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3,3'(1,3-Ethyliminodimethylene)bis(4-hydroxy-6-methoxy-2-methyl)quinoline (**2c**) and related compounds were synthesized. 3,3'-Methylenebis(4-hydroxy-6-methoxy-2-methyl)quinoline (**5**) was prepared and upon treatment with phosphorus oxychloride gave 1,13-dimethyl-5,9-dimethoxy-14*H*-pyrano[3,2-c:5,6-c']diquinoline (**6**), a novel ring system.

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Previous studies have been extended to include the synthesis of some bisaminoquinolines and related compounds as potential antimilarials (7). The rationale for the synthesis of these compounds is that two quinoline rings might be expected to enhance intercalation with DNA beyond that assumed to result from one quinoline ring (1). The increased area of flatness afforded by two quinoline groups might increase potency or reinstate activity in cases of development of resistance (2,3).

In the present work, the Mannich reaction with 4-quinolones gave intermediate Mannich bases used in the synthesis of the desired compounds. Reaction of 2-methyl-4(1*H*)quinolone (**1a**) and its 6-CH_3 (**1b**), 6-OCH_3 (**1c**) and 7-Cl (**1d**) derivatives (4-6) with ethylamine and paraformaldehyde in ethanol under reflux temperature for a long time gave 3,3'(1,3-ethyliminodimethylene)-bis(4-hydroxy-2-methyl)quinoline (**2a**) and its 6-CH_3 (**2b**), 6-OCH_3 (**2c**), and 7-chloro (**2d**) derivatives, respectively.

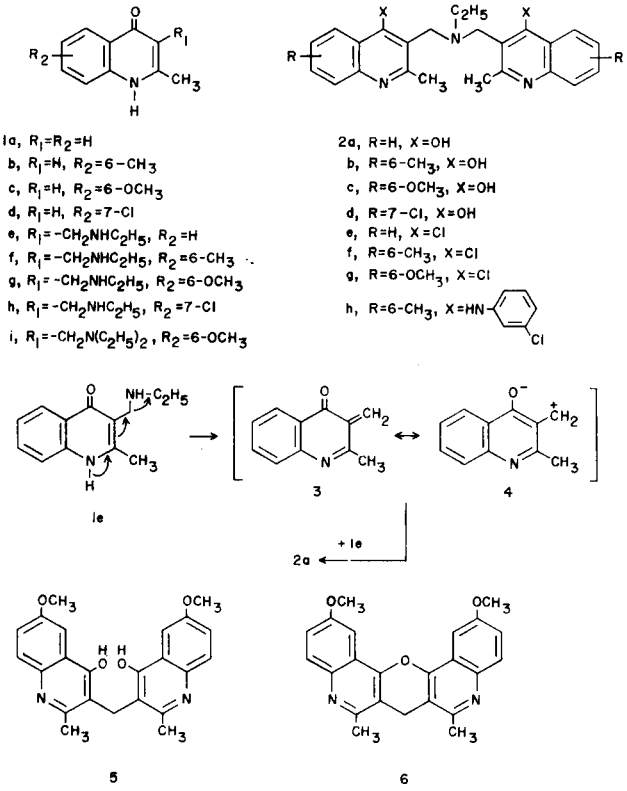
In a previous article (7) it was mentioned that gentle reflux of **1a-d** in alcohol with ethylamine and paraformaldehyde afforded, respectively, the 3-ethylaminomethyl derivatives (**1e-h**). When the same reactants were allowed to heat at reflux temperature for prolonged periods, the same bis-compounds (**2a-d**) were obtained in good yield.

Formation of type **2** compounds may be rationalized on the basis of initial formation of methylene quinone intermediate **3** by the elimination of a mole of ethylamine from **1e** followed by condensation with another mole of **1e** to give **2**. This rationalization is consistent with findings reported with phenolic Mannich bases (8,9).

Heating **2a**, **2b**, and **2c** with phosphorus oxychloride gave the 4-chloro compounds (**2e-g**). When **2f** was condensed with 3-chloroaniline in acidic medium, 4-(3-chloroanilino) derivative **2h** was obtained. Heating compound **2c** at 170° with 4-dimethylaminobenzaldehyde and zinc chloride gave **5** as the main product, together with a small amount of **7**. Heating **2c** in the solid phase gave a quantitative yield of **5**. Consistent with this result is the reported self-condensation of phenolic Mannich bases to form bis(hydroxyaryl)methanes (10). When **5** was allowed to react with phosphorus oxychloride, **6** was obtained.

The Mannich reaction with **1c** using paraformaldehyde and diethylamine gave **1i**. Heating **1i** in the solid phase gave **5** in good yield.

An attempt to prepare an oxazine derivative by reacting **1g** with formaldehyde in alcohol gave only **2c**. This result gives proof of the nonphenolic character of the 4-oxygen function in **1g** and the ease with which self-condensation of **1g** occurs. The ketonic nature of the 4-oxygen function in **1g** is necessary for its condensation to form **2c**, as shown in the mechanism discussed before. The 4-chloro derivatives **8a** and **8b**, prepared by the action of phosphorus oxychloride on **1g** and **1h** (7), are stable substances. They are recovered unchanged after reflux in alcohol for 24 hours. Reaction of **8a** and **8b** with paraformaldehyde, attempted in order to effect cyclization



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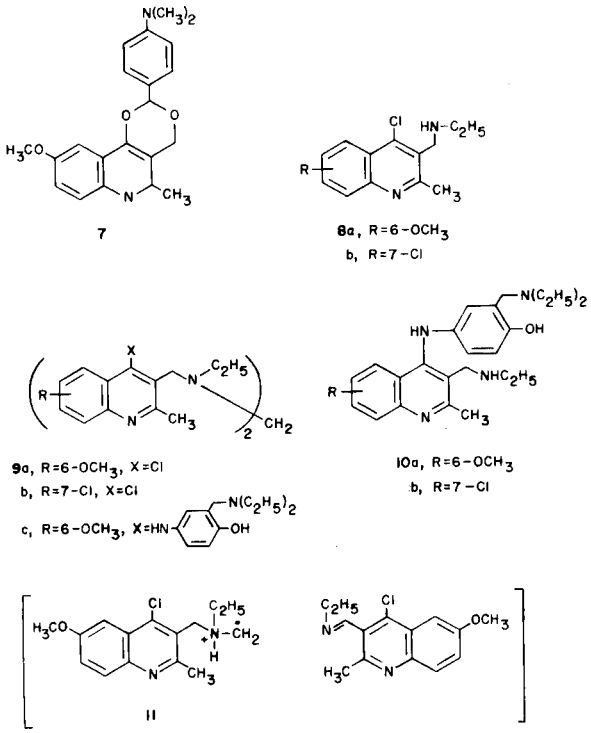

of the secondary amino group with the 2-methyl group, gave instead the 6-methoxy derivative **9a** and 7-chloro derivative **9b**, due to the deactivating effect of the 4-chloro substituent on the 2-methyl group. This is consistent with the fact that 2-methylquinoline readily undergoes the Mannich reaction at the 2-methyl group (11-13), while an attempted Mannich reaction with 4-chloro-2-methylquinoline with paraformaldehyde and diethylamine gave only starting material.

Structure **9a** was confirmed by uv and nmr data. Also, a study of mass spectral fragmentation, although it did not show any trace for a mass corresponding to the molecular weight of **9a**, showed a molecular ion peak at 264. This was rationalized as an instability of such dimers resulting from the effect of heat or electronic bombardment. Thus, a molecular ion peak at 264 would account for the molecular ion **11**. Isotopic analysis of 264 (Cl^{35}) was found to be consistent with **11**. Compound **9a** was condensed with 4-amino-2-diethylaminomethylphenol dihydrochloride (14) to give **9c**. Compounds **8a** and **8b** in a similar condensation gave **10a** and **10b**.

Biological Results.

Compounds **1i**, **2c**, **6** and **9c** were screened for antimalarial activity against blood induced *Plasmodium berghei* infections in mice, and *Plasmodium gallinaceum* in the sporozoite induced chick test, according to Rane (15,16). Screening was carried out in Dr. Rane's laboratory. Compound **9c** was the only compound found active and toxic at 640 mg./kg. dosage.

EXPERIMENTAL

Melting points were taken in capillary tubes on a Mel-Temp block and are uncorrected. Ir spectra were measured with a Perkin-Elmer 377 spectrophotometer. Nmr spectra were recorded relative to standard TMS on a Varian A-60A spectrometer. Satisfactory spectra were obtained for all compounds. Microanalyses were performed by Spang Microanalytical Lab., Ann Arbor, Michigan.

3,3'(1,3-Ethyliminodimethylene)bis(4-hydroxy-2-methyl)quinoline (**2a**).

The 6-CH_3 (**2b**), 6-OCH_3 (**2c**) and 7-chloro (**2d**) derivatives were prepared by two methods.

a.

A mixture of 15.9 g. (0.1 mole) of 2-methyl-4(1*H*)quinolone (**1a**) or its 6-CH_3 (**1b**), 6-OCH_3 (**1c**), 7-Cl (**1d**) derivative, 3 g. of paraformaldehyde and 20 ml. of ethylamine (70% in water) in 150 ml. of absolute alcohol was stirred at room temperature for 15 minutes. The mixture was then refluxed with stirring until precipitation of a white precipitate took place (10-15 hours). The products were insoluble in alcohol, and were purified by washing with alcohol. Analytical samples were obtained by precipitation from acidic alcohol with ammonium hydroxide.

b.

A solution of 3-ethylaminemethyl-2-methyl-4(1*H*)quinolone (**1c**) or its 6-CH_3 (**1f**), 6-OCH_3 (**1g**), 7-Cl (**1h**) derivative was heated under reflux with stirring for 5-7 hours in absolute ethanol, giving the corresponding derivatives (**2a-d**). The yields were identical with those mentioned in Table I.

3,3'(1,3-Ethyliminodimethylene)bis(4-chloro-6-methoxy-2-methyl)quinoline (**2g**).

A mixture of 4.47 g. (0.01 mole) of 3,3'(ethyliminodimethylene)bis(4-hydroxy-6-methoxy-2-methyl)quinoline (**2c**) and 15 ml. of phosphorus oxychloride was heated in an oil bath at 145-150° for 3 hours. Excess phosphorus oxychloride was distilled from the

Table I

Compound	M.p. °C	% Yield	Formula	Analysis Calculated C	H	N	Found C	H	N
2a	348-350	98	$C_{24}H_{25}N_3O_2$	74.39	6.50	10.85	73.93	6.47	10.88
2b	265-268	95	$C_{26}H_{29}N_3O_2$	75.15	7.03	10.11	74.98	6.98	9.99
2c	365-370	89	$C_{26}H_{29}N_3O_4$	69.78	6.53	9.39	69.90	6.61	9.44
2d	355-358	95	$C_{24}H_{23}Cl_2N_3O_2$	63.16	5.08	9.21	62.91	5.16	9.19

reaction mixture. It was kept cool while being diluted with water and basified with sodium hydroxide solution. The white precipitate which formed was washed with hot water and ethyl alcohol to give 4.2 g. (87% yield) of **2g**, m.p. 187-191°. Recrystallization from *n*-propyl alcohol gave m.p. 190-192°.

Anal. Calcd. for $C_{26}H_{27}Cl_2N_3O_2$: C, 64.46; H, 5.62; N, 8.68. Found: C, 64.56; H, 5.63; N, 8.59.

Compounds **2e** and **2f** were also prepared according to the previous method. Compound **2e** was obtained in 82% yield and was recrystallized from alcohol, m.p. 180-182°.

Anal. Calcd. for $C_{24}H_{23}Cl_2N_3$: C, 67.92; H, 5.64; N, 9.90. Found: C, 67.72; H, 5.41; N, 9.89.

Compound **2f** was obtained in 65% yield and was recrystallized from alcohol, m.p. 192-195°.

Anal. Calcd. for $C_{26}H_{27}Cl_2N_3$: C, 69.02; H, 6.07; N, 9.29. Found: C, 69.17; H, 6.10; N, 9.30.

3,3′(Ethyliminodimethylene)bis(3-chloroanilino-2,6-dimethyl)-quinoline (**2h**).

A mixture of 4.52 g. (0.01 mole) of 3-chloroaniline was dissolved in 50 ml. of absolute alcohol. The mixture was acidified with hydrochloric acid and then was refluxed for 10 hours. The reaction mixture, after concentration, was treated with aqueous sodium hydroxide and cooled. The precipitate base was dried to give 5.7 g. (90% yield) of **2h**, m.p. 132-134°. Recrystallization from ether gave m.p. 136-140°.

Anal. Calcd. for $C_{38}H_{37}Cl_2N_3$: C, 71.90; H, 5.88; N, 11.04. Found: C, 72.01; H, 5.78; N, 10.96.

3,3′-Methylene-bis-(4-hydroxy-5-methoxy-2-methyl)quinoline (**5**).

This compound was obtained in quantitative yield upon heating any of compounds **2c** or **1i** in an open flask at 230° for 5 hours. Amine was evolved during heating as suggested by its odor and *p*H paper. After heating, the product was washed with alcohol. It is insoluble in most organic solvents. A sample was purified for analysis and spectral studies by washing several times with alcohol, m.p. 374-377° dec.

Anal. Calcd. for $C_{23}H_{22}N_2O_4$: C, 70.75; H, 5.68; N, 7.18. Found: C, 70.55; H, 5.42; N, 7.11.

1,13-Dimethyl-5,9-dimethoxy-14*H*-pyrano[3,2-*c*:5,6-*c*′]diquinoline (**6**).

A mixture of 3.9 g. (0.01 mole) of **5** and 10 ml. of pure phosphorus oxychloride was heated for one hour at 145°. Excess phosphorus oxychloride was distilled from the reaction mixture. It was kept cool while being diluted with water and basified with sodium hydroxide solution. The precipitate formed was dried to give 3.3 g. (90% yield) of **6**, m.p. 295-298°. Recrystallization from chloroform gave m.p. 302-305°; nmr (trifluoroacetic acid): σ 8.25-7.72 (6H, multiplet, aromatic protons), 4.47 (2H, singlet, $-CH_2-$), 4.20 (6H, singlet, OCH_3, OCH_3) and 3.06 (6H, singlet, $-CH_3$, $-CH_3$).

Anal. Calcd. for $C_{23}H_{20}N_2O_3$: C, 74.17; H, 5.41; N, 7.52. Found: C, 74.26; H, 5.40; N, 7.43.

3-Diethylaminomethyl-6-methoxy-2-methyl-4(1*H*)quinolone (**1i**).

A mixture of 1.6 g. of paraformaldehyde, 20 ml. of diethylamine and 25 ml. of ethyl alcohol was heated until the paraformaldehyde dissolved. To this solution was added 9.4 g. (0.05 mole) of 6-methoxy-2-methyl-4(1*H*)quinolone (**1c**) dissolved in the least amount of ethanol and the mixture was allowed to reflux for 10 hours. The reaction mixture was concentrated and cooled to give 12.3 g. (90% yield) of **1i**, m.p. $>300°$ dec. Recrystallization from ethanol did not change the melting point.

Anal. Calcd. for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.94; H, 8.12; N, 10.08.

3,3′-(2,4-Diethyl-2,4-diazapentane-1,5)bis(4-chloro-6-methoxy-2-methyl)quinoline (**9a**).

A mixture of 5.3 g. (0.02 mole) of 3-ethylaminomethyl-4-chloro-6-methoxy-2-methylquinoline (**8a**) and 0.06 g. of paraformaldehyde in 100 ml. of absolute ethyl alcohol was refluxed for 10 hours. The reaction mixture was concentrated and then was cooled. A viscous material precipitated, which on recrystallization from aqueous alcohol gave a solid product 3.5 g. (63% yield) of **9a**, m.p. 158-162°. Recrystallization from ether gave m.p. 165-168°.

Anal. Calcd. for $C_{29}H_{34}Cl_2N_4O_3$: C, 64.32; H, 6.33; N, 10.35. Found: C, 64.12; H, 6.25; H, 10.26.

3,3′(2,4-Diethyl-2,4-diazapentane-1,5)bis(4,7-dichloro-2-methyl)-quinoline (**9b**).

A mixture of 3.06 g. (0.01 mole) of 4,7-dichloro-3-ethylaminomethyl-2-methylquinoline (**8b**) hydrochloride and 0.3 g. paraformaldehyde was dissolved in 50 ml. of absolute ethanol. The mixture was basified with alcoholic potassium hydroxide and then refluxed for 6 hours. The reaction mixture after concentration was diluted with water and kept at room temperature for 24 hours. The precipitate formed gave 2.5 g. (91% yield) of **9b**, m.p. 159-161°. Recrystallization from ether gave m.p. 165-167°.

Anal. Calcd. for $C_{27}H_{28}Cl_4N_4$: C, 58.92; H, 5.13; N, 10.18. Found: C, 58.94; H, 5.15; N, 10.29.

3,3′(2,4-Diethyl-2,4-diazapentane-1,5)bis[4(3-diethylaminomethyl-4-hydroxyanilino)-6-methoxy-2-methyl]quinoline hydrochloride (**9c**).

A mixture of 5.5 g. (0.01 mole) of **9a** and 5.35 g. (0.02 mole) of 4-amino-2-diethylaminomethylphenol dihydrochloride was dissolved in 50 ml. of absolute ethyl alcohol. The mixture was refluxed for 6 hours to give 5 g. (46% yield) of yellow solid product **9c** hydrochloride, m.p. 236-239°. Recrystallization from absolute alcohol did not change the melting point.

Anal. Calcd. for $C_{51}H_{74}Cl_6N_8O_4$: C, 56.72; H, 6.91; N, 10.38. Found: C, 57.20; H, 6.81; N, 10.26.

The base was prepared by addition of ammonium hydroxide to an aqueous solution of the salt. Extraction with ether gave **9c**, m.p. 104-106°. Recrystallization from petroleum ether did not change the melting point.

4-(3-Diethylaminomethyl-4-hydroxyanilino)3-ethylaminomethyl-6-methoxy-2-methylquinoline (**10a**).

A mixture of 1.3 g. (0.005 mole) of **8a** and 1.33 g. (0.005 mole) of 4-amino-2-diethylaminomethylphenol dihydrochloride was dissolved in 50 ml. of absolute ethanol. The mixture was refluxed for 6 hours. The reaction mixture after concentration was treated with aqueous sodium hydroxide and it was cooled. The base was precipitated as a viscous material. Recrystallization from petroleum ether (60-75°) gave 1.6 g. (76% yield) of **10a**, m.p. 99-101°.

Anal. Calcd. for $C_{25}H_{34}N_4O_2$: C, 71.06; H, 8.11; N, 13.12. Found: C, 71.10; H, 8.10; N, 13.27.

7-Chloro-4(3-diethylaminomethyl-4-hydroxyanilino)-3-ethylaminomethyl-2-methylquinoline (**10b**).

This compound was prepared from **9b** by the method of **10a**. It was obtained as the free base in 40% yield. It was recrystallized from petroleum ether, m.p. 115-117°.

Anal. Calcd. for $C_{24}H_{31}ClN_4O$: C, 67.51; H, 7.32; N, 13.12.

Found: C, 67.25; H, 7.27; N, 13.01.

2(4-Dimethylaminophenyl)-9-methoxy-5-methyltetrahydroxazino-[5,4-c]quinoline (**7**).

A mixture of 4.47 g. (0.01 mole) of **2g**, 1.49 g. (0.01 mole) of 4-dimethylaminobenzaldehyde and 0.02 g. of fused zinc chloride was heated at 170° for 6 hours. The reaction mixture, after being cooled, was treated with alcohol and sodium hydroxide solution. The crude yellow material which precipitated was treated with diethylformamide in which it partially dissolved. The insoluble part which was the main product was found to be identical with compound **5**. Cooling the solution gave 0.55 g. of **7**, m.p. 296-299°. Another recrystallization from propyl alcohol gave an analytical sample of the same melting point; nmr (trifluoroacetic acid): δ 9.93 (1H, singlet), 8.33-7.53 (7H, multiplet, aromatic protons), 4.56 (2H, singlet, $N(CH_3)_2$) and 3.20 (3H, singlet, $-CH_3$). The mass spectrum showed a molecular ion peak at 350. Isotopic analysis of the 350 peak indicates a molecular formula of $C_{21}H_{22}N_2O_3$.

Anal. Calcd. for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33. Found: C, 72.37; H, 6.47.

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