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STEREOCHEMISTRY OF 1,2-OXAPHOSPHOLANES—I

SYNTHESIS, ^1H AND ^{13}C NMR STUDIES AND EQUILIBRATION OF DIASTEREOMERIC 2-METHOXY-2-OXO-3,5,5-TRIMETHYL-1,2-OXAPHOSPHOLAN-3-OLS

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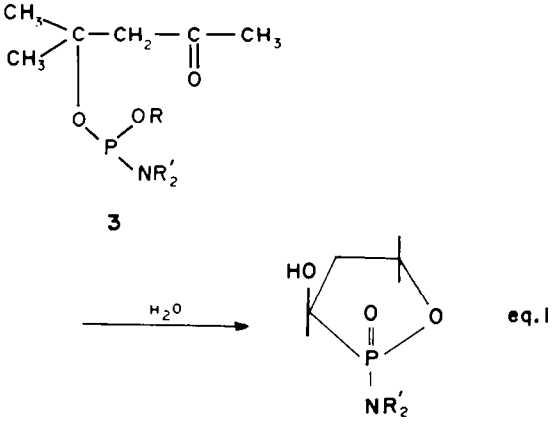
Abstract—Both diasteromers **1A** and **1B** of the title compound were obtained for the first time, as well as the ring-opened product **6**. Pure **1A** and **1B** were equilibrated in the presence of sodium methoxide in methanol to give 45:55 mixture of **1A** and **1B**. The same mixture was produced from **6** with either MeONa/MeOH or HCl/MeOH solutions. Triethylamine-catalyzed cyclisation of **6** led to a 15:85 mixture of **1A** and **1B**. The cis relationship of the OH and P=O groups in **1A** and **7A** was established by ^1H and ^{13}CNMR spectra. Predominant conformations of **1A** and **1B** and their derivatives were deduced from $^3J_{HCCP}$ and $^3J_{CCOP}$ coupling constants. A possible mechanism of the transformations described in the paper is discussed.

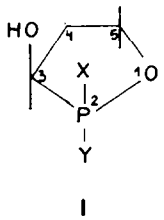
Saturated and α,β-unsaturated γ-lactones have been widely investigated for years[1] mostly due to their occurrence in Nature and significant biological activity. On the other hand simple lactones have been used as building blocks for the synthesis of many natural products. In this area syntheses of enantiomerically pure γ-hydroxymethyl-γ-butyrolactones are the most spectacular.[2]

It is generally agreed, that modification of the chemical structure has been a principal method for the studies on the chemical structure-biological activity relationship. In particular, it includes synthesis and biological evaluation of heteroanalogues of model carbon-compounds. Extending our previous interest in stereochemistry of γ-butenolides[3] we have turned to 1,2-oxaphospholane derivatives which could be considered as P-analogues of γ-lactones. It was anticipated that the synthetic strategy for the preparation of these compounds would be based on chiral building blocks derived from the naturally occuring products which would be used as a starting material. A number of methods for the synthesis of 1,2-oxaphospholane system have been reported.[4] However, the majority of them suffer several drawbacks considering the aim of our projects. For this reason our attention was focused on the reaction developed by Mukhametov and Rizpolozhenskii[4a] which showed that amino-phosphites **3** are readily cyclised to form 1,2-oxaphospholane ring (eqn 1).



eq. 1

The synthesis of 2-methoxy-2-oxo-3,5,5-trimethyl-1,2-oxaphospholan-3-ol (**1**), which was chosen as a model compound for studies on static and dynamic stereochemistry of the 1,2-oxaphospholan-3-ol system, was proposed to be accomplished by appropriate modification of the above pathway. It is noteworthy that previous syntheses[5-7] of **1** resulted in isolation of single diastereomer of m.p. 126–8°. By the comparison of the IR data taken for the series of analogues it was shown that this isomer had the cis configuration of the P=O and OH groups.[5,8]



X = O, OCH_3

Y = OCH_3, O

1

Here, we would like to present the syntheses of both diastereomers of **1** and the ring-opened phosphonate **6**, as well as to discuss stereochemistry of these compounds, their equilibration and finally to make some comments on the possible mechanism of the described transformations.

RESULTS

Our approach to the synthesis of **1** involved condensation of **2** with dimethyl phosphorochloridite (**4**) in the presence of triethylamine to give dimethyl (1,1-dimethyl-3-oxobutyl) phosphite (**5**) and subsequent hydrolysis of **5** with the equivalent amount of water (Scheme 1).

When the phosphite **5** was subjected to hydrolysis a very strong increase of temperature was observed. The ^{31}P NMR spectrum of the crude reaction mixture revealed the presence of three signals at δ42.3, 40.4 and 28.4 ppm in the ratio of 3:1:6, respectively, and the signal at δ135.3 characteristic of phosphites[9a] was not found. Numerous attempts at hydrolysis of **5** always afforded the same mixture consisting of three components but the relative ratios of them changed from 3:1:6 to 5:2:3 depending on the reaction conditions.

However, in all experiments the relative ratios of the cyclic products[4a,10] **1A** and **1B** fluctuated between 7:3 and 6:4.

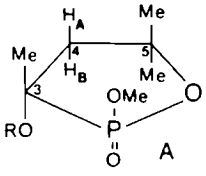
The crude reaction mixture was subjected to column chromatography on silica gel and all three pure components were isolated and studied by the spectroscopic methods. Faster moving compound was identified as **1A** (δ_{31P} 42.3 ppm) based on its melting point (127.5 – 128°)[5] and the ^1H and ^{13}C NMR data (see Discussion). For the second crystalline material (m.p. 63.5 – 64°) structure **1B** (δ_{31P} 40.4 ppm) was deduced because the ^1H and ^{13}C spectra (Tables 1 and 2) of this compound and of **1A** were similar and the chemical shifts in the ^{31}P NMR spectra were very close together. On the other hand, the ^{31}P NMR chemical shift of a colorless oil (δ_{31P} 28.0 ppm) suggested the ring-opened structure for **6**.[9b] Furthermore, the manifestation of diastereotopic methoxy groups on the P atom in its ^1H NMR spectrum with integration twice of that found for **1A**, and the presence of two signals of the methyl carbons coupled to phosphorus (CH_3O–P) in ^{13}C NMR spectrum supported this assignment.

Further evidence for these structural assignments could be obtained from the studies on transformations of **6** and equilibrations of pure diastereomers **1A** and **1B**. First of all, intramolecular transesterification of **6** was attempted in order to obtain 1,2-oxaphospholane ring. For such transformations basic catalysts, e.g. tertiary amines or alkoxides were commonly used.[11] Indeed, when a solution of **6** in methanol was treated with 10 mol% sodium methoxide in methanol, the mixture of **1A** and **1B** in the ratio of 45:55 was formed immediately and almost quantitatively, as judged from the ^{31}P NMR spectra. This reaction provides a very efficient entry to the synthesis of 1,2-oxaphospholan-3-ol system (Scheme 1). Also, triethylamine effectively catalysed cyclisation of **6**. The progress of the reaction was monitored by ^{31}P NMR spectroscopy. Under these conditions almost 20 h were required for the ^{31}P NMR signal of **6** to disappear. Furthermore, the ratio **1A**:**1B** was found to be 15:85, and was constant throughout the observation time. Surprisingly, the cyclisation of **6** could also be accomplished with 3% methanolic hydrogen chloride. The progress of the reaction was again monitored by ^{31}P NMR. It took almost 3 months to achieve the complete conversion of **6** into the mixture of **1A** and **1B** in the ratio of 45:55, as for methoxide-catalysed cyclisation.

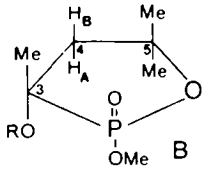
Equilibration of pure diastereomers **1A** and **1B** was also studied by ^{31}P NMR. As for **1A**, when **1B** was treated with 10 mol% solution of sodium methoxide in methanol, it afforded the 45:55 mixture of **1A** and **1B** within 1 h. In contrast to facile cyclisation of **6** in the presence of triethylamine, neither **1A** nor **1B** underwent the equilibration under these conditions.

Methyl ethers of **1A** and **1B** were prepared in order to study the mechanism of the equilibration of 1,2-oxaphospholane system. Thus, pure **1A** was allowed to react with the Purdie reagent[12] for 24 h at room temperature. Unfortunately, the examination of the crude reaction mixture by ^{31}P NMR revealed the presence of 7 organophosphorus components. Diastereomeric methyl ethers **7A** and **7B**, unreacted **1A**, but also **1B** were detected. Numerous attempts at separation of this mixture were conducted but only one diastereomeric methyl ether was obtained for which structure **7A** (Scheme 2) was ascertained (see Discussion).

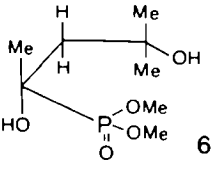
Table 1. ^1H NMR data for 1,2-oxaphospholanes



A



B



6

R	Solvent	Compd	CH_3-C_3-P		CH_3-C_5-O		CH_3-O-P		H_B			H_A		R
			δ	^3J	δ	δ	δ	^3J	δ	J_{BP}	J_{AB}	δ	J_{AP}	δ
H	$CDCl_3$	1A	1.50	15.1	1.39	1.56	3.81	10.6	1.99	1.2	14.1	2.22	25.7	-
		1B	1.60	15.6	1.45	1.51	3.88	10.3	2.15	6.3	14.1	2.24	21.3	-
		6	1.51	15.8	1.35	1.38	3.86 3.79	10.0 10.3	1.77	17.3	15.0	2.19	19.3	-
H	C_6D_6	1A	1.54	15.4	1.08	1.53	3.39	10.3	1.65	0.9	13.8	1.95	26.5	-
		1B	1.68	15.4	1.18	1.39	3.73	10.4	1.88	7.1	13.8	2.06	20.6	-
Me	$CDCl_3$	7A	1.48	15.2	1.37	1.51	3.79	10.6	1.98	1.1	14.1	2.22	24.5	3.51
		7B	1.58	15.6	1.46 /broad/		3.87	10.7	2.06	10.3	14.1	2.34	17.2	3.34
*	$CDCl_3$	8A	1.87	13.8	1.48	1.53	4.00	11.4	2.38	8.0	14.1	2.89	19.3	~8.3
		8B	1.96	14.7	1.48	1.51	3.84	11.1	2.48	12.4	14.5	2.72	13.4	8.1-8.4 AA'BB'

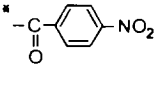
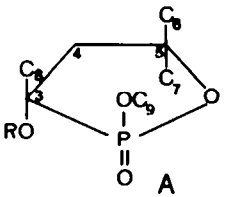


Table 2. ^{13}C NMR data for 1,2-oxaphospholanes



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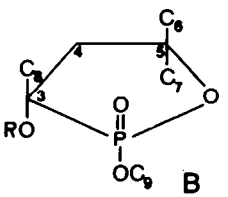

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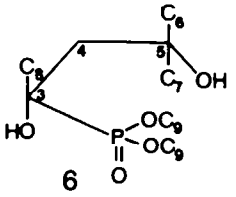
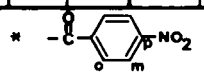


6

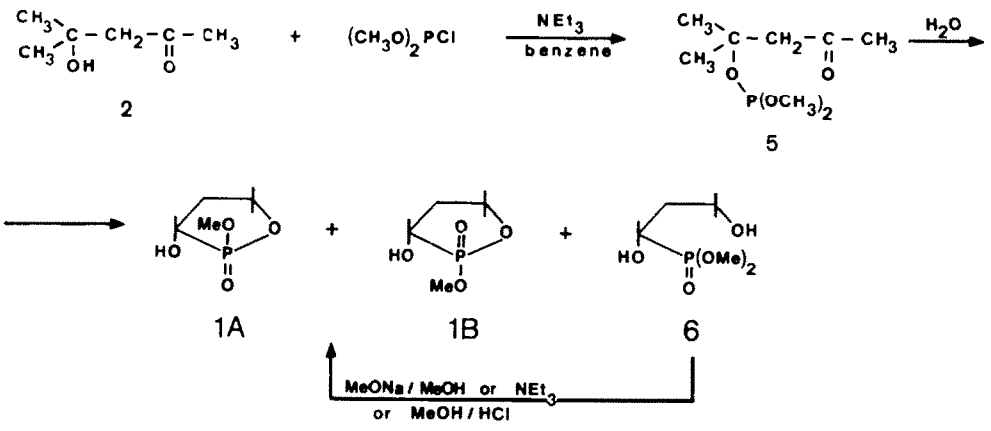
R			δ_{13C}								$^{n}J_{C-P}$							
			C_3	C_4	C_5	$C_{6/7}$		C_8	C_9	R	$^1C_3$	$^2C_4$	$^2C_5$	$^3C_{6/7}$		$^2C_8$	$^2C_9$	^{3}R
H	$CDCl_3$	1A	70.30	50.80	81.71	29.71	30.88	22.52	52.88		136.8	13.2	8.8	0	0	10.3	7.4	
		1B	71.54 s	51.42 t	81.48 s	29.58 q	31.01 q	24.28 q	54.83 q		139.7	14.7	7.4	0	2.9	7.4	7.4	
		6	73.16	46.64	81.86	31.07	32.37	25.03	53.34 54.28		163.3	4.4	10.3	0	0	0	7.4 8.8	
H	C_6D_6	1A	70.51	50.87	81.39	29.84	30.94	22.52	52.75		135.3	13.2	8.8	2.9	0	10.3	7.4	
		1B	71.80	51.48	81.71	29.71	31.07	24.60	55.22		139.7	14.7	8.8	0	0	7.4	7.4	
Me	$CDCl_3$	7A	75.78	49.80	80.62	29.80	30.78	17.25	52.29	52.20	141.5	12.1	6.6	3.3	2.2	8.4	9.9	1.1
		7B	77.25	49.27	80.92	30.24	31.40	19.75	54.58	52.08	140.8	12.8	7.0	0	<0.7	7.0	7.3	6.2
*	$CDCl_3$	8A	78.75 s	49.44 t	79.05 s	30.20 q	31.14 q	21.97 q	54.60 q	163.5	143.1	11.2	6.4	2.9	0	3.4	5.9	5.9
		8B	79.21	50.64	79.83	29.90	30.58	22.00	54.41	163.6	139.2	11.2	5.8	2.0	4.9	4.9	6.3	5.8

* 

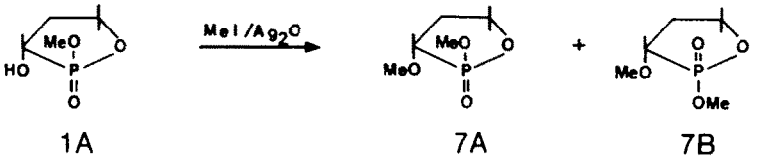
s, t, q - multiplicity from the SFORD experiment - coupling to P omitted.

Chemical shifts of aromatic carbons

	C-1	o	m	p
8A	135.3	131.0	123.5	150.9
8B	135.4	130.9	123.7	151.0
calc.	136.4	129.5	123.7	153.0



Scheme 1.



Scheme 2.

However, when **7A** was treated with 10 mol% of sodium methoxide in methanol, the 6:4 mixture of **7A** and **7B** was obtained. From this mixture pure **7B** was separated. Equilibration of **7B** under the conditions used for **7A** led again to the 6:4 mixture of **7A** and **7B**.

DISCUSSION

Configuration and conformation

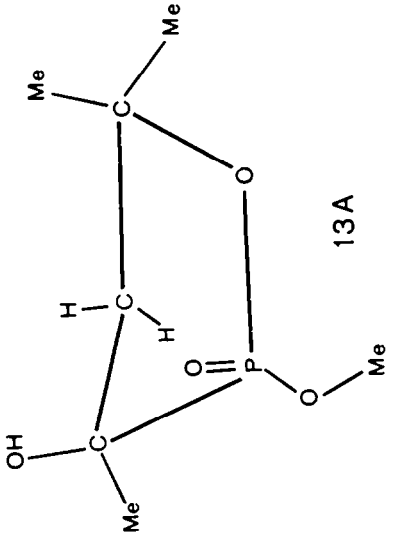
The assignment of the cis arrangement of the OH and P=O groups in **1A** was previously established from the IR studies.[5] Based on the ^1H and ^{13}C NMR spectral data (Table 1 and 2) of pure isomers from the **A** and **B** series this conclusion can now be supported and new assignments can be made.

Deshielding effect of the P=O bond on all kinds of protons cis to the P=O group in the rigid systems is well established.[13] This is observed for the methyl groups in the Me-C_5-P fragment of all compounds of the *B* series (Table 1). This effect, although not too large ($\Delta\delta$ 0.1 ppm) allows the assignment of the cis arrangement of the P=O and methyl (Me-C_5) groups in **1B**, which is unequivocal with the trans configuration of the P=O and O—H groups. Further evidence supporting this assignment comes from the comparison of the ^{13}C NMR chemical shifts of the C_8 and C_9 atoms in **1A** and **1B** (Table 2). For these carbons in **1A** when compared with those in **1B** an upfield shift of *ca* 2 ppm is observed. This shielding can be explained by the steric compression which the methyl and methoxy groups are subjected to in **1A** and not in **1B** and proves the cis arrangement of the P=O and O—H groups in the **A** series. This crowding is even more pronounced for the same carbons in the methyl ethers **7A** and **7B**. It is important for the assignment of configuration of **7A** because the chemical correlation between **1A** and **7A** could not be achieved.

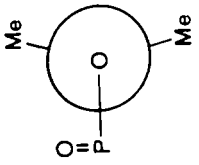
Conformational analyses of 1,2-oxaphospholane derivatives are rare.[8,14] Bergesen[14a] noticed that the coupling constants $^3J_{HCCP}$ of 2-oxo-2-phenyl-3,5,5-trimethyl-1,2-oxaphospholan-3-ol were 10.9 and 11.7 Hz. On that basis he concluded that this compound exists predominantly in the envelope conformation in which the P, C_3, C_4 and C_5 atoms are coplanar, and the O_1 atom is out of the plane. Later, the Russian workers[8] extended this assignment to trans-2-(N,N-diethylamino)-2-oxo-3,5,5-trimethyl-1,2-oxaphospholan-3-ol (9) because the appropriate coupling constants $^3J_{HCCP}$ were 11.0 and 15.2 Hz. On the other hand, for the cis isomer of (9) $^3J_{HCCP}$ of 3.9 and 20 Hz were found. These values allowed the envelope conformation in the chloroform solution to be proposed but in this case the O_1, P, C_3 and C_4 atoms are coplanar and the C_5 atom is out of the plane. The final conclusions regarding the predominant conformations were based on the values of the coupling constants between the H-C_4 and P atom. For the values of $^3J_{HCCP}$ of *ca* 4, 11 and 20 Hz dihedral angles H-C_4-C_3-P of 85 or 93°, 120° and 140 or 160° respectively, were accepted.[8]

Recently, it has been proven that the coupling constant $^3J_{CCCP}$ depends on dihedral angle C-C-C-P and gives the Karplus-type relationship.[15] Therefore, it appeared to be a valuable tool for the conformational analysis. The minimum values of $^3J_{CCCP}$ (*ca* 0 Hz) usually correspond to the dihedral angle C-C-C-P of 90° ± 20°, whereas, maximum coupling is observed for dihedral angles approaching 180°. However, the maximum value of $^3J_{CCCP}$ is characteristic for the class of compounds studied.

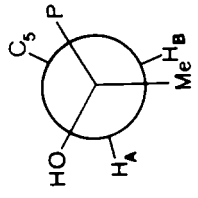
Throughout this paper the values of $^3J_{HCCP}$ and $^3J_{CCOP}$ are used in order to make conclusions about the predominant conformation of 1,2-oxaphospholane ring in the chloroform solution. In **1A**, a surprisingly large $^3J_{H_ACCP}$ of 25.7 Hz is observed in addition to a very small $^3J_{H_BCCP}$ of 1.2 Hz. It is due to the values of the corresponding dihedral angles H-C_4-C_3-P of ca 180° and 90°, as shown in the Newman projections **10A** or alternatively **11A** (Scheme 3). On the other hand, the P-O-C_5-CH_3 dihedral angles in **1A** can be estimated from the analysis of the coupling constants of the C_6 and C_7 to the P atom. Taking into account the values of $^3J_{CCOP}$ (0 Hz) one can conclude that the latter dihedral angles are almost the same (*ca* 90 ±



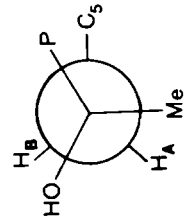
13A



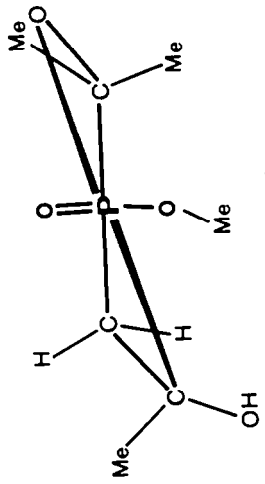
12A



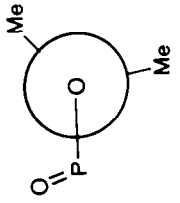
11A



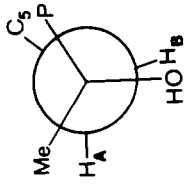
10A



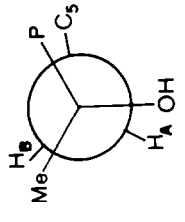
13B



12B



11B



10B

Scheme 3.

20°). Such a situation is envisaged with **12A**. On the basis of the analysis shown above the envelope conformation **13A** is proposed for **1A**.

Additional arguments for the conformation **13A** come from the analysis of the proton chemical shifts of **1A** in the benzene solution. In comparison to the measurements in chloroform substantial upfield shifts of the Me-C_5 ($\Delta\delta$ 0.3 ppm) and of the Me-OP ($\Delta\delta$ 0.4 ppm) groups are found. The chemical shift of the Me-C_3 group is unaffected by benzene. In the proposed conformation only the Me-C_5 *trans* to the P=O group and the Me-OP group should be shielded by the aromatic ring currents[16] if benzene preferably complexes below the 1,2-oxaphospholane ring. In the alternative envelope conformation of **1A** in which the Me-C_3-OH fragment is placed below the plane of the P, O_1, C_5, and C_4 atoms (combination of **10A** and **12a**), it is reasonable to assume that the Me-C_3 group would be shielded additionally. The same predominant conformation **13A** exists for **1A** in benzene although some twisting is likely to occur because two different values of $^3J_{CCOP}$ emerged (Table 2). Substitution of the OH in **1A** by the MeO group has no influence on the H-C_4-C_3-P as well as C-C_5-O-P dihedral angles. Therefore, the conformation of **7A** is essentially the same as that of **1A**.

The conformation of **1B** can be ascertained again from the analysis of the $^3J_{HCCP}$ and $^3J_{CCOP}$. Taking into account the values of the $^3J_{HCCP}$ and $^3J_{CCOP}$ the Newman projections **10B** or **11B** and **12B** (Scheme 3) show the corresponding dihedral angles in **1B**. Thus, one of the two possible conformations of **1B** can be envisioned as **13B**. Evidently, the opposite arrangement of the O_1 and C_3 atoms leads to the alternative twist-envelope conformation of **1B**. However, the large upfield shift of $\Delta\delta$ *ca* 0.3 ppm observed for the Me-C_5 group trans and small one of $\Delta\delta$ *ca* 0.1 ppm for the Me-C_5 group cis to P=O group in benzene solution cannot be explained unequivocally and for this reason it is not possible to take advantage of this observation to indicate the predominant conformation.

Similar twist-envelope conformation is proposed for **8A**. It is highly likely that a different conformational behaviour of the ester **8A** when compared to **1A** and **7A** is caused by the bulky p-nitrobenzoyloxy group.

When the bulkiness of the substituents on the OH group in the **B** series increases the conformation of the 1,2-oxaphospholane ring is being changed. In the methyl ether **7B** the ring is only slightly twisted. Furthermore, in **8B** the coupling constants $^3J_{HCCP}$ are almost equal to each other (12.4 and 13.4 Hz) which proves the eclipsed arrangement of the substituents around the C_3-C_4 bond. In addition, the values of $^3J_{CCOP}$ suggest that the predominant conformation of **8B** in chloroform is the envelope in which the P, C_3, C_4 and C_5 are coplanar and the O_1 atom is out of the plane. Similar conclusions were drawn before[8,14a] for compounds in which groups larger than methoxy were attached to the P atom.

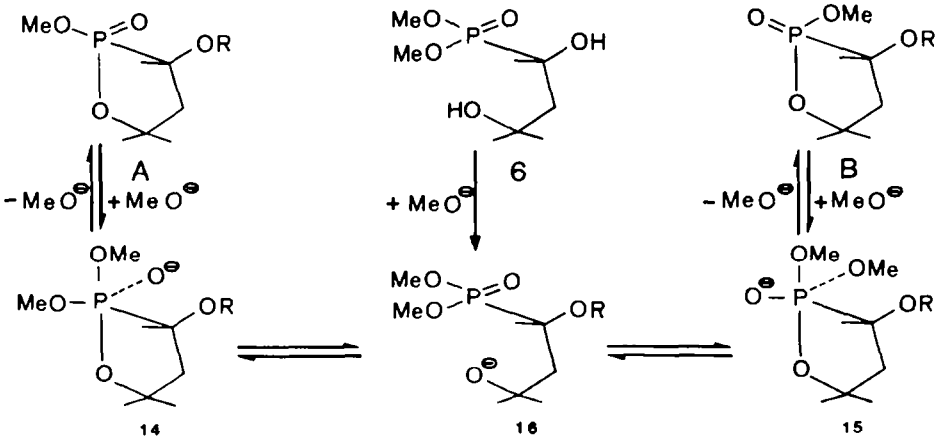
As shown above, the predominant conformation of the 1,2-oxaphospholane derivatives strongly depends on the ring substituents. Because the exact shape of the Karplus-type relationship of the $^3J_{CCOP}$ versus the dihedral angle C-C-O-P in the 1,2-oxaphospholane ring is so far unknown, the limited applicability of this coupling constant in the conformational analysis should be kept in view. The problem is currently under investigation in this laboratory.

Equilibration and mechanism

The process of equilibration of **1A** and **1B** in the presence of basic catalysts can involve breaking either the C_3-P (retro-Abramov reaction) or the P-O_1 bonds or both processes. The observation that the methyl ethers **7A** and **7B** also underwent the equilibration under these conditions allows to exclude the retro-Abramov pathway at least for the latter compounds. Furthermore, taking into account the facile ring closure of the 1,3-dihydroxyphosphonate **6**, the following equilibrium (Scheme 4) is proposed to explain these results.

An apical attack of the methoxide anion leads to the strain-free trigonal bipyramides **14** and **15** in which all the ligands around the P atom are located in the energetically favourable positions.[17] Because pseudorotation in **14** or **15** must either result in an equatorial–equatorial ring or a carbon atom in the apical position, the formation of the intermediate **16** is the only reasonable alternative. Almost equimolar ratios of **1A** and **1B**, as well as **7A** and **7B** produced from **6** or from pure diastereomers in equilibration experiments, reflect the absence of serious nonbonding interactions of the substituents around the P-C_5 bond in the cyclic compounds discussed, because the bulkiness of the interacting groups in the diastereomeric pairs is of the same order.

For **6** even triethylamine is sufficiently basic to



Scheme 4.

promote the formation of an intermediate **16**. Its transformation to **1A** and **1B** might involve trigonal bipyramides similar to **14** and **15** (Scheme 4) but the counterion and solvent in this reaction are different than that in MeONa/MeOH-catalysed cyclisation.

One can suggest that the large excess of **1B** over **1A** is due to kinetic control in the triethylamine-catalyzed cyclisation of **6**. This is in agreement with the observation that as **1A** so **1B** remain intact in the presence of the tertiary amine.

The cylisation of **6** in the presence of methanolic hydrogen chloride can be explained assuming that protonated species **17**, **18** and **19** are involved as intermediates (Scheme 5).

This reaction is also irreversible because **1A** remained unchanged even when it had been refluxed with 3% methanolic hydrogen chloride at *ca* 60° for 5 h.

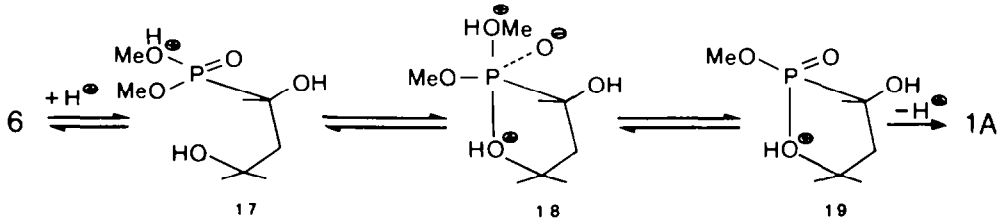
Our results on the cyclisation of α,γ-dihydroxyphosphonate **6** reveal a surprising facility of the 1,2-oxaphospholane ring closure by the O_1–P bond formation. Similar cyclisations were known so far only for γ-hydroxy-α,β-unsaturated phosphonates.[18] However, in all cases the *cis* configuration of the C=C bond accounts for the occurrence of the cyclisation. Here, the saturated chain is also capable of facile cyclisation in spite of absence of any special reason to keep the γ-OH group near the P atom.

Finally, some remarks on the possible mechanism of the reaction shown in Scheme 1 can be made. As long as only one diastereomeric 1,2-oxaphospholane derivative was obtained the intramolecular hydrogen bonding was suspected to control stereochemistry of the ring closure.[4a] The present study calls for an advanced explanation because the two diastereomers and additionally the ring-opened compound **6** were produced simultaneously. Taking into account that the cyclisation of the phosphite **5** took place under *neutral conditions* and that **1A** is unaffected by methanol even when it was refluxed for a half an hour, species **20** and **21** (Scheme 6) are suggested to be involved as intermediates in the reaction under investigation.

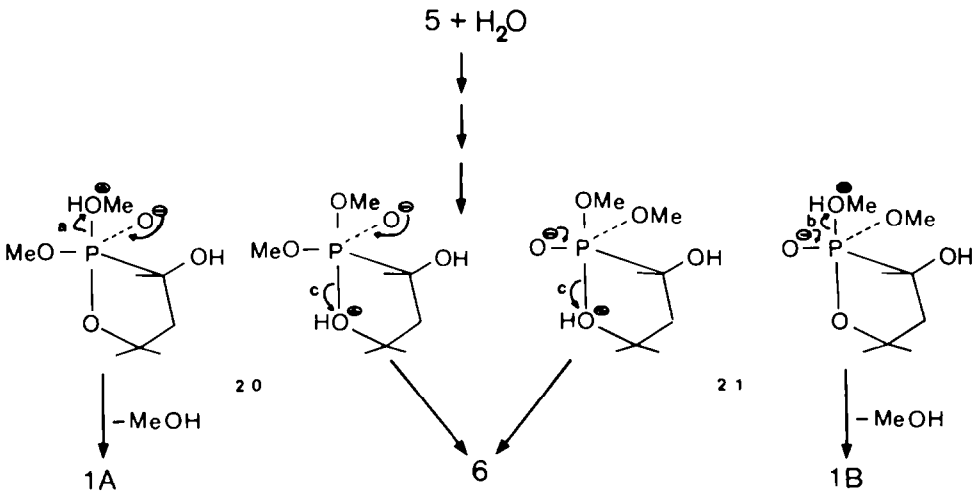
Thus, diastereomeric 1,2-oxaphospholanes **1A** and **1B** could be produced from **20** and **21** by the removal of methanol from the apical position by pathways *a* and *b*, respectively. On the other hand, apical opening by the pathways *c* would form **6** directly. The overall ratio of the products shown in Scheme 1 seems to be the result of the kinetic control because neither **1A** nor **1B** reacted with methanol under neutral conditions. However, pathways of formation of **20** and **21** in the reaction of **5** with water remain unknown so far. Attempts at solution to this question are under way in this laboratory.

EXPERIMENTAL

General. ^{1}H and ^{13}C NMR spectra were taken on Bruker HX 72 at 90 and 22.63 MHz, respectively by operating in the FT mode with TMS as the internal standard. Solutions of *ca* 10 mg of 1,2-oxaphospholane derivatives dissolved in 0.4 ml of $CDCl_3$ were used for ^{1}H observation. Coupling constants $^3J_{PH}$ were calculated according to the described procedure.[19] Selection of the proper solution from the set of two was made by the comparison of the calculated and obtained from ^{31}P-decoupled spectra chemical shifts (with accuracy of 0.02 ppm). The typical conditions for the ^{13}C NMR measurements were as follows: spectral width 6000 Hz, data points 8K/4K. Spectral widths reduced to 1500 Hz and data points 8K/4K were employed to improve the precision of $^3J_{CCOP}$ measurements. ^{31}P NMR spectra were recorded on JEOL JNM FX60 at 24.3 MHz. Chemical shifts are expressed with positive sign when downfield from external



Scheme 5.



Scheme 6.

85% H_3PO_4. IR spectral data were obtained on a Specord 71 IR. Melting points were determined on a Büchi capillary apparatus and are uncorrected.

The following adsorbents were used: column chromatography, Merck silica gel 60 (70-230 mesh); analytical thin layer chromatography, Merck TLC plastic sheets silica gel 60 F_{254}. TLC was performed in the 20:1 $CHCl_3/CH_3OH$ solvent system. Visualization of spots was effected with iodine vapours.

Elemental analyses were performed by Microanalytical Laboratory of Institute of Organic Chemistry, Technical University, Łódź.

All solvents were purified by methods described in the literature. Dimethyl phosphorochloridite was prepared according to the literature procedure.[20] The preparation contained *ca* 5% of trimethyl phosphite as judged from ^1H NMR spectrum and was used without further purification.

Preparation of dimethyl-(1,1-dimethyl-3-oxobutyl) phosphite (5)

To a cooled mixture of 11.6 g (0.1 mol) of diacetone alcohol and 14.0 ml (0.1 mol) of triethylamine dissolved in 100 ml of benzene a solution of 14.0 g (0.11 mol) of dimethyl phosphorochloridite in 10 ml of benzene was added dropwise at 5° under argon atmosphere. Stirring was continued for 1 h at this temp and the reaction mixture was filtrated, washed thoroughly with benzene and evaporated. The crude product was distilled *in vacuo* to yield 12.5 g (60%) of **5**, b.p. 68 – 69°/0.7 mm. ^{31}P NMR ($CDCl_3$): 135.3; ^1H NMR ($CDCl_3$): 1.40 (s, 6H, $(CH_3)_2C$), 2.15 (s, 3H, CH_3CO), 2.70 (s, 2H, CH_2), 3.41 (d, J = 10.0, 6H, CH_3OP); IR (neat): 1720 C=O.

Reaction of **5** *with water*

To magnetically stirred 10.0 g (48.0 mmol) of **5**, water 0.87 ml (48.0 mmol) was added drop by drop with external cooling. Reaction occured immediately and the mixture became viscous. ^{31}P NMR spectrum revealed the presence of three signals: 42.3; 40.4 and 28.4 ppm in the ratio of 3:1:6. Separation was effected by column chromatography with 60:1 $CHCl_3/CH_3OH$.

(2S*, 3S*)-2-methoxy-2-oxo-3,5,5-trimethyl-1,2-oxaphospholan-3-ol.

(**1A**), m.p. 127.5 – 128°; ^{31}P NMR (CH_3OH): 42.3, (C_6H_6): 41.9; IR (KBr): 3320 ν_{OH}, 1245 $\nu_{P=O}$ TLC R_f 0.32. (Found: C, 43.25; H, 7.60; P, 15.68. Calc. for $C_7H_{15}O_4P$: C, 43.30; H, 7.79; P, 15.95%).

(2R*, 3S*) - 2 - methoxy - 2 - oxo - 3,5,5 - trimethyl - 1,2 - oxaphospholan-3-ol.

(**1B**), m.p. 63.5–64°; ^{31}P NMR (CH_3OH): 40.8, (C_6H_6): 39.8; IR (neat): 3320 ν_{OH}, 1220 ν_{P-O}; TLC R_f 0.26. (Found: C, 43.45; H, 7.62; P, 15.61. Calc. for $C_7H_{15}O_4P$: C, 43.30; H, 7.79; P, 15.95).

O,O-Dimethyl 1,3-dihydroxy-1,3-dimethylbutylphosphonate.

(**6**) oil; ^{31}P NMR (CH_3OH): 28.4, (C_6H_6): 28.6; IR (neat): 3320 ν_{OH}, 1220 ν_{P-O}; TLC R_f 0.25. (Found: C, 42.30; H, 8.15; P, 13.50. Calc. for $C_8H_{19}O_5P$: C, 42.47; H, 8.47; P, 13.69%).

General procedure for equilibration of **1A**, **1B**, **7A**, **7B** *and cyclization of* **6**.

1A 88 mg (0.45 mmol) was dissolved in 0.45 ml of methanol (equilibrations) or benzene (cyclization in the presence of NEt_3) in NMR tube and ^{31}P NMR spectrum was taken. Then, 0.045 mmol (10 mol%) of CH_3ONa/CH_3OH solution or NEt_3 was injected. The progress of the reaction was monitored by ^{31}P NMR spectroscopy.

Preparation of p-nitrobenzoates of **1A** and **1B**

p-Nitrobenzoates **8A** and **8B** were obtained from **1A** and **1B** and p-nitrobenzoyl chloride in the presence of pyridine.

8A: m.p. 143 – 143.5°; ^{31}P NMR ($CDCl_3$): 33.5; IR (KBr): 1720 $\nu_{C=O}$, 1285 ν_{P-O}; TLC R_f 0.74. (Found: C, 48.85; H, 5.10; N, 4.17; P, 8.91. Calc. for $C_{14}H_{18}NO_7P$: C, 49.98; H, 5.28; N, 4.08; P, 9.02%).

8B: m.p. 139.5 – 140.5°; ^{31}P NMR (pyridine): 34.85; IR (KBr): 1720 $\nu_{C=O}$, 1280 $\nu_{P=O}$; TLC R_f 0.59. (Found: C, 48.87; H, 5.25; N, 4.20; P, 9.03. Calc. for $C_{14}H_{18}NO_7P$: C, 48.98; H, 5.28; N, 4.08; P, 9.02%).

Methylation of **1A** *with the Purdie reagent*

To 1.73 g (8.91 mmol) of **1A** dissolved in 5 ml of CH_2Cl_2 10 ml of freshly distilled MeI was added. Then Ag_2O 2.97 g (8.91 mmol) was added portionwise. The reaction mixture was stirred for 24 h filtrated, evaporated and distilled in vacuo to give 1.2 g of crude methyl ethers boiling at 120 – 130° (bath)/0.4 mm. Column chromatography with 100:1 $CHCl_3/CH_3OH$ followed by recrystallization of appropriate fractions from $CHCl_3$/hexanes afforded 585 mg (31%) of crystalline (m.p. 70 – 71°) **7A**. ^{31}P NMR ($CDCl_3$): 38.9; IR (KBr): 1250 ν_{P-O}; TLC R_f 0.55. (Found: C, 46.00; H, 7.96; P, 14.86. Calc. for $C_8H_{17}O_4P$: C, 46.15; H, 8.23; P, 14.88%).

Equilibration of **7A**.

In NMR tube 555 mg (2.67 mmol) of **7A** was dissolved in 2 ml of CH_3OH and 0.3 mmol of CH_3ONa as a solution in CH_3OH was added. The progress of the equilibration was monitored by ^{31}P NMR. After 5 h the system reached the equilibrium. The reaction mixture was chromatographed using 900 ml 200:1 $CHCl_3/CH_3OH$ as the solvent system. The following compounds were obtained: **1A**: 211 mg (38%) and **1B**: 133 mg (24%) as a colorless mobile oil; ^{31}P NMR ($CDCl_3$): 38.7; IR (neat): 1250 ν_{P-O}; TLC R_f 0.50. (Found: C, 46.42; H, 8.47; P, 14.49. Calc. for $C_8H_{17}O_4P$: C, 46.15; H, 8.23; P, 14.88%).

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