Cyclic Organophosphorus Compounds. Part XIII.[1] Stereospecific Formation of 4-Substituted 1,3,2-Dioxaphosph(v)orinans from Bicyclic Phosphorus(III) Esters

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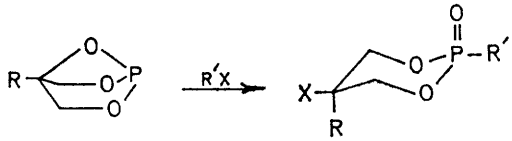
2,7,8-Trioxa-1-phosphabicyclo[3,2,1]octane and its 4,4-dimethyl derivative have been prepared by transesterification. Both compounds undergo stereospecific ring opening when treated with benzyl or triphenylmethyl chlorides, methyl toluene-*p*-sulphonate, *N*-chloropiperidine, or *N*-chloromorpholine. Attempts to prepare 2,6,7-trioxa-1-phosphabicyclo[2,2,1]heptane have been unsuccessful.

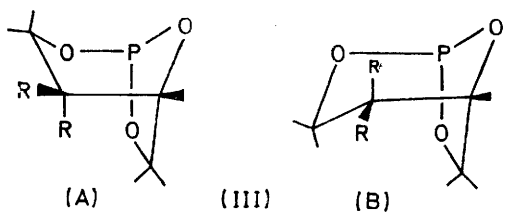
THE stereospecific ring opening of 2,6,8-trioxa-1-phosphabicyclo[2,2,2]octanes by alkyl halides and related compounds is well authenticated and involves rupture of a six-membered phosphite ring.[2] The greater stability of the 1,3,2-dioxaphosph(III)orinan (six-membered) ring compared with that of the unsubstituted or monosubstituted 1,3,2-dioxaphosph(III)olan (five-membered) ring towards alkyl halides in the Arbuzov reaction [3] suggests that 2,6,7-trioxa-1-phosphabicyclo[2,2,1]heptanes (I) should undergo ring opening specifically of the smaller ring to yield *cis*-5-halogeno-1,3,2-dioxaphosph(v)orinans (II)



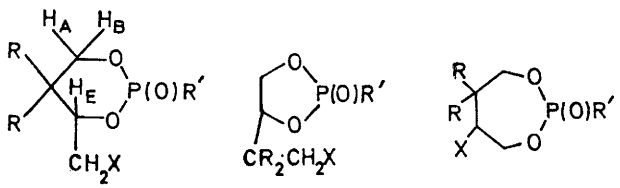
(I) (II)

(the term *cis* refers to the configurational relationship between the phosphoryl and the halogeno-group). Although the successful preparation of 2,6,7-trioxa-1-phosphabicyclo[2,2,1]heptane has been claimed,[4] our attempts to prepare it by the recorded route as well as by other standard procedures were all unsuccessful.

Butane-1,2,4-triol and 3,3-dimethylbutane-1,2,4-triol react readily with trimethyl phosphite in the presence of triethylamine to give phosphites formulated as the cage structures (III; R = H or Me).[5] Of the two conformations, (A) and (B), the latter seems the more likely, interactions between the 5-hydrogen atom and the 4-substituents then being at a minimum, and this conclusion is supported by a detailed analysis of the ^{1}H and ^{31}P n.m.r. spectra.[6]



(A) (III) (B)



(IV) (V) (VI)

The reactions between 2,7,8-trioxa-1-phosphabicyclo-[3,2,1]octane (III; R = H) and benzyl and triphenylmethyl chlorides, *N*-chloropiperidine, and *N*-chloromorpholine, and between (III; R = Me) and benzyl and triphenylmethyl chlorides, *N*-chloropiperidine, and methyl toluene-*p*-sulphonate, all gave single products,

[1] Part XII, R. S. Edmundson, C. I. Forth, and T. A. Moran, *J. Chem. Soc.* (*C*), 1971, 2452.

[2] See R. S. Edmundson and E. W. Mitchell, *J. Chem. Soc.* (*C*), 1970, 752, and references therein. See also K. D. Berlin, C. Hildebrand, A. South, D. M. Hellwege, M. Peterson, E. A. Pier, and J. G. Verkade, *Tetrahedron*, 1964, **20**, 3239.

[3] R. G. Harvey and E. R. de Sombre, *Topics Phosphorus Chem.*, 1964, **1**, 57. See also A. N. Pudovik, G. P. Medvedeva, and V. I. Kuketkova, *Zhur. obshchei Khim.*, 1961, **31**, 2650; A. E. Arbuzov and N. A. Razumova, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1958, 1061.

[4] D. B. Denny and S. L. Varga, *Tetrahedron Letters*, 1966, 4935.

[5] R. S. Edmundson and E. W. Mitchell, *Chem. Comm.*, 1966, 482.

[6] M. Kainosho and A. Nakamura, *Tetrahedron*, 1969, **25**, 4071.

analytical data for which are summarised in Table 1. Formulation of the products as 1,3,2-dioxaphosph(v)-orinans (IV) rather than as 1,3,2-dioxaphosph(v)olans (V) or 1,3,2-dioxaphosph(v)epins (VI) is based upon the following arguments.

(*a*) The products are well defined, with molecular weights consistent with a monocyclic structure. The high stability of six-membered phosphite rings relative to unsubstituted and monosubstituted five-membered rings in the Arbuzov reaction is well established.[3] Data available for seven-membered rings suggest that formation of a phosphonate with retention of the ring is of little importance, the main products being polymers.[7] Thus structure (VI) is probably excluded.

(*b*) The products are stable under aqueous conditions. Unsubstituted and monosubstituted five-membered rings containing either trivalent or pentavalent phosphorus are readily hydrolysed under aqueous conditions.[8] Unsubstituted six-membered phosphate and phosphonate rings are more stable, and substituted six-membered rings may be retained in strongly acid media.[9] The little available information on the hydrolytic stability of seven-membered phosphate rings suggests that they also are considerably more stable than five-membered ones.[10]

(*c*) The 60 MHz ^{1}H n.m.r. spectra of the esters obtained from the phosphite (III; R = H) show a high-field multiplet at *ca.* 2 p.p.m. and a low-field area of absorption, which we assign to the C-5 protons, and to the C-6 methylene and C-4 methine protons respectively (Table 2) by analogy with the spectra of 4-phenyl-1,3,2-dioxaphosph(v)orinan and its 5,5-dideuterio-derivative.[11] For the compounds with R′ = piperidino or morpholino, the chloromethyl resonance consists of a system of partly overlapping doublets with splittings (direct measurement) of *ca.* 6 and 7·5 Hz, split further by *ca.* 0·5 Hz. The spectrum presented earlier for the compound (IV; R = H, R′ = CH_2Ph, X = Cl)[5] was thus deceptively simple with regard to the chloromethyl resonance.

The presence of the 5-methyl groups simplifies the spectra, sometimes to a considerable extent, and an important feature of such spectra is the absence of the high-field multiplet characteristic of the products from (III; R = H), thus confirming its assignment to the 5-methylene group. Nevertheless, even for some of the

TABLE 1

Compound (IV) R	R′	X	M.p. (B.p.)	Solvent	Yield (%)	Found (%) C	H	P(N)	Formula	Required (%) C	H	P(N)
H	CH_2Ph	Cl	159° (185—192° at 0·2 mmHg)	PhH	22	50·6	5·5	11·6	$C_{11}H_{14}ClO_3P$	50·65	5·4	11·9
H	CPh_3	Cl	223·5—224°	Me_2CO	34	67·1	5·35	7·2	$C_{23}H_{22}ClO_3P$	66·9	5·35	7·5
H	NC_5H_{10}	Cl	91—92	$CHCl_3$–petroleum	30	42·8	6·9	(5·25)	$C_9H_{17}ClNO_3P$	42·6	6·75	(5·5)
H	NC_4H_8O	Cl	142·5	AcOEt	68	37·5	5·9	(5·15)	$C_8H_{15}ClNO_4P$	37·6	5·9	(5·25)
Me	CH_2Ph	Cl	134	PhH–petroleum	28	54·05	6·2	10·95	$C_{13}H_{18}ClO_3P$	54·05	6·25	10·75
Me	CPh_3	Cl	191—192	CCl_4	91	65·6 [a]	5·6	7·15	$C_{25}H_{26}ClO_3P$	68·5	5·95	7·0
Me	Me	$SO_3C_7H_7$	140	AcOEt	40	48·0	6·25	8·85	$C_{14}H_{21}O_6PS$	48·25	6·1	8·9
Me	NC_5H_{10}	Cl	123	AcOEt–petroleum	54	47·65	7·6	10·5	$C_{21}H_{21}ClNO_3P$	46·9	7·5	11·0

[a] This compound gave low value for % C after repeated recryst. from a variety of solvents.

TABLE 2

Compound (IV) R	R′	X	I.r. [a] (cm^{-1}) ν(P=O)	ν(POC)	^{1}H N.m.r.
H	CH_2Ph	Cl	1264	1073, 1066, 1014	1·7—2·3 (H_CH_D), 3·33 (CH_2Ph, *J* 21 Hz), 3·3—4·0 (H_B), 3·6 (CH_2Cl), 3·7—4·8 (H_E,H_A)
H	CPh_3	Cl	1250	1054, 1032, 1005	1·8—2·3 (H_CH_D), 3·6 (CH_2Cl), 3·5—4·7 (H_AH_B,H_E)
H	NC_5H_{10}	Cl	1270, 1250	1067, 1010	1·63 (6H, pip), 2·0—2·4 (H_CH_D), 2·95—3·35 (4H, pip), 3·7—3·8 (CH_2Cl), 4·1—4·8 (H_AH_B,H_E)
H	NC_4H_8O	Cl	1260, 1250	1070, 1010	2·0—2·3 (H_CH_D), 3·65—3·8 (CH_2Cl, overlap with morpholine), 3·9—4·8 (H_AH_B,H_E)
Me	CH_2Ph	Cl	1262	1071, 1030	0·74 (CH_3), 1·10 (CH_3), 3·32 (CH_2Ph, *J* 21 Hz), other areas overlap. In PhH, 0·23 (CH_3), 0·74 (CH_3), 3·07 (CH_2Ph)
Me	CPh_3	Cl	1237	1082, 1040, 1021	[c] 0·64 $(CH)_3$, 1·23 (CH_3), *ca.* 3·4 (CH_2Cl)
Me	Me	$SO_3C_7H_7$	1260	*d*	[c] 0·94 (5-CH_3), 1·08 (5-CH_3), 1·51 (PCH_3, *J* 16·5 Hz)
Me	NC_5H_{10}	Cl	1262	*d*	[c] 0·98 (CH_3), 1·14 (CH_3), 1·60 (6H, pip), 2·9—3·3 (4H, pip)

[a] For KBr discs. [b] For 10—20% w/v solutions in $CDCl_3$ (unless otherwise stated) with Me_4Si as internal standard; δ in p.p.m. [c] Overlap of methylene resonances. [d] Uncertain because of complexity of 1100—1000 cm^{-1} region.

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[8] R. S. Edmundson and A. J. Lambie, *J. Chem. Soc.* (*B*), 1967, 577; T. R. Fukuto and R. L. Metcalf, *J. Medicin. Chem.*, 1965, **8**, 759; J.-P. Vives, A. Munoz, J. Navech, and F. Mathis, *Bull. Soc. chim. France*, 1965, 2544.

[9] R. S. Edmundson, *Tetrahedron*, 1965, **21**, 2379; J.-P. Majoral, J. Devillers, and J. Navech, *Compt. rend.*, 1969, **268**, *C*, 1077.

[10] A. Munoz, J. Navech, J.-P. Vives, and J.-P. Majoral, *Bull. Soc. chim. France*, 1967, 3343; H. G. Khorana, G. M. Tener, R. S. Wright, and J. G. Moffatt, *J. Amer. Chem. Soc.*, 1957, **79**, 430.

[11] M. Tsuboi, F. Kuriyagawa, K. Matsuo, and Y. Kyogoku, *Bull. Chem. Soc. Japan*, 1967, **40**, 1813; M. Kainosho, A. Nakamura, and M. Tsuboi, *ibid.*, 1969, **42**, 1713.

monocyclic esters with R = Me, overlap of the H_A, H_B, and H_E resonances with each other and with that of the chloromethyl group renders a detailed interpretation difficult. For the structure (V; R = Me) the chloromethyl group would be expected to display a two-proton singlet or at most a doublet with small ($^5J_{PH}$) splitting, provided that there is no restriction to rotation of the chloromethyl group about its bond of attachment to the ring. Although the presence of the high-field multiplet for the monocyclic esters with R = H does not preclude structure (VI) (which would then possess the P–O–CH_2–CH_2 unit, the source of the absorption), replacement of those particular protons by methyl groups [*i.e.* to give (VI; R = Me)] would lead to molecules which should show considerable changes in the remaining, simplified, methylene absorption upon variation in temperature, by virtue of their considerable flexibility (Dreiding models). While the spectra of some other 5,5-dimethyl-1,3,2-dioxaphosph(v)orinans show pronounced changes with lowering of temperature,[2] that of *cis*-4-chloromethyl-5,5-dimethyl-2-oxo-2-piperidino-1,3,2-dioxaphosphorinan showed only slight alteration with lowering of temperature, a variation which appears to be associated with the resonance of the chloromethyl group.

We thus conclude that the products obtained by ring opening of 2,7,8-trioxa-1-phosphabicyclo[3,2,1]octane and its 4,4-dimethyl derivative are best represented as *cis*-4-substituted 1,3,2-dioxaphosph(v)orinans (IV).

A more detailed discussion of the stereochemical implications of the coupling constant data recorded for the compounds herein described, and for other 5,5-dimethyl-1,3,2-dioxaphosph(v)orinans obtained by the Arbuzov reaction, is to be published later.

The phosphite (III; R = Me) was oxidised with dinitrogen tetroxide and the resulting phosphate was hydrolysed, presumably selectively at the five-membered ring [see (*b*)] to give 5,5-dimethyl-2-hydroxy-4-hydroxymethyl-2-oxo-1,3,2-dioxaphosphorinan (IV; R = Me, X = R′ = OH), isolated as its cyclohexylammonium salt.

EXPERIMENTAL

Petroleum used had b.p. 60—80°. I.r. spectra were determined for potassium bromide discs or liquid films with a Perkin-Elmer 237 spectrometer. ^{1}H N.m.r. spectra were determined for solutions (10—20% w/v) in [^{2}H]chloroform (tetramethylsilane as internal standard) with a Varian A60 spectrometer. All extracts were dried with anhydrous sodium sulphate and solutions were evaporated at 50—55° under reduced pressure.

Attempts to prepare 2,6,7-*Trioxa*-1-*phosphabicyclo*[2,2,1]-*heptane*.—(a) *By use of trimethyl phosphite*. A mixture of trimethyl phosphite (62 g) and dry glycerol (46 g) was stirred and heated gradually to 90—100° (bath); methanol (94%) distilled over. The temperature was then raised to 140° during 5 h. Attempted distillation of the residue produced only a hard resinous material.

Denney and Varga's procedure (in which silicone oil was used as diluent) was repeated. Methanol (100%) was removed by distillation, but the residue again resinified.

(b) *By use of phosphorus trichloride*. Phosphorus trichloride (34 g) in dioxan (30 ml) was added dropwise to glycerol (23 g) and pyridine (60 g) in dioxan (100 ml) at 0°; the mixture was then stirred at ambient temperature for 2 h. Dry ether was added to ensure complete precipitation of pyridinium hydrochloride. The mixture was chilled, filtered rapidly, and evaporated to leave a residue which was not (i.r. spectrum) the cyclic phosphite.

(c) *By use of tris(dimethylamino)phosphine*. When glycerol was stirred with the phosphine (1 mol. equiv.) in boiling ether (or chloroform or benzene), or without solvent, dimethylamine was steadily evolved. Subsequent removal of solvent left a liquid which resinified on further heating.

Repetition of some of the foregoing experiments with 2-methylglycerol gave similar results.

2,7,8-*Trioxa*-1-*phosphabicyclo*[3,2,1]*octane*.—A mixture of butane-1,2,4-triol (42·8 g; dried and freshly distilled), trimethyl phosphite (70 g), and triethylamine (5 drops) was stirred and heated. At 95° (bath) methanol (95%) began to distil over and the mixture thickened rapidly. Further distillation [150—160° (bath)] gave 2,6,7-*trioxa*-1-*phosphabicyclo*[3,2,1]*octane* (42 g, 79%), b.p. 52° at 0·6 mmHg, which solidified. A sample of b.p. 83° at 35 mmHg, n_D^{21} 1·4753, $\nu_{max.}$ 1075, 1045, and 980 (POC) cm^{-1}, was analysed (Found: C, 36·05; H, 5·45; P, 23·0. $C_4H_7O_3P$ requires C, 35·8; H, 5·2; P, 23·15%).

3,3-*Dimethylbutane*-1,2,4-*triol*.—A solution of diethyl 1,1-dimethyl-2-oxosuccinate (47·0 g) in ether was added dropwise to lithium aluminium hydride (25 g) in boiling ether. The mixture was stirred at reflux for 2 h, then cooled and the excess of hydride was decomposed with moist ether and ethyl acetate. The mixture was acidified with 2N-sulphuric acid and extracted continuously with ether. The dried extract was distilled to give the *triol* (20·0 g, 69%), b.p. 127—130° at 0·1 mmHg, n_D^{20} 1·4743, m.p. 66—68° (Found: C, 53·85; H, 10·3. $C_6H_{14}O_3$ requires C, 53·75; H, 10·45%). The *trisphenylurethane* had m.p. 159—160° (from benzene–petroleum) (Found: C, 65·8; H, 5·65. $C_{27}H_{29}N_3O_6$ requires C, 66·0; H, 5·9%).

4,4-*Dimethyl*-2,7,8-*trioxa*-1-*phosphabicyclo*[3,2,1]*octane*.—3,3-Dimethylbutane-1,2,4-triol (4·5 g) and trimethyl phosphite (4·1 g) when heated together (*cf.* previous reaction) gave the bicyclic *phosphite* (4·5 g, 83%), b.p. 76—80° at 0·8 mmHg, n_D^{23} 1·4617, $\nu_{max.}$ 1392, 1370 (CMe_2), 1075, 1030, and 1010 (POC) cm^{-1} (Found: C, 44·45; H, 7·2; P, 18·9. $C_6H_{11}O_3P$ requires C, 44·45; H, 6·8; P, 19·15%).

Reactions of 2,7,8-*Trioxa*-1-*phosphabicyclo*[3,2,1]*octane*.—Reaction conditions for this bicyclic phosphite (and for the 4,4-dimethyl derivative) are now described; physical properties and analytical data for the products are listed in Table 1.

(a) *With benzyl chloride*. The phosphite (6·7 g) and benzyl chloride (6·3 g) were heated together at 200° (bath) for 1 h. The *product* (2·3 g) was obtained by distillation.

(b) *With chlorotriphenylmethane*. The chloride (2·8 g) and the phosphite (1·4 g) were heated together at 180° (bath) for 4 h. The residue was chromatographed on silica gel (for t.l.c.) with chloroform to give an *oil* (1·4 g), which solidified on trituration with petroleum.

(c) *With N-chloropiperidine*. Freshly prepared *N*-chloropiperidine (1·3 g) in carbon tetrachloride (5 ml) was added to the phosphite (1·35 g) in carbon tetrachloride (5 ml). After 20 h at ambient temperature the mixture still contained unchanged phosphite (smell). It was diluted with

chloroform, washed with water, dried, and evaporated, and the residue was chromatographed on silica gel (for t.l.c.) with chloroform to give the *product* (0·75 g).

(d) *With N-chloromorpholine.* In a similar reaction with *N*-chloromorpholine, the yield of *product* was 1·7 g.

Reactions of 4,4-*Dimethyl*-2,7,8-*trioxa*-1-*phosphabicyclo*-[3,2,1]*octane*.—(a) *With benzyl chloride.* The phosphite (2·0 g) and benzyl chloride (2·0 g) were heated together at 120—200° (bath) for 7 h. The gummy residue was chromatographed (benzene–ether) on silica gel (for t.l.c.) to give the *product* (1·0 g).

(b) *With chlorotriphenylmethane.* The chloride (2·8 g) and the phosphite (1·8 g) were heated together at 140° (bath) for 2 h; the solid residue crystallised from carbon tetrachloride to give the *product* (4·2 g).

(c) *With methyl toluene*-p-*sulphonate.* A mixture of the phosphite (3·2 g) and methyl toluene-*p*-sulphonate (3·7 g) was heated at 80—100° (bath) for 6 h, at 100—120° for 6 h, and then at 160—180° for 5 h. The residue was chromatographed on silica gel (for t.l.c.) with ethyl acetate to give the *product* (0·7 g).

(d) *With* N-*chloropiperidine.*—*N*-Chloropiperidine (1·2 g) and the phosphite (1·6 g) in carbon tetrachloride (15 ml) when treated as for the unsubstituted phosphite gave the *product* (1·55 g).

5,5-*Dimethyl*-2-*hydroxy*-4-*hydroxymethyl*-2-*oxo*-1,3,2-*dioxaphosphorinan*.—A solution of 4,4-dimethyl-2,7,8-trioxa-1-phosphabicyclo[3,2,1]octane (5·3 g) in dichloromethane (50 ml) was treated with gaseous dinitrogen tetroxide until a permanent colouration was obtained; excess of oxidant was removed with a stream of nitrogen. The solvent was removed to yield an oil (6·15 g), which was shaken with sodium hydroxide solution (2N; 25 ml) until dissolution was complete. The solution was passed through Zeo-Carb 225 (H^+ form) and the eluant was neutralised with cyclohexylamine. Evaporation left the cyclohexylammonium salt of the *cyclic phosphoric acid* (2·1 g), m.p. 234—236° (from ethanol) (Found: C, 48·9; H, 9·15; P, 10·45. $C_{12}H_{26}NO_5P$ requires C, 48·8; H, 8·9; P, 10·45%).

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