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N-(2-Benzoxazolyl)anthranilic Acid and 3-(2-Hydroxyphenyl)-quinazoline-2,4-dione (I)

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The hydrolysis of 12H-benzoxazolo[2,3-b]quinazolin-12-one (I) yields N-(2-benzoxazolyl)anthranilic acid (III) and 3-(2-hydroxyphenyl)quinazoline-2,4-dione (IV). Unequivocal syntheses of both III and IV are described.

The ease of preparation of 12H-benzoxazolo[2,3-b]quinazolin-12-one (3) (I) prompted us to investigate the reactions of this substance as a means to novel compounds. Whereas Katz (4) and McCarty (5) reported the isolation of only N-(2-benzothiazolyl)anthranilic acid from the hydrolysis of II, we isolated two products from I.

The action of aqueous sodium hydroxide on I yielded N-(2-benzoxazolyl)anthranilic acid (III) and 3-(2-hydroxyphenyl)quinazoline-2,4-dione (IV) when the hydrolysis was stopped immediately after a clear solution was obtained, but only one product (IV) when the hydrolysis was continued for four hours. Aqueous sodium bicarbonate had no effect on I but aqueous sodium carbonate gave the same results as aqueous sodium hydroxide. When treated with dilute aqueous hydrochloric acid, both I and III gave a quantitative yield of IV; however, III could be converted to I on treatment with acetic anhydride.

The quinazolone structure (IV) was assigned to the product on the basis of analysis, infrared data and comparison with the product obtained by an unequivocal synthesis from ethyl anthranilate (V).

It is speculated that the hydrolysis rearrangement of I to IV proceeds either via the ring-opening, ring-closure sequence (Fig. 1) or by a one-step hydrolysis of I (Fig. 2). The fact that III can be isolated from the reaction provides some evidence for the former sequence. The relative ease with which the benzoxazole nucleus can be hydrolyzed has been documented in the literature (6-9). The cyclization of substituted uramidobenzoates or uramidobenzoic acids related to VIII by either acid or base catalysis also has been recognized (10-14).

The reaction of 2-chlorobenzoxazole with anthranilic acid under anhydrous conditions using benzene and triethylamine provided an unequivocal synthesis of N-(2-benzoxazolyl)anthranilic acid (III).

The physical characteristics of III were not in agreement with those obtained by Sam and Plampin (3) for the product of the reaction of anthranilic acid with 2-chlorobenzoxazole in ethanol. The latter product, on the contrary, was found to be identical with 3-(2-hydroxyphenyl)quinazoline-2,4-dione (IV).

EXPERIMENTAL (15)

N-(2-benzoxazolyl)anthranilic acid (III). Method A.

A mixture of 7.1 g. (0.03 mole) of I in 100 ml. of 5% sodium hydroxide was placed on a steam bath, shaken intermittently until all of the material had dissolved (2 hrs.) and then filtered. The cooled filtrate precipitated 2.5 g. of sodium N-(2-benzoxazolyl)anthranilate which was removed by filtration and added to 20 ml. of cold 5% hydrochloric acid. The resulting solid was removed by filtration and recrystallized from ethanol-water to yield 2.0 g. (26%) of the product, m.p. 182-183°. The infrared spectrum showed strong absorption at 1630 cm^{-1} , 1580 cm^{-1} , and 1565 cm^{-1} , which is characteristic of N-substituted anthranilic acids and benzoxazoles (16).

Anal. Calcd. for $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_3$: C, 66.13; H, 3.96; N, 11.02. Found: C, 66.32; H, 4.12; N, 10.84.

Method B.

To a solution of 6.85 g. (0.05 mole) of anthranilic acid and 4.35 g. (0.05 mole) of triethylamine in 150 ml. of anhydrous benzene was added dropwise with stirring 7.68 g. (0.05 mole) of 2-chlorobenzoxazole. The solution was refluxed two hrs., cooled, filtered, and the benzene layer was washed with water and 5% hydrochloric acid. The solvent was removed *in vacuo* giving 9.5 g. (75%) of III, m.p. 182-183°. A mixed melting point with the product obtained in Method A showed no depression. The infrared absorption spectra were identical.

3-(2-Hydroxyphenyl)quinazoline-2,4-dione (IV).

This compound was prepared by the following methods and identified by mixed melting points and infrared spectra.

A. The basic filtrate from the preparation of III above was acidified. The formed precipitate of IV (4.5 g., 59%) was removed by filtration and recrystallized from methanol; m.p. 309-310°, γ max (KBr) 1725, 1650, 758 cm^{-1} (characteristic of 3-substituted quinazolinediones) (17).

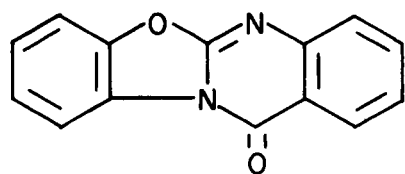
Anal. Calcd. for $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_3$: C, 66.13; H, 3.96; N, 11.02. Found: C, 66.10; H, 3.84; N, 11.01.

B. A solution of III (2.0 g., 0.008 mole) in 100 ml. of 5% sodium hydroxide was heated on a steam bath for 4 hr. The solution was cooled, acidified with concentrated hydrochloric acid and the precipitated solid (1.5 g., 75%) removed by filtration and recrystallized from methanol; m.p. 309-310°.

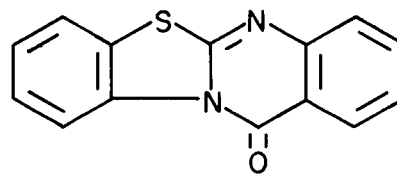
C. A mixture of I (5.0 g., 0.02 mole) and 100 ml. of 10% hydrochloric acid was refluxed for 2.5 hr. The resulting solid was removed by filtration and recrystallized from methanol to yield 4.8 g. (95%) of product, m.p. 309-310°.

D. A mixture of III (2.0 g., 0.008 mole) and 100 ml. of 10% hydrochloric acid was refluxed 4 hr. The resulting solid was removed by filtration and recrystallized from methanol to yield 1.8 g. (90%) of product, m.p. 309-310°.

E. To a cooled solution (5-10°) of 150 ml. of anhydrous benzene containing 9.9 g. (0.1 mole) of phosgene and 29.8 g. (0.2 mole) of N,N-diethylaniline was added dropwise with stirring, a solution of 16.5 g. (0.1 mole) of ethyl anthranilate in 50 ml. of anhydrous benzene. The solution was kept at 5-10° for one-half hr. and then at room temperature for one hr. The solution was again cooled to 5-10° and 10.9 g. (0.1 mole) of *o*-aminophenol was added as a solid. After stirring at room temperature for 3 hr., the solution was filtered and the filtrate was washed with water, 5% hydrochloric acid, and water, respectively. The solvent was removed *in vacuo* and the gummy residue dissolved in 200 ml. of 5% sodium hydroxide and heated on a steam



I



II

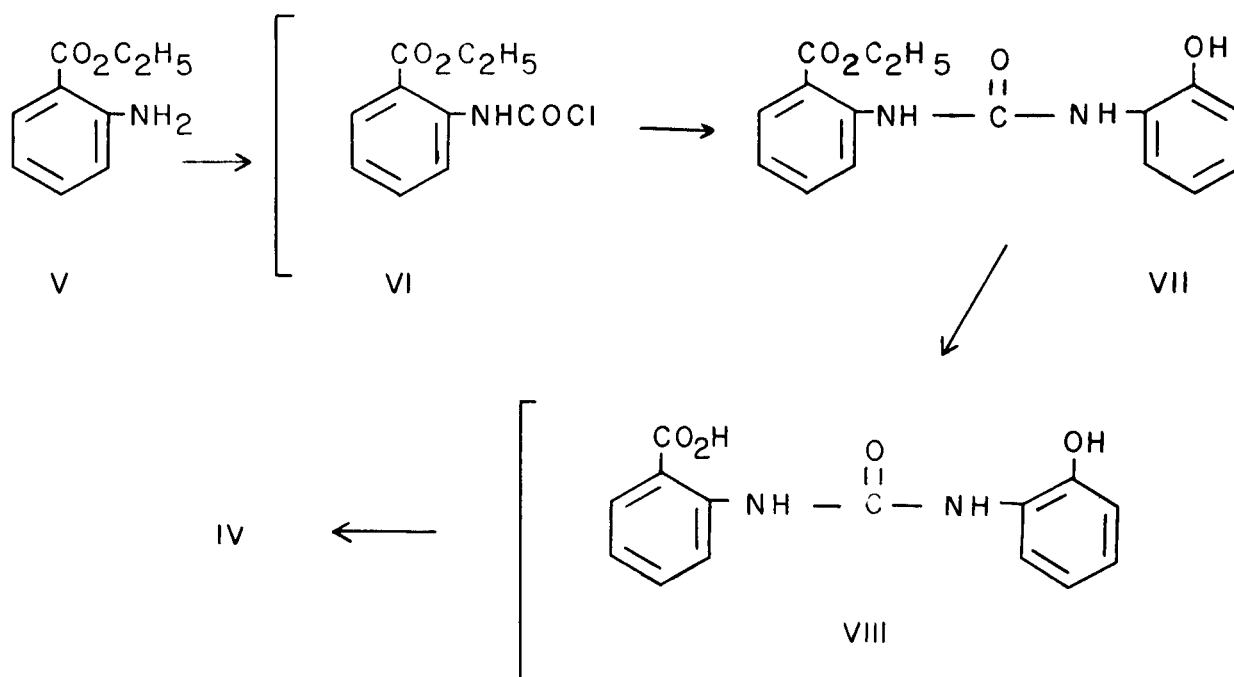
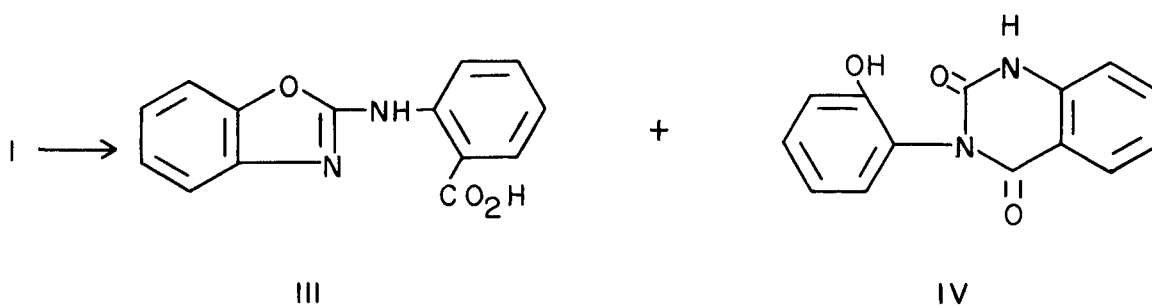


Fig. 1

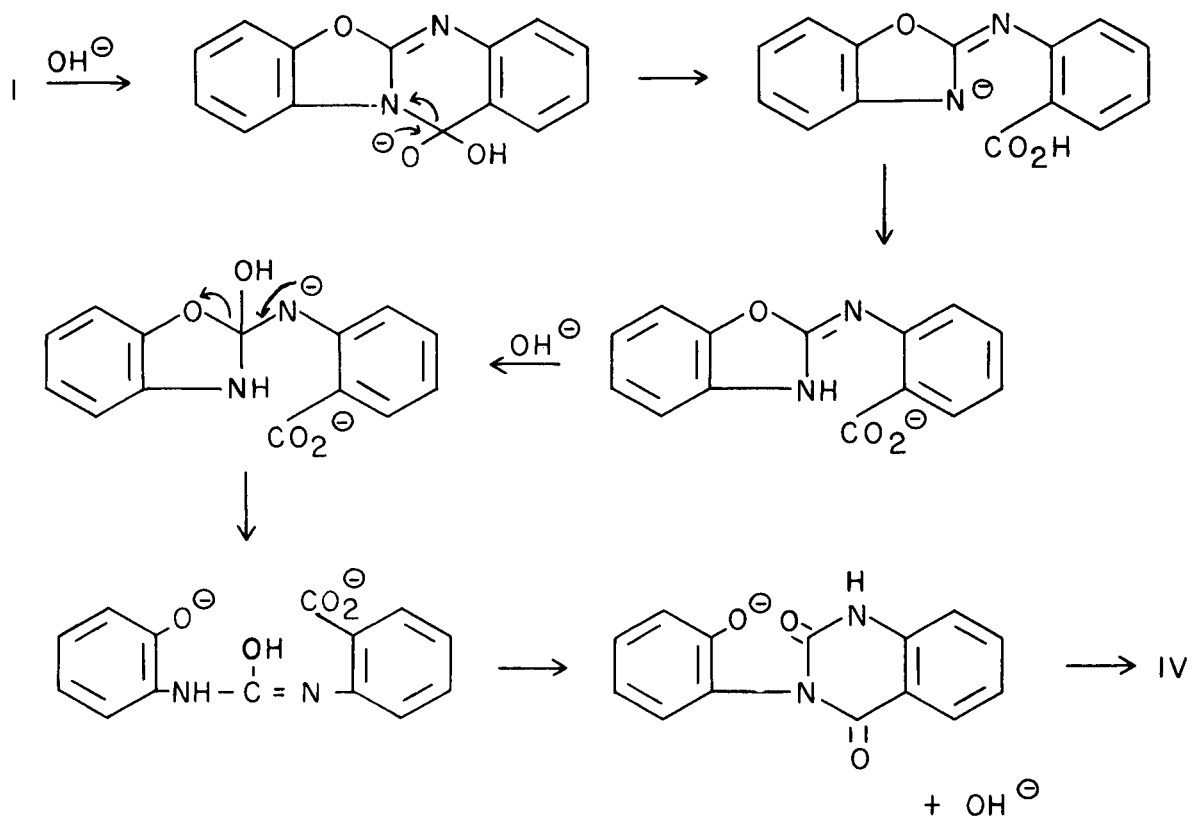
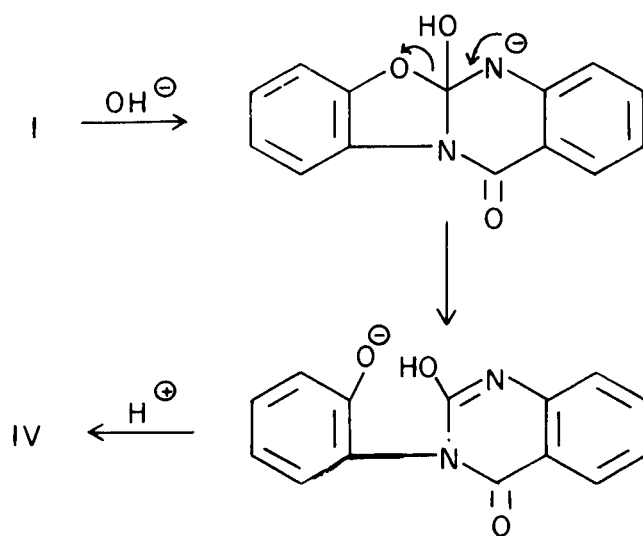


Fig. 2



bath for 2 hr. The solution was cooled, filtered, and the filtrate acidified with concentrated hydrochloric acid. The solid was removed by filtration and recrystallized from methanol to yield 6.8 g. (66%) of product, m.p. 309-310°.

F. The procedure described by Sam and Plampin (3) for the preparation of I was followed using 41.4 g. (0.3 mole) of anthranilic acid, 300 ml. of glacial acetic acid, and 46.1 g. (0.3 mole) of 2-chlorobenzoxazole. After refluxing 3 hr., the solution was concentrated *in vacuo*. The solid was removed by filtration, washed with water, 5% sodium hydroxide, and water, respectively, and recrystallized from methanol to yield 21 g. (30%) of I, m.p. 253-255° (lit. m.p. 253-253.5°). The combined washings of the water and sodium hydroxide solutions were acidified with concentrated hydrochloric acid to yield 40 g. (53%) of IV, m.p. 308-310°, after recrystallization from methanol. 12H-Benzoxazolo[2,3-b]quinazolin-12-one.

Two grams (0.008 mole) of N-(2-benzoxazolyl)anthranilic acid (III) was placed in 50 ml. of acetic anhydride and refluxed gently for 30 min. The solvent was removed *in vacuo* and the residue recrystallized from methanol to yield 1.5 g. (79%) of product, m.p. 253-255°. A mixed melting point with the product obtained in method F for the preparation of IV above showed no depression. The infrared absorption spectra were identical.

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