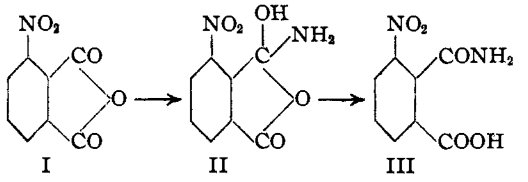
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE BUREAU OF DAIRY INDUSTRY, UNITED STATES DEPARTMENT OF AGRICULTURE]

The Formation of Unsymmetrical Acid Amides

BY BEN H. NICOLET

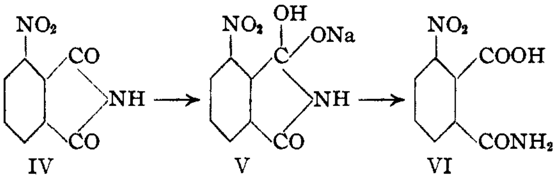
When the anhydride of a dibasic acid reacts with ammonia or with an amine, a monoamide is formed. If the anhydride happens to be unsymmetrical, a question arises as to which carboxyl group will undergo amide formation.

A brief consideration of reaction mechanisms leads to results of a certain interest, and suggests a method (perhaps of general application) by which *either* of the amides may be prepared as desired. For instance, in the case of 3-nitrophthalic anhydride (I), in which, for the purposes of this discussion, the nitro group serves only to label the two carboxyl groups as different, one would be inclined to assume that *one* C=O group would add ammonia (which one is not material in the present discussion) to form a product of the type II,[1] which might then be expected to yield an amide of the structure III.



The amide which results has actually the structure III.[2]

When the imide IV is allowed to react with alkali, the addition should, logically, occur on the *same* C=O group (it will be recalled that no assumptions have been made as to *which* this would be). The result should, however, be the *other* of the two possible monoamides (VI).[3]



In the case of *d*-camphoric acid, although the dissymmetry is here rather slight, being due to a single methyl group, similar results have been observed. The anhydride with ammonia gives *chiefly* the α-amide (45–55%, as compared with 20–25% of the isomer).[4] But the imide gives the β-amide, with only a very little of the α-derivative.[5]

A monoanilide of 3-nitrophthalic acid has been made from the phenylimide.[3] A different monoanilide has now been prepared from the anhydride I.

In further pursuit of the same effect, 3-nitrophthal-phenylimide was found to give with ammonia an amide-anilide (probably the 2-amide-1-anilide). The isomer, probably 3-nitrophthal-1-amide-2-anilide, was obtained by warming the imide with an excess of aniline.

The results thus far given are purely chemical. The principle involved would, however, have certain biochemical applications of considerable interest. It is intended to carry out similar experiments on suitable derivatives of aspartic and glutamic acids, in the hope of increasing the scope of available peptide syntheses.

Experimental Part

Preparation of Materials

3-Nitrophthalimide (IV) was prepared from the amide (III), and 3-nitrophthal-phenylimide from the monoaniline salt of the acid, in both cases by heating at about 190° until effervescence had ceased, and then recrystallizing from acetone and alcohol.

3-Nitrophthalic Acid-2-anilide.—The acid was heated with a slight excess of acetic anhydride to form the anhydride. To this mixture, when the reaction was complete, was added a moderate excess of aniline (at room temperature). After half an hour, water was added, and an excess of hydrochloric acid over that required for complete precipitation. The product, which separated as an oily gum, was removed and crystallized from acetone; m. p. 154°.

Anal. (Kjeldahl) Calcd. for $C_{14}H_{10}O_5N_2$: N, 9.8. Found: N, 10.0, 9.99.

The same material, from dilute alcohol, gave a product of m. p. 172°.

Anal. (Kjeldahl) Calcd. for $C_{14}H_{10}O_5N_2 \cdot 0.5H_2O$: N, 9.6. Found: N, 9.63, 9.55.

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(1) Formulas II and V are meant to imply nothing in detail as to the mechanism of the reaction beyond the idea that an addition of some sort involving the carbonyl group in question, precedes the opening of the anhydride (or imide) ring to form the amides ultimately obtained.

(2) E. Chapman and H. Stephen, *J. Chem. Soc.*, **127**, 1795 (1925).

(3) As a matter of fact, the amide VI has been prepared in the way indicated by Bogert and Boroschek [THIS JOURNAL, **23**, 748 (1901)], and its structure, which was wrongly assigned by the above authors, who adduced no direct evidence, definitely determined by Kahn [*Ber.*, **35**, 3862 (1902)].

(4) Noyes and Taveau, *Am. Chem. J.*, **32**, 287 (1904).

(5) Noyes, *ibid.*, **16**, 310, 503 (1894).

No effort was made to identify specifically the water present, but the products were interconvertible. A mixture of the two had approximately the average m. p. (165°).

A sample of the isomeric 1-anilide made for comparison from the phenylimide, m. p. 181°; a mixture with the 2-anilide (m. p. 154°) m. p. 153°. The melting points are too far apart for a definite depression to be expected.

3-Nitrophthalic Acid-1-anilide-2-amide.—Four grams of the phenylimide was dissolved in 20 cc. of absolute alcohol containing 3 cc. of concentrated ammonium hydroxide, the mixture warmed for half an hour at 50°, and then diluted and acidified. The product, from acetone, m. p. 200–204° (depending on the rate of heating) with effervescence.

Anal. (Kjeldahl) Calcd. for $C_{14}H_{11}O_4N_3$: N, 14.74. Found: N, 14.79.

3-Nitrophthalic Acid-1-amide-2-anilide.—The imide (IV) remained unchanged after warming for an hour at 100° with 1 mole of aniline in 20 cc. of benzene. After two hours with 4 moles of aniline without solvent, reaction had taken place. Crystallized from acetone or from alcohol, the product showed m. p. 228–230°.

Anal. (Kjeldahl) Calcd. for $C_{14}H_{11}O_4N_3$: N, 14.74. Found: N, 14.58.

Summary

1. In the case of unsymmetrical acid anhydrides and acid imides, the assumption that the ring is opened in each case at the bond connected to the *same* carbonyl group, requires that when (as is usually the case) one of the two possible amides is chiefly formed from the anhydride and ammonium hydroxide, *the other* amide should result from the alkaline hydrolysis of the imide.

2. Over the limited range studied, this principle is confirmed.

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[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

Studies in Thiophenol Chemistry. II. A Reaction between Aromatic Mercaptals and Formaldehyde

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Since their discovery fifty years ago by E. Baumann, the thioacetals[1] have been classed among the more inert organic compounds. Although recent work has greatly enlarged our knowledge of those thioacetals derived from mercaptans and ketones (the so-called mercaptoles) little has been done with the mercaptals, or aldehyde derivatives, which appear to be much less reactive.

In the continuation of a study of the general problem of thiophenol–formaldehyde condensations[2] it has been found that a reaction takes place between aromatic mercaptals and formaldehyde in acid media, yielding crystalline products. These are of particular interest in view of the reactivity and tendency to rearrangement exhibited by the analogous acetals, which play an important part in many mechanisms suggested[3] for the formation of phenol-formaldehyde resins.

Slow Reaction of Mercaptals with Formaldehyde.—If formaldehyde diphenylmercaptal, $CH_2(SC_6H_5)_2$, is prepared by direct condensation as described in the Experimental Part of this paper, it separates from solution as a colorless oil which may be crystallized, and melts after purification at 36°. If, however, the oily product is not removed from the flask but is allowed to remain in contact with acetic acid, hydrogen chloride and excess formaldehyde over a period of several months it is slowly converted into a solid, waxy mass having properties quite unlike those of the mercaptal. This change will not take place unless there is present more than enough formaldehyde to combine completely with the thiophenol employed in the initial condensation. By raising the temperature to the boiling point of acetic acid the reaction may be brought about in a few hours, and since the products obtained are the same they are described together in the next section.

Rapid Reaction of Mercaptals with Formaldehyde in Hot Acid Solution.—When various pure, crystalline mercaptals are dissolved in glacial acetic acid, treated with a moderate excess of formaldehyde, the solution then saturated with hydrogen chloride and refluxed for several hours, there separate from solution crystalline products of much higher melting point than the original

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(1) The literature concerning these compounds is summarized by A. Schönberg in Vol. 19 of Ahrens' *Sammlung* (1933); additional references are given by Malisoff, Marks and Hess in *Chem. Rev.*, **7**, 508 (1930).

(2) Dougherty and Taylor, THIS JOURNAL, **55**, 4588 (1933).

(3) Scheiber and Sändig, "Die künstlichen Harze," Stuttgart, 1929, p. 133.