Antimalarial Agents. 6-[[(Dialkylamino)alkyl]amino]-5,8-dimethoxyquinaldines (1,2)

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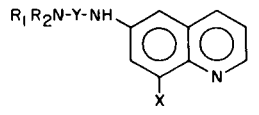
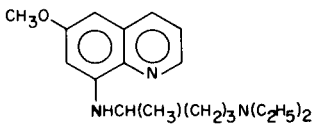
In 1942 Schönhöfer reported that 6-[[4-(diethylamino)-1-methylbutyl]amino]-8-methoxyquinoline (Ia) showed



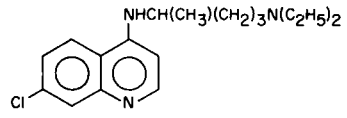
I

	X	NH-Y-NR$_1$R$_2$
a	OCH$_3$	NHCH(CH$_3$)(CH$_2$)$_3$N(C$_2$H$_5$)$_2$
b	OCH$_3$	NH(CH$_2$)$_3$N(C$_2$H$_5$)$_2$
c	OCH$_3$	NH(CH$_2$)$_3$N[(CH$_2$)$_2$]$_2$O
d	H	NHCH(CH$_3$)(CH$_2$)$_3$N(C$_2$H$_5$)$_2$

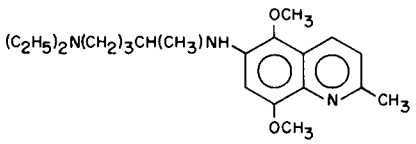


II

modest activity against *Plasmodium relictum* in canaries, but was much less potent than the 8-amino-6-methoxy isomer pamaquine (II) (3). During the World War II antimalarial program several other basically-substituted 6-aminoquinoline derivatives (Ib-d) were synthesized and tested against avian malarias (4,5). 6-[[3-(Diethylamino)-propyl]amino]-8-methoxyquinoline (SN-3,354) (Ib) was inactive against *Plasmodium cathemerium* in the canary at the level tested (< 1.5 quinine), 8-methoxy-6-[[3-(4-morpholino)propyl]amino]quinoline (SN-3,309) (Ic) was ineffective against *Plasmodium gallinaceum* in the chick (<0.04 quinine), while 6-[[4-(diethylamino)-1-methylbutyl]-amino]quinoline (SN-11,529) (Id) was 0.3 and 0.6 times as potent as quinine against *P. gallinaceum* in the chick and *Plasmodium lophurae* in the duck, respectively (4,5). By contrast, it was recently disclosed in the patent literature that 6-(aminoalkylamino)quinoline derivatives substituted with ether groups at both the 5- and 8-positions of the quinoline ring are more potent antimalarials than chloroquine (III) (6). Another cursory report stated that one of these compounds, namely 6-[[4-(diethylamino)-1-methylbutyl]amino]-5,8-dimethoxyquinaldine (B-505) (IV), produced radical cures of *P. gallinaceum* infections in canaries, although it proved to be too toxic for human trials (7,8).



III



IV

In anticipation that certain 6-(aminoalkylamino)quinoline derivatives might ultimately prove useful in connection with malaria problems encountered by the armed forces in Southeast Asia, we have synthesized several 6-[[(dialkylamino)alkyl]amino]-5,8-dimethoxyquinaldine prototypes (VIIa-c) for broad antimalarial evaluation against normal and drug-resistant plasmodia.

The 6-(aminoalkylamino)-5,8-dimethoxyquinaldines (VIIIa-c) were prepared according to the scheme outlined in Chart I. Application of the Skraup reaction to 2,5-dimethoxy-4-nitroaniline (V) and crotonaldehyde utilizing arsenic acid and 85% phosphoric acid (9) afforded 5,8-dimethoxy-6-nitroquinaldine (VI) in 47% yield. Hydrogenation of VI over Raney nickel gave 6-amino-5,8-dimethoxyquinaldine (VII) (72%). Intermediates VI and VII were mentioned in reference 6, but no preparative details are given in the literature. Condensation of the anion of VII, prepared with sodamide, with 2-chlorotriethylamine, 3-diethylaminopropyl chloride, and 3-(chloromethyl)-1-methylpiperidine in xylene afforded 6-[[2-(diethylamino)-ethyl]amino]-5,8-dimethoxyquinaldine (VIIIa) (22%), 6-[[3-(diethylamino)propyl]amino]-5,8-dimethoxyquinaldine (VIIIb) (56%), and 5,8-dimethoxy-6-[[(1-methyl-3-piperidyl)methyl]amino]quinaldine (VIIIc) (9%), respectively, isolated as the β-resorcylic acid salts.

In preliminary antimalarial studies the 6-[[(dialkylamino)alkyl]amino]-5,8-dimethoxyquinaldines (VIIIa-c) were administered subcutaneously in a single dose to mice infected with *Plasmodium berghei* (10,11). Surprisingly, these substances were toxic for mice at doses as low as

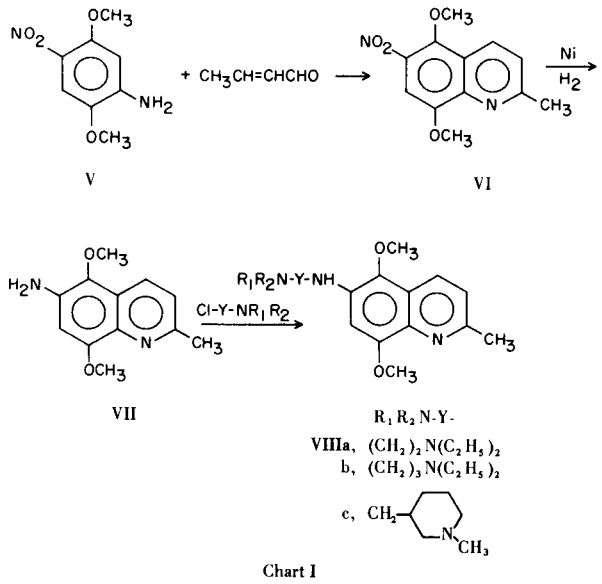


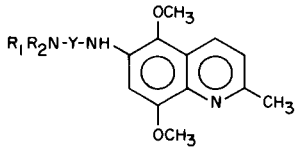
Chart I

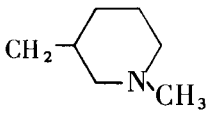
10-40 mg./kg., and produced little or no increase in the mean survival time of mice at maximum tolerated doses ranging from 5 to 20 mg./kg. In contradistinction, compounds VIIIa and b were highly active when given continuously in the diet for 6 days to mice infected with another strain of *P. berghei* (12,13). The SD_{90} (daily dose required for 90% suppression of the parasitemia) for VIIIa, VIIIb, and quinine was 10.5 mg./kg., 1.3 mg./kg., and 74.5 mg./kg., respectively. Thus WR-27799 (VIIIb) was approximately 57 times as potent as quinine against *P. berghei* by drug-diet, although it was toxic for mice at doses only four-fold higher than the SD_{90} dose.

In a third study, the 6-[[(dialkylamino)alkyl]amino]-5,8-dimethoxyquinaldines (VIIIa-c) were evaluated against *P. gallinaceum* infections in white Leghorn cockerels (14). Chicks were given an intravenous injection of 0.2 ml. of heparinized blood infected with *P. gallinaceum* and having a minimum of 80-90% parasitized red blood

TABLE I

Effects of 6-[[(Dialkylamino)alkyl]amino]-5,8-dimethoxyquinaldines Against *Plasmodium gallinaceum* in the Chick

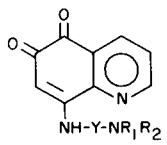


Compd. No.	WR	-Y-NR$_1$R$_2$	Single s.c. dose (mg./kg.) (a)	MST of chicks (days) Treated	Control	ΔST (b)	No. of chicks Cured (c)	Toxic (d)
VIIIa	34410	$(CH_2)_2N(C_2H_5)_2$	30	8.2	3.8	4.4	0	0
			60	6.8	3.8	3.0	1	0
			120	6.8	3.8	3.0	1	0
VIIIb	27799	$(CH_2)_3N(C_2H_5)_2$	30	18.8	3.8	15.0	0	0
			60	20.4	3.8	16.6	0	0
			120	15.0	3.8	11.2	0	3
VIIIc	34413		30	17.4	3.8	13.6	0	0
			60	16.5	3.8	12.7	1	0
			120	19.5	3.8	15.7	1	2

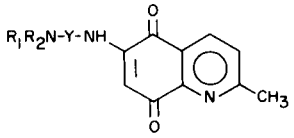
(a) Compounds were tested as the β-resorcylic acid salts and doses were not adjusted for free base content. (b) ΔST represents the difference between the mean survival time (days) of treated and untreated (control) chicks. (c) When any chick in the treated group survives to 30 days. (d) Deaths occurring within 48 hours after infection are attributed to drug action, and are counted as toxic deaths.

cells. The parasitized blood was drawn by cardiac puncture from donor birds infected 72 hours earlier with *P. gallinaceum*. Donor strains were maintained in separate groups of chicks, 14-16 days old, that also received inoculations of heparinized infected blood. In every experiment 100% of the untreated control birds died within 72-96 hours post-infection. Candidate substances were administered to chicks in a single subcutaneous dose in peanut oil immediately after infection. In this test, as in the mouse test, the antimalarial activity of candidate compounds was assessed by comparing the maximum survival times of treated malaria-infected chicks with the survival times of untreated malaria-infected controls. A compound was arbitrarily considered to be active against malaria if it produced increases in the survival times of treated chicks that were at least 100% over the survival times of untreated controls. As summarized in Table I, each of the 6-aminoquinaldines (VIIIa-c) was active against *P. gallinaceum* in chicks based on these criteria.

It has been postulated that the antimalarial action of pamaquine (II) and other 8-amino-6-methoxyquinolines is due to quinoid products (IX) to which they are converted in the host organism (3,15-19). It is therefore reasonable to propose that the 6-[[(dialkylamino)alkyl]amino]-5,8-dimethoxyquinaldines (VIII) may also be converted to active quinone metabolites such as X in the host. Indeed, probable differences in metabolic disposition arising from variations in drug regimen and host provide one plsusible explanation for the variable antimalarial effects of the 6-aminoquinaldines noted above.



IX



X

6-[[3-(Diethylamino)propyl]amino]-5,8-dimethoxyquinaldine di-β-resorcylate (WR-27799) (VIIIb) was subsequently tested against representative drug-resistant lines of *P. berghei* in the mouse to determine whether or not the 6-amino-5,8-dimethoxyquinaldines might represent a unique chemical type with respect to apparent mode of action. In a parallel study WR-27799 was administered by the drug-diet method to mice infected with the sensitive parent line P and the following drug-resistant lines: line T, completely (> 300-fold) resistant to cycloguanil; line S, completely (> 600-fold) resistant to 4,4′-sulfonyldianiline (DDS); and line C, 77-fold resistant to chloroquine (13). Groups of 10 mice were employed throughout, and treatment extended over a 6-day period starting the day before infection. The SD_{90}'s in mg./kg./day were as follows: line P, 2.4; line T, 3.1: line S, 2.4; line C, 5.2. Thus, WR-27799 was essentially fully as active against the cycloguanil- and DDS-resistant lines as against the sensitive parent line, with only a low order of cross-resistance (2.2-fold) against the chloroquine-resistant line. These results suggest that the principal mode of action of WR-27799 and the other 6-amino-5,8-dimethoxyquinaldines may be different from that of chloroquine, cycloguanil, and DDS, and encourages further chemical work in the series in anticipation that related compounds with a satisfactory therapeutic index can be discovered. In this regard it is interesting to note that many of the 4- and 8-aminoquinolines synthesized and tested in the search for useful drugs in these series were also very toxic and exhibited poor therapeutic indices in experimental animals (4,5).

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are corrected.

5,8-Dimethoxy-6-nitroquinaldine (VI).

A mixture of 99.1 g. (0.5 mole) of 2,5-dimethoxy-4-nitroaniline (V) (Eastman Kodak), 142 g. (1.0 mole) of arsenic acid, and 500 ml. of 85% phosphoric acid in a three-neck 2 l. round bottom flask was heated to 90° on a steam bath with vigorous stirring. The external heat was removed and 52.5 g. (0.75 mole) of crotonaldehyde was added dropwise over 60 minutes at such a rate as to maintain the reaction temperature between 92-95°. After the addition was complete, the mixture was heated at 97° for 30 minutes, poured into 2 l. of iced water, and made alkaline with 1 l. of concentrated ammonium hydroxide. The crude product was removed by filtration, pressed dry with a rubber dam, and dried *in vacuo* at 70° overnight. The crude product was extracted with boiling cyclohexane using a Soxhlet extractor until no yellow color was evident in the effluent. The pot extract was chilled to give 32.7 g. of desired product, m.p. 152-156°. Concentration of the liquors gave an additional 25.4 g., m.p. 150-154°. Total yield, 58.1 g. (47%). An analytical sample was prepared by recrystallization from cyclohexane, m.p. 158-160°.

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.05; H, 4.88; N, 11.29. Found: C, 58.14; H, 5.13; N, 11.21.

6-Amino-5,8-dimethoxyquinaldine (VII).

5,8-Dimethoxy-6-nitroquinaldine (VI) (4.8 g., 0.019 mole) in 100 ml. of 2-propanol was hydrogenated over 1 g. of Raney nickel at 25° and an initial hydrogen pressure of 51 p.s.i.g. The catalyst was collected by filtration and the solvent was removed under vacuum. The residue solidified on standing and was recrystallized from benzene to give 3.0 g. (72%) of desired product as yellow crystals, m.p. 155-157°.

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.46; N, 12.83. Found: C, 66.05; H, 6.29; N, 13.12.

6-[[2-(Diethylamino)ethyl]amino]-5,8-dimethoxyquinaldine Sesqui-β-resorcylate (WR-34410) (VIIIa).

To a stirred solution of 21.8 g. (0.1 mole) of 6-amino-5,8-dimethoxyquinaldine (VII) in 250 ml. of xylene was added 8.0 g.

(0.1 mole) of sodamide (50% suspension in xylene). The reaction mixture was heated under reflux for 1.75 hours. Nitrogen was passed through the system until no further ammonia evolution was observed. To the reaction mixture was then added 15.0 g. (0.1 mole) of 2-chlorotriethylamine (obtained from the hydrochloride salt and not distilled) and the mixture was heated under reflux for 20.5 hours. Water was added to the reaction mixture and the xylene layer was separated. The aqueous layer was extracted with ether. The combined ether and xylene extracts were dried over sodium sulfate and the solvents removed *in vacuo* to yield 27.8 g. of residual oil. Vapor phase chromatography showed this oil to be 27% starting material and 73% alkylated product.

An ether solution containing 3 equivalents of β-resorcylic acid was added to a rapidly stirred solution of the crude product in ether. The salt was isolated by filtration, washed well with ether, and dried. The salt was dissolved in water and the base regenerated by adding a 10% sodium hydroxide solution. The base was removed by ether extraction and the ether extract was dried over sodium sulfate. This process was repeated four times to yield 13.5 g. (22%) of the pure sesqui-β-resorcylate salt, m.p. 90° dec. A small sample of the analyzed product was converted to the base, as above, and shown by vapor phase chromatography to be 99% pure.

Anal. Calcd. for $C_{18}H_{27}N_3O_2 \cdot 1.5C_7H_6O_4 \cdot 0.5H_2O$: C, 61.38; H, 6.69; N, 7.53; H_2O, 1.62. Found: C, 60.92; H, 6.83; N, 7.23; H_2O (Karl Fischer), 1.72.

6-[[3-(Diethylamino)propyl]amino]-5,8-dimethoxyquinaldine Di-β-resorcylate (WR-27799) (VIIIb).

To a solution of 15.5 g. (0.071 mole) of 6-amino-5,8-dimethoxyquinaldine (VII) in 200 ml. of xylene was added 5.6 g. (0.072 mole) of sodamide (50% suspension in xylene). The reaction mixture was stirred and heated at reflux under nitrogen for 1.75 hours, at which time the ammonia liberation had ceased. To the reaction mixture was added 11.7 g. (0.072 mole) of distilled 3-diethylaminopropyl chloride and the mixture was heated under reflux for an additional 18.5 hours. The cooled reaction mixture was diluted with water, the organic layer was removed, and the aqueous layer was extracted again with xylene. The combined xylene extracts were dried over sodium sulfate and concentrated on a rotary evaporator to remove the xylene and unreacted 3-diethylaminopropyl chloride. The residual crude product (22.0 g.) was distilled using an oil diffusion pump. After removing the forerun, b.p. up to 113°/0.008 mm., four additional fractions were collected: **2**, b.p. 113-115°/0.008 mm. (2.1 g.); **3**, b.p. 135-166°/0.008 mm. (2.3 g.); **4**, b.p. 166-170°/0.008-0.003 mm. (6.0 g.); and **5**, b.p. 173-180°/0.01-0.003 mm. (4.8 g.). Vapor phase chromatography showed fraction **4** to be 20% starting material and 80% alkylated product. Fraction **5** was dissolved in 200 ml. of ether and added to 3 equivalents of β-resorcylic acid in 500 ml. of ether. The solid β-resorcylic acid salt was filtered and dried *in vacuo;* yield, 8.5 g., m.p. 74-77° dec.

Anal. Calcd. for $C_{19}H_{29}N_3O_2 \cdot 2C_7H_6O_4$: C, 61.96; H, 6.46, N, 6.57. Found: C, 61.87; H, 6.60; N, 6.90.

Fractions **2**, **3**, and **4** were combined and converted to the β-resorcylic acid salt (17.1 g.).

Anal. Calcd. for $C_{19}H_{29}N_3O_2 \cdot 2C_7H_6O_4$: C, 61.96; H, 6.46; N, 6.57. Found: C, 61.44; H, 6.50; N, 6.45.

The combined yield of 6-[[3-(diethylamino)propyl]amino]-5,8-dimethoxyquinaldine di-β-resorcylate was 25.6 g. (56%).

5,8-Dimethoxy-6-[[(1-methyl-3-piperidyl)methyl]amino]quinaldine Di-β-resorcylate (WR-34413) (VIIIc).

To a stirred solution of 10.0 g. (0.0458 mole) of 6-amino-5,8-dimethoxyquinaldine (VII) in 130 ml. of xylene was added 3.6 g. (0.0462 mole) of sodamide (50% suspension in xylene). The mixture was heated under reflux with nitrogen flowing through the system for 1 hour, when the libration of ammonia had ceased. To the reaction mixture was then added 7.1 g. (0.0481 mole) of 3-(chloromethyl)-1-methylpiperidine (isolated from the hydrochloride salt and not distilled) and the mixture was heated under reflux for 21.5 hours. The reaction mixture was cooled, diluted with water, and ether was added to the mixture to effect a separation of the organic and aqueous layers. The organic layer was removed and the aqueous layer was extracted again with ether. The organic layers were combined, washed with water, and dried over sodium sulfate. The solvents were removed leaving a residual oil. The crude product was shown by vapor phase chromatography to contain 45% of the unchanged quinaldine, 23% of the unchanged piperidine, and 32% of the desired alkylated product.

To a stirred ether solution of the crude product was added three equivalents of β-resorcylic acid dissolved in ether. The salt was isolated by filtration, washed well with ether, and dried. The salt was dissolved in water and 10% sodium hydroxide solution was added to regenerate the base. The base was isolated by ether extraction and the extract was dried over sodium sulfate. The salt was reformed and washed well with ether and dried. A small portion was converted to the base as above and shown by vapor phase chromatography to contain 2% of the unchanged quinaldine, 90% of the desired product and 8% of a low boiling material, probably ether. After thorough drying the anhydrous salt weighed 2.5 g. (9%), m.p. 130° dec.

Anal. Calcd. for $C_{19}H_{27}N_3O_2 \cdot 2C_7H_6O_4$: C, 62.15; H, 6.16; N, 6.59. Found: C, 62.14; H, 6.65; N, 6.79.

Acknowledgments.

The authors are indebted to Dr. Leo Rane of the University of Miami and to Dr. Paul E. Thompson of Parke, Davis and Company for the antimalarial testing. We also wish to thank Mr. C. E. Childs and associates for the microanalyses and vapor phase chromatography studies, and Dr. J. M. Vandenbelt and co-workers for determination of the spectral data.

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(11) For a description of the test method, see T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, 10, 431 (1967).

(12) Selected compounds were kindly evaluated by drug-diet against *P. berghei* in mice by Dr. Paul E. Thompson and co-workers, Research Laboratories, Parke, Davis and Co., Ann Arbor, Mich.

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(14) Antimalarial screening against *Plasmodium gallinaceum* in chicks was carried out by Dr. Leo Rane of the University of Miami, and test results were supplied through the courtesy of Dr. David P. Jacobus of the Walter Reed Army Institute of Research.

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Received November 6, 1968 Ann Arbor, Michigan 48106