[Contribution from the Battelle Memorial Institute and Hefco Laboratories]

THE INTERACTION OF 5,7-DIBROMOISATOIC ANHYDRIDE WITH ANILINE

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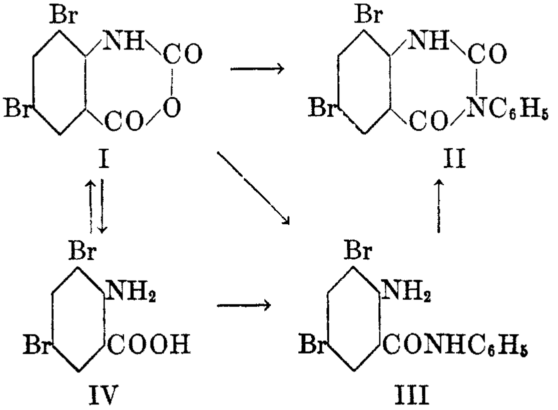
The literature affords examples of reactions of aniline with isatoic anhydride (1) and its 4-nitro (2), N-methyl (3), 5-methyl (4), and N-β,β'-diphenylisopropyl (5) derivatives;[1] the observed products were *o*-aminobenzanilides in all instances. The formation of benzoylene ureas on treating 5,7-dihalogenoisatoic anhydrides with aqueous ammonia or ethylamine (7, 8) suggested that an analogous reaction would occur with aniline, and this possibility has been realized experimentally.

When 5,7-dibromoisatoic anhydride (I) is heated with aqueous solutions of aniline, 3,5-dibromo-2-aminobenzanilide (III) and 3-phenyl-6,8-dibromobenzoylene urea (II) are formed in variable amounts which increase with the concentration of the aniline. The reaction conditions are essentially heterogeneous, and the precipitating particles of the products (II, III) adsorb aniline from the solutions to form oily agglomerations which prevent complete decomposition of the solid anhydride (I). These mixtures were separated quantitatively by washing out the excess aniline with dilute hydrochloric acid and treating the residual solids with aqueous sodium hydroxide solution; the latter dissolves the benzoylene urea (II) and hydrolyzes unreacted anhydride (I) to 3,5-dibromoanthranilic acid (IV), leaving residues of the crude anilide (III). The benzoylene urea (II) precipitates in a pure form on passing carbon dioxide into the alkaline solutions, and the pure anthranilic acid (IV), equivalent to the unreacted anhydride (I), is recovered by acidifying the carbonated solutions. The anilide (III) is the dominant product, especially when the experiments are conducted in solvents which provide homogeneous mixtures, and only in aqueous media were



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[1] This brief nomenclature is simply a retention of the numbering system of the parent isatin. *Cf.* (6).

appreciable yields of the benzoylene urea (II) obtained. When a large excess of aniline was used as solvent only an isolable amount of the benzoylene urea (II) was produced, but in glacial acetic acid solution the anilide (III) was the sole product. These results are summarized in Table I. Attempts to effect reactions between aniline and solutions of the anhydride (I) in 1,2-dimethoxyethane and in chlorobenzene were unsuccessful.

The reactions with aqueous aniline, outlined above, parallel those (8) of the anhydride (I) with aqueous ethylamine. With aqueous ammonia, however, the reactions (7) are somewhat anomalous; 6,8-dibromobenzoylene urea and the corresponding anthranilic acid (IV) are formed to the exclusion of 3, 5-dibromo-2-aminobenzamide, and an analogous behavior has been observed (9) with 7-bromoisatoic anhydride. But like the anilide (III), 3,5-dibromo-2-aminobenzamide is formed when the anhydride (I) is heated with ammonium acetate in glacial acetic acid.

The constitutions of the aniline products (II, III) are indicated by the synthesis of 3,5-dibromo-2-aminobenzanilide (III) from 3,5-dibromoanthranilic acid (IV), phosphorus pentachloride, and aniline in benzene, and the conversion of this product into 3-phenyl-6,8-dibromobenzoylene urea (II) by the action of phosgene in glacial acetic acid.

TABLE I

PRODUCTS FROM 5,7-DIBROMOISATOIC ANHYDRIDE AND ANILINE

SOLVENT AND CONCENTRATION OF ANILINE	3,5-DIBROMO-2-AMINOBENZANILIDE (III), %	3-PHENYL-6,8-DIBROMOBENZOYLENE UREA (II), %	5,7-DIBROMOISATOIC ANHYDRIDE (I) ACCOUNTED FOR, %
0.1 *M* in water	30.7	17.5	101.0
0.35 *M* in water	46.9	36.1	103.2
Pure aniline	95.3	Detectable	95.3+
0.07 *M* in acetic acid	98.5	—	98.5

5,7-Dibromoisatoic anhydride (I) was prepared by passing phosgene into solutions of 3,5-dibromoanthranilic acid (IV) in glacial acetic acid, a method (*cf.* 10) which has also been applied successfully (9) to 3-bromo-, 5-bromo-, and 4-chloro-anthranilic acids. Under the same conditions phosgene failed to react with 3-nitro-, 3,5-dinitro-, and N-(2,4-dinitrophenyl)-anthranilic acids, and with 3,5-dinitro-2-aminobenzamide.

The analyses were performed by J. S. McNulty and J. W. Compton.

EXPERIMENTAL

5,7-Dibromoisatoic anhydride (I). A solution of 2 g. of 3,5-dibromoanthranilic acid (11) in 100 cc. of glacial acetic acid was treated with phosgene at room temperature until 11.8 g. of the gas had been absorbed. After standing overnight the mixture, which contained suspended crystals, was gradually heated to boiling, allowed to cool and crystallize, and slowly diluted with 300 cc. of water. The separated solid, washed with water and dried, amounted to 1.950 g. (89.6%) of good quality product, m.p. 260–262°. Attempts to improve the yield by using less acetic acid and by passing phosgene into initially hot solutions were unsuccessful. The presence of pyridine in the reaction mixtures decreased the yields.

5,7-Dibromoisatoic anhydride is conveniently crystallized from glacial acetic acid; 1 g. to 25–30 cc., recovery 85%. Large, white prisms, m.p. 265–267° (corr.) with slight evolution of gas. Like the material obtained by oxidation of tetrabromoindigo (7, 8), this product reacts with aqueous ethylamine to give 3-ethyl-6,8-dibromobenzoylene urea and 3,5-dibromo-2-aminobenzethylamide.

Anal. Calc'd for $C_8H_3Br_2NO_3$: N, 4.36. Found: N, 4.29, 4.33.

Interaction of 5,7-dibromoisatoic anhydride (I) *with aniline*: *3,5-Dibromo-2-aminobenzanilide* (III) *and 3-phenyl-6,8-dibromobenzoylene urea* (II). (*a*) *With pure aniline.* A mixture of 0.5 g. of dibromoisatoic anhydride and 0.37 g. of freshly distilled aniline effervesced mildly on heating and turned yellow but did not liquify completely. A further quantity, 0.58 g., of aniline was added and the heating continued until the solids dissolved. The mixture crystallized quickly on cooling. It was treated with 10 cc. of 1.0 *M* hydrochloric acid and the undissolved solids were separated and washed with 15 cc. of 1.0 *M* hydrochloric acid and finally with water. Diluting the hydrochloric acid filtrate with water produced a slight, crystalline precipitate which was combined with the undissolved solids to give 0.572 g. of white, finely crystalline material. This was suspended in 25 cc. of aqueous, 1.0 *M* sodium hydroxide solution, collected, washed with water, and dried, yielding 0.549 g., 95.3%, of pure 3,5-dibromo-2-aminobenzanilide, m.p. 218°. The alkaline filtrate and washings, acidified with acetic acid, deposited a sparse, flocculent precipitate which was removed, washed with water, dried, and dissolved in boiling alcohol. From the inspissated alcoholic solution, on standing, 3-phenyl-6,8-dibromobenzoylene urea separated in rosets of small prisms, m.p. 282–283°.

(*b*) *With aqueous solutions of aniline.* This reaction is heterogeneous and fails to go to completion because the insoluble products form an oily agglomeration with aniline which surrounds the remaining crystals of the isatoic anhydride. Dibromoisatoic anhydride (0.5 g.) was refluxed with 50 cc. of a freshly prepared and filtered, aqueous, 0.1 *M* solution of aniline during two hours. The solids rapidly became voluminous and flocculent, and soon agglomerated as described above. On shaking the cold reaction mixture with 8 cc. of dilute, 1:1 hydrochloric acid the presence of unreacted anhydride was indicated by its rapid settling rate. The total solids, washed with water and dried, amounted to 0.545 g. This material was digested with 50 cc. of boiling benzene; the suspension was allowed to cool and the heavy crystalline residue separated by decantation and washing with benzene to recover 0.028 g., 5.6%, of dibromoisatoic anhydride, m.p. 261–263° and identical (mixture melting point) with a specimen of dibromoisatoic anhydride prepared (7) from tetrabromoindigo. Evaporation of the benzene decantate and washings left a white residue which was shaken with 25 cc. of warm, 1.0 *M* sodium hydroxide solution; the suspension was filtered and the alkali-insoluble component washed with water and dried, yielding 0.177 g., 30.7%, of crude 3,5-dibromo-2-aminobenzanilide, m.p. 203–206°. Addition of acetic acid to the combined filtrate and washings precipitated a mixture, 0.327 g., m.p. 211–223°, of phenyldibromobenzoylene urea and dibromoanthranilic acid; this was redissolved in 25 cc. of aqueous, 0.3 *M* sodium hydroxide, diluted to 50 cc., and treated with a stream of carbon dioxide to give a crystalline precipitate, 0.108 g. (17.5%) after washing and drying, of pure 3-phenyl-6,8-dibromobenzoylene urea, m.p. 281.5–283°. From the alkaline filtrate and washings acetic acid precipitated 0.217 g. (47.2%) washed and dried, of pure 3,5-dibromoanthranilic acid, m.p. 232–233°. Total products recovered, 101.0%.

An immediate reaction was evident on adding 50 cc. of an aqueous, 0.35 *M* solution of aniline to 0.5 g. of dibromoisatoic anhydride. After refluxing for two hours the mixture was allowed to cool and was shaken with 8 cc. of dilute, 1:1 hydrochloric acid. The insoluble material, 0.606 g. after washing and drying, was suspended in 25 cc. of warm, 1.0 *M* sodium hydroxide solution, and the fraction undissolved by this treatment was collected, washed with 50 cc. of water, and dried to give 0.270 g. (46.9%) of crude dibromoaminobenzanilide, m.p. 200–202°. Passing carbon dioxide through the combined filtrate and washings precipitated 0.223 g. (36.1%) of phenyldibromobenzoylene urea, m.p. 282.5–283.5°. Acidification of the final, carbonated filtrate with acetic acid precipitated 0.093 g. (20.2%) of dibromoanthranilic acid, m.p. 232–233°. Total products recovered, 103.2%.

(*c*) *With aniline in glacial acetic acid.* A solution of 0.2 g. of freshly distilled aniline in 10 cc. of glacial acetic acid was added to a solution of 0.2 g. of dibromoisatoic anhydride in 20 cc. of glacial acetic acid. The mixture was heated to 100°, allowed to cool, and poured into 200 cc. of water. The precipitate which separated was quite pure anilide, 0.227 g. (98.5%), m.p. 214–216°. This product did not yield any soluble material to hot, aqueous sodium hydroxide solution. Identical results were obtained when the reaction mixture was allowed to stand at room temperature during 48 hours, without heating.

By substituting ammonium acetate for the aniline in the procedure just described, and heating the reaction mixture, there was obtained a yield of 77.5% of crude 3,5-dibromo-2-aminobenzamide. This product was crystallized from alcohol and compared (m.p. and mixture m.p. 211–212°) with an authentic specimen of the amide prepared (8) from 3,5-dibromoanthranilic acid, phosphorus pentachloride, and ammonium carbonate in benzene.

(*d*) *With aniline in 1,2-dimethoxyethane and in chlorobenzene.* 1,2-Dimethoxyethane is a good solvent for 5,7-dibromoisatoic anhydride, but attempts to effect a reaction with aniline in the freshly distilled, peroxide-free material at room temperature and at 85° were unsuccessful. The anhydride was recovered unchanged, 64%, on pouring the solutions into dilute (1:25) hydrochloric acid.

5,7-Dibromoisatoic anhydride is readily soluble in boiling chlorobenzene and crystallizes quickly on cooling. Adding aniline to the solution did not modify this behavior. The mixture was treated with dilute hydrochloric acid, allowed to evaporate spontaneously, and the unchanged anhydride recovered, 89%, by washing the residue with water.

3,5-Dibromo-2-aminobenzanilide (III) crystallizes from alcohol or, better, glacial acetic acid in large, glistening white needles, m.p. 216–217° (corr.). It is soluble in benzene and insoluble in hot water. It dissolves in concentrated hydrochloric acid but is very resistant to hydrolysis by hot hydrochloric acid or hot, aqueous sodium hydroxide solutions.

Anal. Calc'd for $C_{13}H_{10}Br_2N_2O$: N, 7.57. Found: N, 7.62, 7.60.

3-Phenyl-6,8-dibromobenzoylene urea (II) separates from alcohol (0.1 g. in 40 cc., recovery 80%) as a white mat of fine needles resembling a vegetable mold. The crystals from glacial acetic acid are more compact and easier to handle. The compound melts sharply at 288.5° (corr.) and is soluble in benzene, Cellosolve, or carbon tetrachloride. It dissolves in aqueous ammonia and is insoluble in boiling, concentrated hydrochloric acid.

Anal. Calc'd for $C_{14}H_8Br_2N_2O_2$: N, 7.07. Found: N, 6.98, 6.95.

3,5-Dibromo-2-aminobenzanilide (III) *from 3,5-dibromoanthranilic acid* (IV). A suspension of 0.2 g. each of dibromoanthranilic acid and phosphorus pentachloride in 10 cc. of dry benzene was allowed to stand overnight and finally heated in water at 85° until the solids dissolved; a minor amount of fine solid separated on cooling. A solution of 1 g. of aniline in 10 cc. of benzene was added and the resulting white precipitate was removed, washed with benzene, and dried. This precipitate dissolved almost completely in water and the small amount of undissolved material was not diminished by additions of hydrochloric acid. The yellow benzene filtrate and washings were evaporated on a steam-bath and the brownish, crystalline residue was washed with dilute hydrochloric acid and combined with the undissolved material mentioned above. The total material, 0.430 g., was shaken with an aqueous solution of sodium hydroxide and the fraction undissolved by this treatment, 0.260 g., was crystallized once from alcohol to give 0.068 g. (27%) of large needles, m.p. 209–210°. Recrystallizations from alcohol, benzene, and, more successfully, glacial acetic acid, finally gave a pure product which was shown to be identical (m.p. and mixture m.p.) with the 3,5-dibromo-2-aminobenzanilide prepared from 5,7-dibromoisatoic anhydride.

3-Phenyl-6,8-dibromobenzoylene urea (II) *from 3,5-dibromo-2-aminobenzanilide* (III). A white, finely acicular solid rapidly separated on passing 0.52 g. of phosgene into a solution of 0.1 g. of the dibromoanilide in 10 cc. of glacial acetic acid. The suspension was gradually heated to boiling under a condenser, allowed to cool, and diluted with a large volume of water. The solid was collected, washed with water, and dissolved in 50 cc. of aqueous, 0.15 *M* sodium hydroxide. Addition of 10 cc. of 30% acetic acid to the filtered solution threw down a pulpy, white precipitate, 0.103 g. (93%), m.p. 283–285°, after washing with water and drying, which was crystallized from alcohol and found to be identical (mixture m.p.) with the 3-phenyl-6,8-dibromobenzoylene urea prepared from 5,7-dibromoisatoic anhydride.

SUMMARY

5,7-Dibromoisatoic anhydride and aniline react incompletely in an aqueous medium to give 3,5-dibromo-2-aminobenzanilide and 3-phenyl-6,8-dibromobenzoylene urea. Dissolved in a large excess of aniline the anhydride gives a high yield of the anilide and only an isolable amount of the benzoylene urea. In glacial acetic acid solution the yield of anilide is almost quantitative; on substituting ammonium acetate for aniline, under these conditions, 3,5-dibromo-2-aminobenzamide is formed.

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