

primary isotope effects and is, therefore, separate from the evidence based on the absolute magnitudes of the secondary isotope effects.

From these two pieces of evidence, we conclude that the proton is almost completely transferred to oxygen in the transition state for E2 elimination by HO<sup>-</sup> in H<sub>2</sub>O on C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>CH<sub>2</sub>N<sup>+</sup>(CH<sub>3</sub>)<sub>2</sub>. For the corresponding sulfonium ion, the proton is less completely transferred, and for the bromide, the proton is still less completely transferred. This work demonstrates how primary and secondary isotope effects in the same reaction can complement one another.

The rates of elimination of β-phenylethyl compounds substituted in the ring lead to good Hammett ρ correlations. The chloride, bromide, iodide, tosylate, and dimethylsulfonium leaving groups all give ρ values between 2 and 3 with sodium ethoxide in ethanol at 30°, these large values indicating considerable carbanion character in the transition states.<sup>7</sup> Although large ρ values could conceivably be due to other factors than carbanion character, e.g., to the incipient double bond conjugated with the ring in the transition state, our results show that the proton is substantially transferred in these transition states.

We plan to extend this method to other systems because it should help to explain the Hofmann-Saytzeff orientation effects which are currently ascribed to steric influences<sup>8</sup> by some investigators and to electrical influences by other investigators.<sup>9</sup>

(7) W. H. Saunders, Jr., and R. A. Williams, *J. Am. Chem. Soc.*, **79**, 3712 (1957); W. H. Saunders, Jr., C. B. Gibbons, and R. A. Williams, *ibid.*, **80**, 4099 (1958); C. H. DePuy and D. H. Fromsdorf, *ibid.*, **79**, 3710 (1957); C. H. DePuy and C. A. Bishop, *ibid.*, **82**, 2532, 2535 (1960). The ρ value for trimethylammonium under the same conditions is even larger, 3.77 (W. H. Saunders, Jr., and D. G. Bushman, unpublished).

(8) H. C. Brown, in "The Transition State," Special Publication No. 16, The Chemical Society, London, 1962, pp. 143-144.

(9) D. V. Banthrophe, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 4054 (1960).

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### The Hydrolysis of Five-Membered Cyclic Phosphotriesters to Cyclic Phosphodiester<sup>1</sup>

Sir:

The alkaline hydrolysis of methyl ethylene phosphate is much faster than that of trimethyl phosphate and occurs with P-O fission and *ring opening*.<sup>2</sup> The heat of saponification of methyl ethylene phosphate exceeds that of dimethyl 2-hydroxyethyl phosphate by about 5.5 kcal./mole.<sup>2c</sup> Several hypotheses have been advanced to explain these kinetic and thermodynamic observations.<sup>2,3</sup>

Recently, Covitz and Westheimer<sup>3</sup> found that the hydrolysis of methyl ethylene phosphate in acid solution gave predominantly methyl 2-hydroxyethyl hydrogen phosphate, and, in addition, some ethylene hydrogen phosphate (from 5 to 30%). There was, therefore, some preservation of the five-membered ring.

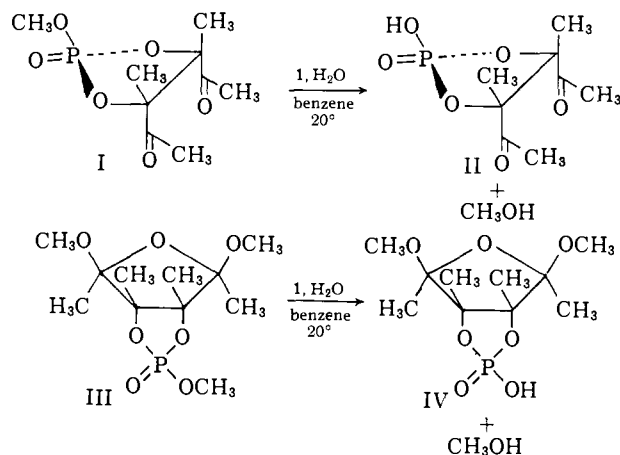
We have observed that certain five-membered cyclic phosphotriesters (I, III) react very rapidly with one mole equivalent of water in aprotic solvents at 20°, yielding *cyclic phosphodiester* II and IV almost ex-

(1) We gratefully acknowledge the support of the Cancer Institute of the National Institutes of Health (CY-4769), the National Science Foundation (G 19509), and the Petroleum Research Fund of the American Chemical Society (286-A).

(2) (a) P. Haake and F. H. Westheimer, *J. Am. Chem. Soc.*, **83**, 1102 (1961), and references therein; (b) R. E. Wall, Thesis, Harvard University, 1960; (c) E. T. Kaiser, M. Panar, and F. H. Westheimer, *J. Am. Chem. Soc.*, **85**, 602 (1963).

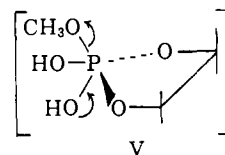
(3) F. Covitz and F. H. Westheimer, *ibid.*, **85**, 1773 (1963).

clusively. The cyclic diesters were readily isolated in crystalline form; they were converted into the original triesters by diazomethane and were characterized also as cyclohexylammonium and piperidinium salts.

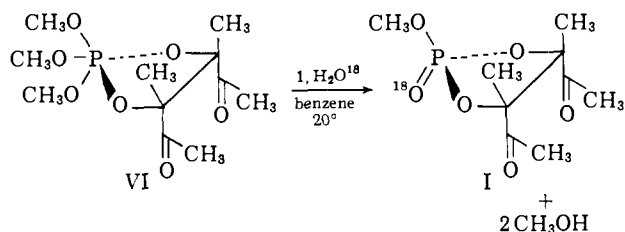


Trimethyl phosphate and dimethyl phosphoacetoin<sup>4</sup> were not affected by water in benzene solution under comparable conditions.

It seems possible that the formation of cyclic phosphodiester from cyclic phosphotriester, at least in aprotic solvents, may proceed by way of an oxyphosphorane intermediate V. In other words, it may be possible under certain conditions to hydrate the phosphoryl group of a cyclic phosphate ester.



If an oxyphosphorane V is indeed an intermediate in the hydrolysis of a cyclic triester to a cyclic diester, the collapse of the oxyphosphorane must occur with preservation of the five-membered ring, since an open-chain diester should not cyclize under the experimental conditions. Some information on the mode of collapse of cyclic oxyphosphoranes analogous to V can be obtained from a study of the hydrolysis of the crystalline pentaalkoxyphosphorane VI in aprotic solvents, using water enriched with O<sup>18</sup>. We had previously shown,<sup>5</sup> using unlabeled water, that this hydrolysis is extremely fast and gives rise to the cyclic phosphotriester I.



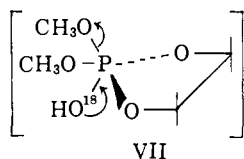
The experiments with labeled water have shown that the oxygen atom of the water becomes attached to the phosphorus of the phosphate ester, presumably as a phosphoryl group, PO. Precisely how this happens remains a problem on the mechanism of substitution at quintuply-connected phosphorus; however, the results suggest the participation of an oxyphosphorane VII in the hydrolysis of the pentaalkoxyphosphorane VI. Evidently, VII tends to collapse with preservation of the five-membered ring, since the product is a cyclic phosphate I. Therefore, the oxyphosphorane V,

(4) F. Ramirez, B. Hansen, and N. B. Desai, *ibid.*, **84**, 4588 (1962).

(5) F. Ramirez, N. B. Desai, and N. Ramanathan, *ibid.*, **85**, 1874 (1963).

postulated in the hydrolysis of the cyclic triesters to the cyclic diesters, should also collapse with preservation of the five-membered ring.

It was shown that no oxygen from the water was incorporated into the carbonyl function of the ester I. These conclusions are based on mass spectrometry of the intact ester.



In discussing the behavior of phosphorus esters, Westheimer and co-workers<sup>3</sup> have recently stressed the possible effect on phosphate stability of p-d double bonding between the ester oxygens and the phosphorus atom. They point out that resistance of a ring to this double bonding should result in lower stabilization for cyclic phosphates than for open chain phosphates. A difference in stability among phosphates, for this or for other reasons, may be, at least partly, responsible for the behavior of our cyclic and open-chain phosphotriesters toward water in aprotic solvents. It may be possible to hydrate the phosphoryl group of the less stable cyclic ester but not that of the more stable open chain esters.

Benzene solutions of the cyclic triesters I and III were treated with one mole equivalent of water at 20°; stirring was continued for about 5 min. in the former and 90 min. in the latter case (to disappearance of turbidity). Removal of solvent and of methanol left residues which were triturated with ether and then recrystallized.

The diketol triester I has been described.<sup>5</sup> The ketal triester III had m.p. 89–90° (hexane); infrared (CCl<sub>4</sub>,  $\mu$ ) PO at 7.70, POC– at 9.43 and 9.56, no OH or CO; H<sup>1</sup> n.m.r. (CDCl<sub>3</sub>,  $\tau$ ) doublet CH<sub>3</sub>OP at 6.16,  $J_{HP}$  12.3 c.p.s., one singlet CH<sub>3</sub>O–C– at 6.73, one CH<sub>3</sub>–C– at 8.56, the other at 8.64; intensities: 1:1:4:4:4. *Anal.* Calcd. for C<sub>11</sub>H<sub>21</sub>O<sub>7</sub>P: C, 44.6; H, 7.2; P, 10.5. Found: C, 44.2; H, 7.2; P, 11.1.

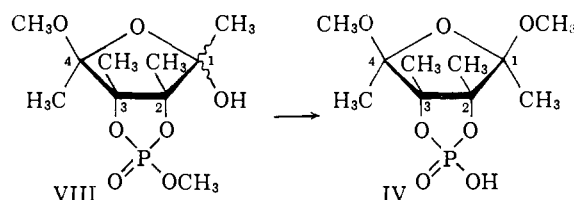
Diketol diester II had m.p. 138–140° (ethyl acetate-hexane); infrared (CHCl<sub>3</sub>,  $\mu$ ) broad P(O)OH with minimum at 3.7, CO at 5.85, PO at 7.97, POC– at 9.77. *Anal.* Calcd. for C<sub>8</sub>H<sub>13</sub>O<sub>6</sub>P: C, 40.6; H, 5.5; P, 13.2; mol. wt., 236. Found: C, 40.4; H, 5.5; P, 13.3; neut. equiv., 224.

The cyclohexylammonium salt had m.p. 179–180° (CH<sub>2</sub>Cl<sub>2</sub>-ether); CO at 5.85 and 5.88  $\mu$  (CH<sub>2</sub>Cl<sub>2</sub>). *Anal.* Calcd. for C<sub>14</sub>H<sub>26</sub>O<sub>6</sub>NP: C, 50.2; H, 7.8; N, 4.2. Found: C, 50.3; H, 7.9; N, 3.9.

Ketal diester IV had m.p. 115–116° (acetonitrile); infrared (CCl<sub>4</sub>,  $\mu$ ) broad P(O)OH with minimum at 3.8, PO at 8.00, POC– at 9.71, and no CO; H<sup>1</sup> n.m.r. (CDCl<sub>3</sub>,  $\tau$ ) acidic H<sup>1</sup> at –2.57, one singlet CH<sub>3</sub>OC– at 6.73, one CH<sub>3</sub>–C– at 8.60, the other at 8.63. *Anal.* Calcd. for C<sub>10</sub>H<sub>19</sub>O<sub>7</sub>P: C, 42.6; H, 6.7; P, 11.0. Found: C, 42.6; H, 6.7; P, 11.3. Cyclohexylammonium salt had m.p. 189–191° (CH<sub>2</sub>Cl<sub>2</sub>-ether); no CO in infrared. *Anal.* Calcd. for C<sub>16</sub>H<sub>32</sub>O<sub>7</sub>NP: C, 50.4; H, 8.5; N, 3.7; P, 8.1. Found: C, 50.7; H, 9.1; N, 3.8; P, 8.3.

The preparation of the ketal phosphodiester IV is of intrinsic interest. IV was obtained when a solution of the hemiketal phosphotriester<sup>5</sup> VIII in anhydrous acetonitrile was kept several hours at 20°. This is a new type of molecular rearrangement of a furanose-2,3-cyclic phosphate in which the C-1-hydroxyl group exchanges places with the methoxyl group attached to

the phosphorus. The details of this rearrangement are being investigated.



Treatment of the diester IV with diazomethane provided the triester III used in the hydrolysis experiments.

**Acknowledgment.**—The authors gratefully acknowledge the cooperation and advice of Professor E. Eliel (University of Notre Dame) in proton n.m.r. spectroscopy. They appreciate the opportunity of examining the manuscripts of Kaiser, Panar, and Westheimer<sup>2c</sup> and of Covitz and Westheimer<sup>3</sup> before publication.

(6) Alfred P. Sloan Fellow, 1961–1963.

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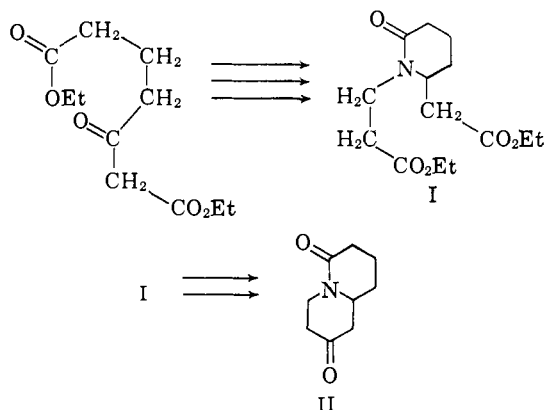
RECEIVED JUNE 14, 1963

### Total Synthesis of *d,l*-Matrine

Sir:

We wish to report the application of our quinolizidine synthesis<sup>1,2</sup> to the total synthesis of *d,l*-matrine (IV) the principal alkaloid of *Sophora flavescens* Ait. The stereochemistry and structure of matrine have been put forth by several groups of workers.<sup>3–5</sup>

Diethyl-3-oxo-pimalate<sup>6</sup> was condensed with the ethyl ester of  $\beta$ -alanine by refluxing a mixture of the two (0.27 mole of diester to 0.29 mole of  $\beta$ -alanine ester) in benzene and removing the water formed *via* azeotropic distillation. The solvent was removed *in vacuo* and



the crude product was reduced with Adams catalyst at 2000 p.s.i. in ethanol solution containing several drops of acetic acid. The crude reduction product obtained after removing the solvent was heated *in vacuo* at steam-bath temperature for 6 hr. to effect lactamization. Distillation afforded I (65% over-all yield), b.p.

- (1) K. P. Singh and L. Mandell, Abstracts of the 138th National Meeting of the American Chemical Society, New York, N. Y., September, 1960, p. 62.
- (2) L. Mandell and K. P. Singh, *J. Am. Chem. Soc.*, **83**, 1766 (1961).
- (3) F. Bohlman, W. Weise, D. Raktze, and C. Arndt, *Ber.*, **91**, 2167, 2177 (1958).
- (4) K. Tsuda, *et al.*, *ibid.*, **69**, 429 (1936); *J. Org. Chem.*, **21**, 1481 (1956).
- (5) E. Ochai, S. Okuda, and H. Minato, *J. Pharm. Soc. Japan*, **72**, 1481 (1956).
- (6) Prepared *via* a modification of the procedures of B. Riegel and W. M. Lillienfeld, *J. Am. Chem. Soc.*, **67**, 1273 (1945), and J. H. Hunter and J. A. Hogg, *ibid.*, **71**, 1924 (1949).