[Contribution from the Chemistry Department, University of Kentucky]

N-Sulfinyl Amines. Reaction with Carboxylic Acids[1]

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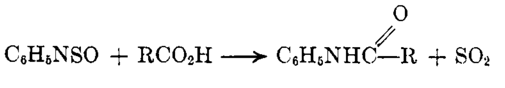
The previously reported reaction of *N*-sulfinylaniline with carboxylic acids to give acyl anilides has been shown to require the presence of hydrogen chloride. The sequence of steps involved in the overall reaction and the role of hydrogen chloride are described.

Carré and Libermann[2] reported that carboxylic acids react with *N*-sulfinylaniline to form the corresponding anilides:



$$C_6H_5NSO + RCO_2H \longrightarrow C_6H_5NH\overset{O}{\overset{\|}{C}}—R + SO_2$$

As part of our study of the chemistry of *N*-sulfinyl amines, attempts were made to carry out the above reaction. It was found that when a solution of *N*-sulfinylaniline in acetic acid was refluxed as described by Carré and Libermann no sulfur dioxide was evolved and no acetanilide could be isolated from the solution. Since these results were contrary to those reported by Carré and Libermann, variations in the reaction conditions were studied and various other acids which reportedly reacted with *N*-sulfinylaniline were also tried, but without success.

N-Sulfinylaniline may be prepared by the action of thionyl chloride on aniline hydrochloride. This suggests the possibility that traces of either thionyl chloride or hydrogen chloride, or both, might be present as impurities in *N*-sulfinylaniline. To test the possibility that one of these impurities might have been acting as a catalyst in the experiments of Carré and Libermann the following experiments were performed.

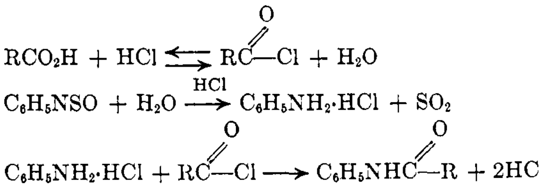
When a mixture of *N*-sulfinylaniline and acetic acid containing a small amount of thionyl chloride was refluxed, there was obtained a 90% yield of acetanilide.

To show the possible catalytic effect of hydrogen chloride a mixture of *N*-sulfinylaniline and acetic acid was exposed to dry hydrogen chloride gas for a few minutes and then allowed to stand with suitable protection from moisture. A precipitate which almost immediately started to form completely dissolved in three days. At the end of seven days a new precipitate had formed. This second precipitate was identified as acetanilide and represented an 83% yield.

These results thus show the catalytic effect of both thionyl chloride and hydrogen chloride on the reaction of *N*-sulfinylaniline with acetic acid. Since thionyl chloride reacts with the carboxylic acid to give hydrogen chloride as one of the products, it appears that the catalytic effect of thionyl chloride is simply due to the fact that it does give rise to hydrogen chloride under the conditions used in the reaction.

A consideration of the possible role of hydrogen chloride as a catalyst for these reactions leads to the following possibilities:

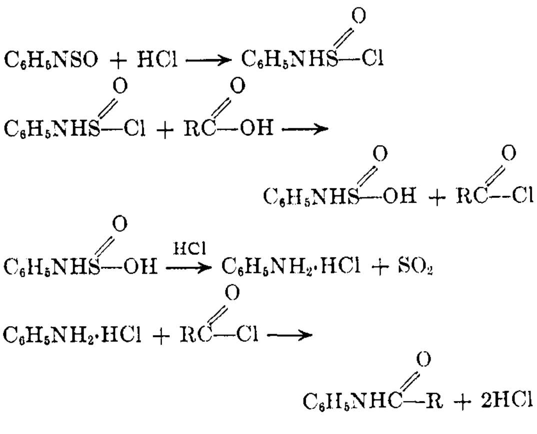
I.



$$RCO_2H + HCl \rightleftarrows R\overset{O}{\overset{\|}{C}}—Cl + H_2O$$
$$C_6H_5NSO + H_2O \xrightarrow{HCl} C_6H_5NH_2\cdot HCl + SO_2$$
$$C_6H_5NH_2\cdot HCl + R\overset{O}{\overset{\|}{C}}—Cl \longrightarrow C_6H_5NH\overset{O}{\overset{\|}{C}}—R + 2HC$$

The possibility of the first step's taking place has to be considered, since the removal of water by reaction with C_6H_5NSO in the second step could drive the equilibrium of the first step to completion:

II.



$$C_6H_5NSO + HCl \longrightarrow C_6H_5NH\overset{O}{\overset{\|}{S}}—Cl$$
$$C_6H_5NH\overset{O}{\overset{\|}{S}}—Cl + R\overset{O}{\overset{\|}{C}}—OH \longrightarrow C_6H_5NH\overset{O}{\overset{\|}{S}}—OH + R\overset{O}{\overset{\|}{C}}—Cl$$
$$C_6H_5NH\overset{O}{\overset{\|}{S}}—OH \xrightarrow{HCl} C_6H_5NH_2\cdot HCl + SO_2$$
$$C_6H_5NH_2\cdot HCl + R\overset{O}{\overset{\|}{C}}—Cl \longrightarrow C_6H_5NH\overset{O}{\overset{\|}{C}}—R + 2HCl$$

III. In a variation of sequence II the initial step need not be represented as above, but simply as the formation of a "complex" between hydrogen chloride and *N*-sulfinylaniline. $C_6H_5NSO + HCl \rightarrow C_6H_5NSO\cdot HCl$. This complex, which may or may not have the structure shown in sequence II, might then react directly with the carboxylic acid

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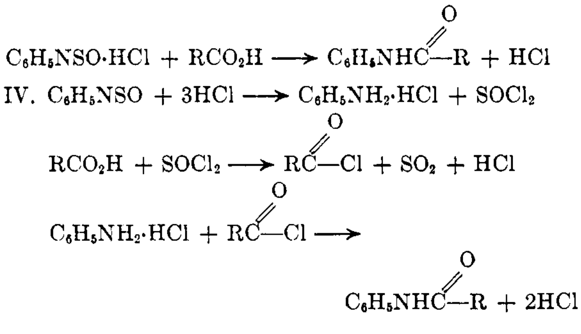
[1] This research was supported by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command, under contract No. AF49(638)-49. Reproduction in whole or in part is permitted for any purpose of the United States Government.

(2) P. Carré and D. Libermann, *Compt. rend.*, **194**, 2218 (1932).

(3) A. Michaelis, *Ber.*, **24**, 745 (1891).



$$C_6H_5NSO\cdot HCl + RCO_2H \longrightarrow C_6H_5NHC(=O)\text{—}R + HCl$$

$$\text{IV. } C_6H_5NSO + 3HCl \longrightarrow C_6H_5NH_2\cdot HCl + SOCl_2$$

$$RCO_2H + SOCl_2 \longrightarrow RC(=O)\text{—}Cl + SO_2 + HCl$$

$$C_6H_5NH_2\cdot HCl + RC(=O)\text{—}Cl \longrightarrow C_6H_5NHC(=O)\text{—}R + 2HCl$$

The first step in this sequence is essentially the reverse of the reaction usually used to prepare *N*-sulfinylaniline. It has been reported[2,3] that this reverse reaction does take place when dry hydrogen chloride is passed into pure *N*-sulfinylaniline. The subsequent steps are known reactions.

Of the above four sequences, three (I, II, and IV) postulate the presence of aniline hydrochloride as an intermediate. Several experiments indicate that aniline hydrochloride is indeed formed prior to the formation of acetanilide in the catalyzed reaction of *N*-sulfinylaniline with acetic acid. When a slight excess of thionyl chloride was added to a solution of *N*-sulfinylaniline in acetic acid there was almost immediate formation of crystals. These crystals were shown to be aniline hydrochloride. When this same mixture was allowed to stand overnight and then worked up as described above, acetanilide was obtained. These results explain the observations described earlier for the hydrogen chloride catalyzed reaction of *N*-sulfinylaniline with acetic acid in which the precipitate which formed at the start of the reaction later dissolved and was replaced by a new precipitate.

In an experiment under the above conditions, it was shown that in less than 15 min. a 64% yield of aniline hydrochloride was obtained. This result is particularly significant in demonstrating that aniline hydrochloride is an intermediate in the formation of acetanilide because this yield of aniline hydrochloride is nearly as great as would have been the yield of acetanilide if the reaction had been allowed to continue.

In a similar experiment the passage of dry hydrogen chloride into a solution of *N*-sulfinylaniline in xylene gave an 88% yield of aniline hydrochloride.

The above experiments established the presence of aniline hydrochloride as an intermediate in the overall sequence of reactions. On this basis, sequence III can be ruled out. Of the remaining possibilities only sequence IV involves the intermediate formation of thionyl chloride. Efforts to isolate thionyl chloride from some of the experiments described above in which aniline hydrochloride was formed were inconclusive. In order to show that thionyl chloride is formed from *N*-sulfinylaniline, a solution of *N*-sulfinylaniline in cyclohexane was exposed to dry hydrogen chloride for a short while and then distilled. The presence of thionyl chloride in the distillate was shown by means of vapor phase chromatography. To show that thionyl chloride is also formed in acetic acid the cyclohexane of the above experiment was replaced by acetic acid with essentially the same results.

The above experiments confirm the earlier observations[3,4] that the reaction given in step 1 of sequence IV can take place. Moreover, our experiments show that this reaction can occur under the same conditions in which *N*-sulfinylaniline reacts with carboxylic acids.

Since sequence IV is the only sequence in which both aniline hydrochloride and thionyl chloride are intermediates, it can be concluded that the steps involved in the reaction of *N*-sulfinyl amines with carboxylic acids are correctly described by sequence IV. It is not necessary that all of the acetanilide be formed from the reaction of aniline hydrochloride with acetyl chloride, since some reaction may take place directly with the acetic acid.

Anilides of the following acids were obtained by refluxing the acid with *N*-sulfinylaniline and a drop of thionyl chloride: formic, 44% yield; benzoic, 30% yield; chloroacetic, 65% yield, glutaric, trace of dianilide. These reactions are not peculiar to *N*-sulfinylaniline. The *N*-sulfinyl derivatives of *p*-nitroaniline and cyclohexyl amine are converted to the corresponding *N*-acetyl derivatives by refluxing in acetic acid containing a trace of thionyl chloride. The reaction of *p*-nitro-*N*-sulfinylaniline with acetic acid is more vigorous than the corresponding reaction of *N*-sulfinylaniline. Immediate reaction is noted and a 92% yield of *p*-nitroacetanilide is obtained. *N*-sulfinylcyclohexylamine gives only a 31% yield under similar conditions.

EXPERIMENTAL[5]

Acetanilide from N-sulfinylaniline and acetic acid. Thionyl chloride catalyst. To a solution of 5 g. (0.036 mole) of *N*-sulfinylaniline[3] in 15 ml. of glacial acetic acid was added 0.2 ml. (0.33 g., 0.003 mole) of thionyl chloride. The solution was refluxed for 2 hr., poured into water, and extracted with chloroform to give 4.4 g. (90%) of acetanilide, m.p. 113–114°, undepressed by mixture with an authentic sample.

Miscellaneous anilides. The following anilides were prepared as above from 1.2 g. of *N*-sulfinylaniline, 1 drop of thionyl chloride and the indicated amount of acid. Formanilide, m.p. 45–46° (44%) from 5 ml. formic acid. Benzanilide, m.p. 156–160° (30%) from 2.17 g. benzoic acid. ω-Chloroacetanilide, m.p. 133–134° (65%) from 1.76 g. chloroacetic acid. Glutaric dianilide, m.p. 221–223° (trace) from 0.94 g. glutaric acid.

Acetanilide from N-sulfinylaniline and acetic acid. Hydrogen chloride catalyst. A solution containing 1.2 g. (0.009 mole) of *N*-sulfinylaniline in 5 ml. of acetic acid was exposed to dry hydrogen chloride for 10 min. The solution was protected from moisture and allowed to stand. A precipitate which started to form almost immediately had completely dis-

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(4) P. Carré and D. Libermann, *Bull. soc. chim. France*, 6, 579 (1939).

(5) Melting points were taken on a Fisher-Johns melting point block and are corrected.

solved at the end of 3 days. At the end of 7 days a new precipitate had formed. The mixture was then poured into water and extracted with chloroform to give 1.0 g. (83%) of acetanilide, m.p. 113–114°.

p-Nitroacetanilide from p-nitro-N-sulfinylaniline. To 5 ml. of glacial acetic acid and 0.1 ml. (0.17 g., 0.0015 mole) of thionyl chloride was added 1 g. (0.005 mole) of *p*-nitro-*N*-sulfinylaniline.[3] Immediate formation of crystals was noted, and after 15 min. of heating the mixture was completely solid. An additional 5 ml. of acetic acid was added and the mixture was allowed to stand for 30 min. The reaction mixture was then diluted with 100 ml. of water and extracted with chloroform. The solid which did not dissolve was removed by filtration and combined with that obtained from evaporation of the chloroform to give 0.9 g. (92%) of *p*-nitroacetanilide, m.p. 215–216°.[6]

N-Cyclohexylacetamide. A mixture of 5 ml. of acetic acid, 1.09 g. (0.0075 mole) of *N*-sulfinylcyclohexyl amine[7] and 0.1 ml. (0.17 g., 0.0015 mole) of thionyl chloride was refluxed for 2 hr., cooled, and extracted with chloroform to give 0.33 g. (31%) of *N*-cyclohexylacetamide, m.p. 103–104°.[8]

Aniline hydrochloride from N-sulfinylaniline. To a solution of 1.2 g. (0.009 mole) of *N*-sulfinylaniline in 5 ml. of acetic acid at 25° was added 1.65 g. (0.017 mole) of thionyl chloride. There was an immediate vigorous reaction resulting in the precipitation of 0.85 g. (74%) of aniline hydrochloride, m.p. 195–198°, undepressed by mixture with an authentic sample.

In another experiment a slow stream of dry hydrogen chloride was passed for 1 hr. into 10 g. (0.07 mole) of *N*-sulfinylaniline dissolved in 30 ml. of dry xylene at 25° to give 8.2 g. (88%) of aniline hydrochloride.

Detection of thionyl chloride. Solutions of *N*-sulfinylaniline in cyclohexane and in acetic acid were exposed to dry hydrogen chloride for 15 min. and then distilled. Vapor phase chromatography of both distillates and of authentic mixtures showed the presence of thionyl chloride.

LEXINGTON, KY.

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(6) A. Kaufmann, *Ber.*, **42**, 3482 (1909).

(7) Donald Trimnell, Thesis, University of Kentucky, 1958.

(8) A. Baeyer, *Ann.*, **278**, 104 (1894).

[CONTRIBUTION FROM THE PIONEERING RESEARCH DIVISION, TEXTILE FIBERS DEPARTMENT, E. I. DU PONT DE NEMOURS & CO., INC.]

Reaction of an Isocyanate and a Carboxylic Acid in Dimethyl Sulfoxide

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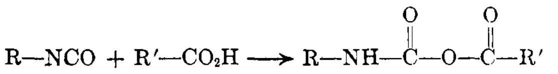
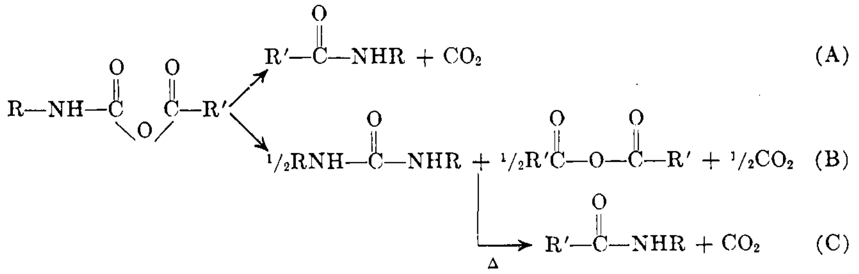
The reaction of an aromatic isocyanate or diisocyanate with benzoic acid in dimethyl sulfoxide as solvent has been found to give the urea or high molecular weight polyurea derived from the amine or diamine precursor of the isocyanate. The dimethyl sulfoxide takes part in the reaction also, forming the methylthiomethyl ester of benzoic acid. This fact, plus the observed stoichiometry of the reaction (2:1:1 for isocyanate:carboxylic acid:sulfoxide), precludes the operation in this case of the usual isocyanate-carboxylic reaction. A mechanism is proposed which accounts for the products formed.

Previous work[1] on the reaction of an isocyanate with a carboxylic acid in equimolar amounts has shown that the first product of the reaction is a mixed carbamic-carboxylic anhydride, which, in most cases, is not stable but in some instances can be isolated:



$$R—NCO + R'—CO_2H \longrightarrow R—NH—\overset{\overset{O}{\|}}{C}—O—\overset{\overset{O}{\|}}{C}—R'$$

The decomposition of the mixed anhydride proceeds by two paths to give an amide in A (below), and in B a symmetrical urea and the anhydride of the acid.[2] Carbon dioxide is evolved in both cases. The products of path B, on heating to higher temperatures (135° or more) can react with each other to give the amide, path C.[2] Thus, under forcing conditions, the ultimate product of the reaction is the amide:



$$R—NH—\overset{\overset{O}{\|}}{C}\diagdown_{O}\diagup\overset{\overset{O}{\|}}{C}—R' \longrightarrow R'—\overset{\overset{O}{\|}}{C}—NHR + CO_2 \quad (A)$$

$$\longrightarrow {}^1/_2RNH—\overset{\overset{O}{\|}}{C}—NHR + {}^1/_2R'\overset{\overset{O}{\|}}{C}—O—\overset{\overset{O}{\|}}{C}—R' + {}^1/_2CO_2 \quad (B)$$

$$\xrightarrow[\Delta]{} R'—\overset{\overset{O}{\|}}{C}—NHR + CO_2 \quad (C)$$

This over-all reaction has been used to prepare amides in good yields.[3]

We would like to report here an unusual variant of the above reactions. If two moles of phenyl

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(1) W. Dieckmann and F. Breest, *Ber.*, **39**, 3052 (1906).

(2) C. Naegli and A. Tyabji, *Helv. Chim. Acta*, **17**, 931 (1934); **18**, 142 (1935).

(3) C. L. Ayre, G. Dinga, and R. Pflaum, *J. Org. Chem.*, **20**, 695 (1955).