

PREPARATION, STEREOCHEMISTRY AND SOME REACTIONS OF 1,3,2-OXAZAPHOSPHOLANES

D.B. COOPER, J.M. HARRISON and T.D. INCH*

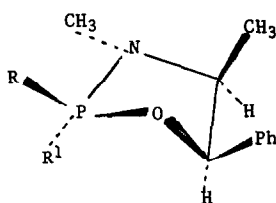
Chemical Defence Establishment, Porton Down, Salisbury, Wiltshire, England

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Although reactions between (-)ephedrine \square 2-(S)-methylamino-1-(R)-phenylpropan-1-ol \square and $RPOCl_2$ (R = Cl, alkyl, aryl, alkoxy, aryloxy) can in principle afford pairs of 1,3,2-oxazaphospholanes epimeric at phosphorus, most reports describe only one product from highly stereoselective reactions.¹ We now report that in benzene in the presence of triethylamine at room temperature, (-)ephedrine with $POCl_3$, $MePOCl_2$ and $PhPOCl_2$ affords the isomeric pairs $1a$ and $1b$, $2a$ and $2b$, and $3a$ and $3b$ respectively. (Characteristic experimental data for these compounds and for other 1,3,2-oxazaphospholanes described in this paper are listed in Table 1. N.m.r. data are listed in Table 2). The reaction mixtures were processed by standard procedures² and the isomers separated by chromatography over silica in the solvents indicated. Yields of $2a$ and $2b$ were low because some decomposition occurred during chromatography. The major chloridate ($1a$) was converted into essentially only $4a$ when treated at room temperature with methanol containing triethylamine and into essentially only $5a$ when treated at room temperature with sodium phenoxide in benzene. Similarly the minor chloridate $1b$ was converted into $4b$ and $5b$. Yields for the conversions of $1a$ and $1b$ into the methoxy and phenoxy derivatives are listed in Table 1.

Tentative conformational and configurational assignments for the 1,3,2-oxazaphospholanes were based on n.m.r. data. Since there is a Karplus type relation between P-O-C-H vicinal couplings and the corresponding dihedral angles³, and provided the effect of substituents on nitrogen do not grossly affect similar relations for P-N-C-H couplings⁴ it is not unreasonable to suggest that the 1,3,2-oxazaphospholane ring in compounds $1a$, $2a$, $3a$, $4a$ and $5a$ is in a ¹E conformation⁵, illustrated in Table 1, with oxygen out of the plane of the other four atoms. In this conformation the P-O-C-H dihedral angle approaches 90°, consistent with a small $J_{P,H-5}$ and the P-N-C-H dihedral angle is > 120°, consistent with a large $J_{P,H-4}$. The coupling constant data for compounds $1b$, $2b$, $3b$, $4b$ and $5b$ are consistent with similar but slightly less puckered conformations. The configurations at phosphorus in compounds $1 - 5$ were assigned on the basis

Table 1.



Compound	R	R ¹	Yield (%)	m.p. °	$[\alpha]_D^{20}$	Chromatography Solvent/R _f
1a	Cl	O	65	88 - 89 ^a	-64	Benzene-acetone (9:1)/0.4
1b	O	Cl	6	111 - 113 ^a	-26	Benzene-acetone (9:1)/0.6
2a	CH ₃	O	9	83 - 84 ^a	-81	Benzene-ethylacetate-acetone (2:1:2)/0.3
2b	O	CH ₃	12	119 - 120 ^b	-65	Benzene-ethylacetate-acetone (2:1:2)/0.25
3a	Ph	O	33	134 - 136	-54	Benzene-acetone (7:3)/0.3
3b	O	Ph	28	159 - 161 ^b	-40	Benzene-acetone (7:3)/0.4
4a	OCH ₃	O	91	Syrup	-110	Benzene-acetone (7:3)/0.25
4b	O	OCH ₃	85	Syrup	-37	Benzene-acetone (7:3)/0.4
5a	OPh	O	83	97 - 98 ^a	-102	Benzene-acetone (9:1)/0.3
5b	O	OPh	91	131 ^b	-34	Benzene-acetone (9:1)/0.4
6a	4-NO ₂ -Ph	O	75	117 ^a	-135	Benzene-acetone (4:1)/0.4

^a from di-isopropyl ether.^b from acetone-di-isopropyl ether.

that in phosphorus containing rings protons in a 1,3-cis relation to a P=O group are deshielded.^{2,6} Thus, since H-4 and H-5 are at lower field in the "a" series than in the "b" series the P=O group must be cis to H-4 and H-5 in the "a" series.⁷ The deshielding effect is greater for H-5 than for H-4, a result which is to be expected in a ¹E conformation in which P=O and H-5 are closer than P=O and H-4.

The formation of $\overset{4a}{\sim}$ and $\overset{5a}{\sim}$ from $\overset{1a}{\sim}$ and the formation of $\overset{4b}{\sim}$ and $\overset{5b}{\sim}$ from $\overset{1b}{\sim}$ shows that displacement of chlorine from phosphorus in 2-chloro-1,3,2-phospholan-2-ones proceeds with retention of configuration. Although there was little doubt of the validity of this conclusion from the physical data available (in addition to the evidence from the n.m.r. data the specific rotations in the "a" series are consistently lower than in the "b" series), supporting evidence was obtained when $\overset{1a}{\sim}$ was converted into $\overset{6a}{\sim}$ by treatment with sodium

4-nitrophenoxide in benzene, and $6a$ was then converted into $4a$ by treatment with MeOH/Et₃N. The result that chlorine displacement occurs with retention of configuration is consistent with similar reactions in other small ring phosphorus compounds⁸ and it is reasonable to postulate that the displacement of chlorine involves initial attack at phosphorus opposite either the ring oxygen or nitrogen atoms to form a trigonal bipyramidal intermediate which undergoes pseudorotation before chlorine leaves from an apical position.

Table 2. N.m.r. parameters for 2-substituted 1,3,2-oxazaphospholan-2-ones

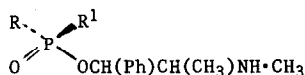
Compound	Chemical Shifts (ppm)				H-4, H-5	Coupling Constants (Hz)			
	NMe	CH ₃	H-4	H-5		P, H-4	P, H-5	PNCH ₃	CH ₃
1a	2.85	0.83	3.85	5.84	6.5	26	~1	13	6.5
1b	2.67	0.80	3.70	5.54	7	14	7	13	7
2a	2.78	0.68	3.69	5.74	5.8	12.2	1-2	9.5	6.5
2b	2.67	0.80	3.55	5.43	6	14	4.5	10	6.5
3a	2.74	0.80	3.83	5.95	6	14	~1	10	6.5
3b	2.58	0.88	3.76	5.62	6	11	5.5	11	7
4a	2.71	0.77	3.70	5.63	6.4	20	1.9	10.5	6.5
4b	2.68	0.79	3.64	5.52	6.5	14	3.6	11	6.5
5a	2.78	0.58	3.61	5.65	6	14	~1	10	6.5
5b	2.72	0.72	3.51	5.28	5.5	10	4	10	6.5

N.m.r. spectra were measured at 100 MHz in CDCl₃.

Ring opening reactions of 1,3,2-oxazaphospholanes have been little studied but limited reports suggest that P-N bond cleavage rather than P-O bond cleavage may be expected under basic hydrolytic conditions⁹ (whereas in acyclic amidates only slow P-O bond cleavage is observed). No information about the stereochemistry of the P-N bond breaking reaction was available. When $2a$ and $2b$ were treated with N sodium methoxide in methanol for 10 min. at room temperature the ring opened products 7 and 8 which result from P-N bond cleavage were obtained (see Table 3 for structures and n.m.r. parameters). Compounds 7 and 8 decomposed rapidly on storage presumably via aziridine intermediates¹⁰ both in the reaction mixtures and after isolation. Compounds 7 and 8 were also obtained after appropriate processing when $2a$ and $2b$ respectively were treated with methanolic hydrogen chloride. Similarly compound 9 was obtained on treatment of $4a$ with either sodium ethoxide/ethanol or with ethanol/HCl and compound 10 was obtained from the ethoxy analogue of $4a$ on treatment with sodium methoxide or MeOH/HCl. Since acid promoted P-N bond breaking reactions may be expected to proceed with inversion of configuration it

followed that base promoted P-N bond breaking reactions also proceed with inversion of configuration in 1,3,2-oxazaphospholanes. (Similar results which will be reported elsewhere have been obtained in 1,3,2-oxazaphosphorinanes.¹¹ For these compounds more direct evidence that acid catalysed P-N cleavage occurs with inversion of configuration has been obtained). These results imply that under basic conditions direct nucleophilic attack at phosphorus occurs opposite the ring nitrogen atom with almost immediate P-N bond fission occurring rather than initial attack opposite the ring oxygen atom with P-N breaking taking place only after pseudo-rotation of the trigonal bipyramid intermediate.

Table 3. N.m.r. parameters for 2-(S)-methylamino-1-(R)-phenylpropan-1-yl phosphates



Compound	R	R ¹	CH(CH ₃)	PCH ₃	NH·CH ₃ ^a	POCH ₃	CH(Ph) ^b	CH ₃ CH ₂
7	OCH ₃	CH ₃	1.03	1.48	2.42	3.38	5.38	-
8	CH ₃	OCH ₃	1.08	1.27	2.43	3.70	5.33	-
9	OC ₂ H ₅	OCH ₃	1.08	-	2.44	3.68	5.34	1.17
10	OCH ₃	OC ₂ H ₅	1.08	-	2.43	3.56	5.33	1.32

^aThe CH₃ signal was a singlet clearly indicating the absence of a P-N bond.

^bA Quartet with J_{H,H} = 4.9 Hz, J_{P,H} = 9.1 Hz. Couplings were independent of configuration at phosphorus.

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