Table I. Antiarthritic Activity and Plasma Au Concentration

Compd	Expt	Dose, mg/kg/day (calcd as Au)	Vehicle[a]	Hindleg vol, % redn from adj control[b]			Serum Au, μg/ml
				Injected leg		Uninjected leg,	
				Day 3	Day 16	Day 16	
1	1	18 po	T	24[f]	32[f]	52[f]	4.9
	5	15 im	B	16[f]	23[f]	19[e]	13.7
3	2	5 po	T	[c]	7[d]	[c]	1.2
	1	18 po	T	11[f]	14[e]	[c]	2.2
	2	20 po	T	[c]	[c]	[c]	2.3
	1	27 po	T	10[e]	[c]	[c]	3.5
	3	40 po	T	26[f]	25[f]	28[f]	4.8
	1	40 po	T	19[f]	14[e]	17[d]	4.0
	1	60 po	T	21[f]	37[e]	42[e]	6.7
5	4	20 po	T	[c]	[c]	[c]	0.0
8	4	20 po	T	[c]	[c]	[c]	0.0
	5	15 im	P	[c]	[c]	[c]	1.5
9	4	20 po	T	[c]	[c]	[c]	0.0
	5	11 im	P	[c]	[c]	[c]	3.1
10[g]	1	20 po	T	33[f]	40[f]	41[f]	
	2	20 po	T	26[f]	29[f]	41[f]	
	3	20 po	T	28[f]	33[f]	45[f]	
	4	20 po	T	30[f]	33[f]	34[f]	
	5	20 po	T	33[f]	41[f]	43[f]	

[a] T, tragacanth; B, benzyl alcohol; P, polyethylene glycol. [b] Per cent reduction from adjuvant control = (hindleg volume of untreated adjuvant control rat − hindleg volume of drug-treated rat)/hindleg volume of untreated adjuvant control rat. [c] No significant reduction in paw volume. [d] $0.01 < p < 0.05$. [e] $0.001 < p < 0.01$. [f] $p < 0.001$. [g] Prednisolone.

spectra were obtained on a Varian T-60 instrument (Me_4Si). Analyses are indicated by the symbols of the elements and were within 0.4% of the theoretical values. Diethyl(2-thioethyl)phosphine was obtained from Edward Lanpher, Orgmet, Inc., Haverhill, Mass.

Di-μ-(diethylphosphinoethylthio)-digold (3). To a solution of 8.50 g (0.0565 mol) of diethyl(2-thioethyl)phosphine[2] in 40 ml of EtOH was added a solution of 2.26 g (0.0565 mol) of NaOH in 40 ml of 50% H_2O–EtOH, followed by a solution of 19.8 g (0.056 mol) of chloro(triethylphosphine)gold in 60 ml of a $CHCl_3$–EtOH (2:1) solution. After stirring for 1 hr, the filtered solution was evaporated to dryness and the residue extracted with about 200 ml of $CHCl_3$. The dried $CHCl_3$ was concentrated under vacuum to give a yellow oil which crystallized on cooling. The solid was washed with Et_2O and then recrystallized from MeOH to give 15.2 g (77.0%) of white crystals: mp 136–138°; mass spectrum, molecular ion at m/e 692 containing two atoms of sulfur; osmometric molecular weight ($CHCl_3$) calcd 692.4, found 723.7; nmr ($CDCl_3$) δ 1.20 (complex multiplet, 12 H, CH_3), 2.10 (complex multiplet, 12 H, CH_2P), 3.37 (doublet of triplets, 4 H, J = 21, 6 Hz, CH_2S). *Anal.* ($C_{12}H_{28}Au_2P_2S_2$) C, H, P.

Poly-μ-[1,2-bis(diphenylphosphinoethane)]-μ-(1,2-ethanedithio)-digold (5). A solution of 2.16 g (2.5 mmol) of μ-[1,2-bis(diphenylphosphine)ethane]-bis(chlorogold)[3] in 25 ml of CH_2Cl_2 was added in two portions to a solution of 0.24 g (2.5 mmol) of 1,2-ethanedithiol in 30 ml of H_2O–EtOH (2:1) containing 0.20 g (5 mmol) of NaOH. A white solid formed after all the reagents were added. The mixture was stirred under N_2 for 45 min and filtered, and the white solid was washed with $CHCl_3$. Drying gave 1.50 g (68%) of a solid, mp 219–221°, which was practically insoluble in all the common solvents tried for recrystallization: mass spectrum, ion of highest mol wt, m/e 462, containing two atoms of sulfur by isotope measurements. *Anal.* ($C_{28}H_{28}Au_2P_2S_2$) C, H, P.

Di-μ-(N,N-di-n-propyldithiocarbamato)-digold (8). The literature[4] procedure gave **8**, mp 219–220°, in 64% yield: mass spectrum, molecular ion at m/e 746. *Anal.* ($C_{14}H_{28}Au_2N_2S_4$) C, H, N.

Di-μ-(ethyl xanthate)-digold (9). AuCl was prepared by adding 1.22 g (0.01 mol) of thiodiglycol in 20 ml of H_2O to a solution of 1.97 g (0.005 mol) of $HAuCl_4$ in 50 ml of saturated aqueous NaCl. Potassium ethyl xanthate (0.80 g, 0.005 mol), dissolved in 20 ml of MeOH, was added to give a yellow solid which was collected by filtration and washed with H_2O and MeOH. Soxhlet extraction with CS_2 gave 0.75 g (47%) of a yellow solid: mp 168–170°; mass spectrum, molecular ion at m/e 636. *Anal.* ($C_6H_{10}Au_2O_2S_4$) C, H, S.

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Synthesis and Biological Properties of [2-L-β-(Pyrazolyl-3)alanine]-Luteinizing Hormone-Releasing Hormone

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The replacement of the imidazole moiety by the isosteric pyrazole ring system in peptides that contain histidine has become a useful means of evaluating the role played by that amino acid in determining biological activity. Thus, β-(pyrazolyl-3)alanine has been substituted for histidine in the RNase S peptide[1] resulting in a material which binds competitively and strongly with the S protein to give a complex which is, however, devoid of enzymatic activity. Substitution of the amino acid for the histidine residues in angiotensin II,[2] β-corticotropin,[3,4] and thyrotropin-releasing hormone[5] gave compounds which retained appreciable hormonal activity.

In view of the apparent importance of the histidine residue of LH-RH in maintaining high levels of biological po-

† This note is dedicated to Alfred Burger in recognition of his many significant contributions to medicinal chemistry.

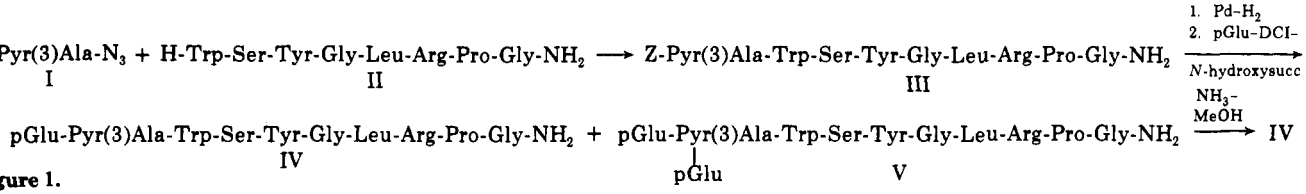

Figure 1.

Table I. LH-RH Activity of [Pyr(3)Ala^2]-LH-RH in Ovariectomized, Estrogen–Progesterone Treated Rats

Sample	Dose, ng/rat[a]	Mean LH, ng/ml ± S.E.	Potency (%) with 95% confidence limits
Saline		4.3 ± 0.8	
Natural	0.5	11.5 ± 1.6	100
LH-RH	2.5	33.3 ± 1.8	
[Pyr(3)Ala^2]-	20	40.8 ± 6.1	19 (8–99)
LH-RH	100	80.6 ± 11.8	

[a] Four rats per group.

tency, it was of interest to synthesize and assay the (pyrazolyl-3)alanine analog.

Synthesis. The principal precursors in the synthetic route outlined in Figure 1 were the LH-RH C-terminal octapeptide (II), which was synthesized by a version of the solid-phase method which has been described previously,[6,7] and N^{α}-benzyloxycarbonyl-β-(pyrazolyl-3)alanine hydrazide, a derivative prepared from the parent amino acid. The hydrazide, upon conversion to the azide (I), was coupled to the octapeptide to give the benzyloxycarbonyl nonapeptide (III). After removal of the protecting group by hydrogenolysis, a 2:1 excess of pyroglutamic acid was coupled to the nonapeptide in the presence of DCI and *N*-hydroxysuccinimide.[8] Thin-layer chromatography of the reaction mixture revealed the unexpected presence of roughly equal amounts of two products which could not be separated by normal column chromatographic techniques. Amino acid analysis of this mixture showed correct ratios for all residues other than glutamic acid which was present in a 1.5 molar excess. In view of the normal 1:1 adduct formed between pGlu and the LH-RH C-terminal nonapeptide under similar conditions,[9] it was concluded that, in this case, some coupling had occurred between pGlu and the pyrazole NH group resulting in a mixture of peptides IV and V. Since many *N*-imidazole-substituted groups are readily removed under basic conditions, it seemed probable that the *N*-pyrazole-substituted pGlu might also be sufficiently labile to be cleaved by treatment with ammonia in methanol. Monitoring of the reaction mixture by tlc indicated rapid conversion of one of the components to the other within a few hours. Ion-exchange chromatography of the reaction products gave the required, homogeneous [Pyr(3)Ala^2]-LH-RH (IV).

Biological Results. The LH-RH activity of [Pyr(3)Ala^2]-LH-RH (Table I) was determined *in vivo* by the stimulation of LH release at two dose levels of 20 and 100 ng administered to ovariectomized rats (four per group) pretreated with estrogen and progesterone, followed by radioimmunoassay[10] for LH. The serum LH contents were compared with those found after administration of controls with saline and 0.5 and 2.5 ng doses of LH-RH isolated from natural sources.

The biological potency of the analog was calculated to be a rather high 19% which clearly demonstrated that the properties peculiar to the imidazole ring of histidine are not essential for triggering of LH release to take place. This conclusion is supported by recent data accumulated from modifications of position 2. Deletion[11] and also replacement of histidine with amino acids having nonfunctional[12,13] or even functional[13] side chains that are not aromatic in character result in peptides which are almost devoid of activity; however, incorporation[13] of phenylalanine in this position gives a peptide which is 1–2% active. Thus, aromaticity is of some importance in promoting LH release. Tryptophan[14] placed in position 2 results in a very high 40% retention of potency, presumably as a result of the combined effects of the ring systems and the slightly basic indole amine group. One can conclude that as long as aromatic side chains having some degree of basicity are present in position 2, then significant intrinsic levels of activity will remain.

Experimental Section

Amino acid derivatives, unless otherwise stated, were purchased from Bachem, Inc., Marina del Rey, Calif. Microchemical analyses were performed by PCR, Inc., Gainesville, Fla., on samples which were dried *in vacuo* over P_2O_5. Amino acid analyses were carried out on samples which were hydrolyzed (18 hr) in 6 *M* HCl containing 4% thioglycolic acid.[15] Solid-phase reactions took place in a Beckman 990 peptide synthesizer. The following tlc systems were employed: R_f^1, *n*-BuOH–AcOH–H_2O (4:1:5, upper phase); R_f^2, *n*-BuOH–EtOAc–AcOH–H_2O (1:1:1:1); R_f^3, EtOAc–Pyr–AcOH–H_2O (5:5:1:3). Sample sizes of *ca.* 20 μg were spotted on Brinkmann precoated layers and solvent fronts allowed to travel 10–15 cm.

H-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH$_2$ (II). *tert*-Butyloxycarbonyl-protected amino acids (3.0 mmol) were coupled successively in the presence of DCI (3.0 mmol) to a 2% cross-linked divinylbenzene-glycine resin (2.94 g, 1.0 mmol of glycine) by previously described[6,7] procedures. *tert*-Butyloxycarbonyl-protecting groups were eliminated at each coupling stage by treatment with 1 *M* HCl in AcOH, the functional side chains of serine and tyrosine being protected with benzyl groups and arginine by a tosyl group. The dried octapeptide-resin weighed 3.93 g (110% based on initial glycine content of resin). This material was suspended in dry MeOH (100 ml); the mixture was saturated with dry ammonia at 0° and allowed to stir for 18 hr at room temperature in a tightly stoppered flask. Ammonia was partially removed at the water pump, the mixture filtered, and the resin cake extracted with DMF (three 15-ml portions). Methanol was distilled from the filtrates *in vacuo* and the protected peptide precipitated by the addition of EtOAc. The white powder (907 mg) exhibitied a single spot to Ehrlich reagent, ninhydrin, and I_2 vapor: R_f^1 (silica) 0.63; amino acid analysis gave Trp 1.00, NH_3 1.21, Arg 1.05, Ser 0.74, Pro 1.02, Gly 2.09, Leu 1.00, Tyr 0.95. *Anal.* ($C_{65}H_{80}N_{13}O_{12}S$) C, H, N.

The protected peptide (200 mg), anisole (3.5 ml), and HF (20 ml) were stirred at 0° for 45 min. After rapid removal of the excess HF *in vacuo*, the sticky peptide was extracted into 0.1 *M* AcOH (50 ml) and the solution washed with EtOAc (three 15-ml portions). Lyophilization of the aqueous layer gave a white powder which was chromatographed on a column (2.7 × 91 cm) of Sephadex G-25 in 0.2 *M* AcOH. Fractions between 480 and 580 ml were collected and lyophilized to give the required octapeptide II (80 mg, 54%): $[\alpha]^{28}D$ −32° (*c* 1.00, 0.1 *M* AcOH) [lit.[16] $[\alpha]^{28}D$ −36.1° (*c* 1.0, 1 *M* AcOH)]; single spot to Ehrlich reagent, ninhydrin, and I_2 vapor; R_f^1 (cellulose) 0.59; R_f^2 (silica) 0.53; R_f^3 (silica) 0.77; amino acid analysis gave Trp 0.97, NH_3 1.21, Arg 1.00, Ser 0.83, Pro 1.01, Gly 2.10, Leu 1.00, Tyr 0.96.

N^{α}-Benzyloxycarbonyl-β-(pyrazolyl-3)alanine Hydrazide. (Pyrazolyl-3)alanine methyl ester dihydrochloride monohydrate[1] (0.316 g) and triethylamine (0.40 ml) were stirred at 0° in chloroform (4 ml). To the mixture were added benzyloxycarbonyl chloride (0.14 ml) and triethylamine (0.18 ml). After 5 min, a further aliquot of benzyloxycarbonyl chloride (0.14 ml) was added and the mixture stirred for 30 min at room temperature. The solution was washed with water (three 5-ml portions) and evaporated to

dryness. The residue was dissolved in ethanol (1 ml) and hydrazine hydrate (0.16 ml) was added. After stirring for 12 hr the solvents were removed *in vacuo* and ether was added to the oily residue to produce a white, semisolid material. Tlc of this showed two widely separated, hydrazide reagent positive components, the slowest moving of which was ninhydrin positive and believed to be Pyr(3)Ala hydrazide. The components were readily resolved by elution on a column (1.4 × 25 cm) of silica gel with 15% methanol in chloroform. The amorphous derivative (145 mg, 37%), mp 96–98°, $[\alpha]^{27}D$ − 11.8° (*c* 0.75, MeOH) [lit.[17] $[\alpha]^{23}D$ −10.6° (*c* 2.42, 80% DMF)] showed one spot to hydrazide reagent and I_2 vapor: R_f^1 (silica) 0.55. *Anal.* ($C_{14}H_{17}N_5O_3$) C, H, N.

Z-Pyr(3)Ala-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2 (III). Benzyloxycarbonyl(pyrazolyl-3)alanine hydrazide (54 mg) was dissolved in DMF (1 ml) and cooled to −20°. Isoamyl nitrite (25 μl) and 5.9 *M* HCl in dioxane (100 μl) were then added and the mixture was stirred for 10 min followed by neutralization with triethylamine (70 μl). An ice-cold solution of the octapeptide II (80 mg) and triethylamine (12 μl) in DMF (200 μl) was added to the above mixture and stirring was continued for 30 min at −20°, 1 hr at −10°, and 24 hr at room temperature. The DMF was removed *in vacuo* whereupon tlc of the reaction mixture showed virtually complete conversion. The material was applied on a small column (1.3 × 37 cm) of CM-cellulose equilibrated with 0.002 *M* NH_4Ac buffer at pH 4.6. A pH and concentration gradient was begun immediately by introducing 0.1 *M* NH_4Ac through a 100-ml mixing flask containing starting buffer. The nonapeptide was located in fractions between 175 and 215 ml by measurement of OD at 280 nm. Lyophilization to constant weight yielded peptide III (58 mg, 57%): $[\alpha]^{28}D$ −46° (*c* 1.0, 0.1 *M* AcOH); single spot to Ehrlich reagent and I_2 vapor; R_f^1 (silica) 0.29; amino acid analysis gave Trp 0.93, NH_3 1.21, Arg 0.98, Ser 0.79, Pro 1.00, Gly 2.00, Leu 1.00, Tyr 0.90, Pyr(3)Ala 0.99.

pGlu-Pyr(3)Ala-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2 (IV). The benzyloxycarbonyl nonapeptide III (38 mg) was hydrogenated for 5 hr in 0.1 *M* AcOH (3 ml) over Pd black to give an almost quantitative yield of the free nonapeptide. This exhibited a single spot to Ehrlich reagent, ninhydrin, and I_2 vapor: R_f^1 (silica) 0.15; amino acid analysis gave Trp 0.99, NH_3 1.10, Arg 0.93, Ser 0.81, Pro 0.99, Gly 2.02, Leu 1.03, Tyr 0.89, Pyr(3)Ala 1.00; amino acid ratios in a leucine aminopeptidase digest are Trp 0.96, Arg not found, Gly 1.12, Pyr(3)Ala 1.01, Leu 1.05, Tyr 0.97.

The nonapeptide (28 mg) and pyroglutamic acid (8.1 mg) were dissolved in DMF (1 ml). *N*-Hydroxysuccinimide (7.2 mg) followed by DCI (14 mg) were added to the solution which was stirred (18 hr). Removal *in vacuo* of the DMF and purification of the mixture on CM-cellulose under the conditions described gave a symmetrical peak eluting between 325 and 335 ml. Tlc of an aliquot of this material (27 mg) gave a pattern of two spots of almost equal intensity and R_f when visualized with Ehrlich reagent and I_2 vapor: R_f^1 (silica) 0.14 and 0.17; amino acid analysis gave Trp 0.95, NH_3 1.13, Arg 1.01, Ser 0.81, Glu 1.50, Pro 0.97, Gly 1.98, Leu 1.03, Tyr 0.97, Pyr(3)Ala 0.99.

The mixture (26 mg) was then dissolved in DMF (0.5 ml) and 0.5 ml of methanol saturated with ammonia was added. After stirring for 5 hr, volatile components were removed *in vacuo* and and the products remaining were chromatographed on CM-cellulose. Lyophilization of fractions containing peptide to constant weight yielded [Pyr(3)Ala^2]-LH-RH (IV) (21 mg): $[\alpha]^{27}D$ −59° (*c* 0.81, 0.1 *M* AcOH); single spot to Ehrlich reagent and I_2 vapor; R_f^1 (silica) 0.16; R_f^1 (cellulose) 0.66; R_f^2 (silica) 0.55; R_f^3 (silica) 0.79; amino acid analysis gave Trp 1.00, NH_3 1.20, Arg 0.98, Ser 0.81, Glu 0.98, Pro 1.01, Gly 2.00, Leu 1.03, Tyr 0.92, Pyr(3)Ala 1.02.

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Potential Antileprotic Agents. 1. Inhibition of a Model Mycobacterial System by Diaryl Sulfones

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The development of a new antileprotic agent poses particular problems in view of the fact that the etiologic agent of human leprosy, *Mycobacterium leprae*, cannot be cultured in bacteriologic media. However, a correlation has been observed between minimum inhibitory concentrations (MIC) for *Mycobacterium* species 607, determined *in vitro*, and dietary MIC's for *M. leprae* growing in the mouse footpad.[1,2] Clinical therapeutic practice in the treatment of leprosy is largely dependent on the use of 4,4′-diaminodiphenyl sulfone (DDS)[3] or hydrolyzable derivatives.[4] In an effort to establish the structure–activity requirements of diaryl sulfones relative to our mycobacterial model system we have prepared a series of DDS analogs and evaluated them as growth inhibitors of *M.* sp. 607.

From the data presented in Table I it can be seen that DDS is superior to the other analogs. This result was not unexpected in view of the findings of previous investigators primarily obtained with tuberculin assay media.[5] The activity of the *N*-formyl and *N*-acetyl derivatives of DDS is probably attributable to hydrolysis back to DDS. However, the action of the 4-amino-4′-hydroxy analog is quite interesting. It is possibly caused by similarity of steric and electronic parameters when compared with DDS and would be reflected in active site binding or transport properties. The decrease of activity in the methyl ether suggests a steric interference with binding or blockage of active transport, since electronic properties would approximate the hydroxy compound. Tests conducted against *M. leprae* in the mouse footpad assay‡ show the hydroxy

† This note is dedicated to Alfred Burger in recognition of his many significant contributions to medicinal chemistry.

‡ Dr. L. Levy, U. S. Public Health Service Hospital, San Francisco, private communication.