anesulfonyl chloride (5.0 g, 0.033 mol) was added dropwise over a period of 20 min while cooling on ice. The reaction mixture was stirred for 5 h. Then H_2O was added and the product crystallized out. The solid was filtered off and recrystallized from PhH, yielding **7** (10.6 g, 87%, mp 111.7 °C). Anal. ($C_{15}H_{16}Cl_2N_2O_5S$) C, H, N.

***cis*-1-Acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine (I).** To a suspension of NaH (50%) dispersion (0.6 g, 0.012 mol) in Me_2SO, **7** (2.4 g, 0.011 mol) was added. After stirring the suspension for 1 h, **8** (4.1 g, 0.010 mol) was added and stirring was continued for 5 h at 80 °C. The reaction mixture was cooled and water was added. After extraction of the mixture with CH_2Cl_2, the organic layer was dried ($MgSO_4$) and evaporated to afford an oily residue, which was crystallized from 4-methyl-2-pentanone to afford I (3.2 g, 59%, mp 146.0 °C). Anal. ($C_{26}H_{28}Cl_2N_4O_4$) C, H, N.

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Antimalarials. 11. Synthesis of 3- and 5-Aminoquinolines as Potential Antimalarials

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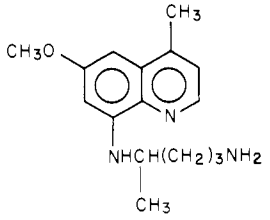
A series of 3-quinolinediamines (**1g**, **2c**, and **3e**) structurally related to primaquine and 4-methylprimaquine have been prepared and tested for antimalarial activity against *Plasmodium berghei* in mice and antileishmanial activity against *Leishmania donovani* in the hamster. All were inactive. In addition, three 5-quinolinediamines (**4b**, **5**, and **6**) were prepared. All were inactive against *Leishmania donovani* in hamsters. One of the examples, **6**, was curative against *Plasmodium cynomolgi* in the rhesus monkey.

In the preceding paper in these series,[1] we reported the preparation of a series of 4-substituted primaquine analogues based in part on a report[2] that 4-methylprimaquine (I) was superior to primaquine itself against *Plasmodium*



I

cynomolgi in the rhesus monkey. None of the 4-substituted primaquine analogues was superior to 4-methylprimaquine, however. We then felt that it would be of interest to prepare selected examples in the 3-amino- and 5-aminoquinoline areas. A very limited number of 3- and 5-quinolinediamines were prepared during the World War II program and reported by Wiselogle.[3] All were inactive in the antimalarial tests conducted. However, none contained methyl and/or methoxy substituents, which were subsequently found to enhance antimalarial activity, nor did they contain the highly effective (4-amino-1-methylbutyl)amino side chain.

Chemistry. Three examples were prepared in each series of 3-/5-NHR quinolines. The first analogue (**1g**) closely resembles 4-methylprimaquine, with the exception that the diamine side chain is in the 3 position of the quinoline nucleus. The synthetic sequence is shown in Scheme I and involved previously reported[1,4-7] procedures.

The second example (**2c**) was prepared similarly from 2-amino-4,5-dimethoxyacetophenone.[8] The third example in the 3-quinolinediamine series (**3e**) is the 4-demethyl analogue of **2c** and was prepared as shown in Scheme II. 2-Nitro-4,5-dimethoxybenzaldehyde was converted to the cyclic ethylene acetal **3a**. Catalytic reduction with Raney nickel afforded the intermediate **3b**. This intermediate is presumably formed via partial cleavage of the ethylene acetal to yield a benzaldehyde, which subsequently condenses with the intermediate aniline. We are unable to explain the stability of the second ethylene acetal function. Nevertheless, spectral and analytical data are consistent with the structure proposed for **3b**. Treatment of **3b** with methazonic acid gives rise to the desired 3-nitroquinoline **3c**. This latter intermediate was identical with an authentic sample prepared via condensation of 2-amino-4,5-dimethoxybenzaldehyde and methazonic acid.[9] The remainder of the sequence is identical with that described for the preparation of **1g**.

Three examples (**4b**, **5**, and **6**) were prepared in the 5-aminoquinoline series and all are 8-methoxy-5-quinolinediamines. Condensation of 2-methoxy-5-nitroaniline with acrolein afforded the requisite 5-nitro-8-methoxyquinoline,[10] which was reduced with hydrazine and Raney nickel to yield 5-amino-8-methoxyquinoline. Condensation of the 5-aminoquinoline with the appropriate side-chain intermediates afforded the three target 5-quinolinediamines.

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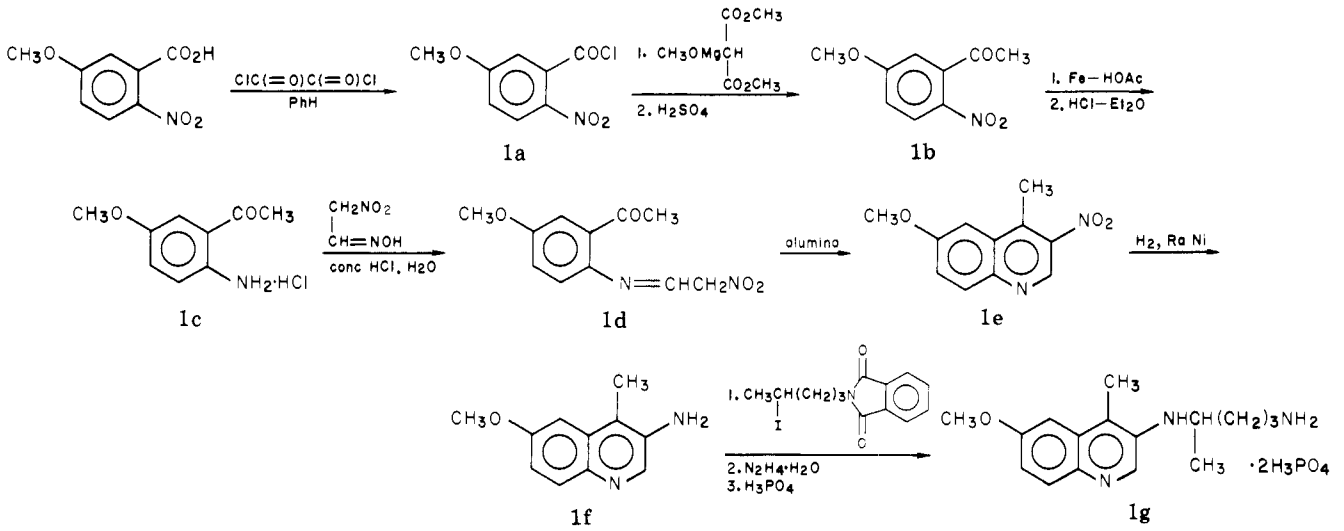
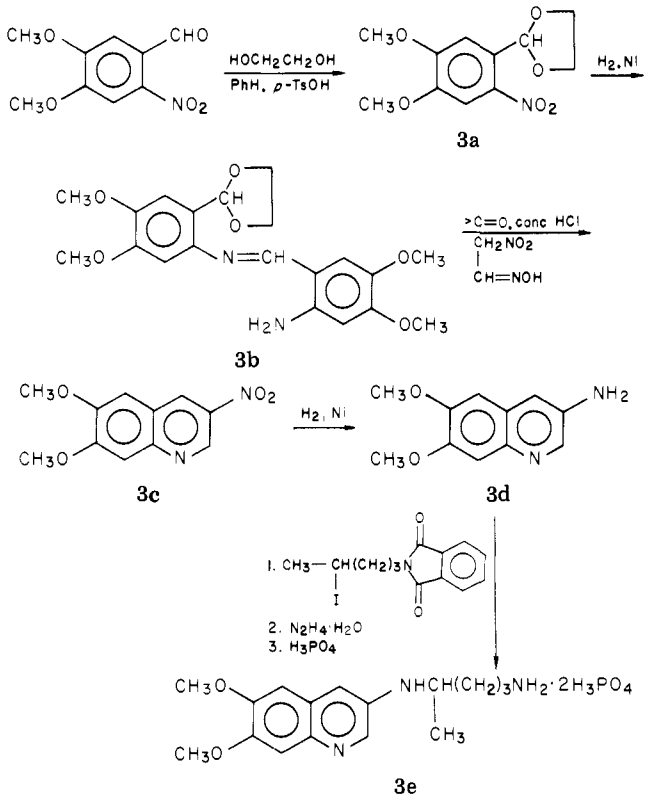
Scheme I



Scheme II



Biological Activity. The six target compounds were tested for suppressive antimalarial activity against *Plasmodium berghei* in mice.[11,12] All were inactive at the highest dosage level tested (640 mg/kg). The compounds were also evaluated for antileishmanial activity against *Leishmania donovani* in hamsters by the well-established 8-day testing method.[13,14] All six compounds were inactive in this screen as well. In addition, compounds **4b**, **5**, and **6** were tested for radical curative antimalarial activity against *Plasmodium cynomolgi* in the rhesus monkey.[15] Only compound **6** was active in this screen with 1/1 cure at 10 mg/kg (×6), clearly inferior to primaquine and 4-methylprimaquine.

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, Ind. NMR spectra were determined on a Varian Model T60A spectrometer. Ethanol used in the work was specially denatured grade 3A alcohol (90% ethanol, 5% 2-propanol, and 5% methanol, v/v). Commercial Raney nickel was supplied by W. R. Grace Co. (no. 30).

2-Nitro-5-methoxybenzoyl Chloride (1a). A mixture of 2-nitro-5-methoxybenzoic acid[4] (36.0 g, 0.18 mol) in dry C_6H_6 (150 mL) containing oxalyl chloride (44.4 g, 0.35 mol) was refluxed on a steam bath for 3 h. The solvent and excess oxalyl chloride were removed under reduced pressure, and the resulting chloride, a yellow oil (39.0 g, 0.18 mol), was used as such in the next reaction.

2-Nitro-5-methoxybenzoylmalonic Acid Dimethyl Ester. To 4.8 g (0.2 g-atom) of magnesium turnings in a dry flask were added absolute MeOH (6 mL) and dry CCl_4 (1 mL). The flask was heated for a short time to initiate the reaction. As soon as the reaction began, anhydrous Et_2O (350 mL) was added cautiously with stirring. A mixture of dimethyl malonate (26.0 g, 0.2 mol), anhydrous Et_2O (70 mL), and absolute MeOH (23 mL) was added with stirring at such a rate that rapid boiling was maintained. The reaction mixture was refluxed for 5 h, during which time most of the Mg had reacted. To the refluxing gray solution was added 2-nitro-5-methoxybenzoyl chloride (39.0 g, 0.18 mol, prepared above) in dry C_6H_6 (70 mL) over a period of 30 min. Refluxing was continued until the green solution became too viscous to stir. The reaction mixture was cooled and treated with cold dilute sulfuric acid (17 mL of concentrated H_2SO_4 in 123 mL of H_2O) until all the solid was dissolved. The Et_2O phase was seperated and the aqueous phase was extracted with Et_2O. The Et_2O extracts were combined, washed with H_2O, and dried over sodium sulfate. The Et_2O was removed, and the resulting solid was crystallized from Et_2O to give 58.0 g (97%) of the title compound, mp 80–82 °C. Anal. ($C_{13}H_{13}NO_8$) C, H, N.

2-Nitro-5-methoxyacetophenone (1b). The title compound was prepared from the above intermediate via the procedure of Makino and Takahashi:[5] yield 67%; mp 67–69 °C, lit.[5] 67 °C.

2-Amino-5-methoxyacetophenone Hydrochloride (1c). 2-Nitro-5-methoxyacetophenone (22.0 g, 0.113 mol) was added portionwise over a 1-h period to a stirred mixture of iron dust (34 g), acetic acid (132 mL), and H_2O (132 mL). After the addition was complete, the reaction mixture was refluxed for 1 h on a steam bath. The mixture was cooled, extracted with Et_2O, washed with H_2O, and dried (Na_2SO_4). The Et_2O was evaporated to give an oil, which was azeotroped with C_6H_6 several times to remove traces of acetic acid. The resulting yellow oil (20.8 g) was dissolved in Et_2O (400 mL) and the solution was acidified with HCl gas. The solid was filtered and washed with Et_2O to give 21.5 g (95%) of the title compound, mp 174–176 °C dec. Anal. ($C_9H_{12}ClNO_2$) C, H, N.

5-Methoxy-2-[(2-nitroethylidene)amino]acetophenone (1d). A solution of 2-amino-5-methoxyacetophenone hydrochloride (20.0 g, 0.10 mol) in H_2O (800 mL) containing 60 mL of concentrated HCl was treated with methazonic acid[6] (12.0 g, 0.11 mol). The reaction mixture was allowed to stir at room temperature for 12

h and the precipitated yellow solid was collected by filtration. The solid was crystallized from hot EtOH to give 19.0 g (81%) of the title compound, mp 173–175 °C. Anal. ($C_{11}H_{12}N_2O_4$) C, H, N.

3-Nitro-4-methyl-6-methoxyquinoline (1e). A solution of 5-methoxy-2-[(2-nitroethylidene)amino]acetophenone (18.0 g, 0.09 mol) in Me_2CO (800 mL) was stirred with activated alumina (145 g) for 12 h at room temperature. The alumina was removed by filtration and the filtrate was evaporated to dryness. The residual solid, on crystallization from EtOH, afforded 15.0 g (90%) of the title compound, mp 132–133 °C.

3-Amino-4-methyl-6-methoxyquinoline (1f). The above 3-nitroquinoline (9.5 g, 0.044 mol) was dissolved in dioxane–ethanol (1:1, 700 mL) with warming. Raney nickel (ca. 4 g) was added and the mixture was hydrogenated at 40 psig for 30 min. The catalyst was removed by filtration through a Celite bed, and the filtrate was concentrated to dryness. The residual solid was crystallized from C_6H_6 to afford 7.7 g (95%) of the title compound, mp 130–131 °C. Similarly prepared were **2b** and **3d** (Table I).

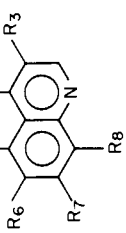
4-Methyl-6-methoxy-3-[(4-amino-1-methylbutyl)amino]-quinoline Diphosphate (1g). A mixture of 3-amino-4-methyl-6-methoxyquinoline (8.0 g, 0.043 mol), 1-phthalimido-4-iodopentane (IPP; 14.5 g, 0.043 mol), triethylamine (TEA; 14.29 g, 0.043 mol), and 2-ethoxyethanol (8 mL) was heated with stirring at 110 °C for 1 h. The mixture was then treated twice at 1-h intervals with IPP (14.5 g) and TEA (4.29 g) and kept at 110 °C for 3 h. The reaction mixture was cooled, extracted with $CHCl_3$, shaken with 5% NaOH, washed with H_2O, and dried (Na_2SO_4). The solvent was removed to give a dark viscous oil. The crude product was chromatographed over silica gel (EM Laboratories). Elution with $CHCl_3$ containing 10% MeOH and concentration of the solvent gave the desired phthalimido intermediate as an orange oil, which solidified on trituration with Et_2O to afford 4.0 g (30%). The crude phthalimido intermediate (6.5 g, 0.016 mol) was dissolved in EtOH (150 mL) containing 75% hydrazine hydrate (2.21 mL) and refluxed for 3 h. The mixture was concentrated to dryness. The residual solid was shaken with $CHCl_3$ and 20% aqueous KOH. The organic phase was washed with H_2O, dried (K_2CO_3), and concentrated to dryness. The resulting oil (4.4 g) was dissolved in EtOH (100 mL), and 1 M H_3PO_4 in EtOH (33 mL) was added with stirring. The solid was filtered and crystallized from EtOH–H_2O to give 6.42 g (83%) of the title compound, mp 232–233 °C. After drying under reduced pressure at 80 °C, the compound analyzed as a hemihydrate and, after block drying at 200 °C, the compound analyzed as anhydrous. Similarly prepared were **2c**, **3e**, and **6**.

2-Nitro-4,5-dimethoxybenzaldehyde Ethylene Acetal (3a). A mixture of 2-nitro-4,5-dimethoxybenzaldehyde (27.0 g, 0.128 mol), ethylene glycol (10 mL), and *p*-toluenesulfonic acid (2.8 g) in dry C_6H_6 (600 mL) was refluxed for 12 h. A Dean–Stark trap was used to remove H_2O formed during the condensation. The reaction mixture was cooled and treated with H_2O (200 mL) and 10% aqueous $NaHCO_3$ (100 mL). The organic phase was seperated, washed with H_2O, dried (Na_2SO_4), and concentrated to dryness. The resulting yellow solid was crystallized from C_6H_6–Et_2O to afford 27.0 g (83%) of the title compound as yellow needles, mp 123–124 °C. Anal. ($C_{11}H_{13}NO_6$) C, H, N.

4,5-Dimethoxy-2-[(2-amino-4,5-dimethoxybenzylidene)-amino]benzaldehyde Ethylene Acetal (3b). A solution of 2-nitro-4,5-dimethoxybenzaldehyde ethylene acetal (10.0 g, 0.039 mol) in dioxane–ethanol (160 mL, 1:3, v/v) containing wet Raney nickel (ca. 6 g) was hydrogenated at 30 psig for 30 min. The catalyst was filtered (Celite) and the filtrate was concentrated in vacuo at room temperature to give a yellow oil, which solidified on standing. The yellow solid was crystallized from EtOH to afford 7.0 g (92%) of the title compound, mp 223–225 °C (shrinking at 212 °C). Anal. ($C_{20}H_{24}N_2O_6$) C, H, N.

3-Nitro-6,7-dimethoxyquinoline (3c). A solution of the above Schiff base (19.0 g, 0.049 mol) in Me_2CO (1.1 L) was treated with H_2O (180 mL), methazonic acid (19.0 g, 0.18 mol), and concentrated HCl (63 mL). The reaction mixture was allowed to stir for 3 days at room temperature. The precipitated solid was removed by filtration to give 8.0 g of crude product. The mother liquor was concentrated to a small volume, diluted with H_2O, and neutralized with concentrated NH_4OH (pH ~8). The resulting precipitate was filtered and air-dried to afford an additional 8.0

Table I



no.	R_3	R_4	R_5	R_6	R_7	R_8	% yield	mp, °C (solvent)	formula	anal.[a]
1e	NO_2	CH_3	H	OCH_3	H	H	90	132–133 (EtOH)	$C_{11}H_{10}N_2O_3$	C, H, N
1f	NH_2	CH_3	H	OCH_3	H	H	95	130–131 (C_6H_6)	$C_{11}H_{12}N_2O$	C, H, N
1g	$NHC(CH_3)H(CH_2)_3NH_2$	CH_3	H	OCH_3	H	H	25[b]	232–235[c] (EtOH–H_2O)	$C_{16}H_{30}N_3O_{9.5}P_2$	C, H, N, P
2a	NO_2	CH_3	H	OCH_3	OCH_3	H	91	206–208[d]		
2b	NH_2	CH_3	H	OCH_3	OCH_3	H	92	202–204 (C_6H_6)	$C_{12}H_{14}N_2O_2$	C, H, N
2c	$NHC(CH_3)H(CH_2)_3NH_2$	CH_3	H	OCH_3	OCH_3	H	80[e]	220–221[f] (EtOH–H_2O)	$C_{17}H_{33}N_2O_{11}P_2$	C, H, N, P
3c	NO_2	H	H	OCH_3	OCH_3	H	57	213–215[g] (EtOH-Me_2CO)		
3d	NH_2	H	H	OCH_3	OCH_3	H	85	257–259[h] (EtOH)	$C_{11}H_{13}ClN_2O_2$	C, H, N, Cl
3e	$NHC(CH_3)H(CH_2)_3NH_2$	H	H	OCH_3	OCH_3	H	32[i]	202–204[j] (EtOH–H_2O)	$C_{16}H_{32}N_2O_{11.5}P_2$	C, H, N, P
4a	H	H	NH_2	H	H	OCH_3	88	156–158 (C_6H_6)	$C_{10}H_{10}N_2O$	C, H, N
4b	H	H	$NHC(CH_3)H(CH_2)_3N(C_2H_5)_2$	H	H	OCH_3		[k]	$C_{19}H_{36}Cl_3N_3O_3$	C, H, N, Cl
5	H	H	$NH(CH_2)_2N(C_2H_5)_2$	H	H	OCH_3	86	116–118[l] (*i*-PrOH)	$C_{16}H_{26}Cl_2N_3O_{1.5}$	C, H, N, Cl
6	H	H	$NHC(CH_3)H(CH_2)_3NH_2$	H	H	OCH_3	48[m]	258–260 (EtOH–H_2O)	$C_{15}H_{22}ClN_3O$	C, H, N, Cl

[a] Analytical results are within ±0.4% of theory unless otherwise noted. [b] From 1e. [c] Diphosphate hemihydrate. [d] Lit.[7] mp 207–208 °C. [e] From 2b. [f] Diphosphate monohydrate. [g] Lit.[7] mp 207–208. [h] Hydrochloride salt. [i] From 3d. [j] Diphosphate sesquihydrate. [k] Vitreous trihydrochloride dihydrate. [l] Dihydrochloride hemihydrate. [m] From 4a.

g of crude product. The crude product (16.0 g) was crystallized from EtOH–Me_2CO to give 13.0 g (57%) of the title compound, mp 213–215 °C, lit.[7] 207–208 °C.

8-Methoxy-5-aminoquinoline (4a). Hydrazine hydrate (75%, 17.8 mL) was added dropwise to a cold (5 °C) stirred slurry of 8-methoxy-5-nitroquinoline[10] (16.0 g, 0.078 mol) and wet Raney nickel (ca. 4 g) in EtOH (480 mL). The temperature was maintained below 20 °C during the addition. After the addition was complete, the reaction mixture was allowed to warm to room temperature and held there for 15 min. The catalyst was filtered (Celite), and the filtrate was concentrated to dryness. The resulting solid was crystallized from C_6H_6 to yield the title compound (12.0 g, 88%) as yellow needles, mp 156–158 °C (shrinking at 154 °C).

5-[[4-(Diethylamino)-1-methylbutyl]amino]-8-methoxyquinoline Trihydrochloride Dihydrate (4b). A mixture of 5-amino-8-methoxyquinoline (14.0 g, 0.08 mol), 5-(diethylamino)-2,2-diethoxypentane (22.0 g, 0.095 mol), and NH_4Cl (1.0 g) was heated at 155 °C for 0.5 h. An additional amount of the diethyl ketal (4.0 g) was added, and the mixture was kept at 155 °C for another 0.5 h. The reaction mixture was cooled, and anhydrous EtOH (30 mL) was added, followed by a slurry of $NaBH_4$ (5.6 g) in anhydrous EtOH (20 mL). After the addition was complete, the mixture was heated on a steam bath for 1 h. The reaction mixture was concentrated to dryness, and the residue was dissolved in Et_2O and washed with 10% aqueous KOH and H_2O (twice). The ethereal phase was dried (K_2CO_3) and concentrated, and the excess diethyl ketal was removed in vacuo (0.05 mm). The yield of the crude product was 22.5 g. This material (22.5 g) was chromatographed over silica gel (400 g, EM (4.4 Elution with $CHCl_3$–MeOH (9:3, v/v) and evaporation of the solvent afforded 12.5 g of pure product as the free base.

A portion of the free base (5.7 g) was dissolved in 2-propanol (15 mL) and the solution was treated with 1 N HCl (52 mL, 2.9 equiv). The deep purple solution was concentrated to dryness and azeotroped with H_2O (twice) to remove any 2-propanol. The residue was dissolved in H_2O and the solution was lyophilized (twice) to yield 6.0 g (deep purple solid, extremely hygroscopic) of the title compound.

5-[[(Diethylamino)ethyl]amino]-8-methoxyquinoline Dihydrochloride Hemihydrate (5). A mixture of 5-amino-8-methoxyquinoline (6.0 g, 0.035 mol), diethylaminoethyl chloride (7.03 g, 0.052 mol), and 2-ethoxyethanol (6 mL) was heated with stirring at 105 °C for 2 h. Additional diethylaminoethyl chloride (2.5 g, 0.018 mol) was added, and the mixture was heated for 1 h. The mixture was cooled, diluted with $CHCl_3$, and washed with 10% aqueous K_2CO_3. The $CHCl_3$ layer was dried (K_2CO_3) and concentrated to dryness. The residual dark oil was chromatographed over silica gel (200 g, EM Laboratories). Elution with $CHCl_3$–MeOH (93:7, v/v) and concentration of the solvent gave 4.45 g of the title compound as the free base. The free base (4.45 g) was dissolved in 2-propanol (10 mL) and the solution was treated with 1 M 2-propanol–HCl. The residual gum was crystallized from 2-propanol to yield the title compound (4.4 g, 86%) as a deep purple solid, mp 116–118 °C.

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(12) The testing was done at the Dr. Leo Rane Laboratory, University of Miami, Miami, Fla. The test results were supplied through the courtesty of Drs. T. R. Sweeney and R. E. Strube of the Walter Reed Army Institute of Research, Washington, D.C. In the primary test against *P. berghei*, five mice were infected with a lethal dose of *P. berghei* 3 days prior to administration of the chemical. Routinely, the chemical was administered subcutaneously in sesame or peanut oil. The mean survival time (MST) of infected control mice is 6.2 ± 0.5 days. Extension in survival time (ΔMST) of the chemically treated mice is interpreted as evidence of antimalarial activity.
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