Streptonigrin and Related Compounds IV. Precursors for the A-Ring

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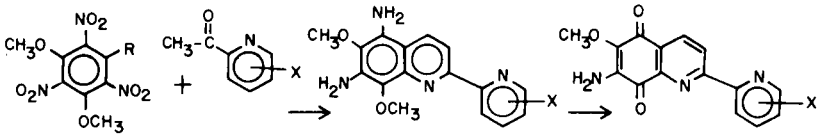
The synthesis of streptonigrin or its tricyclic (ABC) analogues by the Friedlander condensation requires a 2-nitrobenzaldehyde with all the necessary functionalities. A number of alternative syntheses are examined. It is shown that oxidation of 8-amino-5,6-dimethoxy-2,2-pyridylquinoline leads to 8-amino-2,2-pyridylqunoline-5,6-dione instead of 6-methoxy-2,2-pyridylquinoline-5,8-dione. The synthesis of two useful precursors: 4-bromo-3-hydroxy-5,6-dimethoxy-2-nitrobenzaldehyde and 4-bromo-3-hydroxy-5-methoxy-2-nitrobenzaldehyde is described.

J. Heterocyclic Chem., **16**, 1241 (1979).

In part III the synthesis of some tricyclic analogues of streptonigrin, which retain the typical substitution pattern of rings A, B and C (1), was described. The synthesis consisted of two stages: a) construction of the 2,2-pyridylquinoline skeleton, and b) generation of the 7-amino-6-methoxyquinoline-5,8-dione system. Because of the low reactivity of the 7-position of quinoline-5,8-dione, the introduction of the 7-amino function requires an indirect approach such as through halogenation, azidation and reduction. The conditions for the halogenation are such that substitution of either the C or D rings, which may carry nucleophilic substituents, becomes an important problem. It is therefore obvious that the use of an aldehyde component in the Friedlander condensation which contains the appropriate substituent at this position can greatly facilitate this step. This is also an important pracitcal necessity because the ketone components which serve as the C ring or C-D ring precursors are generally available only through multistep syntheses (2,3), and minimizing the number of steps after the condensation is desirable. In this paper, a number of alternatives to the 3-hydroxy-5-methoxybenzaldehyde used in the earlier synthesis are examined and two new potentially more practical routes are described.

Essentially, the problem involves the synthesis of a 2-nitrobenzaldehyde with a 5-methoxyl group, a substituent (or substituents) at the 3- and/or 6-positions which can generate the quinone system and a substituent in the 4-position which can facilitate the eventual conversion to the 7-amino-5,8-dione system. These criteria require not only the preparation of a tetra or a penta substituted benzaldehyde with a preordered substitution pattern, but also one that is reactive enough and leads to unambiguous products. As an example of the problem of reactivity, one of the compounds considered early in the program was the aldehyde **1** which will be expected to form the quinoline **2** through condensation with a suitably substituted 2-acetylpyridine. Oxidation of **2** can directly lead to 7-amino-6-methoxyquinoline-5,8-dione **3**. The Friedlander condensation can proceed in either direction to lead to the same product **2**.

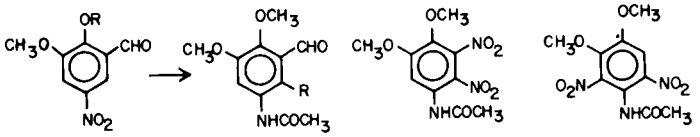
Nitration of orcinol followed by methylation readily gave the necessary precursor **4** for the preparation of **1**. However, many attempts to convert **4** to **1** either directly or indirectly, failed. In most cases, the only product was that resulting from partial demethylation; this approach was therefore abandoned.



1, R = CHO
4, R = CH_3

2

3



6, R = H
7, R = CH_3

5, R = NO_2
9, R = NH_2

8

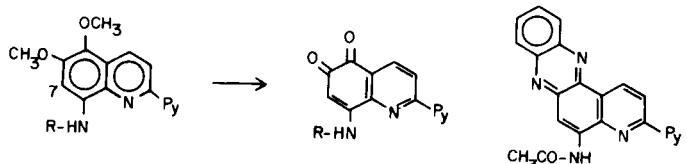
8a

0022-152X/79/061241-08$02.25

As an alternative, the aldehyde **5** was prepared from 2-hydroxy-3-methoxy-benzaldehyde *via* **6** (4) and **7**, essentially in three composite steps with an overall yield of 68%.

The position of the nitro group was ascertained from its ability to form a quinoline. Attempts to brominate **5** were not successful. Nitration of **5** with nitronium tetrafluoroborate gave a nitro derivative **8**, $C_{10}H_{11}N_3O_7$, m/e 285, which, however, no longer possessed the aldehyde function. This product was different from **8a**, prepared by the nitration of 3,4-dimethoxyacetanilide.

Condensation of the amino aldehyde **9** with 2-acetylpyridine directly gave the 2,2-pyridylquinoline **10**, $C_{18}H_{17}N_3O_3$, in 60% yield. Nitration of **10** with nitric acid gave an orange crystalline solid, $C_{16}H_{11}N_3O_3$, in 90% yield. Its nmr spectrum showed that the 7-position was still free but the methoxyl signals were absent. The structure **11** was proposed for this compound. The presence of an *ortho*-quinone function was confirmed by reaction with *o*-phenylenediamine, which formed **12**. Hydrolysis of **11** gave the aminoquinone **13**.



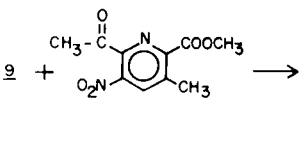
10 , R = CH_3CO

11 , R = CH_3CO

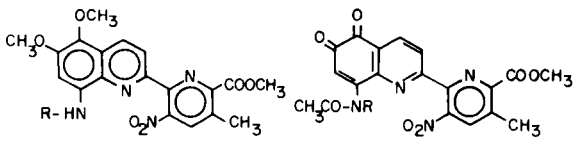
13 , R = H

12

Condensation of **9** with 6-carbomethoxy-5-methyl-3-nitro-2-acetylpyridine (**14**) (2) gave the 2,2-pyridylquinoline **15** in 60% yield. This product has the nitro group in ring C which protects this ring from possible future halogenation. Nitration of **15** was carried out using nitronium tetrafluoroborate at -25° with the hope of introducing the 7-nitro function. An orange crystalline product was obtained in 85% yield, for which the structure **16** was proposed. This product was essentially neutral but on treatment with diazomethane, it gave a pale yellow crystalline product **17** (M^+ 424.1020 ± 0.0025; Calcd. for $C_{20}H_{16}N_4O_7$: 424.1017).



14



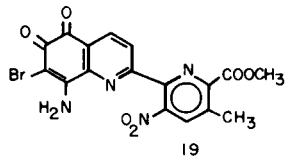
15 , R = CH_3CO

18 , R = H

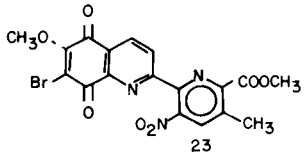
16 , R = H

17 , R = CH_3

Because of the anonalous course of the nitration which failed to introduce the desired functionality, **15** was hydrolyzed to the 8-aminoquinoline **18**, which is expected to be more reactive toward halogenation. On treatment with bromine, this compound gave a reddish brown quinone for which the structure **19** was proposed, based on spectral and analytical data. It was neutral and did not react with diazomethane; these properties precluded the hydroxy-*p*-quinonimine structure.

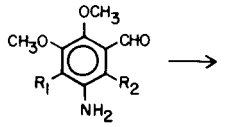


19



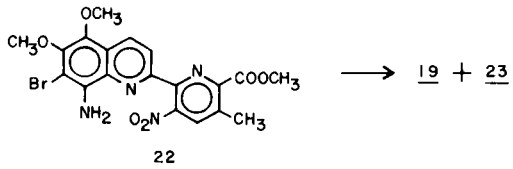
23

In another attempt, the aldehyde **9** was deacetylated, and the product **20** brominated to give **21**. The yield of **21** was low (25%) due to the competing oxidation. The reduced bromoaldehyde **21** condensed smoothly with **14** to form the quinoline **22** directly in 65% yeild. This product was stable to Fremy's salt but was oxidized to a quinonoid product by periodic acid or ceric ammonium nitrate. The product was found to be a mixture of **19** and **23** in approximately a 1:1 ratio.



20 , R_1 = H, R_2 = NO_2

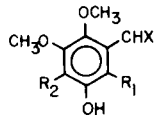
21 , R_1 = Br, R_2 = NO_2



22

These experiments showed that the 8-amino-5,6-dimethoxyquinoline system has a greater tendency to form an orthoquinone through the loss of two methoxyls instead of a paraquinone through the loss of an amino and methoxyl groups. With a view that the presence of an 8-hydroxy-5,6-dimethoxyquinoline system could avoid this, 3-nitro-5,6-dimethoxybenzaldehyde **7** was converted to 3-hydroxy-5,6-dimethoxybenzaldehyde **24** in an overall yield of 50% *via* conversion to the dimethylacetal **25a**, reduction to the amine **25b** and thermal decomposition of the diazonium salt. The use of the recently described procedure (5) for the conversion of a diazonium salt to a phenol through the action of cuprous oxide and cupric nitrate gave significant amounts of non-phenolic by-products. Nitration of **24** gave a 70% yeild of 3-hydroxy-

5,6-dimethoxy-2-nitrobenzaldehyde **26**. The position of the nitro group was proved by the formation of the quinoline **27** through direct condensation with 2-acetylpyridine in alkaline dithionite, although the yield was low (25%). Under conditions of bromination, **27** was converted first to the quinone **28** and then, to the bromoquinone **29**. Azidation to **30**, followed by reduction gave the known 7-amino-6-methoxy-2,2-pyridylquinoline-5,8-dione **31** (6).



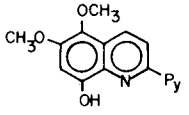
24 , $R_1 = R_2 = H$, X = O

26 , $R_1 = NO_2$, $R_2 = H$, X = O

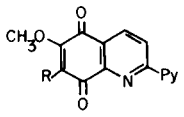
32 , $R_1 = NO_2$, $R_2 = H$, $X = (OCH_3)_2$

33 , $R_1 = NO_2$, $R_2 = Br$, $X = (OCH_3)_2$

34 , $R_1 = NO_2$, $R_2 = Br$, X = O



27



28 , R = H

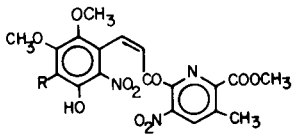
29 , R = Br

30 , $R = N_3$

31 , $R = NH_2$

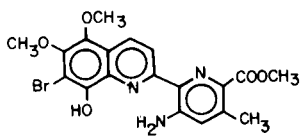
Bromination of **26** was not possible because of the ease of oxidation to the corresponding acid. Conversion to the dimethyl acetal **32**, followed by bromination in pyridine to give **33** and acid hydrolysis gave the desired 4-bromo-3-hydroxy-5,6-dimethoxy-2-nitrobenzaldehyde **34** in a 45% yield from **26**.

As indicated earlier (6), direct Friedlander condensation with an aminoaldehyde containing phenolic hydroxyls was not satisfactory and a two-step method was found to be preferable. Accordingly, **34** was condensed with **14** to give the chalcone **35** in a 75% yeild. Alternatively, **26** and **14** gave the chalcone **36** in a comparable yield, and **36** underwent bromination readily to form **35**. Thus, either **26** or **34** can serve for the preparation of the chalcone **35**. Reductive cyclization of **35** proceeded in a 90% yeild to the quinoline **37**.



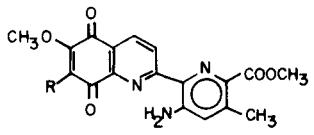
35 , R = Br

36 , R = H



37

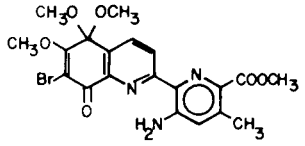
Although unaffected by Fremy's salt, **37** was oxidized readily by periodic acid to the bromoquinone **38**. However, the major product of the reaction was a pale yellow crystalline solid, $C_{20}H_{20}BrN_3O_6$ (M^+ 477.0477; Calcd. 477.0514), which was non-phenolic and non-quinonoid. Its nmr spectrum showed no change from that of **37**, with regard to rings B and C, but showed signals for four methoxyls, two of which had the chemical shift of τ 6.87. From this data and the molecular formula which represented **38** + C_2H_6O, the structure **39** was proposed. This structure was confirmed by the ready conversion of **39** to **38** by treatment with acid. It is unusual that the dimethyl acetal of the quinone was formed as the major product when the reaction was carried out in a methanol/chloroform/water system with periodic acid for fifteen minutes.



38 , R = Br

40 , $R = N_3$

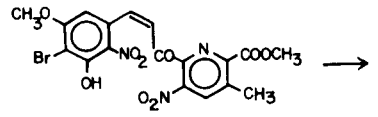
41 , $R = NH_2$



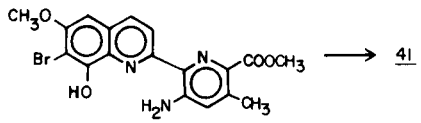
39

The quinone **38** was converted *via* the azide **40** to the desired 7-amino-6-methoxyquinoline-5,8-dione **41** in a yield of 60%. Thus, the preparation of **41** could be accomplished from **14** in five steps, in an overall yield of 35%, which is significantly better than the previous scheme.

The scheme based on 3,5-dihydroxybenzaldehyde and its derivatives used earlier has several limitations. In addition to the starting material being not readily accessible, it is highly susceptible to self condensation. There is no selectivity in partial methylation, which, therefore gives low yields of the monomethyl ether. Further, nuclear substitution generates mixtures of isomers which are difficult to separate and characterize. However, the availability of 4-bromo-3,5-dihydroxybenzoic acid (7, ICN Pharmaceuticals) prompted a reinvestigation of this scheme with some changes. Instead of attempting to partially methylate this compound, the selective demethylation of the completely methylated ester **42** with sodium ethanethiolate in dimethylformamide (8) was studied. The reaction gave a smooth, selective demethylation in 78% yeild to give 4-bromo-3-hydroxy-5-methoxybenzoic acid **43**. Acetylation and Rosenmund reduction of the acid chloride proceeded in an overall yield of 70% to give **44**. Deacetylation to **45** and nitration gave a mixture of **46** and **47**, of which the desired 2-nitro derivative **46** was the major product. The dinitro derivative **48** was also readily prepared. Nitration of the acetyl derivative **44** with nitronium fluoroborate also gave the 2-nitro derivative **49** as the major product. This makes **49** an even more attractive intermediate because it requires one less step than **46** and can be used directly in the subsequent condensation. The four-step scheme for the preparation of



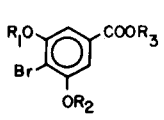
51

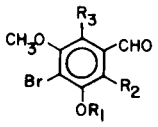


50

49 gave an overall yield of 40% from the commercially available 4-bromo-3,5-dihydroxy benzoic acid.

The usefulness of **46** and **49** was tested by using them in the synthesis of **41**. The quinoline **50** was obtained *via* the chalcone **51**. Oxidation of **50** with Fremy's salt gave the bromoquinone **38** from which **41** was prepared as before. The overall yield of **41** was 35% based on the ketone **14**.





42, $R_1 = R_2 = R_3 = CH_3$

43, $R_1 = CH_3$, $R_2 = R_3 = H$

43a, $R_1 = CH_3$, $R_2 = CH_3CO$, $R_3 = H$

44, $R_1 = COCH_3$, $R_2 = R_3 = H$

45, $R_1 = R_2 = R_3 = H$

46, $R_1 = R_3 = H$, $R_2 = NO_2$

47, $R_1 = R_2 = H$, $R_3 = NO_2$

48, $R_1 = H$, $R_2 = R_3 = NO_2$

49, $R_1 = COCH_3$, $R_3 = H$, $R_2 = NO_2$

EXPERIMENTAL

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. The following instruments were used for the spectra recorded: Beckman 25 (uv), Beckamn-Acculab 3 (ir), Varian T-60 (nmr) with tetramethylsilane as internal standard, DuPont 490 chemical ionization (mass spectra) and Hitachi-Perkin Elmer RMU-6E (high resolution mass spectra). Thin-layer chromatography was carried out using silica gel Merck HF 254 + 366. Column chromatography was performed using a 1:1 mixture of silicic acid (Mallinckrodt 275-325 mesh) and cellulose (tlc grade, Brown and Co.).

3,5-Dimethoxy-2,4,6-trinitrotoluene (**4**).

A solution of trinitroorcinol (9) (13 g.) in ethyl acetate (150 ml.) was treated with a slight excess of diazomethane. After 16 hours, it was concentrated to dryness and the solid crystallized from ether-hexane, m.p. 65-66°; yield, 13 g. (90%).

Anal. Calcd. for $C_9H_9N_3O_8$: C, 37.64; H, 3.16; N, 14.63. Found: C, 37.95; H, 3.04; N, 14.82.

3-Acetylamino-5,6-dimethoxy-2-nitrobenzaldehyde (**5**).

A mixture of **7** (4) (2.1 g.) and sodium dithionite (6 g., 3.6 moles) in 2:1 pyridine/water (8 ml.) was boiled under reflux for 15 minutes. Acetic anhydride (25 ml.) was added through the condenser in small protions and the heating continued for 10 minutes. The cooled mixture was diluted with chloroform (100 ml.) and let stand at 5° for 15 minutes. After filtration, the filtrate was concentrated to dryness. The residual solid was dissolved in a mixture of nitromethane (5 ml.) and chloroform (20 ml.) and stirred with 90% nitric acid (1.5 ml.) for 10 minutes. Water was added, the solvent layer separated, washed once with aqueous bicarbonate and concentrated to dryness. The pale yellow solid was crystallized from ethanol, m.p. 184-186°; yield, 1.94 g. (75%); nmr (deuteriochloroform): τ -0.16 (s, 1H), 0.1 (s, broad, 1H), 1.64 (s, 1H), 6.05 (s, 3H), 6.17 (s, 3H), 7.75 (s, 3H).

Anal. Calcd. for $C_{11}H_{12}N_2O_6$: C, 49.25; H, 4.51; N, 10.45. Found: C, 49.45; H, 4.73; N, 10.22.

3,4-Dimethoxy-5,6-dinitroacetanilide (**8**).

A solution of **7** (0.26 g.) in a mixture of nitromethane (10 ml.) and dichloromethane (10 ml.) was cooled to -25° and stirred with nitronium tetrafluoroborate (0.18 g.). After 10 minutes, ice was added, the solvent layer separated, washed with aqueous bicarbonate and concentrated to dryness. The solid was crystallized from ethanol-ether, m.p. 160-162°; yield, 0.25 g., ms: M^+ 285; nmr (deuteriochloroform): τ -0.83 (s, broad 1H), 0.70 (s, 1H), 6.0 (s, 3H), 6.10 (s, 3H), 7.76 (s, 3H).

Anal. Calcd. for $C_{10}H_{11}N_3O_7$: C, 42.11; H, 3.89; N, 14.73. Found: C, 42.25; H, 4.12; N, 14.98.

3-Acetylamino-2-amino-5,6-dimethoxybenzaldehyde (**9**).

A mixture of **7** (0.52 g.), sodium dithionite (1.3 g.) and sodium carbonate (0.3 g.) in 1:1 aqueous methanol (10 ml.) was boiled under reflux for 10 minutes. The cooled mixture was made slightly basic, saturated with sodium chloride and extracted with chloroform. The extract on concentration gave a yellow solid which was crystallized from ether, m.p. 112-114°; yield, 0.31 g. (65%).

Anal. Calcd. for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.92; N, 11.76. Found: C, 55.67; H, 5.85; N, 11.41.

8-Acetylamino-5,6-dimethoxy-2,2-pyridylquinoline (**10**).

A mixture of **9** (0.47 g.) and 2-acetylpyridine (0.25 g.) in tetrahydrofuran (5 ml.) was cooled to 0° and stirred with 2*N* potassium hydroxide (10 ml.) for 6 hours. It was diluted with water, extracted wtih chloroform and the extract concentrated to dryness. The solid was crystallized from ether, m.p. 148-149°; yield, 0.38 g. (60%); nmr (deuteriochloroform): τ 0.25 (broad, 1H), 1.2-2.8 (m, 7H), 5.95 (s, 3H), 6.0 (s, 3H), 7.62 (s, 3H).

Anal. Calcd. for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 13.00. Found: C, 67.01; H, 5.52; N, 12.84.

8-Acetylamino-2,2-pyridylquinoline-5,6-dione (**11**).

A solution of **10** (0.5 g.) in chloroform (30 ml.) was stirred with 90% nitric acid (0.3 ml.) at 25° for 20 minutes. The solid which separated was filtered, and washed with chloroform and water. It was recrystallized from aqueous dimethylformamide, m.p. 262-264°; yield, 0.42 g. (93%); nmr (DMSO-d_6/trifluoroacetic acid): τ 1.28 (broad, 1H), 0.8-1.98 (m, 6H), 2.0 (s, 1H), 7.45 (s, 3H).

Anal. Calcd. for $C_{16}H_{11}N_3O_3$: C, 65.52; H, 3.78; N, 14.33. Found: C, 65.21; H, 3.58; N, 14.66.

Reaction with *o*-phenylenediamine.

A solution of **11** (0.1 g.) in acetic acid (4 ml.) was boiled under reflux with *o*-phenylenediamine (0.05 g.) for 10 minutes. The solution was diluted with water, neutralized with sodium bicarbonate and extracted wtih ether twice, followed by chloroform.

The chloroform extract was concentrated to dryness and the yellow solid was crystallized from dimethylformamide, m.p. 272-274°; yield, 0.12 g.

Anal. Calcd. for $C_{22}H_{15}N_5O$: C, 72.31; H, 4.14; N, 19.17. Found: C, 72.65; H, 4.05; N, 19.32.

8-Amino-2,2-pyridylquinoline-5,6-dione (**13**).

To 0.35 g. of **11** in tetrahydrofuran (20 ml.) was added 6*N* sulfuric acid (5 ml.) and the mixture boiled under reflux for 1 hour. After cooling and neutralization with sodium bicarbonate, the mixture was extracted wtih chloroform. Concentration of the solvent extract gave a red crystalline solid which was recrystallized from methanol-chloroform (1:1), m.p. >300°; yield, 0.22 g.

Anal. Calcd. for $C_{14}H_9N_3O_2$: C, 66.92; H, 3.61; N, 16.73. Found: C, 66.61; H, 3.72; N, 16.45.

8-Acetylamino-5,6-dimethoxy-2(6-carbomethoxy-5-methyl-3-nitro)-2-pyridylquinoline (**15**).

A mixture of **9** (0.48 g.) and **14** (0.5 g.) in tetrahydrofuran (5 ml.) was cooled to 0° and stirred with precooled 2*N* potassium hydroxide (12 ml.) for 4 hours at 0°. The mixture was acidified and the solid (which was the acid corresponding to **15**) was filtered and crystallized from methanol-chloroform (3:1), m.p. 236-238°; yield, 0.52 g. (60%).

Anal. Calcd. for $C_{20}H_{18}N_4O_7$: C, 56.33; H, 4.26; N, 13.14. Found: C, 56.14; H, 4.22; N, 12.85.

The acid from the preceding experiment was taken up in 1:1 methanol-chloroform (50 ml.) and treated with a slight excess of diazomethane. After 15 minutes, the solution was concentrated to dryness and the yellow solid crystallized from acetone-methanol (1:4), m.p. 235-237°; yield, 0.52 g. (95%); ms: M^+ 440; nmr (deuteriochloroform): τ 0.87 (s, broad, 1H), 1.27 (s, 1H), 1.54 (s, 2H), 2.25 (s, 1H), 6.0 (s, 3H), 6.10 (s, 3H), 7.37 (s, 3H), 7.6 (s, 3H).

Anal. Calcd. for $C_{21}H_{20}N_4O_7$: C, 57.27; H, 4.58; N, 12.72. Found: C, 56.95; H, 4.42; N, 12.48.

8-Acetylamino-2(6-carbomethoxy-5-methyl-3-nitro)-2-pyridylquinoline-5,6-dione (**16**).

A solution of **15** (0.44 g.) in nitromethane (10 ml.) and dichloromethane (20 ml.) was cooled to -25° and stirred with nitronium tetrafluoroborate (0.15 g.) for 15 minutes. Ice was added and the solvent layer washed once with aqueous bicarbonate and concentrated to dryness. The orange solid was crystallized from dimethyl-formamide-methanol (1:4), m.p. 267-269°; yield 0.35 g. (85%).

Anal. Calcd. for $C_{19}H_{14}N_4O_7$: C, 54.28; H, 5.75; N, 13.33. Found: C, 54.45; H, 5.68; N, 12.96.

3-Acetylmethylamino-2(6-carbomethoxy-5-methyl-3-nitro)-2-pyridylquinoline-5,6-dione (**17**).

Ethereal diazomethane was added to a solution of **16** (0.21 g.) in a mixture of chloroform and methanol (10 ml. each). After 16 hours, the pale yellow crystalline solid which separated was filtered, m.p. 255-257°; yield, 0.16 g. (80%); ms: M^+ 424.1020; Calcd. 424.1017.

Anal. Calcd. for $C_{20}H_{16}N_4O_7$: C, 56.60; H, 3.80; N, 13.20. Found: C, 56.88; H, 3.72; N, 13.01.

8-Amino-5,6-dimethoxy-2-(6-carbomethoxy-5-methyl-3-nitro)-2-pyridylquinoline (**18**).

A solution of **15** (0.44 g.) in methanol (50 ml.) was treated with 6*N* sulfuric acid (5 ml.) under reflux for 3 hours. After partial concentration, it was partitioned between chloroform and aqueous bicarbonate. The solvent layer was concentrated to dryness and the yellow solid crystallized from methanol-ether, m.p. 182-184°; yield, 0.32 g. (80%).

Anal. Calcd. for $C_{19}H_{18}N_4O_6$: C, 57.28; H, 4.55; N, 14.07. Found: C, 57.45; H, 4.42; N, 13.78.

8-Amino-7-bromo-2-(6-carbomethoxy-5-methyl-3-nitro)-2-pyridylquinoline-5,6-dione (**19**).

Bromination of **18** (0.2 g.) was carried out in a mixture of acetic acid (1 ml.) and chloroform (20 ml.) with bromine (0.15 ml.) at 25° for 1 hour. The mixture was diluted with water and the solvent layer washed wtih aqueous ascorbic acid (0.5 g.). Concentration of the solvent gave a red crystalline solid, recrystallized from acetone-ether, m.p. 258-260°; yield, 0.15 g. (65%); ms: M^+ 445.9943; Calcd. 445.9921.

Anal. Calcd. for $C_{17}H_{11}Br\ N_4O_6$: C, 45.65; H, 2.48; Br, 17.87; N, 12.53. Found: C, 45.39; H, 2.44; Br, 17.55; N, 12.41.

3-Amino-5,6-dimethoxy-2-nitrobenzaldehyde (**20**).

A solution of **5** (1 g.) in tetrahydrofuran (20 ml.) was boiled under reflux with 6*N* sulfuric acid (2 ml.) for 2 hours. The solution was diluted with water (50 ml.) and extracted with chloroform. Concentration of the solvent extract gave a bright yellow solid, crystallized from methanol-ether, m.p. 170-172°; yield, 0.75 g. (90%); nmr (deuteriochloroform): τ 0 (s, 1H), 3.50 (s, 1H), 6.07 (s, 3H), 6.27 (s, 3H), 6.17 (broad, 2H).

Anal. Calcd. for $C_9H_{10}N_2O_5$: C, 47.79; H, 4.46; N, 12.39. Found: C, 47.60; H, 4.41; N, 12.11.

3-Amino-4-bromo-5,6-dimethoxy-2-nitrobenzaldehyde (**21**).

Bromine (0.3 ml.) was dissolved in pyridine (3 ml.) at 0° and this was added to a solution of **20** (0.2 g.) in pyridine (3 ml.). After 10 minutes at 0°, the mixture was diluted with ice and dilute sulfuric acid and extracted with chloroform. The extract was washed with aqueous ascorbic acid (0.5 g. in 10 ml.) and concentrated to dryness. It was taken up in benzene and subjected to chromatography on silicic acid. The major band, on concentration, gave a yellow crystalline solid, m.p. 118-120°; yield, 0.45 g. (32%); ms: M+ 304; nmr (deuteriochloroform): τ 0 (s, 1H), 5.40 (s, broad, 2H), 6.0 (s, 3H), 6.20 (s, 3H).

Anal. Calcd. for $C_9H_9Br\ N_2O_5$: C, 35.43; H, 2.97; N, 9.18. Found: C, 35.56; H, 2.91; N, 8.87.

8-Amino7--bromo-5,6-dimethoxy-2(6-carbomethoxy-5-methyl-3-nitro)-2-pyridylquinoline (**22**).

A mixture of **21** (0.4 g.) and sodium dithionite (1.5 g.) in 1:1 aqueous methanol (6 ml.) was refluxed until the reduction was complete. To the cooled reaction mixture was added 6*N* sulfuric acid dropwise to *p*H 1-2 to decompose the excess reagnet. Nitrogen was bubbled through for 10 minutes to drive the sulfur dioxide. It was then cooled to 0°, treated with the ketone **14** (0.25 g.), followed by precooled 2*N* potassium hydroxide (15 ml.). After 4 hours of stirring at 0°, the mixture was acidified and extracted with ethyl acetate twice. The extract was washed with aqueous sodium bicarbonate twice and the aqueous layers acidified and reextracted with ethyl acetate. Partial concentration of the solvent layer, esterification with diazomethane and concentration to dryness gave **22** as a yellow crystalline solid. It was recrystallized from acetone-methanol, m.p. 175-177°; yield, 0.3 g. (60% based on the ketone); ms: M^+ 476; nmr (deuteriochloroform): τ 1.57 (s, 2H), 2.14 (s, 1H), 4.97 (s, broad, 2H), 5.94 (s, 6H), 6.04 (s, 3H), 7.30 (s, 3H).

Anal. Calcd. for $C_{19}H_{17}Br\ N_4O_6$: C, 47.82; H, 3.59; Br, 16.74; N, 11.74. Found: C, 47.61; H, 3.48; Br, 16.50; N, 11.41.

Oxidation of (**22**).

To a solution of **22** (0.28 g.) in methanol (2 ml.) and dilute sulfuric acid (1*N*, 10 ml.) was added sodium metaperiodate. After 2 hours of stirring, the mixture was extracted with chloroform, the extract concentrated and the product subjected to chromatography on silicic acid (20 g.) in benzene. The first band on recovery and crystallization from methanol-chloroform was found to be identical with **19**. The second band, eluted wtih 1-2% acetone in benzene, crystallized from chloroform-methanol as reddish-brown needles, m.p. >300°; ms: M^+ 461.

Anal. Calcd. for $C_{18}H_{12}Br\ N_3O_7$: C, 46.77; H, 2.62; Br, 17.67; N, 9.09. Found: C, 46.45; H, 2.51; Br, 17.31; N, 8.72.

3-Nitro-5,6-dimethoxybenzaldehydedimethylacetal (**25a**).

A mixture of **7** (4.21 g.) and Dowex-50-H$^+$ (10 g.) in methanol (200 ml.) was boiled under reflux for 20 hours. The mixture was filtered, the filtrate made slightly basic and the mixture was concentrated to a small volume, which was diluted with water. The solid was filtered and crystallized from ether, m.p. 90-92°; yield, 4.2 g. (93%); nmr (deuteriochloroform): τ 3.50, 3.55, 3.67, 3.72 (ab-quartet, J = 3 Hz, 2H), 4.40 (s, 1H), 6.17 (s, 3H), 6.20 (s, 3H), 6.64 (s, 6H).

Anal. Calcd. for $C_{11}H_{15}NO_6$: C, 51.36; H, 5.88; N, 5.45. Found: C, 51.45; H, 5.72; N, 5.31.

3-Amino-5,6-dimethoxybenzaldehydedimethylacetal (**25b**).

A solution of **25a** (26 g.) in a mixture of tetrahydrofuran (50 ml.) and ethanol (50 ml.) was subjected to catalytic hydrogenation in a Parr apparatus with 5% palladium on carbon (2 g.) for 6 hours. The mixture was filtered and the filtrate concentrated to an oil which became crystalline on the addition of hexane. It was filtered and recrystallized from ether-hexane, m.p. 78-80°; yield, 21 g. (95%); nmr (deuteriochloroform): τ 3.54, 3.59, 3.70, 3.75 (ab-quartet, J = 3 Hz, 2H), 4.44 (s, 1H), 6.20 (s, 3H), 6.24 (s, 3H), 6.34 (broad, 2H), 6.64 (s, 6H).

Anal. Calcd. for $C_{11}H_{17}NO_4$: C, 58.13; H, 7.54; N, 6.16. Found: C, 58.41; H, 7.32; N, 6.39.

3-Hydroxy-5,6-dimethoxybenzaldehyde (**24**).

To a solution of the amino acetal **25b** (5.5 g.) in 3*N* sulfuric acid (50 ml.), cooled to 5°, was added, dropwise, aqueous sodium nitrite (1.8 g. in 10 ml.). After 15 minutes, the excess nitrous acid was decomposed by the addition of ammonium sulfamate (0.8 g.). The reaction mixture was added dropwise to boiling water (1 l.) with stirring. The cooled mixture was extracted with ether and the extract concentrated to dryness. The solid was crystallized from benzene, m.p. 143-145°; yield 3 g. (65%); nmr (deuteriochloroform): τ -0.33 (s, 1H), 1.84 (broad, 1H), 3.20 (s, 1H), 6.07 (s, 3H), 6.10 (s, 3H).

Anal. Calcd. for $C_9H_{10}O_4$: C, 59.33; H, 5.53. Found: C, 59.61; H, 5.48.

3-Hydroxy-5,6-dimethoxy-2-nitrobenzaldehyde (**26**).

A cooled (0-5°) and vigorously stirred solution of **24** (1.8 g.) in chloroform (30 ml.) was treated wtih 90% nitric acid (0.8 ml.) for 10 minutes. Water was added, the solvent layer separated and washed once with 1*M* phosphate buffer (*p*H 7, 15 ml.). The solvent layer was concentrated to dryness, taken up in benzene (20 ml.) and the solution applied to a column of silicic acid (50 g.) in benzene. The major band, eluted with benzene, was concentrated to dryness and the yellow solid crystallized from ether-hexane, m.p. 123-125°; yield, 1.7 g. (70%); nmr (deuteriochloroform): τ -1.0 (s, 1H), 0.23 (s, 1H), 3.33 (s, 1H), 6.00 (s, 3H), 6.17 (s, 3H).

Anal. Calcd. for $C_9H_9NO_6$: C, 47.58; H, 3.99; N, 6.17. Found: C, 47.51; H, 3.92; N, 6.33.

3-Hydroxy-5,6-dimethoxy-2-nitrobenzaldehyde Dimethylacetal (**32**).

A solution of **26** (5 g.) in methanol (200 ml.) was boiled under reflux in the presence of Dowex-50 resin in H$^+$ form (5 g., 200-400 mesh) for 48 hours. The mixture was filtered, and the filtrate concentrated to dryness. The yellow solid was recrystallized from acetone-ether, m.p. 121-123°; yield, 5 g. (85%); nmr (deuteriochloroform): τ 3.39 (s, 1H), 4.37 (s, 1H), 6.09 (s, 3H), 6.17 (s, 3H), 6.50 (s, 6H).

Anal. Calcd. for $C_{11}H_{15}NO_7$: C, 48.35; H, 5.53; N, 5.13. Found: C, 48.12; H, 5.35; N, 5.42.

4-Bromo-3-hydroxy-5,6-dimethoxy-2-nitrobenzaldehyde Dimethylacetal (**33**).

To a solution of **32** (0.54 g.) in pyridine (3 ml.) was added *N*-bromosuccinimide (0.6 g.) and the mixture stirred at 25° in the dark for 2 hours. It was acidified with 6*N* sulfuric acid in the presence of ice and extracted wtih chloroform. The solvent layer was shaken once with aqueous sodium bisulfite and concentrated to dryness. The residual solid was purified by chromatography on silicic acid (25 g.) in benzene. The yellow major band which was eluted with benzene was concentrated to dryness. The solid was recrystallized from ether-hexane, m.p. 67-69°; yield, 0.23 g. (65%); nmr (deuteriochloroform): τ -0.21 (s, 1H), 4.54 (s, 1H), 6.14 (s, 3H), 6.20 (s, 3H), 6.64 (s, 6H).

4-Bromo-3-hydroxy-5,6-dimethoxy-2-nitrobenzaldehyde (**34**).

A solution of **33** (0.35 g.) in tetrahydrofuran (10 ml.) was allowed to stand with 6*N* sulfuric acid (2 ml.) at 25° for 1 hour. The was diluted with water (30 ml.) and extracted wtih chloroform. The extract was concentrated to dryness and the solid crystallized from ether-hexane, m.p. 127-128°; yield, 0.24 g. (80%); nmr (deuteriochloroform): τ -0.2 (s, 1H), 5.94 (s, 6H); ms: M^+ 305.

Anal. Calcd. for $C_9H_8BrNO_6$: C, 35.31; H, 2.63; Br, 26.11; N, 4.58. Found: C, 35.49; H, 2.58; Br, 25.81; N, 4.22.

8-Hydroxy-5,6-dimethoxy-2,2-pyridylquinoline (**27**).

A mixture of **26** (0.45 g.) and sodium dithionite (1.5 g.) in 1:1 aqueous methanol (5 ml.) was boiled under reflux for 10 minutes. It was cooled to 0°, treated with 2-acetylpyridine (0.3 g.) and 2*N* potassium hydroxide (12 ml.). The mixture was stirred in a nitrogen atmosphere for 6 hours. It was extracted with ether and the aqueous layer acidified to *p*H 4 and extracted wtih chloroform. The solvent extract on concentration and chromatography on silicic acid (20 g.) in 2% acetone in benzene gave **27** as a very pale yellow crystalline solid, m.p. 137-139°; yield, 0.15 g. (26%); nmr (deuteriochloroform): τ 1.17-2.84 (m, 5H), 1.45 (s, 2*H*), 2.97 (s, 1H), 6.0 (s, 3H), 6.07 (s, 3H).

Anal. Calcd. for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.33; H, 4.91; N, 9.58.

6-Methoxy-2,2-pyridylquinoline-5,8-dione (**28**).

Bromine (0.1 ml.) was added to a solution of **27** (0.28 g.) in acetic acid (1 ml.) and chloroform (10 ml.). After 30 minutes of stirring, water was added, the solvent layer washed successively with aqueous sodium bisulfite and sodium bicarbonate and concentrated to dryness. The yellow crystalline solid was recrystallized from ethanol-ether, m.p. 262-264°; yield, 0.24 g. (90%); ms: m^+ 266.

Anal. Calcd. for $C_{15}H_{10}N_2O_3$: C, 67.66; H, 3.79; N, 10.52. Found: C, 67.65; H, 3.71; N, 10.22.

7-Bromo-6-methoxy-2,2-pyridylquinoline-5,8-dione (**29**).

Bromination of **27** (0.28 g.) was carried out as under **28** but with bromine (0.2 ml.) for 24 hours. The reaction mixture was

washed with aqueous sodium bisulfite and sodium bicarbonate and concentrated to dryness. The yellow solid was crystallized from ethanol, m.p. 190-192°; yield, 0.28 g. (82%); ms: M^+ 344.

Anal. Calcd. for $C_{15}H_9BrN_2O_3$: C, 52.25; H, 2.62; N, 8.11. Found: C, 51.95; H, 2.58; N, 7.85.

7-Amino-6-methoxy-2,2-pyridylquinoline-5,8-dione (**31**).

A mixture of **29** (0.17 g.) in dimethylformamide (2 ml.) was stirred with sodium azide (0.1 g.) for 15 minutes. The resulting azido quinone was directly reduced by treatment with aqueous sodium dithionite (0.5 g.). The pale yellow reaction mixture was extracted wtih ethyl acetate, whereby air-oxidation took place, leading to a purplish-red extract. Concentration of the extract and crystallization from methanol-chloroform gave a purplish-red crystalline solid, m.p. 172-174°; mixed m.p. with an authentic sample (6), 172-174°. Its chromatographic and spectral properties were also identical with those of the reference sample.

6-Carbomethoxy-3′-hydroxy-5′,6′-dimethoxy-5-methyl-2′,3-dinitro--1-azachalcone (**36**).

A mixture of **26** (0.45 g.) and **14** (0.48 g.) in tetrahydrofuran (3 ml.) was cooled to -5° and treated with precooled 2*N* potassium hydroxide (10 ml.). The mixture was stirred at -5 to 0° for 1 hour. The semisolid reaction mixture was acidified and extracted with ethyl acetate twice. The extract was washed twice with 0.5*M* phosphate buffer (*p*H 7, 25 ml.). The combined aqueous layers were acidified and extracted with ethyl acetate. Concentration of the solvent layer gave a yellow crystalline solid which was esterified by stirring wtih methanolic sulfuric acid (50 ml., 0.5% v/v) for 24 hours. Partial concentration gave a crystalline solid which was filtered and recrystallized from acetone-methanol, m.p. 150-152°; yield, 0.68 g. (75%); nmr (deuteriochloroform): τ -0.83 (s, 1H), 1.97 (s, 1H), 2.62 (s, 1H), 2.79 (s, 1H), 3.50 (s, 1H), 6.07 (s, 6H), 6.33 (s, 3H), 7.37 (s, 3H).

Anal. Calcd. for $C_{19}H_{17}N_3O_{10}$: C, 51.01; H, 3.83; N, 9.39. Found: C, 51.35; H, 3.78; N, 9.68.

4′-Bromo-6-carbomethoxy-3′-hydroxy-5′,6′-dimethoxy-3-methyl-2′,3-dinitro-1-azachalcone (**35**).

To a solution of **36** (0.45 g.) in pyridine (10 ml.) was added a freshly prepared solution of bromine (0.25 ml.) in pyridine (3 ml.) at 0°. After 5 minutes, an aqueous solution of ascorbic acid (0.5 g. in 10 ml.), ice and enough 6*N* sulfuric acid to give a *p*H of 1-2 were added. The mixture was extracted with chloroform. The extract was concentrated and purified by chromatography on silicic acid (20 g.) in benzene. The first band on concentration gave the product as an orange yellow crystalline solid, m.p. 130-132°; yield, 0.37 g. (70%); nmr (deuteriochloroform): τ 1.99 (s, 1H), 2.65 (s, 1H), 2.70 (s, 1H), 6.02, (s, 3H), 6.07 (s, 3H), 6.27 (s, 3H), 7.33 (s, 3H).

Anal. Calcd. for $C_{19}H_{16}BrN_3O_{10}$: C, 43.36; H, 3.06; Br, 15.19; N, 7.99. Found: C, 43.23; H, 3.15; Br, 14.81; N, 7.65.

Alternatively, condensation of **34** (0.61 g.) and **14** (0.5 g.) by the procedure described under **36**, followed by esterification with methanolic sulfuric acid gave a crystalline solid, m.p. 130-132°; yield, 0.8 g. (75%), which was identical with **35**, prepared by the bromination of **36**.

7-Bromo-8-hydroxy-5,6-dimethoxy-2-(3-amino-6-carbomethoxy-5-methyl)-2-pyridylquinoline (**37**).

A mixture of **35** (0.53 g.) and sodium dithionite (1.2 g.) in 1:1 aqueous methanol (15 ml.) was boiled under reflux for 30 minutes, after which time the initial red color changed to pale yellow. To this solution was added methanolic sulfuric acid (6*N*, 12 ml.) and the boiling was continued for 3-5 minutes. Cooling and neutralization with sodium bicarbonate gave a greyish-white solid which was filtered and crystallized from methanol, m.p. 210-212°; yield, 0.4 g. (90%); nmr (deuteriochloroform): τ 1.17, 1.32, 1.45, 1.60 (ab-quartet, J = 9 Hz, 2H), 3.07 (s, 1H), 5.94 (s, 3H), 6.00 (s, 6H), 7.37 (s, 3H); ms: M^+ 447.

Anal. Calcd. for $C_{19}H_{18}BrN_3O_5$: C, 50.90; H, 4.04; Br, 17.83; N, 9.37. Found: C, 50.61; H, 4.22; Br, 17.49; N, 9.11.

Oxidation of **37**.

A solution of **37** (0.45 g.) in a mixture of methanol and chloroform (15 ml. each) was stirred with sodium metaperiodate (0.5 g.) in 1*N* sulfuric acid (2-3 ml.). After 15 minutes the starting material was absent. The mixture was filtered to separate the reddish-brown crystalline solid **38** which was formed. The filtrate was diluted with water and extracted wtih chloroform. The solvent layer was concentrated to a small volume and subjected to chromatography on silicic acid (25 g.) in benzene. The first band gave more of the reddish-brown quinone **38**; total yield 0.09 g. It was identical with an authentic sample of 7-bromo-6-methoxy-2-(3-amino-6-carbomethoxy-5-methyl)-2-pyridylquinoline-5,8-dione **38**.

The second and major band, **39**, crystallized as pale yellow rectangular plates from methanol, m.p. 217-219°; yield, 0.25 g.; ms: M^+ 477.0477; nmr (deuteriochloroform): τ 1.09, 1.24, 1.95, 2.10 (ab-quartet, J = 9 Hz, 2H), 2.67 (broad, 2H), 3.04 (s, 1H), 5.59 (s, 3H), 6.09 (s, 3H), 6.87 (s, 6H), 7.42 (s, 3H).

Anal. Calcd. for $C_{20}H_{20}BrN_3O_6$: C, 50.22; H, 4.21; Br, 16.71; N, 8.79. Found: C, 49.89; H, 4.10; Br, 16.38; N, 8.51.

Conversion of **39** to **38**.

A solution of **39** (0.2 g.) in tetrahydrofuran (15 ml.) was stirred wtih 6*N* sulfuric acid (3 ml.) for 30 minutes at 60°. It was cooled, diluted with water (25 ml.) and the reddish-brown solid filtered. It was recrystallized from methanol-chloroform, m.p. >300; yield, 0.15 g. Its chromatographic and spectral properties were identical with those of **38**.

4-Bromo-3-hydroxy-5-methoxybenzoic Acid (**43**).

A solution of ethanethiol (20 g.) in dimethyl formamide (50 ml.) was added with stirring to sodium hydride (12 g. of 50% dispersion in oil) in dimethylformamide (100 ml.). After the mixture was stirred for 30 minutes, **42** (7) (5.5 g.) in dimethylformamide (30 ml.) was added and the mixture boiled under reflux for 5 hours. After cooling, it was added to water, acidified and extracted with ether. The ethereal layer was reextracted with aqueous sodium bicarbonate. The aqueous layer was acidified and extracted with ether. The solvent layer was dried over sodium sulfate and concentrated to dryness. The solid was recrystallized from ether-hexane, m.p. 274-276°; yeild, 3.9 g. (78%); nmr (deuteriochloroform/10% DMSO-d_6): τ 0.0-2.4 (broad, 2H), 2.76 (d, 1H J = 0.5 Hz), 2.98 (d, 1H, J = 0.5 Hz), 6.10 (s, 3H).

Anal. Calcd. for $C_8H_7BrO_4$: C, 38.89; H, 2.85; Br, 32.35. Found: C, 38.68; H, 2.81; Br, 32.02.

4-Bromo-3-acetoxy-5-methoxybenzoic Acid (**43a**).

Compound **43** (12.5 g.) was converted to the acetyl derivative by reaction with acetic anhydride (10 ml.) and pyridine (10 ml.) at 25° for 6 hours. Addition of water and filtration gave the acetate which was crystallized from aqueous methanol, m.p. 195-197°; yield, 14 g. (90%).

Anal. Calcd. for $C_{10}H_9BrO_5$: C, 41.53; H, 3.13. Found: C, 41.32; H, 3.01.

4-Bromo-3-acetoxy-5-methoxybenzaldehyde (**44**).

A suspension of **43a** (16.5 g.) in benzene (100 ml.) was

boiled under reflux with thionyl chloride (9 ml.) for 1 hour. It was concentrated to near dryness, more benzene (50 ml.) was added and the solution concentrated once more. The residual acid chloride was taken up in xylene (150 ml.), treated with palladium-barium sulfate (4 g.) and heated at 160-170° with hydrogen being bubbled through the mixture. After 5-6 hours, the mixture was filtered, the filtrate concentrated to dryness and the solid crystallized from ether, m.p. 143-145°; yield, 11 g. (73%).

Anal. Calcd. for $C_{10}H_9BrO_4$: C, 43.98; H, 3.32; Br, 29.27. Found: C, 44.12; H, 3.22, Br, 28.91.

4-Bromo-3-hydroxy-5-methoxybenzaldehyde (**45**).

A suspension of **44** (5 g.) in 5*N* ammonium hydroxide (30 ml.) was stirred at 25° until a clear solution resulted. It was acidified, extracted wtih ether and the extract concentrated to dryness. The solid was recrystallized from aqueous methanol, m.p. 130-132°; yield, 3.8 g. (90%); nmr (deuteriochloroform/10% DMSO-d_6): τ 0.27 (s, 1H), 2.84, 2.87, 3.04, 3.07 (ab-quartet, J = 2 Hz), 6.04 (s, 3H); ms: M^+ 230.

Anal. Calcd. for $C_8H_7BrO_3$: C, 41.58; H, 3.06; Br, 34.59. Found: C, 41.23; H, 2.88; Br, 34.21.

Nitration of **45**.

A solution of **45** (2.5 g.) in a nitromethane-dichloromethane mixture (25 ml. each) was stirred wtih 90% nitric acid (0.5 ml.) at 40° for 10 minutes. Ice was added, the solvent layer separated and the aqueous layer extracted with chloroform. The combined solvent layer was washed with 1*M* phosphate buffer (*p*H 7, 25 ml.) and concentrated to dryness. Fractional crystallization from benzene gave the major product, **46**, m.p. 182-183°; yield, 1.25 g.; nmr (deuteriochloroform): τ -0.2 (s, 1H), 3.14 (s, 1H), 5.95 (s, 3H); ms: M^+ 275.

Anal. Calcd. for $C_8H_6BrNO_5$: C, 34.80; H, 2.19; N, 5.07. Found: C, 34.58; H, 2.04; N, 4.88.

The minor product from the crystallization was **47**, m.p. 156-158°; yield, 0.6 g.; nmr (deuteriochloroform): τ 0.09 (s, 1H), 2.65 (s, 1H), 5.95 (s, 3H); ms: M^+ 275.

Anal. Calcd. for $C_8H_6BrNO_5$: C, 34.80; H, 2.19; N, 5.07. Found: 35.08; H, 2.11; N, 5.15.

The buffer wash was acidified, extracted with chloroform and the solvent layer concentrated to dryness. The orange crystalline solid was recrystallized from acetone-ether, m.p. 116-117°; yield, 0.18 g.; nmr (deuteriochloroform): τ 0.2 (s, 1H), 5.92 (s, 3H).

Anal. Calcd. for $C_8H_5BrN_2O_7$: C, 31.41; H, 1.57; N, 8.73. Found: C, 31.38; H, 1.49; N, 8.41.

4′-Bromo-6-carbomethoxy-3′-hydroxy-5′-methoxy-3-methyl-2′,3-dinitro-1-azachalcone (**51**).

Condensation of **46** (0.5 g.) and **14** (0.5 g.) was carried out as described under **36**. After recovery and esterification, the product was crystallized from methanol, m.p. 167-168°; yield, 0.67 g. (68%), nmr (deuteriochloroform): τ 1.64 (s, 1H), 2.35, 2.45 (d, 2H), 3.09 (s, 1H), 5.94 (s, 3H), 5.97 (s, 3H), 7.29 (s, 3H).

Anal. Calcd. for $C_{18}H_{14}BrN_3O_9$: C, 43.56; H, 2.84; Br, 16.14; N, 8.46. Found: C, 43.53; H, 2.61; Br, 15.85; N, 8.30.

7-Bromo-8-hydroxy-6-methoxy-2-(3-amino-6-carbomethoxy-5-methyl)-2-pyridylquinoline (**50**).

Conversion of **51** (0.5 g.) to **50** was carried out as described under **37**. The product was crystallized from chloroform-methanol, m.p. 230-232°; yield, 0.37 g. (90%); ms: M^+ 417.

Anal. Calcd. for $C_{18}H_{16}BrN_3O_4$: C, 51.68; H, 3.85; N, 10.01. Found: C, 51.57; H, 3.89; N, 10.33.

7-Bromo-6-methoxy-2-(3-amino-6-carbomethoxy-5-methyl)-2-pyridylquinoline-5,8-dione (**38**).

To a solution of **50** (0.42 g.) in dimethylformamide (25 ml.) and acetic acid (4 ml.) was added Fremy's salt (1 g.) in water (10 ml.). After 4 hours of stirring, another 1 g. portion of the reagent was added. After 20 hours, the solid was filtered, washed and crystallized from chloroform-methanol. The product was identical with **38** described earlier in the experimental.

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REFERENCES AND NOTES

(1) K. V. Rao, *J. Heterocyclic Chem.*, **14**, 653 (1977).

(2) K. V. Rao and P. Vankateswarlu, *ibid.*, **12**, 731 (1975).

(3) T. K. Liao, P. J. Wittek and C. C. Cheng, *ibid.*, **13**, 1283 (1976).

(4) W. Davies, *J. Chem. Soc.*, **123**, 1583 (1923).

(5) D. Cohen, A. G. Dietz, Jr. and J. R. Miser, *J. Org. Chem.*, **42**, 2053 (1977).

(6) K. V. Rao, *J. Heterocyclic Chem.*, **12**, 725 (1975).

(7) J. R. Cannon, T. M. Cresp, B. W. Metcalf, M. V. Sargent, G. Vinciguerra and J. A. Elix, *J. Chem. Soc. C*, 3495 (1971).

(8) G. I. Feutrill and R. N. Mirrington, *Tetrahedron Letters*, 1327 (1970).

(9) A. J. Birch, R. A. Massey-Westropp, R. W. Rickards and H. Smith, *J. Chem. Soc.*, 360 (1958).