Assignment of cis-trans Geometry in Diastereomeric 2-Benzyl-4-methyl-1,3,2-dioxaphosphorinans and their 2-Oxo- and 2-Seleno-Derivatives

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2-X-2-Benzyl-4-methyl-1,3,2-dioxaphosphorinans, Synthesis, Spectral Characteristic, Configurations

Michaelis-Arbuzov reaction of diastereoisomeric 2-methoxy-4-methyl-1,3,2-dioxaphosphorinans with benzyl halides is non-stereospecific. Cis- and trans-2-benzyl-2-oxo-4-methyl-1,3,2-dioxaphosphorinans were separated and analysed by means of IR, 31P and 13C NMR spectroscopy. 2-Benzyl-2-seleno-4-methyl-1,3,2-dioxaphosphorinans were synthesized and stereospecifically converted to 2-oxo-analogues. Stereochemistries are assigned to the geometrical isomers of all new compounds described in this paper. Application of direct spin-spin coupling constant values for structural elucidation is emphasized.

Due to the lack of the proper model-compound until 1970 the stereochemistry of Arbuzov reaction was obscure. Resolution of enantiomeric isopropyl methylphosphinate and related compounds via stereospecific inclusion in cycloamyloses allowed to carry out the first successfull synthesis of optically active organophosphorus PIII compounds with at least one ester group attached to phosphorus moiety. Thus, optically active ethyl phenylphosphonate when treated with trimethylchlorosilane gave ethyl trimethylsilyl phenylphosphonite. Its alklylation with an excess of methyl iodide proceeds with high stereospecificity and with almost complete retention of the configuration at the P atom.

Similar conclusion was drawn by Bentrude and Hargis who used the only one geometric isomer of 2-methoxy-5-tert-butyl-1,3,2-dioxaphosphorinan for the investigation of the stereospecificity of Michaelis-Arbuzov reaction.

However, 2-methoxy-4-methyl-1,3,2-dioxaphosphorinans (I) which due to the presence of two centres of chirality at P and C-4 atoms can exist as cis- and trans-isomers, were found to react with alkyl halides in the non-stereospecific way. This observation was originally explained by Simpson as the result of the intermediacy of the product of α-addition of the alkyl halide to the starting phosphate, with the structure of trigonal bipyramid, which under experimental conditions undergoes pseudorotation or "permutational isomerisation" of the process being responsible for the loss of stereospecificity of the whole reaction.

In spite of Simpson's observation it was reported from this laboratory that under proper reaction conditions Arbuzov reaction of isomeric cis- and trans-I with elemental chlorine or bromine proceeds with full retention of configuration at the P atom.

Recently B. A. Arbuzov et al. have reported the results on stereospecificity of the reaction of I with methyl iodide. Both cis- and trans-2,4-dimethyl-2-oxo-1,3,2-dioxaphosphorinans (2) were prepared with full stereospecificity, but the temperature of reaction between 1 and methyl iodide was not allowed to arise above 50 °C. Catalytic amounts of methyl iodide were used for the initiation of the rearrangement of 1 into 2. Conformation of the resulting 2 was determined on the basis of dipole-moment data and IR spectroscopy.

Since independent studies on Michaelis-ArBusov and Michaelis-Becker reactions leading to
cis- and trans-2 were undertaken in this laboratory, we compared the results of mentioned studies with our structural determination of 2 based on 1H and 13C NMR spectroscopic analysis and especially, spin-spin coupling constants through one bond between 13C and 31P nuclei. Our conclusions concerning cis-trans geometry assignment of 2 are in full agreement with these drawn by Arbuzov.

However reaction of 1 with benzyl halides, which generally require more drastic conditions, proceeded in the non-stereospecific way. Even under more drastic conditions the yield of 2-benzyl-2-oxo-4-methyl-1,3,2-dioxaphosphorinans (3) was moderate and the product consisted of a mixture of both isomers with chemical shifts δ31P = -19 ppm and δ31P = -24.5 ppm, in the ratio close to equimolar.

The ratio of isomers of 3 was determined from integrated 31P and 1H NMR spectra and both isomers were identified by means of gas-chromatography-mass-spectrometry. The isomer with δ31P = -19.0 ppm was isolated from reaction mixture as crystalline substance m.p. 119-120 °C. Second isomer, δ31P = -24.5 ppm was isolated as a high-boiling oily liquid.

The same compounds were obtained in Michaelis-Becker reaction of both cis- and trans-2-hydro-2-oxo-4-methyl-1,3,2-dioxaphosphorinans (4) with benzyl iodide in the presence of equimolar amount of sodium hydride. The total yields were not higher than 64%, but depending upon the conditions, reactions were rather stereospecific. Thus starting from trans-4 the ratio of crystalline:liquid 3 was 90:10. Reverse ratio was obtained when cis-4 was reacted with benzyl iodide. Physical data of both isomeric 3 are collected in Table I and 13C NMR spectra are tabulated in Table II.

It is important to note that in 1H NMR spectra of both 3 the values of spin-spin coupling constants between phosphorus and protons of C-4 methyl group are the same (4Jₚ-H = 1.9 Hz) and suggest equatorial disposition of C-4 methyl groups in both isomers. The lower value of phosphoryl absorption in the IR spectrum of liquid isomer and lower absolute value of spin-spin coupling constant be-

Table I. Physical data of 2-oxo(3)- and 2-seleno(5)-2-benzyl-4-methyl-1,3,2-dioxaphosphorinans. 1H and 31P NMR spectra were recorded in CDCl₃ soln. except of 31P spectra of both 5, recorded in C6D₆ solution. IR spectra of both 3 were measured in benzene solution and those of 5 in KBr pellets.

<table>
<thead>
<tr>
<th>Compound</th>
<th>m.p. or b.p.</th>
<th>δ31P [ppm]</th>
<th>1JP-77Se [Hz]</th>
<th>4JP-H(CH₃-C₄) [Hz]</th>
<th>3JP-H [Hz]</th>
<th>rP = O or rP = Se [cm⁻¹]</th>
</tr>
</thead>
<tbody>
<tr>
<td>cis-3</td>
<td>82-84 °C/0.05 Torr</td>
<td>-0.5</td>
<td>1.9</td>
<td>22</td>
<td>1260</td>
<td></td>
</tr>
<tr>
<td>trans-3</td>
<td>119-120 °C</td>
<td>-15</td>
<td>1.9</td>
<td>20</td>
<td>1290</td>
<td></td>
</tr>
<tr>
<td>trans-6</td>
<td>75-78 °C/0.05 Torr</td>
<td>-15</td>
<td>-</td>
<td>7</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>cis-5</td>
<td>93-94 °C</td>
<td>-96.9</td>
<td>883</td>
<td>1.6</td>
<td>17</td>
<td>516</td>
</tr>
<tr>
<td>trans-5</td>
<td>107-108 °C</td>
<td>-92.0</td>
<td>909</td>
<td>1.0</td>
<td>15</td>
<td>524</td>
</tr>
</tbody>
</table>

Table II. 13C data of 2-oxo(3)- and 2-seleno(5)-2-benzyl-4-methyl-1,3,2-dioxaphosphorinans. Spectra of 3 were recorded in CDCl₃ soln., and 6 and 5 in C6D₆ soln. using TMS as an internal standard. Standard deviations of δ values ± 0.1 ppm and for coupling constants ± 1.5 Hz. For atom notations see Scheme I.

<table>
<thead>
<tr>
<th>Compound</th>
<th>C-7 [ppm]</th>
<th>C-5 [ppm]</th>
<th>C-6 [ppm]</th>
<th>C-4 [ppm]</th>
<th>CH₃ [ppm]</th>
<th>1JC-7-P [Hz]</th>
<th>3JC-5-P [Hz]</th>
<th>2JC-6-P [Hz]</th>
<th>2JC-4-P [Hz]</th>
<th>3JCH₃-P [Hz]</th>
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<tr>
<td>trans-3</td>
<td>32.4</td>
<td>33.4</td>
<td>66.4</td>
<td>75.5</td>
<td>29.7</td>
<td>128.0</td>
<td>7.4</td>
<td>5.9</td>
<td>5.9</td>
<td>6.5</td>
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<tr>
<td>cis-3</td>
<td>34.2</td>
<td>33.1</td>
<td>65.2</td>
<td>73.5</td>
<td>22.1</td>
<td>138.3</td>
<td>4.4</td>
<td>7.4</td>
<td>7.4</td>
<td>7.4</td>
</tr>
<tr>
<td>trans-6</td>
<td>36.4</td>
<td>36.2</td>
<td>61.0</td>
<td>66.9</td>
<td>23.3</td>
<td>45.6</td>
<td>4.4</td>
<td>4.4</td>
<td>1.9</td>
<td>7.4</td>
</tr>
<tr>
<td>trans-5</td>
<td>45.5</td>
<td>32.8</td>
<td>64.8</td>
<td>75.6</td>
<td>22.3</td>
<td>78.0</td>
<td>8.8</td>
<td>8.8</td>
<td>10.3</td>
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<td>cis-5</td>
<td>46.3</td>
<td>34.8</td>
<td>63.8</td>
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<td>85.3</td>
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between benzyl carbon and phosphorus atoms in $^{13}$C NMR spectrum of crystalline compound as compared to that of liquid one allowed us to determine trans-geometry for the crystalline-3 and cis-geometry for the liquid-3.

Because the relationship between absolute value of $J_{P-X}$ and spatial orientation of aliphatic substituents has been checked on one above described case of pair of 2, it was necessary to carry out the additional experiments which would give another set of data on the validity of observed dependence

$1^1J_{P-X_{ax}} < 1^1J_{P-X_{eq}}$.

Thus we decided to synthesize both the 2-benzyl-2-seleno-4-methyl-1,3,2-dioxaphosphorinans (5) and to elucidate their geometries on independent way. Chemical correlation between corresponding isomers of 3 and 5 would offer an additional proof for correctness of cis-trans geometry assignments in family of 2-chalcogen-2-benzyl-4-methyl-1,3,2-dioxaphosphorinans. Reaction of benzyl dichlorophosphine and butandiol-1,3 in the presence of triethylamine gave only trans-2-benzyl-4-methyl-1,3,2-dioxaphosphorinan (6) (only one peak in gelpc and signal in $^{31}$P NMR spectrum at $\delta_{31P} = -159$ ppm were observed). It was assumed that benzyl group, like other alkyl substituents, prefers to occupy an axial position. Spectral characteristic included in Table II supports this determination. Of special value is spin-coupling between phosphorus and carbon-5 (4.4 Hz). It is known that this coupling strongly depends on orientation of the lone pair at phosphorus and for cis-isomer $^3J_{P-CS}$ was expected to be of order of 10 Hz. Oxidation of 6 with tert-butylhydroperoxide was non-stereospecific (see Scheme I - route a). However, addition of elemental selenium to distilled 6 (the process which is known to proceed with retention of configuration) gave a mixture of two isomers 5 with $\delta_{31P} = -92.0$ ppm and $\delta_{31P} = -97.0$ ppm in the ratio 90:10 respectively.

The isomers 5 were separated by column chromatography on Silica-gel (50-100 mesh). Physical and spectroscopic data of both pure 5 are included in Table I and II. In agreement with our expectations, the order of absolute values of spin-spin coupling constants between phosphorus and carbon-13 and phosphorus and selenium-77 for the pair of diastereomeric compounds agrees with relationship $1^1J_{P-X_{ax}} < 1^1J_{P-X_{eq}}$; $X = ^{77}$Se, $^{13}$C. This allowed us to assign the configuration around the phosphorus atom of preponderant isomer of 5 as trans and the minor one as cis. Such determination is also consistent with the established empirical rule, that stretching frequencies of equatorial substituents are higher than those of their axial analogues.

Both cis- and trans-5 were converted to 2-oxoderivatives 3 using hydrogen peroxide as the oxidizing agent. It was found in this laboratory that conversion $P=S e \rightarrow P=O$, when P atom is involved in dioxaphosphorinanyl ring system is fully stereospecific and proceeds with retention of configuration.

\[ \begin{align*}
\text{trans-5} & \rightarrow \text{cis-5} \\
\text{trans-3} & \rightarrow \text{cis-3}
\end{align*} \]

Scheme I. From route (a): trans-3 (67\%_0) + cis-3 (33\%_0). Addition of selenium to 6 gave 90\%_0 of trans-5 and 10\%_0 cis-5.

As it is shown in Scheme I trans-5 after treatment with $H_2O_2$ gave exclusively trans-3. On the same way cis-5 was converted into cis-3. It is worthwhile to mention, that $^{31}$P chemical shift values for the cis-isomers are lower than those for the trans-isomers. Although few expections were noticed, in certain families of compounds chemical shift order can be used as tentative criterium of cis-trans geo-

* In the light of our recent X-ray structure determination of diastereoisomeric 2-tert-butylamino-2-seleno-
4-methyl-1,3,2-dioxaphosphorinans this regularity when $X = \text{selenium-77}$ seems to be well documented.

We believe, that in conformationally non-labile compounds the structure in solid state and in solution in the non-polar solvent is nearly the same.

T. Bartczak, A. Christensen, R. Kinas, and W. J. Stec, manuscript in preparation.
metry of diastereomeric pairs of phosphorus heterocycles.

Inspection of the Table II shows the difference between $^{13}$C NMR spectra in both diastereoisomeric pairs of 3 and 5. As earlier noticed by Borisenko et al.\textsuperscript{18}, vicinal coupling constants are of special interest due to their applicability to conformational studies of 2-oxo-1,3,2-dioxaphosphorinanyl derivatives. However, conclusions should be drawn very carefully, because the order of changes in values of $^3J_{P-C_5}$ and $^3J_{P-CH_3}$ when going from cis- to trans-isomer does not depend only on the dihedral angle but also on the chemical surrounding of the phosphorus nucleus. In the case of 2-hydro-2-oxo-4-methyl-1,3,2-dioxaphosphorinans trans-isomer (equatorial both 2-oxygen and 4-methyl) $^3J_{P-C_5}$ has lower value (6.1 Hz) than that of cis-one (9.9 Hz)\textsuperscript{18}, when opposite situation exists in the pair of 2\textsuperscript{8}, 3 and 5 (Table II). Detailed discussion of $^{13}$C NMR spectra of the family of 4-methyl-1,3,2-dioxaphosphorinans will be published separately.

Although we were not able to perform of full conformational analysis of both pairs of 3 and 5 due to the complexity of their $^1$H NMR spectra, the determination of cis-trans geometry within those two pairs seems to be unambiguous. However, in the case of trans-5 the chair-chair equilibrium in chloroform solution has to be considered due to the value of $^3J_{PCC(CH)}$ (1 Hz suggests axial orientation of C4-methyl)\textsuperscript{19} and lower than the average value of $^3J_{PCCCH}$ (2.8 Hz)$^{11}$.

Experimental

All m.ps and b.ps are uncorrected, solvents and commercial reagents were distilled and dried by conventional methods before use. $^1$H NMR spectra were recorded at 60 MHz with a Jeol C-60H spectrometer, equipped with Hetero-Spin-Decoupler JNH-SD-HC, with TMS as an internal standard. $^{31}$P NMR spectra were obtained on the same instrument operating at 24.3 MHz with external $H_3PO_4$ or (PhO)$_2$P as the reference. Negative chemical shift values are reported for compounds absorbing at lower fields than $H_3PO_4$. $^{13}$C NMR measurements were recorded on a Bruker-HX72 spectrometer using TMS as an internal standard. Mass spectra were obtained on a LKB-9000S spectrometer at 70 eV ionizing energy. cis- and trans-2-methoxy-4-methyl-1,3,2-dioxaphosphorinans were synthesized according to MIKOLAJCZYK,\textsuperscript{20} trans- and cis-2-hydro-2-oxo-4-methyl-1,3,2-dioxaphosphorinans were obtained by NIFANTIEV method\textsuperscript{21}.

1. Reaction of trans-2-methoxy-4-methyl-1,3,2-dioxaphosphorinan (1) with benzyl chloride. Trans- and cis-2-benzyl-2-oxo-4-methyl-1,3,2-dioxaphosphorinans (3)

The equimolar amounts (0.066 M) of 4 and benzyl chloride were heated together for 8 hours on the oil bath at 170 °C. Evaporation of volatile materials left an oil, which solidified upon standing in refrigerator. n-Pentane was added and crystals were filtered off (3.6 g) and recrystallized from ethyl acetate, m.p. 119–120 °C; $^3J_{P(CH)}(CHCl_3) = -19$ ppm. Mass spectrum (direct inlet): Mol.ion 226 (26%); base peak 91; main peaks: 55, 91, 129, 135, 144, 172.

Elemental analysis: C$_{11}$H$_{13}$O$_3$P

Calcd C 58.4 H 6.6 P 13.7; Found C 58.8 H 7.0 P 13.4.

($^1$H NMR, $^{13}$C NMR and IR data see Table I and II) Compound was identified as trans-3.

Evaporation of solvent from the filtrate and examination of raw material (12.2 g) using $^{31}$P NMR and GCMS techniques had shown the presence of the following compounds:

1) $^3J_{P(CH)} = -19.0$ ppm (12%) – identical with trans-3.
2) $^3J_{P(CH)} = -23.0$ ppm (68%); Mol.ion 226 (20%); base peak 91; main peaks: 55, 91, 129, 135, 144, 172, 211; identified as cis-3.
3) $^3J_{P(CH)} = -28.0$ ppm (20%); Mol.ion 150 (3.4%); base peak 54; main peaks: 135, 123, 97, 79, 57, 47, 43; identified as 2,4-dimethyl-2-oxo-1,3,2-dioxaphosphorinan (2).

Distillation of the mixture allowed the separation of fraction b.p. 82–84 °C/0.05, which contained 92% of cis-3 and 8% trans-3.

2. Preparation of cis- and trans-2-benzyl-2-oxo-4-methyl-1,3,2-dioxaphosphorinans (3) (Michaelis–Becker procedure)

To the solution of trans-2-hydro-2-oxo-4-methyl-1,3,2-dioxaphosphorinan (0.1 M) in benzene (100 ml) sodium hydride (0.1 M) was added portionwise at temperature below 35 °C.

When evolution of hydrogen ceased, the solution of benzyl chloride (0.1 M) in benzene (30 ml) was added dropwise at room temperature and stirring was continued for 3 hours. Water (25 ml) was added and precipitated crystals were filtered off (5.2 g, m.p. 112–113 °C). Filtrate was washed with 5% HCl, 5% NaHCO$_3$ soln. and water and dried over anhydrous MgSO$_4$. Removal of solvent left an oil which solidified upon standing in refrigerator. Second crop of crystals was filtered off and combined with first fraction. Recrystallization from ethyl acetate gave trans-3, m.p. 119–120 °C, analytical data as described under 1). The yield of trans-3 42%.

Oily residue was distilled under reduced pressure and fraction with 96–98 °C/0.1 (4 g) was collected.
$^{31}$P NMR spectrum has shown the presence of cis-3 (86%) and trans-3 (14%). Total yield of both cis- and trans-3 was 64%.


To the solution of trans-2-hydro-2-oxo-4-methyl-1,3,2-dioxaphosphorinan (4) (13.6 g, 0.1 M) and benzyl iodide (21.8 g, 0.1 M) in dioxane (150 ml) 0.1 M of sodium hydride was added portionwise at temperature below 35 °C. Stirring was continued for 3 hours. Precipitated sodium iodide was filtered off, solvent evaporated and residue was diluted with chloroform. The solution was washed with 5% HC1, 5% NaHCO3 soln. and dried over anhydrous MgSO4.

Evaporation of solvent gave oily residue which partly solidified after standing in refrigerator. This residue consisted the mixture of both isomers of 3 in the ratio cis-3 to trans-3 = 10:90 (examined by means of $^{31}$P NMR). The total yield of both 3 was 45%. In the same manner starting from cis-2-hydro-2-oxo-4-methyl-1,3,2-dioxaphosphorinan (4) the mixture of isomers of 3 in the ratio cis-3 to trans-3 79:21 was obtained (the yield of both isomers 30%).

4. Synthesis of trans-2-benzyl-4-methyl-1,3,2-dioxaphosphorinan (6)

To the solution of benzyldichlorophosphine (12) (δ$_{31}$P = —180 ppm, 0.1 M, 19.3 g) in benzene (150 ml) the mixture of triethylamine (0.2 M, 20.2 g) and butandiol-1,3 (0.1 M, 9.0 g) was added at temperature below —10 °C. Stirring was continued for half an hour at room temperature. Triethylamine hydrochloride was filtered off and benzene was removed from the filtrate.

The crude product was distilled under reduced pressure, b.p. 75—78°/0.05. The yield 10.0 g (50%); m.p. 107—108 °C. The yield of 6 was 64%.

Fraction I.

m.p. 93—94 °C (1.0 g); δ$_{31}$P = —96.9 ppm.

Mass spectrum: Mol.ion 290 (17%); base peak 91; main peaks: 55, 77, 91, 119, 135, 172, 209, 236.

Elemental analysis for C$_7$H$_5$O$_2$PSe
Calcd C 54.7 H 4.2 P 10.7.
Found C 54.2 H 4.0 P 10.0.

Identified as cis-5.

Fraction II.

m.p. 107—108 °C (3.5 g); δ$_{31}$P = —92.0 ppm.


Elemental analysis for C$_7$H$_5$O$_2$PSe
Calcd C 54.7 H 4.2 P 10.7.
Found C 54.2 H 4.0 P 10.0.

Identified as trans-5.

6. Reaction of cis- and trans-2-benzyl-2-seleno-4-methyl-1,3,2-dioxaphosphorinans (5) with hydrogen peroxide

Hydrogen peroxide (1 ml of 30% H$_2$O soln.) was dropped to the acetone solution of cis- or trans-5 (0.5 g, 0.005 M, respectively). Immediate precipitation of elemental selenium was observed. Selenium was filtered off (yield 100%), acetone evaporated and residue solved in CHCl$_3$. Examination by means of $^{31}$P NMR has shown that from trans-5 exclusively trans-3 and from cis-5 only cis-3 were obtained.

7. Oxidation of trans-2-benzyl-4-methyl-1,3,2-dioxaphosphorinan (6) with tert-butylhydroperoxide tert-Butylhydroperoxide (0.5 g, 0.0055 M) was dropped into the solution of trans-2-benzyl-1,3,2-dioxaphosphorinan (6) (1.0 g, 0.005 M) in benzene (10 ml). Solvents were evaporated and residue was examined by $^{31}$P NMR. Product consisted the mixture of cis- and trans-3 in ratio 33:67 respectively.

Authors are indebted to Prof. J. Michalski for his interest in this work.

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