group absorption at 5.8 μ in the infrared spectrum. The visible spectrum showed peaks at 740, 697, 660, 630, 606, and 579 mμ in cyclohexane. This spectrum agrees both in position and relative intensity with the spectrum of 6-methyl azuloate reported by Müller[8] to possess maxima at 743, 697, 666, 636, 606, and and 578 mμ. The spectrum of ethyl 6-azuloate is not in the literature, but the visible spectra of the methyl and ethyl esters of 5 azuloic acid are identical, and we assume this to be the case for the 6-esters as well.

5-Azuloic Acid.—A solution of ethyl 5-azuloate and 3 N sodium hydroxide in 50% ethanol was refluxed for 5 hr. The solution was then flooded with water and extracted with ether to remove any remaining ester. The water layer was then acidified and extracted with ether. The ether layer was dried over magnesium sulfate and the solvent was removed yielding a viscous blue oil. The oil was chromatographed on silica gel. Benzene removed a blue band which yielded a blue oil on removal of the solvent. This blue oil proved to be 5-azuloic acid. The infrared spectrum showed a carbonyl group absorption at 5.85 μ. The visible spectrum showed peaks at 679, 645, 617, 588, 566, 542, and 523 mμ in ethanol. The spectrum agrees both in position and relative intensity with that reported by Müller[8] with maxima at 679, 645, 617, 588, 566, 542, and 523 mμ. The neutralization equivalent was 180 compared with the calculated value of 172.

6-Azuloic Acid.—This acid was prepared in a manner analogous to the 5-azuloic acid. The crude acid was a blue-green oil which was chromatographed on silica gel. The column was eluted with benzene which removed a blue band and then eluted with benzene ether which removed a green band. The solvent was removed from the green portion and the 6-azuloic acid was obtained as a green oil. The infrared spectrum showed a carbonyl group absorption at 5.85 μ. The visible spectrum shows peaks at 750 698, 660, and 580 mμ in ethanol. This spectrum agrees both in position and relative intensity with that in the literature[8] with peaks at 750, 698, 665, 633, and 580 mμ. The neutralization equivalent was 171 compared with the calculated value of 172.

Ethyl 1-Azuloate.—To 1.1 g. of 1-azuloic acid dissolved in 75 ml. of anhydrous ether was added 2 ml. of thionyl chloride. The solution was then refluxed for 12 hr. after which 25 ml. of absolute ethanol was added and allowed to reflux overnight. The ether and ethanol were then distilled off, and the residue was dissolved in ether. The ether was washed twice with sodium carbonate and then dried over magnesium sulfate. The ether was removed on a steam bath and the dark blue oil was chromatographed on silica gel. The column was eluted with petroleum ether and then benzene. A red band developed first and was discarded. This was followed by a deep purple band which gave a purple oil in approximately 30% yield on removal of the solvent. This purple oil proved to be ethyl 1-azuloate and showed a carbonyl group absorption at 5.85 μ. The visible spectrum showed peaks at 686, 645, 620, 588, and 545 mμ. This spectrum agrees with the spectrum of methyl 1-azuloate, reported by Anderson,[2b] with maxima at 686, 650, 590, and 544 mμ.
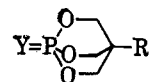
The Synthesis of Bicyclic Esters of Phosphorus Acids

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Recently Verkade and Reynolds,[1] Neunhoffer and Maiwald,[2] and Wadsworth and Emmons[3] published the

I, Y = none; R = CH₃	VII, Y = Se; R = C₂H₅
II, Y = O; R = CH₃	VIII, Y = O; R = C₆H₅
III, Y = S; R = CH₃	IX, Y = S; R = C₆H₅
IV, Y = none; R = C₂H₅	X, Y = O; R = CH₂O—C₆Cl₅
V, Y = O; R = C₂H₅	XI, Y = S; R = CH₂O—C₆Cl₅
VI, Y = S; R = C₂H₅	XII, Y = S; R = CH₂O—C₆Br₅
	XIII, Y = O; R = NO₂

synthesis of bicyclic esters of phosphorus acids. We wish to report our own independent study.
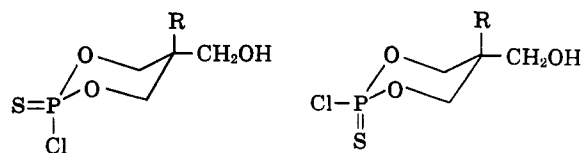
In this laboratory, the previously unknown compounds VII to XII have been synthesized, and the compounds I to VI also have been independently synthesized. Most of the compounds were prepared by a procedure modified from that of Zetzsche and Zurbrugy.[4] Thus, I was prepared in 50% yield by the reaction of phosphorus trichloride and 2-ethyl-2-(hydroxymethyl)-1,3-propanediol in the presence of ether. The product was thermally stable permitting purification by distillation. When phosphorus oxychloride or phosphorus thiotrichloride were used instead of phosphorus trichloride, the products were the bicyclic phosphate and thiophosphates derived from the corresponding triol. The phosphates and thiophosphates were not distillable, but they were stable in water and were high-melting solids. Thus, they could be isolated from aqueous or organic solution without difficulties.

The bicyclic phosphites have been reported to be converted by hydrogen peroxide[1,2,5] and by peracetic acid[3] to the corresponding phosphate, and by sulfur[1,2] and by a mercaptan[3] to the corresponding thiophosphates. We further found that I behaved like triphenyl phosphite in being stable to pure oxygen at room temperatures,[6] but it was instantly oxidized by ozone to yield V. Analogous to the conversion of phosphine to phosphine selenide,[7] I was converted to VII by selenium in the presence of sodium selenide.

A particularly interesting feature of this reaction is that the triols react with the phosphorus trihalides without forming cross-linked polymers as the main products, and satisfactory results can be obtained without using high-dilution technique and lowest possible temperatures.

The formation of the bicyclic esters may involve either one or both of the two intermediates[8] (Chart I), which will further close by either a front or a back-side attack of the OH group on P–Cl to give bicyclic products. However, a study of the formation of 1-phospha-

CHART I

(1) J. G. Verkade and L. I. Reynolds, *J. Org. Chem.*, **25**, 663 (1960).
(2) O. Neunhoffer and W. Maiwald, *Chem. Ber.*, **95**, 108 (1962).
(3) W. S. Wadsworth and W. D. Emmons, *J. Am. Chem. Soc.*, **84**, 610 (1962).
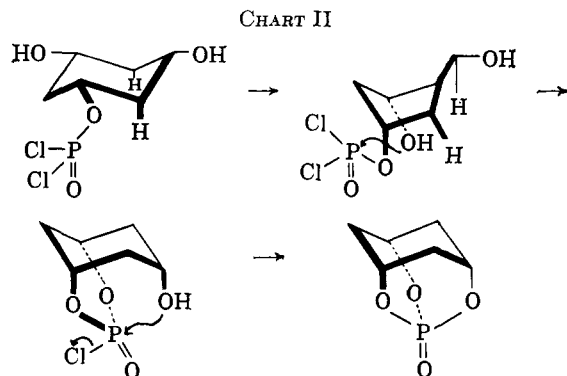(4) F. Zetzsche and E. Zurbrugy, *Helv. Chim. Acta*, **9**, 298 (1926).
(5) H. Stetter and K. Steinacker, *Ber.*, **85**, 451 (1952).
(6) W. S. Knowles and G. E. Thompson, *Chem. Ind.* (London), 121 (1959).
(7) G. M. Kosolopoff. "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1959, p. 99.
(8) Compounds of this type, such as *cis*- and *trans*-2-chloromethyl-2-ethyl-1,3-propylene benzylphosphonates, were actually isolated.[3]

2,8,9-trioxaadamentane 1-oxide[5] seems to suggest that a back-side attack[9] of OH on the P–Cl bond is more likely in the last step as shown in Chart II.[10]

Experimental[11]

4-Ethyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane 1-Oxide (V).—Ten grams of VII was dissolved in 20 ml. of carbon tetrachloride and 20 ml. of hexane. The solution was treated with ozone at room temperature. A crystalline solid formed instantly by feeding gas above the magnetically stirred liquid. This gave 7.0 g. of solid precipitate, m.p. 200–207°, and 4.0 g. solid, m.p. 180–200°, from the residue of the solution, quantitative yield. This higher melting product was recrystallized twice from boiling water and then crystallized from acetone to give a solid, m.p. 207–208°, lit. m.p. 207°[2] and 202°.[3]

4-Ethyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane 1-Selenide (VII).—Ten grams of IV was mixed with selenium (3.0 g.) and benzene (50 g.) It was stirred and refluxed for 1 hr., but no evidence of reaction was observed. After 0.01 g. of sodium selenide was added to the refluxing mixture, the selenium dispersion suddenly coagulated and the solution became transparent and colorless. This mixture was stirred and refluxed for an additional 2 hr., and then kept at 25° overnight. Crystals had formed. These were redissolved by heating and the unused selenium was removed by filtration. The filtrate was concentrated to obtain crystals melting at 172–194°. These were recrystallized twice from 2-methoxyethanol to give 3.6 g. of product, m.p. 207–210°, yield 27.8%.

Anal. Calcd. for $C_6H_{11}O_3PSe$: C, 29.90; H, 4.60; P, 12.85. Found: C, 30.56; H, 4.76; P, 12.75.

4-Phenyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane 1-Oxide (VIII).—The following procedure is used for all the next five reactions, the only change being the polyols and the phosphorus halides used. To a two-necked, 50-ml., round-bottom flask equipped with drying tube and dropping funnel, with magnetic stirring and external cooling, there were added 5.0 ml. of pyridine and 1.0 g. of α,α,α-toluenetrimethanol. After the mixture was homogeneous, a solution of 1.0 g. of phosphorus oxychloride in 20.0 ml. of dry ether was added dropwise at room temperature. Stirring was continued for 0.5 hr. and the mixture was kept at room temperature overnight to ensure completion of the reaction, whereupon solvent was removed from the mixture on steam bath *in vacuo.* Chloroform (20 ml.) and water (20 ml.) were added. The chloroform solution of the product was separated and again evaporated to dryness. The residue was dissolved in acetone to give a turbid solution which was then filtered through a short silica gel packed column. The residue of the filtrate was crystallized three times from methanol-acetone to give 0.25 g. of product, m.p. 247–248°, 20.2% yield.

Anal. Calcd. for $C_{10}H_{11}O_4P$: C, 53.10; H, 4.90; P, 13.70. Found: C, 53.04; H, 5.00; P, 13.82.

4-Phenyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane 1-Sulfide (IX).—The same procedure except for the use of phosphorus thiotrichloride was used. The product weighed 0.30 g., m.p. 207–209°, yield 22.5%.

Anal. Calcd. for $C_{10}H_{11}O_3PS$: C, 49.58; H, 4.58; P, 12.79; S, 13.24. Found: C, 49.21; H, 4.80; P, 12.70; S, 13.03.

4-(Pentachlorophenoxymethyl)-2,6,7-trioxa-1-phosphabicyclo-[2.2.2]octane 1-Sulfide (XI).—The procedure was the same as that above but with (pentachlorophenoxy)methanetrimethanol and phosphorus thiotrichloride as reagents, 0.30 g., m.p. 218–222°, yield 27.1%.

Anal. Calcd. for $C_{11}H_8Cl_5O_4PS$: C, 29.72; H, 1.81; P, 6.97. Found: C, 29.83; H, 1.52; P, 6.47.

4-(Pentachlorophenoxymethyl)-2,6,7-trioxa-1-phosphabicyclo-[2.2.2]octane 1-Oxide (X).—The reagents used were (pentachlorophenoxy)methanetrimethanol and phosphorus oxychloride, giving 0.6 g., m.p. 241.5–242°, yield 52.2%.

Anal. Calcd. for $C_{11}H_8Cl_5O_5P$: C, 30.84; H, 1.88; Cl, 41.38; P, 7.23. Found: C, 30.66; H, 1.97; Cl, 41.30; P, 7.18.

4-(Pentabromophenoxymethyl)-2,6,7-trioxa-1-phosphabicyclo-[2.2.2]octane 1-Sulfide (XII).—The reagents used were (pentabromophenoxy)methanetrimethanol and phosphorus oxychloride, giving 0.6 g., m.p. 234–239°, 54.6%.

Anal. Calcd. for $C_{11}H_8Br_5O_4PS$: C, 19.81; H, 1.21; P, 4.46. Found: C, 20.07; H, 1.75; P, 4.59.

Structures of the Isomeric 20-Hydroxy-4,16-Pregnadien-3-ones

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In a recent communication, the photolysis of a steroidal nitrite derived from a 20-hydroxy-4,16-pregnadien-3-one was described.[2a] The starting alcohol was obtained, together with its C-20 isomer, from the reduction of the 3-methyl enol ether[2b] of 4,16-pregnadiene-3,20-dione with lithium aluminum hydride, followed by removal of the enol ether protecting group. The material in question was eluted as the more polar of the two alcohols from a Florisil column, and the 20α-stereochemistry was assigned since it could also be obtained by microbiological oxidation from the known 5,16-pregnadiene-3β,20α-diol.[3] It was subsequently discovered that the optical rotatory dispersion curve of the derived nitrite resembled that of the 20β-analog in the corresponding 16-saturated series in possessing a negative Cotton effect.[4] Conversely, the nitrite derived from the less polar alcohol demonstrated a positive Cotton effect, as does the 20α-analog in the 16-saturated series. It was felt at the time, however, that any doubt cast on the stereochemical assignment by O.R.D. measurements should not be given too much weight since each situation had to be considered strictly *sui generis* because of the conformational lability of the nitrite

(9) Some tetrasubstituted phosphorus compounds are known to afford products with inverted configurations on phosphorus atom: L. Horner, H. Winkler, A. Rapp, A. Mentrup, H. Hoffmann, and R. Beck, *Tetrahedron Letters,* **No. 5,** 191 (1961); L. Horner and H. Winkler, *ibid.,* **No. 3,** 179 (1964); **No. 9,** 455 (1964).

(10) This is based on the assumption that the solvated oxygen atom is bulkier than the chlorine atoms, and the oxygen atom demands to stay at the least sterically hindered configuration.

(11) Melting points are not corrected. Analyses were by Dr. Galbraith, Knoxville, Tenn.

(1) G. D. Searle and Co.

(2) (a) A. L. Nussbaum, R. Wayne, E. Yuan, O. Zagneetko, and E. P. Oliveto, *J. Am. Chem. Soc.,* **84,** 1070 (1962); (b) A. L. Nussbaum, E. Yuan, D. Dinçer, and E. P. Oliveto, *J. Org. Chem.,* **26,** 3925 (1961).

(3) (a) A. Ercoli and P. de Ruggieri, *Farmaco* (Pavia), *Ed. Sci.,* **7,** 11, 129, 287 (1952); *Chem. Abstr.,* **46,** 10186 (1952); **47,** 2129, 3325 (1953). (b) E. L. Shapiro, D. Gould, and E. B. Hershberg, *J. Am. Chem. Soc.,* **77,** 2912 (1955).

(4) C. Djerassi, I. T. Harrison, O. Zagneetko, and A. L. Nussbaum, *J. Org. Chem.,* **27,** 1173 (1962). See also C. Djerassi, H. Wolf, and E. Bunnenberg, *J. Am. Chem. Soc.,* **85,** 2835 (1963).