1963).
342. D. E. Worall, J. Amer. Chem. Soc., 42, 1055 (1920).
343. D. E. Worall, J. Amer. Chem. Soc., 40, 415 (1918).
344. J. Goerdeler and H. W. Pohland, Chem. Ber., 96, 526 (1963).
345. J. Goerdeler and H. Horn, Chem. Ber., 96, 1551 (1963).
346. G. Barnikow and H. Kunzek, J. prakt. Chem., [4], 29, 323 (1963).
347. J. Goerdeler and J. Gnad, Chem. Ber., 98, 1531 (1965).
348. G. Barnikow and J. Böetius, Z. Chem., 5, 104 (1965); Chem. Abs., 63, 5546 (1965).
349. G. Barnikow, V. Kath, and D. Richter, J. prakt. Chem., [4], 30, 63 (1965).
350. A. N. Borisevich, A. D. Grabenko, and T. S. Pel'kis, USSR P. 170 966 (1965).
351. E. Bullock and R. J. Abraham, Canad. J. Chem., 37, 1391 (1959).
352. J. Goerdeler and U. Kreuser, Chem. Ber., 97, 2209 (1964).
353. G. Barnikow and H. Kaufmann, Z. Chem., 5, 156 (1965); Chem. Abs., 63, 37 (1965).
354. B. Kumely and M. Tišler, Veštnik sloven, kem. Društa, 5, 69 (1958); Chem. Zentr., 12804 (1961).
355. A. D. Grabenko and T. S. Pel'kis, Zhur. Obshch. Khim., 30, 1222 (1960).
356. L. Gattermann, J. prakt. Chem., [2], 59, 3528 (1892).
357. K. K. Ginwals and J. P. Trivedi, J. Indian chem. Soc., 40, 897 (1963); Chem. Abs., 60, 4056 (1964).
358. F. Mayer and A. Mombour, Ber., 62, 1921 (1929).
359. H. Rievier and S. Kunz, Helv. chim. Acta, 15, 376 (1932).
360. K. V. Answers and C. Berger, Ber., 27, 1735 (1894).
361. P. A. S. Smith and R. O. Kan, J. Org. Chem., 29, 2261 (1964).
362. F. Friedmann and L. Gattermann, Ber., 25, 3525 (1892).
363. S. Hunig, K. Hübner, and E. Benzing, Chem. Ber., 95, 926, 937 (1962).
364. W. Ried and K. Käppeler, Annalen, 673, 132 (1964).
365. G. Bianchetti, P. dalla Grace, and D. Pocar, Gazz. chim. ital., 94, 606 (1964).
366. D. H. Glemens, A. J. Bell, and J. L. O'Brien, J. Org. Chem., 29, 2932 (1964).
367. R. Huisgen, R. Grashey, J. M. Vernon, and R. Kunz, Tetrahedron, 21, 3311 (1965).
368. J. E. Baldwin, G. V. Kaiser, and J. A. Ramersberger, J. Amer. Chem. Soc., 87, 4114 (1965).
369. P. Karrer and E. Weiss, Helv. chim. Acta, 12, 554 (1929).
370. K. Tust and L. Gattermann, Ber., 25, 3528 (1892).
371. S. Lur'e and L. Gatsenko, Zhur. Obshch. Khim., 22, 262 (1952).
372. A. Albert, "Chemie der Heterocyclen"; Verlag Chemie, Weinheim Bergstr., 1962.
373. F. Boberg and M. Marei, Annalen, 666, 88 (1963).
374. R. Mayer and J. Jentzsch, Angew. Chem., 74, 292 (1962); Angew. Chem. Internat. Edit., 1, 217 (1962).
375. R. Huisgen and J. Witte, Chem. Ber., 91, 972 (1958).
376. J. Witte and R. Huisgen, Chem. Ber., 91, 1129 (1958).
377. I. Kopecky, Chemie (Prag), 10, 901 (1958); Chem. Zentr., 4-0791 (1964).
378. Kereszky, Wolf, and Z. Foldi, Hungarian P. 135 418 (1949); Chem. Abs., 48, 10060 (1954).