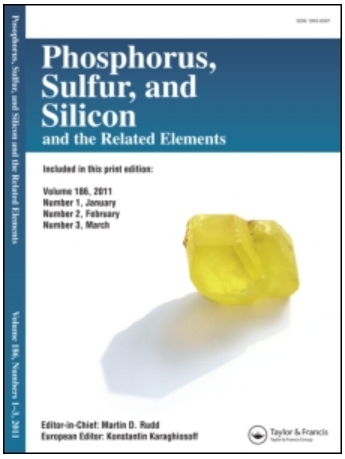

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SYNTHESIS AND CONFORMATIONAL ANALYSIS OF SOME NEW 5-BROMO-5-NITRO-2R-2-OXO-1,3,2-DIOXAPHOSPHORINANE DERIVATIVES

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5-Bromo-5-nitro-2-R-2-oxo-1,3,2-dioxaphosphorinane derivatives (R=CH_3, OC_6H_5, *p*-CH_3—C_6H_4O, *m*-CH_3—C_6H_4O, *p*-O_2N—C_6H_4O, OH) have been obtained by the reaction of 2-bromo-2-nitro-1,3-propanediol with phosphonic dichlorides, phosphoric dichlorides and phosphorus oxychloride. By the 2-chloro- and 2-aryloxy-1,3,2-dioxaphosphorinanes alkaline hydrolyses, the P—OAr and P—Cl bonds were broken exclusively and 5-bromo-5-nitro-2-hydroxy-2-oxo-1,3,2-dioxaphosphorinane was formed. The chair configurations at phosphorus atom of the above compounds were proved by NMR and IR spectral analysis. Thermodynamic data (K, ΔG, ΔH and ΔS) have been determined for 2-methylphosphorinane derivative and equilibrium constants and conformational energies for 2-chloro- and 2-aryloxy-phosphorinane derivatives have been calculated.

INTRODUCTION

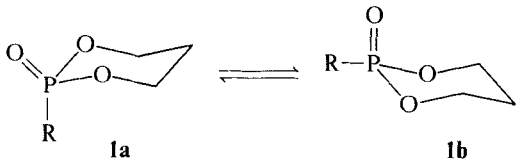
The cyclic esters of the phosphorus acids represent a subclass of organic compounds of fundamental importance.

The majority of the investigation beginning from 1960 in the field of the 1,3,2-dioxaphosphorinane compounds has been concerned with structure determination and stability of these derivatives.[1–73]

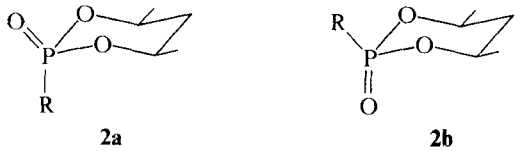
The investigations of 2-R-2-oxo-1,3,2-dioxaphosphorinanes reported in the literature fall into two broad categories:

a) Studies of configurations around phosphorus and ring conformational equilibria of mobile systems such as 1.

b) Assignments of configurations around the phosphorus of rings with reduced mobility such as 2a and 2b.



1a **1b**



2a **2b**

Several instrumental techniques (^{1}H NMR, ^{13}C NMR, ^{31}P NMR. infrared and dipole moment measurements) have been used for determinations of phosphorus stereochemistry and ring conformations in solution.

Coupling constants among ring protons and between phosphorus and ring protons have been found to be both valuable for the determinations of conformer distribution in compounds of type (**1**), and for assignments of stereochemistry around phosphorus.[10,22,52]

Mosbo and Verkade have demonstrated that the C_4 and C_6 axial protons are shifted considerably further downfield in compounds with the (**2b**) configuration than in those with (**2a**).[54,70]

^{31}P NMR data have indicated that chemical shifts of (**2a**) isomers are generally upfield as compared to (**2b**) analogues.[53,54]

Kainosho and coworkers[23] first reported that infrared phosphoryl stretching frequencies could give information about the placement of the P=O group in the ring. The absorption band of the equatorial P=O band (**2a**) was found at higher frequency than the axial band (**2b**). This technique has been extensively employed for identification of stereochemistry around phosphorus as well as for determinations of conformer equilibria.[51,52b,55]

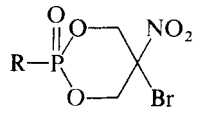
Based on the ^{1}H NMR and ^{31}P NMR chemical shifts, infrared P=O bond measurements as well as dipole moment studies, Mosbo and Verkade have calculated the conformational distributions

of the 2-R-2-oxo-1,3,2-dioxaphorphorinane derivatives, where R=CH_3, H, OCH_3, $N(CH_3)_2$.[70]

During the last ten years, the majority of the studies in the field of cyclic phosphorus compounds with six atoms in the ring, have referred to the 1,3,2-dioxaphosphorinane derivatives, with alkyl, halogen-alkyl, aryl and aralkyl groups as ring substituents. Ring C_5-substituted 2-R-2-oxo-1,3,2-dioxaphosphorinanes with electron attracting groups, as: halogen[28] and NO_2,[69,74-77] have been much less studied.

RESULTS AND DISCUSSION

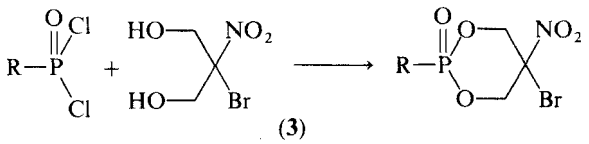
The object of the present paper is the preparation and the conformational study by means of NMR and IR measurements of the 5-bromo-5-nitro-2-R-2-oxo-1,3,2-dioxaphosphorinane derivatives represented by the general formula **A**:



A

R	
CH_3	**3**
Cl	**4**
C_6H_5O	**5**
p-CH_3—C_6H_4O	**6**
m-CH_3—CH_4O	**7**
p-O_2N—CH_4O	**8**
OH	**9**

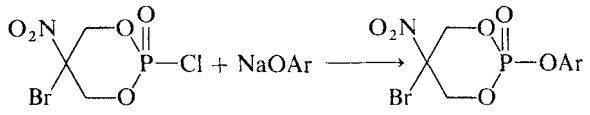
The 5-bromo-5-nitro-2-R-2-oxo-1,3,2-dioxaphosphorinane derivatives represented by the formula A are obtained from the reactions of the 2-bromo-2-nitro-1,3-propanediol with the dichloride derivatives of the phosphonic and phosphoric acids:



(3)

R=CH_3, Cl, OC_6H_5, p-CH_3—C_6H_4O, m-CH_3—C_6H_4O, p-O_2N—C_6H_4O

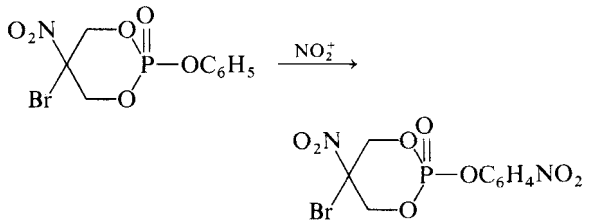
The dioxaphosphorinane compounds **5–8** may also be obtained by the reaction of the 5-bromo-5-nitro-2-chloro-2-oxo-1,3,2-dioxaphosphorinane derivative with the corresponding sodium aryloxides:



(4)

Ar = OC_6H_5, p-CH_3—C_6H_4O, m-CH_3—C_6H_4O, p-O_2N—C_6H_4O

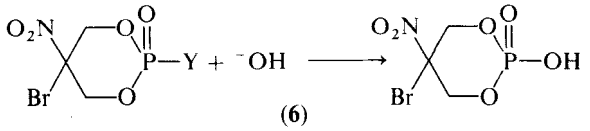
The 5-bromo-5-nitro-2-p-nitrophenoxy-2-oxo-1,3,2-dioxaphosphorinane derivative is obtained in good yield (80%) by the nitration of 5-bromo-5-nitro-2-phenoxy-2-oxo-1,3,2-dioxaphosphorinane:



(5)

Alkaline hydrolysis of 2-R-2-oxo-1,3,2-dioxaphosphorinanes shows in almost all cases strong stability of the phosphorinane ring; the substituents linked to phosphorus are usually hydrolysed.

The compounds **4–8** hydrolyse in a basic medium chiefly by breaking the P—Ar and P—Cl bonds, forming 5-bromo-5-nitro-2-hydroxy-2-oxo-1,3,2-dioxaphosphorinanes:



(6)

Y = Cl, OC_6H_5, p-O_2N—C_6H_4O, p-CH_3—C_6H_4O, m-CH_3—C_6H_4O

The NMR and IR data, together with other physical data of 1,3,2-dioxaphosphorinanes (melting points and elementary analysis) are collected in the Table II and Table III.

Determination of Configuration and Conformation of 5-bromo-5-nitro-2-R-2-oxo-1,3,2-dioxaphosphorinanes **3–9**

The IR absorption spectra of the 5-bromo-5-nitro-2-R-2-oxo-1,3,2-dioxaphosphorinanes **3–9**, show two absorption bands in the P=O region, suggesting a mixture of two stereoisomers.

TABLE I

I.R. spectral characteristics, reaction outputs, melting points and elemental analysis data for 5-bromo-5-nitro-2-R-2-oxo-1,3,2-dioxaphosphorinane derivatives.

Compd	Yield %	Mp (°C)	Elemental analyses Cald. (found) P%	C%	H%	N%	Cl%	IR spectral characteristics νP=O (cm^{-1}) Pellet	(KBr) solution	νP—O—C (cm^{-1})	νAr—NO_2 (cm^{-1})	νC_5—NO_2 (cm^{-1})	νP—CH_3 (cm^{-1})	νP—OH (cm^{-1})	νP—Cl (cm^{-1})
3a			11.92	18.46	2.69	5.38	—	1275	1295			1535	1320	—	—
	60	160–161, 5							benzen	1070	—	1570	—	—	—
3b			(11.89)	(18.80)	(3.01)	(5.60)	—	1230	1260			(1380)	—	—	—
4a			11.05	12.83	1.42	4.99	12.65	1280	1295			1530	—	—	500
	28	184–185							chloroform	1060	—	1570	—	—	—
4b			(11.56)	(15.20)	(1.97)	(5.21)	(13.20)	1330	1345			1570	—	—	—
												(1385)			
5a	56[a]		9.17	31.95	2.66	4.14	—	1280	1290	1065	—	1545	—	—	—
		149–150, 5							dioxan			1590			
5b	69[b]		(9.57)	(32.30)	(2.92)	(4.60)	—	1300	1310			(1385)	—	—	—
6a	49[a]		8.80	34.09	3.12	3.97	—	1280	1290			1530	—	—	—
									dioxan	1055	—	1570	—	—	—
6b	49[b]		(8.30)	(34.62)	(3.65)	(4.34)	—	1305	1320			(1360)	—	—	—
7a	42[a]		8.80	34.09	3.12	3.97	—	1250	1270			1525	—	—	—
									dioxan	1060	—	1565	—	—	—
7b	62[b]		(9.00)	(34.30)	(3.64)	(4.40)	—	1300	1315			(1370)	—	—	—
8a	60[a]		8.09	28.19	2.08	3.65	—	1180	1200		1530	1540	—	—	—
	78[b]	164–165							dioxan	1070		1570	—	—	—
8b	80[c]		(8.53)	(28.60)	(2.50)	(4.00)	—	1230	1240		(1350)	(1390)	—	—	—
9a	39	230–231	11.83	13.74	1.90	5.34	—	1280	1285 1295[d] 1320[d]			1590	—	2400	—
9b			(12.05)	(14.20	(2.30)	(5.76)	—			1110		(1395)	—	1070	—
									DMSO						

[a] Compounds obtained by reaction (**3**).
[b] Compounds obtained by reaction (**4**).
[c] Compounds obtained by nitration (**5**).
[d] Valence bands, for 2-hydroxy-1,3,2-dioxaphosphorinane derivative, in DMSO at 80°C.

TABLE II

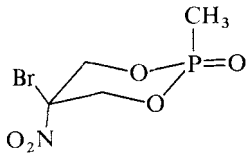
^1H and ^{31}P chemical shifts and coupling constants for 5-bromo-5-nitro-2-R-2-oxo-1,3,2-dioxaphosphorinane derivatives

Compd.	δ ^1H (ppm)			δ ^{31}P (ppm) H_3PO_4 85%	J(Hz)					Solvent	Temp. (°C)
	$H_{4a,6a}$	$H_{4e,6e}$	CH_3		P H_{6e}	P H_{6a}	P CH_3	$^1H-^1H$ geminal	$H_{4e,6e}$		
3a	4.57	3.95	1.60							$DMSO-D_6$	21
			1.61	−19.0	15.0	3.5	—	−10.5	2.6	$DMSO-D_6$	40
			1.61				18.0			$DMSO-D_6$	61
3b	4.05	0.55	1.39							$DMSO-D_6$	21
			1.40	−27.3	14.5	4.0	—	−10.9	2.9	$DMSO-D_6$	40
			1.40							$DMSO-D_6$	61
4a	3.50	3.20	—	113.0						$CDCl_3$	0
	3.52	3.21			23.0	2.9	–	−12.5	3.2	$CDCl_3$	20
4b	4.25	3.90	—	115.2						$CDCl_3$	41
	4.50	4.20								$CDCl_3$	60
5a	5.05	4.80	—	123.5	21.5	3.0	—	−10	2.8	$DMSO-D_6$	25
5b	5.25	5.15	—	125.8						Acetone-D_6	
6a	5.25	4.90	—	125.6	22.0	2.8	—	−11.5	3.5	$CDCl_3$	25
6b				127.5							
7a	5.40	0.00	—	124.5	21.6	1.6	—	−10.6	3.0	$CDCl_3$	25
7b				126.0							
8a	5.10	0.95	—	110.5	20.3	1.4	—	−9.6	2.5	$CDCl_3$	25
8b				113.2							
9	4.80	0.75	—	116.5	10.5	10.5	—	—	—	$CDCl_3$	25

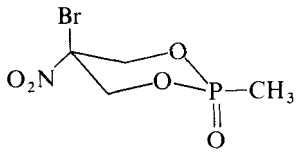
3a, **3b**: J and δ values from computer assisted analysis using LAOCM[3], sample in $DMSO-D_6$; (**4–8**)**a**, **b**; **9**: J and δ values from first-order analysis; $J_{^1H-H}$ assumed negative and other J values assumed positive.

The band with the highest frequency is assigned to the equatorially orientated P=O group (**3a**), while the lower frequency band to the axially orientated P=O group (**3b**).

It was shown that the lower frequency band of the 2-methylphosphorinane derivative was by far the stronger:

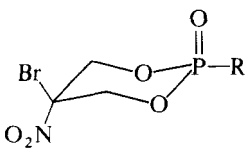


(**3a**)

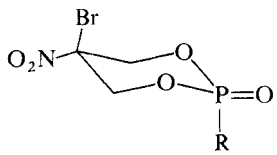


(**3b**)

For 2-chloro and 2-aryloxy-1,3,2-dioxaphosphorinanes, the higher frequencies bands have been found to be the more intense:



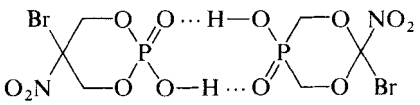
(**4a–8a**)



(**4b–8b**)

These observations suggest that in the case of 2-chloro and 2-aryloxy-1,3,2-dioxaphosphorinanes the isomers with equatorially orientated P=O group (**4b–8b**) are in excess, while in the case of the 2-methyl-1,3,2-dioxaphosphorinane, the isomer with the axially orientated phosphoryl group dominates (**3b**).

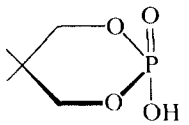
In the 2-hydroxy-1,3,2-dioxaphosphorinane derivative, no free vibration bands occur in the P=O region in solid state or in solution. A broad absorption band at 1280 cm^{-1} points to the existence of dimeric association:



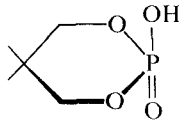
When the IR spectrum is obtained in DMSO at 80°C, two distinct P=O bands appear at 1295 cm^{-1} and 1320 cm^{-1}, suggesting the presence of a mixture of two diastereoisomeric compounds (**9a, 9b**).

The P=O band at the highest frequency corresponds to the stereoisomer with equatorially orientated phosphoryl group, while the other corres-

ponds to the stereoisomer with axially orientated phosphoryl group:



(9a)



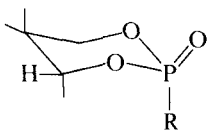
(9b)

In the spectra of compounds (**3–8**), two bands can be assigned to the NO_2 group in the region 1520–1590 cm^{-1}. The band at the lower frequency corresponds to the axially orientated nitro group, while the band at higher frequency to the equatorially orientated NO_2 group.

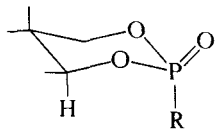
The orientation of the nitrogroups in the stereoisomers (**3a–8a**) and (**3b–8b**) have been established, on the basis of the intensity of the nitro group IR absorption bands, the phosphoryl group IR intensities as well as the chemical shift of the proton in the 4 and 6 positions in the ring.

Table II summarizes the main ^1H and ^{31}P NMR data of the compounds **3–9**.

The magnitude of the $^1H—^1H$ and $^{31}P—O—C—^1H$ coupling constants points to chair conformation of the 5-bromo-5-2-R-2-oxo-1,3,2-dioxaphosphorinanes (**3–9**):



J_{trans}



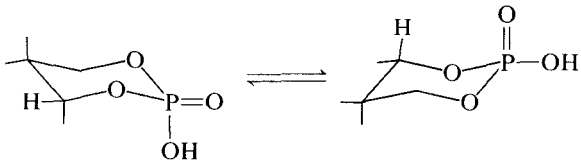
J_{gauche}

$J_{180}\ P—O—C—H_e \gg J_{60}\ P—O—C—H_a$

The fact that the equatorial hydrogen-phosphorus coupling constants ($^JP—O—C—H_e$) are much greater than those with axial hydrogen ($^JP—O—C—H_a$) suggests their dependence on the magnitude of the dihedral angles formed by the planes of the P=O bonds and C—H bonds.

When the NMR spectra are recorded at 100 MHz in different solvents ($CDCL_3$, acetone-D_6) at low temperatures, the transformation of the 1,3,2-dioxaphosphorinanes (**3–8**) into other conformations was not demonstrated.

The NMR spectrum of the 5-bromo-5-nitro-2-hydroxy-2-oxo-1,3,2-dioxaphosphorinane (**9**), suggests that this derivative undergoes rapid interconversion at room temperature between equally populated chair conformers as in (**10**).



J_t (**10**) J_g

Thus the phosphorus coupling constants with equatorial and axial hydrogen are equal $^JP—O—C—H_e = {}^JP—O—C—H_a = 10.5$ Hz and correspond to the average of J_t and J_g (**10**).

The chemical shifts of the methyl protons (1.60 and 1.40 ppm), and those of the ^{31}P, confirm the presence of two isomers of the 5-bromo-5-nitro-2-R-2-oxo-1,3,2-dioxaphosphorinanes (**3–9**), Although the ^1H NMR analysis of the minor components was not possible.

The conformational distributions have been calculated on the basis of the 2-methyl,2-chloro and 2-aryloxy-1,3,2,-dioxaphosphorinane phosphoryl groups IR-bands intensities. For the 2-methyl-1,3,2-dioxaphosphorinane derivative, the distribution has been calculated also using the ^{31}P chemical shift by the method described by Mosbo and Verkade:[70]

$$Y\delta_A + (1 - Y)(\delta_B) = \delta_{31P}$$

Y = mol fraction of isomer with equatorially orientated P=O group. The data obtained are summarized in Table III.

TABLE III

Mole fractions of various conformers of 5-bromo-5-nitro-2-R-2-oxo-1,3,2-dioxaphosphorinanes. (3–8).

Compd.	R	From ν(P=O)	From $\delta\ ^{31}P$	
3	CH_3	0.23	0.27	isomer fraction with equatorial P=O group
4	Cl	0.06	—	
5	C_6H_5O	0.04	—	isomer fraction with axial P=O group
6	p-CH_3-C_6H_4O	0.06	—	
7	m-CH_3-C_6H_4O	0.13	—	
8	p-O_2N-C_6H_4O	0.11	—	

From the data given in Table III it is seen that the same isomer ratio of equatorially and axially orientated P=O groups were obtained for the 2-methyl-1,3,2-dioxaphosphorinane derivative by both procedures.

Conformational Interconversion Equilibria

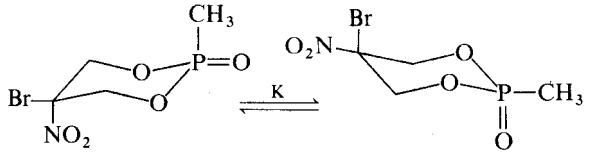
The chair–chair conformational interconversion could be studied via the 5-bromo-5-nitro-2-R-2-oxo-1,3,2-dioxaphosphorinanes (**3–8**) IR-spectra in solution at different temperatures. The equilibrium constants as well as the thermodynamic parameters ΔG, ΔH and ΔS, have been calculated at 25°C, on the basis of the phosphoryl group—IR bands intensities.

$$K = \frac{A_b}{A_a} \cdot \frac{\alpha_a}{\alpha_b}$$

A = areas of the $\nu_{P=O}$ bond α_a, α_b = molar extinction coefficients.

$$\log \frac{A_b}{A_a} = -\frac{\Delta H}{4.6} \cdot \frac{1}{T} + K$$

The data obtained are recorded in Table IV.



(**11**)

TABLE IV

Thermodynamic data for the equilibrium mixture of 5-bromo-5-nitro-2-methyl-2-oxo-1,3,2-dioxaphosphorinane conformers

t(°C)	K	ΔG (Kcal/mol)	ΔH (Kcal/mol)	ΔS (Kcal/mol)
5	0.39			
25	0.30	+0.725	−1.98	−9.07
40	0.25			
70	0.18			

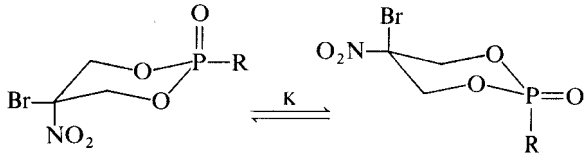
The (α_a, α_b) molar extinction coefficients were determined for dioxaphosphorinane systems with reduced mobility (4,6-dimethyl-2-oxo-2-methyl-1, 3,2-dioxaphosphorinane):

$\alpha_a = 138$

$\alpha_b = 143$

From the data presented in Table IV can be seen that the conformational equilibrium is shifted by rising temperature towards the isomer with the phosphoryl group axially orientated.

The 2-chloro and 2-aryloxy-1,3,2-dioxaphosphorinanes equilibrium constants and ΔG have been also calculated at 25°C. The data obtained are recorded in Table V.



(**12**)

TABLE V

Thermodynamic data for the conformational equilibria of 2-chloro and 2-aryloxy-1,3,2-dioxaphosphorinane derivatives (4–8).

Compd.	R	K	ΔG (Kcal/mol)
4	Cl	0.063	+1.63
5	C_6H_5O	0.042	+1.87
6	p-CH_3-C_6H_4O	0.063	+1.63
7	m-CH_3-C_6H_4O	0.149	+1.14
8	p-O_2N-C_6H_4O	0.123	+1.23

The ratio α_a/α_b was considered as being ≈ 1.

The 2-chloro- and 2-aryloxy-1,3,2-dioxaphosphorinane derivatives equilibria are strongly shifted towards the isomers with equatorially orientated phosphoryl group (see Table III).

CONCLUSIONS

Some new 5-bromo-5-nitro-2-R-2-oxo-1,3,2-dioxaphosphorinane derivatives have been prepared. The existence of mixtures of two stereoisomers in chair conformation has been established by NMR- and JR-spectroscopy.

The equilibria of 5-bromo-5-nitro-2-R-2-oxo-1,3,2-dioxaphosphorinane derivatives are strongly shifted towards one of the isomers. Thus, for the 2-methyl phosphorinane derivative, the equilibrium is shifted towards the isomer with an equatorially orientated methyl group, whereas the other derivatives are shifted towards the isomer with an equatorially orientated phosphoryl group.

EXPERIMENTAL SECTION

The melting points were determined with an Boetius instrument and represent uncorrected values.

The elementary analyses were performed on a Carlo-Erba 1100 analyser and the IR spectra in KBr pellet or solution at different temperatures, on a Perkin Elmer 457 spectrophotometer.

^{1}H NMR spectra were recorded at 100 MHz with a modified Varian HA-100 spectrophotometer operating in the "locked" frequency-sweep mode, and at 60 MHz with a Varian A-60

spectrometer. Tetramethylsilane was used as internal standard. ^{31}P NMR spectra were recorded on a Varian HA-100 spectrometer, operating at 40,477 MHz with external H_3PO_4 or P_4O_6 as the reference. Negative chemical shift values are reported for compounds absorbing at lower fields than H_3PO_4 or P_4O_6.

Synthesis of the 5-Bromo-5-Nitro-2-R-2-Oxo-1,3,2-Dioxaphosphorinane Derivatives **3–9**

These compounds were obtained by the reactions of the phosphonic and phosphoric acids dichloride ($R—P(O)Cl_2$; $R=CH_3$, Cl, C_6H_5O, p-$O_2N—C_6H_4O$, m-$CH_3—C_6H_4O$, p-$CH_3—C_6H_4O$) with 2-bromo-2-nitro-1,3-propanediol.

To the solution of dichloride derivative (0.05 m) in dioxane (250 ml), was added dropwise with stirring during 3 hours a solution of 2-bromo-2-nitro-1,3-propanediol (0.05 m) in dioxane (40 ml). The temperature was maintained at 50°C, with continuous passage of nitrogen. The products obtained were separated according to procedure (a) for compound **3**; (b) for compound **4** and (c) for compounds **5–8**.

a) The reaction mixture is concentrated to 50 ml *in vacuo* at 20 mm Hg. The 2-methylphosphorinane derivative was precipitated from the distillation residue by adding 100 ml of anhydrous ethylether, followed by preparative chromatography separation using an Al_2O_3-silicagel column.

b) After cooling the reaction mixture, part of the 2-chlorophosphorinane derivative have precipitated and was filtrated off. The liquid was concentrated to 20 ml *in vacuo*. The residue was filtered again and the precipitate, which contained the majority of compound **4**, was purified by washing two or three times with ethylether, then by column chromatography (Al_2O_3-silicagel).

c) The reaction mixture was concentrated to 50 ml. *in vacuo*. From the distillation residue the compounds **5–8** were precipitated by addition of water. The precipitate has been dried and washed three times with anhydrous ethyl ether and purified by column chromatography. (Al_2O_3-silicagel).

Synthesis of the Compounds **5–8** *by the Reaction of the 2-chlorophosphorinane Derivative with Sodium Aryloxides*

The reactions were performed in acetonitrile at 25°C, with 0.05 moles of 2-chlorophosphorinane derivative, and 0.05 moles of sodium aryloxides. The reaction products were purified according to procedure (c).

Synthesis of 5-Bromo-5-Nitro-2-p-Nitrophenoxy-2-Oxo-1,3,2-Dioxaphosphorinane Derivative, via Nitration of the 2-phenoxy Phosphorinane

To the stirred, cooled (5°C) 2-phenoxyphosphorinane derivative solution (0.05 m) in methanol (200 ml), was added dropwise a nitration mixture, over 3 hours. The mixture has been stirred further for two hours at 20°C. The methanol has been removed *in vacuo* and the phosphorinane derivative extracted from the residue with 100 ml dioxane. The dioxane solution was treated as in procedure (c).

The Alkaline Hydrolysis of the Compounds **4–8**

The derivatives (0.01 m) were added under continuous stirring at 25°C to a solution of NaOH (0.015 m) in water (20 ml) and dioxane or ethyl alcohol (40 ml).

After 3 hours, the solvents were removed *in vacuo*; the resulting solid is mostly the sodium salt of the 2-hydroxyphosphorinane derivative. This salt was dissolved in water (10 ml) and 10 ml of a 25% HCl solution was added under stirring.

The 2-hydroxyphosphorinane derivative **9** was extracted from the aqueous solution with chloroform in four portions of 25 ml each. From the previously dried organic layer the acid **9** was separated by removing the chloroform *in vacuo*.

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