39. Relative Configuration and Conformation of 5-(Dimethoxyphosphoryl)-2-methoxy-1,2λ^5-oxaphospholan-2-ones by Multinuclear NMR Spectroscopy

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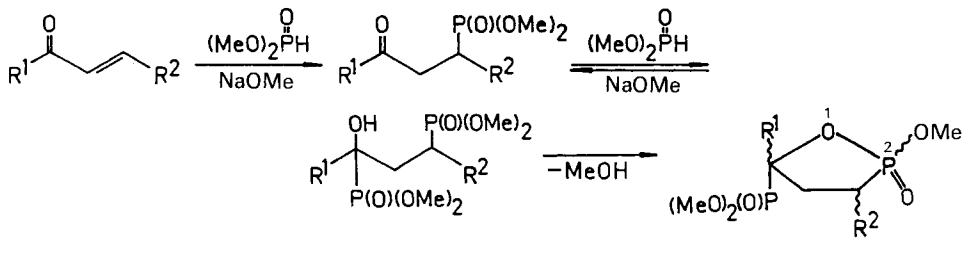
Information on the hitherto unknown relative configuration and on the conformation of the title compounds in solution can be derived from nuclear *Overhauser* effects and coupling constants. Whereas the bridged 5-(dimethoxyphosphoryl)-2-methoxy-1,2λ^5-oxaphospholan-2-ones **6** and **7** are sterically strained and, therefore, conformationally rigid, the C(3)-unsubstituted compound **1** does not show a preferred solution conformation. Phenyl substituents at C(3) (compounds **2–5**) tend to adopt a pseudoequatorial position, this way leading to a definite conformation of the respective compounds. The influence of the conformation on the NMR spectra is discussed. ^{31}P-NMR spectroscopy is ideally suited for the characterization and quantification of the isomers **2–5** present in the reaction mixture.

1. Introduction. – During the last decade, 1,2λ^5-oxaphospholan-2-ones have attracted considerable attention because of their potential biological activity (cytotoxity in hepatoma tissue cultures, cholesterinase inhibition, *etc.*) [1] [2]. Configurational and conformational studies using ^{1}H-, ^{13}C-, and ^{31}P-NMR spectroscopy have been performed [3–5] making extensive use of the well-known influence of the dihedral angle of P–C bonds on the vicinal C,P coupling constants [6] [7]. In general, envelope- or half-chair-type arrangements have been found for the substances under investigation.

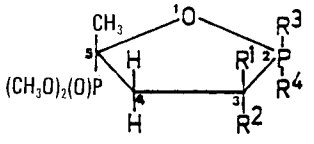
In the context of a synthetic study on *P,P'*-(1-hydroxyalkane-1,3-diyl)bis[phosphonates], a series of 5-(dimethoxyphosphoryl)-2-methoxy-1,2λ^5-oxaphospholan-2-ones could be isolated from the base-catalyzed reaction of various acyclic and cyclic α,β-unsaturated ketones with 2 equiv. of dimethyl phosphite according to the *Scheme* [8]. Using enones with $R^2 \neq H$, three chiral centers are created at C(3), C(5), and P(2) (in this order) in the course of the reaction. With monocyclic products and without restriction of the

Scheme



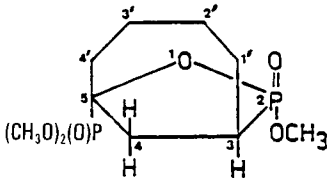
relative arrangement of R^1 and R^2, the formation of four diastereoisomeric pairs of enantiomers is possible.

Applying the standard reaction conditions given in [8] on 4-phenylbut-3-en-2-one (R^1 = Me, R^2 = Ph) as starting material, all theoretically possible diastereoisomers **2–5** could be produced, although in rather different amounts (**2**/**3**/**4**/**5** *ca.* 50:15:10:25). The precursor cycloheptenone yielded the bicyclic product **6** with high diastereoselectivity, whereas compound **7** could be isolated enantioselectively from the chiral educt 5α-cholest-1-en-3-one.



	R^1	R^2	R^3	R^4
1	H	H	=O[a])	CH_3O[a])
2	Ph	H	CH_3O	=O
3	Ph	H	=O	CH_3O
4	H	Ph	CH_3O	=O
5	H	Ph	=O	CH_3O

[a]) Substituents are interchangeable.



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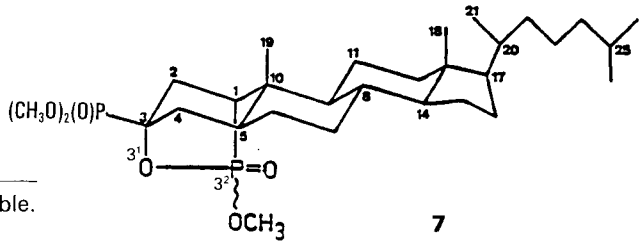

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During these investigations, ^{31}P-NMR spectroscopy proved to be a valuable tool for the identification and quantification of isomers in the crude reaction mixtures [8]. In the course of our attempts to establish an unambiguous assignment of the ^{31}P-resonances of compounds **2–5**, we have also examined the conformational behaviour of these and related compounds (**1**, **6**, **7**) in solution by NMR spectroscopy. The results of this investigation are given in the present paper[1]).

2. Results. – The NMR-spectroscopic assignment of compounds **1–5** is based on the ^{13}C spectra which can be interpreted straightforwardly with the help of chemical-shift, multiplicity, and coupling arguments. Using ^{1}H,^{13}C-correlated spectroscopy, the infor-

[1]) Throughout the text and in the *Tables*, the relative positions of the substituents at C(3) and C(4) are given by the subscripts α and β (below and above the plane defined by the heterocyclus; *cf.* nomenclature of steroids), especially to avoid the use of the unhandy descriptors *pro-R* and *pro-S* for the protons at C(4). For the sake of clarity, compound **6** was numbered in the same way as compounds **1–5**.
Systematic names: 5-(dimethoxyphosphoryl)-2-methoxy-5-methyl-1,2λ^5-oxaphospholan-2-one (**1**), (2*RS*,3*SR*,5*RS*)-5-(dimethoxyphosphoryl)-2-methoxy-5-methyl-3-phenyl-1,2λ^5-oxaphospholan-2-one (**2**), (2*RS*,3*RS*,5*SR*)-5-(dimethoxyphosphoryl)-2-methoxy-5-methyl-3-phenyl-1,2λ^5-oxaphospholan-2-one (**3**), (2*RS*,3*RS*,5*RS*)-5-(dimethoxyphosphoryl)-2-methoxy-5-methyl-3-phenyl-1,2λ^5-oxaphospholan-2-one (**4**), (2*RS*,3*SR*,5*SR*)-5-(dimethoxyphosphoryl)-2-methoxy-5-methyl-3-phenyl-1,2λ^5-oxaphospholan-2-one (**5**), (2*RS*,3*SR*,5*SR*)-3,5-butano-5-(dimethoxyphosphoryl)-2-methoxy-1,2λ^5-oxaphospholan-2-one (= (1*RS*,6*RS*,7*SR*)-1-(dimethoxyphosphoryl)-7-methoxy-8-oxa-7λ^5-phosphabicyclo[4.2.1]nonan-7-one; **6**), and 3β-(dimethoxyphosphoryl)-3^1-methoxy-3α,1α-(epoxyphosphorano)-5α-cholestane-3^2-one (**7**).

mation content of the ^{13}C spectra can be transferred to the protons which in turn yield the assignment of the P-atoms and the CH_3O groups *via* $^1H,^{31}P$-correlated spectroscopy (*Tables 1–3*).

Table 1. *^1H-NMR Chemical Shift Values* (ppm) *of* **1–3**, **5**, *and* **6**

	1	**2**	**3**	**5**[a])	**6**
H_α–C(3)	*ca.* 1.94	3.96	3.94	–	2.23
H_β–C(3)	1.80	–	–	3.55	–
H_α–C(4)	2.51	3.01	3.00	3.02	2.66
H_β–C(4)	*ca.* 2.00	2.47	2.46	2.35	2.16
CH_3–C(5)	1.45	1.69	1.72	1.65	–
CH_3O–P(2)	3.67	3.51	3.84	3.43	3.77
$(CH_3O)_2P$–C(5)	3.68, 3.70	3.91, 3.93	3.85, 3.92	3.82, 3.83	3.78, 3.81
Ph	–	7.30–7.40	7.25–7.45	7.20–7.34	–
$CH_2(1')$	–	–	–	–	1.62, 1.73
$CH_2(2')$	–	–	–	–	1.55, 1.85[b])
$CH_2(3')$	–	–	–	–	1.62, 1.79
$CH_2(4')$	–	–	–	–	1.78[b]), 2.07

[a]) The chemical shifts of **5** were obtained from a mixture **2**/**5** with **5** in large excess (> 10:1).
[b]) Protons connected to H_β–C(4) by NOESY cross peaks.

Table 2. *^{13}C-NMR Chemical Shift Values* (ppm) *of* **1–6**[a])

	1	**2**	**3**	**4**[c])	**5**	**6**
C(3)	17.49	38.56	38.39	36.40	36.18	27.68
C(4)	30.60	37.64	40.39	39.00	35.53	31.49
C(5)	80.37	78.81	79.29	78.55	78.75	83.22
CH_3–C(5)	23.35	24.76	25.15	21.80	22.99	–
CH_3O–P(2)	52.75	53.60	54.07	53.44[b])	53.96	52.38
$(CH_3O)_2P$–C(5)	53.34, 53.81	54.06, 45.41	53.38, 54.51	53.80[b]), 55.08[b])	53.96, 54.20	53.70, 54.06
Buteno, C(1')	–	–	–	–	–	26.10
C(2')	–	–	–	–	–	24.31
C(3')	–	–	–	–	–	22.88
C(4')	–	–	–	–	–	35.00
Ph, C(1')	–	132.53	133.61	133.28	131.93	–
C(2'), C(6')	–	127.63	128.50	[d])	127.76	–
C(3'), C(5')	–	128.70	128.80	[d])	128.80	–
C(4')	–	127.42	127.50	[d])	127.60	–

[a]) The assignment of the arom. C(2') to C(6') was performed with the help of C,P coupling constants (*cf. Table 6*).
[b]) Values are interchangeable.
[c]) The values of **4** were obtained from a mixture **2**/**4**/**5**.
[d]) Unknown.

Table 3. *^{31}P-NMR Chemical Shift Values* (ppm) *of* **1–7**

	1	**2**	**3**	**4**[a])	**5**	**6**	**7**
P(2)	49.51	41.36	41.98	43.86	42.22	54.23	48.18[b])
P–C(5)	23.92	24.01	24.02	22.98	23.53	24.49	22.03[c])

[a]) Values of **4** were obtained from a mixture **2**/**4**/**5**.
[b]) $P(3^2)$.
[c]) *P*–C(3).

For the determination of the relative configurations of compounds **1**–**5**, the configuration at C(5) was arbitrarily defined to be *S*. Starting with CH_3–C(5), the relative positions of the substituents at C(3) and C(4) could be unambiguously established using NOE difference spectroscopy. Attempts to use the dihedral dependance of ^2J(P,H) [9] to derive the position of the phosphoryl O-atom at P(2) relative to H–C(3) failed. However, the influence of the anisotropy effect of the Ph ring at C(3) on CH_3O–P(2) strongly suggests a *cis*-relationship between the Ph and the CH_3O substituent in compounds **2** and **5**. This will be discussed in more detail later. No decision could be made concerning the relative configuration at P(2) for compound **1**.

A somewhat different situation occurs for the bicyclic compound **6**. The butano-bridge leads to a strained structure and defines both the relative configuration at C(3) and the conformation of the heterocyclus. Therefore, compound **6** can be used as a test substance for the influence of the conformation on the H,P, C,P, and P,P coupling constants, respectively. The ^{13}C-NMR spectroscopic assignment of the butano bridge was achieved by an INADEQUATE experiment.

The preferred conformation of compounds **1**–**5** in solution was mainly deduced from coupling constants (*Tables 4–7*) and their dependence on dihedral angles. Whenever there

Table 4. *H,H Coupling Constants* (Hz) *of* **1**–**3**, **5**, *and* **6**

	$J(3\alpha,4\alpha)$	$J(3\alpha,4\beta)$	$J(3\beta,4\alpha)$	$J(3\beta,4\beta)$	$J(4\alpha,4\beta)$	$J(3\alpha,3\beta)$
1	9.0	9.0	9.0	9.0	–13.8	–13.8
2	8.1	13.9	–	–	–13.9	–
3	8.5	14.0	–	–	–14.0	–
5	–	–	13.5	7.8	–13.5	–
6	7.6	0.0	–	–	–13.8	–

Table 5. *H,P Coupling Constants* (Hz) *of* **2**, **3**, **5**, *and* **6** (absolute values)

	2	**3**	**5**	**6**
$J(3\alpha,P(2))$	23.0	18.0	–	15.0
$J(3\beta,P(2))$	–	–	19.5	–
$J(4\alpha,P(2))$	33.6	29.7	2.2	0.0
$J(4\beta,P(2))$	1.8	2.1	31.7	30.0
$J(3\alpha,P–C(5))$	0.0	0.0	–	< 0.5
$J(3\beta,P–C(5))$	–	–	0.0	–
$J(4\alpha,P–C(5))$	11.7	10.0	13.6	14.7
$J(4\beta,P–C(5))$	29.0	26.1	0.0	0.0
$J(CH_3–C(5),P–C(5))$	13.8	11.9	13.2	–
$J(CH_3O–P(2),P(2))$	10.8	10.5	9.8	8.5
$J((CH_3O)_2P–C(5),P–C(5))$	10.3, 10.3	9.0, 8.9	9.1, 9.2	9.1, 9.6

were any ambiguities in the assignment of the H,P and C,P coupling constants to the respective P-atoms, double (^{1}H) or triple (^{13}C) resonance experiments were performed. In all cases, the results were in accordance with information derived from NOE difference spectroscopy.

As to the steroid derivative **7**, no experiments beyond routine 2D NMR spectroscopy were performed for assignment purposes (*Tables 8* and *9*). The A ring being the only

Table 6. *C,P Coupling Constants* (Hz) *of* **1–6** (absolute values)

	1	**2**	**3**	**4**	**5**	**6**
J(C(3),P(2))	121.3	118.4	119.9	122.1	119.2	120.5
J(C(3),*P*–C(5))	3.6	0.0	0.0	6.2	5.8	8.1
J(C(4),P(2))	< 1.0	3.3	5.8	5.9	4.7	3.7
J(C(4),*P*–C(5))	< 1.0	3.3	2.9	0.0	1.5	1.5
J(C(5),P(2))	8.7	5.8	6.5	6.6	5.1	8.7
J(C(5),*P*–C(5))	177.3	175.1	174.4	178.6	179.5	175.9
J(*C*H_3–C(5),P(2))	1.5	2.2	2.9	0.0	0.0	–
J(*C*H_3–C(5),*P*–C(5))	4.4	4.4	4.4	4.6	4.4	–
J(*C*H_3O–P(2),P(2))	6.5	7.3	6.5	6.6[a])	7.3	7.2
J((*C*H_3O)$_2$P–C(5),*P*–C(5))	7.3, 6.5	7.3, 7.3	7.3, 6.5	7.8[a]), [b])[a])	7.3, 6.9	7.3, 7.1
J(C(1′),P(2))	–	5.8	4.4	4.5	6.5	–
J(C(2′,6′),P(2))	–	7.5	8.0	[b])	6.8	–
J(C(3′,5′),P(2))	–	2.9	2.2	[b])	2.7	–
J(C(4′),P(2))	–	2.9	2.9	[b])	2.9	–
J(C(1′),P(2))	–	–	–	–	–	3.5
J(C(1′),*P*–C(5))	–	–	–	–	–	0.0
J(C(2′),P(2))	–	–	–	–	–	2.6
J(C(2′),*P*–C(5))	–	–	–	–	–	0.0
J(C(3′),P(2))	–	–	–	–	–	0.0
J(C(3′),*P*–C(5))	–	–	–	–	–	15.0
J(C(4′),P(2))	–	–	–	–	–	1.3
J(C(4′),*P*–C(5))	–	–	–	–		3.8

[a]) Values are interchangeable. [b]) Unknown.

Table 7. *P,P Coupling Constants* (Hz) *of* **1–7**

	1	**2**	**3**	**4**	**5**	**6**	7
J(P(2), *P*–C(5))	21.6	13.8	10.4	32.2	26.0	24.6	32.1

Table 8. *^{1}H-NMR Chemical Shift Values* (ppm) *and H,H and H,P* (absolute values) *Coupling Constants* (Hz) *of the A-Ring Region of* **7**

δ		J(H,H)		J(H,P)	
H–C(1)	2.10	J(1,2α)	= 4.5	J(1,P(3^2))	= 5.0
H_α–C(2)	2.45	J(1,2β)	= 1.2	J(1,*P*–C(3))	= 2.0
H_β–C(2)	2.22	J(2α,2β)	= –13.2	J(2α,P(3^2))	= 2.5
H_α–C(4)	1.88	J(2α,4α)	= 2.6	J(2α,*P*–C(3))	= 12.1
H_β–C(4)	1.60	J(4α,4β)	= –14.0	J(2β,P(3^2))	= 31.4
H–C(5)	2.24	J(4β,5)	= 13.8	J(2β,*P*–C(3))	< 0.5
C*H*$_3$O–P(3^2)	3.71			J(C*H*$_3$O–P(3^2),P(3^2))	= 9.9
(C*H*$_3$O)$_2$P–C(3)	3.76, 3.78			J((C*H*$_3$O)$_2$P–C(3), *P*–C(3))	= 9.5, 9.4

Table 9. *C,P Coupling Constants* (Hz) *of* **7** (absolute values)

J(C(1),P(3^2)) = 117.2	J(C(3),*P*–C(3)) = 181.0	J(C(19),P(3^2)) = 18.1
J(C(1),*P*–C(3)) = 7.5	J(C(4),*P*–C(3)) = 3.0	J(*C*H$_3$O–P(3^2),P(3^2)) = 7.0
J(C(2),*P*–C(3)) = 3.0	J(C(5),P(3^2)) = 1.5	J((*C*H$_3$O)$_2$P–C(3),*P*–C(3)) = 7.0, 7.0
J(C(3),P(3^2)) = 4.2	J(C(5),*P*–C(3)) = 10.0	

Table 10. *^{13}C-NMR Chemical Shift Values* (ppm) *of* **7**[a])

C(1)	36.88	C(7)	31.15	C(13)	42.67	C(19)	14.12	C(25)	27.94
C(2)	32.39	C(8)	35.70	C(14)	55.61[c])	C(20)	35.70	C(26)	22.50[e])
C(3)	81.63	C(9)	47.45	C(15)	23.77[d])	C(21)	18.59	C(27)	22.74[e])
C(4)	34.18	C(10)	38.01	C(16)	28.13	C(22)	36.06	CH_3O–P(3^2)	52.25
C(5)	39.33	C(11)	21.21	C(17)	55.98[c])	C(23)	23.96[d])	$(CH_3O)_2$P–C(3)	53.72, 53.99
C(6)	26.81	C(12)	39.37[b])	C(18)	12.10	C(24)	39.44[b])		

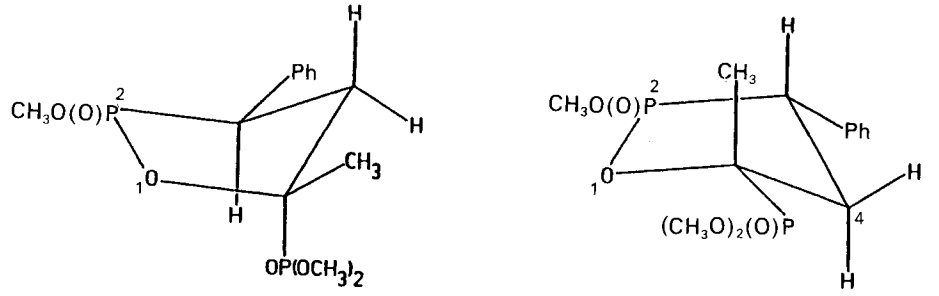
[a]) The assignment of resonances due to other than A-ring C-atoms stems from a comparison with [10].
[b])–[e]) Values marked with the same superscript are interchangeable.

region of interest, the assignment of the ^{13}C-NMR spectrum for the rest of the molecule was derived from a comparison with values from the literature [10] (*Table 10*).

3. Discussion. – The conformational behaviour of 5-membered cyclic compounds is usually described by a phenomenon called pseudorotation [11]. This process leads to a series of conformers interchanging rapidly on the NMR time scale. On the other hand, sterically crowded substituents tend to adopt a pseudoequatorial position to avoid 1,3-diaxial interactions as is known for 6-membered rings. This effect can be expected to be especially pronounced for the Ph substituent at C(3) in compounds **2**–**5**, bearing in mind the rather high value of -2.9 kcal·mol^{-1} for the conformational free energy of the Ph group in cyclohexane [12]. Obviously, this is the case for compounds **2**, **3**, and **5** (for **4**, *vide infra*). In any of them, H–C(3) experiences spin-spin couplings both with a *trans* and a *gauche* proton at C(4) (*Table 4*). Therefore, the coupling pattern for the spin system H–C(3), H_α–C(4), and H_β–C(4) is the same in all three cases. The two envelope conformations deduced from this information for the couples **2**,**3** and **4**,**5**, respectively, are given in *Fig. 1* and are supported by NOE difference measurements and by heteronuclear coupling constants. As to compound **4**, a problem arises insofar as this minor component of the reaction mixture could never be obtained as a pure substance [8]. Due to the complex *m*'s caused by H,H and P,H couplings, the ^{1}H-NMR spectrum of **4** in mixtures with other isomers refused analysis. Nevertheless, it was possible to determine the ^{13}C-NMR parameters of **4** from a mixture **2**/**4**/**5**. Therefore, vicinal coupling constants between C- and P-atoms can be used to check if compound **4** fits into the set of isomers as has been implicitly stated above. This is obviously the case.

The minor component **4** fits into the group of **2**, **3**, and **5**, as can be seen, *e.g.*, from ^3J(C(3), *P*–C(5)) and $^3J(CH_3$–C(5),P(2)) (*Table 6*). The values found for ^3J(P,C) are in perfect accordance with the proposed conformations as can easily be verified using a suitable molecular model (*e.g.* ball-and-stick or *Dreiding* model).

The well-known dependence of ^3J(P,H) and ^3J(P,C) on the dihedral angle [13] is reflected by the values of $^3J(H$–C(4),P(2)), ^{3}J(*H*–C(4),*P*–C(5)), ^3J(C(3),*P*–C(5)), and $^3J(CH_3$–C(5),P(2)) of **2**–**5**. Molecular-model considerations immediately show the almost planar arrangement of the fragments H_α–C(4)–C(3)–P(2) in **2** and **3** and H_β–C(4)–C(3)–P(2) in **4** and **5**, respectively, yielding coupling constants in the region of *ca.* 30 Hz. On the other hand, the nearly perpendicular position of P(2) relative to H_β–C(4) in **2** and **3** and to H_α–C(4) in **4** and **5** results in small or immesurable values for the respective vicinal coupling constants (*Table 5*). As can be seen from *Fig. 1*, the envelope-type arrangements cause the $(CH_3O)_2$P(O) substituent to adopt a pseudoaxial position in **2** and **3** and a pseudoequatorial position in **4** and **5**. This fact provides a means for cross-checking the proposed structures. If the assumed conformations are correct, the dihedral angle of the fragment H_β–C(4)–C(5)–P ought to be nearly 180° in **2** and **3** and *ca.* 90° in **4** and **5**, whereas H_α–C(4) and *P*–C(5) should be *gauche* in both groups of compounds. The values of the respective ^3J's given in *Table 5* clearly support these assumptions.



2,3 **4,5**

Fig. 1. *Preferred conformations of compounds* **2–5** *in* $CDCl_3$ *solution at 300 K as deduced from* $J(H,H)$, $J(H,P)$, *and* $J(C,P)$

The homonuclear P,P spin-spin coupling in **2–5** can take place in two ways: *via* O(1) and C(5) or *via* C(3), C(4), and C(5). The first possibility represents a vicinal coupling and can be expected to show the usual dihedral-angle dependence, whereas the second coupling path (^4J, long range) should only contribute to a minor extent to the overall coupling. In **2** and **3**, the dihedral angle between P(2) and *P*–C(5) is in the region of 90°, and the contribution of ^3J(P(2),*P*–C(5)) is small. With **4** and **5**, on the other hand, a dihedral angle of *ca.* 150° can be expected from the conformation deduced above. Therefore, the contribution of ^3J(P(2),*P*–C(5)) to the overall coupling will be notably larger in this case. If, as a first approximation, the value of ^4J(P(2),*P*–C(5)) is assumed to be nearly equal in all four compounds under investigation, the conformational differences between the two pairs of isomers **2**, **3** and **4**, **5** should result in clearly different values for J(P,P) due to the difference in ^3J(P,P). As can be seen from *Table 7*, this is indeed the case. ^{31}P-NMR spectroscopy, therefore, provides a simple means for the characterization of this class of compounds, even in mixtures with partially overlapping P-resonances.

No comments have been made so far on the relative configuration at P(2). Theoretically, ^2J(P,H) in cyclic phosphine oxides is known to exhibit an angular relationship on the relative positions of the proton and the phosphoryl O-atom [9]. However, this effect seems not to be very pronounced with the title compounds, at least in the case of compounds **2**, **3**, and **5**. As can be seen from *Table 5*, the coupling constants in question do not differ significantly. Moreover, the ^{1}H-NMR signals of H_α–C(3) (**2**, **3**) and H_β–C(3) (**5**) are partially overlapped by the CH_3O resonances, rendering an exact analysis difficult.

Looking at the ^{1}H-NMR spectra of compounds **2**, **3**, and **5**, one immediately notices a characteristic highfield shift of *ca.* 0.4 ppm for one of the CH_3O resonances in **2** and **5** (*Fig. 2*). It can be shown by 2D ^{1}H,^{31}P-correlated spectroscopy that the signals in question arise from the CH_3O group attached to P(2). As the relative configurations at C(3) and C(5) in **2** and **3** are already known, this phenomenon can only be caused by the different configuration at P(2) and has obviously to be ascribed to the anisotropy effect of the Ph substituent. Similar highfield shifts have already been observed for related compounds and were used for tentative configurational assignments [3b]. Theoretical considerations [14] show that the observed effect is in accordance with the idealized geometries of **2** and

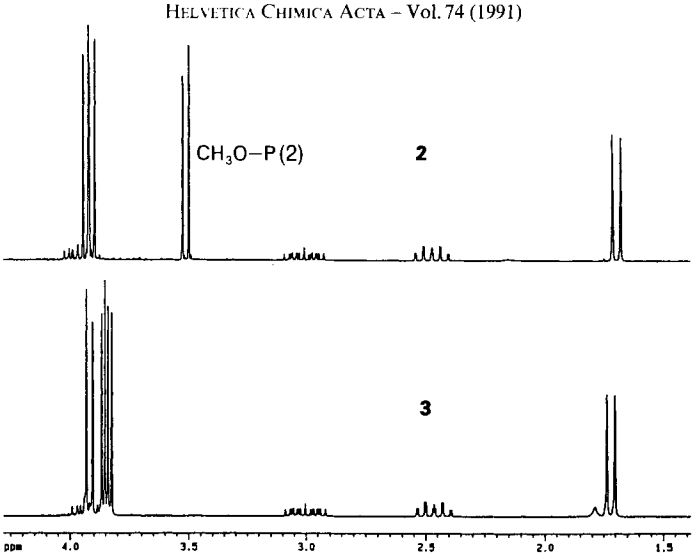


Fig. 2. *^{1}H-NMR spectra of* **2** *and* **3**

5 as given in *Fig. 1*. For compound **5**, the explanation of the highfield shift by the anisotropy effect could be proved to be correct by the observation of an NOE enhancement of the aromatic protons on irradiation of CH_3O–P(2).

The C(3)-unsubstituted compound **1** can give rise to two diastereoisomeric pairs of enantiomers. The reaction leads to a large excess of one diastereoisomer, the other one being visible in the ^{31}P-NMR spectrum as a small impurity (*cf. Exper. Part*). As can be seen from *Table 4*, the vicinal H,H coupling constants are perfectly averaged, thus indicating that no preferred conformation is present. This evidence is supported by the values of 3.6 Hz for ^3J(C(3),*P*–C(5)) and 1.5 Hz for $^3J(CH_3$–C(5),P(2)) which are intermediate with respect to the values found for the couples **2**,**3** and **4**,**5** (*Table 6*) and by the homonuclear P,P spin-spin coupling (*Table 7*). Obviously, the substituents at P(2) and C(5) are of little importance in the context of a fixed geometry of the oxaphospholane **1**. This is in accordance with values of the conformational free energy given for CH_3 [15] and CH_3O [16] substituents in cyclohexane. No data dealing with phosphoryl substituents were found in the literature. As a consequence of the increased mobility of **1** with respect to **2**–**5**, it has not been possible to determine the configuration at P(2) relative to C(5).

The butano-bridged 1,2λ^5-oxaphospholan-2-one **6** can be regarded as a rigid counterpart of compound **1**. The four-membered chain between C(3) and C(5) renders the molecule rather immobile, fixes the relative configurations at these centers and forces H_α–C(3) into a pseudoequatorial position, similar to that occupied by the Ph substituent at C(3) in compounds **4** and **5**. Compound **6** should, therefore, behave very similarly to these species with respect to the H,P, C,P, and P,P coupling constants and can serve as an ideal model compound for the verification of their correct interpretation. As can be seen by a comparison of the respective values for $^3J(H_\alpha$–C(4),P(2)), $^3J(H_\beta$–C(4),P(2)), $^3J(H_\beta$–C(4),*P*–C(5)) (*Table 5*), ^3J(C(3),*P*–C(5)) (*Table 6*), and J(P(2),*P*–C(5)) (*Table 7*), this is indeed the case, and the conformations given for **2**–**5** have, therefore, to be assumed to be correct.

It seems noteworthy to mention a special feature of **6**, concerning H_β–C(4). Both dihedral angles H_β–C(4)–C(3)–H_α and H_β–C(4)–C(5)–P are in the region of 90°, leading to vanishing values for $^3J(H_\beta\text{–}C(4),H_\alpha\text{–}C(3))$ and $^3J(H_\beta\text{–}C(4), P\text{–}C(5))$. Therefore, the coupling pattern of H_β–C(4) is surprisingly – and, on the first impression, confusingly – simple containing only the geminal homonuclear coupling to H_α–C(4) and the vicinal heteronuclear coupling to P(2) which leads to four sharp resonances of equal intensity (*Fig. 3*).

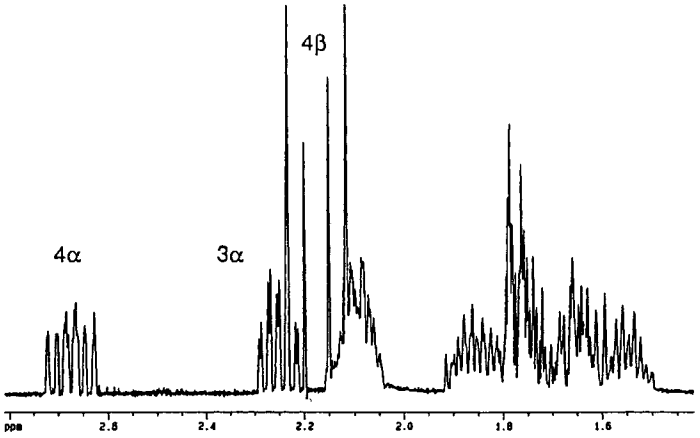


Fig. 3. *Partial ^{1}H-NMR spectrum of* **6**. Note the simple splitting pattern of H_β–C(4).

The relative configuration of compound **6** at P(2) could be established by 2D NOE spectroscopy. A NOESY cross peak correlating the resonances of H_α–C(3) and CH_3O–P(2) demonstrates the CH_3O substituent to be α-oriented. The corresponding β-isomer could not be detected in the reaction mixture.

Although the geometry of the oxaphospholane ring of **6** is fixed by the butano-bridge, the four-membered aliphatic chain itself introduces a new region of conformational interest. Molecular-model considerations show that four nearly or completely unstrained arrangements can be found for the bridge which can be converted into each other with little effort. The NMR spectra, however, indicate conformational homogeneity [17]. Obviously, only one of the possible conformers is present in $CDCl_3$ at room temperature. The large value of $^3J(C(3'),P\text{–}C(5))$, indicating an antiperiplanar relationship of C(3′) and *P*–C(5), together with cross peaks connecting one of the protons at C(2′) and C(4′), respectively, with H_β–C(4) in a NOESY spectrum, point to the conformation given in *Fig. 4*. Because of the thermal instability of **6**, no investigations on the mobility of the butano bridge at elevated temperatures could be performed.

The reaction of 2 equiv. of dimethyl phosphite with 5α-cholest-1-en-3-one yields the 1,3-annelated compound **7** [8] which can be regarded as a lower homologue of **6** with respect to the bridge connecting C(1) and C(3) (C(3) and C(5), resp., in **6**) of the oxaphospholane moiety. Theoretically, α- or β-orientation of the oxaphospholane ring is possible, but β-annelation appears unlikely because of the angular CH_3(19) group. In the first case, the chair conformation of the A-ring of the steroid is only slightly disturbed, whereas a ring formation in the β region forces the A-ring to adopt a boat-like geometry. A W-coupling of 2.6 Hz between H_α–C(2) and H_α–C(4) (*Table 8*) indicates a planar partial structure element H_α–C(2)–C(3)–C(4)–H_α which can only be achieved by an

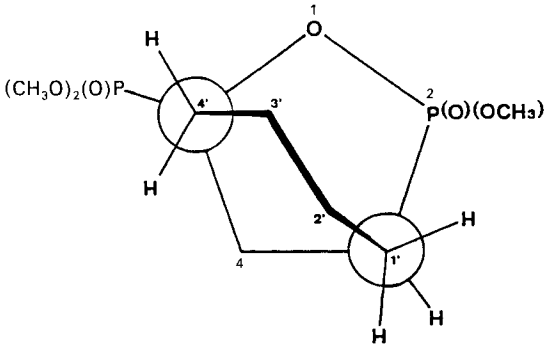


Fig. 4. *Preferred conformation of the butano bridge in* **6** *in* $CDCl_3$ *solution at 300 K*

α-type ring closure. This evidence is supported by a large difference in the values of the vicinal coupling constants of H–C(1) with H_α–C(2) and H_β–C(2) (*Table 8*). In the case of a β-oriented oxaphospholane, these couplings ought to be about equal due to the nearly equal dihedral angles H–C(1)–C(2)–H_α and H–C(1)–C(2)–H_β. We, therefore, conclude that the structure proposal given in [8] is correct. All other homo- and heteronuclear coupling constants of **7** agree with the given structure (*Tables 8* and *9*). It has to be mentioned, however, that this would also be the case for the boat conformation of ring A, provided the subscripts α and β are interchanged. The relative configuration at P(3^2) could not be established without ambiguity.

The ^{31}P-NMR spectrum of **7** immediately shows the close relationship between the bridged compounds **6** and **7**. The high chemical-shift value of the ring P-atom (P(2) and P(3^2), resp.; *Table 3*) reflects the strained structure in both cases. Within experimental error, the J(P,P) value of **7** is equal to the one found for **4** (*Table 7*). The conformation of the bridged oxaphospholane part of **7** obviously closely resembles the structure of **4**. This is in accordance with the fact that the propano bridge in **7** leads to a more strained structure than the butano bridge in **6**. Therefore, the tendency to force the oxaphospholane ring to adopt the envelope conformation proposed for compounds **4** and **5** is more pronounced in **7** than in **6**.

4. Conclusions. – Multinuclear NMR spectroscopy has proved to be a powerful tool for the investigation of the solution conformation of substituted 5-(dimethoxyphosphoryl)-2-methoxy-1,2λ^5-oxaphospholan-2-ones. The conformational behaviour of compounds **2**–**5** is mainly governed by the tendency of the sterically demanding Ph substituent to adopt a pseudoequatorial position, thereby decreasing the mobility of the heterocyclus. Once the influence of the structural parameters on the NMR spectra is known, the relative configurations of the reaction products can be told directly from the ^{1}H- and ^{31}P-NMR spectra. Whereas the relative positions of the Ph substituent at C(3) and the CH_3O group at P(2) are expressed by the anisotropy shift of the CH_3O resonances of **2** and **5** (*Fig. 2*), the relative configuration at C(3) can be detected *via* the value of J(P,P) (*Table 7*). As all ^{31}P resonances of **2**–**5** can be unambiguously assigned using ^{1}H,^{31}P-correlated spectroscopy, the ^{31}P-NMR spectrum provides a simple and efficient means for the identification and quantification of the components present in the reaction mixture (*Fig. 5*). Compounds **2** and **5**, which have been reported to be the main products in the

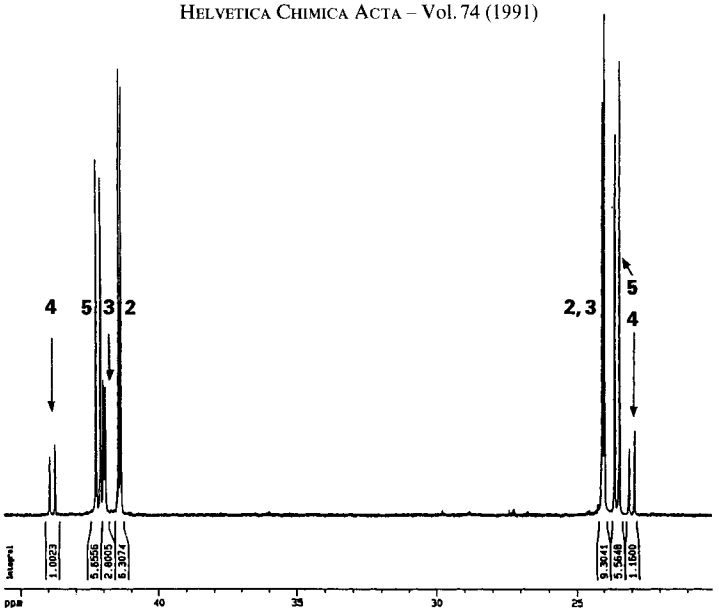


Fig. 5. *^{31}P-NMR spectrum of a mixture of* **2–5**. The spectrum was generated artificially by coadding the spectra of **3** and of a mixture **2**/**4**/**5**.

formation of the isomeric mixture [8], are now established to possess a *cis* relationship of the Ph and CH_3O substituents at C(3) and P(2), respectively.

The unsubstituted 1,2λ^5-oxaphospholan-2-one **1** exhibits a pronounced mobility in the region of the atoms C(3) and C(4). From evidence collected so far, we suppose **1** to be present as two half-chair conformers interconverting rapidly on the NMR time scale (*Fig. 6*). This is in accordance with earlier investigations on related compounds [3a] [4].

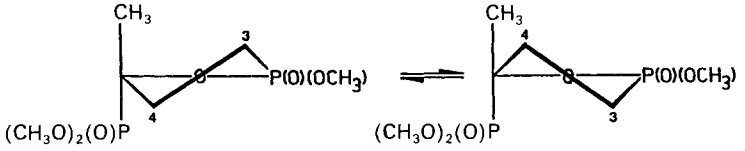


Fig. 6. *Interchanging half-chairs of* **1** *in $CDCl_3$ solution at 300 K*

In compounds **6** and **7**, the conformation of the oxaphospholane ring is fixed by a butano or propano bridge, respectively. The strain exerted by these structural elements is expressed in the ^{31}P chemical shift values of the ring P-atom as well as in the homonuclear P,P coupling constants (*Tables 3* and *7*). The rigid structures of **6** and **7** and the NMR spectroscopic parameters connected therewith permit a cross-check on the conformations deduced for **2–5**.

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Experimental Part

Syntheses. Compounds **2**–**7** have been described elsewhere [8]. Compound **1** could be prepared by cyclization of tetramethyl *P,P'*-(1-hydroxypropane-1,3-diyl)bis[phosphonate] [8]. Heating in toluene soln. in the presence of TsOH afforded a 9:1 mixture of diastereoisomers in very low yield. Column chromatography (silica gel) yielded small amounts of the unstable main component **1** which was identified and characterized solely by NMR spectroscopy [18].

NMR Spectra: Bruker AM 400 WB NMR spectrometer (9.4 T; ^{1}H; 400.13 MHz; ^{13}C: 100.61 MHz; ^{31}P: 161.98 MHz) equipped with an *Aspect 3000* on-line computer; long-time stability was achieved by a deuterium lock channel; with the exception of reverse-detected experiments, samples were spun with *ca.* 20 Hz; data processing on a separate computer (*Aspect X32*). Samples in 5-mm tubes, $CDCl_3$ solns. at 300 K, 2.5M for the INADEQUATE experiment and 30 mM in all other cases; for NOE difference and NOESY measurements, O_2 was removed by a stream of Ar; δ's in ppm from internal TMS for ^{1}H and ^{13}C and from external H_3PO_4 (85%) for ^{31}P.

For all experiments, software supplied by the manufacturer was used [19]. Proton-spin systems were calculated and fitted to the experimental $^1H\{^{31}P\}$ spectra using the PANIC algorithm [20]. Heteronuclear coupling constants were taken directly from the NMR spectra, assuming the respective spin systems to be of first order. Coupling constants are estimated to be correct within ±0.2 Hz.

^{31}P-Broad-band-decoupled ^{13}C spectra and ^{1}H and ^{13}C spectra decoupled selectively from P(2) or P–C(5) ($P(3^2)$ or P–C(3) in the case of **7**) were recorded with the help of a second synthesizer (*B-SV 3 BX*) and a probehead designed specifically for ^{1}H,^{13}C,^{31}P triple resonance experiments. ^{31}P-Broadband-decoupled ^{1}H spectra were achieved using reverse detection of ^{1}H and GARP decoupling of ^{31}P [21] [22]. C-Multiplicities were detected by the SEFT sequence [23].

2D-NMR spectroscopic techniques used included H,H-COSY [24], XH-COSY with direct (^{1}H,^{31}P correlation) [25] and reverse (^{1}H,^{13}C correlation) [21] detection, NOESY [26], and INADEQUATE [27]. Typical parameters were 1 K data points in $F2$ and 128 (XH-COSY) or 256 (H,H-COSY) experiments in $F1$. In any case, zero filling in $F1$ was applied. A squared sine bell shifted by $\pi/2$ rad was used as a filter function except with the ^{1}H,^{31}P-correlated spectra where exponential weighting was applied. H,H-COSY and INADEQUATE spectra were symmetrized after *Fourier* transformation. The S/N ratio of the reverse detected correlated spectra was improved by subtracting the mean T_1 noise from the transformed data matrix.

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