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STEREOCHEMISTRY OF ORGANOPHOSPHORUS CYCLIC COMPOUNDS—II

STEREOSPECIFIC SYNTHESIS OF *CIS*- AND *TRANS*-2-HALOGENO-2-OXO-4-METHYL-1,3,2-DIOXAPHOSPHORINANS AND THEIR CHEMICAL TRANSFORMATIONS

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Abstract—*cis*- and *trans*-2-Chloro-2-oxo-4-methyl-1,3,2-dioxaphosphorinans have been obtained by stereospecific reactions of diastereomerically pure 2-methoxy-4-methyl-1,3,2-dioxaphosphorinans or 2-hydrogen-2-oxo-4-methyl-1,3,2-dioxaphosphorinans with chlorine and sulphuryl chloride, respectively. Similarly, the action of the corresponding brominating agents on isomeric phosphites and phosphonates afforded pure *cis*- and *trans*-2-bromo-2-oxo-4-methyl-1,3,2-dioxaphosphorinans. It has been shown that halogenolysis proceeds with retention of configuration at the P atom. On the basis of the ^{1}H- and ^{31}P-NMR spectra conformation of the halogenoanhydrides obtained has been discussed briefly.

It has been also found that model nucleophilic substitution reactions occur with inversion of configuration at the P atom in the cyclic halogenoanhydrides.

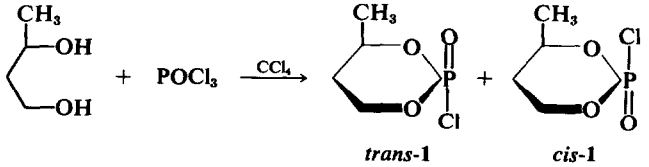
In addition to optically active phosphorus compounds cyclic tri- and tetravalent phosphorus compounds play an important part in the development of dynamic phosphorus stereochemistry. In recent years studies on stereospecific syntheses of geometrical isomers of cyclic phosphorinan systems and their conformations became the principal point of interest in many research establishments.[2-6] It should be emphasized that in contrast to optically active acyclic trivalent phosphorus compounds, which are known only in the form of tertiary phosphines,[7] many geometrical isomers of cyclic trivalent phosphorus P^{III} compounds can be synthesized. The fact that these compounds are relatively readily available makes it possible to study the mechanisms of their transformations and their stereochemistry on a much wider scale than in the case of the acyclic compounds.

In previous work we have described the stereospecific synthesis of geometrical isomers of cyclic phosphorus thio- and selenoacids derivatives of 4-methyl-1,3,2-dioxaphosphorinan.[8] The present paper concerns the stereospecific synthesis of *cis*- and *trans*-2-halogeno-2-oxo-4-methyl-1,3,2-dioxaphosphorinans. These compounds are a convenient starting material for the synthesis of other derivatives and can be utilized to study the stereochemistry of nucleophilic substitution at the P atom. Optically active phosphoryl halides have played an important part in the development of dynamic phosphorus stereochemistry.[2,9,10]

RESULTS AND DISCUSSION

2-Chloro-2-oxo-4-methyl-1,3,2-dioxaphosphorinan (**1**) can exist as one of two geometrical *cis*- and *trans*- isomers in which the Me group at the C_4 atom and the phosphoryl O atom can be in positions *cis* or *trans* with respect to one another.[11] Compound **1** has been described as a homogenous substance,[12] and in two recent papers by Blackburn[13] and Navech[14] regarding NMR studies on cyclic phosphorus compounds only one of the geometrical isomers of chloride **1** has been characterized.

We have now found that the product of the reaction of phosphorus oxychloride with butan-1,3-diol in carbon tetrachloride is a mixture of two diastereoisomeric *cis*- and *trans*-2-chloro-2-oxo-4-methyl-1,3,2-dioxaphosphorinans (**1**). It is a colourless liquid decomposing on attempted distillation under normal conditions (pressure $< 10^{-2}$ mm Hg).



trans-**1** *cis*-**1**

SCHEME 1

Consequently, in chemical transformations we used the crude product which gave correct elemental analysis.

Both isomeric chlorides (1) can be readily identified by their ^{1}H- and ^{31}P-NMR spectra. In the ^{31}P-NMR spectrum of the product of the above reaction there are two resonance signals at +3·5 and +5·7 ppm (H_3PO_4), corresponding to the two isomers. In the IR spectrum there are also two bands in the phosphoryl group absorption region at 1312 and 1305 cm^{-1}.

The formation of two geometrical isomers of 2-chloro-2-oxo-4-methyl-1,3,2-dioxaphosphorinan (1) in the reaction is confirmed, since the reaction of 1 with methanol and with dimethylamine produces mixtures of geometrical isomers of 2-methoxy- and 2-N,N-dimethylamino-2-oxo-4-methyl-1,3,2-dioxaphosphorinan respectively having almost the same composition of isomers as observed in the starting chloride (1).

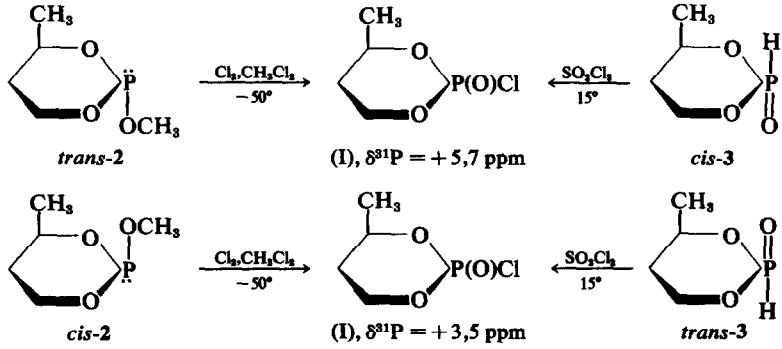
Since phosphorus chloroanhydrides are very reactive we did not attempt separation of the mixture of *cis*- and *trans*-isomers, but we investigated stereospecific synthesis of diastereomeric chlorides (1) and bromides (4).

Stereospecific synthesis of cis- *and* trans-2-*halogeno*-2-*oxo*-4-*methyl*-1,3,2-*dioxaphosphorinans*

The most generally used methods of synthesis of dialkyl phosphorochloridates are based on chlorinolysis of trialkyl phosphites and dialkyl phosphonates,[15] but the mechanisms of these reactions and in particular their stereochemistry have not been adequately investigated. This was an additional reason for undertaking the present work.

The necessary starting materials, i.e. *cis*- and *trans*-2-methoxy-4-methyl-1,3,2-dioxaphosphorinan (2)[8] and *cis*- and *trans*-2-hydrogen-2-oxo-4-methyl-1,3,2-dioxaphosphorinan (3)[8,16] have been prepared as almost 100% pure geometrical isomers. This made it possible for us to undertake the chlorination in order to obtain pure diastereomers of chloride 1.

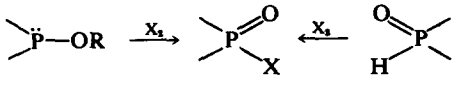
The chlorination was performed by introducing theoretical amounts of chlorine in methylene chloride to solutions of *cis*- or *trans*-2-methoxy-4-methyl-1,3,2-dioxaphosphorinan (2) at −50°. In both cases the stereospecificity of chlorination was complete, since from the ester of *trans*-2 we obtained one pure diastereomer of chloride 1 having $\delta^{31}P = +5{\cdot}7$ ppm. On the other hand a mixture of esters of 2 consisting of 89% *cis*-2 and 11% *trans*-2 gave a mixture of chlorides consisting of the two isomers in the ratio 87:13 in which chloride 1 having $\delta^{31}P = +3{\cdot}5$ ppm was the predominant component.



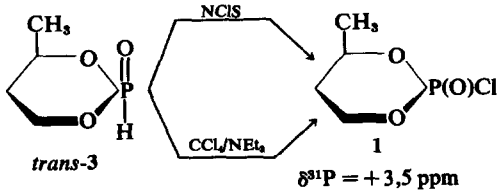
SCHEME 3

Similarly we obtained diastereomerically pure chlorides 1 from the corresponding cyclic *cis*- and *trans*-phosphonates (3) by reaction with sulphuryl chloride in methylene chloride at 15°. The more stable crystalline *trans*-phosphonate (3) gave a pure isomer of chloride 1 having $\delta^{31}P = +3{\cdot}5$ ppm, whereas *cis*-phosphonate (3) gave chloride 1 having $\delta^{31}P = +5{\cdot}7$ ppm.*

In the chlorination of phosphonates by means of N-chlorosuccinimide, NCIS, and carbon tetrachloride in the presence of triethylamine, the reaction of *trans*-3 and NClS, like that with sulphuryl chloride, was completely stereospecific. Its product was the diastereomeric chloride 1 having $\delta^{31}P =$



SCHEME 2

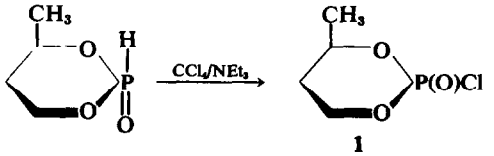


SCHEME 4

*Note added in proof: After this paper was submitted for publication, the reaction of *cis*- and *trans*-3 with SO_2Cl_2 was reported by Nifantev.[31]

+3·5 ppm. The disadvantage of this modification of the chlorination was the difficulty in complete separation of the resulting phthalimide from the product.

Complete stereospecificity of the reaction was observed also in the action of triethylamine in carbon tetrachloride solution on crystalline *trans*-phosphonate (3). On the other hand the chlorination of the less stable *cis*-phosphonate (3) with this reagent gave a mixture consisting of comparable amounts of two isomeric chlorides 1.



cis-3–94% *trans*-3–6%

I

1
48% δ = +5,7 ppm
52% δ = +3,5 ppm

SCHEME 5

This result suggests that under the reaction conditions epimerisation of chloride 1, $\delta^{31}P + 5{\cdot}7$ to chloride 1 $\delta^{31}P + 3{\cdot}5$ takes place.

We obtained similar results in the bromination of phosphites (2) and phosphonates (3). Brominations of *trans* phosphite (2) with bromine and of *cis*-phosphonate (3) with N-bromosuccinimide were completely stereospecific and gave one of the two geometrical isomers of 2-bromo-2-oxo-4-methyl-1,3,2-dioxaphosphorinan (4) having $\delta^{31}P = +19$ ppm. The second isomer of bromide (4) having $\delta^{31}P = +14$ ppm was formed by bromination of *cis*-2 phosphite with bromine and of *trans*-phosphonate (3) with N-bromosuccinimide. Thus bromination of phosphite (2) consisting of 88% *cis*-2 and 12% *trans*-2 with bromine gave a mixture of bromides (4) having $\delta^{31}P = +14$ and +19 consisting of 87% of the former and 13% of the latter. Bromination of 100% pure *trans*-3 phosphonate with N bromosuccinimide gave a mixture of 94% bromide (4) having $\delta^{31}P = +14$ ppm and 6% (4) having $\delta^{31}P = 19$ ppm.

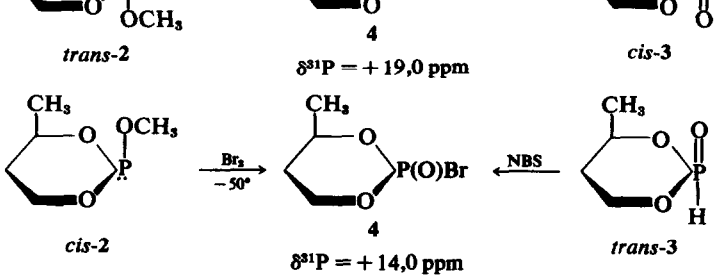
Geometrical isomers of bromoanhydride (4), like chlorides (1), are oily high boiling liquids that cannot be distilled under normal conditions. However, the crude products give correct elemental analyses and therefore we used them for further transformations without purification. Some of the spectral properties of *cis*- and *trans*-halogenoanhydrides (1 and 4) are collected in Table 1.

Preliminary analysis of NMR spectra of the substrates, and particularly those of phosphonates (3) and 2-halogenoanhydrides makes it possible to draw conclusions regarding the configurations of diastereomeric chlorides (1) and bromides (4) and hence to determine the stereochemistry of the reactions. At this stage of our discussion it is of interest to compare ^{31}P-NMR spectra of *trans*- and *cis*-phosphonates (3) and those of the corresponding chlorides 1 (Fig 1).

Figure 1 shows that the appearance of the resonance signal of the more stable crystalline phosphonate is almost the same as that of the corresponding chloride (1) $\delta^{31}P + 3{\cdot}5$ ppm. Based on similarities of apparent splitting patterns this fact can be rationalised assuming that the relative positions of the methyl and phosphoryl groups in these two compounds are the same. Thus during the transformation 3 → 1 the halogen atom replaces the H atom, i.e. the reaction takes place with retention of the configuration at the P atom.† This reasoning leads to the conclusion that chloride 1 having $\delta^{31}P + 5{\cdot}7$ has configuration *cis*, its isomer having $\delta^{31}P + 3{\cdot}5$ has configuration *trans*, and bromides having $\delta^{31}P + 19$ and +14 have configurations *cis* and *trans*, respectively.

Such configurations of diastereomeric halogenoanhydrides and the retention of configuration at the P atom are in agreement with the results of chlorination and bromination of the corresponding methyl phosphites (2). The more stable phosphite *trans*-2

†Retention of configuration at the P atom has also been found by Aaron[17] in the reaction between optically active O-isopropyl-methylphosphonate and chlorinating agents.



SCHEME 6

Table 1. Some ^1H- and ^{31}P-NMR data of 2-halogeno-2-oxo-4-methyl-1,3,2-dioxaphosphorinans

Compound	$\delta^{31}P$* ppm	δ^1H of CH_3—C ppm	$^3J_{CH_3-CH}$ Hz	$^4J_{PH}$ Hz	νPO cm^{-1}
trans-1	+3·5	−1·48 (CCl_4)	6·6	3·0	1312
cis-1	+5·7	−1·53 ($CDCl_3$)	6·8	1·35	1305
trans-4	+14·0	−1·0 ($CDCl_3$)	6·4	3·0	1305
cis-4	+19·0	−0·95 ($CHCl_3$)	6·3	< 1	1315

*As neat liquids, H_3PO_4 as external standard.

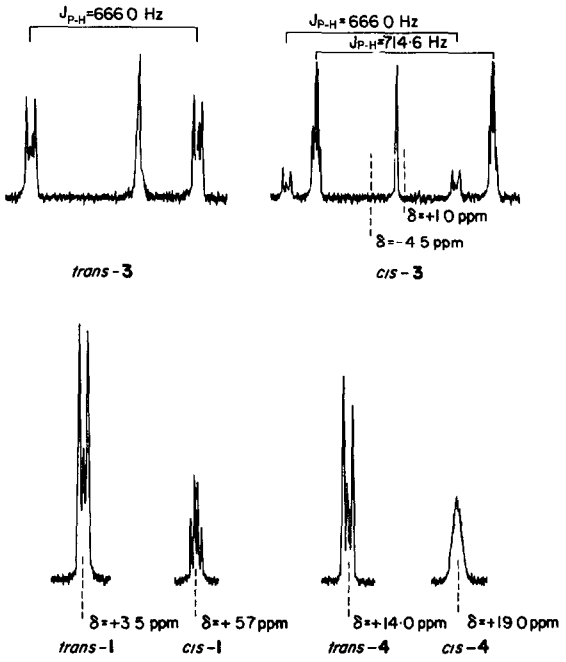


Fig 1. ^{31}P NMR spectra of diastereoisomeric 2-hydrogen-2-oxo-4-methyl-1,3,2-dioxaphosphorinans (3) and 2-halogeno-2-oxo-4-methyl-1,3,2-dioxaphosphorinans obtained with a Jeol C-60H NMR spectrometer using 8 mm high-resolution spinning sample-tubes with H_3PO_4 as an external standard.

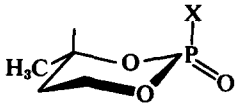
gives *cis*-chloride (1) and *cis*-bromide (4) in which the relative positions of the exocyclic O atom and the C_4 Me group remain unchanged.

The reaction of esters (2) with chlorine is an example of the Arbuzov type reactions,[18] in which according to the generally accepted views the rate determining step is the formation of a quasi-phosphonium salt. There is no doubt that in this step the configuration at the P atom is retained. Since in the second step, consisting of the attack of the chloride anion on the methoxyl C atom, the configuration at the P atom is untouched, the final result of the transformation is the retention of the configuration (diligostatic system).

However, the existence of pentacovalent phosphorus intermediate in the considered reaction is also possible. The formation of an adduct containing a pentavalent P atom in similar reactions has been indicated by other authors.[19] If it also applies to our case the fact that chlorination and bromination of *cis*- and *trans*-phosphites (2) are completely stereospecific would indicate that the life time of such a transitional intermediate is so short that pseudorotation cannot take place.

The reasoning regarding the stereochemistry of the P atom can be extended to reactions of phosphonates (3) with other chlorinating agents, i.e. CCl_4/Et_3N and SO_2Cl_2, assuming that the phosphite form is the reactive species.

The NMR data shown in Table 1 also throw some light on the conformation of the halides. It appears that halogenoanhydrides (1 and 4) having the *trans* configuration and coupling constants $^4J_{PH} = 3$ Hz should exist in the chair conformation in which the Me group and the phosphoryl O atom are in equatorial positions.[5]

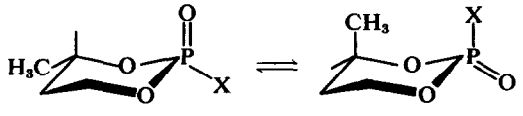


X=Cl,Br

SCHEME 7

Such conformation should be the most stable of the four possible chair conformations for both geometrical isomers, since it is known that the phosphoryl group has a pronounced tendency to occupy the equatorial position.[20,21]

In the case of the isomeric *cis*-halides the much lower values of the corresponding coupling constant suggest that these compounds can exist as a mobile equilibrium mixture of conformers as shown.



SCHEME 8

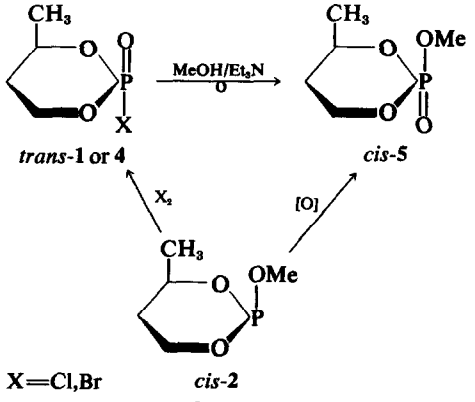
The fact that halogenoanhydrides (1 and 4) having the *trans* configuration are more stable explains the formation of mixtures of *cis*- and *trans*-isomers

in the cases when pure *cis*-isomer could be expected. When a chloride ion is present in the reaction mixture (e.g. in the reaction with CCl_4/Et_3N), it is probable that epimerisation of the isomer *cis*-**1** to the thermodynamically more stable isomer *trans*-**1** takes place as a result of chlorine–chlorine exchange at the P atom.[22]

Chemical transformations of diastereoisomeric 2-chloro-2-oxo-4-methyl-1,3,2-dioxaphosphorinans

We used the diastereomerically pure chlorides (**1**) in our studies on the stereochemistry of nucleophilic substitution at the P atom. First we investigated reactions of chlorides (**1**) with methanol in the presence of triethylamine, leading to *cis*- and *trans*-2-methoxy-2-oxo-4-methyl-1,3,2-dioxaphosphorinans (**5**). The choice of this reaction was suggested by the fact that geometrical features of the products are fairly well known. The data reported by Denney,[23] Bodkin and Simpson,[5] and in our earlier work[24] indicate that isomer **5** having shorter retention time in GLPC and $\delta_{OMe} = -3{\cdot}52$ (benzene) has *cis* configuration, whereas isomer (**5**) having longer retention time and $\delta_{Me} = -3{\cdot}55$ has *trans* configuration.

The transformations carried out in the present work in order to determine the stereochemistry of the examined reaction are shown in Scheme 9:



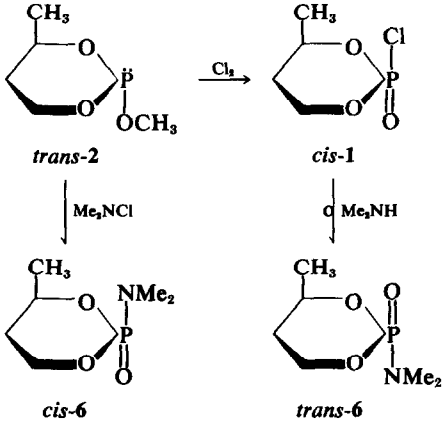
trans-**1** or **4** *cis*-**5** *cis*-**2**

SCHEME 9

We also carried out the same cycle of transformations starting with isomeric *trans*-**2**, *cis*-**1** and *cis*-**4** leading to *trans*-phosphate (**5**).

Since a good yield of *cis*-phosphate (**5**) is obtained from the reaction of *trans*-chloride (**1**) with methanol in the presence of Et_3N it appears that in the course of the reaction inversion of the configuration at the P atom takes place. This conclusion was confirmed by oxidation of the starting *cis*-phosphite (**3**) to *cis*-ester (**5**) with N_2O_4 which occurs with retention of the configuration at the P atom.[25]

The cycle of transformations shown in Scheme 10 proves that in the nucleophilic substitution of halogen in *cis*-chloride (**1**) with dimethylamine inversion of the configuration takes place.*



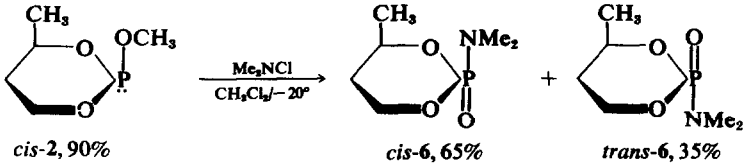
trans-**2** *cis*-**1** *cis*-**6** *trans*-**6**

SCHEME 10

We have found that the reaction of *cis*-chloride (**1**) obtained from *trans*-phosphite (**2**) with dimethylamine leads to *trans*-2-N,N-dimethylamino-4-methyl-2-oxo-1,3,2-dioxaphosphorinan (**6**). The *cis*-isomer can be obtained by the action of N-chlorodimethylamine on *trans*-phosphite (**3**) and it appears that this reaction probably takes place with the retention of configuration at the P atom.†

However, in contrast to the fully stereospecific reaction of *trans*-phosphite (**2**) with chloramine the reaction of *cis*-phosphite (**2**) with this reagent leads to the formation of a mixture of diastereomeric amides (**6**) in which the *cis*-isomer is the larger component.

In our opinion the lack of stereospecificity in the last reaction could be rationalised assuming that a



cis-**2**, 90% *cis*-**6**, 65% *trans*-**6**, 35%

SCHEME 11

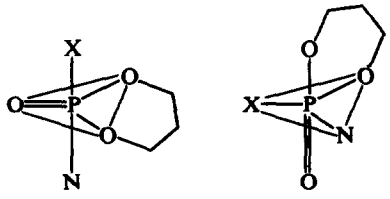
*Inversion of configuration at the phosphorus atom has also been found in the reaction of *cis*- and *trans*-**1** with aniline.[26]

†Sulphenyl chlorides react with diastereomeric cyclic phosphites (**2**) and phosphonates (**3**) with the same steric course e.g. retention at the P atom.[27]

pentacovalent phosphorus adduct is formed as a transitional compound, and that during the pseudorotation of this compound the decomposition resulting in the formation of the more stable *cis*-**6** isomer is favoured. Bodkin and Simpson[19] offered a similar explanation of the low stereospecificity of Arbuzov reactions of diastereomeric 2-ethoxy-1,3,2-dioxaphosphorinans.

The fact that there is complete inversion of configuration in the reactions of diastereomeric chlorophosphorinans (**1**) with nucleophilic reagents is very important in the stereochemistry of nucleophilic substitution at the P atom.[2]

The most probable structure of the transition state or the intermediate adduct is a trigonal bipyramid in which the substitution can take place in the diaxial or in the diradial positions, since only in such cases the stereochemical consequence of the substitution is the inversion of configuration at the P atom.



X – Leaving group
N – nucleophile

SCHEME 12

In the case of cyclic 5-membered phosphorus compounds the ring usually occupies the axial and radial positions, since the diradial position of the ring would cause a large steric strain.[28] However, in the case of 6-membered rings both positions of the ring in the trigonal bipyramid, i.e. diradial and axial-radial are equally probable,[29] and at the present time it is difficult to assign one of the two possible structures.

EXPERIMENTAL

NMR spectra were obtained on a Jeol C-60 H instrument at 60 MHz observing frequency for ^{1}H and 24·3 MHz for ^{31}P nuclei. ^{1}H-NMR spectra were recorded on samples in spinning 5-mm o.d. precission glass tubes using TMS as internal standard. ^{31}P-NMR spectra were measured as neat liquid, unless specified otherwise, on samples in 8 mm glass tubes and are listed in ppm relative to the chemical shift of 85% phosphoric acid contained in a concentric capillary in the NMR tube. Heteronuclear Spin Decoupler JNM-SD-HC was used for precise ^{31}P chemical shift determinations. A positive shift is taken to occur at an applied magnetic field greater than that of the standard. IR spectra were recorded with UR-10 Carl Zeiss (Jena) Spectrometer. GLPC analyses were conducted with Varian Aerograph 1520.

Diastereoisomeric purities were determined from integrated ^{1}H- and ^{31}P-NMR spectra and GLPC analyses. *cis*- and *trans*-**3** were prepared according to Nifanteev[16] and Mikolajczyk,[8] respectively. The preparation of *cis*- and *trans*-**2** has been described.[8] N-chlorodimethylamine was obtained according to Bock and Kompa.[30]

1. trans-2-*Chloro*-2-*oxo*-4-*methyl*-1,3,2-*dioxaphosphorinan* (**1**) *from chlorinolysis of* trans-**3** *with* SO_2Cl_2. SO_2Cl_2 (3·4 g; 0·025 m) was added dropwise at 15° into a stirred soln of *trans*-**3** (2·8 g; 0·02 m) in 60 ml CH_2Cl_2. The exothermic reaction was controlled by external cooling with an ice–water bath. When SO_2Cl_2 was added the mixture was allowed to come to room temp and degassed under vacuum. Removal of CH_2Cl_2 and excess of SO_2Cl_2 (10^{-2} mm Hg, water-bath 35°) gave colourless liquid, n_D^{20} 1·4530, which decomposed during attempts of distillation; yield 3·4 g (100%); IR (film) 1312 cm^{-1} (PO); ^{1}H-NMR (CCl_4) $\delta = -1{\cdot}48$ ppm (quartet, 3H,CH_3—C), $^3J_{HH} = 6{\cdot}6$ Hz, $^4J_{PH} = 3{\cdot}0$ Hz; ^{31}P-NMR (neat) $\delta = +3{\cdot}5$ ppm. (Found: C, 27·0; H, 5·01; P, 17·3. Calc. for $C_4H_8O_3PCl$: C, 28·1; H, 4·7; P, 18·2%).

2. *Reaction of* trans-**1** *with* MeOH *in the presence of* Et_3N. MeOH (0·65 g; 0·02 m) was dropped into soln of *trans*-**1** (3·4 g; 0·02 m) in a mixture of Et_3N (2·02 g; 0·02 m) and CCl_4 (40 ml) at 5° and stirring was continued at room temp for 6 hr. Et_3N . HCl was filtered off, the filtrate washed with 5% HCl (10 ml) and 2 × 5 ml H_2O, dried over $MgSO_4$ and evaporated. The residue was distilled *in vacuo* to afford a mixture containing 94% of *cis*- and 6% *trans*-**5**, 3·0 g (90%); b.p. 80–95°/0·5 mm Hg, n_D^{20} 1·4390, IR (film) 1288 cm^{-1} (PO), ^{1}H-NMR (benzene) $\delta = -1{\cdot}18$ ppm (quartet 3H, CH_3—C), $^3J_{HH} = 6{\cdot}5$ Hz, $^4J_{PH} = 1{\cdot}86$ Hz; $\delta = -3{\cdot}52$ ppm (doublet, 3H, CH_3O), $^3J_{PH} = 11{\cdot}7$ Hz; ^{31}P-NMR (neat) $\delta = +5{\cdot}1$ ppm.

3. *Reaction of* trans-**1** *with* Me_2NH. Me_2NH (1·8 g; 0·04 m) in benzene (25 ml) was added dropwise at temp of 5° to soln of *trans*-**1** (3·4 g; 0·02 m) in benzene (50 ml) with vigorous stirring and then allowed to stand overnight at room temp. Me_2NH . HCl was filtered off, the filtrate washed with 5% HCl (5 ml) and 2 × 5 ml H_2O, dried over anhyd $MgSO_4$ and solvent removed under reduced pressure. Distillation *in vacuo* afforded a mixture of 96% *cis*- and 4% *trans*-**6**; 3·3 g (92%) b.p. 90°/0·8 mm Hg, n_D^{20} 1·4522; IR (film) 1256 cm^{-1} (PO); ^{1}H-NMR ($CDCl_3$) $\delta = -1{\cdot}35$ ppm (quartet, 3H, CH_3—C), $^3J_{HH} = 6{\cdot}6$ Hz, $^4J_{PH} = 2{\cdot}2$ Hz; $\delta = -2{\cdot}52$ ppm (doublet, 6H, $(CH_3)_2N$—), $^3J_{PH} = 10{\cdot}4$ Hz. ^{31}P-NMR (neat) $\delta = -7{\cdot}5$ ppm. (Found: C, 40·5; H, 7·8; P, 16·6; N, 7·4. Calc. For $C_6H_{14}O_3PN$: C, 40·2; H, 7·8; P, 17·3; N, 7·1%).

4. *Chlorinolysis of* cis-2-*hydrogen*-2-*oxo*-4-*methyl*-1,3,2-*dioxaphosphorinan* (**3**). cis-2-*Chloro*-2-*oxo*-4-*methyl*-1,3,2-*dioxaphosphorinan* (**1**). Treatment of *cis*-**3** (4·2 g; 0·03 m) (94% *cis* and 6% *trans*) in CH_2Cl_2 (50 ml) with SO_2Cl_2 (5 g; 0·037 m) as described for *trans*-**1** gave a theoretical amount of *cis*-**1**, n_D^{20} 1·4591; IR (film) 1305 cm^{-1} (PO), ^{1}H-NMR ($CDCl_3$) $\delta = -1{\cdot}53$ ppm (quartet 3H, CH_3—C), $^3J_{HH} = 6{\cdot}8$ Hz, $^4J_{PH} = 1{\cdot}35$ Hz; ^{31}P-NMR (neat) $\delta = +3{\cdot}5$ ppm (6%) and $\delta = +5{\cdot}7$ ppm (94%). (Found: C, 28·6; H, 5·0; P, 16·7; Calc. for $C_4H_8O_3PCl$: C, 28·1; H, 4·7; P, 18·2%).

5. *Reaction of* cis-**1** *with* MeOH *in the presence of* Et_3N. Essentially the same procedure as in exp. 2 yielded from **1** (94% *cis* and 6% *trans*) **5** containing 85% *trans*- and 15% *cis*-isomers with overall yield 86%. b.p. 90°/0·8 mm Hg, n_D^{20} 1·4365; IR (film) 1296 cm^{-1} (PO), ^{1}H-NMR (benzene) $\delta = -1{\cdot}12$ ppm (quartet, 3H, CH_3—C), $^3J_{HH} = 6{\cdot}5$ Hz, $^4J_{PH} = 2{\cdot}5$ Hz; $\delta = -3{\cdot}55$ ppm (doublet, 3H, CH_3O), $^3J_{PH} = 11{\cdot}4$ Hz; ^{31}P-NMR (neat) $\delta = +6{\cdot}4$ ppm.

6. *Reaction of* cis-**1** *with* Me_2NH. Reaction of *cis*-**1** (94% *cis*- and 6% *trans*) with Me_2NH as described under

3) gave **6** (85% *trans* and 15% *cis*); yield 72%, b.p. 97–103°/1·2 mm Hg, $n_D^{20} = 1{\cdot}4555$; IR (film) 1258 cm^{-1} (PO); ^{1}H-NMR (benzene) $\delta = -1{\cdot}17$ ppm (quartet, 3H, CH_3—C), $^3J_{HH} = 6{\cdot}6$ Hz, $^4J_{PH} = 1{\cdot}7$ Hz; $\delta = -2{\cdot}45$ ppm (doublet, 6H $(CH_3)_2N$—), $^3J_{PH} = 11{\cdot}1$ Hz; ^{31}P-NMR (neat) $\delta = -4{\cdot}5$ ppm. (Found: C, 40·1; H, 7·7; P, 16·8; N, 7·0; Calcd. for $C_6H_{14}O_3PN$: C, 40·2; H, 7·8; P, 17·3; N, 7·1%).

7. *Halogenolysis of* 2-*methoxy*-4-*methyl*-1,3,2-*dioxaphosphorinan* (**2**). Into the soln of 0·02 m of X_2 (Cl_2 or Br_2) in 40 ml of CH_2Cl_2 immersed in Dry Ice-acetone bath equimolar amount of **2** in 10 ml of CH_2Cl_2 was added at such a rate as to maintain a temp below −50°. The Dry-Ice bath was removed and water bath was kept at room temp for 1 hr. The solvent was removed under reduced pressure and raw product analysed by means of ^{31}P-NMR. The products were converted into **5** or **6** according to procedure described under 3 or 4, respectively, and analysed as raw, undistilled materials by means of ^{1}H-NMR and GLPC.

(a) Chlorinolysis of diastereomerically pure *trans*-**2** gave only *cis*-**1** $\delta^{31}P = +5{\cdot}7$ ppm. Its subsequent reaction with Me_2NH gave phosphoramidate **6** (92% *trans*- and 8% *cis*-).

(b) *cis*-**2** contaminated with 11% *trans*-**2** gave phosphorochloridate **1** consisting a mixture of 87% *trans*-**1**, $\delta = +3{\cdot}5$ ppm and 13% *cis*-**1**, $\delta = +5{\cdot}7$ ppm. Treatment of this product with Me_2NH gave **6** (88% *cis*- and 12% *trans*-).

(c) Reaction of *trans*-**2** with bromine yielded *cis*-**4** as the single product, $\delta^{31}P = +19{\cdot}0$ ppm. ^{1}H-NMR ($CHCl_3$) $\delta = -0{\cdot}95$ ppm, broadened doublet, 3H, CH_3—C), $^3J_{HH} = 6{\cdot}3$ Hz, $^4J_{PH} = 1$ Hz; IR (film) 1315 cm^{-1} (PO) (Found: C, 23·1; H, 3·7; P, 15·03; Calcd. for $C_4H_8O_3PBr$: C, 22·4; H, 3·7; P, 14·4%).§ This product reacted with MeOH/NEt_3 to give **5** (76% *trans*- and 24% *cis*-).

(d) Treatment of *cis*-**2** (92% of *cis*- and 8% *trans*-) with Br_2 yielded *trans*- (87%) and *cis*- (13%) **4**, $\delta^{31}P = +14{\cdot}0$ ppm (*trans*-) and $+19{\cdot}0$ ppm (*cis*-). ^{1}H-NMR ($CDCl_3$) $\delta = -1{\cdot}0$ ppm (quartet, 3H, CH_3—C), $^3J_{HH} = 6{\cdot}4$ Hz, $^4J_{PH} = 3$ Hz; IR (film) 1305 cm^{-1} (PO). (Found: C, 22·7; H, 3·8; P, 14·7; Calcd. for $C_4H_8O_3PBr$: C, 22·4; H, 3·7; P, 14·4%).* Work-up with MeOH/NEt_3 gave **5** (85% *cis*- and 15% *trans*-) and treatment with Me_2NH yielded **6** (84% *cis*- and 16% *trans*).

8. *Reaction of* trans-**3** *with* CCl_4/NEt_3. NEt_3 (2·02 g; 0·02 m) was added at room temp to the soln of *trans*-**3** (2·8 g; 0·02 m) (contaminated with 14% of *cis*-isomer) in 50 ml of CCl_4 and the mixture left overnight at this temp. Filtration and evaporation gave a mixture of 86% *trans*-**1** ($\delta^{31}P = +3{\cdot}5$ ppm) and 14% of *cis*-**1** ($\delta^{31}P = +5{\cdot}7$ ppm).

9. *Reaction of* cis-**3** *with* CCl_4/NEt_3. NEt_3 (2·02 g; 0·02 m) was added dropwise at a temp below 30° to the soln of *cis*-**3** (2·8 g; 0·02 m) (94% *cis*- and 6% *trans*-) in 50 ml of CCl_4. The reaction was much more vigorous than in the case of *trans*-**3**. After 10 min the solvent was evaporated and residue analysed by means ^{31}P-NMR proving it to consist of a mixture of 48% of *cis*-**1** and 52% *trans*-**1**. Its treatment with Me_2NH in benzene soln yielded a mixture of 51% of *trans*-**6** and 49% of *cis*-**6**.

10. *Direct transformation of* trans-**3** *into* cis-**4**. Into the soln of *trans*-**3** (2·8 g; 0·02 m) contaminated with 8% of *cis*-**3** in 50 ml of CCl_4 a mixture of MeOH (0·9 g; 0·03 m) and NEt_3 (2·1 g; 0·02 m) was added and mixture allowed to stand overnight at room temp. Subsequent work-up as described under exp. 2 gave phosphate (**5**) (87% *cis*- and 13% *trans*-).

11. *Reaction of* N-*haloimides of succinic acid with* trans-**2**. Into the soln of *trans*-**3** (1·4 g; 0·01 m) in 40 ml of CCl_4 was added stoichiometric amount of NClS. The resulting mixture was stirred at room temp for 0·5 hr, the succinimide filtered off, the filtrate evaporated and analysed by means ^{31}P-NMR. Only *trans*-**1** was detected. Similarly *trans*-**3** was brominated with NBS to give a mixture of 94% of *trans*-**4**, $\delta^{31}P = +14$ ppm and 6% *cis*-**4**, $\delta^{31}P = +19$ ppm.

12. *Reaction of* N-*chlorodimethylamine with* trans-**2**. Into the soln of *trans*-**2** (1·5 g; 0·01 m) in CH_2Cl_2 (20 ml) was added soln of stoichiometric amount $ClNMe_2$ in CH_2Cl_2 at temp below −20°. Cooling bath was removed and mixture allowed to warm-up to temp + 10°. Trace amounts of a ppt were filtered off, the solvent removed and the residue analysed by means of GLPC and ^{1}H-NMR. The resulting phosphoramidate (**6**) contained 91% of *cis*- and 9% of *trans*-isomers.

13. *Reaction of* N-*chlorodimethylamine with* cis-**2**. Starting from *cis*-**2** (89% *cis*- and 11% *trans*-) (as described under exp. 12) a mixture of 65% *cis*- and 35% *trans*-**6** was obtained. The reaction did not occur at a temp below −10° but above 0° it is very vigorous. In the series of four experiments a similar ratio of *cis*/*trans*-**6** was recorded.

14. *Reaction of butandiol*-1,3 *with phosphorus oxychloride*. Into the mixture of butandiol-1,3 (18 g; 0·2 m) in CCl_4 (120 ml) equimolar amount of $POCl_3$ was slowly dropped (*ca* 20′) and with vigorous stirring the mixture was refluxed for 6 hr. After cooling the mixture was degassed and solvent removed under reduced pressure. The resulting mixture contained 76% of *trans*-**1** $\delta^{31}P = +3{\cdot}5$ ppm and 24% of *cis*-**1** $\delta^{31}P = +5{\cdot}7$ ppm. In series of four experiments a similar ratio *trans*/*cis* isomers was recorded.

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*Chemical shift values of the pure *cis*- and *trans*-bromides (**4**) found in this work are different from those reported by Navech[14] for the mixture *cis*- and *trans*-**4** (33%, $\delta^{31}P = -19{\cdot}1$ ppm, 67%, $\delta^{31}P = -22{\cdot}0$ ppm).

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