Synthesis and Structural Assignment of 5,6-Dihydro-8-hydroxy-9-methoxy-1*H*,7*H*-benzo[*ij*]quinolizine-1,7-dione

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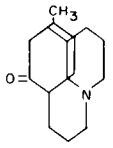
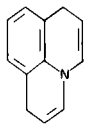
The compound 5,6-dihydro-8-hydroxy-9-methoxy-1*H*,7*H*-benzo[*ij*]quinolizine-1,7-dione (**4a**) was synthesized from 3-(1,4-dihydro-6,7-dimethoxy-4-oxo-1-quinolyl)propionic acid (**3a**, free base), involving spontaneous demethylation with ring closure. The structural assignment of **4a** was based on an analogous, unequivocal synthesis of 5,6-dihydro-9-ethoxy-8-hydroxy-1*H*,7*H*-benzo[*ij*]quinolizine-1,7-dione hydrochloride (**4b**).

The benzo[*ij*]quinolizine ring structure is basic to the Lycopodium family of alkaloids (1), as illustrated by Lycopodine. There are four known ring isomers of the benzo[*ij*]quinolizine (BQ) system, namely 1*H*-; 1*H*,5*H*-; 1*H*,7*H*-; and 1*H*,8*H*-BQ (2,3,4). The present work covers the synthesis of 5,6-dihydro-8-hydroxy-9-methoxy-1*H*,7*H*-benzo[*ij*]quinolizine-1,7-dione (**4a**) and the assignment of structure.



Lycopodine



1*H*,7*H*-BQ

Compound **4a** was synthesized in a three step sequence (Scheme I) starting with 6,7-dimethoxy-4-quinolinol (**1a**) (5). The alkylation of **1a** with acrylonitrile by the method of Colonge and Guzot (6) gave only 3-(6,7-dimethoxy-4-oxo-1-quinolyl)propionitrile (**2a**), the structure of which was proven by infrared spectral data. The nitrile **2a** was readily hydrolyzed to 3-(1,4-dihydro-6,7-dimethoxy-4-oxo-1-quinolyl)propionic acid hydrochloride (**3a**). Milder conditions of the hydrolysis of **2a** gave the intermediate propionamide **5**. The ring closure of **3a** (free base) in hot PPA occurred with concurrent demethylation to give the monomethyl, monohydroxy ketone **4a**, which readily formed an oxime derivative (**10**).

The question of possible ring closure of the acid **3a** on the 2-position of the quinoline (versus the 8-position to give **4a**) was resolved by a comparison of the nmr-spectra of **3a** and **4a**.

Although the structure of the cyclization product was supported by elemental analysis and by the infrared and nmr spectra (see Experimental Section) the question of the relative positions of the 8,9-(hydroxy,methoxy) groups remained unresolved. Demethylation in an analogous cyclization was previously reported (7); ring closure of ethyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-isoquinolinepropionate to 2,3,9,9a-tetrahydro-6-hydroxy-5-methoxy-1-methyl-1*H*-benzo[*d,e*]quinolin-7(8*H*)one occurred, and demethylation was reported *ortho* to the generated ketone. Hence compound **4a** was tentatively assigned the 8-hydroxy-9-methoxy structure **4a**.

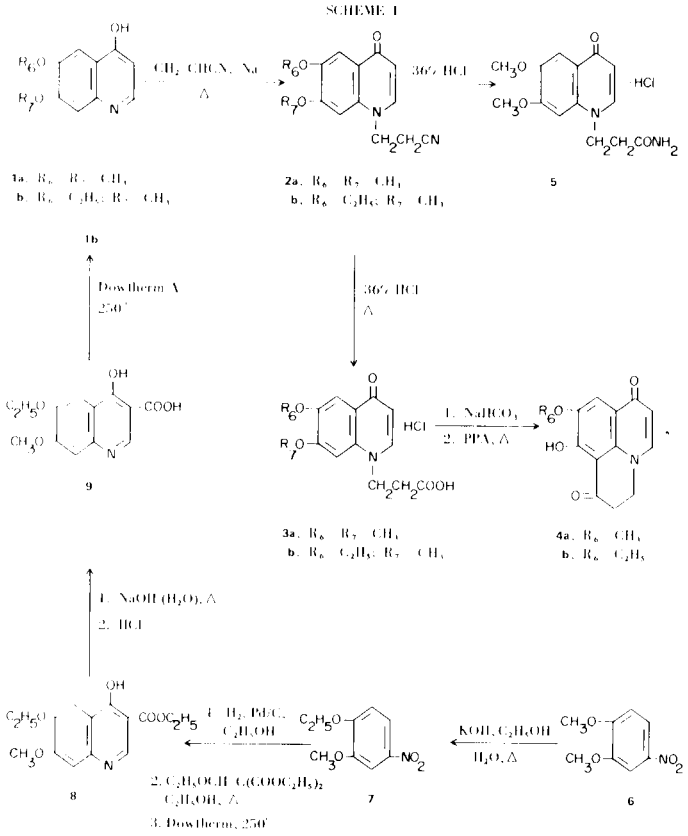
In order to establish the structure of **4a** unequivocally, the compound 3-(1,4-dihydro-6-ethoxy-7-methoxy-4-oxo-1-quinolyl)propionic acid (**3b**, free base) was chosen as a model for ring closure with PPA (Scheme I). Thus ring closure of **3b**, with demethylation at position 8, would give 5,6-dihydro-9-ethoxy-8-hydroxy-1*H*,7*H*-benzo[*ij*]-quinolizine-1,7-dione (**4b**, free base).

An unambiguous synthesis of **3b** was carried out in sequence (Scheme I), starting with nitroveratrole. The 4-ethoxy-3-methoxynitrobenzene (**7**) was prepared through nucleophilic displacement by ethoxide ion on nitroveratrole (**6**) (8). That the methoxy group *para* to the nitro group of nitroveratrole was displaced has been substantiated through the studies of Oliverio on the lability of the *ortho*- and *para*-positions of nitroanisoles relative to the stability of the *meta*-position (9).

In the reaction sequence (Scheme I) the quinoline **1b** was prepared by well established procedures (10). Conversion of **1b** to **2b** was performed as described above.

The sequence (Scheme I) was completed with ring closure of the model compound **3b**, which gave the expected quinolizine-1,7-dione **4b** with the 9-ethoxy-substituent in place. The structure **4b** was supported by elemental analysis and by infrared and nmr spectra (see Experimental Section).

SCHEME I



Since cleavage has been shown to occur at the 8-position during cyclization of **3b** to **4b**, by analogy the product of ring closure of **3a** has been assigned the 8-hydroxy-9-methoxy structure **4a**.

EXPERIMENTAL

Infrared spectra were obtained with a Perkin-Elmer Infracord 137 and nmr spectra were determined in hexadeuterodimethylsulfoxide using tetramethylsilane as an internal standard on a Varian A-60A spectrometer. Melting point data were obtained on a Fisher-Johns hot stage and are uncorrected.

3-(6,7-Dimethoxy-4-oxo-1-quinolyl)propionitrile (**2a**).

To a mixture of 6,7-dimethoxy-4-quinolinol (**1a**) (5) (200 g., 0.97 mole) and acrylonitrile (1200 ml.) was added sodium (2.0 g., 0.0087 g.-atom) at room temperature, with mechanical stirring. The reaction mixture was heated (steam bath) for 2.5 hours and subsequently stirred overnight at room temperature. The solid from the cooled crystalline mixture was collected by filtration and washed well with 2-propanol and ether, m.p. 194-195°, yield: 240 g. (96%); ir (Nujol) μ: 6.13 (C=O); 4.42 (C≡N).

Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.38; H, 5.57; N, 11.03.

3-(1,4-Dihydro-6,7-dimethoxy-4-oxo-1-quinolyl)propionic Acid Hydrochloride (**3a**).

A mixture of **2a** (378 g., 1.46 moles) and concentrated hydrochloric acid (1500 ml.) was heated (steam bath) for 2 hours, with mechanical stirring. The mixture was added to cold water (2000 ml.), and then stored at room temperature overnight. The crystalline solid was collected by filtration and washed with 2-propanol and ether; yield, 480 g. Recrystallization of the product (80 g.) from methanol gave **3a**; m.p. 255-257°, yield: 47 g. (61%); ir (Nujol) μ: 6.16 (C=O); 5.80 (COOH); nmr (δ): 2.94 and 4.90 (pair triplets, CH_2CH_2); 3.90 and 4.05 (singlets, $2CH_3O$); 7.22 and 8.66 (pair doublets, $J_{2,3}$ = 7.0 ± 0.1 Hz, CH-CH); 7.37 and 7.47 (singlets, 2 aromatics); 7.97 (two deuterium oxide-exchangeable protons).

Anal. Calcd. for $C_{14}H_{15}NO_5 \cdot HCl$: C, 53.59; H, 5.14; N, 4.47. Found: C, 53.56; H, 5.15; N, 4.51.

5,6-Dihydro-8-hydroxy-9-methoxy-1*H*,7*H*-benzo[*ij*]quinolizine-1,7-dione (**4a**).

A mixture of **3a** (683 g., 2.18 moles) and water (1000 ml.) was treated with a solution of sodium bicarbonate (190 g., 2.26 moles) with rapid stirring. The mixture was stirred at room temperature for 3 hours, stored overnight, and filtered. The resultant crystalline **3a** (free base) was washed with saturated aqueous sodium chloride (400 ml.), 2-propanol, and ether, m.p. 108-120°, yield, 487 g. (81%).

To PPA (3900 g.) at 60-70° was added **3a** (free base, 487 g., 1.76 moles) over a 1 hour period with mechanical stirring. The reaction mixture was heated (steam bath) at 92-94° for 7 hours, cooled to 60-70° and poured into a slurry of ice (9000 ml.) and water (2500 ml.) with moderate stirring. The yellow crystalline solid was collected by filtration and washed with water (1.5 l.), 2-propanol (1 l.) and ether. Recrystallization of the product (239 g.) from 2% hydrochloric acid (1 l.) gave **4a**; m.p. 224-226°, yield: 184 g. (68%). A second recrystallization from 90% *N,N*-dimethylformamide (methanol) gave analytically pure **4a**; m.p. 256-258°; ir (Nujol) μ: 6.12 (C=O, 7 position); 6.19 (C=O, 1-position); no O-H absorption at 3.0-3.2; nmr (δ): 3.07 and 4.35 (pair triplets, CH_2CH_2); 3.81 (singlet, CH_3O); 5.96 and 7.72 (pair doublets, $J_{2,3}$ = 7.7 ± 0.0 Hz, CH-CH); 7.56 (singlet, 1 aromatic).

Anal. Calcd. for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.86; H, 4.65; N, 5.66.

3-(1,4-Dihydro-6,7-dimethoxy-4-oxo-1-quinolyl)propionamide Hydrochloride Hemihydrate (**5**).

A mixture of **2a** (105 g., 0.41 mole) and concentrated hydrochloric acid (600 ml.) was stirred at room temperature for 6 hours, and then stored overnight. The crystalline product was collected by filtration and washed with 2-propanol and ether; m.p. 161-164°, yield, 77 g. (58%). Recrystallization from methanol (500 ml.) with charcoal gave **5**, m.p. 158-160°, yield: 23 g. (18%); ir (Nujol) μ: 6.07 ($CONH_2$); 6.20 (C=O); 3.0 (NH_2, broad).

Anal. Calcd. for $C_{14}H_{16}N_2O_4 \cdot HCl \cdot \frac{1}{2}H_2O$: C, 52.26; H, 5.64; N, 8.71. Found: C, 52.24; H, 5.88; N, 8.54.

5,6-Dihydro-8-hydroxy-9-methoxy-1*H*,7*H*-benzo[*ij*]quinolizine-1,7-dione 7-Oxime (**10**).

A mixture of hydroxylamine hydrochloride (124 g., 1.78 moles) and water (260 ml.) was treated with 10% sodium hydroxide (313 ml.), **4a** (124 g., 0.51 mole), and methanol (500 ml.). The reaction mixture was heated at 85-90° for 1.5 hours, stored for 2 hours with stirring, and filtered. The resultant product was washed with water (250 ml.), 2-propanol (60 ml.) and ether; m.p. 330° dec., yield, 102 g. (76%); ir (μ): 6.20 (C=O); 3.21 and 3.30 (O-H).

Anal. Calcd. for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.77. Found: C, 60.17; H, 4.63; N, 10.27.

4-Ethoxy-3-methoxynitrobenzene (**7**).

A solution of nitroveratrole (200 g., 1.09 moles) in ethanol (2500 ml.) and 10% potassium hydroxide (200 ml.) was refluxed for 57 hours. The solvent was evaporated under reduced pressure; the residue was dissolved in water (2000 ml.) and neutralized with concentrated hydrochloric acid. The product was collected by filtration. Recrystallization from 2-propanol gave **7**; m.p. 84-85° [lit. (8) m.p. 85-86°], yield: 173 g. (80%).

Ethyl 6-Ethoxy-4-hydroxy-7-methoxy-3-quinolinecarboxylate (**8**).

A mixture of **7** (35.0 g., 0.18 mole), 10% Pd/C (2.4 g.) and ethanol (200 ml.) was subjected to hydrogenation for 1 hour; a pressure drop of 90% of theory was observed. The reaction mixture was filtered of catalyst, and the resultant solution was treated with diethyl ethoxymethylenemalonate (39 g., 0.18 mole) and refluxed in a nitrogen atmosphere for 1 hour. Solvent was removed under reduced pressure, Dowtherm A (11) (250 ml.) was added, and the solution maintained at reflux until all the ethanol product was distilled. The reaction mixture was cooled overnight and the resultant tan solid was collected by filtration and washed with hexane; m.p. 277-285°, yield: 45.8 g. (87%). Three recrystallizations from *N,N*-dimethylformamide gave analytically pure **8**; m.p. 292-294°.

Anal. Calcd. for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.45; H, 5.81; N, 4.99.

6-Ethoxy-4-hydroxy-7-methoxyquinoline-3-carboxylic Acid (**9**).

A mixture of **8** (254 g., 0.88 mole) and 10% sodium hydroxide (400 ml.) was refluxed for 19 hours. The hot solution (treated with charcoal) was filtered, cooled in an ice bath, and treated with concentrated hydrochloric acid (100 ml.). The product was collected by filtration, m.p. 254-255°, yield, 120 g. (52%).

Anal. Calcd. for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.29; H, 5.09; N, 5.53.

6-Ethoxy-7-methoxy-4-quinolinol (**1b**).

To Dowtherm A (1000 ml.) at 235-240° was added gradually **9** (120 g., 0.46 mole). The mixture was then refluxed for 2¼ hours. The reaction mixture was cooled and the product was collected by filtration and washed with hexane; m.p. 233-236°, yield, 70 g. (70%).

The hydrochloride of **1b** was prepared by treatment with aqueous hydrochloric acid in methanol. Recrystallization from methanol gave an analytical sample, m.p. 274-275°.

Anal. Calcd. for $C_{12}H_{13}NO_3$·HCl: C, 56.36; H, 5.52; N, 5.49; Cl, 13.87. Found: C, 56.32; H, 5.54; N, 5.56; Cl, 13.91.

3-(1,4-Dihydro-6-ethoxy-7-methoxy-4-oxo-1-quinolyl)propionitrile (**2b**).

The compound was prepared from **1b** by the same method as employed in the synthesis of **2a**; m.p. 286-288°, yield, 40 g. (34%).

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.36; H, 5.98; N, 10.47.

3-(1,4-Dihydro-6-ethoxy-7-methoxy-4-oxo-1-quinolyl)propionic Acid Hydrochloride (**3b**).

The compound was prepared from **2b** by the same method as employed in the preparation of **3a**; m.p. 252-255°, yield, 65 g. (100%); ir (Nujol) μ: 5.85 (COOH); 6.10 (C=O); nmr (δ): 1.47 and 4.20 (triplet and quartet, CH_3CH_2); 4.08-4.32 (coalesce with ethyl quartet, CH_3O); 3.03 and 5.02 (pair triplets, CH_2CH_2); 7.37 and 8.84 (pair doublets, $J_{2,3}$ = 6.9 ± 0.1 Hz); 7.54 and 7.63 (singlets, 2, aromatic); 11.87 (broadened, 2, COOH and NH).

Anal. Calcd. for $C_{15}H_{17}NO_5$·HCl: C, 54.97; H, 5.54; N, 4.27. Found: C, 55.07; H, 5.52; N, 4.37.

5,6-Dihydro-9-ethoxy-8-hydroxy-1*H*,7*H*-benzo[*ij*]quinolizine-1,7-dione Hydrochloride (**4b**).

The free base of **3b** was prepared as follows: A cold mixture of **3b** (36 g., 0.11 mole) and saturated aqueous sodium chloride (400 ml.) was treated with sodium bicarbonate (10.1 g., 0.12 mole) with hand stirring. Intermittent stirring was continued over 1 hour, then the product was collected by filtration and washed with saturated aqueous sodium chloride (25 ml.), ice water (3 x 15 ml.), 2-propanol (2 x 20 ml.) and ether; yield, 42 g.

A mixture of the finely ground free base of **3b** (37 g.) and PPA (400 g.) was heated (steam bath) for 6 hours, stored at room temperature overnight, and then added to ice (1.1 l.) with stirring. The aqueous solution was neutralized with 50% sodium hydroxide (170 ml.) at 15-35°. The resultant phosphate salt was collected by filtration, washed with cold water (5 x 20 ml.), and then treated with 10% hydrochloric acid (105 ml.) with cooling. The hydrochloride salt was collected by filtration and extracted with hot methanol (3.5 l.). Concentration of the extract to a volume of 200 ml., with subsequent storage in the refrigerator, gave **4b**; m.p. 225-228°, yield, 10 g. (31%); ir (Nujol) μ: 6.00 (C=O, 7-position); 6.11 (C=O, 1-position); 3.2 (OH, very weak); ir (chloroform) μ: 6.12 (C=O, 7-position); 6.27 (C=O, 1-position); 3.0 (OH, broad); nmr (δ): 1.42 and 4.19 (triplet and quartet, CH_3CH_2); 3.22 and 4.70 (pair triplets, CH_2CH_2); 6.80 and 8.40 (pair doublets, $J_{2,3}$ = 6.9 ± 0.1 Hz, CH=CH); 7.68 (singlet, 1, aromatic).

Anal. Calcd. for $C_{14}H_{13}NO_4$·HCl: C, 56.86; H, 4.77; N, 4.74. Found: C, 56.45; H, 4.78; N, 4.52.

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