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).

Acknowledgment. This work was supported by the U.S. Army Medical Research and Development Command under Contract DADA17-69-C-9065. This is contribution number 1581 from the Army Research Program on Antiparasitic Drugs. The advice and timely suggestions of Dr. E. A. Steck formerly of the Walter Reed Army Institute of Research are gratefully acknowledged. Mouse testing was performed by Dr. Arba Ager of the Rane Laboratory, University of Miami, FL. Monkey testing was performed by Drs. David E. Davidson, John Brown, Frank Chapple, and Richard Whitemere of the Armed Forces Research Institute, Bangkok, Thailand.

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.

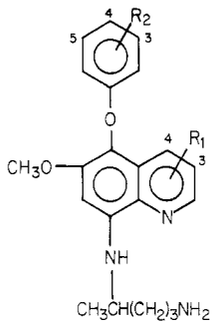
Chemistry. The preparative routes were essentially those described in paper 1 of this series.[1] Details have been tabulated under Experimental Section.

(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).

0022-2623/82/1825-1097$01.25/0

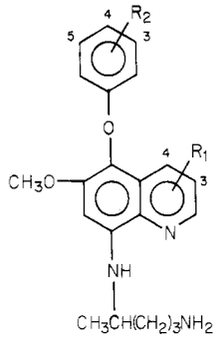
Table I. Blood Schizonticidal Antimalarial Activity (*Plasmodium berghei*, Mouse)[a]



				cures (C),[b] toxic Deaths (T),[c] or Δ MST[d]					
compd	R_1	R_2	dose: 10 mg/kg	20 mg/kg	40 mg/kg	80 mg/kg	160 mg/kg	320 mg/kg	640 mg/kg
primaquine				4.0	5.0	9.4	2T	5T	5T
4-methylprimaquine							9.0	10.0	1T
6a	4-CH_3	H	8.7	4C	3C	4C	4C	3T	2T
6b	H	3-CF_3		0.5	1.3	4.1	7.1	13.5	5C
6c	H	4-CF_3O		−0.3	−0.3	−0.3	0.5	0.7	1T
6d	H	4-CH_3O		0.4	0.4	1.6	6.0	8.6	4C
6e	H	2,4-Cl_2		0.4	0.4	0.8	2.2	4.4	10.4
6f	H	3,4-Cl_2		1.2	0.8	0.4	6.0	1C	1C
6g	H	3,5-$(CF_3)_2$		0.7	0.3	0.3	1.5	6.3	7.9
6h	4-CH_3	3,5-$(CF_3)_2$	1.7	4.3	3C	5C	5C	5C	5C
6i	H	4-F, 3-CF_3		−0.2	0.8	3.4	4.6	12.2	2C
6j	3-CH_3	4-F, 3-CF_3		5.9	9.9	4C	5C	4C	1T
6k	4-CH_3	4-F, 3-CF_3	1C	1C	5C	5C	5C	5C	5C
6l[e]	H	H		0.3	1.5	1.7	5.1	7.5	2C
6m[e]	H	4-Cl		0.7	4.7	5.5	7.1	8.1	2C
6n[e]	H	4-F		2.1	5.7	7.5	8.9	5C	5C

[a] Tests were carried out by the Rane Laboratory, University of Miami, FL, using blood-induced, *P. berghei* infected mice (five animals per group) via the method of Osdene et al.[4] Test data were supplied by Drs. H. A. Musallam, R. O. Pick, E. A. Steck, T. R. Sweeney, and R. E. Strube of WRAIR. [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] These data, reported earlier,[1] are included here for comparison.

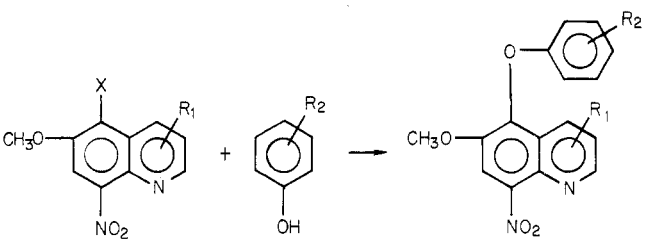
Table II. Radical Curative Antimalarial Activity (*Plasmodium cynomolgi*, Rhesus Monkey)[a]



				cure/no. of animals							
compd	R_1	R_2	dose: 0.125 mg/kg	0.25 mg/kg	0.316 mg/kg	0.5 mg/kg	0.75 mg/kg	1 mg/kg	3.16 mg/kg	10 mg/kg
primaquine				0/8	0/2	10/12	9/9			
4-methylprimaquine					0/4			2/2		
6b	H	3-CF_3	0/1	3/5		2/2		1/1		
6c	H	4-CF_3O						0/1		1/1
6d	H	4-CH_3O						0/1		1/1
6e	H	2,4-Cl_2						0/3	2/2	1/1
6f	H	3,4-Cl_2						1/3	2/2	1/1
6g	H	3,5-$(CF_3)_2$						0/1	1/1	1/1
6i	H	4-F, 3-CF_3			2/2			1/1		
6m[b]	H	4-Cl		0/1		0/2	5/6	3/3		1/1
6n[b]	H	4-F	0/5	3/8		5/5				
6o[b]	H	4-CH_3CONH				0/1		0/1		

[a] Tests were carried out using sporozoite-induced, *P. cynomolgi* infected rhesus monkeys according to the procedure of Schmidt et al.[5] [b] These data, reported earlier,[1] are included for comparison.

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

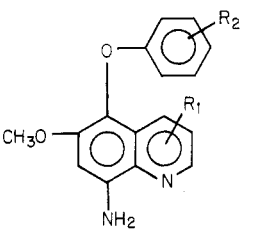


1 [a] 2 [b] 3

compd	R_1	R_2	mp, °C (solvent)	yield, %	formula [c]
3a	4-CH_3	H	169-171 (C_6H_6-hexane)	41	$C_{17}H_{14}N_2O_4$
3b	H	3-CF_3	155-157 (EtOH)	84	$C_{17}H_{11}F_3N_2O_4$
3c	H	4-CF_3O	111-113 (ligroin)	42	$C_{17}H_{11}F_3N_2O_5$
3d	H	4-CH_3O	116-122 (EtOH) [d]	35	$C_{17}H_{14}N_2O_5$
3e	H	2,4-Cl_2	148-151 (MeOH-Et_2O)	49	$C_{16}H_{10}Cl_2N_2O_4$
3f	H	3,4-Cl_2	147-148.5 (EtOH)	38	$C_{16}H_{10}Cl_2N_2O_4$
3g	H	3,5-$(CF_3)_2$	196-198 (C_6H_6-hexane)	34	$C_{18}H_{10}F_6N_2O_4$
3h	4-CH_3	3,5-$(CF_3)_2$	228-230 (C_6H_6)	40	$C_{19}H_{12}F_6N_2O_4$
3i	H	4-F, 3-CF_3	165-166 (EtOH)	90	$C_{17}H_{10}F_4N_2O_4$
3j	3-CH_3	4-F, 3-CF_3	229-230 (C_6H_6)	55	$C_{18}H_{12}F_4N_2O_4$
3k	4-CH_3	4-F, 3-CF_3	175-176 (MeOH)	31	$C_{18}H_{12}F_4N_2O_4$

[a] 5-Bromo-6-methoxy-8-nitroquinoline was prepared as described by Elderfield et al.[2] [b] 3,5-Bis(trifluoromethyl)phenol was made via the method of Wolfe.[6] Synthesis of 4-(trifluoromethoxy)phenol and 4-fluoro-3-(trifluoromethyl)phenol is described under Experimental Section. The remaining phenols were obtained commercially. [c] All compounds except **3d** (previously reported, see ref 7) were analyzed for C, H, and N. [d] Literature[7] mp 121-122 °C.

Table IV. 8-Amino-6-methoxy-5-phenoxyquinolines



4

compd	R_1	R_2	mp, °C (solvent) [a]	yield, %	formula [b]
4a	4-CH_3	H	used without purification		
4b	H	3-CF_3	104-106 (Et_2O-PE)	78	$C_{17}H_{13}F_3N_2O_2$
4c	H	4-CF_3O	99-101 (PE)	75	$C_{17}H_{13}F_3N_2O_3$
4d	H	4-CH_3O	111-112 (EtOH) [c]	62	$C_{17}H_{16}N_2O_3$
4e	H	2,4-Cl_2	89-90 (Et_2O-PE)	60	$C_{16}H_{12}Cl_2N_2O_2$
4f	H	3,4-Cl_2	117-119 (MeOH-H_2O)	94	$C_{16}H_{12}Cl_2N_2O_2$
4g	H	3,5-$(CF_3)_2$	139-141 (Et_2O-PE)	93	$C_{18}H_{12}F_6N_2O_2$ [d]
4h	4-CH_3	3,5-$(CF_3)_2$	136-138 (hexane)	70	$C_{19}H_{14}F_6N_2O_2$
4i	H	4-F, 3-CF_3	87-88 (C_6H_6)	76	$C_{17}H_{12}F_4N_2O_2$
4j	3-CH_3	4-F, 3-CF_3	119-119.5 (hexane)	81	$C_{18}H_{14}F_4N_2O_2$
4k	4-CH_3	4-F, 3-CF_3	120-121 (C_6H_6)	76	$C_{18}H_{14}F_4N_2O_2$

[a] PE = petroleum ether. [b] All compounds except **4a** and **4d** (previously reported, see ref 7) were analyzed for C, H, and N. [c] Literature[7] mp 115-116 °C. [d] C: calcd, 52.74; found, 53.59.

Biology. We have confirmed that 5-phenoxy groups greatly attenuate the toxicity of primaquine (Table I). With the exception of compounds **6a,c,j**, the 5-phenoxyprimaquines produced no toxic lethality at the highest dose tested (640 mg/kg), and even compounds **6a,c,j** were less toxic than primaquine itself.

Among the demethyl derivatives (Table I, R_1 = H), the most active blood schizonticides were those with R_2 equal to 4-F (**6n**) or 3-CF_3 (**6b**). A compound containing both 4-F and 3-CF_3 (**6i**) was less active than either of the singly substituted derivatives.

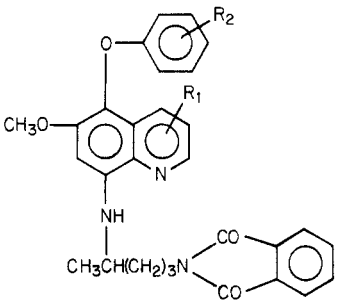
The activity range over the entire demethyl series was relatively narrow. However, introduction of a methyl group on the pyridine ring of various 5-phenoxyprimaquines effected a dramatic increase in blood schizonticidal activity. This is seen to good advantage in comparing **6a** with **6l**, **6g** with **6h**, and in examining the trio **6i,j,k**. Data for the last three compounds would seem to suggest that the methyl group is more effective at position 4 than at position 3. 4-Methylprimaquine, in the absence of a 5-phenoxy group, was quite unimpressive.

A number of the 5-phenoxyprimaquines were also evaluated against persistant tissue schizonts of *Plasmodium cynomolgi* in the radical curative test (Table II). The best of these were the fluorine-containing derivatives, **6b,i,n**, which were more active than primaquine.

Experimental Section

Melting points were determined in capillary tubes in an electrically heated Thiele-Dennis apparatus and are uncorrected.

Table V. 6-Methoxy-8-[(1-methyl-4-phthalimidobutyl)amino]-5-phenoxyquinolines

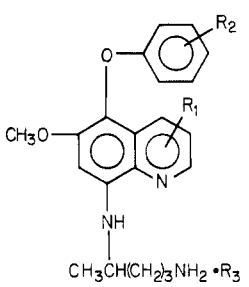


5

compd	R_1	R_2	mp, °C (solvent)	yield, %	formula [a]
5a	4-CH_3	H	166–169 (C_6H_6)	32	$C_{30}H_{29}N_3O_4$
5b	H	3-CF_3	112–115 (Et_2O)	58	$C_{30}H_{26}F_3N_3O_4$ [b,c]
5c	H	4-CF_3O	used without purification		
5d	H	4-CH_3O	170–172 (Et_2O-MeOH)	*d*	$C_{30}H_{31}ClN_3O_5$ [e]
5e	H	2,4-Cl_2	189–191 (MeOH)	76	$C_{29}H_{26}Cl_3N_3O_4$ [e]
5f	H	3,4-Cl_2	125–127 (Et_2O)	74	$C_{29}H_{25}Cl_2N_3O_4$ [f]
5g	H	3,5-$(CF_3)_2$	204–206 (Et_2O)	42	$C_{31}H_{26}ClF_6N_3O_4$ [e]
5h	4-CH_3	3,5-$(CF_3)_2$	159–160 (Et_2O)	20	$C_{32}H_{27}F_6N_3O_4$
5i	H	4-F, 3-CF_3	used without purification		
5j	3-CH_3	4-F, 3-CF_3	149–150 (MeOH)	*g*	$C_{31}H_{27}F_4N_3O_4$
5k	4-CH_3	4-F, 3-CF_3	used without purification		

[a] Except as noted, all compounds were analyzed for C, H, and N. [b] C: calcd, 65.56; found, 66.10. [c] Another fraction was isolated whose IR spectrum suggested a dimorph, mp 97–100 °C. Anal. ($C_{30}H_{26}F_3N_3O_4$) C, H, N. [d] Main fraction used without purification. [e] Analyzed as the hydrochloride. [f] C: calcd, 63.28; found, 62.58. [g] Major fraction was used without purification.

Table VI. 8-[(4-Amino-1-methylbutyl)amino]-6-methoxy-5-phenoxyquinolines



6

compd	R_1	R_2	R_3	mp, °C (solvent)	yield, %	formula [a]
6a	4-CH_3	H	citrate	155–158 (*i*-PrOH)	36	$C_{28}H_{35}N_3O_9$
6b	H	3-CF_3	citrate	149 (MeOH-Et_2O)	77	$C_{28}H_{32}F_3N_3O_9$
6c	H	4-CF_3O	citrate	110–140 (EtOH)	82	$C_{28}H_{32}F_3N_3O_{10}$
6d	H	4-CH_3O	citrate·0.5H_2O	135–137 (EtOH)	47 [c]	$C_{28}H_{36}N_3O_{10.5}$
6e	H	2,4-Cl_2	H_3PO_4	197–199 (MeOH)	29	$C_{21}H_{26}Cl_2N_3O_6P$
6f	H	3,4-Cl_2	hemifumarate	140–153 (*i*-PrOH)	80	$C_{23}H_{25}Cl_2N_3O_4$
6g	H	3,5-$(CF_3)_2$	$2H_3PO_4$	173–180 (MeOH-Et_2O)	53	$C_{23}H_{29}F_6N_3O_{10}P_2$
6h	4-CH_3	3,5-$(CF_3)_2$	citrate	163–164 (*i*-PrOH)	86	$C_{30}H_{33}F_6N_3O_9$
6i	H	4-F, 3-CF_3	hemifumarate	155–157 (MeOH-Et_2O)	34 [c]	$C_{24}H_{25}F_4N_3O_4$
6j	3-CH_3	4-F, 3-CF_3	fumarate	140–142 (MeOH)	50	$C_{27}H_{29}F_4N_3O_6$
6k	4-CH_3	4-F, 3-CF_3	citrate·0.5H_2O	*b* (MeOH-Et_2O)	30	$C_{29}H_{34}F_4N_3O_{9.5}$

[a] All compounds were analyzed for C, H, and N. [b] Indefinite melting range beginning at 84 °C. [c] Based on 8-NH_2 precursor.

Elemental analyses (Micro-Analysis, Inc., Wilmington, DE) were within ±0.4% of the theoretical values unless otherwise noted. Synthetic details are presented in Tables III-VI.

2-Fluoro-5-hydroxybenzotrifluoride. 5-Amino-2-fluorobenzotrifluoride (29 g, 0.16 mol, Marshallton Research Laboratories, Inc.) was added to a hot (80–90 °C) solution of 100 mL of concentrated H_2SO_4 and 200 mL of H_2O. The solution was cooled to 10 °C and treated with a solution of $NaNO_2$ (13.1 g, 0.17 mol) in 20 mL of H_2O at a rate that kept the temperature below 10 °C. On completion of addition, the pale yellow solution was stirred at 5 °C for 0.5 h, treated with 1.5 g of urea in 10 mL of H_2O, and stirred at 5 °C for another 0.5 h. The diazo solution was then added, dropwise, to a steam-distillation apparatus that contained a boiling solution of 100 g of $CuSO_4$·5H_2O in 100 mL of H_2O. (During addition, the internal temperature gradually rose from 105 to 125 °C.) Steam distillation was continued for 2 h after diazo addition was complete. The distillate (ca. 500 mL) was saturated with NaCl, and the aqueous and oil layers were separated. The aqueous layer was thoroughly extracted with Et_2O, and the extracts were combined with the oil layer. The ethereal solution was washed with saturated NaCl (2 × 100 mL), dried (Na_2SO_4), and concentrated. The residual oil was vacuum distilled to give 22.4 g (77%) of the phenol, bp 84–92 °C (14 mm). The analytical sample boiled at 86 °C (15 mm). Anal. ($C_7H_4F_4O$) C, H.

4-(Trifluoromethoxy)phenol. 4-(Trifluoromethoxy)aniline

(40 g, 0.22 mol, Pierce Chemical Co.) was converted to the phenol, in 63% yield, in the manner described above: bp 91–93 °C (20 mm); n^{24}_D 1.4440 [lit.[3] bp 92 °C (25 mm); n^{25}_D 1.4469].

Acknowledgment. We are grateful to Drs. H. A. Musallam, R. O. Pick, E. A. Steck, and T. R. Sweeney of WRAIR for assistance, suggestions, and enthusiasm during the course of our research, to Drs. David E. Davidson, Arba Ager, John L. Brown, Frank D. Chapple, Richard E. Whitmire, and Leon Schmidt for performing biological tests, to Drs. H. A. Musallam of WRAIR and P. Blumbergs of Ash Stevens, Inc., for making available 5-chloro-6-methoxy-3-methyl-8-nitroquinoline and 5-chloro-6-methoxy-4-methyl-8-nitroquinoline and to Janice Conlon, Beth Bauer, and Suzanne Olivieri for technical assistance. This investigation was supported by the U.S. Army Medical Research and Development Command under Contract No. DADA 17-70-C-0101 and is Contribution no. 1644 to the Army Research Program on Antiparasitic Drugs.

(3) W. A. Sheppard, *J. Org. Chem.*, **29**, 1 (1964).
(4) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).
(5) L. H. Schmidt, R. N. Rossan, R. Fradkin, and J. Woods, *Bull. W.H.O.*, **34**, 783 (1966).
(6) J. K. Wolfe, U.S. Patent 2547679 (1951).
(7) W. M. Laver C. Rondestvedt, R. T. Arnold, N. L. Drake, J. Van Hook, and J. Tinker *J. Am. Chem. Soc.*, **68**, 1546 (1946).

Hypobetalipoproteinemic Agents. 3. Variation of the Polycyclic Portion of 4-(1-Adamantyloxy)aniline

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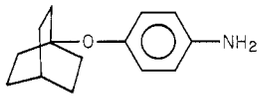
We have replaced the adamantyl moiety of the hypobetalipoproteinemic 4-(1-adamantyloxy)aniline (**2**) with 1- and 4-diamantyl, *cis*- and *trans*-9-decalyl, and 1,1-dimethylbutyl, -hexyl, and -octyl. The compounds were easily accessible by our previous route. Only the diamantyl compounds, **8** and **11**, were active, suggesting that some as yet unidentified, special geometrical and/or associative (electronic) aspects of the tertiary bi- and polycyclooxyanilines are required for the hypobetalipoproteinemic activity of these agents.

We have previously reported the hypobetalipoproteinemic activity of agents related to 4-(1-bicyclo[2.2.2]-octyloxy)aniline (**1**)[1] and the more potent 4-(1-



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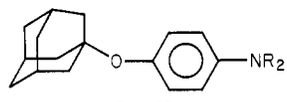


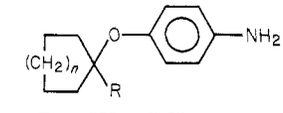
2, R = H
3, R = $(CH_2)_5$

adamantyloxy)aniline (**2**).[2] This activity consists of a reduction of the atherogenic heparin precipitating lipoproteins (HPL) and also the HPL to cholesterol ratio in the cholesterol–cholic acid fed rat.[3] Ultracentrifugation studies with the piperidine **3** have demonstrated that not only are the atherogenic, lower density (d <1.040 g/mL) lipoproteins reduced as desired, but the high density lipoproteins (1.040 < d < 1.21 g/mL), which may well be antiatherogenic,[4-6] are increased. The extensive investigation of compounds related to **2** included variation in the bridging oxygen atom and substitution on the aromatic ring and on nitrogen.[2] Two other changes in the polycyclooxy portion of **1** and **2** produced compounds **4**[1] which

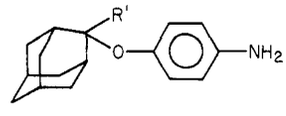
Table I. Hypobetalipoproteinemic Activity of *p*-Aminophenyl Ethers in Diet-Induced Hypercholesterolemic Rats[a]

no.	dose, (mmol/kg)/day	T/C		
		Chol	HPL	HPL/Chol
8	0.17	0.53*	0.35*	0.66*
11	0.17	0.31*	0.19*	0.62*
14[b]	0.18	0.92	0.89	0.97
17[b]	0.18	1.38*	1.24	0.90*
20[b]	0.22	0.84	0.78	0.92
23[b]	0.19	1.02	0.96	0.94
26[b]	0.17	0.98	0.84	0.86*

[a] Chol = total serum cholesterol; HPL = heparin precipitating lipoproteins; T/C signifies the mean value for the treated rats divided by that for the control rats; an asterisk denotes a response significantly different ($p < 0.05$) from control means; compounds were dosed at 50 (mg/kg)/day. Food intake and weight gain were considered normal (>73% and >63% of control values, respectively) during the experiments. [b] Data reported for the hydrochloride salt.



4, R = CH_3, C_2H_5, n = 1, 2



5a, R′ = H
b, R′ = CH_3

were inactive, **5a**[2] which was active, and **5b**[2] the activity of which is considered indeterminant due to subnormal weight gain. Thus, there seemed to be some unique structural characteristic of the bicyclic and tricyclic portions of **1** and **2**, respectively, responsible for their hypo-

(1) C. E. Day, P. E. Schurr, D. E. Emmert, R. E. TenBrink, and D. Lednicer, *J. Med. Chem.*, **18**, 1065 (1975).
(2) D. Lednicer, W. E. Heyd, D. E. Emmert, R. E. TenBrink, P. E. Schurr, and C. E. Day, *J. Med. Chem.*, **22**, 69 (1979).
(3) C. E. Day, P. E. Schurr, W. E. Heyd, and D. Lednicer in "Atherosclerosis Drug Discovery", C. E. Day, Ed., Plenum Press, New York, 1976, p 31.
(4) T. Gordon, W. P. Castelli, M. C. Hjortland, W. B. Kannel, and T. R. Dawber, *Amer. J. Med.*, **62**, 707 (1977).
(5) C. J. Glueck, P. Gartside, R. W. Fallat, J. Sielski, and P. M. Steiner, *J. Lab. Clin. Med.*, **88**, 941 (1976).
(6) G. J. Miller and N. E. Miller, *Lancet*, 16 (1975).
(7) P. E. Schurr, J. R. Schultz, and C. E. Day in "Atherosclerosis Drug Discovery", C. E. Day, Ed., Plenum Press, New York, 1976, p 215.

0022-2623/82/1825-1101$01.25/0