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STEREOCHEMISTRY OF THE BASE-CATALYZED METHANOLYSIS OF 2-PHENYL-TETRAHYDROPYRROLO-1,3,2-OXAZAPHOSPHOLES

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Summary: Diastereomerically pure bicyclic oxazaphospholes were prepared from L-prolinol and phenylphosphonic or thiophosphonic dichloride and their absolute configurations were determined based on the interpretation of NMR spectra. The base-catalyzed methanolysis of those compounds was found to proceed by exclusive P-O bond cleavage with complete inversion of configuration.

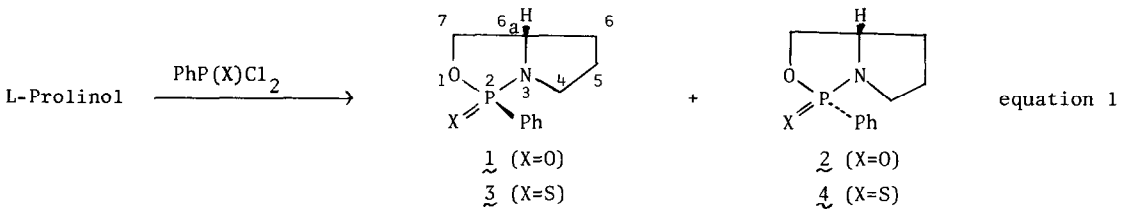
The solvolysis of phosphorus amide esters of acyclic and six membered structures[1] has been well known to proceed by P-N bond cleavage under acidic conditions and by P-O bond cleavage under basic conditions, both exclusively. On the contrary, the solvolysis of the five-membered oxazaphospholes has been reported to be rather different in that the P-N bond cleavage seems more or less predominant even under the basic condition: Hudson et al.[2] studied the alkaline hydrolysis of 2-substituted 2-oxo-1,3,2-oxazaphospholanes and observed the concomitant P-O and P-N bond cleavage in different ratios depending on the substituents on nitrogen. Inch et al.[3] has recently made extensive investigations on the solvolysis of 2-substituted 1,3,2-oxazaphosphole-2-ones and 2-thiones derived from *l*-ephedrine and observed the exclusive P-N bond cleavage with the inversion of configuration both in base- and acid-catalyzed solvolysis. They pointed out that the P-N bond within the 1,3,2-oxazaphospholidine ring is sufficiently weak to undergo the direct S_N2 type displacement.

Here we describe the first stereochemical study on the base-catalyzed solvolysis of bicyclic oxazaphospholes, disclosing that the position of the bond fission is completely different from that of monocycles. Exclusive P-O bond cleavage with complete inversion of configurations was observed.

During the course of our investigation aimed at establishing the utility of amino acid derivatives as the chiral source of optically active organophosphorus compounds[4], we found that the 2-phenyl-tetrahydropyrrolo-1,3,2-oxazaphospholes[5] could be easily prepared by the reaction of L-prolinol and phenylphosphonic dichloride or phenylthiophosphonic dichloride and were stable enough to be submitted to the chromatographic diastereomeric separation.

When phenylphosphonic dichloride was treated with L-prolinol (1 equiv) in the presence of triethylamine (2 equiv) in anhydrous THF at room temperature, the corresponding 2-phenyl-1,3,2-oxazaphosphole-2-oxide was obtained as a mixture of diastereomers in 80-90 % yield. The mixture

was easily separated by flash column chromatography (silica gel, AcOEt) to afford the diastereoisomers 1, $[\alpha]_D^{17}$ +76° (c 1.5), and 2, $[\alpha]_D^{17}$ -4.2° (c 1.8).[6] (equation 1). By the same reaction of L-prolinol with phenylthiophosphonic dichloride followed by the flash chromatography (silica gel, benzene), the diastereomers of 2-thio compound were obtained: 3, bp 180-185°/0.09 Torr, $[\alpha]_D^{14}$ +102° (c 1.0), and 4, bp 180-185°/0.1 Torr, $[\alpha]_D^{14}$ +1.4° (c 2.2).[7] The yields and the NMR data[8] of 1~4 are shown in Table 1.



1 (X=O)
3 (X=S)
2 (X=O)
4 (X=S)

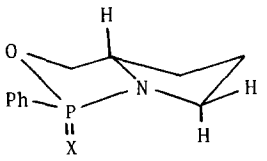
equation 1

Table 1 Yields and NMR Data of Oxazaphospholes

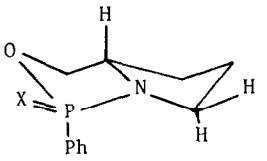
Oxazaphospholes	Yield (%)	NMR δppm (Hz) 4α	4β	5,6	6a	7α	7β
1	40-60	3.76 (m)	2.96 (m)	1.7-2.2	4.15 (br m)	4.35 (octet, 20.0 8.0, 6.0)	3.92 (sextet, 8.0, 8.0, 3.6)
2	10-35	3.06 (m)	2.88 (m)	1.5-2.2	4.28 (br m)	4.76 (octet, 15.0, 9.0, 6.0)	4.08 (sextet, 9.0, 9.0, 4.0)
3	35-45	3.90 (m)	2.96 (m)	1.7-2.2	4.15 (br m)	4.40 (octet, 22.4, 9.0, 6.2)	3.83 (sextet, 9.0, 9.0, 4.0)
4	40-45	3.08 (m)	2.88 (m)	1.5-2.2	4.26 (br m)	4.72 (octet, 17.0, 9.0, 6.0)	4.06 (sextet, 9.0, 9.0, 4.0)

Structure assignment of these oxazaphospholes was made by rationalizing the NMR data on the basis of their configurations. Since the fused 5/5 ring system with bridge-head nitrogen should exist in the energetically favorable cis fused configuration,[9] nonplanar structures of a pair of the diastereomers are depicted as (i) and (ii) below.

When we compared the chemical shifts of C_4-protons within a pair of diastereomers, characteristic low field shifts are notable with 4α H: Δ 0.70 ppm for 1 and 2 and Δ 0.82 ppm for 3 and 4. Such a deshielding should be ascribed to the known effect of P=O or P=S at 1,3 cis position.[3, 10] Therefore, the compounds 1 and 3 must have configuration i, and hence the configuration ii should



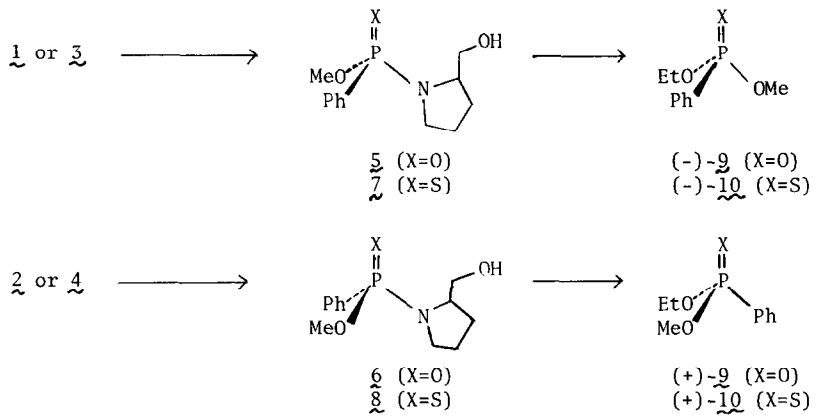
(i)



(ii)

be assigned to the compounds 2 and 4. The above assignment was also supported by the low field 6a protons of 2 and 4 compared from those of 1 and 3. Now that bicyclic oxazaphospholes with the tentatively assigned absolute configurations in hands, we then studied the base-catalyzed methanolysis of these compounds 1~4[11]. All methanolysis were conducted in the presence of NaOMe (1 equiv) and the reactions were completed after 5-10 min at 0°. Only the P-O cleaved amidates 5~8 were obtained almost quantitatively and in diastereomerically pure state[12] (equation 2).

To elucidate the stereochemistry of the above P-O fission reactions, the phosphonamidates 5~8 were then subjected to acid-catalyzed ethanolysis (0.5 M H_2SO_4-EtOH, 30-40 min at reflux) to give the corresponding ethyl methyl phosphonates 9 or 10. The yields and the optical rotations of the products are shown in Table 2.



equation 2

Table 2 Phosphonates obtained from Oxazaphospholes

Starting oxazaphosphole	Ph-P(X)(OMe)(OEt)				
	X	bp °C/Torr	yield (%)	$[\alpha]_D$ (c, temp)	ee (%)
1	O	85-92/0.03	81	-3.2°(1.41, 28)	>91
2	O	85-90/0.06	24[13]	+3.2°(1.43, 28)	>91
3	S	65-70/0.06	58	-7.7°(2.60, 27)	∿100
4	S	65-70/0.06	59	+7.3°(2.60, 27)	∿97

Since we have recently determined[14] the absolute configurations of 9 and 10 by the chemical correlations with (-)-O,S-dimethyl phenylphosphonothioate and the protic acid-catalyzed solvolysis of P-N bond proceeds with complete inversion of configuration[15], the stereochemical course of the NaOMe catalyzed methanolysis of 1~4 should be concluded as stereospecific inversion of configuration. From the above results, the following conclusions are reached.

1) In base-catalyzed alcoholysis, the bicyclic oxazaphospholes undergo the complete P-O bond cleavage with inversion of configuration which is a sharp contrast to that reported for the monocyclic oxazaphospholes. Detailed mechanistic investigation including kinetics is required to find out the reasons for this interesting difference.

2) L-prolinol proved to be a good chirality source for the preparation of various chiral phosphonic esters. The investigation along this line is in progress in this laboratory.

References and Notes

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2) a) J. A. Boudreau, C. Brown, and R. F. Hudson, *Chem. Commun.*, 1975, 679. b) C. Brown, J. A. Boudreau, B. Hewitson, and R. F. Hudson, *J. Chem. Soc. Perkin II*, 1976, 888.

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d) Y. Kobayashi, T. Koizumi, and E. Yoshii, *Chem. Pharm. Bull.*, 27, 1641(1979).

5) All new compounds gave satisfactory elemental analyses and spectral data. All $[\alpha]_D$ measurements were taken in CCl_4.

6) TLC of 1 and 2 : Merck Kieselgel 60 F_{254}, AcOEt, R_f 0.47 for 1 and R_f 0.32 for 2. Both compounds were unstable when submitted to the microdistillation, and used without further purification and elemental analyses.

7) TLC of 3 and 4: Merck Kieselgel 60 F_{254}, benzene, R_f 0.50 for 3 and 0.25 for 4.

8) The assignment of protons at 6, 6a, and 7 positions was confirmed by the comparison of NMR with those of 7 position deuteriated 3 and 4.

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10) J. Devillers, M. Cornus, and J. Navech, *Organic Magnetic Resonance*, 6, 211(1974).

11) The acid-catalyzed methanolysis (1 % H_2SO_4-MeOH) of compounds 1~4 provided the diastereomerically pure P-N bond cleaved products.

12) Both diastereomers were distinguishable by TLC and/or NMR. P-O cleavage was confirmed by the acetylation of 5~8 to give the acetates which exhibited ester carbonyl band at ∿1740 cm^{-1}.

13) The low yield of the phosphonate is probably due to the instability of the compound 7.

14) T. Koizumi, H. Takagi, and E. Yoshii, submitted to *Chemistry Letters*.

15) T. Koizumi, Y. Kobayashi, and E. Yoshii, *Heterocycles*, 9, 1723(1978) and references cited therein.

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