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Hydrogenation of 3-(2-Nitrobenzoyl)-2-benzoxazolinone to 1-Hydroxy-3-(2-hydroxyphenyl)quinazoline-2,4-dione (1)

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The preparations of the compounds noted in the title are described. The reduction of 1-hydroxy-3-(2-hydroxyphenyl)quinazoline-2,4-dione (III) catalyzed by Raney nickel provided 3-(2-hydroxyphenyl)quinazoline-2,4-dione (VI).

The catalytic hydrogenation of 3-(2-nitrobenzoyl)-2-benzoxazolinone (I) in the presence of 5% palladium on carbon and an equivalent amount of hydrochloric acid yielded a product which we considered to be either 3-(2-aminobenzoyl)-2-benzoxazolinone (II), 1-hydroxy-3-(2-hydroxyphenyl)quinazoline-2,4-dione (III) or 2'-hydroxy-2-aminobenzanilide (V).

Structures II and V were ruled out on the basis of analysis and physical-chemical characteristics; structure V also was unequivocally synthesized beginning with 2'-hydroxy-2-nitrobenzanilide (IV). Structure III was confirmed by reducing III to 3-(2-hydroxyphenyl)quinazoline-2,4-dione (VI). The structure of VI has already been reported in an earlier paper (3).

It is speculated that the rearrangement of I to III proceeds via the partial reduction of the nitro group to a hydroxylamino group (VII), which then attacks the carbonyl group of the benzoxazolinone portion of the molecule as shown in the flow sheet.

Hayashi *et al.*, (4) have shown that the hydrogen bond between the adjacent N-hydroxy group and the carbonyl group in the 2-position of similar compounds (VIII) forms a cyclic hydroxyamic acid-type structure (IX) which is highly resistant to reduction catalyzed by palladium-carbon but not to Raney nickel. Compound III likewise was resistant to palladium-carbon catalyzed hydrogenation.

The action of aqueous sodium hydroxide on III yielded azobenzene-2,2'-dicarboxylic acid (X) and 2-aminophenol (XI). The reaction of 2-nitrobenzoic acid with zinc dust in sodium hydroxide provided an unequivocal synthesis of X (5).

The formation of an azo compound from the hydrolysis of III is similar to known reactions which yield azo compounds. For example, the aqueous basic hydrolysis of benzisoxazolinone (XII) also yields azobenzene-2,2'-dicarboxylic acid (X) (6). It is conceivable that both III and XII yield the hydroxylamino compounds (XIII and VII, respectively), as the intermediates in the formation of the azo compounds. The formation of azobenzene during the reduction of nitrobenzene with metal amalgams in aqueous basic solutions (7, 8) is another example of the formation of an azo compound in basic solutions.

The methylation of VI with excess methyl sulfate provided the N,O-dimethyl derivative, XIV.

All attempts to oxidize VI to III via peracids have been unsuccessful. Starting material was recovered in all cases, the phenolic hydroxyl group as well as the NH group being resistant to oxidation.

Although the preparation of 1-hydroxyquinazoline-2,4-dione (IX) has been described (9), the method utilized does not include the direct oxidation of quinazoline-2,4-dione to IX.

EXPERIMENTAL (10)

3-(2-Nitrobenzoyl)-2-benzoxazolinone I.

To a cooled solution (0-5°) of 13.5 g. (0.1 mole) of 2-benzoxazolinone in 100 ml. of pyridine was added dropwise with stirring 18.5 g. (0.1 mole) of 2-nitrobenzoyl chloride. The reaction mixture was stirred for one-half hour at 0-5° and then refluxed gently for 15 min. The solution was cooled, poured into 250 ml. of cold water, and the solid removed by filtration. Recrystallization of the solid from ethanol gave 25 g. (89%) of product, m.p. 166-167°; ν max (KBr) 1710, 1780 cm^{-1} .

Anal. Calcd. for $\text{C}_{14}\text{H}_9\text{N}_2\text{O}_5$: C, 59.16; H, 2.84; N, 9.86. Found: C, 59.35; H, 2.89; N, 10.38.

1-Hydroxy-3-(2-hydroxyphenyl)quinazoline-2,4-dione III.

A suspension of 14.2 g. (0.15 mole) of 3-(2-nitrobenzoyl)-2-benzoxazolinone in 150 ml. of 95% ethanol and 10 ml. of concentrated hydrochloric acid was reduced in a Parr hydrogenator at 40 psi using 5% palladium-carbon catalyst. After the reduction was complete (30 min.) the catalyst was removed by filtration and the solvent distilled *in vacuo* (water aspirator). The residue, which solidified on standing overnight, was recrystallized from water to give 12 g. (89%) of product, m.p. 284-285° dec., ν max (KBr) 752, 1390, 1600, 1640, 1690, 3300 cm^{-1} .

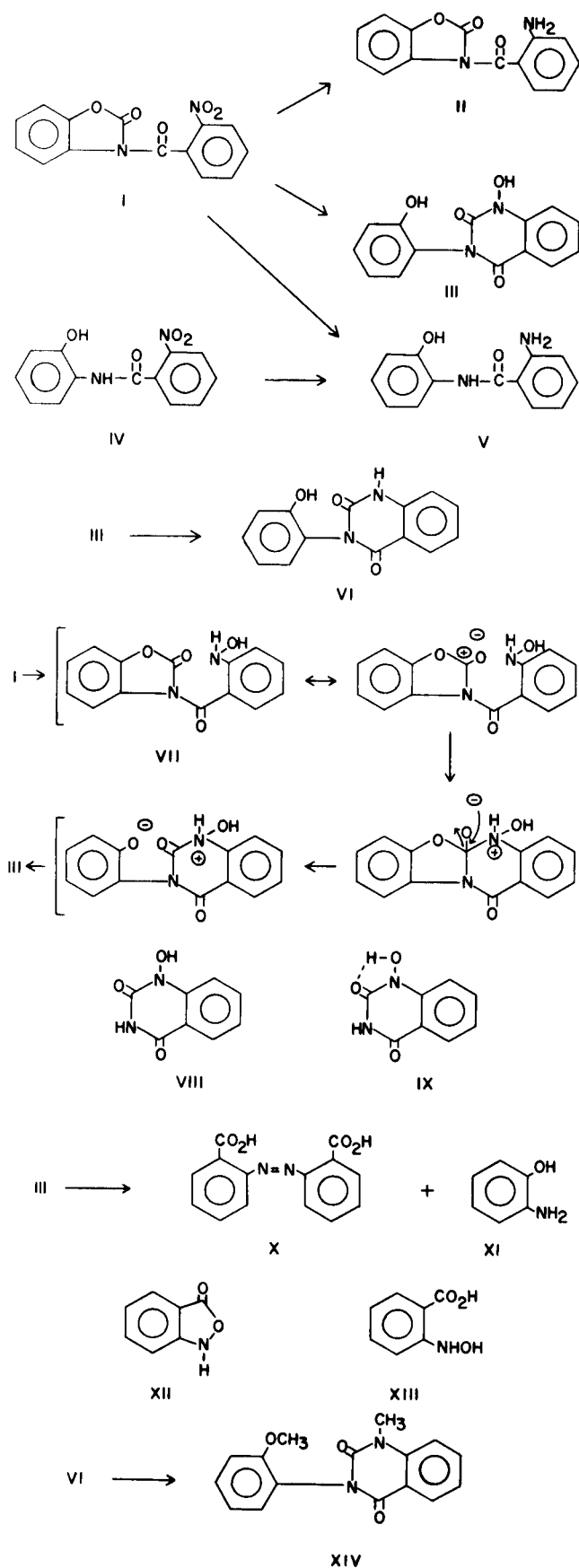
Anal. Calcd. for $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_4$: C, 62.07; H, 3.73; N, 10.37. Found: C, 62.07; H, 3.75; N, 10.19.

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

The procedure described by Hayashi *et al.* (4) was followed. A suspension of 1.0 g. (0.004 mole) of 1-hydroxy-3-(2-hydroxyphenyl)quinazoline-2,4-dione in 50 ml. of methanol was reduced on a Parr hydrogenator at 40 psi using Raney nickel catalyst. After the reduction was complete (3 hrs.), the catalyst was removed by filtration and the solvent distilled *in vacuo* (water aspirator). The residue was recrystallized from methanol to give 0.7 g. (78%) of product, m.p. 308-310°. A mixture melting point with an authentic sample (3) showed no depression. The infrared absorption spectra were identical.

Azobenzene-2,2'-dicarboxylic Acid, X. Method A.

The procedure described by Vogel (5) for the preparation of azobenzene was followed. To a stirred solution of 16 g. (0.4 mole) of sodium hydroxide in 38 ml. of water and 125 ml. of methanol was added 16.7 g. (0.1 mole) of *o*-nitrobenzoic acid. Zinc dust (13 g.) was added and the mixture stirred and refluxed 10 hr. The mixture was filtered while hot and the filtrate was cooled, neutralized with 10% hydrochloric acid, and refiltered. The filtrate was made strongly acidic with 20 ml. of concentrated hydrochloric acid and the solid removed by filtration and recrystallized from ethanol-water to give



9.0 g. (67%) of product, m.p. 252-253° dec. (Lit. (11) m.p. 245-245.5°).

Method B.

Five grams (0.018 mole) of 1-hydroxy-3-(2-hydroxyphenyl)quinazolinone-2,4-dione in 100 ml. of 10% sodium hydroxide was refluxed 6 hr. and then allowed to stand for 24 hr. The solution was neutralized with 10% hydrochloric acid and extracted with ether. The neutral aqueous solution was made strongly acidic with 10 ml. of concentrated hydrochloric acid and the solid removed by filtration and recrystallized from ethanol-water to give 1.8 g. (75%) of product, m.p. 252-253° dec. A mixture melting point with the product obtained in Method A showed no depression. The infrared absorption spectra were identical. 2-Aminophenol. XI.

The ether extract obtained from the preparation of azobenzene-2,2'-dicarboxylic acid, Method B, was evaporated to dryness and the residue recrystallized from water to give 1.0 g. (50%) of product, m.p. 170-171°. A mixture melting point with an authentic sample (commercial product) showed no depression. The infrared absorption spectra were identical.

3-(2-Methoxyphenyl)-1-methylquinazolinone-2,4-dione. XIV.

To a stirred solution containing 2.1 g. (0.05 mole) of sodium hydroxide, 100 ml. of water and 6.35 g. (0.025 mole) of 3-(2-hydroxyphenyl)quinazolinone-2,4-dione was added dropwise 6.3 g. (0.05 mole) of dimethyl sulfate. The clear solution turned cloudy after the methyl sulfate was added. After 10 min. a fine white precipitate appeared. The solution was stirred for 1 hr., heated to 80-90° for 15 min., cooled and filtered. The precipitate was washed with water (2 x 100 ml.) and recrystallized from ethanol to yield 5.2 g. (74%) of product, m.p. 180-185°. Recrystallization of the material two more times from ethanol gave a product melting at 192-193°.

Anal. Calcd. for $C_{18}H_{14}N_2O_5$: C, 68.07; H, 5.00; N, 9.93. Found: C, 68.55; H, 4.79; N, 10.48.

2-Hydroxy-2'-nitrobenzanilide. IV. Method A.

To a cooled solution (5-10°) of 10.9 g. (0.1 mole) of 2-aminophenol in 100 ml. of pyridine was added with stirring 18.5 g. (0.1 mole) of 2-nitrobenzoyl chloride. The mixture was stirred for 1 hr. at 5-10° and then refluxed gently for 15 min. The solution was cooled, poured into 250 ml. of cold water, and made acidic with concentrated hydrochloric acid. The solid was removed by filtration and recrystallized from ethanol-water to yield 18 g. (70%) of product, m.p. 205-206°.

Anal. Calcd. for $C_{13}H_{10}N_2O_4$: C, 60.46; H, 3.90; N, 10.85. Found: C, 60.38; H, 4.08; N, 10.85.

Method B.

Three grams (0.011 mole) of 3-(2-nitrobenzoyl)-2-benzoxazinone in 100 ml. of 10% sodium hydroxide was refluxed 15 min. The solution was cooled and acidified with concentrated hydrochloric acid. The precipitated solid was removed by filtration and recrystallized from ethanol-water to give 2.5 g. (90%) of product, m.p. 205-206°. A mixture melting point with the product obtained in Method A showed no depression. The infrared absorption spectra were identical.

2-Amino-2'-hydroxybenzanilide. V.

A solution of 3.0 g. (0.012 mole) of 2-hydroxy-2'-nitrobenzanilide in 100 ml. of 95% ethanol was reduced on a Parr hydrogenator at 40 psi using platinum oxide catalyst. After the reduction was complete (30 min.), the catalyst was removed by filtration and the solvent distilled *in vacuo*. The residue was recrystallized from ethanol-water to give 2.5 g. (96%) of product, m.p. 139-140°.

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.40; H, 5.30; N, 12.28. Found: C, 68.44; H, 5.43; N, 12.17.

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