Synthesis of 2-Dialkylamino-6- and -7-hydroxy-5,8-dioxoquinolines[1a]

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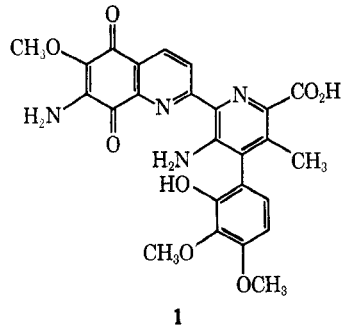
A synthetic route to 2-substituted 6- and -7-hydroxy-5,8-dioxoquinolines has been evaluated. Reaction of 5,7-dinitro-8-hydroxycarbostyril (**4**) with phosphorus oxychloride followed by reaction with piperidine or morpholine gave the 2-substituted 5,7-dinitro-8-quinolinols **5d** and **5e**. Catalytic hydrogenation, oxidation, and acid hydrolysis gave the corresponding 7-hydroxy-5,8-dioxoquinolines **9a** and **9b**. A similar sequence was used to proceed from 5-hydroxy-6,8-dinitrocarbostyril (**12**) *via* 2-chloro-6,8-dinitro-5-quinolinol (**13a**) and 2-piperidino-6,8-dinitro-5-quinolinol (**13b**) to 2-piperidino-6-hydroxy-5,8-dioxoquinoline (**14a**).

The potential importance of the antibiotic and antitumor agent streptonigrin (**1**) suggested an extension of our earlier study of the 6- and 7-hydroxy-5,8-dioxocarbostyrils[2] to preparation of 2-aminoquinolinequinones. Introduction of a secondary amine appeared relatively easy and could be expected to improve the solubility of such quinones. Even more desirable[3] would be elaboration of two isomeric quinolinequinones bearing 6-methoxy-7-amino or 6-amino-7-methoxy groups, but this objective, as noted in the sequel, was not realized.

In an extension of earlier work,[2] quinone **2** was readily brominated to give bromoquinone **3**. All attempts to



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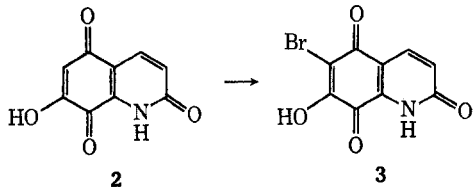
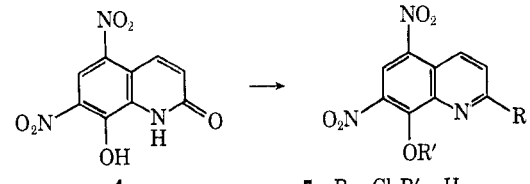


2 **3**

displace the bromo group with amines or azide ion were unsuccessful.[4] Attempts to form a methoxyquinone using either diazomethane or the Fischer esterification method were similarly unsuccessful with either quinone **2** or **3**. Also, once the quinone was elaborated, transformations at the 2 position became more difficult. Thus, modification of the 2 position at an earlier stage of the synthesis was undertaken.

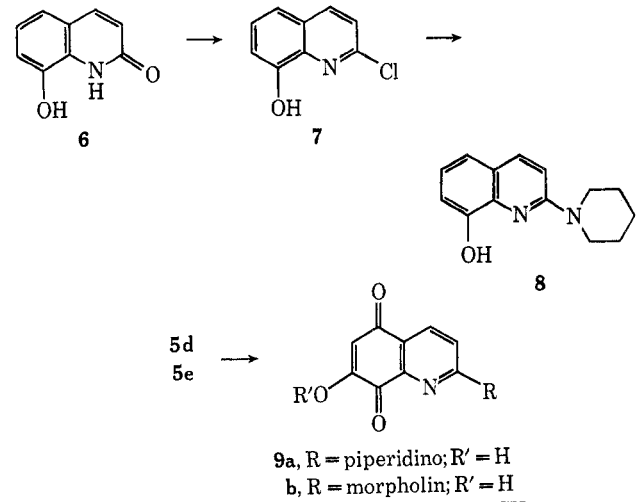
To provide a reactive group at the 2 position, 5,7-dinitro-8-hydroxycarbostyril (**4**) was treated with phosphorus oxychloride to afford the dinitrophenol **5a**. Reaction of phenol **5a** or the ammonium salt **5b** with excess piperidine under mild conditions led to the piperidine salt **5c**. After prolonged heating, amine **5d** was



4

5a, R = Cl; R′ = H
b, R = Cl; R′ = NH_4^+
c, R = Cl; R′ = piperidinium
d, R = piperidino; R′ = H
e, R = morpholino; R′ = H

was obtained. An alternate synthesis of amine **5d** was needed[5] to confirm the structure. Thus, 8-hydroxycarbostyril (**6**) was heated with phosphorus oxychloride to yield 2-chloro-8-quinolinol (**7**). Nitration led to quinoline **5b**, while heating **7** with piperidine (→**8**) followed by nitration led to amine **5d**. This route to amine **5d** proved less convenient experimentally.



6 **7** **8**

9a, R = piperidino; R′ = H
b, R = morpholin; R′ = H
c, R = piperidino; R′ = CH_3
d, R = morpholino; R′ = CH_3

Conversion of quinoline **5d** to quinone **9a** required considerable experimentation. Although we had isolated several amine derivatives of the nitro group precursor in the case of 7-hydroxy-5,8-dioxocarbostyril (**2**),[2] the corresponding intermediate from reduction of

(1) (a) This study received support from the U. S. Medical R and D Command under Contract DA-49-143-MD-3010 and National Science Foundation Grant GB-4939. The present manuscript is Contribution No. 930 from the Army Research Program on Malaria. (b) National Science Foundation Predoctoral Fellow, 1965–1968.

(2) G. R. Pettit, W. C. Fleming, and K. D. Paull, *J. Org. Chem.*, **33**, 1089 (1968).

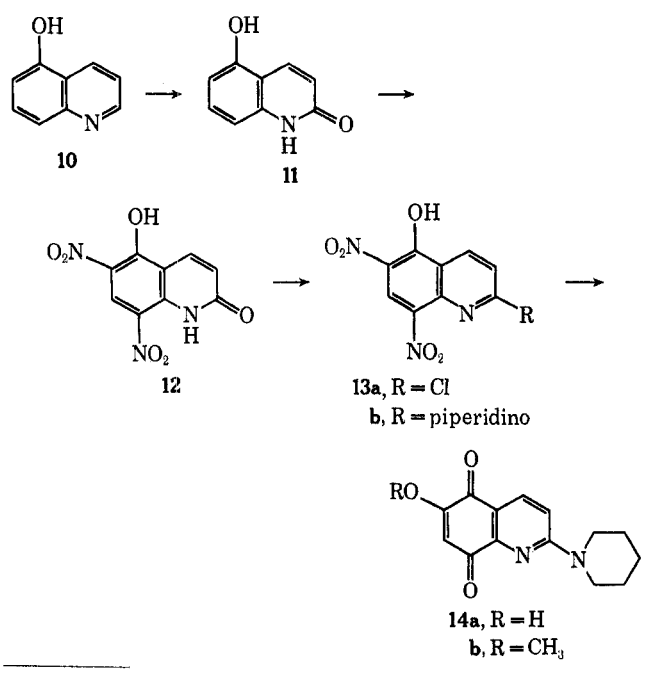
(3) For comments on the possible importance of the aminoquinone structure, see K. V. Rao, K. Bieman, and R. B. Woodward, *J. Amer. Chem. Soc.*, **85**, 2532 (1963).

(4) For an excellent example of the use of bromination to further substitute quinones, see T. K. Liao, W. H. Nyberg, and C. C. Cheng, *Angew. Chem., Int. Ed. Engl.*, **6**, 82 (1967).

(5) The conversion of 6,8-dinitro-5-quinolinol to 5-chloro-6,8-dinitroquinoline by phosphorus oxychloride–phosphorus pentachloride mixtures has been reported: G. M. Bennett and J. F. Grove, *J. Chem. Soc.*, 378 (1945).

nitroquinoline **5d** could not be isolated.[6] Instead, the overall conversion was more readily effected without isolation of intermediates. After catalytic reduction of dinitroquinoline **5d** in dilute acid, the solution was made basic. Oxygen was passed into the solution and a green color formed. Acidification yielded a purple solution which, upon continuous extraction with chloroform, led to a red extract containing quinone **9a**. Heat provided by the refluxing chloroform proved adequate to effect hydrolysis of the aminoquinone intermediate.[7] When morpholine was used in place of piperidine, the sequence proceeded as expected to give 2-(*N*-morpholino)-7-hydroxy-5,8-dioxoquinoline (**9b**).

Quinones **9a** and **9b** were readily methylated to provide ethers **9c** and **9d** using methanol and a trace of sulfuric acid.[8] Unfortunately, attempts to usefully brominate quinones **9a–d** were unsuccessful. Meanwhile, the general reaction sequence used to convert 8-quinolinol to 2-piperidino-7-methoxy-5,8-dioxoquinoline (**9c**) was applied to 5-quinolinol. With one exception, the synthesis proceeded essentially as expected to yield 2-piperidino-6-methoxy-5,8-dioxoquinoline (**14b**). We were unable to form the *N*-oxide of 5-quinolinol as required for a three-step conversion *via* rearrangement in acetic anhydride and hydrolysis to yield 5-hydroxycarbostyril (**11**). Fortunately, fusion of 5-quinolinol with potassium hydroxide gave excellent yields of carbostyril **11**.[9] In contrast to the much milder conditions required to obtain **4**, nitration of 5-hydroxycarbostyril required a mixture of nitric and sulfuric acids to obtain dinitroquinoline **12**.[10] Reaction with phosphorus oxychloride followed by prolonged heating with piperidine gave dinitroquinoline **13b**. After reduction of the nitro groups, conversion of amine **13b** to quinone **14a** required an oxidation step under acidic conditions. Under basic conditions a precipitate formed which apparently resisted oxidation. Oxidation and hydrolysis in hot dilute sulfuric acid gave quinone **14a**. Treatment of the hydroxyquinone **14a** with methanol and a trace of sulfuric acid gave methoxyquinone **14b**. The synthesis developed for obtaining 2-aminoquinolinequinones **9** and **14** appears to present a generally useful route to such substances. When an effective method becomes available for preparation of the corresponding 6- and 7-amine derivatives a more important assessment of streptonigrin structure–activity relationships will be possible. In keeping with this prospect none of the compounds described here and so far tested proved to be active in either antimalarial or antitumor screening.[11]



Experimental Section

Solvent extracts of aqueous solutions were dried over anhydrous sodium sulfate. All analytical samples exhibited a single spot on a thin layer chromatogram. Melting points were observed employing a Kofler melting point apparatus. Infrared (in potassium bromide using a Beckman IR-12 instrument), and proton magnetic resonance (Varian Associates, A-60 spectrometer, trifluoroacetic acid as solvent except where noted) measurements were performed by Miss K. Reimer. Chemical shifts (δ) are in parts per million relative to tetramethylsilane as external standard. Elemental microanalyses were provided by Dr. A. Bernhardt, Mikroanalytisches Laboratorium, 5251 Elbach über Engelskirchen, West Germany.

6-Bromo-7-hydroxy-5,8-dioxocarbostyril (3).—A sample of 7-hydroxy-5,8-dioxocarbostyril (0.25 g) was suspended in methanol (30 ml), and bromine (1.0 ml) was added slowly to the well-stirred solution. The solid rapidly dissolved. After stirring for 2 hr solvent was removed *in vacuo* leaving a red oil. Ethyl acetate (50 ml) was added, and the solvent was again evaporated. The dark solid which remained was dissolved in hot ethyl acetate–methanol and diluted (after filtration) with Skellysolve B until a cloudiness appeared. On cooling a red solid separated (0.19 g, 56%) which decomposed with partial melting above 270°. Another recrystallization by the above procedure gave an analytical sample as a red powder decomposing above 270°: ν_{max} 1685, 1656, 1630, 1602, 1424, 1360, 1297, 1196, 1052, and 697 cm^{-1}; pmr δ 6.70 (d, 1 H, J = 9 Hz) and 8.00 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_9H_4BrNO_4$: C, 40.04; H, 1.48; Br, 29.59; N, 5.18. Found: C, 39.92, 39.98; H, 1.74, 1.86; Br, 29.73; N, 5.26.

2-Chloro-5,7-dinitro-8-hydroxyquinoline Ammonium Salt (5b). Method A.—A mixture of 5,7-dinitro-8-hydroxycarbostyril (1.0 g, **6a**) and phosphorus oxychloride (10 ml) was heated (steam bath) for 2 hr. The solution was poured carefully onto ice (100 g) and concentrated ammonium hydroxide (50 ml) and the solid which formed was collected, yield 1.0 g (88%) of yellow powder melting at 230–237°. Two sublimations gave a pure specimen melting at 233–236°: ν_{max} 1590, 1565, 1518, 1396, 1320, 1270, and 755 cm^{-1}; pmr δ 5.50 (t, 3 H, J = 55 cps), 6.85 (d, 1 H, J = 9 Hz), 8.13 (s, 1 H), and 8.25 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_9H_7ClN_4O_5$: C, 37.71; H, 2.46; Cl, 12.37; N, 19.55. Found: C, 37.82; H, 2.25; Cl, 12.65; N, 19.68.

Method B.—A finely powdered sample of 2-chloro-8-hydroxyquinoline (0.2 g) was suspended in water (25 ml)–concentrated nitric acid (25 ml). The quinoline dissolved; a yellow precipitate formed and then dissolved. The solution was heated on a steam bath for 10 min, cooled, and made basic with concentrated ammonium hydroxide. A greenish yellow solid separated, which was collected and recrystallized from methanol–water to give a yellow powder melting at 240–245°. Sublimation gave a yellow powder melting at 233–236°. The infrared spectrum was identical with that of salt **5b** prepared by method A.

2-Chloro-5,7-dinitro-8-hydroxyquinoline (5a).—A sample of 2-chloro-5,7-dinitro-8-hydroxyquinoline ammonium salt (1.0 g) was recrystallized from ethanol–water containing 6 *N* hydrochloric acid (5 ml). On cooling, 0.84 g (89%) of yellow solid melting at 140–145° separated. Three recrystallizations from

(6) An exception was the isolation of 2-chloro-5,7-diacetamido-8-quinolinol after reductive acetylation of **5a**. No method could be found to convert **5a** to a quinone.

(7) Y. T. Pratt and N. L. Drake, *J. Amer. Chem. Soc.*, **79**, 5024 (1957).

(8) Y. T. Pratt and N. L. Drake, *ibid.*, **77**, 37 (1955).

(9) E. Lellman, *Ber.*, **20**, 2172 (1887).

(10) For an alternate synthesis of **12**, see J. N. Ashley, W. H. Perkins, and R. Robinson, *J. Chem. Soc.*, 382 (1930).

(11) Screening was performed under auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, and the U. S. Medical R and D Command.

ethanol–water gave the analytical sample as a yellow powder melting at 143–145°: ν_{max} 1588, 1526, 1413, 1360, 1322, 1260, 1100, 961, and 746 cm^{-1}; pmr δ 6.85 (d, 1 H, J = 9 Hz), 8.13 (s, 1 H), and 8.25 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_9H_4ClN_3O_5$: C, 40.09; H, 1.50; Cl, 13.15; N, 15.59. Found: C, 40.14; H, 1.65; Cl, 13.07; N, 15.42.

2-Chloro-5,7-dinitro-8-hydroxyquinoline Piperidinium Salt (5c).—A mixture of 5,7-dinitro-8-hydroxycarbostyril (**6a**, 0.5 g) and phosphorus oxychloride (10 ml) was heated (steam bath) for 1 hr. Excess phosphorus oxychloride was removed *in vacuo*, and piperidine (5 ml) in tetrahydrofuran (25 ml) was cautiously added, followed by water (100 ml). Cooling led to 0.5 g (81%) of yellow crystals melting at 205–210°. Three recrystallizations from ethanol–water gave an analytical sample as tiny yellow needles melting at 211–213°: ν_{max} 1612, 1579, 1504, 1400, 1306, and 1274 cm^{-1}; pmr δ 1.30–1.55 (broad m, 4 H), 7.55 (d, 1 H, J = 9 Hz), 8.90 (s, 1 H), and 8.95 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_{14}H_{15}ClN_4O_5$: C, 47.40; H, 4.26; Cl, 9.99; N, 15.79. Found: C, 47.75; H, 4.13; Cl, 9.83; N, 15.82, 15.72.

2-(N-Piperidino)-5,7-dinitro-8-hydroxyquinoline (5d). Method A.—A mixture of 5,7-dinitro-8-hydroxycarbostyril (1.0 g) and phosphorus oxychloride (10 ml) was heated at steam bath temperature for 1 hr. Excess phosphorus oxychloride was removed *in vacuo*. Tetrahydrofuran (20 ml) and piperidine (30 ml) in water (100 ml) were added. The solution was heated at reflux for 36 hr, tetrahydrofuran was distilled, and the mixture was acidified with concentrated hydrochloric acid. After cooling, the crude product (melting at 260–265°) separated and one recrystallization from tetrahydrofuran–water gave 1.03 g (81%) of yellow needles melting at 263–265°. Three recrystallizations from the same solvent afforded an analytical sample: yellow needles; mp 263–265°; ν_{max} 3215, 2960, 1650, 1610, 1528, 1330, 1273, 1242, 1174, and 751 cm^{-1}; pmr δ 0.95–1.25 (broad m, 6 H), 2.95–3.30 (broad m, 4 H), 6.95 (d, 1 H, J = 10 Hz), 7.75 (s, 1 H), and 7.88 (d, 1 H, J = 10 Hz).

Anal. Calcd for $C_{14}H_{14}N_4O_5$: C, 52.83; H, 4.43; N, 17.60. Found: C, 52.91; H, 4.52; N, 17.30.

Method B.—A sample of 2-piperidino-8-hydroxyquinoline (0.2 g) was suspended in water (25 ml). Concentrated nitric acid (25 ml) was added slowly and the resulting solution was allowed to stand for 15 min. After concentrated ammonium hydroxide was added, the precipitate which formed was collected and recrystallized twice from tetrahydrofuran–water to give a yellow powder melting at 260–265°. The product was identical by infrared spectral comparison with quinoline **5d** prepared by method A.

2-Chloro-8-hydroxyquinoline (7).—A mixture of 8-hydroxycarbostyril (2.0 g) and phosphorus oxychloride (10 ml) was heated on a steam bath for 1 hr. The resulting solution was poured slowly onto ice (100 g) and concentrated ammonium hydroxide (50 ml). A white solid formed and was removed by filtration. The solid melted at 270–280° and proved nearly insoluble in a variety of organic solvents, but dissolved readily in concentrated hydrochloric acid (100 ml). After heating for 1 hr at steam-bath temperature, the acid solution was cooled and made basic with concentrated ammonium hydroxide. A white precipitate formed and was collected, yield 1.44 g (67%) of solid melting at 80–83°. Three recrystallizations from methanol–water gave a pure sample of colorless needles melting at 82–83° (lit.[12,13] mp 63–64°): ν_{max} 1575, 1502, 1464, 1374, 1365, 1318, 1241, 1206, 1123, 1085, 832, 750, and 718 cm^{-1}; pmr δ 6.30–6.75 (broad m, 3 H), 6.80 (d, 1 H, J = 9 Hz),[14] and 7.80 (d, 1 H, J = 9 Hz).

Anal. Calcd for C_9H_6ClNO: C, 60.19; H, 3.34; Cl, 19.77; N, 7.80. Found: C, 60.33; H, 3.43; Cl, 19.77; N, 8.00.

2-(N-Piperidino)-8-hydroxyquinoline (8).—A solution composed of 2-chloro-8-hydroxyquinoline (0.5 g), piperidine (10 ml), and dioxane (100 ml) was heated at reflux for 48 hr. Although thin layer chromatography (chloroform mobile phase) indicated only starting material, colorless crystals were observed separating from solution. Most of the solvent was evaporated *in vacuo* and water (100 ml) was added. The resulting solution was extracted with chloroform (two 50-ml portions) and the extract was washed with 6 N hydrochloric acid (two 30-ml portions). The acid solution was treated with Norit-A, filtered, and made basic with concentrated ammonium hydroxide and, on cooling, an oil slowly separated. The aqueous solution was carefully decanted and the oil was crystallized from methanol–water to give an oily, dark solid. A second recrystallization gave 0.29 g (46%) of tan crystals melting at 68–70°. Two more recrystallizations from methanol–water gave an analytical sample as clear plates melting at 71–73°: ν_{max} 3350, 2940, 2860, 1640, 1615, 1575, 1523, 1482, 1450, 1422, 1336, 1282, 1260, 1242, 1131, 828, 749, 742, and 572 cm^{-1}; pmr δ 1.30–1.60 (m, 6 H), 3.30–3.60 (m, 4 H), 6.82 (partially obscured d, 1 H, J = 9 Hz), 6.95 (narrow m, 3 H), and 7.83 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.50; H, 7.19; N, 12.24.

2-(N-Morpholino)-5,7-dinitro-8-hydroxyquinoline (5e).—A mixture of 5,7-dinitro-8-hydroxycarbostyril (1.0 g) and phosphorus oxychloride (10 ml) was heated (steam bath) for 1 hr. Excess phosphorus oxychloride was removed *in vacuo*. The residue was diluted with dioxane (50 ml) and cooled, and a solution of morpholine (20 ml) in water (100 ml) was added. The solution was heated at reflux for 36 hr, cooled, and acidified with concentrated hydrochloric acid. The solid which separated was collected, yield 1.13 g (79%) of yellow powder melting at 274–277°. Three recrystallizations from tetrahydrofuran–water gave a pure sample as tiny yellow needles melting at 280–283°: ν_{max} 1610, 1577, 1523, 1436, 1360, 1310, 1270, 1110, 1013, 918, 811, and 735 cm^{-1}; pmr δ 3.70 (apparent singlet, 8 H), 7.35 (d, 1 H, J = 10 Hz), 8.65 (s, 1 H), and 8.85 (d, 1 H, J = 10 Hz).

Anal. Calcd for $C_{13}H_{12}N_4O_6$: C, 48.75; H, 3.78; N, 17.50. Found: C, 49.18; H, 3.99; N, 17.08.

2-(N-Piperidino)-7-methoxy-5,8-dioxoquinoline (9c).—A mixture of 2-(N-piperidino)-5,7-dinitro-8-hydroxyquinoline (0.3 g), water (100 ml), 6 N hydrochloric acid (5 ml), and 10% palladium-on-carbon catalyst (0.03 g) was stirred under a slightly positive pressure of hydrogen for 18 hr. The solution was filtered and made slightly basic with sodium bicarbonate, and oxygen was bubbled slowly through the solution for 20 min. A dark green color formed, which changed to purple on addition of concentrated sulfuric acid (10 ml). The solution was placed in an insulated continuous extraction apparatus and extracted with chloroform for 5 hr. The deep red chloroform solution was replaced with a fresh portion of chloroform, and the mixture was extracted for an additional 18 hr. Extraction of the combined chloroform extract with saturated sodium bicarbonate solution (two 40-ml portions) gave a blue-green extract. The basic extract was acidified with 6 N hydrochloric acid and extracted with ethyl ether (125 ml) to give a bright orange solution, which was concentrated to a red solid.[15] A solution of the latter material in ether (20 ml) was filtered, cyclohexane (20 ml) was added, and the solution was concentrated until a precipitate started to form. After cooling, the dark solid which separated was recrystallized twice from ether–hexane to give a sample suitable for spectral data, but satisfactory elemental analyses were not obtained. Such specimens decomposed above 200° without melting, and appeared to decompose slowly to a colorless powder when heated in solvents. The quinone exhibited ν_{max} 3420, 3260 (broad), 1694, 1655, 1630, 1599, 1503, 1383, and 1199 cm^{-1}; pmr δ 1.35–1.65 (broad m, 6 H), 3.35–3.65 (broad m, 4 H), 6.12 (s, 1 H), 7.20 (d, 1 H, J = 10 Hz), and 8.03 (d, 1 H, J = 10 Hz).

A sample of crude 2-(N-piperidino)-7-hydroxy-5,8-dioxoquinoline prepared from 0.3 g of 2-(N-piperidino)-5,7-dinitro-8-hydroxyquinoline was dissolved in methanol (50 ml). Concentrated sulfuric acid (3 drops) was added, and the solution was heated at reflux for 1 hr. The solution was concentrated to about 20 ml, diluted with water (180 ml), and extracted with ethyl ether (two 75-ml portions). The ether solution was washed (two 50-ml portions) with saturated sodium bicarbonate solution and concentrated to give 0.14 g (55% overall from nitro quinoline **5d**) of a red powder melting at 150–170°. Two recrystallizations from ether–cyclohexane gave an analytical sample as tiny red needles melting at 178–180°: ν_{max} 2930, 1705, 1652, 1627, 1591, 1514, 1424, 1244, 1056, 972, and 825 cm^{-1}; pmr ($CDCl_3$) δ 1.55–1.85 (broad m, 6 H), 3.55–3.85 (broad m,

(12) M. Hamana and K. Funakoshi, *Yakugaku Zasshi*, **84**, 28 (1964); *Chem. Abstr.*, **61**, 3068*f* (1964).

(13) This compound is mentioned without details in U. S. Patent 2,524,725 (1950); *Chem. Abstr.*, **45**, 3272*f* (1951).

(14) The assignment must be considered tentative, since the doublet is partially obscured by the broad multiplet.

(15) The product obtained at this stage was suitable for conversion to the more stable 2-piperidino-7-methoxy-5,8-dioxoquinoline.

4 H), 3.90 (s, 3 H), 6.05 (s, 1 H), 6.85 (d, 1 H, J = 9 Hz), and 8.05 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.16, 66.27; H, 5.89, 5.92; N, 10.82.

2-(*N*-Morpholino)-7-methoxy-5,8-dioxoquinoline (9d).—A mixture of 2-(*N*-morpholino)-5,7-dinitro-8-hydroxyquinoline (0.3 g), water (50 ml), 6 *N* hydrochloric acid (5 ml), and palladium-on-carbon catalyst (0.03 g) was stirred under slightly positive pressure of hydrogen for 12 hr. The product was treated and isolated by the continuous extraction procedure summarized for obtaining quinone **9a**. The ethyl acetate (150 ml) extract was concentrated to a red powder decomposing with partial melting above 200°.[16] Two recrystallizations from tetrahydrofuran–cyclohexane gave a red powder decomposing at 200–210° with partial melting. This material did not give satisfactory elemental analyses, but spectral data were in good agreement with the assigned structure: ν_{max} 1701, 1654, 1595, 1505, 1327, 1255, 1115, and 945 cm^{-1}; pmr δ 3.70 (apparent singlet, 8 H), 6.12 (s, 1 H), 7.30 (d, 1 H, J = 10 Hz), and 8.15 (d, 1 H, J = 10 Hz).

A crude sample of 2-(*N*-morpholino)-7-hydroxy-5,8-dioxoquinoline (prepared from 0.3 g of 2-morpholino-5,7-nitro-8-hydroxyquinoline) was dissolved in methanol (50 ml) and treated with concentrated sulfuric acid (2 drops) as described for the preparation of methyl ether **9c**. In this case ethyl acetate was employed for extraction. Concentration of the ethyl acetate led to 0.14 g (54% overall from 2-morpholino-5,7-dinitro-8-hydroxyquinoline) of red powder melting at 245–255°.

Two recrystallizations from methanol–ethyl acetate–cyclohexane gave a pure sample as tiny orange needles melting at 262–264°: ν_{max} 1702, 1643, 1620, 1591, 1506, 1415, 1262, 1241, 1116, 1056, 977, and 821 cm^{-1}; pmr ($CDCl_3$) δ 3.80 (apparent singlet, 8 H), 3.90 (s, 3 H), 6.05 (s, 1 H), 6.85 (d, 1 H, J = 9 Hz), and 8.15 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.40; H, 5.21; N, 10.04.

5-Hydroxycarbostyril (11).—A mixture of 5-hydroxyquinoline (3.0 g) and potassium hydroxide (20 g) was placed in a 50-ml stainless steel beaker and heated at 300°. The frothing black mixture was heated for 3 hr, when a clear black solution was obtained. The solution was cooled and dissolved in water (150 ml), and excess concentrated hydrochloric acid was added to give 2.70 g (81%) of tan powder melting at 300–340°. Three recrystallizations from methanol–water gave an analytical sample as straw-colored needles melting at 336–341° (lit.[10] mp 320° dec): ν_{max} 1651 (broad), 1620 (broad), 1553, 1436, 1360, 1289, 1257, 1143, and 792 cm^{-1}; pmr δ 6.30–7.30 (complex multiplet, 4 H), and 8.40 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_9H_7NO_2$: C, 67.08; H, 4.38; N, 8.69. Found: C, 66.88; H, 4.54; N, 8.62.

5-Hydroxy-6,8-dinitrocarbostyril (12).—A sample of 5-hydroxycarbostyril (1.0 g) was dissolved in concentrated sulfuric acid (10 ml). Then concentrated nitric acid (10 ml) was added slowly with cooling (ice bath). The resulting solution was maintained at 45° for 10 min. After cooling, the solution was poured slowly onto ice (150 g), and the yellow powder which separated was collected to give 1.4 g (89%) melting at 230–270°. Three recrystallizations from methanol–water gave a pure sample as yellow needles melting at 268–271° (transition from needles to cubes with partial melting between 240 and 250°, lit.[11] mp 260°): ν_{max} 3270, 1687, 1631, 1602, 1460, 1312, 1141, 1102, 1001, and 812 cm^{-1}; pmr δ 6.75 (d, 1 H, J = 10 Hz), 8.15 (d, 1 H, J = 10 Hz), and 9.05 (s, 1 H).

Anal. Calcd for $C_9H_5N_3O_6$: C, 43.04; H, 2.01; N, 16.73. Found: C, 43.06; H, 2.41; N, 16.85.

2-(*N*-Piperidino)-6,8-dinitro-5-hydroxyquinoline (13b).—A mixture of 5-hydroxy-6,8-dinitrocarbostyril (10 ml) was heated (steam bath) with phosphorus oxychloride (10 ml) for 1 hr. The solution was poured onto ice (200 g) with constant shaking, and the yellow solid which separated was collected to give 0.42 g (78%), mp 115–120°. Three recrystallizations from acetone–water gave the chloro derivative (presumed to be **13a**)[17] as yellow needles melting at 138–140°: ν_{max} 1598, 1545 (broad), 1350, 1292, 1120, and 791 cm^{-1}; pmr (acetone) δ 7.25 (d, 1 H, J = 9 Hz), 8.30 (s, 1 H), and 8.35 (d, 1 H, J = 9 Hz).

A solution of the product (**13a**, 0.3 g) in water (100 ml)–dioxane (20 ml)–piperidine (10 ml) was heated (reflux) for 24 hr. The dark solution was cooled, acidified with concentrated hydrochloric acid, and extracted (six 50-ml portions) with ethyl acetate.[18] Evaporation of solvent left a yellow oil which soon crystallized. The solid was triturated with hot acetone (20 ml) and water (40 ml). After cooling, the yellow residue was collected to yield 0.17 g (48%) of yellow crystals melting at 215–220°. Three recrystallizations from acetone–water gave a pure sample as yellow needles melting at 223–225°: ν_{max} 1620 (broad), 1535, 1394, 1343, 1269, 1227, 1186, and 788 cm^{-1}; pmr δ 1.45–1.65 (m, 6 H), 3.43–3.75 (m, 4 H), 7.10 (d,[19] 1 H, J = 10 Hz), 8.35 (d, 1 H, J = 10 Hz), and 9.05 (s, 1 H).

Anal. Calcd for $C_{14}H_{14}N_4O_5$: C, 52.83; H, 4.43; N, 17.60. Found: C, 53.16; H, 4.25; N, 17.86.

2-(*N*-Piperidino)-6-hydroxy-5,8-dioxoquinoline (14a).—A sample of 2-(*N*-piperidino)-6,8-dinitro-5-hydroxyquinoline (0.2 g) was suspended in water (100 ml) containing 6 *N* hydrochloric acid (5 ml) and 10% palladium-on-carbon catalyst (0.02 g). After stirring under a slightly positive pressure of hydrogen for 18 hr and filtering, the solution was adjusted to pH 2.0 with sodium bicarbonate. Oxygen was bubbled through the solution for 15 min, and the solution was made basic with sodium bicarbonate, oxygenated for an additional 15 min, and acidified with concentrated sulfuric acid (10 ml). The thick green precipitate dissolved to give a very dark solution which was heated at reflux for 25 min, cooled, and partially neutralized with concentrated ammonium hydroxide. Extraction with ethyl acetate (three 75-ml portions) gave a deep red solution which was in turn extracted with 50 ml of saturated sodium bicarbonate solution. The intense red bicarbonate solution was acidified with 6 *N* hydrochloric acid and extracted with ethyl acetate (three 50-ml portions). Evaporation of the ethyl acetate left 0.11 g (68%) of red power melting at 200–205°. Two recrystallizations from tetrahydrofuran–cyclohexane gave the analytical sample as tiny dark red needles melting at 205–208°: ν_{max} 3330, 1665, 1637, 1585 (broad), 1505, 1393, 1313, 1250, 1190, 1090, 1026, 952, 801, and 765 cm^{-1}; pmr ($CDCl_3$) δ 1.55–1.85 (broad m, 6 H), 3.25–3.95 (broad m, 4 H), 6.20 (s, 1 H), 6.75 (d, 1 H, J = 9 Hz), and 8.05 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.06; H, 5.46; N, 10.84. Found: C, 65.06; H, 5.39; H, 10.70.

2-(*N*-Piperidino)-6-methoxy-5,8-dioxoquinoline (14b).—To a solution of 2-(*N*-piperidino)-6-hydroxy-5,8-dioxoquinoline (0.10 g) in methanol (50 ml) was added 1 drop of concentrated sulfuric acid. The solution was heated at reflux for 1 hr, concentrated to about 10 ml, diluted with water (100 ml), and extracted with ethyl acetate (three 50-ml portions). The organic extract was washed with saturated sodium bicarbonate solution and evaporated to yield 0.09 g (95%) of red needles melting at 205–208°. Two recrystallizations from tetrahydrofuran–cyclohexane gave a pure specimen as shiny red needles melting at 207–209°: ν_{max} 2930, 1671, 1590 (broad), 1505, 1421, 1294, 1243, 1099, 848, and 799 cm^{-1}; pmr ($CDCl_3$) δ 1.60–1.80 (broad m, 6 H), 3.70–3.95 (broad m, 4 H), 3.90 (s, 3 H), 6.10 (s, 1 H), 6.80 (d, 1 H, J = 9 Hz).

Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 65.91; H, 5.90; N, 9.83.

Registry No.—**3**, 31568-85-1; **5a**, 31568-86-2; **5b**, 31568-87-3; **5c**, 31568-88-4; **5d**, 31568-89-5; **5e**, 31568-90-8; **7**, 31568-91-9; **8**, 31570-94-2; **9c**, 31570-95-3; **9d**, 31570-96-4; **11**, 31570-97-5; **12**, 31570-98-6; **13a**, 31570-99-7; **13b**, 31571-00-3; **14a**, 31571-01-4; **14b**, 31571-02-5.

(16) This material is suitable for conversion to 2-morpholino-7-methoxy-5,8-dioxoquinoline.

(17) Satisfactory combustion analyses were not obtained for this compound.

(18) The emulsion formed at this point may be eliminated by adding a few milliliters of tetrahydrofuran.

(19) This doublet showed considerable secondary splitting, but the doublet at δ 8.35 was quite sharp. The corresponding doublet in 2-(*N*-piperidino)-5,7-dinitro-8-hydroxyquinoline showed very faint splitting.