into ice-water and extracted with Et_2O. The Et_2O solution was dried ($MgSO_4$) and evaporated to afford **12** (0.44 g) as a solid: mp 69–70 °C (95%); IR ($CHCl_3$) 3470, 1730, 1640, 1590 cm^{-1}; NMR ($CDCl_3$) 0.85 (t, 3 H, J = 6 Hz, CH_3), 3.65 (s, 3 H, $-COOCH_3$), 6.55 (d, 1 H, J = 16 Hz, -CH=CHCO), 7.70 (d, 1 H, J = 16 Hz, -CH=CHCO), 8.82 ppm (s, 1 H, NH). Anal. ($C_{24}H_{33}NO_3$) C, H, N.

Methyl 2-(*trans*-3-Hydroxy-1-octenyl)-3-indoleheptanoate (13). To a solution of **12** (0.3 g, 0.78 mmol) in MeOH (20 mL) solid $NaBH_4$ (0.1 g, 2.6 mmol) was added portionwise at 0 °C. After 1 h the mixture was diluted with water and extracted with Et_2O. Usual workup gave **13** (0.25 g) as an oil after chromatographic purification on silica gel (eluent: petroleum ether–Et_2O, 3:1) (83%): IR ($CHCl_3$) 3480, 3400–3350, 1730, 1610 cm^{-1}; NMR ($CDCl_3$) 0.85 (t, 3 H, J = 6 Hz, CH_3), 3.65 (s, 3 H, $-COOCH_3$), 4.1–4.5 (br, 1 H, CHOH), 5.95 (dd, 1 H, J = 16 Hz, J = 7 Hz, -CH=CHCHOH), 6.65 (d, 1 H, J = 16 Hz, -CH=CHCHOH), 8.60 ppm (br, 1 H, NH).

2-(*trans*-3-Hydroxy-1-octenyl)-3-indoleheptanoic Acid (1). The hydroxy ester **13** (0.2 g, 0.52 mmol) in MeOH (16 mL) was refluxed with 16 mL of an aqueous 10% solution of K_2CO_3 for 2 h. The solution was concentrated in vacuo, diluted with water, and acidified with 2 N HCl. The precipitated solid was collected by filtration and crystallized from Et_2O to yield 0.14 g of **1**: mp 106–107 °C (73.7%); IR ($CHCl_3$) 3480, 1710, 1610 cm^{-1}; NMR ($CDCl_3$) 0.87 (t, 3 H, J = 6 Hz, CH_3), 4.25 (m, 1 H, CHOH), 6.02 (dd, 1 H, J = 16 Hz, J = 7 Hz, -CH=CHCHOH), 6.60 (d, 1 H, J = 16 Hz, -CH=CHCHOH), 8.97 ppm (br, 1 H, NH). Anal. ($C_{23}H_{33}NO_3$) C, H, N.

Bioassay. The rat stomach fundus strip was suspended in an organ bath (4 mL) at 36 °C in Krebs solution gassed with 95% O_2 and 5% CO_2 containing 3×10^{-9} mol/L of cyproheptadine as antagonist of 5-hydroxytryptamine and histamine and 2.8×10^{-6} mol/L of indomethacin as endogenous PGs synthesis inhibitor. Drug or PGE_1 standards were added to the bathing solution as soon as the preparation reached a constant tone. Contractions were recorded on a smoked kymograph paper using an auxotonic lever with a 1 × 20 magnification. The baseline load was 1 g, maximal 3 g. The dose cycle was 10 min, with a contact time of 90 s.

The terminal ileum was set up in a 3-mL bath in oxygenated Tyrode solution at 30 °C, containing 3×10^{-9} mol/L of cyproheptadine. The assay was done at 5-min intervals, with a contact time of 30 s. Contractions were recorded with an isotonic lever with a 1 × 20 magnification, writing on a smoked drum. Tissues were loaded at 0.4–0.7 g.

The amount of PGE_1-like activity of analogue **1** was obtained by bracketing its response between those of two known doses of PGE_1 standards. Compound **1** and PGE_1 standards were dissolved in ethanol, diluted in Krebs or Tyrode solution, and added to the organ baths in a volume of 0.1 mL to give the following final concentrations: compound **1**, $2.70–13.5 \times 10^{-7}$ mol/L, and PGE_1 standards, $0.70–14.0 \times 10^{-9}$ mol/L, in the rat fundus bath; and compound **1**, $3.6–17.9 \times 10^{-7}$ mol/L, and PGE_1 standards, $0.94–18.8 \times 10^{-9}$ mol/L, in the guinea-pig ileum bath.

The log dose–response curve for PGE_1 was linear for both the smooth muscles in the tested concentration range. According to Tolman et al.,[9] antagonist activity of compound **1** was determined by comparing the magnitude of rat fundus strip contractions induced by 11.3×10^{-9} mol/L of PGE_1, in the presence and in the absence of different concentrations of the indole analogue ($2.15–21.5 \times 10^{-6}$ mol/L). The approximate IC_{50} was obtained from the concentration–response curve of analogue **1** as an inhibitor of PGE_1-induced rat fundus strip contractions in four separate preparations.

Rat Liver Homogenate Prostaglandin Assay. Adenylate cyclase activity of rat liver homogenates was assayed by an indirect method[10] measuring the cAMP produced by transformation of ATP under catalysis of the enzyme.

Rat liver homogenates were incubated for 10 min at 37 °C in a medium containing (mol/L) ATP, 4×10^{-3}; $MgSO_4 \cdot 7H_2O$, 15×10^{-3}; Tris-HCl, 0.1 (pH 8.0); GTP, 5×10^{-4}; EGTA, 1×10^{-4}; theophylline, 5×10^{-3}; PGE_1, 2.8×10^{-5}; compound **1**, $6.7–13.4 \times 10^{-3}$; and NaCl, 0.9% for blanks. The final volume was 0.4 mL.

The reaction was terminated by immersing the tubes in boiling water for 2 min. Tubes were frozen at −20 °C. After thawing, samples were centrifuged at 1200g for 10 min and the supernatants assayed for cAMP according to the method of Brown et al.[11] The experiment was replicated four times. Proteins were measured according to the method of Lowry et al.[12]

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Synthesis and Xanthine Oxidase Inhibitory Analysis of 1*H*-Pyrrolo[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (3,7-Dideazaxanthine) and Two of Its Derivatives

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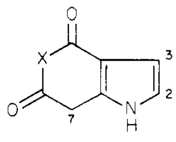
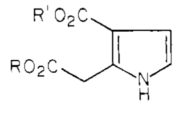
The synthesis of 1*H*-pyrrolo[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (3,7-dideazaxanthine) (**1**), 5-methyl-1*H*-pyrrolo-[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (1-methyl-3,7-dideazaxanthine) (**2**), and 1,7-dihydropyrano[4,3-*b*]pyrrole-4,6-dione (1-oxa-1,3,7-trideazaxanthine) (**3**) has been accomplished from 3-alkoxycarbonylpyrrole-2-acetates (**4**, **11**, and **12** for **1** and **2**) and from 3-carboxypyrrole-2-acetic acid (**6** for **3**). Compounds **1** and **2** have been found to be weak inhibitors of the noncompetitive type for xanthine oxidase while **3** showed no inhibitory properties toward this enzyme.

Investigations into deazapurines and their nucleosides have produced much revealing information about the biological roles of the ring nitrogen atoms in the metabolic functions of purine systems while also providing several derivatives of potential biological significance.[4-6] In our effort to organize and rationalize these diverse results for use in drug design, it became apparent that no biological data pertinent to this goal were available for the dideazapurines wherein one pyrimidine and one imidazole –N= of the purine nucleus had each been replaced by a –CH= moiety. Our approach to this situation was to consider the xanthine oxidase inhibitory analysis of appropriate dideaza analogues of xanthine with allopurinol[7] in mind. Thus, 1*H*-pyrrolo[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (3,7-dideazaxanthine, **1**),[8] 5-methyl-1*H*-pyrrolo-



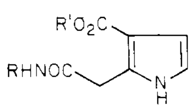
1, X = NH
2, X = NMe
3, X = O



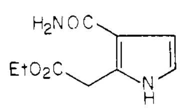
4, R = R′ = Et
5, R = H; R′ = Et
6, R = R′ = H
11, R = Me; R′ = Et
12, R = R′ = Me

[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (1-methyl-3,7-dideazaxanthine, **2**), and 1,7-dihydropyrano[4,3-*b*]pyrrole-4,6-dione (1-oxa-1,3,7-trideazaxanthine, **3**), as an isosteric deaza analogue of **1**, have been synthesized and evaluated as inhibitors for xanthine oxidase.

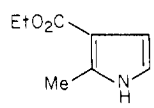
Chemistry. The synthesis of **1** began with ethyl 3-ethoxycarbonylpyrrole-2-acetate (**4**) which was prepared,[9] along with 3-ethoxycarbonylpyrrole-2-acetic acid (**5**) and 3-carboxypyrrole-2-acetic acid (**6**), from aminoacetaldehyde hydrochloride and diethyl 1,3-acetonedicarboxylate. Diester **4** was converted into 3-ethoxycarbonylpyrrole-2-acetamide (**7**) with ammonium hydroxide which, in turn,



7, R = H; R′ = Et
13, R = H; R′ = Me
14, R = Me; R′ = Et



7i



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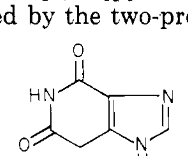
upon treatment with sodium hydroxide solution cyclized to **1**.

In view of the anticipated[10a] increased reactivity of the aliphatic carbonyl of **4** (vs. its aromatic carbonyl) toward nucleophiles, it was reasonable to assume[10b] that **7** (rather than its isomeric **7i** which would also cyclize to **1**) was the product of ammonolysis of **4**. However, it was considered worthwhile to prove that **7** was indeed the correct structural assignment. Thus, acid hydrolysis of the ester amide (**7** or **7i**) led to an ester acid (not identified) which was subsequently decarboxylated to 3-ethoxycarbonyl-2-methylpyrrole (**8**).[11] This verifies that **7** is the amide precursor to **1** since **7i** could not have produced **8**.

The structural assignment of **1** as the diketo tautomer, similar to 1*H*-imidazo[4,5-*c*]pyridine-4,6(5*H*,7*H*)-dione (**9**),[10a] was supported by the two-proton singlet at δ 4.1



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assignable to the two protons at C_7 of **1**. This structure was further corroborated by (1) the infrared spectral data of **1** in which two carbonyl bands were discernible in the ν 1720–1685-cm^{-1} region and (2) the mass spectral analysis which demonstrated m/e 150 (M^+), 107 (M^+ – CONH), and 79 [M^+ – $(CO)_2NH$] as a pattern characteristic of cyclic imides.[12]

In order to achieve a greater abundance of **1** the by-products in the synthesis of **4** (i.e., **5** and **6**) were converted into the diesters **11** and **12** with diazomethane. These systems were transformed into amides **7** and **13**, respectively, and then to **1** in yields comparable to the **4** → **7** → **1** process.

This same approach was extended to realizing **2** by treating **4** with aqueous methylamine to obtain **14** (cf. **7**) as the major product along with a small amount of **2**. Cyclization of **14** thus obtained yielded additional amounts of the desired **2**.

Finally, the synthesis of the oxygen isosteric analogue of **1** (i.e., **3**) was accomplished by an acetic anhydride mediated dehydration of **6**.

As with **1**, the spectral data (see the Experimental Section) for **2** and **3** support the dicarbonyl tautomers as shown.

Biological Results. Each of the new xanthine analogues was subjected to evaluation for inhibitory activity toward xanthine oxidase by employing the spectrophotometric method used by Baker and Hendrickson.[13] In this manner compound **3** demonstrated no inhibition capabilities for xanthine oxidase while the concentrations needed (i.e., $\sim 100K_m$) to permit analysis of the inhibitory characteristics for **1** and **2** indicated that they are very weak inhibitors of this enzyme. Furthermore, inspection of the Lineweaver–Burk plots[14-16] for **1** and **2** shows that they are of the noncompetitive type with K_{is} values[17,18] of 0.0925 mM for **1** and 0.1195 mM for **2**. Therefore, as might be anticipated, these data indicate that **1**, as the closest structural analogue of xanthine, possesses the greatest inhibitory potential of this series of compounds. Unfortunately, this potential does not seem worthy of further exploitation as a source of xanthine oxidase inhibitors. However, the implications of these data on the biological significance of the nitrogen atoms of xanthine and their role in substrate–enzyme interaction are quite revealing and are the subject of further scrutinization of this laboratory.

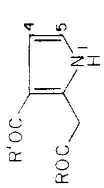
Experimental Section

All melting points (uncorrected) were obtained on a Thomas-Hoover melting point apparatus. Infrared spectra were recorded on a Beckman AccuLab 3 spectrophotometer and the ultraviolet spectra and absorbance values were determined on a Cary Model 14 recording spectrophotometer. The proton magnetic resonance spectra were obtained on a Varian EM-360 spectrometer and are reported in parts per million downfield from Me_4Si as an internal standard. The ^1H NMR spin multiplicities are indicated by the symbols s (singlet) and t (triplet). The mass spectra were determined on a Varian MAT CH-7 instrument at Indiana University, Bloomington, Ind. Elemental analyses (indicated by the symbols of the elements) were preformed by Het-Chem-Co., Harrisonville, Mo., and were within ±0.4% of the theoretical values.

3-Ethoxycarbonylpyrrole-2-acetamide (7). Compound **4**[9] or **11** (0.0133 mol) was added in small portions to 50 mL of refluxing 28% NH_3 solution. After the addition was complete, the brownish solution was refluxed for an additional 10 min and filtered and the filtrate cooled in an ice bath. This cooled solution was acidified (litmus) with 20% H_2SO_4 and chilled overnight in a refrigerator. The resulting white solid which separated was obtained by filtration and purified and characterized as **7** (see Table I).

1*H*-Pyrrolo[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (3,7-Dideazaxanthine, 1). In a manner analogous to that used in preparing **9**[10a] a mixture of **7** (2.12 g, 0.0108 mol) and 12 mL of 95% EtOH in a three-necked 100-mL flask was heated to 80 °C in an oil bath, at which time a clear solution formed. Then, 13 mL of 10% aqueous NaOH was added. Immediately the color started becoming pink. After 10 min, the flask was removed from the oil bath, cooled in ice for 1 h, acidified (litmus) drop by drop with

Table I. 2,3-Disubstituted Pyrroles



compd	yield, %	mp or bp (mm), °C[a] [solvent]	formula[b]	IR, cm⁻¹ [c] (ν CO)	¹H NMR data, chemical shifts in δ [d,e] R	R'	CH$_2$	H-1	H-4	H-5
7 (R = NH$_2$; R' = OEt)	62[f] 79[g]	143–144 [BP]	$C_9H_{12}N_2O_3$	1685 1660	6.8 (br) 7.2 (br)	1.2 (t) 4.15 (q)	3.7	11.2 (br)	6.3 (t)	6.6 (t)
11 (R = OMe; R' = OEt)	100	88 (5)	$C_{10}H_{13}NO_4$	1740 1665	3.65	1.26 (t) 4.13 (q)	4.03	11.02 (br)	6.53 (t)	6.74 (t)
12 (R = R' = OMe)	96	70–71 [P]	$C_9H_{11}NO_4$	1725 1620	3.63	3.6	3.93	11.35 (br)	6.4 (t)	6.75 (t)
13 (R = NH$_2$; R' = OMe)	76	184–186 [BP]	$C_8H_{10}N_2O_3$	1680 1660	6.85 (br) 7.2 (br)	3.67	3.73	11.25 (br)	6.3 (t)	6.63 (t)
14 (R = NHMe; R' = OEt)	76	151 [B]	$C_{10}H_{14}N_2O_3$	1685 1660	2.82 (d) 7.48 (br)	1.36 (t) 4.4 (q)	4.05	11.14 (br)	6.78 (m)	6.78 (m)

[a] All white crystals except 11 (yellow liquid). Solvent of crystallization: BP, benzene–petroleum ether; P, petroleum ether; B, benzene. [b] C, H, and N analyses for all compounds were within ±0.4% of the theoretical value. [c] As compressed potassium bromide disks. [d] In Me$_2$SO-d_6 as solvent (except 14 which was performed in CDCl$_3$) with Me$_4$Si as an internal standard. [e] Singlet unless stated otherwise; br, broad; d, doublet; t, triplet; q, quartet; m, multiplet. [f] From 4. [g] From 11.

20% HCl, and, finally, cooled in ice again for 1.5 h. The tiny pink solid which separated was obtained by filtration and recrystallized from glacial AcOH as buff-colored needles of 1 (1.37 g, 9.1 mmol, 84%): mp >300 °C; ¹H NMR (Me$_2$SO-d_6) δ 4.1 (s, 2 H, CH$_2$), 6.75 (t, J = 3.0 and 2.7 Hz, 1 H, H-3), 7.25 (t, J = 3.0 and 2.7 Hz, 1 H, H-2), 11.2 (br, 1 H, pyrrole NH), 12.3 (br, 1 H, imide NH); IR (KBr) 3300–3170 (br, NH), 1715–1690 cm^{-1} (two C=O); UV λ_{max} nm (ε) at pH 7 (EtOH) 241 (8300), 279 (6540); UV λ_{max} at pH 1 245 (5000), 290 (4000); UV λ_{max} at pH 11 267 (10 940), 315 (9120); mass spectrum (70 eV) m/e (peak assignment, rel intensity) 150 (M$^+$, 100%), 107 (M$^+$ – CONH, 54), 79 [M$^+$ – (CO)$_2$NH, 73]. Anal. ($C_7H_6N_2O_2$) C, H, N.

Methyl 3-Ethoxycarbonylpyrrole-2-acetate (11). Compound 5[9] (11.82 g, 0.06 mol) was placed in 225 mL of dry Et$_2$O and a cold ethereal solution of diazomethane[20] (0.066 mol) was added in small portions with stirring over a period of 5–6 min. The mixture was stirred for an additional 30 min at which time the yellow color of the diazomethane had disappeared. After decomposing the excess diazomethane with glacial AcOH, the solution was stirred for an additional 5 min and then the solvent was evaporated on a rotary evaporator to result in an oil which was purified and characterized as 11 (see Table I).

Methyl 3-Methoxycarbonylpyrrole-2-acetate (12). In a manner analogous to that for preparing 11, 6[9] (1.19 g, 0.01 mol) produced a semisolid, upon removal of the Et$_2$O and AcOH, which was extracted repeatedly with petroleum ether (bp 40–60 °C) followed by concentrating the combined petroleum ether extracts to 25 mL and cooling this solution overnight in a refrigerator. The pale yellow solid which separated was isolated by filtration and purified and characterized as 12 (see Table I).

3-Methoxycarbonylpyrrole-2-acetamide (13). Following the procedure described earlier for realizing 7, 12 (400 mg, 2 mmol) was converted into 13 (see Table I).

3-Ethoxycarbonylpyrrole-2-(*N*-methyl)acetamide (14). To 20 mL of boiling aqueous (40%) CH$_3$NH$_2$ solution 4[9] (1 g, 4.4 mmol) was added in small portions with the solution becoming reddish brown in color. The mixture was refluxed for an additional 5 min and filtered, and the filtrate was cooled and acidified (litmus) with 3 N H$_2$SO$_4$ to a bluish green solution from which needles began precipitating. After keeping the mixture at room temperature for 1 h, the bluish solid was isolated by filtration and air-dried. This product was dissolved in 35 mL of benzene, the benzene solution boiled with charcoal and filtered, and the filtrate concentrated to half of its original volume and cooled. After about 0.5 h, tiny green crystals identified as 2 (0.1 g, 0.61 mol, 13.9%), mp >300 °C, separated. The IR spectrum of this sample was identical with that of the authentic sample of 2 prepared by the procedure given below.

While 2 was being obtained by filtration, white needles began forming in the filtrate. After 1 h, the resulting solid was isolated by filtration and characterized as 14 (see Table I).

5-Methyl-1*H*-pyrrolo[3,2-*c*]pyridine-4,6(5*H*,7*H*)-dione (1-Methyl-3,7-dideazaxanthine, 2). In a manner analogous to that for synthesizing 1, 14 (1.5 g, 7.1 mmol) produced light blue needles of 2 (1.06 g, 6.1 mmol, 86% from AcOEt): mp >300 °C; ¹H NMR (Me$_2$SO-d_6) δ 3.1 (s, 3 H, NCH$_3$), 3.98 (s, 2 H, CH$_2$), 6.4 (t, J = 3.0 and 2.7 Hz, 1 H, H-3), 6.85 (t, J = 3.0 and 2.7 Hz, 1 H, H-2), 11.32 (br, 1 H, pyrrole NH); IR (KBr) 3200 (NH), 1690 and 1650 cm^{-1} (C=O); UV λ_{max} nm (ε) at pH 7 241 (4180), 283 (2790), 350 (774); UV λ_{max} at pH 1 245 (4490), 286 (3483); UV λ_{max} at pH 11 268 (3590), 308 (3715). Anal. ($C_8H_8N_2O_2 \cdot 0.5H_2O$)[21] C, H, N.

1,7-Dihydropyrano[4,3-*b*]pyrrole-4,6-dione (1-Oxa-1,3,7-trideazaxanthine, 3). Compound 6[9] (1 g, 5.9 mmol) was heated under reflux with Ac$_2$O (1.09 g, 10.7 mmol) for 15 min. The reaction mixture was cooled to room temperature and the green solid which separated was collected by filtration and washed with a few milliliters of petroleum ether, dried, and recrystallized from AcOEt to obtain 3 as white crystals (0.89 g, 5.9 mmol, 100%): mp 197–198 °C; ¹H NMR (Me$_2$SO-d_6) δ 4.15 (s, 2 H, CH$_2$), 6.45 (t, J = 3.0 and 2.7 Hz, 1 H, H-3), 6.95 (t, J = 3.0 and 2.7 Hz, 1 H, H-2), 10.7 (br, 1 H, pyrrole NH); IR (KBr) 3380 (NH), 1765 and 1725 cm^{-1} (C=O). Anal. ($C_7H_5NO_3$) C, H, N.

Xanthine Oxidase Inhibition Assays. Using xanthine oxidase from buttermilk (Sigma) and a Gilford 240 single beam spectrophotometer the method of Baker and Hendrickson[13] was employed by dissolving **1–3** in 10 mM aqueous NaOH solution.

Acknowledgment. This investigation was supported by U.S. Public Health Service Research Grant No. CA 17878 from the National Cancer Institute and such assistance is gratefully acknowledged. The assistance of Dr. J. O. Tsokos and Dr. L. P. Solomonson with the biological evaluation and interpretation of the results for **1–3** is also appreciated.

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(2) Department of Chemistry.
(3) Department of Biology.
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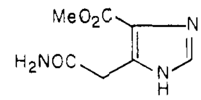

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Cyclic Analogues of Luteinizing Hormone-Releasing Hormone with Significant Biological Activities

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There is evidence that, in its receptor-binding conformation, the N and C terminus of LH-RH may be in close proximity and two cyclic analogues of the hormone were synthesized to test the hypothesis. Cyclic [β-Ala[1],D-Ala[6],Gly[10]]- and [6-aminohexanoic acid[1],D-Ala[6],Gly[10]]-LH-RH were prepared by treatment of their linear precursor peptides with dicyclohexylcarbodiimide in the presence of 1-hydroxybenzotriazole in dilute dimethylformamide solution. Although the linear peptides possessed no detectable LH-releasing activity in ovariectomized rats, the cyclic β-Ala analogue had 1.2% the activity of LH-RH, whereas the longer chain cyclic 6-aminohexanoic acid analogue had 0.65% activity. These results support the concept of an important interaction between the ends of the LH-RH molecule possibly involving hydrogen-bond formation between the pyrrolidone carbonyl group of pyroglutamic acid and the glycinamide group.

It is now reasonably well established by analogue studies and free-energy analysis[2,3] that the active conformation of LH-RH contains a type II β bend hinged around glycine in position 6. A notable consequence of this is that the substitution of D-amino acids,[4] particularly those with bulky side chains,[5] results in large increases in gonadotropin-releasing activity presumably due to the stabilization of the β bend. With this configuration at the center of the chain, the LH-RH molecule assumes a "U" shape in which the <Glu residue in position 1 and glycinamide in position 10 are in quite close proximity.

Structure–activity studies[6] on <Glu strongly suggest that the pyrrolidone carbonyl group contributes to full biological activity by taking part in hydrogen-bond formation either with a complimentary group on the receptor or with some part of the LH-RH chain itself. Slight alterations to Momany's CC conformer[3] for LH-RH, which was derived from computer minimum free-energy calculations and a consideration of analogue activities, readily enable <Glu and glycinamide to approach close enough for hydrogen-bond formation between the γ-carbonyl group and the glycine NH_2 group.

If there is such an interaction between the termini of LH-RH, then it should be possible to covalently link the ends of the peptide chain and at least retain appreciable biological activity. At best, if the optimum stereochemical

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