Influence of Phosphorus Derivatization on the Conformational Behavior of Model Compounds for 3′,5′-xylo-cAMP Studied by ^{1}H NMR Spectroscopy

Rob J. M. Hermans* and Henk M. Buck

Department of Organic Chemistry, Eindhoven University of Technology, P.O. Box 513, NL-5600 MB Eindhoven, The Netherlands

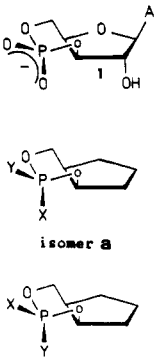
Received August 7, 1987

A number of epimeric pairs of 3-X-3-Y-*cis*-2,4-dioxa-3-phosphabicyclo[4.3.0]nonanes (**2**, X = OCH_3, Y = O; **3**, X = OCH_3, Y = S; **4**, X = OPh, Y = O; **5**, X = OPh, Y = S; **6**, X = Cl, Y = O; **7**, X = Cl, Y = S; **8**, X = $N(CH_3)_2$, Y = O; **9**, X = $N(CH_3)_2$, Y = S; **10**, X = S^-, Y = O; **11**, X = O^-, Y = O) has been prepared as model compounds for 3′,5′-xylo-cAMP (**1**). The influence of the nature and orientation of the exocyclic phosphorus substituents on the phosphate ring conformation has been determined by ^{1}H NMR. It is shown that the cis phosphates **2a–7a** and the trans phosphates **8b** and **9b** populate the same chair conformation as was found for 3′,5′-xylo-cAMP. However, the phosphate rings of their epimers exist as an equilibrium between this chair conformation and a distorted-boat conformation. The mole fraction of the latter conformer depends on the nature of the exocyclic phosphorus substituent and varies from 0.14 for the phosphoramidate **9a** to 0.86 for the chlorophosphonate **7b**. For the phosphates **10a**, **10b**, and **11**, the conformation of the dioxaphosphorinane ring is strongly affected by the exact location of the negative charge on the phosphate group.

Introduction

The conformations of natural 3′,5′-cyclic nucleotides, e.g., 3′,5′-cAMP and 3′,5′-cGMP, have been extensively studied by X-ray[1] and NMR methods.[2–5] It was shown that the trans (1,2) fusion of the six-membered phosphate ring to a five-membered sugar ring produces a rigid bicyclic system with the phosphate ring in a chair conformation. Recently, however, it was demonstrated that the dioxaphosphorinane ring of neutral phosphate and phosphoramidate derivatives of thymidine 3′,5′-cyclic monophosphate exists as an equilibrium between a chair and twist conformation.[6] A similar observation was made on the phosphate ring conformation of a number of phosphorus-derivatized 3′,5′-cyclic nucleotide model compounds.[7] The mole fraction of twist conformer in these uncharged phosphates was found to vary with the nature and orientation of the exocyclic substituents on the phosphorus atom and amounted up to 0.8 for some chloro derivatives.[6,7] For the structurally related 9-(β-D-xylofuranosyl)adenine 3′,5′-cyclic monophosphate (3′,5′-xylo-cAMP, **1**), in which the phosphate ring is cis (1,2) fused to the sugar ring, a chair conformation, although different from the one mentioned before, has been found.[8]

In this paper, we report the results of an ^{1}H NMR study of the conformation of the phosphate ring of a series of epimeric 3-oxo- and 3-thioxo-*cis*-2,4-dioxa-3-phosphabicyclo[4.3.0]nonanes **2a,b–10a,b** and **11**, which are simple model compounds for **1**. The major objective of this research has been to assess the influence of phosphorus-derivatization on the dioxaphosphorinane ring conformation in cis (1,2) fused bicyclic systems like **1**. A comparison



	X	Y		X	Y
2	OCH_3	O	**7**	Cl	S
3	OCH_3	S	**8**	$N(CH_3)_2$	O
4	OPh	O	**9**	$N(CH_3)_2$	S
5	OPh	S	**10**	S^-	O
6	Cl	O	**11**	O^-	O

is made with the results of conformational studies on other cis (1,2) fused bicyclic 1,3,2-dioxaphosphorinanes.[8–11]

Results and Discussion

Synthesis. The cis compound **2a** (singly bonded substituent cis to H_1) was obtained by stereochemically retentive NO_2/N_2O_4 oxidation[12] of phosphite **14a**. Reaction of this phosphite with elemental sulfur, also proceeding with retention of configuration, afforded thiophosphate **3a**. Phosphite **14a** (methoxy group cis to H_1) was prepared by transesterification of (1*RS*,2*RS*)-2-hydroxycyclopentanemethanol (**13**) with trimethylphosphite (**12**) in 100% stereomeric purity. Treatment of the stereomerically pure cis chlorophosphonite **15**,[13] obtained from **13** and phosphorus trichloride, with methanol in the presence of triethylamine according to the general method of Verkade et al.[12a] gave phosphite **14b** as major component (>80%). Reaction of this compound with NO_2/N_2O_4 and S_8 afforded the phosphates **2b** and **3b**, respectively. (The methyl phosphite **14b** isomerized under influence of traces of trifluoroacetic acid into the thermodynamically more stable **14a** (Scheme I).

(1) (a) Watenpaugh, K.; Dow, J.; Jensen, L. H.; Furburg, S. *Science (Washington, D.C.)* **1968**, *159*, 206. (b) Coulter, C. L. *Acta Crystallogr., Sect. B* **1969**, *25*, 2055. (c) Chwang, A. K.; Sundaralingam, M. *Acta Crystallogr., Sect. B* **1974**, *30*, 1233. (d) Varughese, K. I.; Lu, C. T.; Kartha, G. *J. Am. Chem. Soc.* **1982**, *104*, 3398.

(2) Blackburn, B. J.; Lapper, R. D.; Smith, I. C. P. *J. Am. Chem. Soc.* **1973**, *95*, 2873.

(3) Lapper, R. D.; Mantsch, H. H.; Smith, I. C. P. *J. Am. Chem. Soc.* **1973**, *95*, 2878.

(4) Lee, C.-H.; Sarma, R. H. *J. Am. Chem. Soc.* **1976**, *98*, 3541.

(5) Robins, M. J.; MacCoss, M.; Wilson, J. S. *J. Am. Chem. Soc.* **1977**, *99*, 4660.

(6) (a) Sopchik, A. E.; Bentrude, W. G. *Tetrahedron Lett.* **1980**, *21*, 4679. (b) Nelson, K. A.; Bentrude, W. G.; Setzer, W. N.; Hutchinson, J. P. *J. Am. Chem. Soc.* **1987**, *109*, 4058. (c) Sopchik, A. E.; Bajwa, G. S.; Nelson, K. A.; Bentrude, W. G. In *Phosphorus Chemistry*; ACS Symposium Series 171; Quin, L. D., Verkade, J. G., Eds.; American Chemical Society: Washington, DC, 1981; pp 217–220.

(7) Hermans, R. J. M.; Buck, H. M., *J. Org. Chem.* **1987**, *52*, 5150.

(8) MacCoss, M.; Ezra, F. S.; Robins, M. J.; Danyluk, S. S. *Carbohydr. Res.* **1978**, *62*, 203.

(9) Neser, J.-R.; Tronchet, J. M. J.; Charollais, E. J. *Can. J. Chem.* **1983**, *61*, 1387.

(10) Nifant'ev, E. E.; Elepina, L. T.; Borisenko, A. A.; Koroteev, M. P.; Aslanov, L. A.; Ionov, V. M.; Sotman, S. S. *Zh. Obshch. Khim.* **1978**, *48*, 2453.

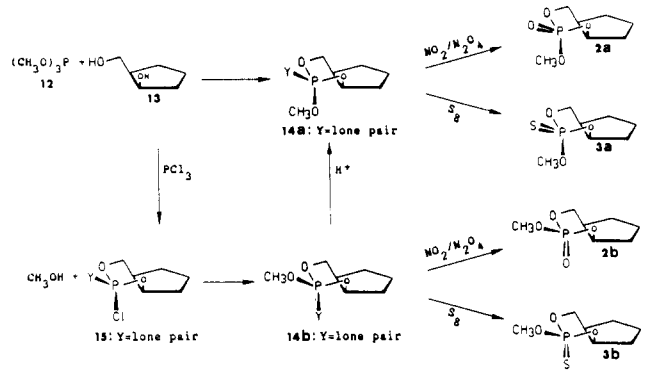
(11) Morr, M.; Ernst, L.; Mengel, R. *Liebigs Ann. Chem.* **1982**, 651.

(12) (a) Mosbo, A. J.; Verkade, J. G. *J. Am. Chem. Soc.* **1973**, *95*, 4659. (b) Michalski, J.; Okruscek, A.; Stec, W. *J. Chem. Soc. D* **1970**, 1495. (c) Denney, D. Z.; Chen, G. Y.; Denney, B. D. *J. Am. Chem. Soc.* **1969**, *91*, 6838.

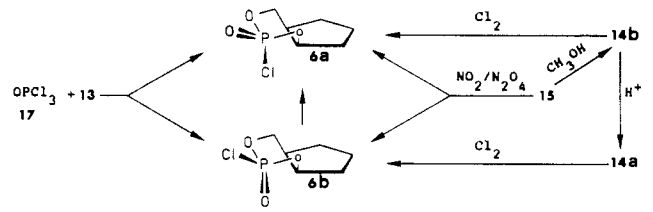
(13) The chloro substituent is believed to be cis to H_1 by the strong similarity of the couplings of H_{5a} and H_{5b} to those of the cis phosphites **14a** and **16a** (see Experimental Section).

0022-3263/88/1953-2077$01.50/0

Scheme I



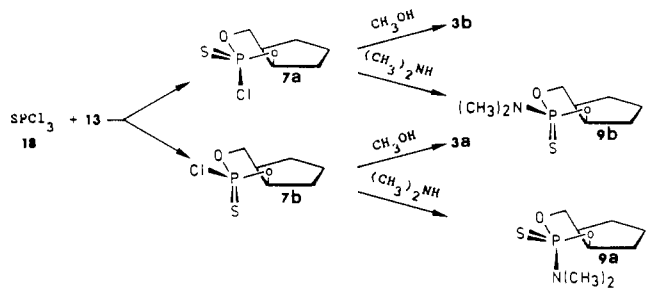
Scheme II



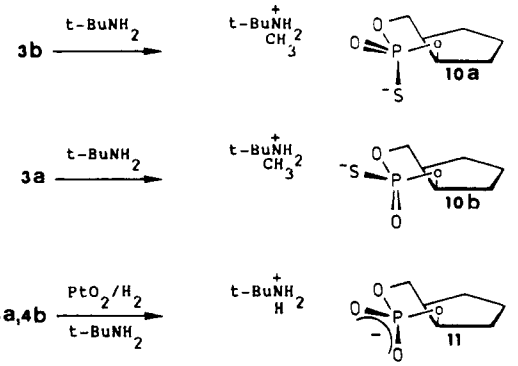
The phenoxy compounds **4a** and **4b** were synthesized from the corresponding phosphites **16a** and **16b**, respectively, by stereoretentive NO_2/N_2O_4 oxidation. Reaction of phenyl dichlorophosphinate with diol **13** as described by Penney and Belleau[14] gave a 53/47 mixture of **4a** and **4b** (determined by integration of the ^{31}P NMR signals). Heating the phosphites **16a** and **16b** with equimolar amounts of S_8 afforded the thioxophosphorinanes **5a** and **5b**, respectively. Phosphite **16b** was obtained by reaction of chlorophosphonite **15** with phenol. Acid-induced stereomutation of this kinetically preferred isomer gave **16a**. The reaction between phosphorus oxychloride **17** and diol **13** in the presence of γ-collidine yielded a mixture containing two main components with ^{31}P chemical shifts of 5.4 and 1.0 ppm in the ratio 36/64.[15] A mixture of both components in the ratio 30/70 was also formed on oxidation of chlorophosphonite **15** (Scheme II). Upon standing several weaks, both ratios changed to 9/91. In addition, new signals appeared as a result of the decomposition of both components. In contrast, the compound with the downfield shift was formed almost exclusively (ratio 91/9) upon chlorination of phosphite **14a**. In addition, reaction of **14b** with chlorine gave the compound with ^{31}P resonance at 1.0 ppm in 80% excess. Since both reactions are known to proceed with inversion of configuration at phosphorus in comparable systems,[16] the resonance at 5.4 and 1.0 ppm could be attributed to **6b** and **6a**, respectively.

Reaction of thiophosphoryl chloride **18** with diol **13** afforded a mixture of two components with ^{31}P resonances at 71.7 and 63.7 ppm in the ratio 46/52, which could be separated by column chromatography. The phosphate with downfield shift could be identified as **7b**, since it was stereospecifically transformed into **3a** upon methanolysis, which has been found to proceed with complete configurational inversion at phosphorus in bicyclic 1,3,2-dioxaphosphorinanes.[7,17,18] In an analogous way, the signal at 63.7 ppm could be assigned to **7a** (Scheme III).

Scheme III



Scheme IV



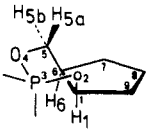
The dimethylamino derivatives **8a,b** and **9a,b** were obtained by the reaction of the corresponding chlorophosphonates with dimethylamine, which is known to proceed with complete inversion of configuration at phosphorus.[7,18] Thus, a 68/32 mixture of **6a** and **6b** afforded a 31/69 mixture of **8a** and **8b**, while aminolysis of the pure chloridates **7a** and **7b** resulted in pure **9b** and **9a**, respectively. The charged phosphates **10a** and **10b** were obtained from **3b** and **3a**, respectively, by stereospecific demethylation with *tert*-butylamine (Scheme IV).[19] Compound **11** was prepared by hydrogenolysis of a mixture of **4a** and **4b** as described in ref 14.

Assignment of Configuration at Phosphorus. Assignment of the cis and trans configurations at phosphorus in the dioxaphosphorinanes **2a,b–10a,b** was made on the basis of their stereospecific way of synthesis (vide supra). As was reported earlier for other isomeric pairs of bicyclic 1,3,2-dioxaphosphorinanes,[7,18,20–22] the cis orientation of the singly bonded substituent results in a ^{31}P chemical shift (see Experimental Section) upfield of that for the trans isomer except for the phosphates **9a** and **9b**. The reverse order observed for these two compounds is, however, exactly parallel to what was noted for structurally related thiophosphoramidates.[7,20]

^{1}H NMR Conformational Analysis. The ^{1}H NMR parameters of the phosphate ring of the compounds **2a,b–9a,b** (in acetone-d_6) and of **10a,b** and **11** (in methanol-d_4) are listed in Table I. The chemical shifts and spin–spin coupling constant data for H_{5a} and H_{5b} were obtained by iterative fitting of expansions of the H_{5a} and H_{5b} patterns of the 200-MHz ^{1}H NMR spectra, using the PANIC program.[23] For the H_1 proton, the first-order

(14) Penney, C. L.; Belleau, B. *Can. J. Chem.* **1978**, *56*, 2396.
(15) Positive ^{31}P chemical shifts in ppm downfield from external 85% H_3PO_4.
(16) Edmundson, R. S.; Johnson, O.; Jones, D. W.; King, T. J. *J. Chem. Soc., Perkin Trans. 2* **1985**, 69.
(17) Hall, C. R.; Inch, T. D. *Tetrahedron* **1980**, *36*, 2059.
(18) Bouchu, D.; Dreux, J. *Phosphorus Sulfur* **1982**, *13*, 25.
(19) (a) Smith, D. J.; Ogilvie, K. K.; Gillen, M. F. *Tetrahedron Lett.* **1980**, *21*, 861. (b) Sopchik, A. E.; Bentrude, W. G. *Tetrahedron Lett.* **1981**, *22*, 307.
(20) Bouchu, D. *Phosphorus Sulfur* **1983**, *15*, 33.
(21) Maryanoff, B. E.; Hutchins, R. O.; Maryanoff, C. A. *Top. Stereochem.* **1979**, *11*, 187.
(22) Gorenstein, D. G.; Rowell, R.; Findlay, J. *J. Am. Chem. Soc.* **1980**, *102*, 5077.
(23) PANIC program: Copyright Bruker Spectrospin A. G., Switzerland.

Table I. Selected ^{1}H NMR Spectral Parameters for 1,[a] 2a,b–10a,b, and 11 at 300 K



	δ			J, Hz					
compd	5a	5b	1[b]	5a,5b	5a,P	5a,6	5b,P	5b,6	Σ1[c]
1[a]	4.62	4.65	4.83	−13.5	21.6	1.5	1.9	2.0	<2.9
2a[d]	4.26	4.54	4.85	−11.6	21.3	1.9	2.8	2.9	7.4
3a[d]	4.21	4.61	4.90	−11.5	21.6	2.2	3.5	3.5	6.5
4a[d]	4.36	4.75	5.07	−11.7	22.6	1.8	2.2	3.0	6.7
5a[d]	4.37	4.85	5.13	−11.5	22.7	2.0	3.3	3.5	~8
6a[d]	4.53	4.77	5.09	−11.9	28.2	1.5	3.3	2.8	6.7
7a[d]	4.49	4.82	5.09	−11.9	28.8	1.5	4.3	2.9	9.6
8a[d]	4.11	4.36	4.79	−11.3	15.6	4.8	8.7	4.3	17.5
9a[d]	4.13	4.51	4.81	−11.3	19.6	3.0	5.6	3.6	11.2
10a[e]	4.00	4.62	4.78	−11.4	24.0	1.0	5.2	2.8	~4
11[e]	4.00	4.46	4.70	−11.4	19.4	2.0	4.9	3.0	~4
2b[d]	4.20	4.64	5.04	−11.5	16.6	4.9	9.0	4.3	14.0
3b[d]	4.18	4.60	4.94	−11.5	19.8	4.3	9.3	4.2	13.1
4b[d]	4.14	4.52	5.02	−11.4	12.4	7.0	14.0	5.2	19.7
5b[d]	4.19	4.62	5.00	−11.5	17.9	5.4	11.5	4.6	15.1
6b[d]	4.22	4.55	5.14	−11.5	9.9	9.3	24.3	6.5	27.4
7b[d]	4.19	4.53	5.07	−11.4	11.4	10.2	25.0	6.7	24.2
8b[d]	4.11	4.57	4.85	−11.6	19.1	2.9	4.6	3.5	6.8
9b[d]	4.15	4.72	4.91	−11.6	24.7	1.6	4.1	3.0	6.7
10b[e]	3.90	4.39	4.72	−11.3	16.3	5.1	10.9	4.7	12.4

[a] In D_2O from ref. 8. [b] First-order analysis. [c] $\Sigma 1 = J_{1,P} + J_{1,6} + J_{1,9a} + J_{1,9b}$. [d] In acetone-$d_6$. [e] In methanol-$d_4$.

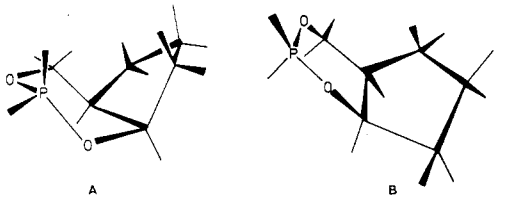


Figure 1. Possible chair conformations of the phosphate ring of **2a,b–10a,b** and **11**.

chemical shift value and the sum of the couplings to H_1 are presented in Table I. The relevant parameters of 3′,5′-xylo-cAMP (**1**) in D_2O are given for comparison.[8]

Uncharged Phosphorinanes 2a,b–9a,b. Inspection of Dreiding models indicated two possible chair forms of the six-membered phosphate ring in the compounds **2a,b–10a,b** and **11**. These are depicted in Figure 1.

The magnitude of the various coupling constants to H_{5a} and H_{5b} in both conformers was estimated from the dihedral angles by using the empirically generalized Karplus relation[24,25] for $^3J_{HCCH}$ couplings and relation 1 for $^3J_{POCH}$ couplings (eq 1). This $^3J_{POCH}$ vs Φ_{PH} relationship, pro-

$$^3J_{POCH} = 18.1 \cos^2 \Phi - 4.8 \cos \Phi \quad (1)$$

posed by Lee and Sarma[4] was chosen since it had been used extensively and successfully for structurally related compounds.[8,9] The values of $J_{5a,P}$, $J_{5a,6}$, $J_{5b,P}$, and $J_{5b,6}$ thus obtained are listed in Table II.

Table II. Dihedral Angles Φ and the Corresponding Calculated Coupling Constants of the Conformers A and B

	conformer A		conformer B	
dihedral angle	Φ, deg	J, Hz	Φ, deg	J, Hz
$PO_4C_5H_{5a}$	−60	$J_{5a,P} = 2.3$	180	$J_{5a,P} = 22.9$
$H_6C_6C_5H_{5a}$	180	$J_{5a,6} = 11.5$	−60	$J_{5a,6} = 1.9$
$PO_4C_5H_{5b}$	180	$J_{5b,P} = 22.9$	60	$J_{5b,P} = 2.3$
$H_6C_6C_5H_{5b}$	−60	$J_{5b,6} = 4.1$	60	$J_{5b,6} = 1.9$

Comparing the data in Tables I and II it was clear that the phosphate rings of **2a–7a**, **8b**, and **9b** populated chair conformer B. The small differences between observed and calculated proton–proton coupling constants originated from small deviations of the ideal chair conformation B. The main reason for the differences in $J_{5a,P}$ and $J_{5b,P}$ values was the susceptibility of these coupling constants to the electronegativity of the substituents attached to the phosphorus atom.[7] In conformation A, the phosphorus and H_1 are in an antiperiplanar orientation, thus $J_{1,P} > 20$ Hz would be predicted. In contrast, dihedral angle $PO_2C_1H_1$ in conformation B is about 90°, leading to a very small $J_{1,P}$ value. Although the magnitude of $J_{1,P}$ was not known for **2a–7a**, **8b**, and **9b**, it was obvious from the sum of the couplings to H_1 that it was far less than 10 Hz (for **7a**, the largest coupling to H_1 is about 3.5 Hz). This presented another argument in favor of conformation B. The population of the chair conformer B is consistent with the preference of the electronegative OCH_3 (**2a**, **3a**), OPh (**4a**, **5a**), and Cl (**6a**, **7a**) for an axial position at phosphorus (in the chair form A, these substituents would be equatorially located). The relatively large dimethylamino group and its consequent preference for an equatorial position lead to adoption of the chair conformation B by the phosphoramidates **8b** and **9b**. The isomers **2b–7b**, **8a**, and to a lesser extent also **9a** showed coupling patterns that were quite different from those of their epimers and not consistent with chair form B being the only conformer populated. An equilibrium between the conformers A and B seemed to be a likely assumption for two reasons. First,

(24) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.

(25) In this generalized equation, the standard Karplus relation is extended with a correction term which accounts for the influence of electronegative substituents on $^3J_{HH}$

$$^3J_{HH} = 13.22 \cos^2 \Phi - 0.99 \cos \Phi + \sum[0.87 - 2.46 \cos^2 (\xi_i \Phi + 19.9|\Delta\chi_i|)]\Delta\chi_i$$

Φ is the proton–proton torsion angle, $\Delta\chi_i$ is the difference in electronegativity between the substituent and hydrogen according to the electronegativity scale of Huggins, and ξ_i is a substituent orientation parameter.

Table III. Mole Fraction x(A) of Conformer A of 2b–7b, 8a, and 9a at 300 K in Acetone-d_6

	x(A) calcd from			
compd	$J_{5a,P}$(obsd)	$J_{5a,6}$(obsd)	$J_{5b,P}$(obsd)	$J_{5b,6}$(obsd)
2b	0.23	0.32	0.32	0.88
3b	0.09	0.23	0.30	0.70
4b	0.46	0.54	0.56	1.38
5b	0.23	0.36	0.40	1.10
6b	0.69	0.78	0.86	2.17
7b	0.67	0.86	0.87	2.53
8a	0.19	0.22	0.24	0.73
9a	0.22	0.14	0.30	0.40

Table IV. Selected Coupling Constants of 7b at Various Temperatures in Acetone-d_6

	J, Hz					
T, K	5a,5b	5a,P	5a,6	5b,P	5b,6	$\sum 1^a$
330	−11.4	11.7	9.8	24.4	6.6	24.2
300	−11.4	11.4	10.2	25.0	6.7	24.2
270	−11.2	11.1	10.6	25.7	6.8	24.6
240	−11.2	10.9	10.8	26.5	6.9	24.8
210	−11.3	10.2	11.3	27.2	7.1	24.8
195	−11.3	10.1	11.5	27.5	7.2	24.7
180	−11.2	9.9	11.7	27.8	7.2	24.4

[a] $\sum 1 = J_{1,P} + J_{1,6} + J_{1,9a} + J_{1,9b}$.

in conformer A, the various substituents would be located in their preferred position on phosphorus. Second, the observed couplings of **2b–7b**, **8a**, and **9a** were intermediate between those expected for conformers A and B (Table II). The mole fraction x(A) was estimated from $J_{5a,P}$(obsd) and $J_{5b,P}$(obsd) (Table I) by using eq 2 and 3, where $J_{5a,P}$(A)

$$J_{5a,P}(\text{obsd}) = x(\text{A})J_{5a,P}(\text{A}) + (1 - x(\text{A}))J_{5a,P}(\text{B}) \quad (2)$$

$$J_{5b,P}(\text{obsd}) = x(\text{A})J_{5b,P}(\text{A}) + (1 - x(\text{A}))J_{5b,P}(\text{B}) \quad (3)$$

and $J_{5b,P}$(A) are the J_{PH} coupling constants to H_{5a} and H_{5b}, respectively, in conformer A and $J_{5a,P}$(B) and $J_{5b,P}$(B) those in conformer B. The $J_{5a,P}$ and $J_{5b,P}$ values of conformer A of **2b–7b**, **8a**, and **9a** were assumed to be equal to the corresponding coupling constants of their trans fused analogues of which the phosphate ring populates conformer A.[7] The $J_{5a,P}$ and $J_{5b,P}$ couplings of conformer B were given the values of $J_{5a,P}$ and $J_{5b,P}$ found for **2a–7a**, **8b**, and **9b** which populated entirely this conformer (vide supra). The results thus obtained are presented in Table III. In addition, x(A) calculated in an analogous procedure from the $J_{5a,6}$ and $J_{5b,6}$ values of **2b–7b**, **8a**, and **9a** is also given.

Although the mole fractions calculated from $J_{5a,P}$, $J_{5b,P}$, and $J_{5a,6}$ were in fairly good agreement, the values obtained from $J_{5b,6}$ clearly revealed that the initial assumption of an equilibrium between the chair conformers A and B could be rejected. Participation of a nonchair conformer instead of conformer A could afford an alternative explanation for the observed coupling constants of **2b–7b**, **8a**, and **9a**. With this assumption, it was clear from the results in Table I that the mole fraction of this nonchair conformer was maximal for the chlorophosphonates **6b** and **7b**. Therefore, **7b** was chosen for a variable temperature ^{1}H NMR study in the range 180–330 K in order to establish the exact geometry of the nonchair conformer. Some relevant results are listed in Table IV.

From the results in Table IV it was clear that the contribution of the nonchair conformer had increased upon lowering the temperature. Assuming that the equilibrium between conformer B and the nonchair conformer was shifted completely to the latter one at 180 K, the dihedral angles of this conformer could be deduced from the observed coupling constants. Using the generalized Karplus relation, values of $\Phi H_6C_6C_5H_{5a}$ = 180° and $\Phi H_6C_6C_5H_{5b}$ = −40° were obtained. Dihedral angles $\Phi PO_4C_5H_{5a}$ and $\Phi PO_4C_5H_{5b}$ were calculated with eq 4, which was derived

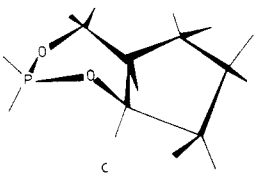


Figure 2. Distorted-boat conformation C.

Table V. Mole Fraction x(C) of Conformer C of 2b–7b, 8a, and 9a at 300 K in Acetone-d_6

	x(C) calcd from			
compd	$J_{5a,P}$(obsd)	$J_{5a,6}$(obsd)	$J_{5b,P}$(obsd)	$J_{5b,6}$(obsd)
2b	0.33	0.31	0.28	0.33
3b	0.31	0.22	0.11	0.19
4b	0.59	0.53	0.57	0.52
5b	0.42	0.35	0.29	0.30
6b	0.87	0.76	0.87	0.84
7b	0.88	0.85	0.92	0.88
8a	0.25	0.22	0.25	0.22
9a	0.08	0.14	0.30	0.14

$$^3J_{POCH} = 22.9 \cos^2 \Phi - 5.9 \cos \Phi \quad (4)$$

from the $J_{5a,P}$ values of 28.8 Hz found for **7a** ($\Phi PO_4C_5H_{5a}$ = 180°) and 2.8 Hz found for the trans fused analogue of **7a** ($\Phi PO_4C_5H_{5a}$ = −60°).[7] According to this relation, the values of $J_{5a,P}$ = 9.9 Hz and $J_{5b,P}$ = 27.9 Hz in **7b** corresponded to dihedral angles of $\Phi PO_4C_5H_{5a}$ = −37° and $\Phi PO_4C_5H_{5b}$ = −169°. The sum of the coupling constants to H_1 was 24.4 Hz, composed of values of 4.9, 5.3, 6.8, and 7.4 Hz. Although it was not known which value arose from coupling of H_1 to phosphorus, it could be calculated from eq 4 that dihedral angle $PO_2C_1H_1$ fell in the narrow range of −46° to −54° or −110° to −117°. Inspection of Dreiding models clearly revealed that only a small dihedral angle (∼−50°) was compatible with the distorted-boat conformation C (Figure 2), which was constructed on the basis of the dihedral angles calculated from the couplings to H_{5a} and H_{5b}.

Conformation C is intermediate between A and B. The PO_4C_5 side of C strongly resembles that of conformation A while the PO_2C_1 side has maintained the chairlike arrangement of B. In fact, conformation C results from A by tilting O_2 upwards and from B by flipping of the PO_4C_5 fragment. Using the $J_{5a,6}$ and $J_{5b,6}$ values of conformer B (taken to be equal to those found for **2a–7a**, **8b**, and **9b**) and conformer C (11.6 and 7.2 Hz, respectively) as limiting values, the mole fraction x(C) of the equilibrium B ⇄ C at 300 K was calculated for the phosphates **2b–7b**, **8a**, and **9a**. In addition, x(C) was also calculated from the observed $J_{5a,P}$ and $J_{5b,P}$ values. In this case, the values of $J_{5a,P}$ and $J_{5b,P}$ found for **2a–7a**, **8b**, and **9b** were used for conformer B. Due to the dependence of the $^3J_{POCH}$ couplings to the electronegativity of the substituents on the phosphorus atom, the values of 27.9 ($J_{5a,P}$) and 9.9 Hz ($J_{5b,P}$) for conformer C could only been used for compound **7b**. Therefore, the values of these coupling constants for conformation C of **2b–6b**, **8a**, and **9a** were calculated by using Karplus relations[26] which were derived from the values of $J_{5a,P}$ and $J_{5b,P}$ observed for **2a–6a**, **8b**, and **9b** ($\Phi PO_4C_5H_{5a}$ = 180°; $\Phi PO_4C_5H_{5b}$ = 60°) and for the trans fused analogues of these compounds ($\Phi PO_4C_5H_{5a}$ = −60°;

(26) Karplus relation used for: **2b**, ^3J_PH = 15.5 cos^2 Φ − 6.7 cos Φ; **3b**, $^3J_{PH}$ = 16.5 cos^2 Φ − 6.2 cos Φ; **4b**, $^3J_{PH}$ = 15.9 cos^2 Φ − 7.0 cos Φ; **5b**, $^3J_{PH}$ = 17.3 cos^2 Φ − 6.2 cos Φ; **6b**, $^3J_{PH}$ = 20.8 cos^2 Φ − 7.4 cos Φ; **7b**, $^3J_{PH}$ = 22.9 cos^2 Φ − 5.9 cos Φ; **8a**, $^3J_{PH}$ = 15.7 cos^2 Φ − 6.0 cos Φ; **9a**, $^3J_{PH}$ = 19.1 cos^2 Φ − 5.6 cos Φ; **10b**, $^3J_{PH}$ = 19.6 cos^2 Φ − 4.8 cos Φ.

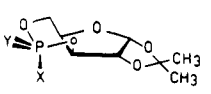
$\Phi PO_4C_5H_{5b}$ = 180°).[7] The mole fractions x(C) thus obtained (Table V) were in very good agreement. This enabled to regard the postulate of the presence of an equilibrium between the conformers B and C in **2b–7b**, **8a**, and **9a** as fully justified.

The variations in x(C) in Table V are the result of the balance between the preferences of Cl, OPh, and OCH_3 for an axial and of $N(CH_3)_2$ for an equatorial position at phosphorus favoring conformation C and the 1,3-steric and eclipsing interactions favoring chair conformer B. The distinct preference of the chloro group for an axial position is strong enough to force the chair conformation of **6b** and **7b** almost completely into the distorted-boat conformation C with Cl pseudoaxial. In case of OPh and OCH_3, the driving force for reorientation of these substituents is decreased as a result of the decreased electronegativity. This results in a smaller percentage of conformer C for **2b–5b** relative to **6b** and **7b**. The equatorial-seeking nature of the dimethylamino group is not strong enough to effect the conversion B → C to a large degree. As a result, x(C) for **8a** and **9a** is quite small. Replacement of the doubly bonded oxygen by sulfur affects the equilibrium B ⇄ C only significantly in the isomers having exocyclic substituents with a moderate preference for an axial or equatorial position. This cannot be explained by a decreased preference of sulfur for an equatorial position relative to oxygen since in that case one would expect a larger value of x(C) for **9a** if compared with **8a**. The reason for the absence of conformer A in the isomers **2b–7b**, **8a**, and **9a** are the strong steric interactions between the phosphate ring and the cis-annelated five-membered ring in this conformer.

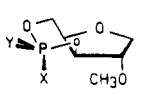
Charged Phosphates 10a,b and 11. The compounds **10a,b** and **11** resemble **1** most closely, since in these compounds the phosphate group is negatively charged. In **11**, the negative charge is delocalized between the two exocyclic oxygen atoms as in **1**. In **10a** and **10b**, however, the negative charge is localized on the sulfur atom.[27] The results in Table I indicate an exclusive population of the conformer B by **10a** and **11**. In contrast, the coupling pattern of **10b** point to an equilibrium of conformers B and C. Using the appropriate equations,[26] values of x(C) = 0.50 (from $J_{5a,P}$(obsd)), x(C) = 0.38 (from $J_{5a,6}$(obsd)), x(C) = 0.31 (from $J_{5b,P}$(obsd)) and x(C) = 0.43 (from $J_{5b,6}$(obsd)) are obtained. These results show that a negatively charged sulfur atom in a cis position results in the same conformation of the phosphate ring as a delocalized charge. However, introduction of a trans located negatively charged sulfur atom leads to a clearly different conformation. In fact, the value of x(C) for **10b** is intermediate between those of **2b** and **4b** in which the singly bonded substituents are OCH_3 and OPh, respectively.

Comparison with Other Cis (1,2) Fused Bicyclic Phosphates. The compounds **2a–7a**, **8b**, **9b**, **10a**, and **11** populate entirely chair conformer B. Coupling patterns indicative of chair conformation B have been found previously for the comparable cis fused phosphates **1**,[8] **19a**,[9] **20a**,[10] and **21**.[10] The chair structure of the latter was also confirmed by the results of an X-ray investigation.

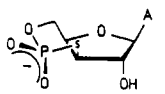
From the observations made on **1** and **11** it is evident that the replacement of an adenosine fragment in **1** by a cyclopentane ring does not result in a significant change of the dioxaphosphorinane ring conformation. Comparison of the results found for **4a** and **8b** with those for **19a**[9] and



19a: X=OPh, Y=O
19b: X=O, Y=OPh



20a: X=H, Y=O
20b: X=O, Y=H



22

21: X=O, Y=N(C_2H_5)$_2$

21[10] also reveals the invariability of the dioxaphosphorinane ring conformation to the composition of the cis fused five-membered ring in isomers having the singly bonded exocyclic substituent in the preferred orientation. The phosphorus containing rings of the isomers **19b**[9] and **20b**[10] have been found to exist as an equilibrium between chair form B and a nonchair conformer. For the phosphate ring of 3′-thio-3′,5′-xylo-cAMP (**22**), a twist-boat conformation has been established.[11] The structures of these nonchair forms are, however, completely different from conformation C.

Experimental Section

All solvents and materials were reagent grade and were used as received or purified as required. All reactions involving phosphorus compounds were routinely run under an atmosphere of dry nitrogen. ^{1}H NMR spectra were run in the FT mode on a Bruker AC-200 spectrometer at 200.1 MHz, 32K data base, 3000-Hz SW, and 5.10-s acquisition time. A standard computer simulation–iteration procedure[23] was employed to obtain accurate values for spin–spin coupling constants, and chemical shifts. ^{13}C NMR spectra were recorded on a Bruker AC-200 at 50.3 MHz. Chemical shifts in parts per million for ^{1}H and ^{13}C are referenced to TMS. ^{31}P NMR spectra were run on a Bruker AC-200 spectrometer at 81.0 MHz. Positive ^{31}P chemical shifts are in δ (parts per million) downfield from external 85% H_3PO_4. Melting points are uncorrected. Column chromatography was performed by using silica gel (type 60 Merck) as the stationary phase. TLC was performed on silica gel 60 F-254 (Merck). Detection was effected by exposure to iodine vapor.

(1*RS*,2*RS*)-2-Hydroxycyclopentanemethanol (13). This compound was prepared from cyclopentanone by the method of Penney and Belleau:[14] bp 90 °C (1.1 mm); ^{1}H NMR (acetone-d_6) δ 1.40–2.00 (m, 7 H, CH_2, CH), 3.46–3.97 (m, 4 H, C*H*$_2$OH, CHO*H*, CH_2O*H*), 4.22–4.34 (m, 1 H, C*H*OH); ^{13}C NMR (acetone-d_6) δ 22.7 (CH_2), 26.4 (CH_2), 35.8 (CH_2), 47.6 (CH_2), 62.8 (CH_2OH), 74.6 (CHOH).

3β-Chloro-*cis*-2,4-dioxa-3-phosphabicyclo[4.3.0]nonane (15). A solution containing diol **13** (2.32 g, 20.0 mmol) and triethylamine (4.05 g, 40.0 mmol) in methylene chloride (60 mL) and a separate solution containing phosphorus trichloride (2.75 g, 20.0 mmol) in methylene chloride (60 mL) were added dropwise at equal rates to 100 mL of methylene chloride at 0 °C in 45 min. The mixture was stirred further at 0 °C for 30 min and at 25 °C for 2 h. The solvent was removed at 25 °C (30 mm) and the residue triturated with ether (100 mL) and filtered. The ether solution was evaporated and the residue purified by vacuum distillation to yield 1.23 g (6.8 mmol, 34%) of **15**: bp 92 °C (2.0 mm); ^{31}P NMR (acetone-d_6) δ 155.1; ^{1}H NMR (acetone-d_6) δ 1.40–2.30 (m, 7 H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 3.93–4.05 (m, 1 H, H_{5a}, $J_{5a,5b}$ = −11.8 Hz, $J_{5a,P}$ = 10.4 Hz, $J_{5a,6}$ = 1.4 Hz), 4.75–4.88 (m, 2 H, H_{5b}, H_1, $J_{5a,5b}$ = −11.8 Hz, $J_{5b,P}$ = 5.6 Hz, $J_{5b,6}$ = 2.9 Hz); ^{13}C NMR (acetone-d_6) δ 22.1 (C_7), 25.4 (C_8, J = 1.0 Hz), 34.1 (C_9, J = 2.9 Hz), 42.1 (C_6, J = 5.5 Hz), 62.0 (C_5, J = 3.9 Hz), 76.6 (C_1, J = 4.1 Hz).

3β-Methoxy-*cis*-2,4-dioxa-3-phosphabicyclo[4.3.0]nonane (14a). Equimolar quantities of trimethyl phosphite (**12**) and diol **13** were mixed and heated until methanol began to reflux. The mixture was then stirred at room temperature overnight. Methanol was removed and the residue distilled at 64–68 °C (3.0 mm): ^{31}P NMR (acetone-d_6) δ 133.2; ^{1}H NMR (acetone-d_6) δ 1.56–2.20 (m, 7 H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 3.51 (d, 3 H, OCH_3, J = 10.9 Hz), 3.55–3.67 (m, 1 H, H_{5a}, $J_{5a,5b}$ = −11.1 Hz, $J_{5a,P}$ = 10.0 Hz, $J_{5a,6}$ = 1.0 Hz), 4.50–4.59 (m, 1 H, H_{5b}, $J_{5a,5b}$ = −11.1 Hz, $J_{5b,P}$ = $J_{5b,6}$ = 2.8 Hz), 4.60–4.64 (m, 1 H, H_1); ^{13}C NMR (acetone-d_6) δ 22.4 (C_7), 25.6 (C_8), 34.6 (C_9, J = 3.3 Hz), 42.3 (C_6,

(27) (a) Iyengar, R.; Eckstein, F.; Frey, P. A. *J. Am. Chem. Soc.* **1984** *106*, 8309. (b) Frey, P. A.; Sammons, R. D. *Science (Washington, D.C.)* **1985**, *228*, 541. (c) Frey, P. A.; Reimschussel, W.; Paneth, P. *J. Am. Chem. Soc.* **1986**, *108*, 1720.

J = 6.0 Hz), 49.7 (OCH_3, J = 17.8 Hz), 58.7 (C_5, J = 2.4 Hz), 73.0 (C_1, J = 2.6 Hz).

3α-Methoxy-*cis*-2,4-dioxa-3-phosphabicyclo[4.3.0]nonane (14b). Phosphite **14b** was prepared by the general method of Verkade et al.[12a] To a stirred solution of chlorophosphonite **15** (180 mg, 1.0 mmol) in 15 mL of anhydrous ether maintained at −10 °C was added dropwise with stirring a solution containing 0.9 equiv of methanol (28.8 mg, 0.9 mmol) and 1.0 equiv of triethylamine (101.2 mg, 1.0 mmol) in 10 mL of anhydrous ether. After removal of the triethylamine hydrochloride salt, the product was concentrated and not further purified: ^{31}P NMR (acetone-d_6) δ 134.2 (**14b**, 84%) and 133.2 (**14a**, 16%); ^{1}H NMR (acetone-d_6) δ 1.19–2.20 (m, 6 H, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 2.30–2.50 (m, 1 H, H_6), 3.50 (d, 3 H, OCH_3, J = 10.6 Hz), 3.73–3.87 (m, 1 H, H_{5a}, $J_{5a,5b}$ = −10.9 Hz, $J_{5a,P}$ = 9.0 Hz, $J_{5a,6}$ = 6.3 Hz), 3.90–4.05 (m, 1 H, H_{5b}, $J_{5a,5b}$ = −10.9 Hz, $J_{5b,P}$ = 11.3 Hz, $J_{5b,6}$ = 7.8 Hz), 4.33–4.39 (m, 1 H, H_1); ^{13}C NMR (acetone-d_6) δ 22.2 (C_7), 27.4 (C_8), 34.2 (C_9, J = 2.7 Hz), 40.0 (C_6, J = 6.4 Hz), 49.1 (OCH_3, J = 10.0 Hz), 60.8 (C_5), 84.5 (C_1, J = 2.0 Hz).

3β-Phenoxy-*cis*-2,4-dioxa-3-phosphabicyclo[4.3.0]nonane (16a). Cis phosphite **16a** was prepared by acid-induced stereomutation of **16b**: bp 110–113 °C (0.9 mm); ^{31}P NMR (acetone-d_6) δ 126.0; ^{1}H NMR (acetone-d_6) δ 1.40–2.12 (m, 7 H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 3.71–3.83 (m, 1 H, H_{5a}, $J_{5a,5b}$ = −11.4 Hz, $J_{5a,P}$ = 10.1 Hz, $J_{5a,6}$ = 1.0 Hz), 4.72–4.81 (m, 1 H, H_{5b}, $J_{5a,5b}$ = −11.4 Hz, $J_{5b,P}$ = $J_{5b,6}$ = 2.9 Hz), 4.81–4.85 (m, 1 H, H_1), 7.00–7.44 (m, 5 H, Ar H); ^{13}C NMR (acetone-d_6) δ 22.3 (C_7), 25.6 (C_8, J = 0.7 Hz), 34.6 (C_9, J = 3.4 Hz), 42.2 (C_6, J = 5.9 Hz), 59.7 (C_5, J = 2.6 Hz), 74.1 (C_1, J = 2.6 Hz), 120.5 (Ar C, J = 7.9 Hz), 123.9 (Ar C, J = 1.1 Hz), 130.5 (Ar C), 153.8 (Ar C, J = 6.3 Hz).

3α-Phenoxy-*cis*-2,4-dioxa-3-phosphabicyclo[4.3.0]nonane (16b). This compound was prepared from **15** and phenol according to the procedure described for the synthesis of **14b**. The crude product consisted of 87% of **16b** and was not further purified: ^{31}P NMR (acetone-d_6) δ 128.2; ^{1}H NMR (acetone-d_6) δ 1.24–2.16 (m, 6 H, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 2.45–2.64 (m, 1 H, H_6), 3.73–3.83 (m, 1 H, H_{5a}, $J_{5a,5b}$ = −11.1 Hz, $J_{5a,P}$ = 9.6 Hz, $J_{5a,6}$ = 6.5 Hz), 4.10–4.20 (m, 1 H, H_{5b}, $J_{5a,5b}$ = −11.1 Hz, $J_{5b,P}$ = 11.4 Hz, $J_{5b,6}$ = 5.8 Hz), 4.37–4.47 (m, 1 H, H_1), 7.00–7.40 (m, 5 H, Ar H); ^{13}C NMR (acetone-d_6) δ 21.1 (C_7), 27.0 (C_8), 33.2 (C_9, J = 1.8 Hz), 38.7 (C_6, J = 6.3 Hz), 59.9 (C_5, J = 1.4 Hz), 76.6 (C_1, J = 5.3 Hz), 121.1 (Ar C, J = 7.6 Hz), 124.2 (Ar C), 130.4 (Ar C), 151.3 (Ar C, J = 7.0 Hz).

3β-Methoxy-3α-oxo-*cis*-2,4-dioxa-3-phosphabicyclo[4.3.0]nonane (2a). A solution of NO_2/N_2O_4 in CH_2Cl_2 (1 g/40 mL) was added dropwise to a stirred solution of methyl phosphite **14a** (100 mg, 0.57 mmol) in 15 mL of methylene chloride at −78 °C until a faint greenish blue color appeared in the solution (TLC (hexane/ether, 5/4) indicated that no starting material remained). The mixture was allowed to come to room temperature. The solvent was evaporated and the residue purified by column chromatography using 2-butanone as eluent to give 40 mg (0.21 mmol, 37%) of **2a** as a colorless liquid. Anal. Calcd for $C_7H_{13}O_4P$: C, 43.76; H, 6.82. Found: C, 43.90; H, 6.95. ^{31}P NMR (acetone-d_6) δ −1.4; ^{1}H NMR (acetone-d_6) δ 1.60–2.42 (m, 7 H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 3.73 (d, 3 H, OCH_3, J = 10.9 Hz), 4.19-4.31 (m, 1 H, H_{5a}), 4.51–4.57 (m, 1 H, H_{5b}), 4.83–4.86 (m, 1 H, H_1); ^{13}C NMR (acetone-d_6) δ 22.4 (C_7), 25.4 (C_8), 34.5 (C_9, J = 8.3 Hz), 40.8 (C_6, J = 6.4 Hz), 53.5 (OCH_3, J = 5.6 Hz), 69.1 (C_5, J = 6.4 Hz), 85.6 (C_1, J = 7.3 Hz).

3α-Methoxy-3β-oxo-*cis*-2,4-dioxa-3-phosphabicyclo[4.3.0]nonane (2b). This compound was prepared by oxidation of methyl phosphite **14b** with NO_2/N_2O_4 analogous to the procedure described for **2a**. Column chromatography of the crude product (eluent, 2-butanone) yielded **2b** as a colorless liquid. Anal. Calcd for $C_7H_{13}O_4P$: C, 43.76; H, 6.82. Found: C, 44.10; H, 7.05. ^{31}P NMR (acetone-d_6) δ 1.6; ^{1}H NMR (acetone-d_6) δ 1.60–2.15 (m, 6 H, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 2.30–2.50 (m, 1 H, H_6), 3.78 (d, 3 H, OCH_3, J = 11.3 Hz), 4.11–4.28 (m, 1 H, H_{5a}), 4.57–4.70 (m, 1 H, H_{5b}), 5.00–5.08 (m, 1 H, H_1); ^{13}C NMR (acetone-d_6) δ 22.8 (C_7), 26.3 (C_8), 34.5 (C_9, J = 8.1 Hz), 40.7 (C_6, J = 5.3 Hz), 55.4 (OCH_3, J = 6.4 Hz), 68.9 (C_5, J = 5.0 Hz), 84.5 (C_1, J = 5.6 Hz).

3β-Methoxy-3α-thioxo-*cis*-2,4-dioxa-3-phosphabicyclo[4.3.0]nonane (3a). (a) Reaction of Phosphite 14a with Sulfur. A solution of 200 mg (1.14 mmol) of phosphite **14a** and 36.5 mg (1.14 mmol) of elemental sulfur in 5 mL of benzene was heated for 24 h under reflux. The progress of the reaction was monitored by TLC (eluent, hexane/ether, 5/4). The product was chromatographed by using the same eluent: yield, 23.1 mg (1.11 mmol, 97%); mp 54.7–57.8 °C. Anal. Calcd for $C_7H_{13}O_3PS$: C, 40.38; H, 6.29. Found: C, 40.62; H, 6.17. ^{31}P NMR (acetone-d_6) δ 68.4; ^{1}H NMR (acetone-d_6) δ 1.66–2.14 (m, 6 H, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 2.14–2.30 (m, 1 H, H_6), 3.74 (d, 3 H, OCH_3, J = 13.4 Hz), 4.14–4.26 (m, 1 H, H_{5a}), 4.57–4.64 (m, 1 H, H_{5b}), 4.88–4.91 (m, 1 H, H_1); ^{13}C NMR (benzene-d_6) δ 22.4 (C_7), 25.6 (C_8), 34.5 (C_9, J = 8.3 Hz), 40.8 (C_6, J = 7.1 Hz), 54.1 (OCH_3, J = 5.0 Hz), 68.4 (C_5, J = 8.0 Hz), 84.9 (C_1, J = 7.9 Hz).

(b) Reaction of Methanol with 7b. A solution of 250 mg (1.42 mmol) of **7b** in 15 mL of anhydrous methanol was stirred for 1 week at room temperature. Methanol was then evaporated. The residue was dissolved in 25 mL of benzene. After washing with sodium carbonate, drying (Na_2SO_4), and evaporation of the solvent, pure **3a** was obtained.

3α-Methoxy-3β-thioxo-*cis*-2,4-dioxa-3-phosphabicyclo[4.3.0]nonane (3b). (a) **3b** was prepared from phosphite **14b** and S_8 according to the procedure described for **3a**. Column chromatography (eluent, hexane/ether, 5/4) of the crude product yielded **3b** as a colorless liquid. Anal. Calcd for $C_7H_{13}O_3PS$: C, 40.38; H, 6.29. Found: C, 40.52; H, 6.50. ^{31}P NMR (acetone-d_6) δ 71.7; ^{1}H NMR (acetone-d_6) δ 1.64–2.02 (m, 6 H, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 2.25–2.44 (m, 1 H, H_6), 3.80 (d, 3 H, OCH_3, J = 13.5 Hz), 4.09–4.27 (m, 1 H, H_{5a}), 4.53–4.67 (m, 1 H, H_{5b}), 4.90–4.97 (m, 1 H, H_1); ^{13}C NMR (acetone-d_6) δ 22.4 (C_7), 26.5 (C_8), 34.4 (C_9, J = 8.9 Hz), 41.3 (C_6, J = 5.6 Hz), 55.2 (OCH_3, J = 6.2 Hz), 68.3 (C_5, J = 5.3 Hz), 83.6 (C_1, J = 5.6 Hz).

(b) Reaction of **7a** with methanol according to the procedure described for **3a** afforded pure **3b**.

3β-Phenoxy-3α-oxo-*cis*-2,4-dioxa-3-phosphabicyclo[4.3.0]nonane (4a). This compound was prepared by oxidation of the phenyl phosphite **16a** with NO_2/N_2O_4 at −78 °C analogous to the procedure described for the preparation of **2a**. The progress of the reaction was monitored with TLC (eluent, hexane/ether, 5/4). The crude product was purified by column chromatography using the same eluent. The viscous product solidified upon standing: mp 86.6–89.7 °C. Anal. Calcd for $C_{12}H_{15}O_4P$: C, 56.70; H, 5.95. Found: C, 56.98; H, 6.00. ^{31}P NMR (acetone-d_6) δ −8.6; ^{1}H NMR (acetone-d_6) δ 1.65–2.14 (m, 6 H, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 2.20–2.42 (m, 1 H, H_6), 4.29–4.47 (m, 1 H, H_{5a}), 4.73–4.82 (m, 1 H, H_{5b}), 5.04–5.08 (m, 1 H, H_1), 7.07–7.50 (m, 5 H, Ar H); ^{13}C NMR (acetone-d_6) δ 22.3 (C_7), 25.3 (C_8), 34.4 (C_9, J = 8.3 Hz), 40.7 (C_6, J = 6.5 Hz), 69.8 (C_5, J = 6.7 Hz), 86.6 (C_1, J = 7.6 Hz), 120.4 (Ar C, J = 5.1 Hz), 125.6 (Ar C), 130.6 (Ar C), 151.7 (Ar C, J = 6.3 Hz).

3α-Phenoxy-3β-oxo-*cis*-2,4-dioxa-3-phosphabicyclo[4.3.0]nonane (4b). (a) This compound was prepared by oxidation of **16b** with NO_2/N_2O_4 according to the procedure described for **4a**. It was obtained as a viscous liquid. Anal. Calcd for $C_{12}H_{15}O_4P$: C, 56.70; H, 5.95. Found: C, 56.98; H, 6.20. ^{31}P NMR (acetone-d_6) δ −5.2; ^{1}H NMR (acetone-d_6) δ 1.38–2.14 (m, 6 H, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 2.24–2.64 (m, 1 H, H_6), 4.05–4.21 (m, 1 H, H_{5a}), 4.44–4.60 (m, 1 H, H_{5b}), 4.96–5.07 (m, 1 H, H_1), 7.14–7.50 (m, 5 H, Ar H); ^{13}C NMR (acetone-d_6) δ 22.8 (C_7), 26.4 (C_8), 34.1 (C_9, J = 7.3 Hz), 40.1 (C_6, J = 5.3 Hz), 69.4 (C_5, J = 5.7 Hz), 84.7 (C_1, J = 6.3 Hz), 121.1 (Ar C, J = 4.5 Hz), 125.9 (Ar C), 130.4 (Ar C), 151.7 (Ar C, J = 7.0 Hz).

(b) A mixture of **4a** and **4b** (ratio 53/47) was obtained by reaction of phenyl phosphorodichloridate with **13** according to the procedure of Penney and Belleau.[14] Both isomers were separated by column chromatography using chloroform as eluent.

3β-Phenoxy-3α-thioxo-*cis*-2,4-dioxa-3-phosphabicyclo[4.3.0]nonane (5a). Thiophosphate **5a** was prepared by the reaction of phenyl phosphite **16a** with elemental sulfur according to the procedure described for the preparation of **3a**. Column chromatography of the crude product afforded **5a** as a white solid: mp 88.8–90.3 °C. Anal. Calcd for $C_{12}H_{15}O_3PS$: C, 53.33; H, 5.59. Found: C, 53.68; H, 5.99. ^{31}P NMR (acetone-d_6) δ 60.1; ^{1}H NMR (acetone-d_6) δ 1.68–2.15 (m, 6 H, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 2.23–2.44 (m, 1 H, H_6), 4.27–4.45 (m, 1 H, H_{5a}), 4.81–4.90 (m, 1 H, H_{5b}), 5.08–5.22 (m, 1 H, H_1), 7.15–7.53 (m, 5 H, Ar H); ^{13}C NMR (acetone-d_6) δ 22.4 (C_7), 25.6 (C_8), 34.6 (C_9, J = 8.3 Hz), 40.9 (C_6, J = 7.1 Hz), 69.2 (C_5, J = 8.4 Hz), 86.0 (C_1, J = 9.3 Hz), 120.4

(Ar C, J = 5.1 Hz), 125.8 (Ar C, J = 1.5 Hz), 130.5 (Ar C, J = 1.0 Hz), 152.0 (Ar C, J = 6.9 Hz).

3α-Phenoxy-3β-thioxo-*cis*-2,4-dioxa-3-phosphabicyclo[4.3.0]nonane (5b). This compound was prepared from **16b** and S_8 according to the procedure described for **5a**. It was obtained as a viscous liquid. Anal. Calcd for $C_{12}H_{15}O_3PS$: C, 53.33; H, 5.59. Found: C, 53.73; H, 5.92. ^{31}P NMR (acetone-d_6) δ 65.1; ^1H NMR (acetone-d_6) δ 1.46–2.11 (m, 6 H, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 2.33–2.53 (m, 1 H, H_6), 4.10–4.28 (m, 1 H, H_{5a}), 4.55–4.69 (m, 1 H, H_{5b}), 4.96–5.04 (m, 1 H, H_1), 7.13–7.53 (m, 5 H, Ar H); ^{13}C NMR (acetone-d_6) δ 22.8 (C_7), 26.5 (C_8), 34.4 (C_9, J = 8.7 Hz), 41.1 (C_6, J = 5.6 Hz), 68.9 (C_5, J = 5.9 Hz), 84.1 (C_1, J = 6.1 Hz), 122.1 (Ar C, J = 4.5 Hz), 126.3 (Ar C, J = 2.0 Hz), 130.4 (Ar C, J = 1.7 Hz), 151.6 (Ar C, J = 8.6 Hz).

3β-Chloro-3α-oxo- and 3α-Chloro-3β-oxo-*cis*-2,4-dioxa-3-phosphabicyclo[4.3.0]nonanes (6a and 6b). (a) By Reaction of Phosphorus Oxychloride with 13. A solution of diol **13** (580 mg, 5.0 mmol) and γ-collidine (1.21 g, 10.0 mmol) in dichloromethane (10 mL) and a solution of phosphorus oxychloride (760 mg, 5.0 mmol) in dichloromethane (10 mL) were added dropwise at equal rates to 15 mL of dichloromethane stirred at 0 °C in 20 min. The mixture was stirred further at 0 °C for 15 min and at room temperature for 3 h. The solvent was removed and the residue triturated with ether and filtered. Evaporation of the ether gave 0.95 g of a colorless viscous liquid, which consisted of 57% of **6a** and 32% of **6b**. Upon standing at room temperature, the percentage of cyclic phosphates decreased to 65%. The ratio **6a**/**6b** changed to 91/9.

6a: ^{31}P NMR (acetone-d_6) δ 1.0; ^1H NMR (acetone-d_6) δ 1.50–2.19 (m, 6 H, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 2.25–2.50 (m, 1 H, H_6), 4.42–4.63 (m, 1 H, H_{5a}), 4.72–4.82 (m, 1 H, H_{5b}), 5.06–5.10 (m, 1 H, H_1); ^{13}C NMR (acetone-d_6) δ 22.1 (C_7), 25.2 (C_8), 34.1 (C_9, J = 9.2 Hz), 40.6 (C_6, J = 6.9 HZ), 71.2 (C_5, J = 7.2 Hz), 88.8 (C_1, J = 8.6 Hz).

6b: ^{31}P NMR (acetone-d_6) δ 5.4; ^1H NMR (acetone-d_6) δ 1.47–2.15 (m, 6 H, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 2.75–2.94 (m, 1 H, H_6), 4.13–4.29 (m, 1 H, H_{5a}), 4.44–4.66 (m, 1 H, H_{5b}), 5.07–5.21 (m, 1 H, H_1); ^{13}C NMR (acetone-d_6) δ 22.6 (C_7), 26.7 (C_8, J = 0.9 Hz), 33.1 (C_9, J = 5.9 Hz), 39.1 (C_6, J = 5.9 Hz), 70.8 (C_5, J = 6.9 Hz), 87.6 (C_1, J = 8.9 Hz).

(b) By Oxidation of Chlorophosphonite 15. Oxidation of chlorophosphonite **15** with NO_2/N_2O_4 at −10 °C in CD_2Cl_2 yielded a mixture containing **6a** and **6b** as main components in the ratio 70/30.

(c) By Reaction of the Phosphite 14b with Chlorine. A solution of **14b** (100 mg, 0.57 mmol) in 2 mL of CD_2Cl_2 was added dropwise to a solution of chlorine (40.3 mg, 0.57 mmol) in 3 mL of CD_2Cl_2 stirred magnetically at −78 °C. After the addition was complete, ^{31}P NMR indicated the presence of **6a** and **6b** (ratio 90/10) as major components.

(d) By Reaction of Phosphite 14a with Chlorine. Chlorination of **14a** at −78 °C in CD_2Cl_2 analogous to the procedure described above afforded **6a** and **6b** as main components in the ratio 9/91 as indicated by ^{31}P NMR.

3β-Chloro-3α-thioxo- and 3α-Chloro-3β-thioxo-*cis*-2,4-dioxa-3-phosphabicyclo[4.3.0]nonanes (7a and 7b). A solution of 1.16 g (10.0 mmol) of diol **13** and 1.58 g (10.0 mmol) of dry pyridine in 25 mL of dry toluene was added dropwise to a stirred solution of 1.69 g (10.0 mmol) of thiophosphoryl chloride in 50 mL of toluene held at 40 °C. After the addition was completed, the mixture was stirred for 2.5 h at 40 °C. The pyridine hydrochloride salt was filtered off and the organic phase washed twice with 15 mL of water. After drying on calcium chloride, toluene was evaporated to give 1.92 g of a colorless viscous oil consisting of **7a** (50%), **7b** (42%), and other phosphates (8%). Column chromatography of this mixture, eluting with hexane/ether (5/4) afforded pure **7a** and **7b**.

7a: liquid. Anal. Calcd for $C_6H_{10}ClO_2PS$: C, 33.89; H, 4.74; Found: C, 34.00; H, 4.91. ^{31}P NMR (acetone-d_6) δ 63.7; ^1H NMR (acetone-d_6) δ 1.50–2.13 (m, 6 H, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 2.25–2.48 (m, 1 H, H_6), 4.37–4.59 (m, 1 H, H_{5a}), 4.77–4.87 (m, 1 H, H_{5b}), 5.06–5.11 (m, 1 H, H_1); ^{13}C NMR (acetone-d_6) δ 22.0 (C_7), 25.3 (C_8), 33.8 (C_9, J = 7.6 Hz), 40.6 (C_6, J = 7.6 Hz), 70.7 (C_5, J = 9.5 Hz), 88.0 (C_1, J = 10.3 Hz).

7b: liquid. Anal. Calcd for $C_6H_{10}ClO_2PS$: C, 33.89; H, 4.74; Found: C, 34.10; H, 5.00. ^{31}P NMR (acetone-d_6) δ 71.7; ^1H NMR (acetone-d_6) δ 1.40–1.96 (m, 6 H, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 2.73–2.95 (m, 1 H, H_6), 4.10–4.27 (m, 1 H, H_{5a}), 4.42–4.64 (m, 1 H, H_{5b}), 5.01–5.13 (m, 1 H, H_1); ^{13}C NMR (acetone-d_6) δ 23.0 (C_7), 27.4 (C_8, J = 0.9 Hz), 33.8 (C_9, J = 7.6 Hz), 40.2 (C_6, J = 5.4 Hz), 70.4 (C_5, J = 8.4 Hz), 85.8 (C_1, J = 9.1 Hz).

3β-(Dimethylamino)-3α-oxo- and 3α-(Dimethylamino)-3β-oxo-*cis*-2,4-dioxa-3-phosphabicyclo[4.3.0]nonanes (8a and 8b). Dimethylamine was bubbled through a solution of 400 mg (2.03 mmol) of **6a** and **6b** (ratio 68/32) in 5 mL of CD_2Dl_2 at 0 °C. The progress of the reaction was monitored by ^{31}P NMR. After 1 h, all starting material had been converted to **8a** and **8b** in the ratio 31/69. The solvent was evaporated and the residue triturated with ether and filtered. Concentration of the filtrate yielded a viscous oil. Column chromatography (eluent, 2-butanone) gave in order of elution 70 mg (0.34 mmol, 17%) of **8a** and 150 mg (0.73 mmol, 36%) of **8b**.

8a: viscous liquid. Anal. Calcd for $C_8H_{16}NO_3P$: C: 46.83; H, 7.86; N, 6.83. Found: C, 46.58; H, 8.16; N, 6.51. ^{31}P NMR (acetone-d_6) δ 9.4; ^1H NMR (acetone-d_6) δ 1.52–2.02 (m, 6 H, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 2.22–2.45 (m, 1 H, H_6), 2.63 (d, 6 H, $N(CH_3)_2$, J = 10.7 Hz), 4.02–4.19 (m, 1 H, H_{5a}), 4.30–4.42 (m, 1 H, H_{5b}), 4.74–4.83 (m, 1 H, H_1); ^{13}C NMR (acetone-d_6) δ 22.8 (C_7), 26.4 (C_8), 34.7 (C_9, J = 6.2 Hz), 36.5 ($N(CH_3)_2$, J = 3.0 Hz), 40.1 (C_6, J = 6.2 Hz), 68.1 (C_5, J = 6.1 Hz), 83.9 (C_1, J = 7.7 Hz).

8b: mp 91.2–94.4 °C. Found: C, 46.48; H, 8.04; N, 6.51; ^{31}P NMR (acetone-d_6) δ 11.9; ^1H NMR (acetone-d_6) δ 1.60–2.00 (m, 6 H, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 2.05–2.25 (m, 1 H, H_6), 2.66 (d, 6 H, $N(CH_3)_2$, J = 9.8 Hz), 4.02–4.29 (m, 1 H, H_{5a}), 4.52–4.29 (m, 1 H, H_{5b}), 4.81–4.93 (m, 1 H, H_1); ^{13}C NMR (acetone-d_6) δ 22.7 (C_7), 25.9 (C_8), 34.8 Hz (C_9, J = 8.8 Hz), 36.3 ($N(CH_3)_2$, J = 4.5 Hz), 40.6 (C_6, J = 5.5 Hz), 67.1 (C_5, J = 5.0 Hz), 82.3 (C_1, J = 5.5 Hz).

3β-(Dimethylamino)-3α-thioxo-*cis*-2,4-dioxa-3-phosphabicyclo[4.3.0]nonane (9a). Dry dimethylamine was bubbled through a solution of 250 mg (1.18 mmol) of **7b** in 3 mL of benzene-d_6 kept at 10 °C. The reaction was followed with ^{31}P NMR. After about 1 h, the precipitated salts were removed by filtration and washed with a little benzene. The combined filtrate and washings were washed with 3 × 2 mL of water, dried over Na_2SO_4, and evaporated in vacuo. The residue was chromatographed (eluent, hexane/ether, 5/4) to give **9a** as a white solid: mp 79.8–81.8 °C. Anal. Calcd for $C_8H_{16}NO_2PS$: C, 43.43; H, 7.29; N, 6.33. Found: C, 43.83; H, 7.76; N, 6.03. ^{31}P NMR (acetone-d_6) δ 78.2; ^1H NMR (acetone-d_6) δ 1.62–1.98 (m, 6 H, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 2.13–2.32 (m, 1 H, H_6), 2.52 (d, 6 H, $N(CH_3)_2$, J = 13.3 Hz), 4.04–4.21 (m, 1 H, H_{5a}), 4.45–4.56 (m, 1 H, H_{5b}), 4.77–4.86 (m, 1 H, H_1); ^{13}C NMR (acetone-d_6) δ 22.4 (C_7), 25.9 (C_8), 34.4 (C_9, J = 7.2 Hz), 36.9 ($N(CH_3)_2$, J = 2.4 Hz), 40.6 (C_6, J = 7.0 Hz), 67.6 (C_5, J = 7.9 Hz), 84.0 (C_1, J = 9.1 Hz).

3α-(Dimethylamino)-3β-thioxo-*cis*-2,4-dioxa-3-phosphabicyclo[4.3.0]nonane (9b). This compound was prepared from **7a** and dimethylamine according to the procedure described for the synthesis of **9a**. It was obtained as a viscous liquid. Anal. Calcd for $C_8H_{16}NO_2PS$: C, 43.43; H, 7.29; N, 6.33. Found: C, 43.75; H, 7.69; N, 5.98; ^{31}P NMR (acetone-d_6) δ 77.8; ^1H NMR (acetone-d_6) δ 1.75–1.98 (m, 6 H, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 2.08–2.20 (m, 1 H, H_6), 2.80 (d, 6 H, $N(CH_3)_2$, J = 11.4 Hz), 4.05–4.24 (m, 1 H, H_{5a}), 4.67–4.76 (m, 1 H, H_{5b}), 4.89–4.92 (m, 1 H, H_1); ^{13}C NMR (acetone-d_6) δ 22.6 (C_7), 26.0 (C_8), 34.5 (C_9, J = 9.1 Hz), 36.7 ($N(CH_3)_2$, J = 5.6 Hz), 41.0 (C_6, J = 6.1 Hz), 67.1 (C_5, J = 4.8 Hz), 82.7 (C_1, J = 5.5 Hz).

3β-Thioxo-3α-oxo-*cis*-2,4-dioxa-3-phosphabicyclo[4.3.0]-nonane *N*-Methyl-*tert*-butylammonium Salt (10a). A solution of **3b** in *tert*-butylamine was refluxed for 48 h. The excess *tert*-butylamine was removed by evaporation and the resulting white solid recrystallized from methanol/ether: mp 194.3–198.0 °C dec. Anal. Calcd for $C_{11}H_{24}NO_3PS$: C, 46.96; H, 8.60; N, 4.98. Found: C, 47.49; H, 8.80; N, 5.10. ^{31}P NMR (methanol-d_4) δ 55.7; ^1H NMR (methanol-d_4) δ 1.34 (s, 12 H, CH_3), 1.58–2.08 (m, 7 H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 3.91–4.09 (m, 1 H, H_{5a}), 4.56–4.66 (m, 1 H, H_{5b}), 4.73–4.85 (m, 1 H, H_1); ^{13}C NMR (methanol-d_4) δ 23.1 (C_7), 26.6 (C_8), 28.1 ($(CH_3)_3C$), 35.0 (C_9, J = 9.2 Hz), 42.4 (C_6, J = 5.8 Hz), 52.4 ($(CH_3)_3C$, CH_3N), 67.5 (C_5, J = 4.9 Hz), 82.5 (C_1, J = 5.8 Hz).

3α-Thioxo-3β-oxo-*cis*-2,4-dioxa-3-phosphabicyclo[4.3.0]-nonane *N*-Methyl-*tert*-butylammonium Salt (10b). Deme-

thylation of **3a** with *tert*-butylamine as described for **10a** gave **10b**. It was recrystallized from methanol/ether: mp 159.9–162.6 °C dec. Anal. Calcd for $C_{11}H_{24}NO_3PS$: C, 46.96; H, 8.60; N, 4.98. Found: C, 46.36; H, 8.44; N, 5.23. ^{31}P NMR (methanol-d_4) δ 59.8; ^1H NMR (methanol-d_4) δ 1.36 (s, 12 H, CH_3), 1.56–1.99 (m, 6 H, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 2.05–2.26 (m, 1 H, H_6), 3.81–3.97 (m, 1 H, H_{5a}), 4.32–4.46 (m, 1 H, H_{5b}), 4.70–4.76 (m, 1 H, H_1); ^{13}C NMR (methanol-d_4) δ 23.6 (C_7), 27.3 (C_8), 27.8 ($(CH_3)_3C$), 35.3 (C_9, J = 8.8 Hz), 42.5 (C_6, J = 4.9 Hz), 52.7 ($(CH_3)_3C$, CH_3N), 66.5 (C_5, J = 6.3 Hz), 80.9 (C_1, J = 7.6 Hz).

3,3-Dioxo-*cis*-2,4-dioxa-3-phosphabicyclo[4.3.0]nonane *tert*-Butylammonium Salt (11). A mixture of phenyl phosphate triesters **4a** and **4b** was dissolved in spectrograde methanol, and the phenyl groups were removed by hydrogenolysis in a Parr apparatus at 50 psi, using PtO_2 (100 mg/g of triester) as catalyst. After removal of the catalyst, the methanolic solution was neutralized with *tert*-butylamine. The solvent was removed by rotary evaporation, and the residue was crystallized from methanol/ether: mp 176.7–178.9 °C dec. Anal. Calcd for $C_{10}H_{22}NO_4P$: C, 47.80; H, 8.83; N, 5.57. Found: C, 48.28; H, 8.50; N, 5.20. ^{31}P NMR (methanol-d_4) δ 1.6; ^1H NMR (methanol-d_4) δ 1.36 (s, 12 H, CH_3), 1.58–2.08 (m, 7 H, H_6, H_{7a}, H_{7b}, H_{8a}, H_{8b}, H_{9a}, H_{9b}), 3.91–4.08 (m, 1 H, H_{5a}), 4.41–4.51 (m, 1 H, H_{5b}), 4.65–4.78 (m, 1 H, H_1); ^{13}C NMR (methanol-d_4) δ 23.3 (C_7), 26.5 (C_8), 27.9 ($(CH_3)_3C$), 35.2 (C_9, J = 9.0 Hz), 42.3 (C_6, J = 5.0 Hz), 52.5 ($(CH_3)_3C$), 67.3 (C_5, J = 5.1 Hz), 82.1 (C_1, J = 5.7 Hz).

Catalyzed Reaction of Diazodiphenylethanone and Related Diazo Ketones with Enaminones as a Source of Pyrroles

Marcos N. Eberlin and Concetta Kascheres*

Universidade Estadual de Campinas, Instituto de Quimica, Caixa Postal 6154, 13081 Campinas, São Paulo, Brazil

Received April 2, 1987

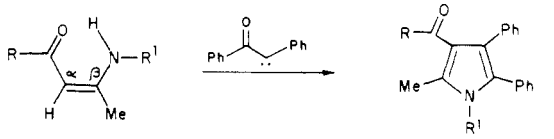
The reaction of copper(II)-stabilized keto carbenes (**1**, **7**, **8**), derived from diazo ketones, with enaminones leads to the formation of pyrroles. The cyclic enaminones **3** react with the keto carbenes on nitrogen to form products **5**, **9**, **11**, and/or pyrroles **6**, **10**, and **12**. Treatment of the initially formed addition products **5**, **9**, and **11** with KOH in ethanol leads to formation of the corresponding pyrroles for the cyclic six-membered enaminones **3a,c** but not for the five-membered **3d**. The acyclic enaminones **2** react with keto carbene **1** to form the pyrroles **4** directly. It has been shown, by using keto carbenes with different substituents (**7** and **8**), that **2d** reacts preferentially on the vinylogous Cα position to form pyrroles **13** and/or **14**.

As part of a study on the reactions of enaminones with various electrophiles, we report the reactions of several enamino ketones and esters with copper(II)-stabilized keto carbenes derived from diazo ketones.

Analysis of the products from the reactions of the keto carbene **1**, formed from the decomposition of diazodiphenylethanone in the presence of copper(II) acetylacetonate, with the acyclic enaminones **2** in refluxing methylene chloride showed the formation of pyrroles **4** (Table I). The mechanism could involve electrophilic attack of the keto carbene on the N and/or the Cα position of the enaminone system, followed by cyclization and loss of water.

When the cyclic enaminones **3** were reacted with diazodiphenylethanone under the same conditions, the principal product formed, with the exception of **3b**, was the product of reaction of **1** on nitrogen (**5**, Table II, entries 1–4). With **3b**, which is the only cyclic enaminone that is not primary, the pyrrole **6b** was formed directly. Heating **5** in refluxing benzene or toluene did not lead to the formation of pyrrole, nor did the use of refluxing acetic acid. We suspected that the cyclization of **5** was being impeded by intramolecular hydrogen bonding between N–H and the exocyclic carbonyl group (as shown in Table II), suggesting that treatment with base might be effective in facilitating cyclization by removing this proton. In fact, treatment of **5a** and **5c** with a solution of potassium hydroxide in ethanol, followed by neutralization, led to the formation of the pyrroles **6a** and **6c** respectively, in very high yields (Table III, entries 1, 2). However, the reaction of the five-membered cyclic product **5d** led to the formation of a complex mixture with no evidence of pyrrole formation. Perhaps the increased strain of fusing two five-membered rings slows down the formation of pyrrole and favors intermolecular processes.

Table I. Pyrroles Formed in the Reactions of Acyclic Enaminones 2 with Keto Carbene 1



2 **4**

R	R^1	2	4	yield, %
Me	H	**a**	**a**	21
Me	Me	**b**	**b**	37
OEt	H	**c**	**c**	14
OEt	Me	**d**	**d**	71

These reactions were extended to include the keto carbenes **7** and **8**. Thus, the reactions of the cyclic enaminones **3a,c,d** with 1-diazo-1-phenyl-2-propanone in the presence of $Cu(acac)_2$ yielded the product of reaction of keto carbene **7** on nitrogen (**9a,c,d**) and pyrroles **10a,c** (Table II, entries 5–7). As in the case of compounds **5a** and **5c**, treatment with base converted **9a** and **9c** to the pyrroles **10a** and **10c**, respectively, in very high yields (Table III, entries 3, 4). Again the five-membered cyclic product **9d** did not produce a pyrrole under these conditions. When the keto carbene **8**, derived from 2-diazo-1-phenyl-1-propanone, was used, **3a** and **3c** yielded analogous products **11a** and **11c** (Table II, entries 8, 9), which upon treatment with base formed pyrroles **12a** and **12c**, respectively (Table III, entries 5, 6). However, in the reaction

0022-3263/88/1953-2084$01.50/0