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Further Studies on the Synthesis of Substituted Ureas

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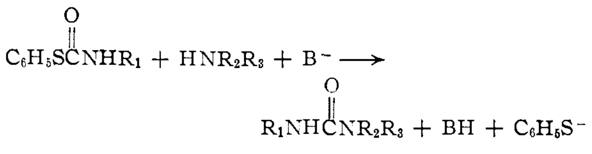
The base-catalyzed reaction of S-phenylthiocarbamate, or N-monosubstituted derivatives thereof, with ammonia, or with primary or secondary amines, or with certain amides or hydrazines, to give the corresponding substituted ureas or semicarbazides has been shown to be of preparative interest and to be capable of modification to permit the use of alternative reagents and of extension to the synthesis of the analogous thioureas. Possible mechanisms for this reaction have been considered.

In a previous communication from these laboratories[2] it was suggested that the reaction



$$C_6H_5S\overset{O}{\overset{\|}{C}}NHR_1 + HNR_2R_3 + B^- \longrightarrow R_1NH\overset{O}{\overset{\|}{C}}NR_2R_3 + BH + C_6H_5S^-$$

where R_1, R_2 and R_3 are hydrogen atoms or alkyl or aryl groups, could be applied to the synthesis of many mono-, di- and trisubstituted ureas. It is the purpose of this communication to show that the above reaction can be so used and that it is capable of modification and extension.

S-Phenylthiocarbonyl chloride[3] reacts with ammonia or with primary or secondary amines to form the corresponding amides.[3] While the amides obtained from secondary amines are relatively stable in the presence of both acids and bases[2,3] those formed from ammonia or primary amines are readily decomposed in alkaline medium.[2,3] Therefore, in the preparation of amides of the latter types it is desirable to add a solution of two moles of the amine to one of the acid chloride except in those cases where the amine has a pK_B greater than *ca.* 8 where the reverse order of addition is equally satisfactory. Although the above procedure requires a second mole of the amine for neutralization of the hydrogen chloride formed during the reaction it should be noted that the yields obtained by this method are generally greater than 90% of the theoretical.

The addition of two moles of the amine to one of the acid chloride was found to proceed rapidly and smoothly in dioxane or absolute ethanol solutions. The amides so formed were recovered either by pouring the reaction mixtures into cold water, or by their evaporation to dryness, extraction of the neutral residue with either benzene or toluene and subsequent precipitation of the amides from these solutions by the addition of ligroin. The amides were purified by recrystallization from mixtures of toluene and ligroin after it was found that recrystallization from hot aqueous ethanol frequently led to products which did not give satisfactory analyses and which appeared to be contaminated by hydrolysis products of the original amides. The properties of a series of representative N-monosubstituted-S-phenylthiocarbamates are given in Table I.

For the synthesis of the various substituted ureas the requisite S-phenylthiocarbamate, derived from either ammonia or a primary amine, was dissolved in dioxane or absolute ethanol,[2] and to this solution was added the appropriate primary or secondary amine and a base such as triethylamine. After the reaction mixture had been allowed to stand for 1 hour at *ca.* 25° the urea was isolated by one of the several methods described below.[4] Triethylamine was found to be the most satisfactory catalyst for general use because it is a sufficiently strong base to function as an effective proton acceptor in the reaction under discussion, it is freely soluble in the usual reaction media, and it can be removed readily from the reaction mixture by distillation. Where the added amine has a pK_B of less than *ca.* 6 it may of course be added in excess so as to assume the role of both reactant and catalyst. Sodium hydroxide, while convenient in certain cases, *e.g.*, with α-amino acids,[2] does not appear to be as generally useful as triethylamine.

Water-insoluble ureas are conveniently isolated in yields greater than 90% by a procedure in which the reaction mixture is poured into water containing an excess of 1 *N* hydrochloric acid, the suspension so formed steam distilled until the residual suspension is practically odorless, the precipitated urea collected, washed with aqueous sodium carbonate and with water and finally recrystallized from toluene or absolute ethanol. If the steam distillation is omitted several recrystallizations from toluene are necessary to obtain an odorless product. A more general method of isolation is based upon the removal of the solvent, the tertiary amine catalyst and thiophenol by evaporation of the reaction mixture to dryness on a steam-bath, and under an inert atmosphere, followed by recrystallization of the residue from toluene or aqueous-ethanol. In those cases where the added amine is a gas and can also serve as the catalyst, the reaction is conveniently conducted by passing the gas into a toluene solution of the appropriate amide followed by subsequent precipitation of the urea by the addition of ligroin.

In many instances the ureas may be prepared without the actual isolation of the intermediate S-phenylthiocarbamate.[2] In addition to the procedure described earlier[2] the following method may be applied. S-Phenylthiocarbonyl chloride, and a onefold excess of ammonia or a primary

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[1] To whom inquiries regarding this article should be sent.

[2] W. H. Schuller and C. Niemann, THIS JOURNAL, **75**, 3425 (1953).

[3] H. Rivier, *Bull. soc. chim.*, [4] **1**, 733 (1907).

[4] The use of anhydrous dioxane or ethanol is not obligatory provided that the reaction proceeds rapidly at room temperature. For those cases where it does not anhydrous solvents are required for the attainment of good yields of the ureas.

amine are allowed to react in a water-insoluble solvent, the amine hydrochloride removed by extraction of the reaction mixture with dilute aqueous hydrochloric acid, the non-aqueous phase dried, the second amine, and triethylamine if necessary, added to this solution and the urea isolated as described above. If a symmetrical disubstituted urea is to be prepared, the above procedure may be modified by allowing the acid chloride to react with two moles of the requisite primary amine in the presence of an excess of triethylamine.

Some of the ureas prepared from S-phenylthiocarbamate, or N-monosubstituted derivatives thereof, are listed in Table II. In general, the yields were 90% or greater. In addition to a comparison of the melting points of the various ureas with those given in the literature[5–24] all of the ureas listed in Table II which contained a phenyl group were prepared also from phenyl isocyanate in order that a direct comparison of the melting point could be made in these cases.

The extension of the base-catalyzed reaction of S-phenylthiocarbamate, or of N-monosubstituted derivatives thereof, with ammonia, or with primary or secondary amines, to the synthesis of analogous compounds was demonstrated by the synthesis of N-phenyl-N'-benzoylurea[22] from N,S-diphenylthiocarbamate and benzamide,[25] by the preparation of 1,4-diphenylsemicarbazide[23] from the same carbamate and phenylhydrazine, and by the synthesis of N,N'-diphenylthiourea[24] from N,S-diphenyldithiocarbamate and aniline. In all three cases triethylamine was used as the base and in the latter instance the dithiocarbamate was prepared by the reaction of phenyl isothiocyanate with thiophenol rather than by the reaction of aniline with the known S-phenyldithiocarbonyl chloride.[3]

A further modification was made by the replacement of N,S-diphenylthiocarbamate with O,N-diphenylcarbamate in the synthesis of N-phenyl-N'-*n*-butylurea[9] from *n*-butylamine, and with N-phenyl-S-(β-phenethyl)-thiocarbamate in a synthesis of N,N'-diphenylurea[11] from aniline. However, with these latter carbamates, and in contrast to the S-phenylthiocarbamates, it was necessary to conduct the reactions at 80°, rather than at 25°, in order to obtain good yields of the ureas in the course of one hour.

At least three reaction mechanisms can be advanced for the base-catalyzed reaction of S-phenylthiocarbamate, or the N-monosubstituted derivatives thereof, with primary or secondary amines to give, in either dioxane or ethanol solutions at 25°, the corresponding mono-, di- or trisubstituted ureas. As has been noted previously[2] the reaction may be formulated in terms of a 1,2-elimination reaction[26–28] to give an intermediate isocyanate which then participates in a 1,2-addition reaction with the amine to give the urea. However, it should be recalled that in contrast to the Hofmann reaction, where an isocyanate is believed to be an intermediate and where urethans are produced if the reactions are conducted in alcoholic solvents,[29] the reaction of N-ethyl-S-phenylthiocarbamate, and of N,S-diphenylthiocarbamate, with ethylamine in absolute ethanol gave *sym*-diethylurea and N-ethyl-N'-phenylurea in yields of 90 and 100%, respectively.[2] Furthermore, when a solution of N,S-diphenylthiocarbamate in either absolute ethanol or a mixture of anhydrous isopropyl alcohol and dioxane was treated at 25° with an excess of triethylamine the amide was recovered unchanged. Finally, all attempts to convert N,S-diphenyl-, N-*p*-chlorophenyl-S-phenyl- and N-*p*-nitrophenyl-S-phenylthiocarbamate into the corresponding isocyanates by reaction of the amides with triethylamine in anhydrous dioxane, either in the absence or presence of 2,4-dinitrochlorobenzene or acrylonitrile, were totally unsuccessful. While it is true that the above observations do not exclude rigorously the possibility that an isocyanate is an intermediate in the reaction under consideration, it is clear that at present there is no evidence to support such a view.

The formal similarity of the reaction under discussion to the aminolysis of esters,[30,31] thioesters,[32] S-alkylisothioureas,[33] imidic esters,[34] dithiouracils[35] and S-alkylpyrimidines[36] suggests that the former reaction may be formulated in a manner analogous to that proposed for the aminolysis of esters and thioesters,[30–32] *i.e.*, as a nucleophilic attack of the amine, or the corresponding anion, upon a neutral molecule. However, there are several facts that are difficult to explain on the basis of such a mechanism. The principal difficulty resides in the fact that N-disubstituted-S-phenylthiocarbam-

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(5) T. L. Davis and K. C. Blanchard, THIS JOURNAL, **51,** 1790 (1929).

(6) *Idem, ibid.*, **45,** 1816 (1923).

(7) P. P. T. Sah and K. Chang, *Ber.*, **69B**, 2762 (1936).

(8) R. Stolle and F. Henke-Stark, *J. prakt. Ckem.*, [2] **124**, 261 (1930).

(9) J. W. Boehmen, *Rec. trav. chim.*, **55,** 379 (1936).

(10) A. E. Dixon, *J. Chem. Soc.*, **67,** 556 (1895).

(11) J. R. Scott and J. B. Cohen, *ibid.*, **121,** 2034 (1922).

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(14) K. Feist, W. Awe, J. Schultz and F. Klett, *Arch. Pharm.*, **272,** 100 (1934).

(15) R. Stolle, *J. prakt. Chem.*, [2] **117,** 185 (1927).

(16) W. Gebhardt, *Ber.*, **17,** 3033 (1884).

(17) R. A. Henry and W. M. Dehn, THIS JOURNAL, **71,** 2297 (1949).

(18) P. Sabatier and J. B. Senderens, *Ann. chim.*, [8] **4,** 319 (1905).

(19) W. Gebhardt, *Ber.*, **17**, 2088 (1884).

(20) P. P. T. Sah, *Rec. trav. chim.*, **59**, 231 (1940).

(21) S. V. Niementowski, *Ber.*, **43**, 3012 (1910).

(22) H. Lakra and F. B. Dains, THIS JOURNAL, **51**, 2220 (1929).

(23) M. Busch and O. Limpach, *Ber.*, **44**, 560 (1911).

(24) W. Autenrieth and H. Hefner, *ibid.*, **58**, 2151 (1925).

(25) In this instance it was necessary to conduct the reaction at the boiling point of the reaction mixture rather than at 25°.

(26) E. D. Hughes and C. K. Ingold, *Trans. Faraday Soc.*, **37**, 657 (1941).

(27) M. L. Dhar, E. D. Hughes, C. K. Ingold, A. M. M. Mandour, G. A. Maw and L. I. Woolf, *J. Chem. Soc.*, 2093 (1948).

(28) N. Kornblum and H. E. De La Mare, THIS JOURNAL, **73**, 880 (1951).

(29) E. S. Wallis and J. F. Lane, *Org. Reactions*, **3,** 267 (1946).

(30) M. Gordon, J. G. Miller and A. R. Day, THIS JOURNAL, **70,** 1946 (1948).

(31) R. Baltzly, I. M. Berger and A. A. Rothstein, *ibid.*, **72,** 4149 (1950).

(32) R. Schwyzer, *Helv. Chim. Acta*, **36**, 414 (1953).

(33) B. Rathke, *Ber.*, **17,** 297 (1884).

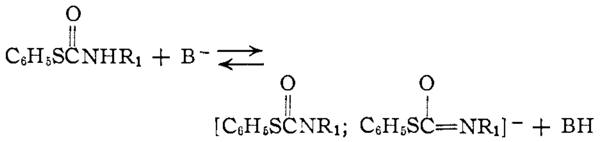
(34) R. L. Shriner and F. W. Newmann, *Chem. Revs.*, **35**, 351 (1944).

(35) P. B. Russell, G. B. Elion, E. A. Falco and G. H. Hitchings, THIS JOURNAL, **71**, 2279 (1949).

(36) G. W. Kenner in "Thorpes Dictionary of Applied Chemistry," 4th edition, Vol. 10, Longman's Green and Co., London, 1950, pp. 317–325.

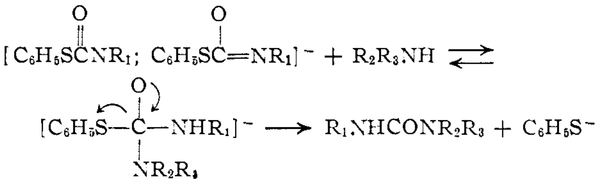
ates are extremely stable in both acids and bases[2] and it was not surprising to find in this study that N-methyl-N-phenyl-S-phenylthiocarbamate was recovered unchanged after treatment with an excess of diethylamine either at 25° or at the refluxing temperature of the reaction mixture. Since it is known that the aminolysis of esters,[31] imidic esters,[34] dithiouracils[35] and S-alkylpyrimidines[36] is notably sensitive to steric hindrance the reaction of diethylamine with N-pentamethylene-S-phenylthiocarbamate was investigated both at 25° and at the refluxing temperature of the reaction mixture. In both cases the original amide was recovered in nearly quantitative yields. Although it is known that electron-releasing groups in the immediate neighborhood of the carboxyl function will decrease the rate of ammonolysis of esters[30] and that esters of α-substituted carboxylic acids undergo ammonolysis with difficulty[37] there appears to be no valid explanation, in terms of the above reaction mechanism, of why, for example, N-ethyl-S-phenylthiocarbamate should react with a primary or secondary amine under the conditions specified and the N-pentamethylene compound should not, particularly in view of the fact that a number of esters of thioacetic acid are rapidly and completely aminolyzed by aniline even under slightly acidic conditions.[32]

The clear requirement for the presence of an amide hydrogen atom in the thiocarbamate in order that subsequent reaction to form a urea be observed led to the suggestion[2] that the first step in the over-all reaction is the formation of a resonance-stabilized intermediate ion, *i.e.*



$$\mathrm{C_6H_5S\overset{O}{\overset{\|}{C}}NHR_1 + B^- \rightleftarrows [C_6H_5S\overset{O}{\overset{\|}{C}}NR_1;\ C_6H_5S\overset{O}{\overset{|}{C}}{=}NR_1]^- + BH}$$

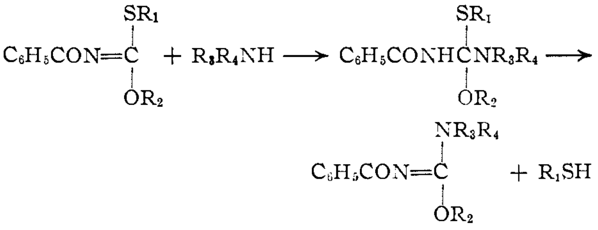
which is then attacked by the primary or secondary amine with the concomitant elimination of thiophenate ion resulting in the formation of the urea, *i.e.*



$$\mathrm{[C_6H_5S\overset{O}{\overset{\|}{C}}NR_1;\ C_6H_5S\overset{O}{\overset{|}{C}}{=}NR_1]^- + R_2R_3NH \rightleftarrows}$$
$$\mathrm{[C_6H_5S{-}\overset{O}{\underset{NR_2R_3}{C}}{-}NHR_1]^- \longrightarrow R_1NHCONR_2R_3 + C_6H_5S^-}$$

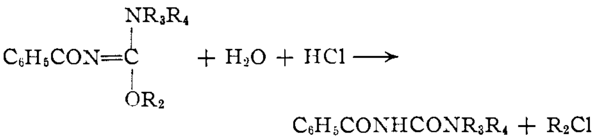
This formulation is compatible with all of the known experimental facts relative to the behavior of the S-phenylthiocarbamates, provides an adequate explanation of the lack of reactivity of the O-alkylcarbamates under conditions where the corresponding S-aryl- and S-alkylthiocarbamates and the O-arylcarbamates are readily converted into ureas,[2] is compatible with the fact that S-arylthiocarbamates are more reactive than the corresponding S-alkylthiocarbamates or O-arylcarbamates, and is capable of extension to explain the behavior of compounds which are analogs of the thiocarbamates.

The reaction mechanism given immediately above also derives support from the investigations of Wheeler and co-workers[38,39] who found that the reaction



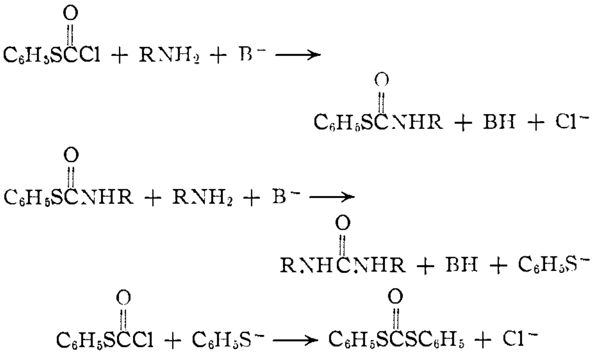
$$\mathrm{C_6H_5CON{=}\overset{SR_1}{\underset{OR_2}{C}} + R_3R_4NH \longrightarrow C_6H_5CONH\overset{SR_1}{\underset{OR_2}{C}}NR_3R_4 \longrightarrow C_6H_5CON{=}\overset{NR_3R_4}{\underset{OR_2}{C}} + R_1SH}$$

was both general and facile and that the O-alkylisourea so formed reacts with cold aqueous hydrochloric acid to give an alkyl halide and a practically quantitative yield of the substituted urea, *i.e.*



$$\mathrm{C_6H_5CON{=}\overset{NR_3R_4}{\underset{OR_2}{C}} + H_2O + HCl \longrightarrow C_6H_5CONHCONR_3R_4 + R_2Cl}$$

The stoichiometry of the reaction of phenylthiocarbonyl chloride with a simple primary amine in the presence of an excess of base may be represented by the equations



$$\mathrm{C_6H_5S\overset{O}{\overset{\|}{C}}Cl + RNH_2 + B^- \longrightarrow C_6H_5S\overset{O}{\overset{\|}{C}}NHR + BH + Cl^-}$$
$$\mathrm{C_6H_5S\overset{O}{\overset{\|}{C}}NHR + RNH_2 + B^- \longrightarrow RNH\overset{O}{\overset{\|}{C}}NHR + BH + C_6H_5S^-}$$
$$\mathrm{C_6H_5S\overset{O}{\overset{\|}{C}}Cl + C_6H_5S^- \longrightarrow C_6H_5S\overset{O}{\overset{\|}{C}}SC_6H_5 + Cl^-}$$

Thus it is evident that under the above conditions two moles of the acid chloride will react with two moles of the primary amine to give one mole of the corresponding urea and one mole of diphenyl dithiocarbonate. If more than two moles of the acid chloride are added to the original reaction mixture, the amount in excess of two moles does not appear to react as is apparent from the persistence of an oily emulsion of the acid chloride even after prolonged agitation. However, if the simple primary amine is replaced by an equivalent amount of an α-amino acid it appears that an unlimited amount of the acid chloride can be consumed, if sufficient base is present, except in those cases where the urea is periodically removed from the reaction mixture.[2] In a particular experiment in which six moles of the acid chloride was allowed to react with two moles of DL-phenylalanine, in the presence of an excess of aqueous sodium hydroxide, there was obtained three moles of diphenyldithiocarbonate and, after acidification of the reaction mixture, one mole of the urea and two moles of carbon dioxide. These facts may be

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(37) R. Fischer and A. Dilthey, *Ber.*, **35**, 844 (1902).

(38) H. L. Wheeler and B. Barnes, *Am. Chem. J.*, **24**, 60 (1900).

(39) H. L. Wheeler and T. B. Johnson, *ibid.*, **24**, 185 (1900); **26**, 408 (1901).

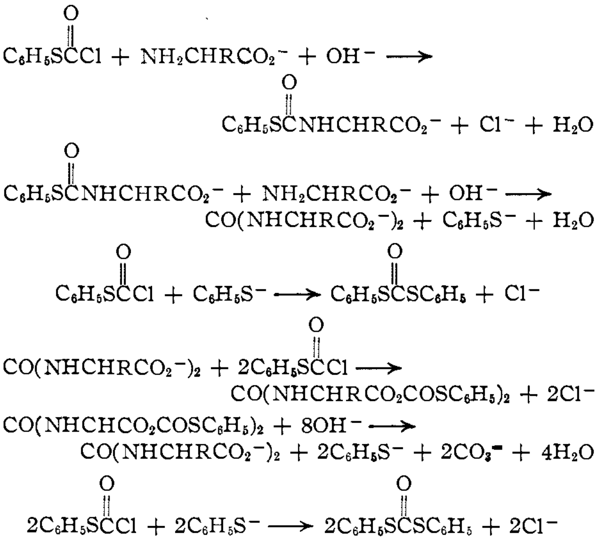
TABLE I

N-MONOSUBSTITUTED S-PHENYLTHIOCARBAMATES[a,b] ($R_1HNCOSC_6H_5$)

R_1	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Methyl	103–104	57.5	58.2	5.4	5.6	8.4	7.9
Ethyl	81–82	59.6	59.8	6.1	6.2	7.7	7.7
Cyclohexyl	113–113.5	66.4	66.4	7.3	7.3	6.0	5.9
Phenyl	125.5–126	68.2	68.2	4.9	4.8	6.1	6.1
p-Chlorophenyl	141–141.5	59.4	59.4	3.8	3.8	5.3	5.3
p-Ethoxyphenyl	144.5–145	65.9	66.0	5.5	5.5	5.1	5.0
p-Nitrophenyl	142.2–142.8	56.9	56.9	3.7	3.7	10.2	10.1
o-Carbomethoxyphenyl	117.5–118.3	62.7	62.8	4.6	4.6	4.9	4.9
α-Pyridyl	151.2–152	62.6	62.7	4.4	4.4	12.2	12.1

[a] Batty and co-workers (British Patents 599,178 and 599,179; *C. A.*, **42**, 7331, 7332 (1948)) appear to have prepared a number of N-substituted-S-phenyl- and S-(*p*-tolyl)-thiocarbamates, but detailed information concerning their synthesis and properties is not available. [b] Several N-disubstituted-S-phenylthiocarbamates also were prepared, *i.e.*, N-methyl-N-phenyl-S-thiocarbamate[2,3] and N-pentamethylene-S-phenylthiocarbamate, m.p. 60–60.5°. *Anal.* Calcd. for $C_{12}H_{15}ONS$: C, 65.2; H, 6.8; N, 6.3. Found: C, 65.2; H, 6.7; N, 6.2.

explained, at least in part, in terms of the following equations.



$$C_6H_5S\overset{O}{\overset{\|}{C}}Cl + NH_2CHRCO_2^- + OH^- \longrightarrow C_6H_5S\overset{O}{\overset{\|}{C}}NHCHRCO_2^- + Cl^- + H_2O$$

$$C_6H_5S\overset{O}{\overset{\|}{C}}NHCHRCO_2^- + NH_2CHRCO_2^- + OH^- \longrightarrow CO(NHCHRCO_2^-)_2 + C_6H_5S^- + H_2O$$

$$C_6H_5S\overset{O}{\overset{\|}{C}}Cl + C_6H_5S^- \longrightarrow C_6H_5S\overset{O}{\overset{\|}{C}}SC_6H_5 + Cl^-$$

$$CO(NHCHRCO_2^-)_2 + 2C_6H_5S\overset{O}{\overset{\|}{C}}Cl \longrightarrow CO(NHCHRCO_2COSC_6H_5)_2 + 2Cl^-$$

$$CO(NHCHCO_2COSC_6H_5)_2 + 8OH^- \longrightarrow CO(NHCHRCO_2^-)_2 + 2C_6H_5S^- + 2CO_3^{=} + 4H_2O$$

$$2C_6H_5S\overset{O}{\overset{\|}{C}}Cl + 2C_6H_5S^- \longrightarrow 2C_6H_5S\overset{O}{\overset{\|}{C}}SC_6H_5 + 2Cl^-$$

The above phenomenon is not only of practical interest in connection with the synthesis of ureas derived from the α-amino acids by the technique outlined above and described in detail earlier[2] but it also suggests two interesting possibilities, *i.e.*, one, that of stopping the reaction at the mixed anhydride stage by limiting the amount of base present in the reaction system and to thereby gain an intermediate that would be useful for the subsequent synthesis of derivatives of the carboxyl function present in these ureas, and two, that the role of the urea in catalyzing the hydrolytic degradation of phenylthiocarbonyl chloride may be of sufficient general interest so as to justify a detailed study of the mechanism of this reaction. It is not known at present whether the particular urea in this study has any special function in the hydrolytic degradation of phenylthiocarbonyl chloride or whether the same reaction can be observed with any carboxylic acid.

Experimental[40,41]

S-Phenylthiocarbonyl Chloride.[8]—This acid chloride was prepared from phosgene and thiophenol by the method of Rivier[8] and fractionally distilled to give a product of b.p. 95–97° (8 mm.).

Phenoxycarbonyl Chloride.—To an ice-cold and well-stirred solution of 61 g. (0.62 mole) of phosgene, previously washed by successive passage through cottonseed oil and concentrated sulfuric acid, in 250 ml. of toluene was added, at the rate of *ca.* 5 ml. a minute, a solution of 47 g. (0.5 mole) of phenol in 500 ml. of 1 *N* aqueous sodium hydroxide, the reaction mixture stirred for an additional hour at 0°, the layers separated, the non-aqueous layer dried over magnesium sulfate and freed of excess phosgene by aeration of the dried solution. The solvent was removed *in vacuo* and the residue fractionally distilled to give 26.0 g. (33.3%) of phenoxycarbonyl chloride, b.p. 63–63.5° (7 mm.). The distillate crystallized to give the solid acid chloride, m.p. 38.0–38.5°. Reaction of the solid acid chloride with aniline gave a practically quantitative yield of O,N-diphenylcarbamate, *vide post.*

N,S-Diphenylthiocarbamate.—To an ice-cold and well-stirred solution of 13.8 ml. (0.10 mole) of phenylthiocarbonyl chloride in 100 ml. of dry dioxane was added dropwise 18.6 ml. (0.20 mole) of aniline, the reaction mixture allowed to stand at 25° for two hours, the slurry slowly poured with vigorous stirring into a mixture of 300 ml. of water and 100 g. of ice, the precipitated solid collected, washed with 300 ml. of 2 *N* hydrochloric acid and then with 500 ml. of water and finally air-dried. This product was recrystallized from a mixture of toluene and 60–80° ligroin to give 20.0 g. (87.5%) of N,S-diphenylthiocarbamate, m.p. 123.3–124°. The mother liquor was concentrated to give an additional 1.6 g. of product which brought the total yield to 94%.

The other thiocarbamates listed in Table I, with the exception of N-methyl-S-phenylthiocarbamate, were prepared essentially as described above.

N-Methyl-S-phenylthiocarbamate.—Dry gaseous methylamine, 0.06 mole, was passed slowly into a cold solution of 4.14 ml. (0.03 mole) of phenylthiocarbonyl chloride in 15 ml. of dry dioxane, the reaction mixture allowed to stand at 25° for 15 minutes, the precipitated methylammonium chloride collected, the colorless filtrate evaporated to dryness at 60° and the solid residue recrystallized from toluene to give 3.5 g. (70%) of N-methyl-S-phenylthiocarbamate, m.p. 103–104°.

N-Phenyl-S-(β-phenethyl) Thiocarbamate.—A mixture of 1.19 g. (0.01 mole) of phenyl isocyanate, 1.38 g. (0.01 mole) of β-phenethylmercaptan and 5 drops of anhydrous pyridine was allowed to stand at 25° for 16 hours. The solid reaction product was then recrystallized from a mixture of 60–80° ligroin and toluene to give 2.50 g. (97%) of N-phenyl-S-(β-phenethyl)-thiocarbamate, m.p. 109.5–110.5°.

Anal. Calcd. for $C_{15}H_{15}NOS$ (257.4): C, 70.0; H, 5.9; N, 5.4. Found: C, 70.2; H, 5.9; N, 5.1.

O,N-Diphenylcarbamate.—Redistilled aniline, 3.4 g. (0.038 mole), was added dropwise and with vigorous agitation to a solution of 3 g. (0.019 mole) of phenoxycarbonyl chloride in 20 ml. of dioxane, the reaction mixture allowed to stand for ten minutes and then poured into ice-water. To this suspension was added 15 ml. of 2 *N* hydrochloric acid, the mixture stirred, the solid collected, washed with 2 *N* hydrochloric acid and with water and air-dried. The crude

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(40) All melting points are corrected.

(41) Microanalyses by Dr. A. Elek.

product was recrystallized from aqueous ethanol to give 3.4 g. (95%) of O,N-diphenylcarbamate, m.p. 126.3–126.8°, with no depression of the m.p. by admixture of the same urethan prepared from phenol and phenyl isocyanate.

Preparation of Substituted Ureas.—The preparations which follow are representative of those which were used for the synthesis of the various ureas which are listed in Table II. In general all of these ureas were prepared in yields greater than 90% of the theoretical.

TABLE II

UREAS PREPARED FROM N-SUBSTITUTED S-PHENYLTHIOCARBAMATES

Urea	M.p., °C. Found	Lit.	Ref.
N-*n*-Butyl	94–95	96	5
N-Phenyl	144.6–145.6	147	6
N-*p*-Anisyl	166–167	164–165	7
N-*p*-Phenethyl	160–161	160–161	7
N-*p*-Nitrophenyl	237–238	238	8
N-Phenyl-N'-methyl	145–146	151	9
N-Phenyl-N'-allyl	115.5–116	115.5	10
N-Phenyl-N'-*n*-butyl	130–131	130	9
N,N'-Diphenyl	238–239	237–238	11
N-Phenyl-N'-*p*-chlorophenyl	237–238	237–238	12
N-Phenyl-N'-*p*-nitrophenyl	211–212	212	13
N-Phenyl-N'-α-pyridyl	185–186	187	14
N-Phenyl-N',N'-dimethyl	127.5–128	134	15
N-Phenyl-N',N'-diethyl	84–85	85	16
N-Phenyl-N',N'-tetramethylene	133–134	133–134	17
N-Phenyl-N',N'-pentamethylene	171–172	171–172	17
N-Phenyl-N',N'-dicyclohexyl	167–168	169	18
N-*p*-Phenethyl-N'-*n*-butyl	145–146	146	9
N-*p*-Chlorophenyl-N'-*n*-butyl	171–172	173	9
N-α-Pyridyl-N'-*n*-butyl	87–88	88	9
N-Methyl-N,N'-diphenyl	104–105	104	19
N-Methyl-N-phenyl-N'-*p*-nitrophenyl	122–123	123	20
Imidazole-N-carboxylic acid anilide[a]	114–115	114.5–115.5	17
Indole-N-carboxylic acid anilide[a]	135–136	136	17
Tetrahydroquinoline-N-carboxylic acid anilide[a]	96–97	96	17
Morpholine-N-carboxylic acid anilide[a]	161–162	161.5–162	17
2-Hydroxybenzimidazole[a]	310	310–312	21
N-Phenyl-N'-benzoyl	210–211	210	22
1,4-Diphenyl semicarbazide[a]	177.8–178.5	177	23
N,N'-Diphenylthio	153–154	154	24

[a] In these cases a more convenient alternative nomenclature has been used to describe the urea.

N-Phenyl-N'-α-pyridylurea.—To a solution of 1.14 g. (0.005 mole) of N,S-diphenylthiocarbamate in 15 ml. of dry dioxane was added 0.47 g. (0.05 mole) of α-aminopyridine and 1.0 ml. (0.007 mole) of triethylamine, the reaction mixture allowed to stand at 25° for several hours, the solvent removed by evaporation at *ca.* 60° in a stream of illuminating gas, the solid residue triturated with 20 ml. of 60–80° ligroin, the solid collected, repeatedly washed with ligroin and air-dried. The crude product was recrystallized from aqueous ethanol to give 1.03 g. (97%) of N-phenyl-N'-α-pyridylurea, m.p. 179–180° with no depression of the m.p. upon admixture with the same urea prepared by the reaction of α-aminopyridine with phenyl isocyanate.

Piperidine-N-carboxylic Anilide.—Piperidine, 1.0 ml. (0.01 mole), was added to a solution of 0.57 g. (0.0025 mole) of N,S-diphenylthiocarbamate in 10 ml. of toluene, the exothermic reaction allowed to proceed to completion, the crystalline reaction product triturated with 2 ml. of 60–80° ligroin, the suspension cooled in an ice-bath, the solid collected, washed with a warm 1:1 mixture of ligroin and toluene, the filtrate and washings combined, evaporated to dryness, the residue taken up in ligroin, the solid collected, washed with ligroin and air-dried. Recrystallization of the crude product from aqueous ethanol gave 0.48 g. (95%) of product m.p. 168–169° which upon an additional recrystallization from the same solvent gave piperidine-N-carboxylic anilide, m.p. 171–172°, with no depression of the m.p. when mixed with an authentic sample prepared from piperidine and phenyl isocyanate.

N-Phenyl-N',N'-dimethylurea.—An excess of dry dimethylamine was passed into a solution of 0.57 g. (0.0025 mole) of N,S-diphenylthiocarbamate in 15 ml. of toluene until the formation of a crystalline precipitate had ceased. An equal volume of 60–80° ligroin was added to the suspension, the latter cooled in an ice-bath, the solid collected and washed with 1:1 mixture of ligroin and toluene to give 0.33 g. (81%) of N-phenyl-N',N'-dimethylurea, m.p. 127.5–128°. Admixture of this product with an authentic sample prepared from dimethylamine and phenyl isocyanate failed to depress the m.p.

N-Phenyl-N'-*n*-butylurea.—To 0.54 g. (0.0025 mole) of O,N-diphenylcarbamate in 10 ml. of dry dioxane was added 0.5 ml. (0.005 mole) of *n*-butylamine, the mixture heated under refluxing conditions for 1 hour, the cooled reaction mixture poured into 75 ml. of water, the solid collected, washed with 2 *N* hydrochloric acid and with water and dried *in vacuo* to give 0.45 g. (94%) of product, m.p. 126–127°. Recrystallization of this product from a mixture of benzene and ligroin gave N-phenyl-N'-*n*-butylurea, m.p. 127.8–128.2° which was not depressed when admixed with an authentic sample prepared from phenyl isocyanate and *n*-butylamine.

***sym*-Diphenylurea.**—A mixture of 0.52 g. (0.002 mole) of N-phenyl-S-(β-phenethyl)-thiocarbamate, 0.2 g. (0.002 mole) of aniline and 0.2 ml. of triethylamine in 5 ml. of dry dioxane was heated at 80° for 1 hour. The cooled reaction mixture was poured into a mixture of 20 g. of ice and 50 ml. of 2 *N* hydrochloric acid, the precipitate collected, washed with water, and dried to give 0.43 g. (100%) of *sym*-diphenylurea, m.p. 230–232°. A similar experiment conducted at 25° gave only 0.2 g. (45%) of *sym*-diphenylurea after extraction of the unreacted thiocarbamate with hot carbon tetrachloride.

N-Phenyl-N'-benzoylurea.—To 1.14 g. (0.005 mole) of N,S-diphenylthiocarbamate and 0.70 g. (0.0058 mole) of benzamide in 5 ml. of anhydrous dioxane was added 5 ml. of triethylamine and the reaction mixture heated under refluxing conditions for 2 hours. The cooled reaction mixture was poured into ice-water, the solid collected, dried, and recrystallized from aqueous ethanol to give 0.96 g. (80%) of N-phenyl-N'-benzoylurea, m.p. 210–211° dec.

1,4-Diphenyl Semicarbazide.—To a solution of 0.57 g. (0.0025 mole) of N,S-diphenylthiocarbamate and 0.25 ml. (0.0025 mole) of phenylhydrazine in 10 ml. of dry dioxane was added 0.7 ml. (0.005 mole) of triethylamine, the reaction mixture allowed to stand at 25° for 1 hour, the clear solution poured into 50 ml. of water and 30 g. of crushed ice, the precipitated solid collected, washed with 70 ml. of 2 *N* hydrochloric acid and then with 50 ml. of water and then air-dried. Recrystallization of this product from 50% aqueous ethanol gave 0.52 g. (93%) of 1,4-diphenylsemicarbazide, m.p. 177.8–178.5° with no depression of the m.p. when mixed with an authentic sample prepared from phenylhydrazine and phenyl isocyanate.

N,N'-Diphenylthiourea.—To 0.61 g. (0.0025 mole) of N,S-diphenyldithiocarbamate, prepared from thiophenol and phenyl isothiocyanate, in 10 ml. of dry dioxane was added 0.93 ml. (0.01 mole) of aniline and 1.4 ml. (0.01 mole) of triethylamine, the reaction mixture allowed to stand for 1 hour, the clear solution diluted with 30 ml. of 60–80° ligroin, the solid collected and dried to give 0.47 g. (82%) of thiocarbanilide, m.p. 153–154° with no depression of the m.p. when mixed with an authentic sample.

N-Phenyl-N',N'-diethylurea.—Aniline, 2 ml. (0.022 mole), was added to a solution of 1.4 ml. (0.01 mole) of phenylthiocarbonyl chloride in 15 ml. of benzene, the reaction mixture stirred for 10 minutes, 25 ml. of 2 *N* hydrochloric acid added, the mixture again stirred, the non-aqueous phase separated, washed with water and dried over sodium sulfate. To this solution was added 3.0 ml. (0.03 mole) of diethylamine, the reaction mixture allowed to stand for 30 minutes, the solvent removed on a steam-bath, the crystalline residue triturated with 10 ml. of 60–80° ligroin, the solid collected, washed with 30 ml. of ligroin to give 1.76 g. (92%) of N-phenyl-N',N'-diethylurea, m.p. 80–82° with no depression of the m.p. when mixed with an authentic sample prepared from phenyl isocyanate and diethylamine.

Identification of Products Formed in Reaction of N,S-Diphenylthiocarbamate with Aniline.—To a solution of 0.57 g. (0.0025 mole) of N,S-diphenylthiocarbamate and 0.9 ml. (0.01 mole) of aniline in 10 ml. of dry dioxane was added

1.4 ml. (0.01 mole) of triethylamine, the mixture allowed to stand for 45 minutes at 25°, the clear solution washed into a distilling flask with 250 ml. of water containing 15 ml. of 2 *N* sulfuric acid, the contents of the flask steam distilled, the distillate (50 ml.) extracted with ether, the ethereal extract dried over magnesium sulfate, the solvent removed and the oily residue allowed to react with dinitrochlorobenzene in the presence of alkali[42] to give 0.36 g. (68%) of 2,4-dinitrodiphenyl sulfide, m.p. 118–119°. The residue remaining after the steam distillation was filtered, the solid washed with water, dried, and recrystallized from ethanol to give 0.52 g. (98%) of *sym*-diphenylurea, m.p. 233–234°.

Attempted Reaction of N,S-Diphenylthiocarbamate with Isopropyl Alcohol and with Ethanol.—To a solution of 0.57 g. (0.0025 mole) of N,S-diphenylthiocarbamate in 0.5 ml. of dry isopropyl alcohol and 10 ml. of anhydrous dioxane was added 0.5 ml. of triethylamine, the reaction mixture allowed to stand at 25° for 45 minutes, then poured into 50 ml. of ice water, the precipitate recovered and dried to give 0.48 g. of the original amide, m.p. 124–125°. Practically the same result was obtained when the solution of isopropyl alcohol and dioxane was replaced by absolute ethanol.

Attempted Reaction of N-Phenyl-N-methyl-S-phenylthiocarbamate with Several Primary and Secondary Amines.—A solution of 0.61 g. of N-phenyl-N-methyl-S-phenylthiocarbamate in 15 ml. of diethylamine was allowed to stand at 25° for 3 hours, the solution then heated under refluxing conditions for 2 hours, cooled, and the solvent removed in a stream of illuminating gas to give 0.61 g. of the original amide, m.p. 69–70°. Essentially the same results were obtained when the amide was treated with a toluene solution of methylamine at 25°, a toluene solution of aniline and triethylamine at 25°, and a dioxane solution of N-methylaniline and triethylamine at the temperature of the refluxing reaction mixture.

Attempted Reaction of N-Pentamethylene-S-phenylthiocarbamate with Diethylamine.—To a solution of 2.21 g. (0.01 mole) of N-pentamethylene-S-phenylthiocarbamate in 15 ml. of dry toluene was added 5.1 ml. (0.05 mole) of diethylamine, the solution allowed to stand overnight and then heated under refluxing conditions for 2 hours. The solvent was evaporated in a stream of illuminating gas, the oily residue triturated with 20 ml. of 2 *N* hydrochloric acid, the solid collected, washed with water and air-dried to give 2.22 g. of product, m.p. 60–62°. Recrystallization of this material from 60–80° ligroin gave 1.59 g. (72%) of the original amide, m.p. 59–60°.

Attempted Reaction of N-Phenylurethan with Aniline.—To a solution of 0.83 g. of N-phenylurethan in 10 ml. of anhydrous dioxane was added 1.0 ml. of aniline and 1.4 ml. of triethylamine, the reaction mixture allowed to stand at 25° for 5 hours, poured into 50 ml. of ice-water, the crystalline solid collected and dried to give 0.80 g. of the original urethan, m.p. 48–49°.

Reaction of Phenylthiocarbonyl Chloride with DL-Phenylalanine.—S-Phenylthiocarbonyl chloride, 12.95 g. (0.075 mole), was weighed into a small separatory funnel and the acid chloride was added in small portions to a vigorously stirred solution of 4.13 g. (0.025 mole) of DL-phenylalanine in 15 ml. of 3 *N* aqueous sodium hydroxide and 10 ml. of water. When *ca.* one-fifth of the acid chloride had been added, an additional 10 ml. of the aqueous alkali was introduced into the reaction mixture followed by more of the acid chloride until *ca.* 4 g. of the latter remained in the funnel. Since no reaction was apparent at this stage, stirring was discontinued and the reaction mixture allowed to stand overnight. After an interval of 9 hours, during which time a precipitate had separated, an additional 15 ml. of 3 *N* alkali was added followed by the remainder of the acid chloride which was added dropwise and with stirring. After all of the acid chloride had been added, a final portion of 10 ml. of 3 *N* alkali was added and the reaction mixture stirred for an additional 8 hours. The solid was then collected, washed with water and dried to give 9.20 g. (99.5%) of diphenyl dithiocarbonate, m.p. 43.5–44°. The alkaline filtrate was quantitatively transferred to a flask equipped with a dropping funnel and an absorption train for the collection of carbon dioxide. The system was swept free of air by a stream of nitrogen, the carbon dioxide absorption tube weighed, the solution carefully acidified with 2 *N* sulfuric acid to *p*H 5 and the evolved carbon dioxide swept into the absorption tube by a stream of nitrogen. The amount of carbon dioxide collected, corrected for the amount of carbonate present in the added alkali and that remaining in solution at 20° was 1.11 g. or 0.025 mole. The solid which had precipitated from the alkaline solution upon acidification was collected, washed with water and dried to give 4.27 g. (96%) of N,N′-carbonylbis-DL-phenylalanine. Thus from the reaction of 2 moles of the α-amino acid with 6 moles of the acid chloride in the presence of an excess of aqueous sodium hydroxide there was obtained 1 mole of the urea, 3 moles of diphenyldithiocarbonate and 2 moles of carbon dioxide.

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[JOINT CONTRIBUTION FROM THE SAMUEL C. HOOKER LABORATORY OF THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY AND THE INSTITUTO DE QUIMICA DE LA UNIVERSIDAD NACIONAL AUTONOMA DE MEXICO]

Alkaloid Studies. IV.[1] The Isolation of Reserpine, Serpentine and Ajmaline from *Rauwolfia heterophylla* Roem. and Schult.[2]

BY CARL DJERASSI, MARVIN GORMAN,[3] A. L. NUSSBAUM[4] AND JESUS REYNOSO

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The alkaloids reserpine, serpentine and ajmaline have been isolated from the Mexican and Guatemalan *Rauwolfia heterophylla*. The presence of γ-sitosterol and sucrose also has been noted.

Alkaloids have been encountered in a number of Asian and African *Rauwolfia* species,[5,6] but the majority of the work has centered on *Rauwolfia serpentina* Benth. which has been employed in India for the treatment of hypertension and other clinical conditions.[5-7] Enormous interest in the Indian *R. serpentina* was created recently by the isolation by

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