was warmed to reflux temperature and stirred for 1 h. After this time $H_2O$ and $Et_2O$ were added. The organic layer was dried and evaporated to give 30.8 g of an oil. Distillation of the oil gave 12.5 g of 1,5-dibromopentane (85 °C, 0.07 mmHg) and a residue, which was purified by column chromatography; on elution with $CHCl_3$, 6.2 g of 10-bromo-1-phenyl-5-oxa-2-thiadecane was obtained. A solution of KCN (1.5 g, 23 mmol) in $H_2O$ (63 mL) was added to a solution of the above alkyl bromide (6.2 g, 20 mmol) in EtOH (145 mL) and the mixture was stirred at reflux temperature for 4 h. After this time, the EtOH was removed, $H_2O$ was added, and the compound was extracted with $Et_2O$. The organic layer was dried and evaporated to give 4.9 g of 11-phenyl-7-oxa-10-thiaundecanenitrile (38%). A solution of this nitrile (4.9 g, 18 mmol) in dioxane (50 mL) was added to a suspension of $LiAlH_4$ (2.1 g, 56 mmol) in dioxane (100 mL) and the resulting mixture was stirred at reflux temperature for 3 h. After cooling, 3 mL of $H_2O$, 3 mL of dioxane, 4 mL of 2 N NaOH, and 9 mL of $H_2O$ were successively added. The mixture was filtered and the filtrate evaporated to dryness. The residue was dissolved in $CHCl_3$ and extracted with 10% HCl. The aqueous layer was basified with 2 N NaOH and washed with $CHCl_3$. The chloroform extracts were dried and evaporated to give 3.29 g of an oil. This oil was distilled and the fraction collected between 175 and 200 °C (0.05 mmHg) yielded 2.26 g of **53** (44%).

**(b) Bis[2-[(6-aminohexyl)oxy]ethyl] Disulfide (54).** Under $N_2$ atmosphere, small pieces of Na (4.5 g, 195 mmol) were added to a solution of **53** (0.5 g, 1.8 mmol) in EtOH (56 mL). The reaction was strongly exothermic. When spontaneous boiling ceased, the solution was maintained at reflux temperature until all of the Na had dissolved (40 min). The solution was cooled and solid $CO_2$ was added. The resulting white paste was diluted with EtOH and $CH_2Cl_2$ and filtered, and the solid was washed with $CH_2Cl_2$. The organic layers were evaporated to dryness, and the residue was dissolved in EtOH. Over this ethanolic solution was added 0.1 N aqueous $I_2$ until no decoloration was observed, and the mixture was stirred for 1 h. The solution was evaporated, and the residue was dissolved in $H_2O$, basified with 2 N NaOH, and extracted with $CH_2Cl_2$. The organic layer was dried and evaporated to give the disulfide **54** (0.3 g, 90%).

**(c) Bis[2-[[6-[(arylmethyl)amino]hexyl]oxy]ethyl] Disulfides 30 and 31.** A solution of disulfides **54** (0.3 g, 0.9 mmol) and the suitable aldehyde (benzaldehyde or *o*-methoxybenzaldehyde) (1.9 mmol) in dry benzene (50 mL) was stirred at reflux temperature for 15 h in a system equipped with a Dean-Stark trap. After this time the solvent was evaporated and the residue dissolved in MeOH. To this methanolic solution was added $NaBH_4$ (0.08 g, 2.1 mmol) and the mixture was stirred at reflux temperature for 30 min. The mixture was cooled, acidified with 2 N HCl, and washed with $Et_2O$. The aqueous solution was basified with 2 N NaOH and extracted with $CHCl_3$. The chloroform extracts were dried and evaporated to give the expected disulfides **30** or **31**.

**General Procedure for Preparation of *N*,*N*'-Bis[(arylmethoxy)hexyl]cystamines 32-38. Method F. (a) [(Arylmethoxy)hexyl]amines 56a-c.** A solution of the suitable alcohol **55a-c** (80 mmol) in anhydrous THF (20 mL) was slowly added to a suspension of NaH (100 mmol) and 1,6-dibromohexane (200 mmol) in THF (60 mL). The resulting mixture was stirred at reflux temperature for 30 min, then poured into $H_2O$, and extracted with $Et_2O$. The organic layer was washed with $H_2O$, dried, and evaporated to give an oil. Upon distillation, excess 1,6-dibromopentane and a residue identified as the corresponding bromo ether were isolated. The bromo ether and potassium phthalimide (50 mmol) in DMF (50 mL) were heated at 100 °C for 5 h. After this time the mixture was poured into $H_2O$ and extracted with $Et_2O$. The organic layer was washed with $H_2O$, dried, and evaporated to give the corresponding phthalimide. A solution of this phthalimide (80 mmol) and 80% hydrazine hydrate (104 mmol) in EtOH (300 mL) was heated for 3 h at reflux temperature. The solvent was removed, the residue was dissolved in 5 N NaOH, and the desired product was extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and evaporated to give the corresponding amines **56a-c**.

**(b) Cystamines 32-38.** A solution of the suitable amine (**56a-c**, ethylamine, *tert*-butylamine, benzylamine, or piperidine) (75 mmol) in benzene (20 mL) was stirred at reflux temperature for 1 h in a system equipped with a Dean-Stark trap.

The solution was cooled at 0 °C and a thiirane (63 mmol) in benzene (20 mL) solution was slowly added. The resulting mixture was refluxed for 3 h. The solvent was evaporated, the residue was dissolved in $H_2O$, and 2 N HCl was added until a pH of 8-9 was reached. A solution of $K_3Fe(CN)_6$ (8 mmol) in $H_2O$ (25 mL) was added. The mixture was allowed to stand, and after a 30-min period, NaOH pellets (6 g, 150 mmol) were added. A sufficient amount of NaCl was next added to saturate the solution. The aqueous solution was washed with $CH_2Cl_2$, and the organic extracts were dried and evaporated to give disulfides **32-38**. These compounds were purified by crystallization of a solid derivative.

**Pharmacology.** The following protocol[1a] was applied for the relative potencies listed in Table I. Male rats weighing 200-250 g were killed by a sharp blow on the head and both vasa deferentia were isolated. These were mounted individually in organ baths of 30-mL vol containing Krebs bicarbonate buffer (113 mmol of NaCl, 4.7 mmol of KCl, 2.4 mmol of $CaCl_2$, 1.2 mmol of $MgSO_4$, 1.2 mmol of $KH_2PO_4$, 25 mmol of $NaHCO_3$, and 11.5 mmol of dextrose). The medium was maintained at 32 °C while being aerated with 95% $O_2$-5% $CO_2$. The loading tension was 0.50 g, and the contractions were recorded by means of force transducers connected to a Omni-Scribe recorder. The tissues were allowed to equilibrate for 1 h, and the medium was changed prior to addition of the antagonists. After a 30-min incubation period, the bath was drained and the tissues were washed with the bath solution for 30 min. Cumulative concentration-response curves for NE were constructed after treatment with each antagonist. The decrease in maximum response was expressed in percent of the control value. The percent blockade for each compound is expressed as the mean ± SEM of five separate experiments.

**Acknowledgment.** We thank Dr. F. López-Calahorra, for his work and encouragement in the initial step, A. Morón, E. Naudó, E. Bardají, and L. Bennasar for their assistance with the synthetic work, and also the Department of Pharmacology, Autónoma University of Barcelona, for the use of their facilities.

# Modifications of Primaquine as Antimalarials. 4. 5-Alkoxy Derivatives of Primaquine

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Thirty-two 5-alkoxyprimaquines have been synthesized and evaluated as blood schizonticides (*Plasmodium berghei*, mouse) and tissue schizonticides (*Plasmodium cynomolgi*, monkey). Several of these compounds were extremely active in both screens. Such a broad spectrum of antimalarial efficacy offers the possibility of a single drug that could cure the various relapsing and nonrelapsing malarias.

The major forms of human malaria are caused by the parasites *Plasmodium falciparum* and *Plasmodium vivax*. Elimination of the blood form of falciparum malaria clears the body of this disease. Vivax malaria, however, gives rise

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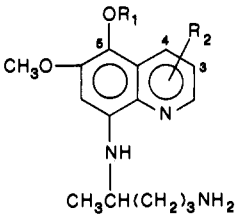
**Table I.** Blood Schizonticidal Antimalarial Activity (*Plasmodium berghei*, Mouse)[a]




| | | | cures (C),[b] toxic deaths (T),[c] or ΔMST;[d] dose (mg/kg): | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| no. | $R_1$ | $R_2$ | 2.5 | 5 | 10 | 20 | 40 | 80 | 160 | 320 | 640 |
| | primaquine | | | | | 4.0 | 5.0 | 9.4 | 2T | 5T | 5T |
| | 2-methylprimaquine | | | | | 3.1 | 5.5 | 7.3 | 8.3 | 1T | 5T |
| | 3-methylprimaquine | | | | | 5.7 | 7.5 | 1T | 2T | 5T | 5T |
| | 4-methylprimaquine | | | | | 3.1 | 4.9 | 5.5 | 9.0 | 10.0 | 3C |
| **7a** | $C_2H_5$ | H | | | | | 0.3 | | 3T | | 5T |
| **7c** | $n$-$C_3H_7$ | H | | | 3.7 | 4.5 | 8.3 | 1T | 5T | 5T | 5T |
| **7d** | $n$-$C_4H_9$ | H | | | 4.1 | 6.5 | 6.7 | 2T | 3T | | 5T |
| **7e** | $n$-$C_5H_{11}$ | H | | | 4.3 | 4.7 | 6.1 | 4.7 | 4T | 5T | 2T |
| **7f** | $n$-$C_6H_{13}$ | H | | | | 3.7 | 6.5 | 1C | 1C | 0.1 | 1T |
| **7g** | $n$-$C_8H_{17}$ | H | | | | 2.9 | 6.7 | 8.1 | 12.1 | 6.3 | 1T |
| **7h** | $n$-$C_{10}H_{21}$ | H | | | | 0.1 | 0.1 | 2.9 | 5.7 | 9.3 | 2C |
| **7i** | $n$-$C_3H_7$ | 4-$CH_3$ | 6.0 | 1C | 1C | 3C | 3T | | 5T | | 5T |
| **7j** | $n$-$C_4H_9$ | 4-$CH_3$ | | | 11.0 | 5C | 3C | 4T | 5T | 5T | 5T |
| **7k** | $n$-$C_5H_{11}$ | 4-$CH_3$ | 2C | 5C | 5C | 4C | 1C | 2T | 4T | 5T | 5T |
| **7l** | $n$-$C_6H_{13}$ | 4-$CH_3$ | 1C | 1C | 1C | 5C | 5C | 4C | 3T | 5T | 5T |
| **7m** | $n$-$C_7H_{15}$ | 4-$CH_3$ | 7.9 | 3C | 3C | 5C | 4C | 2C | 1T | 5T | 5T |
| **7n** | $n$-$C_8H_{17}$ | 4-$CH_3$ | 7.8 | 12.0 | 5C | 5C | 5C | 5C | 2C | 0.4 | 2T |
| **7o** | $n$-$C_9H_{19}$ | 4-$CH_3$ | 7.9 | 9.7 | 2C | 3C | 5C | 5C | 4C | 4C | 4C |
| **7p** | $n$-$C_{10}H_{21}$ | 4-$CH_3$ | | | 1.8 | 2C | 3C | 4C | 4C | 5C | 4C |
| **7q** | $n$-$C_{11}H_{23}$ | 4-$CH_3$ | | | 3.7 | 1.0 | 1C | 2C | 5C | 5C | 5C |
| **7r** | $n$-$C_{12}H_{25}$ | 4-$CH_3$ | | | 2.0 | 3.2 | 6.4 | 7.6 | 4C | 5C | 5C |
| **7s** | $n$-$C_6H_{13}$ | 3-$CH_3$ | | | 0.2 | 8.2 | 2C | 1C | 7.6 | 3T | 4T |
| **7t** | $n$-$C_6H_{13}$ | 2-$CH_3$ | | | 2.7 | 6.0 | 1C | 11.4 | 3C | 3T | 3T |
| **7u** | 2-$C_6H_{13}$ | 3-$CH_3$ | | | 6.1 | 2C | 3C | 1C | 5T | 5T | 5T |
| **7v** | 3-$C_6H_{13}$ | 3-$CH_3$ | | | | 5.3 | 1C | 1C | 4T | 5T | 5T |
| **7w** | $n$-$C_6H_{13}$ | 2,4-$(CH_3)_2$ | | 7.3 | 1C | 2C | 5C | 5T | 5T | 5T | 5T |
| **7x** | $C_6H_5O(CH_2)_4$ | 4-$CH_3$ | 8.0 | 1C | 10.2 | 5C | 5C | 5T | 5T | 5T | 5T |
| **7y** | $C_6H_5O(CH_2)_6$ | 4-$CH_3$ | | 7.3 | 2C | 4C | 5C | 4C | 2C | 2T | 2T |
| **7z** | $C_6H_5O(CH_2)_8$ | 4-$CH_3$ | | | 0.6 | 3.0 | 9.4 | 4.4 | 3C | 2T | 1T |
| **7aa** | $C_6H_{11}CH_2$ | 4-$CH_3$ | 9.2 | 7.8 | 1C | 4C | 3C | 1C | 2C | 4T | 5T |
| **7bb** | cyclopentyl | 4-$CH_3$ | 6.1 | 6.9 | 6.9 | 1C | 2C | 1C | 5T | 5T | 5T |
| **7cc** | $CH_2$=$CHCH_2CH_2$ | 4-$CH_3$ | 7.5 | 8.1 | 7.5 | 8.8 | 1C | 0.0 | 5T | 5T | 5T |
| **7dd** | $CH_3(CH_2)_3O(CH_2)_2$ | 4-$CH_3$ | 3.3 | 4.3 | 3C | 4C | 2C | 4T | 3T | 4T | |
| **7ee** | $CH_3O(CH_2)_6$ | 4-$CH_3$ | 6.9 | 1C | 3C | 2C | 2C (3T) | | 5T | | 5T |
| **7ff** | $C_6H_5CH_2O(CH_2)_6$ | 4-$CH_3$ | 1C | 2C | 4C | 2T | 5T | | | | |
| | $CH_3$ | 4-$CH_3$[e] | | | | 5.7 | 7.1 | 8.9 | 1T | 4T | 5T |

[a] Test data were supplied by Drs. H. A. Musallam and E. A. Steck of Walter Reed Army Institute of Research. Tests were carried out by the Rane Laboratory, University of Miami with blood-induced, *P. berghei* infected mice (five animals per group) via the method of Osdene et al.[5] [b] The number of mice surviving at 60 days postinfection. [c] Deaths prior to the 6th day. [d] 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). [e] See ref 8.

to a reservoir of tissue forms that can cause relapse through intermittent reinvasion of cleared blood. Primaquine, a potent tissue schizonticide, is the clinical drug of choice for the radical cure of refractory, relapsing malaria. Despite its preeminence, primaquine suffers from several serious deficiencies; it has minimal blood schizonticidal activity and a therapeutic index low enough to make its use hazardous. Earlier papers in this series[1,2] described the dramatic attenuation of these drawbacks by addition to the primaquine molecule of a methyl group at position 4 and a phenoxyl group at position 5. In an extension of this research, we have synthesized a number of 5-alkoxyprimaquines with methyl groups at various positions on the pyridine ring.

## Chemistry

Scheme I outlines the general preparative route. Alkylation of 1[3] was effected in hexamethylphosphoric triamide, in the presence of triethylamine and propylene oxide, by an adaptation of Fujita's method.[4] The sequence leading from **3** to **7** was identical with the one described earlier.[1,2] Preparation of the intermediates **3a** and **3b** was carried out by using the inverted method shown in Scheme II. This method failed with alcohols containing more than two carbon atoms. Preparative data are presented in Tables III–V and methods are exemplified in the Experimental Section.

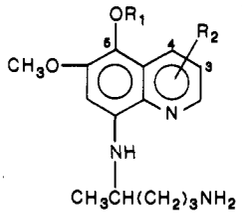
## Biological Evaluation and Discussion

The 32 target compounds were evaluated in the suppressive, blood schizonticidal test (trophozoite-induced

(1) Chen, E. H.; Saggiomo, A. J.; Tanabe, K.; Verma, B. L.; Nodiff, E. A. *J. Med. Chem.* **1977**, *20*, 1107.
(2) Nodiff, E. A.; Tanabe, K.; Chen, E. H.; Saggiomo, A. J. *J. Med. Chem.* **1982**, *25*, 1097.

(3) We are grateful to Dr. H. A. Musallam of WRAIR for making these starting materials available.
(4) Fujita, Y. Japanese Patent 69 12,887 (June 10, 1969); *Chem. Abstr.* **1969**, *71*, 101529.

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




| no. | $R_1$ | $R_2$ | cures/no. of animals; daily dose [mg/kg (×7)]: 0.1 | 0.316 | 1.0 | 3.16 | 10.0 |
|---|---|---|---|---|---|---|---|
| | primaquine | | 0/2 | 0/2 | 1/2 | | |
| | 3-methylprimaquine | | 0/2 | 0/2 | 2/2 | | |
| | 4-methylprimaquine | | | 0/4 | 2/2 | | 2/2 |
| **7b** | $CF_3CH_2$ | H | | 0/1 | 1/1 | | |
| **7c** | $n$-$C_3H_7$ | H | 0/2 | 2/2 | 3/3 | | 1/1 |
| **7d** | $n$-$C_4H_9$ | H | | 2/4 | 2/2 | | T |
| **7e** | $n$-$C_5H_{11}$ | H | 0/2 | 1/2 | 1/1 | | |
| **7f** | $n$-$C_6H_{13}$ | H | | 0/2 | 3/3 | | 1/1 |
| **7g** | $n$-$C_8H_{17}$ | H | 0/2 | 0/1 | 2/2 | | |
| 7h | $n$-$C_{10}H_{21}$ | H | | | 0/1 | | 1/1 |
| 7i | $n$-$C_3H_7$ | 4-$CH_3$ | 0/2 | 2/2 | 1/1 | | |
| **7j** | $n$-$C_4H_9$ | 4-$CH_3$ | 0/2 | 2/2 | 1/1 | | |
| **7k** | $n$-$C_5H_{11}$ | 4-$CH_3$ | 3/4 | | 2/2 | | |
| 7l | $n$-$C_6H_{13}$ | 4-$CH_3$ | 5/5 | 3/3 | 1/1 | 0/1 | |
| **7m** | $n$-$C_7H_{15}$ | 4-$CH_3$ | 0/2 | 2/2 | 4/4 | | T |
| **7n** | $n$-$C_8H_{17}$ | 4-$CH_3$ | | 0/1 | 1/1 | | T |
| **7o** | $n$-$C_9H_{19}$ | 4-$CH_3$ | 0/2 | 0/2 | 1/1 | | T |
| **7p** | $n$-$C_{10}H_{21}$ | 4-$CH_3$ | | | 0/1 | 0/1 | 1/1 |
| **7q** | $n$-$C_{11}H_{23}$ | 4-$CH_3$ | | | 0/1 | 2/2 | 1/1 |
| **7r** | $n$-$C_{12}H_{25}$ | 4-$CH_3$ | 0/1 | | 0/1 | | |
| **7s** | $n$-$C_6H_{13}$ | 3-$CH_3$ | 0/2 | 0/2 | 3/4 | | |
| 7t | $n$-$C_6H_{13}$ | 2-$CH_3$ | 0/2 | 1/1 | 0/1 | | |
| **7u** | 2-$C_6H_{13}$ | 3-$CH_3$ | | | 1/1 | | |
| **7v** | 3-$C_6H_{13}$ | 3-$CH_3$ | 0/1 | | 0/1 | | |
| **7w** | $n$-$C_6H_{13}$ | 2,4-$(CH_3)_2$ | 2/4 | 2/3 | 1/1 | | |
| **7x** | $C_6H_5O(CH_2)_4$ | 4-$CH_3$ | 0/2 | | | | |
| **7y** | $C_6H_5O(CH_2)_6$ | 4-$CH_3$ | 0/1 | 0/2 | 1/1 | | |
| **7z** | $C_6H_5O(CH_2)_8$ | 4-$CH_3$ | 1/2 | 0/3 | 2/2 | | |
| 7aa | $C_6H_{11}CH_2$ | 4-$CH_3$ | 0/1 | 0/1 | 2/2 | | 1/1 |
| **7bb** | cyclopentyl | 4-$CH_3$ | 0/2 | 2/2 | 2/2 | | T |
| **7cc** | $CH_2$=$CHCH_2CH_2$ | 4-$CH_3$ | 0/1 | 1/1 | 1/1 | | |
| **7dd** | $CH_3(CH_2)_3O(CH_2)_2$ | 4-$CH_3$ | 1/3 | 2/2 | 1/1 | | T |
| 7ee | $CH_3O(CH_2)_6$ | 4-$CH_3$ | 0/2 | 0/1 | 2/2 | | |
| **7ff** | $C_6H_5CH_2O(CH_2)_6$ | 4-$CH_3$ | 1/3 | 3/5 | 2/2 | | |
| | $CH_3$ | 4-$CH_3$[c,d] | | | | | |

[a] Data were provided by Drs. H. A. Musallam and E. A. Steck, Walter Reed Army Institute of Reserach. [b] Tests were carried out by the SEATO Medical Research Laboratory, Bangkok, with sporozoite-induced *P. cynomolgi* infected rhesus monkeys according to the procedure of Schmidt et al.[6] [c] See ref 8. [d] 11/13C at 0.125 mg/kg, 3/4C at 0.25 mg/kg, 1/1C at 0.5 mg/kg.

*Plasmodium berghei* infection in mice)[5] (Table I)and in the radical curative, tissue schizonticidal test (sporozoite-induced *Plasmodium cynomolgi* infection in rhesus monkeys)[6] (Table II). In the tables, $R_1$ equals $n$-alkyl, isoalkyl, cycloalkyl, alkenyl, cycloalkylmethyl, phenoxyalkyl, alkoxyalkyl, and (benzyloxy)alkyl; $R_2$ equals H, 2-$CH_3$, 3-$CH_3$, 4-$CH_3$, and 2,4-$(CH_3)_2$. Included for comparison, are primaquine, its pyridine ring methyl derivatives, and LaMontagne's[8] compound, 5-methoxy-4-methylprimaquine.

**Blood Schizonticidal Activity (Table I).** Among the desmethyl compounds, the best combination of activity and nontoxicity occurred when $R_1$ was the $n$-decyl group (**7h**). However, even this compound was relatively unimpressive with only two cures at 640 mg/kg. On moving from $R_1$ = decyl down through this homologous series, toxicity increased until when $R_1$ was butyl or smaller, toxicity was greater than that for primaquine itself. The toxicity increase was not accompanied by any significant increase in activity.

Introduction to the 5-alkoxyprimaquines of a 4-$CH_3$ group generally produced a very pronounced increase in activity in the lower half of the dosage range without diminishing toxicity at the elevated doses. Exceptions were the long-chain compounds with $R_1$ = nonyl (**7o**), decyl (**7p**), undecyl (**7q**), and dodecyl (**7r**). These four derivatives caused no toxic deaths at the highest dose tested.

Following are a number of additional structure–activity relationships:

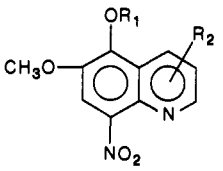
1. Comparison of the 5-hexoxy derivatives, **7l**, **7s**, and **7t**, suggests that the 2-$CH_3$ and 3-$CH_3$ groups are almost equivalent and have a lesser effect on both activity and toxicity than the 4-$CH_3$ group.

2. The 2,4-dimethyl-5-alkoxyprimaquine was more toxic than the corresponding 4-$CH_3$ analogue (**7w** vs. **7l**).

3. Primaquines, bearing a branched-chain alkoxy at position 5, were more toxic than their straight-chain

(5) Osdene, T. S.; Russell, P. B.; Rane, L. *J. Med. Chem.* **1967**, *10*, 431.
(6) Schmidt, L. N.; Rossan, R. N.; Fradkin, R.; Woods, J. *Bull. W.H.O.* **1966**, *34*, 783.
(7) Fuson, R. C.; Bauman, R. A.; Howard, E., Jr.; Marvell, E. N. *J. Org. Chem.* **1947**, *12*, 799.
(8) LaMontagne, M. P.; Markovac, A.; Khan, M. S. *J. Med. Chem.* **1982**, *25*, 964.

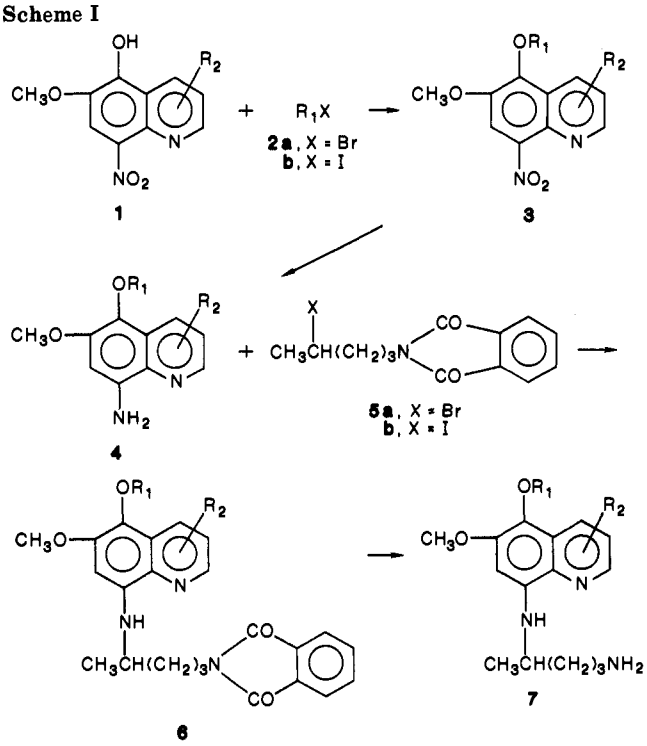
**Table III.** 5-Alkoxy-6-methoxy-8-nitroquinolines



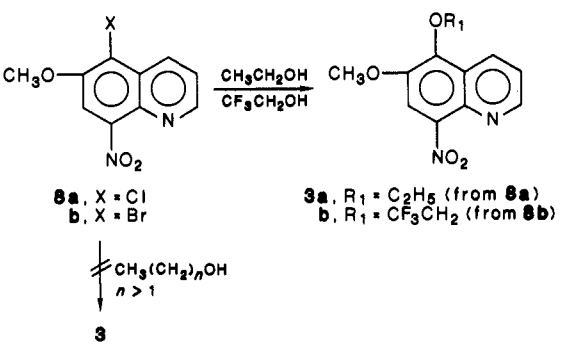
| no. | $R_1$ | $R_2$ | $R_1X$[a] | mp, °C (solvent) | yield, % | formula[b] |
|---|---|---|---|---|---|---|
| **3a** | $C_2H_5$ | H | OH | 95–97 (ligroin) | 80 | $C_{12}H_{12}N_2O_4$ |
| **3b** | $CF_3CH_2$ | H | OH | 120–121 ($Et_2O$) | 43 | $C_{12}H_9F_3N_2O_4$ |
| **3c** | $n$-$C_3H_7$ | H | Br | 105–106 (MeOH) | 62 | $C_{13}H_{14}N_2O_4$ |
| **3d** | $n$-$C_4H_9$ | H | Br | 71–73 (MeOH) | 70 | $C_{14}H_{16}N_2O_4$ |
| **3e** | $n$-$C_5H_{11}$ | H | I | 66–67 (ligroin) | 73 | $C_{15}H_{18}N_2O_4$ |
| **3f** | $n$-$C_6H_{13}$ | H | Br | 53–55 (MeOH–$H_2O$) | 65 | $C_{16}H_{20}N_2O_4$ |
| **3g** | $n$-$C_8H_{17}$ | H | Br | 52–54 (pet. ether) | 75 | $C_{18}H_{24}N_2O_4$ |
| **3h** | $n$-$C_{10}H_{21}$ | H | I[c] | 56 (ligroin) | 56 | $C_{20}H_{28}N_2O_4$ |
| **3i** | $n$-$C_3H_7$ | 4-$CH_3$ | Br | 97–101 (ligroin) | | *d* |
| **3j** | $n$-$C_4H_9$ | 4-$CH_3$ | Br | 68–73 (ligroin) | | *d* |
| **3k** | $n$-$C_5H_{11}$ | 4-$CH_3$ | Br | 56–57 (ligroin) | 43 | $C_{16}H_{20}N_2O_4$ |
| **3l** | $n$-$C_6H_{13}$ | 4-$CH_3$ | Br | 53–54 (pet. ether) | 57 | $C_{17}H_{22}N_2O_4$ |
| **3m** | $n$-$C_7H_{15}$ | 4-$CH_3$ | I | 56–57 (pet. ether) | 68[f] | $C_{18}H_{24}N_2O_4$ |
| **3n** | $n$-$C_8H_{17}$ | 4-$CH_3$ | Br | 60–62 (pet. ether) | 53 | $C_{19}H_{26}N_2O_4$ |
| **3o** | $n$-$C_9H_{19}$ | 4-$CH_3$ | Br | 60–61 (pet. ether) | 42 | $C_{20}H_{28}N_2O_4$ |
| **3p** | $n$-$C_{10}H_{21}$ | 4-$CH_3$ | I | 52–54 (ligroin) | 58 | *d* |
| **3q** | $n$-$C_{11}H_{23}$ | 4-$CH_3$ | Br | 59–60 (pet. ether) | 37 | $C_{22}H_{32}N_2O_4$ |
| **3r** | $n$-$C_{12}H_{25}$ | 4-$CH_3$ | Br | 55–57 (pet. ether) | 42 | $C_{23}H_{34}N_2O_4$ |
| **3s** | $n$-$C_6H_{13}$ | 3-$CH_3$ | Br | 84–85 (ligroin) | 59 | *d* |
| **3t** | $n$-$C_6H_{13}$ | 2-$CH_3$ | Br | 32–34 *e* | | *d* |
| **3u** | 2-$C_6H_{13}$ | 3-$CH_3$ | Br[c] | *e* | | *d* |
| **3v** | 3-$C_6H_{13}$ | 3-$CH_3$ | Br[g] | 60–61 (pet. ether) | 73 | $C_{17}H_{22}N_2O_4$[h] |
| **3w** | $n$-$C_6H_{13}$ | 2,4-$(CH_3)_2$ | Br | 66–67 (ligroin) | 50 | $C_{18}H_{24}N_2O_4$ |
| **3x** | $C_6H_5O(CH_2)_4$ | 4-$CH_3$ | Br | 87–88 (hexane–$Et_2O$) | 37 | $C_{21}H_{22}N_2O_5$ |
| **3y** | $C_6H_5O(CH_2)_6$ | 4-$CH_3$ | Br[i] | 60–61 ($Et_2O$) | 51 | $C_{23}H_{26}N_2O_5$ |
| **3z** | $C_6H_5O(CH_2)_8$ | 4-$CH_3$ | Br[i] | 68.5–70 (hexane) | 63 | $C_{25}H_{30}N_2O_5$[j] |
| **3aa** | $C_6H_{11}CH_2$ | 4-$CH_3$ | Br | 89–90.5 (hexane) | 30 | $C_{18}H_{22}N_2O_4$ |
| **3bb** | cyclopentyl | 4-$CH_3$ | Br | 71–73 (hexane) | 32 | $C_{16}H_{18}N_2O_4$ |
| **3cc** | $CH_2$=$CHCH_2CH_2$ | 4-$CH_3$ | Br[k] | 85–87 (hexane) | 37 | $C_{15}H_{16}N_2O_4$ |
| **3dd** | $CH_3(CH_2)_3O(CH_2)_2$ | 4-$CH_3$ | Br[l] | 45–47 (hexane) | 37 | $C_{17}H_{22}N_2O_5$ |
| **3ee** | $CH_3O(CH_2)_6$ | 4-$CH_3$ | Br[m] | 45–46.5 (hexane) | 32 | $C_{18}H_{24}N_2O_5$ |
| **3ff** | $C_6H_5CH_2O(CH_2)_6$ | 4-$CH_3$ | Br[l] | *e* | | *d* |

[a] With the noted exceptions, the alkyl halides were purchased from Aldrich Chemical Co., Milwaukee, WI. [b] All compounds were analyzed for C, H, and N. [c] Pfaltz and Bauer, Stamford, CT. [d] Used without analysis. [e] Used without recrystallization. [f] The yield with 1-bromoheptane instead of 1-iodoheptane was 52%. [g] Eastern Chemical Corp., Hauppauge, NY. [h] C: calcd, 64.13; found, 63.56. [i] Fairfield Chemical Co., Inc., Blythewood, SC. [j] C: calcd, 68.47; found, 67.75. [k] Fluka Chemical Corp., Hauppage, NY. [l] Experimental. [m] Drake, N. L. *J. Am. Chem. Soc.* **1946**, *68*, 1536.

**Scheme I**



**Scheme II**



analogues (**7v** and **7u** vs. **7s**).

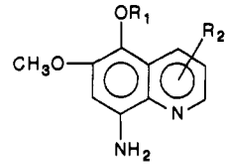
4. The unsaturated derivative (**7cc**) was slightly less active and toxic than the saturated compound (**7j**).

5. The 4-methyl-5-cycloalkoxyprimaquine (**7bb**) was less active and a bit less toxic than the corresponding 4-methyl-5-$n$-alkoxyprimaquine (**7k**).

6. Replacement of a terminal hydrogen of a 5-$n$-alkoxy group with a phenoxyl moiety had little effect on activity or toxicity (**7y** vs. **7l**, **7x** vs. **7j**, **7z** vs. **7n**).

7. Replacement of a terminal hydrogen of a 5-$n$-alkoxy group with an alkoxy moiety diminished activity and increased toxicity (**7ee** vs. **7l**).

**Table IV.** 5-Alkoxy-8-amino-6-methoxyquinolines




| no. | $R_1$ | $R_2$ | mp, °C (solvent) | yield, % | formula[a] |
|---|---|---|---|---|---|
| **4a** | $C_2H_5$ | H | 132.5–133.5 (ligroin) | 71 | $C_{12}H_{14}N_2O_2$ |
| **4b** | $CF_3CH_2$ | H | 95–96 ($Et_2O$) | 76 | $C_{12}H_{11}F_3N_2O_2$ |
| **4c** | *n*-$C_3H_7$ | H | 73–74 (hexane) | 72 | $C_{13}H_{16}N_2O_2$ |
| **4d** | *n*-$C_4H_9$ | H | 80–81 (ligroin) | 82 | $C_{14}H_{18}N_2O_2$ |
| **4e** | *n*-$C_5H_{11}$ | H | 55–56 (ligroin) | 82 | $C_{15}H_{20}N_2O_2$ |
| **4f** | *n*-$C_6H_{13}$ | H | *b* | | |
| **4g** | *n*-$C_8H_{17}$ | H | 63–64 (pet. ether) | 89 | $C_{18}H_{26}N_2O_2$ |
| **4h** | *n*-$C_{10}H_{21}$ | H | 65 (pet. ether) | 54 | $C_{20}H_{30}N_2O_2$ |
| **4i** | *n*-$C_3H_7$ | 4-$CH_3$ | 88–89 (ligroin) | 80 | $C_{14}H_{18}N_2O_2$ |
| **4j** | *n*-$C_4H_9$ | 4-$CH_3$ | 65–68 (pet. ether) | 91 | $C_{15}H_{20}N_2O_2$ |
| **4k** | *n*-$C_5H_{11}$ | 4-$CH_3$ | 65–66 (ligroin) | 85 | $C_{16}H_{22}N_2O_2$ |
| **4l** | *n*-$C_6H_{13}$ | 4-$CH_3$ | 69–71 (ligroin) | 67 | $C_{17}H_{24}N_2O_2$ |
| **4m** | *n*-$C_7H_{15}$ | 4-$CH_3$ | 68–69 (ligroin) | 88 | $C_{18}H_{26}N_2O_2$ |
| **4n** | *n*-$C_8H_{17}$ | 4-$CH_3$ | 54–55 (pet. ether) | 85 | $C_{19}H_{28}N_2O_2$ |
| **4o** | *n*-$C_9H_{19}$ | 4-$CH_3$ | 57–58 (pet. ether) | 85 | $C_{20}H_{30}N_2O_2$ |
| **4p** | *n*-$C_{10}H_{21}$ | 4-$CH_3$ | 51–52 (pet. ether) | 95 | $C_{21}H_{32}N_2O_2$[d] |
| **4q** | *n*-$C_{11}H_{23}$ | 4-$CH_3$ | 58–59 (pet. ether) | 57 | $C_{22}H_{34}N_2O_2$ |
| **4r** | *n*-$C_{12}H_{25}$ | 4-$CH_3$ | 55–56 (pet. ether) | 84 | $C_{23}H_{36}N_2O_2$ |
| **4s** | *n*-$C_6H_{13}$ | 3-$CH_3$ | 61–63 (ligroin) | 71 | *c* |
| **4t** | *n*-$C_6H_{13}$ | 2-$CH_3$ | 77–77.5 (pet. ether) | 88 | $C_{17}H_{24}N_2O_2$ |
| **4u** | 2-$C_6H_{13}$ | 3-$CH_3$ | 74–76 (MeOH–$H_2O$) | 78 | $C_{17}H_{24}N_2O_2$[e] |
| **4v** | 3-$C_6H_{13}$ | 3-$CH_3$ | 103–103.5 (ligroin) | 98 | $C_{17}H_{24}N_2O_2$ |
| **4w** | *n*-$C_6H_{13}$ | 2,4-$(CH_3)_2$ | 74–75 (pet. ether) | 79 | $C_{18}H_{26}N_2O_2$ |
| **4x** | $C_6H_5O(CH_2)_4$ | 4-$CH_3$ | 84–85 (hexane) | 90 | $C_{21}H_{24}N_2O_3$ |
| **4y** | $C_6H_5O(CH_2)_6$ | 4-$CH_3$ | 77–78 (pet. ether) | 63 | $C_{23}H_{28}N_2O_3$[f] |
| **4z** | $C_6H_5O(CH_2)_8$ | 4-$CH_3$ | 59–61 (pet. ether) | 93 | $C_{25}H_{32}N_2O_3$ |
| **4aa** | $C_6H_{11}$-$CH_2$ | 4-$CH_3$ | 83–83.5 (pet. ether) | 97 | $C_{18}H_{24}N_2O_2$ |
| **4bb** | cyclopentyl | 4-$CH_3$ | *h* (hexane) | 83 | $C_{16}H_{20}N_2O_2$[g] |
| **4cc** | $CH_2$=$CHCH_2CH_2$ | 4-$CH_3$ | 78–79 (hexane) | 46 | $C_{15}H_{18}N_2O_2$ |
| **4dd** | $CH_3(CH_2)_3O(CH_2)_2$ | 4-$CH_3$ | b | | |
| **4ee** | $CH_3O(CH_2)_6$ | 4-$CH_3$ | 39–41 (pet. ether) | 81 | $C_{18}H_{26}N_2O_3$ |
| **4ff** | $C_6H_5CH_2O(CH_2)_6$ | 4-$CH_3$ | b | | |

[a] All compounds were analyzed for C, H, and N. [b] Used without purification. [c] Used without analysis. [d] C: calcd, 73.21; found, 72.74. [e] H: calcd, 8.39; found, 8.89. [f] N: calcd, 7.36; found, 6.90. [g] C: calcd, 70.56; found, 69.95. [h] Indefinite.

8. The most toxic compound in Table I (2T at 20 mg/kg) is the (benzyloxy)hexoxy derivative (**7ff**).

9. 5-Methoxy-4-methylprimaquine[8] was toxic at 160–640 mg/kg. It was marginally active at 20–80 mg/kg.

**Radical Curative Activity (Table II).** With the exception of the *n*-decoxy derivative (**7h**), all of the desmethyl 5-*n*-alkoxy homologues were curative at 1.0 mg/kg. Among these, the propoxy, butoxy, and pentoxy derivatives (**7c**, **7d**, and **7e**, respectively) were also curative at 0.316 mg/kg, making them somewhat more active than primaquine and 4-methylprimaquine.

Addition of a 4-methyl group to the propoxy and butoxy derivatives effected no pronounced change. However, the effect of the 4-methyl group on the *n*-pentoxy and *n*-hexoxy derivatives was dramatic. The resulting compounds (**7k** and **7l**) were extremely active, producing multiple cures at 0.1 mg/kg. This is of particular importance because **7k** and **7l** were also very effective blood schizonticides (Table I).

In moving through the homologous 4-methyl-5-*n*-alkoxy series, from $C_6$ (**7l**) to $C_{12}$ (**7r**), activity gradually dropped with the $C_{10}$, $C_{11}$, and $C_{12}$ compounds noncurative at 1.0 mg/kg.

The 2,4-$(CH_3)_2$ analogue (**7w**) of **7l** cured two/four mice at 0.1 mg/kg, but the 2-$CH_3$ (**7t**) and 3-$CH_3$ (**7s**) analogues of **7l** were less active.

An analogue of **7l** in which the 5-alkoxy chain was interrupted by an oxygen atom (**7dd**) was partially curative at 0.1 mg/kg.

5-Methoxy-4-methylprimaquine[8] was curative at 0.125, 0.25, and 0.5 mg/kg.

## Conclusion

Radical cure of the various human malarias requires a drug of low toxicity that can eliminate both the blood and tissue forms of the disease. Although we have not completely eliminated toxicity, two of our compounds, 4-methyl-5-*n*-pentoxyprimaquine (**7k**) and 4-methyl-5-*n*-hexoxyprimaquine (**7l**) are remarkably effective blood *and* tissue schizonticides. Such a broad spectrum of antimalarial efficacy offers the possibility of a single drug that can cure all of the relapsing and nonrelapsing forms of malaria. Our research is continuing.

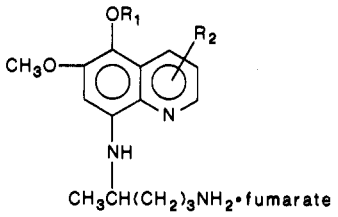
## Experimental Section

Melting points were determined in capillary tubes in an electrically heated Thiele-Dennis apparatus and are uncorrected. Elemental analyses (Micro Analysis, Inc., Wilmington, DE) were within ±0.4% of the theoretical values unless otherwise noted. Infrared spectra were obtained for all compounds as Nujol mulls on a Perkin-Elmer 137B Infracord instrument and were consistent with the assigned structures.

The preparations detailed below are typical of those outlined in Schemes I and II.

**5-(Hexyloxy)-6-methoxy-4-methyl-8-nitroquinoline (3l) (Table III).** A stirred mixture of 5-hydroxy-6-methoxy-4-methyl-8-nitroquinoline[3] (2.4 g, 0.01 mol), *n*-hexyl bromide (3.3 g, 0.02 mol), triethylamine (0.3 g), and hexamethylphosphoric triamide (2 mL) was heated at 140–150 °C, under $N_2$, while

**Table V.** 5-Alkoxy-8-[(4-amino-1-methylbutyl)amino]-6-methoxyquinolines




| no. | $R_1$ | $R_2$ | mp, °C (solvent)[a] | yield, % | formula[b] |
|---|---|---|---|---|---|
| **7a** | $C_2H_5$ | H | 154–156[c] | 60 | $C_{21}H_{29}N_3O_6$ |
| **7b** | $CF_3CH_2$ | H | 169–171[c] | 56 | $C_{21}H_{27}F_3N_2O_{6.5}$[d] |
| **7c** | $n$-$C_3H_7$ | H | 165–166[e] | 49 | $C_{22}H_{31}N_3O_6$ |
| **7d** | $n$-$C_4H_9$ | H | 157–159 | 62 | $C_{23}H_{33}N_3O_6$ |
| **7e** | $n$-$C_5H_{11}$ | H | 158–160 | 95 | $C_{24}H_{35}N_3O_6$ |
| **7f** | $n$-$C_6H_{13}$ | H | 157–158 | 65 | $C_{25}H_{37}N_3O_6$ |
| **7g** | $n$-$C_8H_{17}$ | H | 152–154 | 33 | $C_{27}H_{41}N_3O_6$ |
| **7h** | $n$-$C_{10}H_{21}$ | H | 156–161 | 51 | $C_{29}H_{45}N_3O_6$ |
| **7i** | $n$-$C_3H_7$ | 4-$CH_3$ | 143–146 | 67 | $C_{23}H_{33}N_3O_6$ |
| **7j** | $n$-$C_4H_9$ | 4-$CH_3$ | 146–150 | 23 | $C_{24}H_{35}N_3O_6$ |
| **7k** | $n$-$C_5H_{11}$ | 4-$CH_3$ | 151–153 | 30 | $C_{25}H_{37}N_3O_6$ |
| **7l** | $n$-$C_6H_{13}$ | 4-$CH_3$ | 147–149 | 41 | $C_{26}H_{39}N_3O_6$ |
| **7m** | $n$-$C_7H_{15}$ | 4-$CH_3$ | 145–148 | 37 | $C_{27}H_{41}N_3O_6$ |
| **7n** | $n$-$C_8H_{17}$ | 4-$CH_3$ | 148–152 | 71 | $C_{28}H_{43}N_3O_6$ |
| **7o** | $n$-$C_9H_{19}$ | 4-$CH_3$ | 150–153 | 46 | $C_{29}H_{45}N_3O_6$ |
| **7p** | $n$-$C_{10}H_{21}$ | 4-$CH_3$ | 150–154 | 46 | $C_{30}H_{47}N_3O_6$ |
| **7q** | $n$-$C_{11}H_{23}$ | 4-$CH_3$ | 146–152 | 37 | $C_{31}H_{49}N_3O_6$ |
| **7r** | $n$-$C_{12}H_{25}$ | 4-$CH_3$ | 147–155 | 24 | $C_{32}H_{51}N_3O_6$ |
| **7s** | $n$-$C_6H_{13}$ | 3-$CH_3$ | 148–152 | 40 | $C_{26}H_{39}N_3O_6$ |
| **7t** | $n$-$C_6H_{13}$ | 2-$CH_3$ | 146–147 | 36 | $C_{26}H_{39}N_3O_6$ |
| **7u** | 2-$C_6H_{13}$ | 3-$CH_3$ | 151–153 | 51 | $C_{26}H_{39}N_3O_6$ |
| **7v** | 3-$C_6H_{13}$ | 3-$CH_3$ | 150–152 | 60 | $C_{26}H_{39}N_3O_6$ |
| **7w** | $n$-$C_6H_{13}$ | 2,4-$(CH_3)_2$ | 149–151 | 41 | $C_{27}H_{41}N_3O_6$ |
| **7x** | $C_6H_5O(CH_2)_4$ | 4-$CH_3$ | 145–148 | 45 | $C_{30}H_{39}N_3O_7$ |
| **7y** | $C_6H_5O(CH_2)_6$ | 4-$CH_3$ | 143–145 | 25 | $C_{32}H_{43}N_3O_7$ |
| **7z** | $C_6H_5O(CH_2)_8$ | 4-$CH_3$ | 143–145 | 41 | $C_{34}H_{47}N_3O_7$ |
| **7aa** | $C_6H_{11}CH_2$ | 4-$CH_3$ | 157–160 | 64 | $C_{27}H_{39}N_3O_6$ |
| **7bb** | cyclopentyl | 4-$CH_3$ | 164–166 | 63 | $C_{25}H_{35}N_3O_6$ |
| **7cc** | $CH_2$=$CHCH_2CH_2$ | 4-$CH_3$ | 162–165 | 82 | $C_{24}H_{33}N_3O_6$ |
| **7dd** | $CH_3(CH_2)_3O(CH_2)_2$ | 4-$CH_3$ | 148–149 | 43 | $C_{26}H_{39}N_3O_7$ |
| **7ee** | $CH_3O(CH_2)_6$ | 4-$CH_3$ | 144–146 | 47 | $C_{27}N_{41}N_3O_7$ |
| **7ff** | $C_6H_5CH_2O(CH_2)_6$ | 4-$CH_3$ | 147–149 | 23 | $C_{33}H_{45}N_3O_7$ |

[a] With the few noted exceptions, all compounds were crystallized from $Me_2CO$. [b] All compounds were analyzed for C, H, and N. [c] *i*-PrOH. [d] Isolated as hemihydrate. [e] $Me_2CO$–MeOH.

propylene oxide (2 mL) was slowly added (10 min). After 1.5 h at 140–150 °C, 1 additional mL of propylene oxide was added. The reaction was continued for another hour, cooled, diluted with $Me_2CO$ (100 mL), and filtered to remove 0.1 g of unreacted 5-OH compound. The dark filtrate was concentrated and the residue was dissolved in $Et_2O$. The ethereal solution was extracted with dilute NaOH, washed with $H_2O$, dried ($K_2CO_3$), and treated with carbon. Removal of the solvent left a residue which, on crystallization from petroleum ether (bp 20–40 °C), gave 1.8 g (57%) of **3l** as pale yellow crystals, mp 48–51 °C. Solution in $C_6H_6$, passage through a silica gel column, and recrystallization from petroleum ether (carbon) gave the analytical sample, mp 53–54 °C.

**8-Amino-5-(hexyloxy)-6-methoxy-4-methylquinoline (4l) (Table IV).** A stirred mixture of **3l** (10 g, 0.03 mol), degreased 40-mesh iron filings (20 g), $H_2O$ (80 mL), acetic acid (10 mL), and dibutyl ether (10 mL) was heated at 100 °C for 6 h, cooled, and filtered. The dark solid residue was dried and extracted with a total of 800 mL of $Et_2O$. The extract was treated with carbon and the solvent was evaporated. Extraction of the residue with petroleum ether (bp 20–40 °C) and cooling of the extract in dry ice–acetone gave 7 g of the amino compound. Recrystallization from ligroin (bp 60–90 °C) provided 5.8 g (67%) of pure **4l** as yellow crystals, mp 69–71 °C.

**5-(Hexyloxy)-6-methoxy-4-methyl-8-[(1-methyl-4-phthalimidobutyl)amino]quinoline (6l).** A stirred mixture of 5.8 g (0.02 mol) of **4l** and 6 g (0.02 mol) of 4-bromo-1-phthalimidopentane (BPP) (**5a**) was maintained at 140–150 °C while triethylamine (3 g) was added, dropwise, during 0.5 h. Additional quantities of BPP (6 g in a single portion) and $Et_3N$ (3 g, dropwise) were introduced twice more at 1.5-h intervals. The mixture was allowed to cool, diluted with $Me_2CO$ (100 mL), and filtered to remove $Et_3N$·HBr. The filtrate was treated with carbon and the solvent was evaporated. Extraction of the residue with $Et_2O$ and treatment of the filtered extract with ethereal hydrogen chloride produced a red-orange semisolid. This material was dissolved in $CHCl_3$, basified with dilute NaOH, dried ($Na_2SO_4$), and passed through a silica gel column. Evaporation of the eluate gave 9.5 g (90%) of an oil whose IR spectrum was consistent with the ascribed structure. The oil was used without further purification.

**8-[(4-amino-1-methylbutyl)amino]-5-(hexyloxy)-6-methoxy-4-methylquinoline Fumarate (7l) (Table V).** A stirred mixture of 7.5 g (0.015 mol) of **6l**, 95% hydrazine (15 mL), and ethanol (500 mL) was heated under reflux for 4.5 h, cooled, and filtered. The filtrate was evaporated to dryness, in vacuo, and the residue was extracted with $Et_2O$. The filtered extract was washed with 30% KOH (4 × 50 mL) and $H_2O$ and dried ($Na_2SO_4$). Treatment with 80 mL of 1.5% isopropanolic fumaric acid gave 4.2 g of crude fumarate, mp 128–135 °C. Crystallization from $Me_2CO$ (carbon) provided 3 g (41%) of pure **7l**, mp 147–149 °C.

**5-Ethoxy-6-methoxy-8-nitroquinoline (3a) (Table III).** To a stirred refluxing solution of 3.63 g (0.055 mol) of 85% KOH in 500 mL of ethanol was added 12 g (0.05 mol) of 5-chloro-6-methoxy-8-nitroquinoline (**8a**)[7]. Heating was stopped, 5.5 g (0.055 mol) of $Et_3N$ was added, and the tan suspension was heated under reflux for 12 h. The resulting brown solution was cooled and 0.6 g of **8a** was removed by filtration. The filtrate was taken to dryness, in vacuo, and the residue was washed with $H_2O$ to give 12 g of crude product as brown crystals, mp 88–95 °C. Recrystallization from ligroin (bp 90–120 °C) (carbon) provided 10 g

(80%) of **3a** as yellow crystals, 95–97 °C.

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**Registry No.** 1 ($R_2$ = H), 5323-58-0; 1 ($R_2$ = 4-$CH_3$), 81358-81-8; 1 ($R_2$ = 3-$CH_3$), 108191-07-7; 1 ($R_2$ = 2-$CH_3$), 108191-08-8; 1 ($R_2$ = 2,4-$(CH_3)_2$), 108191-09-9; **3a**, 81358-67-0; **3b**, 81358-68-1; **3c**, 81358-71-6; **3d**, 81358-76-1; **3e**, 108190-29-0; **3f**, 81358-87-4; **3g**, 81359-03-7; **3h**, 81359-08-2; **3i**, 108190-30-3; **3j**, 108190-31-4; **3k**, 81358-82-9; **3l**, 81358-93-2; **3m**, 81358-98-7; **3n**, 108190-32-5; **3o**, 108190-33-6; **3p**, 108190-34-7; **3q**, 108190-35-8; **3r**, 81359-13-9; **3s**, 108190-36-9; **3t**, 108190-37-0; **3u**, 108214-79-5; **3v**, 108190-38-1; **3w**, 108190-39-2; **3x**, 108190-40-5; **3y**, 108190-41-6; **3z**, 108190-42-7; **3aa**, 108190-43-8; **3bb**, 108190-44-9; **3cc**, 108190-45-0; **3dd**, 108190-46-1; **3ee**, 108190-47-2; **3ff**, 108190-48-3; **4a**, 64992-85-4; **4b**, 81358-69-2; **4c**, 81358-72-7; **4d**, 81358-77-2; **4e**, 108190-49-4; **4f**, 81358-88-5; **4g**, 81359-04-8; **4h**, 81359-09-3; **4i**, 108190-50-7; **4j**, 108190-51-8; **4k**, 81358-83-0; **4l**, 81358-94-3; **4m**, 81358-99-8; **4n**, 108190-52-9; **4o**, 108214-80-8; **4p**, 108190-53-0; **4q**, 108190-54-1; **4r**, 81359-14-0; **4s**, 108190-55-2; **4t**, 108190-56-3; **4u**, 108190-57-4; **4v**, 108190-58-5; **4w**, 108190-59-6; **4x**, 108190-60-9; **4y**, 108190-61-0; **4z**, 108190-62-1; **4aa**, 108190-63-2; **4bb**, 108190-64-3; **4cc**, 108190-65-4; **4dd**, 108190-66-5; **4ee**, 108190-67-6; **4ff**, 108190-68-7; **5a**, 59353-62-7; **5b**, 63460-47-9; **6a**, 64992-87-6; **6b**, 108214-81-9; **6c**, 81358-73-8; **6d**, 81358-78-3; **6e**, 108190-69-8; **6f**, 81358-89-6; **6g**, 81359-05-9; **6h**, 81359-10-6; **6i**, 108190-70-1; **6j**, 108190-71-2; **6k**, 81358-84-1; **6l**, 81358-95-4; **6m**, 81359-00-4; **6n**, 108190-72-3; **6o**, 108190-73-4; **6p**, 108190-74-5; **6q**, 108190-75-6; **6r**, 81359-15-1; **6s**, 108190-76-7; **6t**, 108190-77-8; **6u**, 108190-78-9; **6v**, 108190-79-0; **6w**, 108190-80-3; **6x**, 108190-81-4; **6y**, 108190-82-5; **6z**, 108190-83-6; **6aa**, 108190-84-7; **6bb**, 108190-85-8; **6cc**, 108214-82-0; **6dd**, 108190-86-9; **6ee**, 108190-87-0; **6ff**, 108190-88-1; **7a**, 64992-84-3; **7a**·fumarate, 64992-88-7; **7b**, 81444-45-3; **7b**·fumarate, 81444-46-4; **7c**, 81358-74-9; **7c**·fumarate, 81358-75-0; **7d**, 81358-79-4; **7d**·fumarate, 81358-80-7; **7e**, 108190-09-6; **7e**·fumarate, 108190-89-2; **7f**, 81358-90-9; **7f**·fumarate, 81358-91-0; **7g**, 81359-06-0; **7g**·fumarate, 81359-07-1; **7h**, 81359-11-7; **7h**·fumarate, 81359-12-8; **7i**, 108190-10-9; **7i**·fumarate, 108190-90-5; **7j**, 108190-11-0; **7j**·fumarate, 108214-83-1; **7k**, 81358-85-2; **7k**·fumarate, 81358-86-3; **7l**, 81358-96-5; **7l**·fumarate, 81358-97-6; **7m**, 81359-01-5; **7m**·fumarate, 81359-02-6; **7n**, 108190-12-1; **7n**·fumarate, 108190-91-6; **7o**, 108190-13-2; **7o**·fumarate, 108190-92-7; **7p**, 108190-14-3; **7p**·fumarate, 108190-93-8; **7q**, 108190-15-4; **7q**·fumarate, 108190-94-9; **7r**, 81359-16-2; **7r**·fumarate, 81359-17-3; **7s**, 108190-16-5; **7s**·fumarate, 81358-97-6; **7t**, 108190-17-6; **7t**·fumarate, 108190-95-0; **7u**, 108190-18-7; **7u**·fumarate, 108214-85-3; **7v**, 108190-96-1; **7v**·fumarate, 108190-97-2; **7w**, 108190-19-8; **7w**·fumarate, 108190-98-3; **7x**, 108190-20-1; **7x**·fumarate, 108190-99-4; **7y**, 108190-21-2; **7y**·fumarate, 108214-86-4; **7z**, 108190-22-3; **7z**·fumarate, 108191-00-0; **7aa**, 108190-23-4; **7aa**·fumarate, 108191-01-1; **7bb**, 108190-24-5; **7bb**·fumarate, 108191-02-2; **7cc**, 108190-25-6; **7cc**·fumarate, 108191-03-3; **7dd**, 108190-26-7; **7dd**·fumarate, 108191-04-4; **7ee**, 108190-27-8; **7ee**·fumarate, 108191-05-5; **7ff**, 108190-28-9; **7ff**·fumarate, 108191-06-6; 7 ($R_1$ = $CH_3$, $R_2$ = 4-$CH_3$), 64992-94-5; **8a**, 64992-86-5; **8b**, 5347-15-9; $CF_3CH_2OH$, 75-89-8; *n*-$C_3H_7Br$, 106-94-5; *n*-$C_4H_9Br$, 109-65-9; *n*-$C_5H_{11}I$, 628-17-1; *n*-$C_6H_{13}Br$, 111-25-1; *n*-$C_8H_{17}Br$, 111-83-1; *n*-$C_{10}H_{21}I$, 2050-77-3; *n*-$C_5H_{11}Br$, 110-53-2; *n*$C_7H_{15}I$, 4282-40-0; *n*-$C_9H_{19}Br$, 693-58-3; *n*-$C_{11}H_{23}Br$, 693-67-4; *n*-$C_{12}H_{25}Br$, 143-15-7; 2-$C_6H_{13}Br$, 3377-86-4; 3-$C_6H_{13}Br$, 3377-87-5; $C_6H_5O(CH_2)_4Br$, 1200-03-9; $C_6H_5O(CH_2)_6Br$, 51795-97-2; $C_6H_5O(CH_2)_8Br$, 52176-61-1; $C_6H_{11}CH_2Br$, 2550-36-9; $CH_2$=$CH(CH_2)_2Br$, 5162-44-7; $CH_3(CH_2)_3O(CH_2)_2Br$, 6550-99-8; $CH_3O(CH_2)_6Br$, 50592-87-5; $C_6H_5CH_2O(CH_2)_6Br$, 54247-27-7; $C_7H_{15}Br$, 629-04-9; primaquine, 90-34-6; 2-methylprimaquine, 57695-10-0; 3-methylprimaquine, 64992-44-5; 4-methylprimaquine, 57514-29-1; cyclopentyl bromide, 137-43-9.

# 2′-Fluorinated Arabinonucleosides of 5-(2-Haloalkyl)uracil: Synthesis and Antiviral Activity

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The synthesis of 5-(2-fluoroethyl)-2′-deoxyuridine (FEDU, **4b**), its 2′-fluoro analogue 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-(2-fluoroethyl)-1*H*,3*H*-pyrimidine-2,4-dione (FEFAU, **4k**), and the 2′-fluoro analogue of the potent antiherpes virus compound 5-(2-chloroethyl)-2′-deoxyuridine (CEDU), 5-(2-chloroethyl)-1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-1*H*,3*H*-pyrimidine-2,4-dione (CEFAU, **4i**), is described. The antiviral activities of these compounds were determined in cell culture against herpes simplex virus (HSV) types 1 and 2 and varicella zoster virus (VZV). All compounds were shown to possess significant and selective antiviral activity. FEDU proved less potent than CEDU against VZV replication; however, it was more active against HSV-2. CEFAU showed marked activity against HSV-1, HSV-2, and VZV. The compound containing fluorine at both positions, FEFAU, exhibited the strongest antiviral potency against HSV-1, HSV-2, and VZV. It inhibited HSV-1 at a concentration of 0.03–0.2 μg/mL, HSV-2 at 0.1–0.3 μg/mL, and VZV at 0.03 μg/mL. Neither FEDU nor CEFAU or FEFAU exerted a significant inhibitory effect on cell proliferation at a concentration of 100 μg/mL. Thus, the cytotoxicity of these compounds is as low as that of CEDU and compares favorably to that of previously described 2′-fluoroarabinosyl nucleoside analogues.

5-(2-Bromovinyl)-2′-deoxyuridine (BVDU)[1] and the recently described 5-(2-chloroethyl)-2′-deoxyuridine (CEDU)[2] are two of the most potent and selective antiviral representatives of the large class of 5-substituted pyri-

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