

The Chemistry of 5*H*-Benzoxazolo[3,2-*a*]quinolin-5-ones.  
5*H*-Benzoxazolo[3,2-*a*]quinolin-5-ones as Synthons for the Preparation of  
Novel Quinoline Derivatives

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Received May 18, 1981

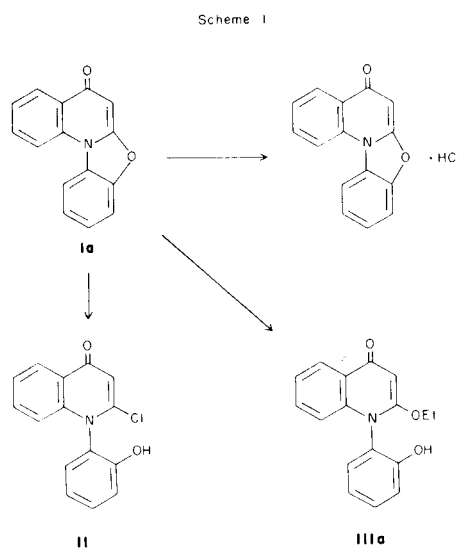
The usefulness of 5*H*-benzoxazolo[3,2-*a*]quinolin-5-ones (I) as synthons for the preparation of otherwise difficultly obtainable quinolin-5-ones is demonstrated. Nucleophilic reagents cleaved the oxazole ring of I at the 7-position, resulting in 1-(2-hydroxyphenyl)-2-substituted 4-(1*H*)quinolinones. Treatment of 5*H*-benzoxazolo[3,2-*a*]quinolin-5-one (Ia) with ethanolic potassium hydroxide gave 1-(2-hydroxyphenyl)-2-ethoxy-4-(1*H*)quinolinone (IIIa), and attempted formylation of Ia with the Vilsmeier-Haak reagent instead gave 2-chloro-1-(2-hydroxyphenyl)-4-(1*H*)quinolinone (II). Likewise, 10-chloro-5*H*-benzoxazolo[3,2-*a*]quinolin-5-ones (Ib) afforded 2-ethoxy- and 2-methoxy-1-(5-chloro-2-hydroxyphenyl)-4-(1*H*)quinolinone (IIIb and IIIc) upon treatment with ethanol and methanol, respectively. Reaction of Ib with 1-phenylpiperazine yielded 1-(5-chloro-2-hydroxyphenyl)-2-(4-phenyl-1-piperazinyl)-4-(1*H*)quinolinone (IV). Alkaline hydrolysis of IIIb gave 1-(2-hydroxy-5-chlorophenyl)-2-(1*H*)quinolinone (V). Treatment of IIIc with epichlorohydrin gave 1-[5-chloro-2-(2-oxiranylmethoxy)phenyl]-2-methoxy-4-(1*H*)quinolinone (VIa) which in turn upon treatment with isopropylamine gave 1-[5-chloro-2-[2-hydroxy-3-(1-methylethylamino)propoxy]phenyl]-2-methoxy-4-(1*H*)quinolinone (VIIa). Similarly, the ethoxy analog (VIIb) was prepared. Reaction of Ib with sodium cyanide in dimethylsulfoxide produced 1-(5-chloro-2-hydroxyphenyl)-1,4-dihydro-4-oxo-2-quinolinecarbonitrile (X) which was hydrolyzed to give the corresponding carboxamide (XIV) and carboxylic acid (XI) depending on the reaction conditions. The latter yielded 2-chloroquino[2,1-*c*][1,4]benzoxazine-6,8-dione (XII) when heated with an excess of acetic anhydride. Treatment of XII with methoxyethylamine gave 1-(5-chloro-2-hydroxyphenyl)-1,4-dihydro-*N*-2(methoxyethyl)-4-oxo-2-quinolinecarboxamide (XV). 1-(5-chloro-2-hydroxyphenyl)-2-(1*H*-tetrazoyl-5-yl)-4-(1*H*)quinolinone (XIII) was prepared from X. When Ib was allowed to react with sodium diethylmalonate, there was obtained [1-(5-chloro-2-hydroxyphenyl)-1,4-dihydro-4-oxo-2-quinolinyl]-propanedioic acid diethyl ester (XVI) which was transformed to 1-(5-chloro-2-hydroxyphenyl)-1,4-dihydro-4-oxo-2-quinolinacetic acid ethyl ester (XVII) upon heating in hexamethylphosphoramide.

*J. Heterocyclic Chem.*, **18**, 1393 (1981).

Previous reports of this series described that reaction of *N*-(2-hydroxyphenyl)anthranilic acids with acetic anhydride gave 5*H*-benzoxazolo[3,2-*a*]quinolin-5-ones (1,2). However, only a very limited study of the chemical properties of these compounds was described (1). This paper illustrates the usefulness of 5*H*-benzoxazolo[3,2-*a*]quinolin-5-ones as synthons for the preparation of otherwise difficultly obtainable quinoline derivatives of potential pharmacological interest.

Treatment of 5*H*-benzoxazolo[3,2-*a*]quinolin-5-ones with nucleophiles caused reaction to occur at the 7-position with resultant cleavage of the oxazole ring. Thus, heating 5*H*-benzoxazolo[3,2-*a*]quinolin-5-one (Ia) with ethanol in the presence of potassium hydroxide gave 1-(2-hydroxyphenyl)-2-ethoxy-4-(1*H*)quinolinone (IIIa, Scheme I).

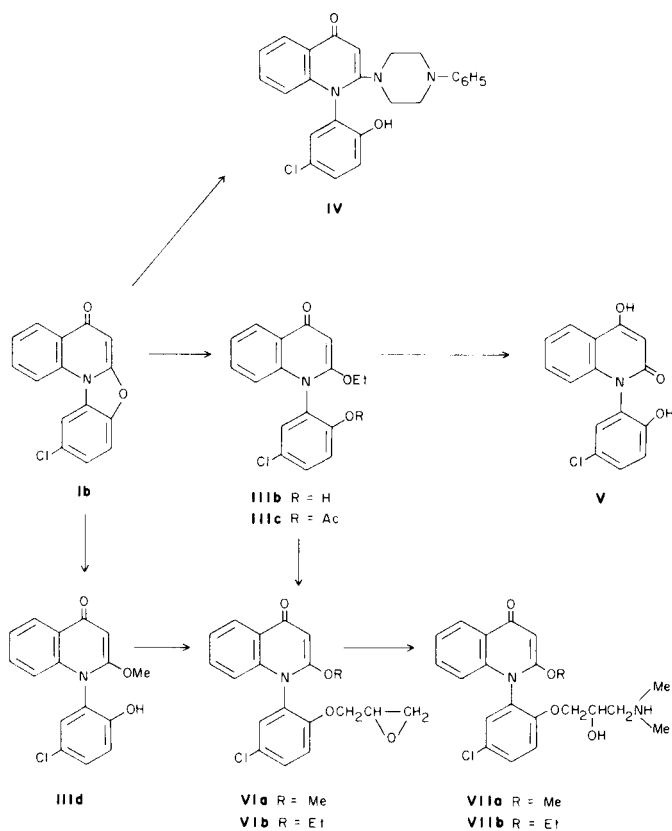
Under similar conditions Ib gave IIIb which in turn yielded V upon treatment with an aqueous base. Treatment of Ib with methanol afforded IIIc which was characterized as a hydrochloride salt (Scheme II). Treatment of IIIb with acetic anhydride afforded the phenolic acetate IIIc (Scheme II). The reaction of Ib with



1-phenylpiperazine yielded 1-(5-chloro-2-hydroxyphenyl)-2-(4-phenyl-1-piperazinyl)-4-(1*H*)quinolinone (IV). In contrast to their reactivity in basic media, 5*H*-benzoxazolo-

-[3,2-*a*]quinolin-5-ones were quite stable toward acids; only its hydrochloride salt was isolated when Ia was heated under reflux for 2.5 hours with dilute hydrochloric acid. The facile cleavage of the oxazole ring was further demonstrated. Thus, attempted formylation of Ia at the 3-position with the Vilsmeier-Haack reagent instead resulted in chlorination with opening of the oxazole ring, giving 2-chloroquinoline II (Scheme I).

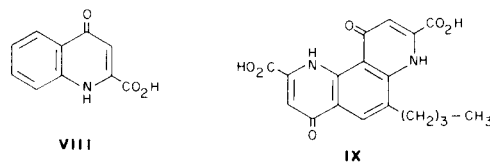
Scheme II



Many aryloxypropanolamines are known to be therapeutically valuable antihypertensive agents which exert their blood pressure lowering effects *via* blockage of  $\beta$ -adrenergic receptors of hypertensive subjects (3). It was thus of interest to synthesize quinolines having such pharmacophobic side chain as an aminopropanoxy group. Treatment of III d with epichlorohydrin afforded 1-[5-chloro-2-(2-oxiranylmethoxy)phenyl]-2-methoxy-4-(1*H*)quinolinone (VIa) in 46% yield. Reaction of the latter with isopropanol gave 1-[5-chloro-2-[2-hydroxy-3-(1-methylethylamino)propoxy]phenyl]-2-methoxy-4-(1*H*)quinolinone (VIIa). In similar fashion, VIIb was synthesized and characterized as a nitric acid salt. Disappointingly, neither VIIa nor VIIb showed antihypertensive activity when tested in animal.

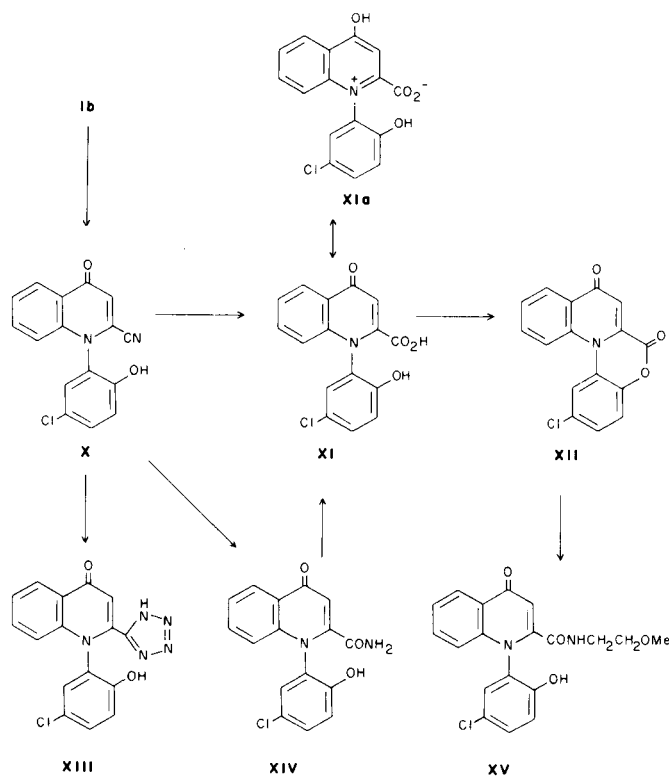
A variety of quinolines derivatives including 1,4-dihydro-

4-oxoquinoline-2-carboxylic acid (VIII) and 6-*n*-butyl-2,8-dicarboxy-4,10-dioxo-1,4,7,10-tetrahydro-1,7-phenanthroline (IX) were shown to possess potent antiallergic properties (5).



It was thus thought worthwhile to prepare quinoline derivatives which carry a carboxylic acid group at the 2-position for evaluation of antianaphylactic activity.

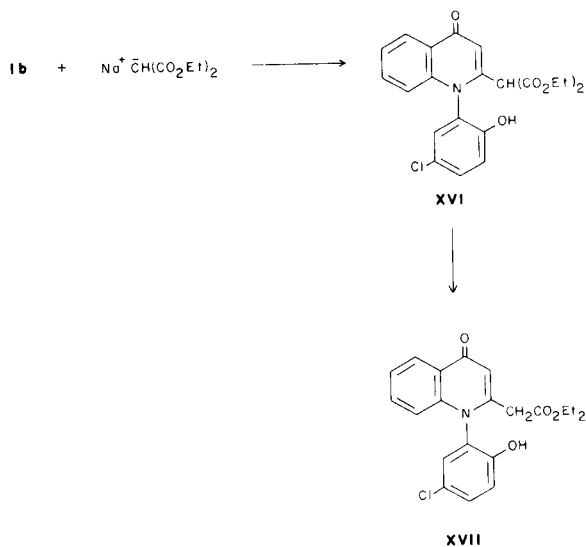
Scheme III



When Ib was allowed to react with sodium cyanide in dimethylformamide there was obtained 1-(5-chloro-2-hydroxyphenyl)-1,4-dihydro-4-oxo-2-quinolinecarbonitrile (X) in quantitative yield. Compound X has a strong tendency to solvate crystallization solvent. It was obtained as an ethanolate when recrystallized from ethanol and precipitated with a half mole of acetonitrile upon recrystallization from acetonitrile. Treatment of X with a boiling aqueous sodium hydroxide solution for 1 hour afforded the corresponding carboxamide XIV. Extension of the reaction time of the basic hydrolysis of X to 6 hours gave the corresponding carboxylic acid XI. The latter was also obtainable from XIV under the basic hydrolysis conditions. The infrared spectrum of XI exhibited strong

bands at  $1605\text{ cm}^{-1}$  and at  $1429\text{ cm}^{-1}$ , ascribable to a carboxylate group in addition to a carboxyl OH stretching vibration band at  $2500\text{ cm}^{-1}$  and a weak carbonyl absorption band at  $1695\text{ cm}^{-1}$ . It appears thus that the compound exists mainly in the more aromatic form such as XIa. Reaction of XI with acetic anhydride resulted in a lactone formation to give 2-chloroquino[2,1-*c*][1,4]benzoxazine-6,8-dione (XII) which in turn yielded 1-(5-chloro-2-hydroxyphenyl)-1,4-dihydro-*N*-(2-methoxyethyl)-4-oxo-2-quinolinecarboxamide (XV) upon treatment with 2-methoxyethylamine (Scheme III). The acidity of the 1*H*-tetrazol-5-yl group is comparable to those of the carboxylic acids (7), and it has been reported that the carboxylic group of some acidic antiallergic compounds may be replaced with the tetrazol function without loss of the biological activity. In fact in some instances, such an allosteric replacement of the carboxylic group resulted in an improvement of the potency of the antiallergic activity (8). Accordingly, X was converted to 1-(5-chloro-2-hydroxyphenyl)-2-hydroxyphenyl)-2-(1*H*-tetrazol-5-yl)-4-(1*H*)quinolinone (XIII) in 97% yield by allowing it to react with sodium azide in the presence of ammonium chloride in dimethylformamide. None of these compounds, however, exhibited significant antiallergic activity in the rat passive cutaneous anaphylaxis test.

Scheme IV



Reaction of Ib with sodium diethylmalonate was studied. When Ib was allowed to react with sodium diethylmalonate which was generated *in situ* in hexamethylphosphoramide, the geminal diester XVI was obtained in 12% yield and a small amount of quinolineacetic acid ethyl ester XVII. The nmr spectrum of the latter showed the methylene proton signal at  $\delta 4.10$  as a singlet, and the presence of an ester function was indicated by its infrared carbonyl absorption band appeared at  $1730\text{ cm}^{-1}$ . Geminal diesters are known to undergo decarbalkox-

ylation upon heating with an inorganic salt in an aprotic solvent such as dimethylsulfoxide or dimethylformamide (9). No such inorganic salt was, however, required for the decarbalkoxylation of XVI. When XVI was simply heated with hexamethylphosphoramide at  $120^\circ$  for 2.5 hours, the removal of the carbethoxy group proceeded smoothly to give XVII in 94% yield (Scheme IV).

## EXPERIMENTAL

Melting points were taken in capillary tubes (Thomas-Hoover melting point apparatus) and are uncorrected. Ir spectra were obtained in potassium bromide pellets using a Perkin-Elmer 21 spectrophotometer. Uv absorption spectra were obtained in ethanol solution using a Perkin-Elmer Model 450-uv-visible NIR spectrophotometer. Nmr spectra were determined on a Jeolco Model C-60HL NMR spectrometer using tetramethylsilane as the internal reference. Combustion elemental analyses were performed by the Analytical Section of these Laboratories using a Perkin-Elmer Model 240 elemental analyzer. Mass spectra were obtained with an Associated Electrical Industries MS-9 high resolution mass spectrometer. The reported yields may be improved under optimal reaction conditions.

### 1-(5-Chloro-2-hydroxyphenyl)-2-ethoxy-4(1*H*)quinolinone (IIIb).

Potassium hydroxide pellets (0.8 g) were dissolved in ethanol (100 ml) with warming on a steam bath. To the ethanol solution was added 10-chloro-5*H*-benzoxazolo[3,2-*a*]quinolin-5-one (Ib, 2.7 g), and the resulting mixture was heated under reflux for 1 hour. The hot reaction mixture was neutralized with concentrated hydrochloric acid and chilled in ice. The precipitate that separated was collected on a filter and washed with ethanol giving the product (2.5 g, 79%), mp  $257\text{--}260^\circ$ . Purification by dissolution in dilute aqueous sodium hydroxide solution and precipitation by acidification improved the mp to  $264\text{--}265^\circ$  dec; ir:  $1626\text{ cm}^{-1}$ ; nmr (DMSO- $d_6$ ):  $\delta$  1.19 (3H,  $\text{CH}_3$ , t), 4.25 (2H,  $\text{CH}_2$ , q), 5.91 (1H, =CH-, s), 6.75-8.36 (7H, aromatic, m) and 10.50 (1H, OH, broad s).

Anal. Calcd. for  $\text{C}_{17}\text{H}_{14}\text{ClNO}_3$ : C, 64.66; H, 4.47; N, 4.44. Found: C, 64.68; H, 4.30; N, 4.36.

### 1-(2-Hydroxyphenyl)-2-ethoxy-4(1*H*)quinolinone (IIIa).

This compound was similarly prepared from 5*H*-benzoxazolo[3,2-*a*]quinolin-5-one (Ia) in 84% yield and purified by recrystallization from ethanol, mp  $244\text{--}246^\circ$ .

Anal. Calcd. for  $\text{C}_{17}\text{H}_{15}\text{NO}_3$ : C, 72.58; H, 5.37; N, 4.98. Found: C, 72.43; H, 5.32; N, 4.92.

### 2-Chloro-1-(2-hydroxyphenyl)-4(1*H*)quinolinone (II).

Phosphorous oxychloride (8.4 g) was added with stirring to dimethylformamide (16 g) chilled in ice, and the resulting mixture was allowed to set at room temperature for 1 hour. 5*H*-benzoxazolo[3,2-*a*]quinolin-5-one (Ia, 2.3 g) was added to the mixture and stirred at room temperature for 1 hour, then heated gently on a steam bath for 3 hours. The reaction mixture was poured into about 250 ml of crushed ice, allowed to set overnight and neutralized with dilute aqueous sodium hydroxide solution. The precipitate was collected on a filter, washed with water and recrystallized from ethanol to give II (0.87 g, 32%), mp  $268\text{--}269^\circ$ ; ir:  $1645\text{ cm}^{-1}$ ; nmr (DMSO- $d_6$ ):  $\delta$  7.60 (1H, =CH-, s), 6.65-8.10 (8H, aromatic, m), and 9.90 (1H, OH, s); ms: (C.I.)  $m/e$  272 ( $\text{MH}^+$ ).

Anal. Calcd. for  $\text{C}_{15}\text{H}_{10}\text{ClNO}_2$ : C, 66.31; H, 3.71; N, 5.15. Found: C, 65.92; H, 3.67; N, 5.00.

### 1-[2-(Acetyloxy)-5-chlorophenyl]-2-ethoxy-4(1*H*)quinolinone (IIIc).

A mixture of IIIb (2.5 g), acetic anhydride (45 ml) and pyridine (5 drops) was heated under reflux for 1.5 hours, then filtered while hot. The filtrate was evaporated on a rotary evaporator under reduced pressure to dryness. The residue was triturated with ether, then recrystallized from tetrahydrofuran to give IIIc (1.2 g, 38%), mp  $162\text{--}164^\circ$ ; ir:  $1770\text{ cm}^{-1}$  and

1631  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{19}\text{H}_{16}\text{ClNO}_4$ : C, 63.78; H, 4.51; N, 3.92. Found: C, 63.92; H, 4.33; N, 3.84.

1-(5-Chloro-2-hydroxyphenyl)-2-(4-phenyl-1-piperazinyl)-4-(1*H*)quinolinone (IV).

A mixture of Ib (2.7 g) and 1-phenylpiperazine (3.5 g) was heated in an oil bath maintaining the temperature of 170° for 2.5 hours. The resulting resinous mixture was dissolved in ca. 10 ml of hot ethanol. Chilling of the solution in ice caused separation of a precipitate which was removed by filtration. The filtrate was diluted with an equal volume of ether and allowed to set at room temperature for several days. The crystalline product that separated was collected on a filter and washed with ethanol, giving IV (1.95 g, 45%), mp 233-235°.

*Anal.* Calcd. for  $\text{C}_{25}\text{H}_{22}\text{ClN}_3\text{O}_2$ : C, 69.36; H, 5.12; N, 9.71. Found: C, 69.21; H, 5.37; N, 9.73.

1-(5-Chloro-2-hydroxyphenyl)-2-methoxy-4-(1*H*)quinolinone Hydrochloride, 1/4 Hydrate (III*d*).

A mixture of Ib (10.8 g), potassium hydroxide pellets (86% purity, 3.26 g) and methanol (250 ml) was heated under reflux for 1 hour. After being cooled to room temperature it was acidified with concentrated hydrochloric acid. Chilling of the resulting solution caused separation of a precipitate (potassium chloride) which was collected on a filter and washed with methanol. The combined filtrate and washing were evaporated on a rotary evaporator under reduced pressure to give an oily residue which solidified on standing. The solid material was collected on a filter and washed with methanol to give a product (13 g, mp 310° dec) which was recrystallized from methanol and ether. On heating, it effervesced at about 190°, then melted with decomposition at 305-307°.

*Anal.* Calcd. for  $\text{C}_{16}\text{H}_{12}\text{ClNO}_3 \cdot \text{HCl} \cdot 1/4\text{H}_2\text{O}$ : C, 56.07; H, 3.97; N, 4.09. Found: C, 55.95; H, 3.69; N, 4.17.

1-(2-Hydroxy-5-chlorophenyl)-2-(1*H*)quinolinone (V).

A mixture of IIIb (3.5 g), 15% aqueous sodium hydroxide solution (50 ml) and water (50 ml) was heated under reflux for 1.5 hours, then filtered. The filtrate was acidified with concentrated hydrochloric acid to pH ca. 4. A precipitate was collected on a filter and washed with water several times, then recrystallized from a small amount of ethanol, mp 303-305° dec; ir: broad band at 2817  $\text{cm}^{-1}$  and 1637  $\text{cm}^{-1}$ ; uv: max:  $\mu\epsilon$  ( $\epsilon$ ) 226.5 (22300), 269.5 (3400), 280 (4200) and 310 (2700).

*Anal.* Calcd. for  $\text{C}_{15}\text{H}_{10}\text{ClNO}_3$ : C, 62.62; H, 3.60; N, 4.87. Found: C, 62.59; H, 3.72; N, 4.92.

1-(5-Chloro-2-(2-oxiranylmethoxy)phenyl)-2-methoxy-4-(1*H*)quinolinone (VIa).

Six g of 1-(5-chloro-2-hydroxyphenyl)-2-methoxy-4-(1*H*)quinolinone, hydrochloride, 1/4 hydrate (III*d*) was added with stirring to an aqueous sodium hydroxide solution which was obtained by dissolving 0.85 g of sodium hydroxide in 70 ml of water. Epichlorohydrin (3.0 g) was added, and the resulting mixture was stirred at room temperature overnight, then heated on a steam bath for 1 hour. The mixture was chilled in ice and the solid product that separated was collected on a filter. The crude product was recrystallized from ethanol, then from tetrahydrofuran to yield 2.9 g (46%) of VIa; mp 203-205°; ir: 3012  $\text{cm}^{-1}$ , 1626  $\text{cm}^{-1}$  and 1250  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{19}\text{H}_{16}\text{ClNO}_4$ : C, 63.78; H, 4.51; N, 3.52. Found: C, 63.55; H, 4.51; N, 3.69.

1-[5-Chloro-2-[2-hydroxy-3-(1-methylethylamino)propoxy]phenyl]-2-ethoxy-4-(1*H*)quinolinone (VIIa).

A mixture of VIa (1.0 g), isopropylamine (5 ml) and methanol (15 ml) was stirred at room temperature for 1 day. The heterogeneous mixture at the beginning become a clear solution. Evaporation of the reaction mixture under reduced pressure gave a resinous residue which solidified upon addition of a small amount of anhydrous ether and scratching, giving analytically pure product (1.05 g, 90%), mp 164-166°; ir: 3333  $\text{cm}^{-1}$ , 3030  $\text{cm}^{-1}$ , 2941  $\text{cm}^{-1}$ , and 1623  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{22}\text{H}_{23}\text{ClN}_2\text{O}_4$ : C, 63.38; H, 6.04; N, 6.72. Found: C, 62.98; H, 6.27; N, 6.79.

1-[5-Chloro-2-(2-oxiranylmethoxy)phenyl]-2-methoxy-4-(1*H*)quinolinone (VIb).

Five and four-tenth g of Ib was added with stirring to an ethanolic potassium hydroxide solution obtained by dissolving 1.5 g of potassium hydroxide pellets (86% purity) in 200 ml of absolute ethanol, and the resulting mixture was heated under reflux for 1 hour. After cooling to room temperature, it was filtered to remove a small amount of a solid material. The filtrate was evaporated on a rotary evaporator under reduced pressure to dryness. The residue was dissolved in water (70 ml). Epichlorohydrin (2.0 g) was added to the aqueous solution and the resulting mixture was allowed to stir at room temperature overnight. The resinous precipitate that separated was collected by decanting the supernatant liquid and allowed to set at room temperature for several days to give a solid product. The crude product was recrystallized from ethyl acetate. The product weighed 2.0 g (27%) and melted at 143-145°; ms: (E.I.) *m/e* 371 ( $\text{M}^+$ ) and 270.

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{18}\text{ClNO}_4$ : C, 64.60; H, 4.88; N, 3.77. Found: C, 64.39; H, 4.99; N, 3.64.

1-[5-Chloro-2-[2-hydroxy-3-(1-methylethylamino)propoxy]phenyl]-2-ethoxy-4-(1*H*)quinolinone, Nitrate (VIIa).

A mixture of VIb (1.5 g), isopropylamine (5 ml) and ethanol (15 ml) was heated under reflux for 3.5 hours, then evaporated under reduced pressure to give a glossy resinous material. The residue was dissolved in ethyl acetate. To the solution was added dropwise nitric acid dissolved in chilled absolute ethanol whereupon a resinous material separated. The supernatant liquid was decanted and the resinous material was triturated with anhydrous ether twice. The residue was dissolved in a small amount of absolute ethanol and the solution was diluted with anhydrous ether until the solution become cloudy. Chilling the mixture in ice caused separation of an oily material. The supernatant liquid was decanted and the residue was triturated with anhydrous ether twice, causing solidification of the oil. The product (0.85 g, 42%) thus obtained melted at 115-118°.

*Anal.* Calcd. for  $\text{C}_{23}\text{H}_{27}\text{ClN}_2\text{O}_4 \cdot \text{HNO}_3 \cdot 3/4\text{H}_2\text{O}$ : C, 54.43; H, 5.86; N, 8.28. Found: C, 54.33; H, 5.59; N, 8.61.

1-(5-Chloro-2-hydroxyphenyl)-1,4-dihydro-4-oxo-2-quinolinecarbonitrile (X).

A mixture of powdered sodium cyanide (1.5 g) and dimethylsulfoxide (70 ml) was heated under nitrogen atmosphere to 80° in an oil bath. To this mixture was added Ib (6.1 g) with vigorous stirring. The temperature of the oil bath was then raised to 120°, and the stirring was continued for 30 minutes. The reaction mixture was poured into ice-water (20 ml). The resulting aqueous solution was neutralized in a hood with dilute hydrochloric acid to pH 5 and chilled. The precipitate that separated was collected on a filter and washed with water several times, giving X (7.5 g, 100%). Recrystallization from ethanol gave an analytical sample which contained one mole of ethanol, mp 223-225° dec; ir: 2222  $\text{cm}^{-1}$ ; uv: max  $\mu\epsilon$  ( $\epsilon$ ) 218.5 (36600), 238 (23000), 249 (25000), 288 (4600), 345 (13500) and 360 (11500).

*Anal.* Calcd. for  $\text{C}_{16}\text{H}_9\text{ClN}_2\text{O}_2 \cdot \text{C}_2\text{H}_5\text{OH}$ : C, 63.07; H, 4.41; N, 8.17. Found: C, 63.14; H, 4.28; N, 8.19.

1-(5-Chloro-2-hydroxyphenyl)-1,4-dihydro-4-oxo-2-quinolinecarboxylic Acid (XI).

A mixture of X•ethanolate (4.0 g), sodium hydroxide (2.0 g) and water (200 ml) was heated under reflux for 6 hours, cooled to room temperature, and acidified with dilute hydrochloric acid to cause separation of a precipitate. The mixture was chilled in ice and the precipitate was collected on a filter and washed with water several times. The product amounted to 3.5 g (94.5%) and melting at 187-189° with effervescence; ir: 2500  $\text{cm}^{-1}$  (broad), 1605  $\text{cm}^{-1}$  and 1429  $\text{cm}^{-1}$ ; uv: max  $\mu\epsilon$  ( $\epsilon$ ) 214 (29800), 230 (26500), 286 (5100), 315 (13000) and 325 (15200).

*Anal.* Calcd. for  $\text{C}_{16}\text{H}_{10}\text{ClNO}_4 \cdot 1/4\text{H}_2\text{O}$ : C, 60.01; H, 3.30; N, 4.37. Found: C, 59.72; H, 3.28; N, 4.76.

1-(5-Chloro-2-hydroxyphenyl)-1,4-dihydro-4-oxo-2-quinolinecarboxamide (XIV).

A mixture of X•ethanolate (1.5 g), sodium hydroxide (0.7 g) and water (70 ml) was heated under reflux for 1 hour, then neutralized with dilute hydrochloric acid to pH ca. 3. The precipitate that separated was collected on a filter and washed with water several times to give XIV (1.3 g, 90%), mp 192-195°. Purification by dissolution in water with addition of dilute aqueous sodium hydroxide solution, and precipitation by acidification with dilute hydrochloric acid afforded a sample, mp 192-194° dec; ir: 1692 cm<sup>-1</sup> and 1629 cm<sup>-1</sup>; uv: max mμ (ε) 214 (31600), 230 (27900), 283 (5300), 315 (14300) and 325 (16300).

*Anal.* Calcd. for C<sub>16</sub>H<sub>11</sub>ClN<sub>2</sub>O<sub>3</sub>•1/4H<sub>2</sub>O: C, 58.37; H, 3.52; N, 8.51. Found: C, 58.61; H, 3.64; N, 8.10.

2-Chloroquino[2,1-*c*][1,4]benzoxazine-6,8-dione (XII).

A mixture of XI (6.5 g) and acetic anhydride (100 ml) was heated under reflux for 2.5 hours, then evaporated on a rotary evaporator under reduced pressure. The residue was triturated with a small amount of ethanol and the solid which was collected on a filter was washed with ethanol, giving XII (3.4 g, 55%), mp 213-215°; ir: 1779 cm<sup>-1</sup> and 1645 cm<sup>-1</sup>; ms: (C.I.) m/e 298 (MH<sup>+</sup>).

*Anal.* Calcd. for C<sub>16</sub>H<sub>11</sub>ClNO<sub>3</sub>: C, 64.55; H, 2.71; N, 4.71. Found: C, 64.87; H, 2.57; N, 4.62.

1-(5-Chloro-2-hydroxyphenyl)-1,4-dihydro-*N*-(2-methoxyethyl)-4-oxo-2-quinolinecarboxamide (XV).

A mixture of XII (1.45 g) and 2-methoxyethylamine (25 ml) was heated under reflux for 1 hour, then the excess amine was removed on a rotary evaporator under reduced pressure to give a resinous material. The residue was dissolved in a small amount of ethanol and the solution was neutralized with concentrated hydrochloric acid, then chilled in ice. The precipitate that separated was collected on a filter, washed with ethanol and recrystallized from ethanol giving XV (1.0 g, 55%), mp 220-222.5°; ir: 1686 cm<sup>-1</sup> and 1626 cm<sup>-1</sup>.

*Anal.* Calcd. for C<sub>19</sub>H<sub>17</sub>ClN<sub>2</sub>O<sub>4</sub>: C, 61.21; H, 4.60; N, 7.52. Found: C, 61.44; H, 4.51; N, 7.52.

1-(5-Chloro-2-hydroxyphenyl)-2-(1*H*-tetrazoyl-5-yl)-4-(1*H*)quinolinone (XIII).

A mixture of X•ethanolate (3.4 g), sodium azide (0.72 g), ammonium chloroide (0.58 g) and dimethylformamide (30 ml) was heated in an oil bath maintaining the temperature of 125 ± 5° for 20 hours, then evaporated on a rotary evaporator under reduced pressure. The residue was dissolved in water with addition of a small amount of dilute aqueous sodium hydroxide solution and filtered. Acidification of the filtrate with dilute hydrochloric acid caused separation of a precipitate which was collected on a filter and washed with water several times, giving the product (3.4 g, 97%) in analytical purity, mp 258-260° dec; ir: 1661 cm<sup>-1</sup> and 1618 cm<sup>-1</sup>.

*Anal.* Calcd. for C<sub>16</sub>H<sub>10</sub>ClN<sub>4</sub>O<sub>2</sub>•3/4H<sub>2</sub>O: C, 54.40; H, 3.28; N, 19.83. Found: C, 54.53; H, 3.40; N, 19.91.

[1-(5-Chloro-2-hydroxyphenyl)-1,4-dihydro-4-oxo-2-quinolinyl]propanedioic Acid Diethyl Ester (XVI).

Sodium hydride (1.0 g of 50% oil dispersion) was washed with hexane 3 times and suspended in hexamethylphosphoramide (60 ml). Diethyl malonate (3.5 g) was added to the solution and the resulting mixture was stirred at room temperature for 20 minutes. 10-Chloro-5*H*benzoxazolo[3,2-*a*]quinolin-5-one (1b, 5.4 g) was added, and the reaction mixture was

stirred at room temperature for 3 hours, then heated in an oil bath maintaining the temperature of 110° for 1.5 hours. The reaction mixture was poured into ca. 250 ml of cold water, whereby a precipitate separated. The precipitate (unreacted starting material, 1.0 g) was removed by filtration. The filtrate was acidified with concentrated hydrochloric acid to pH ca. 3. The precipitate that separated was collected on a filter and washed with water repeatedly. The filter residue was dissolved in hot ethanol, and an insoluble residue was removed by filtration. The filtrate was evaporated on a rotary evaporator under reduced pressure to give a solid residue which was recrystallized from ethanol, giving XVI (1.0 g, 12%), mp 218-220° dec; ir: 1760 cm<sup>-1</sup>, 1739 cm<sup>-1</sup> and 1626 cm<sup>-1</sup>.

*Anal.* Calcd. for C<sub>22</sub>H<sub>16</sub>ClNO<sub>6</sub>: C, 61.47; H, 4.69; N, 3.26. Found: C, 61.51; H, 4.81; N, 3.35.

From the ethanol mother liquor of the XVI recrystallization was obtained a small amount of XVII which was identical to that prepared from XVI.

1-(5-Chloro-2-hydroxyphenyl)-1,4-dihydro-4-oxo-2-quinolinacetic Acid Ethyl Ester (XVII).

A mixture of XVI (0.4 g) and hexamethylphosphoramide (7 ml) was heated in an oil bath maintaining the temperature of 120° for 2.5 hours, then poured into 50 ml of cold water causing a separation of unfilterable fine particles. The mixture was allowed to set overnight. The supernatant liquid was decanted and the solid was collected on a filter, and recrystallized from ethanol, giving XVII (0.3 g, 94%), mp 124-127° dec; ir: 1730 cm<sup>-1</sup> and 1623 cm<sup>-1</sup>; ms: (E.I.) m/e 357, 311 and 270.

*Anal.* Calcd. for C<sub>19</sub>H<sub>16</sub>ClNO<sub>4</sub>: C, 63.78; H, 4.51; N, 3.92. Found: C, 63.59; H, 4.68; N, 4.24.

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