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The Synthesis of Substituted Ureas

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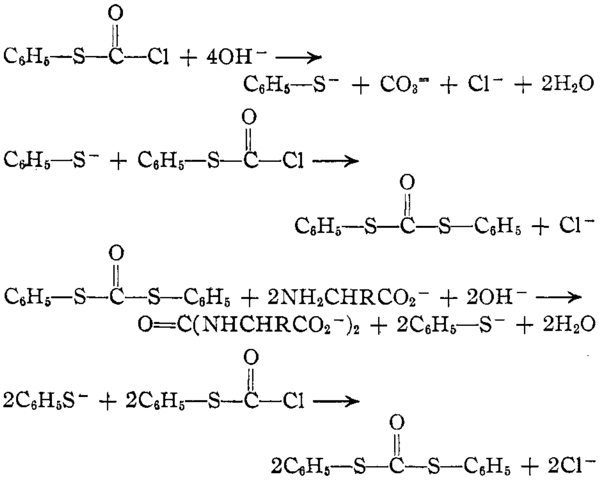
The reaction of phenylthiocarbonyl chloride with D- or L-phenylalanine under Schotten–Baumann conditions has been found to give the corresponding N,N′-carbonyl-bis-phenylalanines in good yields. The nature of this reaction has been examined and its application as a general reaction for the synthesis of mono-, di- and trisubstituted ureas has been indicated.

In the course of the preparation of a number of acylated D- and L-phenylalanines, intended for use in other studies,[2] an attempt was made to acylate L-phenylalanine with phenylthiocarbonyl chloride under Schotten–Baumann conditions despite the earlier report[3] that this practice did not lead to very successful results.

During the stepwise addition of the acid chloride, and a comparable quantity of aqueous sodium hydroxide, to the cold alkaline solution of the α-amino acid an extremely insoluble substance, which was subsequently identified as diphenyl dithiocarbonate, separated from the reaction mixture. After all of the acid chloride, *i.e.*, 1.3 moles per mole of α-amino acid, had been added the precipitated diphenyl dithiocarbonate was collected, and the filtrate acidified to give a crystalline product which proved to be N,N′-carbonyl-bis-L-phenylalanine dihydrate. Since the remaining aqueous solution still contained an appreciable quantity of the α-amino acid the acylation process was repeated and, after the consumption of 3 moles of the acid chloride per mole of α-amino acid, a total of *ca.* 90% of the theoretical amount of the substituted urea was obtained. The reaction of phenylthiocarbonyl chloride with D-phenylalanine under the same conditions was observed to proceed in an analogous manner.

The N,N′-carbonyl-bis-L-phenylalanine dihydrate was converted into the corresponding ethyl ester and the physical constants of this compound were found to be in excellent agreement with those reported previously for the same compound prepared by the reaction of the ethyl ester of L-phenylalanine with phosgene.[4] It is interesting to note that the substituted urea derived from L-phenylalanine was isolated as the dihydrate whereas the enantiomorphic D-compound was obtained as the monohydrate even though both compounds were finally recrystallized from water, and dried, in so far as can be determined, in the same way. The complete dehydration of both of the above compounds required relatively drastic conditions and in the course of this process both substances melted and then resolidified. It will be noted that although the elementary analyses of the anhydrous compounds were in good agreement with the theoretical values, the specific rotations of the anhydrous preparations not only were in disagreement with each other but also differed from the values calculated from the specific rotations of the two hydrates. From the elementary analyses and the specific rotations of the two hydrates and the two anhydrous preparations, and the specific rotations of the corresponding hydantoins,[4] it is clear that the dried products were indeed the anhydrous ureas, and not the corresponding hydantoin monohydrates, and that in the drying process both ureas were partially racemized.

With the identification of diphenyl dithiocarbonate and N,N′-carbonyl-bis-L-phenylalanine as the principal products of the reaction of phenylthiocarbonyl chloride with L-phenylalanine in the presence of aqueous sodium hydroxide, an attempt was made to determine the nature of the reactions leading to the formation of these products. While it is true that N,N′-diphenylurea may be obtained by heating aniline with diphenyl carbonate[5] it is clear that the reaction sequence



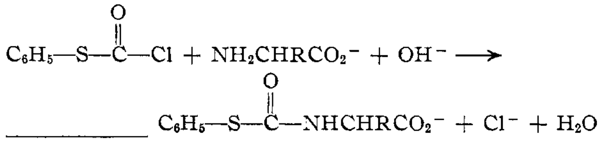
$$C_6H_5{-}S{-}\overset{O}{\overset{\|}{C}}{-}Cl + 4OH^- \longrightarrow C_6H_5{-}S^- + CO_3^{=} + Cl^- + 2H_2O$$

$$C_6H_5{-}S^- + C_6H_5{-}S{-}\overset{O}{\overset{\|}{C}}{-}Cl \longrightarrow C_6H_5{-}S{-}\overset{O}{\overset{\|}{C}}{-}S{-}C_6H_5 + Cl^-$$

$$C_6H_5{-}S{-}\overset{O}{\overset{\|}{C}}{-}S{-}C_6H_5 + 2NH_2CHRCO_2^- + 2OH^- \longrightarrow O{=}C(NHCHRCO_2^-)_2 + 2C_6H_5{-}S^- + 2H_2O$$

$$2C_6H_5S^- + 2C_6H_5{-}S{-}\overset{O}{\overset{\|}{C}}{-}Cl \longrightarrow 2C_6H_5{-}S{-}\overset{O}{\overset{\|}{C}}{-}S{-}C_6H_5 + 2Cl^-$$

can be ruled out on several grounds, *e.g.*, the relative stability of phenylthiocarbonyl chloride in the presence of aqueous sodium hydroxide, the insolubility of diphenyl dithiocarbonate in aqueous media, and the practically quantitative recovery of the latter compound after shaking with a solution of L-phenylalanine in aqueous sodium hydroxide. It therefore appeared that the initial reaction was an acylation of the α-amino acid with the acid chloride[3,6] and that the products isolated were a consequence of subsequent reactions, *i.e.*



$$C_6H_5{-}S{-}\overset{O}{\overset{\|}{C}}{-}Cl + NH_2CHRCO_2^- + OH^- \longrightarrow C_6H_5{-}S{-}\overset{O}{\overset{\|}{C}}{-}NHCHRCO_2^- + Cl^- + H_2O$$

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

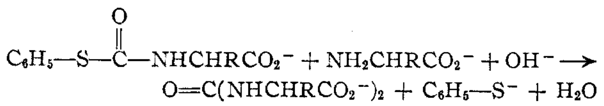
[2] W. H. Schuller and C. Niemann, THIS JOURNAL, **73**, 1644 (1951); **74**, 4630 (1952).

[3] G. C. H. Ehrensvärd, *Nature*, **159**, 500 (1947).

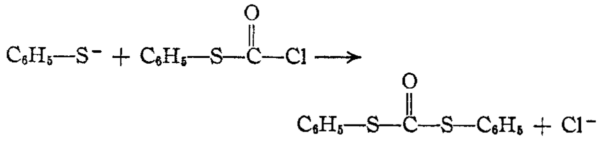
[4] F. Wessely and J. Mayer, *Monatsh.*, **50**, 439 (1928).

[5] H. Eckenroth, *Ber.*, **18**, 516 (1885).

[6] A. Lindenmann, H. H. Khan and K. Hofmann, THIS JOURNAL, **74**, 476 (1952).



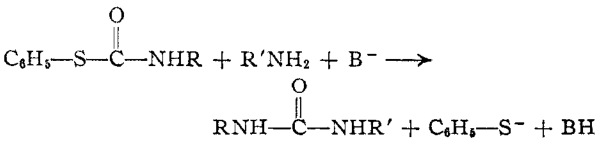
$$C_6H_5{-}S{-}\overset{O}{\overset{\|}{C}}{-}NHCHRCO_2^- + NH_2CHRCO_2^- + OH^- \longrightarrow O{=}C(NHCHRCO_2^-)_2 + C_6H_5{-}S^- + H_2O$$



$$C_6H_5{-}S^- + C_6H_5{-}S{-}\overset{O}{\overset{\|}{C}}{-}Cl \longrightarrow C_6H_5{-}S{-}\overset{O}{\overset{\|}{C}}{-}S{-}C_6H_5 + Cl^-$$

It is known[7] that S-phenylthiocarbamate and N,S-diphenylthiocarbamate, while stable in dilute acid, are readily decomposed by alkali, and Ehrensvärd[3] has reported, without giving any experimental details, that the phenylthiocarbonyl-α-amino acids are likewise decomposed in alkaline solutions in 10–30 seconds. In the course of this investigation it was observed that the addition of 1 mole of phenylthiocarbonyl chloride to 2 moles of ethylamine in absolute ethanol, at 0–25°, gave, after the addition of water to the reaction mixture, a precipitate of diphenyl dithiocarbonate and N-ethyl-S-phenylthiocarbamate, from which the latter compound was isolated in a 13% yield, and a solution from which there was obtained, in addition to ethylammonium chloride, *sym*-diethylurea. However, by reversing the order of addition, *i.e.*, by slowly adding 2 moles of diethylamine to 1 mole of the acid chloride in absolute ethanol an 84% yield of N-ethyl-S-phenylthiocarbamate was obtained. In contrast to the behavior of ethylamine the addition of 1 mole of phenylthiocarbonyl chloride to an ethanol solution of 2 moles of aniline, at 0–25°, gave a 98% yield of N,S-diphenylthiocarbamate.

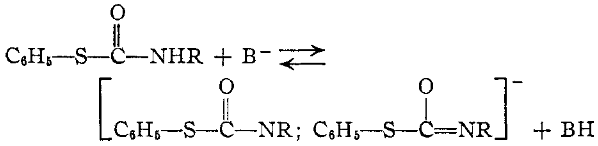
The above results are readily explained in the light of the following observations: N-ethyl-S-phenylthiocarbamate was recovered unchanged from an ethanolic solution of aniline, but reacted at 0–25° with an ethanolic solution of ethylamine to give a 90% yield of *sym*-diethylurea; N,S-diphenylthiocarbamate was recovered unchanged from an ethanolic solution of aniline, but reacted at 0–25° with an ethanolic solution of ethylamine to give a practically quantitative yield of N-ethyl-N′-phenylurea; at 0–25° N,S-diphenylthiocarbamate reacted with aniline in the presence of dioxane and triethylamine to give a practically quantitative yield of *sym*-diphenylurea. Thus it is clear that the reaction



$$C_6H_5{-}S{-}\overset{O}{\overset{\|}{C}}{-}NHR + R'NH_2 + B^- \longrightarrow RNH{-}\overset{O}{\overset{\|}{C}}{-}NHR' + C_6H_5{-}S^- + BH$$

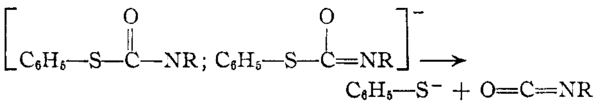
can proceed, at 0–25°, only when a fairly strong base is present in the reaction system. In addition to hydroxyl ion and the aliphatic tertiary amines, the simple aliphatic, but not the aromatic, primary amines are sufficiently strong bases to function as B^- in this reaction.

The role of the base B^- in the above reaction may be deduced from the observation that N-methyl-N-phenyl-S-phenylthiocarbamate is not decomposed by either hot or cold, aqueous sodium hydroxide,[7] or by hot methanolic sodium methoxide. Thus the transformation of an N,S-disubstituted thiocarbamate may be imagined to proceed via the reaction



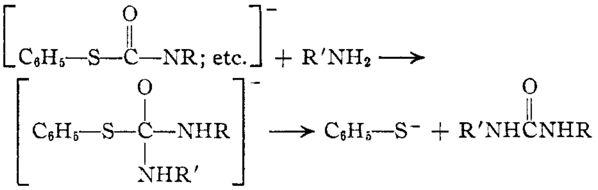
$$C_6H_5{-}S{-}\overset{O}{\overset{\|}{C}}{-}NHR + B^- \rightleftarrows \left[C_6H_5{-}S{-}\overset{O}{\overset{\|}{C}}{-}NR;\ C_6H_5{-}S{-}\overset{O}{\overset{|}{C}}{=}NR\right]^- + BH$$

which will be recognized as representing the formation of the intermediate ion of a typical heterolytic 1:2 elimination reaction.[8,9] The next stage of the reaction is uncertain as it is not known whether the intermediate ion, which is capable of a considerable amount of resonance stabilization, decomposes as in other heterolytic 1:2 elimination reactions,[8,9] *i.e.*



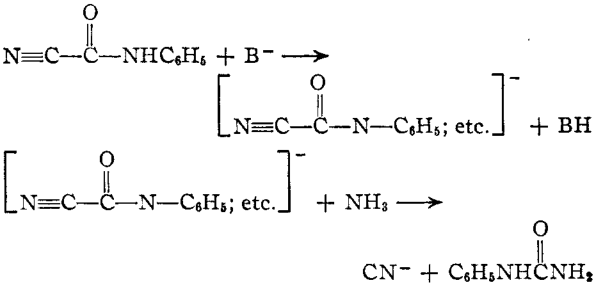
$$\left[C_6H_5{-}S{-}\overset{O}{\overset{\|}{C}}{-}NR;\ C_6H_5{-}S{-}\overset{O}{\overset{|}{C}}{=}NR\right]^- \longrightarrow C_6H_5{-}S^- + O{=}C{=}NR$$

or whether the ion possesses sufficient stability to participate in a second bimolecular reaction involving attack on the electron deficient carbon atom by a molecule of amine, *i.e.*



$$\left[C_6H_5{-}S{-}\overset{O}{\overset{\|}{C}}{-}NR;\ \text{etc.}\right]^- + R'NH_2 \longrightarrow \left[C_6H_5{-}S{-}\underset{\underset{NHR'}{|}}{\overset{O}{\overset{|}{C}}}{-}NHR\right]^- \longrightarrow C_6H_5{-}S^- + R'NH\overset{O}{\overset{\|}{C}}NHR$$

It is of interest to note that the reaction of cyanoformanilide with ammonia to give N-phenylurea[10] may be considered to be an analog of the above reaction, *i.e.*



$$N{\equiv}C{-}\overset{O}{\overset{\|}{C}}{-}NHC_6H_5 + B^- \longrightarrow \left[N{\equiv}C{-}\overset{O}{\overset{\|}{C}}{-}N{-}C_6H_5;\ \text{etc.}\right]^- + BH$$

$$\left[N{\equiv}C{-}\overset{O}{\overset{\|}{C}}{-}N{-}C_6H_5;\ \text{etc.}\right]^- + NH_3 \longrightarrow CN^- + C_6H_5NH\overset{O}{\overset{\|}{C}}NH_2$$

Khan and Hofmann[6] have reported that a number of phenylthiocarbonyl dipeptide esters react with lead acetate, in 70% aqueous ethanol at 80–85°, to give the corresponding hydantoins. While these reaction conditions are different from those employed in the present study it appears that this reaction may be a special case of the more general one which is the subject of this communication. There appears to be little evidence to support the postulate of Lindemann, Khan and Hofmann that an isocyanate is formed as an intermediate in their reaction since a mechanism similar to that described immediately above is also consistent with

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

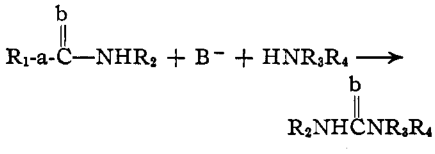
[8] M. L. Dhar, E. D. Hughes, C. K. Ingold, A. M. M. Mandour, G. A. Maw and L. I. Woolf, *J. Chem. Soc.*, 2093 (1948).

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

[10] W. Dieckmann and H. Kämmerer, *Ber.*, **38**, 2977 (1905).

the available evidence and may actually be favored, in the hydantoin case, because of the possible intramolecular nature of the reaction.

A number of essentially qualitative observations in respect to the behavior of certain disubstituted carbamates and thiocarbamates when heated, either alone or in the presence of an organic or inorganic base[11-14] suggest that the reaction observed in this investigation is capable of extension to other cases consistent with the equation



$$R_1\text{-a-}\overset{\overset{\text{b}}{\|}}{\text{C}}\text{—NHR}_2 + \text{B}^- + \text{HNR}_3\text{R}_4 \longrightarrow \text{R}_2\text{NH}\overset{\overset{\text{b}}{\|}}{\text{C}}\text{NR}_3\text{R}_4 + \text{BH} + \text{R}_1\text{-a}^-$$

where R_1 is an aryl group, or its equivalent, when a = O, and either an aryl or an alkyl group when a = S, where R_2, R_3 and R_4 are hydrogen atoms or alkyl or aryl groups and where b = O or S. Representative examples of the above general reaction have been obtained and an account of these and other pertinent observations will be submitted in a separate communication.

Experimental[15,16]

N,N'-Carbonyl-bis-L-phenylalanine.—To a vigorously stirred ice-cold solution of 4.4 g. (0.027 mole) of L-phenylalanine, $[\alpha]^{23}\mathrm{D}$ −34.1° (*c* 1.7% in water), in 15 ml. of 3 *N* aqueous sodium hydroxide and 10 ml. of water, was added, in many small portions over a 2-hour period, 6.05 g. (0.035 mole) of phenylthiocarbonyl chloride[7] and 17 ml. of 3 *N* aqueous sodium hydroxide. When the acid chloride was added to the reaction mixture an emulsion was formed which rapidly disappeared, being replaced by a white solid. After all of the acid chloride and alkali had been added the reaction mixture was stirred for an additional 2 hours at 25°, 15 ml. of water added, the precipitate collected from the strongly alkaline solution, and dried to give 4.0 g. (0.016 mole) of diphenyl dithiocarbonate, m.p. 43.0–43.5°, after two recrystallizations from absolute ethanol. Rivier[7] gives a m.p. of 41° for this compound.

Anal. Calcd. for $C_{13}H_{10}OS_2$ (246.3): C, 63.4; H, 4.1; S, 26.0. Found: C, 63.6; H, 4.4; S, 26.1.

The alkaline filtrate was acidified with concentrated hydrochloric acid to give 2.4 g. of a colorless crystalline precipitate. The filtrate was made alkaline with 3 *N* aqueous sodium hydroxide, and the acylation repeated, this time with 8.0 g. (0.046 mole) of the acid chloride. After removal of the diphenyl dithiocarbonate the filtrate was acidified as before to give an additional 2.0 g. of crystalline precipitate. The filtrate was again made alkaline and the acylation process repeated for a third time with 2.8 g. (0.016 mole) of the acid chloride. In contrast to the behavior noted previously this time the emulsion which formed on the addition of the acid chloride to the reaction mixture did not disappear and very little diphenyl dithiocarbonate was formed. Acidification of the aqueous phase gave no precipitate.

The precipitates collected from the acidified reaction mixtures were combined and recrystallized three times from water, once from a mixture of ethyl acetate and 60–70° ligroin, and again from water, and dried for 24 hours over phosphorus pentoxide at 25° and 1 mm. pressure to give N,N'-carbonyl-bis-L-phenylalanine dihydrate, m.p. 183.5–184° with decomposition, $[\alpha]^{25}\mathrm{D}$ +63.5° (*c* 0.95% in absolute ethanol, $[\alpha]^{25}\mathrm{D}$ +66.8° (*c* 1.9% in absolute ethanol).

Anal. Calcd. for $C_{19}H_{20}O_5N_2 \cdot 2H_2O$ (392.4): C, 58.2; H, 6.2; N, 7.1; neut. equiv., 196. Found: C, 58.2; H, 6.3; N, 7.1; neut. equiv., 195.

Two samples of the recrystallized dihydrate were dried to constant weight (21–25 hours) over phosphorus pentoxide at 139° and 1 mm. pressure; loss in weight calculated for the removal of two molecules of water, 9.18%; found, 9.18, 9.48%. During the drying process the samples melted and then slowly resolidified. The dried material melted, in a sealed capillary tube, at 178–179° with decomposition, $[\alpha]^{30}\mathrm{D}$ +60.8° (*c* 0.95% in absolute ethanol).

Anal. Calcd. for $C_{19}H_{20}O_5N_2$ (356.4): C, 64.0; H, 5.6; N, 7.9. Found: C, 64.1; H, 5.7; N, 7.8.

It will be noted that the yield of the crude N,N'-carbonyl-bis-L-phenylalanine dihydrate was 83%.

N,N'-Carbonyl-bis-D-phenylalanine.—D-Phenylalanine, $[\alpha]^{23}\mathrm{D}$ +29.8° (*c* 1.5% in water), 3.8 g. (0.023 mole) in 18 ml. of 3 *N* aqueous sodium hydroxide was acylated with 7.6 g. (0.044 mole) of phenylthiocarbonyl chloride and 25 ml. of 3 *N* aqueous sodium hydroxide as described for the initial acylation of L-phenylalanine, *vide ante*. The precipitate was recovered from the alkaline solution and dried to give 5.35 g. (0.022 mole) of crude diphenyl dithiocarbonate, m.p. 43–43.5° after two recrystallizations from absolute ethanol. The alkaline filtrate was acidified as before to give 1.8 g. of a colorless crystalline product. As an attempted recrystallition of this material from absolute ethanol gave a sirup, the sirup was dissolved in *N* aqueous sodium hydroxide, the solution acidified with 4 *N* hydrochloric acid, the crystalline precipitate recrystallized five times from water, and dried for 5 hours over phosphorus pentoxide at 25° and 1 mm. pressure to give N,N'-carbonyl-bis-D-phenylalanine monohydrate, m.p. 98–100° with resolidification to give a product m.p. 177–178° with decomposition, $[\alpha]^{25}\mathrm{D}$ −66.3° (*c* 0.37% in absolute ethanol).

Anal. Calcd. for $C_{19}H_{20}O_5N_2 \cdot H_2O$ (374.4): C, 61.0; H, 5.4; N, 7.5. Found: C, 60.8; H, 5.1; N, 7.6.

A sample of the recrystallized monohydrate was dried for 19 hours over phosphorus pentoxide at 139° and 1 mm. pressure. During this treatment the sample melted and then slowly resolidified. The dried product, $[\alpha]^{25}\mathrm{D}$ −24.2° (*c* 0.37% in absolute ethanol), $[\alpha]^{28}\mathrm{D}$ −27.5° (*c* 0.95% in absolute ethanol), $[\alpha]^{25}\mathrm{D}$ −31.8° (*c* 1.73% in absolute ethanol), melted in a sealed capillary tube, at 172.5–174° with decomposition.

Anal. Calcd. for $C_{19}H_{20}O_5N_2$ (356.4): C, 64.0; H, 5.6; N, 7.9. Found: C, 64.1; H, 5.7; N, 7.8.

Diethyl Ester of N,N'-Carbonyl-bis-L-phenylalanine.—Absolute ethanol, 5 ml., was saturated, at 0°, with anhydrous hydrogen chloride and to this solution was added 0.196 g. (0.0005 mole) of N,N'-carbonyl-bis-L-phenylalanine dihydrate. The resulting solution was allowed to stand at 25° for 48 hours, concentrated *in vacuo* to *ca.* 1 ml., the residue chilled in an ice-bath, the crystalline product recovered, washed with cold absolute ethanol and dried over phosphorus pentoxide at 25° and 1 mm. pressure to give 0.052 g. (25%) of the expected diethyl ester, m.p. 142.5°, unchanged after one recrystallization from a mixture of benzene and 60–70° ligroin, $[\alpha]^{22}\mathrm{D}$ +42.3° (*c* 1.18% in absolute ethanol). Wessely and Mayer[4] who prepared the diethyl ester by the reaction of L-phenylalanine ethyl ester with phosgene give the following constants: m.p. 142.5°, $[\alpha]^{25}\mathrm{D}$ +42.28° (*c* 1.18% in absolute ethanol).

Anal. Calcd. for $C_{23}H_{28}O_5N_2$ (412.5): C, 67.0; H, 6.8. Found: C, 66.8; H, 6.7.

Two additional crops of the diethyl ester, of 0.018 and 0.078 g., respectively, were recovered from the mother liquors to give a total yield of 0.148 g. (72%).

Attempted Reaction of Diphenyl Dithiocarbonate with L-Phenylalanine.—To a solution of 1.5 g. (0.009 mole) of L-phenylalanine in 4 ml. of 10 *N* aqueous sodium hydroxide and 21 ml. of water was added 4.52 g. (0.018 mole) of finely powdered diphenyl dithiocarbonate, m.p. 43–43.5°, and the mixture vigorously shaken for 5 hours. The alkaline solution was filtered, the precipitate washed with water, and dried to give 4.4 g. (97%) of diphenyl dithiocarbonate, m.p. 43–43.5°. The alkaline filtrate was acidified with concentrated hydrochloric acid but no precipitate was obtained.

N-Ethyl-S-phenylthiocarbamate. (A).—To an ice-cold solution of 1.43 ml. (0.022 mole) of ethylamine in 5 ml. of absolute ethanol was added, with cooling and vigorous shaking, 1.73 g. (0.01 mole) of phenylthiocarbonyl chloride. The reaction mixture was allowed to stand at 25° for 15

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[11] W. Will, *Ber.*, **15**, 338 (1882).

[12] F. Gumpert, *J. prakt. Chem.*, [2] **32**, 278 (1885).

[13] M. Busch, G. Blume and E. Pings, *ibid.*, [2] **79**, 513 (1909).

[14] T. Wilm and G. Wischin, *Chem. Centr.*, 663 (1868).

[15] All melting points are corrected.

[16] Microanalyses by Dr. A. Elek.

minutes, poured into 15 ml. of ice-water, the biphasic product cooled in a Dry Ice-bath, the solid collected, and dried to give 1.2 g. of product. This material was recrystallized from absolute ethanol to give 0.22 g. of diphenyl dithiocarbonate, m.p. 43°, as the more insoluble fraction, and 0.24 g. (13%) of N-ethyl-S-phenylthiocarbamate, m.p. 81–82°, *vide post*. The solution remaining after the initial collection of the above mixture was evaporated to dryness, *in vacuo*, to give 0.61 g. of a mixture of ethylammonium chloride and *sym*-diethylurea. Extraction of this product with 60–70° ligroin gave 0.18 g. of *sym*-diethylurea, m.p. 109.5° after one additional recrystallization from 60–70° ligroin.

(B).—To an ice-cold and vigorously shaken solution of 2.16 g. (0.0125 mole) of phenylthiocarbonyl chloride in 5 ml. of absolute ethanol was added, in small portions over a 3–4 minute interval, 1.61 ml. (0.025 mole) of ethylamine, the reaction mixture allowed to stand at 25° for 10 minutes, poured into 20 ml. of ice-water, the precipitated oil crystallized by cooling in a Dry Ice-bath, the solid product collected, and dried to give 1.9 g. (84%) of N-ethyl-S-phenylthiocarbamate, m.p. 81–82°, after two recrystallizations from absolute ethanol.

Anal. Calcd. for $C_9H_{11}ONS$ (181.2): C, 59.6; H, 6.1; N, 7.7. Found: C, 59.8; H, 6.2; N, 7.7.

When dry dioxane was used as a solvent, *in lieu* of absolute ethanol, a yield of 83% was obtained.

N,S-Diphenylthiocarbamate.—To a cold and vigorously shaken solution of 1.86 ml. (0.02 mole) of aniline in 10 ml. of absolute ethanol was added, in several portions, 1.73 g. (0.01 mole) of phenylthiocarbonyl chloride, the solution allowed to stand at 25° for 2.5 hours, poured into 25 ml. of ice water, the precipitate collected, washed in turn with dilute hydrochloric acid and with water and dried to give 2.25 g. (98%) of N,S-diphenylthiocarbamate, m.p. 125.5–126° after one recrystallization from 95% ethanol. Rivier[7] gives a m.p. of 122–122.5° for this compound. N,S-Diphenylthiocarbamate was found to be insoluble in hot water, hot *N* hydrochloric acid and only slightly soluble in cold 4.5 *N* aqueous sodium hydroxide. However, when a suspension of N,S-diphenylthiocarbamate in 4.5 *N* aqueous sodium hydroxide was shaken, the solid phase was observed to slowly dissolve. Warming greatly accelerated this process.

N-Methyl-N-phenyl-S-phenylthiocarbamate.—Acylation of N-methylaniline, 1.08 ml. (0.011 mole) with 0.86 g. (0.005 mole) of phenylthiocarbonyl chloride, as described in the preparation immediately above, gave 1.15 g. (95%) of N-methyl-N-phenyl-S-phenylthiocarbamate, m.p. 71–71.5°, after recrystallization from absolute ethanol. Rivier[7] gives a m.p. of 66.0–66.5° for this compound.

Anal. Calcd. for $C_{14}H_{13}ONS$ (243.3): C, 69.1; H, 5.4; S, 13.2. Found: C, 69.5; H, 5.7; S, 13.4.

Reaction of N-Ethyl-S-phenylthiocarbamate with Ethylamine.—To an ice cold and vigorously shaken solution of 0.45 g. (0.0025 mole) of N-ethyl-S-phenylthiocarbamate in 5 ml. of absolute ethanol was added 1.30 ml. (0.02 mole), of ethylamine, the reaction mixture allowed to stand at 25° for 15 minutes, evaporated to dryness in a stream of air, the residue dried at 25° *in vacuo*, triturated with 60–70° ligroin, filtered, and dried to give 0.26 g. (90%) of crude *sym*-diethylurea, m.p. 104–106°; m.p. 109–109.5° after one recrystallization from 60–70° ligroin.

Reaction of N,S-Diphenylthiocarbamate with Ethylamine.—N,S-Diphenylthiocarbamate, 1.15 g. (0.005 mole) in 20 ml. of absolute ethanol was allowed to react with 1.14 ml. (0.002 mole) of ethylamine as described in the preparation immediately above, the reaction mixture evaporated to dryness in a stream of air, the residue triturated with water, the precipitate collected, washed with water and dried to give 0.53 g. (64%) of N-ethyl-N′-phenylurea, m.p. 92–95°. From the mother liquors a second crop of 0.30 g. (36%) of the urea was obtained. The two fractions were combined and recrystallized from aqueous ethanol to give N-ethyl-N′-phenylurea, m.p. 99°.

Stability of N-Ethyl-S-phenyl- and N,S-Diphenylthiocarbamate in the Presence of Aniline.—A solution of 1.12 ml. (0.012 mole) of aniline and 0.54 g. (0.0025 mole) of N-ethyl-S-phenylthiocarbamate in 10 ml. of absolute ethanol was allowed to stand at 25° for 15 minutes, the solution concentrated in a stream of air, 15 ml. of ice-water added to the residue, the *p*H adjusted to *ca.* *p*H 4 with dilute hydrochloric acid, the precipitate collected, washed in turn with *N* hydrochloric acid and with water, and dried to give 0.54 g. (100%) of N-ethyl-S-phenylthiocarbamate, m.p. 81–82°, after one recrystallization from absolute ethanol.

A solution of 0.93 ml. (0.01 mole) of aniline and 0.57 g. (0.003 mole) of N,S-diphenylthiocarbamate in 10 ml. of absolute ethanol when treated as described immediately above gave 0.56 g. (98%) of N,S-diphenylthiocarbamate, m.p. 125.5–126°, after one recrystallization from 95% ethanol.

Reaction of N,S-Diphenylthiocarbamate with Aniline in the Presence of Triethylamine.—Triethylamine, 1.39 ml. (0.01 mole), was added, slowly and with vigorous agitation, to an ice cold solution of 0.58 g. (0.0025 mole) of N,S-diphenylthiocarbamate and 0.93 ml. (0.01 mole) of aniline in 10 ml. of dioxane that had been previously distilled over sodium. The reaction mixture was allowed to stand at 25° for 40 minutes, then poured into 40 ml. of ice-water, the precipitate collected, washed with *N* hydrochloric acid and with water, and dried to give 0.53 g. (100%) of *sym*-diphenylurea, m.p. 240°.

The above reaction was also conducted with ethanol as a solvent and aqueous sodium hydroxide as the base to give a 28% yield of the urea, and with dioxane as the solvent and a lesser quantity of aqueous sodium hydroxide to give a 42% yield of the urea.

Stability of N-Methyl-N-phenyl-S-phenylthiocarbamate in the Presence of Base.—N-Methyl-N-phenyl-S-phenylthiocarbamate was recovered unchanged, in 91% yield from an aqueous ethanol solution of sodium hydroxide that had been allowed to stand at 25° for 20 minutes, in 100% yield from a suspension in 2 *N* aqueous sodium hydroxide that had been heated to boiling for 1 minute, and in 80% yield from a solution in *N* methanolic sodium methylate that had also been boiled for 1 minute.

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