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SYNTHESIS OF 2-PHOSPHONOPYRROLIDINE AND ITS SUBSTITUTION FOR PROLINE IN AN INHIBITOR OF ANGIOTENSIN-CONVERTING ENZYME

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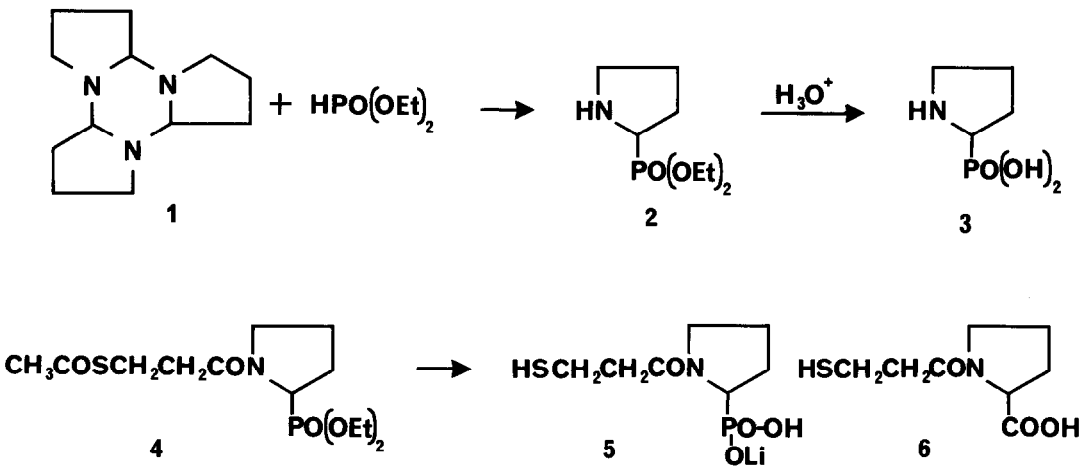
The title compound was synthesized via its diethyl ester from 1-pyrroline trimer and diethyl phosphite. The 3-mercaptopropanoyl derivative inhibited angiotensin converting enzyme with I_{50} = 1.7 μM.

Recently, 1-aminoalkylphosphonic acids have been the subject of numerous reports concerning their synthesis and chemistry as analogs of α-aminocarboxylic acids.[1] We report here a short synthesis of the proline analog 3, *dl*-2-phosphonopyrrolidine, and its incorporation into an inhibitor of angiotensin-converting enzyme (ACE) related to captopril(SQ 14,225).[2]

One general method for the synthesis of 1-aminoalkylphosphonic acid derivatives is the reaction of imino derivatives of carbonyl compounds with phosphorous acid,[1b] its esters,[1c] or halides.[1d] We have applied this method to a simple synthesis of diester 2. 1-Pyrroline trimer 1[3] and diethyl phosphite (3 equiv.), heated together at 85° for 90 min under argon,



undergo complete conversion to 2[4] (^{13}C-NMR($CDCl_3$): 61.0(8),$\underline{CH_2}CH_3$; 53.1(164),C-2; 47.3(10), C-5; 25.8,C-4; 25.1(8),C-3; 15.5(5), $\underline{CH_3}CH_2$).[5] Crude 2 could be distilled (85-8°/0.025 mm, 52% recovery), but was sufficiently pure for further use without distillation.

Diester 2 was hydrolyzed to acid 3 by refluxing in 6N HCl (20 volumes) overnight. Water and HCl were removed *in vacuo*, the residue was applied to an AG-50W (H^+ form) column, and the amino acid was eluted by distilled water. Crystallization (water-ethanol) affords 3[6], mp 275-80°, in 65% yield from crude 2 (^{13}C-NMR(D_2O/dioxane ref): 55.8(144),C-2: 46.8(6),C-5; 26.4,C-4; 23.9(8),C-3). A plot of electrophoretic mobility of 3 vs pH shows that the isoelectric point is below pH 3, with conversion to a dianion at pH 5-6.

3-(Acetylthio)propanoic acid[2] (1 equiv.) was coupled to 2 (1 equiv.) using DCC (1 equiv.) in CH_2Cl_2 (10 min, 0°; overnight, r.t.) to obtain 4 in 62% yield. Amide 4 was then treated with $(CH_3)SiBr$ (2 equiv.) in CH_2Cl_2[7] (0°, 4 hr, under Ar) and the resulting silyl ester stirred with 1N aqueous hydrazine (3 equiv.) for 2 hr. Removal of hydrazine by passage through AG-50W resin yielded the expected phosphonic acid as a hygroscopic glass. Passage through an AG-50W (Li^+) column and lyophilization gave 5, a free-flowing powder.[6] (^{13}C-NMR(D_2O/dioxane): 173.2,C=O; 54.4(151),C-2; 48.0,C-5; 38.0,$\underline{CH_2}C=O$; 26.0,C-4; 24.0(2),C-3; 19.2($HSCH_2$)).[5]

Thiol 5 inhibited ACE of rabbit lung with I_{50} = 1.7 μM.[2,8] The corresponding derivative of L-proline, 6 has I_{50} = 0.20 μM. Thus, it appears that the phosphonic acid function of 5 is a reasonably good replacement for the carboxylic acid function in the mercapto-alkanoyl amino acid series of ACE inhibitors.[9,10]

Notes

1. a) Review: K. Prager and J. Rachon, Z. Chem. 15, 209 (1975). b) D. Redmore, J. Org. Chem. 43, 992,996 (1978). c) D. Redmore in Topics in Phosphorus Chemistry, E.J. Griffith and M. Grayson, Eds., Vol. 8, J. Wiley & Sons, New York 1976. d) J. Oleksyszyn, R. Tyka and P. Mastalerz, Synthesis 1978, 479.
2. D.W. Cushman, H.S. Cheung, E.F. Sabo and M.A. Ondetti, Biochemistry 35, 5484 (1977). Captopril is (S)-1-(3-mercapto-2-methyl-1-oxopropyl)-L-proline.
3. Y. Nomura *et al.*, Chem. Lett. 1977, 693.
4. A. Dehnel and G. Lavielle, Bull. Soc. Chim. Fr. 1978, II-95, report a three-step synthesis of 2 and its piperidine homolog from diethyl aminomethylphosphonate.
5. 15-MHz proton-noise-decoupled spectra run on JEOL FX-60Q. Assignments confirmed by off-resonance decoupled spectra. Chemical shifts in ppm from TMS. C-P couplings in Hertz in parentheses.
6. Satisfactory microanalyses were obtained for 3(C,H,N,P) and 5(C,H,N,P,S).
7. C.E. McKenna *et al.*, Tetrahedron Lett. 1977, 155.
8. D.W. Cushman and H.S. Cheung, Biochem. Pharmacol. 20, 1637 (1971).
9. We expect that the R-enantiomer of 5 is the most active, since there is a known[2] requirement for L-amino acid stereochemistry in inhibitors such as 6.
10. We thank the following colleagues for assistance: D.W. Cushman, H.S. Cheung (ACE inhibition testing); O. Kocy, N. Cole (electrophoresis); M.B. Young (elemental analyses).

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