Cyclic Organophosphorus Compounds. Part XIV.[1] A Proton Magnetic Resonance Study of the Stereochemistry of some 5,5-Di- and 4,5,5-Trisubstituted 1,3,2-Dioxaphosph(v)orinans

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4,4-Dimethyl-2,7,8-trioxa-1-phosphabicyclo[3,2,1]octane and its 5-deuterio-derivative have been prepared and converted by chlorination followed by treatment with piperidine into *trans*-4-chloromethyl-5,5-dimethyl-2-oxo-2-piperidino-1,3,2-dioxaphosphorinan and its 4-deuterio-derivative.† ^{1}H N.m.r. data suggest that this piperidide and the intermediate monocyclic phosphorochloridate, as well as *trans*-5-chloromethyl-5-methyl-2-oxo-2-piperidino-1,3,2-dioxaphosphorinan, exist with the phosphorus-containing ring held in a rigid chair form. On the other hand the *cis*-stereoisomers of 4-chloromethyl-5,5-dimethyl-2-oxo-2-piperidino- (again demonstrated by use of the 4-deuterio-compound), 5-chloromethyl-5-methyl-2-oxo-2-piperidino-, and 2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan probably possess a twist ring.

In Part IX,[2] stereoisomeric 5-halogenomethyl-5-methyl-2-oxo-2-piperidino-1,3,2-dioxaphosphorinans (I; R = NC_5H_{10}, X = Cl or Br) were described. Attempts to assign conformations to the methyl groups (and hence to the halogenomethyl groups) were based primarily on a comparison of the alteration in their chemical shifts upon change of solvent ([^{2}H]chloroform to benzene) and the effect already recorded for the analogous 5,5-dimethyl compounds, but measurements of n.m.r. signal widths were also helpful. Only for the case of *cis*-5-chloromethyl-5-methyl-2-oxo-2-piperidino-1,3,2-dioxaphosphorinan was it possible to suggest the most likely conformational arrangement at the phosphorus atom, by virtue of the stereospecific nature of the preparation of this compound.

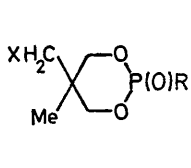
It was surprising that only one stereoisomer (the *cis*-form) of 2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (I; R = X = Cl) could be isolated. All other 1,3,2-dioxaphosphorinans possessing non-

† The terms *trans* and *cis* refer to the configurational relationship between the phosphoryl group and the 4-(or 5-)halogenomethyl groups.

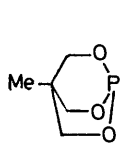
[1] Part XIII, R. S. Edmundson and E. W. Mitchell, *J. Chem. Soc.* (*C*), 1971, 3179.

[2] R. S. Edmundson and E. W. Mitchell, *J. Chem. Soc.* (*C*), 1968, 3033.

identical groups at C-5 exist in two geometrically isomeric forms. The report that treatment of 4-methyl-2,6,7-trioxa-1-phosphabicyclo[2,2,2]octane (II) with sulphuryl chloride gives a 5-chloromethyl-5-methyl cyclic phosphorochloridate (I; R = X = Cl) stereochemically different from that (m.p. 70°) obtained by use of chlorine [3] prompted a re-examination of the stereochemistry of the phosphorochloridate and its derivatives.



(I)



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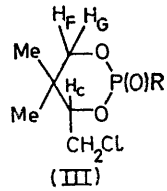

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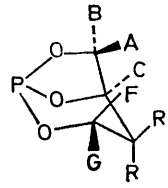
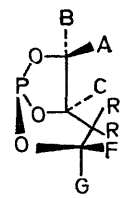
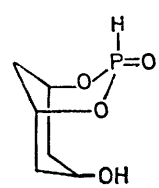


(IVA)



(IVB)



(V)

The phosphite (II) reacts vigorously with sulphuryl chloride but the product has now been shown to be identical to that obtained by using chlorine.[4] Both samples of the phosphorochloridate yield the same *trans*-piperidide, inversion occurring during substitution.

The n.m.r. spectrum of the product from phosphoryl chloride and 2-chloromethyl-2-methylpropane-1,3-diol showed the presence of two cyclic phosphorochloridates (two methyl and two chloromethyl signals). One methyl–chloromethyl pair corresponded to the *cis*-phosphorochloridate (I; R = X = Cl), m.p. 70°. Attempts to separate the two phosphorochloridates chromatographically were only partially successful, possibly because of equilibration between the two geometrical isomers; this has been suggested elsewhere for solutions in polar solvents.[3,4] Equilibration also takes place during distillation of the pure *cis*-phosphorochloridate, the distillate affording a mixture of stereoisomeric piperidides (I; X = Cl, R = NC_5H_{10}), m.p. 136—137°.[5] Such behaviour probably explains our previous failure to isolate the *cis*-phosphorochloridate in pure form, since reaction products were ' purified ' by distillation.

A more detailed analysis of the ^1H n.m.r. spectra of the two phosphorochloridates (I; X = R = Cl), of the piperidides (I; X = Cl, R = NC_5H_{10}) derived stereospecifically from them is now presented (Table 1). Because of the nature of the results, and of the recent observations on the stereospecific formation of 4-substituted *cis*-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinans (III) from 4,4-dimethyl-2,7,8-trioxa-1-phosphabicyclo[3,2,1]octane (IV; R = Me),[1] a similar analysis of the ^1H n.m.r. spectra of a 4-chloromethyl cyclic phosphorochloridate (III; R = Cl) and two stereoisomeric piperidides (III; R = NC_5H_{10}) was carried out. Chlorination (with chlorine itself or sulphuryl chloride) of the bicyclic phosphite (IV; R = Me) gave stereochemically pure *cis*-2-chloro-4-chloromethyl-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinan (III; R = Cl), which yielded the *trans*-piperidide (III; R = NC_5H_{10}), m.p. 127—128° different from the *cis*-form of m.p. 123°

TABLE 1

^1H Chemical shift data for (A) 2-chloro- (I; R = X = Cl) and (B) 2-piperidino- (I; X = Cl, R = NC_5H_{10}) 5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinans

Sample	Composition	(%)	Δ * Me	Δ * CH_2Cl
1	A	74	0·51	0·39
		26	0·37	0·59
2	B	78	0·57	0·32
		22	0·31	0·67
3 †	A	62	(a)0·56	0·40
		38	(b)0·42	0·64
4	B	67	0·59	0·30
		33	0·30	0·73
5	A	73	0·57	0·41
		27	0·43	0·64
6	B	75	0·62	0·34
		25	0·35	0·72

* Δ = δ($CDCl_3$) − δ(PhH). † In $CDCl_3$ $W_{\frac{1}{2}}$ (a) 0·6 Hz, (b) 1·2 Hz.

prepared from compound (IV; R = Me) with *N*-chloropiperidine.

The ^1H n.m.r. spectra (see Discussion section) of the three compounds (III) were complex. Their 4-deuterio-analogues were therefore prepared. Reduction of diethyl 1,1-dimethyl-2-oxosuccinate with sodium borodeuteride followed by reduction of the residual ester groups with lithium aluminium hydride gave the monodeuteriated triol, which was transesterified with trimethyl phosphite giving 4,4-dimethyl-[5-^2H]-2,7,8-trioxa-1-phosphabicyclo[3,2,1]octane, which was employed as described previously.[1] All the deuteriated compounds had physical constants almost identical with those of the corresponding protio-compounds; their i.r. spectra showed in addition bands at 2160—2190 cm^{-1} (w to ms) attributable to the C–D bond.

EXPERIMENTAL

Petroleum used had b.p. 60—80°. I.r. spectra were determined for potassium bromide discs or liquid films between sodium chloride plates with a Perkin-Elmer 237 spectrometer. ^1H N.m.r. spectra were determined for solutions (10—20% w/v) in [^2H]chloroform (tetramethylsilane as internal standard) at ambient temperature with a Varian A60 spectrometer; 100 MHz spectra were determined

[3] W. Wadsworth, jun., and H. Horton, *J. Amer. Chem. Soc.*, 1970, **92**, 3785.

[4] W. Wadsworth, jun., S. Larsen, and H. Horton, in the press.

[5] W. Wadsworth, jun., personal communication. We thank Dr. Wadsworth for pointing out the correction necessary to the m.p.s of the stereoisomeric piperidides; they have m.p. 182 and 155°.

by P.C.M.U. All extracts were dried with anhydrous sodium sulphate and solutions were evaporated at 50—55° under reduced pressure. Silica gel (for t.l.c.) was employed for chromatography.

2-Chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (I; X = R = Cl).—(a) cis-*Stereoisomer* (m.p. 70°). (i) Chlorination of 4-methyl-2,6,7-trioxa-1-phosphabicyclo[2,2,2]octane (II) was carried out as described previously but with twice the volume of ether.[2] Trituration of the oily product with petroleum gave a solid (76%), m.p. 66—69° (from ether–petroleum). Chromatography (benzene–20% ether) of this gave the phosphorochloridate, m.p. 69—71°.

Treatment of this phosphorochloridate with piperidine gave *trans*-2-chloro-5-chloromethyl-5-methyl-2-oxo-2-piperidino-1,3,2-dioxaphosphorinan (I; X = Cl, R = NC_5H_{10}), m.p. 152—153° (from benzene–cyclohexane) (lit.,[3] 152—153°).

(ii) Sulphuryl chloride (redistilled; 6·8 g) in ethanol-free chloroform (15 ml) was added to 4-methyl-2,6,7-trioxa-1-phosphabicyclo[2,2,2]octane (II) (7·4 g) in chloroform (25 ml) at ambient temperature. The mixture was stirred for 1 h and filtered, and the filtrate was evaporated to a semi-solid. Chromatography as in (i) gave a cyclic phosphorochloridate, m.p. 69·5—71·5°, identical (mixed m.p.; i.r., n.m.r., and mass spectra) with that obtained in (i). Treatment of the product with piperidine gave a piperidide, m.p. 151—152°, identical (mixed m.p.; i.r. and n.m.r. spectra) with that obtained as in (i).

Distillation of the *cis*-phosphorochloridate (m.p. 70°) for 0·5 h at 1 mmHg (bath at 200 °C) gave an oil which solidified (m.p. 40—45°; sample 1; the compositions of this sample and others described in the following experiments are given in Table 1 with the relevant n.m.r. data). The phosphorochloridates (sample 1) with piperidine gave a mixture of piperidides, m.p. 130—135° (sample 2).

(b) *Mixed stereoisomers*. A solution of 2-chloromethylpropane-1,3-diol (6·4 g) and triethylamine (10·1 g) in benzene (50 ml) was added to redistilled phosphoryl chloride (4·5 ml) in benzene (50 ml) at ambient temperature. The mixture was set aside for 48 h, then washed with water, dried, and evaporated to an oil (sample 3). This sample of mixed *cis*- and *trans*-phosphorochloridates (I; X = R = Cl) had partially solidified after storage at 0° for 24 h. Sample 3 of the phosphorochloridates gave a mixture of piperidides (sample 4) (I; X = Cl, R = NC_5H_{10}).

Chromatography of the mixed phosphorochloridates from a second preparation (20% ether–benzene as eluant) concentrated the minor component but failed to purify it completely.

The mixed phosphorochloridates were distilled at 2 mmHg and 180—195° (bath); the distillate (sample 5) solidified; it furnished a mixture of piperidides (sample 6).

cis-2-*Chloro*-4-*chloromethyl*-5,5-*dimethyl*-2-*oxo*-1,3,2-*dioxaphosphorinan* (III; R = Cl).—A solution of 4,4-dimethyl-2,7,8-trioxa-1-phosphabicyclo[3,2,1]octane [1] (IV; R = Me) (3·6 g) in dry ether (125 ml) was cooled in ice–water and saturated with chlorine. Excess of chlorine was removed with a nitrogen stream, and the solution was evaporated to leave a solid (3·6 g). This crystallised from benzene–ether (1 : 1) to give cis-2-*chloro*-4-*chloromethyl*-5,5-*dimethyl*-2-*oxo*-1,3,2-*dioxaphosphorinan*, m.p. 113—114·5°, $\nu_{max.}$ 1302 (P=O), 1038, 1025, and 1003 (POC) cm^{-1} (Found: C, 31·0; H, 4·55; P, 13·55. $C_6H_{11}Cl_2O_3P$ requires C, 31·0; H, 4·75; P, 13·3%). An identical sample (m.p., mixed m.p., and i.r. spectrum) was obtained by use of sulphuryl chloride.

trans-4-*Chloromethyl*-5,5-*dimethyl*-2-*oxo*-2-*piperidino*-1,3,2-*dioxaphosphorinan* (III; R = NC_5H_{10}).—The trans-*piperidide*, m.p. 127—128° (from ethyl acetate–petroleum) was obtained in the usual way from the foregoing phosphorochloridate and piperidine; $\nu_{max.}$ 1245 (P=O), 1043, and 1020 (POC) cm^{-1} (Found: C, 47·5; H, 7·55; P, 10·2. $C_{21}H_{21}ClNO_3P$ requires C, 46·9; H, 7·5; P, 11·0%).

4,4-Dimethyl-[5-^{2}H]-2,7,8-*trioxa*-1-*phosphabicyclo*[3,2,1]-*octane* (IV; H_O replaced by ^{2}H).—(a) *3,3-Dimethyl*-[2-^{2}H]*butane*-1,2,4-*triol*. A solution of sodium borodeuteride (0·99 g) in ice-cold deuterium oxide (10 ml) was added dropwise to a solution of diethyl 1,1-dimethyl-2-oxosuccinate (21·6 g) in freshly distilled, peroxide-free tetrahydrofuran (90 ml) at ambient temperature. The mixture was stirred for 3 h, acidified with N-hydrochloric acid, and extracted with ether. The dried extract was evaporated and the resulting diethyl 1,1-dimethyl-2-hydroxy[2-^{2}H]succinate (22·5 g) in ether (50 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (7 g) in ether (150 ml). When the vigorous reaction had subsided the excess of hydride was decomposed with wet ether. The mixture was acidified with N-hydrochloric acid and continuously extracted with ether (60 h). Evaporation of the dried extract gave the [^{2}H]*triol* (11·5 g), which was used without further purification.

(b) A mixture of 3,3-dimethyl[2-^{2}H]butane-1,2,4-triol (11·5 g) and trimethyl phosphite (12 g) containing triethylamine (5 drops) was slowly distilled, giving methanol followed by *4,4-dimethyl*-[5-^{2}H]-2,7,8-*trioxa*-1-*phosphabicyclo*[3,2,1]*octane* (6·5 g), b.p. 50 at 1 mmHg (56° at 0·8 mmHg), which was redistilled at 54° and 1 mmHg; $\nu_{max.}$ 2190 (C–D), 1075, 1030, and 1010 (POC) cm^{-1}.

cis-2-*Chloro*-4-*chloromethyl*-5,5-*dimethyl*-2-*oxo*-[4-^{2}H]-1,3,2-*dioxaphosphorinan* (III; H_O replaced by H).—The [^{2}H]bicyclic phosphite (1·6 g) in ethanol-free chloroform (10 ml) was added to sulphuryl chloride (1·4 g) in chloroform (10 ml). The mixture was stirred for 3 h, the solvent removed, and the *cyclic* [4-^{2}H]*phosphorochloridate*, m.p. 99—101° (2·45 g), was used directly for conversion into the piperidide.

trans-4-*Chloromethyl*-5,5-*dimethyl*-2-*oxo*-2-*piperidino*-[4-^{2}H]-1,3,2-*dioxaphosphorinan* (III; H_O replaced by ^{2}H).—The [^{2}H]*piperidide*, m.p. 127—129° (from benzene–petroleum), $\nu_{max.}$ 2160 (C–D), 1250 (P=O), 1075, 1053, 1033, and 1012 (POC) cm^{-1}, was obtained from the *cis*-[4-^{2}H]-phosphorochloridate in the usual way.

cis-4-*Chloromethyl*-5,5-*dimethyl*-2-*oxo*-2-*piperidino*-[4-^{2}H]-1,3,2-*dioxaphosphorinan* (III; H_O replaced by ^{2}H).—4,4-Dimethyl-[5-^{2}H]-2,7,8-trioxa-1-phosphabicyclo[3,2,1]-octane (1·6 g) in carbon tetrachloride (10 ml) was treated with *N*-chloropiperidine (1·3 g) in the same solvent (5 ml). The mixture was heated over steam for 1 h and worked up in the usual way to give the cis-[4-^{2}H]*cyclic piperidide* (2·0 g), m.p. 122—124·5° (from ethyl acetate), $\nu_{max.}$ 2160 (C–D) and 1260 (P=O) cm^{-1} (the POC region was too complex for definite assignments).

DISCUSSION

If there is no gross distortion in the 5,5-disubstituted 1,3,2-dioxaphosphorinan ring system, the dihedral angles, POCH(*ax*) (gauche) and POCH(*eq*) (anti) will be *ca.* 60 and 180°, respectively, and providing the ring is

conformationally immobile, $J_{POCH(eq)}$ would be expected to be greater than $J_{POCH(ax)}$. Also because of the planar W arrangements, $J_{H(eq)OCCH'(eq)}$ will be greater than $J_{H(ax)OCCH'(eq)}$ [the latter being then same as $J_{H(eq)OCCH'(ax)}$], and $J_{H(ax)OCCH'(ax)}$ would be expected to be small. For a conformationally mobile system, the two coupling constants $J_{POCH(ax,eq)}$ would depend on conformer populations and could be identical. For a boat form of the ring system identical coupling constants could again be found, arising either from a confromationally rigid system where the dihedral angles POCH would each be approximately 120°, or from rapidly interconverting twist forms. Rationalisation of the available ^{1}H n.m.r. data for 1,3,2-dioxaphosph(III)-orinans [6-8] and 1,3,2-dioxaphosph(V)orinans [6,9,10] seems generally to support these principles. For cases where the ring system is known to be conformationally rigid, extreme values of the gauche and anti coupling constants lie within the ranges 1—7 and 17—30 Hz, the limits depending at least partly on the nature of the group attached to the phosphorus atom.[9] Intermediate values of J have been related to conformational mobility.[11]

Table 2 shows the results of ABX analyses * (A is the lower field proton, B the higher field proton, and X is the phosphorus atom) of the ^{1}H n.m.r. spectra for the reported 5-halogenomethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinans and analogous 5,5-dimethyl derivatives (I). Spectra of the 5-halogenomethyl series (I; X = Cl or Br, R = Cl or NC_5H_{10}) show no alteration with temperature between —60 and 100°, and it is therefore believed that these molecules are conformationally stable within this range; conformers of the piperidide (I; R = NC_5H_{10}, X = H) are detectable.[2]

TABLE 2

^{1}H N.m.r. data for 5-substituted 2-oxo-1,3,2-dioxaphosphorinans (I)

	Compound (I) X	R	Solvent	δ(p.p.m.) Me	XCH_2	H_A	H_B	⟨J⟩/Hz $^3J_{PH_A}$	$^3J_{PH_B}$	Σ^3J_{PH}	$J_{H_AH_B}$
a	H	Cl	$CHCl_3$	0·93	1·32	4·25 [a]	4·0 [a]	2·9 [a]	27·5 [a]	30·4 [a]	
			PhH	0·17	0·84						
b	Cl(*cis*)	Cl	$CHCl_3$	0·98	3·78	4·45	4·23	18·0 [b]	12·75 [b]	30·75	11·75
			PhH	0·23	3·29	3·85	3·62	17·5 [b]	14·1 [b]	31·6	11·3
c	Cl(*trans*)	Cl	$CHCl_3$	1·31	3·37						
			PhH	0·88	2·60						
d	H	NC_5H_{10}	(i)$CHCl_3$	0·87	1·21	4·23	3·72	3·05	20·15	23·2	10·7
			PhH	0·34	0·97	4·07	3·38	2·5 [b]	20·7 [d]	23·2	10·8
			(ii)$CHCl_3$	0·94	1·34						
			PhH	0·3	0·9						
e [c]	Cl(*cis*)	NC_5H_{10}	$CHCl_3$	1·24	3·51	4·37	3·89	8·3	15·5 [e]	23·8	11·3
			PhH	0·94	2·93	4·15	3·52	6·55 [f]	17·45	24·0	11·3
f [c]	Cl(*trans*)	NC_5H_{10}	$CHCl_3$	0·91	3·77	4·40	4·10	1·2 [d]	21·0 [g]	22·2	11·1
			PhH	0·38	3·48	4·14	3·47	2·3 [i]	21·3 [h]	23·6	11·3
g [c]	Br(*cis*)	NC_5H_{10}	$CHCl_3$	1·23	3·22	4·34	3·89	8·05 [h]	16·7 [e]	24·7	11·0
h [c]	Br(*trans*)	NC_5H_{10}	$CHCl_3$	0·91	3·64	4·33	4·05	2·9 [d]	17·9 [e]	20·8	11·3

[a] Values from M. Kainosho, A. Nakamura, and M. Tsuboi, *Bull. Chem. Soc. Japan*, 1969, **42**, 1713. [b] Split further by 2·0 Hz. [c] Values of chemical shifts for Me and CH_2X from ref. 2. [d] Split further by 1·4 Hz. [e] Split further by 1 Hz. [f] ±1Hz. [g] Split further by 1·1 Hz. [h] Split further by 1·7 Hz. [i] Split further by 1·2 Hz.

The ^{1}H n.m.r. spectrum (Figure 1a) of the *cis*-phosphorochloridate (Ib) (see Table 2) is similar to that of the corresponding 5-bromomethyl phosphorobromidate

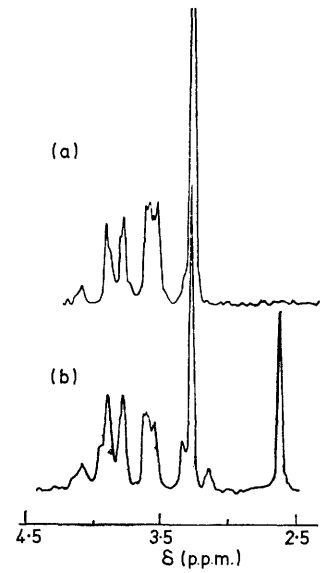


FIGURE 1 60 MHz ^{1}H N.m.r. spectra (methylene region) of (a) pure *cis*-, (b) impure *trans*-2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan

* Carried out by use of the methods given in 'N.m.r. for Organic Chemists,' ed. D. W. Mathieson, Academic Press, 1967, ch. 6 and Appendix, p. 195.

[6] W. G. Bentrude and J. H. Hargis, *J. Amer. Chem. Soc.*, 1970, **92**, 7136.
[7] D. W. White, R. D. Bertrand, G. K. McEwen, and J. G. Verkade, *J. Amer. Chem. Soc.*, 1970, **92**, 7125.
[8] D. W. White, G. K. McEwen, R. D. Bertrand, and J. G. Verkade, *J. Magnetic Resonance*, 1971, **4**, 123.
[9] D. W. White, G. K. McEwen, R. D. Bertrand, and J. G. Verkade, *J. Chem. Soc.* (*B*), 1971, 1454.
[10] J.-P. Majoral and J. Navech, *Bull. Soc. chim. France*, 1971, (*a*) 95; (*b*) 1331; (*c*) 2609.
[11] R. S. Edmundson and E. W. Mitchell, *J. Chem. Soc.* (*C*), 1970, 752.

(I; X = R = Br), with the methylene pattern reversed.[8] ABX analysis was possible in spite of extensive overlap of the two AB quartets with each other and to some extent with the chloromethyl signal. The values of Σ^3J_{PH} for the phosphorochloridate and the phosphorobromidate are similar (31 and 37 Hz) but the individual gauche and anti coupling constants for the latter compound (7 and 30 Hz, respectively) are more suggestive of a chair ring, as confirmed by *X*-ray analysis.

It was not possible to purify the stereoisomeric phosphorochloridate (Ic) (assumed *trans*-configuration) completely and hence to determine the coupling constants more accurately for this; nevertheless the general features of the spectrum of the mixture of *cis*- and *trans*-phosphorochloridates (Figure 1b) suggest that $^3J_{PH_B}$ is greater for (Ic) than for (Ib), probably at the expense of $^3J_{PH_A}$, and is more in keeping with a chair form. Although the formation in the phosphorochloridate (Ib) was initially assumed to be the same as in the 5-bromomethyl phosphorobromidate prepared in a similar manner,[2,3] measurement of band widths at half height would appear to confirm that the difference in stereochemistry between (Ib) and (Ic) lies at C-5, the former having an equatorial or quasi-equatorial methyl group and the latter an axial methyl group. An axial halogen substituent would thus be allowed in both cases, as confirmed for other individual phosphorohalidates by use of alternative techniques.

Such techniques, particularly *X*-ray analysis, have shown that for monocyclic 1,3,2-dioxaphosph(v)orinans (I), the ring is chair shaped, with the phosphorus end flattened and broadened, and with the phosphoryl bond equatorial.[12] An exception to this is 4,6-dimethyl-2-oxo-2-triphenylmethyl-1,3,2-dioxaphosphorinan, reported[13] as having a twist ring conformation; unfortunately ^{1}H n.m.r. data are not available for this compound. Other than polycyclic ester systems containing phosphorus in which the rings are constrained to boat forms by covalent bonding *via* phosphorus, 7-hydroxy-3-oxo-2,4-dioxa-3-phosphabicyclo[3,3,1]-nonane (V) represents the only known example of a derivative of the 1,3,2-dioxaphosphorinan ring system in which the phosphorus-containing ring is boat shaped; again, unfortunately, n.m.r. data are not available.[14]

2,7,8-Trioxa-1-phosphabicyclo[3,2,1]octane (IV; R = H) was first prepared by us,[1,15] but a detailed analysis of the ^{1}H and ^{31}P n.m.r. spectra, requiring double- and triple-irradiation experiments, appeared more recently.[16] These data suggested that conformation (IVA) is preferred but did not completely exclude conformation (IVB), and the molecule exhibited many smaller ^5J couplings considered to be 'through-space' effects.

As for the monocyclic dioxaphosphorinans, replacement of the protons D and E (as designated by the Japanese authors) by methyl groups to give structure (IV; R = Me) [$\delta(CDCl_3)$ 0·78 (Me*eq*) and 1·03 (Me*ax*) (Figure 2)]

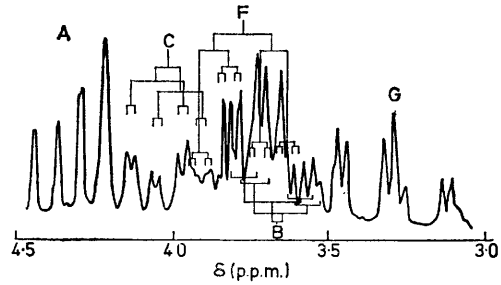


FIGURE 2 60 MHz ^{1}H N.m.r. spectrum (methylene region) of 4,4-dimethyl-2,7,8-trioxa-1-phosphabicyclo[3,2,1]octane

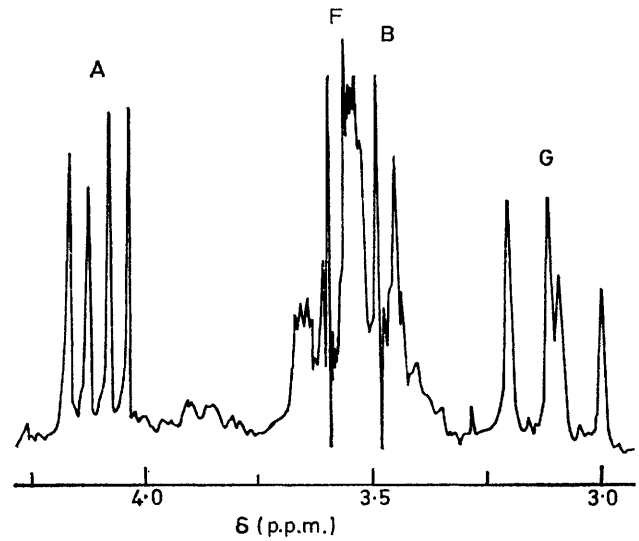


FIGURE 3 100 MHz ^{1}H N.m.r. spectrum (methylene region) of 4,4-dimethyl-[5-^{2}H]-2,7,8-trioxa-1-phosphabicyclo[3,2,1]-octane

and of the methine proton C by deuterium (Figure 3) greatly simplified the reported spectrum, but this was still complex because of overlap of the B and F proton signals. The choice of peaks to link with those of the A and G protons for analytical purposes was initially a matter of trial and error, and *J* values approximating to those quoted[16] for (IV; R = H) were assumed. The systems PAB and PEG were analysed on the assumption that cross ring couplings were small. The chemical shifts calculated for the protons of compound (IV; R = Me) are: A, 4·17 (observed 4·33); B 3·53 (observed 3·53); C (observed 3·87); F, 3·75 (observed 3·63); G 3·32 (observed 3·30) p.p.m., and a comparison of the coupling constants for this system with those found for (IV; R = H) is given in Table 3.

[12] T. A. Beineke, *Acta Cryst.*, 1969, **B25**, 413; H. J. Geise, *Rec. Trav. chim.*, 1967, **86**, 362; M.-ul Haque, C. N. Caughlan, and W. L. Moats, *J. Org. Chem.*, 1970, **35**, 1446; M.-ul Haque, C. N. Caughlan, J. H. Hargis, and W. J. Bentrude, *J. Chem. Soc.* (*A*), 1970, 1786; R. C. G. Killean, J. H. Lawrence, and I. M. Magennis, *Acta Cryst.*, 1971, **B27**, 189; L. Silver and R. Rudman, *ibid.*, 1972, **B28**, 574.

[13] Personal communication reported in ref. 9.

[14] D. M. Nimrod, D. R. Fitzwater, and J. G. Verkade, *Inorg. Chim. Acta*, 1968, **2**, 149.

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

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

The 100 MHz ^{1}H n.m.r. spectra of the two stereoisomeric 4-chloromethyl-5,5-dimethyl-2-oxo-2-piperidino-1,3,2-dioxaphosphorinans (III; R = NC_5H_{10}) and their 4-deuterio-derivatives are compared in Figures 4 and 5. It is evident that each of the [^{2}H]-compounds contains traces of the [^{1}H]-compound.

TABLE 3

Spin–spin coupling constants for the 2,7,8-trioxa-1-phosphabicyclo[3,2,1]octanes (IV) ($CDCl_3$ solutions; values in Hz)

Coupled system	H_AH_B	H_AP	H_BP	H_FH_G	H_FP	H_GP
(IV; R = H) *	8·8	4·4	1·7	12·2	2·5	9·3
(IV; R = Me)	9·0	4·8	2·8	11·35	5·4	9·0

Coupled system	H_CP	H_BH_C	H_AH_C	H_GH_C
(IV; R = H) *	9·6	5·2	0·67	1·1
(IV; R = Me)	9·8	4·8	1	1·8

* Values from ref. 16.

The *cis*-piperidide (III; R = NC_5H_{10}), from *N*-chloropiperidine, showed absorptions at 1·12 (Me*ax*) and 0·98 (Me*eq*) in [^{2}H]chloroform solution. For the [4-^{2}H]-piperidide, the chloromethyl resonance consists of a doublet at 3·64 p.p.m. (J_{POCCH} 2 Hz). Analysis of

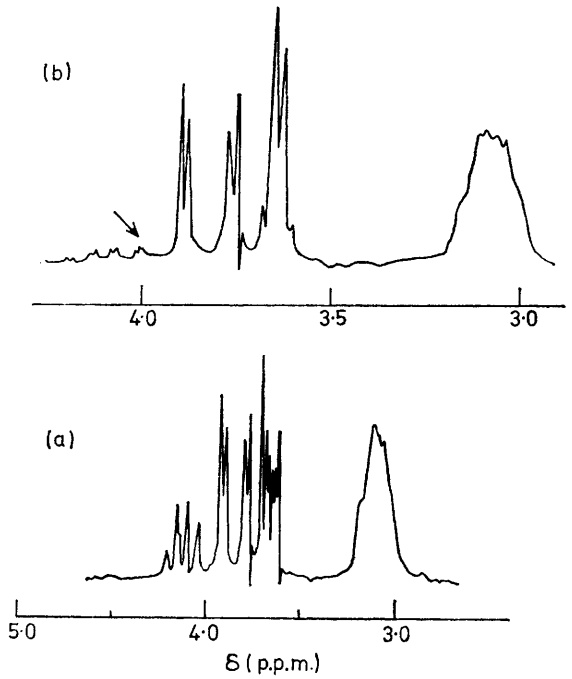


FIGURE 4 100 MHz ^{1}H N.m.r. spectra (methylene region) of (a) *cis*-4-chloromethyl-5,5-dimethyl-2-oxo-2-piperidino-1,3,2-dioxaphosphorinan and (b) its 4-deuterio-derivative

the remaining pattern for the methylene protons was rendered easier by the noticeable intensity of the arrowed peak (Figure 4), this being too great to be attributable to the presence of the isotopic impurity. With J_{FG} assumed to be *ca.* 10—12 Hz, analysis shows δ_F 3·87, δ_G 3·81 p.p.m., J_{FG} 10·8, J_{HFP} 13·2 Hz, and J_{HGP} 12·2 Hz. The signal for H_C at 4·11 p.p.m. was analysed on the assumption that J_{HCP} would then be *ca.* 12—13 Hz; this gave J_{HCP} 11·4 Hz, with further splittings of 6·3 (J_{HC,CH_2Cl}) and 1·15 Hz (probably cross-ring coupling).

Satisfactory analysis of the 60 MHz ^{1}H n.m.r. spectrum of *cis*-2-chloro-4-chloromethyl-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinan (III; R = Cl) proved more difficult. For a solution in [^{2}H]chloroform the methyl signals at

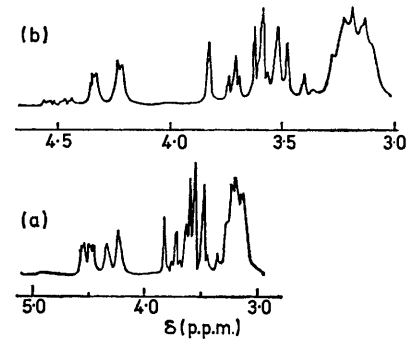


FIGURE 5 100 MHz ^{1}H N.m.r. spectra (methylene region) of (a) *trans*-4-chloromethyl-5,5-dimethyl-2-oxo-2-piperidino-1,3,2-dioxaphosphorinan and (b) its 4-deuterio-derivative

1·21 and 1·02 p.p.m. were of equal height and hence unambiguous conformational assignments to these were not possible. For a solution in benzene (δ_{Me} 0·69 and 0·27 p.p.m.), resolution of the complex methylene–chloromethyl region was not improved. From the spectrum of the [4-^{1}H]-phosphorochloridate it is evident that the chloromethyl signal overlaps with a portion of the B quartet, and also that there is almost complete collapse of the A quartet, rendering analysis less reliable. Again J_{FG} was assumed to be *ca.* 10—11 Hz, and analysis gave J_{FG} 10·8, J_{HFP} 3·0, and J_{HGP} 31·3 Hz, with δ_F 4·27 and δ_G 3·70 p.p.m. Hence from the spectrum of the ^{1}H compound, δ_C = 4·50 p.p.m. and J_{HCP} = 3·5 Hz, while J_{HC,CH_2Cl} = 8·0 Hz. In addition there is a well-defined splitting of 2·35 Hz, probably cross-ring in origin; further splittings are not greater than *ca.* 1 Hz.

A more complex resonance for the chloromethyl–methylene groups was also apparent in both 60 and 100 MHz spectra of the *trans*-piperidide (III; R = NC_5H_{10}) derived from the foregoing cyclic phosphorochloridate. The 60 MHz spectrum provided a more rapid approximate solution to the ABX analysis of the ring methylene region. For a solution in [^{2}H]chloroform (δMe*ax* 1·11 and δMe*eq* 0·91), analysis gave δ_F 4·22, δ_G 3·66 p.p.m., J_{FG} 11·5, J_{HFP} 2·05, J_{HGP} 19·15 Hz. Further analysis of the H_C signal at 4·51 p.p.m. was made possible by assuming that J_{HCP} would be either *ca.* 2 or 20 Hz. Splittings thus found were J_{HC,CH_2Cl} 7·8 Hz, with J_{HCP} 3·1 or 1·7 Hz. The spectrum is unchanged in the temperature range 35 to −50 °C.

For a wide range of 4-methyl, 4,6-dimethyl, 4,4,6-trimethyl, and 4,5,5,6-tetramethyl-1,3,2-dioxaphosph(v)orinans [10,17] the CH,CH_3 splitting is 6·0—6·6 Hz, with

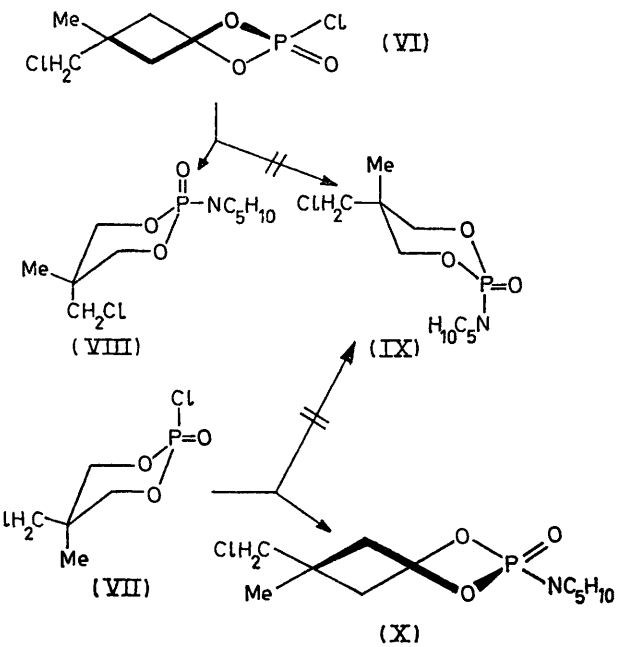
[17] L. D. Hall and R. B. Malcolm, *Chem. and Ind.*, 1968, 92.

J_{POCH_3} $\not>$ 3 Hz, this being greater when the methyl group is in the equatorial position. For 4-isopropyl-5,5-dimethyl-1,3,2-dioxaphosphorinans [10a] the isopropyl group was thought to be equatorial, since the remaining methine proton signal was split by phosphorus to the extent of only 1·2—4·5 Hz, the corresponding coupling constants for the 6-methylene group being 1·4—4·5 (axial proton) and 22·4—31·1 Hz (equatorial proton). For all the recorded compounds, splitting between the side-chain and the adjacent ring methine proton was 3·2—3·8 Hz. Because of the constancy of the coupling constants, stereoisomerism probably results from conformational differences at the phosphorus atom, and the extreme values of J_{POCH} for axial and equatorial protons are indicative of a chair ring.

Of the compounds described here, the conformationally stable (I; X = H, R = Cl or NC_5H_{10}), *trans*-(I; X = Cl or Br, R = NC_5H_{10}), and *cis*-2-chloro-4-chloromethyl-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinan (III; R = Cl) and the *trans*-piperidide (III; R = NC_5H_{10}) derived from it all exhibit coupling constants strongly suggestive of a chair form for the dioxaphosphorinan ring. The remainder [*i.e.* *cis*-(I; X = Cl, R = Cl or NC_5H_{10}), *cis*-(I; X = Br, R = NC_5H_{10}), and *cis*-4-chloromethyl-5,5-dimethyl-2-oxo-2-piperidino-1,3,2-dioxaphosphorinan (III; R = NC_5H_{10})] of those compounds for which a full analysis is reported exhibit numerically more equivalent J_{POCH} values which, it might be argued,[6] result from changes in electron density at the phosphorus atom dependent upon the conformation of attached groups. However, as indicated in the previous paragraph, this argument appears not to apply. Alternatively, the J values indicate that the latter group of compounds possess skew forms of the dioxaphosphorinan ring. Such skew forms have not been completely excluded for certain 5-t-butyl-1,3,2-dioxaphosph(III, V)orinans.[6,18]

Although all the molecules (I) and (III) described here are regarded as being essentially conformationally stable, *trans*-4-chloromethyl-5,5-dimethyl-2-oxo-2-piperidino-1,3,2-dioxaphosphorinan shows slight variation in the ^{1}H n.m.r. spectrum between 30 and −50 °C consistent with a slightly greater degree of molecular freedom than has the corresponding *cis*-isomer.

The stereochemical relationship between the *cis*- (VI) (Ib) and *trans*- (VII) (Ic) phosphorochloridate with a chloromethyl group at C-5 and their derived piperidides is illustrated. During the substitution reaction a pentaco-ordinate species is presumably formed and if the arriving piperidine and departing chlorine atom move in an axial direction (a concept currently accepted), then the intermediate is substituted diequatorially by the dioxaphosphorinan ring. Such a situation allows ready flipping of the phosphorus end of the ring system because of appreciable broadening in the intermediate. The product from the phosphoro-



chloridate (VI) is thus (VIII) and not (IX), nor is the latter produced from what is possibly a chair form (*trans*) phosphorochloridate (VII). The formation of the twist *cis*-piperidide (IX) (Ie) may take place directly from (VII) or *via* a conformationally unstable chair or or boat form.

[2/093 *Received*, 17*th January*, 1972]

[18] W. G. Bentrude and J. H. Hargis, *Chem. Comm.*, 1969, 1113.