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STEREOCHEMISTRY OF ORGANOPHOSPHORUS CYCLIC COMPOUNDS—I[1]

STEREOSPECIFIC SYNTHESIS OF *CIS*- AND *TRANS*-2-HYDROXY-2-THIO(SELENO)-4-METHYL-1.3.2-DIOXAPHOSPHORINANS

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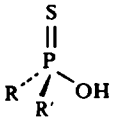
Abstract—Geometrical isomers of 2-hydroxy-2-thio-4-methyl-1,3,2-dioxaphosphorinan (I) and 2-hydroxy-2-seleno-4-methyl-1,3,2-dioxaphosphorinan (V) have been prepared stereospecifically by : (a) demethylation of *cis*- and *trans*-2-methoxy-2-thio-4-methyl-1,3,2-dioxaphosphorinan (IV) and 2-methoxy-2-seleno-4-methyl-1,3,2-dioxaphosphorinan (VI) with trimethylamine, and (b) addition of sulphur and selenium to geometrical isomers of 2-hydrogen-2-oxo-4-methyl-1,3,2-dioxaphosphorinan (VIII). It has been demonstrated that addition of sulphur and selenium to the >P(O)H grouping proceeds with retention of configuration at the P atom.

AMONG stable chiral phosphorus compounds phosphorus monothioacids having two different substituents attached to the phosphorus atom play a significant role in stereochemical investigations. They are readily resolved into optically active forms



through diastereomeric salts with optically active amines and at present more than twenty various optically active phosphorus monothioacids have been described. Because of high reactivity of the >P(S)OH—grouping they prove most suitable as starting materials for the synthesis of other optically active phosphoryl—P(O) and thiophosphoryl—P(S) derivatives.[2]

Interestingly direct proof of the Walden inversion at phosphorus has been recently obtained using optically active O-ethyl ethylphosphonothioic acid[3] and O-methyl isopropylphosphonothioic acid.[4]

However, in contrast to acyclic phosphorus monothioacids the chemistry and especially stereochemistry of their cyclic analogues has received very little attention. In view of the increasing tendency to investigate phosphorus stereochemistry using suitable cyclic model compounds[5] we decided to study the geometrical isomerism in cyclic five- and six-membered phosphorus monothioacid derivatives which occurs when the molecule contains at least one asymmetric centre at a ring carbon atom.

Recently, Eckstein[6] has synthesized uridine 2',3'-O,O-cyclophosphorothioate as a mixture of two diastereomers and Saenger and Eckstein[7] have determined the absolute configuration of one of them by X-ray analysis.

In preliminary communications[8,9] we reported the geometrical isomerism in two cyclic thioacids: 2-hydroxy-2-thio-4-methyl-1,3,2-dioxaphospholan and 2-hydroxy-2-thio-4-methyl-1,3,2-dioxaphosphorinan. We now describe our full results concerning the stereospecific synthesis of *cis*- and *trans*-isomers of the latter as well as its selenium analogue 2-hydroxy-2-seleno-4-methyl-1,3,2-dioxaphosphorinan.

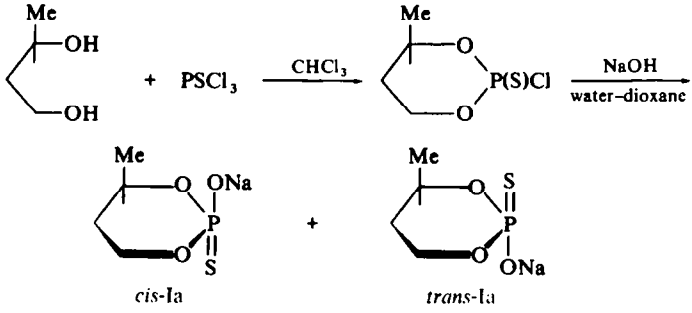
SCHEME 1

The convention is used in the present paper that *cis* refers to the relation between the C_4-methyl group and the exocyclic oxygen atom.

RESULTS AND DISCUSSION

We have found that the sodium salt (Ia) of 2-hydroxy-2-thio-4-methyl-1,3,2-dioxaphosphorinan (I) obtained by alkaline hydrolysis of 2-chloro-2-thio-4-methyl-1,3,2-dioxaphosphorinan (prepared from butan-1,3-diol and $PSCl_3$[10]),* according to Edmundson,[11] is a mixture of two diastereomeric salts, *cis*-Ia and *trans*-Ia. The

SCHEME 2



presence of the *cis*- and *trans*-isomers was confirmed by conversion of the sodium salt into a dicyclohexylammonium salt (Ib) which although analytically pure had very poor melting point, 187–201°, and then by analysis of the ^{1}H- and ^{31}P-NMR spectra which showed two distinct sets of signals corresponding to the two geometrical isomers (Ia). The ^{1}H-NMR spectrum at 100 MHz exhibited two quartets at 1·27 ppm ($J_{H—CH_3}$ 6·2 Hz, $J_{P—CH_3}$ 2 Hz) and 1·28 ppm ($J_{H—CH_3}$ 6·2 Hz, $J_{P—CH_3}$ 1·7 Hz) which can be ascribed to the protons of the C_4-methyl group in both diastereomers. In the ^{31}P–NMR spectrum two signals appeared at − 50·5 and − 54·0 ppm, respectively.

* 2-Chloro-2-thio-4-methyl-1,3,2-dioxaphosphorinan obtained in this way is a mixture of two geometrical isomers as shown by NMR spectra.[12,13]

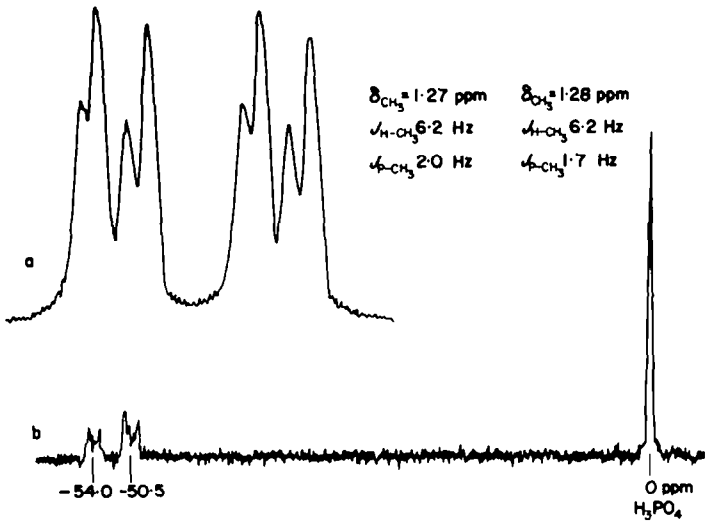


FIG 1. ^{1}H- and ^{31}P-NMR spectra of the mixture of diastereomeric sodium salts *cis*-Ia and *trans*-Ia.

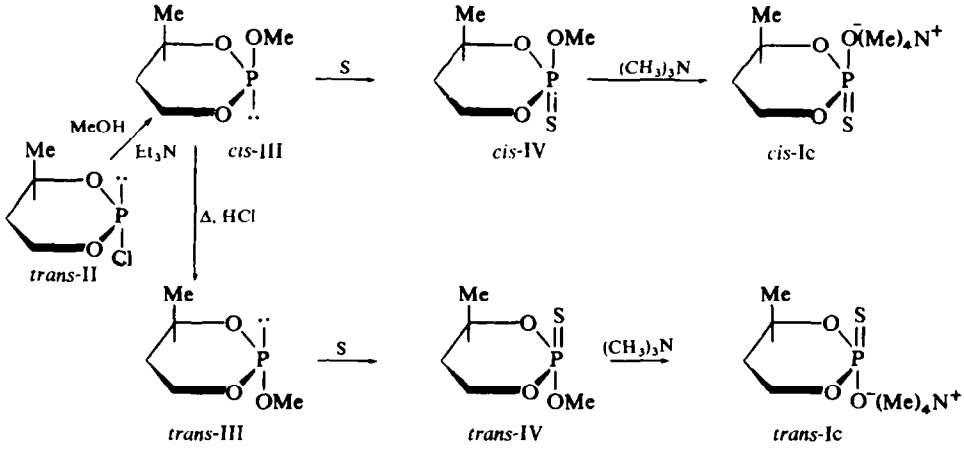
(a) Expanded resonance signal of C_4-methyl protons (100 MHz, D_2O, DSS as internal standard)

(b) ^{31}P-NMR spectrum of *cis*- and *trans*-Ia (24·3 MHz, H_2O using 85% H_3PO_4 as external standard)

Dicyclohexylammonium salt (Ib) can be partially separated into the diastereomeric components by fractional crystallization from an n-propanol-ether mixture. However, very low yields of *cis*-Ib and *trans*-Ib salts were obtained.

To avoid fractional crystallization and to assign the NMR data to the isomers several stereospecific routes were devised to both diastereomeric thioacids (I). The first is shown in Scheme 3.

SCHEME 3



We took advantage of the fact that 2-chloro-4-methyl-1,3,2-dioxaphosphorinan (II) exists entirely as the single, presumably more stable *trans*-isomer[14] and also that the possibility existed for the synthesis of diastereomerically pure 2-methoxy-4-methyl-1,3,2-dioxaphosphorinans (III) and 2-methoxy-2-thiono-4-methyl-1,3,2-dioxaphosphorinans (IV) following the method of Aksnes[15] who prepared in the pure state their *cis*- and *trans*-ethoxy analogues.

Using the same method we have obtained the less-stable phosphite (III), $\delta_{31_P} = -126{\cdot}5$ ppm, by treatment of the cyclic chlorophosphite (II) with MeOH in the presence of excess Et_3N in ether. Addition of sulphur to the undistilled product affords one form of the diastereomeric thiophosphate (IV) having $\delta_{31_P} = -63{\cdot}5$ ppm which was contaminated with small amounts of the other isomer (2–4%). Then, the less-stable phosphite (III) was converted into the more stable isomer, $\delta_{31_P} = -125{\cdot}9$ ppm, by twice distilling at a bath temperature of 100° in the presence of a trace anhydrous HCl.* Reaction of this phosphite (III) with sulphur in ether results in the formation of the pure second thiophosphate (IV) diastereomer having $\delta_{31_P} = -61{\cdot}5$ ppm.

By making the reasonable assumption that chlorophosphite (II) has the *trans*-configuration (*trans*- relationship of the C_4-methyl group and the chlorine atom) and that it reacts with MeOH with inversion of configuration at the P atom[5, 15] we have assigned the *cis*- configuration to the less stable phosphite (III) and the *trans*- configuration to the more stable isomer. Since conversion of the phosphite esters into their corresponding sulphides by addition of sulphur proceeds stereospecifically with retention at phosphorus[16] it was next possible to assign *cis*- and *trans*- configurations to the corresponding thiophosphates (IV) having $\delta_{31_P} = -63{\cdot}5$ and $-61{\cdot}5$ ppm, respectively.

The crucial and last step of the stereospecific synthesis includes the reaction of *cis*- and *trans*-thionoesters (IV) with Et_3N in benzene at room temperature and leads to the formation of the diastereomeric tetramethylammonium salts (Ic). Since configuration at the phosphorus atom is unchanged during the demethylation (it proceeds by nucleophilic attack of the nitrogen atom of Me_3N on the carbon atom of the methoxy-group in the thiophosphate) the spatial relationships between the C_4-methyl group and the exocyclic oxygen atom in diastereomeric tetramethylammonium salts (Ic) obtained are the same as those in the starting thionophosphates (IV). Therefore, the reaction of *cis*-IV with Me_3N gives the tetramethylammonium salt *cis*-Ic, m.p. 203–206°, $\delta_{31_P} = -49.7$ ppm and *trans*-IV treated with Me_3N affords *trans*-Ic, m.p. 122–126° (very hygroscopic), $\delta_{31_P} = -53{\cdot}5$ ppm.

For further characterization *cis*- and *trans*-salts (Ic) were converted into the corresponding *cis*- and *trans*-dicyclohexylammonium, -ammonium, and -diethylammonium salts Ib, Id and Ie, respectively. In all cases the differences in m.ps and ^{31}P–NMR chemical shifts were observed (Table 1).

After this work was completed Bodkin and Simpson[5d] reported results of NMR studies on the conformation of 2-alkoxy-4-methyl-1,3,2-dioxaphosphorinans and confirmed our assumptions concerning the stereochemistry of the chlorophosphite

* In our previous report[9] the low-temperature distillation of *cis*-phosphite III did not cause its isomerization into *trans*-phosphite III and therefore the opposite configurations of thionophosphates (IV), thioacids (I) and phosphonates (VIII) have been erroneously assigned.

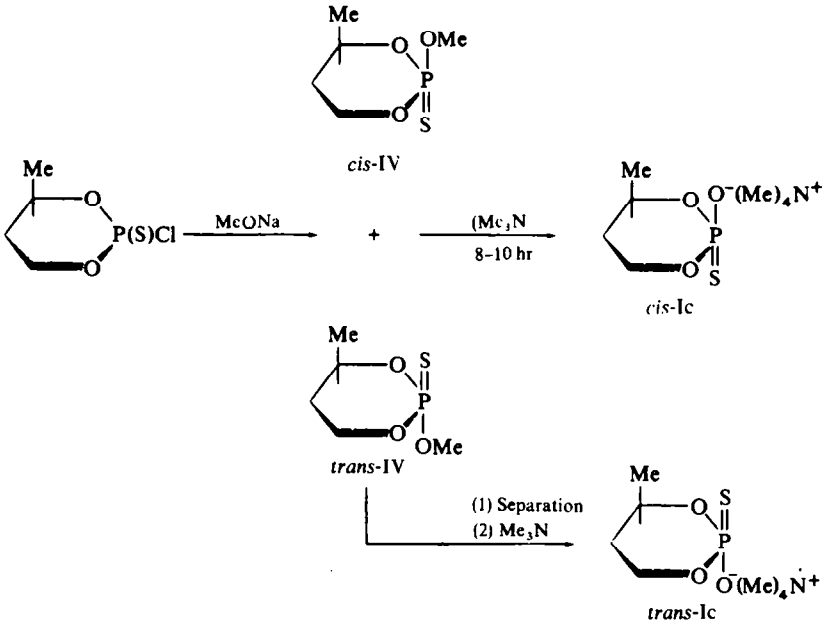
TABLE 1. PHYSICAL AND SPECTRAL DATA OF THE SALTS OF *cis*- AND *trans*-2-HYDROXY-2-THIO-4-METHYL-1,3,2-DIOXAPHOSPHORINAN (I)

Salt	M.p. (solvent)	δ_{31P}, ppm (H_3PO_4, 85%)	Analysis					
			Found			Calc.		
			C	H	P	C	H	P
cis-Ib	208–211° (n-propanol-petroleum ether)	−50·5	54·75	8·8	9·2	54·9	9·2	8·9
trans-Ib	194–196° (n-propanol-petroleum ether)	−53·5	54·4	9·1	9·2			
cis-Ic	203–206° (n-propanol-acetone)	−49·7	39·75	8·3	12·7	39·8	8·35	12·8
trans Ic	122–126°	−53·5	39·8	8·5	13·1			
cis-Id	188–192° (n-propanol-ether)	−50·5	26·0	6·25	17·4	25·9	6·5	16·6
trans-Id	144–147° (n-propanol)	−53·0	25·6	6·6	16·7			
cis-Ie	122–126° (benzene–ether)	−48·6	39·5	7·8	12·9	39·8	8·3	12·9
trans-Ie	117–120° (benzene–ether)	−52·6	39·3	8·0	12·8			

(II) and the isomeric phosphites (III). Therefore, it seems that our assignments of the diastereomeric *cis*- and *trans*- thioacids (I) are at present reliable.

During the demethylation experiments we observed considerable rate differences for both diastereomeric thiophosphates (IV). This fact prompted us to investigate the reaction of Me_3N with the 1:1 mixture of *cis*- and *trans*-IV which occurs in the reaction of 2-chloro-2-thio-4-methyl-1,3,2-dioxaphosphorinan with NaOMe in MeOH.

SCHEME 4



We have found that almost pure tetramethylammonium salt *cis*-Ic precipitates from the reaction after *ca.* 8–10 hr at room temp, and recrystallization affords pure diastereomer *cis*-Ic. Unreacted thiophosphate *trans*-IV can be isolated from the filtrate by solvent evaporation and subsequent distillation. It can be used for obtaining the isomeric tetramethylammonium salt *trans*-Ic. This makes it possible to synthesize *cis*- and *trans*-Ic directly from the mixture of both diastereomeric thiophosphates (IV) without carrying out their stereospecific synthesis.

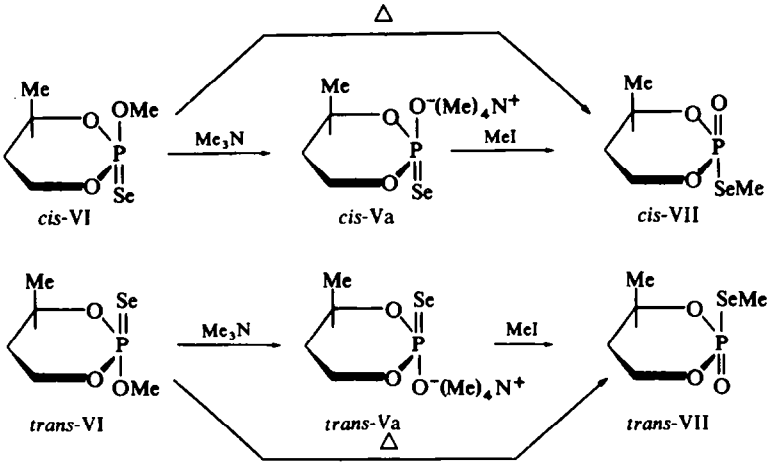
In the course of this work we have synthesized the *cis*- and *trans*-tetramethylammonium salts (Va) of 2-hydroxy-2-seleno-4-methyl-1,3,2-dioxaphosphorinan (V) by the action of Me_3N on the corresponding *cis*- and *trans*-2-methoxy-2-seleno-4-methyl-1,3,2-dioxaphosphorinans (VI)[17] prepared by addition of selenium to the diastereomeric phosphites (III). Thus, demethylation of the *cis*- selenonophosphate (IV) afforded the tetramethylammonium salt *cis*-Va having m.p. 172–173·5°, $\delta_{31_P} = -41{\cdot}3$ ppm; the *trans*-selenonophosphate (VI) gave the salt *trans*-Va which had m.p. 114–117°, $\delta_{31_P} = -45{\cdot}8$ ppm. The corresponding dicyclohexylammonium

salts *cis*-Vb and *trans*-Vb have m.p. and δ_{31_P}-value: 199–202°, − 43·1 ppm and 174–176°, − 45·6 ppm, respectively.

The geometrical isomers of the cyclic selenoacid (V) were further characterized as 2-methylseleno-2-oxo-4-methyl-1,3,2-dioxaphosphorinans (VII) by methylation of *cis*-Va and *trans*-Va with MeI. Apart from the differences in the ^{1}H- and ^{31}P-NMR spectra, the isomeric selenolophosphates (VII) show very distinct physical properties. Whereas *cis*-selenolophosphate (VII) is a crystalline solid, m.p. 58·5–59·5°, δ_{31_P} = − 11·7 ppm, its *trans*-isomer is liquid, b.p. 105–110°/0·2 mm, δ_{31_P} = − 14·0 ppm.

An alternative route to the above diastereomeric selenoloesters (VII) consists in thermal isomerization of the selenonophosphates (VI). This process does not change the relationship between the ring substituents on the phosphorus and carbon atoms. The above transformation are in Scheme 5.

SCHEME 5



Another approach to the stereospecific synthesis of geometrical isomers of thioacid (I) and selenoacid (V) is based on the well-known reaction of dialkylphosphonates with sulphur or selenium in the presence of base leading to the thio- or seleno-acids.[18]

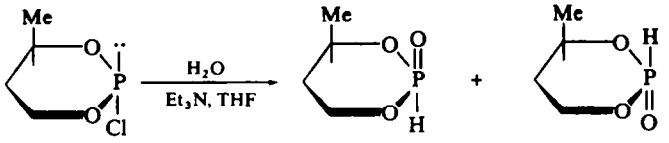
$$(RO)_2\overset{\overset{O}{\|}}{P}—H + S\,(Se) \xrightarrow{Base} (RO)_2\overset{\overset{S\,(Se)}{\|}}{P}—OH$$

However, for this purpose it was necessary to have the geometrical isomers of the corresponding cyclic phosphonate-2-hydrogen-2-oxo-4-methyl-1,3,2-dioxaphosphorinan (VIII). At the beginning of this investigation practically nothing was known about the stereochemistry of $\diagup\!\!\diagdown$P(O)H— containing compounds, although great improvements in this field have been made in the past three years.[19]

We have demonstrated that the phosphonate (VIII) can exist in *cis*- and *trans*-forms which are easily distinguished by ^{1}H- and ^{31}P-NMR spectroscopy.[20] This fact best explains the discrepancies in physical properties of the phosphite (VIII) reported.[21] Similar observation has been made independently by Nifantiev *et al.*[22]

In this work it has been established that hydrolysis of the chlorophosphite (II) with water in the presence of Et_3N affords a mixture of isomeric phosphates (VIII).

SCHEME 6



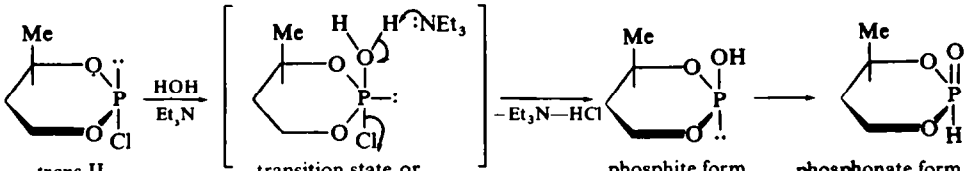
By fractional crystallization we were able to isolate pure predominant isomer having m.p. 55–58° and $\delta_{31_P} = -3{\cdot}1$ ppm. The second phosphonate (VIII)-isomer is a liquid, $\delta_{31_P} = +1{\cdot}0$ ppm, which slowly undergoes isomerization to the more stable crystalline isomer (VIII).

Recently Nifantiev *et al.*[23] have shown by NMR and dipole moment studies that the crystalline isomer (VIII) adopts a chair conformation having equatorial methyl and phosphoryl groups, whereas the less-stable phosphonate (VIII) has an equatorial C_4-methyl group but an axial exocyclic oxygen atom.

SCHEME 7

Considering this assignment it is reasonable to assume that hydrolysis of the chlorophosphite (II) like alkoholysis proceeds with inversion of configuration at P and leads to the more stable isomer according to Scheme 8.

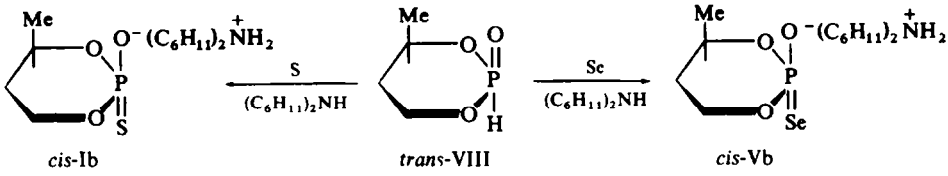
SCHEME 8



A little of the less-stable phosphonate (VIII) observed may be due to thermal epimerization *trans*-VIII → *cis*-VIII during product distillation.

Addition of sulphur and selenium in the presence of dicyclohexylamine to the crystalline phosphonate *trans*-VIII in benzene-ether solution affords diastereomerically pure dicyclohexylammonium salts *cis*-Ib and *cis*-Vb, respectively. Yields were found to be 80–90%.

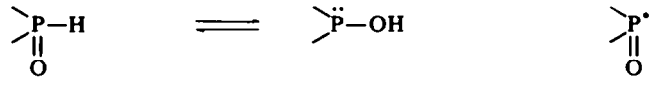
SCHEME 9



cis-Ib *trans*-VIII *cis*-Vb

Analogous experiments with liquid phosphonate isomer (VIII) were less satisfactory but pure dicyclohexylammonium salt *trans*-Ib has been obtained in *ca.* 30% yield.

These experiments clearly demonstrate that addition of sulphur and selenium to the >P(O)H— phosphonates is completely stereospecific and takes place with retention of configuration at the P atom. Sulphur addition to phosphonates is usually considered to proceed *via* an ionic mechanism involving formation of tautomeric



A B C

phosphite B as a reactive species. However Mosher and Irino[24] suggest a radical mechanism for this reaction. In such a case the formation of phosphino-radical C can be expected. The fact that sulphur and selenium addition to the cyclic >P(O)H— compounds are completely stereospecific does not rule out the radical mechanism since under the reaction conditions the cyclic phosphorus radical may be configurationally stable and can add sulphur in a stereospecific manner.

Conformation of the diastereomeric thioacids (I), selenoacids (V) and their derivatives is the subject of our further studies.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. ^{1}H-NMR spectra were obtained on a Varian instrument (100 MHz) or a Jeol spectrometer (60 MHz) with TMS as an internal standard (DSS for D_2O solutions). ^{31}P-NMR spectra were recorded on a Jeol C-60 H instrument at 24·3 MHz with 85% phosphoric acid as external standard. Heteronuclear Spin Decoupler INH–SD–HC was used for precise ^{31}P chemical shift determinations. GLPC analyses were conducted with a Varian 10 gas chromatograph. Diastereomeric purities were determined from integrated ^{1}H and ^{31}P-NMR spectra and GLPC analyses.

2-Chloro-4-methyl-1,3,2-dioxaphosphorinan (II) was synthesized from butan-1,3-diol and PCl_3 in

$CHCl_3$ according to Lucas *et al.*[25] *Cis*-2-hydrogen-2-oxo-4-methyl-1,3,2-dioxaphosphorinan (VIII) was prepared according to Nifantiev *et al.*[23] 2-Chloro-2-thio-4-methyl-1,3,2-dioxaphosphorinan was obtained from butan-1,3-diol and $PSCl_3$ in $CHCl_3$ according to Ziemlanski and Kalaschnikov.[10]

Alkaline hydrolysis of 2-chloro-2-thio-4-methyl-1,3,2-dioxaphosphorinan. The cyclic chloride (1·87 g, 0·01 M) was added in one portion to a solution of NaOH (0·8 g) in water (20 ml) and dioxane (20 ml). After 2 hr solvents were evaporated *in vacuo* and the solid residue extracted with acetone (70 ml). Addition of petroleum ether (50–60°) to the filtered solution precipitated the sodium salt (Ia) of 2-hydroxy-2-thio-4-methyl-1,3,2-dioxaphosphorinan (I); 1·82 g, 96%, decomposition at 255–260° (Found: C, 24·5; H, 4·6; P. 16·1; S, 16·4. Calc. for $C_4H_8O_3PSNa$: C, 25·3; H, 4·2; P, 16·3; S, 16·9%). The sodium salt (I) is a mixture of geometrical isomers as shown by ^1H and ^{31}P-NMR spectra (Fig 1).

The sodium salt was dissolved in water (5 ml) and to the solution 25%–HCl was added, which was then $CHCl_3$ extracted (4 × 25 ml). $CHCl_3$ layer was dried and evaporated to give the crude acid (I). It was dissolved in ether and light petroleum and added to 1·81 g dicyclohexylamine in petroleum ether. Dicyclohexylammonium salt (Ib) was filtered, 2·5 g, 71%, m.p. 187–201°. After recrystallization from n-propanol-petroleum ether it had m.p. 187–196° (Found: C, 55·4; H, 9·2; N, 4·1; P, 8·6; S, 9·0. Calc. for $C_{16}H_{32}NO_3PS$: C, 55·0; H, 9·2; 4·0; P, 8·9; S, 9·2%).

cis-2-*Methoxy*-4-*methyl*-1,3,2-*dioxaphosphorinan* (III). To a solution of 11·2 g (0·0725 M) chlorophospite (II) in 80 ml ether 9·0 g (0·09 M) Et_3N in 20 ml ether and 2·56 g (0·08 M) MeOH in 20 ml ether were added (temperature was kept below 0°). After 1 hr $Et_3N.HCl$ was filtered off and solvent evaporated at room temp. The residue was the nearly pure isomer *cis*-III, $\delta_{31_P} = -126·5$ ppm and can be distilled *in vacuo*, b.p. 20–22°/0·05 mm, n_D^{21} 1·4468, 8·7 g, 80% (94·1% *cis* and 5·9%—*trans* isomer).

trans-2-*Methoxy*-4-*methyl*-1,3,2-*dioxaphosphorinan* (III). This isomer was obtained from *cis*-III by adding a catalytic amount of dry HCl gas followed by twice distilling the mixture under reduced pressure; b.p. 90–92°/60 mm, n_D^{21} 1·4481, $\delta_{31_P} = -125·9$ ppm (100% pure isomer).

cis-2-*Methoxy*-2-*thio*-4-*methyl*-1,3,2-*dioxaphosphorinan* (IV). It was obtained by gradual addition of elemental sulphur to *cis*-III at 0°. From 5·1 g *cis*-III and 1·2 g sulphur after distillation 5 g (80·6%) *cis*-IV was obtained, b.p. 78–80°/0·3 mm, n_D^{20} 1·4902 (Found: C, 32·8; H, 6·0; P, 16·9; S, 17·2. Calc. for $C_5H_{11}O_3P$: C, 32·9; H, 6·1; P, 17·0; S, 17·6%) ^1H-NMR (100 MHz, $CDCl_3$): $\delta_{C-CH_3} = 1·41$ ppm, $J_{P-CH_3} = 2·1$ Hz, J_{H-CH_3} 6·4 Hz, $\delta_{OCH_3} = 3·82$ ppm, J_{P-OCH_3} 13·1 Hz, ^{31}P-NMR (neat) $\delta = -63·5$ ppm.

trans-2-*Methoxy*-2-*thio*-4-*methyl*-1,3,2-*dioxaphosphorinan* (IV). To 19·75 g (0·131 M) *trans*-phosphite (III) 4·6 g (0·14 M) sulphur was gradually added at 0°. After 2 hr the product was distilled to give *trans*-IV, 19·5 g (81%), n_D^{22} 1·4913, b.p. 76–80°/0·03 mm (contains 5% of *cis*-isomer). ^1H-NMR (100 MHz, $CDCl_3$): $\delta_{C-CH_3} = 1·39$ ppm, J_{H-CH_3} 6·3 Hz, J_{P-CH_3} 2·3 Hz, $\delta_{OCH_3} = 3·75$ ppm, J_{P-OCH_3} 13·1 Hz. ^{31}P-NMR (neat) $\delta = -61·5$ ppm.

Tetramethylammonium salt cis-Ic. *cis*-Thionophosphate (IV) (3·0 g, 0·016 M) was dissolved in benzene (25 ml) and treated at room temp with a benzene solution of Me_3N (10·0 g). After two days the precipitated salt *cis*-Ic was filtered (2·8 g, 95%, m.p. 199–201°) and crystallized from n-propanol–ether, m.p. 203–206° (Table 1).

Tetramethylammonium salt trans-Ic. A solution of *trans* thionophosphate (IV) (6·0 g, 0·033 M) and Me_3N (25·0 g) in benzene (80 ml) gives the salt *trans*-Ic, 6·4 g, 88%, m.p. 122–126° (very hygroscopic) (Table 1).

Treatment of an aqueous solution of the above salts *cis*-Ic and *trans*-Ic with Dowex 50 and the eluate with dicyclohexylamine, ammonia and diethylamine yielded the corresponding *cis*- and *trans*- salts Ib, Id and Ie, respectively (Table 1).

Reaction of 2-chloro-2-thio-4-methyl-1,3,2-dioxaphosphorinan with sodium methoxide. A solution of the cyclic chloride (9·35 g, 0·05 M) in ether (20 ml) was added at room temp to NaOMe in MeOH (1·15 g Na in 100 ml MeOH). After 1 hr NaCl was filtered, the solvents evaporated and the residue distilled to afford the thionophosphate (IV), 7·0 g, 77%, b.p. 89–93°/0·6 mm, n_D^{21} 1·4921 (Found: C, 33·19; H, 6·15; P. 16·80; S, 17·56. Calc. for $C_5H_{11}O_3PS$: C, 32·95; H, 6·09; P, 17·00; S, 17·60%). By GLPC analysis it was shown that the product consisted of 48·2% of *cis*-IV and 51·3% of *trans*-IV.

Selective demethylation of the mixture of cis- *and* trans-IV. Ester (IV) obtained above (2·9 g, 0·016 M). in 30 ml benzene was added to a solution of Me_3N in benzene. After 10 hr the precipitated salt was filtered; 1·65 g, 40·6%, m.p. 168–182°. The ^{31}P-NMR spectrum showed only one signal at −49·7 ppm. After crystallization from n-propanol-petroleum ether the salt had m.p. 203–206°.

Tetramethylammonium salt cis-Va. Selenonophosphate (VI) (2·3 g, 0·01 M, 80% *cis*- and 20% *trans*-isomer) was dissolved in benzene (20 ml) and added to a 25% solution (30 ml) of Me_3N in benzene. After 20 hr the tetramethylammonium salt *cis*-Va was filtered, washed with benzene and dried; 1·9 g, 66%,

m.p. 172–173·5° (Found: C, 33·55; H, 7·26; N, 4·51; P, 13·58. Calc. for $C_8H_{20}NO_3PSe$: C, 33·43; H, 7·00; N, 4·87; P, 10·80%). ^{1}H-NMR (60 MHz, D_2O, DSS): δ_{CH_3} = 1·3 ppm, J_{H-CH_3} 6·9 Hz, J_{P-CH_3} 2·04 Hz, δ_{N-CH_3} = 3·23 ppm. ^{31}P-NMR (H_2O): δ = −41·3 ppm.

Dicyclohexylammonium salt cis-Vb. The salt *cis*-Va (1·44 g, 0·005 M) in water was treated with HCl (10%, 3 ml) and the free acid *cis*-V was quickly $CHCl_3$ extracted dried over $MgSO_4$. To this solution dicyclohexylamine (1·0 g, 0·0055 M) was added. After removal of solvent the crude salt *cis*-Vb was crystallized from n-propanol-ether to give the pure *cis*-Vb, 1·6 g, 81%, m.p. 199–202° (Found: C, 49·15; H, 8·65; N, 3·30; P, 9·23. Calc. for $C_{16}H_{32}NO_3PSe$: C, 48·48; H, 8·13; N, 3·53; P, 7·81%). ^{1}H-NMR (60 MHz, D_2O, DSS): δ_{CH_3} = 1·28 ppm, J_{H-CH_3} 6·75 Hz, J_{P-CH_3} 1·95 Hz. ^{31}P-NMR (H_2O): δ = −43·1 ppm.

cis-2-*Methylseleno*-2-*oxo*-4-*methyl*-1,3,2-*dioxaphosphorinan* (VII). To the suspension of *cis*-Va (0·72 g, 0·0025 M) in 20 ml benzene MeI (1·2 g, 0·0075 M) was added. After 24 hr Me_4NI was filtered off and ether washed. Evaporation of filtrate afforded *cis*-VII, 0·55 g, 96%, m.p. 58–59° (Found: C, 26·54; H, 4·76; P. 16·50. Calc. for $C_5H_{11}O_3PSe$: C, 26·20; H, 4·80; P, 13·53%). ^{1}H-NMR (60 MHz, benzene, TMS): δ_{CH_3} = 1·02 ppm, J_{H-CH_3} 6·6 Hz, J_{P-CH_3} 2·4 Hz, δ_{SeCH_3} = 1·99 ppm, J_{P-SeCH_3} 13·5 Hz, ^{31}P-NMR (benzene): δ = −11·7 ppm, $J_{P-Se''}$ 444·7 Hz.

Cis-VII was also obtained from the *cis*-Vb (0·5 g, 0·00125 M) and MeI (0·6 g, 0·0039 M) in benzene; 0·28 g, 96%, m.p. 58–59° (Found: C, 27·15; H, 4·70; P, 13·03%).

Thermal isomerization of cis-VI *into* cis-VII. *cis*-VI (4·58 g, 0·02 M) was distilled at bath temperature 180°. The distillate, b.p. 108–115°/0·2 mm, which solidified, was crystallized from benzene–ether to give the pure *cis*-VII, 4·22 g, 92%, m.p. 58–59·5°.

Tetramethylammonium salt trans-Va. The mixture of *trans*-VI (2·0 g, 0·0087 M) and Me_3N (25% benzene solution, 15 ml) was allowed to stand for 5 days at room temp. The precipitated *trans*-Va was filtered, washed with benzene and dried, 2·2 g, 88%, m.p. 114–117° (very hygroscopic) (Found: C, 33·00; H, 7·33; N, 4·86; P, 14·27%). ^{1}H-NMR (60 MHz, D_2O, DSS): δ_{CH_3} = 1·3 ppm, J_{H-CH_3} 6·74 Hz, J_{P-CH_3} 1·65 Hz, δ_{NCH_3} = 3·20 ppm. ^{31}P-NMR (H_2O): δ = −45·8 ppm.

Dicyclohexylammonium salt trans-Vb. Essentially the same procedure as for *cis*-Vb yielded from *trans*-Va (1·44 g, 0·005 M) the salt *trans*-Vb, 1·62 g, 82%, m.p. 174–176° (MeOH–ether) (Found: C, 48·63; H, 8·36; N, 3·23; P, 8·43%). ^{1}H-NMR (60 MHz, D_2O, DSS): δ_{CH_3} = 1·30 ppm, J_{H-CH_3} 6·6 Hz, J_{P-CH_3} 1·53 Hz. ^{31}P-NMR (H_2O): δ = −45·6 ppm.

trans-2-*Methylseleno*-2-*oxo*-4-*methyl*-1,3,2-*dioxaphosphorinan* (VII). Methylation of *trans*-Va (1·44 g, 0·005 M) with MeI (2·4 g, 0·018 M) in benzene (40 ml) afforded the *trans*-ester (VII) 1·1 g, n_D^{22} 1·5160 (Found: C, 26·10; H, 4·86%). ^{1}H-NMR (60 MHz, benzene, TMS): δ_{CH_3} = 1·0 ppm, J_{H-CH_3} 6·9 Hz, J_{P-CH_3} 1·77 Hz, δ_{SeCH_3} = 1·99 ppm, J_{P-SeCH_3} 15·3 Hz. ^{31}P-NMR (benzene): δ = −14·0 ppm, $J_{P-Se''}$ 476·3 Hz.

Thermal isomerization of trans-VI *into* trans-VII. Distillation of ester *trans*-VI (4·58 g, 0·02 M) at 105–110°/0·2 mm, bath temperature 175°, afforded *trans*-VII, 4·12 g, n_D^{22} 1·5221 (Found: C, 27·11; H, 4·8; P, 13·63).

Hydrolysis of 2-*chloro*-4-*methyl*-1,3,2-*dioxaphosphorinan* (II). A mixture of H_2O (0·9 g, 0·05 M) and Et_3N (5·1 g, 0·054 M) in 5 ml THF was added dropwise at 0° to a stirred solution of chloride (II) (7·73 g, 0·05 M) in 50 ml benzene. After 1 hr Et_3N.HCl was filtered and solvent evaporated. The residue was distilled *in vacuo* to give phosphonate (VIII), 5·8 g, 85%, b.p. 94–97°/0·2 mm. After crystallization from benzene–ether *trans*-2-hydrogen-2-oxo-1,3,2-dioxaphosphorinan (VIII) was obtained, m.p. 55–58° (Found: C, 34·92; H, 7·04; P, 22·08. Calc. for $C_4H_9O_3P$: C, 35·30; H, 6·66; P, 22·72%). ^{1}H-NMR (100 MHz, $CDCl_3$, TMS): δ_{CH_3} = 1·43 ppm, J_{H-CH_3} 6·2 Hz, J_{P-CH_3} 1·8 Hz, δ_H = 6·89 ppm, J_{P-H} 667·3 Hz. ^{31}P-NMR (benzene): δ = −3·1 ppm.

The mother liquids contain a large amount of *cis*-2-hydrogen-2-oxo-4-methyl-1,3,2-dioxaphosphorinan (VIII). ^{1}H-NMR (100 MHz, $CDCl_3$, TMS): δ_{CH_3} = 1·45 ppm, J_{H-CH_3} 6·4 Hz, J_{P-CH_3} 1·4 Hz, δ_H = 6·96 ppm, J_{P-H} 713·2 Hz. ^{31}P-NMR (benzene): δ = +1·0 ppm.

Sulphur addition to trans-VIII. To phosphonate *trans*-VIII (1·36 g, 0·01 M) in benzene (10 ml) and ether (10 ml) dicyclohexylamine (1·8 g, 0·01 M) in ether (10 ml) and sulphur (0·32 g, 0·01 M) were added. The mixture was stirred for 4 hr. The precipitated salt *cis*-Ib was isolated, 3·2 g, 92%, m.p. 206–208°, from n-propanol-ether m.p. 208–211°.

Selenium addition to trans-VIII. A mixture of *trans*-VIII (1·7 g, 0·0125 M), dicyclohexylamine (2·26 g) and selenium (1·0 g) in benzene (25 ml) and ether (10 ml) was stirred at room temp for 3 days. *Cis*-Vb was filtered and purified by twice crystallization from n-propanol-ether, 3·2 g, 81%, m.p. 199–202° (Found: C, 48·52; H, 7·50; N, 3·32; P, 8·03%).

Sulphur addition to cis-VIII. The same procedure as described above yielded from *cis*-VIII (6·45 g,

0·074 M), dicyclohexylamine (8·6 g) and sulphur (1·52 g) in ether (50 ml) the salt *trans*-Ib, 4·4 g, 27%, m.p. 192–196°.

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