Cyclic Organophosphorus Compounds; XIX[1]. A Convenient Synthesis of 7-Aza-2,6-dioxa-1-phosphabicyclo[2.2.2]octanes by the Cyclization of *trans*-2-Amino-5-chloromethyl-2-oxo-1,3,2-dioxaphosphorinanes

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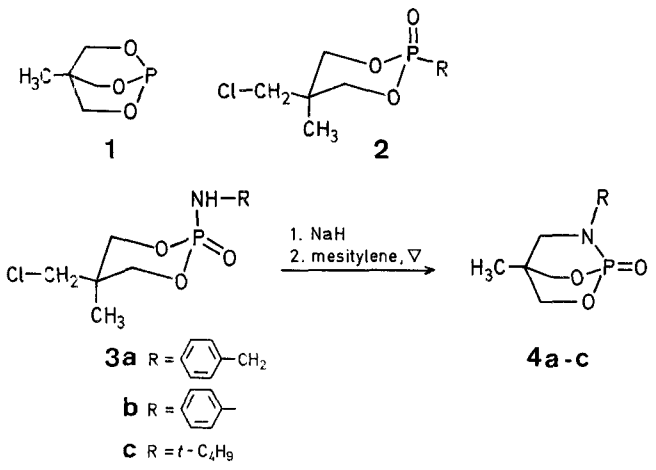
Phosphoramidates and related ester-amides of pentavalent phosphorus, particularly those with electron-attracting groups attached to nitrogen, form anions which easily undergo intermolecular alkylation[2]. Examples of the intramolecular alkylation of acyclic ω-haloalkyl phosphoramidates and phosphonic amides to form 1,3,2-oxazaphosphorinanes or 1,3,2-oxazaphospholidines are widely recorded for a process which also occurs under comparatively mild conditions[3]. The ease of cyclization of the anions from 2-[bis(2-chloroethyl)amino]-2*H*-1,3,2-oxazaphosphorinane 2-oxide (cyclophosphamide)[4] and 5-bromocyclophosphamide[5] has also been recorded, but attempts to bring about the cyclization of 2-[ω-halogenoalkyl] and 2-[ω-halogenoalkoxyl]-1,3,2-oxazaphosphorinanes under similarly mild conditions have been unsuccessful[6].

In a new adaptation of the intramolecular cyclization process, anions derived from *trans*-2-amino-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinanes **(3)** have now been shown to cyclize in boiling mesitylene to give 4-methyl-7-aza-2,6-dioxa-1-phosphabicyclo[2.2.2]octane 1-oxides **(4)**, examples of a hitherto unrecorded phosphorus-containing ring system[7].

Chlorination of 4-methyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane **(1)** by either chlorine or sulphuryl chloride under controlled conditions yields 2-chloro-5*c*-chloromethyl-5*t*-methyl-2*r*-oxo-1,3,2-dioxaphosphorinane (**2**; R = Cl), the molecular geometry of which has been established by analogy with that of the corresponding dibromo compound[8]. Reaction of the phosphorochloridate **2** (having the *cis* configuration)



with amines yields single, isolable, phosphoramidates **3** to which the designation *trans* has been given, based upon a comparison of chemical shift data for methyl and chloromethyl groups in the stereoisomeric compounds **2** and **3**, and also an X-ray analysis of the piperidide derived from (**2**; R = Cl) and piperidine[9]. The ^{1}H-N.M.R. data for three such phosphoramidates have been briefly listed[10], but these compounds are characterized here more fully; the ^{1}H-chemical shifts for the methyl and chloromethyl groups fall within the ranges for the reported[11] *trans* stereoisomeric 1,3,2-dioxaphosphorinanes and coupling constant data are consistent with chair forms. The failure of stereoisomeric amides (exemplified by **2**; R = $C_6H_5CH_2NH$—) to undergo cyclization would appear to confirm, in chemical terms, the stereochemical assignments made to amides in the series **2** and **3**.

The structures of the products **4** are based on microanalytical and spectroscopic data which are detailed in the experimental section. However, it may be noted that whereas **4b** and **4c** exhibit well-separated ^{1}H-N.M.R. signals for ring *O*-methylene and *N*-methylene protons in the ratio 2:1, **4a** shows overlap of the former with the benzylic protons, although their separation can be achieved by the use of perdeuterio-Eu(fod)$_3$[12]. In addition, the two *N*-*t*-butylphosphoramidates **3c** and **4c** provided no molecular ions in their mass spectra obtained under normal conditions, as appears to be customary for such amides[13]; however, application of the fast atom technique does provide the expected [M + 1] and [2 M + 1] ions[14].

The melting points reported are uncorrected. Thin layer and column chromatography were carried out with Merck Kiesel gel. I.R. spectra were determined with a Perkin-Elmer model 681 spectrophotometer. ^{1}H-N.M.R. spectra were determined using a JEOL-MH-100 spectrometer using TMS as internal standard.

Table. *trans*-2-Amino-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinanes **3** and 4-Methyl-7-aza-2,6-dioxa-1-phosphabicyclo[2.2.2]octane 1-Oxides **4**

Product	R	Time of Reflux [h]	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
3a	$C_6H_5CH_2$	2	79	145–146° (benzene, then ethyl acetate)	$C_{12}H_{17}ClNO_3P$ (289.7)	3190 (NH); 1220 (P=O); 1053, 1015, 1000 (POC)	0.88 (s, 3H, CH_3); 3.64 (s, 2H, CH_2Cl); 3.81, 4.2 (q, 2H each, OCH_2, $^3J_{POCH}$ = 2.8, 19.8 Hz, $^3J_{HCH}$ = 11 Hz)
3b	C_6H_5	6.5	95	166–167° (ethyl acetate)	$C_{11}H_{15}ClNO_3P$ (275.7)	3190 (NH); 1245 (P=O); 1050, 1032, 1002 (POC)	1.0 (s, 3H, CH_3); 4.22 (s, 2H, CH_2Cl)
3c	t-C_4H_9	5	76	179–180° (benzene)	$C_9H_{19}ClNO_3P$ (255.7)	3200 (NH); 1245, 1235 (P=O); 1045, 1032, 1000 (POC)	0.9 (s, 3H, CH_3); 1.28 [s, 9H, $C(CH_3)_3$]; 3.64 (s, 2H, CH_2Cl); 3.92, 4.2 (q, 2H each, OCH_2, $^3J_{POCH}$ = 2.4, 20.6 Hz, $^3J_{HCH}$ = 11 Hz)
4a	$C_6H_5CH_2$	8–9	32	122° (carbon tetrachloride)	$C_{12}H_{16}NO_3P$ (257.7)	1300 (P=O); 1040, 1005 (POC)	0.8 (s, 3H, CH_3); 3.12 (d, 2H, NCH_2, $^3J_{PNCH}$ = 6 Hz); 4.24 (m, 4H, $C_6H_5CH_2N$ and OCH_2); 7.3 (s, 5 H_{arom}). In the presence of 0.2 molar perdeuterio-Eu(fod)$_3$: 1.14 (s, 3H, CH_3); 3.76 (d, 2H, NCH_2, $^3J_{PNCH}$ = 5 Hz); 4.85 (d, 2H, OCH_2, $^3J_{POCH}$ = 6 Hz); 5.44 (d, 2H, $C_6H_5CH_2N$, $^3J_{PNCH}$ = 10.3 Hz); 7.4 (m, H_{arom}); 8.3 (m, H_{arom})[b]
4b	C_6H_5	8–9	10	195° (ethyl acetate)	$C_{11}H_{14}NO_3P$ (239.2)	1300 (P=O); 1032 (POC)	1.0 (s, 3H, CH_3); 3.68 (d, 2H, NCH_2, $^3J_{PNCH}$ = 4.5 Hz); 4.28 (d, 2H, OCH_2, $^3J_{POCH}$ = 6.5 Hz)
4c	t-C_4H_9	8–9	46	120–120.5° [ethyl acetate-petroleum ether (60–80 °C)]	$C_9H_{18}NO_3P$ (219.2)	1285 (P=O); 1062, 1040, 1018 (POC)	0.94 (s, 3H, CH_3); 1.36 [s, 9H, $C(CH_3)_3$] 3.48 (d, 2H, NCH_2, $^3J_{PNCH}$ = 5 Hz); 4.36 (d 2H, OCH_2, $^3J_{POCH}$ = 6 Hz)[c]

[a] Satisfactory microanalysis obtained: C ±0.25, H ±0.15, N ±0.15; exception: **4b**, C −0.7.

[b] In benzene solution: δ = 0.16 (s, 3H, CH_3); 2.74 (d, 2H, NCH_2, $^3J_{PNCH}$ = 6 Hz); 3.84 (d, 2H, OCH_2, $^3J_{POCH}$ = 7 Hz); 4.36 ppm (d, 2H $C_6H_5CH_2N$, $^3J_{PNCH}$ = 11 Hz).

[c] In acetone-d_6.

2-Chloro-5*c*-chloromethyl-5*t*-methyl-2*r*-oxo-1,3,2-dioxaphosphorinane (**2**, R = Cl) was prepared according to Refs.[10,15]; m.p. 64–66 °C (from CCl_4).

2-Amino-5*t*-chloromethyl-5*c*-methyl-2*r*-oxo-1,3,2-dioxaphosphorinanes 3; General Procedure:

A solution of the amine (0.04 mol) in benzene (20 ml) is added in one portion to the cyclic phosphorochloridate **2** (4.4 g, 0.02 mol) dissolved in benzene (25 ml) and the mixture is warmed over a steam bath for 2 h. The cooled mixture is diluted with chloroform (50 ml), washed with water (25 ml), dried with sodium sulfate, and the solvent removed under reduced pressure. The residue is crystallised from suitable solvents (Table).

For compound **3b**, the reaction involves aniline (0.02 mol) together with triethylamine (0.02 mol).

7-Aza-4-methyl-1-oxo-2,6-dioxa-1-phosphabicyclo[2.2.2]octanes 4, General Procedure:

Sodium hydride (50% in oil, 0.5 g) is washed several times with toluene, and then covered with mesitylene (50 ml). The appropriate 2-amino-5*t*-chloromethyl-5*c*-methyl-2*r*-oxo-1,3,2-dioxaphosphorinane **3** (0.01 mol) is added and the mixture is warmed until evolution of hydrogen ceases and complete solution of the sodium derivative is achieved. The solution is then heated under reflux for 8–9 h, filtered, and the solvent removed under reduced pressure. The residue is chromatographed using benzene/acetone (7:3, v/v) (for **4a**) or crystallised directly (for **4b** and **4c**).

Mixed Stereoisomers of 2-Chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinane (2):

A mixture of the stereoisomeric cyclic phosphorochloridates is prepared according to Ref.[16].

Stereoisomeric 2-Benzylamino-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinanes (3a):

A solution of benzylamine (43 g, 0.04 mol) in benzene (20 ml) is added in one portion to the mixed stereoisomers of 2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinane (44 g, 0.02 mol) dissolved in benzene (25 ml) and the mixture is warmed over a steam bath for 2 h. The cooled mixture is diluted with chloroform (50 ml), washed with water (50 ml), dried with sodium sulfate, and the solvent removed under reduced pressure. Chromatography of the resulting mixture using butan-2-one and chloroform (3:1, v/v) yields first 2-benzylamino-5*c*-chloromethyl-5*t*-methyl-2*r*-oxo-1,3,2-dioxaphosphorinane (the *cis*-isomer of **3a**); yield: 1.5 g (76%), m.p. 109–110 °C (from benzene) followed by the *trans* isomer of **3a**; yield: 1.8 g (31%); m.p. 143–145 °C.

cis-Isomer of **3a**:

$C_{12}H_{17}ClNO_3P$	calc.	C 49.75	H 5.92	N 4.84
(289.7)	found	49.6	6.0	4.7

I.R. (KBr): ν = 3180 (NH); 1216 (P=O); 1054, 1015, 998 cm^{-1} (POC).

^{1}H-N.M.R. ($CDCl_3$): δ = 1.12 (s, 3H, CH_3); 3.48 ppm (s, 2H, CH_2Cl).

^{1}H-N.M.R. (C_6H_6): δ = 0.72 (s, 3H, CH_3); 2.72 ppm (s, 2H, CH_2Cl).

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[1] Part XVIII; R. S. Edmundson, *Org. Mass Spectrom.*, in the press.
[2] R. S. Edmundson, T. A. Moran, *J. Chem. Soc.* [C] **1970**, 1009 and references therein.
[3] See, for example, P. Savignac, J. Chenault, M. Dreux, *J. Organomet. Chem.* **66**, 63 (1974).
J. F. Brault, P. Savignac, *J. Organomet. Chem.* **66**, 71 (1974).
[4] G. Zon, S. M. Ludeman, W. Egan, *J. Am. Chem. Soc.* **99**, 5785 (1977).
[5] S. M. Ludeman, G. Zon, W. Egan, *J. Med. Chem.* **22**, 151 (1979).
[6] R. S. Edmundson, T. A. Moran, unpublished results.
[7] For a summary of related systems, see: R. S. Edmundson in *Chemistry of Carbon Compounds*, 2nd Edn., S. F. Coffey, Ed., Vol. IVK, Elsevier, Amsterdam, 1979, Chapter 48.
[8] T. A. Beineke, *Acta Crystallograph.* [B] **25**, 413 (1969).
[9] R. E. Wagner, W. Jensen, W. Wadsworth, Q. Johnson, *Acta Crystallograph.* [B] **29**, 2160 (1973).
[10] W. S. Wadsworth, S. Larsen, H. L. Horten, *J. Org. Chem.* **38**, 256 (1973).
[11] For a summary, see: B. E. Maryanoff, R. O. Hutchins, C. A. Maryanoff, *Top. Stereochem.* **11**, 187 (1979).
[12] W. G. Bentrude, H.-W. Tan, K. C. Yee, *J. Am. Chem. Soc.* **94**, 3264 (1972).
A. J. Dale, *Acta Chem. Scand.* **B30**, 255 (1976).
[13] R. S. Edmundson, *Phosphorus Sulfur* **9**, 307 (1981).
R. S. Edmundson, *Org. Mass Spectrom.* **17**, 558 (1982).
[14] M. Barber, R. S. Bordoli, R. D. Sedgwick, A. N. Tyler, *J. Chem. Soc. Chem. Commun.* **1981**, 325.
[15] R. S. Edmundson, E. W. Mitchell, *J. Chem. Soc.* [C] **1968**, 3033.
[16] R. S. Edmundson, *J. Chem. Soc. Perkin Trans.* **1972**, 1660.