Synthesis of Pyrimido[5,4-*c*]quinolines and Related Quinolines as Potential Antimalarials

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3-Ethylaminomethyl-2-methyl-4(1*H*)-quinolone (**1a**) and its 6-CH_3, 6-OCH_3, and 7-Cl derivatives were prepared by means of the Mannich reaction. Conversion to the 4-chloro derivatives and condensation with 3-chloroaniline gave the corresponding 4-(3-chloroanilino) derivatives. Cyclization of 4-(3-chloroanilino)-2,6-dimethyl-3-ethylaminomethylquinoline (**3a**) and its 6-OCH_3 derivative with paraformaldehyde gave 1-(3-chlorophenyl)-3,9-dimethyl-3-ethyltetrahydropyrimido[5,4-*c*]quinoline (**4a**) and the 9-OCH_3 derivative **4b**. Treatment of **4b** with benzaldehyde gave 1-(3-chlorophenyl)-3-ethyl-9-methoxy-5-styryltetrahydropyrimido[5,4-*c*]quinoline (**5**). 3-Benzylaminomethyl-6-methoxy-2-methyl-4(1*H*)-quinolone (**1e**) and 3,3′-(1,3-benzyliminodimethylene)di[2-methyl-4(1*H*)-quinolone] (**6b**) were also synthesized. The compounds were inactive as antimalarials.

A structure of type **5**, owing to the quinoline and tetrahydropyrimidine moieties, is designed to have a dual mode of antimalarial action and, thus, attack the parasite at two different metabolic sites. The same substance might be expected to possess a synergistic effect or an effect greater than that to be expected from either moiety alone. Owing to the flat quinoline of **5**, it might be expected to intercalate with DNA in the manner of the antimalarial chloroquine.[1,2] The tetrahydropyrimidine system might be expected to inhibit the enzyme dihydrofolate reductase in the same manner as pyrimethamine and trimethoprim.[3] The alicyclic tertiary nitrogen might serve as a conductophoric grouping as in the terminal side-chain nitrogen of chloroquine, but it would not be able to reach the phosphate groups of DNA as with chloroquine. It has been reported by Rubtsov[4] that the styryl group at the 2 position in 4-aminoquinolines increases antimalarial properties. Thus, introduction of the 2-styryl grouping, conceived as a means of removal of the three-dimensional dystherapeutic 2-methyl group and extension of the flatness of the quinoline ring, may be considered as a desirable structural alteration of the weakly effective 4-aminoquinaldine antimalarials. Introduction of the 3-chloroanilino moiety was intended to test whether or not a free hydrogen at the nitrogen of **5** is essential to antimalarial activity.

Chemistry. In the Mannich reaction with 2-methylquinoline, condensation occurs at the 2-methyl group,[5-7] while with 2-methyl-4(1*H*)-quinolone, it takes place at the 3 position.[8,9]

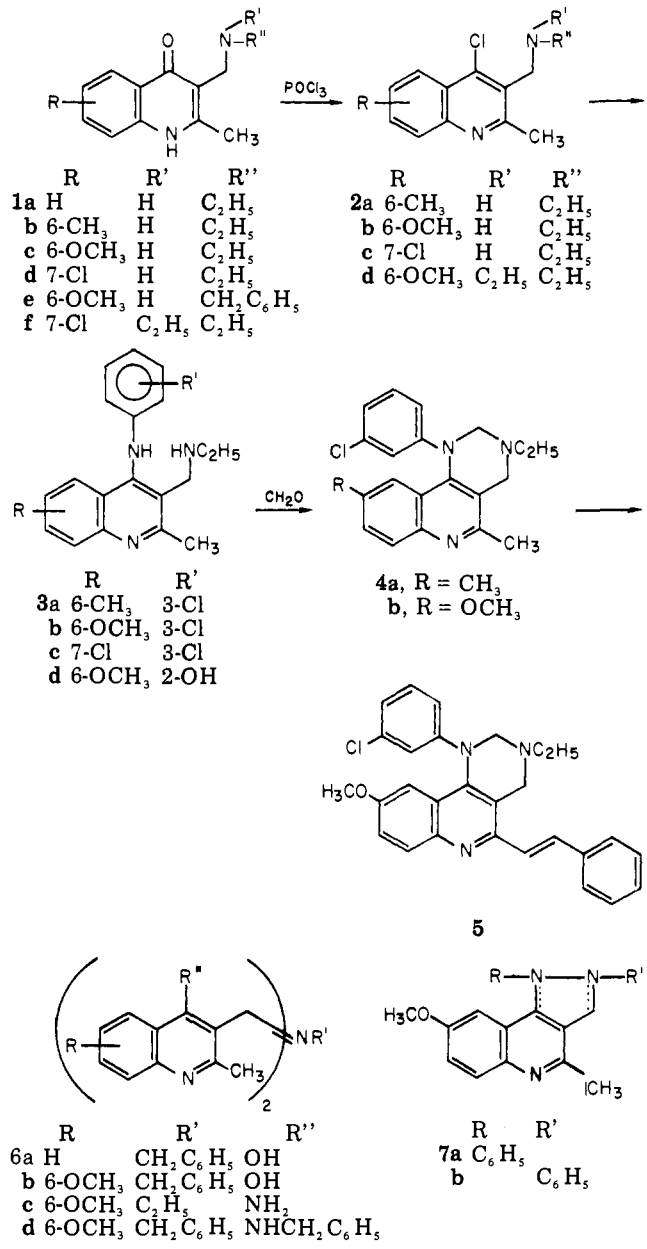
In the present work, 2-methyl-4(1*H*)-quinolone[10] and its 6-methyl,[11] 6-methoxy,[12] and 7-chloro[13] derivatives were allowed to undergo the Mannich reaction with ethylamine and paraformaldehyde. 3-Ethylaminomethyl-2-methyl-4(1*H*)-quinolone (**1a**) and the 6-CH_3 (**1b**), 6-OCH_3 (**1c**), and 7-Cl (**1d**) derivatives were thus obtained. Acetylation of **1c** gave its *N*-acetyl derivative. Treatment of **1b–d** with phosphorus oxychloride gave, respectively, the 4-chloro derivatives **2a–c** (Scheme I).

When **2a–c** were allowed to condense with 3-chloroaniline in acidic medium, 4-(3-chloroanilino) derivatives **3a–c** were obtained. Heating **3a** and **3b** with paraformaldehyde in alcoholic solution gave 1-(3-chlorophenyl)-5,9-dimethyl-3-ethyltetrahydropyrimido[5,4-*c*]quinoline (**4a**) and 1-(3-chlorophenyl)-3-ethyl-9-methoxy-5-methyltetrahydropyrimido[5,4-*c*]quinoline (**4b**). Treatment of **4b** with benzaldehyde in the presence of Ac_2O or fused $ZnCl_2$ as a catalyst gave 1-(3-chlorophenyl)-3-ethyl-9-methoxy-5-styryltetrahydropyrimido[5,4-*c*]-quinoline (**5**).

When benzylamine was used instead of ethylamine in the Mannich reaction with 2-methyl-4(1*H*)-quinolone or its 6-methoxy derivative, dimer **6a** or **6b** was obtained as the main product. However, use of excess benzylamine gave mainly **1e**.

When **2b** was allowed to react with 2-aminophenol in acidic medium, it gave 4-(2-hydroxyanilino)-3-ethylaminomethyl-6-methoxy-2-methylquinoline (**3d**). 7-

Scheme I



	R	R′	R″
1a	H	H	C_2H_5
b	6-CH_3	H	C_2H_5
c	6-OCH_3	H	C_2H_5
d	7-Cl	H	C_2H_5
e	6-OCH_3	H	$CH_2C_6H_5$
f	7-Cl	C_2H_5	C_2H_5

	R	R′	R″
2a	6-CH_3	H	C_2H_5
b	6-OCH_3	H	C_2H_5
c	7-Cl	H	C_2H_5
d	6-OCH_3	C_2H_5	C_2H_5

	R	R′
3a	6-CH_3	3-Cl
b	6-OCH_3	3-Cl
c	7-Cl	3-Cl
d	6-OCH_3	2-OH

4a, R = CH_3
b, R = OCH_3

5

	R	R′	R″
6a	H	$CH_2C_6H_5$	OH
b	6-OCH_3	$CH_2C_6H_5$	OH
c	6-OCH_3	C_2H_5	NH_2
d	6-OCH_3	$CH_2C_6H_5$	$NHCH_2C_6H_5$

	R	R′
7a	C_6H_5	
b		C_6H_5

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Table I. 3-Ethylaminomethyl-2-methyl-4(1*H*)-quinolones

Compd	R	Yield, %	Recrystn solvent	Mp, °C	Formula	Analyses
1a	H	50	Aq EtOH	344–348 dec	$C_{13}H_{16}N_2O$	C, H, N
1b	6-CH_3	80	Aq EtOH	359–361 dec	$C_{14}H_{18}N_2O$	C, H, N
1c	6-OCH_3	94	Aq EtOH	363–367 dec	$C_{14}H_{18}N_2O_2$	C, H, N
1d	7-Cl	85	EtOH	358–360 dec	$C_{13}H_{15}ClN_2O$	C, H, N

Table II. 4-Chloro-3-ethylaminomethyl-2-methylquinolines

Compd	R	Yield, %	Recrystn solvent	Mp, °C	Formula	Analyses
2a	6-CH_3	74	Aq EtOH	54–56	$C_{14}H_{17}ClN_2$	C, H, N
2b	6-OCH_3	55	Aq EtOH	66–67	$C_{14}H_{17}ClN_2O$	C, H, N
2c	7-Cl	60	EtOH	236–239	$C_{13}H_{14}Cl_2N_2 \cdot HCl$	C, H, N

Table III. 4-(3-Chloroanilino)-3-ethylaminomethyl-2-methylquinolines

Compd	R	Yield, %	Recrystn solvent	Mp, °C	Formula	Analyses
3a	6-CH_3	82	Et_2O	139–141	$C_{20}H_{22}ClN_3$	C, H, N
3b	6-OCH_3	56	Et_2O	153–157	$C_{20}H_{22}ClN_3O$	C, H, N
3c	7-Cl	67	EtOH	152–154	$C_{19}H_{19}Cl_2N_3$	C, H, N

Chloro-2-methyl-4(1*H*)-quinolone, when allowed to react with paraformaldehyde and diethylamine, gave 7-chloro-3-diethylaminomethyl-2-methyl-4(1*H*)-quinolone (**1f**). Hydrogenolysis of **1f** gave 7-chloro-2,3-dimethyl-4(1*H*)-quinolone, whose structure was confirmed through independent synthesis.[14]

Dry ammonia was passed into a hot solution of **2b** in phenol, according to analogous procedures.[15] However, only the 4-phenoxy derivative was isolated. When a phenolic solution of **2b** was heated with ammonium carbonate,[16] dimeric compound 3,3′-(1,3-ethyliminodimethylene)di(4-amino-6-methoxy-2-methylquinoline) (**6c**) was obtained in low yield. Condensation of **2b** with phenylhydrazine at 200 °C in mineral oil gave a product whose structure is either of two isomeric compounds, **7a** or **7b**. This result is consistent with the fact that the phenylhydrazones of ketonic Mannich bases form pyrazolines by internal amine exchange.[17,18]

Compound **2b**, upon reaction with benzylamine, gave 3,3′-(1,3-benzyliminodimethylene)di(4-benzylamino-6-methoxy-2-methylquinoline) (**6d**).

Biological. Compounds **1b**,**c**,**f**, **3b**, **4a**,**b**, and **5** were screened for antimalarial activity against blood-induced *Plasmodium berghei* in mice, according to the procedure of Rane.[19] They were found to be inactive at 640 mg/kg dosage. One (**5**) was screened against *Plasmodium gallinaceum* in the sporozoite-induced chick test, also according to Rane, and found to be inactive at 320 mg/kg dosage. All screening was carried out in Dr. Rane's laboratory.

Compounds **1b–f**, lacking a 4-amino function, were not expected to be active. Compounds **3b**, **4b**, and **5** were inactive, possibly because the alicyclic nitrogen could not reach the phosphate groupings of DNA.

Experimental Section

Melting points were taken in capillary tubes on a Mel-Temp block and are uncorrected. IR spectra were measured with a Perkin-Elmer 337 spectrophotometer. NMR spectra were recorded relative to standard Me_4Si on a Varian A-60A spectrometer. Satisfactory spectra were obtained for all compounds. Microanalyses were performed by Spang Microanalytical Lab., Ann Arbor, Mich. All analytical results were within 0.4% of the theoretical values.

3-Ethylaminomethyl-2-methyl-4(1*H*)-quinolones (Table I). The title compounds were obtained from the corresponding 2-methyl-4(1*H*)-quinolone by the following general procedure. A solution of the 2-methyl-4(1*H*)-quinolone derivative (0.1 mol), 0.3 g of paraformaldehyde, and 20 mL of $EtNH_2$ (70% in water) in 150 mL of EtOH was stirred at room temperature for 15 min. The mixture was gently heated without reflux for 1 h and then was refluxed with stirring. The reaction mixture became a clear solution after 3 h of reflux and stirring and then became turbid after another 4 h. It was allowed to cool and was then filtered. The filtrate was poured into H_2O and cooled overnight, whereupon a white precipitate was obtained. Yields and melting points are reported in Table I.

4-Chloro-3-ethylaminomethyl-2-methylquinolines (Table II). The following general method was applied. A mixture of the corresponding 3-ethylaminomethyl-2-methyl-4(1*H*)-quinolone derivative (0.075 mol) and 13.8 g (0.09 mol) of pure $POCl_3$ was heated in an oil bath at 145–150 °C for 3 h. The excess $POCl_3$ was distilled off and the reaction mixture was cooled, while being diluted with H_2O and basified with NaOH solution. During continual cooling, a viscous precipitate was formed. It was extracted with Et_2O. Yields and melting points are reported in Table II.

4-(3-Chloroanilino)-3-ethylaminomethyl-2-methylquinolines (Table III). The following general method was applied. A mixture of the 4-chloro-3-ethylaminomethyl-2-methylquinoline derivative (0.05 mol) and 6.38 g of 3-chloroaniline was dissolved in 100 mL of EtOH. The solution was acidified with concentrated HCl and then was refluxed for 10 h. The reaction mixture after concentration was treated with aqueous NaOH and was cooled. The precipitated base was dried. Yields and melting points are reported in Table III.

1-(3-Chlorophenyl)-3-ethyl-9-methoxy-5-methyltetrahydropyrimido[5,4-*c*]quinoline (4b). A mixture of 7.12 g (0.02 mol) of 4-(3-chloroanilino)-3-ethylaminomethyl-6-methoxy-2-methylquinoline (**3b**) and 0.62 g of paraformaldehyde in 100 mL of absolute EtOH was refluxed for 4 h. The reaction mixture was concentrated and was cooled to give 6 g (81% yield) of a white precipitate of **4b**, mp 124–126 °C. Recrystallization from Et_2O gave white needles: mp 145–147 °C; NMR peaks at δ 7.88–6.50 (7 H, m, aromatic protons), 4.30 and 3.28 (s, 4 H, $-CH_2$), 3.39 (3 H, s, OCH_3), 2.53 (5 H, approximate q, $-CH_2-$ of ethyl group and $-CH_3$), and 1.02 (3 H, t, $-CH_3$ of ethyl group). Anal. ($C_{21}H_{22}ClN_3O$) C, H, N.

1-(3-Chlorophenyl)-3-ethyl-9-methoxy-5-styryltetrahydropyrimido[5,4-*c*]quinoline (5). A mixture of 6.11 g (0.016 mol) of 1-(3-chlorophenyl)-3-ethyl-9-methoxy-5-methyltetrahydropyrimido[5,4-*c*]quinoline (**4b**), 2.55 g of benzaldehyde, and 0.3 g of fused $ZnCl_2$ was heated at 160 °C for 4 h. After the reaction mixture was cooled, it was treated with EtOH and 10% NaOH solution to give 5 g (68.5% yield) of a yellow precipitate, mp 152–155 °C. Recrystallization from EtOH elevated the melting point to 157–159 °C: NMR peaks at δ 8.15–6.49 (14 H, m, aromatic protons), 4.32 and 4.05 (4 H, s, $-CH_2-$, $-CH_2$), 3.40 (3 H, s, OCH_3), 2.54 (2 H, q, $-CH_2-$ of ethyl), and 1.04 (3 H, t, $-CH_3$ of ethyl

group). Anal. ($C_{28}H_{26}ClN_3O$) C, H, N.

1-(3-Chlorophenyl)-5,9-dimethyl-3-ethyltetrahydropyrimido[5,4-*c*]quinoline (4a). A mixture of 3.4 g (0.01 mol) of 4-(3-chloroanilino)-3-ethylaminomethyl-2,6-dimethylquinoline (**3a**) and 0.31 g of paraformaldehyde in 50 mL of absolute EtOH was refluxed for 6 h. The reaction mixture was concentrated and was cooled to give 2.7 g (77% yield) of a white precipitate (**4a**), mp 158–160 °C. Anal. ($C_{21}H_{22}ClN_3$) C, H, N.

3-Benzylaminomethyl-6-methoxy-2-methyl-4(1*H*)-quinolone (1e). A mixture of 18.9 g (0.1 mol) of 6-methoxy-2-methyl-4(1*H*)-quinolone, 3 g of paraformaldehyde, and 10.7 g (0.1 mol) of benzylamine in 150 mL of absolute ethyl alcohol was refluxed with stirring for 10 h. The white precipitate was collected on a filter and set aside. The filtrate was concentrated and was diluted with water. The mixture was cooled to give 1.5 g (5% yield) of **1e**, mp 375–378 °C dec. Recrystallization from aqueous alcohol did not change the melting point. Anal. ($C_{19}H_{20}N_2O_2$) C, H, N.

3,3′-(1,3-Benzyliminodimethylene)di[2-methyl-4(1*H*)-quinolone] (6a). A mixture of 7.95 g (0.05 mol) of 2-methyl-4(1*H*)-quinolone, 5.3 g (0.05 mol) of benzylamine, and 1.5 g of paraformaldehyde was refluxed in 75 mL of absolute ethyl alcohol. The mixture was allowed to reflux with stirring for 24 h. The white precipitate formed gave 10 g (73% yield) of **6a**, mp 344–348 °C dec. An analytical sample was obtained by precipitation from acidic alcohol with NH_4OH. There was no change in melting point. Anal. ($C_{29}H_{27}N_3O_2$) C, H, N.

3,3′-(1,3-Benzyliminodimethylene)di[6-methoxy-2-methyl-4(1*H*)-quinolone] (6b). The main product precipitated during the preparation of **1e** was found to be **6b**. It was obtained in 85% yield, mp 360–365 °C. It was insoluble in most organic solvents. An analytical sample was obtained through precipitation from acidic alcohol with NH_4OH. Anal. ($C_{31}H_{31}N_3O_4$) C, H, N.

3-Ethylacetylaminomethyl-6-methoxy-2-methyl-4(1*H*)-quinolone. A mixture of 2.5 g (0.001 mol) of 3-ethylaminomethyl-6-methoxy-2-methyl-4(1*H*)-quinolone (**1c**) and 20 mL of acetic anhydride was heated at 145 °C for 3 h. The reaction mixture turned to yellowish brown after the heating. It was diluted with water, neutralized with sodium hydroxide solution, and cooled. A yellowish product was obtained, 2 g (70% yield), which gave mp 203–205 °C. Recrystallization from ethyl alcohol gave mp 214–216 °C. Anal. ($C_{16}H_{20}N_2O_3$) C, H, N.

3-Ethylaminomethyl-4-(2-hydroxyanilino)-6-methoxy-2-methylquinoline (3d). A mixture of 2.6 g (0.001 mol) of 3-ethylaminomethyl-4-chloro-6-methoxy-2-methylquinoline (**2b**) and 1.1 g (0.001 mol) of 2-aminophenol was dissolved in 50 mL of absolute ethyl alcohol. The mixture was acidified with concentrated HCl and was refluxed for 10 h. The reaction mixture after concentration was neutralized with sodium hydroxide and was cooled. The yellow precipitated base was dried to give 3 g (89% yield) of **3d**, mp 305–210 °C. Recrystallization from alcohol gave mp 222–224 °C. Anal. ($C_{20}H_{23}N_3O_2$) C, H, N.

7-Chloro-3-diethylaminomethyl-2-methyl-4(1*H*)-quinolone (1f). This compound was prepared by the same method applied to 3-ethylaminomethyl-6-methoxy-2-methyl-4(1*H*)-quinolone (**1c**) by using diethylamine instead of ethylamine. The product obtained gave an 85% yield of **1f**, mp 334–336 °C. Recrystallization from alcohol gave the same melting point. Anal. ($C_{15}H_{19}ClN_2O$) C, H, N.

7-Chloro-2,3-dimethyl-4(1*H*)-quinolone. A mixture of 8.66 g (0.03 mol) of 7-chloro-3-diethylaminomethyl-2-methyl-4(1*H*)-quinolone (**1f**), 5 g of copper chromite, and 150 mL of absolute ethanol was placed in a bomb. Hydrogen was added and the mixture was shaken and heated gradually to 175 °C at an equilibrium pressure of 3000 lb for 4 h, when the calculated amount of hydrogen was consumed (0.045 mol). The bomb was allowed to cool to room temperature. Catalyst was removed by filtration, and the filtrate was concentrated and cooled to give 3 g (48% yield) of a yellowish white precipitate, mp 328–332 °C. It was recrystallized from alcohol, mp 330–332 °C. It was found to be identical with another specimen of the same compound prepared through condensation of *m*-chloroaniline and ethyl α-methylacetoacetate by way of the Conrad–Limpach reaction.[14]

3-Ethylaminomethyl-6-methoxy-2-methyl-4-phenoxyquinoline Hydrochloride. A mixture of 2.64 g (0.01 mol) of 4-chloro-3-ethylaminomethyl-6-methoxy-2-methylquinoline (**2b**) and 1.8 g of phenol was heated at 125 °C for 1 h. The deep blue colored solution was cooled and then was treated with concentrated NaOH solution. The phenoxy compound was extracted with ether and dried. Dry HCl was passed into the solution to give 3 g (83.7% yield) of a red-violet product, mp 221–224 °C. Recrystallization twice from absolute EtOH gave white crystals, mp 236-238 °C. Anal. ($C_{20}H_{23}ClN_2O_2$) C, H, N.

3,3′-(1,3-Ethyliminodimethylene)di(4-amino-6-methoxy-2-methylquinoline) (6c). A mixture of 10.5 g (0.04 mol) of 4-chloro-3-ethylaminomethyl-6-methoxy-2-methylquinoline (**2b**) and 18 g of phenol was heated to 75 °C. Powdered $(NH_4)_2CO_3$ (10 g) was added with stirring. The temperature was then raised to 170 °C and kept there 30 min. After the reaction mixture was cooled, it was treated with concentrated NaOH solution. The base was extracted with Et_2O and was dried over $CaCl_2$. The Et_2O was distilled off, and the viscous substance which remained was distilled under reduced pressure (0.05 mm) and with an internal heat of 185 °C. The viscous oily base was treated with Et_2O, whereupon a solid separated. The Et_2O solution yielded the 4-phenoxy derivative of **2b** (90% yield). The other insoluble substance, obtained in small amount (0.3 g), was considered to have the structure of **6c**, mp 200–205 °C. Recrystallization from EtOH gave an analytical sample, mp 209–211 °C. Anal. ($C_{26}H_{31}O_2N_5$) C, H, N.

8-Methoxy-4-methyl-1-phenyl-2*H*-pyrazolo[4,3-*c*]quinoline (7a or 7b). A mixture of 2.65 g (0.01 mol) of 4-chloro-3-ethylaminomethyl-6-methoxy-2-methylquinoline (**2b**) and 1.08 g (0.01 mol) of phenylhydrazine was gradually heated in 20 mL of paraffin oil. The temperature was raised to 200 °C and kept there for 1 h. The reaction mixture was cooled and a viscous solid was obtained. It was decanted from the oil and then washed with petroleum ether (bp 40–60 °C). Recrystallization from EtOH gave 0.2 g (6.9% yield) of a yellow substance, mp 161–163 °C. Another recrystallization from 95% EtOH gave yellow crystals, mp 169–172 °C. Anal. ($C_{18}H_{15}N_3O$) C, H, N.

3,3′-(1,3-Benzyliminodimethylene)di(4-benzylamino-6-methoxy-2-methylquinoline) (6d). A mixture of 2.64 g (0.01 mol) of 4-chloro-3-ethylaminomethyl-6-methoxy-2-methylquinoline (**2b**), 1.88 g (0.02 mol) of phenol, and 1.3 g (0.0125 mol) of benzylamine was heated at 130 °C for 24 h. The reaction mixture was then dissolved in 20 mL of absolute ethyl alcohol and the solution poured onto 300 mL of ether, whereupon a precipitate was obtained. Dry HCl was passed through the whole mixture. The hydrochloride salt was dissolved in water and then ammonium hydroxide was added. The base was extracted with ether and the solution was dried over magnesium sulfate. The ether was concentrated and the residue was cooled to yield 0.8 g (23% yield) of a white crystalline product (**6d**). Recrystallization from alcohol gave mp 210–211 °C. Anal. ($C_{45}H_{45}N_5O_2$) C, H, N.

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Imidazo[4,5-*f*]quinolines. 4. Synthesis and Anthelmintic Activity of a Series of Imidazo[4,5-*f*]quinolin-9-ols[1]

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A series of 2-arylimidazo[4,5-*f*]quinolin-9-ols has been prepared by a multistep procedure from various 5-aminobenzimidazoles. These compounds possess a significant degree of anthelmintic activity against the mouse tapeworm *Hymenolepis nana*. The most active compound is the 2-(2-furyl) analogue. Additional anthelmintic testing is reported for this compound.

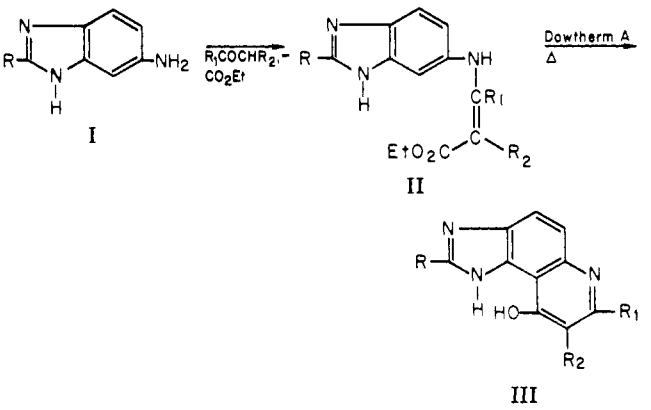
The first paper in this series reported the synthesis of a number of imidazo[4,5-*f*]quinolin-9-ols.[3] As a result of the anthelmintic activity shown by one of these compounds, **7** (Table I), a number of analogues were prepared and tested for anthelmintic activity. This paper reports the synthesis and preliminary anthelmintic evaluation of these new analogues[4] and an improved synthesis and further evaluation of one of them (**1**, furodazole).

Chemistry. The imidazo[4,5-*f*]quinolin-9-ols III (Table I) were prepared (Scheme I) by the condensation of a 5-amino-2-substituted benzimidazole I with the appropriate β-keto ester, followed by thermal cyclization of the resultant benzimidazolylacrylate II in boiling Dowtherm A. The 5-amino-2-substituted benzimidazoles I required for compounds **2–7** were prepared (Scheme II) from 2,4-dinitroaniline. Acylation with the appropriate acid chloride, followed by catalytic hydrogenation and acid-catalyzed cyclization of the intermediate 2,4-dinitrobenzanilides IV, gave the amino compounds I. The 5-aminobenzimidazole I required for compound **1** was prepared from the 5-nitro derivative[5] by catalytic hydrogenation. Intermediates II and IV were isolated but not purified prior to reaction. The 5-amino-2-substituted benzimidazoles I generally were used without isolation.

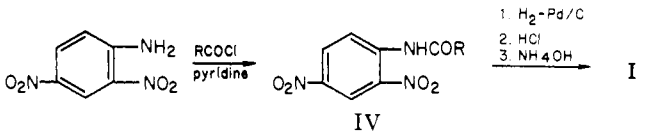
As a result of significant activity shown by **1** (see the biological section), a large quantity of this material was needed for additional anthelmintic evaluation. The preparation of **1** (Scheme I) from the aminobenzimidazole I was well adapted for large-scale synthesis. The preparation of this aminobenzimidazole, however, could not be scaled up conveniently, and alternate syntheses were investigated. The Weidenhagen synthesis of this intermediate[5] had several disadvantages. Two steps are involved (Scheme III): the preparation and isolation of the copper salt **8** and treatment of **8** with hydrogen sulfide to give **9**. Furthermore, the use of hydrogen sulfide on a large scale could create serious environmental problems with waste disposal and odor. In addition, the presence of residual amounts of sulfur in the product caused difficulties in the subsequent reduction step to the amine.

A second synthetic sequence for the preparation of **9** involved the reaction of 2-furancarbonyl chloride with 1,2-diamino-4-nitrobenzene in the classic Phillips synthesis (Scheme IV).[6] Although it has been reported that this sequence is impractical for this type of compound,[5] we were

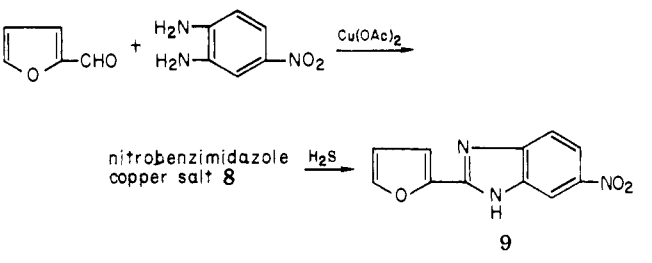
Scheme I



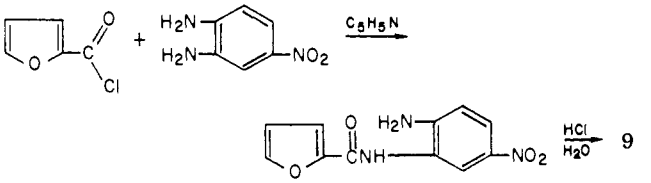
Scheme II



Scheme III



Scheme IV



able to produce **9** in high yield.[4] This sequence, although better adapted to scale-up than the Weidenhagen syn-

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