Synthetic Studies of the Antitumor Antibiotic Streptonigrin. I. Synthesis of the A-B Ring Portion of Streptonigrin

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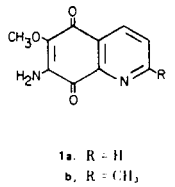
Received June 11, 1976

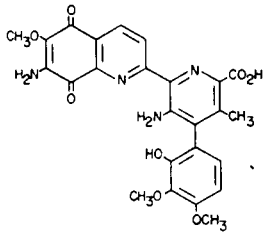
Bromination of 6-methoxy-5,8-quinolinedione gave the 7-bromo derivative in quantitative yield. Treatment of the bromo compound with sodium azide followed by hydrogenation yielded 7-amino-6-methoxy-5,8-quinolinedione, the A-B ring portion of the antitumor antibiotic streptonigrin. The corresponding 2-methyl homolog was prepared in a similar manner from 6-methoxy-2-methyl-8-nitroquinoline, which in turn, was obtained by a Skraup synthesis from 2-nitroanisidine and crotonaldehyde.

J. Heterocyclic Chem., 13, 1063 (1976).

A preliminary account of the synthesis of 7-amino-6-methoxy-5,8-quinolinedione (**1a**), the A-B ring portion of the antitumor antibiotic streptonigrin (**2**), was reported in 1967 (1). Following is a detailed experimental procedure for the preparation of **1a** as well as its 2-methyl homolog **1b**.



1a, R = H
b, R = CH_3



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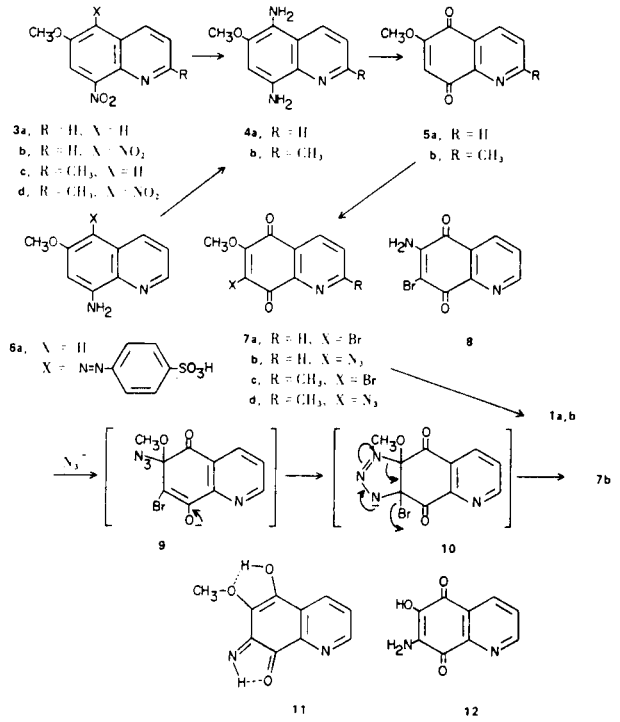
Nitration of 6-methoxy-8-nitroquinoline (**3a**) (2) gave a quantitative yield of the 5,8-dinitro derivative **3b** (3). Reduction of **3b** followed by oxidation of the crude intermediate **4a** with sodium dichromate, as described by Pratt and Drake (4), gave 6-methoxy-5,8-quinolinedione (**5a**). The intermediate **4a** was also prepared by treatment of 8-amino-6-methoxyquinoline (**6a**) with diazotized sulfanilic acid followed by reduction of the phenylazo compound **6b** with sodium hydrosulfite according to the general procedure of Campbell *et al.*, (5).

Bromination of the quinone **5a** with bromine in a mixture of glacial acetic acid and sodium acetate gave a quantitative yield of the 7-bromo derivative **7a**. Attempted replacement of the halogen with an amino group by treatment of **7a** with either aqueous or ethanolic ammonia, however, resulted in the formation of 6-amino-7-bromo-5,8-quinolinedione (8). Preferential replacement of a methoxy group rather than a bromo group by nucleophilic agents in other bromomethoxyquinones was also observed by Marzer (6) as well as by Remers and Weiss (7). It is also in accordance with Pratt's statement that preferential nucleophilic attack occurs at the 6-position of 5,8-quinolinedione, regardless of the nature of substituents at positions 6 or 7 (8).

Replacement of the bromo group in **7a** by an amino group was carried out as follows: Treatment of **7a** with so-



dium azide in aqueous ethanol yielded the 7-azide derivative **7b**. Formation of **7b** from **7a** probably was realized by an addition of an azide ion at the 6-position of the quinolinedione, followed by a triazole ring closure, loss of Br^-, and synchronous ring opening at the 7-position, as depicted in structures **9** and **10**.

Catalytic hydrogenation of **7b** gave a 60% yield of **1a**, the A-B ring moiety of streptonigrin, as dark purple flakes. The spectroscopic characteristics of this product (see Experimental) indicated that **1a** may be tautomeric with structures such as **11**. Analogous tautomerization and hydrogen bonding formation between the 6-OH group of 7-amino-6-hydroxy-5,8-quinolinedione (**12**) and the neighboring groups could perhaps explain the unsuccessful methylation attempts of **12** into **1a** by other investigators (9).

The corresponding 2-methyl homolog **1b** was prepared from 6-methoxy-8-nitroquinaldine (**3c**) (10) *via* 6-methoxy-2-methyl-5,8-quinolinedione (**5b**) (10,11) by a similar synthetic route.

EXPERIMENTAL

6-Methoxy-2-methyl-8-nitroquinoline (**3c**).

A stirred mixture of 336 g. (2 moles) of 2-nitroanisidine, 920 g. (4 moles) of arsenic pentoxide, and 2 liters of 85% phosphoric acid was heated to 100° on a steam bath. The steam bath was removed and 210 g. (3 moles) of redistilled crotonaldehyde was *rapidly* added at such a rate that the temperature of the reaction mixture was maintained at 102-105°. After the addition was complete, the mixture was heated again on the steam bath at 100° for 2 hours and poured onto 5 kg. of crushed ice, with vigorous stirring. The resulting icy mixture was made basic with aqueous ammonia. The solid product was collected by filtration, washed with 4 liters of hot water, and dried to give 192 g. of crude **3c**, m.p. 178-182°. The crude product was powdered, mixed with sand, and extracted with ether using a Soxhlet extractor to give 175 g. (40% yield) of **3c**, m.p. 184-186° [lit. (10), m.p. 183-184°].

5,8-Dinitro-6-methoxy-2-methylquinoline (**3d**).

To a mixture of 96.2 g. (0.44 mole) of **3c** and 75 ml. of concentrated sulfuric acid was added dropwise, with cooling, a solution of 90 g. of fuming nitric acid in 75 ml. of concentrated sulfuric acid. The temperature of the reaction mixture was kept below 40° during the addition. After the addition was complete, the reaction solution was allowed to stand at room temperature for 3 hours. It was then cooled and the *p*H of the solution was adjusted to 5 with 50% sodium hydroxide. After overnight standing at 5°, the precipitated yellow solid was collected by filtration, washed with water and dried to give 111 g. (96% yield) of crude **3d**, m.p. 176-180°. Recrystallization from ethanol yielded an analytically pure sample, m.p. 181.5-183.5°.

Anal. Calcd. for $C_{11}H_9N_3O_5$: C, 50.20; H, 3.45; N, 15.97. Found: C, 50.49; H, 3.57; N, 15.65.

5,8-Diamino-6-methoxyquinoline (**4a**).

A mixture of 25 g. (0.1 mole) of 5,8-dinitro-6-methoxyquinoline (**3b**), 1 g. of platinum oxide, 200 ml. of ethyl acetate, and 40 ml. of absolute ethanol was hydrogenated at 4.3 kg/cm^2 for 3 hours. The reaction mixture was evaporated *in vacuo* to a small volume. To this was added 450 ml. of water and 10 ml. of 12 *N* sulfuric acid. The product, which was found to be identical with that prepared by the sodium hydrosulfite reduction of the 5-phenylazoquinoline **6b**, was oxidized to 6-methoxy-5,8-quinolinedione (**5a**) by the method of Pratt and Drake (4) without further purification.

6-Methoxy-2-methyl-5,8-quinolinedione (**5b**).

A mixture of 26.3 g. (0.1 mole) of **3d**, 150 ml. of water, 20 ml. of hydrochloric acid and 0.5 g. of 10% palladium-on-charcoal was hydrogenated at 3 kg/cm^2 for 20 hours. The reaction mixture was filtered and to the filtrate was added 150 g. of ferric chloride hexahydrate in 100 ml. of water. To this mixture was added 500 ml. of chloroform and the resulting mixture was stirred vigorously for 1 day. The chloroform was separated and the aqueous layer extracted with chloroform (5 x 30 ml.). The chloroform extracts were combined, dried (sodium sulfate) and evaporated to give 15.5 g. (76% yield) of **5b**, m.p. 199-203°. Recrystallization from ethanol yielded an analytical sample, m.p. 204-205°. This product was found to be identical with that prepared by other routes (10,11).

7-Bromo-6-methoxy-5,8-quinolinedione (**7a**).

To a mixture of 1 g. (0.0053 mole) of **5a**, 3.5 g. of anhydrous sodium acetate and 30 ml. of glacial acetic acid was added 0.85 g. (0.0053 mole) of bromine. The mixture was stirred for 24 hours and poured into 350 ml. of cold water. The resulting precipitate (1.4 g.) was collected by filtration, washed with water, and air dried. Recrystallization twice from ethanol gave 0.72 g. (51% yield) of analytically pure **7a**, m.p. 185-187° dec.

Anal. Calcd. for $C_{10}H_6BrNO_3$: C, 44.80; H, 2.25; N, 5.23. Found: C, 44.90; H, 2.41; N, 5.00.

7-Bromo-6-methoxy-2-methyl-5,8-quinolinedione (**7c**).

This compound was prepared from 2 g. (0.01 mole) of **5b**, 6 g. of sodium acetate, 60 ml. of acetic acid and 2 g. (0.025 mole) of bromine in 71% yield in a manner similar to that used in the foregoing experiment, m.p. 175° dec.

Anal. Calcd. for $C_{11}H_8BrNO_3$: C, 46.83; H, 2.86; N, 4.97. Found: C, 47.04; H, 3.10; N, 5.06.

6-Amino-7-bromo-5,8-quinolinedione (**8**).

A suspension of 0.5 g. of **7a** in 40 ml. of saturated ethanolic ammonia was stirred vigorously at room temperature for 3 hours. The resulting brick red powder was collected by filtration, washed repeatedly with ethanol and finally with ether to give an almost quantitative yield of **8**. Recrystallization from dimethylformamide yielded an analytical sample. On heating, it gradually darkened above 250° and decomposed at 314°; uv λ max (*p*H 1): 228 (ϵ, 7,100), 262 nm (ϵ, 3,800); λ max (*p*H 11): 235 (ϵ, 4,000), 268 nm (ϵ, 3,900).

Anal. Calcd. for $C_9H_5BrN_2O_2$: C, 42.72; H, 1.99; N, 11.07. Found: C, 42.90; H, 1.96; N, 10.80.

7-Amino-6-methoxy-5,8-quinolinedione (**1a**).

A mixture of 5.4 g. (0.02 mole) of **7a** and 1.3 g. (0.02 mole) of sodium azide suspended in 180 ml. of 50% ethanol was stirred at room temperature for 3 hours. The resulting orange yellow solid was collected by filtration, washed with water, and air dried. Ether extraction of the filtrate yielded an additional amount of solid to give a near quantitative yield of the azido intermediate **7b**. Recrystallization from aqueous ethanol yielded **7b** as orange yellow flakes, m.p. 131.5-132° dec.; λ max (*p*H 1): 233 (ϵ, 16,800) and

272 nm (ε, 16,900); λ max (*p*H 11): 232 (ε, 18,400) and 269 nm (ε, 15,500); ir (nujol): 1270 (aromatic ether), 1652 (carbonyl), 1680 (carbonyl) and 2130 cm^{-1} (N_3).

Two g. of the azido compound and 0.1 g. of platinum oxide were suspended in 200 ml. of anhydrous methanol and hydrogenated at 4 kg/cm^2 for 2.5 hours. The reaction mixture was filtered through a sintered glass funnel, during which time the filtrate turned dark purple. The filtrate was concentrated *in vacuo* to a small volume. The resulting precipitate was collected by filtration and washed with a small amount of ethyl acetate to give 1.05 g. (61% yield) of crude **1a**, m.p. 190-195°. Recrystallization from ethyl acetate yielded analytically pure **1a** as dark purple flakes, m.p. 202-203° dec.; ir (nujol): 1270, 1700, 3250 and 3500 cm^{-1}; uv λ max (*p*H 1): 232 (ε, 16,300), 271 (13,700) and 475 nm (2,550); uv λ max (*p*H 11): 232 (ε, 17,000), 271 (17,400) and 475 nm (2,800); ir (nujol): 1270 (aromatic ether), 1700 (carbonyl), 3250 (OH), and 3500 cm^{-1} (NH). The single, sharp NH stretching band at 3500 cm^{-1}, the presence of the OH band at 3250 cm^{-1}, and the similar uv absorption spectra at *p*H 1 and 11, suggest that compound **1a** may be tautomeric with structures such as **11**.

Anal. Calcd. for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 59.10; H, 3.89; N, 13.79.

7-Amino-6-methoxy-2-methyl-5,8-quinolinedione (**1b**).

7-Azido-6-methoxy-2-methyl-5,8-quinolinedione (**7d**), the intermediate for the synthesis of **1b**, was prepared from 8.5 g. (0.03 mole) of the corresponding 7-bromo compound **7c** and 2.0 g. of sodium azide in 82% yield in a manner similar to that used for the preparation of **7b**. Catalytic hydrogenation of 6 g. of **7d** in the presence of platinum oxide gave 3.2 g. (62% yield) of **1b**, m.p. 185-187°.

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.79; H, 4.34; N, 12.83.

Acknowledgments.

This investigation was supported by Contract NO1-CM-33743 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education and Welfare. The authors thank Dr. Harry B. Wood, Jr. of NCI and Professor George R. Pettit of Arizona State University for their interest, information and encouragement. They are also indebted to Mrs. Margaret L. Rounds and Mr. John R. Gravatt for performing analyses and instrumental measurements.

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