SULFONYLUREAS AND SULFONYLTHIOUREAS[1]

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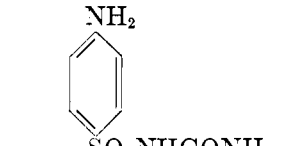
I. Introduction

Although isolated examples of sulfonylureas are recorded in the earlier literature, a more systematic study of the chemistry of sulfonyl derivatives of urea and thiourea is of very recent origin. About 1940, increased interest in this

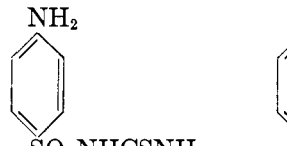
[1] This article reviews the literature, through *Chemical Abstracts*, up to January 1, 1951. The appendix covers subsequent work (up to July 1951) and the additional material has also been incorporated in the tables.

class of compounds was aroused by the expectation that sulfanilylurea (I) and sulfanilylthiourea (II), because of their close structural resemblance to sulfanilamide (III), were compounds of potential chemotherapeutic value. A formal analogy no less striking exists between the highly active sulfathiazole (IV) and sulfanilylthiopseudoureas of type V:



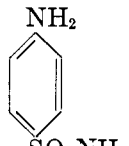
I

Sulfanilylurea



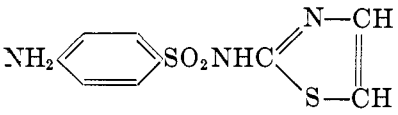
II

Sulfanilylthiourea



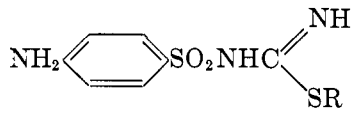
III

Sulfanilamide



IV

Sulfathiazole



V

In 1941 Mayer (118) advanced the hypothesis that tubercle bacilli may be regarded as fungi and that chemicals affecting the latter should also have an effect on the microbes causing tuberculosis. Of the numerous compounds known to retard the development of fungi, a number of sulfur-containing substances were selected for detailed study. Sulfanilylthiourea (II) was found to possess excellent antimycotic, antibacterial, and antitubercle action; it exceeded, with one exception, the other tested compounds in all three modes of activity. The chemotherapeutic usefulness of sulfanilylurea and sulfanilylthiourea was confirmed and firmly established in later investigations. These results stimulated numerous researches which have added more generally to our knowledge of sulfonylureas. The present account attempts to present a comprehensive review of the contributions made to the chemistry of this class of compounds and to refer concisely to their physiological and biochemical properties.[1]

II. Carbamidosulfonic Acids

Carbamidosulfonic acids may be classed among the simplest compounds incorporating the sulfonylurea structure. They are formed from urea or cyanic acid by the most direct methods and are therefore dealt with first.

Urea forms two salts with sulfuric acid: the normal sulfate, $2CO(NH_2)_2 \cdot H_2SO_4$, and the bisulfate, $CO(NH_2)_2 \cdot H_2SO_4$ (13). Excess of concentrated sulfuric acid at 130–140°C. decomposes urea into sulfamic acid, carbon dioxide, and ammonia; the last two products arise probably from the intermediate carbamic acid:

$$\underset{\text{Urea}}{NH_2CONH_2} + HOSO_2OH \rightarrow \underset{\text{Sulfamic acid}}{NH_2SO_2OH} + \underset{\text{Carbamic acid}}{[NH_2COOH]} \rightarrow NH_3 + CO_2$$

Similar results were obtained, at lower temperatures, with fuming sulfuric acid; in this reaction the intermediate occurrence of carbamidosulfonic acid (VI) was demonstrated but the compound was not isolated (13). Chlorosulfonic acid yields stable addition products with urea at low temperatures (45, 87, 88), but also gives rise to sulfamic acid as final product at higher temperatures (42, 167). The decomposition of urea by the above sulfonating agents is used in the large-scale manufacture of sulfamic acid.

$$NH_2CONH_2 + H_2S_2O_7 \rightarrow [NH_2CONHSO_2OH + H_2SO_4]$$

Urea

$$\downarrow$$

$$NH_2SO_2OH + [HOO_2SNHCOOH]$$

$$\downarrow$$

$$NH_2SO_3H + CO_2$$

Sulfamic acid

Salts of carbamidosulfonic acids were first prepared by Baumgarten and Marggraff (14), who melted urea with *N*-pyridinium sulfonic acid at 120°C. By employing the appropriate proportions of the sulfonating agent the pyridinium salts of the monosulfonic (VI) or disulfonic acid (VII) were readily obtained and converted to alkali or alkaline earth salts. The free acids proved highly unstable in aqueous media, however, and were not isolated:

$$NH_2CONHSO_2OH + HOH \rightarrow NH_2CONH_2 + H_2SO_4$$

Carbamidosulfonic acid

The direct action of sulfur trioxide on dry urea also results in carbamidosulfonic acid (VI).

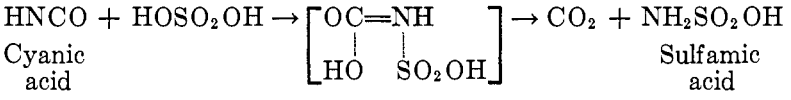
$NH_2CONHSO_2OH$	$HOO_2SNHCONHSO_2OH$
VI	VII
Carbamidosulfonic acid	Carbamidodisulfonic acid

In his detailed studies on cyanic acid, Linhard (109) succeeded in preparing free carbamidosulfonic acid. Cyanic acid reacts additively with many substances, the positive and negative parts of the added molecules being linked to the nitrogen and carbon atoms of the carbonimide structure, respectively:

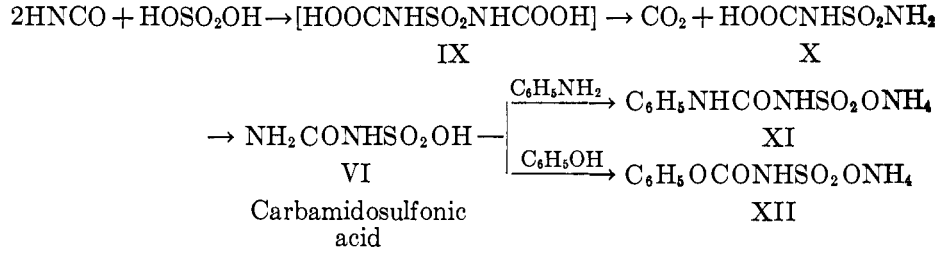
$$\begin{array}{l} HN{=}CO \\ \quad | \\ \quad H \quad NH_2 \end{array} \qquad \begin{array}{l} HN{=}CO \\ \quad | \quad | \\ \quad H \quad OR \end{array}$$

With sulfuric acid, under anhydrous conditions, cyanic acid yields the unstable sulfonated carbamic acid (VIII), which decomposes spontaneously into carbon dioxide and sulfamic acid. Excess of cyanic acid affords the dicarboxylic acid IX; immediate loss of one molecule of carbon dioxide, followed by rearrangement of the resulting sulfonamidocarboxylic acid X (exchange of NH_2 and OH groups), produces a substance which possesses the properties of carbamidosul-

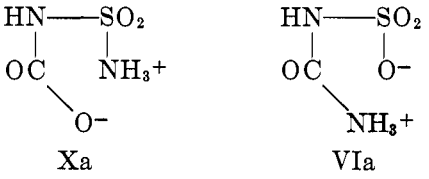
fonic acid (VI). It gives rise, for example, to the ammonium salt of phenylcarbamidosulfonic acid (XI) with aniline, or to the ammonium sulfonate of phenylurethan (XII) with phenol.



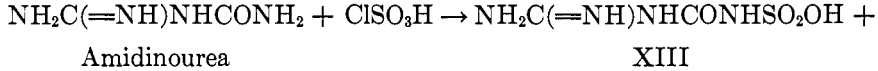
VIII



The facile rearrangement of X into VI may be due to the occurrence of zwitterion structures (Xa and VIa). Owing to the favorable dimensions of the molecule, a ring structure may be approached, in which the polar groups are closely adjacent to one another and may therefore be readily interchanged. The physical properties of the compounds concerned (high melting points, insolubility in nonpolar solvents, etc.) are in agreement with structures involving or approaching ionic lattices.



A sulfonic acid derived from amidinourea, probably of structure XIII, has been prepared from amidinourea sulfate, by dehydration with acetic anhydride or by its interaction with inorganic acid halides. The same compound was obtained more conveniently in the direct sulfonation of amidinourea at 125°C. (106).



Amidinourea XIII

When fused with ammonium sulfamate, urea produces guanidine sulfate (111); with sulfamic acid itself the yields are lower.

III. Methods of Synthesis of Sulfonylureas

In contrast to *N*-carbonylureas, $R'CONHCONH_2$, which are easily prepared by the action of acid halides or anhydrides upon the appropriate urea, sulfonylureas have unexpectedly not been obtained by the analogous reaction involving

sulfonyl halides (75, 99–104; *cf.* Section III, D, 2). Convenient alternative methods for making sulfonylureas have been developed; they are based on the numerous conventional urea syntheses but present, in certain cases, features of special interest. Since most procedures are equally applicable to the preparation of urea and thiourea derivatives, the synthesis of both series has here been considered collectively under the several headings.

The nomenclature adopted is that of *Chemical Abstracts*, according to which the positions in the urea and pseudourea structure at which substitution may occur are distinguished by the following system of numbering:

$$\overset{1}{\mathrm{NH_2}}\overset{2}{\mathrm{C}}\overset{3}{\mathrm{ONH_2}} \qquad \overset{1}{\mathrm{NH}}{=}\overset{2}{\mathrm{C}}(\mathrm{OH})\overset{3}{\mathrm{NH_2}}$$

A. SYNTHESIS FROM SULFONYL ISOCYANATES BY INTERACTION WITH AMINES

Sulfonyl isocyanates can be prepared, with suitable precautions, from sulfonyl chlorides and silver cyanate; they react readily with amines to yield the corresponding sulfonylureas. In 1904 Billeter (22) studied the interaction of benzenesulfonyl isocyanate with ammonia, amines, ethanol, and phenol, and obtained a series of sulfonylureas and sulfonylurethans. This work was, incidentally, the first systematic investigation dealing with compounds of this type. Owing to the difficulties of preparing sulfonyl isocyanates, however, the method has not found wide application. In the only other example reported (65) the experimental procedure was simplified by omitting the isolation of the intermediate sulfonyl isocyanate: the nitrobenzene solution in which it had been formed was used immediately for condensation with the amine.

$$\mathrm{R'SO_2NCO} + \mathrm{RNH_2} \rightarrow \mathrm{R'SO_2NHCONHR}$$

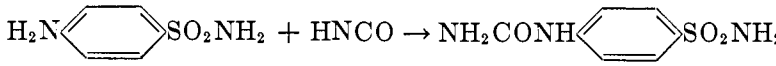
B. SYNTHESIS FROM SULFONAMIDES

Sulfonylureas are obtained from sulfonamides by the methods generally used for converting amines into ureas. The reagents used for this purpose are cyanic acid, isocyanic esters, or substances which decompose into these products under the conditions of the synthesis. Urea, nitrourea, urethan, and carbamyl chloride may serve as sources of the elements of cyanic acid, while their *N*-alkyl- and *N*-aryl substitution products, and certain azides and bromoamides, have been employed in place of isocyanates. The individual reactions are discussed in some detail below.

1. Interaction with cyanic acid

The well-known extension of Wöhler's synthesis, *viz.*, the interaction of cyanic acid with amines, has been successfully applied to the preparation of sulfonylureas. The first compounds of this type described in the literature were, in fact, prepared by this method (36). In contrast to amines, which condense rapidly with cyanates in acid solution, sulfonamides do not interact under these conditions; this is strikingly illustrated by the reaction of sulfanilamide with cyanic

or thiocyanic acid, in which *p*-sulfonamidophenylurea or *p*-sulfonamidophenylthiourea is produced, the sulfonamide group remaining unchanged (see Section IV, A).



p-Sulfonamidophenylurea

Sulfonamides are therefore condensed in neutral or alkaline media, but reaction occurs much more slowly than with amines. Prolonged boiling of either benzene- or *p*-toluenesulfonamide with alkali cyanate in aqueous ethanol, for example, gives good yields of the appropriate arylsulfonylurea (75, 102). A few aliphatic sulfonylureas have also been made by this procedure (80).

$$R'SO_2NH_2 + KCNO \rightarrow R'SO_2NKCONH_2 \rightarrow R'SO_2NHCONH_2$$

Attempts to prepare sulfonylthioureas similarly by the use of potassium thiocyanate were unsuccessful (107). The preparation of sulfanilylthiourea by this method has been claimed in the patent literature (34), but the physical constants of the products were not recorded.

2. Interaction with urea and substituted ureas

Sulfonylureas can often be made from urea itself by its interaction with sulfonamides; owing to the acidic character of the latter reagents, the presence of alkali is again necessary. Prolonged boiling of a mixture of *p*-acetaminobenzenesulfonamide, urea, and sodium carbonate in aqueous ethanol affords nearly theoretical yields of acetylsulfanilylurea (75, 116). The use of arylureas in this reaction gives rise to 1-aryl-3-arylsulfonylureas (R′ = R = Ar); the yields are generally low, however, and the long periods of heating required result in the formation of considerable quantities of carbanilides, $(RNH)_2CO$, as by-products (102). No references to the preparation of sulfonylthioureas by this method appear to be on record.

$$2R'SO_2NH_2 + 2NH_2CONHR + Na_2CO_3 \rightarrow 2R'SO_2N(Na)\cdot CO\cdot NHR + (NH_4)_2CO_3$$

$$R'SO_2NHK + NH_2CONHR \rightarrow R'SO_2N(K)\cdot CO\cdot NHR + NH_3$$

3. Interaction with nitrourea

Davis and Blanchard's (28, 44) convenient method of preparing substituted ureas with the aid of nitrourea has been used for synthesizing sulfonylureas. The sulfonamide is refluxed with sodium nitrourea, or with sodium carbonate and nitrourea, in 80 per cent ethanol until the evolution of nitrous oxide ceases. The desired sulfonylureas are usually obtained in excellent yields (75, 116).

$$R'SO_2NH_2 + NO_2N(Na)CONH_2 \rightarrow R'SO_2N(Na)CONH_2 + N_2O + H_2O$$

4. Interaction with urethans

Urethans decompose into cyanic acid or isocyanic esters and alcohols under suitable conditions and have therefore been successfully used in the preparation

of sulfonylureas. The reaction is carried out by heating a sulfonamide with urethan in the absence of solvents to 100°C. until no more ethanol is evolved (116). In another form of this method the reactants are stirred in glycol monomethyl ether at 110–120°C. for prolonged periods (65). Sulfanilylurea can thus be obtained from *p*-acetamidobenzenesulfonamide and urethan (116), while 1,3-disubstituted products, such as 3-benzyl-1-sulfanilylurea (65), are formed when *N*-substituted urethans are employed.

$$NH_2COOC_2H_5 \rightarrow HNCO + C_2H_5OH$$

$$RNHCOOC_2H_5 \rightarrow RNCO + C_2H_5OH$$

$$R'SO_2NH_2 + NHRCOOC_2H_5 \rightarrow R'SO_2NHCONHR + C_2H_5OH$$

5. Interaction with carbamyl chlorides

Carbamyl chloride and related compounds readily condense with sulfonamides: *p*-nitrobenzenesulfonamide, for example, reacts with carbamyl chloride in dioxane solution in the presence of pyridine to yield *p*-nitrobenzenesulfonylurea (116). Condensation with dialkylcarbamyl chlorides in nitrobenzene at 140–150°C. affords the corresponding trisubstituted ureas (64, 68, 115):

$$R'SO_2NH_2 + R_2NCOCl \rightarrow R'SO_2NHCONR_2 + HCl$$

In a variation of this method, use is made of phosgene and the appropriate amine, without isolating the intermediate carbamyl chloride (65).

$$2RNH_2 + COCl_2 \rightarrow RNHCOCl + RNH_2 \cdot HCl$$

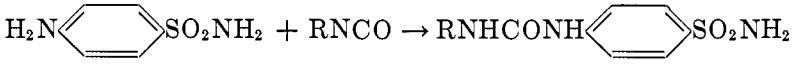
6. Interaction with isocyanic and isothiocyanic esters

The condensation of isocyanic esters with sulfonamides is a convenient method by which the great majority of sulfonylureas bearing a substituent on the amido nitrogen have been prepared:

$$R'SO_2NH_2 + RNCO \rightarrow R'SO_2NHCONHR$$

The reaction may be performed under a variety of conditions with both aliphatic and aromatic isocyanates. Alkali metal salts of sulfonamides react in nitrobenzene (64, 65, 66, 67), acetone (65), or ethanol (35), while free sulfonamides have been condensed in ethanolic sodium hydroxide solution (65) or in the absence of solvents (75, 102). In the last case the addition of triethylamine, particularly in relatively large quantities, accelerates the reaction considerably and results in improved yields (102). The catalyzing influence of tertiary amines in the condensation of isocyanates and hydroxyl-containing compounds is well known and its kinetics have been studied in detail (9). The interaction of isocyanates and amines, on the other hand, proceeds normally so readily that no attempts to employ tertiary amines as catalysts appear to be on record (142). It may be pointed out that in this reaction one of the reactants, *viz.*, the amine, is a base and is likely to be responsible for autocatalytic effects. With sulfonamides, of essentially acidic character, however, the catalytic in-

fluence of a tertiary base becomes significant. The great difference in the velocity with which amino and sulfonamido groups react with isocyanic esters is clearly illustrated by the observation of Roth and Degering (139) that approximately equimolecular proportions of sulfanilamide and isocyanates react to form 1-aryl-3-*p*-sulfonamidophenylureas; the isocyanate is used up preferentially by the primary amino group of the molecule, while the sulfonamido grouping remains unaffected.



Sulfonylthioureas are similarly prepared in excellent yields from sulfonamides and isothiocyanic esters (31, 35, 65).

7. Interaction with acid azides

Substituted azides which give rise to isocyanates with loss of nitrogen under suitable conditions provide yet another method of adding the elements of isocyanate to sulfonamides. For this purpose the azide may be prepared *in situ* and need not be isolated. Thus, phenylacetyl chloride is allowed to react with sodium azide in anhydrous benzene until the evolution of nitrogen ceases; treatment of the resulting solution with sodium *p*-nitrobenzenesulfonamide (and continued heating) yields 1-benzyl-3-*p*-nitrobenzenesulfonylurea (65):

$$R'SO_2NH_2 + RCON_3 \rightarrow R'SO_2NHCONHR + N_2$$

8. Interaction with acid amides

Sulfonylureas are similarly obtainable by the reaction of sulfonamides with *N*-bromoamides in the presence of excess of alkali. The amide, RCONHBr, undergoes the Hofmann rearrangement on heating in the alkaline solution, alkali bromide is simultaneously lost, and the isocyanate thus formed reacts with the sulfonamide.

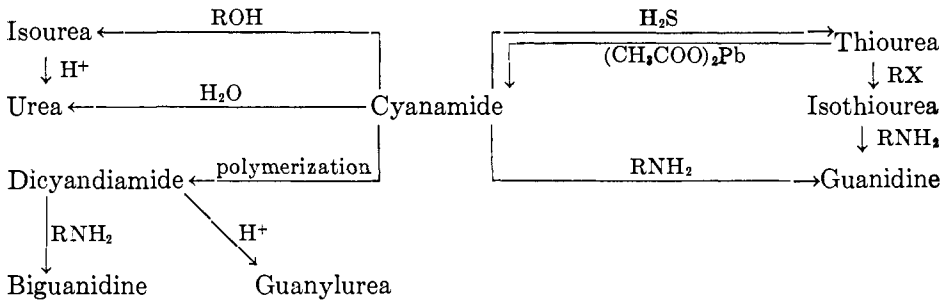
$$RCONHBr \rightarrow \underset{\underset{NBr}{\|}}{RCO^-Na^+} \rightarrow \underset{\underset{NR}{\|}}{BrCO^-Na^+} \rightarrow RNCO + NaBr$$

N-Bromophenylacetamide, for example, has been used for making 1-arylsulfonyl-3-benzylureas (65).

$$R'SO_2NH_2 + RCONHBr \rightarrow R'SO_2NHCONHR + HBr$$

C. SYNTHESIS FROM SULFONYLCYANAMIDES

The versatility of the cyanamide grouping for synthetic purposes is well known. Cyanamides are readily converted to ureas, pseudoureas, thioureas, and guanidines by the addition of water, alcohol, hydrogen sulfide, and ammonia, respectively. Some of the relationships between these and related compounds are illustrated in the following diagram:



Essentially the same connections have been found to exist among the sulfonyl derivatives of these compounds. Since sulfonylcyanamides are prepared without difficulty from sulfonyl chlorides and cyanamide salts (78), they are excellent intermediates for synthetic work in this field. Acetylsulfanilylcyanamide (as its calcium salt), for example, has been prepared (3, 165) in approximately 75 per cent yields by slowly stirring *p*-acetamidobenzenesulfonyl chloride into an aqueous solution of calcium cyanamide at 25–30°C., the product being separated by the addition of a large excess of calcium chloride (107). The sulfonylcyanamide salts so obtained are suitable for immediate conversion to ureas.

1. Addition of water or hydrogen sulfide

Sulfonylcyanamides are rapidly hydrolyzed to the corresponding ureas in 80–90 per cent yields by brief boiling with strong acids (6, 107, 165). They are, of course, unaffected by alkalis; thus, *p*-acetaminobenzenesulfonylcyanamide may be deacetylated by boiling with 10 per cent aqueous sodium hydroxide without damage to the cyanamide group (107).

$$RSO_2NHCN + HOH \rightarrow RSO_2NHCONH_2$$

The analogous addition of hydrogen sulfide was first reported by Leitch, Baker, and Brickmann (107), who heated the reactants in sealed tubes in a rocking furnace at 100°C. for 15 hr. and described the use of hydrogen sulfide gas, in conjunction with an autoclave, for work on a slightly larger scale. Das Gupta and Gupta (43) effected the reaction by suspending the sulfonamide in saturated aqueous ammonium sulfide and setting the mixture aside, at atmospheric pressure, for prolonged periods. Favorable conditions for the addition of hydrogen sulfide include the use of tertiary bases, or ammoniacal ethanol, together with hydrogen peroxide, sulfur, or certain sulfur-containing compounds (e.g., *N*,*N*,*N*′,*N*′-tetramethylthiuram disulfide $[(CH_3)_2NCSS]_2$ or thionyl chloride) as catalysts (150, 151).

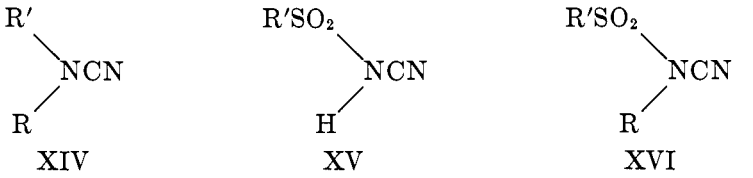
$$R'SO_2NHCN + H_2S \rightarrow R'SO_2NHCSNH_2$$

The conversion of disubstituted cyanamides to thioureas offers no difficulties. Wallach (160) added the elements of hydrogen sulfide to dialkyl- and diarylcyanamides by saturating their ethanolic solutions with ammonia and hydrogen

sulfide. An attempt to extend this reaction to disubstituted sulfonylcyanamides of type XVI, however, has been unsuccessful. Model experiments employing diphenylcyanamide (XIV: R = R′ = C_6H_5) showed that hydrogen sulfide was readily added, with formation of *as*-diphenylthiourea even at atmospheric pressure, when the cyanamide was treated with hydrogen sulfide in the presence of ammonia; heating diphenylcyanamide under pressure with excess of hydrogen sulfide alone, however, gave negative results. The catalytic influence of small quantities of ammonia on the rate of formation of thioureas is well established (81, 151); it presumably operates by the alternate addition of ammonium hydrogen sulfide and loss of ammonia, followed by the regeneration of the acid sulfide.

$$(C_6H_5)_2NCN + NH_4HS \rightarrow \left[(C_6H_5)_2NC(SNH_4)=NH\right] \rightarrow (C_6H_5)_2NC(SH)=NH + NH_3$$

Since aryl(arylsulfonyl)cyanamides (XVI) are very sensitive towards alkalis, the use of bases as catalysts had to be avoided. As observed with diphenylcyanamide, *N*-phenyl-*N*-*p*-toluenesulfonylcyanamide (XVI: R = C_6H_5; R′ = *p*-$CH_3C_6H_4$) failed to react with hydrogen sulfide in the absence of a base but was, on the other hand, rapidly hydrolyzed to *p*-toluenesulfanilide when ammonia was present. Even the weak base pyridine, by itself without action on aryl(arylsulfonyl) cyanamides, caused rapid removal of their cyanogen grouping when used in conjunction with hydrogen sulfide. The results show that the introduction of an aromatic nucleus into a sulfonylcyanamide (XV) renders subsequent addition of hydrogen sulfide more difficult (103).



2. Addition of alcohols and amines

The general method of preparing isoureas by treating cyanamide, dissolved in an excess of the appropriate alcohol, with hydrogen chloride, has been extended to the synthesis of sulfanilyl methyl- and ethylisoureas according to the following equation (165):

$$R'SO_2NHCN + ROH + HCl \rightarrow R'SO_2NHC(OR)=NH \cdot HCl$$

Ammonia and amines may be condensed with sulfonylcyanamides in the usual way (53) and give rise to sulfonylguanidines (107, 165):

$$R'SO_2NHCN + RNH_2 \rightarrow R'SO_2NHC(=NH)NHR$$

Sulfonyl derivatives of biguanidine and guanylurea have also been prepared by a variation of this method (2, 91, 165).

D. SYNTHESIS FROM SULFONYL CHLORIDES

1. Synthesis and hydrolysis of sulfonylpseudoureas

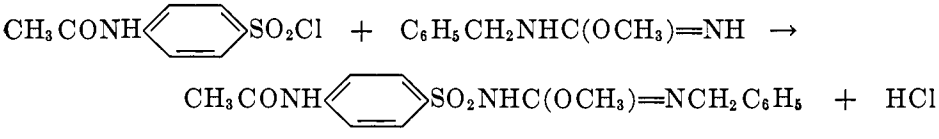
An efficient and convenient route which has been widely employed for the synthesis of sulfonylureas involves the preparation and subsequent hydrolysis of sulfonylpseudoureas. Ethers of pseudoureas, which are required as intermediates in this synthesis, are readily made from cyanamide by the action of hydrogen chloride in the appropriate anhydrous alcohol or from urea by treatment with methyl sulfate; they react with sulfonyl halides to yield salts of sulfonylpseudoureas:

$$NH_2CN + ROH + HCl \rightarrow NH_2C(OR)=NH \cdot HCl$$

$$2NH_2CONH_2 + R_2SO_4 \rightarrow [NH_2C(OR)=NH]_2 \cdot H_2SO_4$$

$$R'SO_2Cl + NH_2C(OR)=NH \cdot HCl + 2NaOH \rightarrow R'SO_2NHC(OR)=NH + 2H_2O + 2NaCl$$

Following the method of Basterfield and Powell (11, 12), Cox and Raymond (40) prepared arylsulfonylpseudoureas by slowly adding alkali to a stirred aqueous suspension of ethylisourea hydrochloride and arylsulfonyl chloride at 0°C.; excellent yields of sulfanilylpseudoureas were obtained by this method with minor modifications (38, 74, 165). Equally favorable results have been observed with substituted pseudoureas (65):



The preparation of sulfonylpseudoureas from sulfonylcyanamides directly has already been mentioned (*cf.* Section III, C, 1).

McKee's general method, originally described for converting 2-methyl-1-phenylpseudourea to phenylurea (112), is applicable to its sulfonyl derivatives (38, 40, 74). 1-Benzenesulfonyl-2-ethylpseudourea, for example, is smoothly split into benzenesulfonylurea and ethyl chloride by brief heating with hydrochloric acid.

$$R'SO_2NHC(OR)=NH + HCl \rightarrow R'SO_2NHCONH_2 + RCl$$

The corresponding sequence of reactions in the thiourea series has also been studied in detail. Pseudothiourea ethers are available from thiourea by direct alkylation with alkyl sulfates (146), alkyl halides (107, 154), chloromethyl ether (56, 155), and similar reagents. Cox's observation (39), in 1942, that pseudothiourea ethers condense readily with aromatic sulfonyl chlorides to form 2-substituted 1-arylsulfonyl-2-thiopseudoureas has been widely applied (4, 19, 41, 56, 72, 73, 92, 93, 107, 165) to the preparation of a large number of derivatives of this type. Additional investigations employing this synthesis aimed at the final conversion of sulfonylthiopseudoureas to the corresponding guanidines (18, 24, 29, 32, 33, 60, 76, 77, 152).

$$2NH_2CSNH_2 + R_2SO_4 \rightarrow [NH_2C(SR)=NH]_2 \cdot H_2SO_4$$

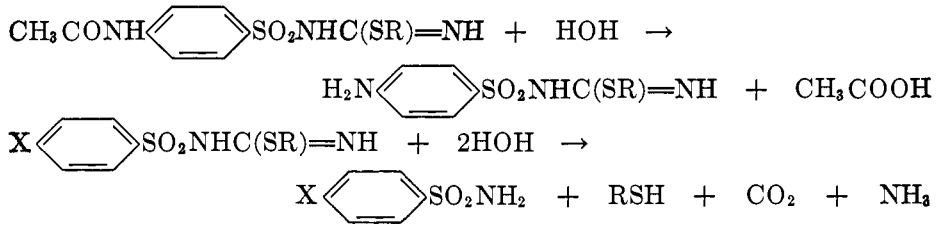
$$NH_2CSNH_2 + RCl \rightarrow NH_2C(SR)=NH \cdot HCl$$

$$R'SO_2Cl + NH_2C(SR)=NH \cdot HCl + 2NaOH \rightarrow R'SO_2NHC(SR)=NH + 2NaCl + 2H_2O$$

As in the urea series, the reaction is conveniently performed by slowly adding a mixture of a slight excess of the pseudourea salt and the sulfonyl chloride to an ice-cold solution of potassium carbonate or hydroxide in aqueous acetone (24) and isolating the product by dilution with water, acidification, or partial evaporation. The use of sodium ethoxide in anhydrous solvents has also been described (56).

S-Acyl derivatives of thiopseudourea, though readily obtained by Dixon and Taylor's method (47) from thiourea and acid chlorides in acetone, do not condense with sulfonyl chlorides in the usual way but give rise to thiolsulfonates of the structure $R'SO_2SR'$. In this reaction the *S*-acylthiopseudourea is probably first reconverted hydrolytically to thiourea, which then acts on the sulfonyl chloride and forms the thiolsulfonate ester, being itself oxidized to dithioformamidine (107) (see Section III, D, 2).

In contrast to the easy hydrolytic conversion of sulfonylpseudoureas to sulfonylureas the analogous reaction in the thiourea series is difficult. Sulfonylthiopseudoureas are fairly resistant towards mineral acids, with which they form salts of varying stability. Like alkylthiopseudoureas, they decompose into (sulfon)amide under the influence of alkalis or strong acids, with evolution of mercaptans (19, 40, 165). Acetylsulfanilylthiopseudoureas, for example, are merely deacetylated when heated with dilute acids, but are decomposed by treatment with sodium hydroxide or concentrated acids (107):



An exception to these observations, reported by Földi, Gerecs, Demjen, and König (56), and independently confirmed by Leitch *et al.* (107), was the behavior of the 2-methoxymethyl ether of acetylsulfanilylthiopseudourea, which gave excellent yields of acetylsulfanilylthiourea on being boiled for 1 min. with very dilute methanolic hydrochloric acid. It was pointed out by Bergmann (19) that the attachment, at the sulfur atom of a thiopseudourea, of a group R which has the tendency to form carbonium ions R^+, facilitates alkyl–sulfur fission instead of the usually observed carbon–sulfur fission under certain circumstances in acid media. Thus, heating 1-acetylsulfanilyl-2-*tert*-butyl-2-thiopseudourea with ethanolic hydrochloric acid did not produce sulfonamide and thiol but gave sulfanilylthiourea, though in low yields. Treatment with hydriodic acid at room temperature was still more effective and removed the *tert*-butyl

radical quantitatively. An electronic interpretation of this and similar observations was advanced.

The problem of obtaining sulfonylthioureas from the corresponding pseudo derivatives by a generally applicable method appears to have been solved finally by the discovery (147) that hydrolysis employing ethanolic sodium hydrogen sulfide in closed vessels gives satisfactory yields of the desired products:

$$R'SO_2NHC(SR)=NH + NaSH \rightarrow R'SO_2NHC(SNa)=NH + RSH$$

2. Interaction with urea derivatives

The interaction of sulfonyl chlorides with urea, first studied by Elander (52), was investigated in some detail by Remsen and Garner (136). Reaction in the absence of solvents at 100°C. was found to occur vigorously with formation of guanylurea sulfonates:

$$R'SO_2Cl + 2NH_2CONH_2 \rightarrow NH_2CONHC(=NH)NH_2 \cdot R'SO_2OH + HCl$$

Salt-like addition products of the formula $R'SO_2Cl \cdot NH_2CONH_2$ were prepared in ethereal solution by Schwartz and Dehn (143).

Sulfonylureas have not been obtained by the action of sulfonic acid halides on ureas, i.e., by the reaction that takes place readily when halides of carboxylic acids are employed. Unsuccessful attempts in this direction were reported by Haak (75); the formation of sulfonic acids and products derived from urea by dehydration and polymerization, such as dicyandiamide, was mentioned, but no details were given. The failure to obtain a sulfonylurea from pyridine-3-sulfonyl chloride and urea has also been referred to (117). The greater reactivity of a carboxylic acid chloride compared with a sulfonyl chloride grouping towards urea is clearly illustrated by the results of the attempts of Bodendorf and Senger (26) to prepare the cyclic ureide XVIII from the dichloride (XVII) of carboxymethanesulfonic (sulfoacetic) acid and urea. It was found that the sulfonyl entity did not react, and that the ureide of carboxymethanesulfonyl chloride (XIX) which was thus formed could not be cyclized to XVIII. The failure of the sulfonyl chloride group of the molecule XIX to react was clearly not due to its intrinsic inertness, since it condensed rapidly with aniline or ethanol to yield the substituted sulfonanilide (XX) or ethyl ester (XXI), respectively:

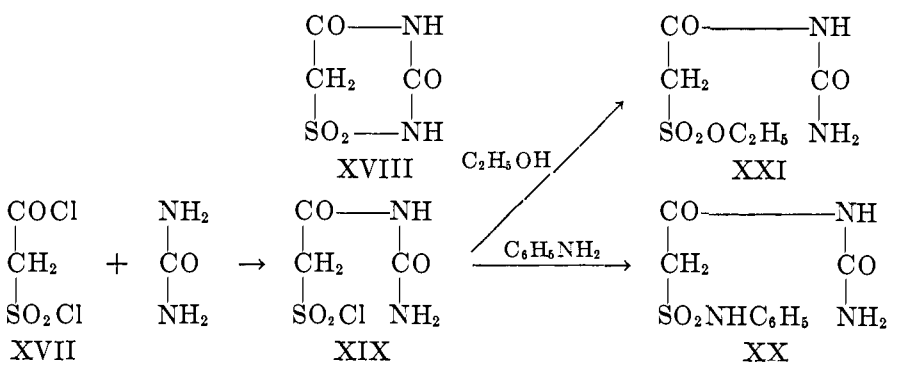


TABLE 1

Synthesis of sulfonylureas

METHOD OF PREPARATION	O_2N-C$_6$H$_4$-$SO_2NHCONH_2$		H_2N-C$_6$H$_4$-$SO_2NHCONH_2$		CH_3CONH-C$_6$H$_4$-$SO_2NHCONH_2$	
	Melting point	Reference	Melting point	Reference	Melting point	Reference
	°C.		°C.		°C.	
$R'SO_2Cl + CO(NH_2)_2$	190 (d)*	(64, 69, 115)	320 (subl.)* 303 (d)	(64, 69, 115) (120)	241–242	(120)
$R'SO_2NH_2 + HNCO$			149–154 158–160	(75) (116)	185–188	(75)
$R'SO_2NH_2 + CO(NH_2)_2$					185–188	(75)
$R'SO_2NHCN + HOH$	178–180	(6)	143–147 140–144	(107) (165)		
$R'SO_2Cl + NH_2C(OR)=NH$†			140–144 140–146	(165) (38)		

* Abbreviations: (d) = melt with decomposition; (subl.) = sublimes.

† Followed by hydrolysis.

Claims for two methods of preparing sulfonylureas from sulfonyl chlorides and urea directly have been advanced but have not been confirmed by subsequent work. It was reported in the patent literature (64, 69, 115) that melting *p*-nitrobenzenesulfonyl chloride with urea, first at 100–120°C. and later at 140°C., gave *p*-nitrobenzenesulfonylurea. However, the constants quoted for this compound, and for the amino derivative obtained therefrom by reduction, differed from those established by several independent methods (*cf.* table 1) and efforts to use this route for making other sulfonylureas have failed. Arylureas were found to be equally unsuitable: the interaction of phenylurea and *p*-toluenesulfonyl chloride under various conditions resulted merely in mutual decomposition, yielding such products as ammonium *p*-toluenesulfonate, *s*-diphenylurea, and *p*-toluenesulfonanilide (102).

A variation of this synthesis, in which the reactants were condensed in aqueous media in the presence of sodium carbonate, has been described (120), but has again not been confirmed (103).

It was recently shown (99, 100) that the condensation of arylureas and excess of aromatic sulfonyl chlorides in pyridine at moderate temperatures does not yield sulfonylureas but occurs with simultaneous dehydration and results in the formation of *N*-aryl-*N*-arylsulfonylcyanamides in excellent yields:

$$2R'SO_2Cl + RNHCONH_2 \rightarrow R'SO_2NRCN + R'SO_2OH + 2HCl$$

Owing to the great readiness with which thiourea derivatives are oxidized, the products of their interaction with sulfonyl halides are more numerous than in the case of ureas. The action of benzenesulfonyl chloride on thiourea in alcoholic solution was first studied by Remsen and Turner (137), who obtained dithioformamidine dihydrochloride and phenyl benzenethiolsulfonate. The production of the former substance had also been observed by McGowan in the reaction between thiourea and methanesulfonyl or trichloromethanesulfonyl chloride (110).

$$2R'SO_2Cl + 4NH_2CSNH_2 \rightarrow [NH_2C(=NH)S]_2 + R'SO_2SR' + 2NH_2CN + 2S + 2HCl + 2H_2O$$

With aromatic thioureas the reaction takes a different course. Fromm and Heyder (59), when attempting to prepare aryl-substituted dithioformamidines from phenylthiourea by the above method, found that ring closure occurred instead, with formation of "Hector's base" (i.e., probably 2,3,4,5-tetrahydro-3,5-diimino-2,4-diphenyl-1,2,4-thiadiazole[2]), a compound that had previously been obtained by the action of various oxidizing agents on phenylthiourea (79).

The interaction of aromatic thioureas with sulfonyl chlorides in pyridine at moderate temperatures (101) results in rapid loss of sulfur and production of arylcyanamide. Some of the cyanamide reacts further with the excess of sulfonyl chloride, as shown by the isolation of *N*-aryl-*N*-arylsulfonylcyanamides, while part of the sulfonyl chloride is converted to the thiolsulfonate during the reaction:

[2] The assigned structure has yet to be confirmed beyond doubt.

$$4R'SO_2Cl + 3C_6H_5NHCSNH_2 \rightarrow 3C_6H_5NHCN + 3S + R'SO_2SR' + 2R'SO_2OH + 4HCl$$

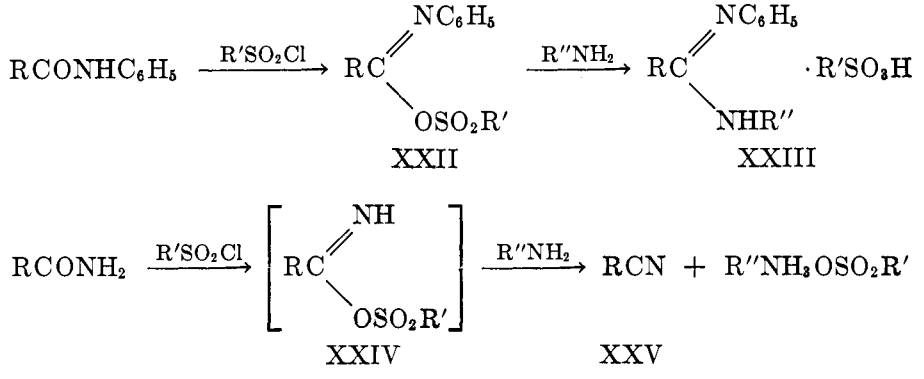
$$R'SO_2Cl + C_6H_5NHCN \rightarrow R'SO_2N(C_6H_5)CN + HCl$$

All experiments that might be expected to furnish sulfonylthioureas by this method have thus given negative results. A successful preparation of sulfanilylthiourea by the condensation of the sulfonyl chloride and thiourea in aqueous alkali has been claimed (120), but the products had anomalous melting points. Leitch, Baker, and Brickman (107) were unable to confirm these results, but obtained *p*-acetaminophenyl *p*-acetaminobenzenethiolsulfonate ($CH_3CONHC_6H_4SO_2SC_6H_4NHCOCH_3$), showing that the reaction proceeded essentially as previously outlined by Remsen and Turner (137). All their efforts to prepare the desired sulfonylureas by varying the reaction conditions gave the thiolsulfonate.

Reaction mechanism

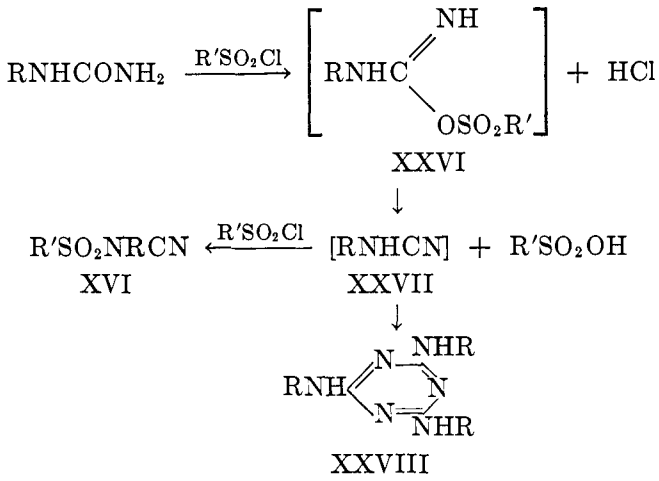
The conversion of aromatic ureas and thioureas into *N*-aryl-*N*-arylsulfonylcyanamides (XVI), rather than sulfonylureas, under the influence of sulfonyl halides has been accounted for by assuming the urea to react in its enolic form, producing unstable intermediate *O*- or *S*-sulfonylpseudoureas (XXVI, XXIX) (100, 104, 124).

Oxley, Peak, and Short (125) have shown that imidosulfonates of formula XXII (obtainable by the addition of a sulfonyl chloride to an *N*-substituted amide in pyridine solution) may be preserved long enough in the solvent to undergo aminolysis with subsequently added amines to form amidinesulfonates (XXIII). Imidosulfonates of type XXIV, however, bearing no substituent on the nitrogen atom, are highly unstable; attempts to prepare *N*-phenylbenzamidine from benzamide and benzenesulfonyl chloride, followed by addition of aniline, were unsuccessful, since the imidosulfonate (XXIV: R = R′ = C_6H_5) decomposed even at −10°C., phenyl cyanide (XXV) being isolated instead.

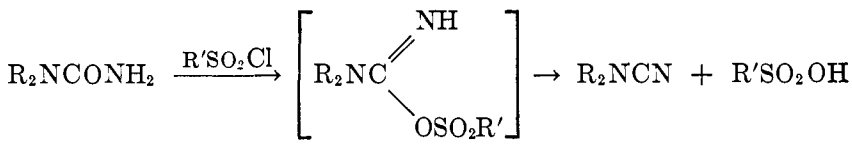


Since *O*-sulfonylpseudoureas (XXVI) show a close resemblance to the imidosulfonate structure (XXIV), their instability and consequent analogous de-

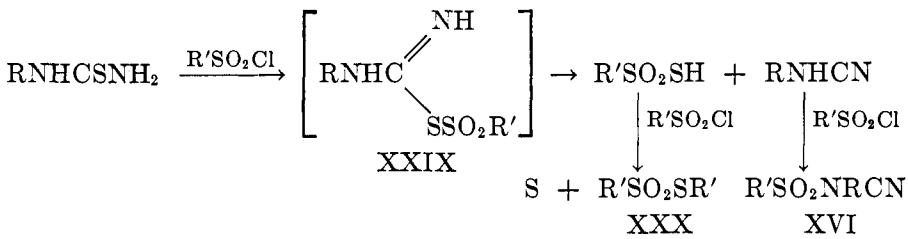
composition into arylcyanamides (XXVII) and sulfonic acids may be postulated; the former reacts further with the excess of sulfonyl chloride to yield sulfonylcyanamides of formula XVI.



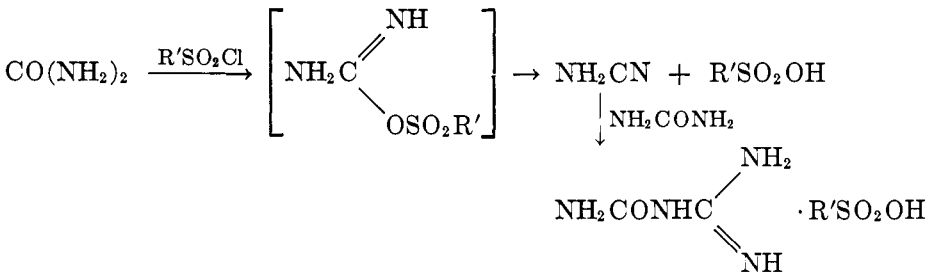
Direct evidence for the intermediate formation of cyanamides in this reaction is provided by the observation (100) that substituted triazines (XXVIII), obviously formed by trimerization of such cyanamides, are sometimes isolated as by-products in this reaction. Also, with 1,1-disubstituted ureas the reaction must of course stop at the cyanamide stage; thus *s*-diphenylurea is converted almost quantitatively to diphenylcyanamide (100):



The results of the interaction of arylthioureas and sulfonyl chlorides are similarly interpreted by the assumption of a comparable decomposition of intermediate labile *S*-sulfonylthiopseudoureas (XXIX) into arylcyanamides and aromatic thiosulfonic acids; there is evidence that reaction of the latter with the excess of sulfonyl chloride present produces the observed aryl arylthiolsulfonate (XXX) and elementary sulfur (100):



Remsen and Garner's synthesis of guanylurea from urea is also brought into line by this mechanism (124).



The failure of ureas and thioureas to afford *N*-sulfonyl derivatives on treatment with sulfonyl halides under the conditions so far examined[3] is in contrast to the behavior of pseudoureas and pseudothioureas (*cf.* Section III, D, 1), guanidines (6, 114), and amidines (10, 63), which undergo this reaction readily in the presence of acid-binding substances. All the above compounds incorporate the —C(=NH)NHR system (R = H or hydrocarbon radical) in their molecules; the structures of the latter group, however, which form *N*-sulfonyl derivatives directly, are distinguished by the absence of the —NHCO— entity which is capable of reacting in the enolic form. This observation appears to provide additional indirect support for the suggestion that it is the enolic hydroxyl group of ureas, or the thiol group of thioureas, that is primarily involved in the reactions with sulfonyl chlorides, and that the observed reaction products arise in the immediate decomposition of the *O*- or *S*-sulfonyl esters (XXVI, XXIX) so formed. If the hydroxyl group is already effectively blocked (as in pseudoureas) or replaced by another structural unit (as in guanidines and amidines), *N*-sulfonyl derivatives are obtained in the usual way.

These considerations do not apply to the corresponding reactions with carboxylic acid chlorides, because urea and its derivatives yield *N*-carbonyl compounds with these reagents under comparable conditions (16, 37, 161). Treatment of thioureas with acyl chlorides in acetone solution produces *S*-carbonylureas, which rearrange to the *N*-substituted isomers on melting or treatment with pyridine (46, 47).

In the interaction of semicarbazide (122, 139, 164) and guanylurea (163) with sulfonyl chlorides the carbamyl function is not concerned, since attack occurs at the 1-amino or the 1-amidino grouping, respectively.

E. MISCELLANEOUS SYNTHESES

1. Interaction of sulfonylureas and amines

1-Aryl-3-arylsulfonyl ureas may be prepared by introducing the second substituent into the preformed sulfonylurea. Thus, prolonged heating of acetylsulfanilylurea with benzylamine hydrochloride in ethanol, or with benzylamine

[3] An exceptional observation that has been reported (193) is discussed in the appendix (page 44).

in dimethylamine, followed by hydrolysis yields 3-benzyl-1-sulfanilylurea. The reaction is equally applicable to sulfonylthioureas (65).

$$R'SO_2NHCONH_2 + RNH_2 \cdot HCl \rightarrow R'SO_2NHCONHR + NH_4Cl$$

2. Interaction of sulfonylurethans and amines

The same products are also obtained by heating the appropriate arylsulfonylurethan and primary amine in glycol monomethyl ether at 100°C. for 20 hr., when condensation occurs with loss of alcohol (65).

$$R'SO_2NHCOOCH_3 + RNH_2 \rightarrow R'SO_2NHCONHR + CH_3OH$$

3. Desulfurization of sulfonylthioureas

In the presence of a mineral acid, most oxidizing agents convert thiourea to dithioformamidine. In neutral media, however, permanganate, hydrogen peroxide, and other oxidizing agents yield urea as the main product. Certain oxides and salts of heavy metals (e.g., lead, mercury, copper, silver) which in alkaline media remove the elements of hydrogen sulfide, forming cyanamides, yield ureas in neutral solution. By the use of ethanolic silver nitrate, for example, 1-acetylsulfanilyl-3-benzylurea has been converted to the corresponding urea compound (65).

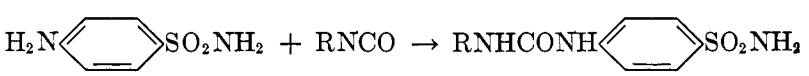
$$R'SO_2NHCSNHR + 2AgNO_3 + H_2O \rightarrow R'SO_2NHCONHR + Ag_2S + 2HNO_3$$

IV. Sulfamylureas

A detailed discussion of sulfamylureas is outside the scope of this review; brief reference to the numerous investigations dealing with these compounds, however, appears justified, because of their chemotherapeutic interest and their relationship to sulfonylureas.

A. SYNTHESES FROM SULFANILAMIDE

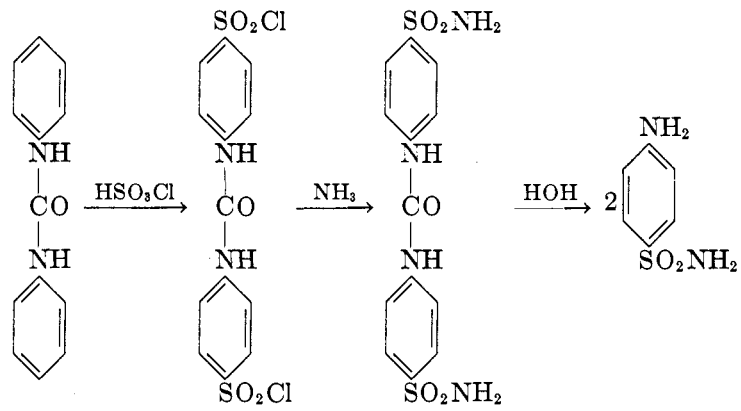
With cyanic acid and its derivatives the primary amino group reacts much more rapidly than does the sulfonamido group (*cf.* Sections III, B, 1 and III, B, 6). Sulfanilamide may therefore be directly converted into a series of *p*-sulfonamidophenylureas. Because of the potential therapeutic value of such products, the condensation has been carried out with a variety of reagents, including alkali cyanates (95, 108), nitrourea (98), and isocyanate esters (139), all of which interact selectively with the amino group. Sulfamylthioureas are similarly made (62, 107, 159).



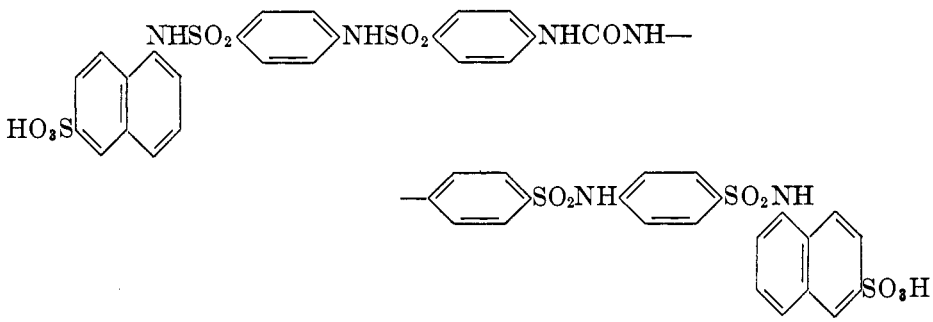
B. SULFONATION OF ARYLUREAS

The sulfonamide group may be introduced into an arylurea by direct sulfonation. The aromatic urea, or preferably its acetyl derivative, is treated with chlorosulfonic acid at low temperatures, the sulfonyl chloride being subsequently

converted to the amide in the usual way (37, 156). Starting with carbanilide, this reaction sequence is particularly important, because the resulting 4,4′-disulfamylcarbanilide may be hydrolyzed directly to sulfanilamide in alkaline media. The large-scale production of the drug by this process has been found useful during shortages of acetylating agents which are required in the alternative manufacturing methods (27, 50, 61, 71, 168):



Several of the other possible routes to sulfamylureas have been employed (90, 144), including, for example, the use of phosgene (133, 134), thiocarbonyl chloride, $CSCl_2$ (51, 113), urea fusion (89), and hydrolysis of cyanamides (54). Mention may be made of a number of analogs of the compound known as Bayer 205 (or Fourneau 309), which contain sulfonyl instead of carbonyl groups (30, 133, 134, 158).



V. Sulfonamidoureas

Sulfonamidoureas may be prepared from sulfonyl chlorides and semicarbazide or thiosemicarbazide in pyridine solution (139) or by thoroughly grinding the components to a paste with sodium acetate (122); analogs of sulfanilamide and Marfanil have been obtained by this method (164):

$$R'SO_2Cl + NH_2NHCONH_2 \rightarrow R'SO_2NHNHCONH_2 + HCl$$

Members of this series bearing an additional substituent may be made by first condensing the sulfonyl chloride with hydrazine hydrate; the resulting sulfonyl-

hydrazine is then allowed to react with an isocyanate ester in dioxane or ethanol solution (139).

$$R'SO_2Cl + NH_2NH_2 \rightarrow R'SO_2NHNH_2 + HCl$$
$$R'SO_2NHNH_2 + RNCO \rightarrow R'SO_2NHNHCONHR$$

VI. Sulfonylurethans

In addition to the method involving sulfonyl isocyanates (*cf.* Section III, A, 1), the synthesis of sulfonylurethans from sulfonamides and sulfonyl chlorides by the action of chloroformic ester (64) and urethan (115), respectively, has been described:

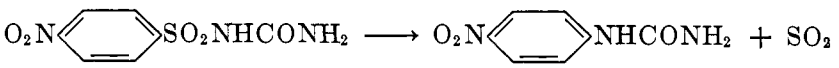
$$\begin{matrix} R'SO_2NH_2 + ClCOOC_2H_5 \\ \qquad\qquad\qquad\qquad\searrow \\ \qquad\qquad\qquad\qquad\quad R'SO_2NHCOOC_2H_5 + HCl \\ \qquad\qquad\qquad\qquad\nearrow \\ R'SO_2Cl + NH_2COOC_2H_5 \end{matrix}$$

VII. Chemical Properties

Sulfonylureas and sulfonylthioureas are crystalline solids of acidic character. Their solubility in water and the common organic solvents varies with the complexity of their structure: compounds containing the free urea grouping (i.e., $R'SO_2NHCONH_2$) may often be crystallized from boiling water; sulfonylureas containing additional substituents (e.g., $R'SO_2NHCONR_2$) are usually soluble in polar solvents, less so in hydrocarbon solvents, and sparingly soluble in water. The solubilities of sulfanilylurea and sulfanilylthiourea in carbon dioxide-free water at 20°C. have been given as 0.233 per cent and 0.055 per cent, respectively (58).

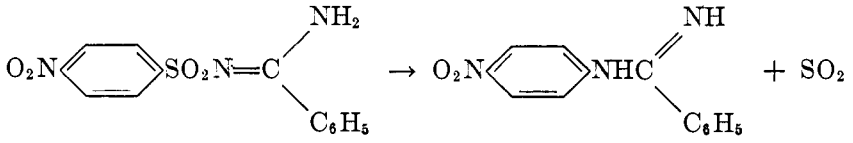
The presence of the sulfonamido radical confers acidic properties on sulfonylureas. They dissolve in alkalis with formation of stable salts which crystallize in the form of lustrous solids, of definite melting points, on the addition of alcohol to their concentrated aqueous solutions (65, 70). Stable nonhygroscopic salts have also been prepared from sulfanilylthiourea and organic bases, including mono-, di-, and triethanolamines (148, 153). Salts of 3-benzyl-1-sulfanilylurea show a considerably lower alkalinity in aqueous solution (5 per cent solution, pH 8.52) than those of other sulfonamide drugs (e.g., 2 per cent solutions of sulfapyridine have a pH of 11.2; 2 per cent solutions of sulfathiazole a pH of 10) (65, 70). Ethanolamine salts of sulfanilylthiourea yield solutions having a pH of 7–7.8 (153).

On short boiling with dilute aqueous sodium hydroxide, *p*-nitrophenylsulfonylurea undergoes a remarkable decomposition into sulfur dioxide and *p*-nitrophenylurea:

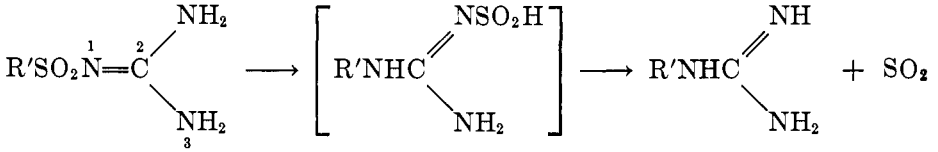


This reaction has been studied more fully with guanidines (7, 8). Benzenesulfonylguanidines containing a nitro group in the para or ortho position are similarly

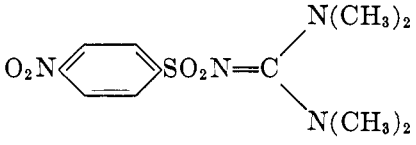
decomposed in alkaline media; bisarylsulfonylguanidines may yield cyanamide as an additional reaction product. The same fission is observed in the thermal decomposition of *N*-*p*-nitrobenzenesulfonylbenzamidine; the sulfonylimino ether XXXIII, however, having a similar structure, is extremely stable to heat (10):



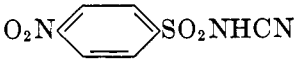
The decomposition of sulfonylguanidines has been interpreted by Backer and Moed (7, 8), who have adduced evidence for a mechanism which involves an intramolecular rearrangement into unstable intermediate aminosulfinic acids:



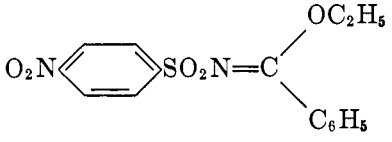
In addition to the influence of activating substituents in the benzene nucleus, the presence of an unsubstituted amino group at carbon atom 2 appears to be necessary for the occurrence of the postulated rearrangement preceding the loss of sulfur dioxide; the mechanism thus agrees satisfactorily with the observation that the tetramethylsulfonylguanidine XXXI, and *p*-nitrophenylsulfonylcyanamide (XXXII), which lack this amino group, are stable towards alkalis, while *p*-nitrophenylsulfonylurea or *p*-nitrophenylsulfonylbenzamidine is readily desulfoxylated.



XXXI



XXXII



XXXIII

Under suitable conditions, sulfonylthioureas are hydrolyzed to sulfonamides. *N*-Carbethoxysulfanilylthiourea, for example, undergoes this fission on prolonged heating with 15 per cent alcoholic ammonia at 150°C. (18).

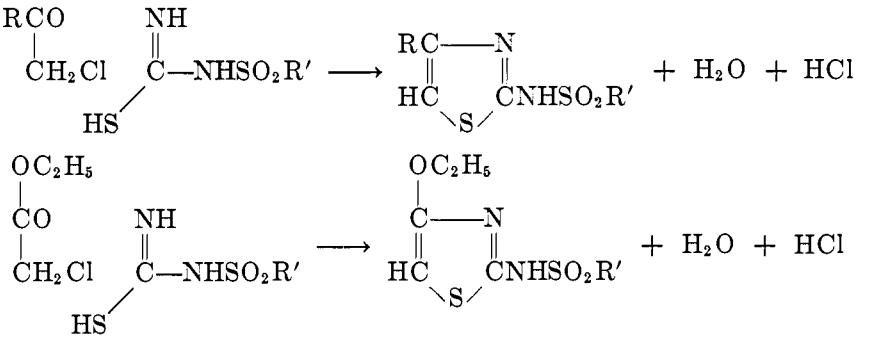
Sulfonylureas decompose above their melting points (6). 1-Aryl-3-arylsulfonylureas are split into the aromatic sulfonamide and isocyanate; arylsulfonylureas yield cyanuric acid as the second decomposition product, probably formed from intermediate isocyanic acid. The course of this thermal decomposition accounts

for the observation that arylsulfonylureas resolidify immediately after fusion and then decompose at a higher temperature (6, 102):

$$R'SO_2NHCONH_2 \rightarrow R'SO_2NH_2 + HNCO \rightarrow C_3H_3N_3O_3$$

$$R'SO_2NHCONHR \rightarrow R'SO_2NH_2 + RNCO$$

Sulfonylthioureas may be converted into substituted thiazoles by the usual methods. The action of sodium sulfanilylthiourea with 1,2-dichloroethyl acetate in aqueous sodium acetate (107), or with dichloroethyl ether in the presence of calcium carbonate (43), yields sulfathiazole. The use of chloroacetone or bromoacetophenone in absolute alcohol affords a 4-alkyl or 4-aryl derivative, while chloroacetic ester gives rise to 4-hydroxylated compounds (56). Various other derivatives of this type have been synthesized by this method (43, 56):



Sulfonylpseudoureas and sulfonylpseudothioureas are stable compounds which may be obtained in the form of lustrous crystalline solids; the solvents most frequently used are methanol, ethanol (anhydrous or aqueous), or butanol, but butyl acetate, acetic acid, or water is sometimes preferred (19, 65, 165). The solubilizing action of pectin has been noted (15). Pseudoureas and pseudothioureas contain the amidino group, $-C(=NH)NH_2$, and are therefore strong monoacid bases; their dissociation constants approach those of primary aliphatic amines. In their sulfonyl derivatives, however, the basic characteristics are considerably reduced, though not completely suppressed, by the presence of the acidic sulfonamide residue. Thus, the hydrochlorides of most sulfanilylthioureas dissociate spontaneously during recrystallization and are therefore prepared from ethanolic hydrochloric acid (19) (*cf.* table 2). Free 1,3-disubstituted sulfonylpseudoureas are directly isolated from acid solution (65).

The hydrolytic fission of sulfonylpseudoureas and their sulfur analogs has already been discussed (*cf.* Section III, D, 1). Their imino group may be acylated: when boiled with acetic anhydride in the presence of sodium acetate, 2-methyl-1-sulfanilylthiopseudourea yields the 3-acetyl derivative (29).

$$R'SO_2NHC(SCH_3)=NH \rightarrow R'SO_2NHC(SCH_3)=NCOCH_3$$

One of the main reasons for the numerous investigations dealing with sulfonylthiopseudoureas is their facile conversion into therapeutically useful sulfonyl-

guanidines. Birtwell, Haworth, Rose, Swain, and Vasey (24, 77) obtained acetylsulfanilylguanidine in 67 per cent yield by passing ammonia through a phenol solution of the corresponding 2-methylthiopseudourea at 110°C.; fusion with dry ammonia and the use of 2-ethyl or 2-benzyl analogs required higher temperatures and gave inferior yields:

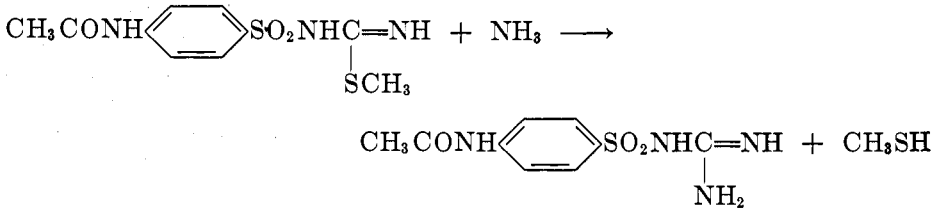
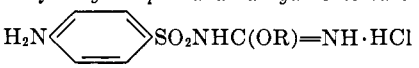


TABLE 2

Sulfanilylthiopseudourea hydrochlorides



R	MELTING POINT OF BASE	MELTING POINT OF HYDROCHLORIDE	BEHAVIOR OF HYDROCHLORIDE
	°C.	°C.	
CH_3	184	226	Dissociates spontaneously Obtained from ethanolic hydrochloric acid
C_2H_5	165	180	
n-C_3H_7	130	175	
n-C_4H_9	115	175–180	
n-C_5H_{11}	125	175	
$CH_2{=}CHCH_2$	174	185	From 10 per cent aqueous HCl
$C_6H_5CH_2$	145	216	Stable; forms free base with NH_3
$C_2H_5OC_6H_4$	141	188	Dissociates spontaneously

Numerous sulfonylguanidines have been prepared (29, 32, 33, 60) by employing various modifications of this method; they include, for example, fusion of the sulfonylthiopseudourea with urea at 210°C. until the evolution of the mercaptan ceases (29), or its interaction with alcoholic or aqueous ammonia under pressure (76). Substituted guanidines are obtainable by the use of alkylamines (18, 152).

VIII. Chemotherapy of Sulfonylureas

The physiological properties of sulfanilylurea (I) and sulfanilylthiourea (II)[4] have been studied in considerable detail and have been reviewed by Northey (123). Pharmacological data have been obtained both in the course of extensive comparative evaluations of sulfonamides (1, 58, 131, 135) and in more specialized investigations. The results of comprehensive physiological and clinical studies

[4] Trade names of these compounds appear occasionally in the literature: Euvernil = sulfanilylurea; Fontamide, Badional, and R.P. 2255 = sulfanilylthiourea; Marbadal = a saltlike addition compound of sulfanilylthiourea and Marfanil ($NH_2CH_2C_6H_4SO_2NH_2$) (48, 97); Supronal = sulfanilylthiourea + Marfanil + Sulfamerazine (97).

have been published by Frisk (58) and Alline (1). Attempts have also been made to relate the antibacterial activity and toxicity of these compounds to their chemical constitution (17, 96).

Sulfonylureas are rapidly, though incompletely, absorbed; they are distributed fairly evenly throughout the body (58, 132) but concentrations considerably higher than the normal blood levels have been observed in certain organs (e.g., kidneys) (1, 131). The concentration in the blood attains its maximum within 2–8 hr. or sooner, after administration, but has dropped practically to zero at the end of 24 hr. (1, 20). The greater part of the drug is eliminated in the urine, between 10 to 20 per cent having undergone acetylation (58). Sulfanilylurea is perhaps the least toxic of the sulfonamides ($L.D._{50}$ for mice = 6.99 g./kg.) (58), but the great tolerance for this drug is largely offset by its very rapid elimination. The suggested dosage is 6 g. per day, but quantities up to 15–20 g. per day appear to be well tolerated (55, 132).

Although the activity *in vitro* of sulfanilylurea against *E. coli* and pneumococci (types I and III) is roughly equal to that of sulfapyridine, its protecting action on infected mice is considerably lower and has been accounted for by its small concentration in the blood. Pichat has demonstrated that tubercle bacilli are killed in 2–3 days by 1:300 solutions, or within 5–20 days by 1:3000 solutions of sulfanilylthiourea. In greater dilution (1:15,000) the growth of the pathogens is retarded but not completely inhibited. The results of clinical trials, however, were not promising (128). When injected into the pleural cavity of tuberculous patients, sulfanilylthiourea was slowly absorbed; a sufficiently high concentration of the drug was therefore retained long enough in the exudate to cause a temporary disappearance of bacilli from the pleural cavity, but the organisms reappeared after a few weeks (129, 130). 3-Benzyl-1-sulfanilylurea, on the other hand, has been claimed to be effective in inhibiting the spread of experimentally induced tuberculosis in guinea pigs (65). While subcutaneous injection of sulfanilylthiourea into mice infected with pneumonia was almost without effect, it was possible to cure the disease by supplying the drug in a fine spray (21). Unfavorable results, due to nonabsorption, were reported on the therapeutic use of sulfanilylthiourea in experimental toxoplasmosis in mice (23).

The clinical use of sulfanilylurea in ophthalmology has been described (55). The treatment of infections of the urinary tract with this drug has been advocated; good results were obtained when a 25 per cent solution was given in cystitis and pyelitis (57, 132).

When administered subcutaneously over two months, sulfanilylthiourea caused a slight degree of thyroid injury in rabbits (5) and produced thyroid hyperemia, enlargement, and hyperplasia in the rat. Hypothyroidism was also indicated by decreases in growth, food intake, and basal oxygen consumption; the effects were prevented by hypophysectomy or by the administration of thyroid powder (86). The antithyroid activity of sulfanilylthiourea, as measured by its inhibiting effect on the uptake of radioactive iodine by the thyroid gland, is slight (145). Several other physiological aspects of sulfanilylthiourea have been investigated (25, 119, 126, 158).

Analogs of Bayer 205 (*cf.* page 20) were found to be inactive against streptococci, staphylococci, and *Eberthella typhosa in vivo* (30).

IX. Analytical

Several methods for detecting and estimating sulfanilylurea and sulfanilylthiourea have been described, and procedures for distinguishing them from other compounds incorporating the sulfanilamide structure are available. Hoffmann and Wilkens (85) have developed a scheme for the separation and identification of sulfonamides, including sulfanilylurea, which is applicable to both solids, solutions, and ampoule liquids. Suitable color reactions, employing sodium nitroprusside (140), sodium nitrite and α-naphthylamine (157), and other specific tests (83, 84) have been suggested. Styphnic acid is a satisfactory reagent for the microcrystalloscopic identification of sulfanilylthiourea (141). Sulfanilylurea may be estimated bromometrically, using potassium bromide–potassium bromate, according to the Koppeschaar method (166).

As is often observed with sulfonamides, the presence of sulfanilylthiourea in urine interferes in a number of standard procedures used in urine analysis. Several investigators (49, 105, 127) have dealt with the detection and determination, in the presence of sulfanilylthiourea, of uric acid, purine bases, sulfur, vitamin C (127), albumin, glucose (105), lactose, acetone, bilirubin, urobilin, and urobilinogen.

The use of sulfanilylthiourea as a reagent for lignin has been suggested. Treatment of the plant tissue with an alkaline solution of this compound, followed by acid, develops an orange color in the presence of lignin (121).

X. Tables of Compounds

The numbers in the columns headed "Method" in tables 3 to 11 correspond to the methods of synthesis listed on page 27.

METHOD	REACTION		CORRESPONDING SECTION AND PAGE OF THIS ARTICLE
1	$R'SO_2NCO + RNH_2$	$\rightarrow R'SO_2NHCONHR$	III, A; page 5
2	$R'SO_2NH_2 + HCNO$	$\rightarrow R'SO_2NHCONH_2$	III, B, 1; page5
3	$R'SO_2NH_2 + RNHCONH_2$	$\rightarrow R'SO_2NHCONHR + NH_3$	III, B, 2; page 6
4	$R'SO_2NH_2 + NH_2CONHNO_2$	$\rightarrow R'SO_2NHCONH_2 + N_2O + H_2O$	III, B, 3; page 6
5	$R'SO_2NH_2 + RNHCOOC_2H_5$	$\rightarrow R'SO_2NHCONHR + C_2H_5OH$	III, B, 4; page 6
6	$R'SO_2NH_2 + R_2NCOCl$	$\rightarrow R'SO_2NHCONR_2 + HCl$	III, B, 5; page 7
7	$R'SO_2NH_2 + RNCO$	$\rightarrow R'SO_2NHCONHR$	III, B, 6; page 7
8	$R'SO_2NH_2 + RCON_3$	$\rightarrow R'SO_2NHCONHR + N_2$	III, B, 7; page 8
9	$R'SO_2NH_2 + RCONHBr$	$\rightarrow R'SO_2NHCONHR + HBr$	III, B, 8; page 8
10	$R'SO_2NHCN + HOH$	$\rightarrow R'SO_2NHCONH_2$	III, C, 1; page 9
11	$R'SO_2Cl + NH_2C(OR)=NH$	$\rightarrow R'SO_2NHC(OR)=NH + HCl$ $\rightarrow R'SO_2NHCONH_2 + RCl$	III, D, 1; page 11
12	$R'SO_2Cl + RNHCONH_2$	$\rightarrow R'SO_2NHCONHR + HCl$	III, D, 2; page 13
13	$R'SO_2NHCONH_2 + RNH_2$	$\rightarrow R'SO_2NHCONHR + NH_3$	III, E, 1; page 18
14	$R'SO_2NHCOOCH_3 + RNH_2$	$\rightarrow R'SO_2NHCONHR + CH_3OH$	III, E, 2; page 19
15	$R'SO_2NHCSNHR$	$\rightarrow R'SO_2NHCONHR$	III, E, 3; page 19
16	$NH_2ArSO_2NH_2 + HCNO$ (etc.)	$\rightarrow NH_2CONHArSO_2NH_2$	IV, A; page 19
17	$ArNHCONH_2 + HSO_3Cl$	$\rightarrow NH_2CONHArSO_2Cl \rightarrow NH_2CONHArSO_2NH_2$	IV, B; page 19
18	$R'SO_2Cl + NH_2NHCONH_2$	$\rightarrow R'SO_2NHNHCONH_2 + HCl$	V; page 20
19	$R'SO_2NHNH_2 + RNCO$	$\rightarrow R'SO_2NHNHCONHR$	V; page 20
20	$R'SO_2NH_2 + ClCOOC_2H_5$	$\rightarrow R'SO_2NHCOOC_2H_5 + HCl$	VI; page 21
21	$R'SO_2Cl + NH_2COOC_2H_5$	$\rightarrow R'SO_2NHCOOC_2H_5 + HCl$	VI; page 21

TABLE 3*

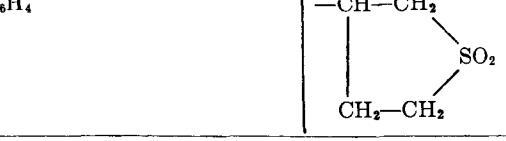
Sulfonylureas

$R'SO_2NHCON\langle^{R}_{R''}$

R′	R	R″	METHOD OF SYNTHESIS	MELTING POINT	REFERENCES
				°C.	
NH_2	$Cl(CH_2)_6$	H	7	128–129	(190)
NH_2	C_6H_5	H	7	151	(190)
$(CH_3)_2N$	$Cl(CH_2)_6$	H	7	94	(190)
$(CH_3)_2N$	C_6H_5	H	7	144–146	(190)
CH_3	$Cl(CH_2)_2$	H	7	174	(190)
CH_3	$Cl(CH_2)_6$	H	7	146–147	(190)
CH_3	C_6H_5	H	7	168	(190)
$ClCH_2$	C_6H_5	H	7	146	(190)
n-C_6H_{13}	H	H	3	A	(80)
n-$C_{16}H_{33}$	H	H	2	156–157	(80)
Alkyl	H	H	2	A	(80)
Cyclo-C_6H_{11}	H	H	2	A	(80)
C_6H_5	H	H	1	167	(22)
			2	170–171	(75)
			11	169–171	(40, 74)
			12	167	(193)
C_6H_5	$Cl(CH_2)_6$	H	7	77–79	(190)
C_6H_5	C_6H_5	H	1	158	(22)
			7	166–167	(102)
			7	158	(190)
C_6H_5	4-$O_2NC_6H_4$	H	7	126–128	(190)
C_6H_5	C_2H_5	C_6H_5	1	123	(22)
C_6H_5	CH_3CO	H	1	155–156	(22)
C_6H_5	C_6H_5CO	H	1	208	(22)
C_6H_5	$C_6H_5SO_2$	H	1	159	(22)
4-$CH_3C_6H_4$	H	H	2	200–202 (d)	(102)
			4	184–188 (d)	(75)
			11	192	(40)

4-$CH_3C_6H_4$	C_6H_5	H	3, 7	172–174	(102)
			7	163–165	(190)
4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	H	3	160–162	(102)
1-$C_{10}H_7$	H	H	11	211	(40)
4-ClC_6H_4	4-ClC_6H_4	H	7	245	(190)
4-ClC_6H_4	3,4-$Cl_2C_6H_3$	H	7	186–188	(190)
4-$O_2NC_6H_4$	H	H	2	A	(116)
			6	198–200	(116)
			10	178–180	(6)
			12	190 (d)	(64, 69, 115)
4-$O_2NC_6H_4$	CH_3	H	7	213	(67)
4-$O_2NC_6H_4$	$C_6H_5CH_2$	H	1, 6, 7	226–232	(65)
			8, 13	224–232	(65)
			B	A	(174)
4-$O_2NC_6H_4$	3,4-$(CH_3)_2C_6H_3CH_2$	H	7	199	(65)
4-$O_2NC_6H_4$	C_2H_5	H	7	175–176	(64, 66, 115)
4-$O_2NC_6H_4$	C_2H_5	C_2H_5	6	A	(64, 69, 115)
4-$O_2NC_6H_4$	Iso-C_5H_{11}	H	7	155	(67)
3-$O_2NC_6H_4$	$Cl(CH_2)_6$	H	7	141–144	(190)
3-$O_2NC_6H_4$	C_6H_5	H	7	152–154	(190)
4-$CH_3CONHC_6H_4$	H	H	2, 3, 4	185–188 (d)	(75)
			12	241–242	(120)
4-$CH_3CONHC_6H_4$	CH_3	H	11	232–233	(74)
4-$CH_3CONHC_6H_4$	CH_3	CH_3	11	A	(74)
			12	>330	(120)
4-$CH_3CONHC_6H_4$	$C_6H_5CH_2$	H	3, 7, 9	214–218	(65, 173)
			13, 14, 15	216–218	(65)
			7, 9, 14	214–217	(172)
4-$CH_3CONHC_6H_4$	4-$CH_3C_6H_4CH_2$	H	7	A	(65)
4-$CH_3CONHC_6H_4$	Cyclo-C_6H_{11}	H	11	A	(74)
4-$CH_3CONHC_6H_4$	$Cl(CH_2)_6$	H	7	172–174	(190)
4-$CH_3CONHC_6H_4$		H	7	214–216	(190)

TABLE 3—*Concluded*

R′	R	R″	METHOD OF SYNTHESIS	MELTING POINT	REFERENCES
				°C.	
4-$CH_3CONHC_6H_4$	C_6H_5	H	7	A	(75)
			11	A	(74)
			7	188–189	(190)
4-$CH_3CONHC_6H_4$	C_6H_5	C_6H_5	12	201	(120)
4-$CH_3OOCNHC_6H_4$	$C_6H_5CH_2$	H	7	185–187	(65)
			7	A	(172)
4-$C_2H_5OOCNHC_6H_4$	$Cl(CH_2)_6$	H	7	139–141	(190)
4-$C_2H_5OOCNHC_6H_4$	C_6H_5	H	7	191–193	(190)
4-$H_2NC_6H_4$	H	H	3	149–154 (d)	(75)
			3	125–127† (d)	(75)
			10	143–147 (d)	(107)
			10	121–124† (d)	(107)
			10, 11	140–144	(165)
			11	140–146	(38, 74)
			12	303 (d)	(120)
			12	320 (subl.)	(64, 69, 115)
			2, 3, 4, 5, 6	158–160 (d)	(116)
4-$H_2NC_6H_4$	CH_3	H	7	173	(64, 67, 115)
4-$H_2NC_6H_4$	CH_3	CH_3	11	158–161	(74)
			12	268–270 (d)	(120)
4-$H_2NC_6H_4$	$C_6H_5CH_2$	H	3, 5, 7, 11, 13, 14	215–218	(65)
			7	217–218	(172)
4-$H_2NC_6H_4$	3,4-$(CH_3)_2C_6H_3CH_2$	H	7	174–175	(65)
4-$H_2NC_6H_4$	C_2H_5	H	7	160	(64, 66, 115)
4-$H_2NC_6H_4$	C_2H_5	C_2H_5	6	170 (d)	(64, 68, 115)
4-$H_2NC_6H_4$	Iso-C_5H_{11}	H	7	150–152	(64, 67, 115)
4-$H_2NC_6H_4$	$Cl(CH_2)_6$	H	7	113–114	(190)
4-$H_2NC_6H_4$		H	7	168–170	(190)

$4\text{-}H_2NC_6H_4$	C_6H_5	H	7	160–161	(190)
$4\text{-}H_2NC_6H_4$	$4\text{-}CH_3C_6H_4$	H	7	195–196	(65)
$4\text{-}H_2NC_6H_4$	$4\text{-}O_2NC_6H_4$	H	7	A	(115)
$4\text{-}H_2NC_6H_4$	$4\text{-}H_2NC_6H_4$	H	7	260 (d)	(25, 64, 115)
$4\text{-}H_2NC_6H_4$	$3\text{-}H_2NC_6H_4$	H	7	174 (d)	(64, 115)
$4\text{-}H_2NC_6H_4$	C_6H_5	C_6H_5	12	216	(120)
$4\text{-}C_6H_5NHCONHC_6H_4$	C_6H_5	H	7	208–210	(190)
$[C_6H_5SO_2NHCONH]_2(CH_2)_6$			7	182	(190)

* The following abbreviations are used:
(d) = melts with decomposition;
(subl.) = sublimes;
A = information not available;
B = special method not included among the syntheses listed.

† Hydrate.

TABLE 4*

Sulfonylthioureas

$R'SO_2NHCSNHR$

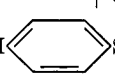
R′	R	METHOD OF SYNTHESIS	MELTING POINT	REFERENCES
			°C.	
$(CH_3)_2N$	C_6H_5	7	109	(190)
CH_3	C_6H_5	7	164–166	(190)
n-C_4H_9	H	2	A	(80)
C_6H_5	H	10	138–139	(150, 169)
		11	138	(147)
		A	134–136	(118)
C_6H_5	$C_6H_5CH_2$	7	144–147	(190)
C_6H_5	C_6H_5	7	138	(190)
3-$O_2NC_6H_4$	CH_2=$CHCH_2$	7	126–127	(190)
4-$C_2H_5OOCNHC_6H_4$	H	11	140, 178 (d)	(19)
4-$C_2H_5OOCNHC_6H_4$	CH_2=$CHCH_2$	7	162–163	(190)
4-SuccinylNHC$_6H_4$	H	A	205	(149)
4-PhthalylNHC$_6H_4$	H	A	224	(149)
4-$CH_3CONHC_6H_4$	H	2	A	(34)
		10	197–198	(43, 107)
		10	200–201, 228	(150, 169)
		11	198–202	(19, 56, 94, 107, 179)
		11	228	(147)
		12	243	(120)
		12	No product	(107)
4-$CH_3CONHC_6H_4$	$C_6H_5CH_2$	7, 13	202–204 (d)	(65)
		7	184–185	(190)
4-$CH_3CONHC_6H_4$	CH_2=$CHCH_2$	7	170–171	(190)
4-$CH_3CONHC_6H_4$	C_6H_5	12	>330	(120)
		7	184–185	(190)
4-$H_2NC_6H_4$	H	A	A	(56)
		A	172, 203	(94, 118)
		2	A	(34)
		10	169–172	(43, 107)
		10	200–201	(150, 151, 169)
		11	182	(19)
		11	200 (d)	(147)
		12	285 (d)	(120)
4-$H_2NC_6H_4$	$C_6H_5CH_2$	7	165–167	(190)
4-$H_2NC_6H_4$	CH_2=$CHCH_2$	7	110–111	(190)
4-$H_2NC_6H_4$	C_6H_5	7	177–178	(35)
		12	276 (d)	(120)
		7	142–144	(190)

* The following abbreviations are used:
(d) = melts with decomposition;
A = information not available.

TABLE 5

Sulfonylpseudoureas

$$R'SO_2NR''—\underset{\displaystyle OR}{\overset{\displaystyle |}{C}}=NH$$

R′	R	R″	METHOD OF SYNTHESIS	MELTING POINT	REFERENCES
				°C.	
C_6H_5	CH_3	H	11	164–165	(74)
C_6H_5	C_2H_5	H	11	101, 110	(12, 40)
C_6H_5	n-C_3H_7	H	11	74	(11)
4-$CH_3C_6H_4$	C_2H_5	H	11	79	(40)
4-$O_2NC_6H_4$	CH_3	H	10	A*, 203–206	(138, 165)
4-$O_2NC_6H_4$	C_2H_5	H	10	A*	(138)
4-$O_2NC_6H_4$	Iso-C_3H_7	H	10	113–114	(138)
4-$CH_3CONHC_6H_4$	CH_3	H	11	188–189	(74)
4-$CH_3CONHC_6H_4$	CH_3	Cyclo-C_6H_{11}	11	195–200	(74)
4-$CH_3CONHC_6H_4$	CH_3	$C_6H_5CH_2$	11	198–200	(65)
4-$CH_3CONHC_6H_4$	C_2H_5	H	11	233–234	(38)
			11	195–200	(74)
4-$H_2NC_6H_4$	CH_3	H	10	172–173	(138, 165)
4-$H_2NC_6H_4$	C_2H_5	H	10	126–128	(138, 165)
4-$H_2NC_6H_4$	Iso-C_3H_7	H	10	104–105	(138)
1-$C_{10}H_7$	CH_3	H	11	152	(11)
1-$C_{10}H_7$	C_2H_5	H	11	145	(40)
CH_3CONH  $SO_2N=C(OCH_3)N(CH_3)_2$			11	136–144	(74)

* A = information not available.

TABLE 6

*Sulfonylthiopseudoureas**

$R'SO_2NR''C(=NH)SR$

R′	R	R″	MELTING POINT	REFERENCES
			°C.	
C_5H_5	CH_3	H	159–160	(39, 41)
C_6H_5	C_2H_5	H	109–110	(41)
4-$CH_3C_6H_4$	CH_3	H	118–120	(19, 39, 41)
4-$CH_3C_6H_4$	$(CH_3)_3C$	H	109–110	(19)
2,4-$(CH_3)_2C_6H_3$	CH_3	H	137–138	(39, 41)
3,4-$(CH_3)_2C_6H_3$	CH_3	H	136–137	(39, 41)
2,5-$(CH_3)_2C_6H_3$	CH_3	H	144–145	(39, 41)
4-ClC_6H_4	CH_3	H	114	(60)
4-$O_2NC_6H_4$	$C_6H_5CH_2$	H	172	(77)
4-$O_2NC_6H_4$	Cyclo-C_6H_{11}	H	163–165	(77)
4-$O_2NC_6H_4$	C_2H_5	H	108–110	(77)
			A†	(170)
4-$CH_3CONHC_6H_4$	CH_3	H	225–226	(24)
			230–232	(39, 41)
			234–236	(29, 77, 107)
4-$CH_3CONHC_6H_4$	CH_3	CH_3CO	92	(29)
4-$CH_3CONHC_6H_4$	$C_6H_5CH_2$	H	168–169	(77, 107)
			170	(19)
			171–173	(72, 73)
			A	(147)
4-$CH_3CONHC_6H_4$	$C_6H_5CH_2$	C_6H_5	205–206	(73)
4-$CH_3CONHC_6H_4$	4-$O_2NC_6H_4CH_2$	H	214–225	(73)
4-$CH_3CONHC_6H_4$	4-$O_2NC_6H_4CH_2$	C_6H_5	201	(73)
4-$CH_3CONHC_6H_4$	4-$CH_3OC_6H_4CH_2$	H	138–140	(73)
4-$CH_3CONHC_6H_4$	CH_3OCH_2	H	166–167 (d)†	(56, 94, 107, 179)
4-$CH_3CONHC_6H_4$	C_2H_5	H	181–182	(32, 33, 41, 72, 170)
			188	(77)
4-$CH_3CONHC_6H_4$	C_2H_5	C_6H_5	209–210	(73)
4-$CH_3CONHC_6H_4$	C_2H_5	4-$CH_3C_6H_4$	204–206	(73)
4-$CH_3CONHC_6H_4$	C_2H_5	4-$CH_3OC_6H_4$	200–201	(73)
4-$CH_3CONHC_6H_4$	C_2H_5	2-$C_{10}H_7$	201–202	(73)
4-$CH_3CONHC_6H_4$	HOC_2H_4	H	236–238	(107)
4-$CH_3CONHC_6H_4$	$C_6H_5C_2H_4$	H	163	(19)
4-$CH_3CONHC_6H_4$	C_3H_7	H	174–175	(19, 72)
4-$CH_3CONHC_6H_4$	C_3H_7	C_6H_5	206–207	(73)
4-$CH_3CONHC_6H_4$	CH_2=$CHCH_2$	H	165	(19)
			173–174	(72)
4-$CH_3CONHC_6H_4$	CH_2=$CHCH_2$	C_6H_5	204	(73)

* All the compounds in this table were prepared by method 11.

† A = information not available.
(d) = melts with decomposition.

TABLE 6—*Concluded*

R′	R	R″	MELTING POINT	REFERENCES
			°C.	
4-$CH_3CONHC_6H_4$	*n*-C_4H_9	H	155–157	(19, 72)
4-$CH_3CONHC_6H_4$	*n*-C_4H_9	C_6H_5	207–208	(73)
4-$CH_3CONHC_6H_4$	$(CH_3)_3C$	H	203	(19)
4-$CH_3CONHC_6H_4$	*n*-C_5H_{11}	H	141	(19)
4-$CH_3CONHC_6H_4$	Iso-C_5H_{11}	H	186	(73)
4-$CH_3CONHC_6H_4$	*n*-C_6H_{13}	H	125–126	(41)
4-$C_2H_5OOCNHC_6H_4$	$(CH_3)_3C$	H	206–207	(19)
4-$H_2NC_6H_4$	CH_3	H	183–185	(19, 41, 39, 107, 165)
4-$H_2NC_6H_4$	$C_6H_5CH_2$	H	143–145	(19, 73, 77, 107)
4-$H_2NC_6H_4$	$C_6H_5CH_2$	C_6H_5	190	(73)
4-$H_2NC_6H_4$	4-$O_2NC_6H_4CH_2$	H	153–155	(73)
4-$H_2NC_6H_4$	4-$O_2NC_6H_4CH_2$	C_6H_5	166 (d)†	(73)
4-$H_2NC_6H_4$	4-$CH_3OC_6H_4CH_2$	H	89–92	(73)
4-$H_2NC_6H_4$	C_2H_5	H	154–156	(72, 165)
			160–161	(41, 77)
			165–168	(19, 118)
			159–160	(170)
4-$H_2NC_6H_4$	C_2H_5	C_6H_5	192–193	(73)
4-$H_2NC_6H_4$	C_2H_5	4-$CH_3C_6H_4$	188–189	(73)
4-$H_2NC_6H_4$	C_2H_5	4-$CH_3OC_6H_4$	194	(73)
4-$H_2NC_6H_4$	C_2H_5	2-$C_{10}H_7$	186–188	(73)
4-$H_2NC_6H_4$	HOC_2H_4	H	171–173	(107)
4-$H_2NC_6H_4$	$C_6H_5C_2H_4$	H	141	(19)
4-$H_2NC_6H_4$	*n*-C_3H_7	H	130	(19)
			133–134	(72)
4-$H_2NC_6H_4$	*n*-C_3H_7	C_6H_5	195–196	(73)
4-$H_2NC_6H_4$	CH_2=$CHCH_2$	H	170–174	(19, 72)
4-$H_2NC_6H_4$	CH_2=$CHCH_2$	C_6H_5	193–194	(73)
4-$H_2NC_6H_4$	*n*-C_4H_9	H	155–116	(19, 72)
4-$H_2NC_6H_4$	*n*-C_4H_9	C_6H_5	191–192	(73)
4-$H_2NC_6H_4$	*n*-C_5H_{11}	H	125	(19)
4-$H_2NC_6H_4$	Iso-C_5H_{11}	H	145–146	(73)
4-$H_2NC_6H_4$	*n*-C_6H_{13}	H	129–130	(41)
4-CNC_6H_4	CH_3	H	132–133	(4)
[4-$H_2NC_6H_4SO_2NHC$(=NH)$SCH_2]_2$			175–177	(73)
[4-$CH_3CONHC_6H_4SO_2NHC$(=NH)$SCH_2]_2$			255	(73)

† (d) = melts with decomposition.

TABLE 7

Sulfamidoureas

$R'SO_2NHNHCONHR$

R′	R	METHOD OF SYNTHESIS	MELTING POINT	REFERENCES
			°C.	
4-$CH_3CONHCH_2C_6H_4$	H	18	193–194 (d)*	(122)
4-$H_2NCH_2C_6H_4$	H	18	225–226 (d)†	(122)
4-$O_2NC_6H_4$	H	18	A*	(164)
4-$CH_3CONHC_6H_4$	H	18	A	(164)
		18	227 (d)	(139)
		18	223–224 (d)	(122)
4-$CH_3CONHC_6H_4$	2-$CH_3C_6H_4$	19	206–207	(139)
4-$CH_3CONHC_6H_4$	4-BrC_6H_4	19	215–216 (d)	(139)
4-$CH_3CONHC_6H_4$	4-$O_2NC_6H_4$	19	214–215 (d)	(139)
4-$H_2NC_6H_4$	H	18	A	(164)
		18	229 (d)	(122)

* (d) = melts with decomposition.
A = information not available.
† Hydrochloride.

TABLE 8

Sulfamidothioureas

$R'SO_2NHNHCSNHR$

R′	R	METHOD OF SYNTHESIS	MELTING POINT	REFERENCES
			°C.	
4-$CH_3CONHC_6H_4$	H	18	A*	(164)
		18	186	(122)
		18	193–194 (d)*	(139)
4-$CH_3CONHC_6H_4$	CH_3	19	228 (d)	(139)
4-$CH_3CONHC_6H_4$	C_2H_5	19	214 (d)	(139)
4-$CH_3CONHC_6H_4$	n-C_3H_7	19	210 (d)	(139)
4-$CH_3CONHC_6H_4$	CH_2=$CHCH_2$	19	212–214 (d)	(139)
4-$CH_3CONHC_6H_4$	n-C_4H_9	19	212–213 (d)	(139)
4-$CH_3CONHC_6H_4$	n-C_5H_{11}	19	204 (d)	(139)
4-$CH_3CONHC_6H_4$	C_6H_5	19	216–217 (d)	(139)
4-$CH_3CONHC_6H_4$	4-$CH_3OC_6H_4$	19	209–210 (d)	(139)
4-$CH_3CONHC_6H_4$	1-$C_{10}H_7$	19	232–233 (d)	(139)
4-$H_2NC_6H_4$	H	18	A	(164)
		18	224–225 (d)	(122)

* (d) = melts with decomposition.
A = information not available.

TABLE 9

Sulfamylureas

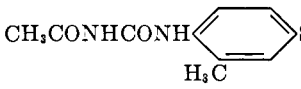
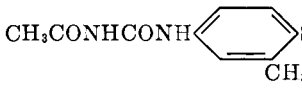
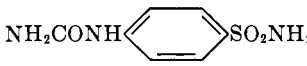
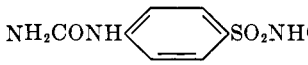
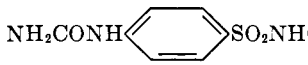
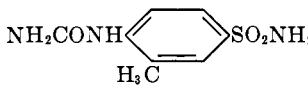
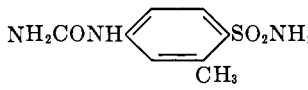
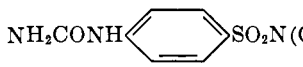
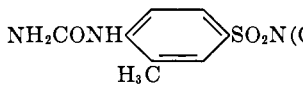
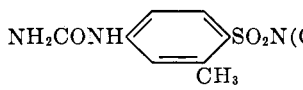
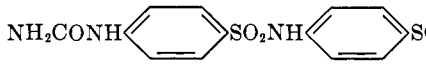
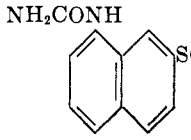
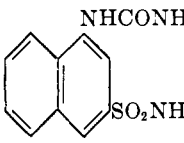
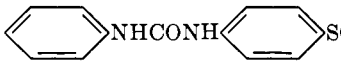
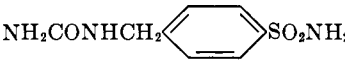
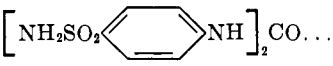
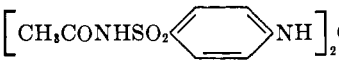
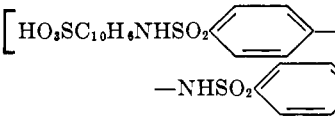
COMPOUND	METHOD OF SYNTHESIS	MELTING POINT	REFERENCES
		°C.	
	17	246–247	(37)
	B*	244	(54)
	17	231–233	(37)
	17	226–227	(37)
	16	A*	(95, 108)
	16	208–209	(98)
	16, 17	202	(156, 180)
	17	206–207	(37)
	B	206–207	(54)
	18	203-204	(156)
	17	207	(156)
	17	223–225	(37)
	17	209–210	(37)
	17	148–149	(37)
	17	165–167	(37)
	17	147–148	(37)

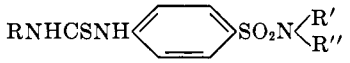
TABLE 9—*Concluded*

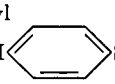
COMPOUND	METHOD OF SYNTHESIS	MELTING POINT	REFERENCES
		°C.	
	17	210 (d)*	(180)
	16	225	(36)
	16	273	(36)
	16	231–233	(139)
	16	258–259	(139)
	16	239–240	(139)
	16 B	197–198 192–193	(82) (188)
	16 17 17 B B	270–271 (d) A 272–274 (d) 238 290 (d)	(144) (50, 61, 71, 168) (27, 156, 194) (90) (89)
	B	320	(90)
	16	A	(133, 134)

* B = special method not included among the syntheses listed.
A = information not available.
(d) = melts with decomposition.

TABLE 10

*Sulfamylthioureas**



R	R′	R″	MELTING POINT	REFERENCES
			°C.	
H	H	H	A†	(51)
			197, 209	(62, 159)
CH_3	H	H	205–206	(139)
C_2H_5	H	H	201–202	(139)
C_3H_7	H	H	182–183	(139)
CH_2=$CHCH_2$	H	H	182	(62)
			189–190	(139)
CH_2=$CHCH_2$	CH_3	CH_3	181	(62)
CH_2=$CHCH_2$	4-$H_2NC_6H_4$	H	175	(62)
CH_2=$CHCH_2$	4-$(CH_3)_2NC_6H_4$	H	161	(62)
CH_2=$CHCH_2$	4-$H_2NSO_2C_6H_4$	H	180–181	(62)
n-C_4H_9	H	H	170–171	(139)
n-C_5H_{11}	H	H	157–158	(139)
C_6H_5	H	H	189–191	(62, 139)
2-$CH_3C_6H_4$	H	H	215–216	(139)
1-$C_{10}H_7$	H	H	193–194	(139)
4-$C_2H_5OC_6H_4$	H	H	A	(51)
4-$HOOCC_6H_4$	H	H	213, 263–268 (d)†	(113)
4-$HOOCC_6H_4$	2-Thiazolyl	H	185, 195–200	(113)
4-$HOOCC_6H_4$	2-Pyridyl	H	175–179	(113)
3-$HOOCC_6H_4$	H	H	A	(51)
4-$NH_2SO_2C_6H_4$	H	H	A	(51)
4-$NH_2SO_2C_6H_4$	2-Thiazolyl	H	214–217	(113)
4-$H_2O_3AsC_6H_4$	H	H	A	(51)
4-$H_2O_3SbC_6H_4$	H	H	A	(51)
2-Pyridyl	H	H	A	(51)
6-CH_3O-8-quinolyl	H	H	189–190	(113)
2-Thiazolyl	2-Pyridyl	H	167–170	(113)
			138–140	(162)

* All compounds listed in this table were prepared by method 16.

† A = information not available.

(d) = melts with decomposition.

TABLE 11

Sulfonylurethans

R′SO_2NHCOOR

R′	R	METHOD OF SYNTHESIS	MELTING POINT	REFERENCES
			°C.	
C_6H_5	C_2H_5	1	109	(22)
4-$CH_3CONHC_6H_4$	C_2H_5	21	172	(120)
4-$H_2NC_6H_4$	C_2H_5	21	270	(120)
		20, 21	133 (d)*	(64, 115)
4-$O_2NC_6H_4$	C_2H_5	20, 21	A*	(64, 115)
C_6H_5	C_6H_5	1	123	(22)

* (d) = melts with decomposition.

A = information not available.

XI. References

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XII. APPENDIX

The chemistry of sulfonylureas has seen few new developments in the period covered by this appendix,[5] since most reports deal with the application and extension of the reactions discussed in the main body of this review. This applies particularly to a number of patents that have recently appeared (169, 170, 172, 173, 179).

The interaction of sulfonamides and isocyanates (*cf.* Section III, B, 6) has been the subject of further experiments. Petersen (189), investigating the fusion of hexamethylene diisocyanate and sulfonamides in the absence of catalysts at 180°C., obtained viscous insoluble resins; in subsequent work (190), sulfonylureas were produced in excellent yields when an isocyanate was added to the sulfonamide in alkaline solution at room temperature (*cf.* 65, 172). As in the corresponding reaction with carbonamides (195), the sulfonamido group must be unsubstituted; benzenesulfonmethylamide, for example, fails to react. Sulfanilamide condenses with two molecules of isocyanate to yield compounds of the formula $RNHCONHC_6H_4SO_2NHCONHR$; it will be recalled that only the N^4-amino group reacts in the absence of alkali (139). Sulfamide ($NH_2SO_2NH_2$) readily affords the expected sulfonylurea, but only one of the amino groups is affected:

$$NH_2SO_2NH_2 + Cl(CH_2)_6NCO \rightarrow NH_2SO_2NHCONH(CH_2)_6Cl$$

Analogous results are observed in the corresponding thiourea series, provided that slightly higher reaction temperatures are employed.

The direct condensation of benzenesulfonyl chloride with urea, in 2 *N* aqueous sodium hydroxide according to the Schotten–Baumann method, has been claimed to produce good yields of benzenesulfonylurea (193). Attempts to employ carbethoxymethanesulfonyl chloride, or the dichloride of carboxymethanesulfonic (sulfoacetic) acid, under the same conditions, however, were unsuccessful (193; *cf.* 26). The above observation would represent the first example of a direct attack of a sulfonyl halide, in the urea system, at the nitrogen in preference to the (unprotected) oxygen atom (*cf.* Section III, D, 2). The intermediate formation of an *O*-sulfonate, $RSO_2OC(=NH)NH_2$, followed by isomerization to the *N*-substituted derivative, well known in the acylthiourea series (46, 47), is unlikely. The *O*-sulfonate may reasonably be expected to show the usual instability of this structure; its immediate decomposition into benzenesulfonic acid and cyanamide, probably followed by the formation of sulfonylcyanamide, would then be the course of the above reaction.

[5] The appendix covers the literature, through *Chemical Abstracts*, up to July, 1951.

A new synthesis (174) of a sulfonylurea involves the interaction of benzylurea with a sulfenyl chloride: the intermediate sulfenyl compound is then oxidized with potassium permanganate.

$$RNHCONH_2 + R'SCl \rightarrow HCl + RNHCONHSR' \xrightarrow{2O} RNHCONHSO_2R'$$

The biological synthesis of a sulfamylurea has been observed (188). *p*-Aminomethylbenzenesulfonamide, when administered orally, is not only acetylated in the body, but appreciable quantities of *p*-sulfonamidobenzylurea are also excreted; the compound arises probably by the condensation of urea with the administered sulfonamide, although the unacetylated drug itself is not detected in the urine.

The chlorosulfonation of arylureas, carbanilide, and arylurethans has been reëxamined (180, 183, 187, 194) and its mechanism studied (192).

CHEMOTHERAPY

The biochemical properties and clinical potentialities of sulfanilylurea and sulfanilylthiourea continue to attract considerable attention. Domagh (171) has stressed the favorable comparison between the effectiveness of drugs incorporating sulfanilylthiourea with that of penicillin and streptomycin against *Clostridium perfrigens*, *Clostridium chauvoei*, and hemolytic staphylococci *in vitro* and *in vivo*. Adequate blood levels of sulfanilylthiourea in patients can be maintained by oral and rectal administration (191). The drug inhibits the growth of pathogenic strains of pleuropneumonia-like organisms and is also effective against saccharomyces, streptococci, staphylococci, and *C. diphtheriae* (184). Enterococci are somewhat sensitive to the action of Marbadal (see footnote 4, page 24); its activity is not inhibited in the presence of *p*-aminobenzoic acid (175). An attempt has been made (185) to relate the activity of sulfonylureas and analogous drugs to the stability of certain of their copper complexes.

The use of sulfanilylthiourea in dentistry has been reviewed (182) and its germicidal power, both alone and in combination with wetting agents, such as sodium dodecylsulfonate, has been assessed (181).

ANALYTICAL

Hoffmann and Wilkins (178) have revised their scheme for the identification, in sulfonamide preparations, of sulfanilylurea and sulfanilylthiourea. Individual tests, including the production of characteristic precipitates with silver nitrate, potassium mercuric iodide (K_2HgI_4), and copper tetraaminosulfate, have been described (176, 177). Attention has been drawn to the fact that sulfanilylthiourea and its derivatives can be determined by the bromometric method (166) only if the thiourea sulfur is first removed by treatment with silver sulfate solution (196). In the production of sulfonamide preparations incorporating sulfanilylthiourea, careful attention must be given to its possible incompatibility with other sulfonamides, since slow interaction with evolution of hydrogen sulfide may occur (186).

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