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Synthesis of Potential Antimalarial Agents. Preparation of Some 6-Amino-5,8-dimethoxyquinolines and the Corresponding 6-Amino-5,8-quinolinediones†

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The condensation of 2,5-dimethoxyaniline with acetylacetone and trifluoroacetylacetone gave the 5,8-dimethoxy derivatives of 2,4-dimethyl- and 4-methyl-2-(trifluoromethyl)quinoline (**12** and **13**), respectively. The direct preparation of 6-aminoquinolines by the cyclization of 4-(4-acetamido-2,5-dimethoxyanilino)-3-penten-2-one was unsuccessful. Also, the direct preparation of 6-nitroquinolines by condensation reactions involving 2,5-dimethoxy-4-nitroaniline was unsuccessful except for the reaction with 3-penten-2-one in the presence of arsenic acid to give 5,8-dimethoxy-2,4-dimethyl-6-nitroquinoline (**10**). A better method for the preparation of **10** and the corresponding 2-(trifluoromethyl) compound **11** involved the nitration of **12** and **13** in trifluoroacetic anhydride. The catalytic hydrogenation of **10** and **11** gave the corresponding 6-aminoquinolines **14** and **15**. Although the condensation of **15** with 5-(diethylamino)-2-pentanone was unsuccessful, the mono- and dialkylation of **14** with 2-(diethylamino)ethyl chloride to give **16** and **17** was successful. Ether cleavage of the 5,8-dimethoxyquinolines **12** and **13** to give the 5,8-dihydroxyquinolines **22** and **23** was effected with HBr. Oxidation of **22** and **23** with dichromate gave the 5,8-quinolinediones **25** and **26**. Oxidative amination of **25** with hydrazoic acid and 2-(diethylamino)ethylamine was shown to give 6-amino- and 6-[[2-(*N,N*-diethylamino)ethyl]amino]-2,4-dimethyl-5,8-quinolinediones (**24** and **28**), respectively. Also, the oxidative addition of *p*-chlorobenzenethiol to **26** gave both the mono- and bis(*p*-chlorophenylthio)-5,8-quinolinediones (**20** and **21**).

Both the 5,8-quinolinedione and 5,8-dimethoxyquinoline systems have provided compounds with antimalarial activity.[1-3] Recently, some 6-[(4-diethylamino-1-methylbutyl)amino]-5,8-dimethoxyquinolines were found to be as well tolerated by mice and canaries as chloroquine and to be as active against *Plasmodium vinckei* and the erythrocytic stages of *Plasmodium cathemerium* as primaquine. Also, no general cross resistance was observed when one of these compounds was tested against a strain of *Plasmodium berghei* fully resistant to chloroquine.[1] In this paper we wish to report our investigations on the preparation of 6-amino-5,8-quinolinediones and 6-amino-5,8-dimethoxyquinolines.

Several methods for the preparation of the 6-aminoquinolines **14** and **15** were investigated. Catalytic hydrogenation of 2,5-dimethoxy-4-nitroacetanilide with Raney nickel in EtOH gave the aniline **1**, which was condensed with acetylacetone at 160° to give the 4-anilino-3-penten-2-one **4**. However, the formation of **9** by treatment of **4** with a variety of reagents was unsuccessful.[4,5]

The second approach involved the condensation of the nitroaniline **2** with acetylacetone to give **5** followed by cyclization of the latter to give **10**. However, only a minor amount of **5** was formed at 150°, which was attributed to the relatively low nucleophilicity of the amino group of **2** when compared with that of **1**. The presence of **5** (M^+ 280) in the reaction mixture was confirmed by isolation of a sample by thick-layer chromatography. No ring closure to **10** was observed when **5** was refluxed in either diphenyl ether or toluene containing piperidine. In contrast, the condensation of **2** with trifluoroacetylacetone at 130° gave a good yield of **6**, which was attributed to the increased electrophilic character of the trifluoroacetyl carbonyl group of trifluoroacetylacetone when compared with that of acetylacetone. Although mass spectral analyses indicated that a trace amount of **11** was formed by treatment of **6** (R = CF_3) with concentrated H_2SO_4 at 100°, no cyclization was observed when **6** (R = CF_3) was treated with ei-

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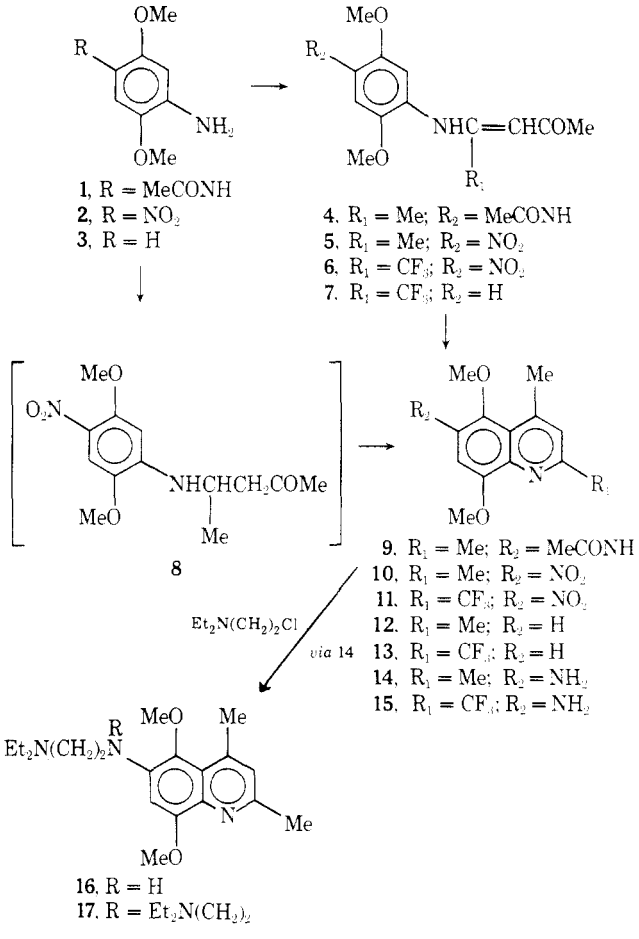
ther refluxing diphenyl ether or hot phosphorus oxychloride. Also, reaction of 6 (R = CF_3) with $BF_3 \cdot Et_2O$ appeared to give only a boron difluoride derivative, identified by the mass spectrum which showed a strong molecular ion at 382 and fragment ions at 367 $(M - Me)^+$, 363 $(M - F)^+$, and 313 $(M - CF_3)^+$.

The successful route to **14** involved the condensation of **2** with 3-penten-2-one in the presence of arsenic acid to give a 16–19% purified yield of **10**, no doubt formed *via* the intermediate **8**.‡ No increase in the yield of **10** was obtained by the use of either a large excess of 3-penten-2-one and shorter reaction time or a large excess of both 3-penten-2-one and arsenic acid. A better method for the preparation of **10** resulted from an investigation of the nitration of 5,8-dimethoxy-2,4-dimethylquinoline (**12**).[7] Although nitration of a suspension of **12** with a mixture of HNO_3–Ac_2O by the procedure of Dann[8] appeared to give mainly degradation products along with a minor amount of **10**, treatment of a suspension of **12** in trifluoroacetic anhydride with fuming nitric acid gave a 58% yield of **10**. The nitration of the 2-(trifluoromethyl)quinoline **13** by a similar procedure gave **11**. The preparation of **13** involved the condensation of **3** with trifluoroacetylacetone to give **7** followed by cyclization of **7** with concentrated H_2SO_4. Column chromatography of the mixture resulting from nitration of **13** gave two by-products. One was identified by elemental analysis and spectral data as the oxime of 5,8-dimethoxy-6-nitro-2-(trifluoromethyl)-4-quinolinecarboxaldehyde, presumably formed by a route involving nitrosation of the 4-methyl group of **11**.§ A second minor by-product was identified by its mass spectrum as 4-methyl-2-(trifluoromethyl)-5,8-quinolinedione, apparently resulting from oxidative demethylation of **11**. Catalytic hydrogenation of **10** and **11** in the presence of Raney nickel gave the desired 6-aminoquinolines **14** and **15** (Scheme I).

The condensation of **15** with 5-(diethylamino)-2-pentanone to give the corresponding azomethine derivative was unsuccessful in either refluxing toluene containing *p*-toluenesulfonic acid or hot diphenyl ether over the temperature range 165–250°. In the latter, decomposition of **15** occurred at the higher temperatures. Apparently the nucleophilicity of the amino group of **15** is reduced by the electron-withdrawing trifluoromethyl group since **14** has been reported to undergo condensation reactions with carbonyl derivatives.[8] Treatment of **14** first with sodium amide and then with 2-(diethylamino)ethyl chloride[10] in refluxing xylene gave an excellent yield of **16**. A second alkylation of **16** with 2-(diethylamino)ethyl chloride in DMSO containing sodium hydride at 65° gave a good yield of **17**. Treatment of **14** with sodium amide and 2-(diethylamino)ethyl chloride in liquid ammonia gave incomplete conversion to a mixture of **16** and **17**, which was indicated by thin-layer chromatography and mass spectral analysis.

In the preparation of 5,8-quinolinediones and related compounds, cleavage of the methoxy groups of **12** with refluxing 48% HBr for 5, 7, and 16 hr gave respectively 75, 85, and 96% conversion to the hydrobromide salt of **22**. The latter was readily methylated in DMAC with dimethyl sulfate in the presence of sodium hydride to give **12** in 90.8%. Similarly, alkylation of **22** with bromoethyl acetate gave a good yield of dialkylated products, **19** and the corresponding product resulting from hydrolysis of one of the side-chain ester functions (mass spectrum). Pure **19** was obtained from the mixture by column chromatography. The nitration of **19** occurred readily in trifluoroacetic anhydride to give **18**; however, hydrolysis of the ester functions with base in EtOH resulted in displacement of one of the hydroxyethoxy groups to give an ethoxyquinoline (see Experimental Section).

Scheme I



The oxidation of **22** with $FeCl_3$ in 5 *N* HCl has been reported to give **25**,[11] but this procedure gave a low yield of product that was difficult to purify. However, treatment of the hydrobromide of **22** with dichromate in H_2SO_4 gave a good yield of **25**. Reduction of **25** with a variety of reagents gave the 5,8-dihydroxyquinoline **22**. Reactions similar to those described above were used for the conversion of **13** to **23** and the latter to **26**.

Addition of hydrazoic acid to **25** gave directly the 6-aminoquinolinedione **24** formed by intramolecular oxidation–reduction of the intermediate 6-azido-5,8-dihydroxyquinoline. Reduction of **24** with diborane gave **27**, which was methylated in DMAC in the presence of sodium hydride with dimethyl sulfate to give **14**. This result indicated that oxidative amination of **25** with hydrazoic acid occurred at the 6 rather than the 7 position of the ring. Also, the oxidative amination of **25** with 2-(diethylamino)ethylamine in EtOH in the presence of $CeCl_3$ gave the 6-aminoquinolinedione **28**.= The structure of **28** was confirmed by reduction to the corresponding 5,8-dihydroxyquinoline (M^+ 303) and alkylation of a solution of the latter in DMAC with dimethyl sulfate in the presence of sodium hydride to give a mixture containing **16** (M^+ 331, tlc). Similarly, oxidative addition of *p*-chlorobenzenethiol to **26** gave a mixture of **20** and **21**, which were separated by column chromatography (Scheme II).

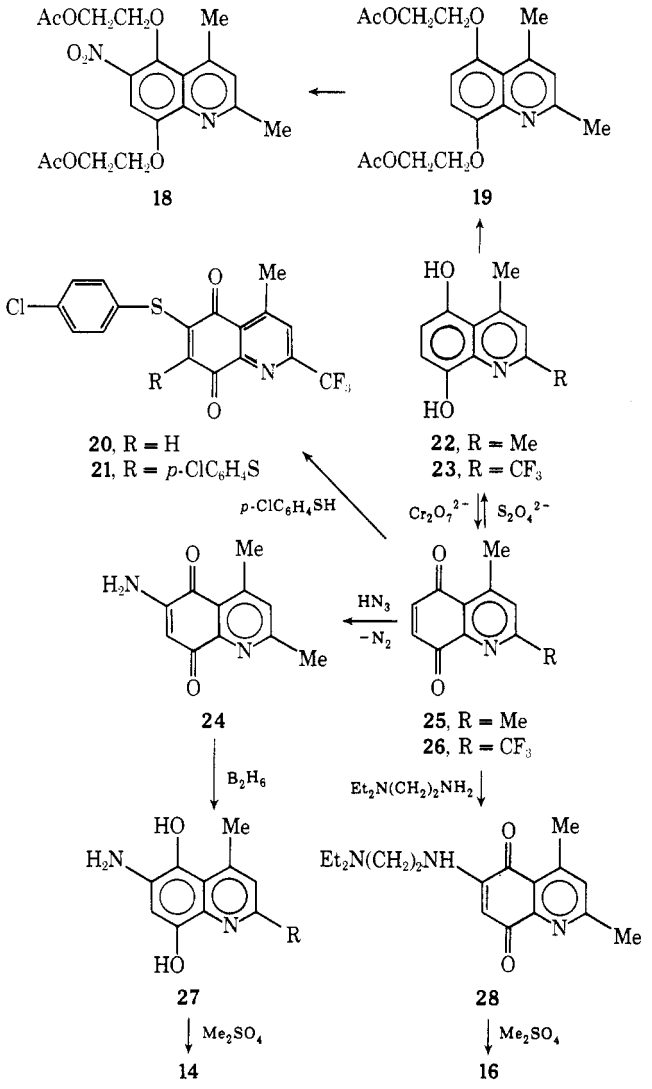
Most of these compounds were tested against lethal,

‡A similar procedure was used for the preparation of the corresponding 2-methylquinoline (see ref 6).

§A related type of reaction with methylpyridines has been observed (see ref 9).

=The oxidative amination of 5,8-quinolinedione in the 6 position with arylamines has been reported (see ref 12).

Scheme II



blood-induced *P. berghei* infections in mice.[13] Borderline activity was observed for **16**, which gave an increase in life span of 5.9 days at a dose of 640 mg/kg. Compounds **11–13, 17, 22, 23, 25, 26,** and **28** were inactive in this test. Only compounds **22, 23, 25,** and **26** were considered to be toxic. Against *Plasmodium gallinaceum* in chicks,[14] activity was observed for **25** (ILS, 5.4 days, 40 mg/kg) and **28** (ILS, 4.9 days, 20 mg/kg); however, both compounds showed toxicity at these doses. Compounds **13, 15, 23, 24,** and **26** were inactive in this test. These compounds were toxic at low doses with the exception of **13** and **24.**

Experimental Section**

4-(2,5-Dimethoxy-4-nitroanilino)-5,5,5-trifluoro-3-penten-2-one (6). A solution of **2** (1.00 g, 5.05 mmol) and trifluoroacetylacetone (5 ml) was refluxed under N_2 in a 130° oil bath for 2 hr and evaporated to dryness *in vacuo* to give a dark yellow solid: yield 1.71 g. The solid was triturated with petroleum ether (100 ml) and dissolved in EtOAc (25 ml); the resulting solution was diluted very slowly with petroleum ether (250 ml) until crystallization occurred. The yellow crystals were collected by filtration, washed with petroleum ether, and dried *in vacuo* over P_2O_5 at room temperature: yield 1.31 g (78.1%); mp 121–123°. A 100-MHz pmr spectrum in DMSO-d_6 solution showed >C=CHC(=O)- absorption at 5.79 ppm and a second, much smaller peak at 5.44 ppm suggesting that this sample is mainly the *trans*-anilinoacetyl isomer containing a small amount of the cis isomer. *Anal.* ($C_{13}H_{13}F_3N_2O_5$) C, H, N.

4-(2,5-Dimethoxyanilino)-5,5,5-trifluoro-3-penten-2-one (7). A solution of **3** (20.0 g, 131 mmol) and trifluoroacetylacetone (40.6 g, 264 mmol) was stirred at room temperature for 1 hr followed by a gentle reflux under N_2 for 1 hr. The volatiles were removed *in vacuo,* and the dark, oily residue was dried for 18 hr over P_2O_5 *in vacuo* to give a soft semisolid. A solution of this crude material in Et_2O (200 ml) was treated with charcoal, filtered through Celite, diluted with hexane (600 ml), and cooled in a Dry Ice–acetone bath. The yellow crystalline solid was collected by filtration and washed quickly with cold hexane. Concentration of the filtrate to about one-fourth volume followed by cooling as described above gave a second crop of yellow solid. The combined crops (36.9 g, 97.4%) were dissolved in Et_2O (100 ml), and the solution was charcoaled, filtered, diluted with hexane (300 ml), and again cooled in Dry Ice to give a bright yellow crystalline solid: yield 35.3 g (93.2%); mp 40–42°. *Anal.* ($C_{13}H_{14}F_3NO_3$) C, H, N.

5,8-Dimethoxy-2,4-dimethyl-6-nitroquinoline (10). In a 300-ml three-necked flask fitted with a thermometer, a condenser, and an addition funnel, a mixture of **2** (9.91 g, 50.0 mmol), solid H_3AsO_4 (14.2 g, 100 mmol), 85% H_3PO_4 (50 ml), and 2 drops of antifoaming agent was heated at 95° (internal temperature) in a preheated oil bath. Dropwise addition of 90% technical grade 3-penten-2-one (12.6 g, 135 mmol) resulted in the immediate initiation of an exothermic reaction. External heat was removed, and a temperature of 95–97° was maintained by the rate of addition. During the last 25% of the addition, the temperature dropped below 95° and external heating was resumed until the addition was complete and for 10 min afterward. The total reaction time was about 25 min. The dark reaction mixture was poured onto ~300 g of ice and adjusted to pH 8 with cold concentrated NH_4OH. The aqueous supernatant was decanted from the precipitated tar, and the latter was washed with cold H_2O and dried *in vacuo* over P_2O_5. The black mass was extracted with boiling EtOAc (3 × 200 ml); the combined extract was charcoaled, filtered through Celite, and evaporated to give a black gum: yield 12.1 g. A solution of this gum in $CHCl_3$ was poured onto a 300-g silica gel column (70–325 mesh); elution with $CHCl_3$ gave two product-containing fractions (4.20 g) that were rechromatographed on a 200-g silica gel column. The two product-containing fractions (total 4.00 g, 30.5%) were recrystallized from isopropyl acetate to give chromatographically homogeneous, bright yellow needles: yield 2.48 g (18.9%); mp 175–177°. A sample from a previous run was dried *in vacuo* over P_2O_5 at 78°: mp 178–179°. *Anal.* ($C_{13}H_{14}N_2O_4$) C, H, N.

Nitration of Quinolines. A solution of fuming nitric acid (5.81 g, sp gr 1.59) in trifluoroacetic anhydride (50 ml) was added dropwise during 15 min to an ice-cold, vigorously stirred suspension of **12** (20.0 g, 92.3 mmol) in trifluoroacetic anhydride (300 ml). The resulting mixture was stirred at room temperature until complete solution occurred (~40 min). This solution was evaporated under reduced pressure, and a solution of the residual dark solid in $CHCl_3$ (200 ml) was washed with saturated Na_2CO_3 solution (2 × 200 ml) and with H_2O (100 ml). Evaporation of the resulting $CHCl_3$ solution gave a yellow solid: yield 22.4 g. A solution of the solid in $CHCl_3$ was chromatographed on a silica gel column (300 g, 70–230 mesh) that was poured and eluted with the same solvent. Fraction I was a chromatographically homogeneous sample of the yellow crystalline 6-nitroquinoline: yield 11.8 g (48.8%); mp 177–178°. Fraction II (4.7 g) contained mainly **10** contaminated with a small amount of unnitrated **12.** Recrystallization of this sample from isopropyl acetate gave an additional amount of homogeneous material: yield 2.3 g (9.6%); mp 175–177°. Fraction III was mainly **12:** yield 2.2 g (11% recovery).

Similarly, the nitration of **13** (19.0 g, 70.2 mmol) with fumic nitric acid (4.42 g) was carried out in trifluoroacetic acid (100 ml) at room temperature for 20 min. Column chromatography (silica gel, $CHCl_3$) gave a homogeneous sample of **11:** yield 13.8 g (62.3%). For analyses a sample was recrystallized from isopropyl acetate and dried *in vacuo* over P_2O_5 at 78°; mp 166–168°. *Anal.* ($C_{13}H_{11}F_3N_2O_4$) C, H, N.

From the column chromatography of **11** two by-products were obtained: 4-methyl-6-nitro-2-(trifluoromethyl)-5,8-quinolinedione (~0.7 g), identified by its mass spectrum (M^+ 286); and 5,8-dimethoxy-6-nitro-2-(trifluoromethyl)-4-quinolinecarboxaldehyde oxime (1.7 g), mp 229–231°, identified by its mass and pmr spectra. *Anal.* ($C_{13}H_{10}F_3N_3O_5$) C, H, N.

**Melting points were determined on a Mel-Temp apparatus. The mass and pmr spectra, respectively, were determined with a Hitachi Perkin-Elmer RMU-6D-3 spectrometer and with a Varian A-60A spectrometer using tetramethylsilane as an internal reference. Silica gel was obtained from Brinkmann Instruments, Inc., and thin-layer chromatograms were usually developed with mixtures of $CHCl_3$ and MeOH. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

The nitration of **19** (780 mg, 2.20 mmol) with fuming nitric acid (136 mg) in trifluoroacetic acid (20 ml) at room temperature for 45 min after column chromatography (silica gel, $CHCl_3$) gave **18**: yield 650 mg (73.9%). An analytical sample was obtained by recrystallizing a 100-mg portion from isopropyl acetate: yield 60 mg; mp 80–81°. *Anal.* ($C_{19}H_{22}N_2O_8$) C, H, N.

5,8-Dimethoxy-4-methyl-2-(trifluoromethyl)quinoline (13). Solid **7** (35.0 g, 121 mmol) was added rapidly portionwise to concentrated H_2SO_4, which had been precooled in an ice–salt bath. The mixture was transferred to a boiling water bath and heated for 15 min. The hot mixture was poured onto ~1500 g of ice, and with external cooling the solution was adjusted to pH 10–11 with 50% NaOH solution. The precipitated solid was collected by filtration and washed repeatedly with H_2O until neutral and free of Na_2SO_4: yield 31.5 g (96.2%). A solution of the crude solid in Et_2O (1 l.) was treated with charcoal, filtered through Celite, diluted with hexane (500 ml), and cooled in Dry Ice–acetone bath. The bright yellow crystals were collected by filtration, washed with cold hexane, and dried *in vacuo* over P_2O_5: yield 28.5 g (86.9%); mp 118–120°. The sample was chromatographically homogeneous. *Anal.* ($C_{13}H_{12}F_3NO_2$) C, H, F, N.

6-Amino-5,8-dimethoxy-2,4-dimethylquinoline Hydrochloride Hydrate (14). A. A solution of **10** (0.50 g, 1.90 mmol) in MeOH (100 ml) was hydrogenated over Raney nickel catalyst (~5 g) in a Parr shaking apparatus at an initial pressure of 3.7 kg/cm². The catalyst was removed by filtration under N_2; the filtrate, which became colored rapidly on contact with air, was chilled in an acetone–Dry Ice bath and evaporated to dryness under oil pump vacuum. The rate of evaporation was sufficient to cause external icing of the flask. The residue was dissolved in EtOH (100 ml) containing a slight excess of ~2 *N* ethanolic HCl to form the hydrochloride salt. The solution was treated with charcoal, filtered through Celite, and concentrated *in vacuo* to about 50 ml. Ether (400 ml) was added very slowly, and the precipitated granular yellow solid was collected under N_2 (extremely hygroscopic) and dried *in vacuo* over P_2O_5 at 65°: yield 0.52 g; melting point indefinite, decomposes gradually above 150°. The yellow solid was reprecipitated from absolute EtOH (40 ml) containing 2 *N* ethanolic HCl (1 ml) by careful addition of dry Et_2O (400 ml). The granular yellow solid was collected by filtration under N_2 and dried *in vacuo* over P_2O_5 at 78°: yield 0.44 g (72%); melting point indefinite, softens gradually 150–160°. The infrared and proton magnetic resonance spectra of this material were consistent with the assigned structure (M^+ 232). *Anal.* ($C_{13}H_{16}N_2O_2 \cdot 1.56HCl \cdot 1.83H_2O$) C, H, Cl, N.

B. A solution of **22**·2HBr resulting from borane reduction of **25** (0.30 g, 1.5 mmol) in dry DMAC (20 ml) was treated with a suspension of NaH (0.18 g, 7.4 mmol, prepared from 0.32 g of 57% oil dispersion) in DMAC (10 ml) followed by dimethyl sulfate (0.28 g, 2.2 mmol) and allowed to stand for 16 hr. The reaction mixture was evaporated to dryness *in vacuo* (oil pump, 40°). Water (50 ml) was added, and when H_2 evolution ceased, the mixture was adjusted to pH 5 with HCl and extracted with $CHCl_3$ (100 ml). The aqueous layer was adjusted to pH 10 and extracted with $CHCl_3$ (2 × 100 ml). The dried $CHCl_3$ extract was evaporated to dryness. A solution of the residual dark oil (0.3 g) in $CHCl_3$–MeOH (99:1) was chromatographed on a silica gel column (200 g). Elution with the same solvent gave several bands, which were collected in eight fractions totaling 0.13 g. Mass and pmr spectra and tlc showed that fraction four (0.06 g, 17%) was the desired **14**. Elution with $CHCl_3$–MeOH (97:3) gave a ninth fraction that was identified as **25** (0.01 g, 3.3%). A black band at the top of the column was not eluted.

6-Amino-5,8-dimethoxy-4-methyl-2-(trifluoromethyl)quinoline dihydrochloride (15) was prepared by a method similar to that described above for **14** from **11** (4.0 g, 12.5 mmol): yield 1.13 g (25%); mp 177–180° dec with prior charring. *Anal.* ($C_{13}H_{13}F_3N_2O_2 \cdot 2HCl$) C, H, Cl, N.

6-[[2-(Diethylamino)ethyl]amino]-5,8-dimethoxy-2,4-dimethylquinoline (16). A suspension of **10** (8.60 g, 32.8 mmol) in EtOH was hydrogenated over Raney nickel as described above to give **14**: yield 7.50 g (99%). A solution of this material in xylene was refluxed with commercial sodium amide (25% excess) for 3 hr. After treatment with 2-(diethylamino)ethyl chloride (100% excess), the mixture was refluxed for 16 hr. The reaction mixture was diluted with H_2O (300 ml); the resulting xylene layer was washed with H_2O (300 ml), dried over Na_2SO_4, and evaporated to give a brown oil. A solution of this oil was eluted with $CHCl_3$–MeOH (95:5) from a silica gel column to give chromatographically homogeneous material as a clear yellow viscous oil: yield 10.4 g (96.8%); M^+ 331. A solution of a portion of the oil (3.30 mmol) in Et_2O (200 ml) was treated dropwise with a solution of β-resorcylic acid (0.510 g, 3.30 mmol) in Et_2O (50 ml). The precipitated yellow solid was collected by filtration, washed liberally with Et_2O, and dried *in vacuo* over P_2O_5: yield 0.97 g. The filtrate was evaporated to dryness. A solution of the solid yellow residue in H_2O (50 ml) was adjusted to pH 11 with NaOH solution and extracted with Et_2O (2 × 100 ml). Based on the weight of the quinoline-free base thus recovered (0.26 g, 0.78 mmol), and equivalent amount of β-resorcylic acid was added under conditions similar to those described above to give a second crop of yellow resorcylate salt: yield 0.23 g. The total yield was 1.20 g; melting point sinters above 85°. A pmr spectrum indicated that the ratio of β-resorcylic acid to quinoline base was greater than 1:1. The approximate composition was calculated from the elemental analysis. Thin-layer chromatography showed two spots corresponding to the quinoline and acid components. *Anal.* ($C_{19}H_{29}N_3O_2 \cdot 1.58C_7H_6O_4$) C, H, N.

6-[[*N,N*-Bis(2-diethylamino)ethyl]amino]-5,8-dimethoxy-2,4-dimethylquinoline (17). Under an atmosphere of dry N_2, a slurry of NaH (0.530 g, 22.2 mmol, prepared from 0.940 g of 57% oil dispersion by washing with petroleum ether) in dry DMSO (50 ml) was added to a solution of **16** (6.70 g, 20.2 mmol) in DMSO (50 ml). The mixture was heated on an oil bath at 65° for 45 min, during which time mild frothing due to gas evolution occurred and a deep red-purple solution was formed. After the addition of freshly distilled 2-(diethylamino)ethyl chloride (4.11 g, 30.3 mmol), the resulting solution was stirred for 2 hr at room temperature and poured into cold H_2O (1 l.). The mixture was extracted with $CHCl_3$ (3 × 250 ml); the extract was washed with H_2O, dried over Na_2SO_4, and evaporated *in vacuo* to give a clear brown oil: yield 9.01 g. A solution of the oil in $CHCl_3$–MeOH (9:1) was chromatographed on a silica gel column (175 g, 70–230 mesh). Elution with $CHCl_3$–MeOH (9:1) gave a yellow band containing mainly **16** and a minor amount of **17**. Elution with $CHCl_3$–MeOH (4:1) gave a diffuse band of **17**, collected in several fractions totaling 4.61 g (53.0%). One of these fractions was chromatographically homogeneous and was shown to be the desired product by its mass (M^+ 430), infrared, and pmr spectra. A solution of this clear yellow oil (2.66 g, 6.18 mmol) in Et_2O (300 ml) and MeOH (1 ml) was treated dropwise with a solution of β-resorcylic acid (1.91 g, 12.4 mmol) in Et_2O (200 ml). The precipitated lemon-yellow solid was collected by filtration under N_2, washed with Et_2O (3 × 50 ml), and dried *in vacuo* over P_2O_5 at 65° for 4 hr: yield 4.10 g (87.8% conversion as the diresorcylate monohydrate); melting point indefinite, sinters gradually above 80°. *Anal.* ($C_{25}H_{42}N_4O_2 \cdot 2C_7H_6O_4 \cdot H_2O$) C, H, N.

5,8-Bis(2-acetoxyethoxy)-2,4-dimethylquinoline (19). A suspension of NaH (0.270 g, 11.1 mmol, prepared from 0.470 g of 57% NaH dispersed in oil by washing with petroleum ether) in dry DMAC (20 ml) was added under N_2 to a solution of **22** hydrobromide (1.00 g, 3.73 mmol) in DMAC (25 ml). After 10 min, the mixture was treated dropwise with a solution of 2-bromoethyl acetate (1.23 g, 7.37 mmol) in DMAC (25 ml). The dark solution was stirred at room temperature for 6 hr, and the volatiles were removed by oil pump evacuation on a 50° oil bath. A solution of the dark residue in $CHCl_3$ (100 ml) was washed with H_2O (2 × 50 ml), dried over Na_2SO_4, and evaporated to give a viscous brown oil that partially crystallized on standing: yield 1.26 g. This reaction was repeated under the same conditions except that an excess of 2-bromoethyl acetate (2.00 g) was used and the reaction time was increased to 18 hr: yield 1.29 g (97.1%). Both crude samples (2.55 g) from the above reactions were dissolved in 98:2 $CHCl_3$–MeOH, and the solution was chromatographed on a silica gel column (300 g). The first major fraction (0.13 g) was identified by mass spectral analysis as a monoalkylated quinoline (M^+ 275). The second fraction was identified by mass spectral (M^+ 361) and pmr analysis as the desired dialkylated quinoline: yield 0.90 g (33.8%); mp 74–75°. *Anal.* ($C_{19}H_{23}NO_6$) C, H, N.

A third major column fraction was identified by mass spectral analysis as the 5- (or 8-) acetoxyethoxy-8- (or 5-) (hydroxyethoxy)-quinoline (M^+ 319). A pmr spectrum indicated that this sample was probably a mixture of both structural isomers: yield 0.40 g (16.9%).

An additional 0.48 g (~18%) of material was collected which was a mixture (tlc) of components two and three. Thus, the total yield of dialkylated material was about 69%.

5,8-Dihydroxy-2,4-dimethylquinoline Monohydrobromide (22). A solution of **12** (87 g, 0.40 mol) in 48% HBr (500 ml) was refluxed under N_2 for 16 hr. Water (500 ml) was added cautiously to the hot reaction mixture; the bright yellow crystalline solid that deposited on cooling was collected by filtration, washed with

ice-cold H_2O (100 ml), and dried *in vacuo* over NaOH pellets and then P_2O_5: yield 106.9 g (98.4%); mp 290–292° with prior charring. *Anal.* ($C_{11}H_{11}NO_2 \cdot HBr$) C, H, Br, N.

Mass spectral and pmr analysis showed that the product contained a trace amount of unhydrolyzed **12**. In other experiments, the ether cleavage was only 75 and 85% complete after 5 and 7 hr of reflux, respectively.

5,8-Dihydroxy-4-methyl-2-(trifluoromethyl)quinoline (23) was prepared by a method similar to that described above for **22** from **13** (0.50 g, 1.8 mmol): yield 0.42 g (93.3%); mp 139–140°. *Anal.* ($C_{11}H_8F_3NO_2$) C, H, N.

6-Amino-2,4-dimethyl-5,8-quinolinedione (24). A suspension of **25** (4.68 g, 25.0 mmol) in absolute EtOH (560 ml) was cooled in an ice bath and treated with solid sodium azide (4.88 g, 75.0 mmol) and concentrated HCl (6.2 ml, ~75 mmol). The ice bath was removed after 15 min, and the red solution was stirred for 20 hr, gradually depositing an orange-red solid and evolving nitrogen. The solid was collected by filtration and triturated with cold H_2O (2 × 50 ml) to remove inorganic salts: yield 3.02 g (59.8%). This sample was recrystallized from EtOH (700 ml). The glistening red needles were recovered in two crops and dried *in vacuo* over P_2O_5: yield 2.29 g (45.4%); melting point charred extensively but melted >400°. *Anal.* ($C_{11}H_{10}N_2O_2$) C, H, N.

Evaporation of the aqueous filtrate to dryness gave a dark solid residue (1.5 g) that was shown to contain **24** by thin-layer chromatography.

2,4-Dimethyl-5,8-quinolinedione (25). A solution of $Na_2Cr_2O_7 \cdot 2H_2O$ (20.0 g, 67.2 mmol) in H_2O (100 ml) was added all at once to a solution of **22** hydrobromide (45.0 g, 157 mmol) and concentrated H_2SO_4 (25 ml) in H_2O (1200 ml). The resulting dark solution was cooled in an ice bath for 30 min. The deposit of tiny crystals that formed was collected by nitration, washed with cold H_2O, and dried *in vacuo* over P_2O_5: yield 17.7 g (56.7%); mp 152–153° dec (lit.[11] mp 156° dec). The filtrate was extracted with $CHCl_3$ (4 × 200 ml); the combined extract was stirred with anhydrous Na_2SO_4, decanted, and allowed to stand over fresh Na_2SO_4. The solution was filtered and evaporated to give a brown residue: yield 9.5 g. A solution of the residue in $CHCl_3$ (100 ml) was treated with charcoal and filtered through Celite. Hexane (600 ml) was added very slowly from an addition funnel until crystallization began, then more rapidly with magnetic stirring. The deposit of shiny yellow needles was collected by filtration, washed with hexane, and dried *in vacuo* over P_2O_5: yield 6.8 g (21.8%); mp 151–153° dec. Evaporation of the filtrate to a volume of ~50 ml followed by dilution with a large volume of hexane gave a third crop of brown needles: yield 1.2 g (3.9%); mp 147–149° dec. The total yield was 25.7 g (82.4%).

4-Methyl-2-(trifluoromethyl)-5,8-quinolinedione (26). A solution of $Na_2Cr_2O_7 \cdot 2H_2O$ (3.50 g, 11.6 mmol) in H_2O (25 ml) was added with stirring to a dark red solution of **23** (5.60 g, 22.9 mmol) and concentrated H_2SO_4 (4.50 g, 46.1 mmol) in H_2O (200 ml). After cooling in ice for 30 min, the fine, crystalline precipitate was collected by filtration, washed with H_2O, and dried *in vacuo* over P_2O_5: yield 4.20 g (76.5%); mp 158–159° with prior sintering. *Anal.* ($C_{11}H_6F_3NO_2$) C, H, N.

6-Amino-5,8-dihydroxy-2,4-dimethylquinoline Dihydrobromide (27). In a flask protected with a drying tube, a suspension of **24** (0.16 g, 0.79 mmol) in dry THF (20 ml) was treated with a solution of 1 *M* borane in THF (3 ml) under N_2. The resulting mixture was stirred for 45 min, warmed at 40–45° for 15 min, cooled, and treated with excess MeOH (10 ml). After H_2 evolution ceased, the clear red solution was cooled in Dry Ice and then evaporated to dryness *in vacuo* (oil pump). A second portion (5 ml) of MeOH was added and evaporated. A suspension of the residue in THF (40 ml) was treated with glacial HOAc (48 mg, 0.8 mmol). After 10 min, 48% HBr (0.5 ml) was added; the initially gummy precipitate became granular after standing for 15 min. The yellow solid was filtered off under N_2, washed with THF, and dried *in vacuo* over P_2O_5: yield 0.25 g (86.5%); mp 240–245° dec. A mass spectrum and tlc confirmed the structure as the desired hydroquinone, containing only a trace of quinone starting material. *Anal.* ($C_{11}H_{12}N_2O_2 \cdot 2HBr$) C, H, Br, N.

6-[[2-(*N,N*-Diethylamino)ethyl]amino]-2,4-dimethyl-5,8-quinolinedione (28). A mixture of **25** (4.00 g, 21.3 mmol), *N,N*-diethylethylenediamine (2.48 g, 21.3 mmol), and $CeCl_3 \cdot 7H_2O$ (0.78 g, 2.1 mmol) in absolute EtOH (200 ml) was stirred vigorously with access to the air for 72 hr. The dark solution was evaporated to dryness; an aqueous solution (500 ml) of the residue was treated with glacial HOAc (2 ml), adjusted to pH ~7 by addition of solid NaOAc, and extracted with $CHCl_3$ (5 × 250 ml). The $CHCl_3$ was dried over Na_2SO_4 and evaporated to give a black gum: yield 5.3 g. A solution of the gum in $CHCl_3$–MeOH (99:1) was chromatographed on a silica gel column (300 g, 70–325 mesh). Elution with $CHCl_3$–MeOH (99:1) gave a fast moving, bright yellow band: yield 85 mg. Mass spectral analysis showed that this was a mixture of **25** (M^+ 187), a dimeric form (M^+ 372), and possibly 6-ethoxy-2,4-dimethyl-5,8-quinolinedione (M^+ 231) and 6-diethylamino-2,4-dimethyl-5,8-quinolinedione (M^+ 258). Elution with $CHCl_3$–MeOH (9:1) gave **28** as a diffuse orange band: yield 3.7 g (58%). A solution of this crude product in MeOH (200 ml) was treated with charcoal, filtered through Celite, and evaporated to dryness. The residue was chromatographed on a silica gel column (250 g) as described above. The chromatographically homogeneous fractions were combined: yield 2.65 g (41.3%); mp 106–108°. *Anal.* ($C_{17}H_{23}N_3O_2$) C, H, N.

A portion of this material was converted to the hygroscopic dihydrochloride salt by precipitation with Et_2O from a solution in EtOH containing a slight excess of HCl. *Anal.* ($C_{17}H_{23}N_3O_2 \cdot 2HCl$) C, H, N.

6-(*p*-Chlorophenylthio)-4-methyl-2-(trifluoromethyl)-5,8-quinolinedione (20) and 6,7-Bis(*p*-chlorophenylthio)-4-methyl-2-(trifluoromethyl)-5,8-quinolinedione (21). Solid *p*-chlorobenzenethiol (1.13 g, 7.80 mmol) was added to a stirred suspension of **26** (1.88 g, 7.80 mmol) and $CeCl_3 \cdot 7H_2O$ (0.29 g, 0.78 mmol) in absolute ethanol (45 ml). The resulting dark mixture was stirred for 2.5 days with access to the air and evaporated to dryness *in vacuo*. A solution of the residue in $CHCl_3$ (200 ml) was extracted with a solution of NaOAc (0.5 g) in H_2O (100 ml), dried over Na_2SO_4, and evaporated to dryness. A solution of the residual red glass (2.8 g) in $CHCl_3$ was chromatographed on a silica gel column (300 g, 200–325 mesh) to give two major components, a fast traveling red band and a slower traveling orange band. Elution of the red band followed by solvent evaporation gave a chromatographically homogeneous reddish purple glass that was identified by mass and pmr spectra as **21**: yield 0.99 g (24.1%); mp 146–147°. *Anal.* ($C_{23}H_{12}Cl_2F_3NO_2S$) C, H, N.

Elution of the orange band gave an orange powder identified by mass and pmr spectra as **20**: yield 0.95 g (31.8%); mp 195–198° dec. *Anal.* ($C_{17}H_9ClF_3NO_2S$) C, H, N.

The combined weights (0.99 and 0.95 g) of **20** and **21** represent an 80.1% yield based on *p*-chlorobenzenethiol.

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