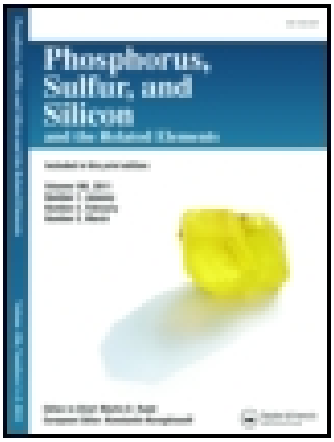

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SYNTHESIS OF 1,3,2-OXAZAPHOSPHOLIIN-4-ONES

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SYNTHESIS OF 1,3,2-OXAZAPHOSPHOLIDIN-4-ONES

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The subject of this paper is the preparation of 1,3,2-oxazaphospholidin-4-ones by reaction of phenyldichlorophosphine with the N-methyl amides of α-hydroxy isobutyric acid and the two chiral carboxylic acids (S) lactic acid and (R,S) mandelic acid, which leads to diastereomeric products. Reaction control by means of ^{31}P n.m.r. demonstrates two surprising findings: the preferred generation of the thermodynamically less stable *cis*-isomer and an epimerization of the phosphorus chirality centre at room temperature.

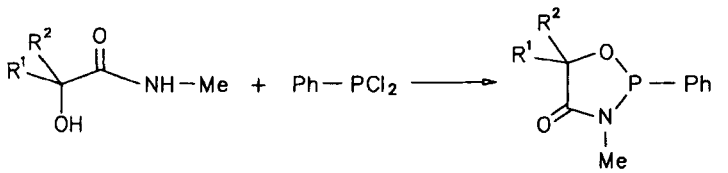
Key words: 1,3,2-oxazaphospholidin-4-one, n.m.r. spectra, phosphorus inversion.

INTRODUCTION

In our studies about pentaco-ordinated phosphoranes,[1] we synthesized spirophosphoranes by Staudinger reaction[2] of cyclic tervalent phosphorus compounds with α- and β-hydroxy carboxylic acid azides. Continuing our research[3] we were interested in distinct derivatives of 1,3,2-oxazaphospholidin-4-one with phosphorus and nitrogen bearing phenyl and methyl substituents respectively. Compounds of that type were not reported in the literature although some procedures describing the preparation of analogous compounds were helpful.[4,5]

RESULTS

The compounds **1**, **2** and **3** were derived as shown in Scheme I by reaction of phenyldichlorophosphine with the appropriate α-hydroxy carboxylic acid amide us-



SCHEME I Synthesis of **1**, **2** and **3**, refluxing one hour in toluene/pyridine. **1** $R^1 = R^2 = CH_3$; **2** R^1 = H, $R^2 = CH_3$; **3** R^1 = H, R^2 = Ph.

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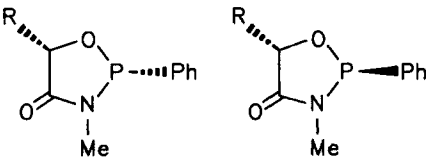
TABLE I

1,3,2-Oxazaphospholidin-4-ones **2** and **3**: *cis/trans* ratio, ^{31}P n.m.r. data and ^{1}H n.m.r. data δ (J_{PH}) of the ring proton



	cis	trans
2 (R = CH_3)	20%	80%
^{31}P-NMR	153.9	145.7
^{1}H-NMR	4.57 (12)	4.54 (0.7)
3 (R = Ph)	15%	85%
^{31}P-NMR	155.8	149.2
^{1}H-NMR	5.51 (10)	5.49(0)

ing toluene as a solvent and pyridine as a base. Purification by Kugelrohr distillation leads to viscid liquids **1** and **2** and a semisolid **3**, respectively. The structures are proved by ^{1}H and ^{13}C n.m.r. (both also ^{31}P-decoupled) and by ^{31}P n.m.r.

The 1,3,2-oxazaphospholidin-4-one **1** is derived from α-hydroxy isobutyric acid N-methyl amide and is represented by two enantiomeres with regard to high inversion barrier of pyramidal phosphorus. Consequently two diastereomeric products are obtained using the N-methyl amides of (S) lactic acid and (R,S) mandelic acid (yielding **2** and **3** respectively) due to the additional centre of chirality. Decisive are the relative orientation of the P-phenyl group and the substituent at the former α-carbon of the amide. After distillation the relative amounts of *cis:trans* isomers are 1:4 for **2** and about 1:5 for **3**. The assignment of the configuration succeeds in comparing the magnitude of the three-bond coupling constant between phosphorus and hydrogen located at C(5): In five-membered heterocycles containing trico-ordinate phosphorus, the $^{3}J_{PH}$ is different for hydrogen atoms *cis* and *trans* relative to the phosphorus lone pair.[6] Consequently the smaller $^{3}J_{PH}$ value belongs to the trans-isomers which are thermodynamically more stable presumably because of less sterical hindrance (Table I).

DISCUSSION

The 1,3,2-oxazaphospholidin-4-ones **2** and **3** are obtained as mixtures of diastereomers, the relative amount is fixed after refluxing the reaction mixture and remains

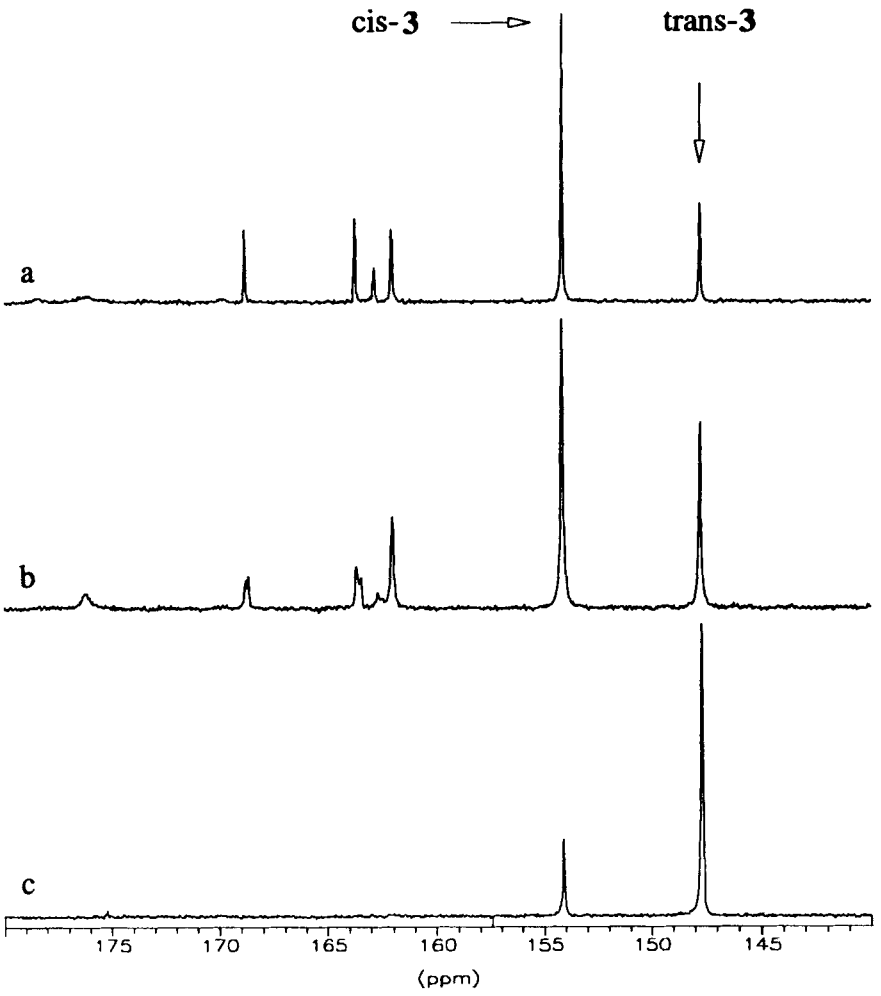


FIGURE 1 Synthesis of **3**: part of ^{31}P-n.m.r. spectra of the reaction mixture after (a) 1.5 hours at −5°C, (b) additional 1.5 hours at 20°C and (c) after refluxing.

unchanged after distillation. Checking the reaction progress of the (R,S) mandelic derivative **3** (the same is true for **2**) by means of ^{31}P n.m.r. brings about a change in the ratio of diastereomers (Figure 1). The first spectra, obtained after allowing the educts to react for 1.5 hours at −5°C, show that the reaction to the thermodynamic less stable *cis*-**3** (δ = 154) was preferred to that of *trans*-**3** (δ = 148). ^{13}C n.m.r. spectra of the reaction mixture gave evidence for this finding. As implied by the second set of spectra the *cis:trans* ratio had changed after stirring the reaction mixture at 20°C for 1.5 hours. The final ratio of diastereomers was achieved after refluxing (spectra (b) in Figure 1).

This sequence of ^{31}P n.m.r. spectra permits two interesting conclusions: First of all a preference for the formation of the *cis*-isomer is a surprising finding for which we have no mechanistic explanation. The same applies to the isomerization at room temperature with respect to the high inversion barriers reported in literature for ter-

valent phosphorus compounds of this type.[6] Owing to difficulties in their separation, it has, until now, not been possible to observe the isomerization of pure diastereomers, therefore no statement about their inversion barriers can be given.

EXPERIMENTAL

^1H n.m.r. and ^{13}C n.m.r. spectra, which were also recorded ^{31}P decoupled, were obtained at 30°C in $CDCl_3$ on a Bruker AM 300 spectrometer with the solvent signals as an internal reference. $^{31}P\{^1H\}$ data is given relative to external 85% H_3PO_4 with positive chemical shifts at low field. EI- and CI-mass spectra were recorded on a Varian MAT 44S spectrometer, while HRMS were measured on a Finnigan MAT 95. Elemental analyses were performed at the Microanalytical Laboratory of the Institute for Physical Chemistry, University of Vienna, Austria.

By reaction of the appropriate ester with methyl amine in a closed vessel and toluene as solvent the N-methyl amides of the following carboxylic acids were obtained: α-hydroxy isobutyric acid (18 hours in an autoclave at 100°C): m.p. 78°C (acetone), (S) lactic acid (18 hours at 20°C): colourless oil after Kugelrohr distillation, (R,S) mandelic acid (18 hours at 20°C): m.p. 96°C (toluene).

Phenyldichorophosphine (FLUKA prakt.) was used without purification. Solvents were dried using standard techniques.

Compounds **1**, **2** and **3** were obtained by the following general procedure; reaction, work-up and distillation must be carried out under an inert atmosphere: To a stirred solution of 3.5 ml (25.6 mmol) of $PhPCl_2$ in 50 ml of toluene a solution of one equivalent of the appropriate N-methyl amide in pyridine (3 ml) was added dropwise at room temperature. After refluxing the mixture for one hour the white precipitate of pyridinium hydrochloride was filtered and the solvent removed under reduced pressure. The residue was distilled (**1** and **2**) or Kugelrohr distilled (**3**). Yields vary from 70 to 80%.

3,5,5-Trimethyl-2-phenyl-1,3,2-oxazaphospholidin-4-one (**1**): boiling point: 85–90°C/0.01 mbar, colourless oil; $^{31}P\{^1H\}$ n.m.r.: 146.0; ^1H n.m.r.: 7.58–7.42 (m, ArH), 2.88 (d, J_{PH} 7, N—CH_3), 1.50 and 1.38 (s, C(5)—CH_3); $^{13}C\{^1H\}$ n.m.r: 176.75 (d, J_{PC} 3, C(4)), 141.11 (d, J_{PC} 50, Ph ipso C), 131.86 (s, Ph), 130.21 (d, J_{PC} 25, Ph), 128.78 (d, J_{PC} 6, Ph), 82.39 (d, J_{PC} 10, C(5)), 27.65 (d, J_{PC} 3, N—CH_3), 26.37 (d, J_{PC} 2, 2 × C(5)—$\underline{C}H_3$); mass spectra (CI with isobutane): m/z 224 (M+1); HREI-MS: molecular formula $C_{11}H_{14}NO_2P$, m/z 223.0762 (calculated), 223.0759 (measurement); Analysis: Found C 58.70, H 6.17, N 6.25, P 13.90. Calculated for $C_{11}H_{14}NO_2P$ (223.21): C 59.19, H 6.32, N 6.28, P 13.88.

3,5-Dimethyl-2-phenyl-1,3,2-oxazaphospholidin-4-one (**2**): boiling point: 85–90°C/0.01 mbar, colourless oil; mass spectra (CI with isobutane): m/z 210 (M+1); HREI-MS: molecular formula $C_{10}H_{12}NO_2P$, m/z 209.0605 (calculated), 209.0600 (measurement); Analysis: Found C 57.08, H 5.83, N 6.70, P 14.78. Calculated for $C_{10}H_{12}NO_2P$ (209.18): C 57.42, H 5.78, N 6.70, P 14.81.

cis-**2** (20%): $^{31}P\{^1H\}$ n.m.r.: 153.0; ^1H n.m.r.: 7.51–7.38 (m, ArH), 4.57 (d, J_{PH} 12, J_{HH} 7, C(5)H, 2.79 (d, J_{PH} 7, N—CH_3), 1.35 (d, J_{HH} 7, C(5)—CH); $^{13}C\{^1H\}$ n.m.r.: 174.31 (d, J_{PC} 4, C(4)), 141.21 (d, J_{PC} 49, Ph ipso C), 132.07 (s, Ph), 130.25 (d, J_{PC} 26, Ph), 128.78 (d, J_{PC} 7, Ph), 75.84 8 (d, J_{PC} 9, C(5), 26.0 (d, J_{PC} 14, N—CH_3), 19.70 (d, J_{PC} 2, C(5)—$\underline{C}H_3$).

trans-**2** (80%): $^{31}P\{^1H\}$ n.m.r.: 145.7; ^1H n.m.r.: 7.51–7.38 (m, ArH), 4.54 (dd, J_{PH} 0.7, J_{HH} 7, C(5)H), 2.85 (d, J_{PH} 8, N—CH_3), 1.44 (d, J_{HH} 7, C(5)—CH); $^{13}C\{^1H\}$ n.m.r.: 175.41 (s, C(4)), 138.89 (d, J_{PC} 46, Ph ipso C), 131.75 (s, Ph), 129.88 (d, J_{PC} 25, Ph), 128.8 (d, J_{PC} 7, Ph), 73.84 (d, J_{PC} 8, C(5), 26.26 (d, J_{PC} 15, N—CH_3), 18.39 (d, J_{PC} 4, C(5)—$\underline{C}H_3$).

3-Methyl-2,5-diphenyl-1,3,2-oxazaphospholidin-4-one (**3**): temperature of Kugelrohr distillation: 190°C/0.01 mbar; mass spectra (EI): m/z 271; HREI-MS: molecular formula $C_{15}H_{14}NO_2P$, m/z 271.0762 (calculated), 271.0759 (measurement); Analysis: Found: C 65.84, H 5.22, N 5.32, P 11.27. Calculated for $C_{15}H_{14}NO_2P$ (271.25): C 66.42, H 5.20, N 5.16, P 11.42.

cis-**3**: $^{31}P\{^1H\}$ n.m.r.: 155.8; ^1H n.m.r.: 7.6–7.2 (m, ArH), 5.51 (d, J_{PH} 10, C(5)H), 2.82 (d, J_{PH} 8, N—CH_3); $^{13}C\{^1H\}$ n.m.r.: 171.78 (d, J_{PC} 4, C(4)), 140.07 (d, J_{PC} 49, P—Ph ipso C), 137.61 (s, C—Ph ipso C), 132.35 (s, P—Ph), 131.07 (d, J_{PC} 27, P—Ph), 128.93 (d, J_{PC} 6, P—Ph), 128.03 (s, Ph—C), 127.83 (s, Ph—C), 125.69 (s, Ph—C), 79.02 (d, J_{PC} 10, C(5)), 26.34 (d, J_{PC} 14, N—CH_3).

trans-**3**: $^{31}P\{^1H\}$ n.m.r.: 149.2; ^1H n.m.r.: 7.6–7.2 (m, ArH), 5.49 (s, C(5)H), 2.89 (d, J_{PH} 8, N—CH_3); $^{13}C\{^1H\}$ n.m.r.: 173.23 (s, (d, C(4)), 139.88 (d, J_{PC} 46, P—Ph ipso C), 136.11 (d, J_{PC} 5, C—Ph ipso C), 132.07 (s, P—Ph), 130.03 (d, J_{PC} 25, P—Ph), 128.57 (s, Ph—C), 128.50 (d, J_{PC} 3, P—Ph), 128.37 (s, Ph—C), 126.60 (s, Ph—C), 78.82 (d, J_{PC} 9, C(5)), 26.09 (d, J_{PC} 15, N—CH_3)

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