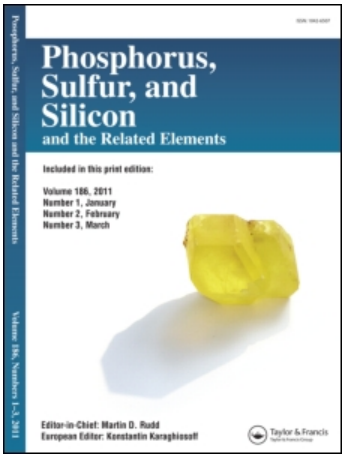

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SYNTHESIS OF DIASTEREOISOMERIC 2,4,7-TRIOXA-3-PHOSPHA-3-R-3-THIONOBICYCLO (4.4.0) DECANES AS A MODEL FOR PHOSPHORUS NUCLEOPHILIC SUBSTITUTION STUDIES

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SYNTHESIS OF DIASTEREOISOMERIC 2,4,7-TRIOXA-3-PHOSPHA-3-R-3-THIONOBICYCLO (4.4.0) DECANES AS A MODEL FOR PHOSPHORUS NUCLEOPHILIC SUBSTITUTION STUDIES

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2,4,7-Trioxa-3-chloro, 3-fluoro, 3-dimethylamino, 3-methoxy, 3-(2-propanoxy)-3-phospha-3-thionobicyclo (4.4.0) decanes (trans fusion) have been prepared. The precursor diol, 2-hydroxymethyl-3-hydroxy-tetrahydropyran (2R*, 3S*), was obtained in two steps from 3,4-dihydro-2H-pyran.

The chloridates **7a** and **7b** were separated by high performance liquid chromatography and the stereochemistry of the nucleophilic substitution at phosphorus (with fluoride anion, dimethylamine, methanol, 2-propanol) for each isomer was studied. The substitution of chlorine was found to occur mostly with inversion of configuration for the two isomers. Equilibrium constants were measured for **7a** ⇌ **7b** and **9a** ⇌ **9b** making it possible to calculate the corresponding standard free energies.

A kinetic study of the 2-propanolysis of **7a** and **7b** showed that **7b** reacted more slowly than **7a**. It was found that the difference between the free energy of activation ($\Delta\Delta G^{\neq}$ $(b - a) = 1$ Kcal/mol) for the two isomers is close to the calculated value of the standard free energy variation $\Delta G°$ $(b - a) = -1.3$ Kcal/mol. The difference between the observed reaction rates is probably due to the relative thermodynamic stabilities of the reactants.

INTRODUCTION

Studies of reaction mechanisms involving tri- or tetra-coordinate phosphorus esters using cyclic model compounds (dioxaphosphorinanes) have attracted a constant interest in the past few years.[1] 1,3,2-dioxaphosphorinanes for which it is possible to state a cis-trans relationship between the phosphorus substituents and those of the carbon-containing fragment of the ring have been extensively employed in stereochemical studies of nucleophilic substitution at thiophosphoryl centers.[2]

In this context we have undertaken to synthesize model compounds in the 2,4,7-trioxa-3-phospha-3-R-3-thionobicyclo (4.4.0) decane series. The precursor diol, synthesized in two steps, led to pairs of diastereoisomers having a rigid ring fusion (trans), which can serve as model compounds for sugar thiophosphates or nucleotides. Such bicyclic model compounds with a trans fusion have been previously described.[3] However, it seems that conclusions drawn from compounds possessing an oxygen atom as part of the ring adjacent to the dioxaphosphorinane cycle are more directly applicable to compounds of biological interest (namely cyclic nucleotides).

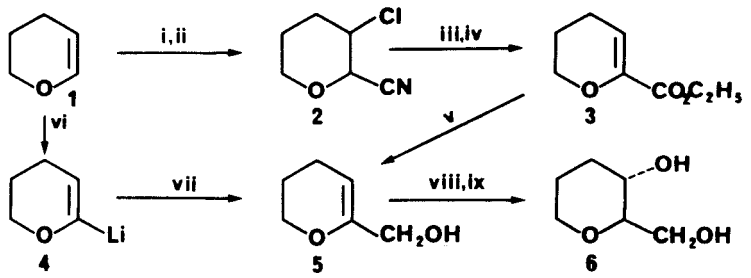
The unambiguous configurational attribution of diastereoisomers with the aid of ^{1}H, ^{13}C and ^{31}P nuclear magnetic resonance[4] or by electron impact induced fragmentation[5] make them interesting compounds for studies of the influence of phosphorus configuration on the stereochemistry of reactions at the phosphorus center.

The elaboration of the semi-preparative separation by high performance liquid chromatography (HPLC) of the chlorine containing derivatives **7a** and **7b** gave us the opportunity to confirm some aspects of nucleophilic substitution at thiophos-

phoryl centers with diastereoisomers, the stereochemistry of which is well established.[6]

RESULTS AND DISCUSSION

Diol Synthesis



Reagents : i, Cl_2, CCl_4; ii, CuCN; iii, KOH, EtOH; iv, EtO_2SO_2; v, $LiAlH_4$; vi, Bu^nLi, Hexane; vii, CH_2O; viii, BH_3, THF; ix, H_2O_2, NaOH.

FIGURE 1

This synthesis applies the successive functionalization of the α and β (with respect to oxygen) vinylic carbons of 3,4-dihydro-2H-pyran **1**. 2-cyano-3-chlorotetrahydropyran **2**[7] treated with alcoholic potassium hydroxide yielded the potassium salt of 3,4-dihydro-6-carboxy-2H-pyran which was esterified with diethylsulfate. The lithium aluminium hydride reduction of the ester led to 3,4-dihydro-6-hydroxymethyl-2H-pyran **5** which could be obtained more directly by reaction of 3,4-dihydro-2H-pyranyl-6-lithium **4** with polyoxymethylene.[8] Hydroboration-oxidation[9] of this ethylenic alcohol selectively gave 2-hydroxymethyl-3-hydroxytetrahydropyran (2R*, 3S*) **6** (80% yield). The trans relative configuration of this compound was established by comparison of the infrared and mass spectra of its bis-3,5-dinitrobenzoate and those of the 2-hydroxymethyl-3-hydroxytetrahydropyran (2R, 3S) obtained from triacetyl-D-glucal.[10] On the other hand, this arrangement was confirmed by the $^3J_{H1-H6}$ value = 9.5–10.0 Hz obtained from the nuclear magnetic resonance spectra of the cyclic phosphorus esters.

Cyclic Phosphorus Compounds

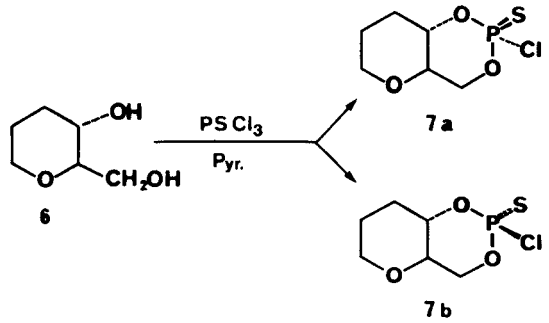


FIGURE 2

2-Hydroxymethyl-3-hydroxytetrahydropyran **6** reacted with $PSCl_3$ in benzene in the presence of pyridine[11] to yield the mixture of 2,4,7-trioxa-3-chloro-3-phospha-3-

thionobicyclo (4.4.0) decanes (1R*, 3S*, 6S*) **7a** and (1R*, 3R*, 6S*) **7b**.[12] Under these reaction conditions **7a** was obtained predominantly (**7a**: 61 to 65%; **7b**: 35 to 39%). This mixture, in acetone in the presence of tetraethylammonium chloride at room temperature, equilibrated to a new mixture which contained 90% of **7b**. The same equilibrium ratio was reached from each pure isomer, providing a standard free energy $\Delta G°_{25°} = -1.3$ Kcal/mol for the reaction **7a** → **7b**. Taking into account the great preference of the chlorine atom for an axial orientation,[13] it was possible to deduce the configuration of the isomers **7a** and **7b** from the observed stability difference. Indeed, an axial orientation of the chlorine atom for **7a** is only possible if the 1,3,2-dioxaphosphorinane ring assumes a less stable nonchair conformation. The spectroscopic data corroborating this configurational attribution were previously described.[6]

The reaction of dimethylamine with **7a** and **7b** led very easily to the thiophosphoramides **8a** and **8b**, with complete configurational inversion[14] at phosphorus. Indeed, the reaction carried out from **7a** afforded exclusively **8b** and **8a** from **7b**. There are many examples in agreement with this result in the 2-oxo-1,3,2-dioxaphosphorinane series.[2j] The 2,4,7-trioxa-3-fluoro-3-phospha-3-thionobicyclo (4.4.0) decanes (1R*, 3R*, 6S*) **9a** and (1R*, 3S*, 6S*) **9b** were obtained from **7a** and **7b** by halogen exchange.[15] The mixture of chloridates **7a** and **7b** (27/73) treated with ammonium fluoride in acetone at room temperature led to **9a** and **9b** (18/82). This mixture, in the presence of an excess of ammonium fluoride, under the same conditions equilibrated rapidly to afford a new mixture containing **9a** (6%) and **9b** (94%). The calculated standard free energy for this reaction **9a** ⇌ **9b** shows a difference of 1.65 Kcal/mol in favor of **9b**. The greater stability of this isomer allowed us to assign to it the configuration indicated for the same reasons as in the case of its chlorinated analogues (the axial preference of the fluorine atom being more pronounced.)[16]

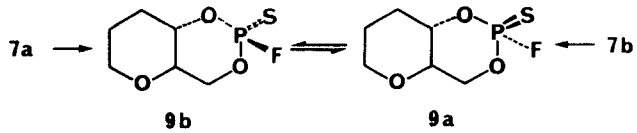


FIGURE 3

This configurational attribution was confirmed unambiguously by nmr and mass spectrometric data.[17] The lack of stereospecificity of the halogen exchange reaction previously observed in 2-thiono-1,3,2-dioxa-phospholane[18] and 2-oxo-1,3,2-dioxaphosphorinane series[2a] can be explained by assuming the formation of a trigonal bipyramidal intermediate (resulting from the attack of fluoride at phosphorus) and its decomposition to give, predominantly, the more stable fluoridate, **9b**, after permutational changes. However, this same exchange reaction accomplished according to the procedure used by Bianchi *et al.*[19] for the preparation of arylsulfonic acid fluorides, allowed us to rule out this assumption. Thus, the reaction of the chloridate **7b** with potassium fluoride in acetonitrile in the presence of 18-crown-6 at room temperature gave the fluoridates, **9a** and **9b**, within fifteen minutes. G.l.c. analysis showed that the amount of **9a** reached a maximum, then decreased until the conversion of **7b** was completed. This observation shows that the reaction first occurred with configurational inversion of the phosphorus atom and that the relatively fast epimerization of **9a** to **9b** allowed us to obtain **9a** in small yield only (<10%). We can consider for this epimerization the transition through a trigonal bipyramidal pentacoordinate phosphorus intermediate[20] the formation of which is

favored by the great nucleophilicity of the fluoride ion and the well-known stabilization of pentacoordinate phosphorus compounds by fluorine.[21]

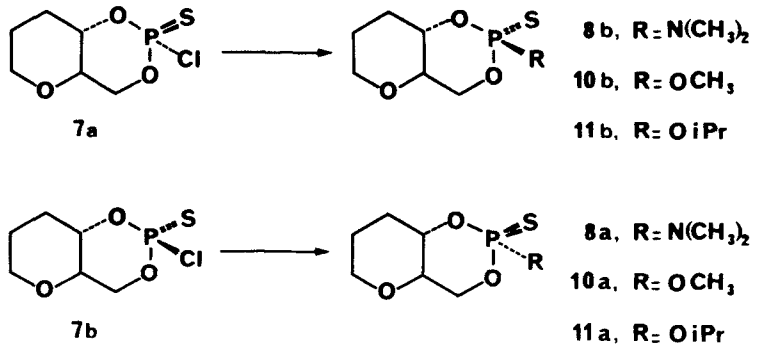


FIGURE 4

We obtained the 2,4,7-trioxa-3-methoxy-3-phospha-3-thionobicyclo (4.4.0) decanes (1R*, 3R*, 6S*) **10a** and (1R*, 3S*, 6S*) **10b** upon reaction with sodium methoxide of the mixture of **7a** and **7b** in moderate yield (65%). The stoichiometric amount of sodium methoxide did not suffice for the complete conversion of **7b** which was esterified less rapidly than **7a**. At the end of the reaction, after a second addition of the sodium methoxide required for the total transformation of **7b**, trimethylthiophosphate was isolated among other products. The substitution reaction of the chlorine atom of **7a** and **7b**, therefore, competes with opening of the dioxaphosphorinane ring, according to Cooper *et al.*[2k] Without base, the methanolysis furnished the esters in good yield (>95%). Here too, the isomer **7a** disappeared from the reaction mixture more rapidly than **7b** (**7a**: t 1/2 = 20 min; **7b**: t 1/2 = 20 h at 23°C). The lower reactivity of **7b** could explain the observed ring opening reactions when a stronger nucleophile such as sodium methoxide was employed, the esters **10a** and **10b** formed during the reaction being able to react with this later under these conditions. Methanolysis carried out with each pure chloridate showed complete configurational inversion of the phosphorus atom. **7a** led exclusively to **10b** and **7b** to **10a**, according to results of Harrison *et al.*[21] in the 2-oxo-1,3,2-dioxaphosphorinane series. In this case, the stereospecificity of chlorine atom substitution is not affected by the conformation adopted by the dioxaphosphorinane ring.

The greater ease of following the progress of the 2-propanolysis reaction of the chloridates **7a** and **7b** by means of g.l.c. analysis allowed us to study more accurately the effect of the conformation of each isomer on the solvolysis kinetics. This was pseudo-first order during the greater part of the reaction. The change in reaction order at the end of the reaction could be explained by the acidification of the reaction mixture. The data for the pseudo-first order reaction are given in the following table.

TABLE I

	T°c	$k_{s^{-1}\times 10^6}$	E *	$\Delta H^{\neq}_{25°}$*	$\Delta S^{\neq}_{25°}$**	$\Delta G^{\neq}_{25°}$*
7a	45.7 56.5	6.33 (0.06) 12.52 (0.17)	13.2 (±0.3)	12.6 (±0.3)	−42.9 (±1)	25.4 (±0.6)
7b	45.7 56.5	1.29 (0.03) 2.82 (0.04)	15.1 (±0.5)	14.5 (±0.5)	−40.1 (±1.6)	26.4 (±0.9)

* Kcal mol^{-1} ** cal mol^{-1}

The difference between the free energy of activation for the two isomers $\Delta\Delta G^{\neq}$ $(b - a) = 1$ Kcal/mol is close to the calculated value of the standard free energy variation $\Delta G°$ $(b - a) = -1.3$ Kcal/mol between **7a** and **7b** in acetone. Therefore, the difference between the observed reaction rates is probably due to the relative thermodynamic stabilities of the reactants. Recently, Gorenstein *et al.*[3c] drew the same conclusion to explain the difference of the hydrolysis rates for a pair of isomeric 2,4-dioxa-3-aryloxy-3-oxobicyclo (4.4.0) decanes (1R*, 6S*).

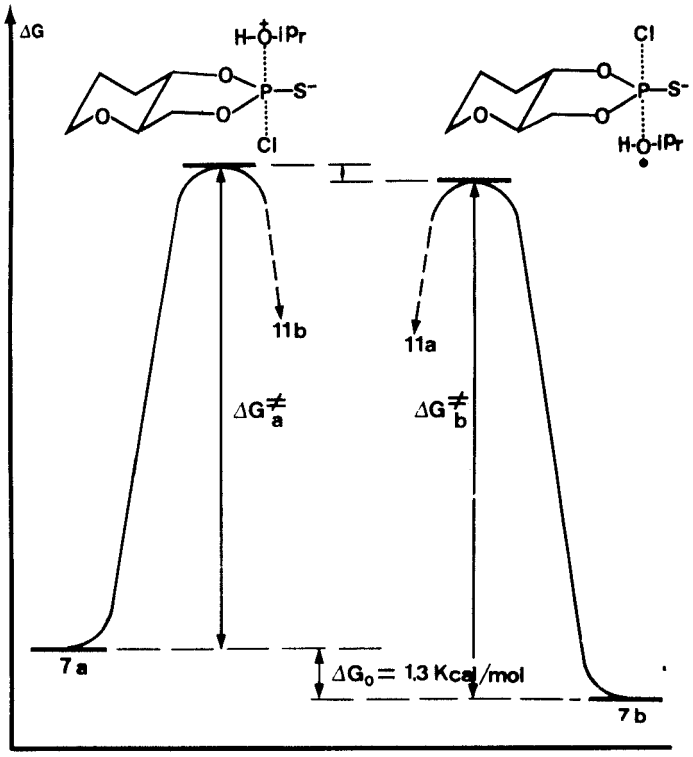


FIGURE 5

This assumption agrees with the work of Cook *et al.*[22] who have shown that in reactions where a pentacoordinate intermediate is suspected, the rate of the reaction is dependent on the nature of the leaving group. It is the decomposition of this intermediate which is the limiting step of the reaction in the case of a poor leaving group, whereas it is the formation of this same intermediate which is the slow step for a good leaving group such as chloride or phenoxide anions.

In conclusion, the synthesis of these compounds in the 2,4,7-trioxa-3-phospha-3-thionobicyclo (4.4.0) decane series provides an excellent model for studying the stereochemistry of reactions at phosphorus. Indeed, we were able to separate the two diastereoisomeric chloridates, **7a** and **7b**, and check with each of them that the substitution of the chlorine atom exclusively takes place with configurational inversion in the case of the nucleophiles used. The synthesis and separation of the fluoro derivatives **9a** and **9b** opens a wide field of investigation of reactions at phosphorus for this class of compounds. The easy configurational attribution by means of mass spectrometry makes them interesting models for such studies. Furthermore, the synthesis process used for the precursor diol may be applied to the preparation of 2-

hydroxymethyl-3-hydroxytetrahydrofuran which leads to bicyclic compounds closely comparable with 3',5'-cyclic nucleotides. The study of the consequences of the ring strain caused by this adjacent ring upon the stereochemistry of this class of compounds is presently in progress.

EXPERIMENTAL SECTION

Microanalyses were conducted by the Service Central d'Analyses du C.N.R.S. LYON. Melting points are uncorrected. IR spectra were obtained on a Perkin-Elmer 257 instrument. ^{1}H NMR spectra were recorded on Varian A60, Varian XL 100 instruments with TMS as internal reference. ^{31}P NMR spectra were obtained on a Varian XL 100 spectrometer. Positive chemical shifts are downfield relative to external 85% H_3PO_4. Mass spectra were determined with a Varian MAT CH5 instrument. Relative abundances are given in parentheses. G.l.c. analyses were run on a Carlo Erba instrument on a 2 m × 2 mm stainless steel column with a 5% SE30 on Chromosorb G packing, dimethylchlorosilane (D.M.C.S.) treated, acid washed (AW). HPLC were performed with "home made" silica (Whatman Partisil 10μ or Merck Lichrosorb SI 60 5μ) columns using a LDC or Waters detector (refractometer).

3,4-Dihydro-6-carbethoxy-2H-pyran **3**

To a stirred solution of potassium hydroxide (117 g, 1.8 mol) in ethanol (400 ml) was added dropwise 2-cyano-3-chlorotetrahydropyran **2** (105 g, 0.72 mol) giving rise to an exotherm reaction. After the addition was completed, the reaction mixture was refluxed for 12 h. Ethanol was evaporated to give the salt of 3,4-dihydro-6-carboxy-2H-pyran which was diluted in anhydrous benzene. Freshly distilled diethyl sulfate (2 mol/mol of salt) was added, then the stirred mixture was refluxed for 12 h. After cooling, water (200 ml) was added and the mixture decanded. After drying, the solvent was removed under reduced pressure. The residue was distilled to give **3** (110 g, 98%), bp (21 mm) 122°C. Anal. Calcd for $C_8H_{13}O_3$: C, 61.52; H, 7.74; Found: C, 61.48; H, 7.58; nmr (CCl_4) δ 5.93 (t, 1H, $J_{H5\,H4'} = 4$ Hz), 4.14 (q, 2H, O—CH_2—CH_3), 4.00 (m, 2H, H_2, $H_{2'}$), 2.15 (m, 2H, H_4, $H_{4'}$), 1.9 (m, 2H, H_3, $H_{3'}$); IR (film) (cm^{-1}): 1725 (C=O), 1645 (C=C); MS (70 eV) 156 (61) ($M^{+\cdot}$), 128 (24) (M-28), 127 (49) (M—C_2H_5), 55 (68) (C_4H_7, C_3H_3O).

3,4-Dihydro-6-hydroxymethyl-2H-pyran **5**

a) *From 3,4-dihydro-6-carbethoxy-2H-pyran* **3** The ester **3** (78.5 g, 0.5 mol) was dissolved in dry diethyl ether (140 ml). The solution was stirred and cooled to ≃0°C. Lithium aluminum hydride (19 g, 0.5 mol) in dry diethyl ether (1 l) was added dropwise at 0°C. After the addition was completed, the reaction mixture was stirred for 1 h. The excess of lithium aluminum hydride was destroyed by slow addition of water. Hydrolysis was achieved by subsequent addition of water under vigorous stirring. The reaction mixture was decanted, the ether layer dried (sodium sulfate) and the solvent was evaporated *in vacuo*. The residue was distilled to give **5** (42.2 g, 74%). The crude product obtained before distillation was quite pure according to t.l.c. and nmr analyses (96% yield), bp (2 mm) 67°C (Lit.[8] bp (14 mm) 92°C). Anal. Calcd for $C_6H_{10}O_2$: C, 63.13; H, 8.83; Found: C, 63.15; H, 8.86; nmr (CCl_4) δ 4.8 (t, 1H, $J_{H5\,H4} = J_{H5\,H4'} =$ 3.7 Hz), 4.05 (m, 2H, H_2, $H_{2'}$), 3.95 (s, 1H, OH), 3.9 (s, 2H, CH_2 OH), 2.0 (m, 2H, H_4, $H_{4'}$), 1.9 (m, 2H, H_3, $H_{3'}$); IR (film) 3400 (OH), 1675 (C=C); MS (70 eV) 114 (7.4) ($M^{+\cdot}$), 84 (6.9) (M—CH_2O), 83 (13) (M—CH_2OH), 72 (19), 71 (20.4) (C_4H_7O), 70 (23.6) (M—C_2H_4O), 69 (7.4), 57 (17), 56 (60.2), 55 (40), 46 (61), 45 (100), 44 (56), 43 (55), 42 (88), 41 (65.4).

b) *From 3,4-dihydro-2H-pyran* **1** It was prepared according to Lebouc *et al.*[8]

2-Hydroxymethyl-3-hydroxy-tetrahydropyran **6**

To a stirred solution of **5** (55 g, 0.48 mol) in anhydrous tetrahydrofuran (300 ml) was added dropwise, under dry nitrogen at 0°C, a 1.9 M solution of borane in tetrahydrofuran (180 ml, 1.02 eq H^-). The reaction mixture was further stirred for 12 h at 25°C. The organoborane formed was oxidized at 30–50°C by adding 3N sodium hydroxide (87 ml) followed by dropwise addition of 30% hydrogen peroxide (58 ml). After the reaction mixture had been stirred for 3 h at room temperature, sodium chloride was added and the organic layer was separated. The aqueous phase was extracted twice with ether and the combined organic layers were dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was

distilled to give **6** (51 g, 80% yield), bp (2 mm) 130–135°C, n_D^{20} = 1,476 (Lit.[10] n_D^{19} = 1.478); nmr (CD_3COCD_3) δ 3.0–4.0 (m, 6H, H_2, H_3, H_6, $H_{6'}$, CH_2OH), 1.4–2.2 (m, 4H, H_4, $H_{4'}$, H_5, $H_{5'}$); IR (film) 3400 (s) ν(OH), 2940 (s), 2860 (s), 1450 (m), 1275 (m), 1210 (m), 1100 (s), 1080 (s), 1050 (s), 1030 (m), 1010 (m), 985 (m), 860 (m); MS (70 eV) m/Z 114 (12) (M—H_2O), 101 (34) (M—CH_2OH), 85 (61), 71 (100) (C_4H_7O), 55 (18), 44 (46), 43 (32), 41 (30). Bisdinitrobenzoate: mp 172°C. Anal. Calcd for $C_{20}H_{16}O_{13}N_4$: C, 46.16; H, 3.09; N, 10.77; Found: C, 46.10; H, 3.21; N, 10.71; IR and MS data were identical with those of C. Chin *et al.*[10]

2,4,7-Trioxa-3-chloro-3-phospha-3-thionobicyclo (4.4.0) decanes (1R, 3S*, 6S*)* **7a** *and (1R*, 3R*, 6S*)* **7b**

These compounds were prepared according to the procedure described in Ref. (11). ^{31}P nmr spectrum and g.l.c. analysis of the crude product showed the presence of two isomers **7a** (δ ^{31}P = 63.9; 61–65%) and **7b** (δ ^{31}P = 59.2; 39–35%). Semi-preparative g.l.c. induced isomerization of **7a** to **7b**. The mixture of **7a** + **7b** showed only one spot in t.l.c. with several systems of elution. The two isomers were thus separated by high performance liquid chromatography over a Partisil 10μ column (Ø int = 10.7 mm; l = 50 cm; mobile phase: hexane, dichloromethane, acetone, 35/15/2). In order of elution **7a** (5.7 g, 50.0%) and **7b** (3.65 g, 32%) were obtained.

7a, liquid, Anal. Calcd for $C_6H_{10}ClO_3PS$: C, 31.52; H, 4.41; Cl, 15.50; Found: C, 31.85; H, 4.18; Cl, 15.43; IR (film) 2950 (w), 2860 (w), 1455 (w), 1430 (w), 1135 (w), 1090 (m), 1050 (s), 1015 (s), 980 (m), 950 (m), 930 (s), 860 (m), 850 (m), 820 (s), 705 (s), 690 (s), 630 (w), 570 (f), 550 (m), 500 (s).

7b, mp 61–63°C, Anal. Found: C, 31.47; H, 4.32; Cl, 15.12; IR (KBr) 2950 (w), 2860 (w), 1455 (w), 1435 (w), 1140 (w), 1105 (w), 1095 (m), 1050 (s), 1020 (s), 980 (m), 960 (s), 935 (s), 865 (w), 850 (w), 830 (m), 705 (s), 615 (w), 550 (m), 520 (w), 490 (m), 445 (w).

2,4,7-Trioxa-3-N,N-dimethylamino-3-phospha-3-thionobicyclo (4.4.0) decanes (1R, 3R*, 6S*)* **8a** *and (1R*, 3S*, 6S*)* **8b**

Dimethylamine (1.8 g, 0.04 mol) in benzene (25 ml) was added dropwise to a stirred solution of **7a** + **7b** (60/40) (4.56 g, 0.02 mmol) in benzene (50 ml) at 5°C. After the addition was completed the reaction mixture was stirred for 12 h. Dimethylamine hydrochloride was filtered off. The organic phase was washed with 5% HCl (5 ml) and twice with water (2 × 5 ml). After drying over sodium sulfate, benzene was evaporated to give a product which slowly crystallized. After filtration and washing with cyclohexane **8b** (1.86 g) was obtained. The mother liquors were concentrated and residual **8b** (0.45 g) was separated from **8a** (1.51 g) over silica by HPLC (SI 60 5μ; Ø int = 4.6 mm; l = 25 cm; mobile phase: hexane, acetone; 100/3), overall yield 80.6%).

8a, mp 64°C, Anal. Calcd for $C_8H_{16}NO_3PS$: C, 40.50; H, 6.80; N, 5.90; Found: C, 40.53; H, 6.72; N, 5.95; IR (film) 2930 (w), 2890 (w), 2850 (w), 1450 (m), 1305 (m), 1280 (w), 1235 (w), 1185 (m), 1140 (w), 1110 (m), 1095 (m), 1055 (s), 1030 (s), 1000 (s), 960 (s), 920 (s), 900 (w), 860 (m), 845 (s), 800 (s), 765 (s), 637 (s), 615 (w), 545 (w), 520 (w), 460 (m); nmr δ ^{31}P 74.4.

8b, mp 112–114°C, Anal. Found: C, 40.60; H, 6.68; N, 5.99; IR (KBr) 2930 (m), 2850 (m), 1450 (m), 1275 (m), 1160 (m), 1140 (w), 1090 (m), 1050 (m), 1015 (s), 970 (s), 960 (s), 930 (s), 900 (w), 865 (w), 855 (w), 815 (s), 755 (s), 645 (w), 605 (w); nmr δ ^{31}P 75.1.

When the reaction was conducted on **7a**, **8b** was obtained exclusively. The same was true for the formation **8a** from **7b**.

2,4,7-Trioxa-3-fluoro-3-phospha-3-thionobicyclo (4.4.0) decanes (1R, 3R*, 6S*)* **9a** *and (1R*, 3S*, 6S*)* **9b**

a) *Reaction of* **7a** + **7b** *with ammonium fluoride in acetone* A mixture of **7a** + **7b** (27/73) (342 mg, 1.5 mmol) and ammonium fluoride (56 mg, 1.5 mmol) in anhydrous acetone (5 ml) was stirred for 24 h at room temperature. Acetone was evaporated and the residue was dissolved in chloroform. After washing with water and drying (Na_2SO_4), the solvent was evaporated to give a mixture of fluoridates **9a** + **9b** (6/94) (207 mg, 65%). **9a** was separated from **9b** over silica by HPLC (Partisil 10μ, Ø int = 10.7 mm, l = 50 cm; mobile phase: hexane, dichloromethane, acetone (35/10/1). **9a** was obtained in greater amount when ammonium fluoride was added in portions. Thus from **7a** + **7b** (23/73) a mixture of **9a** + **9b** (18/82) was obtained. This latter mixture was rapidly isomerized in acetone with an excess of ammonium fluoride to give the thermodynamic mixture (6/94).

b) *Reaction of* **7b** *with potassium fluoride in acetonitrile in the presence of crown ether* A mixture of **7b** (228 mg, 1 mmol), potassium fluoride (59 mg, 1 mmol) and 18-crown-6 (15 mg, 0.062 mmol) in acetonitrile (3 ml) was stirred at 25°C until the transformation of **7b** was completed (t.l.c.). Water (15 ml)

was added and the aqueous phase was extracted twice with chloroform. After drying, the solvent was evaporated. **9a** (13 mg, 6.1%) and **9b** (167.5 mg, 79%) was separated as above.

9a, liquid, Anal. Calcd for $C_6H_{10}O_3PSF$: C, 33.96; H, 4.75; F, 8.95; Found: C, 33.63; H, 4.74; F, 8.88; IR (film) 2950 (w), 2910 (w), 2850 (w), 1450 (w), 1430 (w), 1270 (w), 1130 (w), 1100 (m), 1090 (m), 1055 (s), 1025 (s), 985 (m), 950 (m), 925 (s), 860 (m), 850 (s), 825 (m), 690 (m), 655 (w); nmr δ ^{31}P 56.5.

9b, mp 38°C; Anal. Found: C, 33.77; H, 4.78; F, 8.57; IR (KBr) 2950 (w), 2940 (w), 2910 (w), 2860 (m), 1470 (w), 1460 (w), 1450 (w), 1435 (w), 1315 (w), 1270 (w), 1230 (w), 1155 (w), 1140 (w), 1105 (w), 1095 (m), 1050 (s), 1030 (s), 980 (m), 960 (s), 930 (s), 850 (s), 840 (m), 825 (m), 690 (s); nmr δ ^{31}P 53.1.

2,4,7-Trioxa-3-methoxy-3-phospha-3-thionobicyclo (4.4.0) decanes (1R, 3R*, 6S*)* **10a** *and (1R*, 3S*, 6S*)* **10b**

a) *Reaction of sodium methoxide with* **7a** + **7b** A solution of sodium methoxide (1.2 g, 22 mmol) in methanol (30 ml) was added to a mixture of **7a** (61%) and **7b** (39%) (4.2 g, 18.4 mmol) in dry ether (20 ml) at 10°C. After 1 h ^{31}P nmr showed the presence of unchanged **7b**. Sodium methoxide (0.4 g, 7.4 mmol) was added until the transformation of **7b** was completed. Sodium chloride was then removed by filtration and the solvent evaporated. The residue was dissolved in benzene and washed with water (10 ml). After drying and evaporation of the organic phase **10a** (1.6 g, 39%) was separated from **10b** (1.07 g, 26%) over silica in hexane, ethyl acetate (9/1).

10a, liquid, Anal. Calcd for $C_7H_{13}O_4PS$: C, 37.49; H, 5.84; Found: C, 37.62; H, 5.92; IR (film) 2940 (m), 2890 (w), 2840 (m), 1450 (w), 1435 (w), 1135 (w), 1105 (w), 1090 (m), 1050 (m), 1045 (w), 1020 (s), 960 (m), 925 (s), 865 (m), 855 (m), 815 (s), 660 (w), 640 (w); nmr δ ^{31}P 67.8.

10b, mp 78°C, Anal. Found: C, 37.55; H, 5.86; IR (film). 2940 (m), 2895 (w), 2840 (m), 1450 (w), 1440 (w), 1140 (w), 1105 (w), 1095 (m), 1050 (s), 1015 (s), 985 (w), 960 (s), 930 (s), 900 (w), 865 (m), 855 (m), 830 (s), 820 (s), 670 (m); nmr δ ^{31}P 63.6.

b) *Reaction of methanol with* **7a** + **7b** The mixture of **7a** + **7b** (61/39) (250 mg, 1.1 mmol) in anhydrous methanol (15 ml) was stirred for one week at 25°C. Methanol was then evaporated. The residue was dissolved in benzene (25 ml). After washing with sodium carbonate, drying (Na_2SO_4) and evaporation of the solvent a mixture of **10a** + **10b** (37/63) (230 mg, 95%) was obtained.

2,4,7-Trioxa-3-(2-propanoxy)-3-phospha-3-thionobicyclo (4.4.0) decanes (1R, 3S*, 6S*)* **11a** *and (1R*, 3R*, 6S*)* **11b**

The mixture of **7a** + **7b** (60/40) (240 mg, 1.05 mmol) in anhydrous 2-propanol (40 ml) was heated at reflux for 72 h. After cooling and neutralization with solid sodium bicarbonate, 2-propanol was evaporated. The residue was dissolved in chloroform and washed with water. After drying (Na_2SO_4) and evaporation of the solvent a mixture of **11a** + **11b** (39/61) (245 mg, 92%) was obtained. **11a** was separated from **11b** over silica by HPLC (Partisil 10μ, $\emptyset$ int = 10.7 mm, l = 50 cm; mobile phase: hexane, dichloromethane, acetone, 80/20/1).

11a, liquid, Anal. Calcd for $C_9H_{17}O_4PS$: C, 42.85; H, 6.79; P, 12.28; Found: C, 43.14; H, 6.53; P, 12.78; IR (film) 2980 (m), 2970 (w), 2900 (w), 2860 (w), 1470 (w), 1440 (w), 1390 (w), 1380 (w), 1280 (w), 1260 (w), 1180 (w), 1165 (w), 1145 (m), 1120 (w), 1100 (m), 1065 (s), 1010 (s), 965 (m), 930 (s), 900 (w), 865 (m), 820 (s), 785 (m), 675 (w), 640 (w); nmr δ ^{31}P 65.7.

11b, mp 73–74°C, Anal. Found: C, 43.01; H, 6.60; P, 12.53; IR (KBr) 2960 (w), 2930 (w), 2860 (w), 1450 (w), 1425 (w), 1380 (w), 1365 (w), 1250 (w), 1170 (w), 1140 (m), 1100 (m), 1090 (s), 1050 (s), 1025 (s), 990 (s), 980 (s), 955 (s), 930 (s), 890 (m), 870 (m), 850 (m), 820 (s), 790 (s), 660 (m), 610 (w), 545 (w), 520 (w), 480 (w); nmr δ ^{31}P 60.4.

Kinetics

Kinetic data were obtained for the isopropanolysis of each isomer of **7** at 45.7°C and 56.5°C (±0.1°C). The solutions of **7a** and **7b** in 2-propanol were 10^{-2} to 2.5×10^{-2} M. Solvolysis reactions were followed by g.l.c. analysis (5% SE 30 on Chromosorb G packing, D.M.C.S. treated, AW, 154°C). A pseudo first-order rate law was observed by plotting log $a/a-x$ *vs* time where $a = 100$ at $t = 0$ and $a-x$ is the percentage of chloridate at time t. Rate constants were obtained by measuring the slope of the least-squares lines. The least-squares correlation coefficients were R = 0.9998 (**7a**, 45.7°C) 0.9997 (**7a**, 56.5°C) 0.9976 (**7b**, 45.7°C) 0.9995 (**7b**, 56.5°C).

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