

A NOVEL PHOSPHORYLATION METHOD USING THE RING STRAIN  
OF FIVE-MEMBERED CYCLIC PHOSPHORODIAMIDATE<sup>1)</sup>

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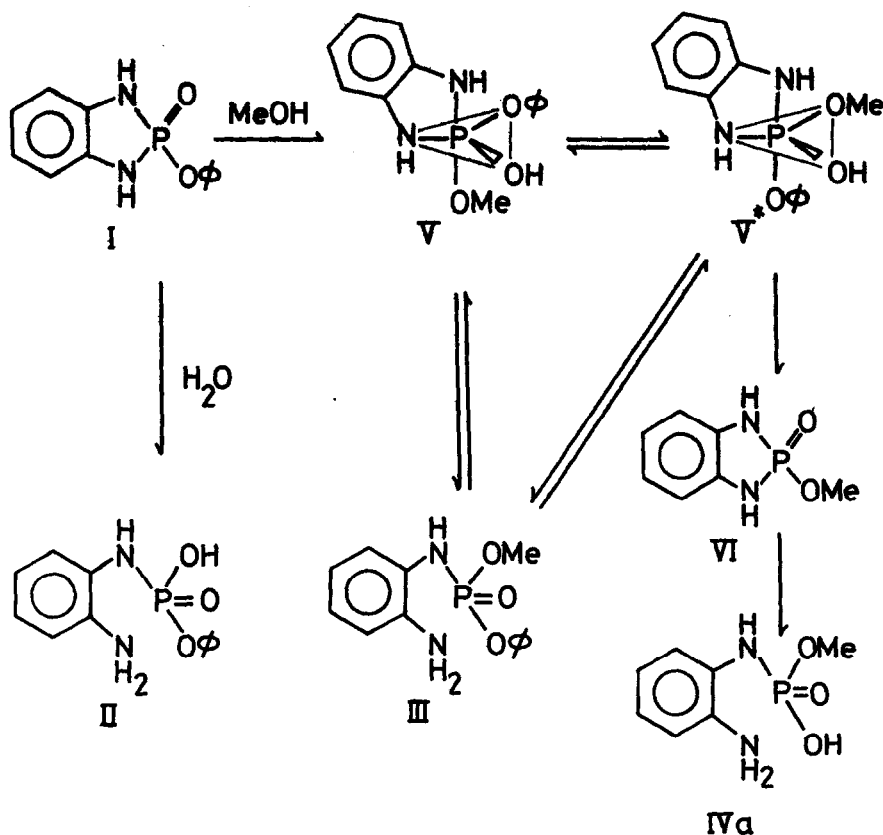
Five-membered cyclic phosphates have been known to be susceptible to hydrolysis and the reason for the high reactivity has been attributed to the ring strain of five-membered ring and the relief of the strain by the formation of a pentacoordinate intermediate<sup>2)</sup>.

During the course of our study on the phosphorus containing heterocyclic compounds, we noticed that unlike ordinary phosphorodiamidates, 2-phenoxy-1,3-dihydro-2H-1,3,2-benzodiazaphosphole-2-oxide (I) reacts easily with water even at room temperature to give phenyl hydrogen N-(2-aminophenyl)phosphoroamidate (II, 50% yield), phenol (27%), and *o*-phenylenediammonium phosphate (34%) respectively<sup>3)</sup>. On the basis of this finding we have reached the idea of using I for the phosphorylation of alcohols. This paper describes the results along this line and presents the first successful attempt to utilize the ring strain energy of five-membered cyclic phosphorodiamidates for the phosphorylation of alcohols<sup>4)</sup>.

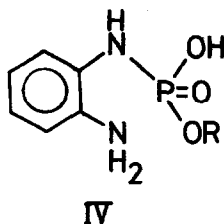
When I was refluxed with one equivalent of methanol in tetrahydrofuran for 2 hours, there were obtained two products after fractional crystallization from aqueous ethanol: methyl phenyl N-(2-aminophenyl)phosphoroamidate (III mp 123-124°, 17% yield) and methyl hydrogen N-(2-aminophenyl)phosphoroamidate (IVa mp 172-173°, 48% yield)<sup>5)</sup>.

Formation of III and IVa is explained by assuming pentacoordinate intermediates and subsequent transformations. Nucleophilic attack of methanol on phosphorus atom from an apical position gives a pentacoordinate intermediate V, which pseudorotates to V\* and its equivalents<sup>6)</sup>. The intermediates V and V\* may afford III by ring opening with apical P-N bond cleavage. By the loss of phenoxy group V\* gives 2-methoxy-1,3-dihydro-2H-1,3,2-benzodiazaphosphole-2-oxide (VI), which is eventually hydrolyzed to IVa during the work-up procedure.

Interestingly the exclusive formation of IVa (62% yield) was observed by a prolonged heating of the reaction mixture ( for 24 hrs ), which suggests that transformation of III to IVa might have occurred. In fact III was converted to IVa by refluxing for 24 hrs in THF and the aqueous work-up. The formation of VI through the pentacoordinate intermediate V and/or V\* should be a logical explanation for this conversion.



The easy formation of the methyl phosphoroamidate IVa by the reaction of I with methanol prompted us to investigate the phosphorylation of other alcohols. Using the same condition as that of methanol (24 hrs reflux in THF), the following results were obtained. In the case of ethanol, ethyl hydrogen N-(2-aminophenyl)phosphoroamidate IVb (mp 166-167°) was obtained in 51% yield.



	b	c	d	e	f	g
R	Et	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	n-C <sub>3</sub> H <sub>7</sub>	i-C <sub>3</sub> H <sub>7</sub>	n-C <sub>4</sub> H <sub>9</sub>	n-C <sub>16</sub> H <sub>33</sub>

Similarly IVc (mp 171-172°, 42%), IVd (mp 164-165°, 32%), IVe (mp 161-163°, 30%), IVf (mp 166-168°, 30%), IVg (mp 140-141°, 48%) were obtained from the corresponding alcohols.

Although the yields are not fully satisfactory and need some improvement<sup>7)</sup>, the result presented here clearly verifies that the idea of using the ring strain for the phosphorylation of alcohols is quite valid. Research along this line is now being in progress together with application to complex alcohols and result will be reported elsewhere.

#### References and Notes

- 1) A part of this study was presented at the 93rd Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April, 1973.
- 2) F. H. Westheimer, Accounts of Chem. Research, 1, 70(1968).  
R. F. Hudson, and C. Brown, Accounts of Chem. Research, 5, 204(1972).

- 3) T. Koizumi, Y. Arai, and E. Yoshii, Chem. Pharm. Bull., 21, 202(1973).
- 4) There have been many interesting papers utilizing the five-membered cyclic phosphates for the preparation of alkyl phosphates.
  - a) T. A. Khwaja, C. B. Reese, and J. C. M. Stewart, J. Chem. Soc. (C), 1970, 2092.
  - b) Y. Kodaira, and T. Mukaiyama, J. Org. Chem., 31, 2903(1966).
  - c) T. Ukita, A. Hamada, and A. Kobata, Chem. Pharm. Bull., 9, 363(1961).
  - d) T. Ukita, N. Imura, K. Nagasawa, and N. Aimi, Chem. Pharm. Bull., 10, 1113(1962).

However, these methods utilized the ring strain for the decomposition of the initially formed five-membered intermediates. In other words, the ring strain energy was not used for the P-OR bond formation itself.

The present method utilizes the ring strain energy of the five-membered cyclic phosphorodiamidate for the formation of P-OR bond itself and in this respect is quite different from those previously reported.

- 5) Satisfactory elemental analyses and spectral data have been obtained on all new compounds. All the yields are based on alcohols employed and are the isolated yields.
- 6) Although many other pseudorotational isomers may be considered, only V and V\* are formulated in order to simplify the discussion.

See K. Mislow, Accounts of Chem. Research, 3, 321(1970) for the topological representation of pseudorotational isomers.
- 7) It seems quite possible to improve the yields by the choice of the reaction conditions. For example, when 3 equivalents of I was used for the reaction with n-propanol, IVd was obtained in 60-70% yield.