CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE JOHNS HOPKINS UNIVERSITY]

THE SYNTHESIS OF 2,6-DIAMINOBENZOIC ACID

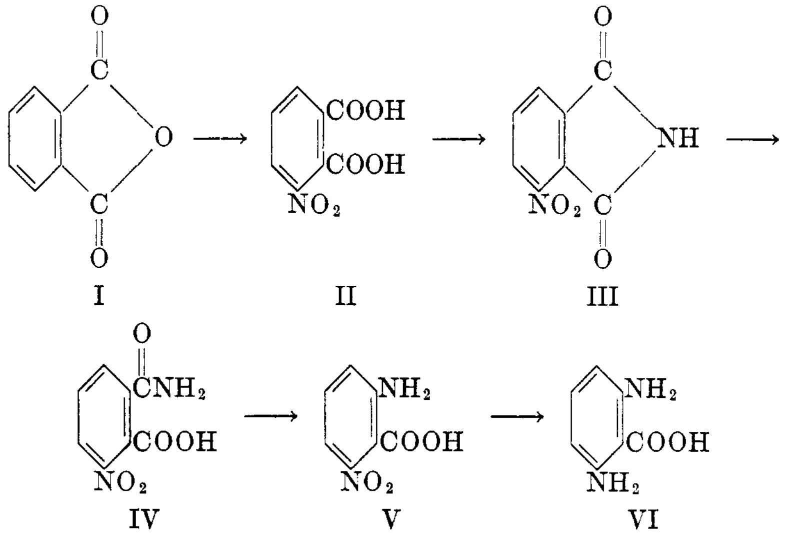
CARL M. MOSER AND THOMAS GOMPF

Received November 8, 1949

Of the unsubstituted diaminobenzoic acids, the 2,3- (1), 2,4- (2), 2,5- (3)' 3,4- (1), and 3,5- (4) have been prepared. There is not, however, any reference in the literature to the preparation of 2,6-diaminobenzoic acid (VI). In connection with another problem this compound was needed, and this manuscript describes the results obtained in the investigation of a method for the synthesis of this acid.

The first approach to be tried envisaged the utilization of 2,6-dinitrotoluene as an intermediate. Holleman and Boeseken (5) have reported the preparation of this compound from 2,4,6-trinitrotoluene by way of reduction to 4-amino-2,6-dinitrotoluene with the use of ammonium sulfide. These authors reported a yield of 20% for this reduction, but in our hands the yield was never above 10%; the isolation of this quantity was so tedious that this approach was abandoned.

6-Nitroanthranilic acid (V) seemed to be an attractive starting material for the desired acid. This compound has been prepared in various ways; the most widely used is as follows:



This method was developed by Kahn (6) and improved by Bogert and co-workers (7) some years ago; there does not appear to have been any further investigation on this series of reactions since then. Since a fairly large quantity of V was desired, each of the steps was carefully reinvestigated to ascertain if any improvement in yield or simplification of procedure could be effected.

The nitration of phthalic anhydride with a nitrating mixture of concentrated nitric acid and concentrated sulfuric acid proceeds very satisfactorily; it is not necessary to use fuming nitric acid as suggested by some workers (8). The nitration of phthalic anhydride with concentrated nitric acid has been carried out by Littmann (9), and the yield of crude product was reported to be 85–90%. Littmann's somewhat involved procedure was considerably simplified and very pure 3-nitrophthalic acid (II) was readily obtained in 26% yield.

The transformation of the acid II to the imide III was carried out according to the procedure of Bogert and Seil (7b). Attempts to transform the imide III directly to the acid V according to the procedure of Seidel and Bittner (10) resulted in a very impure product that could not be readily purified. This observation is in agreement with the report of Bogert and Chambers.

Hydrolysis of the imide to the amido acid IV was carried out by Kahn (6) on a very small scale. When fairly large quantities of the imide were hydrolyzed, it was found that the concentration of imide should not exceed about 5%; otherwise, the product obtained was a mixture from which only the acid II could be isolated on crystallization from water.

With the use of pure IV the acid V could be obtained readily in a high state of purity following the procedure of Bogert and Chambers (7a). If the amido acid was not quite pure, however, an inferior grade of the acid V was obtained; this product could not be readily purified by crystallization.

The reduction of the nitro acid V to the diamino acid VI with the usual metal and mineral acid combination seemed unpromising, for the nitro acid readily loses carbon dioxide in the presence of small amounts of mineral acid. For example, attempts to esterify the nitro acid with the use of hydrogen chloride or sulfuric acid as catalyst result in the formation of *m*-nitroaniline (6).

Reduction of the nitro acid with Adams' catalyst took place in methanol or ethanol, but no crystalline material could be isolated from the reaction mixture. The reduction was satisfactorily accomplished in methanol with the use of Raney nickel catalyst at three atmospheres pressure. The crude acid was obtained in 40% yield.

The diamino acid is not very stable. The pure acid crystallizes from anhydrous ethyl ace ate and hexane in the form of white needles, m.p. 104° (uncorr.). In the course of two days the material has nearly completely decomposed to a green tar. If the acid is dissolved in solvents that contain some water, the solution turns green-black in color, and the acid cannot be isolated again. One sample of the acid was carefully dried under vacuum and, if kept under vacuum, seemed to be stable for about one week. In the usual Dumas apparatus for the determination of nitrogen, micro-bubbles could not be obtained with this acid, apparently indicating rather rapid decomposition.[1]

On benzoylation of this amino acid only the benzamidobenzoyl anthranil (VII) could be isolated in a pure state from the complex reaction mixture. The benzoylation of an anthranilic acid derivative frequently results in a mixture of the benzoyl anthranil and benzamido acid (11).

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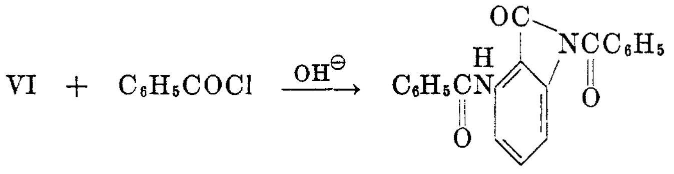
[1] Observation of Mrs. June Long.



VII

A hydrochloride of the amino acid could be obtained, but it was too unstable for a satisfactory analysis.

If this diamino acid could be successfully diazotized, a convenient route to the synthesis of several 2,6-disubstituted benzoic acids would be available. Unfortunately, several attempts to prepare the diazonium salt in the usual manner yielded only intractable tars. It is possible that diazotization under anhydrous conditions might proceed satisfactorily.

Acknowledgement. We are indebted to Mrs. Marjorie Melville for experimental assistance during part of this work.

EXPERIMENTAL[2]

3-Nitrophthalic acid (II). To a mixture of 175 g. of phthalic anhydride and 175 cc. of concentrated nitric acid in a 3-l. round-bottom flask there was slowly added with shaking 175 cc. of concentrated sulfuric acid. The mixture was heated for three hours on the steam-bath, after which it was cooled and poured with constant stirring into 500 cc. of cold water. An additional 60 cc. of water was used to rinse the flask. The suspension was cooled to 10°, filtered, and pressed as dry as possible with the aid of a rubber dam. The filter cake was thoroughly stirred for a few minutes with 200 cc. of ice-water and the precipitate was crystallized from 200 cc. of glacial acetic acid. The solution was allowed to stand at room temperature for 24 hours to ensure complete precipitation. The yield of small, hard prisms, m.p. 216–218° (vac.) [reported (8) 217° (vac.)], was 70 g. (26%).

3-Nitrophthalamic acid (IV). The imide III (96 g.) was shaken with a solution of 56 g. of potassium hydroxide in 2 l. of water until solution had taken place (*ca.* two hours). The solution was cooled and carefully acidified. The precipitate was washed with a small amount of cold water, and dried. The yield of amido acid, m.p. 153–155° with resolidification and remelting 212–213° [reported (6) 152–155° with resolidification and remelting 212°] was 84 g. (80%). If the above reaction was repeated using only 1 l. of water as solvent, the product melted over a wide range, 124–160°. Crystallization from warm water afforded only 3-nitrophthalic acid, m.p. 216–218° (vac.).

2,6-Diaminobenzoic acid (VI). 6-Nitroanthranilic acid (1 g.) was dissolved in 10 cc. of absolute methanol and *ca.* 1 g. of Raney nickel catalyst was added. The reduction was carried out in the Parr apparatus for one hour; the uptake of hydrogen corresponded to 80% of the calculated. The solution was rapidly filtered with suction, and the nickel was washed with a few cc. of methanol. The yellow solution was evaporated to dryness *in vacuo* (best below 20°). The residue remaining after evaporation ranged in color from yellow to greenish-black depending on the temperature of evaporation. Enough warm ethyl acetate was added to dissolve all soluble material, and the product was obtained on the addition of hexane. The yield was 330 mg. (40%). The pure acid, m.p. 103.5–104° (dec.) was obtained as short needles after several recrystallizations from a mixture of ethyl acetate and hexane.

Anal. Calc'd for $C_7H_8N_2O_2$: C, 55.24; H, 5.29.
Found: C, 55.73; H, 5.20.

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[2] Melting points are uncorrected.

Treatment of this acid with benzoyl chloride and dilute alkali in the cold yielded the anthranil VII as the alkali-insoluble product. The compound crystallized from ethyl acetate as long, faintly-yellow needles, m.p. 205–205.5°.

Anal.[3] Calc'd for $C_{21}H_{14}N_2O_3$: N, 8.18. Found: N, 8.48.

No definite product could be isolated from the alkali-soluble material.

A *hydrochloride*, m.p. 160–160.5° (dec.) could be obtained, but it decomposed too rapidly to permit analysis.

The amino acid did not form an oxalate.

SUMMARY

1. The synthesis of 2,6-diaminobenzoic acid by the reduction of 6-nitroanthranilic acid has been reported.

2. The synthesis of 6-nitroanthranilic acid from phthalic anhydride has been reinvestigated.

Baltimore 18, Maryland

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[3] Analysis by Mrs. June Long.