Chart I. Amino Acid Sequences of LH-RH and the Cyclic Analogues

<Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2
1 2 3 4 5 6 7 8 9 10
LH–RH

$NH(CH_2)_2CO$-His-Trp-Ser-Tyr-D-Ala-Leu-Arg-Pro-Gly
cyclic [β-Ala[1],D-Ala[6],Gly[10]]-LH-RH

$NH(CH_2)_5CO$-His-Trp-Ser-Tyr-D-Ala-Leu-Arg-Pro-Gly
cyclic [6-aminohexanoic acid[1],D-Ala[6],Gly[10]]-LH-RH

cyclization, however, their activities increased enormously and the cyclic analogues II and IV (Chart I) were found to have 1.2 and 0.65% the LH-releasing activity of the standard LH-RH preparation, respectively. The best explanation for this is, we believe, that a close proximity exists between the ends of the LH-RH decapeptide chain in its receptor binding conformation, particularly since the shorter chain cyclic peptide was the most potent. It is possible that such an interaction, when worked out in detail, might explain many of the biological properties of some LH-RH agonists and antagonists, many of the more interesting of which contain critical modifications in their N- and C-terminal regions.

Acknowledgment. This work was supported by NIH Contract NICHD 6-2841 and the Veterans Administration.

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Synthesis of 2-Substituted Primaquine Analogues as Potential Antimalarials

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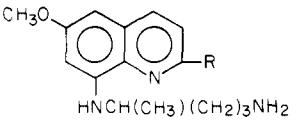
Received March 20, 1978

A series of 2-substituted primaquine analogues has been synthesized and evaluated against *Plasmodium berghei* in the mouse and *Leishmania donovani* in the hamster. Three members (**3a,d,e**) of the series were evaluated against *Plasmodium cynomolgi* in the rhesus monkey. One analogue (**3d**) was evaluated against *Trypanosoma rhodesiense* in the mouse, and two (**3b,e**) were evaluated against *Schistosoma mansoni* in the mouse. Several analogues possessed significant activity against *P. berghei* (**3e,f**) and *L. donovani* (**3a,e**).

Although quite toxic,[1] primaquine (**1**) is an important



1, R = H
2, R = $OCH_2C_6H_5$
3, R = OCH_3, NH_2, $N(CH_3)_2$, Cl, C_2H_5, $CH{=}CH_2$, $NHCOCH_3$

radical curative and causal prophylactic antimalarial agent. Our earlier studies[2] had indicated that 2-benzyloxy analogues, **2**, were less toxic than primaquine, as measured in the Rane mouse screen,[3] and this suggested the possibility that 2-substituted 8-aminoquinolines may offer a lead in the search for more effective and less toxic agents. We have now synthesized and evaluated a number of variously 2-substituted analogues, **3**. Selection of moieties for the 2 position was patterned after those which have shown interest when present at the 4 or 5 position.[4]

Chemistry. Compounds **5a–c** (Scheme I) were prepared by direct nucleophilic displacement of the halogen in 2-chloro-6-methoxy-8-nitroquinoline (**4**)[5] by an appropriate reagent (e.g., sodium methoxide, phenol–ammonia, or dimethylamine). The 2-amino analogue **5b** was converted to the 2-acetamido derivative **5g**, and the 8-nitro group of **5g** and **5c** was reduced with iron–acetic acid[6] to yield **6g** and **6c**. Compound **5f** (Scheme II) was prepared from 6-methoxy-2-methyl-8-nitroquinoline (**8**),[7] via the quaternary salt (**10**) of the Mannich base (**9**).[8] Reduction of **5f** with stannous chloride–hydrochloric acid gave **6f**, whereas reduction with Raney nickel–hydrazine hydrate[9] gave **6e**. Compounds **6a** and **6d**[10] (prepared directly from **4**) were also obtained by Raney nickel–hydrazine hydrate reduction. Alkylation of the amines **6** with 4-bromo-1-phthalimidopentane,[11] utilizing the triethylamine procedure,[12] gave the intermediate phthalimidoalkylaminoquinoline derivatives **7**. These were subjected directly to hydrazinolysis, and the resulting amines **3** were characterized as maleate or fumarate salts. (During hydrazinolysis, the acetamido group present in **7g** and unreacted **6g** was cleaved to give the desired **3b** and amine **6b**.[13]) Pertinent physical and analytical data for all new compounds are summarized in Tables I and II.

Biological Results. The antimalarial test results were provided by the Walter Reed Army Institute of Research. The suppressive activity was assessed against *Plasmodium berghei* in mice by the method of Rane and co-workers.[3,14] As noted in Table I, several **3** analogues were "active", but primaquine-like toxicity, as observed in the Rane test, was still present, except for **3e**. (No mouse data were available for **3b**.) Compounds **3a,d,e** were also tested for radical

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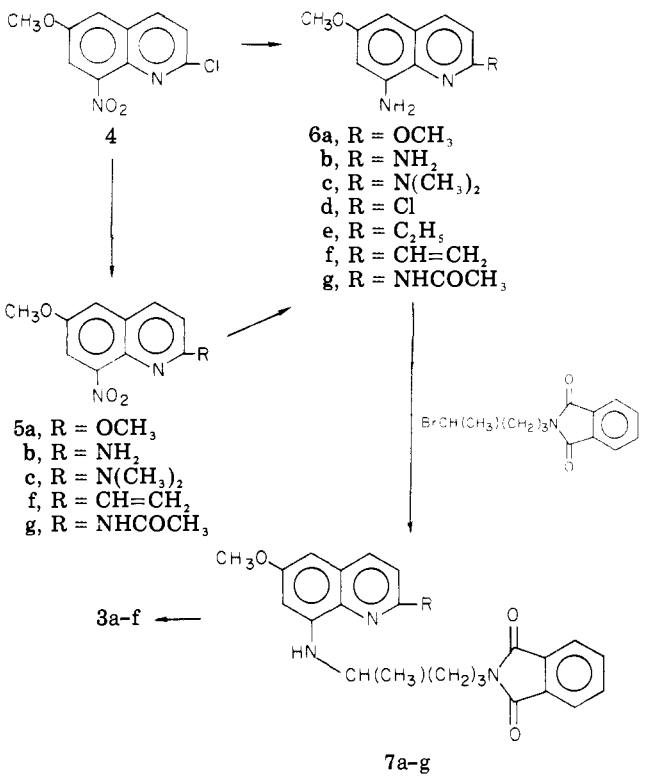
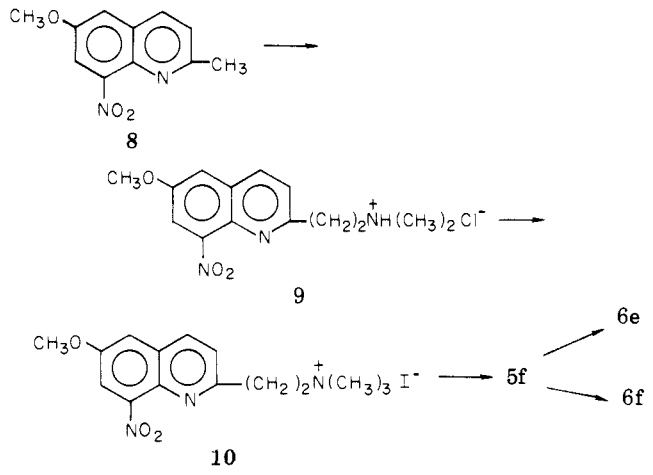
Scheme I



Scheme II

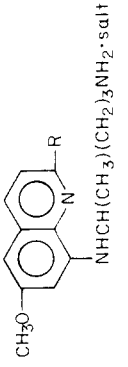


curative antimalarial activity against *Plasmodium cynomolgi* in the rhesus monkey.[15,16] These were found to be inactive.

In other antiprotozoan tests, the antileishmanial activity for **3a–f** was assessed against *Leishmania donovani* in hamsters by the well-established 8-day test method.[17,18] Of the group, **3e** demonstrated the most significant activity (Table I). Compound **3d** was examined for antitrypanosomal activity by the method of Rane[19] against *Trypanosoma rhodesiense* in mice, and it was found to be inactive. Similarly, in the primary screening method[20] employed to evaluate prophylactic activity against *Schistosoma mansoni* in mice, **3b** and **3e** were found to be inactive.

Although **3e** was "active" against *P. berghei* and did not demonstrate primaquine-like toxicity in the Rane test, the data for this series indicated that the possibilities of increasing antiprotozoan effectiveness are limited. The activity patterns of 2-substituted analogues, **3**, were not considered adequate to justify expanded testing or further

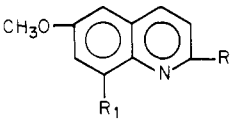
Table I. 2-Substituted Primaquine Analogues



compd	R	salt	mp, °C	% yield	formula	analyses[a]	ΔMST (days) after single sc mg/kg dose[b,c] 80	160	320	640	G[d,e]
3a	OCH_3	maleate	118–119[f]	64.0	$C_{20}H_{27}N_3O_6$	C, H, N	6.1	7.9 (1T)	(5T)	(5T)	2.4 (13)
3b	NH_2	maleate	168–170[g]	27.4	$C_{23}H_{30}N_4O_9$[h]	C, H, N					0.0
3c	$N(CH_3)_2$	fumarate	152–153[i]	20.8	$C_{21}H_{30}N_4O_5$	C, H, N	4.9	5.2 (1T)	(5T)	(5T)	*j*
3d	Cl	maleate	150–152[k]	44.0	$C_{19}H_{24}N_3O_5Cl$	C, H, N, Cl	1.2	3.0 (2T)	4.0 (2.T)	5.5 (3T)	0.3 (208)
3e	C_2H_5	maleate	111–114[i]	26.0	$C_{24}H_{29}N_3O_5$	C, H, N	6.7	8.3	9.9	13.9	10.0 (3.25)
3f	$CH=CH_2$	fumarate	143–145[l,m]	27.8	$C_{21}H_{27}N_3O_5$	C, H, N	2.9	3.3 (2T)	5.3 (2T)	7.9 (2T)	1.6 (52)
1	H	phosphate					9.4	10.8 (2T)	(5T)	(5T)	0.96

[a] Analyses are within ±0.4% of the theoretical value. [b] Activity against *P. berghei*. [c] Increase in mean survival time (MST) in days of the test group is reported. The mean survival time of untreated mice is 6.1 days. A compound is "active" if ΔMST exceeds 6.1 days. Animals that survive to 60 days postinfection are considered "cured" (C). Deaths from days 2 to 5 after drug administration are attributed to drug toxicity (T). [d] *G* = Glucantime index, see ref 18. [e] Data in parentheses represent dose. [f] 95% EtOH. [g] MeOH. [h] Analyzed as the dimaleate. [i] Et_2O–EtOH. [j] 99% inhibitor at 52 mg/kg/day. [k] $CHCl_3$. [l] THF–MeOH–Et_2O. [m] **3f** was also characterized as the maleate; mp 117–120 °C (Et_2O-EtOH).

Table II. Substituted Quinolines



compd	R	R_1	mp, °C	% yield	formula	analyses[a]
5a	OCH_3	NO_2	149-150	95[b,c]	$C_{11}H_{10}N_2O_4$	
5b	NH_2	NO_2	195-197	58[d]	$C_{10}H_9N_3O_3$	C, H, N
5c	$N(CH_3)_2$	NO_2	136-138	93.9[e]	$C_{12}H_{13}N_3O_3$	C, H, N
5f	$CH=CH_2$	NO_2	156-158	89[f]	$C_{12}H_{10}N_2O_3$	C, H, N
5g	$NHCOCH_3$	NO_2	298-301	90	$C_{12}H_{11}N_3O_3$	
6a	CH_3O	NH_2	137-138	97.7[e,g]	$C_{11}H_{12}N_2O_2$	
6b	NH_2	NH_2	203-205	37.3[b]	$C_{14}H_{15}N_3O_5$[h]	C, H, N
6c	$N(CH_3)_2$	NH_2	73-75	94[i]	$C_{12}H_{15}N_3O$	C, H, N
6d	Cl	NH_2	102-104.5	84[e]	$C_{10}H_9N_2OCl$	C, H, N, Cl
6e	C_2H_5	NH_2	239-241	56[f]	$C_{12}H_{15}N_2OBr$[j]	C, H, N
6f	$CH=CH_2$	NH_2	120-122	77[k]	$C_{12}H_{12}N_2O$	C, H, N
6g	$NHCOCH_3$	NH_2	192-194	78[e]	$C_{12}H_{13}N_3O_2$	C, H, N
9	$(CH_2)_2N^+H(CH_3)_2Cl^-$	NO_2	195-196	71[e]	$C_{14}H_{18}N_3O_3Cl$[l]	C, H, N
10	$(CH_2)_2N^+(CH_3)_3I^-$	NO_2	167-168	72[e]	$C_{15}H_{20}N_3O_3I$	C, H, N, I

[a] Analyses are within ±0.4% of the theoretical value. [b] MeOH. [c] Lit.[5] mp 149-150 °C. [d] Sublimed. [e] 95% EtOH. [f] EtOH-$CHCl_3$. [g] Lit.[5] mp 135-136 °C. [h] Analyzed as the maleate salt. [i] Hexane. [j] Analyzed as the HBr salt. [k] Hexane-EtOH. [l] Analyzed for 0.25 mol of H_2O.

extension of the present series.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga., and results were within ±0.4% of the calculated values unless otherwise noted. Satisfactory IR (Perkin-Elmer 467 grating spectrophotometer, KBr) and NMR (Hitachi Perkin-Elmer R20A high-resolution NMR spectrophotometer and Me_4Si as internal reference) spectra were obtained for all new compounds ($CDCl_3$, Me_2SO-d_6). TLC were performed on Eastman chromatogram sheets, type 6060 (silica gel).

2,6-Dimethoxy-8-nitroquinoline (5a). This compound was prepared in a one-step reaction rather than the two-step literature procedure.[5] To a solution of 4.6 g (0.2 mol) of sodium in 300 mL of absolute MeOH was added 28.8 g (0.12 mol) of 2-chloro-6-methoxy-8-nitroquinoline (4),[5] and the mixture was heated at reflux for 27 h under a nitrogen atmosphere. The mixture was poured into cold H_2O, stirred briefly, and filtered. The yellow solid was collected and dried.

2-Amino-6-methoxy-8-nitroquinoline (5b). The procedure of LaMontagne and co-workers[4b] was adapted. A mixture of 50.4 g (0.21 mol) of 4 and 490 g of phenol was heated at 170–180 °C for 1.5 h under an ammonia atmosphere. The mixture was cooled and treated with 50% NaOH solution. The yellow precipitate was collected and dried (34.8 g). The crude product, which was a mixture of **5b** and 6-methoxy-8-nitro-2-phenoxyquinoline, was treated with hot 30% HOAc and filtered. The filtrate was basified with NaOH solution and the yellow precipitate (**5b**) was collected and dried (mp 194–196 °C) for use directly in the next step. The analytical sample was obtained by sublimation.

2-Acetamido-8-amino-6-methoxyquinoline (6g). Compound **5b** was refluxed with Ac_2O for 3 h. The solvent was removed in vacuo and the residue washed thoroughly with 95% EtOH and water (90% yield of **5g**, mp 298–301 °C). A mixture of 10.5 g (0.04 mol) of crude **5g**, 14 g of iron filings, 2 mL of glacial HOAc, and 120 mL of H_2O was stirred on the steam bath for 18 h. The solid residue was filtered off and thoroughly washed with Me_2CO. The Me_2CO washings were concentrated and the residue was eluted through a short silica gel column with CH_2Cl_2. Evaporation of the solvent gave **6g**.

Compound **6c** was prepared similarly (Table II).

2-Dimethylamino-6-methoxy-8-nitroquinoline (5c). A mixture of 24 g (0.1 mol) of 4, 10 g of dimethylamine, 11 g of triethylamine, and 100 mL of DMF was heated at 70–80 °C for 12 h. (A dry ice–Me_2CO trap was placed on top of the H_2O condenser to reduce excessive loss of the dimethylamine.) After 12 h, 20 mL of dimethylamine was added through the condenser to the hot mixture and reflux was continued for another 4 h. The cooled mixture was poured into 1 L of cold H_2O, and the yellow-orange precipitate was collected.

2-(β-Dimethylaminoethyl)-6-methoxy-8-nitroquinoline Hydrochloride (9). A mixture of 75 g (0.344 mol) of 6-methoxy-2-methyl-8-nitroquinoline (**8**),[6] 28.1 g (0.344 mol) of dimethylamine hydrochloride, 11.4 g of paraformaldehyde, and 80 mL of EtOH was heated under reflux for 7 days. The cooled reaction mixture was diluted with Et_2O, and the solid was collected by filtration and recrystallized.

6-Methoxy-8-nitro-2-(β-trimethylaminoethyl)quinoline Iodide (10). Compound **9** (76 g, 0.24 mol) was mixed with 800 mL of 1 N NaOH, and the solution was extracted with Et_2O. The Et_2O extracts were washed with H_2O, dried (Na_2SO_4), and concentrated. The residue was dissolved in 75 mL of EtOH and treated with 34.2 g of MeI, and the mixture was heated under reflux for 0.5 h. The cooled mixture was diluted with Et_2O and the solid was collected by filtration.

6-Methoxy-8-nitro-2-vinylquinoline (5f). A mixture of 73.2 g (0.175 mol) of **10**, 1250 mL of 1 N NaOH, and 1250 mL of $CHCl_3$ was stirred mechanically at room temperature for 6 h. The $CHCl_3$ layer was separated, washed with H_2O, dried (Na_2SO_4), and concentrated.

8-Amino-2-ethyl-6-methoxyquinoline Hydrobromide (6e). To a mixture of 9.5 g (0.04 mol) of **5f**, 5 g of Raney nickel catalyst (wet weight, washed with EtOH, W. R. Grace no. 28), and 250 mL of toluene–95% EtOH (1:1) was added 25 mL of 85% hydrazine hydrate in portions. After the vigorous reaction was over, the mixture was heated under reflux for 5 h. The condenser was removed and the mixture was heated until the vapors were faintly alkaline (additional EtOH added). The mixture was cooled and filtered over Celite, and the filtrate was concentrated in vacuo. The oily residue was dissolved in anhydrous Et_2O and treated with HBr gas. The hydrobromide precipitated as a yellow powder.

6a and **6d**[10] were prepared similarly, but they were isolated as the free bases.

8-Amino-6-methoxy-2-vinylquinoline (6f). To a stirred and cooled mixture of 1.2 g of granular tin, 38.7 g of $SnCl_2 \cdot 2H_2O$, 80 mL of concentrated HCl, and 40 mL of EtOH was added to 10 g of **5f**, in portions such that the temperature never exceeded 10 °C. After the addition was completed, stirring was continued at 10 °C for 1 h and then at 25 °C for 2 h. The mixture was cooled and basified with 40% NaOH solution. The solution was extracted with CH_2Cl_2. The combined extracts were washed with H_2O, dried (Na_2SO_4), and concentrated. The residual oil was eluted through a short silica gel column with CH_2Cl_2 to give a yellow solid upon removal of the solvent.

General Preparation of 2-Substituted 6-Methoxy-8-(4-amino-1-methylbutylamino)quinolines 3. The preparation of 2,6-dimethoxy-8-(4-amino-1-methylbutylamino)quinoline maleate (**3a**) is presented as an example; the remaining derivatives of **3**

were obtained by essentially the same procedure (Table I).

A mixture of 12.3 g (0.06 mol) of **6a**, 17.8 g of (0.06 mol) of 4-bromo-1-phthalimidopentane, and 6.1 g (0.06 mol) of triethylamine was stirred and heated at 135 °C for 20 h. After 1 h, 6.1 g of triethylamine was added; after 6 h, 17.8 g of 4-bromo-1-phthalimidopentane and 6.1 g of triethylamine were added. The mixture was diluted with Et_2O, and the insoluble triethylamine hydrobromide was separated by filtration. The Et_2O filtrate was concentrated and the residue was heated under reflux for 3 h with 500 mL of 95% EtOH and 50 mL of 85% hydrazine hydrate. The EtOH was removed in vacuo, and the residual solid was stirred with 120 g of 50% KOH and Et_2O (200 mL) for about 0.5 h. The Et_2O layer was separated and the aqueous portion was extracted with Et_2O. The combined Et_2O extracts were washed with H_2O and saturated NaCl solution, dried (Na_2SO_4), and concentrated. The residual oil was redissolved in anhydrous Et_2O and treated with a solution of 9 g of maleic acid in MeOH. Dilution with anhydrous Et_2O precipitated the salt as a white powder, which was recrystallized.

Acknowledgment. We gratefully acknowledge the U.S. Army Medical Research and Development Command under Contract No. DADA 17-71-C-1068 for support of this work. This is Contribution No. 1497 from the Army Research Program on Malaria. The authors wish to thank Drs. E. A. Steck, R. E. Strube, and T. R. Sweeney of WRAIR for interest and suggestions during the course of this work.

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(10) We are indebted to Dr. W. P. Wetter for the preparation of intermediate **6d**.

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(13) The 2,8-diamino-6-methoxyquinoline (**6b**) isolated from the hydrazinolysis reaction was characterized as the maleate salt (Table II).

(14) Tests were carried out by the Rane Laboratory, University of Miami, Miami, Fla., using blood-induced *P. berghei* infected mice (five animals per group) in the method described by Osdene and co-workers.[4] Test data were supplied by Drs. T. R. Sweeney, E. A. Steck, and R. E. Strube of the Walter Reed Army Institute of Research.

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(20) Tests were carried out by the Walter Reed Army Institute of Research Laboratory in Brasilia, Brazil. Routinely, five mice are given a single subcutaneous dose (1280 mg/kg) of the drug in peanut oil 2 days after being infected with *S. mansoni* cercariae by tail immersion for 30 min. A compound is active if mice survive to 49 days (mean survival time for untreated animal is 24 days), at which time they are sacrificed and examined for worms.