

## Synthesis of 6,7-Dihydroxy-2-methyl-4-quinazolone

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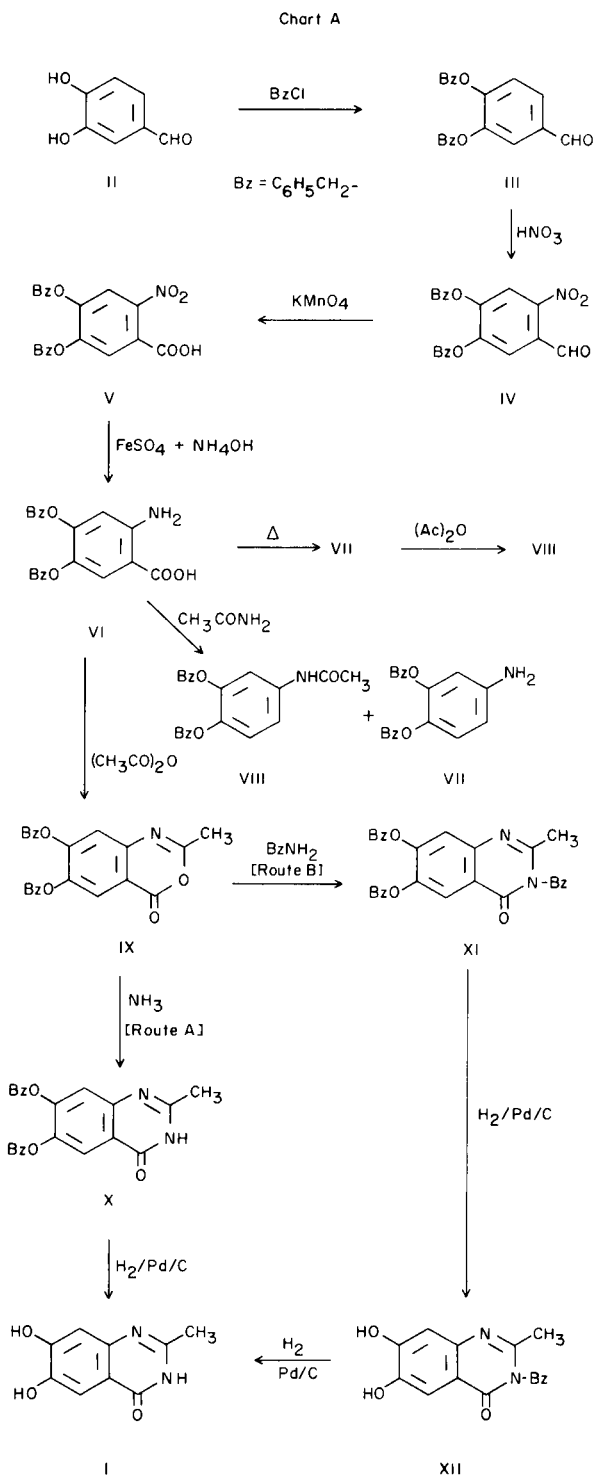
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Interesting physiological activities such as hypnotic (1), anticonvulsant (2), diuretic (3) and hypotensive (4,5) have been ascribed to quinazolone derivatives. Although the chemical literature abounds with the synthesis of quinazolones, the hydroxylated derivatives in the benzene portion have been sparsely described. We had an opportunity to synthesize 6,7-dihydroxy-2-methylquinazoline-4-(3H)-one (I) and it is reported in this note.

The synthetic scheme for I as shown in Chart A was based initially on the commonly utilized Niementowski reaction (6). This involves a fusion of an anthranilic acid with an aliphatic amide. The key intermediate therefore was the anthranilic acid (VI). To prepare it, commercially available 3,4-dihydroxybenzaldehyde (protocatechualdehyde) (II) was benzylated (7) with benzyl chloride to form III in 90% yield. Nitration of III which was also accomplished in a high yield to give IV, was assumed to have occurred in the 2-position based on the analogous nitrations of 3,4-methylenedioxybenzaldehyde (piperonal) and 3,4-dimethoxybenzaldehyde (veratraldehyde) (8). The oxidation of the aldehyde (IV) with potassium permanganate in acetone (9) furnished the nitro acid (V). The anthranilic acid (VI) was obtained by the reduction of V with ferrous sulfate and ammonium hydroxide. This special procedure had to be devised because of the susceptible nature of the benzyl groups in V to hydrogenolysis during catalytic reduction (10) and for the failure of it to undergo reduction chemically with stannous chloride and hydrochloric acid.

The thermal condensation of the anthranilic acid (VI) with acetamide did not produce X as expected. Instead two products were isolated from the reaction. They were identified as 3,4-bisbenzyloxyaniline (11) (VII) and its acetanilide (VIII). The aniline derivative (VII) was formed by the decarboxylation of the anthranilic acid (VI) which as separately shown, occurs readily at the temperature of the condensation. The anilide (VIII) was presumably a result of acylation of the aniline derivative with acetamide.

The next approach to the synthesis of I was made through the 2-methylbenzoxazinone (IX) (acetantranil) method (12). The anthranil (IX) was obtained without difficulty by heating the anthranilic acid (VI) with acetic



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anhydride, however, its conversion to X by the treatment with ethanolic ammonia was slow (4 days). Furthermore when X was debenzylated catalytically, the overall yield of I from IX (route A) was 14 percent. Since hydrogenolysis of the benzyl groups was inevitable in the penultimate step of the synthesis, the preparation of *N,O,O*-tribenzylquinazolone (XI) was considered (route B). This could be stepwise (through XII) debenzylated to I. This method not only afforded I, but the overall yield of I from IX was considerably improved, 36 percent.

#### EXPERIMENTAL

##### 3,4-Bisbenzyloxybenzaldehyde (III).

Following the procedure described by Kametani and Kano (7), 1.45 g. (0.0105 mole) of protocatechualdehyde was caused to react with 3.30 g. (0.0260 mole) of benzyl chloride to give 3.04 g. of 3,4-dibenzyloxybenzaldehyde (90%). One recrystallization of the crude product from ethanol (Norit) afforded a crystalline solid melting at 90-91.5°; reported (7) m.p. 87.5-89°.

##### 4,5-Bisbenzyloxy-2-nitrobenzaldehyde (IV).

To 25 ml. of nitric acid (sp. gr. 1.42) was added in portions with stirring over a period of ten minutes 6.37 g. (0.0200 mole) of 3,4-bisbenzyloxybenzaldehyde. The temperature increased to 40°, and the flask was cooled to 30° in a cold water bath. The mixture was stirred at 30-35° for 30 minutes and was then cooled in an ice-bath and diluted with 50 ml. of ice-water. The product was filtered and washed with ice-water to give 6.51 g. of IV as a yellow solid.

One recrystallization from ethanol and petroleum ether gave a yellow solid which melted at 139-141°.

*Anal.* Calcd. for  $C_{21}H_{17}NO_5$ : C, 69.4; H, 4.72; N, 3.85. Found: C, 69.0; H, 4.95; N, 4.01.

##### 4,5-Bisbenzyloxy-2-nitrobenzoic Acid (V).

A mixture of 7.27 g. (0.0200 mole) of 4,5-bisbenzyloxy-2-nitrobenzaldehyde, 4.74 g. (0.0300 mole) of finely powdered potassium permanganate, 500 ml. of acetone and 50 ml. of water was refluxed with stirring for 6.5 hours and was then allowed to stand at room temperature for two days. The brown mixture was then evaporated to dryness in vacuo, and the residue was treated with 1 liter of 1% sodium carbonate solution. This was warmed on the steam bath and filtered while hot, washing the brown filtrate with 300 ml. of hot water. The filtrate and wash were combined, and 5 *N* hydrochloric acid was added until strongly acidic. The golden solid, 4.53 g. (60%), which precipitated was filtered and washed with water, m.p. 173-174°.

*Anal.* Calcd. for  $C_{21}H_{17}NO_6$ : C, 66.5; H, 4.52; N, 3.69. Found: C, 66.3; H, 4.58; N, 3.73.

##### 4,5-Bisbenzyloxyanthranilic Acid (VI).

To 300 ml. of concentrated ammonium hydroxide was added with stirring simultaneously from two separatory funnels a solution of 11.4 g. (0.0330 mole) of 4,5-bisbenzyloxy-2-nitrobenzoic acid in 180 ml. of acetone and a solution of 58.4 g. (0.210 mole) of ferrous sulfate heptahydrate in 200 ml. of hot water. The solutions were added dropwise over a period of 10 minutes. To the mixture was then added 100 ml. of concentrated ammonium hydroxide, and the mixture was heated on the steam bath and stirred for 30 minutes. The solid which had precipitated was then filtered off, and the brown cake was washed with 200 ml.

of 1 *N* sodium hydroxide. The combined filtrate and wash was warmed over steam treated with Norit, and filtered over Celite. The filtrate was cooled and treated with acetic acid to pH 6.8. The gray solid which precipitated on cooling was filtered, washed with water, 5.02 g. Additional product, 1.52 g., was obtained by washing each of the two filter cakes with 750 ml. of a hot solution of 0.25 *N* sodium hydroxide, and acidifying with acetic acid: total weight, 6.54 g. (62%). The crude products were combined and recrystallized from ethanol and water (Norit) to give a cream solid which melted at 182-183° dec.

*Anal.* Calcd. for  $C_{21}H_{19}NO_4 \cdot 0.5H_2O$ : C, 70.4; H, 5.63; N, 3.91. Found: C, 70.2; H, 5.36; N, 3.87.

Condensation of 4,5-bisbenzyloxyanthranilic Acid and Acetamide to Produce VII and VIII.

A mixture of 1.05 g. (0.00300 mole) of the anthranilic acid and 0.18 g. (0.00300 mole) of acetamide was fused by heating with a heating mantle. As the solids began to melt, and the temperature rapidly increased to 143°, the flask was removed from the heat and cooled to 120°. Heating was then resumed, maintaining the temperature between 125 and 135° for one half hour. An additional 0.18 g. of acetamide was added to the hot solution, and heating was continued at 125-135° for another one half hour.

The dark solution was then dissolved in 10 ml. of ethanol, treated with Norit, and filtered. The brownish-gray solid which crystallized was filtered, washed with cold ethanol and 12 ml. of 5% sodium bicarbonate; 0.20 g., m.p. 151-156°.

Addition of water to the combined filtrate and ethanolic wash gave a precipitate which was filtered off, washed with 50% aqueous ethanol and 10 ml. of 5% sodium bicarbonate; 0.42 g., m.p. 101-103°.

A sample of the higher melting solid was recrystallized from ethanol and water (Norit), to give a white solid melting at 160-160.5°. On the basis of melting points and the comparison of IR spectrum with that of a sample prepared independently, it was identified as 3,4-bisbenzyloxyacetanilide.

Two recrystallizations from ethanol (Norit) of the lower melting solid gave a pink solid which melted at 103-105°. The IR spectrum of this compound was similar to that of 3,4-bisbenzyloxyaniline (11).

##### 3,4-Bisbenzyloxyaniline (VII).

In a 50 ml. flask, 4.54 g. (0.0130 mole) of 4,5-bisbenzyloxyanthranilic acid was heated with a heating mantle. The temperature increased to 153°, and the flask was removed from the heat and cooled to 125°. Heating was then resumed and continued for 1 hour, maintaining the temperature at 125-135°. The warm melt was then dissolved in 25 ml. of boiling 95% ethanol, treated with Norit and filtered. The shiny rosy solid which crystallized on cooling was filtered off, washed with water; 3.27 g. (82%). Three recrystallizations, from 95% ethanol (Norit), from benzene and petroleum ether (Norit), and finally from petroleum ether alone yielded the analytical sample melting at 118-119.5°; reported (11) m.p. 112°.

*Anal.* Calcd. for  $C_{20}H_{19}NO_2$ : C, 78.7; H, 6.27; N, 4.59. Found: C, 78.7; H, 6.49; N, 4.55.

##### 3,4-Bisbenzyloxyacetanilide (VIII).

To 0.92 g. (0.0030 mole) of 3,4-bisbenzyloxyaniline was added 12 ml. of acetic anhydride and the mixture was refluxed on the steam bath for 1.75 hours. The solution was poured into 100 ml. of water, the gummy pink solid was collected by filtration and was recrystallized from 95% ethanol (Norit). The resulting white solid was filtered off, washed with 50% aqueous ethanol; wt. 0.47 g. (45%), m.p. 159-160°.

*Anal.* Calcd. for  $C_{22}H_{21}NO_3$ : C, 76.1; H, 6.09; N, 4.03; Found: C, 76.1; H, 6.20; N, 3.89.

6,7-Bisbenzyloxy-2-methyl-4H-3,1-benzoxazine-4-one (IX).

A mixture of 10.5 g. (0.0300 mole) of 4,5-bisbenzyloxy-anthranilic acid and 78 ml. of acetic anhydride was refluxed on the steam bath for 3 hours and then allowed to stand at room temperature overnight. It was then evaporated to dryness, and the yellow crystalline solid was triturated with 100 ml. of water, filtered off and washed with 50 ml. of water; 11.1 g. (99%). A sample recrystallized from benzene and petroleum ether melted at 175-177°.

*Anal.* Calcd. for  $C_{23}H_{19}NO_4$ : C, 74.0; H, 5.13; N, 3.75. Found: C, 73.8; H, 5.43; N, 3.69.

6,7-Bisbenzyloxy-2-methylquinazolin-4-(3H)one (X).

An ice-cold solution of 3.28 g. (0.00880 mole) of the benzoxazinone prepared by dissolving it in 1500 ml. of boiling ethanol was saturated with ammonia. The flask was stoppered and allowed to stand at room temperature for four days. The solution was then filtered, and the filtrate was evaporated to dryness. Recrystallization of the residue from benzene (Norit) gave 1.10 g. (34%) of a fluffy white solid. The analytical sample was obtained by recrystallizing this solid from chloroform and it melted at 229-231°.

*Anal.* Calcd. for  $C_{23}H_{20}N_2O_3$ : C, 74.2; H, 5.41; N, 7.52. Found: C, 73.8; H, 5.36; N, 7.23.

3-Benzyl-6,7-bisbenzyloxy-2-methylquinazolin-4(3H)one (XI).

A mixture of 3.73 g. (0.0100 mole) of the benzoxazinone and 3.22 g. (0.0300 mole) of benzylamine was fused by heating at 130-145° for 1 hour. The cooled orange solution was triturated with ether, and the precipitated yellow solid, 4.09 g. (88%), was collected by filtration. One recrystallization from methanol (Norit) yielded the analytical sample, m.p. 137-138°.

*Anal.* Calcd. for  $C_{30}H_{26}N_2O_3$ : C, 77.9; H, 5.67; N, 6.06. Found: C, 77.6; H, 5.81; N, 6.07.

3-Benzyl-6,7-dihydroxy-2-methylquinazolin-4(3H)one (XII).

To a solution of 6.94 g. (0.0150 mole) of 3-benzyl-6,7-bisbenzyloxy-2-methylquinazolone dissolved in boiling ethanol was added 10.9 g. of freshly prepared (13) 10% palladium on charcoal. This was hydrogenated at 1 atmosphere until the hydrogen uptake was 97.5% of the calculated 672 ml. (0.03 mole). The catalyst was filtered off and washed with ~ 700 ml. of boiling ethanol. The filtrate and wash were combined and concentrated to ~ 60 ml. This boiling solution was filtered, and to the filtrate was added ~ 200 ml. of water. The pale beige solid, 2.92 g. (69%), which precipitated on cooling was collected by filtration. Two recrystallizations of this crude product from ethanol (Norit) gave a white solid melting at 263-266°. This sample was dried in a drying pistol at 138° for 20 hours, however, a Karl Fisher determination indicated the presence of 1.97% water.

*Anal.* Calcd. for  $C_{16}H_{14}N_2O_3 \cdot 1.97\%H_2O$ : C, 66.7; H, 5.12; N, 9.72. Found: C, 67.3; H, 5.27; N, 9.87, 10.1;  $H_2O$ , (K.F.) 1.97.

6,7-Dihydroxy-2-methylquinazolin-4(3H)one (I).

Procedure 1.

To a solution of 2.14 g. (0.00760 mole) of the 3-benzyl-6,7-dihydroxyquinazolone was added 5 g. of 10% palladium on charcoal prepared as described in the previous experiment. This

mixture was then hydrogenated at 15 pounds for 25.5 hours. The catalyst was filtered off and washed with ~ 600 ml. of boiling ethanol. Evaporation of the filtrate to dryness gave 0.40 g. of a cream-colored solid which did not melt by 350°. An additional sample (total wt., 0.88 g., 60%) of the high melting solid was obtained by washing the catalyst with 3 x 100 ml. of hot DMF and concentrating the filtrate to dryness.

An analytical sample was prepared by dissolving 40 mg. of the above solid in 160 ml. of boiling ethanol, filtering, and concentrating the filtrate to ~ 10 ml. The resulting white solid was filtered off and washed with ethanol, and this procedure was repeated to give 18 mg. of a powdery white solid, m.p. > 350°; dried in a drying pistol at 138° for 19 hours.

*Anal.* Calcd. for  $C_9H_8N_2O_3$ : C, 56.3; H, 4.20; N, 14.6. Found: C, 55.9; H, 4.29; N, 13.8, 13.7. (14).

Procedure 2.

To a suspension of 2.23 g. (0.00600 mole) of the 6,7-bisbenzyloxy-2-methylquinazolone in 75 ml. of ethanol and 75 ml. of acetic acid was added 0.3 g. of 10% palladium on charcoal. This mixture was hydrogenated at 26 pounds pressure for 1 hour. The catalyst was filtered off and washed with 3 x 100 ml. of boiling ethanol. Evaporation of the combined filtrate and wash gave 0.49 g. of a gray solid which did not melt by 350°. Washing the catalyst with 3 x 75 ml. of boiling benzene gave an additional 0.03 g. of product (total wt. 0.52 g., 45%). The IR spectrum of this reaction product is identical to that of the product obtained by the first procedure.

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