




Table I. Rate Constants^a for Hydrolyses in D₂O

Compound	Temp, °C	<i>k</i> (acid)	Temp, °C	<i>k</i> (acid)	Temp, °C	<i>k</i> (base)	Temp, °C	<i>k</i> (base)
II	26	3 × 10 ^{-3b}	100	2 × 10 ^{-6c}	30	6 × 10 ^{5d}	25	1 × 10 ⁻⁵
	100	2 × 10 ⁻⁵			25	1 × 10 ⁻²		
			100	7 × 10 ⁻⁶			25	3 × 10 ⁻⁴
III	100	>3 × 10 ^{-4b}	100	1 × 10 ^{-6c}	30	2 ^{b,d}	91	3 × 10 ^{-5e,e}
	100	9 × 10 ⁻⁶	100	9 × 10 ⁻⁶	25	2 × 10 ⁻⁴	25	2 × 10 ⁻⁴

^a In liters/mole sec; determined by nmr methods unless otherwise noted. ^b First ester group. ^c Second ester group. ^d Determined by use of a pH-Stat. ^e NMR Specialties, Inc., Teflon liner used.

The first ester group of III is nowhere near so labile as that of II. Nevertheless, the rate of its hydrolysis in alkali¹¹ exceeds that of the second ester group (extrapolated to a common temperature) by a factor of about 10⁷ and exceeds that of its monocyclic analog by a factor of 10⁴. The large retardation—about 10³-fold—in the rate of hydrolysis of the second ester group of III compared to that of its monocyclic analog is reasonable on electrostatic grounds provided that the tricyclic system in II and III has the *exo* configuration. The rate of hydrolysis in acid of the first ester group in III exceeds that of the second by a factor of at least 300, and that of its monocyclic analog by a factor of at least 30. Since it is possible that hydrolysis of the ester group in the tricyclic system occurs with P–O cleavage, while that of the monocyclic analog occurs with C–O cleavage, the actual rate difference at phosphorus may be considerably larger than that for the over-all rates. The ester group that hydrolyses rapidly in II and III is presumably the one at position 7 of the phosphabicycloheptane or -heptene system.

If trigonal-bipyramidal intermediates are indeed involved in these hydrolyses, and if the transition state for the hydrolysis of an ester is reasonably symmetrical, then the hydrolysis must take place with pseudo-rotation between one trigonal-bipyramidal intermediate and another, in accordance with previous theory.³ The large difference in rate between the hydrolyses of II and III may be caused by the larger strain in the former; the type of special interactions noted for 7-halobicycloheptenes seems relatively unlikely,¹² since II and III show the same qualitative behavior.

The rate constants here recorded apply, in all cases, to regions where second-order kinetics are obeyed. Most constants were determined by nmr analysis of reactions mixtures in D₂O and are therefore relatively crude numbers; fortunately for the large differences here discussed, high precision is not essential. For all the compounds except II, the entire quartet for the

methylene group of the ethanol produced during hydrolysis was cleanly separated from the multiplet of the methylene group of the corresponding ethyl ester, so that integration of the areas of these peaks was always possible, and the data are therefore as reliable as the integrator of the Varian A-60. For II, the rates were estimated by comparing the heights of the peak for the methyl protons of ethanol with those for the ester.

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Some Substituted 7-Ethoxy-7-phosphabicycloheptene and -heptane 7-Oxides¹

Sir:

Strain in five-membered cyclic phosphates, but not in previously known phosphonates and phosphinates, greatly enhances the rate of hydrolysis *external* to the ring. To test our hypothesis² concerning the cause of this phenomenon further, we have sought esters with maximum strain in a bond angle at phosphorus. We now report the preparation of three highly strained compounds: phosphinic esters with phosphorus at the bridge position³ of bicyclic systems. Their hydrolytic behavior is reported in the accompanying communication.⁴

We had previously³ prepared 1-ethoxyphosphole 1-oxide (I) and found that, although it does not readily react with dienophiles, it dimerizes with a rate constant of about 0.5 l./mole sec at 25°. The Diels–Alder dimer has now been isolated in crystalline form and assigned structure II, where the stereochemistry of the ring junction and of the substituents on phosphorus is uncertain. On hydrogenation, II yields III, where the stereochemistry is likewise uncertain. The synthesis of 3,4-dimethyl-1-ethoxyphosphole 1-oxide (IV) was attempted, since it was expected on the basis of analogy

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(2) E. A. Dennis and F. H. Westheimer, *J. Am. Chem. Soc.*, **88**, 3431, 3432 (1966).

(3) D. A. Usher and F. H. Westheimer, *ibid.*, **86**, 4732 (1964).

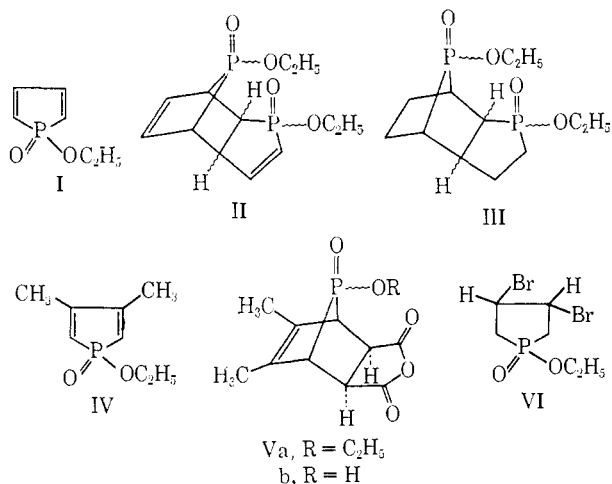
(4) R. Kluger, F. Kerst, D. G. Lee, E. A. Dennis, and F. H. Westheimer, *ibid.*, **89**, 3918 (1967).

(11) Professor Aksnes has written us that further investigations, subsequent to his publication,⁹ have shown that his sample of the ethyl ester of tetramethylenephosphinic acid contains considerable 1,8-dichlorooctane as impurity; this impurity presumably accounts for the incomplete solubility of his material in water. It may also account for most of the discrepancy between his rate and ours. Our rates were measured at 25° in D₂O, Aksnes and Bergesen's at 50° in 50% ethanol. After extrapolation to a common temperature, our rate constant is ten times theirs. Although much of this difference is caused by a solvent effect, a redetermination of the rate of saponification of this ethyl ester at 50° in 50% ethanol gives, in our hands, a rate about 2.5 that reported by the Norwegian investigators.

(12) S. Winstein, M. Shatavsky, C. Norton, and R. B. Woodward, *J. Am. Chem. Soc.*, **77**, 4183 (1955).

with other dienes⁵ to be a better diene and poorer dienophile (and consequently more stable) than the unsubstituted ethoxyphosphole oxide. A crude reaction mixture has been obtained that reacts with maleic anhydride, presumably to form Va, which on hydrolysis forms Vb. The latter has been identified by analysis, analytical mass spectrum, and nmr spectrum. The nmr spectrum in D₂O shows a singlet at δ 3.71 (2 H), a doublet at 2.89 ($J = 11$ cps, 2 H), and a singlet at 1.80 (6 H). The simplicity of the spectrum confirms the assigned structure. Apparently the signal from the bridgehead hydrogen atoms is split by the ³¹P; the lack of interaction between these hydrogen atoms and those adjacent to the carbonyl groups suggests that the compound is the *exo* isomer.⁶

II, III, and V constitute a new class of phosphinates with highly compressed C-P-C bond angles. Their mass spectra show, in addition to the parent ion, a strong peak corresponding to the loss of the bridge, with an accompanying appropriate metastable peak. Presumably O=P(O)C₂H₅ or O=P(O)H is formed as the uncharged cleavage product. These are monomeric metaphosphites, previously postulated⁷ as intermediates in the hydrolysis of phosphites.



II was best prepared from VI, obtained by the bromination of 1-ethoxy-3-phospholene 1-oxide⁸ in chloroform at 0°, needles from ethyl acetate-hexane, mp 47–48°; nmr triplet at δ 1.37 (3 H), multiplets from 1.9 to 3.2 (4 H), and overlapping sextet and quintet 3.82 to 5.20 (4 H); principal infrared bands at 3.31, 7.17, 7.75, 8.00, 8.22, 9.67, 10.40, 11.43, and 12.05 μ . *Anal.* Calcd for C₆H₁₁Br₂O₂P: C, 23.56; H, 3.59; P, 10.12; Br, 52.26. Found: C, 23.49, 23.47; H, 3.75, 3.70; P, 10.27, Br, 52.02.

VI (25 g) in 125 ml of carbon tetrachloride was allowed to react with 25 g of dry triethylamine at 0° for 10 hr to yield triethylammonium bromide (removed by filtration) and a solution of II. The concentrate from the carbon tetrachloride solution was chromatographed over Florisil by elution with 3:1 carbon tetrachloride-ethyl acetate. The fractions were evaporated, and those containing product were dissolved in ethyl ace-

tate and crystallized by the addition of *n*-hexane; rhombic crystals, mp 125–126°; exact mass, calcd 288.0680, found 288.0688; principal infrared bands (KBr) at 3.34, 6.39, 7.20, 7.54, 8.19, 8.33, 9.19, 9.75, 10.54, 11.83, 12.62, 13.06, 13.71, and 14.47 μ ; the nmr spectrum is compatible with that expected for II. *Anal.* Calcd for C₁₂H₁₈O₄P₂: C, 50.00, H, 6.30, P, 21.50. Found: C, 49.36, H, 6.25, P, 21.57.

Crystalline II was hydrogenated in absolute ethanol with 10% platinum on charcoal at 3 atm for 24 hr. After removing solvent, the product was crystallized from ethyl acetate-hexane; needles, mp 80–81°; exact mass: calcd 292.0993, found 292.1009; principal infrared bands (CCl₄) at 3.30, 7.88, 8.04, 8.13, 8.21, 9.19, 9.65, 10.50, and 11.49 μ ; the nmr spectrum is compatible with that expected for III. *Anal.* Calcd for C₁₂H₂₂O₄P₂: C, 49.30, H, 7.59, P, 21.21. Found: C, 49.42; H, 7.50; P, 21.20.

The crude reaction mixture from 1-ethoxy-3,4-dimethyl-2-phospholene 1-oxide⁸ and N-bromosuccinimide was treated with 1 equiv of sodium ethoxide in ethanol; a compound (presumably 1-ethoxy-3,4-dimethylphosphole 1-oxide), λ_{\max} 298 m μ , was generated. After 5 min a slight excess of acetic acid was added; the solution of the phosphole was stable at room temperature for several days, as evidenced by ultraviolet spectroscopy. The solution was evaporated at room temperature, and the carbon tetrachloride soluble portion of the residue was treated with maleic anhydride. Vb formation could be prevented by the use of superdry solvents or accelerated by the addition of a small amount of water or acetic acid. After crystallization from tetrahydrofuran, the compound melted at 261–263°; principal infrared bands (KBr) at 3.30, 5.29, 5.58, 6.88, 7.72, 8.11, 8.50, 9.22, 10.22, 10.70, 10.85, and 14.67 μ . *Anal.* Calcd for C₁₀H₁₁O₃P: C, 49.60, H, 4.58; P, 12.79. Found: C, 49.4; H, 4.54; P, 12.62.

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Biological Activities of Some Terminally Modified Squalene and Squalene 2,3-Oxide Analogs

Sir:

Recent findings in our own^{1,2} and another³ laboratory have shown that squalene 2,3-oxide (I) and not squalene (II) is the substrate which undergoes enzymic cyclization to lanosterol in preparations of rat liver. The cyclase system occurs in the microsomal fraction and requires neither oxygen nor NADPH.² The molecular asymmetry of squalene 2,3-oxide permits new approaches to the study of the mechanism of enzymic cyclization, and it is now possible to synthesize selected analogs of squalene oxide and to test them as substrates for the cyclase system in the expectation that the structures of their products will shed new light on the mode of interaction between this enzyme system and its substrate.

As a first approach to a systematic study of this type

(1) E. E. van Tamelen, J. D. Willett, R. B. Clayton, and K. E. Lord, *J. Am. Chem. Soc.*, **88**, 4752 (1966).

(2) E. E. van Tamelen, J. D. Willett, and R. B. Clayton, *ibid.*, **89**, 3371 (1967).

(3) E. J. Corey and W. E. Russey, *ibid.*, **88**, 4750 (1966).

(5) J. Sauer, D. Lang, and A. Mielert, *Angew. Chem.*, **74**, 352 (1962).

(6) W. D. Kumler, J. N. Shoolery, and F. V. Brutcher, Jr., *J. Am. Chem. Soc.*, **80**, 2533 (1958); J. Meinwald and Y. C. Meinwald, *ibid.*, **85**, 2514 (1963).

(7) E. T. Kaiser, M. Panar, and F. H. Westheimer, *ibid.*, **85**, 602 (1963).

(8) U. Hasserodt, K. Hunger, and F. Korte, *Tetrahedron*, **19**, 1563 (1963); K. Hunger, U. Hasserodt, and F. Korte, *ibid.*, **20**, 1593 (1964).