°C (0.06 mm). Anal. ($C_7H_{10}O_4$) C, H, O.

Benzyl *N*-(±)-*cis*-2-Acetoxycyclobutylcarbamate (15). Compound **13** (2.58 g, 0.016 mol), triethylamine (2.3 mL, 0.016 mol), 3.5 mL (0.016 mol) of diphenylphosphoryl azide, and 16 mL of dry benzene were combined under N_2 at 25 °C; then the mixture was warmed and stirred under reflux for 4 h until the evolution of N_2 ceased. Benzyl alcohol (8.5 mL, 0.082 mol) was added, and the resulting mixture was stirred under reflux for 15 h. The benzene was then removed under reduced pressure, and excess benzyl alcohol was distilled off. The residual oil was taken up in benzene, and this solution was washed with H_2O, saturated $NaHCO_3$, and H_2O and dried (Na_2SO_4). Concentration of the solution gave 4.32 g (100%) of the product as an oil, which was determined by GC to be greater than 99% pure. This was used in the next step without purification. An analytical sample was distilled (with considerable loss by charring), bp 152–154 °C (0.1 mm). Anal. ($C_{14}H_{17}NO_4$) C, H, N.

(±)-*cis*-2-Acetoxycyclobutylamine (16). Compound **15** (1.21 g, 0.0046 mol) was hydrogenolyzed at 25 °C in 50 mL of EtOAc and 2 mL of glacial AcOH over 0.5 g of 10% Pd/C at an initial pressure of 50 psig. The theoretical amount of H_2 was consumed in 1 h; hydrogenation was continued for 40 h. The catalyst was removed, and the solvent was evaporated. The residual material was taken up in 20 mL of EtOAc, this solution was washed with saturated Na_2CO_3 (19 mL, 0.041 mol), and this washing was washed twice with EtOAc. The combined organic phases were washed with 10 mL of H_2O, which was back-extracted twice with EtOAc, and the combined EtOAc solutions were evaporated. Distillation of the yellow, oily residue through a short-path apparatus gave 0.44 g (74%) of product: bp 79–80 °C (1.0 mm); MS, *m/e* 129 (M^+).

(±)-*cis*-2-Acetoxycyclobutyltrimethylammonium Iodide (4). Freshly prepared **16** (0.2 g, 0.0016 mol), 0.81 mL (0.0034 mol) of tri-*n*-butylamine, and 7 mL of EtOAc were combined at 0 °C, and 0.32 mL (0.0051 mol) of MeI was added. The mixture was stirred at 25 °C for 18 h in the dark. The white precipitate that formed was collected on a filter under N_2 and was washed on the filter with EtOAc. Recrystallization of the residue on the filter from 1-butanol–heptane gave 0.269 g (58%) of white needles, homogeneous by TLC (R_f 0.19, silica GF, MeOH): mp 174–176.5 °C; IR ($CHCl_3$) 3000 (strong, C–H *as*), 1740 (acetoxy C=O), 1440 (m, C–H *bend*), 1429 (vw, C–H *bend*), 1420 (m, C–H *bend*) cm^{-1}; MS, *m/e* 157 ($M^+ - CH_3I$); NMR (CD_3OD) δ 2.0–2.3 (m, superimposed singlet at δ 2.05, total integration 7 H, $\overline{NCHCH_2CH_2CCHO}$), 2.05 (s, $COCH_3$), 3.2 (s, 9 H, NCH_3), 4.05–4.45 (m, 1 H, $\overline{NCHCH_2CH_2CHO}$), 5.1–5.4 (m, 1 H, $\overline{NCHCH_2CH_2CHO}$). Anal. ($C_9H_{18}INO_2$) C, H, N.

Recrystallization of (±)-*trans*-2-Acetoxycyclobutyltrimethylammonium Iodide (3). An authentic sample was recrystallized twice from 1-butanol–heptane to afford white crystals, homogeneous by TLC (R_f 0.53, silica GF, MeOH): mp 166–167.5 °C. [lit[3] mp 164–166 °C]. The IR spectrum ($CHCl_3$) was identical with that recorded for **4** with the following exceptions: 1433 (m, C–H *bend*), 1415 (w, C–H *bend*) cm^{-1}; NMR (CD_3OD) δ 2.0–2.3 (m, superimposed singlet at δ 2.05, total integration 7 H, $\overline{NCHCH_2CH_2CHO}$), 2.05 (s, $COCH_3$), 3.2 [s, 9 H, $N(CH_3)_3$], 4.05–4.5 (m, 1 H, $\overline{NCHCH_2CH_2CHO}$), 5.1–5.4 (m, 1 H, $\overline{NCHCH_2CH_2CHO}$).

(±)-*cis*-2-Aminocyclobutanol (5). A solution of 0.1 g (0.007 mol) of **16** in 10 mL of benzene was added dropwise to a solution of 70% *Red-Al* (0.67 mL, 0.0023 mol, Aldrich Chemical Co.) in 10 mL of benzene. The mixture was stirred under N_2 under reflux for 4 h, and then the excess *Red-Al* was destroyed by careful addition of EtOH. The volatiles were removed under reduced pressure, and the residue was dissolved in 10% NaOH. Liquid/liquid extraction of this solution with Et_2O for 4 days, followed by concentration of the organic solution, gave a brown oil. An ion-exchange column was prepared: Amberlite IRC-50 (40.0 g, Mallinckrodt) was washed with 10% glacial AcOH in EtOAc, EtOAc (4 times), and 2-PrOH (4 times) and was packed into a glass column. A solution of the brown oil in 2 mL of 2-PrOH was placed on the column, and impurities were eluted with 400 mL of 2-PrOH. The product was then eluted with 350 mL of 10% Et_3N in 2-PrOH. The eluate was evaporated to give an oily residue, homogeneous by GC. Crystallization from Et_2O–petroleum ether (bp 35–60 °C) gave 0.31 g (46%) of product, mp 56–59 °C (lit.[4] mp 58–60 °C).

Notes

Antimalarials. 14. 5-(Aryloxy)-4-methylprimaquine Analogues. A Highly Effective Series of Blood and Tissue Schizonticidal Agents

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A series of five 5-(aryloxy)-4-methylprimaquine analogues has been prepared and evaluated for antimalarial activity. The compounds were tested for suppressive activity against *Plasmodium berghei* in mice and for radical curative activity against *Plasmodium cynomolgi* in the rhesus monkey. The compounds were not only significantly superior to primaquine as radical curative agents but also were suprisingly highly effective as suppressive agents.

Primaquine, over the years, has been the clinical drug of choice with widespread use in the treatment of relapsing *Plasmodium vivax* and *P. ovale* malaria. Primaquine, used clinically as the diphosphate salt, is a radical curative drug that is effective in clearing tissue parasites but has minimal suppressive activity; i.e., it is relatively ineffective as a blood schizonticide. In man, the toxicity of primaquine precludes administration of a single curative dose. Thus, to achieve a radical cure of *P. vivax* in man, the drug is ordinarily given in divided doses over 14 or 21 days and is accompanied by a 3-day course of chloroquine to clear the blood of schizonts.

As part of early attempts to improve primaquine, the side chain was variously modified as part of the extensive Army World War II Program, but no significant improvement was achieved.

Later in 1955, Elderfield and co-workers[1] reported the

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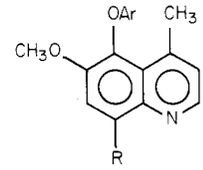
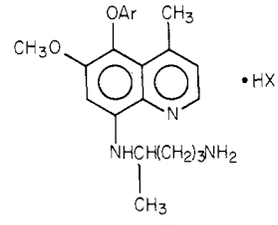
Table I. Physical Data



no.	Ar	R	mp, °C (solvent)	yield, %	formula	anal.[a]
4a	C_6H_4-*m*-CF_3	NO_2	208-210 ($EtOCH_2CH_2OH$)	69	$C_{18}H_{13}F_3N_2O_4$	F
4b	C_6H_3-*o*,*p*-Cl_2	NO_2	166-168 ($EtOCH_2CH_2OH$)	64	$C_{17}H_{12}Cl_2N_2O_4$	Cl
4c	C_6H_3-*m*,*p*-Cl_2	NO_2	187-189 ($EtOCH_2CH_2OH$)	65	$C_{17}H_{12}Cl_2N_2O_4$	Cl
4d	C_6H_4-*p*-OCH_3	NO_2	158-160 ($EtOCH_2CH_2OH$)	68	$C_{13}H_{16}N_2O_5$	
4e	C_6H_4-*p*-F	NO_2	183.5-185 ($EtOCH_2CH_2OH$)	59	$C_{17}H_{13}FN_2O_4$	F
5a	C_6H_4-*m*-CF_3	NH_2	116-117 (ligroin)	76	$C_{18}H_{15}F_3N_2O_2$	F
5b	C_6H_3-*o*,*p*-Cl_2	NH_2	115-117.5 (cyclohexane)	84	$C_{17}H_{14}Cl_2N_2O_2$	
5c	C_6H_3-*m*,*p*-Cl_2	NH_2	132-134 (cyclohexane)	82	$C_{17}H_{14}Cl_2N_2O_2$	Cl
5d	C_6H_4-*p*-OCH_3	NH_2	185-187 ($C_6H_5CH_3$)	58	$C_{18}H_{18}N_2O_3$	
5e	C_6H_4-*p*-F	NH_2	144.5-145.5 (cyclohexane)	78	$C_{17}H_{15}FN_2O_2$	F
6a	C_6H_4-*m*-CF_3	$NHCH(CH_3)(CH_2)_3Pth$	143-145 (EtOH)	57	$C_{31}H_{28}F_3N_3O_4$	F
6b	C_6H_3-*o*,*p*-Cl_2	$NHCH(CH_3)(CH_2)_3Pth$	170-172 ($EtOCH_2CH_2OH$)	90	$C_{30}H_{23}Cl_2N_3O_4$	
6c	C_6H_3-*m*,*p*-Cl_2	$NHCH(CH_3)(CH_2)_3Pth$	158.5-160.5 (Et_2O)	54	$C_{30}H_{23}Cl_2N_3O_4$	
6d	C_6H_3-*p*-OCH_3	$NHCH(CH_3)(CH_2)_3Pth$	189-191 (EtOH)[b]	71	$C_{31}H_{32}ClN_3O_5$	F
6e	C_6H_4-*p*-F	$NHCH(CH_3)(CH_2)_3Pth$	123-126 (EtOH)	61	$C_{30}H_{28}FN_3O_4$	
7a	C_6H_4-*m*-CF_3	$NHCH(CH_3)(CH_2)_3NH_2$	102-103 (Et_2O-MeOH)[c]	94	$C_{27}H_{32}F_3N_3O_6$	F
7b	C_6H_3-*o*,*p*-Cl_2	$NHCH(CH_3)(CH_2)_3NH_2$	203-206 (EtOH-H_2O)[d]	76	$C_{22}H_{29}Cl_2O_6P$	P
7c	C_6H_3-*m*,*p*-Cl_2	$NHCH(CH_3)(CH_2)_3NH_2$	199-201 (EtOH-H_2O)[d]	92	$C_{22}H_{29}Cl_2N_3O_6P$	P
7d	C_6H_4-*p*-OCH_3	$NHCH(CH_3)(CH_2)_3NH_2$	162-163 (EtOH-H_2O)[d]	84	$C_{23}H_{32}N_3O_7P$	P
7e	C_6H_4-*p*-F	$NHCH(CH_3)(CH_2)_3NH_2$	113 (EtOH-MeOH)[d]	58	$C_{22}H_{29}FN_3O_6P$	F, P

[a] In addition to C, H, N. [b] Hydrochloride salt. [c] Succinate salt. [d] Phosphate salt.

Table II. Radical Curative Activity of 4-Methyl-5-(aryloxy)primaquine Analogues. SEATO Primate Antimalarial Study



compd	dose of salt:[c]	*P. cynomolgi* (rhesus monkey), sporozoite-induced test[a,b] 0.1	0.316	1.0	molar primaquine index[d]
7a		0/2C	2/2C	2/2C	4.8
7b		0/3C	1/2C	3/3C	1.3
7c		0/3C	1/2C	3/3C	1.3
7d		0/2C	2/2C	3/3C	4.3
7e		0/3C	2/2C	3/3C	4.2
primaquine diphosphate			0/2C	1/2C[e]	1.0

[a] See ref 6. [b] C = cure. [c] In (mg/kg)/day (× 7) po. [d] Ratio of moles of primaquine diphosphate to achieve 100% cures divided by moles of test compound to achieve 100% cures. [e] 6/6C at 1.3 (mg/kg)/day (× 7).

synthesis of 4-methylprimaquine, which, more recently, has been tested in modern and well-developed test systems and represents one example with radical curative activity superior to that of primaquine. Subsequent modifications of the 4-substituent[2] failed to yield a superior analogue. Chen and co-workers[3] reported the preparation of a series of 5-phenoxyprimaquine analogues. The best example was slightly more effective than the parent drug as a tissue schizonticidal agent. In terms of blood schizonticidal activity, it was comparable to primaquine at the lower dose levels and was curative and nontoxic at the higher levels (320 and 640 mg/kg). In the previous paper in this series,[4] we reported the preparation of a series of 5-alkoxy-4-methylprimaquine analogues. The best example in this series was significantly more effective than primaquine in terms of both blood and tissue schizonticidal activity. However, the toxicity characteristic of the 8-aminoquinolines was not overcome. We presently report the preparations of a series 4-methyl-5-(substituted-phenoxy)primaquine analogues that exhibit remarkable blood and tissue schizonticidal activity accompanied by a significant decrease in toxicity relative to primaquine and 4-methylprimaquine as measured in the Rane mouse model.

Chemistry. The key intermediate in the preparation of the target compounds described herein was 5-chloro-

(1) Elderfield, R. C.; Mertel, H. E.; Mitch, R. T.; Wempen, I. M.; Werble, E. *J. Am. Chem. Soc.* **1955**, *77*, 4816.
(2) LaMontagne, M. P.; Markovac, A.; Menke, J. R. *J. Med. Chem.* **1977**, *20*, 1122.
(3) Chen, E. H.; Saggiomo, A. J.; Tanabe, K.; Verma, B. L.; Nodiff, E. A. *J. Med. Chem.* **1977**, *20*, 1107.
(4) LaMontagne, M. P.; Markovac, A.; Khan, M. S. *J. Med. Chem.* **1982**, *25*, 964.

Table III. Suppressive Antimalarial Activity Data

	P. berghei, Rane mouse test, five mice[a]							
dose:[b]	5	10	20	40	80	160	320	640
7a	6.9 (A)	2C	5C	5C	5C	5C	5C	1C, 4T
7b	5.0	1C	5C	5C	5C	5C	4C, 1T	3C, 2T
7c	4C	5C	5C	5C	5C	5C	5C	5C
7d	5.5 (A)	5.9 (A)	1C	5C	5C	5C	5C	2C, 3T
7e	7.0 (A)	3C	4C	5C	5C	5C	4C, 1T	3C, 2T
primaquine			2.2	4.2	6.4 (A)	7.0 (A)	5T	5T
primaquine diphosphate			4.0	5.0	9.4 (A)	10.8 (A), 2T	5T	5T

[a] Activity determined by Rane Laboratories, University of Miami, as described by Osdene and co-workers.[7] Mean survival time (MST) of infected controls was 6.1 days. Increase in survival time (ΔMST) of mice treated with a single dose of compound administered subcutaneously 72 h after infection is considered evidence of antimalarial activity if the increase is at least 100%. Number of cures (C) is the number of mice surviving, out of five, at 60 days postinfection. A = active; T = toxic. [b] Dose in mg/kg (×1).

6-methoxy-4-methyl-8-nitroquinoline (**3**). Treatment of 5,6-dimethoxy-4-methyl-8-nitroquinoline (**1**) with ethanolic hydrochloric acid as described by Fuson et al.[5] afforded the 5-hydroxy-6-methoxy-4-methyl-8-nitroquinoline (**2**), which upon treatment with phosphorous oxychloride afforded **3**. Reaction of **3** with the sodium salt of the appropriate phenol afforded the 5-aryloxy intermediates **4a–e**. Reduction of the 8-nitro group with hydrogen and Raney nickel and side-chain introduction involved procedures previously described (see Table I).[2]

Biological Activity Data. Target compounds **7a–e** were evaluated for radical curative antimalarial activity against *P. cynomolgi* in the rhesus monkey.[6] The data are shown in Table II along with the data for primaquine diphosphate. The most active examples are **7a**,**d**,e, which are 100% curative at a dose of 0.316 (mg (salt)/kg)/day (×7); primaquine is inactive at this level and is 100% curative only at a dose level of 1.3 (mg/kg)/day (×7). The compounds were also evaluated for suppressive activity against *P. berghei* in mice,[7] and the results are shown in Table III. As can be seen, all five examples exhibit a very high level of activity in this screen. One example is curative at 5 mg/kg and **7a**,**d**,e are active at this level. The least active example (**7b**) is curative at 10 mg/kg. Compound **7a** was further evaluated for suppressive activity against *P. cynomolgi* in the rhesus monkey.[8] Whereas primaquine diphosphate suppressed but did not cure parasitemia at dosages ranging from 31.6 to 1.0 (mg/kg)/day (×7), compound **7a** was 100% curative at 1.0 (mg/kg)/day (×7) and was suppressive but not curative at doses as low as 0.0316 (mg/kg)/day (×7).

In Table IV is shown a comparison between primaquine and compound **7a** as radical curative drugs when used in conjunction with chloroquine as a suppressive adjuvant. As discussed earlier, the toxicity of primaquine precludes administration of a single curative dose, and in order to achieve a radical cure of *P. vivax* in man, multiple doses are required coupled with the administration of chloroquine to maintain the blood clear of schizonts. Accordingly, testing was performed to establish whether a single dose of compound **7a** was effective as both a tissue and blood schizonticide and whether the coadministration of chloroquine was necessary and/or desirable. The results are shown in Table IV.

Table IV. Combination Drug Therapy Including Chloroquine as a Suppressive Adjuvant. *P. cynomolgi* (Rhesus Monkeys) Radical Curative Studies

mg/kg, po, of base (× 1)[a]	primaquine + chloroquine[b]	7a	7a + chloroquine
14	2C	1C	
7	2C, 1SF, 1R	2C	
3.5	2C, 1SF, 1R	1C, 1SF	
1.75	2R	4SF	2C
0.875		3SF, 1R	4C
0.4375		4R	4R

[a] Primaquine or 7a administered in salt form but calculated as the free base. [b] Chloroquine (phosphate) added as 5 mg/kg of salt (× 7). C = cure; SF = suppressive failure (blood not cleared); R = relapse (tissues not cleared).

The data show the primaquine at a dose level of 3.5 mg/kg (×1) in combination with chloroquine was effective, although a relapse was observed in one of the four animals. Compound **7a**, without chloroquine, was equally active at this dose level. On the other hand, the coaddition of chloroquine demonstrates that the fully curative dose level of compound **7a** can be reduced to 0.875 mg/kg compared to 14 mg/kg for primaquine. On this basis the molar primaquine index with chloroquine coadministration is 19. These ratios clearly demonstrate the superiority of compound **7a** over primaquine against *P. cynomolgi* in the rhesus, which is regarded as predictive of the efficacy of the drugs against *P. vivax* in man.

The above results are both surprising and remarkable in that all previously prepared 8-aminoquinolines possessed only very limited suppressive antimalarial activity. Also the present compounds possess blood schizonticidal activity comparable, and in some cases superior, to the more active amino alcohols (e.g., the 4-pyridylcarbinolamines[9] and the 9-phenanthrylcarbinolamines[10]). Further investigation of this class of highly active antimalarial agents is in progress.

Experimental Section

All melting points and boiling points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 237B spectrometer. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, IN. NMR spectra were determined on a Varian Model T60A spectrometer. Ethanol used in this work was specially denatured grade 3A alcohol (90% ethanol, 5% 2-propanol,

(5) Fuson, R. C.; Bauman, R. A.; Howard, Jr., E.; Marvell, E. N. *J. Org. Chem.* **1947**, *12*, 799.
(6) Schmidt, L. H., Rossan, R. N., Fisher, K. F. *Am. J. Trop. Med. Hyg.* **1963**, *12*, 494.
(7) Osdene, J. S.; Russell, P. B.; Rane, L. *J. Med. Chem.* **1967**, *10*, 431.
(8) Davidson, D. E.; Johnsen, D. O.; Tanticharoenyos, P.; Hickman, R. L.; Kinnamon, K. E. *Am. J. Trop. Med. Hyg.* **1976**, *25*, 26.
(9) LaMontagne, M. P.; Markovac, A.; Blumbergs, P. *J. Med. Chem.* **1974**, *17*, 519.
(10) Nodiff, E. A.; Saggiomo, A. J.; Shinbo, M.; Chen, E. H.; Otomasu, H.; Kondo, Y.; Kikuchi, T.; Verma, B. L.; Matsuura, S.; Tanabe, K.; Tyagi, M. P.; Morosawa, S. *J. Med. Chem.* **1972**, *15*, 775.

and 5% methanol, v/v). Commercial Raney nickel was purchased from W.R. Grace Co. (no. 30). Silica gel was purchased from EM Labs (70–230 mesh).

5-Hydroxy-6-methoxy-4-methyl-8-nitroquinoline (2). 4-Methyl-5,6-dimethoxy-8-nitroquinoline[4] (6.21 g, 25 mmol) was dissolved in EtOH (100 mL) containing concentrated HCl (4.7 mL). The mixture was heated under reflux for 21 h, cooled to 10 °C, and filtered. The solid was washed with cold (10 °C) EtOH (18 mL), followed by petroleum ether (15 mL), and air-dried to yield 5.41 g (92%) of the title compound, mp 253–257 °C dec. Anal. ($C_{11}H_{10}N_2O_4$) C, H, N.

5-Chloro-6-methoxy-4-methyl-8-nitroquinoline (3). A solution of the above 5-hydroxyquinoline (5.25 g, 0.022 mol) in $POCl_3$ (75 mL) was heated at 80 °C for 2 h. The reaction mixture was poured onto ice and basified with excess NH_4OH. The tan solid was filtered to give 5.8 g of crude product. This material was purified via column chromatography over silica gel and eluted with $CHCl_3$. The fast-moving yellow band was collected and concentrated to give 3.9 g (69%) of the title compound, mp 167–169 °C. Anal. ($C_{11}H_9ClN_2O_3$) C, H, Cl, N.

6-Methoxy-4-methyl-8-nitro-5-[3-(trifluoromethyl)phenoxy]quinoline (4a). To a solution of 3-(trifluoromethyl)phenol (4.1 g) in 2-ethoxyethanol (45 mL) containing KOH (1.37 g) was added the above 5-chloroquinoline (5.7 g, 0.023 mol). The mixture was heated at reflux for 8 h and allowed to cool overnight. The solid was filtered and washed well with cold EtOH to give 5.9 g (69%) of the title compound, mp 206–208 °C. An analytical sample was prepared via crystallization from 2-ethoxyethanol, mp 208–210 °C. Similarly prepared were compounds **4b–e** (Table I).

8-Amino-6-methoxy-4-methyl-5-[3-(trifluoromethyl)-phenoxy]quinoline (5a). A solution of 4-methyl-5-[3-(trifluoromethyl)phenoxy]-6-methoxy-8-nitroquinoline (5.9 g, 15.6 mmol) in ethanol–dioxane (4:3, v/v, 350 mL) containing wet Raney nickel (ca. 4 g) was reduced at 45 psig for 1.25 h. The catalyst was filtered, and the filtrate was concentrated to dryness. The residual solid was crystallized from ligroin (bp 60–80 °C) to afford 4.1 g (75%) of the title compound mp 113–115 °C. A sample recrystallized once again gave an analytical sample, mp 116–117 °C.

Similarly prepared were compounds **5b–e** (Table I).

6-Methoxy-4-methyl-8-[(4-phthalimido-1-methylbutyl)-amino]-5-[3-(trifluoromethyl)phenoxy]quinoline (6a). A mixture of the above 8-aminoquinoline (3.0 g, 8.6 mmol), 4-iodo-1-phthalimidopentane (IPP; 3.0 g, 8.7 mmol), Et_3N (1.2 mL), and 2-ethoxyethanol (1 mL) was heated at 105 °C for 2.5 h, after which time an additional quantity of IPP (3 g) and Et_3N (1.2 mL) was added. After an additional 4 h at 105 °C, the mixture was cooled and dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with 10% aqueous KOH and H_2O, dried, and concentrated to dryness. The residue was dissolved in Et_2O and excess ethereal HCl was added. The Et_2O was decanted, and the gum was triturated in fresh Et_2O (×2). The gum was then shaken with Et_2O and 10% aqueous K_2CO_3. The Et_2O was removed, and the residue was heated in EtOH (15 mL). The mixture was cooled, and the solid was filtered to give 1.65 g of the title compound. The filtrate was concentrated to dryness, and the residue was triturated in hot ligroin (bp 60–80 °C, 50 mL). The ligroin was decanted from a little insoluble gum and concentrated to dryness to afford 1.5 g of additional crude product. The combined crops were crystallized from EtOH (75 mL) to give 2.75 g (57%) of pure title compound, mp 143–145 °C.

Similarly prepared were compounds **6b–e** (Table I).

8-[(4-Amino-1-methylbutyl)amino]-6-methoxy-4-methyl-5-[3-(trifluoromethyl)phenoxy]quinoline Succinate (7a). A solution of the above phthalimide (4.9 g, 8.7 mmol) in EtOH (110 mL) containing hydrazine hydrate (75%, 1.48 mL) was heated at reflux for 6 h. The EtOH was removed under reduced pressure, and the residue was shaken with Et_2O and 10% aqueous KOH. The Et_2O layer was washed with H_2O (×2) and dried (K_2CO_3). To the dried Et_2O solution was added a solution of succinic acid (1.03 g, 1 mol equiv) in EtOH (100 mL) containing CH_3OH (4 mL) to solubilize the succinic acid. After the solution was left standing overnight, the solid was filtered to yield 4.5 g (94%) of the title compound, mp 102–103 °C (eff).

Similarly prepared were compounds **7b–e** (Table I).

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Modifications of Primaquine as Antimalarials. 3. 5-Phenoxy Derivatives of Primaquine

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Various 5-phenoxy derivatives of primaquine have been prepared that are somewhat more effective and considerably less toxic than the parent compound in blood and tissue schizonticidal screens. Addition of a methyl group to the pyridine ring of the 5-phenoxyprimaquines has produced a number of antimalarials with potent activity against both blood and tissue schizonts.

Antimalarial enhancement of primaquine by 5-phenoxylation was described earlier.[1] In an effort to achieve the optimal substitution pattern for this series, we have synthesized the compounds included in Table I. Having found that 4-methylprimaquine[2] was less toxic than its parent, we were particularly interested in those primaquines that combined a 5-phenoxy with a pyridine ring methyl group.

Chemistry. The preparative routes were essentially those described in paper 1 of this series.[1] Details have been tabulated under Experimental Section.

(1) E. H. Chen, A. J. Saggiomo, K. Tanabe, B. L. Verma, and E. A. Nodiff, *J. Med. Chem.*, **20**, 1107 (1977).

(2) R. C. Elderfield, H. E. Mertel, R. T. Mitch, I. M. Wempen, and E. Werble, *J. Am. Chem. Soc.*, **77**, 4816 (1955).

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