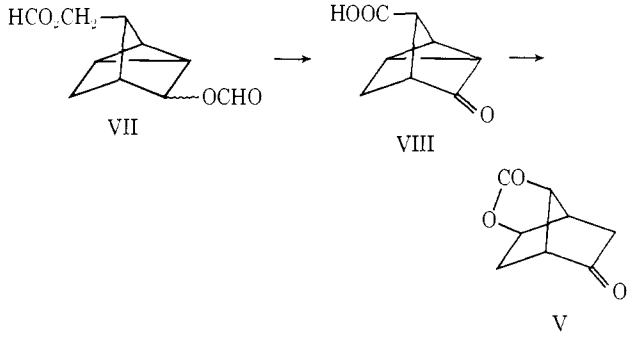
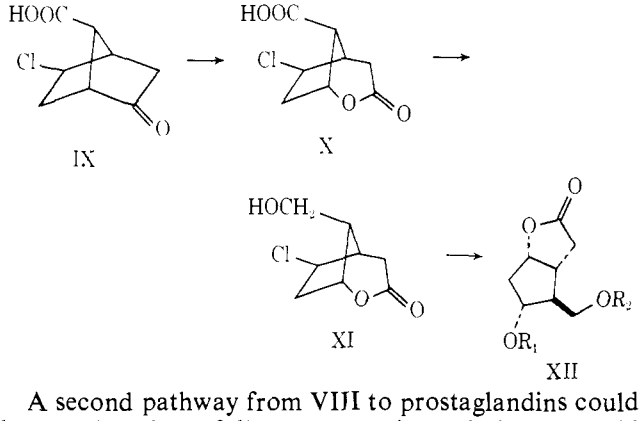
Jones reagent at 0° led directly to the keto acid VIII,[3] mp 144–145°, in 72% yield.[7] The acid VIII upon heating with 20% aqueous sulfuric acid or perchloric acid at 150° for 10 hr (or 50% aqueous acid at 150° for 1 hr) afforded the desired lactone V, mp 195–196° in 85% yield.




The optically active acid VIII was readily secured in the absolute configuration required for prostaglandin synthesis by resolution of (±)-VIII with L-(−)-α-methylbenzylamine. The optically pure salt, obtained in *ca.* 75% yield after two or three recrystallizations, had mp 154–155°, $[\alpha]^{25}D$ +59° (*c* 1, $CH_3OH$), and yielded the desired dextrorotatory keto acid VIII, mp 137–138°, $[\alpha]^{25}D$ +74° (*c* 1, $CH_3OH$). From the dextro acid VIII optically active keto lactone V, mp 195–197°, $[\alpha]^{25}D$ +266° (*c* 1, $CH_3OH$), was obtained as described above for the racemic form and converted to optically active dilactone VI, mp 209.5–210.5°, $[\alpha]^{25}D$ +59.7° (*c* 0.5, $CHCl_3$).

The conversion of these optically active intermediates to prostaglandins in natural optically active form can be achieved using the methods of side-chain elaboration which have already been described.[1] The details of these transformations will be reported in a separate publication.




A second pathway from VIII to prostaglandins could be developed as follows. Reaction of the (+)-acid VIII[3] with boiling aqueous hydrochloric acid (with steady introduction of gaseous HCl) for 1 hr produced cleanly (80%) the chloro acid IX,[3] mp 151–152°, $[\alpha]^{25}D$ +12° (*c* 1, $CH_3OH$). This was transformed cleanly by Baeyer–Villiger oxidation using *m*-chloroperbenzoic acid in methylene chloride in the presence of sodium bicarbonate (2 equiv) to the chloro lactone acid X,[3] mp 165.5–168°, $[\alpha]^{25}D$ −70° (*c* 1, in $CH_3OH$). The acid X was then converted in high yield to the corresponding primary alcohol XI,[3] mp 129–131°, $[\alpha]^{25}D$ −65° (*c* 1, $CHCl_3$), by sequential treatment with (1) ethyl chloroformate (1 equiv)–triethylamine (1 equiv) in ether at 0° to form the mixed anhydride and (2) ethanolic sodium borohydride at −20° or zinc borohydride in THF at 25°.

Conversion of XI to the tetrahydropyranyl ether and treatment with a mixture of 1 equiv of aqueous base, THF, and 20 equiv of 30% hydrogen peroxide as buffer produced the hydroxy lactone XII,[3] $R_1$ = H and $R_2$ = THP (80% yield), which was readily transformed into the hydroxy *p*-phenylbenzoate XII, $R_1$ = *p*-$C_6H_5C_6H_4CO$ and $R_2$ = H, mp 131°, $[\alpha]^{25}D$ −87° (*c* 1, $CHCl_3$), by acylation with *p*-phenylbenzoyl chloride–pyridine and acidic cleavage of the tetrahydropyranyl group. The hydroxy lactone ester XII, $R_1$ = *p*-$C_6H_5C_6H_4CO$ and $R_2$ = H, so obtained was identical with material which earlier had been synthesized and converted into prostaglandins.[1c]

(7) We have recently learned that Professor J. K. Sutherland of the University of Manchester, in an independent study, has also arrived at the synthesis of VIII *via* the Prins route from norbornadiene and, further, that he has succeeded in developing a route from VIII to prostaglandins which is different from those reported herein.

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## Solid State Conformation of the C-Terminal Tripeptide of Oxytocin, L-Pro-L-Leu-Gly-$NH_2 \cdot 0.5H_2O$

*Sir:*

The C-terminal tripeptide of oxytocin, L-Pro-L-Leu-Gly-$NH_2$ (I), has been postulated as the factor inhibiting the release of melanocyte-stimulating hormone (MSH).[1,2] Other workers,[3-6] however, have been unable to verify this proposed role for the tripeptide. Whatever its possible role as a biologically important molecule, I is experimentally and theoretically interesting in terms of molecular conformation both in isolation and in the oxytocin molecule.

Walter, *et al.*,[7] have postulated a solution conformation for I based on 300-MHz pmr studies carried out in dimethyl-$d_6$ sulfoxide. Based on the observed differences in chemical shift of the two N–H protons of the glycinamide moiety it was concluded that intramolecular hydrogen bonding between the trans carboxamide proton and the prolyl carbonyl oxygen results in a preferred solution structure. The basic conformational feature of the proposed solution model, a ten-membered β-turn structure, is observed in the present X-ray investigation.

I·0.5$H_2O$ ($C_{13}H_{25}O_3N_4 \cdot 0.5H_2O$), supplied by Dr. V.

(1) M. E. Celis, S. Taleisnik, and R. Walter, *Proc. Nat. Acad. Sci. U.S.*, **68**, 1428 (1971).
(2) R. M. G. Nair, A. J. Kastin, and A. V. Schally, *Biochem. Biophys. Res. Commun.*, **43**, 1376 (1971).
(3) A. Bower, M. E. Hadley, and V. J. Hruby, *Biochem. Biophys. Res. Commun.*, **45**, 1185 (1971).
(4) W. Vale, G. Grant, and R. Guillemin, "Frontiers in Neuroendocrinology," W. F. Ganong and L. Martini, Ed., Oxford University Press, London, 1973, in press.
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(6) M. E. Hadley, A. Bower, and V. J. Hruby, *Yale J. Biol. Med.*, in press.
(7) R. Walter, I. Bernal, and L. F. Johnson, "Chemistry and Biology of Peptides," Ann Arbor Science Publishers, Ann Arbor, Mich., 1972, pp 131–135.

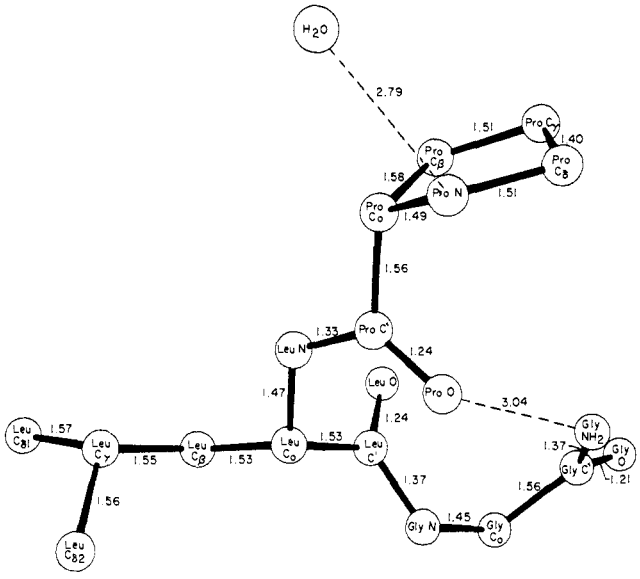


Figure 1. Molecular conformation of L-Pro-L-Leu-Gly-$NH_2 \cdot 0.5H_2O$.

J. Hruby, crystallizes in the hexagonal space group $P6_122$ (or $P6_522$). The unit cell dimensions and crystal data are: $a = b = 10.605$ (3) and $c = 50.366$ (11) Å, $\gamma = 120°$, $V = 4905.6$ Å$^3$, and $Z = 12$ (also see ref 7). The calculated density is 1.19 g cm$^{-3}$ which compares with a measured[7] density of 1.20 (2) g cm$^{-3}$. Intensity data were collected on a Picker FACS-I computer-controlled diffractometer using Cu K$\alpha$ radiation, filtered with a monochromator. The structure was solved using acentric direct method procedures in the space group $P6_122$ (*vide infra*). The program MULTAN[8] was used with local modifications to handle hexagonal symmetry. Three cycles of full-matrix least-squares refinement with anisotropic thermal parameters for all nonhydrogen atoms except the water oxygen atom (isotropic) has resulted in $R = 0.090$ and $R_w = 0.098$. A total of 1200 data having $F_o^2 > 3\sigma(F_o^2)$ were used in the refinement process. The water molecule occupies site b (point symmetry 2) of the space group $P6_122$. The $C_\beta$, $C_\gamma$, and $C_\delta$ atoms of the proline residue exhibit high anisotropic thermal motion, and bond lengths and angles involving these atoms should not be considered accurate at this stage of the analysis.

A careful check of this region of the molecule using difference Fourier techniques did not reveal a statically disordered $C_\gamma$ atom as had been found in the proline residue of the tripeptide L-Leu-L-Pro-Gly.[9] The majority of the hydrogen atoms have been located, although no refinement of their positional or thermal parameters has yet been carried out. Details of the molecular structure are presented in Figure 1.

The bond distances shown in Figure 1 and the bond angles presented in Table I are in good agreement with similar dimensions in other peptides determined by X-ray methods.[9-11]

(8) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. B*, 26, 274 (1970).
(9) Y. C. Leung and R. E. Marsh, *Acta Crystallogr.*, 11, 17 (1958).
(10) R. E. Marsh and J. Donohue, *Advan. Protein Chem.*, 22, 235 (1967).
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**Table I.** Bond Angles (Degrees)

| | Angle | Prolyl | Leucyl | Glycyl |
|---|---|---|---|---|
| Peptide unit | N–$C_\alpha$–C' | 110.6 | 108.1 | 114.0 |
| | $C_\alpha$–C'–N | 114.5 | 116.0 | |
| | $C_\alpha$–C'–O | 121.7 | 121.2 | 116.4 |
| | N–C'–O | 123.8 | 122.8 | 125.9 |
| | C'–N–$C_\alpha$ | 119.5 | 119.2 | |
| Av angle in side chain | C–C–C | 106.9[a] | 110.4 | |

[a] Includes angles involving the ring N.

The molecule reveals an interesting system of intra- and intermolecular hydrogen bonding involving all the heteroatoms of the structure. A weak intramolecular hydrogen bond involving the Pro(O) and Gly-$NH_2$ (3.04 Å) determines the overall compact structural feature of the molecule. The Pro(O) is involved in a second intermolecular hydrogen bond (2.99 Å) to the Pro(N) of a symmetry-related molecule. Gly(O) bonds to Leu(N) of a symmetry-related molecule (2.85 Å). The water is involved in four hydrogen bonds. Two pairs of contacts involving Gly(N) (2.98 Å) and Pro(N) (2.79 Å) are observed. The disposition of the hydrogen atoms in the contacts involving the water molecule is such that the Gly(N) hydrogen atom is donated in the Gly(N)···O($H_2O$) hydrogen bond and the water hydrogen atoms are donated in the Pro(N)···O($H_2O$) hydrogen bonds. Finally, the Gly($NH_2$)···Leu(O) is the longest contact in the set of hydrogen bonds with a contact distance of 3.08 Å. The model proposed by Walter, *et al.*,[7] postulated that the water molecule was involved in hydrogen bonding through the glycine carbonyl. While this may be a possible scheme in solution, it is clear that it is not the scheme in the crystal. A strong hydrogen bond involves the water molecule and the proline nitrogen atom. The sense of this hydrogen bond (*i.e.*, O–H···N) implies that the lone-pair density on the nitrogen atom makes it a good acceptor atom in hydrogen bond formation in this molecule. In addition, the NH of the proline is also involved in a long hydrogen bond despite its apparent low electrophilicity.[7]

Atoms of the peptide unit are planar in one peptide bond but significantly nonplanar in the other. The dihedral angle, $\Delta\omega$,[12] which is 0° for a planar peptide bond, is 0.1° in the leucylglycinamide bond and −9.0° in the prolylleucyl bond.

The conformation of the peptide chain can be described by $\psi$ and $\phi$, the torsion angles about the bonds in the chain. The values are: $\psi$(Pro) = 152.9°, $\phi$(Leu) = −61.2°, $\psi$(Leu) = 127.8°, and $\phi$(Gly) = 71.8°.

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(12) G. N. Ramachandran and A. S. Kolaskar, *Biochim. Biophys. Acta*, 303, 385 (1973).

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