Tetrahedron Letters No. 22, pp 1913 - 1916, 1977. Pergamon Press. Printed in Great Britain.

THE HYDROLYSIS OF HETEROATOM CONTAINING BENZOPHOSPHOLES

Toru Koizumi*, Yutaka Watanabe, Yuichi Yoshida, Kei Takeda, and Eiichi Yoshii

Faculty of Pharmaceutical Sciences, University of Toyama, Gofuku, Toyama 930, Japan

(Received in Japan 21 February 1977; received in UK for publication 21 April 1977)

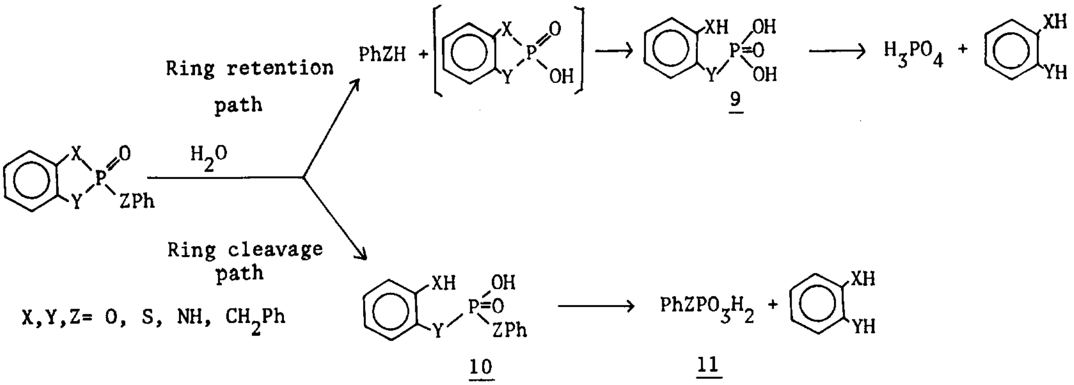
Previously we introduced new phosphorylating reagents, 1,3-diaza1) and 1,3-oxaza-2) 2-phenoxy-benzophosphole-2-oxides, and their phosphorylating ability was attributed to the intrinsic instability of the nitrogen containing vinylenephosphate-type ring itself. So far, the chemistry of such heteroatom containing five-membered phosphate analogues has been little studied , in contrast to those of ethylenephosphates3) and vinylenephosphates.4) Only recently the alkaline hydrolysis of O,S-ethylenephosphorothioates5) and 2-oxo-1,3,2-oxazaphospholanes6) have been studied and the results are interpreted in terms of the Westheimer's pentacoordinate intermediate mechanism.

In order to obtain the more detailed information on the effect of the heteroatoms on the solvolysis we investigated the hydrolysis of heteroatom containing benzophospholes under neutral condition with the limited amount of water. This communication describes the results of product analysis which suggest the reactivity and the position of the bond fission are strongly dependent on the heteroatoms introduced.

Eight benzophospholes listed in the Table were synthesized either by the reaction of phenylphosphorodichloridate7) with 1,2-disubstituted benzene (method A) or by the reaction of 2-chloro-2-oxo-benzophosphole with phenol or aniline (method B), both of which have been reported in our previous papers.8)

Hydrolysis was then carried out in tetrahydrofuran with three equivalents of water at ambient temperature and the products were isolated as follows: phenol, by silicagel chromatography; phosphates derivatives, as appropriate ammonium salt.
In the cases of 2-anilino- and 2-benzyl-benzodiazaphosphole-2-oxides, the starting material was recovered unchanged under the present hydrolytic condition.

The classification of the products[9] indicated in the Table was made by tentatively following the Westheimer's pentacoordinate intermediate mechanism and according to the equation shown below. Namely, exocyclic cleavage (ring retention path) was considered to provide phenol or aniline and the remaining fragments (9 , H_3PO_4), whereas endocyclic cleavage (ring cleavage path) to afford the products (10, 11) retaining the original phenyl ester group.

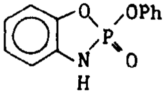
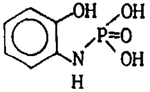
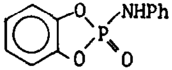
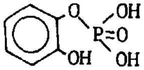
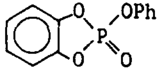
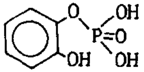
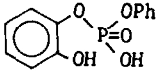
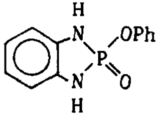
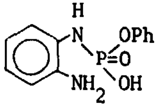
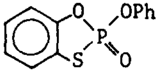
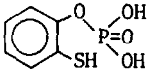
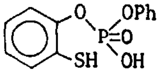
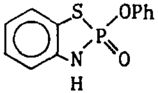
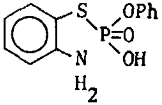
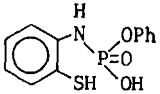
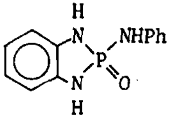
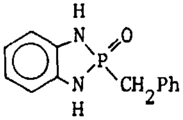


From the survey of the Table, the following conclusion might be reached.

1) *The ease of the hydrolysis is considerably affected by the heteroatoms both at exocyclic and endocyclic position.*—— The increase in numbers and the decrease in the electronegativity of the heteroatoms result in the low reactivity of the substrates. (e. g. 7, 8)

2) *The course of the reaction (ring retention path or ring cleavage path) is highly dependent on the heteroatoms introduced.*—— The extreme two cases are the hydrolysis of 2-phenoxy-benzoxazaphosphole-2-oxide 1, and 2-phenoxy-benzothiazaphosphole-2-oxide 6. In the case of 1 (as well as 2) only ring retention products were isolated[10]. Considering the fact that 1 reacts with o-aminophenol to give the corresponding pentacoordinate compounds[11], it is quite reasonable to conclude that the hydrolysis of 1 should proceed through the Westheimer's pentacoordinate intermediate mechanism. On the contrary, the thiazaphosphole 6 gave almost predominant ring cleavage products. Although the pentacoordinate intermediate mechanism might still be operating in this case, the participation of the direct displacement mechanism (S_N 2 like *In Line* mechanism) is another possibility[12].

Table The Product Analysis of the Hydrolysis of Benzophospholes

Benzophospholes		mp or bp$^{a)}$ (mmHg)	Products from ring retention path			Products from ring cleavage path	
	1	bp 210°(0.001)$^{b)}$	PhOH 85%		62%$^{d)}$	-----	
	2	mp 152-154° $^{c)}$			64%$^{e)}$	-----	
	3	bp 160°(0.7)$^{c)}$	PhOH 68%		71%$^{e)}$		21%$^{e)}$
	4	mp 156-157°$^{b)}$	PhOH 27%	H_3PO_4	34%$^{f)}$		51%
	5	bp 170°(0.15)$^{b)}$			30%$^{g)}$		45%$^{g)}$
	6	bp 235°(0.2) $^{b)}$	PhOH 8%	H_3PO_4	7%$^{d)}$	$PhOPO_3H_2$  	4%$^{d)}$ 0.7%$^{d)}$ 78%$^{d)}$
	7	mp 245-250°$^{b)}$	No reaction				
	8	mp 221-223°$^{b)}$	No reaction				

a) bath temperature b) prepared by method A c) prepared by method B d) as cyclohexylammonium salt
e) as anilinium salt f) as o-phenylenediamine salt g) isolated as methylated form with diazomethane

References and Notes

1) T. Koizumi, Y. Arai, and E. Yoshii, *Tetrahedron Letters*, 1973, 4763.

2) T. Koizumi, Y. Yoshida, Y. Watanabe, and E. Yoshii, *Chem. Pharm. Bull.*, 23, 1381(1975).

3) F. Westheimer, *Accounts of Chemical Research*, 1, 70(1968).

4) a) P. Gillespie, F. Ramirez, I. Ugi, and D. Marquarding, *Angew. Chem. Intern. Ed.*, 12, 91 (1973). b) F. Ramirez, J. F. Marecek, and I. Ugi, *Synthesis*, 1975, 99.
c) F. Ramirez, and J. F. Marecek, *J. Org. Chem.*, 40, 2849(1975).

5) a) D. C. Gay and N. K. Hamer, *J. Chem. Soc., Perkin II*, 1972, 929.
b) D. C. Gay, and N. K. Hamer, *J. Chem. Soc. Chem. Commun.*, 1970, 1564.

6) a) C. Brown, J. A. Boudreau, B. Hewitson, and R. F. Hudson, *J. Chem. Soc., Perkin II*, 1976, 888. b) D. B. Cooper, J. M. Harrison, and T. D. Inch, *Tetrahedron Letters*, 1974, 2697.

7) Benzylphosphonic dichloride was employed in the case of 2-benzyl-benzodiazaphosphole-2-oxide.

8) a) T. Koizumi, Y. Arai, and E. Yoshii, *Chem. Pharm. Bull.*, 21, 202(1973).
b) T. Koizumi, Y. Watanabe, Y. Yoshida, and E. Yoshii, *Tetrahedron Letters*, 1974, 1075.

9) All products gave satisfactory elemental analysis and spectral data.

10) Similar solvolysis with complete ring retention was observed during the phosphorylation of alcohols with 2-phenoxy-benzoxazaphosphole-2-oxide. see ref. 2.

11) We have previously reported that the reaction of 1 with o-aminophenol gave bis-(o-phenyleneoxyamino)-2-aminophenoxy phosphorane and bis-(o-phenyleneoxyamino)phenoxyphosphorane, suggesting that this could be a strong support for the Westheimer's pentacoordinate intermediate mechanism. T. Koizumi, Y. Watanabe, Y. Yoshida, and E. Yoshii, *Tetrahedron Letters*, 1974, 1075.

12) It is of interest because *In Line* mechanism has been suggested only for the catalysis of Pancreatic RNase. W. Saenger, *Angew. Chem. Intern. Edit.*, 12, 591(1973).