extracts were dried ($MgSO_4$) and concentrated *in vacuo*. An HCl salt of the residue was prepared; yield 3.80 g (24%), mp 178–180°. *Anal.* ($C_{23}H_{26}ClN_3O_3 \cdot HCl \cdot 2H_2O$) C, H, N.

3-[β-Keto-γ-(3-hydroxy-2-pyridyl)propyl]-4-quinazolone (3c).—A solution of **2c** (1.91 g, 0.004 mole) in 100 ml of distilled H_2O was hydrogenated over 0.3 g of 5% Pd–C at atmospheric pressure and temperature. After 18 hr the catalyst was removed, a saturated solution of $NaHCO_3$ was added, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ solution was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was converted to an HCl salt.

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Synthesis and Antimalarial Activity of Amodiaquine Analogs[1]

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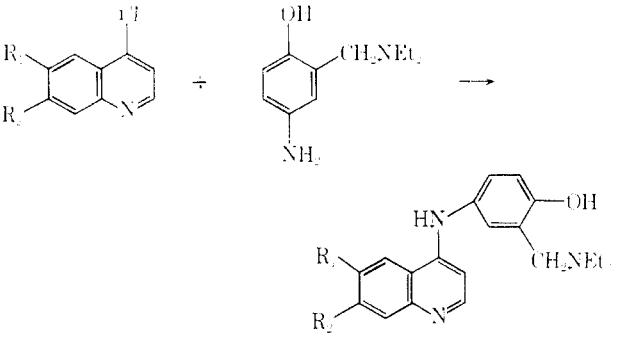
Ever since the initial discovery that certain α-dialkylamino-*o*-cresols possessed antimalarial activity,[3] chemists have tried to incorporate this moiety in a host of candidate drugs. One such agent, 7-chloro-4-(3-diethylaminomethyl-4-hydroxyanilino)quinoline or amodiaquine, was first prepared by Burckhalter's group.[4] Today, amodiaquine is one of the most widely used drugs for the strains of parasites susceptible to its schizontocidal properties. It displays gametocytocidal action against *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae* but not against *Plasmodium falciparum*.[5] Substituted analogs of amodiaquine have been prepared, but virtually none of these appeared to be superior to the parent compound.[4,6]

We wish to report the synthesis of three related 4-aminoquinolines bearing the same pendant phenolic Mannich base at C-4 as amodiaquine. In primary mouse screens against *Plasmodium berghei* and in *Plasmodium gallinaceum* infected chicks, these materials displayed impressive antimalarial acitivity.

The synthetic route in all cases involved displacement upon the corresponding 4-chloroquinoline by the deacetylated, *in situ* generated 4-hydroxy-3-diethylaminomethylaniline. The requisite 4-chloroquinolines were prepared by standard methods from the 2-carbomethoxy-4(1H)-quinolones[7] by saponification, decarboxylation, and chlorination. The selection of the 6-methoxy- and 7-halo-containing functions for incorporation in these candidate materials was predicted by their demonstrated potency in many other aminoquinoline antimalarials.



1, $R_1 = OCH_3$; $R_2 = Cl$
2, $R_1 = OCH_3$; $R_2 = F$
3, $R_1 = OCH_3$; $R_2 = CF_3$
amodiaquine, $R_1 = H$; $R_2 = Cl$

Biological Activity.—Shown in Table I are comparison data for amodiaquine[8] and our synthetic analogs in the Rane mouse and chick profiles. From this primary screening it would appear that **1** and **2** are somewhat more active against *P. berghei* than amodiaquine itself. These substances effected four cures out of five test animals at the 160-mg/kg level *vs.* three for amodiaquine. Comparison at the 40-mg/kg level in the mouse screen permitted the same conclusion. The trifluoromethyl analog **3** is less active than the comparison compounds.

Experimental Section[9]

Melting points were obtained in microcapillaries on a Mel-Temp apparatus and are uncorrected. Nmr spectra were obtained on a Varian A-60 spectrometer and are reported in δ ppm units *vs.* TMS standard.

6-Methoxy-7-trifluoromethyl-4(1H)-quinolone.—A solution of 0.04 mole of methyl 6-methoxy-7-trifluoromethyl-4(1H)-quinolone-2-carboxylate[7] in 40 ml of 10% (w/w) aqueous NaOH was refluxed for 1.5 hr, filtered while hot, cooled to ice-bath temperatures, and neutralized with 6 *N* HCl. The precipitated acid was collected, washed well (H_2O), vacuum dried, and added as a powder in small portions to 50 ml of boiling Ph_2O. After the addition process, which required approximately 1 hr to minimize frothing, the medium was heated for an additional 10 min, cooled, diluted with 800 ml of 30–60° petroleum ether, and filtered. The crude product (7.3 g or 75%) was purified by thorough washing with hot petroleum ether and double vacuum sublimation, mp 256–264° dec. *Anal.* ($C_{11}H_8F_3NO_2$) C, H, N.

4-Chloro-6-methoxy-7-trifluoromethylquinoline.—A mixture of 0.46 mole of 6-methoxy-7-trifluoromethyl-4(1H)-quinolone and 200 ml of $POCl_3$ was refluxed for 2 hr. Excess $POCl_3$ was removed by vacuum distillation and the residue was cooled and poured over 300 g of chopped ice. After 1 hr, the solution was adjusted to pH 9 with aqueous NH_3 and the precipitated halo heterocycle was isolated by filtration, yield 106 g (88%). An analytical sample was prepared by vacuum sublimation, mp 153–155°. *Anal.* ($C_{11}H_7ClF_3NO$) C, H, N.

4-Chloro-6-methoxy-7-fluoroquinoline.—A solution of 0.16

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(2) NDEA Predoctoral Fellow 1968–1969.

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(8) Testing data in the Rane mouse screen for amodiaquine (Camoquin® or SN 10,751 are equivalent names) was provided by Dr. Bing T. Puon of the Walter Reed Army Institute of Research.

(9) Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements are within ± 0.4% of the theoretical values.

TABLE I

Compd	Test system[a]	Dose, mg/kg	Cures[b]
Amodiaquine	M	40	0
	M	160	3
	M	640	5
1	M	20	0
	M	40	1
	M	80	2
	M	160	4
	M	640	5
	C	80	0
	C	160	0
	C	320	1
2	M	20*	0
	M	40	1
	M	160	4
	M	640	5
	C	80	0
	C	160	0
	C	320	1
3	M	20*	0
	M	40*	0
	M	80	0
	M	160	2
	M	320	2
	M	640	4
	C	80	0
	C	160	0
	C	320	0

[a] Compounds screened against *P. berghei* in mice (M) by Dr. L. Rane; see T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967). A test system against blood-induced *P. gallinaceum* infection in white Leghorn cockerel chicks (C) has also been employed. Details of this chick screen will appear in a forthcoming publication from Dr. Rane's laboratory. [b] Number of animals out of five surviving to 60 days postinfection in mice or 30 days postinfection in chick. When mean survival time increase is 100% greater than normal survival time of the untreated infected test animals (7.0 ± 0.5 days in mice and 3.5 ± 0.5 days in chickens) the compound is defined as "active." Compounds were all classed as "active" except at those doses designated with an asterisk.

mole of methyl 6-methoxy-7-fluoro-4(1H)-quinolone-2-carboxylate[10] and 140 ml of 10% (w/w) aqueous NaOH solution was refluxed for 1.5 hr, filtered hot, cooled to ice-bath temperatures, and neutralized with 6 *N* HCl. The acid was thoroughly dried *in vacuo*, powdered, and added in small portions to 180 ml of boiling Ph_2O over a 70-min period. The cooled mixture was diluted with 2 l. of 30–60° petroleum ether and filtered to isolate the quinolone. This was converted directly to the corresponding 4-chloro compound by refluxing for 3 hr with 60 ml of $POCl_3$. Excess $POCl_3$ was removed by vacuum distillation and the remaining solution was added cautiously to 500 g of chopped ice. Neutralization (NH_4OH), filtration, and washing (H_2O) gave 20 g (59% based on methyl 6-methoxy-7-fluoro-4(1H)-quinolone-2-carboxylate) of 4-chloro-6-methoxy-7-fluoroquinoline. An analytical sample was prepared by double vacuum sublimation, mp 153–154°. The nmr spectrum (DMSO-d_6) revealed an *o*-F to proton coupling (H_8–F) at δ 7.92 ppm of 12 Hz, and a *m*-F to proton coupling (H_5–F) at 7.61 ppm of 9 Hz clearly ruling out the 5-fluoro-6-methoxy possibility. *Anal.* ($C_{10}H_7ClFNO$) C, N,N.

6-Methoxy-7-chloro-4-(3-diethylaminomethyl-4-hydroxyanilino)quinoline (1).—A solution of 5.9 g (0.025 mole) of *p*-acetamido-α-diethylamino-*o*-cresol[4] and 13 ml of 6 *N* HCl was refluxed for 1 hr and then neutralized with 50% NaOH to pH 6. An equimolar quantity of 4,7-dichloro-6-methoxyquinoline[11] and 25 ml of DMF[12] was then added. The mixture was heated at 90° for 24 hr before being cooled and diluted with H_2O. After filtration the solution was made slightly basic with NaOH and the precipitated solid was collected and taken up in $CHCl_3$. The $CHCl_3$ phase was washed (dilute aqueous NaOH, H_2O), dried ($MgSO_4$), and evaporated to dryness. The solid residue was recrystallized from MeOH (charcoal) to yield 4.5 g (47%) of yellow crystals. Several more recrystallizations from MeOH produced analytical material, mp 236–245° dec. *Anal.* ($C_{21}H_{24}ClN_3O_2$) C, H, N.

Compound **2**.—Application of the above procedure to 4-chloro-6-methoxy-7-fluoroquinoline gave the aminoquinoline as a light tan solid in 64% yield. After three recrystallizations from MeOH, analytical material was obtained, dec pt 246–247°, but no formation of a liquid phase up to 315°. *Anal.* ($C_{21}H_{24}FN_3O_2$) C, H, N.

6-Methoxy-7-trifluoromethyl-4-(3-diethylaminomethyl-4-hydroxyanilino)quinoline (3).—The amination of 4-chloro-6-methoxy-7-trifluoromethylquinoline as described above gave a 74% yield of the desired aminoquinoline as pale yellow needles, mp 218–224° dec. *Anal.* ($C_{22}H_{24}F_3N_3O_2$) C, H, N.

(10) In ref 7, a mixture of the 6-methoxy-7-fluoro- and the 5-fluoro-6-methoxyquinolinates was prepared. These isomers could not be separated, and a mixture was therefore employed for the synthetic sequence described above. An nmr analysis (*vide infra*) on the final 4-chloroquinoline obtained by the sequence showed that the isolated material was pure 4-chloro-6-methoxy-7-fluoroquinoline.

(11) H. R. Snyder, H. E. Freier, P. Kovacic, and E. M. Van Heyningen, *J. Am. Chem. Soc.*, **69**, 371 (1947).

(12) A larger quantity of DMF or higher reaction temperatures should be avoided because dimethylamination of the 4-Cl can occur under these conditions see: N. D. Heindel and P. D. Kennewell, *Chem. Commun.*, 38 (1969).

Arylglyoxal N,N-Disubstituted Hydrazones with Antiviral and Antifungal Activity

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In continuation of our study of aromatic glyoxals as antiviral agents, we prepared a series of N,N-disubstituted hydrazones of *para*-substituted phenylglyoxals. All compounds were subjected to the usual pharmacological screening, as well as to antiviral, antibacterial, and antifungal activity tests. The acute toxicity of the compounds was determined intraperitoneally in mice. The results are listed in Table I.

No activity was observed when the compounds were tested for smooth-muscle relaxing activity and for coronary vasodilator activity. Compounds **3**, **5**, **7**, and **26** showed anticonvulsant activity at doses of $0.2LD_{50}$ in electroshock, intraperitoneally in mice. In tests for antiinflammatory activity on the rat's formalin paw edema, **1**, **2**, **8**, **10**, **13**, **14**, **26**, **29**, **30**, **36**, **37**, **39**, and **41** were active intraperitoneally at 100–200 mg/kg.

All compounds were also tested in embryonated eggs infected with A-PR8 virus and vaccinia virus. Compounds **15** and **39** were active against A-PR8 virus, and **15** was also active against vaccinia virus (Table II).

The two active compounds are derivatives of diphenyl, which emphasizes the importance of this supporting moiety for antiviral activity.[1,2]

No compound showed antibacterial activity nor was any active against *Candida albicans*. Some product were active against *Trichophyton mentagrophytes*, gypseum type (2538) (Table III), namely N,N-dimethyl- and N,N-diethylhydrazones of 4-chloro-, 4-nitro-, 4-phenoxy-, and 4-phenylphenglyoxals; among the cyclic

(1) G. Cavallini and E. Massarani, *J. Med. Chem.*, **1**, 365 (1959).
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