Professor B. Nygård for valuable discussions on polarography and for providing facilities for the polarographic measurements.

References

(1) H. E. Paul and M. F. Paul, *Exp. Chemother.*, 2, 310 (1964).
(2) K. Miura and H. K. Reckendorf, *Progr. Med. Chem.*, 5, 320 (1967).
(3) D. R. McCalla, A. Reuvers, and C. Kaiser, *J. Bacteriol.*, 104, 1126 (1970).
(4) T. Sasaki, *Pharm. Bull.*, 2, 104 (1954).
(5) B. J. Lindberg, *Ark. Kemi*, 32, 317 (1970).
(6) E. Åkerblom, *Chem. Scr.*, in press.
(7) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York and London, 1969, p 134.
(8) U. E. Matter, C. Pascual, E. Pretsch, A. Pross, W. Simon, and S. Sternhell, *Tetrahedron*, 25, 691 (1969).
(9) E. Åkerblom, *Acta Chem. Scand.*, 21, 1437 (1967).
(10) E. Åkerblom, *Acta Chem. Scand.*, 21, 843 (1967).
(11) E. M. Peresleni, Yu. N. Sheinker, and N. P. Zosimova, *Zh. Fiz. Khim.*, 39, 926 (1965).
(12) A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, 71, 525 (1971).
(13) C. Hansch, A. Leo, and D. Nikaitani, *J. Org. Chem.*, 37, 3090 (1972).
(14) K. Skagius and B. Zetterberg, *Antibiot. Chemother.*, 11, 37 (1961).
(15) J. Meyer-Rohn, *Advan. Antimicrob. Antineoplastic Chemother., Proc. Int. Congr. Chemother., 3rd*, 563 (1964).
(16) H. J. Bachmann, R. J. Shirk, H. W. Layton, and G. A. Kemp, *Antimicrob. Ag. Chemother.*, 524 (1969).
(17) E. J. Lien, C. Hansch, and S. Anderson, *J. Med. Chem.*, 11, 430 (1968).
(18) K. Butler, H. L. Howes, J. E. Lynch, and D. K. Pirie, *J. Med. Chem.*, 10, 891 (1967).
(19) E. Kutter, H. Machleidt, W. Reuter, R. Sauter, and A. Wildfeuer, *Arzneim.-Forsch.*, 22, 1045 (1972).
(20) I. Saikawa and T. Maeda, *Yakugaku Zasshi*, 88, 369 (1968).
(21) H. A. Burch and W. O. Smith, *J. Med. Chem.*, 9, 405 (1966).
(22) H. A. Burch, *J. Med. Chem.*, 13, 288 (1970).
(23) E. B. Åkerblom and D. E. S. Campbell, *J. Med. Chem.*, 16, 312 (1973).
(24) K. Skagius, *Nitro Compounds, Proc. Int. Symp., 1963*, 475 (1964).
(25) S. Nakamura and M. Shimizu, *Chem. Pharm. Bull.*, 21, 130 (1973).
(26) K. Iwamoto, K. Oda, S. Muranishi, H. Sezaki, and K. Kakemi, *Chem. Pharm. Bull.*, 20, 1131 (1972).

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

Carroll Temple, Jr.,* Jerry D. Rose, and John A. Montgomery

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205. Received December 7, 1973

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-

ther refluxing diphenyl ether or hot phosphorus oxychloride. Also, reaction of 6 (R = CF$_3$) with BF$_3$·Et$_2$O 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$_2$O 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$_2$SO$_4$. 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 an-

---

‡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).

Scheme I
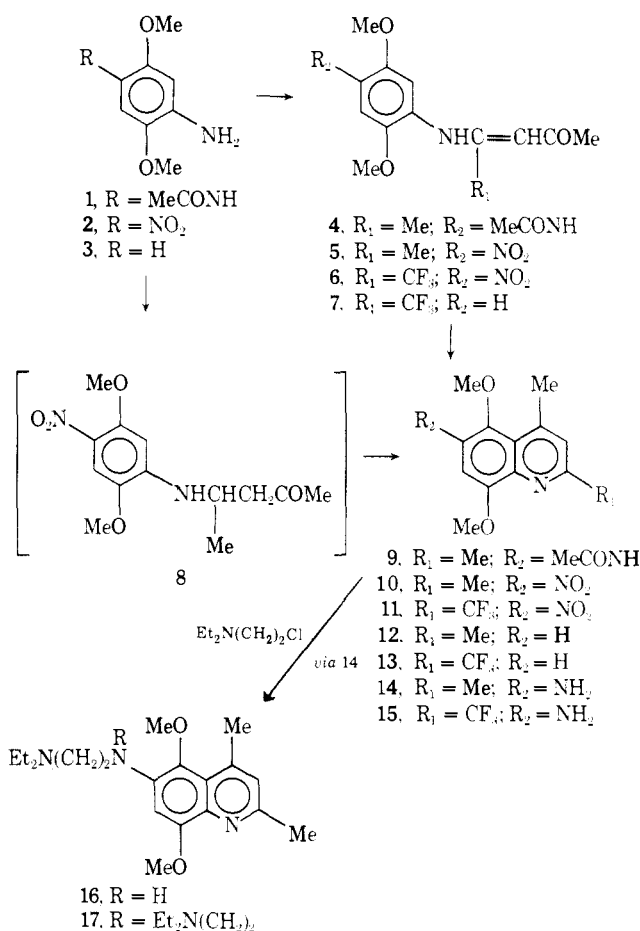
hydride to give 18; however, hydrolysis of the ester functions with base in EtOH resulted in displacement of one of the hydroxyethoxy groups to give an ethoxyquinoline (see Experimental Section).

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$_2$SO$_4$ 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,

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

Scheme II

20, R = H
21, R = p-ClC$_6$H$_4$S

22, R = Me
23, R = CF$_3$

24

25, R = Me
26, R = CF$_3$

27

28

14

16
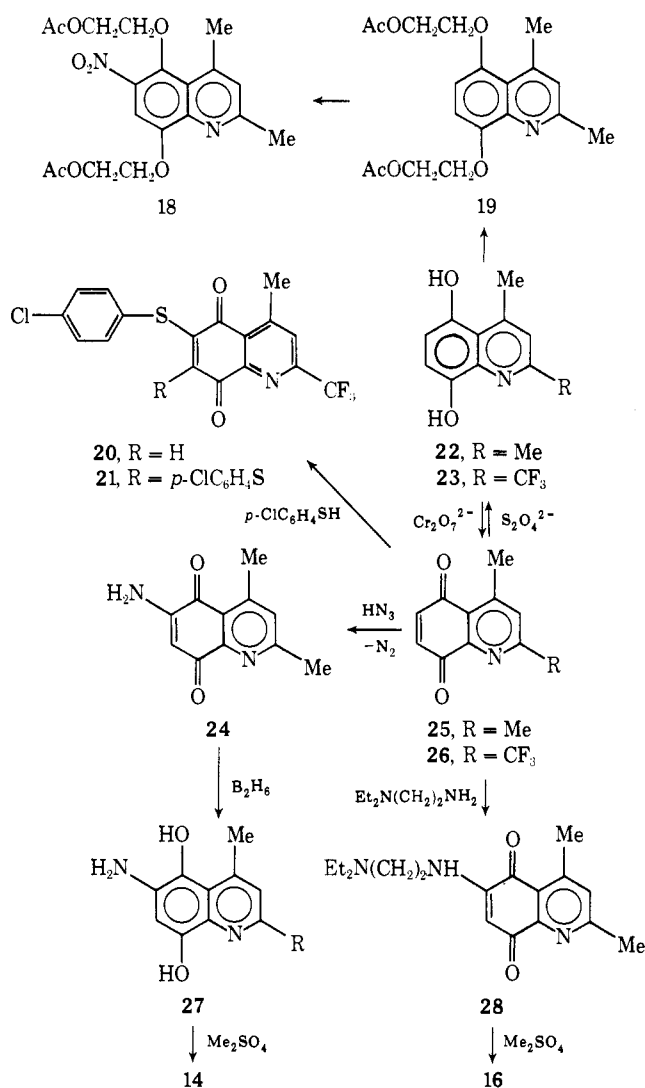
blood-induced *P. berghei* infections in mice.[13] Borderline activity was observed for 16, which gave an increase in life span of 5.9 days at a dose of 640 mg/kg. Compounds 11–13, 17, 22, 23, 25, 26, and 28 were inactive in this test. Only compounds 22, 23, 25, and 26 were considered to be toxic. Against *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$_2$O$_5$ 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$_3$N$_2$O$_5$) 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$_2$O$_5$ *in vacuo* to give a soft semisolid. A solution of this crude material in Et$_2$O (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$_2$O (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$_3$NO$_3$) 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$_3$AsO$_4$ (14.2 g, 100 mmol), 85% H$_3$PO$_4$ (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$_4$OH. The aqueous supernatant was decanted from the precipitated tar, and the latter was washed with cold H$_2$O and dried *in vacuo* over P$_2$O$_5$. 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$_2$O$_5$ at 78°: mp 178–179°. *Anal.* (C$_{13}$H$_{14}$N$_2$O$_4$) 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$_2$CO$_3$ solution (2 × 200 ml) and with H$_2$O (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$_2$O$_5$ at 78°; mp 166–168°. *Anal.* (C$_{13}$H$_{11}$F$_3$N$_2$O$_4$) 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$_3$N$_3$O$_5$) C, H, N.

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$_2$O$_8$) 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$_2$SO$_4$, 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$_2$O until neutral and free of Na$_2$SO$_4$: yield 31.5 g (96.2%). A solution of the crude solid in Et$_2$O (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$_2$O$_5$: yield 28.5 g (86.9%); mp 118–120°. The sample was chromatographically homogeneous. *Anal.* (C$_{13}$H$_{12}$F$_3$NO$_2$) 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/cm^2. 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$_2$O$_5$ 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$_2$O (400 ml). The granular yellow solid was collected by filtration under N$_2$ and dried *in vacuo* over P$_2$O$_5$ 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$_2$O$_2$·1.56HCl·1.83H$_2$O) 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$_3$N$_2$O$_2$·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$_2$O (300 ml); the resulting xylene layer was washed with H$_2$O (300 ml), dried over Na$_2$SO$_4$, 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$_2$O (200 ml) was treated dropwise with a solution of β-resorcylic acid (0.510 g, 3.30 mmol) in Et$_2$O (50 ml). The precipitated yellow solid was collected by filtration, washed liberally with Et$_2$O, and dried *in vacuo* over P$_2$O$_5$: yield 0.97 g. The filtrate was evaporated to dryness. A solution of the solid yellow residue in H$_2$O (50 ml) was adjusted to pH 11 with NaOH solution and extracted with Et$_2$O (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$_3$O$_2$·1.58C$_7$H$_6$O$_4$) 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$_2$O (1 l.). The mixture was extracted with CHCl$_3$ (3 × 250 ml); the extract was washed with H$_2$O, dried over Na$_2$SO$_4$, 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$_2$O (300 ml) and MeOH (1 ml) was treated dropwise with a solution of β-resorcylic acid (1.91 g, 12.4 mmol) in Et$_2$O (200 ml). The precipitated lemon-yellow solid was collected by filtration under N$_2$, washed with Et$_2$O (3 × 50 ml), and dried *in vacuo* over P$_2$O$_5$ 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$_4$O$_2$·2C$_7$H$_6$O$_4$·H$_2$O) 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$_2$O (2 × 50 ml), dried over Na$_2$SO$_4$, 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.

References

(1) V. E. Fink, P. Nickel, and O. Dann, *Arzneim.-Forsch*, 1775 (1970).

(2) P. Nickel, L. Schrimpl, E. Fink, and O. Dann, *Justus Liebigs Ann. Chem.*, 744, 119 (1971).

(3) T. H. Porter, F. S. Skelton, and K. Folkers, *J. Med. Chem.*, 15, 34 (1972).

(4) E. Roberts and E. B. Turner, *J. Chem. Soc.*, 1832 (1927).

(5) K. Campbell and I. Schaffner, *J. Amer. Chem. Soc.*, 67, 86 (1945).

(6) E. F. Elslager, M. P. Hutt, and L. M. Werbel, *J. Heterocycl. Chem.*, 6, 99 (1969).

(7) F. Lions, W. H. Perkins, Jr., and R. Robinson, *J. Chem. Soc.*, 1158 (1925).

(8) O. Dann, Belgium Patent 755,975 (1971).

(9) H. F. Ferrer and J. P. Lawrence, *J. Org. Chem.*, 37, 3662 (1972).

(10) G. A. C. Gough and H. King, *J. Chem. Soc.*, 2437 (1938).

(11) R. Long and K. Schofield, *J. Chem. Soc.*, 3161 (1953).

(12) Y. T. Pratt, *J. Org. Chem.*, 27, 3905 (1962).

(13) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, 10, 431 (1967).

(14) T. H. Porter, C. M. Bowman, and K. Folkers, *J. Med. Chem.*, 16, 115 (1973).