analyses; and Mr. T. K. Elzey for the NMR measurements.

## References and Notes


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# Modifications of Primaquine as Antimalarials. 1. 5-Phenoxy Derivatives of Primaquine

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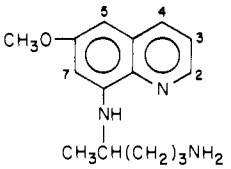
Various 5-phenoxy derivatives of primaquine have been prepared which are more active and less toxic than the parent compound in murine and monkey antimalarial screens. An improved method for the phthalimido alkylation of amines is described.

Primaquine, a derivative of 8-aminoquinoline, is an important radical curative and causal prophylactic anti-

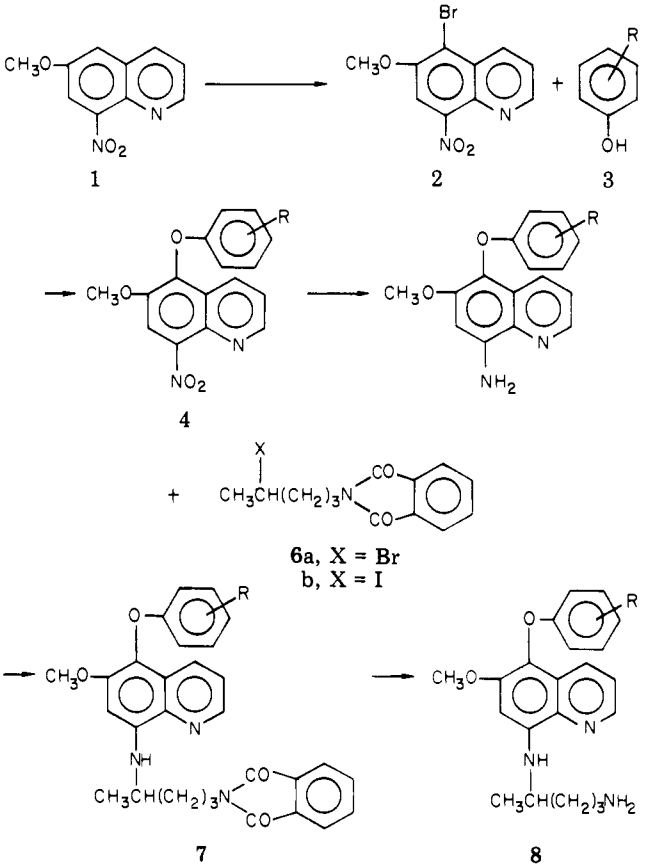


primaquine

malarial agent which suffers from excessive toxicity.[1] We have therefore undertaken a program of molecular modification designed to improve its therapeutic index. Since the highest therapeutic index among the 8-aminoquinolines in the Coatney compilation[2] belonged to a 5-phenoxy derivative, we have initiated our program with the synthesis of a group of 5-phenoxyprimaquines.

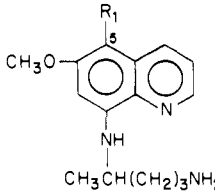
**Chemistry.** The preparative route (Scheme I) was an adaptation of one described by Elderfield et al.[3] and it proceeded, in the main, quite smoothly. However, a persistent, early stumbling block was the resistance of the amino derivatives **5** to phthalimido alkylation with 4-bromo-1-phthalimidopentane (**6a**). The classical phthalimido alkylation methods either failed completely or gave unsatisfactory yields of the penultimate 8-phthalimidoalkylamino intermediates **7**. Thus, the reaction between **5** and **6a**, in refluxing ethanol, as suggested by Elderfield,[3] provided little or none of the desired compounds. Equally unproductive were variations which included a phosphate buffer[3] or sodium iodide[4] or which utilized solvents other than ethanol.[4,5] Direct fusions of **5** and **6a** were also in vain.[3,6] We ultimately devised a method which involved incremental addition of at least 2 equiv each of **6a** and triethylamine and which produced satisfactory yields of **7** in every instance. A further improvement, which in preliminary work has increased yields and reduced reaction times, was the substitution of the iodide **6b** for the bromide **6a**.

Scheme I



**Biology.** Table I compares primaquine and its 5-phenoxy derivatives (**8a–c**) in the murine blood schizonticidal antimalarial screen. In contrast to primaquine,

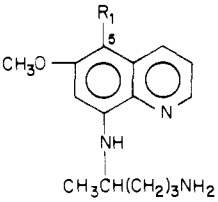
Table I. Blood Schizonticidal Antimalarial Activity[a] (*P. berghei*, Mouse)



| Compd[b] | $R_1$ | $R_2$ | Cures (C),[c] toxic deaths (T),[d] or ΔMST[e] at dose, mg/kg 20 | 40 | 80 | 160 | 320 | 640 |
|---|---|---|---|---|---|---|---|---|
| Primaquine | H | $2H_3PO_4$ | 4.0 | 5.0 | 9.4 | 2T | 5T | 5T |
| 8a | $C_6H_5O$ | $H_3PO_4 \cdot 0.5H_2O$ | 0.3 | 1.5 | 1.7 | 5.1 | 7.5 | 9.9 |
| 8b | 4-$ClC_6H_4O$ | $H_2O$ | 0.7 | 4.7 | 5.5 | 7.1 | 8.1 | 2C |
| 8c | 4-$FC_6H_4O$ | Citrate·$0.5H_2O$ | 2.1 | 5.7 | 7.5 | 8.9 | 5C | 5C |

[a] Tests were carried out by the Rane Laboratory, University of Miami, Fla., using blood-induced, *P. berghei* infected mice (five animals per group) by the method described by Osdene et al.[7] Test data were supplied by Drs. E. A. Steck, R. E. Strube, and T. R. Sweeney of Walter Reed Army Institute of Research. [b] No data available for compound 8d. [c] The number of mice surviving at 60 days postinfection. [d] Deaths prior to the sixth day. [e] Increase in mean survival time over controls; a compound is considered active if MST of the treated group is more than twice that of the control group (MST of control group, 6.1 days).

Table II. Radical Curative Antimalarial Activity[a] (*P. cynomolgi*, Rhesus)



| Compd[b] | $R_1$ | $R_2$ | Cures/no. of animals or day of relapse[c] at dose, mg/kg 0.125 | 0.25 | 0.5 | 0.75 | 1 | 10 |
|---|---|---|---|---|---|---|---|---|
| Primaquine | H | $2H_3PO_4$ | | 0/8 | 10/12 | 9/9 | | |
| 8b | 4-$ClC_6H_4O$ | $H_2O$ | | 0/1 | 0/2 | 5/6 | 3/3 | 1/1 |
| 8c | 4-$FC_6H_4O$ | Citrate·$0.5H_2O$ | 0/5 | 3/8 | 5/5 | | | |
| 8d | 4-$CH_3CONHC_6H_4O$ | HCl | | | 9 | | 10 | |

[a] Tests were carried out by Dr. L. H. Schmidt, Southern Research Institute, Birmingham, Ala., using sporozoite-induced, *P. cynomolgi* infected rhesus monkeys.[8] [b] Data unavailable for 8a. [c] Monkeys that do not relapse in 90 days are considered cured.

which was toxic at 160 mg/kg, **8a–c** were nontoxic at the highest dose tested (640 mg/kg). Compounds **8a–c** were all either active or curative but the best of these was the fluoro derivative **8c**. The latter had about the same activity level as primaquine at the lower doses but was completely curative at 320 and 640 mg/kg. Those analogues with halogen atoms (**8b** and **8c**) were more effective than the unsubstituted phenoxy compound **8a**. No mouse data were available for **8d**. The halogen-bearing congeners **8b** and **8c** produced radical cures in the monkey screen (Table II). The fluoro derivative **8c** was once again dominant, surpassing in activity primaquine itself. However, if the lipophilic halogen groups were replaced with the hydrophilic acetamido (**8d**), activity was eliminated. Monkey data for **8a** were unavailable.

## Experimental Section

Melting points were determined in capillary tubes in an electrically heated Thiele-Dennis apparatus and are uncorrected. Elemental analyses (Micro-Analysis, Inc., Wilmington, Del.) were within ±0.4% of the theoretical values unless otherwise noted. Satisfactory IR spectra were obtained for all compounds as Nujol mulls on a Perkin-Elmer 137B Infracord. The starting materials (**1** and **3** in Scheme I) were commerically available.

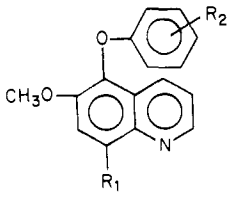
The following preparations exemplify those used to synthesize the compounds included in Table III.

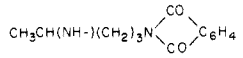
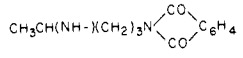
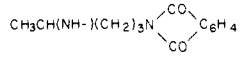
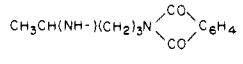
**5-(4-Acetamidophenoxy)-6-methoxy-8-nitroquinoline (4d).** To a stirred mixture of 7.5 g (0.05 mol) of 4-acetamidophenol, 60 mL of EtOH, 2 g of NaOH, and 5 mL of $H_2O$ were added 60 mL of dioxane and 14.2 g (0.05 mol) of 5-bromo-6-methoxy-8-nitroquinoline (**2**).[3] The mixture was heated under reflux overnight, cooled, and filtered to give 11 g of pale yellow solid. This material was extracted with boiling $C_6H_6$ and the $C_6H_6$-insoluble residue was crystallized from $Me_2CO$ (Darco) to give 8.5 g of **4d** as yellow crystals.

**5-(4-Acetamidophenoxy)-8-amino-6-methoxyquinoline (5d).** A stirred mixture of 3.5 g (0.01 mol) of **4d**, 2.2 g of Fe filings (40 mesh), 10 mL of $H_2O$, 0.5 mL of HOAc, and 0.5 mL of *n*-$Bu_2O$ was heated at 100 °C for 17 h, cooled, and filtered. The filter cake was extracted with boiling $Me_2CO$ and the extract was concentrated to give 2.8 g of **5d**. Recrystallization from $Me_2CO$, followed by vacuum sublimation [230 °C (0.3 mm)], afforded the analytical sample.

**6-Methoxy-8-(1-methyl-4-phthalimidobutylamino)-5-phenoxyquinoline (7a).** A stirred mixture of 10.6 g (0.04 mol) of 8-amino-6-methoxy-5-phenoxyquinoline (**5a**) and 15 g (0.05 mol) of 4-bromo-1-phthalimidopentane (**6a**) was maintained at 150 °C while $Et_3N$ (5 g, 0.05 mol) was added in portions during 1.5 h. After an additional 1.5 h at 150 °C, 9 g (0.03 mol) of **6a** was added in a single portion followed by 3 g (0.03 mol) of $Et_3N$ in small portions during 1 h. After another 2 h, 6 g (0.02 mol) of **6a** and 2 g (0.02 mol) of $Et_3N$ were added in the usual manner. Stirring was continued (2 h) at 150 °C until TLC revealed only a trace of unreacted **5a**. The mixture was allowed to cool, diluted with $Me_2CO$ (200 mL), and filtered to remove $Et_3N$·HBr. The filtrate was concentrated under reduced pressure and the residue was extracted with 850 mL of $Et_2O$. The filtered extract was treated with ethereal HCl to give crude **7a**·HCl as an orange-red solid. The free base was released by treatment with ethereal $Et_3N$ and

Table III. 8-Substituted 6-Methoxy-5-phenoxyquinolines



| Compd | $R_1$ | $R_2$ | Mp, °C (solvent) | Yield, % | Formula[a] |
|---|---|---|---|---|---|
| 4a | $NO_2$ | H | 136-139 (95% EtOH)[b] | 56 | $C_{16}H_{12}N_2O_4$ |
| 4b | $NO_2$ | 4-Cl | 180-181 (EtOH) | 57 | $C_{16}H_{11}ClN_2O_4$ |
| 4c | $NO_2$ | 4-F | 177-179 (MeOH) | 59 | $C_{16}H_{11}FN_2O_4$ |
| 4d | $NO_2$ | 4-$CH_3CONH$ | 265-267 ($Me_2CO$) | 50 | $C_{18}H_{15}N_3O_5$ |
| 5a | $NH_2$ | H | 121-122 (95% EtOH)[c] | 85 | $C_{16}H_{14}N_2O_2$ |
| 5b | $NH_2$ | 4-Cl | 117-118 (MeOH) | 89 | $C_{16}H_{13}ClN_2O_2$ |
| 5c | $NH_2$ | 4-F | 87-88 ($C_6H_6$-hexane) | 65 | $C_{16}H_{13}FN_2O_2$ |
| 5d | $NH_2$ | 4-$CH_3CONH$ | 225-227 ($Me_2CO$) | 87 | $C_{18}H_{17}N_3O_3$ |
| 7a |  | H | 126-128 (EtOH) | 65[d] | $C_{29}H_{27}N_3O_4$[f] |
| 7b |  | 4-Cl | 75-77 | 70,[d] 84[e] | $C_{29}H_{29}BrClN_3O_5$[g,h] |
| 7c |  | 4-F | 85 (Petr ether) | 85[d] | $C_{29}H_{26}FN_3O_4$ |
| 7d |  | 4-$CH_3COHN$ | *i* | 65[d] | *i* |
| 8a | $CH_3CH(NH_2)(CH_2)_3NH_2 \cdot H_3PO_4 \cdot 0.5H_2O$ | H | 167-180 (EtOH-MeOH) | 64 | $C_{21}H_{29}N_3O_{6.5}P$ |
| 8b | $CH_3CH(NH_2)(CH_2)_3NH_2 \cdot H_2O$ | 4-Cl | 82-85 ($Et_2O$) | 58 | $C_{21}H_{26}ClN_3O_3$ |
| 8c | $CH_3CH(NH_2)(CH_2)_3NH_2 \cdot$citrate$\cdot 0.5H_2O$ | 4-F | 133-137 (MeOH) | 39 | $C_{27}H_{33}FN_3O_{9.5}$ |
| 8d | $CH_3CH(NH_2)(CH_2)_3NH_2 \cdot HCl$ | 4-$CH_3CONH$ | 202-207 (EtOAc) | 46 | $C_{23}H_{29}ClN_4O_3$ |

[a] All compounds except 4a and 5a (previously reported, see footnote *b*) were analyzed for C, H, and N. [b] Lit. mp 137-139 °C [W. M. Lauer, C. Rondestvedt, R. T. Arnold, N. L. Drake, J. V. Hook, and J. Tinker, *J. Am. Chem. Soc.*, **68**, 1546 (1946)]. [c] Lit. mp 124-125 °C (see footnote *b*). [d] Obtained with bromide (**6a**). [e] Obtained with iodide (**6b**). [f] C: calcd, 72.35; found, 72.81. [g] Analyzed as hydrobromide hydrate, mp 214-215 °C. [h] N: calcd, 6.83; found 6.26. [i] Used without purification.

crystallized to give 12.5 g of yellow solid.

**4-Iodo-1-phthalimidopentane (6b).** A stirred mixture of 60 g (0.203 mol) of **6a**, 34 g (0.225 mol) of NaI, and 250 mL of $Me_2CO$ was heated at reflux, in the dark, for 67 h. The mixture was allowed to cool and filtered to remove 15.5 g of NaBr. The filtrate was concentrated to dryness, treated with 120 mL of $CHCl_3$, and filtered to remove another 8 g of inorganic salt. The $CHCl_3$ solution was washed sequentially with dilute $Na_2S_2O_3$, $H_2O$, dilute $NaHCO_3$, and $H_2O$, then dried ($MgSO_4$), and concentrated to give 55 g (80%) of **6b**. This material was used without further purification.

**5-(*p*-Chlorophenoxy)-6-methoxy-8-(1-methyl-4-phthalimidobutylamino)quinoline (7b).** A stirred mixture of 3 g (0.01 mol) of 8-amino-5-(*p*-chlorophenoxy)-6-methoxyquinoline (**5b**), 3.5 g (0.01 mol) of **6b**, and 1 g (0.01 mol) of $Et_3N$ was heated at 145 °C for 0.5 h, treated with a mixture of 3.5 g (0.01 mol) of **6b** and 1 g (0.01 mol) of $Et_3N$ during 15 min, and maintained at 145 °C for an additional 1.75 h. The mixture was concentrated in vacuo and the residue was extracted with 450 mL of boiling $Et_2O$. The extract was slowly treated with $Et_2O$–HCl and a small amount of pale-yellow precipitate was discarded. Continued treatment with $Et_2O$–HCl gave 5.2 g (95%) of **7b**·HCl as an orange-red solid. Basification with $NH_4OH$ provided an 84% yield of the free base.

**8-(4-Amino-1-methylbutylamino)-6-methoxy-5-phenoxyquinoline Phosphate Hemihydrate (8a).** A mixture of 11.5 g (0.024 mol) of **7a**, 12 mL of 95% hydrazine, and 400 mL of EtOH was heated under reflux for 15 h, cooled, and filtered to remove phthal hydrazide. The filtrate was brought to dryness in vacuo and the residue was extracted with warm $Et_2O$ (total, 700 mL). The extract was filtered, washed with 30% KOH (3 × 100 mL) and $H_2O$ (3 × 50 mL), and dried ($MgSO_4$). To the stirred, dry extract was slowly added a solution of 3 g of 85% $H_3PO_4$ in 20 mL of EtOH. The resulting tacky orange-red solid was separated by decantation and boiled with 400 mL of EtOH. The suspension was cooled and the yellow solid was ground and again boiled with EtOH (200 mL) for 0.5 h. Cooling, filtering, and drying gave 7 g of **8a** with the melting range, 167–180 °C. An analytical sample, prepared by crystallization from EtOH–MeOH (80:20), displayed the same melting range.

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