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Synthesis of Some 4-Substituted 8-Amino-6-methoxyquinolines as Potential Antimalarials

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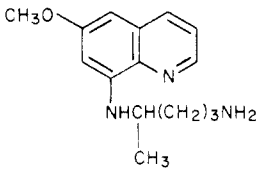
The 4-vinyl, 4-ethyl, and three 4-[β-(arylthio)ethyl] derivatives of primaquine and other 8-aminoquinoline antimalarial agents were prepared for antimalarial evaluation. 8-[(4′-Amino-1′-methylbutyl)amino]-4-ethyl-6-methoxyquinoline (4-ethylprimaquine), which showed activity approximately equal to that of primaquine against *Plasmodia cynomolgi* in Rhesus monkey, was the most active of the compounds tested. 4-Ethylprimaquine was also less toxic than primaquine, as measured in the Rane mouse screen.

In an earlier report,[1] we pointed out the value of 8-aminoquinolines, such as primaquine (**1**), for the radically



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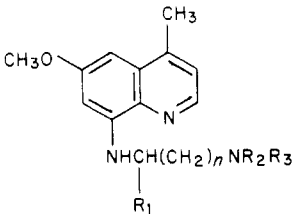
curative treatment (complete eradication of the parasites) of *Plasmodium vivax* malaria and described the synthesis and antimalarial activity of several reduced 8-aminoquinoline analogues.

The major drawback to the use of primaquine (**1**) is its relative toxicity and rapid excretion. A survey of the earlier literature[2-4] reveals that the type of toxicity induced by the 8-aminoquinolines depends largely upon the structure of the 8-amino side chain. However, nuclear substituents appear to have a greater influence upon relative toxicity. For example, several 8-[[(dialkylamino)alkyl]amino]-6-methoxy-4-methylquinolines (**2**) were reported to possess



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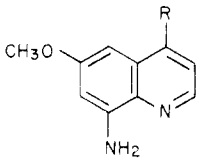
high antimalarial activity combined with reduced toxicity relative to the unsubstituted analogues.[5,6] Based on the above, we initiated a program which involved the synthesis of 4-vinyl, 4-ethyl and 4-[β-(arylthio)ethyl]-8-aminoquinoline analogues.

Chemistry. In order to achieve the synthesis of the desired target compounds, it was first necessary to devise synthetic schemes for the preparation of 8-amino-6-methoxy-4-vinylquinoline (**3a**), 8-amino-4-[(arylthio)-ethyl]-6-methoxyquinoline (**3b–d**), and 8-amino-4-ethyl-6-methoxyquinoline (**3e**). Scheme I outlines the reaction scheme used to prepare the compounds **3a–d**. Subjection of 6-methoxy-4-methyl-8-nitroquinoline (**4**)[5] to the Mannich reaction gave 4-[β-(dimethylamino)ethyl]-6-



3a, R = $CH{=}CH_2$
b, R = $CH_2CH_2SC_6H_4$-*p*-F
c, R = $CH_2CH_2SC_6H_4$-*p*-OCH_3
d, R = $CH_2CH_2SC_6H_4$-*p*-Cl
e, R = CH_2CH_3

methoxy-8-nitroquinoline hydrochloride (**5**). Neutralization of **5** followed by treatment with methyl iodide gave 6-methoxy-8-nitro-4-[β-(trimethylamino)ethyl]quinoline iodide (**6**). Treatment of **6** with aqueous sodium hydroxide gave 6-methoxy-8-nitro-4-vinylquinoline (**7**). Condensation of **6** with *p*-fluorothiophenol and *p*-methoxythiophenol in DMF containing potassium carbonate gave the 4-[(arylthio)ethyl]-6-methoxy-8-nitroquinolines **8**, X = F and OCH_3, respectively. Reduction of **7** and **8** (X = OCH_3) with stannous chloride and hydrochloric acid yielded **3a** and **3c**, respectively. Catalytic reduction of **8** (X = F) using Raney nickel catalyst gives **3b**. The addition of *p*-chlorothiophenol to **3a** gives the addition product **3d**.

Two synthetic procedures for the preparation of 8-amino-4-ethyl-6-methoxyquinoline (**3e**) were developed and are shown in Scheme II. In one case (method A), 4-methoxy-2-nitroaniline (**9**) was converted to 4-ethyl-6-methoxy-8-nitroquinoline (**10**) by a modified Skraup reaction. Reduction of **10** with stannous chloride and hydrochloric acid or catalytically gave the desired amine **3e**. The amine **3e** was also prepared by catalytic reduction of 6-methoxy-8-nitro-4-vinylquinoline (**7**; method B, Scheme II). Scheme III outlines the procedures used to attach the side chain to the 8-aminoquinolines **3a–e**. The results obtained are listed in Table I. The alkylation of **3** with 4-bromo- or 4-iodo-1-phthalimidopentane in the presence of triethylamine,[7,8] followed by removal of the phthaloyl-protecting group with hydrazine, gave the 8-[(4′-amino-1′-methylbutyl)amino]quinolines **11**. If 4-bromo-1-phthalimidobutane or 6-chloro-1-phthalimidohexane was used in place of the 4-bromo-1-phthalimidopentane for the alkylation of **3a**, the 8-[(4′-aminobutyl)amino]quinoline (**12**) and 8-[(6-aminohexyl)amino]quinoline (**13**) were obtained, respectively, after treatment with hydrazine. The condensation of **11e** with acetone, followed by re-

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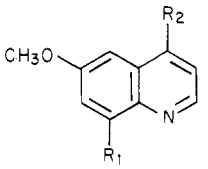
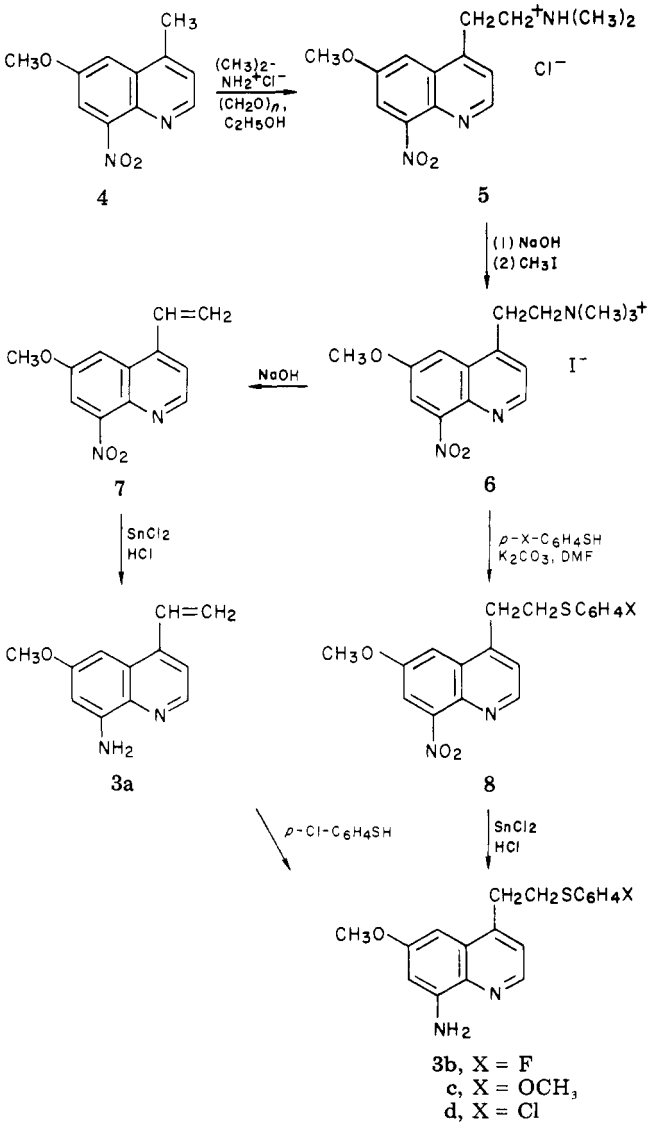
Table I. 8-Aminoquinolines



compd	R_1	R_2	mp, °C (recryst solv)	yield,[a] %	formula[b]
11a	$NHCH(CH_3)(CH_2)_3NH_2$·fumarate	CH_2=CH-	143-146 (MeOH-MeCN)[c]	27	$C_{12}H_{27}N_3O_5$
11b	$NHCH(CH_3)(CH_2)_3NH_2$·fumarate/ 0.5H_2O	p-$FC_6H_4SCH_2$-CH_2-	138-140 (EtOH)	71	$C_{27}H_{33}FN_3O_{5.5}S$
11c	$NHCH(CH_3)(CH_2)_3NH_2$·H_3PO_4	p-$CH_3OC_6H_4SCH_2$-CH_2-	187-190 (EtOH-H_2O)	56	$C_{24}H_{37}N_3O_6PS$
11d	$NHCH(CH_3)(CH_2)_3NH_2$·fumarate	p-$ClC_6H_4SCH_2$-CH_2-	153-155 (H_2O)	75	$C_{27}H_{32}ClN_3O_5S$
11e	$NHCH(CH_3)(CH_2)_3NH_2$·2HBr	CH_3CH_2-	216-217 (EtOH-Et_2O)	42	$C_{17}H_{27}Br_2N_3O$
12	$NHCH_2(CH_2)_2CH_2NH_2$·2HBr/ 0.5EtOH	CH_3CH_2-	108-109 (EtOH)	55	$C_{17}H_{28}Br_2N_3O_{1.5}$
13	$NHCH_2(CH_2)_4CH_2NH_2$·HBr/ 0.5EtOH	CH_3CH_2-	95[c] (EtOH)	36	$C_{19}H_{32}BrN_3O_{1.5}$

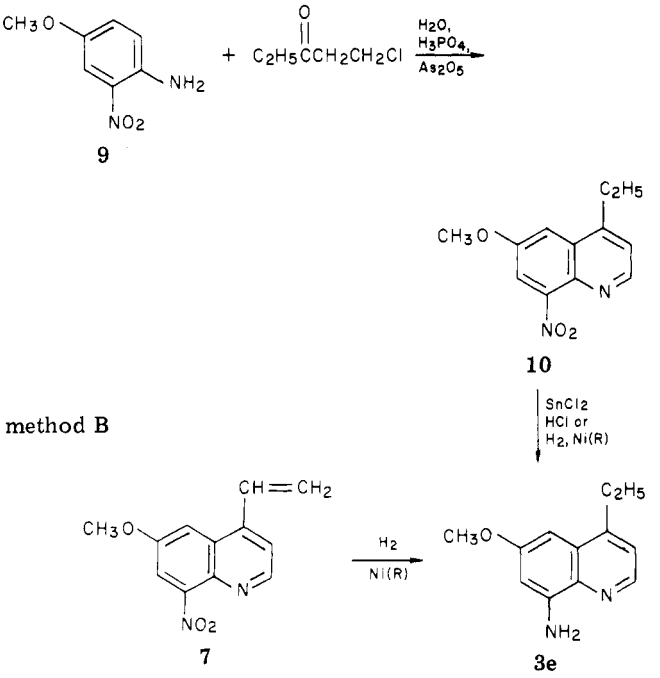
[a] Yield is based on starting amine 3 unless otherwise noted. [b] Analysis for C, H, N, S, and halogen when present are within ±0.4% of the theoretical value. [c] The compound melts with decomposition.

Scheme I



duction with sodium borohydride, gave **14**. Treatment of **3e** with 2,2′-diethoxy-5-(diethylamino)pentane, followed by reduction with sodium borohydride, gave the pamaquine analogue **15**. The alkylation of **3e** with 1,6-dichlorohexane gave **16**, which yields **17** on treatment with piperazineethanol. Alkylation of **3e** with 6-(diethylamino)hexyl bromide gave **18**.

Scheme II



Biological Testing. The data in Table II compares the activities of compounds **11a,c–e**, **12–15**, **17**, and **18** to those of primaquine (**1**) in the blood schizonticidal antimalarial screen.[9] Compounds **11a** and **11e** were the most active compounds tested. Compound **11a** showed three cures at 160 and 320 mg/kg and two cures at 640 mg/kg but was toxic at the two higher dose levels. Compound **11e** was active at 160 mg/kg and showed two and five cures, respectively, at 320 and 640 mg/kg. Primaquine is active at 80 mg/kg but toxic at high dose levels. Thus, **11a** and **11e** are slightly less active than primaquine at dose levels up to 80 mg/kg but are less toxic than primaquine at higher dose levels. It is also interesting to note that compound **12**, which differs from **13** by only two methylene

Scheme III

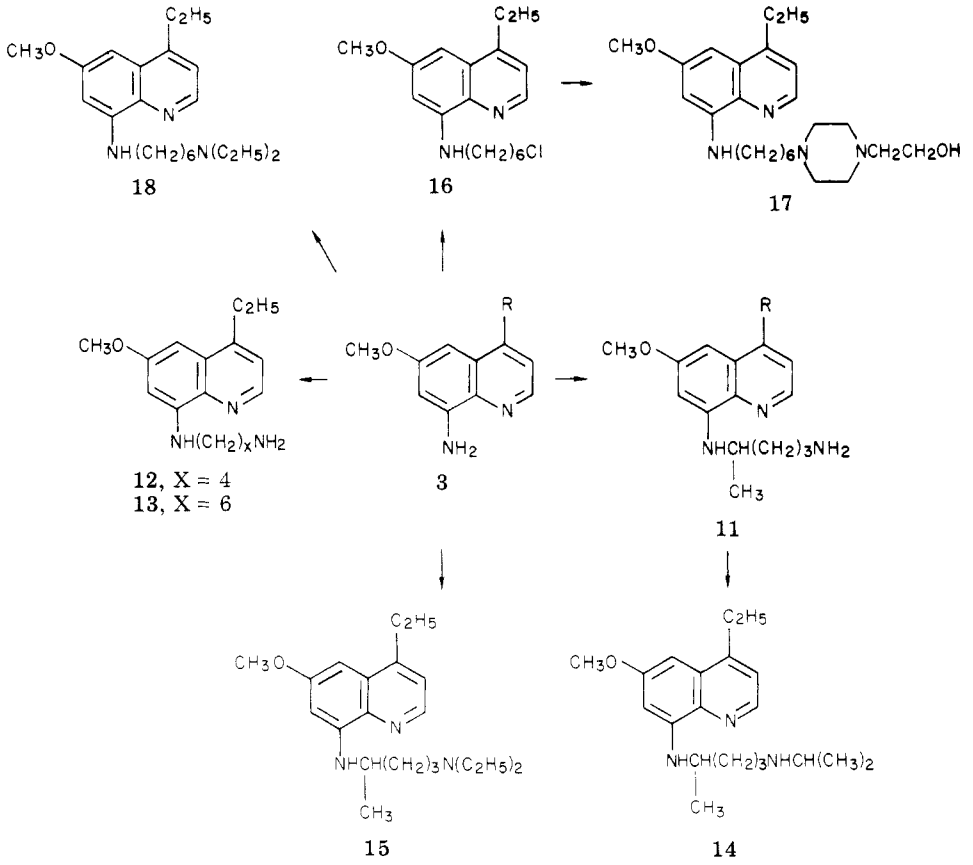


Table II. Antimalarial Activity against *P. berghei* in Rodents[a]

compd	ΔMST, C or T:[b] dose, mg/kg					
	20	40	80	160	320	640
11a	1.1	1.7	5.9	8.7 (3C)	7.7 (3C, 1T)	2C, 3T
11c	0.1	0.3	2.1	2.7	6.1	7.5
11d	2.3	3.3	6.3	7.7	8.9	14.6 (2C)
11e	2.8	3.8	5.2	6.4	11.5 (2C)	5C
12	0.9	1.7	2.1	2.9	6.3	7.9
13		0.8	4.8 (2T)	5T		
14	−0.3	2.3	3.5	6.7	10.5 (2C)	2C, 3T
15	1.1	1.5	3.7	6.6	2T	5T
17	0.1	0.7	2.7	2.5	4.1	5T
18	0.5	1.7	3.3	5.5	6.7	7.9
1	4.0	5.0	9.4	2T	5T	5T

[a] Tests were carried out by the Rane Laboratory, University of Miami, Miami, Fla., using blood-induced *P. berghei* infected mice (five animals per group) by the method described by Osdene et al.[9] Test data were supplied by Drs. E. A. Steck and R. E. Strube of Walter Reed Army Institute of Research. [b] ΔMST, mean survival time over controls (6.2 ± 0.5 days). A compound is considered active if MST of the treated group is more than twice that of the control group: C, number of cures (mice surviving 60 days); T, number of toxic deaths occurring on days 2–5 after infection.

units in the 8-amino side chain, is not toxic at 640 mg/kg, whereas toxicity at both 80 and 160 mg/kg was noted for **13**.

Compounds **11a**, **11b**, and **11e** were tested for radical curative activity against *P. cynomolgi* in Rhesus monkeys[10] (Table III). Compound **11e** shows activity approximately equal to that of primaquine. Compounds **11a** and **11b** which showed 1/2 cures at 0.5 mg/kg were slightly less active than primaquine.

Compound **11c** was tested for causal prophylatic activity against sporozoite-induced *P. berghei yoelii* in rodents. Tests were carried out by the Rane Laboratory, University of Miami, Miami, Fla., using sporozoite-induced *P. berghei yoelii* infected mice.[11,12] The test compound was dissolved or suspended in 0.5% hydroxyethylcellulose–0.1% Tween-80 and administered either orally (po) or subcutaneously (sc) at three dose levels to groups of five mice. Activity was evidenced by survival of drug-treated mice to 30 days. Survival of two or more mice in the treated group may be considered as an indication of activity. Compound **11c** showed 2/5 curves at a dose of 160 mg/kg (po) but was inactive at doses of 40 and 10 mg/kg (po). The compound was also inactive at doses of 160, 40, and 10 mg/kg (sc).

The above animal test data indicated that the addition of a 4-ethyl- or 4-vinyl substituent to the primaquine structure diminished toxicity while retaining high activity

Experimental Section

Melting points were determined on a Kofler hot-stage microscope using a calibrated thermometer. IR spectra were measured with a Perkin-Elmer Model 267 or 467 grating infrared

Table III. Antimalarial Activities against *P. cynomolgi* in Rhesus Monkeys[a,b]

compd	dose, mg/kg[c]	cures[d]	relapses[e]
11a	0.25	0/1	7
	0.5	1/2	10
	1.0	1/2	24
11b	0.25	0/1	13
	0.5	1/2	7
	1.0	0/2	6, 7
11e	0.125	0/1	9
	0.25	0/2	7, 80
	0.5	3/4	28
	1.0	1/2	37
1	0.375	0/2	11, 14
	0.5	10/12	11, 22
	0.75	4/4	

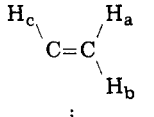
[a] Data were supplied by Dr. E. A. Steck, Walter Reed Army Institute of Research. [b] Tests were carried out by Dr. L. H. Schmidt, Southern Research Institute, Birmingham, Ala.[10] [c] Dose administered via stomach tube once daily for 7 days with 2.5 mg of base/kg of chloroquine. [d] Monkeys that did not relapse in 90 days are considered cured. [e] The number given is the days between the end of treatment and relapse.

spectrophotometer. NMR spectra were recorded on a Varian Model HA-100 spectrometer using tetramethylsilane as an internal standard. MS were determined on an AEI-MS 902 spectrometer. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Ill., or Integral Microanalytical Laboratories, Inc., Raleigh, N.C. Where analyses are indicated by the symbols of the elements, the analytical results were within ±0.4% of the theoretical values.

4-[β-(Dimethylamino)ethyl]-6-methoxy-8-nitroquinoline Hydrochloride (5). A mixture of 5 g (22 mmol) of 6-methoxy-4-methyl-8-nitroquinoline (4), 1.79 g (22 mmol) of dimethylamine hydrochloride, 0.76 g of paraformaldehyde, and 5 mL of ethanol was refluxed for 7 days. The cooled reaction mixture was filtered, and the resulting solid was recrystallized from an ethanol and water mixture to give 5.18 g (76%) of **5**, mp 238–241 °C. The analytical sample prepared by recrystallization from an *N,N*-dimethylformamide and ether mixture had mp 243–244 °C dec; IR (KBr) 2700–2200 (NH^+), 1530 and 1368 cm^{-1} (NO_2). Anal. ($C_{14}H_{18}ClN_3O$) C, H, N. If the reaction was carried out at 110 °C in a Parr Teflon-lined digestion bomb, the reaction time could be reduced to 15 h and the yield increased to 82%.

6-Methoxy-8-nitro-4-[β-(trimethylamino)ethyl]quinoline Iodide (6). The hydrochloride **5** (6.6 g, 21 mmol) was converted to the free amine by treatment with sodium hydroxide (1 N) and chloroform extraction. The light brown amine was dissolved in 8 mL of THF in a Parr Teflon-lined bomb and stirred vigorously while 2.5 g of methyl iodide was added rapidly. The mixture formed a thick paste immediately, which was heated at 95 °C for 1 h to complete the reaction. The tan product which resulted after washing with ether weighed 6.7 g (76%) and had mp 203–205 °C dec. Anal. ($C_{15}H_{20}IN_3O_3$) C, H, N. This reaction has been repeated several times with yields varying from 70 to 74%.

6-Methoxy-8-nitro-4-vinylquinoline (7). 6-Methoxy-8-nitro-4-[β-(trimethylamino)ethyl]quinoline iodide (**6**; 44.3 g, 0.106 mol) was suspended in a mixture of 750 mL of 1 N NaOH and 750 mL of chloroform and stirred vigorously at 25 °C for 6 h. (All of the solid had dissolved.) The chloroform layer was separated, washed with H_2O, and dried (Na_2SO_4). Concentration gave a brown solid, which was recrystallized from a methylene chloride–hexane mixture to give 24.0 g (98%) of **7** as pale yellow crystals, mp 151–153 °C. The analytical sample prepared by recrystallization from the same solvent system had mp 152–154 °C; IR (CH_2Cl_2) 1620 and 1585 (C=C), 1535 and 1358 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 3.94 (s, CH_3O–), 5.68 (q, i H_a, $J_{a,c}$ = 12 and $J_{a,b}$ = 1.2 Hz), 5.94 (q, i H_b, $J_{b,c}$ = 17.2 Hz), 7.09–7.62 (m, 3, 5, and 7 H and ii H_c) 8.76 (d, 2 H). Anal. ($C_{12}H_{10}N_2O_3$) C, H, N.



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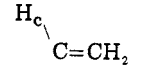

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4-[2′-[(*p*-Fluorophenyl)thio]ethyl]-6-methoxy-8-nitroquinoline (8, X = F). A mixture of 3.5 g (8.4 mmol) of **6**, 10 mL of DMF, 2.5 g of potassium carbonate, and 1.2 g (9.4 mmol) of *p*-fluorothiophenol was thoroughly mixed and heated at 90 °C for 10 h. After cooling to room temperature, the solution was poured into 200 mL of water with stirring. Filtration afforded 2.98 g (93%) of **8** (X = F) as a tan product. An analytical sample recrystallized from methanol had mp 114 °C. Anal. ($C_{18}H_{15}FN_2O_3S$) C, H, N, S.

4-[2′-[(*p*-Methoxyphenyl)thio]ethyl]-6-methoxy-8-nitroquinoline (8, X = OCH_3). A mixture of 4.2 g (10 mmol) of **6**, 2.5 g of potassium carbonate, 1.5 g of *p*-methoxythiophenol, and 30 mL of DMF was stirred at room temperature while a stream of nitrogen was blown on the surface of the liquid. After 20 h, the product was poured into water, and the sticky precipitate obtained was washed with water and extracted with methylene chloride. The solid obtained on evaporation of the solvent was recrystallized from ethanol to give 2.5 g (74%) of **8** (X = OCH_3): mp 90–95 °C; NMR ($CDCl_3$) δ 3.1 (s, CH_2CH_2), 3.73, 3.75 (2 s, OCH_3), 6.7 (d, $H_{3'}$, $H_{5'}$), 6.98 (d, H_5), 7.25 (d, H_2, $H_{6'}$), 7.4 (d, H_7), 8.55 (d, H_2). Anal. ($C_{19}H_{18}N_2O_4S$) C, H, N, S.

8-Amino-6-methoxy-4-vinylquinoline (3a). To a suspension of 1.21 g of granular tin, 38.7 g of $SnCl_2$, 80 mL of concentrated hydrochloric acid, and 40 mL of ethanol cooled to 0 °C was added 10.0 g (43.5 mmol) of 6-methoxy-8-nitro-4-vinylquinoline (**7**) portionwise such that the temperature never exceeded 10 °C. After the addition, the temperature was brought to 10 °C for 1 h and then 25 °C for 2 h, whereupon the reduction was complete. The reaction was basified (with cooling) and extracted with methylene chloride. The extracts were washed (H_2O), dried (Na_2SO_4), and concentrated to give a dark oil. The oil was eluted through a short Woelm Al_2O_3 (grade III) column with 10% THF/C_6H_6 to give 7.78 g (89%) of the title compound as a bright yellow oil, which crystallized on cooling: IR (CH_2Cl_2) 3482, 3375 cm^{-1} (NH_2); NMR ($CDCl_3$) δ 3.83 (s, CH_3O), 5.50 (q, i H_a, J_{ac} = 11 and J_{ab} = 1.3 Hz), 5.83 (q, i H_b, J_{bc} = 16.2 Hz), 6.51 and 6.59 (2 d, 5 and 7 H), 7.06–7.40 (m, 3 H, i H_c), and 8.47 ppm (d, 2 H).

A portion was converted to the hydrobromide in the standard manner; recrystallization from an ethanol–ether mixture gave the analytical sample, mp 210–213 °C dec. Anal. ($C_{12}H_{13}BrN_2O$) C, H, N.

8-Amino-4-[2′-[(*p*-fluorophenyl)thio]ethyl]-6-methoxyquinoline (3b). The nitro compound **8** (X = F; 2.5 g) was dissolved in 200 mL of methanol with heating. To the cooled solution, 3 g of Raney nickel was added, and the mixture was hydrogenated at room temperature on a Parr hydrogenator. After filtration of the catalyst and removal of the solvent, 1.7 g (74%) of the amine **3b** was obtained as a yellow oil. The compound was used without further purification.

8-Amino-4-[2′-[(*p*-methoxyphenyl)thio]ethyl]-6-methoxyquinoline (3c). To a mixture of 25 mL of ethanol, 50 mL of concentrated hydrochloric acid, and 4.9 g of stannous chloride cooled with an ice bath, a solution of 2 g of **8** (X = OCH_3) in 20 mL of THF was added dropwise with stirring. A deep red color resulted, and a red precipitate separated. After 1 h at 40 °C, the mixture was basified and the product extracted with methylene chloride. The extract was washed with water, dried with sodium sulfate, and evaporated to give 1.6 g (87%) of **3c** as a syrup: NMR ($CDCl_3$) δ 3.1 (s, CH_2CH_2), 3.70, 3.73 (2 s, OCH_3), 6.2 (d, H_5), 6.7, 7.3 (2 d, $H_{3'}$, $H_{5'}$, $H_{2'}$, $H_{6'}$), 8.33 (d, H_2). This product was used without further purification.

8-Amino-4-[2′-[(*p*-chlorophenyl)thio]ethyl]-6-methoxyquinoline (3d). To a solution of 8-amino-6-methoxy-4-vinylquinoline (**3a**; 2.00 g, 10 mmol) in 100 mL of EtOH was added a solution of *p*-chlorothiophenol in 100 mL of EtOH. The resulting solution was stirred at room temperature. After about 5 min, a white crystalline material was slowly formed. After stirring for 2 h, the crystals were collected by filtration and washed with

EtOH. Recrystallization from EtOH (95%) gave 2.48 g of off-white crystals: mp 137–139 °C; NMR ($CDCl_3$–CD_2Cl_2) δ 3.20 (s, QCH_2CH_2, 4 H), 3.77 (s, CH_3O, 3 H), 6.38 and 6.52 (two d, 5 and 7 H, $J_{5,7}$ = 3 Hz), 7.11 (d, 3 H, $J_{2,3}$ = 4.2 Hz), 7.26 (s, Ar H, 4 H), 8.44 (d, 2 H). Anal. ($C_{18}H_{17}ClN_2OS$) C, H, N.

4-Ethyl-6-methoxy-8-nitroquinoline (10). A homogeneous mixture of 50 g (0.3 mol) of 4-methoxy-2-nitroaniline, 40 g of technical 1-chloropentanone, and 90 mL of phosphoric acid was heated at 90 °C for 1 h with stirring. Some HCl evolution was noticeable. Arsenic pentoxide (40 g) was added all at once and stirring with heating continued for 2.5 h at 70–90 °C. The dark mixture was diluted with 900 mL of water and filtered. Upon basification of the filtrate with concentrated ammonia, a light-brown product precipitated which was thoroughly washed with water and methanol. The quinoline derivative remained as a light brown crystalline product which melted at 150–152 °C, yield 27 g. An additional 6 g could be recovered from the methanol washings, bringing the total yield to 33 g (48%). The product was sufficiently pure for further synthesis. The analytical sample prepared by recrystallization from methylene chloride–hexane had mp 158.5–159 °C; IR (CH_2Cl_2) 1535, 1358 cm^{-1} (NO_2). Anal. ($C_{12}H_{12}N_2O_3$) C, H, N.

The yield of **10** was 46% when the more expensive ethyl vinyl ketone was used in place of 1-chloropentanone. When sulfuric acid was used in place of phosphoric acid, the yield dropped to 11%.

8-Amino-4-ethyl-6-methoxyquinoline (3e). Method A. To a suspension of 1.72 g of granular tin, 54.8 g of $SnCl_2$, 108 mL of concentrated HCl, and 200 mL of ethanol cooled to 0 °C was added 14.33 g (0.062 mol) of **10** portionwise such that the temperature never exceeded 10 °C. After the addition, the temperature was brought to 10 °C for 45 min and then 25 °C for 30 min, whereupon the reduction was complete. The reaction was basified (with cooling) and then extracted with methylene chloride. The extracts were washed (H_2O), dried (Na_2SO_4), concentrated, dried again, and chromatographed on Woelm Al_2O_3 (grade III) eluting with 25% THF–C_6H_6 to give 9.85 g (79%) of **3e** as a yellow oil, which on recrystallization from methylene chloride–hexane had mp 72–74 °C. The analytical sample prepared by recrystallization from methylene chloride–hexane had mp 74–75 °C; IR (CH_2Cl_2) 3490, 3380 cm^{-1} (NH_2). Anal. ($C_{12}H_{14}N_2O$) C, H, N.

Catalytic reduction of **10** in methanol using Raney nickel catalyst gave an 83% yield of **3e**.

Method B. A solution of 500 mg (2.17 mmol) of 6-methoxy-8-nitro-4-vinylquinoline (**7**) in 35 mL of ethanol containing a catalytic amount of Raney nickel was hydrogenated in a Parr hydrogenator until hydrogen ceased to be absorbed. The catalyst was separated by filtration and the filtrate concentrated on a rotary evaporator. The remaining residue was recrystallized from a methylene chloride and hexane mixture to give 0.30 g (60%) of **3e**, mp 74–75 °C.

General Procedure for 4-Substituted 8-[(Aminoalkyl)amino]-6-methoxyquinolines 11a–e, 12, and 13. The appropriate 8-aminoquinoline (~2 g) was heated with stirring at 105–110 °C under argon while a solution of 2 equiv of 4-bromo- or 4-iodo-1-phthalimidopentane, 4-bromo-1-phthalimidobutane, or 6-chloro-1-phthalimidohexane in 2 g of triethylamine[13] was added very slowly over a period of about 24 h. The pasty mixture was extracted with 30 mL of benzene, cooled, filtered, and concentrated under vacuum. The remaining yellow-brown syrup was purified by passing through a column of 200 g of silica gel 60 (Merck) or aluminum oxide (Woelm) using chloroform as the eluent. The pure alkylated amine recovered as a yellow syrup was refluxed with 4 equiv of hydrazine in 50 mL of ethanol. After 2–3 h, the cooled mixture was filtered and the filtrate concentrated under vacuum. The residue was treated with methylene chloride and filtered, and the filtrate was concentrated under vacuum. The free alkylated aminoquinolines were converted to their salts by standard procedure. Individual examples are described in Table I.

4-Ethyl-8-[[4′-(isopropylamino)-1′-methylbutyl]amino]-6-methoxyquinoline (14) Dihydrobromide. A solution of 2.9 g (0.01 mol) of **11e** free base in 50 mL of acetone containing 0.4 g of sulfuric acid and 10 g of molecular sieves (Linde 4Å) was stirred at 25 °C for 16 h. The product obtained after filtration and removal of the excess acetone was dissolved in methanol and treated with 2 equiv of sodium borohydride. After 1 h, the reaction mixture was concentrated to a liquid, which was dissolved in chloroform, washed with water, and dried (Na_2SO_4). The liquid obtained on removal of the chloroform was chromatographed on Woelm (grade III) alumina using a 1:1 mixture of chloroform and ethyl acetate as the eluent. The product fraction weighted 1.4 g (42%): NMR ($CDCl_3$) δ 0.99 [d, $CH(CH_3)_2$], 1.27 (d, $CHCH_3$), 1.33 (t, CH_3CH_2), 2.92 (g, CH_3CH_2), 3.86 (s, OCH_3), 6.16, 6.34, 7.06, 8.36 (4 d, H_5, H_7, H_3, H_2). A small sample of **14** was converted to the dihydrobromide salt, mp >100 °C dec. Anal. ($C_{22}H_{38}Br_2N_3O$) C, H, Br, N.

8-[[4′-(Diethylamino)-1′-methylbutyl]amino]-4-ethyl-6-methoxyquinoline (15) Citrate. A mixture of 5 g (0.025 mol) of **3e**, 7 g of 2,2-diethoxy-5-(diethylamino)pentane, and 0.4 g of *p*-toluenesulfonic acid was heated at 140 °C overnight while a continuous stream of argon was passed through the mixture. After 20 h, the brown reaction material was cooled, dissolved in chloroform, and extracted with sodium carbonate solution. The organic phase was evaporated to a syrup and treated with an excess of sodium borohydride in ethanol at room temperature. The reaction was completed in 20 min. Excess borohydride was destroyed with acetic acid, and the resulting product was evaporated to dryness. A chloroform extract of the residue was purified by silica gel chromatography (chloroform–ethanol eluent) to give 1.5 g (18%) of **15**. A solution of **15** (1.5 g) in ether was added to an alcoholic solution (10 mL) of 0.9 g of citric acid. A yellow-brown material precipitated. Addition of a sufficient amount of ethanol and heating on a water bath with stirring produced light yellow crystals. Cooling at 0 °C overnight completed the crystallization. The citrate of **15** (1.97 g) after washing with ethanol–ether had mp 98–102 °C dec. Anal. ($C_{27}H_{41}N_3O_8$) C, H, N.

4-Ethyl-8-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]hexyl]amino]-6-methoxyquinoline (17) Dimaleate. A suspension of 4 g (0.02 mol) of **3e**, 6 g of sodium bicarbonate, 15 g of 1,6-dichlorohexane, and 7 mL of dimethylformamide was heated with stirring under argon at 110–120 °C. After 2 h, 50 mg of sodium iodide was added and heating continued for 24 h. The reaction product was taken up in methylene chloride, extracted several times with water, and evaporated to a syrup, which was chromatographed on silica gel using methylene chloride and ethyl acetate as eluent. Pure **16** was obtained as a light yellow crystalline solid: yield 2.9 g (46%); NMR ($CDCl_3$) δ 1.3 (t, CH_3CH_2), 2.94 (q, CH_3CH_2), 3.52 (t, CH_2Cl), 3.86 (s, OCH_3), 6.2, 6.39, 7.08, 8.36 (4 d, H_5, H_7, H_3, H_2).

A 1.7-g sample of **16** was heated with 5 g of piperazineethanol at 120 °C overnight. The crude product was dissolved in chloroform and extracted three times with water. Removal of the chloroform gave 2.7 g of brown syrup, which after chromatography on silica gel (chloroform–methanol eluent) yielded 1.9 g (87%) of **17**. An alcoholic solution (20 mL) of this product was combined with a solution of 0.9 g of maleic acid in 10 mL of ethanol. A light yellow salt crystallized immediately. A total of 2.3 g of **17** maleate was recovered, mp 142–143 °C dec. Anal. ($C_{32}H_{46}N_4O_{10}·0.5H_2O$) C, H, N.

8-[[6′-(Diethylamino)hexyl]amino]-4-ethyl-6-methoxyquinoline (18) Dihydrobromide. To a 5-g (0.025) sample of **3e** heated under argon in an oil bath at 125 °C, a solution of 7 g of diethylaminohexyl bromide hydrobromide in 16 mL of DMF was added dropwise with stirring over a 90-min period. Heating was continued for 70 min, and then the product was treated with 1 N sodium hydroxide and extracted with chloroform. Evaporation of the extract gave a brown syrup which was chromatographed on silica gel using ethyl acetate–20% ethanol as eluent. The product was dissolved in benzene, filtered, and evaporated to yield 4 g (63%) of **18**. This was converted to the dihydrobromide salt, mp 178–180 °C. Anal. ($C_{22}H_{37}Br_2N_3O$) C, H, Br, N.

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(12) Test data were supplied by Dr. E. A. Steck, Walter Reed Army Institute of Research.
(13) In the synthesis of **12** and **13**, sodium hydrogen carbonate (5 g) was used in place of triethylamine as base, and DMF (8 mL) was used as solvent. Sodium iodide (50 mg) was added to the reaction mixture for the synthesis of **13**, and the temperature was reduced to 60–70 °C for the synthesis of **12**.

Synthesis and Pharmacological Evaluation of *cis*-3,4,4a,9a-Tetrahydro-1*H*-pyrano[3,4-*b*]benzofuran-1-ones. Tricyclic Analogues Related to the Antilipidemic Drug Clofibrate[1]

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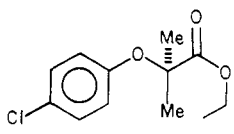
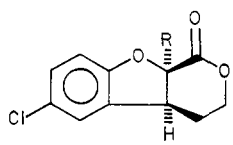
The chemistry and pharmacology of two δ-lactones, *cis*-6-chloro-9a-methyl-3,4,4a,9a-tetrahydro-1*H*-pyrano[3,4-*b*]benzofuran-1-one (**2**) and the 9a-demethyl analogue **3**, are reported. Lactones were prepared from dihydrobenzofuran precursors possessing geometrical configurations confirmed both by synthesis and ^{1}H NMR spectroscopy. All *cis*-dihydrobenzofurans exhibited J_{vic} = 9.0–10.8 Hz, whereas their trans isomers exhibited J_{vic} = 5.0–6.0 Hz in agreement with predictions based on the Karplus equation. The pharmacological profiles for **2** and **3** were compared to that of clofibrate (**1**) in normal male Sprague–Dawley rats. Using equimolar doses (0.4 mmol/kg, po, twice daily for 7 days), **1** exhibited both anticholesterolemic and antitriglyceridemic activity, lactone **2** exhibited only antitriglyceridemic activity, and **3** was inactive as an antilipidemic agent. No correlation was observed for inhibition of hepatic HMG-CoA reductase activity and serum cholesterol lowering.

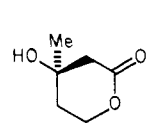
As part of a continuing study concerned with antilipidemic drug development,[3-6] we describe in this article the synthesis and pharmacological properties of *cis*-6-chloro-9a-methyl-3,4,4a,9a-tetrahydro-1*H*-pyrano[3,4-*b*]-benzofuran-1-one (**2**) and its demethyl analogue **3**. These



1



2, R = Me
3, R = H



(*R*)-**4**

compounds are 6-5-6 tricyclic δ-lactones structurally related to clofibrate (**1**). Analogue **2** differs from the molecular weight of **1** by 4 H atoms and may be visualized as a compound in which one of the *gem*-dimethyl groups of **1** is concomitantly bonded ortho on the phenyl ring and to the β-carbon of the ethyl function. Furthermore, one enantiomorph of each of these tricyclic lactones **2** and **3** also has a structural resemblance to mevalonolactone [(*R*)-**4**]. Thus, these molecules were constructed in the hope that they would have increased affinity over **1** for HMG-CoA reductase[7] or other enzymes involved in the biochemical transformation of (*R*)-**4** and its precursors to cholesterol.

Synthetic Aspects. Key intermediate diacid *trans*-**11** served as the precursor to *cis*-**11** and was prepared from aldehyde **5** according to methods similar to those reported by Koelsch[8,9] and Shimizu[10,11] in the preparation of the dechloro analogue. In large scale preparations, diacid **6** (282 g, 1 mol) was converted to the isomeric mixture **9** in 69% yield without isomer separation. Whereas *cis*- and *trans*-**9** could not be separated by conversion to and fractional crystallization of their respective isomeric nitrile acids **10**, diacid *trans*-**11** could be isolated as a high-melting crystalline product devoid of contamination by the cis isomer. A small sample of the cis isomer was obtained from the mother liquor resulting from crystallization of *trans*-**11**.

Diacid *trans*-**11** was isomerized to *cis*-**11** using Shimizu's[11] method. Thus, treatment of *trans*-**11** with NH_4OH afforded epimerized imide **12** in 46% yield. Yields severely decreased when more than 2 g of *trans*-**11** was employed. Conditions for hydrolysis of **12** to *cis*-**11** exclusive of epimerization are critical. Hydrolysis in 10% aqueous NaOH solution for 1 h afforded *cis*-**11** in 74% yield. Isomerization under longer reaction conditions yielded appreciable

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