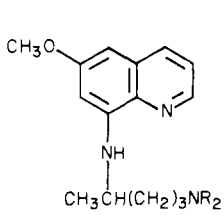
Synthesis and Antimalarial Activity of 8-[(1-Alkyl-4-aminobutyl)amino]-6-methoxy-4-methylquinolines

Shou-Jen Yan, Ping-Lu Chien, and C. C. Cheng*[1]

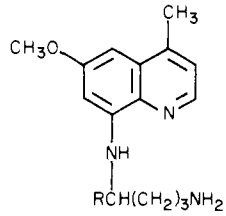
Midwest Research Institute, Kansas City, Missouri 64110. *Received July 24, 1980*

Three analogues of the causal prophylactic antimalarial primaquine were prepared and their antimalarial activity was evaluated. 8-[(1-Ethyl-4-aminobutyl)amino]-6-methoxy-4-methylquinoline (**2a**) demonstrated activity against *Plasmodium berghei* in mice at 20 mg/kg, with all animals cured at 320 mg/kg, and is without toxicity at 640 mg/kg. It also possessed outstanding causal prophylactic activity against *Plasmodium cynomolgi* in rhesus monkeys at very low dosages.

Primaquine (**1a**) and (**1b**) are two of the most widely



1a, R = H
b, R = CH_2CH_3



2a, R = CH_2CH_3
b, R = $(CH_2)_2CH_3$
c, R = $CH(CH_3)_2$

studied antimalarials in the 8-aminoquinoline series.[2-4] Although primaquine has a better chemotherapeutic index than pamaquine, toxicity possessed by the former compound is still serious enough to keep it from becoming a far from ideal drug.[5]

In connection with our efforts in searching for better antimalarial agents, three analogues of **1a** were synthesized and evaluated for their antimalarial activity. These compounds (**2a–c**) are so designed that only the lipophilicity of the original compound is modified. The important triangular feature, composed of three electronegative atoms substituted at positions 1, 2, and 4 of a benzene ring, which is common to many compounds possessing casual prophylactic activity,[6] is kept intact.

Chemistry. Condensation of *N*-(4-bromohexyl)-phthalimide, prepared from potassium phthalimide and 1,4-dibromohexane[7] (**6b**), with 8-amino-6-methoxy-4-methylquinoline[8] (**3**) in the presence of diiopropylamine at elevated temperature[9] gave 8-[(1-ethyl-4-phthalimidobutyl)amino]-6-methoxy-4-methylquinoline (**5a**) (Scheme I). Hydrazinolysis[10] of **5a** afforded the desired compound **2a**. Compound **2b** was prepared in a similar manner from **3** and *N*-(4-bromoheptyl)phthalimide (**4b**). The latter was, in turn, prepared from potassium phthalimide and 1,4-dibromoheptane[11] (**6d**). Although both the aforementioned dibromoalkanes **6b** and **6b** are known compounds, they were prepared by methods different from those reported in the literature, and detailed procedures are given under Experimental Section.

For the preparation of compound **2c** a different approach was used, since the analogous condensation of **3** with the corresponding bromophthalimide resulted in dehydrobromination of the latter. 6-Bromo-2-methylhexan-3-one (**9b**) was prepared by addition of isopropylmagnesium bromide to cyclopropyl cyanide (11), followed by cleavage of the cyclopropyl ring of the resulting cyclopropyl isopropyl ketone (**10b**) with HBr. The bromo ketone **9b** was converted to the phthalimido derivative **7**, and the latter, in the presence of excess $NaBH_3CN$, was condensed with **3** accordng to the reductive alkylation procedure of Borch et al.[12] to give **5c**, which was converted to **2c** in the usual manner.

Table I. Antimalarial Activity against *Plasmodium berghei*[a]

	MST, days after a single sc dose					
compd	20 mg/kg	40 mg/kg	80 mg/kg	160 mg/kg	320 mg/kg	640 mg/kg
1a·$2H_3PO_4$[b]	+2.2	+4.2	+6.4	+7.0 (2 toxic)	5 toxic	5 toxic
1a·$2H_3PO_4$[c]	+4.0	+5.0	+9.4	+10.8 (2 toxic)	5 toxic	5 toxic
2a·$2H_3PO_4$[a]	+7.3	+7.9	+9.7	+11.5	5 cures	5 cures
2b·$2H_3PO_4$[a]	+3.1	+4.1	+5.7	+6.3	+9.1	+12.3
2c·$2H_3PO_4$[a]	+3.4	+5.2	+6.8	+7.8 (1 cure)	+7.2	1 cure

[a] Reference 14. [b] Reference 16. [c] Reference 10.

Biological Activity and Discussion. Compound **2a** possesses good blood-schizonticidal antimalarial activity against *Plasmodium berghei* in mice with no detectable toxicity. This compound is active at 20 mg/kg, with five out of five cures at 320 mg/kg, and is nontoxic even at a dose of 640 mg/kg. A comparison of the activity of this compound with that of primaquine in the same *P. berghei* system is given in Table I.

Compounds **2b** and **2c** are less active than **2a** but still superior to primaquine. The fact that compound **2c** is slightly more active than compound **2b** revealed that the optimum number of carbon atoms in the straight carbon

(1) Corresponding address: Mid-America Cancer Center, The University of Kansas Medical Center, Kansas City, Kansas 66103.

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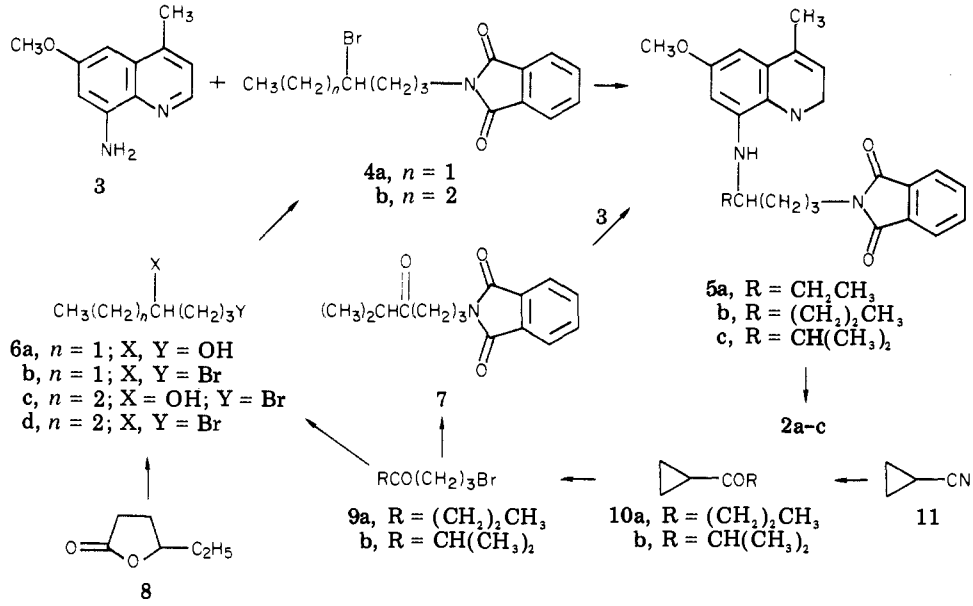
Scheme I



side chain of compounds of this type is six. Compound **2a** was also found to exhibit outstanding casual prophylactic antimalarial activity against *P. cynomolgi* in rhesus monkeys. The compound gave 6/7 cures at a dosage of 0.125 mg/kg and 4/4 cures at 0.25 mg/kg.[13]

Experimental Section

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

***N*-(4-Bromohexyl)phthalimide (4a).** A mixture of 24.7 g (0.1 mol) of 1,4-dibromohexane[7] (**6b**), 27.8 g (0.15 mol) of potassium phthalimide, and 200 mL of Me_2CO was stirred and refluxed for 44 h. The white precipitate was separated by filtration, washed with Me_2CO (2 × 50 mL), and discarded. The combined Me_2CO solution was evaporated to yield a slightly yellow liquid residue. This was dissolved in 10 mL of C_6H_6 as the eluant. The first 60-mL fraction was discarded. The following 2000-mL fraction contained 24.3 g (79% yield) of **4a**: NMR ($CDCl_3$) δ 1.10 (3 H, t, J = 7 Hz, CH_3), 1.50–2.01 (6 H, m, CH_2 at C-2, C-3, and C-5), 3.50–3.82 (2 H, m, CH_2 at C-1), 3.90–4.25 (1 H, m, CH), 7.80 (4 H, s, aromatic H); IR (neat) 1700 and 1705 (CO), 721 (1,2-disubstituted benzene ring) cm^{-1}. Anal. ($C_{14}H_{16}BrNO_2$) C, H, N.

8-[(1-Ethyl-4-phthalimidobutyl)amino]-6-methoxy-4-methylquinoline (5a). In a steel vessel was placed a solution of 17.3 g (0.092 mol) of 8-amino-6-methoxy-4-methylquinoline[8] (**3**) in 20 mL of 2-ethoxyethanol and 22 mL of EtOH containing 42.6 g (0.137 mol) of **4a** and 13.7 g (0.137 mol) of bis(1-methylethyl)amine. The steel vessel was heated to 150 °C during 6 h and was maintained at that temperature for an additional 13 h. The container was then cooled in an ice–H_2O bath and opened. The dark brown reaction mixture was transferred into a beaker and stirred with 1 L of Et_2O for 1 h. The precipitated amine HCl salt was separated by filtration, washed with 100 mL of Et_2O, and discarded. The combined Et_2O solution was evaporated to yield a dark brown residue, which was dissolved in 20 mL of $CHCl_3$ and column chromatographed over 500 g of silica gel (Woelm, activity I) using $CHCl_3$ as the eluant. The elution fractions were monitored with TLC (silica gel, $CHCl_3$–Me_2CO, 9:1) to give 20 g (51.4% yield) of **5a** as a yellow liquid: IR (neat) 3360 (NH), 1760 and 1700 (CO) cm^{-1}.

8-[(1-Ethyl-4-aminobutyl)amino]-6-methoxy-4-methylquinoline (2a). A mixture of 13.9 g (0.033 mol) of **5a**, 10 mL of 85% $N_2H_4 \cdot H_2O$, and 500 mL of EtOH was stirred and refluxed for 6 h. A white precipitate, which started to form after 30 min of reflux, was separated by filtration, washed with EtOH (2 × 50 mL), and discarded. The combined EtOH solution was evaporated in vacuo to yield a greenish yellow liquid. This was shaken with a mixture of 150 mL of Et_2O and 30 mL of 30% KOH. The Et_2O layer was separated and the aqueous layer extracted with two additional 150-mL portions of Et_2O. The combined Et_2O solution was washed with H_2O (2 × 100 mL) and saturated NaCl solution (100 mL) and dried ($MgSO_4$). Evaporation of Et_2O gave 5.1 g (54% yield) of crude **2a**. A portion was purified by distillation using a Kugelrohr distillator, at an oven temperature of 130–140 °C at 0.06–0.1 mm, to give analytically pure **2a**: mass spectrum, m/e 287 (M^+); IR (neat) 3360 (NH) cm^{-1}. Anal. ($C_{17}H_{25}N_3O$) C, H, N.

The diphosphate of **2a** was prepared as follows: To a stirred solution of 2.2 g of **2a** in 80 mL of 2-PrOH was added 3 g of 85% H_3PO_4 in 30 mL of 2-PrOH. The resulting yellow phosphate was separated and dissolved in 120 mL of boiling 95% EtOH. After the solution cooled, 2.6 g (70% yield) of the diphosphate of **2a**, mp 173–176 °C dec, was collected by filtration. An analytical sample, mp 172–175 °C dec, was prepared by an additional recrystallization from 95% EtOH [dried at 25 °C (0.1 mm) overnight]. Anal. ($C_{17}H_{25}N_3O \cdot 2H_3PO_4$) C, H, N, P. When the dried sample was exposed in air overnight, the resulting solid was analyzed as a dihydrate. Anal. ($C_{17}H_{25}N_3O \cdot 2H_3PO_4 \cdot 2H_2O$) C, H, N.

1-Cyclopropylbutan-1-one (10a). To a stirred suspension of 9 g of Mg and 250 mL of anhydrous Et_2O was added, under N_2, 5 g of propyl bromide to initiate the Grignard reaction. As the reaction commenced, the remaining 40 g of propyl bromide was added dropwise to the reaction suspension at such a rate that the Et_2O refluxed gently. The dark solution thus obtained was stirred for an additional hour, followed by the dropwise addition of 25 g of cyclopropyl cyanide (**11**). The reaction mixture was gently refluxed throughout the addition and then was allowed to stir at room temperature overnight. The resulting clear solution was poured into a mixture of 500 mL of 1 M H_2SO_4 and 200 g

(13) Tests were conducted by Dr. L. H. Schmidt of Southern Research Institute, Birmingham, Ala., using sporozoite-induced *P. cynomolgi* infected rhesus monkeys. Monkeys that do not relapse in 90 days are considered cured.

(14) Tests were conducted by Mrs. Leo Rane of the Rane Laboratory, University of Miami, Fla., using blood-induced *P. berghei* infected mice (five animals per group). Increase in mean survival time (ΔMST) is reported. The mean survival time of untreated mice is 6.1 days. Animals that survive to 60 days postinfection are considered cured. Deaths from days 2–5 after drug administration are attributed to drug toxicity. For details of test results, see ref 15.

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of crushed ice. The Et_2O layer was separated and the aqueous layer extracted with Et_2O. The solution was dried ($MgSO_4$) and evaporated to give 33.5 g (81% yield) of **10a**[17] as a colorless liquid. Its IR spectrum (neat) showed a carbonyl absorption at 1700 cm^{-1}. No nitrile absorption was observed.

1-Bromoheptan-3-one (9a). A mixture of 29.5 g (0.267 mol) of **10a** and 250 mL of 48% HBr was stirred at room temperature for 20 h. The resulting organic layer was separated and diluted with 200 mL of Et_2O. The Et_2O solution was washed with 5% $NaHCO_3$ (2 × 100 mL), dried ($MgSO_4$), and evaporated to yield a liquid which, upon distillation at 86 °C (3.5 mm), gave 34.4 g (66% yield) of **9a** [lit.[18] bp 66 °C (1.5 mm)].

1-Bromo-4-hydroxyheptane (6c). The a solution of 20.4 g (0.105 mol) of **9a** in 105 mL of tetrahydrofuran at 2 °C was added dropwise, with stirring, 105 mL of 1 M BH_3–THF in 90 min. The temperature of the reaction mixture was kept below 10 °C during the addition and remained at the same temperature for 90 min after the addition. The cooling bath was then removed and the mixture was allowed to warm up to room temperature in 1 h. It was cooled again to 2 °C and to the mixture was added dropwise 30 mL of EtOH to decompose the excess BH_3. The resulting solution was acidified with 2 mL of 60% ethanolic HCl and evaporated in vacuo below 40 °C. The liquid residue was dissolved in 200 mL of Et_2O, and the resulting solution was washed with 5% $NaHCO_3$ (30 mL) and H_2O. After drying ($MgSO_4$), the Et_2O solution was evaporated to yield crude **6c**. This was distilled at 80 °C (0.3 mm) to give 12.2 g (58% yield) of **6c**. Its IR spectrum (neat) had a strong absorption at 3560–3050 cm^{-1}. No carbonyl absorption was observed. This compound was rather unstable on standing. It was therefore used immediately for the preparation of **6d**.

***N*-(4-Bromoheptyl)phthalimide (4b).** This compound was prepared in 82% yield (10.1 g) from 10.1 g (0.039 mol) of 1,4-dibromoheptane[11] (**6d**), 14.4 g (0.078 mol) of potassium phthalimide, and 150 mL of Me_2CO in a manner similar to that for the preparation of **4a**, except that the initial reflux time was 3 days and that $CHCl_3$ rather than C_6H_6 was used as the eluant. The product eluted was originally a liquid, which solidified on standing, mp 46–50 °C. Anal. ($C_{15}H_{18}BrNO_2$) C, H, N.

6-Methoxy-4-methyl-8-[(1-propyl-4-aminobutyl)amino]quinoline (2b). A stirred solution of 1.1 g of 6-methoxy-4-methyl-8-[(1-propyl-4-phthalimidobutyl)amino]quinoline (**5b**), prepared in 30% yield from **3** and **4b** in a manner similar to that for the preparation of **5a**, was refluxed with 0.8 mL of 85% N_2H_4 in 25 mL of EtOH for 2 h. The workup was the same as that for **2a**. The yield of **2b** was 40% (0.3 g). Its IR, NMR, and mass spectra were in accord with the structural assignment. Compound **2b** (0.3 g) was dissolved in 1 mL of 2-PrOH and converted into its diphosphate with the addition of 0.3 g of 85% H_3PO_4 to give, after recrystallization from 95% EtOH, 0.1 g of analytically pure sample, mp 142–144 °C. Anal. ($C_{18}H_{27}N_3O·2H_3PO_4·2H_2O$) C, H, N, P.

6-Bromo-2-methylhexan-3-one (9b). To a freshly prepared 2-propylmagnesium bromide solution (from 50 g of 2-propyl bromide, 9 g of Mg, and 300 mL of Et_2O) was added dropwise, with stirring, a solution of 25 g (0.37 mol) of cyclopropyl cyanide (**11**) in 30 mL of Et_2O under N_2 over a period of 30 min. After the addition, the mixture was stirred by room temperature for 2 h and the excess Grignard reagent decomposed with H_2O. The resulting mixture, which contained **10b**, was poured into 100 mL of cold H_2O and 150 mL of 48% HBr. After 1 h, the Et_2O layer was separated and the aqueous phase extracted with 300 mL of Et_2O. The combined Et_2O solution was washed (H_2O), dried (Na_2SO_4), and evaporated. The residue thus obtained was stirred with 100 mL of 48% HBr at room temperature for 1 day. The oily layer was separated and the aqueous layer extracted with Et_2O (2 × 200 mL). The combined organic layer was washed thoroughly with H_2O, dried (Na_2SO_4), and evaporated to give 38 g (53% yield) of the desired product **9b** as a light tan liquid. Its NMR and IR spectra confirmed the structural assignment.

2-Methyl-6-(phthalimido)hexan-3-one (7). A mixture of 19.3 g (0.1 mol) of **9b** and 18.5 g (0.1 mol) of potassium phthalimide in 100 mL of DMF was heated at 70 °C with stirring for 1 day. The reaction mixture was poured into 500 mL of H_2O, and the precipitated solid product was collected by filtration. The crude product was dissolved in 50 mL of $CHCl_3$, and the insoluble phthalimide was removed by filtration. The filtrate was chromatographed over Al_2O_3, and the product was eluted with $CHCl_3$ to give 13 g (50% yield) of **7**. An analytical sample was prepared by recrystallization from MeOH, white crystals, mp 81–82 °C. Anal. ($C_{15}H_{17}NO_3$) C, H, N.

6-Methoxy-4-methyl-8-[[1-(1-methylethyl)-4-aminobutyl]amino]quinoline (2c). A mixture of 13 g (0.05 mol) of **7**, 10 g (0.053 mol) of **3**, and 6 g (0.095 mol) of $NaBH_3CN$ in 200 mL of MeOH containing a small amount of anhydrous HCl was stirred at room temperature for 3 days. To the mixture was added an additional 3 g of $NaBH_3CN$ in MeOH, and stirring was continued for another 4 days. The reaction mixture was poured into 400 mL of cold H_2O, and the MeOH was evaporated under reduced pressure. The resulting aqueous solution was extracted with Et_2O (4 × 100 mL). The combined Et_2O extracts were washed (H_2O), dried (Na_2SO_4), and evaporated. The residue was chromatographed four times over Al_2O_3 to give 8 g of the phthalimido derivative **5c** as a yellow oil. This was heated with 10 mL of 65% N_2H_4 in 200 mL of EtOH for 2 h. The solid was separated by filtration and the filtrate was concentrated under reduced pressure. The residue **2c** was dissolved in 300 mL of Et_2O, and the Et_2O solution was washed (H_2O), dried (Na_2SO_4), and evaporated to dryness. The oily residue thus obtained was dissolved in 50 mL of 2-PrOH and treated with a solution of H_3PO_4 in 2-PrOH until precipitation of the phosphate salt was complete. The yellow solid was collected by filtration and washed with 2-PrOH to give, after drying, 6.5 g (24.3% overall yield) of **2c** as a diphosphate, mp 181–185 °C. A sample was prepared by recrystallization from MeOH, yellow crystals, mp 189–191 °C. Anal. ($C_{18}H_{27}N_3O·2H_3PO_4·2H_2O$) C, H, N.

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