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

NH(CH₂),CO-His-Trp-Ser-Tyr-D-Ala-Leu-Arg-Pro-Gly cyclic [\beta-Ala1,D-Ala6,Gly10]-LH-RH

NH(CH₂),CO-His-Trp-Ser-Tyr-D-Ala-Leu-Arg-Pro-Gly cyclic [6-aminohexanoic acid¹,D-Ala⁶,Gly¹⁰]-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.

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Synthesis of 2-Substituted Primaguine Analogues as Potential Antimalarials

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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



radical curative and causal prophylactic antimalarial agent. Our earlier studies² 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, phenolammonia, 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 acid⁶ 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 hydrate⁹ gave 6e. Compounds 6a and 6d¹⁰ (prepared directly from 4) were also obtained by Raney nickelhydrazine 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 7gand 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

Scheme I





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 Rane¹⁹ against Trypanosoma rhodesiense in mice, and it was found to be inactive. Similarly, in the primary screening method²⁰ 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

					NHCH(C	CH ₃)(CH ₂) ₃ NH ₂ ·sα	i† ∆MS	ST (days) after	single sc mg/k	g dose ^{b,c}	
compd	R	salt	mp, °C	% yield	formula	analyses ^a	80	160	320	640	$G^{d,e}$
3a	OCH,	maleate	118-119 ^f	64.0	C ₂₀ H ₂₇ N ₃ O ₆	C, H, N	6.1	7.9 (1T)	(5T)	(5T)	2.4(13)
3b	\mathbf{NH}_2	maleate	168-170	27.4	C ₂₃ H ₃₀ N ₄ O ₉ "	С, н, N					0.0
3c	N(CH ₃),	fumarate	152 - 153'	20.8	$C_{21}H_{30}N_4O_5$	С, Н, N	4.9	5.2(11)	(1.9)	(.1.9)	1
3d	с С	maleate	$150-152^{k}$	44.0	C, H, N, O, CI	C, H, N, CI	1.2	3.0(2T)	4.0(2.T)	5.5 (3T)	0.3(208)
3e	C.H.	maleate	$111 - 114^{i}$	26.0	C,,H,NO	C, H, N	6.7	8.3	9.9	13.9	10.0(3.25)
3f	CH=CH.	fumarate	$143-145^{l,m}$	27.8	C"H"NO	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
¹ Analyse rvival tim	s are within ≟ e of untreate	0.4% of the theo d mice is 6.1 day	oretical value. b /s. A compound	Activity aga is "active" i	inst <i>P. berghei.</i> c f Δ MST exceeds 6	Increase in mean .1 days. Animal	t survival t is that sur	ime (MST) in c vive to 60 days	lays of the test postinfection	group is repor are considered	ted. The mean "cured" (C). $f_{OEC} = f_{OEC}$
who from		after during a dual	states and see of the	Thirted to dry			JUDAY SPE				1 0/07 - do

2-Substituted Primaquine Analogues

Table I.

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^m 3f was also characterized as the maleate; mp Deaths from days 2 to 5 after drug administration are attributed to drug toxicity (1). To = Cucantum index, see ref 10. # MeOH. ^h Analyzed as the dimaleate. ^t Et₂O-EtOH. ^j 99% inhibitor at 52 mg/kg/day. ^k CHCl₃. ^l THF-MeOH-Et₂O. 117-120 °C (Et₂O-EtOH). De g] su

				L		
compd	R	\mathbf{R}_{i}	mp, °C	% yield	formula	analyses ^a
5a 5b 5c 5f 5g	OCH ₃ NH ₂ N(CH ₃) ₂ CH=CH ₂ NHCOCH ₃	NO ₂ NO ₂ NO ₂ NO ₂ NO ₂	$149-150 \\ 195-197 \\ 136-138 \\ 156-158 \\ 298-301 \\ 1000000000000000000000000000000000$	950,0 58 ^d 93.9 ^e 89 ^f 90	$C_{11}H_{10}N_{2}O_{4}$ $C_{10}H_{9}N_{3}O_{3}$ $C_{12}H_{13}N_{3}O_{3}$ $C_{12}H_{10}N_{2}O_{3}$ $C_{12}H_{10}N_{2}O_{3}$	C, H, N C, H, N C, H, N
6a 6b 6c 6d 6e 6f	$CH_{3}O$ NH_{2} $N(CH_{3})_{2}$ Cl $C_{2}H_{3}$ $CH=CH_{2}$	NH ₂ NH ₂ NH ₂ NH ₂ NH ₂ NH ₂	$137-138 \\ 203-205 \\ 73-75 \\ 102-104.5 \\ 239-241 \\ 120-122$	$97.7^{e,s}$ 37.3^{b} 94^{i} 84^{e} 56^{f} 77^{k}	C ₁₁ H ₁₂ N ₂ O ₂ C ₁₄ H ₁₅ N ₃ O ₅ ^h C ₁₂ H ₁₅ N ₃ O C ₁₀ H ₂ N ₂ OCI C ₁₂ H ₁₅ N ₂ OBr ⁱ C ₁₂ H ₁₅ N ₂ OBr ⁱ	C, H, N C, H, N C, H, N, Cl C, H, N C, H, N
6g 9 10	$\begin{array}{c} \text{NHCOCH}_3\\ (\text{CH}_2)_2\text{N}^+\text{H}(\text{CH}_3)_2\text{Cl}^-\\ (\text{CH}_2)_2\text{N}^+(\text{CH}_3)_3\text{I}^- \end{array}$	NH ₂ NO ₂ NO ₂	192-194 195-196 167-168	78 ^e 71 ^e 72 ^e	$\begin{array}{c} C_{12}H_{13}N_{3}O_{2}\\ C_{14}H_{18}N_{3}O_{3}Cl^{l}\\ C_{15}H_{20}N_{3}O_{3}I \end{array}$	C, H, N C, H, N C, H, N, I

CH_20-

^a Analyses are within ±0.4% of the theoretical value. ^b MeOH. ^c Lit.^s mp 149-150 °C. ^d Sublimed. ^e 95% EtOH. ^f EtOH-CHCl₃. ^g Lit.^s 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 H₂O.

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 $\pm 0.4\%$ 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 Me₄Si as internal reference) spectra were obtained for all new compounds (CDCl₃, Me₂SO-d₆). 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 H₂O was stirred on the steam bath for 18 h. The solid residue was filtered off and thoroughly washed with Me₂CO. The Me₂CO washings were concentrated and the residue was eluted through a short silica gel column with CH₂Cl₂. 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-Me₂CO 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- $(\beta$ -**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 Et₂O, 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 Et₂O. The Et₂O extracts were washed with H₂O, dried (Na₂SO₄), 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 Et₂O 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 Et₂O 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 $SnCl_2:2H_2O$, 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 (Na₂SO₄), 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-(4amino-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 4bromo-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 Et₂O 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 Et₂O (200 mL) for about 0.5 h. The Et₂O 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 (Na₂SO₄), and concentrated. The residual oil was redissolved in anhydrous Et₂O and treated with a solution of 9 g of maleic acid in MeOH. Dilution with anhydrous Et₂O precipitated the salt as a white powder, which was recrystallized.

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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.