B was methyl sulfite (9%, assuming one mole of disulfide produces two of sulfite); sapon. equiv. 55 (calcd. 55), infrared spectrum identical with that of authentic material.[11] However, it contained considerable impurity (analysis, n^{25}D, vile atypical odor) which could not be removed.

D was methyl ethanesulfinate (II, 31%). It had strong infrared absorption at 993–1000 cm.$^{-1}$ and 1139 cm.$^{-1}$. The sapon. equiv. after 1.5 hr. of heating was 117–119 (calcd. 108), and the sulfinate salt obtained after neutralization and evaporation gave, with 2,4-dinitrochlorobenzene, ethyl 2,4-dinitrophenyl sulfone in 80% yield, m.p. 156–157° (reported, 156°).[12] The sapon. equiv. cannot be relied upon; thus, heating for 0.8 hr. gave 198–200 and for 2.5 hr., 143–149. The best II afforded by distillation still was not pure; b.p. 62° (29 mm.), n^{25}D 1.4383. Other material with n^{25}D 1.4387 had d^{25}_{4} 1.093, MD calcd. 26.58[8] found 26.00.

Anal. Calcd. for $C_3H_8O_2S$: C, 33.31; H, 7.46; S, 29.65. Found: C, 33.90; H, 7.71; S, 30.26.

(b) **Omission of Water Washing.**—The reaction was like that of (a), but after the 10 hr. of reflux, a slight excess of lead tetraacetate (starch-iodide test) was destroyed with a few drops of ethylene glycol. Chloroform was distilled and lead diacetate was removed occasionally by filtration after chilling. Since the yield was only 17%, this approach was unpromising.

(c) **With Reduction in Temperature and Proportion of Lead Tetraacetate.**—A solution of lead tetraacetate (0.25 mole) in chloroform (450 ml.) was added to ethyl disulfide (9.17 g., 0.075 mole) in chloroform (140 ml.)-methanol (76 ml.) during 4 hr. at 25–30°. After 6 hr., the solution was poured into water. The washed and dried chloroform layer upon distillation (47-cm. column) gave 1.13 g. (7%) of methyl sulfite, 9.35 g. of crude II (58%, n^{25}D 1.4353–1.4479), and 1.2 g. of higher boiling material (infrared absorption at 1758 cm.$^{-1}$ suggested acetoxylated substances). Redistillation of II gave the usual yield, however: 4.99 g. (31%), b.p. 68° (39 mm.), n^{25}D 1.4377–1.4397, infrared spectrum in agreement with that of II as reported above. After saponification (1 hr.; sapon. equiv. 113–116), ethyl 2,4-dinitrophenyl sulfone was obtained in 72% yield.

Essentially the same reaction at 0°, followed by 9 hr. of stirring at 25°, gave virtually the same result as at 25°.

(d) **With n-Butyl Alcohol.**—When the reaction of (c) at 25° was repeated with *n*-butyl alcohol instead of methanol, *n*-butyl sulfite resulted in 5% yield; infrared spectrum identical with that of commercial material. *n*-Butyl ethanesulfinate apparently resulted in *ca.* 9% yield (infrared spectrum) but could not be purified by distillation.

(e) **With Reduced Proportions of Methanol.**—A reaction like that of (c) at 25° but with only 13 ml. (0.32 mole) of methanol gave II in 23% yield, n^{25}D 1.4370–1.4399, and nearly an equal weight of higher boiling material.

Reduction of the methanol to 0.15 mole, about one-half the theoretical amount, resulted after distillation in seventeen fractions which were combined into three groups. Vapor phase chromatography (162°, 10% Carbowax 400 on Fluoropak 80) indicated that one group consisted of II with at least five impurities, and another of two principal components with four impurities.

Reaction of Other Disulfides.—A solution of lead tetraacetate (0.25 mole) in chloroform (450 ml.) was added (2 hr.) to benzyl disulfide (18.91 g., 0.077 mole) in chloroform (140 ml.)-methanol (76 ml.) at 25°. After a stirring period of 22 hr. at 25°, isolation was effected as usual. Distillation of oil obtained (32.2 g.) gave four groups of fractions: (1) Methyl sulfite (identified by its infrared spectrum; 1.33 g., 8% conversion). (2) Benzaldehyde (1.96 g., 12% conversion assuming one mole of disulfide yields two of benzaldehyde); identity was established by the infrared spectrum and by conversion (66%) to the 2,4-dinitrophenylhydrazone, m.p. 241.5–243.5° (reported, 242–244.5°).[13] (3) Benzaldehyde dimethylacetal (n^{25}_{D} 1.4872–1.4915); infrared spectrum and n^{25}_{D} (1.4919), after purification, essentially identical with those of authentic material (n^{25}D 1.4927); converted to benzoic acid and benzaldehyde 2,4-dinitrophenylhydrazone; yield 4.42 g., 19% conversion, assuming one mole of disulfide produces two of the acetal. (4) A mixture which could not be separated.

From undistilled residue, chromatography separated benzyl disulfide (24% recovery).

Essentially the procedure of (a) with *t*-butyl disulfide gave product which became black and evolved sulfur dioxide upon distillation. A distillate had strong infrared absorption at 1136 cm.$^{-1}$ and 990–1000 cm.$^{-1}$ but also had intense carbonyl absorption (1740 cm.$^{-1}$) and was not studied further.

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[11] H. H. Szmant and W. Emerson, *J. Am. Chem. Soc.*, **78**, 454 (1956).

[12] R. W. Bost, P. K. Starnes, and E. L. Wood, *ibid.*, **73**, 1968 (1951).

[13] D. Buckley, S. Dunstan, and H. B. Henbest, *J. Chem. Soc.*, 4901 (1957).

Reactions between Acids and Thiourea. II.[1] The Formation of Anilides from Acids and s-Diphenylthiourea[2]

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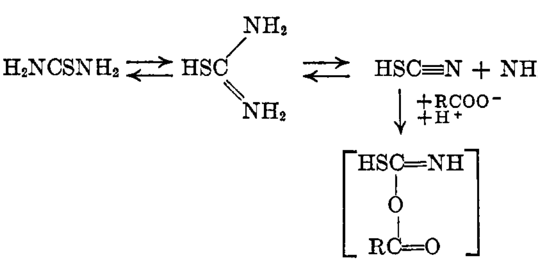
In a previous communication[1] the formation of amides by heating an equimolecular mixture of an acid and thiourea was described. A mechanism was suggested, based upon the intermediate formation of an addition product from the carboxylic acid and from the thiocyanic acid assumed to originate from the decomposition of thiourea (equation 1). This mechanism was proposed in analogy to that postulated by Rahman[1] for the formation of amides from acids and urea[3] in which the formation of an intermediate product from the carboxylic acid and from the isocyanic acid formed by thermal decomposition of urea was suggested. The difference between the two proposed mechanisms is that in the thermal decomposition of urea, isocyanic acid has been assumed to be the reactive tautomer, while in the decomposition of thiourea, thiocyanic acid is postulated to be the prevailing form in the equilibrium.



(1)

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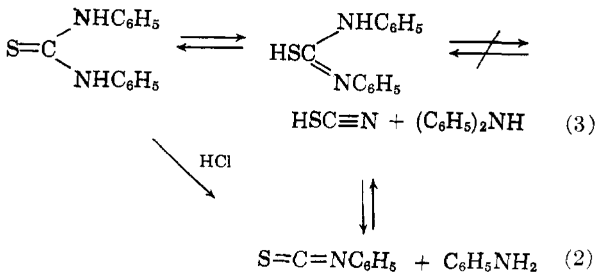
[1] Part I, A. Rahman, M. A. Medrano, and O. P. Mittal, *Rec. trav. chim.*, **79**, 188 (1960).

[2] Presented in the Latin-American Symposium on Synthetic Organic Chemistry, Bahía Blanca, September, 1961.

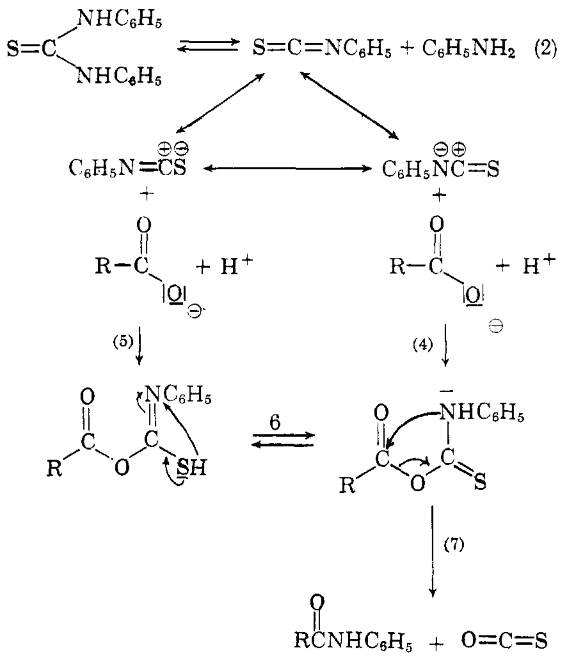
[3] A. Rahman, *Rec. trav. chim.*, **75**, 164 (1956).

The present work was undertaken with the twofold object (1) of extending the reactions of thioureas with carboxylic acids to form anilides, and (2) of examining the earlier proposed mechanisms for these reactions for the purpose of determining whether thiocyanic acid or isothiocyanic acid is the reacting intermediate. If *s*-diphenylthiourea is employed in place of thiourea in the reaction with carboxylic acid, the intermediates should be either phenyl isothiocyanate and aniline (equation 2) or thiocyanic acid and diphenylamine (equation 3). The products from thiocyanic acid would be amides while the products from phenyl isothiocyanate would be anilides.



In the present work, phenylacetic, diphenylacetic, palmitic, stearic, and benzoic acids gave the respective anilides in yields ranging from 54 to 95%, when heated in equimolecular mixtures with diphenylthiourea at 180°. Succinic acid and its anhydride, as expected, furnished N-phenylsuccinimide in 74% yield.

In view of these results it is reasonable to assume that the thermal decomposition of diphenylthiourea yields aniline and phenyl isothiocyanate and that the latter represents the reacting moity in the reaction between carboxylic acid and diphenylthiourea at elevated temperatures, resulting in the formation of anilides. The well known decomposition of *s*-diphenylthiourea into phenyl isothiocyanate and aniline by heating with hydrochloric acid may be noted in this connection. Additional information about the mechanism operating in the formation of anilides was obtained by carrying out reactions between phenyl isothiocyanate and the same carboxylic acids as were used for interactions with *s*-diphenylthiourea. Anilides were obtained in all cases in over 80% yield. Succinic acid and its anhydride again furnished N-phenylsuccinimide. These results lead to the postulation of the following over all mechanism for the formation of anilides in reactions between carboxylic acids and *s*-diphenylthiourea or for that matter phenyl isothiocyanate.



The presence of aniline in the reaction product was confirmed by the coupling reaction with β-naphthol. During the reaction, the characteristic odor of hydrogen sulfide, a small deposition of sulfur in the condenser, combustion with a blue flame of the outcoming gases, and the formation of a precipitate of barium carbonate on passing the outcoming gases into baryta, were observed and may be considered as a result of the formation of carbon oxysulfide as a by-product and of its further decomposition as follows:

$$\mathrm{OCS} + \mathrm{H_2O} \longrightarrow \mathrm{CO_2} + \mathrm{H_2S}$$

$$2\ \mathrm{OCS} \rightleftharpoons 2\ \mathrm{CO} + 2\ \mathrm{S} \rightleftharpoons \mathrm{CO_2} + \mathrm{CS_2}$$

Further confirmatory evidence in favor of the fact that in the formation of anilides from *s*-diphenylthiourea the reactive entity is phenyl isothiocyanate and not phenyl thiocyanate was provided by the nonformation of anilides upon heating a mixture of phenylacetic acid and phenyl thiocyanate. The acid was recovered completely from the reaction mixture. Diphenylacetic acid also gave a negative result.

In view of the lack of evidence in favor of the fact that the formation of amides using thiourea and of anilides using *s*-diphenylthiourea in conjunction with carboxylic acids, takes place through two different mechanisms, it is reasonable to modify the mechanism reported earlier[1,2] for the formation of amides and consider the above mechanism as a general one also applicable to the formation of amides.

It is interesting in this connection to consider the mechanism of amide formation from acid and urea based on the postulation of an intermediate addition product from carboxylate ion and isocyanic acid (from decomposition of urea) proposed by Rahman[3] and the suggestion that the formation of anilides[4] from acids and diphenylurea, yielding phenyl isocyanate upon decomposition, proceeds *via* a similar mechanism. This lends a wider scope to the mechanism outlined under equations 2 to

(4) A. Rahman and M. O. Farooq, *Ber.*, **86**, 945 (1953).

7, since it may also be considered valid for the formation of amides from acids and urea as well as to that of anilides from acids and *s*-diphenylurea.

Experimental[5]

The experimental details described below for the preparation of phenylacetanilide represent a typical case and serve as a model for other cases except for small differences in the maximum temperature employed and the total time allowed for the reaction. The identity of the anilides was confirmed by analysis and mixed melting point determinations with authentic samples prepared from aniline and the respective acid chlorides.

Preparation of Phenylacetanilide.—An intimate mixture of 6.8 g. (0.05 mole) of well dried diphenylacetic acid and an equimolecular quantity (11.4 g.) of *s*-diphenylthiourea was placed in a flask fitted with an air condenser, and was heated gradually in an oil bath. In the course of about 1 hr. the temperature was raised to 180–185° when the actual reaction commenced marked by effervescence and frothing and deposition of some yellow solid (sulfur) in the reflux tube. The reaction was allowed to proceed for another hour, the temperature of bath being maintained between 180–190°. The reaction mixture was cooled and taken up in ether. After extraction with dilute hydrochloric acid, the ethereal solution was washed with water and dried over anhydrous magnesium sulfate. Evaporation of the ether and crystallization of the residue from ethanol gave 9.4 g. (90%) of diphenylacetanilide, m.p. and mixed m.p. with an authentic sample[4] of 117–118°. The aqueous hydrochloric acid extract of the ethereal solution of the reaction product gave a positive coupling reaction with β-naphthol.

Preparation of N-Phenylsuccinimide.—A mixture of 5 g. (0.05 mole) of succinic anhydride and an equimolecular quantity (11.4 g.) of *s*-diphenylthiourea was heated at 180–185° for about 2 hr. The cooled reaction mixture was triturated with small portions of ether to remove aniline and the residue was crystallized from ethanol. This gave 6.5 g. (74%) of N-phenylsuccinimide with a m.p. and mixed m.p. with an authentic sample[4] of 155°.

Preparation of Benzanilide from Phenyl Isothiocyanate.—An intimate mixture of 3.66 g. (0.03 mole) of benzoic acid and an equimolecular quantity of phenyl isothiocyanate (4.05 g.) was heated at 180–185° for about 2 hr. A slight deposition of sulfur in the condenser and the evolution of hydrogen sulfide from the out-coming vapors was noted and confirmed. The reaction mixture was allowed to cool and was then taken up in hot alcohol. Treatment of the hot alcoholic solution with active charcoal and evaporation of the solvent from the filtered solution gave 5.2 g. (89%) of benzanilide which on recrystallization from ethanol melted at 162–163° and did not show any depression on admixture with the sample of benzanilide prepared from *s*-diphenylthiourea and an authentic sample prepared from benzoyl chloride and aniline.

TABLE I

Acids	Yields of the Anilides, %	M.p., °C.
Phenylacetic	85	117–118
Diphenylacetic	91	181–182
Benzoic	89	162–163
Succinic	57 (Imide)	154–155
Palmitic	81	86–87
Stearic	84	82–83

The preceeding table summarizes the yields of the anilides obtained from phenyl isothiocyanate and acids other than benzoic acid. The identity of the anilide in each case was confirmed both by mixed melting point determination with samples prepared from *s*-diphenylthiourea and with an authentic sample prepared from the respective acid chloride and aniline and by elemental analysis. It may be noted that the melting point of pure stearic acid anilide prepared by the above two methods and from the acid chloride and aniline, was found to be 82–83° and not 93° as reported in the literature.

Acknowledgment.—The authors wish to express their thanks to "Consejo Nacional de Investigaciones Científicas y Técnicas," Buenos Aires, for a research grant in connection with this work.

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[5] Melting points are uncorrected.

Alternative Approaches to 1-Substituted Thymines

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Syntheses of the cyclopentane isostere of thymidine and other 1-(hydroxycyclopentyl)thymines[1] required 1-(3-cyclopenten-1-yl)thymine (V) as a key intermediate. For the synthesis of this compound we found that a route to 1-substituted thymines reported by Shaw and Warrener[2] was quite satisfactory, except for the last step, closure of the pyrimidine ring. This note describes an improved ring closure method, as well as an alternative approach to acylurea intermediates.

In a modification of the published route, methyl 3-methoxy-2-methylacrylate was saponified and the resulting sodium salt converted directly to the acid chloride, bypassing an intervening[2] isolation of the free acid. Conversion of the acid chloride to the acyl isocyanate I and then to the ethoxycarbonylamide[2] III proceeded smoothly. In a subsequent reaction of III with an equivalent amount of 3-cyclopenten-1-ylamine[3] in hot aqueous sodium hydroxide, a condensation–cyclization gave the desired 1-(3-cyclopenten-1-yl)thymine (V), but the yield was only 23%. It seems likely that saponification of the starting ethoxycarbonylamide (III) or of a noncyclized intermediate was a competing side reaction. Other workers have found that in an analogous cyclization with benzylamine as the amine component the yield of 1-benzylthymine was 24%,[4] and even with large excesses of ammonia or methylamine the yields of thymine and 1-methylthymine were 42 and 44%,

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[1] K. C. Murdock and R. B. Angier, Abstracts of Papers, 141st Meeting, American Chemical Society, Washington, D. C., March, 1962, p. 22-N; *Tetrahedron Letters*, 415 (1962); *J. Am. Chem. Soc.*, in press.

[2] G. Shaw and R. N. Warrener, *J. Chem. Soc.*, 153, 157 (1958).

[3] K. C. Murdock and R. B. Angier, *J. Org. Chem.*, **27**, 2395 (1962).

[4] M. H. Benn, B. Chatamra, and A. S. Jones, *J. Chem. Soc.*, 1014 (1960).