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Structural studies of phosphorinanes

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by

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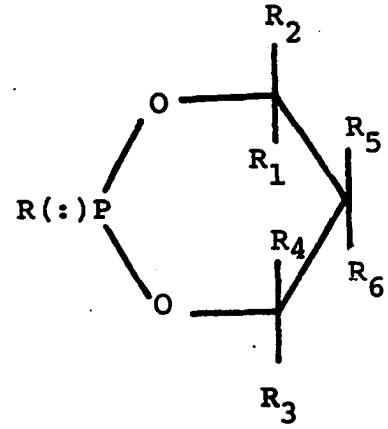
PART I. SOLUTION STUDIES

INTRODUCTION

In this and the following sections of this part, many phosphorinanes are discussed. The compounds are listed in Tables 1-6 and are grouped here for the convenience of the reader. Table 1 lists monocyclic tricoordinate 1,3,2-dioxaphosphorinanes, Table 2 polycylic phosphites, Table 3 monocyclic tetracoordinate 1,3,2-dioxaphosphorinanes, Table 4 polycyclic tetracoordinate 1,3,2-dioxaphosphorinanes and Table 5 contains other phosphorinanes except for the 1,3,5-dioxaphosphorinanes found in Table 6.

The biological importance and toxic properties of organophosphorus compounds are well documented (1-5). The unknown steric and stereochemical dependencies of biological reactions can be investigated through the use of compounds in which geometrical contraints limit some of the complicating rotational motions and provide chemically active groups in different electronic and geometric environments. Six-membered ring organophosphorus compounds not only meet these requirements as model compounds, but are important biological agents themselves. Thus, cyclic adenosine monophosphate, 205, is known to be a secondary messenger in mammalian cells (6) and cyclophosphamide, 206, which will be discussed in more detail in Part II, is employed in the treatment of a variety of cancers (7). There are two major problems to be solved concerning ring compounds: (1) the ring conformation which could be chair, boat, or twist

Table 1. Tricoordinate 1,3,2-dioxaphosphorinanes



Compound[a]	R	R_1	R_2	R_3	R_4	R_5	R_6	Ref.[b]
1	MeO	H	H	H	H	H	H	8,this work
2	PhO	H	H	H	H	H	H	8
3	Cl	H	H	H	H	H	H	8
4	MeO	H	H	H	H	Me	Me	9,10,11,23
5	t-BuO	H	H	H	H	Me	Me	9,10
6	PhO	H	H	H	H	Me	Me	11,23
7	PhS	H	H	H	H	Me	Me	9,10
8	Me_2N	H	H	H	H	Me	Me	11
9	Me	H	H	H	H	Me	Me	26

10	Ph	H	H	H	H	Me	Me	9,10,11,26
11	F	H	H	H	H	Me	Me	9,10,11
12	Cl	H	H	H	H	Me	Me	9,10,11
13	Br	H	H	H	H	Me	Me	9,10
14a,b	MeO	H	H	H	H	H	Me	28
15	Cl	H	H	H	H	H	Me	12
16	Cl	H	H	H	H	H	Ph	12
17a,b	MeO	H	H	H	H	H	t-Bu	13,14
18a,b	MeHN	H	H	H	H	H	t-Bu	15
19a,b	Me_2N	H	H	H	H	H	t-Bu	15,16
20	t-Butyl	H	H	H	H	H	t-Bu	44
21a,b	Me	H	H	H	H	H	t-Bu	17
22a,b	Ph	H	H	H	H	H	t-Bu	18
23	Cl	H	H	H	H	H	t-Bu	13,14

[a]The letters a,b following the compound number indicate geometrical isomers.

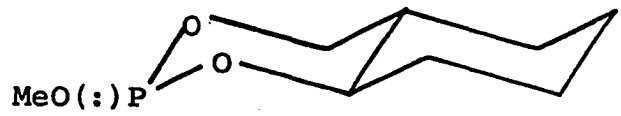
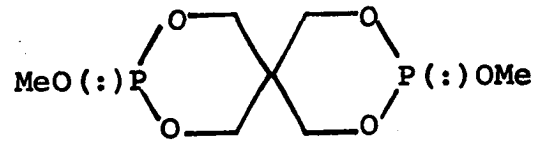
[b]Ref. are the reference numbers of literature reports of each compound. Numbers in parentheses following "This work" refer to published accounts of the work appearing in this thesis.

Table 1 (Continued)

Compound[a]	R	R_1	R_2	R_3	R_4	R_5	R_6	Ref.[b]
24a,b	MeO	H	H	H	H	Me	CH_2Cl	9,10,24
25a,b	F	H	H	H	H	Me	CH_2Cl	9,10
26a,b	Cl	H	H	H	H	Me	CH_2Cl	9,10
27a,b	Br	H	H	H	H	Me	CH_2Cl	9,10
28a,b	MeO	H	H	H	H	Me	NO_2	25
29a,b	MeO	H	H	H	H	Me	CH(Me)OMe	29
30a,b	Cl	H	H	H	H	Me	CH(Me)OMe	29
31a,b	Br	H	H	H	H	Me	CH(Me)OMe	20
32a,b	MeO	H	Me	H	H	H	H	28,29,this work (73,167)
33a,b	EtO	H	Me	H	H	H	H	19,20,23
34a,b	i-PrO	H	Me	H	H	H	H	20
35	t-BuO	H	Me	H	H	H	H	20
36a,b	Me_2N	H	Me	H	H	H	H	This work (73,167)
37	Cl	H	Me	H	H	H	H	9,10,12,19,20,22, 28,30

38a,b	MeO	H	Me	H	Me	H	H	11,21,22,28 This work (73,167)
39a,b	Me_2N	H	Me	H	Me	H	H	This work (73,167)
40	Cl	H	Me	H	Me	H	H	9,10,11,21,22
41	MeO	H	Me	Me	H	H	H	9,10

Table 2. Tricoordinate polycyclic compounds

Compound[a]	Structural formula	Ref.[b]
42a,b		22
43		22
44		9,10

[a]The letters a,b following the compound number indicate geometrical isomers.

[b]Ref. are the reference numbers of literature reports of each compound.

Table 2 (Continued)

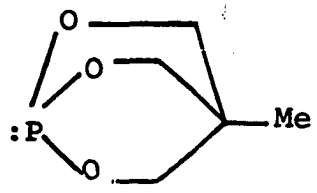
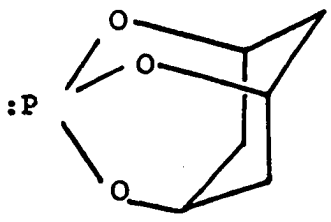
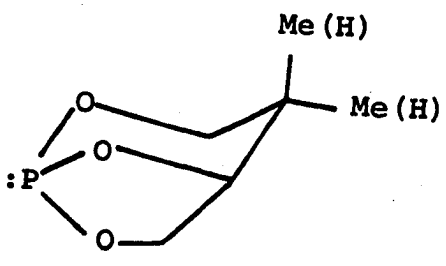
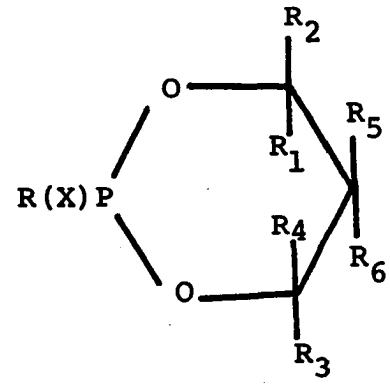
Compound[a]	Structural formula	Ref.[b]
45		111
46		31
47		41

Table 3. Tetracoordinate 1,3,2-dioxaphosphorinanes



Compound[a]	R	X	R_1	R_2	R_3	R_4	R_5	R_6	Ref.[b]
48	HO	O	H	H	H	H	H	H	61
49	MeO	O	H	H	H	H	H	H	10,84, this work
50	PhO	O	H	H	H	H	H	H	48,62,79,80,86, 106,107
51	Me_2N	O	H	H	H	H	H	H	This work
52	H	O	H	H	H	H	H	H	This work
53	Me	O	H	H	H	H	H	H	This work
54	$HO(Me)_2C$	O	H	H	H	H	H	H	This work
55	Ph	O	H	H	H	H	H	H	78,79,82

56	HO	O	H	H	H	H	Me	Me	63,88,107
57	MeO	O	H	H	H	H	Me	Me	10,27,77,78,79, 84
58	MeO	S	H	H	H	H	Me	Me	27
59	EtO	O	H	H	H	H	Me	Me	77,78,79,80
60	n-PrO	O	H	H	H	H	Me	Me	85
61	i-PrO	O	H	H	H	H	Me	Me	77
62	n-BuO	O	H	H	H	H	Me	Me	85
63	t-BuO	O	H	H	H	H	Me	Me	10,27,84,103
64	PhO	O	H	H	H	H	Me	Me	27,45,47,48,78, 79,80,82,85,86, 107
65	PhO	S	H	H	H	H	Me	Me	79,86
66	p-anisyl	O	H	H	H	H	Me	Me	77
67	3,5-dimethyl-phenoxy	O	H	H	H	H	Me	Me	77
68	2,6-dimethyl-phenoxy	O	H	H	H	H	Me	Me	77

[a]The letters a,b following the compound number indicate geometrical isomers.

[b]Ref. are the reference numbers of literature reports of each compound. Numbers in parentheses following "This work" refer to published accounts of the work appearing in this thesis.

Table 3 (Continued)

Compound[a]	R	X	R_1	R_2	R_3	R_4	R_5	R_6	Ref.[b]
69	2,6-di-t-Bu-4-methyl-phenoxy	O	H	H	H	H	Me	Me	77
70	n-PrHN	O	H	H	H	H	Me	Me	85
71	t-BuHN	O	H	H	H	H	Me	Me	27,85
72	n-PentHN	O	H	H	H	H	Me	Me	85
73	Me_2N	O	H	H	H	H	Me	Me	48,78,79,85,86
74	Me_2N	S	H	H	H	H	Me	Me	27
75	$C_5H_{10}N$	O	H	H	H	H	Me	Me	50
76	H	O	H	H	H	H	Me	Me	10,84, this work (168)
77	Me	O	H	H	H	H	Me	Me	10,27,54,74,84, 103
78	Me	Me	H	H	H	H	Me	Me	26
79	s-Bu	O	H	H	H	H	Me	Me	27,103
80	t-Bu	O	H	H	H	H	Me	Me	27,103
81	$HO(Me)_2C$	O	H	H	H	H	Me	Me	This work (168)
82	Cl_3C	O	H	H	H	H	Me	Me	27,103

83	$PhCH_2$	O	H	H	H	H	Me	Me	27,54,103
84	2,4,6-trimethyl-$C_6H_2CH_2$	O	H	H	H	H	Me	Me	27
85	Ph(Me)CH	O	H	H	H	H	Me	Me	27,54,103
86	Ph(NHPr)CH	O	H	H	H	H	Me	Me	27
87	Ph_3C	O	H	H	H	H	Me	Me	10,27,54,84,103
88	Ph	O	H	H	H	H	Me	Me	10,27,48,63,74, 78,79,80,82,84, 107
89	Ph	S	H	H	H	H	Me	Me	79
90	Cl	O	H	H	H	H	Me	Me	10,27,50,65,73, 78,79,80,84,86, 88,107
91	Cl	S	H	H	H	H	Me	Me	27,79,80,86,88
92	Br	O	H	H	H	H	Me	Me	88
93	i-PrO	O	H	H	H	H	Et	Et	27
94	t-BuNH	O	H	H	H	H	Et	Et	27
95	Ph	O	H	H	H	H	Et	Et	78,79,80,82
96	Ph	S	H	H	H	H	Et	Et	79
97	Me_2N	O	H	H	H	H	Ph	Ph	48,79,86
98	PhO	O	H	H	H	H	Ph	Ph	45,47,48,79,86
99	PhO	S	H	H	H	H	Ph	Ph	48,79

Table 3 (Continued)

Compound[a]	R	X	R_1	R_2	R_3	R_4	R_5	R_6	Ref.[b]
100	Ph	O	H	H	H	H	Ph	Ph	78,79,80,82
101	Ph	S	H	H	H	H	Ph	Ph	79
102	Cl	O	H	H	H	H	Ph	Ph	78,79,86
103	Cl	S	H	H	H	H	Ph	Ph	86
104	PhO	O	H	H	H	H	Me	i-Pr	45
105a,b	MeO	O	H	H	H	H	H	Me	28
106a,b	MeO	O	H	H	H	H	H	t-Bu	13,38,39,52
107a,b	MeO	S	H	H	H	H	H	t-Bu	13,39,52
108a,b	MeHN	S	H	H	H	H	H	t-Bu	15
109a,b	Me_2N	O	H	H	H	H	H	t-Bu	15,16
110a,b	Me	O	H	H	H	H	H	t-Bu	14,17,38,52,76
111a,b	t-Bu	O	H	H	H	H	H	t-Bu	51
112a,b	Ph	O	H	H	H	H	H	t-Bu	18
113a,b	PhO	O	D	D	H	H	H	Ph	106
114a,b	MeO	O	H	H	H	H	Me	CH_2Cl	56
115a,b	MeO	BH_3	H	H	H	H	Me	CH_2Cl	24

116a,b	$C_5H_{10}N$	O	H	H	H	H	Me	CH_2Cl	50,53,54
117a,b	C_6H_{11}	O	H	H	H	H	Me	CH_2Cl	54
118a,b	$PhCH_2$	O	H	H	H	H	Me	CH_2Cl	54,103,111
119a,b	Ph(Me)CH	O	H	H	H	H	Me	CH_2Cl	54
120	Ph_3C	O	H	H	H	H	Me	CH_2Cl	10,34,54,84
121a,b	Cl_3C	O	H	H	H	H	Me	CH_2Cl	54
122a,b	Cl	O	H	H	H	H	Me	CH_2Cl	50
123a,b	$Cl_2C=CHO$	O	H	H	H	H	Et	CH_2Cl	111
124a,b	$C_5H_{10}N$	O	H	H	H	H	Et	CH_2Cl	10,56,57,84,95
125a,b	$PhCH_2$	O	H	H	H	H	Et	CH_2Cl	10,54,57,84,111
126	Ph(Me)CH	O	H	H	H	H	Et	CH_2Cl	54
127a,b	Cl	O	H	H	H	H	Et	CH_2Cl	50,111
128a,b	Br	O	H	H	H	H	Et	CH_2Cl	111
129	Ph_3C	O	H	H	H	H	n-Pr	CH_2Cl	10,84
130	$PhCH_2$	O	H	H	H	H	Cl	CH_2Cl	54
131	Br	O	H	H	H	H	H	CH_2Br	10,84
132a,b	$C_5H_{10}N$	O	H	H	H	H	Me	CH_2Br	50,53
133a,b	Me	O	H	H	H	H	Me	CH_2Br	10,25,54,84
134	Et	O	H	H	H	H	Me	CH_2Br	10,84

Table 3 (Continued)

Compound[a]	R	X	R_1	R_2	R_3	R_4	R_5	R_6	Ref.[b]
135	n-Pr	O	H	H	H	H	Me	CH_2Br	10,84
136a,b	$PhCH_2$	O	H	H	H	H	Me	CH_2Br	25,54
137	Ph(Me)CH	O	H	H	H	H	Me	CH_2Br	54
138	Ph_3C	O	H	H	H	H	Me	CH_2Br	10,54,84
139	Br	O	H	H	H	H	Me	CH_2Br	10,55,84
140	Me	O	H	H	H	H	Me	CH_2I	10,84
141	n-Pr	O	H	H	H	H	Me	CH_2I	10,84
142	$HO(Me)_2C$	O	H	H	H	H	Me	CH_2OH	10,84
143a,b	Me	O	H	H	H	H	Me	CH_2OTs	54
144a,b	$PhCH_2$	O	H	H	H	H	Me	CH_2OTs	25,54
145a,b	Me	O	H	H	H	H	Me	CH(Me)OMe	29
146	$(Me_4N)^{+-}O$	O	H	Me	H	H	H	H	83,87
147a,b	$(Me_4N)^{+-}O$	S	H	Me	H	H	H	H	83,87
148a,b	$(C_6H_{11})_2N^{+-}O$	S	H	Me	H	H	H	H	83,87
149a,b	HO	S	H	Me	H	H	H	H	87
150a,b	HO	Se	H	Me	H	H	H	H	87

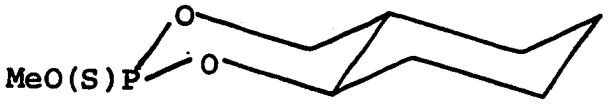
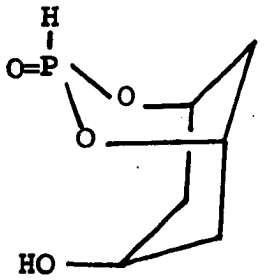
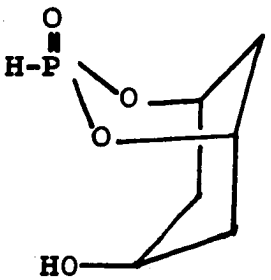
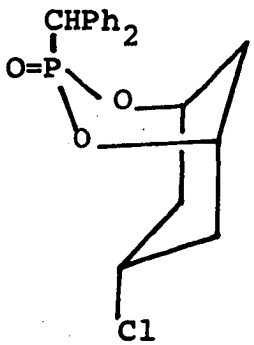
151a,b	MeO	O	H	Me	H	H	H	H	28,92,117,118 this work (73, 167)
152a,b	MeO	S	H	Me	H	H	H	H	20
153a,b	EtO	S	H	Me	H	H	H	H	19,20,30
154a,b	i-PrO	S	H	Me	H	H	H	H	20
155a,b	i-BuO	S	H	Me	H	H	H	H	20
156a,b	PhO	O	H	Me	H	H	H	H	45,47,79,86,105
157a,b	PhO	S	H	Me	H	H	H	H	86
158a,b	MeSe	O	H	Me	H	H	H	H	88
159a,b	PhHN	O	H	Me	H	H	H	H	83,114
160a,b	Me_2N	O	H	Me	H	H	H	H	93,this work (73,167)
161a,b	H	O	H	Me	H	H	H	H	48,69,71,88,89, this work (168)
162a,b	Me	O	H	Me	H	H	H	H	59,60, this work
163a,b	Et	O	H	Me	H	H	H	H	59,60
164a,b	$HO(Me)_2C$	O	H	Me	H	H	H	H	This work (168)
165a,b	Cl	O	H	Me	H	H	H	H	78,79,86,92,114
166a,b	Cl	S	H	Me	H	H	H	H	86
167a,b	Br	O	H	Me	H	H	H	H	86,92,114

Table 3 (Continued)

Compound[a]	R	X	R_1	R_2	R_3	R_4	R_5	R_6	Ref.[b]
168	$K^{+-}O$	O	H	Ph	H	H	H	H	88
169	Cl	O	H	Ph	H	H	H	H	88
170	Cl	S	H	Ph	H	H	H	H	88
171a,b	MeO	O	H	Me	H	Me	H	H	28, this work (73,167)
172a,b	MeO	S	H	Me	H	Me	H	H	22
173a,b	MeO	BH_3	H	Me	H	Me	H	H	32
174a,b	PhO	O	H	Me	H	Me	H	H	49,108
175a,b	Me_2N	O	H	Me	H	Me	H	H	This work (73, 167)
176a,b	H	O	H	Me	H	Me	H	H	This work (168)
177a,b	Me	O	H	Me	H	Me	H	H	This work
178	$HO(Me)_2C$	O	H	Me	H	Me	H	H	This work (168)
179	Ph_3C	O	H	Me	H	Me	H	H	33,34
180	Cl	O	H	Me	H	Me	H	H	79
181	PhO	O	H	Me	Me	H	H	H	46,49,108
182	PhO	O	Me	Me	H	H	H	H	46,79

183a,b	PhO	O	Me	Me	H	Me	H	H	45,47,48,49,79, 105
184	PhO	S	Me	Me	H	Me	H	H	49
185a,b	H	O	Me	Me	H	Me	H	H	71
186	Cl	O	Me	Me	H	Me	H	H	49,79
187	Cl	S	Me	Me	H	Me	H	H	49
188a,b	PhO	O	H	Me	H	Me	H	Me	78,79,81
189a,b	PhO	O	H	Me	H	Me	Me	H	78,79,81
190a,b	PhO	O	Me	H	H	Me	H	Me	78,79,81
191a,b	PhO	O	H	i-Pr	H	H	Me	Me	45,47,48,78,79 86
192	PhO	S	H	i-Pr	H	H	Me	Me	79,86
193	Cl	O	H	i-Pr	H	H	Me	Me	78,86
194	Cl	S	H	i-Pr	H	H	Me	Me	79,86
195a,b	$C_5H_{10}N$	O	H	CH_2Cl	H	H	Me	Me	50
196	Cl	O	H	CH_2Cl	H	H	Me	Me	50
197a,b	PhO	O	H	Me	H	Me	Me	Me	49,78,79
198	PhO	O	Me	Me	Me	Me	H	H	45,79,82
199	Ph	O	Me	Me	Me	Me	H	H	82,79

Table 4. Tetracoordinate polycyclic compounds

Compound[a]	Structural formula	Ref.[b]
200a,b		22
201a		66,90
201b		66,90
202		91

[a]The letters a,b following the compound number indicate geometrical isomers.

[b]Ref. are the reference numbers of literature reports of each compound.

Table 4 (Continued)

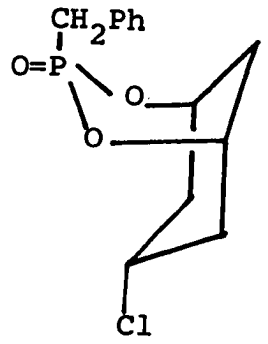
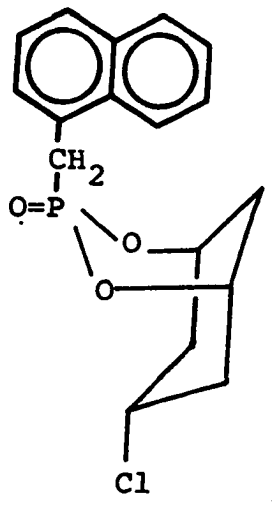
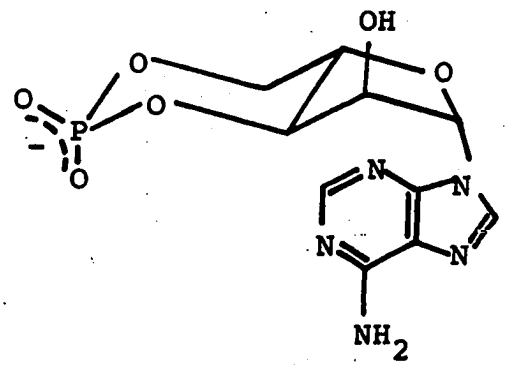
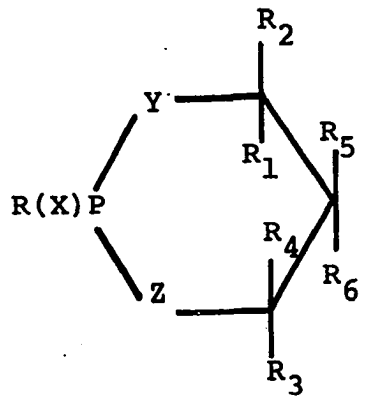
Compound[a]	Structural formula	Ref.[b]
203		91
204		91
205		6

Table 5. Other 1,3,2-Y,Z-phosphorinanes



Compound[a]	Y	Z	R	X	R_1	R_2	R_3	R_4	R_5	R_6	Ref.[b]
206	O	NH	$(CH_2CH_2Cl)_2N$	O	H	H	H	H	H	H	172, this work (171)
207a,b	O	CH_2	MeO	O	H	H	H	H	H	Me	119
208a,b	O	CH_2	EtO	O	H	H	H	H	H	Me	119,120
209a,b	O	CH_2	MeO	O	H	Me	H	H	H	H	119,121
210a,b	O	CH_2	EtO	O	H	Me	H	H	H	H	119,120,121
211a,b	O	CH_2	EtO	O	H	H	H	Me	Me	H	122
212a,b	O	CHMe	EtO	O	H	H	H	H	H	H	123
213	S	S	MeO	:	H	H	H	H	Me	Me	126
214	S	S	Me	:	H	H	H	H	Me	Me	126
215	S	S	Et	:	H	H	H	H	Me	Me	126

216	S	S	t-Bu	:	H	H	H	H	Me	Me	126
217	S	S	Ph	:	H	H	H	H	Me	Me	126
218	S	S	PhO	O	D	D	H	H	Me	Me	102
219	S	S	MeO	:	H	H	H	H	H	t-Bu	126
220	S	S	Me	:	H	H	H	H	H	t-Bu	126
221	S	S	Et	:	H	H	H	H	H	t-Bu	126
222	S	S	t-Bu	:	H	H	H	H	H	t-Bu	126
223a,b	S	S	Ph	:	H	H	H	H	H	t-Bu	126
224	NMe	NMe	MeO	:	H	H	H	H	H	H	127
225	NMe	NMe	Me	:	H	H	H	H	H	H	127
226	NMe	NMe	Et	:	H	H	H	H	H	H	127
227	NMe	NMe	Ph	:	H	H	H	H	H	H	127
228	NMe	NMe	Cl	:	H	H	H	H	H	H	127
229	NMe	NMe	MeO	:	H	H	H	H	Me	Me	127
230	NMe	NMe	Me	:	H	H	H	H	Me	Me	127
231	NMe	NMe	Et	:	H	H	H	H	Me	Me	127

[a]The letters a,b following the compound number indicate geometrical isomers.

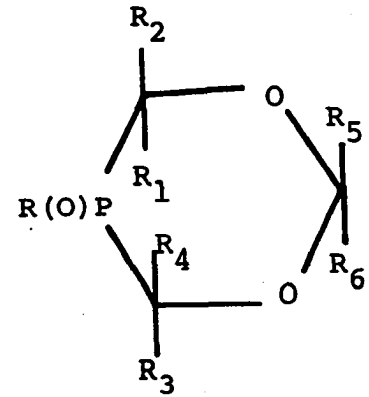
[b]Ref. are the reference numbers of literature reports of each compound. Numbers in parentheses following "This work" refer to published accounts of the work appearing in this thesis.

Table 5 (Continued)

Compound[a]	Y	Z	R	X	R_1	R_2	R_3	R_4	R_5	R_6	Ref.[b]
232	NMe	NMe	Ph	:	H	H	H	H	Me	Me	127
233	NMe	NMe	Cl	:	H	H	H	H	Me	Me	127
234	CH_2	CH_2	H	:	H	H	H	H	H	H	129,130
235	CH_2	CH_2	H	S	H	H	H	H	H	H	130
236	CH_2	CH_2	H	Me	H	H	H	H	H	H	130
237	CH_2	CH_2	Me	:	H	H	H	H	OMe	OMe	131,132
238	CH_2	CH_2	Ph	:	H	H	H	H	OMe	OMe	131
239	CH_2	CH_2	Me	:	H	H	H	H	O[c]		133
240a,b	CH_2	CH_2	Me	:	H	H	H	H	H	OH	132,134
241a,b	CH_2	CH_2	Me	:	H	H	H	H	Et	OH	134,135
242a,b	CH_2	CH_2	Et	:	H	H	H	H	Et	OH	134
243a,b	CH_2	CH_2	Me	:	H	H	H	H	t-Bu	OH	132
244a,b	CH_2	CH_2	Me	:	H	H	H	H	Ph	OH	134
245a,b	CH_2	CH_2	Me	:	H	H	H	H	CH_2OH	OH	134
246a,b	CH_2	CH_2	Me	:	H	H	H	H	$CH_2C(O)Et$	OH	134

[c]Carbonyl group at C4 position.

Table 6. 1,3,5-Dioxaphosphorinanes



Compound	R	R_1	R_2	R_3	R_4	R_5	R_6	Ref.[a]
247	$PhCH_2$	Ph	H	Ph	H	Ph	H	136
248	$PhCH_2$	Ph	Ph	H	H	H	Ph	136
249	HO	Me,H		Me,H		Me,H		137
250	MeO	Me,H		Me,H		Me,H		137

[a]Ref. are the reference numbers of literature reports of each compound.

depending on the prevailing stereo-electronic conditions and (2) the preferred disposition of exocyclic substituents. These will first be discussed in relation to 1,3,2-dioxaphosphorinanes, for which the greatest amount of work has been reported, and then to other saturated phosphorus heterocycles.

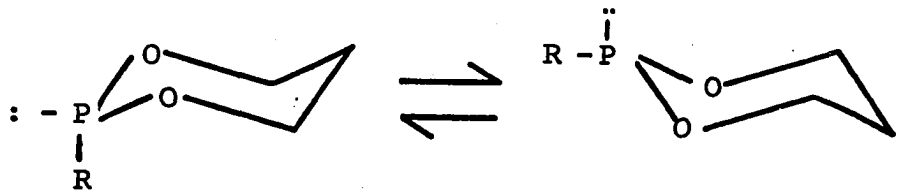
2-R-1,3,2-dioxaphosphorinanes

Ring conformation

No crystal structure determinations have been reported for 1,3,2-dioxaphosphorinanes containing trivalent phosphorus, presumably because most are liquids at room temperature. A considerable number of nmr spectral studies have been undertaken to determine the ring conformations in solution.

Analyses of nmr spectra of compounds 1-3 (8), 5 (9, 10), 7 (9, 10), 8 (11), 11 (9, 10, 11), 12 (9, 10, 11), 13 (9, 10, 11), 15 (12), 16 (12), 17a (13, 14), 18a,b (15), 19a,b (15,16), 21a (17), 22a,b (18), 23 (13, 14), 26a,b (9, 10), 27a,b (9, 10), 37 (12, 19, 20), 38b (9, 10, 21, 22), 42 (22), 43 (22), and 44 (9, 10, 11) have been accomplished by observation at one temperature only and all have been assigned a chair conformation. Spectra of compounds 4 (9, 10, 11, 23), 6 (10, 22), 24a,b (9, 10, 24), 25a,b (9, 10), 28a,b (25), 32a (20), 33a (19, 20), 34a (20), 35 (20), 38a (9, 10, 21, 22), 40 (9, 10, 21, 22) and 41 (9, 10) have been obtained at various temperatures and concluded to exist in either a single rigid chair conformation or an equilibrium of two chair conformations

indicated below for I and II which does not change appreciably within the temperature ranges (typically to -50°C) investigated. Conversely, variable temperature experiments and



I II

spectral analysis of compounds 9 (26), 10 (9, 10, 11, 26) 17b (13, 14), 21b (17), 32b (20), 33b(19, 20), and 34b (20) indicated changes in nmr spectral parameters consistent with conformational changes generally assumed to be chair-chair interconversions as indicated above for I and II.

Isomers

In addition to isomerism at phosphorus induced by chair-chair interconversions, isomerism can arise from substitution at one or more of the ring carbon positions. Thus, compounds 14-40 and 42-43 could in theory be prepared as two isomers differing in configuration either at phosphorus or at the substituted carbon. Interconversion of these isomers would necessitate bond cleavage at either phosphorus or carbon followed by bond re-formation.

Edmundson and Mitchell (27) found that the two methyl groups at the C5 position of compound 57 differed in chemical shift and peak width at half height. They concluded

that the broader, downfield methyl peak was due to axial methyl protons on the basis of unresolved residual coupling to the axial protons of C4 and C6 since these lie in a W configuration. By similar reasoning the a,b isomers of compounds 24 (9, 24), 25 (9), 26 (9), 27 (9), 28 (25), 29 (29), 30 (29) and 31 (29), have been assigned as differing in C5 configuration with consistent phosphorus configuration for each pair, whereas compounds 17 (13, 14), 18 (15), 19 (15, 16), 32 (20, 28), 33 (19, 20, 30), 34 (20), 35 (20), 38 (9, 21, 22) and 42 (22) are isomeric at phosphorus with consistent carbon configuration. Compounds 36a,b and 39a,b, also isomeric at phosphorus, are described in detail in the Discussion section of this part. Carbon versus phosphorus isomerization is dependent on the energetics of the preferred configuration of the sites. Thus, in the first series of compounds, isomeric at C5, the configurational preference of phosphorus is of greater thermodynamic importance than that of C5. The contrasting behavior of the latter series of isomeric compounds apparently arises from steric instability of compounds with opposite carbon configuration. Thus, compounds 32-37 would require axially disposed methyl groups at the C4 position resulting in severe 1,3 interactions with the axial proton of C6. Severity of interaction is amplified for compounds 37-39 which would require diaxial methyl groups in the C4 and C6 positions. Pnmr analyses of these types of compounds indicate the predominance of a single carbon conformation with the methyl substituents

equatorial. The stereochemistry of C4 and C5 in 41 would also be difficult to change owing to the presence of a six-membered ring fused at these positions. The energetic balance of isomeric compounds 14 (28), 17 (13, 14), 18 (15), 19 (15, 16), 21 (17) and 22 (18) are more difficult to predict and C5 versus phosphorus isomerism for 14 has not been determined. Generally the tert-butyl group prefers an equatorial orientation. Consequently, the thermodynamically stable isomers of compounds 17, 21, and 22, and both isomers of 18 and 19 contain equatorial tert-butyl groups. The unstable isomers of 17, 21, and 22, however, are conformationally mobile at room temperature indicating that the opposing preferred C5 and phosphorus geometries are energetically similar. At low temperature the unstable isomer of 17 does form one major stable conformation in which the tert-butyl group is axial.

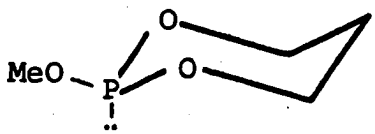
Isomers of the chloro compounds 15 (12), 16 (12), 23 (13, 14), 37 (12, 19, 20, 28, 30), 40 (9, 22, 23), although expected, have not been observed. Furthermore, pnmr spectra of the 2-chloro compounds 12 (9, 11), 26 (9), 30 (29), and 41 (9) and to a greater extent those of the 2-bromo compounds 13 (9) and 27 (9) exhibit decreased broadening of spectral lines upon cooling and/or dilution. Employing a mechanism previously proposed for five-membered rings, White et al. (9) postulated that these observations indicated an intermolecular exchange mechanism in which an incoming halide ion displaces the original halide

resulting in an inversion of phosphorus configuration. The result of this mechanism is ready establishment of equilibrium of phosphorus and carbon substituent conformations. The presence of only one isomer of each of the compounds 15, 16, 23, 37 and 40 indicates a preference of one configuration at both phosphorus and carbon since a mechanism to form the other isomers is readily available. The other 2-chloro and 2-bromo compounds can exist as isomers because the energy differences between C5 configurations are small. The authors further stated that the order of the rate of exchange of various phosphorus substituents is greatest for bromo followed by chloro and then fluoro with methoxy least of the four.

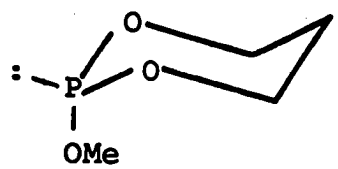
Phosphorus and ring carbon stereochemistry

Although the stereochemistry of ring carbons can be established with relative ease from coupling constant values, phosphorus stereochemistry is more difficult to determine. Gagnaire and Robert (23) postulated an equatorial OMe (III below) for compound 4 on the basis of coupling constants. They reasoned that since the $J(POCH_{eq})$ value of 6 Hz for compound 46 (which can be construed as a six-membered ring with an axial substituent) was much different from that of the $J(POCH_{eq})$ value of 10.8 Hz for 4, the configuration must be opposite. Furthermore, $J(POCCH_{ax})$ and $J(POCCH_{eq})$ values of about zero and 0.5 Hz, respectively, for 46 (31) differed significantly from 0.5 and 3.6 Hz for the stable isomer 38a (21),

reinforcing their postulation of opposite configurations. They also proposed a similar equatorial preference for compounds 6, 8, 10, 11, and 12 (11) and 40 (21) largely on the basis of least steric interaction. Bogat-skii et al. (29) also stated that the OMe disposition was equatorial in compounds 29a and b, but the basis for the assignment was not given.



III

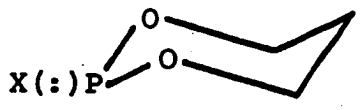


IV

Other evidence contradicts the above methyl assignment (configuration III) and supports the configurational assignment depicted by IV above. White, McEwen and Verkade (24) reported dipole moments of the BH_3 adducts of 24a,b (compounds 115a,b) which are isomeric at C5 and found them to be consistent with axial OMe and equatorial BH_3. Dipole moment measurements have also been obtained for compounds 152a,b, 153a,b, 154a,b and 155 prepared from the stereoretentive reaction of sulfur with phosphites 32a,b, 33a,b, 34a,b and 35 (19, 20). Differences of about 1.3 Debye were observed for each isomer pair of the first three compounds. The thio derivatives of the stable phosphites of each pair (a isomers) and of 35, for which only one isomer could be prepared, were concluded to contain an axial alkoxy group because of the larger molecular moments induced by an

equatorial versus an axial phosphoryl sulfur. The crystal structure of compound 173 (32), prepared with presumed stereoretention of the methoxy group from diborane and 38a was found to have an axial methoxy group. The crystal structure of compound 179 (33, 34), obtained from the Michaelis-Arbusov reaction of triphenylmethyl chloride and unstable phosphite 38b which occurs with stereoretention of the exocyclic oxygen (see references 35-37 for reviews of the Michaelis-Arbusov reaction mechanism), indicated an equatorial oxygen. Axial methoxy orientation was also concluded to be the stable configuration by Bentrude and coworkers from the crystal structure of the Michaelis-Arbusov reaction product (110b) of unstable phosphite 17b with methyl iodide since it possessed equatorial phosphoryl oxygen (38). A crystal structure determination of the phosphate 106b derived from the presumed stereoretentive (39) oxidation of the same unstable phosphite 17b by tert-butyl peroxide indicated equatorial tert-butyl and methoxy groups (40). Although Gagnaire and coworkers encountered difficulties when making assignments on the basis of nmr spectral parameters, two other groups have indicated axial alkoxy preference by nmr techniques. Thus, Bergesen and Albriktsen proposed that configuration on the basis of similarity of couplings in compounds 1 and 2 to those of 47 (8) which has been shown to have the structure indicated in the table (41), namely a six-membered ring with an axial substituent. Haemers et al. (22) concluded that the stable isomers 38a and 42a contained equatorial

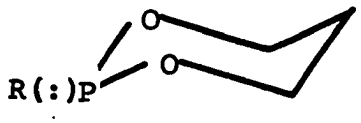
methoxy groups by the difference in chemical shifts of the C4 and C6 axial protons in a versus b isomers. For both 38 and 42 the proton absorptions of the a isomers were shifted further downfield than those of the b isomers which these authors concluded to be due to deshielding by the methoxy group when axially disposed.



V

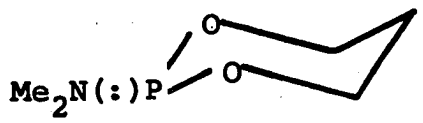
In contrast to the original postulation of equatorial preference of halogens (compound type V above where X is F, Cl or Br) by the French workers (cf. p. 30), several other groups of workers have come to the opposite conclusion. As with the phosphites, the similarity of the coupling constants of 3 and 47 led Bergesen and Albriktsen (8) to assign the chloro orientation as axial. From chemical shift data Haemers et al. (22) made the same assignment for 40 and 42 as did Bergesen and Albriktsen (12) for compounds 15, 16, and 37. Perhaps the most convincing argument, however, was presented by Bodkin and Simpson (19) who pointed to the fact that since the reaction of methanol with 37 probably proceeds by inversion of configuration as suggested by Aksnes (30) and since it is known to yield unstable phosphite containing an equatorial methoxy

group, the chloro group must have an axial disposition.



VI

The preferred phosphorus stereochemistries of the two isomeric phosphonites 21a,b (17) and 22a,b (18) (compound type VI above) have also been determined. The isomers 21a and b were stereoretentively oxidized with NO_2 to 110a,b and compared to the compounds obtained by the Michaelis-Arbusov reaction described above. Axial methyl was found to be the preferred configuration (17). Similarly 22a, the stable phenyl phosphonite, was found to be axially substituted since its NO_2 oxidation produced was of opposite configuration to that obtained from the Michaelis-Arbusov reaction of 17b with iodobenzene (18).



VII

Several techniques have been used by Bentrude and Tan (15, 16) to ascertain that the preferred stereochemistries of the compounds 18a,b and 19a,b (compound type VII above) are

equatorial amino as opposed to axial substituent for all other compounds discussed above. For both of the compounds, equilibria between the isomers can be established and in both cases the b isomers were predominant. Bentrude and coworkers have found that axial substituents consistently exhibit a greater upfield ^{31}P chemical shift than their equatorial analogues (42) and the shifts for the b isomers appear downfield of those for the a isomers. Upfield ^{13}C chemical shifts of carbons γ to axial substituents have been noted for cyclohexane systems (43) and the chemical shifts for the C4 and C6 carbons of a isomers are upfield of the b isomers. The stereoretentive oxidation of 19a,b with NO_2 results in compounds 109a,b for which the chemical shifts of axial proton at C4 and C6 are upfield of the equatorial protons for the a isomer and reversed for the b isomer as expected for equatorial and axial phosphoryl groups, respectively. Finally, the coupling constants $J(POCH_{eq})$ for b isomers are about twice as large as those for which the substituent is known to be axial, and very similar to that for compound 20 which is believed to be equatorially substituted due to steric interaction (44).

Rationalizations for differing phosphorus stereochemistries dependent on substituent type will be deferred to the Discussion section of this part.

2-R-2-oxo-1,3,2-dioxaphosphorinanes

Ring conformations

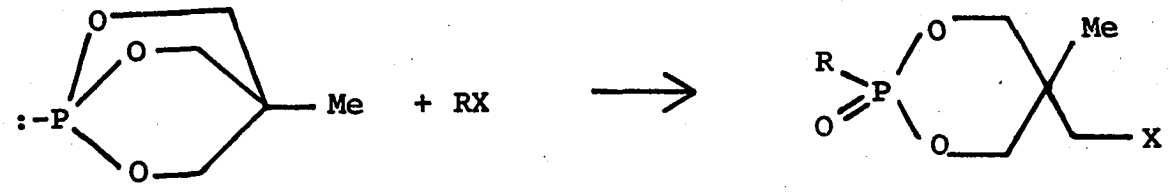
The chemical and structural investigations of tetravalent phosphorus compounds have been more extensive than for trivalent compounds. Analyses of nmr spectra have been performed on a majority of the compounds listed in Table 3 and reference numbers to the analyses are included in the table. Most of the compounds have been found to exist in either a single chair form or an equilibrium of two chairs. These aspects will not be treated here, however, and some of the conformational consequences of steric interactions are now discussed. Compound 198 which contains four methyl groups in the C4 and C6 positions does not exist in a chair conformation (45) presumably because that would necessitate sterically prohibitive diaxial methyl interactions, whereas a twist conformation would partially eliminate such interactions. Compound 181 probably also exists in a twist conformation for similar reasons. Although the a isomers of compounds 156 (45, 47, 48) and 183 (45, 47, 49), and the b isomer of 195 (50) all exist in chair forms, the b isomers of the former two and the a isomer of the latter are somewhat distorted. The distortions apparently arise from an unstable phosphorus configuration which induces a ring flip which in turn would result in an unstable configuration of carbon substituents. Compound 111a is the only reported example of a compound which appears to be in a boat conformation (51).

Compounds 107b (52), 116a (50, 51, 52), 122b (53), and 132a (53) all exist in twist forms for no obvious reason. In earlier variable temperature work many authors assumed that if the pnmr spectra did not change, there was only one chair conformer present. More recent work reported by many of these same authors, however, indicate that this is an inaccurate assumption since the results could also be explained by little or no change in the equilibrium ratio of two chair conformers in the temperature ranges employed. The nmr spectra of some compounds do change with temperature indicating conformational mobility. The significance of these results will be discussed later in considering the phosphorus stereochemistry.

Isomers

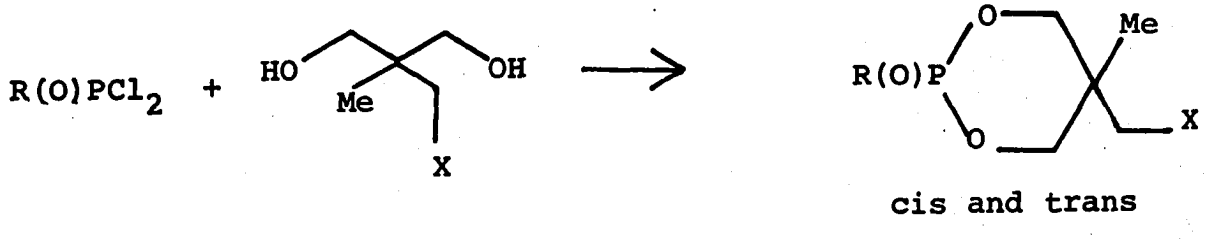
As in the case of trivalent phosphorus compounds discussed previously, tetravalent phosphorus compounds can exist as stereoisomers if at least one ring carbon is substituted. Compounds for which two isomers have been observed are indicated in Table 2 by a,b following the compound number.

The reaction of bicyclic compounds such as 45, 46 and 47 with RX where X is a halogen, and R is halogen, alkyl, aryl, or amino, proceeds by the Michaelis-Arbusov mechanism (see references 35, 36, 37 for reviews of the mechanism) to produce compounds for which the relative cis or trans stereochemistry of carbon and phosphorus are known. The reaction is indicated below for compound 45, where cis and trans refer to

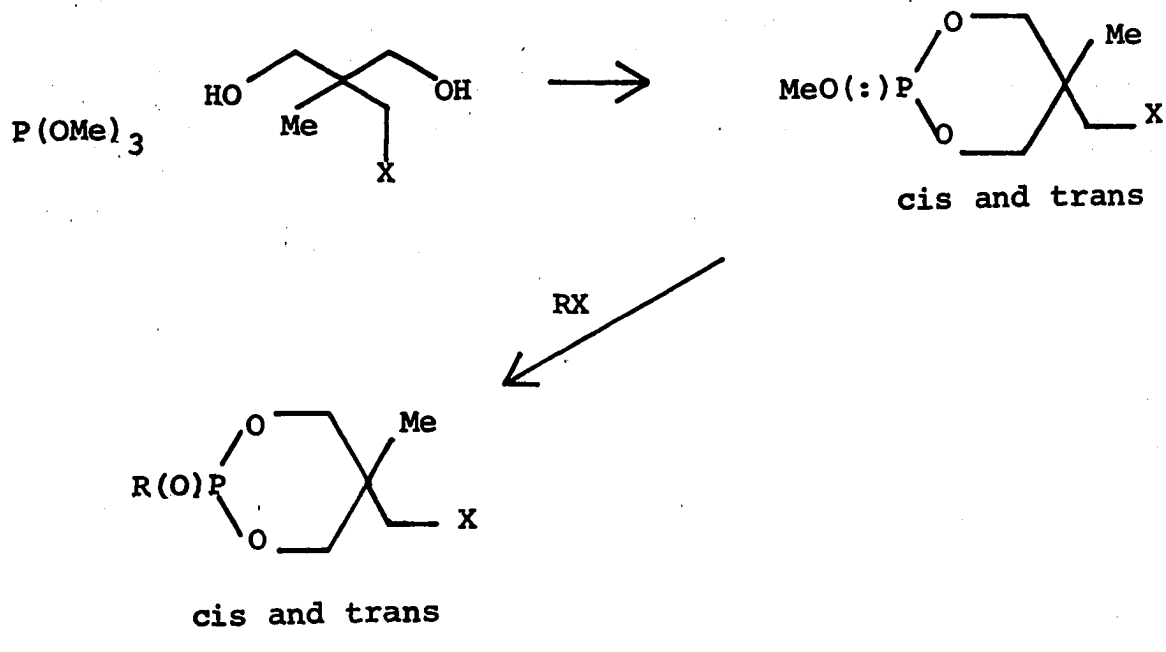


45

the relationship of R and the halomethyl group. The x-ray structure determination of the reaction product of bromine with 45 has been reported and the bromomethyl group at C5 was found to be trans to the bromo group at phosphorus (55) as expected from the mechanism. A mixture of cis and trans compounds can be obtained from the appropriate dialcohol and phosphorus reagent (reaction 1), by synthesis of the phosphite from dialcohol and trimethylphosphite and subsequent reaction with RX (reaction 2), or by nucleophilic displacement reactions

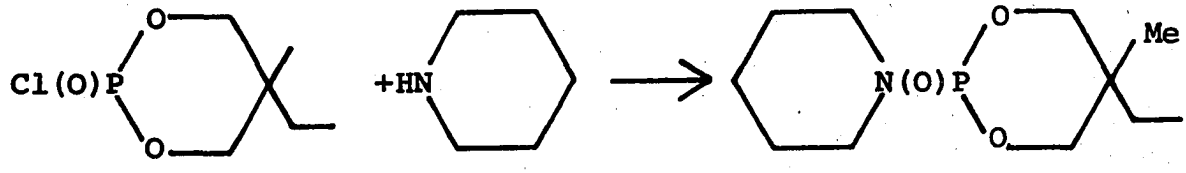


Reaction 1



Reaction 2

at phosphorus such as reaction 3. By these types of procedures compounds 114-141, 195-196, 202-204 have been synthesized with known relative geometries. There has been



Reaction 3

some confusion in the literature concerning the isomers of compound 124, however. Wadsworth and Horton (56) reported three isomers for 124, two of which contained the same relative C5 and phosphorus geometry, but were of opposite ring conformation. More recently, however, Duff and Trippett reported that upon repeating this work only two isomers, cis and trans, were actually present (57). Isomers of the other compounds can be prepared as mixtures by Reaction 1, 2, or 3 using the appropriate diolcohol or by oxidation of trivalent isomer mixtures with NO_2, peroxides or sulfur. Pure isomers can be prepared from stereospecific oxidations of isomerically pure trivalent compounds by NO_2 (see Discussion), tert-butyl peroxide (39), or sulfur (58). Although the Michaelis-Arbusov reaction (Reaction 2) is generally presumed to proceed with retention of oxygen configuration, Bodkin and Simpson have found that reaction of compounds 33a,b and 34a,b with methyl or ethyl iodide to give products 162a,b and 163a,b results in some loss of stereospecificity (59, 60). This was not the case with triphenylmethyl chloride, nor does it appear to be true in the reaction of methyl phosphites with methyl iodide (see Experimental) and it can be used to prepare isomerically pure methyl- and triphenylmethylphosphonates.

Instrumental methods for determination of stereochemistry

Many different techniques have been used to determine the preferred phosphorus stereochemistry of tetravalent 1,3,2-dioxaphosphorinanes. Each method will be discussed with a few specific examples and then the results of the methods will be compared according to compound type.

The most obvious procedure for determination of phosphorus stereochemistry is that of x-ray diffraction. All of the structures reported in the literature, namely, compounds 48 (61), 50 (62), 56 (63), 88 (64), 90 (65), 110a (38), 139 (55), 179 (33, 34) and 201a (66), are in chair conformations somewhat flattened at phosphorus, with equatorial phosphoryl oxygens except compound 201a which is boat and will be discussed later. There is evidence that when the phosphorus substituent is NR_2, the oxygen is axial (67). The solid state configurations cannot necessarily be extended to solution, however, since crystal packing forces may be influential in phosphoryl orientation. The rest of the methods discussed below are all solution studies.

One of the simplest nmr procedures employed is the observation of chemical shifts of axial C4 and C6 protons. For two isomers differing only in stereochemistry at phosphorus it has been reasoned that those with axial phosphoryl oxygen or thiono phosphoryl sulfur will be shifted further downfield. Although in many cases this method has predicted the same

phosphorus geometry as other techniques, an incorrect assignment based solely on this method was reported for 161a,b (68). Peak width measurement of C5 methyl proton absorptions has been used for compounds of the 5,5-dimethyl and 5-alkyl-5-substituted methyl type. For the former category of compounds, the two methyl groups are not chemically equivalent, and if there is not an equal distribution of ring conformers one methyl will have more axial character than the other. At room temperature equivalent methyl groups have only been observed for compound 78 which is symmetrically substituted at phosphorus (26). Edmunson and Mitchell (27) found one of the methyl groups of compound 57 to be broader than the other and assigned it as axial on the basis of decoupling of the residual planar W coupling to the C4 and C6 axial protons. The chemical shift of the axial methyl in deuteriochloroform was found to be downfield of the equatorial methyl for this compound, whereas the relationship for compound 87 containing a large triphenylmethyl substituent at phosphorus was reversed. They reasoned that since the steric requirements of 87 precluded axial orientation, it and the other similarly behaving aralkyl phosphonates investigated must be equatorial. The cause of the chemical shift inversion was believed to be from shielding of the axial groups by the phenyl groups. They also found that $\Delta\delta$ values (defined as chemical shifts in deuteriochloroform minus those in benzene) were smaller for axial than equatorial

methyl groups in all cases. Axial broadening and $\Delta\delta$ criteria have also been applied to the determination of C5 stereochemistry in 5-methyl-5-halomethyl compounds (53) where $\Delta\delta$ (equatorial Me) > $\Delta\delta$ (axial CH_2X) and $\Delta\delta$ (equatorial CH_2X) > $\Delta\delta$ (axial Me). When the relative stereochemistry of C5 and phosphorus are known as in the Michaelis-Arbusov reactions of bicyclic phosphites with RX (cf. p. 36), determination of C5 geometry yields the phosphorus configuration. Thus compound trans-122 shown to have axial chloromethyl at C5 also contains axial chloro at phosphorus. Comparison of the peak width of the thus determined equatorial methyl group in that compound to those of the isomeric phosphoramidates 116a,b indicated the trans isomer (a) of the latter (prepared by Michaelis-Arbusov reaction) to be dissimilar and the cis isomer (b) similar. This indicated axial and equatorial C5 methyl groups respectively, requiring equatorial phosphorus substitutents and axial phosphoryl oxygens for both compounds.

Coupling constant data can also be employed to determine substitution at C4 and C6 positions. Thus, the C4 methyl group has been found to be equatorial in both isomers of 161 (69) because of the large coupling of the C4 axial proton to the axial C5 proton. If the methyl were axial in either isomer, the necessarily equatorial C4 proton would have a much smaller coupling to the C5 axial proton. Unless synthetic reactions are employed whose stereochemical pathways are

known, however, no direct information can be obtained regarding the phosphorus configuration.

Similar to large differences in vicinal diaxial coupling compared to vicinal axial-equatorial coupling of protons is the dihedral angle dependency of phosphorus coupling to axial and equatorial protons, alkyl groups, or ^{13}C nuclei at C4 and C6. Coupling to equatorial protons or groups of protons is much larger than to axial ones (see reference 70 for a study of these phenomena). Borisenko et al. (71) have reported a dihedral angle dependence of $J(POC^{13}C)$ for compounds 161a,b and 185a,b where coupling to carbons of axial methyl groups at C4 and C6 were 0-1.8 Hz and to equatorial methyl group carbons were 4.5-9.1 Hz. Bentrude and Tan (15, 16) have found unusually large $J(POCH_{ax})$ coupling constants for compounds in which the substituent is known to be equatorial, being almost double those of the same compound with opposite phosphorus configuration and indicative of a substituent orientation effect on coupling constants. To date this has only been used by these authors to corroborate configurational assignments for 109a,b.

Two types of information can be obtained through the use of lanthanide shift reagents. Yee and Bentrude (72) have demonstrated that coupling constants and chemical shifts can be obtained from otherwise complex spectra using europium shift reagents with compounds containing phosphoryl oxygen. In this thesis is described the first report of the use of

tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione) europium(III) ($Eu(fod)_3$) in the direct determination of phosphorus stereochemistry via chemical shift (73), but the results will be deferred to the Discussion section. Dale (74) has also used chemical shifts of C4 and C6 axial protons to indicate phosphorus stereochemical preference. Yee and Bentrude found that coordination of the phosphorus compound to the shift reagent occurs at the phosphoryl oxygen (72). The difference in chemical shift in the presence and absence of shift reagent, $\Delta\delta$, is dependent on the angle θ and distance R from the europium moiety as given by the expression $\Delta\delta = k(3\cos^2\theta - 1)/R^3$ where k is a collection of constants (75). The C4 and C6 axial protons, being in closer proximity to the europium in a compound containing an axial phosphoryl oxygen, will exhibit a greater downfield shift than the same compound containing an equatorial phosphoryl oxygen. Care must be exercised in the interpretation of LIS data in potentially mobile systems, however, since Bentrude, Tan and Yee (76) have observed a change in the phosphoryl orientation from equatorial to axial in compound 110a upon complexation with shift reagent. This could result in erroneous assignments if undetected.

Bentrude and coworkers have found that for isomeric pairs of compounds, those with axial phosphorus substituent and equatorial phosphoryl oxygen have ^{31}P chemical shifts consistently upfield of the equatorially substituted isomers

(44). This criterion must be used with caution, however, since an exception to this for the hydrogen phosphonates 161a,b and 176a,b (see Discussion) has been found in the present research.

The final nmr procedure to be discussed for determination of substituent stereochemistry is that of ^{13}C chemical shift measurements as observed by Bentrude and Tan (15, 16). It has been found in cyclohexane systems that the chemical shift of a ring carbon γ to an axial substituent is further upfield than the same carbon γ to the equatorial group in the isomeric compound (43). This has been extended to the 1,3,2-dioxaphosphorinane system in the assignment of equatorial orientation of the dimethylamino group in 109b and axial position in 109a.

Dipole moment measurements have been used by a few authors to determine phosphorus stereochemistry for compounds containing a BH_3 group on phosphorus (24), a phosphoryl oxygen (68, 69), and a phosphoryl sulfur (19, 20). For all the compounds studied the P-X moment involving these groups was expected to be larger than the P-R moment resulting in greater molecular moments for compounds with axial R and equatorial X than those with opposite configuration (see also Discussion). This method appears quite valuable when comparing isomeric compounds, but some difficulties may be encountered when assignments are based solely on comparison of measured values to calculated values (cf. p. 54).

Unlike nmr spectra and dipole moment measurements, infrared spectra are not time averaged with respect to ring conformational changes and they can readily yield a quantitative measure of conformer equilibria. Kainosho and coworkers were the first to report that equatorial phosphoryl groups absorbed at higher frequencies than the axial conformers of the same compound, and have assigned the preferred stereochemisteries of some compounds on the basis of relative conformer phosphoryl intensities (77). Majoral and coworkers (78) extended this work and attempted to obtain an empirical relationship of predictive value for phosphoryl frequencies. The equation $\bar{\nu}(P=O) = 1174 + 26\Sigma\sigma^* - 25\Sigma x$, where Σx is the sum of the chloride and SR groups bonded to phosphorus and σ^* is the Taft constant empirically derived for various substituents on phosphorus has been used for acyclic systems. Upon comparison of this equation to cyclic systems they obtained the equations

$$\bar{\nu}(P=O)_{ax} = 1174 + 26\Sigma\sigma^* - 25\Sigma x$$

$$\bar{\nu}(P=O)_{eq} = 1200 + 26\Sigma\sigma^* - 25\Sigma x$$

reflecting the finding of the Japanese workers. Values for Taft constants are listed in Table 7 and a summary of the absorption regions are given in Table 8 (79). The French workers have reported increases in equatorial phosphoryl conformers with increased solvent polarity (80). Thermodynamic

Table 7. Taft constants for phosphoryl stretching frequencies of 2-R-2-oxo-1,3,2-dioxaphosphorinanes[a]

R	σ*	Σσ*[b]
MeO	1.46	4.16
EtO	1.35	4.05
PhO	2.38	5.08
Me_2N	0.65	3.35
Ph	0.6	3.30
Cl	2.94	5.64

[a]Ref. 78.

[b]Σσ* includes two times the value of EtO presumed for the dialcoxy portion of the ring.

Table 8. Vibrational frequency ranges for 2-R-2-oxo-1,3,2-dioxaphosphorinanes[a]

Orientation of P=O	Disposition of R			
	PhO	Me_2N	Ph	Cl
Equatorial	1316-1323		1284-1286	1316-1323
Axial	1290-1297	1252-1258	1258-1260	1288-1290

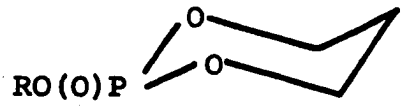
[a]Ref. 79.

parameters ΔG, ΔH, and ΔS, determined from variable-temperature infrared spectra for the interconversion of chair conformers (reference 81 for original work), have agreed well with the results of nmr studies (80, 82).

One report has been published of attempts to distinguish the phosphorus atoms of isomeric compounds 159a and b by inner-orbital photoelection spectroscopy, but the results were inconclusive (83).

This concludes the discussion of instrumental techniques. The results found in the literature will now be discussed with respect to preferred phosphorus configuration by substituent.

Phosphates (VIII)



VIII

The stereochemistry of the phosphate 49 has been determined from infrared studies to consist essentially of one conformer which contains an axial methoxy group and an equatorial phosphoryl oxygen (84). The same has been found for 57 from the C5 methyl chemical shifts (27) and infrared spectra (77, 78, 79, 84). The latter method allowed calculation of 93% equatorial phosphoryl conformation in pyridine (78). Isomers of compound 106 have been prepared by presumed stereoretentive oxidation

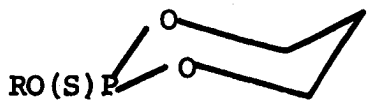
of the phosphites and thus the relative stereochemistry of the tert-butyl group at C5 and the methoxy at phosphorus became known. The phosphorus geometry of the a isomer was found to be equatorial in phosphoryl oxygen and equatorial in C5 tert-butyl, and the b isomer axial in phosphoryl and equatorial in tert-butyl from C4 and C6 proton chemical shifts and C4 and C5 proton coupling, although the b isomer was conformationally quite mobile (52). The ethyl, n-propyl, iso-propyl, n-butyl and tert-butyl phosphates (compounds 60-64) have all been found to have predominately equatorial phosphoryl oxygen by comparison of coupling constants (84) to 106a which is known to contain equatorial phosphoryl (51), from dipole moment measurements (85), and by infrared studies (77-80). In non-polar solvents the predominant phosphorus configuration of compound 59 was found to be equatorial phosphoryl oxygen, and the use of polar solvents increased the amount of that configuration (80) to 92% in pyridine (78). The numerous studies of compounds 50, 64, 95, and 98 resulted in the same conformational conclusions from nmr coupling constants (84), 5,5-dimethyl chemical shifts for 64 (27), dipole moment measurements (85), and infrared studies (45, 47, 48, 78-80, 86) with the latter method demonstrating solvent dependency for compounds 50 and 64 (80). A distribution of 94% equatorial phosphoryl for 64 (78) in pyridine was determined from infrared spectra. Compounds 181, 182, and 197 are all capable of readily under-

going conformational changes as are the phenyl phosphates discussed above although they contain at least one axial C4 or C6 methyl group. The former two compounds behave normally, containing equatorial phosphoryl oxygen as shown by infrared studies (46, 49, 79) with that configuration constituting about 84% of 189 (46) in pyridine. Although 181 is not appreciably distorted since equatorial and axial methyl groups are readily distinguished in the nmr spectra (49), distortion is observed for 198 by nmr spectroscopy (45) and is demonstrated in the ir spectrum by a smaller difference in frequency of what might best be referred to as pseudoaxial and pseudoequatorial phosphoryl oxygens with the latter predominating (79). Compounds 152, 171, 183, 188-191, and 197 all exist as a,b isomers. Compounds 156a and b both contain equatorial phosphoryl oxygen based on the great similarity of ^{31}P chemical shifts and infrared stretching frequencies (79, 86). This means the preference for equatorial phosphoryl is greater than the instability caused by the 1,3 steric interactions, although the axial methyl group of the b isomer did cause some ring distortion (86). Although both isomers of 183 have been observed, the b isomer was present in such low abundance that no assignment was made. The a isomer contained two equatorial methyl groups as shown by nmr spectroscopy and equatorial phosphoryl oxygen (45, 47, 48). As with compound 181, compound 190 contains one axial and one equatorial methyl group at the

C4 and C6 positions regardless of ring conformation, but the position of the C5 methyl group can be axial or equatorial resulting in isomers. Both isomers exhibit equatorial phosphoryl according to the ir spectra (81). Compounds 191a,b contain equatorial iso-propyl groups at the C4 positions as demonstrated by nmr coupling constants implying a difference in phosphorus configuration. The a isomer has equatorial and the b isomer axial phosphoryl oxygen as suggested by infrared spectral data (45, 47, 48, 79, 86). In this case the steric interactions of the isopropyl groups are sufficiently strong to overcome the phosphorus stereochemical preference. The remaining four phenyl phosphate isomer pairs 171a,b, 188a,b, 189a,b and 197a,b all contain diequatorial methyl groups in the C4 and C6 positions as shown by nmr spectroscopy (49, 81). The a isomers have equatorial and the b isomers axial phosphoryl oxygens as postulated from the ir spectra. It is germane to mention at this point that preferred stereochemical assignments cannot be made for the last five isomeric compounds alone unless equilibrium ratios of isomers can be obtained. The infrared stretching frequencies of the phenyl phosphate derivatives 66, 67, 68 demonstrate the predominance of equatorial phosphoryl oxygen configuration, but compound 69 which has the very bulky substituted phenoxy group exhibits an approximately equal distribution of the two configurations (77) because of 1,3 interactions with the C4 and C6 axial protons

when the phosphoryl is equatorial and the substituent axial.

Thiophosphates (IX)



IX

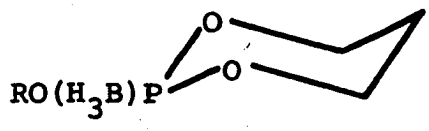
Thiophosphates have not been investigated as comprehensively as phosphates. This is probably due in part to the difficulty in the assignment of thiono phosphoryl stretching frequencies compared to the phosphoryl frequencies. Only two studies give any justification for an equatorial thiono phosphoryl being favored. One of these is based on the chemical shift differences of the 5,5-dimethyl groups in compound 58 (27), while the other study involved compounds 107a,b prepared by the presumably stereochemically retentive sulfuration of the isomerically pure phosphites with elemental sulfur. The a isomer containing equatorial thiono phosphoryl was predominantly in a single chair conformation with the tert-butyl group equatorial as indicated by the nmr spectrum. The other isomer, however, was not a single chair but underwent ring flipping including non-chair conformations (52). This indicates the relative instability of the axial thiono phosphoryl compared to the equatorial orientation. Isomers of 172 and 200 (22) have been isolated and configurational assignments

made on the basis of C4 and C6 axial proton chemical shifts. Isomers of 153, 154 and 155 have also been prepared and isolated with configurational assignments postulated from dipole moment measurements and corroborated by thiono phosphoryl stretching frequencies (19, 20). In neither of these studies could the preferred phosphorus stereochemistry be deduced, however.

Other phosphate-like compounds

Discussion of the remaining phosphate-like compounds has been delayed until now because there has been very little work with these systems and the chemical implications are unique. The phosphate anions 146 (83, 87) and 168 (88) probably do not contain a sure phosphoryl oxygen and a totally anionic oxygen, nor is the charge likely to be evenly distributed between the two oxygens. The distribution of charge between the axial and equatorial oxygens is not known, however, nor is it known between oxygen and sulfur in the isomeric compounds 147a,b and 148a,b (83, 87). Isomers of 149 and 150 have been synthesized by stereospecific reactions and although the relative geometries are known, the absolute configurations are not (87). Compounds 158a,b were also prepared stereospecifically by reaction of selenium with phosphite which then underwent the interesting reaction of methyl transfer. Here too, the relative but not absolute geometries are known (87).

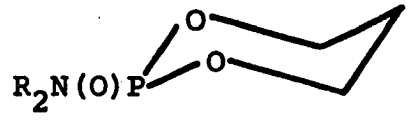
Borane adducts (X)



X

Besides the crystal structure mentioned previously only one investigation has been made of the preferred geometry of borane adducts of phosphorus. Dipole moment measurements of 115a,b indicate the preference of equatorial borane group in both isomers, implying isomerization at the C5 carbon (24).

Phosphoramidates (XI)



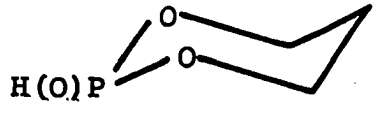
XI

Considerably fewer 2-dialkylamino-2-oxo-1,3,2-dioxaphosphorinanes have been investigated than the phosphates discussed above or the phosphonates discussed below. Kainosho and Shimozawa (85) have reported dipole moment measurements for primary amine derivatives 70, 71, and 72 and concluded the phosphoryl oxygen to be equatorial in all cases. The assignments are of dubious value, however, since they were based on

comparison of measured moments with calculated values of equatorial and axial phosphoryl conformers, a procedure which is hazardous at best. They also made the false assumption that the nitrogen atoms were tetrahedral (see Discussion) for their calculations. The dipole moment of 73, a secondary amine derivative, although not differing greatly from those of 70, 71 and 72 was the basis for assignment of axial phosphoryl oxygen (85). Majoral, Navech and coworkers in several papers assigned the geometry of phosphorus to be axial phosphoryl for both compounds 73 (48, 78, 86) and 97 (48, 86) on the basis of the single observed phosphoryl stretching frequency. In a later publication (79) the French workers were less certain of their original assignments, however, because of the questions raised by the reports of the Japanese workers. Bentrude and Tan have prepared and isolated the isomeric compounds 109a,b and assigned the stereochemistry of a as equatorial and b as axial phosphoryl on the basis of presumed stereoretentive oxidation of compounds 19a,b, axial C4 and C6 chemical shifts, $J(POCH_{eq})$ coupling constants and ^{31}P and γ ^{13}C chemical shifts (15, 16). The nmr spectral parameters of 109b led them to assign a predominantly single chair conformer, whereas 109a existed as more than one conformer implying the axial phosphoryl orientation, 109b, as the more stable phosphorus conformation. The relative geometries of C5 to phosphorus of compounds 116 and 132 are known from preparation of the trans

isomers from the Michaelis-Arbusov reaction of 45 with N-halopiperidine (cf. p. 36). The C5 geometry was assigned on the basis of peak widths and chemical shifts of the methyl and halomethyl groups. The phosphorus configuration was deduced to be axial phosphoryl oxygen for both isomers of both compounds (53). The isomeric sulfide derivatives 108a,b have been synthesized by the presumed stereoretentive reaction of sulfur with 18a,b, but no preferred phosphorus stereochemistry was stated (15). Equatorial thiono phosphoryl has been postulated for compound 74 from 5,5-dimethyl chemical shifts (27).

Hydrogen phosphonates (XII)

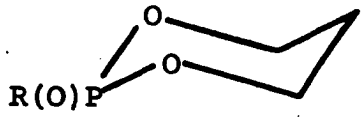


XII

There has been some confusion in the literature concerning the phosphorus stereochemistry of hydrogen phosphonates 161a,b. Mikolajczyk reported the two isomers as containing axial and equatorial phosphoryl oxygen, respectively, on the basis of axial C4 and C6 chemical shifts (68). Nifant'ev and coworkers also investigated the properties of the two isomers (88), and from nmr data determined the stereochemistry at C4 to be equatorial methyl in both cases. Through the use of dipole

moment measurements the phosphorus configuration was found to be opposite to that described above (69). Although other tetracoordinate phosphorus compounds do not readily isomerize at phosphorus, the hydrogen phosphonates do so when heated or in the presence of catalytic amounts of acid or base (see Discussion and reference 89). Nifant'ev and Borisenko found the rate of interconversion to be first order in phosphonate and that the a isomer (equatorial phosphoryl) was the more stable isomer at room temperature (89). The conformations of compounds 201a,b are believed to be those indicated in Table 4 with the phosphorus ring boat because of possible steric interactions with the known axially disposed hydroxyl group. The latter conclusion was reached from nmr coupling constants (90). The stereochemistry at phosphorus was determined for the b isomer to be axial phosphoryl and equatorial hydrogen on the basis of long range coupling of the phosphorus hydrogen to the colinear C5 axial proton of the phosphorus six-membered ring (90). Long range coupling of this nature has been observed by these authors in other rigid systems where colinearity is present (30). The a isomer was assumed at that time to have the opposite configuration (axial hydrogen and equatorial phosphoryl oxygen) and the assumption was validated by the crystal structure determination of that compound (66).

Alkyl phosphonates (XIII)



XIII

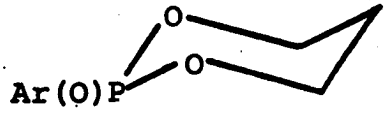
From the analysis of the nmr spectrum of compound 77 it was concluded that there was no great preference for phosphorus substituent orientation, whereas nmr spectra of compounds 133a (trans) and 141 (trans) contained predominantly equatorial phosphoryl oxygen (84). The authors believed that the preference in the latter two compounds was actually at C5 with the halomethyl group axially oriented in both compounds (84). The cis isomers which would then be expected to have the same C5 geometry and opposite phosphorus stereochemistry were not reported. Equatorial phosphoryl oxygen preference has been postulated for 77 from 5,5-dimethyl chemical shifts (27), but axial from LIS effects on the C4 and C6 axial protons (74). The latter method must be viewed with caution, however, because changes in conformation can occur upon complexation with shift reagents (cf. p. 44). Isomers of 111 have been obtained and the b isomer exists in a chair conformation with diequatorial tert-butyl groups. The a isomer, however, was found to exist in a boat conformation with both tert-butyl

groups equatorial. In this case ΔG for the difference between chair and boat conformations was estimated to be about 1 kcal/mole. The reason for equatorial tert-butyl at phosphorus is apparently the possible steric interactions of the large tert-butyl group with the C4 and C6 axial protons (50). The phosphoryl oxygen of the trichloromethyl phosphonate 84 has been postulated to be equatorial by 5,5-dimethyl chemical shifts (27).

It has been argued that the only possible orientation of triphenylmethyl is equatorial because of the steric bulk of that group (27). The similarity of the 5,5-dimethyl groups in that compound, 87, to those of 83, 84, 85, and 86 have led Edmundson and Mitchell to conclude axial phosphoryl for the latter four as well (27). A europium shift reagent study of 83 also indicated axial phosphoryl oxygen (74). Infrared spectral results for compounds 87, trans-120 and trans-138 implied the presence of two conformers (84) in contrast to the postulate above (in reference 27). The latter authors did believe, however, that the steric bulk of the triphenylmethyl group precluded the existence of a chair conformation with the triphenylmethyl group axial and thus the other conformer or conformers probably included non-chair forms (84). The stereochemistry of the trans isomers of 118, 119, 136 and 144, and compounds 120, 126 and 138 prepared by Michaelis-Arbusov reactions were all assigned as equatorial CH_2X and axial methyl

at C5 by chloroform-benzene $\Delta\delta$ values. This requires axial phosphoryl in these compounds as well as the cis isomers of 118, 119, 136 and 144 which displayed opposite C5 geometry (54). These results are consistent with the results of the 5,5-dimethyl compounds studied by the same authors as discussed above (27). Compounds 202, 203 and 204, prepared by the Michaelis-Arbusov reaction with 47 have been assigned the structures indicated in Table 4. The halo group has been shown by nmr coupling constants to be equatorial while the relative stereochemistry of phosphorus to that carbon is known by the reaction mechanism leaving only the phosphorus six-membered ring conformation in doubt. The authors reasoned that it must be boat with the substituent axial because of the steric interactions present in a chair conformer (91).

Aryl phosphonates (XIV)

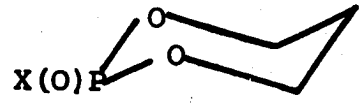


XIV

The infrared stretching frequencies reported in several studies of 55 (78, 79, 82), 88 (48, 78-82, 84), 95 (80, 82) and 100 (78-80, 82) all indicate the presence of more than one phosphoryl oxygen assumed to be due to two interconverting

chair forms in equilibrium. In polar solvents such as pyridine the equatorially oriented phosphoryl has been found to predominate, whereas in non-polar solvents such as carbon disulfide or benzene, axial phosphoryl has been observed as the major conformation (78, 80). Variable-temperature infrared spectra have been observed and ΔG values at 25° calculated to be 1.1 kcal/mole are in good agreement with those determined by nmr spectroscopy (82). Equatorial phosphoryl has been assigned to 88 on the basis of 5,5-dimethyl chemical shift differences (27). Axial preference for 86 has been inferred from europium shift studies in carbon tetrachloride and deuteriochloroform, although more of the equatorial conformer is found in the latter solvent than the former (74). The form of 199 is a distorted chair with equatorial phosphoryl predominating (79). Isomers of 112 have been prepared from presumed stereoretentive oxidation of the phenyl phosphonites 22a,b and the relative geometries determined by comparison to the Michaelis-Arbusov product of stable phosphite 14a with iodobenzene to give 112b. Both isomers have an equatorial tert-butyl group at the C5 position as determined by nmr spectroscopy and thus have opposite phosphorus stereochemistry with 112a containing equatorial and 112b axial phosphoryl oxygens (18). The stable phosphorus geometry cannot be inferred from this study.

Phosphorohalidates (XV)



XV

The infrared spectra of 90 reported in several papers all indicate the presence of one predominant conformation containing equatorial phosphoryl (78-80, 86), which was also found in the crystal structure (65), although the French authors did observe some evidence for another conformer. The same geometry has been proposed on the basis of 5,5-dimethyl chemical shifts (27) and by europium shift reagent experiments (74). Only one phosphoryl stretching frequency has been observed for compound 102 which was assigned to equatorial phosphoryl (78, 79, 86). The reaction of phosphorus oxychloride with the appropriate diol produced only a single isomer for compounds 165a (78, 86), 179 (79), 186 (49, 79) and 193 (78, 86) although two isomers might be expected. In all cases the phosphoryl stretching frequencies indicated equatorial phosphoryl oxygen. Isomers of 165 prepared by stereoselective syntheses have been reported by other authors who postulated equatorial phosphoryl for the thermodynamically stable isomer, but did not speculate as to the phosphorus configuration of the other isomer (92). The chloro sulfide 91 has been postulated to have an equatorial phosphoryl

sulfur from 5,5-dimethyl chemical shifts (27). Isomers 166a,b have been obtained and shown by nmr to possess equatorial C4 methyl in both cases, implying opposite phosphorus stereochemistry (86).

The two trans compounds 131 and 139 contain equatorial phosphoryl groups as deduced from infrared spectra (84) which is consistent with the crystal structure of 139 (55). Isomers of 167 have been prepared and nmr spectral analysis indicated the C4 methyl group to be equatorial in the a isomer but axial in b. The necessarily identical phosphorus configurations were found to be equatorial P=O from the infrared spectral data (86).

Summary of preferred phosphorus stereochemistry

To summarize the trends observed, the following statements seem appropriate: (a) 2-Substituent-2-oxo-1,3,2-dioxaphosphorinanes are usually found to exist in chair-chair equilibria, (b) Phosphate esters show a great preference for equatorial phosphoryl oxygen, while phosphoramidates prefer axial phosphoryl orientations, (c) Hydrogen phosphonates prefer equatorial phosphoryl oxygens, while alkyl and aryl phosphonates do not exhibit any great preference in phosphorus configuration, (d) Halogenated compounds prefer equatorial phosphoryl dispositions. Possible reasons for the varying preferences will be discussed in the Discussion section.

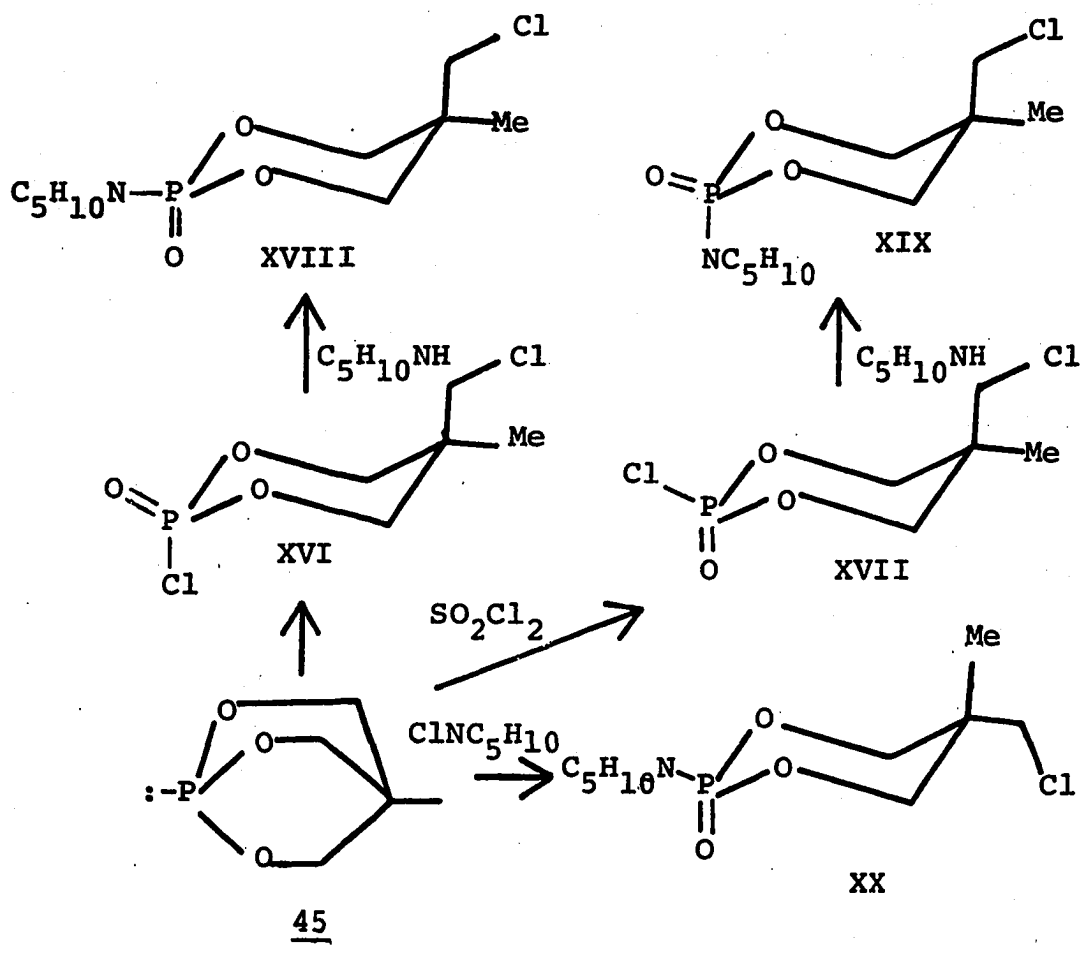
Other investigations

A few other investigations are worthy of mentioning here. Majoral and coworkers have found a generally linear relationship of ^{31}P chemical shifts to phosphoryl stretching frequencies (79, 86). These include phosphates, phosphoramidates, alkyl and aryl phosphonates and phosphorahalidates, although the hydrogen phosphonates do not follow the pattern. The ^{31}P chemical shifts of axially and equatorially oriented phosphoryl oxygen in hydrogen phosphonates are opposite to those of the other compounds, whereas their respective phosphoryl stretching frequencies are similar (see Discussion for hydrogen phosphonate ^{31}P chemical shift and infrared stretching frequency data).

As discussed with respect to trivalent and tetravalent phosphorus compounds, in some cases isomers can be synthesized in which the phosphorus configurations are opposite but the remainder of the ring substituents are identically oriented (e.g. phosphites 38a,b and phosphates 171a,b). The substituents in such isomers are obviously in different steric and chemical environments and would be expected to be in different electronic environments as well. The basicities of axial vs. equatorial lone pairs have been investigated for phosphites 38a,b through the use of the borane adducts 173a,b (93). From the argument that higher B-H stretching frequencies occur when BH_3 is coordinated to a poorer base (94), it has been concluded that

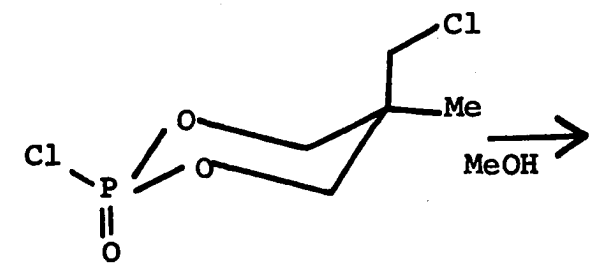
the equatorially oriented lone pair is less basic than an axial lone pair (93). The implication of greater positive charge on phosphorus in the former compound (i.e., less basic lone pair) is also indicated in the phenol shifts of compounds 161a,b (69) which are less for the equatorially oriented (less basic) phosphoryl oxygen of compound 161a. Majoral and coworkers have also observed phenol shifts but came to no conclusions from the results except that data for phosphoramidates did not fit with those for the other compounds investigated (78). They apparently did not realize the difference in basicity of equatorial versus axial phosphoryl in the phosphoramidates containing the latter and the other compounds for former oxygen orientation.

Recently two papers (56, 95) from the same laboratory have appeared in the literature proposing an $S_N1(P)$ mechanism which involves a trivalent phosphorus cation intermediate. Some of the assumptions and reasons for postulating the mechanism seem questionable, however, and these will be discussed. The original communication (56) suggested the existence of three "isomers" of compound 116 synthesized as indicated below. Although the incorrectness of this postulate has been alluded to previously (cf. p. 39) it will be discussed more fully here. The problem lies in the synthesis of XVII and XVIII. First, there is no evidence for the existence of a dominant equatorial chloro orientation in compounds of type XVII where the ring is

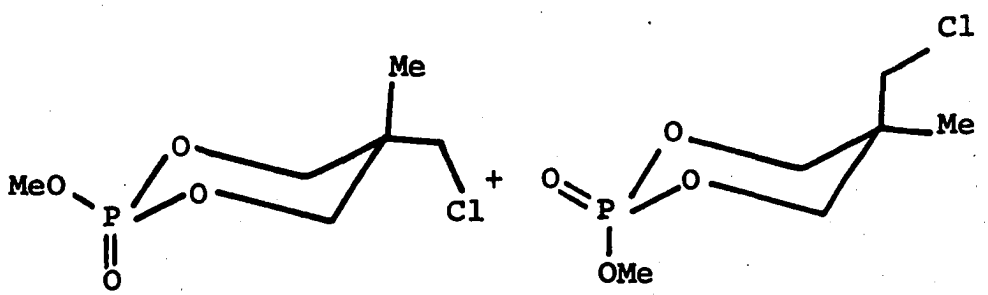


free to undergo conformational change. Second, there is evidence indicating the preferences of equatorial dialkylamino groups for compounds of type XIX where geometric constraints do not limit the conformation to axial disposition. The chemical shift data for XVII and XIX indicate the C5 configurations to be correct as written, requiring opposite phosphorus stereochemistry. Isomer XIX is therefore the same as XVIII, and XVII the same as XVI. Further evidence for this

assignment is that the chemical shifts of the two pairs XIX and XVIII, and XVII and XVI are within experimental error of each other. The only difference (lower melting points for XVII and XIX) is consistent with impure compounds. Duff and Trippett (57) repeated the work and concluded XVII to be the same as XVI and XIX the same as XVIII. As originally postulated XIX is related to XX by a chair-chair interconversion and no evidence in the literature suggests such interconversion to be subdued at room temperature. In the original paper the authors also indicated the reaction given below. They stated

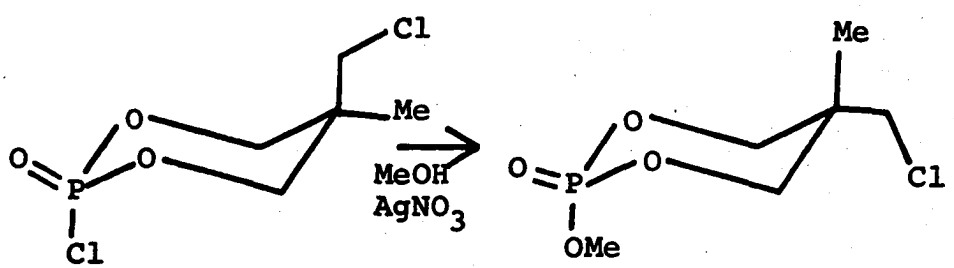


XVII

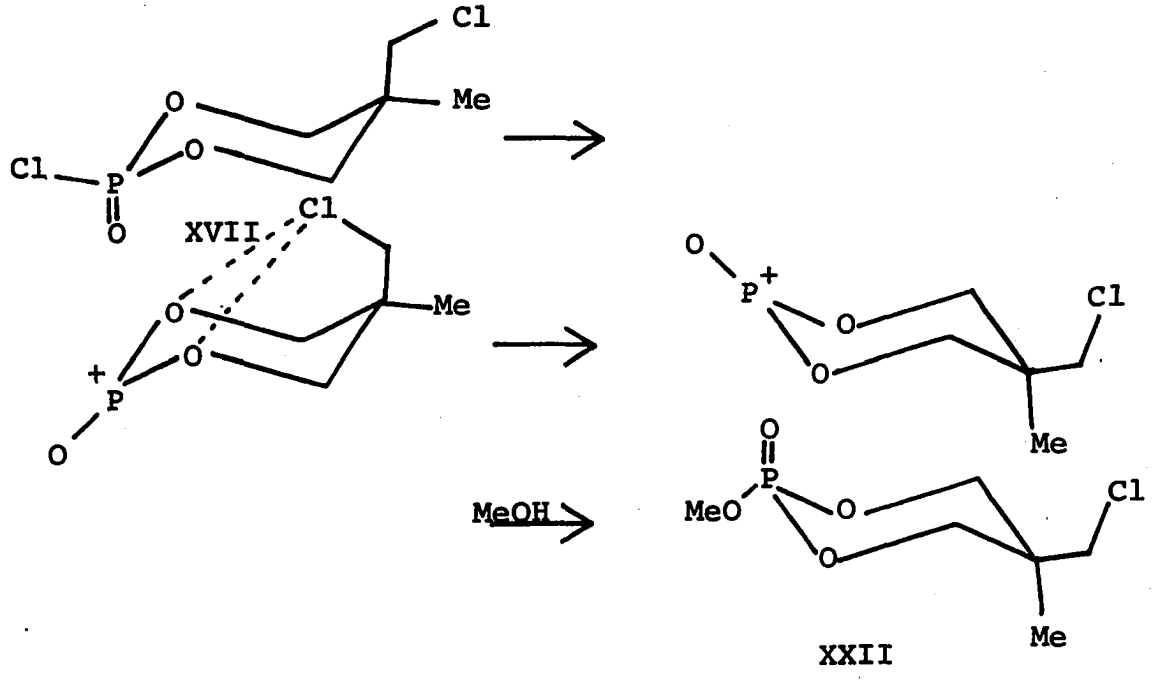


XXII XXIII

that the reaction of the chloro compound with piperidine yielded only one product but with methanol two were obtained and this constituted their initial evidence for the existence of an $S_N1(P)$ mechanism in the case of the methanol reaction. The starting material XVII in the above reaction is incorrectly drawn and should be the same as XVI. The "isomers" XXII and XXIII, related by a ring interconversion are probably also incorrect since methoxy groups prefer axial orientations. The nmr spectra published do indicate the presence of two isomers which are probably XXIII and the compound of opposite phosphorus configuration of XXII which will be numbered XXIV. It was stated that the reaction of XVII with methanol in the presence of an equivalent of silver nitrate produced XXII only. Actually, the reaction of XVI must have produced the S_N2 inversion product XXIV only, whereas formation of compound XXIII does not proceed by inversion. These results are opposite those stated by the authors. The mechanism given for



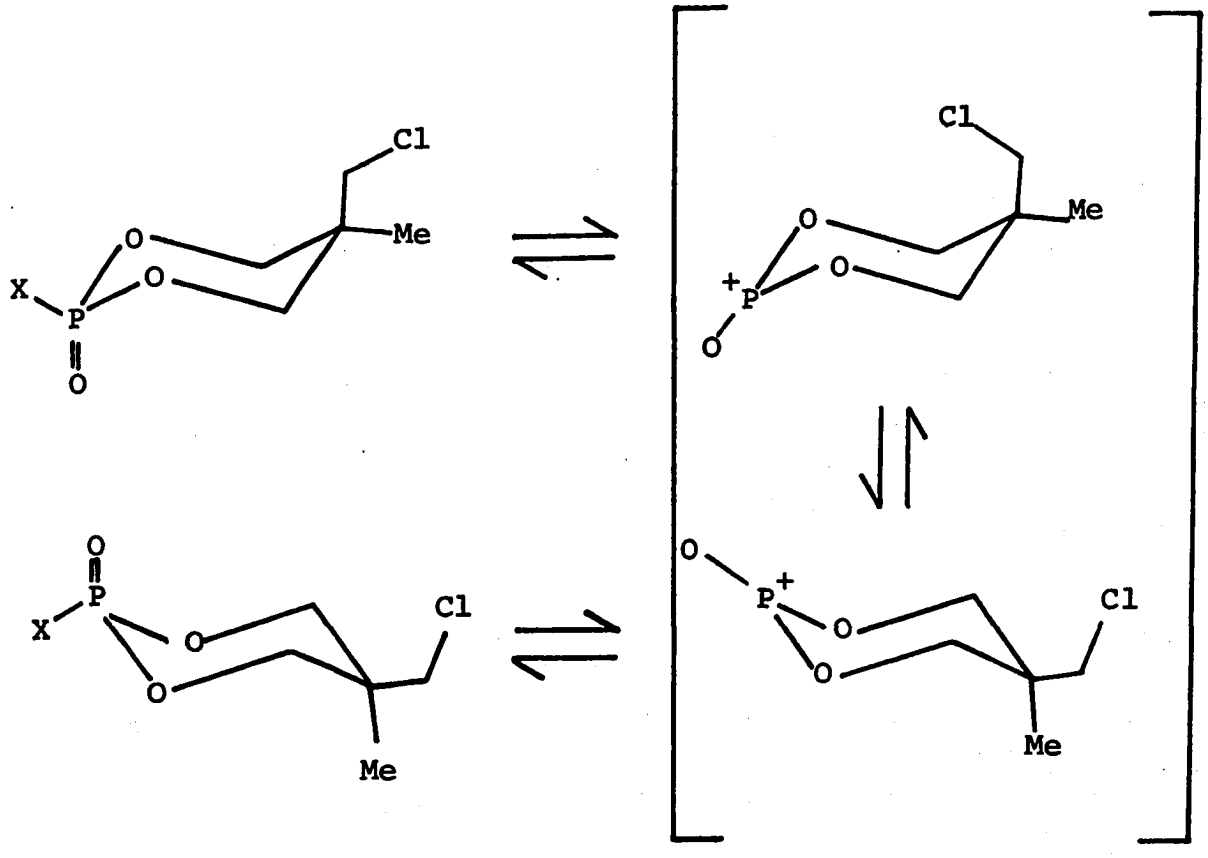
for formation of XXII is therefore completely unnecessary but is given below. Referring to formation of XXII they said that,



XXII

"The developing positive charge would decrease the dipole interaction (of C5 chloromethyl with the oxygen lone pairs), thus allowing conformational mobility at the five position." Since they believed XXII to be produced in the presence of silver nitrate, the $S_N1(P)$ mechanism was necessary, when in fact the silver ion apparently only assisted in the expected S_N2 type of reaction to form XXIV. The question that needs to be answered is how compound XXIII was formed in the absence of silver nitrate since it apparently is not the S_N2 product. It

might be thought that this was the result of impure starting material containing C5 isomeric chloro compounds, but the same isomeric distribution would also be expected for the silver nitrate reaction. The question remains unanswered. The $S_N1(P)$ mechanism has been used in the second paper (95) as indicated below. They reported that when X was amino, alkoxy, or phenoxy



no isomerization occurred even upon heating to 200°, but when X was phosphate (such as in pyrophosphate), 4-nitrophenoxy, 2,4-dinitrophenoxy or chloro, solvent dependent isomerism did occur and could be followed by the observation of the methyl

and chloromethyl chemical shifts which differ when axially or equatorially oriented. They interpreted the results in terms of isomerization due to ionization, allowing the phosphorus configuration to invert. They also said the ratio at equilibrium (ca. 2.5:1, depending on solvent) favored the compound on the left. For the compounds which underwent isomerization they indicated the geometry to be as drawn, "due to the preference of the substituent at phosphorus for the equatorial position." No evidence or reference was given for that statement, and nowhere in recent literature is there evidence that any phosphate or halo compound prefers equatorial orientation, but instead prefers axial orientation. The two isomers are incorrectly depicted with the C5 geometry probably correct, but the phosphorus geometry reversed. There also is no reason to require the $S_N1(P)$ mechanism. The isomerization could be a bimolecular S_N2 reaction since no evidence was given to the contrary, or a very small percentage of compound could ionize and the phosphorus of another molecule be subjected to an S_N2 attack by the anion of ionization. The isomerization of benzoyl phosphates (X = OBz) was found to be acid catalyzed, but was not further investigated. Isomerism occurred more rapidly in more polar solvents which is consistent with an $S_N1(P)$ mechanism, but is also consistent with slight ionization followed by S_N2 attack at phosphorus. In dimethylformamide benzoyl phosphates react to produce pyrophosphate and benzoyl

anhydride (previously reported in reference 96). Wadsworth (95) repeated the experiment and concluded that the mechanism involved the reaction of phosphoryl cation with phosphate anion, the respective products of the $S_N1(P)$ ionization and $S_N1(P)$ derived benzoate anion with benzoyl phosphate. He believed this and not nucleophilic attack at phosphorus to be the mechanism of pyrophosphate formation since it had been shown by other workers that both charged and uncharged nucleophiles attack the starting benzoyl phosphate with C-O but no P-O bond scission (97).

There is no compelling reason to believe the necessity of an $S_N1(P)$ mechanism from the two papers described, especially considering the disregard of reported phosphorus stereochemistry necessary in interpreting the stereochemistry of the reactions studied.

Other references

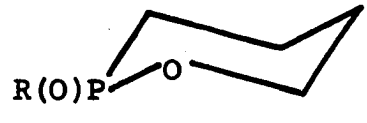
There are several references not used in the previous discussions regarding either trivalent or tetravalent 1,3,2-dioxaphosphorinase which are added here for completeness. Many are older references listing instrumental data without stating any conclusions pertinent to the discussion, others are syntheses of compounds without structural implications, and some will be discussed in the Discussion because they are not directly applicable in this section but are included here for reader convenience. By main topic these are: ^{31}P chemical shifts

(98-100), infrared stretching frequencies (101-104), syntheses (105-114), Michaelis-Arbusov reactions (115, 116), and oxidation reactions (99, 117, 118).

Other Phosphorinane Compounds

The following discussion concerns phosphorinane compounds (listed in Tables 5 and 6) other than 1,3,2-dioxaphosphorinanes. The first compound, 206, will be discussed in Part II, the remainder will be discussed by Y, Z type indicated in the Tables.

2-R-2-oxo-1,2-oxaphosphorinanes (XXV)



XXV

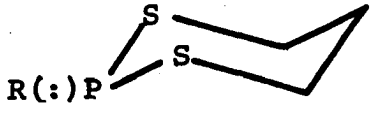
The 2-substituent-2-oxo-1,2-oxaphosphorinanes 207a,b (119), 208a,b (119, 120), 209a,b (119, 121), 210a,b (119-121), 211a,b (122), and 212a,b (123) all exist as isomer pairs. The general method of synthesis is reaction of dihalide (usually dibromide) with trimethylphosphite to produce the isomeric mixture from which isomers can usually be separated by gas chromatography (119-123). From infrared stretching frequencies the geometries of the C5 methyl groups of 207a,b and 208a,b were postulated

to be solely equatorial for a isomers and at least sometimes axial for b isomers. The presence of a peak in the region of 585-650 cm^{-1} for each b isomer was assumed to be due to axial methyl, whereas the a isomers lacked such a band. The single phosphoryl stretching frequency for each a isomer was assumed to indicate a single conformer, whereas the two bands for the corresponding b isomers were taken as indicative of two conformers (119, 120). The relative phosphorus and C5 geometries were assigned on the basis of the Auwers-Skita rule (124,125) which states that cis isomers of 1,4 and trans 1,3 substituted cyclohexanes have higher refractive indices and higher densities. This certainly does not seem to be sufficient evidence for configurational assignment if for no other reason than the lack of any evidence indicating that the chemical and physical properties of cyclohexane systems resemble those of phosphorinanes. In reference 119 the authors acknowledge these as tentative assignments, but in later papers they referred to them as firm assignments. The implications of the stereochemical assignments are that the a isomers contain equatorial C5 methyl and equatorial phosphoryl oxygen in a single stable chair conformer, whereas the b isomers undergo facile chair-chair interconversions. The C6 methyl configuration of both isomers of 209 and 210 has been postulated as equatorial due to lack of bands in the 570-770 cm^{-1} region, and similarity of C6 methyl chemical shifts and $J(POCCH_3)$ coupling constants.

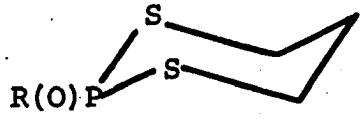
The assignments of phosphorus configurations were largely based on the Auwers-Skita rule described above and the similarity of GLC retention times to the previously assigned stereochemistries of 208a,b (also from the Auwers-Skita rule). The a isomer was proposed to have both C6 methyl and phosphoryl oxygen equatorially oriented and the b isomer equatorial C6 methyl and axial phosphoryl oxygen. They indicated the presence of only one ring conformer for both isomers and did not attempt to rationalize the presence of two phosphoryl stretching frequencies for b isomers (119, 121). Compounds 211a,b prepared from the meso dibromide can exist as four different isomers although two are simply ring conformers of the other two. The b isomer exhibited two absorptions in the 585-650 cm^{-1} region indicating the presence of two different axial methyl groups resulting from two ring conformers. The two phosphoryl stretching frequencies observed are consistent with the existence of two conformers. The a isomer possessed a single methyl absorption in the 585-650 cm^{-1} region which was assumed to mean only one conformer containing axial C5 and equatorial C6 methyl groups. The phosphorus configuration of a was assigned as equatorial phosphoryl for no apparent reason. From equilibria studies the a isomer was found to be the more stable by a value of ΔG of about 0.3 kcal/mole at room temperature (122). The isomers 212a,b were determined to contain equatorial and axial C3 methyl groups, respectively,

from the infrared spectra. The geometries of C3 relative to P were based on the Auwers-Skita rule, and the similarity of behavior to previously investigated 1,2-oxaphosphorinanes (also assigned from the Auwers-Skita rule). The lack of change in nmr spectra in the range -90 to 40° implied to the authors the existence of rigid chairs with the phosphoryl oxygens equatorial in both isomers. Since both isomers exhibited single phosphoryl bands which absorbed at identical frequencies, the assignment of single chair conformers with the same phosphoryl oxygen orientations was substantiated.

2-R- and 2-R-2-oxo-1,3,2-dithiaphosphorinanes (XXVI, XXVII)



XXVI



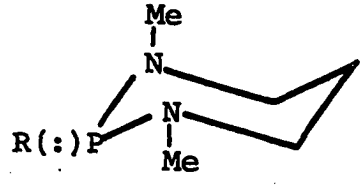
XXVII

The ring conformations of 213-215 and 217 have been concluded to be essentially rigid chairs in which one phosphorus configuration predominates as shown by the nmr spectra of the 5,5-dimethyl groups for which the broader, down-field peak was assigned as axial (126). Compound 216, however, exhibited C5 methyl groups of very similar chemical shift and nearly identical peak width indicative of a different ring conformation or conformations. The authors concluded the

substituents to be axially oriented in compounds 213-215 and 217 from these observations: (a) Chemical shifts of the C4 and C6 axial protons were deshielded in 213 compared to 214 and 215 due to axial methoxy oxygen, (b) C4 and C6 axial protons were shielded in 217 because of the proximity of the axial phenyl group, (c) Nuclear Overhauser effects on 214 were consistent with that assignment. In the latter experiment axial 2-methyl orientation was implied since irradiation of that nmr signal resulted in a 7% enhancement of the C4 and C6 axial protons indicating a close spatial relationship of those protons to the methyl group. Isomers of 223 were obtained and the a isomer was isolated pure although b could not be so obtained. Equilibration experiments indicated an 85.5:15.5 ratio of a:b at 200° and a ΔG of isomerization favoring a of 1.9 kcal/mole at 25°. An nmr spectral analysis of the a isomer indicated an equatorial tert-butyl group. Axial phenyl orientation was assigned because of the preferred geometry of the 5,5-dimethyl compound 217 discussed above. The absolute geometries of the b isomers were not postulated although the relative geometries must be trans (i.e., opposite of a). Compounds 219-222, although listed in a figure in the communication (126), were not discussed. The compound with the bulky tert-butyl phosphorus substituent, 216, was concluded to have a different phosphorus configuration or ring conformation in which the substituent was either equatorial or the ring was

twisted. The pnmr spectra of the isomers 218a,b were consistent with equatorial C5 phenyl groups for both a and b isomers (102). This indicates a greater stereochemical preference at C5 than phosphorus for the dithia compounds in contrast to the 1,3,2-dioxaphosphorinane analogues 113a,b for which the phenyl is equatorial in a and axial in b. The ^{31}P chemical shifts are consistent with this idea differing by about 11.2 p.p.m. for the dithia compounds containing opposite phosphorus configurations, but only 1.2 p.p.m. for the dioxa compounds, which possesses the same phosphorus configuration The phosphorus stereochemistries of 218 a and b were not established.

2-R-1,3,2-diazaphosphorinanes (XXVIII)



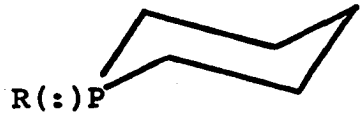
XXVIII

Nmr spectral analyses of compounds 224-233 indicated one predominant chair conformation with the exception of the chloro compounds 228 and 234 (127). The spectra of these compounds changed upon dilution, an observation discussed previously for the dioxa systems, indicating intermolecular chloride exchange. The dilute samples of the chloro compounds behaved

like most of the non-halogen analogues in that predominantly single conformers were observed. This is illustrated in the 5,5-dimethyl compounds 229-234 by two well separated C5 methyl groups differing in peak width. The authors pointed out that in contrast to $J(POCH_{ax})$ and $J(POCH_{eq})$ of dioxa compounds which vary little with substituent (being generally in the range 2.1-5.7 and 10.0-11.3, respectively) the coupling constants $J(PNCH_{ax})$ and $J(PNCH_{eq})$ vary considerably with substituent ranging from 0-10.3 and 5.3-11.0 Hz, respectively. The couplings are dependent on ring conformational equilibria, however, and perhaps a more appropriate remark is that the sum of the couplings for the dioxa systems are generally very similar (except when the substituent is amino) (9), whereas in the diaza systems the sums range from 5.3 Hz for 232 to 20.7 Hz for 234. Conversely, the couplings $J(PNCH_3)$ are quite independent of substituent. The authors discussed the N-methyl orientation at some length and concluded they were likely to be equatorial at both nitrogens. What they failed to recognize was the fact that structural studies of compounds with nitrogen directly bonded to phosphorus all indicate nitrogen to be planar as long as there is no steric interaction to preclude the possibility (see reference 128 for a detailed summary of this work and Part II of this thesis). The idea of axial and equatorial N-methyl groups is therefore an unsubstantiated concept. No unambiguous assignments of phosphorus configuration

could be made from available data, but an equatorial substituent is consistent with some observations. Thus, no shielding was found for the C4 and C6 axial protons compared to the C4 and C6 equatorial protons in compounds 227 and 232. Also, virtually no nuclear Overhauser effect enhancement of the C4 and C6 axial proton absorptions was seen upon irradiation of the phosphorus methyl resonances of 225 and 230, but a 5% enhancement of the N-methyl peaks was observed.

1-R-Phosphorinanes (XXIX)



XXIX

Nomenclature rules require the phosphorus to be in the one position for these compounds, but the two position for all previously discussed compounds.

The axial preference of the phosphorus proton has been indicated for phosphorinane 234 (129, 130). The pnmr spectrum shows no change in the temperature range -50 to -80° indicating one major chair conformation. P-H subspectrum broadening observed above -50° was concluded to be due to hydrogen exchange (130). The axial orientation of at least 95% abundance was deduced from $J(HPCH_{eq})$ and $J(HPCH_{ax})$ couplings,

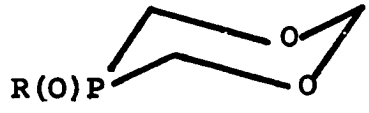
the latter being larger. The spectra of 235 and the iodide salt of 236 did not change upon sample cooling to -70° and -60°, respectively. The hydrogen atom was concluded to be axial in the former compound from coupling data, but no conclusive evidence could be cited for preferred orientation in the latter.

The crystal structure determination of compound 238 specified the phenyl group at the somewhat flattened phosphorus to be axial. Proton nmr spectral studies also indicated one predominant configuration in solution since two methoxy resonances were observed (131). The methyl derivative 237, however, does not exist as a single predominant conformer in solution as the pnmr spectrum exhibited only one type of methoxy group (132). A crystal structure of the phosphorinane 239 also showed axial phenyl substituent and flattening at phosphorus (133).

Isomers of 240 (132, 134), 241 (134, 135), 242 (134), 243 (132) and 244-246 (134) have been observed. Proton nmr spectra of 240a,b indicated the C4 axial proton to be in the same axial position in both isomers thus requiring opposite phosphorus configuration. The 6 p.p.m. ^{31}P chemical shift difference also indicated a difference in phosphorus stereochemistry. Equilibration studies indicated the energy difference for interconversion of isomers to be about zero. Compounds 243a,b have been separated by GLC and were found to differ at phosphorus

as suggested by a 10 p.p.m. ^{31}P chemical shift difference. The authors tentatively assigned the phosphorus geometry of a to be axial methyl and b equatorial methyl on the basis of a downfield chemical shift of the axially oriented group. The remaining compounds were investigated several years ago and no definitive evidence was advanced that indicated stereochemical preferences. Similarities in ir spectra were taken to indicate similar C4 geometries in isomeric compounds, but more unambiguous proof is lacking.

5-R-5-oxo-1,3,5-dioxaphosphophosphorines (XXX)



XXX

Discussion of compounds 247-250 has been delayed until now because of their greater similarity to phosphorinanes than 1,3,2-dioxaphosphorinanes. In these compounds the phosphorus is in the number 5 position of the ring. The two isomeric compounds 247 and 248 were prepared from benzaldehyde, phosphine and a catalytic amount of p-toluenesulfonic acid (136). The isomers differed greatly in nmr and ir spectra and were determined to have diequatorial C4 and C6 and axial C2 phenyl groups for 247 and diequatorial C2 and C4 and axial C6

phenyl groups for 248. The phosphorus geometry was assigned as axial benzyl, but no evidence was presented for that assumption (136). No stereochemical assignments were made for any of the substituents of compounds 249 and 250, since the paper was a synthetic report (137).

Summary

If the somewhat questionable assignments of 2-alkoxy-2-oxo-1,2-oxaphosphorinanes are correct, the configurational preferences are similar to those of the 1,3,2-dioxaphosphoranes, whereas the 1,3-dithia compounds appear to exhibit lesser degrees of configurational preference. Results from 1,3,2-diazaphosphorinane studies are too ambiguous for generalization. Phosphorinanes show a preference for axial substituents.

EXPERIMENTAL

Materials

All solvents and other materials not specifically mentioned were reagent grade or better and in most cases were stored over Linde 3A Molecular Sieves. Anhydrous ether was obtained by refluxing over and distillation from lithium aluminum hydride onto molecular sieves. Dry pyridine was obtained by distillation from potassium hydroxide onto fresh potassium hydroxide. Trimethyl phosphite, phosphorus trichloride, and trisdimethylamino phosphine, obtained from Aldrich Chemical Corporation, were generally used without further purification. The dialcohols 1,3-propanediol and 1,3-butanediol, also obtained from Aldrich Chemical Corporation, were vacuum distilled prior to use. The 80 atom percent ^{18}O-enriched water used in phosphoryl stretching frequency studies was obtained from Bio-Rad Laboratories. The shift reagent tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione) europium(III) ($Eu(fod)_3$) was obtained from Norell Chemical Company, Inc.

Molecular weight determinations were performed by Alfred Bernhardt Mikroanalytisches Laboratories, West Germany.

NMR Spectra

All ^1H spectra were obtained from either benzene or chloroform solutions as specified. Chemical shifts are given in ppm (δ) relative to internal tetramethylsilane, with a

positive shift indicating a resonance at an applied magnetic field smaller than that of the standard. Coupling constants are given in cycles per second (Hz). Spectra were obtained on a Varian Associates A-60 spectrometer operating at 14,000 gauss, a Varian Associates HA-100 spectrometer operating at 23,500 gauss, or an Hitachi Perkin-Elmer R20-B spectrometer operating at 14,000 gauss. ^{31}P chemical shifts relative to 85% phosphoric acid were obtained either directly or by ^{1}H INDOR techniques on an HR 60 spectrometer. Shifts occurring at higher applied field were taken to be positive.

Spectra of solutions 0.2M in sample and 0.1M in tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione) europium(III) (Eu(fod$_3$) in deuteriochloroform were obtained on the Varian Associate HA-100 spectrometer. Nmr spectra of phosphites and phosphosphoramidites did not exhibit shifts in the presence of Eu(fod)$_3$, although the oxidized species did.

Infrared Spectra

Infrared spectra were obtained on a Beckman model 12 instrument. Both liquids and solids were run using ca. 0.05M benzene solutions in demountable cells (Barnes Engineering Co.) with sodium chloride windows, and 0.1 mm spacers. All spectra were obtained in the double beam mode with solvent in the reference beam and calibrated with polystyrene.

With the exception of compounds 52, 161a,b and 176a,b for which ^{18}O enriched compounds were synthesized, phosphoryl stretching frequencies were assigned by observation of absorption shifts to lower energy upon saturating the benzene solutions with iodine.

Variable temperature infrared spectra were obtained on a Beckman Model 8 employing a sample cell whose temperature could be controlled with water circulating through a surrounding jacket. Reported temperatures are probably no more accurate than $\pm 3°C$ at the extremes.

Dipole Moment Measurements

Dielectric measurements were determined with the heterodyne beat apparatus described by Vandenbroucke et al. and the data treatment is similar to theirs (138). Generally, four solutions of each compound ranging in concentration from about 1 to 10×10^{-3} mole fraction in benzene prepared under nitrogen were employed.

Mass Spectra

Routine mass spectra were obtained on an Atlas CH-4 Mass spectrometer while high resolution spectra were provided by an AEI MS-902 spectrometer. All compounds, whether liquids or solids, were run as solids. In the former case this was accomplished by adsorption on ground molecular sieves. When

spectra were obtained from liquids run as liquids, fragmentation was so extensive that parent peaks often could not be observed.

Preparations

Trivalent compounds were handled in a nitrogen atmosphere, and water was scrupulously avoided in all reactions in which it was not called for as a reactant. Where products can be prepared isomerically pure and the configurations are known (see Discussion section), α-β nomenclature is employed where α refers to equatorial and β to axial substituent orientations.

In several of the distillations used to obtain isomerically pure compounds a 16" platinum spinning band column (Nester/Faust Manufacturing Corporation) was employed.

Meso-2,4-pentanediol

The slightly modified preparation of this compound originally reported by Pritchard and Vollmer (139) has been previously described (9).

2-Chloro-4,6-dimethyl-1,3,2-dioxaphosphorinane (40)

The synthesis of this compound from PCl_3 and meso-2,4-pentanediol has been described previously (9).

2-Chloro-4-methyl-1,3,2-dioxaphosphorinane (37)

This compound was prepared identically to 40 above from PCl_3 and 1,3-butanediol.

2-Chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane (12)

This compound was prepared identically to 40 above from PCl_3 and 2,2-dimethyl-1,3-propandiol.

2-Chloro-1,3,2-dioxaphosphorinane (3)

This compound was prepared identically to compound 40 above from PCl_3 and 1,3-propanediol.

2-β-Methoxy-4,6-α,α-dimethyl-1,3,2-dioxaphosphorinane (38a)

This compound was synthesized as described previously (9) from meso-2,4-pentanediol and trimethyl phosphite.

2-β-Methoxy-4,6-α,α-dimethyl-1,3,2-dioxaphosphorinane (38b)

Although the synthesis of this compound described previously (9) results in contamination of the desired product with stable isomer 38a, a few minor modifications of that procedure leads to pure 38b. To a stirred solution of phosphorochloridite 40 in diethyl ether was added dropwise with stirring a solution containing a 5% deficit of the molar amount of methanol and a 5% excess of triethylamine in diethyl ether. After filtration under nitrogen, the ether was removed under vacuum and the product vacuum distilled at $\leq$ 25°C and 0.1 to 0.3 mm of Hg. The temperature of the distillation flask did not exceed 40°C. The phosphite obtained in 90% yield can be stored for a month or longer at -78°C without substantial conversion to the stable isomer.

2-β-Methoxy-4-α-methyl-1,3,2-dioxaphosphorinane (32a)

The synthesis was accomplished in the same manner as for 38a using trimethyl phosphite and 1,3-butanediol.

2-α-Methoxy-4-α-methyl-1,3,2-dioxaphosphorinane (32b)

This synthesis was accomplished in the same manner as 38b above from phosphorochloridite 37 and methanol.

2-Methoxy-1,3,2-dioxaphosphorinane (1)

This compound was prepared in the same manner as compound 38a above from 1,3-propanediol and trimethyl phosphite.

2-β-Dimethylamino-4,6-α,α-dimethyl-1,3,2-dioxaphosphorinane (39a) and 2-α-dimethylamino-4,6-α,α-dimethyl-1,3,2-dioxaphosphorinane (39b)

These isomers were prepared in ca. 1:10 ratio of 39a:39b by two different procedures.

(a) A solution of 5.0 g (0.048 mol) of meso-diol and 7.8 g (0.048 mol) of trisdimethylaminophosphine was heated at 55°C for 3 hours under a nitrogen atmosphere. The temperature was then raised to 65° for 10 hours and then to 85° until no more dimethylamine could be detected leaving the reaction. Rapid heating resulted in formation of considerable quantities of polymer and poor yields of desired compound. The product obtained in about 60% yield was vacuum distilled at 44-46°C and 2 mm of Hg.

(b) Into a solution of 7.8 g (0.046 mol) of phosphorochloridite 40 and 200 ml of diethyl ether maintained at about -25°C was bubbled with stirring an excess of 0.092 moles of dimethylamine gas diluted to about 50% by dry nitrogen. Upon completion, the dimethylamine hydrochloride was removed by filtration under nitrogen, the ether removed under vacuum, and the product distilled in 60% yields or better. Pnmr spectra prior to and following distillation of product indicated a ratio of 1:10 for 39a:39b.

2-β-Dimethylamino-4-α-methyl-1,3,2-dioxaphosphorinane (36a) and 2-α- dimethylamino-4-α-methyl-1,3,2-dioxaphosphorinane (36b)

These compounds were prepared in a ca. 1:10 ratio of 36a:36b by the procedure (a) for the syntheses of 39a and 39b, although a somewhat poorer yield was realized.

2-β-Methoxy-2-α-oxo-4,6-α,α-dimethyl-1,3,2-dioxaphosphorinane (171a)

This compound was prepared by NO_2 oxidation of the phosphite 38a at 0°C in carbon tetrachloride solution. Recrystallization from diethyl ether yielded compound 171a (m.p. 57-58°) essentially quantitatively and it displayed a parent peak of 180 m/e in the mass spectrum.

2-α-Methoxy-2-β-oxo-4,6-α,α-dimethyl-1,3,2-dioxaphosphorinane (171b)

This compound was prepared by the NO_2 oxidation of 38b as described above for 171a. Purification was accomplished by vacuum distillation (b.p. 86° at 0.2 mm of Hg) giving an essentially quantitative yield of compound which exhibited a mass spectrum parent peak of 180 m/e.

2-β-Methoxy-2-α-oxo-4-α-methyl-1,3,2-dioxaphosphorinane (151a)

This compound was prepared similarly to 171a above from NO_2 oxidation of 32a. Purification by vacuum distillation (b.p. 116° at 0.25 mm of Hg) gave an essentially quantitative yield of compound exhibiting a mass spectrum parent peak of 166 m/e.

2-α-Methoxy-2-β-oxo-4-α-methyl-1,3,2-dioxaphosphorinane (151b)

This compound was obtained from 32b as described above for 171a by NO_2 oxidation. Purification by vacuum distillation (b.p. 86° at 0.25 mm of Hg) gave essentially quantitative yields of compound which displayed m/e of 166 in the mass spectrum.

2-Methoxy-2-oxo-1,3,2-dioxaphosphorinane (49)

This compound was prepared from the NO_2 oxidation of phosphite 1 as described above for 171a. Distillation at 96° and 0.3 mm of Hg afforded an essentially quantitative yield of compound which displayed a parent peak m/e of 152.

2-α-Dimethylamino-2-β-oxo-4,6-dimethyl-1,3,2-dioxaphosphorinane (175a) and 2-β-dimethylamino-2-oxo-4,6-α,α-dimethyl-1,3,2-dioxaphosphorinane (175b)

These compounds were prepared by two procedures.

(a) The isomers were prepared by the NO_2 oxidation of the phosphoramidites 39a,b as described above for the phosphate 171a. This resulted in an essentially quantitative yield of a 1:10 ratio of 175a:175b which is the same as the ratio of isomers of the starting material.

(b) A mixture of isomers of 175a:175b of ca. 2:3 ratio was obtained by treatment of 38a with excess N-chlorodimethylamine. The amine starting material was prepared in benzene by the procedure of Heasley, Kovacic and Lange (140) and used without further purification. To a solution of 9.9 g (0.06 mol) of phosphite 38a dissolved in 50 ml of benzene was added dropwise with stirring the benzene solution of N-chlorodimethylamine. After addition, the solution was stirred 0.5 hr., then heated to reflux for 0.75 hr. It was found that a repetition of this procedure was necessary to completely react all the phosphite and to insure high yields (ca. 60%) of the desired product. The solution was filtered, the benzene removed under vacuum, and the isomers separated by vacuum distillation employing a platinum spinning band column (b.p. 175a, 82° at 0.1 mm of Hg; b.p. 175b, 63° at 0.1 mm of Hg). An impurity of an unknown nature could not be separated from

either isomer, but constituted less than 5% of the total product. The mass spectra of both isomers displayed parent peaks of 193 m/e.

2-β-Dimethylamino-2-α-oxo-4-α-methyl-1,3,2-dioxaphosphorinane (160a) and 2-α-dimethylamino-2-β-oxo-4-α-methyl-1,3,2-dioxaphosphorinane (160b)

These compounds were prepared by the procedure (b) described above for 175a,b. A ca. 5% impurity was also found in these compounds that could not be removed employing a platinum spinning band column. Boiling points of 82° and 66° at 0.25 mm of Hg were observed for 160a and 160b, respectively. Mass spectra of the two isomers exhibited parent peaks of 179 m/e.

2-Dimethylamino-2-oxo-1,3,2-dioxaphosphorinane (51)

This compound was prepared by reaction of N-chlorodimethylamine and phosphite as described above for 175a,b. Purification was accomplished by vacuum distillation at 82° and 0.3 mm of Hg, although here too a ca. 5% impurity was observed which could not be removed employing a platinum spinning band column. The parent peak of 165 m/e was observed in the mass spectrum.

2-β-Methyl-2-α-oxo-4,6-α,α-dimethyl-1,3,2-dioxaphosphorinane (177a)

This compound was prepared by stirring a solution comprised of phosphite 38b and an equal volume of methyl

iodide for 10 hr. at room temperature. After removal of the methyl iodide under vacuum, the product was sublimed at ca. 55° and 0.3 mm of Hg in nearly quantitative yield. The mass spectrum displayed a parent peak of 164 m/e.

2-α-Methyl-2-β-oxo-4,6-α,α-dimethyl-1,3,2-dioxaphosphorinane (177b)

The synthesis of this compound was the same as that for 177a above from 38a and methyl iodide except that sublimation was at 40° at 0.3 mm of Hg. The mass spectrum indicated a parent peak of 164 m/e.

2-β-Methyl-2-α-oxo-4-α-methyl-1,3,2-dioxaphosphorinane (162a)

This synthesis was accomplished identically to that of 177a from 32b and methyl iodide. Purification was accomplished by vacuum distillation at 93° and 0.3 mm of Hg. The mass spectrum showed a parent peak of 150 m/e.

2-α-Methyl-2-β-oxo-4-α-methyl-1,3,2-dioxaphosphorinane (162b)

This preparation was the same as that for 177a above from 32a and methyl iodide. The nearly quantitative yield of compound with a boiling point of 57° at 0.15 mm of Hg displayed a mass spectral parent peak of 150 m/e.

2-Methyl-2-oxo-1,3,2-dioxaphosphorinane (54)

This synthesis from 1 and methyl iodide was performed in the same manner as that for 177a. The mass spectrum of the

purified product (sublimed at 55° at 0.3 mm of Hg) exhibited a parent peak of 136 m/e.

2-β-Hydro-2-α-oxo-4,6-α,α-dimethyl-1,3,2-dioxaphosphorinane (176a) and 2-α-hydro-2-β-oxo-4,6-α,α-dimethyl-1,3,2-dioxaphosphorinane (176b)

To a solution of 21.9 g (0.13 mol) of 40 dissolved in 20 ml of dioxane was added dropwise with stirring 2.5 ml (about 0.13 mol) of water in 20 ml of dioxane. After completion of addition, the dioxane was removed under vacuum. The liquid product was formed in about 90% yield of which ca. 70% was 176a and 30% isomer 176b. A synthesis of 176a,b in which a small excess of pyridine was mixed with the water-dioxane solution resulted in essentially the same yield of diester and the same distribution of isomers.

To obtain pure isomer 176b the above mixture was vacuum distilled (74°C at 0.55 mm of Hg) using a platinum spinning band column with a pot temperature in excess of 140°. A slow reflux was maintained at the column head and a reflux ratio of one employed. The product which readily supercools was sublimed twice at ca. 0.1 mm of Hg and 40° (m.p. 38-39°C). Compound 176b was obtained in quantitative yield with respect to the diester mixture (owing to complete conversion of 176a to 176b) and it gave a high resolution mass spectrum parent peak of 150.043957 m/e (theoretical 150.044581 m/e) as expected. The molecular weight was determined by osmometry

in chloroform solvent to be 153 amu.

Upon heating 176b to 145° for 12 hrs. a mixture of ca. 75% 176a and 25% 176b was obtained which gave a molecular weight of 151 amu from osmometric measurement in chloroform solvent. Repeated fractional crystalization from hot heptane led to isolation of pure 176a (m.p. 50-52°C). A low resolution mass spectrum exhibited a parent peak of 150 m/e.

2-β-Hydro-2-α-oxo-4-α-methyl-1,3,2-dioxaphosphorinane (161a) and 2-α-hydro-2-β-oxo-4-α-methyl-1,3,2-dioxaphosphorinane (161b)

The method of preparation of these two compounds was the same as for 176a,b above. The reaction yielded 80-85% 161a and 20-15% 161b in a solid mixture (total yield ca. 90%) which upon repeated recrystallization from hot heptane gave pure 161a (m.p. 52-54°C). Isomer 161b was prepared from the isomer mixture as described above for 176b but with a boiling point of 78°C at 0.45 mm of Hg. Although 161b remained a liquid, supercooling cannot be ruled out. During one preparation, a solid was observed in the platinum spinning band column which melted and did not solidify on distillation when the column temperature was raised. The parent peaks of both isomers were identified from their mass spectra. The synthesis of 161a,b has been described previously (113, 141a), but the ratio of the isomers was not fully determined.

2-Hydro-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinane (76)

The synthesis was accomplished as described above for 176a,b and it has also been described elsewhere (113, 141a).

2-Hydro-2-oxo-1,3,2-dioxaphosphorinane (52)

The preparation of this compound was accomplished as described above for 176a,b and it has also been described elsewhere (113, 141a).

^{18}O-enriched hydrogen phosphonates

Enrichment to ca. 80% ^{18}O at the phosphoryl oxygen was accomplished by the same procedure for compounds 176a,b, 161a,b and 52. The following example is for 176a,b. To 224 mg of 40 (1.33 mmoles) dissolved in 2 ml of dioxane was added with stirring 23 µl of ca. 80% ^{18}O-enriched water. After one hour the solvent was removed under vacuum and the product used without further purification. For infrared comparison purposes the compounds were also prepared using water of normal isotope distribution by this procedure as well as by the more rigorous methods described above for the individual compounds.

2-α-[2'(2'-Hydroxypropyl)]-2-β-oxo-4,6-α,α-dimethyl-1,3,2-dioxaphosphorinane (185)

To a few grams of 176b was added a two to three-fold molar excess of acetone, and 2 to 3 drops of concentrated $HClO_4$. After stirring the solution for 36 hours, the acetone

was removed under vacuum and the white crystalline precipitate was filtered and washed three times with small quantities of acetone. The yield of the product (mp = 125-128°) was essentially quantitative. A high resolution mass spectrum of the parent peak gave a value for m/e of 208.084103, calculated as 208.086445 for the compound as formulated and it exhibited a major fragment due to loss of acetone.

The acetone could be removed from 185 to reform 176b by heating to 110° followed by applying vacuum until 185 was observed to sublime up to the walls of the flask. Air was then admitted and the sublimate scraped down. After twice repeating this sequence, the residue was heated to 130° and vacuum distilled to obtain pure 176b.

The isomeric compound which would contain an axial 2-isopropyl group and equatorial phosphoryl could not be synthesized under these conditions. Even after 2 wks no product was observed from 176a, acetone, and a catalytic amount of acid.

2-α-[2'(2'-Hydroxypropyl)]-2-β-oxo-4-α-methyl-1,3,2-dioxaphosphorinane (164)

The synthesis from 161b and acetone differed from that of 185 only in that the product was an oil for several weeks before eventually crystallizing (m.p. 109-110°). The parent ion was observed in its mass spectrum and there was again a major fragment from loss of acetone. The other isomer could

not be synthesized by the same procedure from 161a and acetone.

2-[2'(2'-Hydroxypropyl)]-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinane (81)

This compound was prepared identically to that for 185 (m.p. 181-183°C). Its mass spectrum exhibited a parent peak of 208 m/e and a major fragment of 150 amu due to loss of acetone.

2-[2'(2'-Hydroxypropyl)]-2-oxo-1,3,2-dioxaphosphorinane (54)

This compound was also prepared identically to that of 185. The product was an oil which did not crystallize and purification was not attempted.

Other Investigations

Reaction of phosphite 38a with HBr

The triester 38a was dissolved in 3 ml of D_3-acetonitrile to give a ca. 30% solution in a three-neck indented 25 ml flask equipped with reflux condenser and magnetic stirrer. After flushing the system and solution with nitrogen, anhydrous HBr diluted with nitrogen to about 50% was bubbled through the solution while maintaining the reaction at 65°C. After 2 hrs. the reaction was complete as evidenced by the pnmr spectrum which revealed a ca. 1:1 mole ratio of 176a:176b. Methyl bromide was also observed in the pnmr spectrum. Under identical conditions pure 176b isomerized to form a 1:1 mixture

whereas 176a gave a ca. 90:10 ratio of 176a:176b.

Determination of thermodynamic and kinetic data for 176a,b

Heating pure 176b at various temperatures resulted in the formation of equilibrium mixtures of 176a and 176b. A total of five points at 10° increments from 120 to 160°C gave isomer ratio extrema for 176a/176b of 4.39 (81.4% 176a) and 2.30 (69.7% 176a), respectively. (See Discussion section for table of this data.) The time required for obtaining equilibrium ranged from no more than 72 hrs. for the former to 12 hrs. for the latter. A least squares analysis yielded a slope of 9.65×10^2 and an intercept of -1.82 for a plot of log K vs. 1/T. From the slope a value of -4.4 ± 1.5 kcal/mole was obtained for $\Delta H°$ of the reaction 176b forming 176a using the relationship $\log K = (-\Delta H°/2.303\ R)\frac{1}{T} + I$ where K is the ratio of 176a to 176b and I is the intercept. A value for ΔS was calculated as -8.3 cal/deg·mole. The reaction was found to be acid catalyzed and a sixth point was obtained at 40°C under catalytic conditions. Unfortunately, the reaction had a half life of approximately 36 hours and after only four half lives there was severe decomposition. To obtain K_{eq}, the values of the known K's were plotted vs time and the curved line extrapolated to the asymptotic approach of K_{eq}. The value so obtained was used in a least squares analysis which included the data obtained at higher temperatures and the enthalpy and entropy recalculated to give $\Delta H° = -3.7 \pm 1.5$ kcal/mole and

$\Delta S°$ = -6.4 cal/deg·mole. The value for $\Delta G°$ calculated at 40° via the relationship $\Delta G° = -RT\ (2.303)\ \log K_{eq}$ was -1.6 kcal/mole.

The product distribution in converting 176b to 176a was observed at 150° after four different time periods (total time 9.17 hours). (See Discussion section for table). A least squares analysis of a plot of $-\log[(C-C_\infty)/(C_0-C_\infty)]$ vs t gave a slope of 0.158 from which a value for the first order rate constant k_{obs} of 0.363 hr^{-1} (or 6.05×10^{-3} min^{-1}) was calculated ($t_{1/2}$ = 1.91 hr).

Hydrolysis of hydrogen phosphonates 176a,b

To a ca. 1:1 mixture of 176a:176b dissolved in D_3-acetonitrile and containing a catalytic quantity of $HClO_4$ was added sufficient water to completely hydrolyze half of the starting material to phosphorous acid and dialcohol. After 24 hrs. the pnmr spectrum indicated the complete absence of 176b, whereas the amount of 176a was essentially unchanged. The same results were observed when the acid was omitted.

Hydrolysis of phosphoramidates 175a,b

To 0.5 ml of a 1 M solution of water in acetonitrile containing one drop of concentrated perchloric acid was added sufficient 175b to give a 1 M solution. A solution of 175a was similarly prepared and both solutions were placed in a 75°C constant temperature bath. After one hour both solutions

were ca. 30% hydrolyzed as shown by their pnmr spectra. However, the spectrum of the sample of 175a indicated 33% of the unhydrolyzed phosphoramidate was 175b. After 2.5 and 5 hrs. the spectra showed a similar 175a:175b ratio although hydrolysis had progressed. Monitoring the sample of 175b revealed no detectable appearance of 175a throughout the same period. No further hydrolysis was observed after 5 hrs.

RESULTS AND DISCUSSION

The Results and Discussion are organized into two parts. The first deals with compounds containing either 4-methyl or 4,6-dimethyl ring substituents. These compounds can be prepared as isomers and the data leading to phosphorus configurational assignments are presented. Although equilibration of isomers can usually be obtained for trivalent compounds such as the phosphoramidites 39a,b so that the thermodynamically preferred phosphorus configuration can be determined, isomeric tetravalent phosphorus compounds generally do not readily equilibrate. With the exception of the hydrogen phosphonates which do equilibrate, preferred stereochemisteries cannot generally be inferred from these compounds.

Since isomers of non-substituted compounds are not obtained but ring conformational changes can readily occur, comparison of these compounds to the isomeric compounds leads to quantitative determination of preferred stereochemistry. From dipole moment measurements, ^{31}P chemical shifts, and infrared phosphoryl stretching frequencies conformational ratios can be calculated and these experiments are discussed in the second part.

2-R- and 2-R-2-oxo-1,3,2-dioxaphosphorinanes with Ring Carbon Substituents

Proton nmr spectral parameters for all compounds of this class investigated in this work are listed in Table 9, dipole

Table 9. ^{1}H nmr data for 4-methyl and 4,6-dimethyl-1,3,2-dioxaphosphorinanes

Compound	δR^a	δR_1^a	δR_2^a	δR_3^a	δR_4^a	δR_5^a	δR_6^a	J(POCCH$_3$)	J(HCCH$_3$)	J(PR)[b]
32a	3.52d	4.4m	1.20d	4.4	4.4m	1.8m	1.8m	-	6.0	11.6
32b	3.50d	4.1m	1.38d	4.1m	4.1m	1.9m	1.9m	-	6.4	11.5
38a	3.52d	4.2m	1.20d	4.2m	1.20d	1.9m	1.9m	-	6.4	12.0
38b	3.51d	4.2m	1.20d	4.2m	1.20d	1.9m	1.9m	-	6.8	10.8
39a	2.47d	4.2m	1.21d	4.2m	1.21d	1.9m	1.9m	-	6.8	8.2
39b	2.68d	4.2m	1.25d	4.2m	1.25d	1.9m	1.9m	-	6.4	8.8
151a	3.73d	4.4m	1.37dd	4.4m	4.4m	1.9m	1.9m	2.5	6.1	11.0
151b	3.73d	4.5m	1.40dd	4.5m	4.5m	2.0m	2.0m	1.9	6.2	11.0
171a	3.80d	4.5m	1.38dd	4.5m	1.38dd	1.8m	1.8m	2.2	6.2	11.8
171b	3.78d	4.7m	1.38dd	4.7m	1.38dd	1.8m	1.8m	2.2	6.2	10.8
160a	2.65d	4.3m	1.42dd	4.3m	4.3m	1.9m	1.9m	1.6	6.2	10.8
160b	2.68d	4.3m	1.33dd	4.3m	4.3m	1.8m	1.8m	2.2	6.2	9.9
175a	2.66d	4.4m	1.38dd	4.4m	1.38dd	1.8m	1.8m	2.2	6.2	11.0
175b	2.71d	4.6m	1.33dd	4.6m	1.33dd	1.8m	1.8m	2.2	6.2	10.0
161a	6.89d	4.5m	1.42dd	4.5m	4.5m	1.8m	1.8m	1.9	6.2	670
161b	7.00d	4.5m	1.45dd	4.5m	4.5m	1.8m	1.8m	1.3	6.3	712
176a	6.90d	4.6m	1.41dd	4.6m	1.41dd	1.8m	1.8m	1.7	6.2	664
176b	6.95d	4.6m	1.39dd	4.6m	1.39dd	1.8m	1.8m	1.8	6.2	719
162a	1.53d	4.6m	1.35dd	4.6m	4.6m	1.9m	1.9m	1.6	6.5	18.4
162b	1.55d	4.5m	1.36dd	4.5m	4.5m	1.8m	1.8m	1.6	6.3	18.5
177a	1.56d	4.5m	1.38dd	4.5m	1.38dd	1.8m	1.8m	1.7	6.5	17.1
177b	1.52d	4.7m	1.32dd	4.7m	1.42dd	1.8m	1.8m	1.6	6.6	18.2
164	1.48d[c] 3.33s[d]	4.5m	1.22dd	4.5m	4.5m	1.8m	1.8m	1.6	6.3	15.8[c]
178	1.48d[c] 3.48s[d]	4.7m	1.35dd	4.7m	1.35dd	1.8m	1.8m	1.5	6.3	15.6[c]

[a] $CDCl_3$ solutions relative to TMS internal standard, R's are protons or groups of protons as indicated in Tables 1 and 3, s = singlet, d = doublet, m = multiplet.

[b] J(PR) refers to coupling constant of phosphorus to substituent protons.

[c] Methyl protons of HO(C$\underline{H}_3$)$_2$C-.

[d] OH proton of $\underline{H}$O(CH$_3$)$_2$C-.

moment measurement data are listed in Table 10, and measured dipole moments, ^{31}P chemical shifts and phosphoryl stretching frequencies are in Table 11.

Evidence for stereoretentive oxidation of phosphorus in 2-methoxy-1,3,2-dioxaphosphorinanes

The reaction of phosphites with NO_2 has been assumed in the literature to be stereoretentive. Since the stereochemistry of this reaction is important for configurational assignments to be discussed, evidence for retentive reaction is presented here. Denney et al. (141b) pointed out earlier that NO_2 oxidizes bicyclic phosphites such as 45 and moncyclic phosphites such as 38a,b with similar ease. Thus it seemed reasonable to suppose that since the former compounds are unable to undergo inversion, it was unnecessary for the latter to do so in order to oxidize. Michalski et al. (118) concluded that NO_2 oxidation of 32a and b to 151a and b, respectively, occurred with retention of phosphorus configuration although acyclic phosphines apparently did not. Because the arguments in the literature were not unequivocal, further experimental evidence has been sought. The data discussed below accord well with stereoretentive NO_2 oxidation of moncyclic phosphites, supporting the earlier postulates (118, 141).

From earlier work Vandenbroucke et al. (142) concluded that despite the larger electronegativity of oxygen, the P-O

Table 10. Dipole moment data for 4-methyl and 4,6-dimethyl-1,3,2-dioxaphosphorinanes

Compound	Mole fraction $\chi x10^3$	Dielectric constant, ϵ[a]	$\frac{\partial \epsilon}{\partial \chi}$	$\frac{\partial n}{\partial \chi}$[b]	P_o[c]
32a	12.43	2.416	11.40	-0.10	173.7
	5.896	2.342			
	2.984	2.308			
	1.542	2.292			
32b	13.85	2.430	11.24	-0.10	171.4
	6.477	2.348			
	3.220	2.311			
	1.646	2.293			
38a	11.48	2.414	11.89	-0.11	181.4
	5.789	2.346			
	2.565	2.308			
	1.244	2.292			
38b	11.56	2.417	12.19	-0.10	185.4
	5.242	2.340			
	2.893	2.311			
	1.422	2.294			
151a	11.52	2.806	45.85	-0.056	683.1
	5.342	2.520			
	2.726	2.400			
	1.361	2.341			
151b	13.13	2.711	33.22	-0.078	496.5
	6.906	2.503			
	2.228	2.348			
	1.088	2.311			

171a	9.594	2.762	51.04	-0.13	763.3
	5.035	2.527			
	2.191	2.383			
	1.176	2.333			
171b	9.775	2.568	29.98	-0.10	449.3
	4.593	2.412			
	3.288	2.373			
	1.541	2.321			
160a	9.674	2.650	38.95	-0.076	581.5
	4.656	2.453			
	2.066	2.352			
	1.004	2.313			
160b	8.737	2.466	21.85	-0.058	326.9
	4.421	2.372			
	1.997	2.319			
	0.9406	2.296			
175a	9.884	2.730	46.15	-0.092	688.8
	5.435	2.521			
	1.971	2.362			
	0.9532	2.319			
175b	9.483	2.486	22.20	-0.12	335.0
	4.654	2.380			
	2.889	2.339			
	1.544	2.310			

[a]All data were collected from compounds in benzene solution at 25.00 ± 0.02°C.

[b]The indices of refraction, n, were measured at 25.0 ± 0.2°C.

[c]Orientation polarization.

Table 10 (Continued)

Compound	Mole fraction $\chi \times 10^3$	Dielectric constant, ε [a]	$\frac{\partial \varepsilon}{\partial \chi}$	$\frac{\partial n}{\partial \chi}$ [b]	P_o [c]
161a	12.17	2.886	49.82	-0.048	741.6
	6.410	2.602			
	3.541	2.457			
	1.827	2.371			
161b	15.30	2.853	37.64	-0.044	560.7
	7.737	2.570			
	3.763	2.419			
	1.946	2.350			
176a	11.68	2.927	55.65	-0.080	829.5
	5.965	2.610			
	3.202	2.456			
	1.610	2.367			
176b	11.80	2.691	35.25	-0.074	526.5
	6.349	2.501			
	2.419	2.360			
	1.257	2.320			
162a	10.80	2.827	51.54	-0.055	767.4
	5.324	2.542			
	2.703	2.408			
	1.361	2.342			
162b	12.57	2.560	22.61	-0.079	339.0
	6.815	2.430			
	2.524	2.333			
	1.187	2.303			

177a	9.211	2.797	56.6	-0.081	843.7
	4.690	2.540			
	2.604	2.424			
	1.804	2.376			
	1.281	2.349			
	0.08782	2.324			
	0.05372	2.306			
177b	10.94	2.529	23.48	-0.066	351.4
	5.598	2.407			
	3.658	2.360			
	1.557	2.308			

Table 11. Dipole moments, ^{31}P chemical shifts and phosphoryl stretching frequencies of 4-methyl and 4,6-dimethyl-1,3,2-dioxaphosphorinanes[a]

Compound	μ[b]	^{31}P[c]	$\bar{\nu}$(P=O)[d]
32a	2.91	-129	-
32b	2.90	-132	-
38a	2.98	-126	-
38b	2.01	-133	-
39a	-	-137	-
39b	-	-141	-
151a	5.78	6.8	1309s (94)
151b	4.93	5.2	1288m,1270m
171a	6.11	7.1	1304s (143)
171b	4.69	5.0	1289m, 1271m
160a	5.33	-3.5	1301m, 1260s
160b	4.00	-6.6	1257s (94)
175a	5.80	-3.5	1301m, 1260s
175b	4.05	-6.6	1257s (88)
161a	6.02	-2.8	1298s (84)
161b	5.24	+1.7	1293vw,1270s
176a	6.37	-2.9	1296s (79)
176b	5.07	+1.3	1294vw,1267s
162a	6.13	-20.4	1284s (88)
162b	4.07	-27.7	1254s (110)
177a	6.42	-19.4	1285s (138)
177b	4.15	-28.0	1251s (143)
164	-	-	1249
178	-	-24.2	1247

[a]All measurements were made on benzene solutions with the exception of 164 and 178 which were made in $CDCl_3$.

[b]Given in Debye units with a precision of $\pm$0.05 D.

[c]Given in ppm relative to external 85% H_3PO_4.

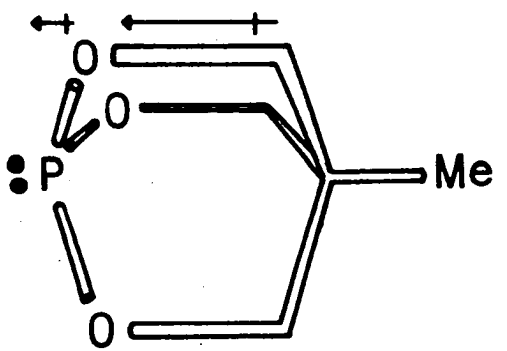
[d]Given in cm^{-1}, s = strong, m = medium, w = weak, v = very. The numbers appearing in parentheses are calculated extinction coefficients in units of l/mol.cm.

group moment was in the direction of phosphorus as shown in Figure 1a. This anomaly was attributed to constraint of the oxygen lone-pair density to enhance the molecular moment along the C_{3v} axis and pi election transfer from oxygen to phosphorus. The latter effect is expected to be augmented in the bicyclic phosphate (Figure 1b). It is seen in Figure 1c that opening the caged phosphate to form a six-membered ring phosphate would not be expected to alter the molecular moment appreciably except when the methoxy group is in the "extended" position. Even if the extended form of the molecule were the main component, the molecular dipole would still be approximately along the phosphorus-phosphoryl axis since one C-O bond moment is a comparatively small contribution to the overall moment. Figure 1d shows that a decrease in molecular moment is expected when the configuration at phosphorus is inverted. The conformers shown in Figures 1c and 1d are well represented by isomers 171a and 171b, respectively. The experimental dipole moment of 171a is 6.11D (Table 11) which as expected (if the configuration shown is correct) is less than that of the bicyclic phosphate 45 (7.10 D ref. 143). In further accord with the hypothesis is the measured moment of 171b which is even less (4.69 D, Table 11).

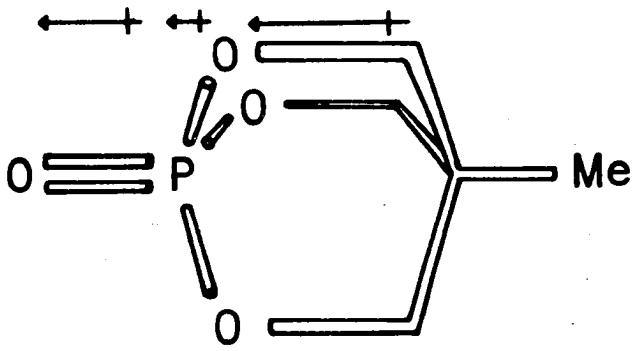
Further confirmation for NO_2 oxidation of 38a,b with retention of configuration comes from the lanthanide induced shift (LIS) studies of 151a,b. The method of preparation of

Figure 1. Molecular dipole moment components in

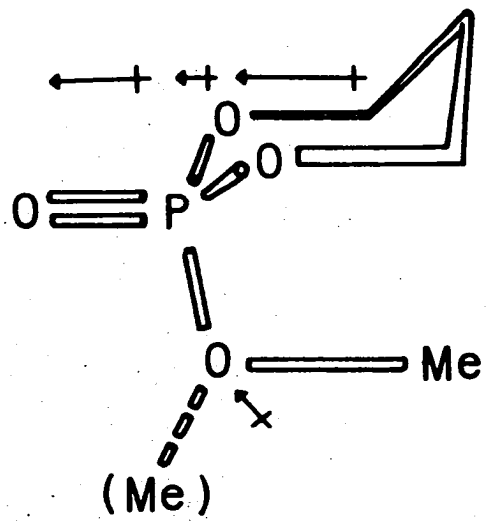
(a) A bicyclic phosphite
(b) A bicyclic phosphate
(c) Equatorially oriented phosphoryl oxygen of a six-membered ring phosphate
(d) Axially oriented phosphoryl oxygen of a six-membered ring phosphate



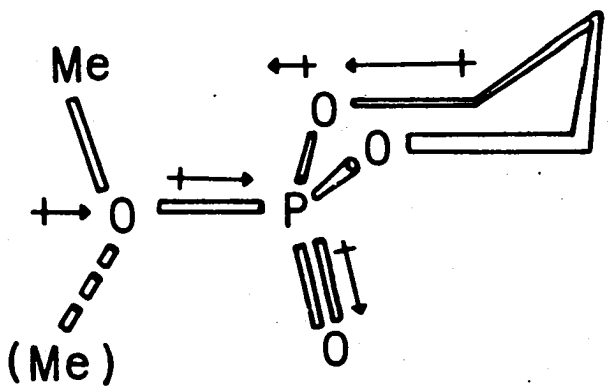
(a)



(b)



(c)



(d)

these isomers is exactly analogous to that of 171a,b from which they differ only in the absence of one ring methyl group. The LIS experiments are more informative for 151a,b than for 171a,b as is now explained. In the presence of $Eu(fod)_3$ protons are shifted according to the relationship $\Delta\delta = k(3\cos^2\theta-1)/R^3$ (75) where k is a collection of constants, θ is the angle and R the distance of the proton to the europium center. As noted in the Introduction section, complexation occurs at the phosphoryl oxygen (72). Dreiding models of 151a,b indicate that the C4 and C6 axial and C6 equatorial protons are of similar distances to the metal for isomer a assuming that the lanthanide complex is located near the phosphoryl oxygen along the P=O axis. In 151b, however, the two axial protons are considerably closer to the shift reagent than in 151a, but the C6 equatorial protons are about the same distance in both isomers. The nmr shifts for these protons in 151a,b (Table 12) are entirely in agreement with these considerations, lending further credence to the conclusion that NO_2 oxidation of the parent phosphites (32a,b or 38a,b) occurs with retention.

2-Alkoxy-2-oxo-1,3,2-dioxaphosphorinanes

The ^{31}P chemical shifts of 171a,b in Table 11 show that if their configurational assignments based on dipole moment arguments are correct, an equatorial P=O leads to a ^{31}P chemical shift which is upfield of that associated with an axial P=O.

Table 12. ^{1}H chemical shift $\Delta\delta$[a] data for 2-R-2-oxo-4-methyl-1,3,2-dioxaphosphoranes

Compound	R	R_1	R_2	R_3	R_4	R_5	R_6
151a	4.58	3.3	1.30	3.0	2.2	1.5	2.4
151b	3.94	5.1	1.37	4.5	2.2	1.6	2.6
160a	2.64	2.3	1.90	2.3	1.6	1.5	2.6
160b	3.73	5.3	1.19	4.6	2.2	1.4	2.8
161a	-[b]	1.6	1.2	1.6	1.6	1.4	2.2
161b	-[b]	4.6	1.3	4.1	1.7	2.0	2.6
162a	3.64	1.9	1.61	1.9	1.9	1.6	2.6
162b	3.50	4.5	1.09	4.5	1.6	1.4	2.3

[a] $\Delta\delta$ refers to the chemical shift in the presence of $Eu(fod)_3$ minus that in the absence of $Eu(fod)_3$.

[b] A very large shift occurred which was out of instrumental range.

That this is very probably a general phenomenon (except for hydrogen phosphonates) is indicated by the results of Bentrude and Tan (44) who have found this to be true for a variety of analogous systems.

As discussed in the Introduction section, Kainosho and coworkers originally (77) and Majoral and coworkers later (78) found stretching frequencies to be of higher energy in compounds wherein the phosphoryl group was postulated to be

equatorially disposed than in those wherein it was believed to be axial. Thus $\bar{\nu}(P=O)$ for 171a and 151a are at higher energy than 171b and 151b. The strong evidence presented here for the stereoretentive NO_2 oxidation lends considerable support to the conclusions drawn in earlier work on more tenuous grounds. An interesting feature of the phosphoryl stretching frequencies is the presence of only one band for 171a and 151a but two bands for 171b and 151b. The origin of the doubling in trialkylphosphates has been reviewed by several authors (144, 145, 146, p. 201, 147, p. 54). In some cases where the splitting is relatively small (e.g., 15 cm^{-1} for trimethylphosphate) rotational isomerism has been postulated. However, in other instances a much larger splitting of up to 50 cm^{-1} is observed. In these cases the doubling has been attributed to Fermi resonance of the P=O band with an overtone (146, p. 201). Since the splittings for compounds 171b and 151b, (18 and 19 cm^{-1}, respectively) are similar to those of trimethylphosphate, it seems reasonable to assign the presence of the two bands to rotational isomerism of the methoxy group. That compounds 171a and 151a do not exist as rotational isomers is not unreasonable. Dreiding models of these compounds indicate severe steric interactions of the methoxy protons with the C4 and C6 axial protons when in the conformations indicated by the solid line in Figure 1c. The likelihood of rotational isomers is therefore reduced for these isomers. The extended

form, depicted by the dashed lines in the figure, probably predominates and thus only one phosphoryl frequency is observed. This postulate is consistent with the significantly lowered dipole moments of 171a (6.11 D, Table 11) and 151a (5.78 D, Table 11) compared to the bicyclic phosphate (7.10 D, ref. 143) as alluded to above. No steric interactions exist for the b isomers, and rotational isomers would be expected.

2-Dialkylamino-2-oxo-1,3,2-dioxaphosphorinanes

In view of the fact that a P=O bond moment exceeds that of the $PNMe_2$ as well as that of the POMe group by a factor of a least two (148), the determining factor in the magnitude of the molecular moments of 175a,b is the disposition of the P=O link on the ring. The evidence for this was discussed above for 171a,b and the magnitudes of the dipole moments of 175a and 175b (Table 11) strongly suggest that the P=O orientations in 175a and 171a as well as in 175b and 171b are the same.

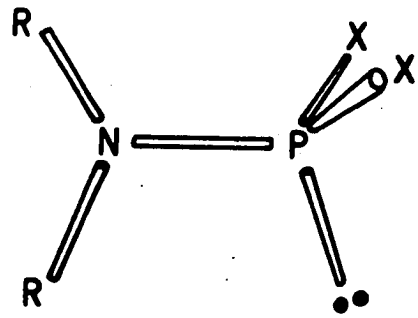
Strong support for the correctness of these assignments for the isomers 175a,b stems from LIS studies on 160a,b. The results shown in Table 12 very nicely parallel those discussed earlier for 151a,b. Noteworthy is the observation that compounds 39a,b displayed no appreciable LIS and this strengthens the basis for the supposition that lanthanide complexation takes place on the phosphoryl oxygen in 151a,b and 160a,b.

The relative ^{31}P chemical shifts of 175a and b in Table 11 also parallel those of 171a and b. Since the configurations of the latter were established with substantial certainty in the previous discussion, the inference which can be drawn from the ^{31}P data is that the configurations of 175a,b are also substantiated. Thus the a isomers contain equatorial phosphoryl and axial phosphorus substituent while the b isomers are opposite. The ^{31}P chemical shifts of 160a and b and 151a and b indicate similar assignments for these related compounds.

The phosphoryl stretching frequencies listed in Table 11 for the phosphoramidates are at first glance somewhat ambiguous. The single frequency for the b isomers of 160 and 175 is very similar to the stronger of the two absorptions of the a isomers. This is in contrast to the large difference expected for axial vs equatorial phosphoryl groups. There is consistent evidence that a nitrogen directly bonded to phosphorus assumes a planar configuration barring steric problems. Most of the structural studies reported in the literature have dealt with trivalent phosphorus compounds and a more detailed discussion of the results is deferred until later. The important point here is that the nitrogen plane has been found to bisect the X-P-X angle (Figure 2) and it eclipses the phosphorus-lone pair vector. A similar result has been observed for 206 as reported in Part II of this thesis wherein the exocyclic nitrogen plane bisects the ring N-P-O angle and eclipses the phosphoryl bond. This

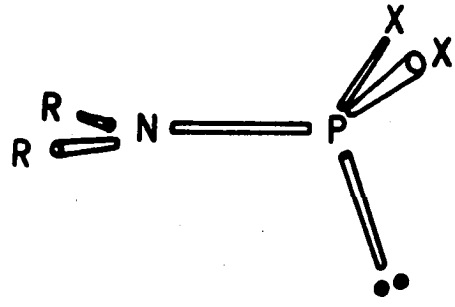
Figure 2. Orientations of R_2N plane to phosphorus substituents

(a) Bisecting of X-P-X angle and eclipsing of P-:
(b) Rotation of 90° about P-N bond



R=H, Me
X=F, Cl

(a)



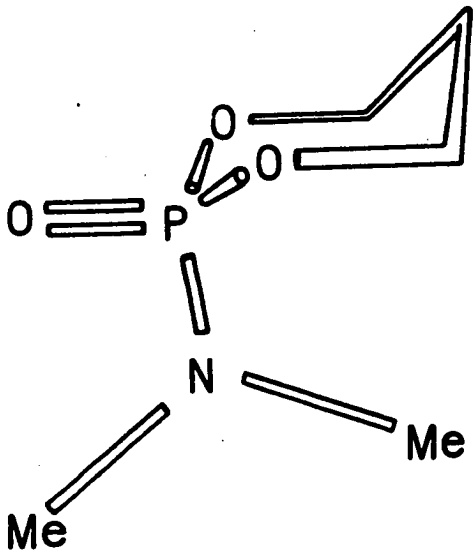
R=H, Me
X=F, Cl

(b)

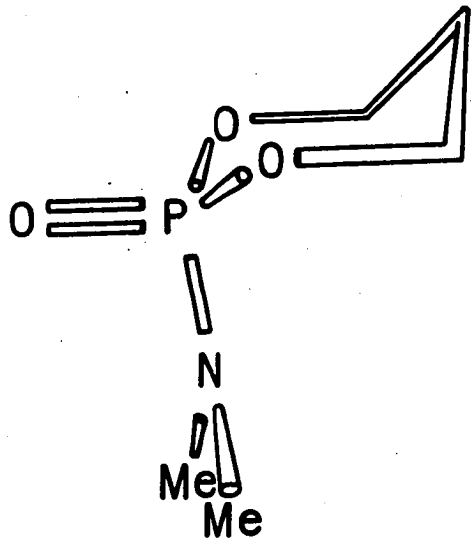
apparently stable co-planar relationship of the nitrogen configuration and the phosphorus substituent (oxygen or lone pair) is probably also true for the phosphoramidates 160a,b and 175a,b. The presence of only one type of N-Me group from pnmr spectra indicates rapid rotation about the P-N bond on the nmr time-scale. From structural studies discussed above, however, the preferred orientations would be as indicated in Figure 2a and this apparently results in only one phosphoryl stretching frequency for the b isomers because of a comparatively low concentration of rotational isomer due to a 90° rotation about the P-N bond (Figure 2b). The situation for the a isomers is further complicated, however, by the fact that in a chair conformation with the preferred nitrogen orientation (Figure 3a), severe steric interactions occur between the N-methyl protons and the C4 and C6 axial protons. Two conformational changes could alleviate this problem: (a) Rotation about the P-N bond by 90° could produce a stable chair conformation with disfavored nitrogen conformation (Figure 3b) and/or (b) formation of a half-chair (as is found from the x-ray structural determination of 179 (33, 34)) could lead to a relatively unstable ring conformation while maintaining the preferred nitrogen conformation (Figure 3c). The presence of two such rotational-conformation isomers (or some combination of them) in 160a and 175a can explain the presence of the two phosphoryl stretching frequencies. Indeed, the higher energy frequency for each a isomer is in the region expected for

Figure 3. Orientations of Me_2N plane with respect to the six-membered ring in a phosphoramidate

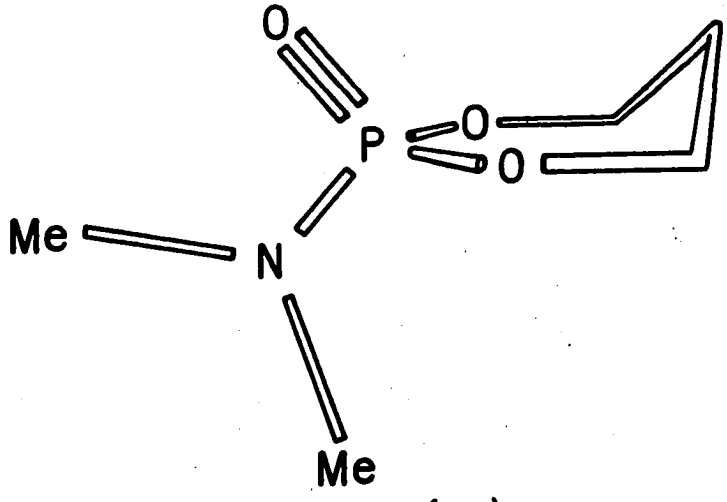
(a) Stable nitrogen plane configuration with stable chair ring conformation
(b) Unstable nitrogen plane configuration with stable chair ring conformation
(c) Stable nitrogen plane configuration with unstable half-chair ring conformation



(a)



(b)



(c)

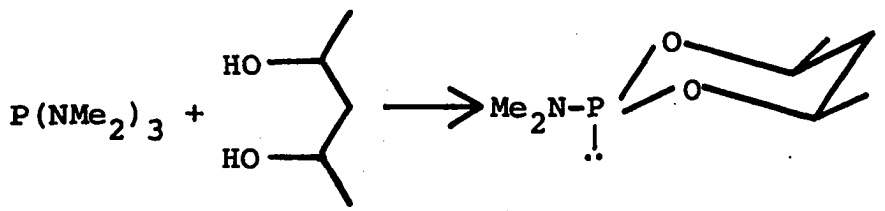
equatorial P=O and the low energy frequency is the same as that observed for 179 (9). Although temperature variation would be expected to cause a change in such rotational-conformational ratios, this was not observed in the infrared spectra of 175a in the range of 30° to 68°C. Variable low temperature ^{31}P nmr spectra of a mixture of 175a and b did indicate a chemical shift change for 175a and no change for 175b, consistent with the presence of rotational-conformational isomers.

The evidence described above indicates the phosphorus configuration of 160b and 175b to be axial P=O and equatorial P-NMe_2. The corresponding a isomers possess the opposite geometry at phosphorus although appreciable concentrations of rotational-conformational isomers may be present.

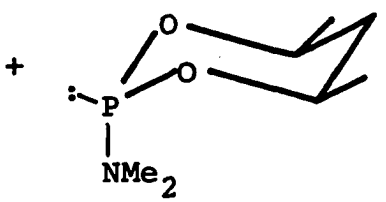
From the data so far described, no conclusions can be drawn regarding the preferred phosphorus stereochemistry for the phosphoramidates 160a,b and 175a,b. However, during the course of hydrolysis of 175a and 175b (see Experimental section) it was noticed that considerable isomerization of 175a to 175b accompanied hydrolysis of 175a while no 175a was detected in the sample of 175b under the same conditions. This seems to imply a greater stability of the axial P=O orientation of 175b compared to the equatorial (or pseudo equatorial) disposition of this group in 175a.

2-Dialkylamino-1,3,2-dioxaphosphornanies

Isomers 39a and b are produced in essentially the same ratio (1:10) by transesterification (reaction 4) and by the reaction of the cyclic phosphorochloridite 40 with excess dimethyl amine (reaction 5) as discussed in the Experimental section. In contrast to this, the reaction of the diol with

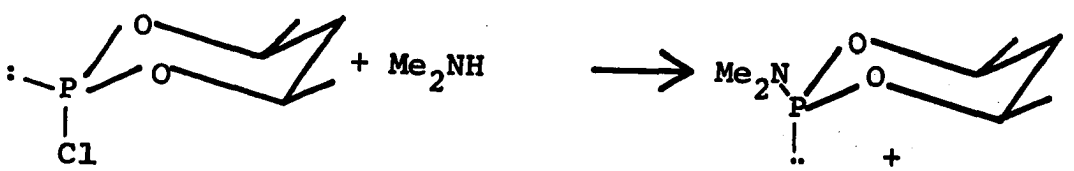


39b

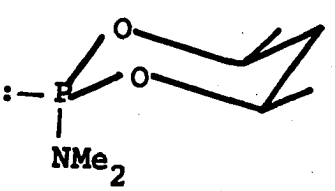


39a

Reaction 4

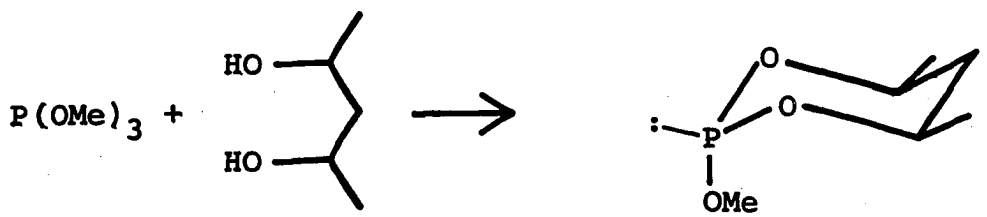


40



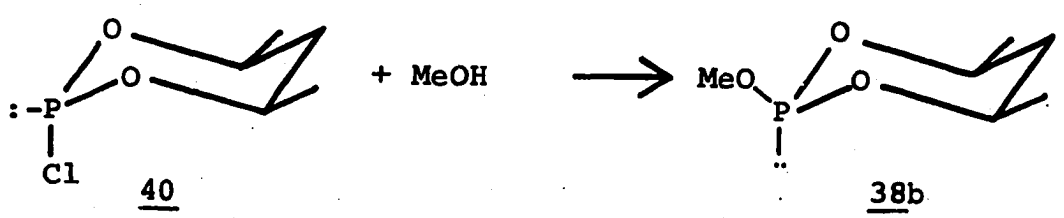
Reaction 5 39b and a

trimethylphosphite (reaction 6) gives pure 38a while the phosphorochloridite reacts with methanol to form only 38b (reaction 7). Thus, isomerization of 39a and b is apparently much more facile under these reaction conditions than that of 38a and b and deductions regarding phosphorus stereochemistry



38a

Reaction 6

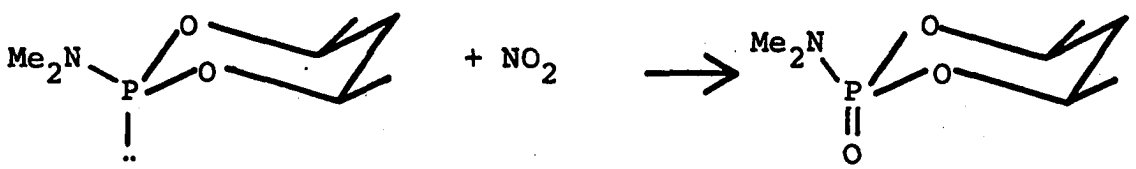


40 38b

Reaction 7

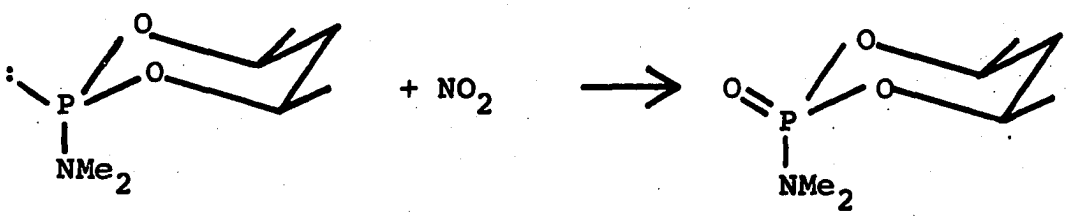
in 39a and b based on the stereospecificity of phosphorochloridite and amine reactions are not possible. While the reaction of N-chlorodimethylamine with the thermodynamically stable phosphite 38a might have been expected to form 175b owing to stereospecificity of the Michaelis-Arbusov reaction, isomerization to a ca. 2:3 ratio of 175a to 175b rendered stereochemical assignments made on this basis tenuous as well.

The stereochemical assignments of the phosphoramidites 39a,b can be made from their stereoretentive oxidation with NO_2 to yield 175a,b (reactions 8 and 9). That the NO_2



39b 175b

Reaction 8



39a 175a

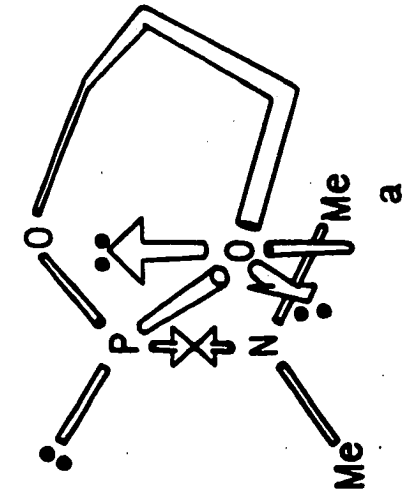
Reaction 9

oxidation is stereoretentive was indicated from the formation of the phosphates 171a and 171b from the phosphites whose absolute configuration were known (see Introduction section). Oxidation of an equilibrium mixture of ratio 1:10 for 39a:39b produced a 1:10 ratio of 175a:175b. Thus the configuration of 39a is axial P-NMe_2-equatorial lone pair and 39b axial lone pair-equatorial P-NMe_2. The ^{31}P data listed in Table 11 are consistent with these assignments in that the a isomer chemical shifts of 38 and 39 are upfield of their respective b isomers. Values for the ^{31}P chemical shifts previously reported in the literature (9) for compounds 38a and b are incorrect and should be reversed.

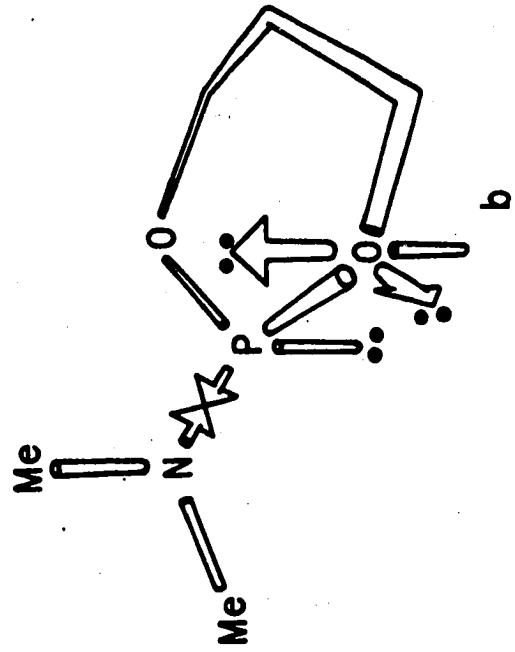
Unlike the situation for 38a,b wherein no detectable amounts of 38b are present at equilibrium (9), the equilibrium ratio of 39a to 39b is about 1:10 showing that the more stable phosphorus configurations are opposite in the isomeric phosphites and phosphoramidites. That the 1:10 ratio of 39a to 39b is very likely the equilibrium ratio is suggested by the observation of this ratio in two different reactions (reactions 4 and 5, see Experimental section) which were carried out at rather different temperatures and also by the constancy of this ratio after heating the mixture to 120° for 18 hrs. or upon vacuum distillation on a spinning band column.

An interpretation which can be given for the greater thermodynamic stability of axial OMe and equatorial NMe_2 in the trivalent phosphorus heterocycles lies in the gauche effect (wherein polar sigma bond pairs and electron pairs are stabilized by a gauche relationship, ref. 149) which has been modified to accommodate electronic changes occurring upon the introduction of a phosphorus atom into the ring system. It is reasonable to suppose that the hybridization around oxygen and nitrogen in OR and NR_2, respectively, is roughly sp^2 when these atoms are attached to phosphorus because the exocyclic POC angle in $MeOP(OCHPh)_2$ is 117.5° (150) and the nitrogen in Me_2NPF_2 (151, 152) Me_2NPCl_2 (153) and H_2NPF_2 (154) possesses a nearly trigonal planar configuration (Figure 2a). Although no structural data are available for POC angles in six-membered ring trivalent phosphorus compounds, there is no reason to expect them to be very far below 120° in view of the 117.5° exocyclic POC angle mentioned above. Further evidence for this supposition comes from the recent crystal structure determination of <u>trans</u>-$P(OCH_2)_3PFe(CO)_3P(OCH_2)_3P$ in which this angle in the PC_3 coordinated polycycle is very nearly 120° (155). Thus as depicted in Figure 4, the ring oxygens are involved in pi bonding to the phosphorus (as shown by shortening of this link compared to the sum of the covalent radii involved, ref. 151, 155) and the non-bonding vicinal electron pairs are not quite eclipsed in the a configuration which is

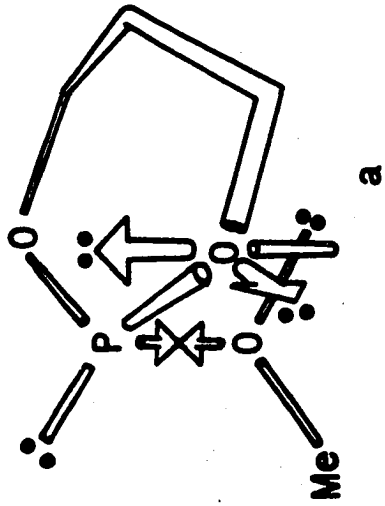
Figure 4. Preferential phosphorus substituent rotamers in some trivalent phosphorus systems. The vectors represent p or hybrid sp orbitals relevant to the gauche effect



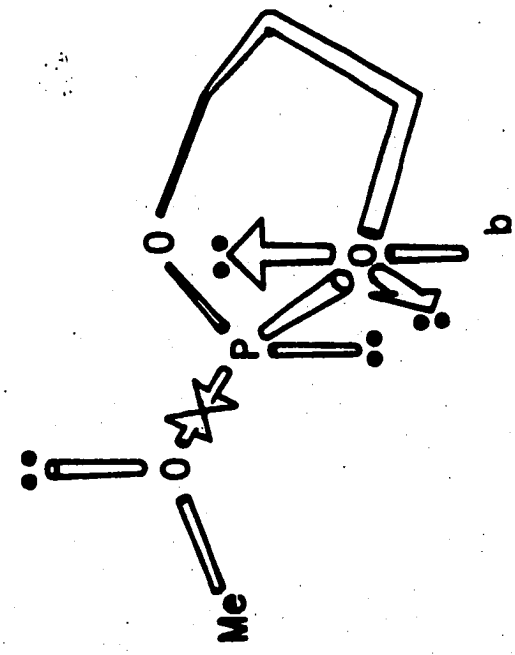
a



b



a



b

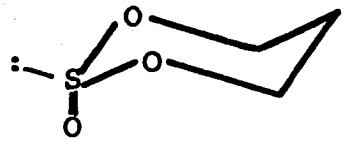
the more stable one in the case of the OMe compound (Figure 4). Although the b conformation would be more favored because of a more gauche relationship between the non-bonding lone pairs, it must be remembered that the electron pair in the p orbital on oxygen is capable of spanning the P-O link in a pi molecular orbital. The electron-electron repulsion resulting from the close proximity of the bottom half of this pi MO to the phosphorus lone pair in b could be destabilizing relative to a for the phosphite case.

The rotameric conformations of the OMe and NMe_2 groups shown in the a and b phosphorus stereochemistries in Figure 4 are apparently favored since they have been observed for Me_2NPF_2 (151, 152), Me_2NPCl_2 (153) and H_2NPF_2 (154) (Figure 2a). A factor in stabilizing this rotameric conformation is the mutual repulsion of both halves of the N-P pi MO and the phosphorus lone pair density. (An inductive effect from PH_2 to nitrogen rather than d orbital participation of phosphorus has been postulated to account for stabilization of the planar nitrogen configuration in H_2NPH_2, see ref. 156 and references therein. In phosphates and phosphites, however, the phosphorus atom is considerably more electronegative and pi bonding appears to be influential, see ref. 157.) Despite the flattening of the ring at phosphorus owing to near 120° POC ring angles, 1,3 steric interactions between one of the nitrogen methyls in a with axial hydrogens may still be responsible for

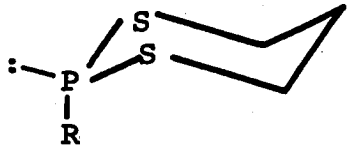
the greater stability of b. In the case of the OMe group, the oxygen lone pair is energetically lower when trans to the phosphorus lone pair than when cis and the oxygen lone pair may even be attracted to the axial protons, the combined effect stabilizing a relative to b (Figure 4).

The greater preference of an isopropyl group for the axial position (158) would seem to militate against the above steric argument. It is to be noted, however, that unlike the NMe_2 group which presumably because of N-P pi bonding requirements adopts the rotameric conformation shown in b (Figure 4), the isopropyl group can minimize the 1,3 interactions in order to maximize the gauche effect. The same may be true of the phenyl group (18) barring conjugation influences sufficiently strong to drive it into the same conformation adopted by an axial NMe_2 (Figure 4). Some evidence for the preferred rotameric conformation of the phenyl group plane being parallel to the plane formed by the C4 and C6 carbons and C4 and C6 axial protons (as opposed to the preferred nitrogen configuration discussed above) is the upfield shift noted for the axial protons on C4 and C6 (9, 18) brought about by the shielding region of the aromatic ring.

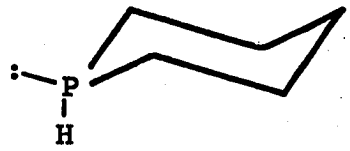
Other systems in which the predominant species is concluded to be that wherein the heteroatom substituent is axial are shown below. All of these cases, along with the trivalent phosphorus systems just discussed, have in common a lone pair



Ref. 159

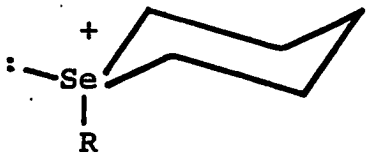


Ref. 126

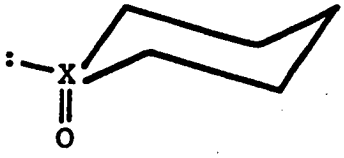


Ref. 130

Ref. 160

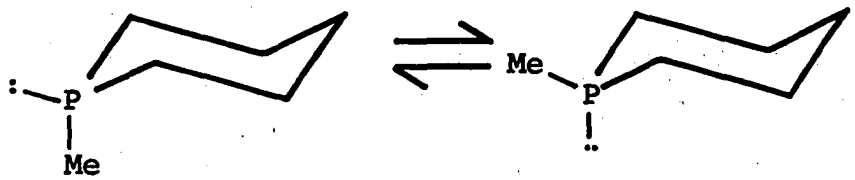


Ref. 161



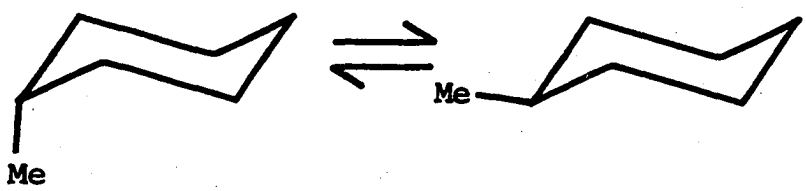
X=S, Ref. 162
X=Se, Ref. 161

as well as an axial substituent of the single heteroatom. It appears that the dioxa and dithia compounds shown could be governed by a modified gauche effect involving pi bonding from the chalcogen to the unique hetero atom. The remaining systems are dominated by a more straightforward gauche effect in which the heteroatom lone pair is gauche with respect to two C-H bond pairs. The hydrogen-phosphorinane 234 shown above contains axial hydrogen as the preferred configuration in the temperature range -50 to -80°C (130). Above -50° hydrogen exchange was rapid, precluding determination of the configuration at room temperature. Contrastingly, 1-methyl-phosphorinane exhibits an equilibrium between XXXI and XXXII in a ratio of 0.50 at -130°C (163). Extrapolation of low temperature



XXXI XXXII

conformer distributions to room temperature resulted in a calculated ratio of XXXI to XXXII of 1.8 at 25°C (163). The contrary behavior of 1-methyl-phosphorinane appears to be the result of opposing energetics of the gauche effect and 1,3 steric interactions of the methyl group, wherein the latter predominates at low temperatures. That the gauche effect is likely to be operative, is seen in the comparison of the relatively large ratio of XXXI to XXXII of 0.50 at -130°C compared to that of XXXIII to XXXIV of 0.01 at -110°C for methyl cyclohexane (164). Because methyl cyclohexane possesses no lone pair electrons, it cannot exhibit gauche effects.



XXXIII XXXIV

2-Hydro-2-oxo-1,3,2-dioxaphosphorinanes

As alluded to previously, the hydrogen phosphonate isomers 161a and b and 176a and b are interesting systems in that they are the only tetravalent phosphorus compounds studied that readily undergo isomerization.

Hydrolysis of 2-chloro-1,3,2-dioxaphosphorinane in acidic (HCl is formed in the reaction) or basic media (excess pyridine) produced 70% 176a and 30% 176b which suggests dominance of S_N2 mechanisms similar to those shown in Figure 5 if the stereochemical assignment of 176a is correct (cf. p. 149). Evidence for the likelihood of the configuration shown for 40 has been discussed in the Introduction (cf. p. 32).

Although 176a can be purified by repeated crystallization of the reaction mixture, 176b is obtained pure by vacuum distillation of a mixture of the two isomers. Proof of their monomeric nature is found in their molecular weights measured in solution (see Experimental section).

The equilibrium between the two isomers indicated by the distillation experiment was followed in the range 120-160° by means of nmr integration of the downfield half of the P-H protons and the enthalpy for interconversion of 176a to 176b was calculated to be 4.4 ± 1.5 kcal/mole (see data in Table 13). Equilibrium at room temperature is reached undetectably slowly and even at 74° where 176b distilled from the mixture, equilibrium establishment was sufficiently slow to allow it to

Figure 5. Acidic and basic pathways of S_N2 mechanism of formation of hydrogen phosphonate (176a) from phosphorochloridite (40)

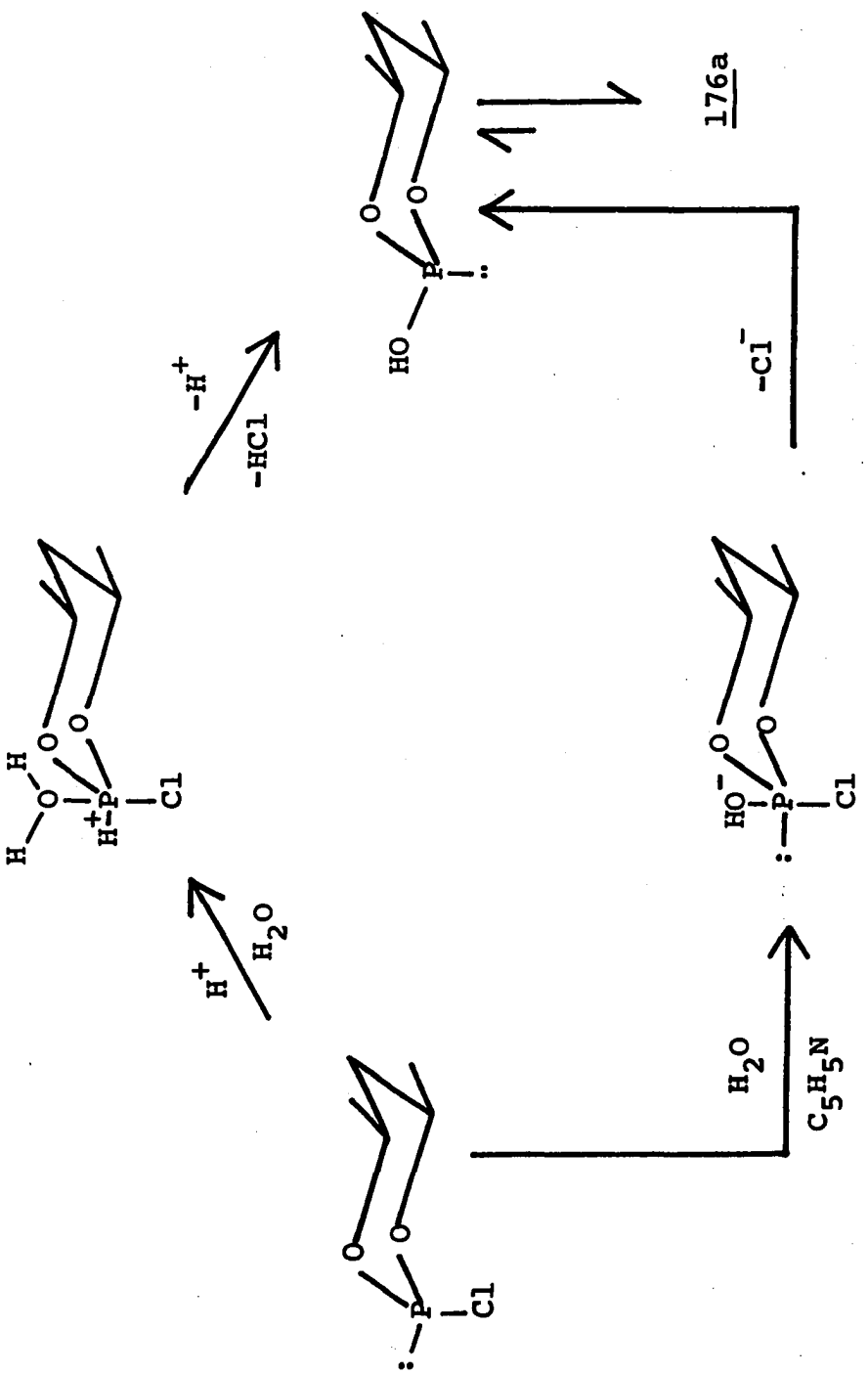

176a
-Cl⁻
-H⁺
-HCl
H⁺
H₂O
H₂O
C₅H₅N

Table 13. Thermodynamic data for the equilibria of 176a and 176b[a]

Temperature[b]	K_{eq}[c]
40[d]	7.18[d]
120	4.39
130	3.85
140	3.19
150	3.05
160	2.30

[a] ca. 1.5 M mesitylene solutions.

[b] In degrees C.

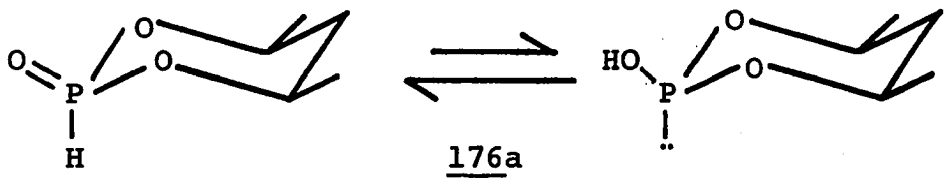
[c] K_{eq} equals the amount of 176a divided by the amount of 176b. The data is for the reaction 176b forming 176a.

[d] Acid catalyzed equilibrium at 40° as described in text.

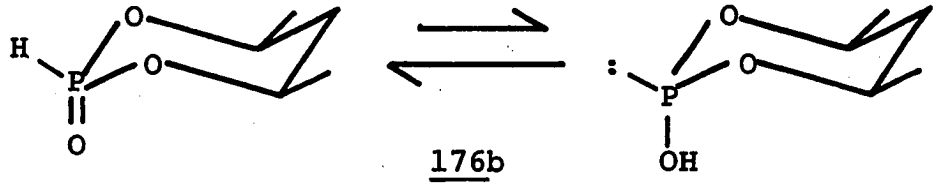
be obtained pure. In fact, 72 hr are required for equilibrium to occur at 120°. The free energy difference at 40° is $\Delta G°$ = 1.6 ± 1 kcal/mole favoring 176a over 176b in the acid-catalyzed equilibrium.

It seems quite reasonable to assume that tautomers of 176a and 176b are probably important (Figure 6) in the equilibrium process and some evidence for tautomerism is presented later. (A single ring cleavage would not account for isomerization although its involvement in the 176a-176b equilibrium

Figure 6. Keto-enol equilibria of isomeric hydrogen phosphonates 176a and b



176a



176b

cannot be ruled out. It seems unduly complicated to invoke the necessity of two simultaneous ring cleavages to cause isomerization). The conversion of 176b to 176a at 150° was found to be first order (data Table 14). The data listed in Table 14 for the two concentrations are qualitatively similar and thus are also consistent with a first order mechanism. The quantitative difference is likely due to the inaccuracy of the intergration of the downfield half of the P-H doublet in the pnmr spectra of the more dilute sample. A value of k = 0.363 hr^{-1} calculated from the data for the more concentrated sample is taken to be a more accurate representation of the first order rate constant than k = 0.249 calculated from the more dilute sample. Similar results for the transformation of 161b to 161a were found by Nifant'ev and Borisenko (89).

Table 14. Reaction rate data for formation of 176a from 176b[a]

Time[b]	$-\log[(c_o - c_\infty)/(c_o - c_\infty)]$[c]	
	1.5 M solution	0.4 M solution
2	0.206	0.304
4	0.453	0.547
6	0.815	0.804
9.17	1.318	1.077

[a]Measured at 150°C in mesitylene.

[b]Time given in hours.

[c]The slope of the plot of $-\log[(c - c_\infty)/(c_o - c_\infty)]$ vs time, where c = concentration of 176b at that time, c_∞ = concentration of 176b at infinite time, and c_o = initial concentration of 176b, gives k/2.303.

These workers further stated that the activation energy for the conversion of 161b to 161a was 23.0 ± 0.8 kcal/mole (88). Such an activation energy value is quite low for a phosphorus inversion process (about 50 kcal/mol, ref. 165) even if an anionic species is involved (about 30 kcal/mole ref. 165) as suggested by the Russian workers (89). Postulating other possible mechanisms at this time, however, would be too speculative.

The catalysis of isomerization by aqueous acid can be understood in terms of an S_N2 attack by water (Figure 7). It should be pointed out that evidence for a similar bimolecular pathway for the facile interconversion of isomers 122a and b has been put forth since isomerization is accelerated in the presence of halide ion (see Introduction and ref. 9). Since the keto form might be expected to predominate, the mechanism in Figure 8 for the acid-catalyzed interconversion is a viable alternative.

The stereochemistry at phosphorus in 176a and 176b is strongly implied by the Michaelis-Arbusov-like reaction of 38a with gaseous HBr. Although 176b would be expected to

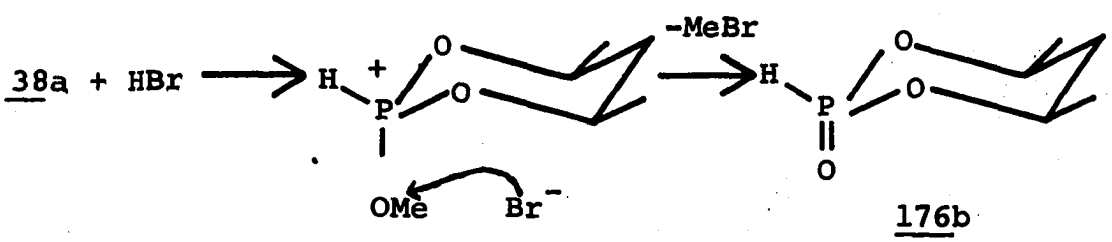


Figure 7. Enol-intermediate isomerization mechanism of hydrogen phosphonates 176a and b

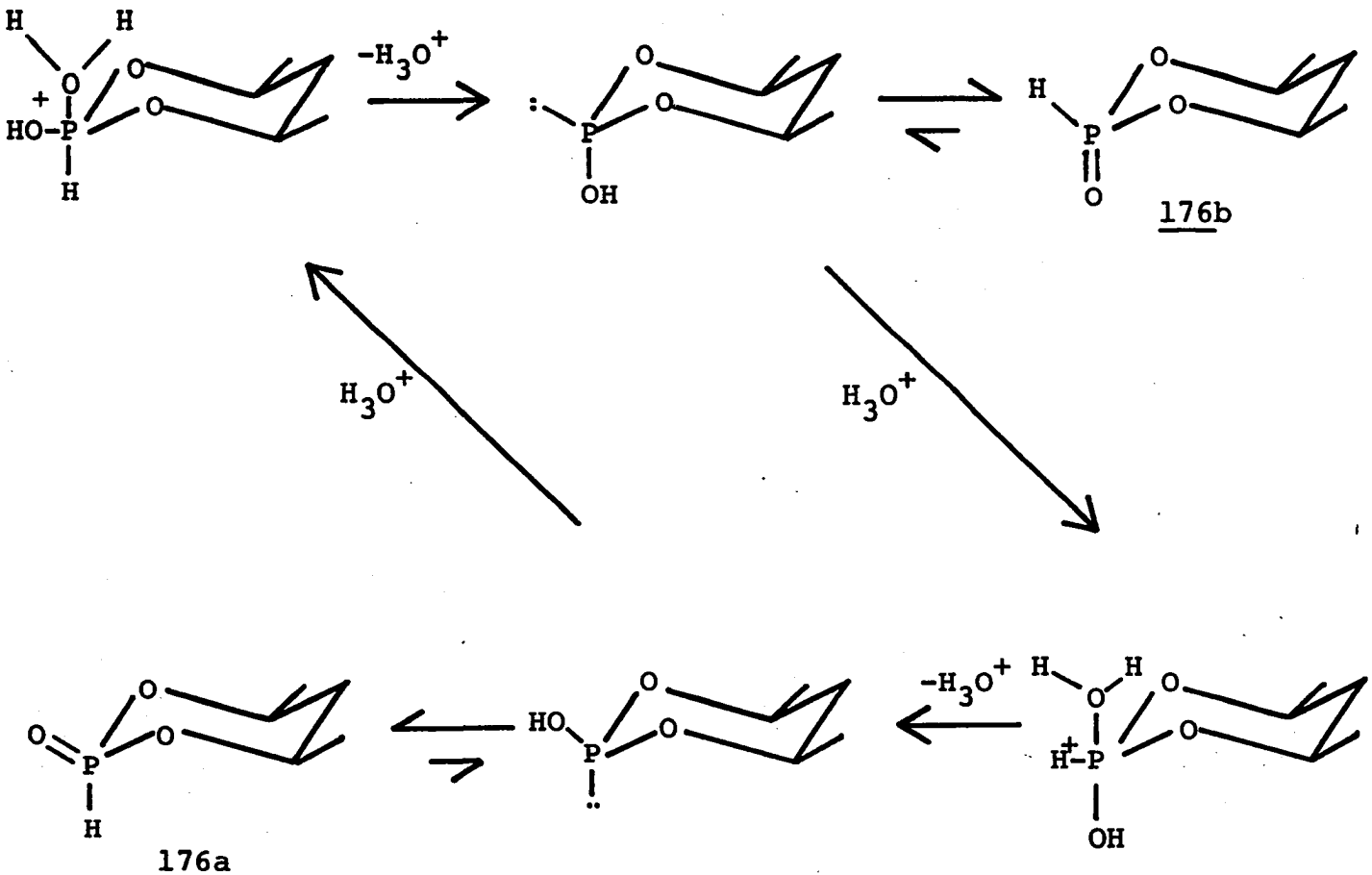
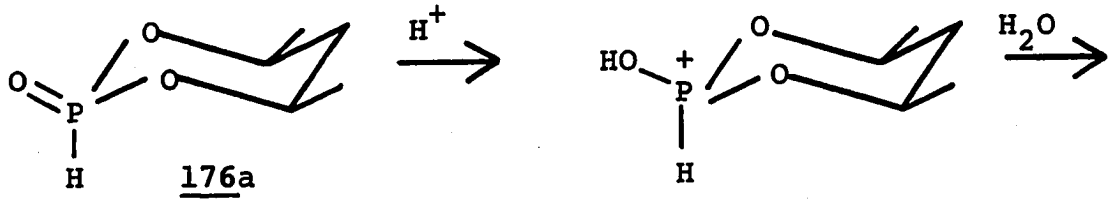
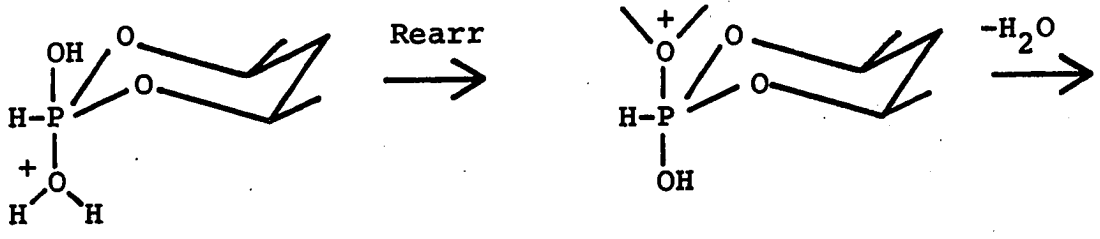
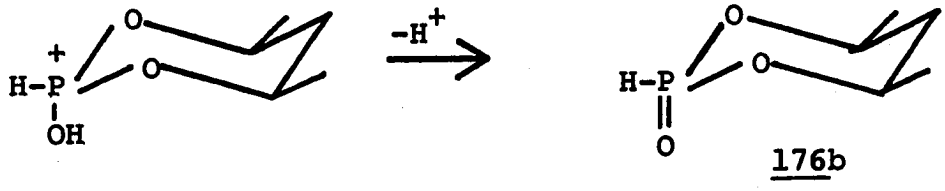

$-H_3O^+$
176b
H_3O^+
H_3O^+
$-H_3O^+$
176a

Figure 8. Keto-intermediate isomerization mechanism of hydrogen phosphonates 176a and b



176a





176b

constitute the major product, a ca. 50-50 mixture of 176b to 176a was formed. This result suggests that at 65° isomerization of 38a to 38b (in which case the latter could react with HBr to form 176a) and/or isomerization of 176b to 176a was occurring. Although the second process is undetectably slow at 65° using pure 176b, it is catalyzed by aqueous $HClO_4$ and a ca. 50-50 mixture of 176a and 176b is formed in the same length of time the HBr reaction was allowed to take place. Furthermore, when a mixture of 38a and 176b was treated with HBr by the same procedure, a 1:1 ratio of 176b to 176a was obtained. Thus isomerization of the starting material does not seem to be important, for no 38b was detected at any point during this reaction. Excess HBr could well be responsible for partial conversion of 176b to 176a if trace amounts of water were present.

Of importance to the configurational assignment of 176b in the HBr reaction is the fact that equilibrium was not attained during reaction. Even at 120°, equilibrium occurs with only about 20% 176b present and so more than a two-fold excess of 176b was formed in the HBr reaction than could be accommodated at equilibrium at 65°. Extrapolation of the equilibrium data obtained in the 120-160° range indicates an equilibrium point of about 10% 176b and 90% 176a. Acid-catalyzed equilibrium approached at 40° after 5 days (see Experimental section) using pure 176b or 176a corroborates

the extrapolated result.

The $Eu(fod)_3$ LIS data (Table 11) reported for isomers 161a and b are consistent with the assignment of equatorial phosphoryl for 161a and 176a and axial phosphoryl for 161b and 176b on the same basis as discussed previously for the phosphates and phosphoramidates. They also imply a chair conformation.

Dipole moment measurements (Table 11) also support the assignments, although both 161b and 176b are somewhat larger than expected. This latter fact will be taken up again shortly.

The infrared stretching frequencies (Table 11) also accord well with the configurational assignments with the equatorial P=O displaying a higher frequency than the axial isomer. Two phosphoryl stretching frequencies are listed for both 161b and 176b, but the assignments are not certain. Although two bands are observed for the two pure isomers (the higher energy peaks being much less intense), ^{18}O-enrichment studies did not permit conclusive detection of the presence of those bands since they lie in the region of the intense P=O frequency of the corresponding a isomers. Moreover, studies of the ^{18}O-enriched compounds were restricted to mixtures of isomers. It is not unreasonable to believe the higher energy peak in the b isomers to be due to the presence of a conformer possessing a more equatorial P=O configuration (e.g. twist or boat). Such

a conformer could also explain the rather large dipole moment observed for the b isomers.

If as demonstrated in other 1,3,2-dioxaphosphorinanes the ^{31}P chemical shifts are always upfield for equatorial P=O isomers, the configurational assignments for the 2-hydro-2-oxo-1,3,2-dioxaphosphorinanes 161a,b and 176a,b are incorrect (Table 11). All other evidence discussed above, however, suggests that the assignments are correct. Although these are the only known cases of inverted behavior, the implication is that care must be exercised in making configurational assignment on the basis of ^{31}P chemical shifts alone.

A few years ago, it was reported that the isomeric compounds 161a and b were formed upon hydrolysis of the parent 2-chloro compound 37 in the presence of base (68). The configurational assignments reported here for these isomers are opposite to those arrived at in the earlier report, however. The original assignment was based on the tenuously small deshielding (0.02 ppm) of the predominantly equatorial ring methyl group when cis to P=O (161a) than when trans (161b), as might be expected if P=O groups deshielded analogously to S=O groups (166). Repetition of this work and further studies lead to the conclusion that application of the P=O deshielding criterion yields incorrect assignments in this case. The grounds for this contention are: (a) isomers 161a and 161b possess melting points, boiling points, (see

Experimental) J(P-H) values (Table 15), P=O stretching frequencies (Table 11), P-H stretching frequencies (Table 15), ^{31}P chemical shifts and dipole moments (Table 11) which compare closely with those of isomers 176a and 176b whose configuration were deduced from data discussed above. (b) Like 176b, 161b can be distilled in pure form from a mixture of 161a and b, and at 145° the a/b isomer equilibrium ratio is about 3:1 in both pairs of compounds. (c) The chemical properties (cf. p. 152) of 176a and 161a are very similar as are those of 176b and 161b but configurations a and b do exhibit contrasting chemical behavior. (d) The proton chemical shifts in the presence of $Eu(fod)_3$ are consistent with this assignment as discussed above. The same conclusions reported in this thesis were also reached in a more recent Russian report (69) on the basis of the measured dipole moment of these isomers which are within experimental error of those reported here.

Table 15. P-H nmr and ir data for 2-hydro-2-oxo-4-methyl- and -4,6-dimethyl-1,3,2-dioxaphosphorinanes[a]

Compound	$\bar{\nu}$(P-H)[b]	J(P-H)[c]
161a	2414	670
161b	2477	712
176a	2406	664
176b	2470	719

[a]From $CDCl_3$ solutions.

[b]Given in cm^{-1}.

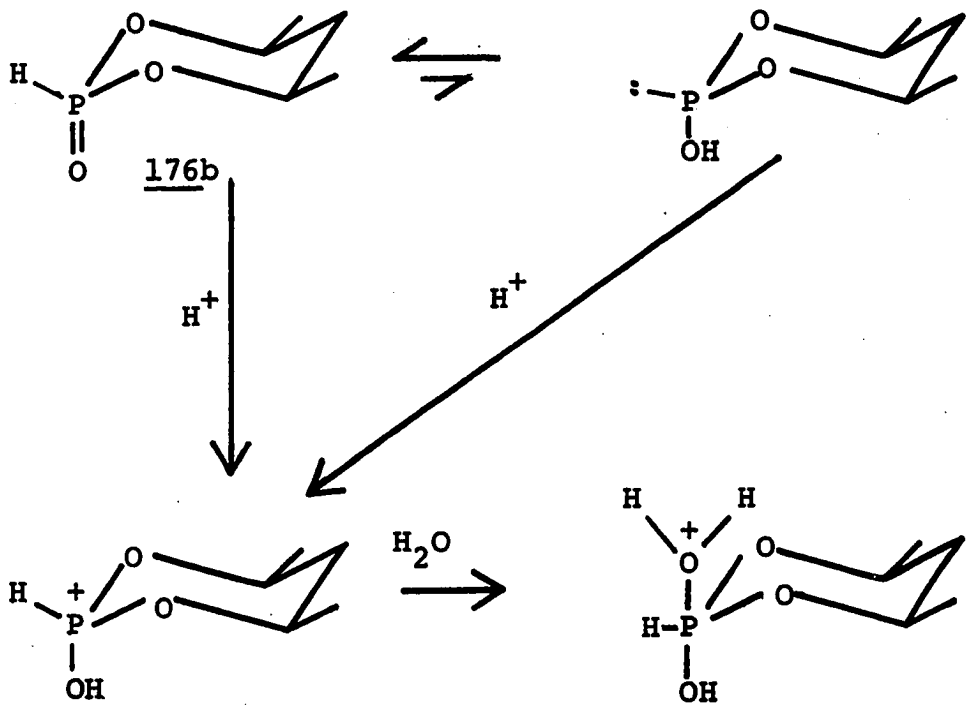
[c]Given in cycles per second (Hz).

Acetone insertion products of 2-hydro-2-oxo-1,3,2-dioxaphosphorinanes

The behaviors of 161a, 161b, 176a, and 176b toward water and acetone are rather remarkable. When an equimolar mixture of 161a and 161b or 176a and 176b is allowed to react with enough water (in the absence or presence of acid) to hydrolyze half the diester completely to phosphorous acid and diol, the b isomers are completely destroyed (Figure 9). After 24 hr at room temperature the a isomers remain essentially intact as shown from the pnmr spectra. Furthermore, 161b and 176b react quantitatively with acetone in the presence of a catalytic amount of aqueous acid over a period of 36 hr to form 164 and 178, respectively, (Figure 10) while no reaction was observed for 161a and 176a. Although an earlier report (167) disclosed the reaction of acetone with other six-membered ring hydrogen phosphonates to form similar products (167), the stereospecific dependence of acetone attack on the configuration of phosphorus is reported here. While the configurations at phosphorus in the acetone reaction products 164 and 178 are somewhat uncertain, they are apparently the same in these two compounds as judged from the ^{31}P chemical shifts and P=O stretching frequencies (Table 11).

The hydrolyses and the acetone reactions of 161b and 176b may reflect a greater ease of tautomer formation on the part of the b isomers. Thus like OR groups (see Introduction

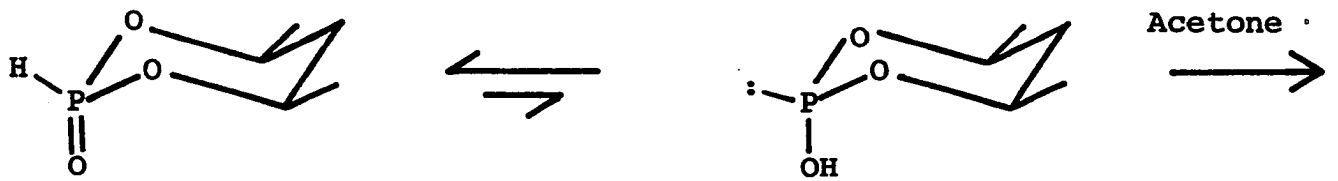
Figure 9. Mechanism of hydrolysis of hydrogen phosphonate 176b to form phosphorous acid and meso-diol



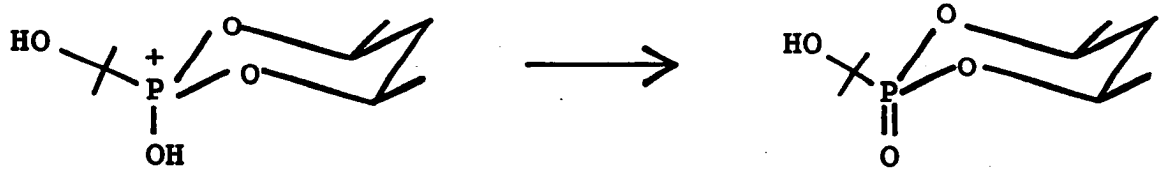
$H(O)P(OH)_2$ +

Phosphorous Acid Meso-diol

Figure 10. Mechanism for formation of acetone insertion product of hydrogen phosphonate 176b



176b



178

section and following discussions), an OH group may be thermodynamically more stable in the axial than in the equatorial position demanded by the a isomers (Figure 6). Moreover, equatorial attack of the b tautomer by electrophiles such as H^+ in the hydrolysis (probably followed by water attack on P and cleavage of a ring P-O bond) (Figure 9) and a carbonyl carbon in the acetone reaction (followed by proton attack at the carbonyl oxygen) (Figure 10) is perhaps somewhat more sterically favored than axial attack on the a tautomers. The available evidence seems to suggest that the configuration of 164 and 178 is axial P=O , but the assignment is not unambiguous. This question will be again treated after discussion of the compounds lacking C4 and C6 methyl groups.

2-Alkyl-2-oxo-1,3,2-dioxaphosphorinanes

The stereochemistries of the methyl phosphonates 177a and 177b are known since they are prepared from the Michaelis-Arbusov reaction of methyl iodide with 38b and 38a, respectively. Although Bodkin and Simpson have found some lack of exocyclic oxygen stereoretention when the isomeric ethyl and isopropyl cyclic phosphites 33a,b and 34a,b were reacted with methyl or ethyl iodide (59, 60), this was not observed by the present author for 32a,b or 38a,b with methyl iodide. The a isomers 162a and 177a are thus believed to contain equatorial phosphoryl oxygen and the b isomers axial P=O from the dipole moments and phosphoryl stretching frequencies listed

in Table 11 since they are as expected for these configurational assignments. The ^{31}P chemical shifts are similar to analogous phosphate and phosphoramidate isomers (though dissimilar to the isomeric hydrogen phosphonates) with equatorial P=O isomers displaying the higher field chemical shift.

2-R- and 2-R-2-oxo-1,3,2-dioxaphosphorinanes without Ring Carbon Substituents

Proton nmr spectral parameters for all compounds of this class investigated in this work are listed in Table 16, dipole moment measurement data are listed in Table 17, and measured dipole moments, ^{31}P chemical shifts and phosphoryl stretching frequencies are to be found in Table 18. P-H nmr and ir data are given in Table 19.

2-Hydro-2-oxo-1,3,2-dioxaphosphorinanes

The first compound to be considered is the hydrogen phosphonate 52 since the preferred stereochemistry and equilibrium distribution are known for compounds 176a and b from the previously described thermodynamic data. The dipole moments, ^{31}P chemical shifts, and infrared phosphoryl stretching frequencies are listed in Table 18.

For calculation of the conformer distribution from dipole moment data the equation $(Y)(\mu_A)^2 + (1-Y)(\mu_B)^2 = (\mu)^2$ was employed. It was assumed that the dipole moment of 176a (μ_A) was identical to the dipole moment of the conformer of 52

Table 16. ^1H nmr data for 2-R-2-oxo-1,3,2-dioxaphosphorinanes

Compound	δR^a	δR_1^a, δR_2^a, δR_3^a, δR_4^a	δR_5^a	δR_6^a	$J(PR)^b$
1	3.50d	4.0m	2.0m	2.0m	12.0
49	3.80d	4.4m	2.0m	2.0m	11.2
51	2.68d	4.3m	2.0m	2.0m	10.2
52	6.91d	4.4m	2.0m	2.0m	673
76	6.90d	3.9m	0.95s	1.35s	675
53	1.73d	4.4m	2.0m	2.0m	17.5
81	1.53d[c]	4.2m	1.07s	1.10s	15.5
	2.98s[d]				

[a] $CDCl_3$ solutions relative to TMS internal standard. R's are protons or groups of protons as indicated in Tables 1 and 3, s = singlet, d = doublet, m = multiplet.

[b] J(PR) refers to coupling constant of phosphorus to substituent protons.

[c] Methyl protons of $HO(C\underline{H}_3)_2C$-.

[d] OH proton of $\underline{H}O(CH_3)_2C$-.

containing the equatorial P=O orientation, and that the dipole moment of 176b (μ_B) was the same as that of the opposite conformation. Knowledge of the measured moment of 52 (μ) therefore allowed calculation of the fraction (Y) of 52 containing equatorial phosphoryl oxygen. The results are given in Table 20 with estimated precisional errors in parentheses.

Table 17. Dipole moment data for 2-R-2-oxo-1,3,2-dioxaphosphorinanes

Compound	Mole fraction $\chi \times 10^3$	Dielectric constant, ε[a]	$\frac{\partial \varepsilon}{\partial \chi}$	$\frac{\partial n}{\partial \chi}$[b]	P_o[c]
1	17.57	2.442	9.496	-0.060	143.6
	8.911	2.360			
	3.319	2.307			
	1.714	2.292			
49	16.72	3.002	43.57	-0.048	648.9
	7.817	2.612			
	4.040	2.449			
	1.987	2.361			
51	10.68	2.503	21.28	-0.075	319.2
	5.335	2.389			
	2.081	2.319			
	1.086	2.299			
52	13.44	2.919	47.29	0.000	701.9
	7.117	2.623			
	5.182	2.529			
	2.622	2.406			
53	12.28	2.687	33.97	-0.050	506.4
	6.575	2.492			
	5.119	2.442			
	2.764	2.365			

[a]All data were collected from compounds in benzene solution at 25.00 ± 0.02°C.

[b]The indices of refraction, n, were measured at 25.0 ± 0.2°C.

[c]Orientation polarization.

Table 18. Dipole moments, ^{31}P chemical shifts and phosphoryl stretching frequencies of 2-R-2-oxo-1,3,2-dioxaphosphorinanes[a]

Compound	μ[b]	^{31}P[c]	$\bar{\nu}$(P=O)[d]
1	2.65	-139	----
49	5.63	6.7	1310s
51	3.95	-6.22	1255s
52	5.86	-2.26	1303s, 1281vw
76	--	-24.2	1296s, 1269vw
53	4.98	-24.2	1288m, 1255s
81	--	-22.3	1288m, 1258s

[a]All measurements were made on benzene solutions with the exception of 81 made in $CDCl_3$.

[b]Given in Debye units with a precision of $\pm$ 0.05D.

[c]Given in ppm relative to external 85% H_3PO_4.

[d]Given in cm^{-1}, s = strong, m = medium, w = weak, v = very.

Table 19. P-H nmr and ir data for 2-hydro-2-oxo-1,3,2-dioxaphosphorinanes[a]

Compound	$\bar{\nu}$(P-H)[b]	J(P-H)[c]
52	2395, 2437	673
76	2409, 2440	675

[a]In $CDCl_3$ solutions.

[b]Given in cm^{-1}. The low energy peak was much more intense for both compounds.

[c]Given in cycles per second (Hz).

Table 20. Conformer fractions of 2-R-2-oxo-1,3,2-dioxaphosphorinanes[a]

Compound	From μ	From ^{31}P	From $\bar{\nu}$(P=O)
49	0.63(0.09)	0.8(0.1)	0.8(0.2)
51	0.0(No estimate)	0.12(0.06)	0.19(0.09)
52	0.58(0.08)	0.85(0.1)	0.8(0.2)
53	0.32(0.05)	0.43(0.02)	0.4(0.1)[b] 0.35(0.1)[c]

[a]The method of calculation is described in the text. The data refer to the fraction of equatorial conformer in solution. The numbers in parentheses are the errors as calculated from limits on precision.

[b]Calculated assuming the extinction coefficient of 177b to be the same as the lower energy peak of 53.

[c]Calculated assuming the extinction coefficient of 177a to be the same as the higher energy peak of 53.

Since the ring methyl groups of 176a and b are symmetrically substituted, no ring distortions affecting the dipole moments are expected for these compounds. Compounds with a single exocyclic methyl group such as 161a,b were not used in these calculational studies since distortion is more likely and ring conformation changes by way of flipping are sterically less disfavored. Substitution of a methyl group for a hydrogen does not introduce a significant change in the local dipole moment since the group moment is (3 cos 70.5°)(C-H) = (1.004)(C-H) which is well within the experimental error of the carbon-

hydrogen moment. Introduction of the methyl substituents may cause a change in ring angles which would affect dipole moments, but no corrections have been made for this possibility. Another source of error is the assumption that 176a and b are conformationally pure. Although there is no reason to believe that this is not the case for 176a, 176b apparently displays two phosphoryl stretching frequencies indicative of more than one conformation (cf. p. 149). The reasonable assumption that no intermediate conformer of 52 makes a significant contribution to the dipole moment has also been made.

The conformational distribution of 52 was calculated from ^{31}P chemical shift data using the equation $(Y)(\delta_A)+(1-Y)(\delta_B) = \delta$ (Table 20) using similar assumptions to those for dipole moment data. The chemical shift of 176a (δ_A) was assumed to be the same as the conformer of 52 containing equatorial P=O and that for 176b (δ_B) the same as the axial P=O conformer of 52. The same two error sources are also present. Substitution of a methyl for a hydrogen may cause changes in ring angles, thus causing a change in chemical shift, and 176a and/or 176b may not be conformationally pure.

The infrared spectrum of 52 displayed two phosphoryl stretching frequencies (Table 18), indicative of two ring conformations. The higher energy absorption was assigned to the equatorial P=O and was assumed to have the same extinction coefficient as that calculated for 176a. The

concentration of that conformer was calculated and the fraction of total compound in that conformation determined (Table 20). Any error introduced by assuming identical extinction coefficients is probably overshadowed by the large error in the determination of the absorbances from the non-linear baselines of the spectra.

The conformer distributions calculated from ^{31}P chemical shifts and P=O stretching frequencies are similar, but higher than those calculated from dipole moment data. This is consistent for all four compounds (Table 20) and the cause is unknown. The equilibrium distribution for 176a and b at 40° is about 90% 176a and 10% 176b, in much better quantitative agreement with the former two methods of calculation than with the dipole moment method. All three procedures give the same qualitative result that equatorial phosphoryl is preferred.

Acetone insertion products of 2-hydro-2-oxo-1,3,2-dioxaphosphorinanes

Although the preferred stereochemistry of 52 and therefore probably 76 as well, is equatorial phosphoryl oxygen, the chemistry of these two compounds more closely resembles that of 176b which contains axial P=O. The hydrolyses of 52 and 76 under similar conditions to those of 176b proceed at similar rates which are much more rapid than that for 176a (cf. p. 152). Like 176b, 52 and 76 also react quantitatively with acetone in ca. 36 hrs yielding compounds 54 and 81, respectively, whereas

176a does not react (cf. p. 152). The difference in behavior of 52 and 76 compared to 176a is probably a result of the equilibrium between conformers for 52 and 76 allowing the conformer with axial phosphoryl to undergo reactions similar to those of 176b which are disfavored for equatorial P=O configurations of 52, 76 and 176a. Compound 54 could not be purified and remained as an oil, but compound 81 was crystalline showing two infrared P=O stretching frequencies (Table 18). The more intense, lower-energy absorption indicates preference for axial phosphoryl oxygen. This is consistent with the steric argument presented earlier for the lack of product from 176a and acetone since 176a possesses an equatorial P=O . The ^{31}P chemical shift is also listed in Table 18, but with no known equatorial P=O analogue for comparison, the significance of the chemical shift cannot be judged.

2-Alkoxy-2-oxo-1,3,2-dioxaphosphorinanes

Conformer distributions were calculated for the phosphate 49 (Table 20) from the data in Table 18 by the same procedures described for 52. The results from ^{31}P chemical shift values and P=O stretching frequencies are probably more accurate than the dipole moment calculations since that was observed to be true for the hydrogen phosphonate 52. All three methods yield data which qualitatively corroborate the same conclusions drawn previously in the literature for analogous

compounds that an equatorial phosphoryl oxygen is preferred (see Introduction).

2-Dialkylamino-2-oxo-1,3,2-dioxaphosphorinanes

The dimethylamino compound 51 exhibits a behavior opposite to that of the hydrogen phosphonate and phosphate compounds in that axial P=O is preferred (Table 20). This difference can be ascribed to the steric problems presented earlier in discussion of the phosphoramidites 39a,b. The tentative evidence of preferred axial P=O from hydrolysis data (cf. p. 124) is thus substantiated by the dipole moment, ^{31}P chemical shift and phosphoryl stretching frequency data for 51. An indication of the presence of error in calculation of the conformer ratio derived from P=O stretching frequency data is now demonstrated with 51 as an example. Only one peak was observed in the spectrum of 51 indicating 100% axial P=O. From a determination of the extinction coefficient of 175b and assignment of this value to that peak of 51, the value given in Table 20 was obtained. Either the peak from the other conformer is so weak as to be unobserved, or the calculations are inaccurate.

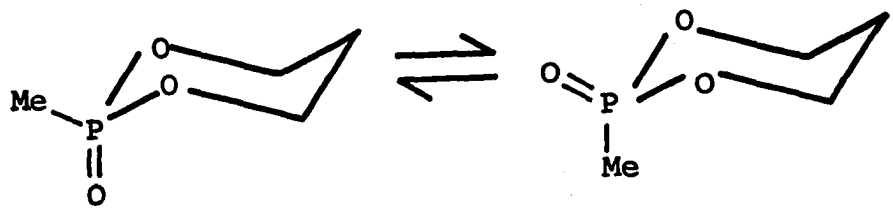
As mentioned in the Introduction, axial P=O preference was initially reported by Majoral and coworkers (48,78,86) for compounds 73 and 97, but they later questioned this conclusion (79) because of the inconsistencies presented by Kainosho et al. (85) for compounds 70, 71, 72 and 73. Bentrude and Tan

have recently indicated the greater stability of axial P=0 disposition from compounds 109a and b (15, 16).

2-Alkyl-2-oxo-1,3,2-dioxaphosphorinanes

From the many reports cited in the Introduction, phosphonates do not display a major conformational preference. The distributions calculated for the methyl phosphonate 53 (Table 20) are consistent with those findings. Two values are listed from P=0 stretching frequency data arising from calculations assuming the extinction coefficient of 177a to be the same as the equatorial P=0 of that conformer of 53 and assuming the extinction coefficient of 177b to be the same as that of the axial P=0 of 53. All the calculations indicate a somewhat favored axial phosphoryl orientation.

It is important to note that all of the calculations are based on distributions at or near room temperature with benzene as the only solvent. Majoral and coworkers have found the infrared P=0 intensity to be dependent on temperature and solvent (46, 80, 82). Although benzene has been the only solvent used for the measurements reported here, variable temperature infrared spectra have been obtained for compound 53. From the data listed in Table 21 values of ΔH and ΔS were calculated as -1.34 kcal/mol and -5.38 cal/mol·deg, respectively, for the interconversion indicated below, with ΔG° = +0.16 at 25°C. Formation of the equatorial P=0 conformer is therefore favored at lower temperatures, but the solvent did not permit



53

Table 21. Thermodynamic data for the conformer equilibria of 2-methyl-2-oxo-1,3,2-dioxaphosphorinane[a]

Temperature (°C)	K_{eq}[b]
5	0.76
15	0.68
31	0.62
40	0.57
50	0.53
60	0.52
68	0.47

[a]Benzene solutions.

[b]K_{eq} equals the amount of equatorial phosphoryl conformer divided by the amount of axial phosphoryl conformer. The data is for the reaction of the latter to the former conformer.

investigations at temperatures below 5°. Low-temperature ^{31}P chemical shifts were essentially unchanged from those measured at 25°C. This is probably due to the use of the very polar solvent $CFCl_3$ which could cause the equatorial P=O conformer to predominate at all temperatures employed.

2-R-2-oxo-1,3,2-dioxaphosphorinanes with Ring Carbon Substituents Re-examined

With the greater certainty of the preferred phosphorus stereochemistry in the various phosphosphorinanes now established, it is interesting and instructive to consider once again some of the data for the 4-methyl and 4,6-dimethyl-1,3,2-dioxaphosphorinanes. The coupling constants $J(POCCH_3)$ given in Table 9 range from 1.6 to 2.5 for all 4,6-dimethyl isomers investigated (171a,b, 175a,b, 176a,b and 177a,b), for the 4-methyl isomers containing preferred phosphorus conformations (151a, 160b, 161a and 162b), and for 162a which probably differs little in energy from 162b. The 4-methyl isomers with unstable configurations (151b, 160a, and 161b), however, all have coupling constants 0.6 Hz smaller. Although the differences of 0.6 Hz are too small to make a quantitative analysis meaningful, the indication is that these compounds do contain a significant contribution of other conformers which may arise from ring flipping or twisting. The dipole moment data are fairly consistent with this postulate. Compounds 175b and 160b, have measured dipole moments within experimental

error of each other, whereas the unstable configurations 175a and 160a differ substantially. The same is also true, however, for 177b and 162b compared to 177a and 162a where both pairs would be expected to be similar. For the remaining two compound types, the 4,6-dimethyl isomers represent dipole moment extrema with the 4-methyl isomers intermediate. The conclusion is that 4,6-dimethyl isomers are probably better model compounds for axial and equatorial substituents than are the 4-methyl compounds, since the latter are more apt to exist as ring flipped or twisted conformers.

Summary

The phosphorus stereochemistry of the isomer pairs of both 4-methyl and 4,6-dimethyl substituted 2-methoxy-2-oxo- (151a,b and 171a,b), 2-dimethylamino-2-oxo- (160a,b and 175a,b), 2-dimethylamino- (36a,b and 39a,b), 2-hydro-2-oxo- (161a,b and 176a,b), and 2-methyl-2-oxo-1,3,2-dioxaphosphorinanes (162a,b and 177a,b) have been assigned from dipole moment measurements, ^{31}P chemical shifts, infrared stretching frequencies and LIS experiments. Both dipole moment measurements and LIS experiments gave unambiguous results for the compounds containing a phosphoryl oxygen and appear to be reliable methods for determining phosphorus stereochemistry for these non-mobile compounds. ^{31}P chemical shifts were inconsistent in that compounds 151a,b, 171a,b, 160a,b, 175a,b, 36a,b, 39a,b, 162a,b

and 177a,b all exhibited higher field shifts for those isomers with equatorial P=O or lone pair (a isomers) but for 161a,b and 176a,b the opposite was true. Infrared phosphoryl stretching frequencies were also ambiguous because of the observation of two bands for the isomers 151b, 171b, 160a and 175a.

Preferred geometries were assigned for 2-methoxy-2-oxo- (49) 2-dimethylamino-2-oxo- (51), 2-hydro-2-oxo- (52) and 2-methyl-2-oxo-1,3,2-dioxaphosphorinane (53) by quantitative comparison of their dipole moments, ^{31}P chemical shifts and phosphoryl stretching frequencies to those of the corresponding isomeric 2-R-2-oxo-4,6-dimethyl-1,3,2-dioxaphosphorinanes. Although the precision of the calculations from dipole moment data was the greatest, the accuracy is believed to be the poorest of the three methods since the calculated conformer distribution for 52 from this method was in poor agreement with the equilibrium isomer distribution of 176a and 176b from thermodynamic data. The calculated conformer distribution for 52 calculated from ^{31}P chemical shift and infrared data did give reasonable agreement with the equilibrium isomer distribution of 176a and 176b. All measurements were obtained in benzene solution at room temperature only except for variable temperature infrared spectra obtained for 53. The three methods gave the same qualitative results for 2-methoxy-2-oxo- and 2-hydro-2-oxo-1,3,2-dioxaphosphorinanes which showed a

preference for equatorial phosphoryl oxygen and axial substituent, while 2-dimethylamino-2-oxo-1,3,2-dioxaphosphorinane displayed the opposite tendency. The 2-methyl-2-oxo-1,3,2-dioxaphosphorinane showed a somewhat greater preference for axial phosphoryl oxygen at room temperature but increasing equatorial oxygen preference as the temperature was lowered.

The majority of the work described in this thesis concerning the evidence for stereoretentive oxidation of phosphorus in 2-methoxy-1,3,2-dioxaphosphorinanes and the stereochemical assignments of the 4-methyl and 4,6-dimethyl ring substituted 2-dimethylamino-2-oxo- (160a,b and 175a,b) and 2-dimethylamino-1,3,2-dioxaphosphorinanes (36a,b and 39a,b) has been published (73) or is in press (167). Most of the work concerning the 4-methyl and 4,6-dimethyl ring substituted 2-hydro-2-oxo-1,3,2-dioxaphosphorinanes (161a,b and 176a,b), the acetone insertion products of these compounds (164 and 178) and the acetone insertion product of 2-hydro-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinane has also been reported (168).

SUGGESTIONS FOR FUTURE WORK

In the manner indicated in the Discussion, the conformational distributions of 49, 51 and 52 have been assigned at essentially one temperature only and in only one nonpolar solvent. Observation of the phosphoryl stretching frequencies of 53 suggested a dependence on temperature, although the experimental conditions were not sufficiently rigorous that accurate thermodynamic parameters could be calculated. Variable temperature infrared spectra should be obtained for 53 as well as compounds 49, 51 and 52 in order to determine the thermodynamic stability of the preferred geometries quantitatively. Since preferred geometry is dependent on solvent polarity, this variable should also be studied employing solvents such as chloroform and/or acetonitrile. The disadvantage of the former solvent is the formation of weak hydrogen bonds between the solvent and the phosphoryl oxygen. Variable temperature ^{31}P nmr spectral studies would provide a check in the determination of conformer distributions calculated from variable temperature infrared studies.

The presence of rotational isomerism was suggested for those compounds containing methoxy and dimethylamino substituents as an explanation for the presence of more than one phosphoryl stretching frequency. The validity of this postulate could possibly be elucidated by low temperature infrared and pnmr spectral studies. If the rotation can be

stopped, the methoxy compounds 151a and b, and 171a and b should display one type of methyl group in the pnmr spectra and only one phosphoryl stretching frequency. Conversely, the dimethylamino compounds, 160b and 175b, although exhibiting only one phosphoryl frequency, should contain two types of N-methyl groups if the nitrogen plane bisects the O-P-O angle as suggested in the Discussion. If the nitrogen plane takes an orientation 90° from the bisecting position, the methyl groups would be equivalent. Compounds 160a and 175a could likewise result in pnmr N-methyl non-equivalence if they exist in a half-chair form, whereas equivalence would be observed if they are in a chair form.

Pnmr spectral analysis performed on compounds 160a and 175a would also help elucidate the stable ring conformation. Pnmr spectral analysis of all 4-methyl-1,3,2-dioxaphosphorinanes would aid in resolving the question of whether the unstable isomer of these compounds possesses an axial 4-methyl group as alluded to in the Discussion.

Since there are no reports of studies designed to assign the stable configurations of 1,3,2-azaoxaphosphorinanes, investigations of these compounds would be of importance for comparison with 1,3,2-dioxaphosphorinanes and 1,3,2-diazaphosphorinanes. The most reliable method for determining the phosphorus geometry of the 4-methyl and 4,6-dimethyl compounds is probably the measurement of dipole moments if both isomers

can be obtained. It is further suggested that infrared and ^{31}P data for such compounds be used to quantitatively assess the stereochemistries of compounds lacking ring methyl substituents in similar spectral investigations.

PART II. THE X-RAY CRYSTAL STRUCTURE OF CYCLOPHOSPHAMIDE

INTRODUCTION

The carcinostatic properties of cyclophosphamide, 206, in the treatment of *in vivo* tumors have been widely studied. (The entire issue of the journal quoted in reference 7 is devoted to chemical and clinical research on 206. Reference 170 is a very recent report of both *in vivo* and *in vitro* studies.)

As discussed at some length in Part I, the presence of the ring implies that the phosphorus substituents may assume axial or equatorial positions. Thus, one purpose of the structural determination was to ascertain the preferred phosphorus stereochemistry in the solid state. Also, the similarity of this compound to 51, 160a and b, and 175a and b allows adjudication of the validity of certain assumptions concerning the latter compounds. Thus, the assumption that the exocyclic nitrogens are planar with that plane bisecting the O-P-O angle and eclipsing the P=O bond was employed as a factor favoring the preferred axial P=O stereochemistry.

A preliminary report of the following structural determination was published (171) within a month of an independent report of the same research by other workers (172).

EXPERIMENTAL

A sample of the compound was kindly supplied by Dr. W. A. Zygmunt of Mead Johnson Research Center, Evansville, Indiana and colorless crystals were obtained by slow evaporation of an ether-heptane solution. Microscopic examination revealed that the crystals were acicular with sharply defined faces. A crystal was selected and mounted in a thin-walled Lindemann glass capillary under nitrogen atmosphere to avoid absorption of water. Preliminary Weissenberg and precession photographs exhibited no other symmetry than $\bar{1}$ and no systematic extinctions consistent with a triclinic space group. Successful refinement employing the space group $P\bar{1}$ indicated it to be the correct choice. The unit cell parameters are a = 8.65(1), b = 13.39(1), c = 6.01(1)Å, α = 96.3(1), β = 100.3(1) and γ = 106.7(1)° obtained by a least-squares fit to independent reflection angles whose centers were determined by left-right, top-bottom beam splitting of a previously aligned Hilger-Watts four-circle diffractometer (Mo - K_α radiation, λ = 0.7107 Å). Any error in the instrumental zero was eliminated by centering the reflection at both +2θ and -2θ. A density of 1.74 g/cm^3 was calculated for two molecules per unit cell.

Data were collected at room temperature utilizing a Hilger-Watts four-circle diffractometer equipped with a scintillation counter and using Zr-filtered Mo K_α radiation.

Within a 2θ sphere of 60° all data in each of four unique octants were recorded using the θ-2θ scan technique with a take-off angle of 8°. Background counts of one-half the aggregate time were taken before and after each scan. A total of 2799 reflections were measured in this way.

As a general check on electronic and crystal stability, the intensities of these standard reflections were measured periodically during data collection. Although these reflections did decrease slowly in intensity, it was felt to be quite acceptable and no correction was applied.

The standard deviations of the $|F_o|$'s were estimated by the procedure of Stout and Jensen (173). Of the 2799 reflections, 1198 had $F_o^2 < 3.0\sigma(F_o^2)$, and these were considered unobserved and were not used in refinement.

Phases were assigned by an iterative application of Sayre's equation and all fourteen non-hydrogen atoms of the molecule were apparent in the subsequent E synthesis. (The library of programs used are given in references 174-177.) These positions were then refined by full-matrix least-squares techniques with isotropic thermal parameters to a conventional discrepancy index ($R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$) of 0.242 and a weighted R factor of $\omega R = (\Sigma\omega(|F_o| - |F_c|)^2/\Sigma\omega|F_o|^2)^{1/2} = 0.320$ after three cycles, whereupon one atom due to a water of hydration was observed. After inclusion of this atom, four cycles produced a conventional R of 0.155 and a weighted R of

0.194. The scattering factors were those of Hanson et al. (178). A difference electron density map at this stage showed that all the non-hydrogen atoms had been accounted for, but some anisotropic motion, particularly of the heavier atoms, was quite evident. Accordingly, anisotropic refinement was begun and after four cycles the values of R and ωR of 0.087 and 0.118, respectively, were obtained. All hydrogen atoms were then located from a difference electron density map and after one cycle invariant in hydrogen positions and thermal parameters, a final R of 0.072 and ωR of 0.092 were obtained. A final electron density difference map showed no peaks higher than 0.3 $e/\mathring{A}^3$. A final statistical analysis of the F_o and F_c values as a function of the indices, the scattering angle, and the magnitude of F_o showed no unusual trends and suggests that the relative weighting scheme is a reasonable one.

RESULTS AND DISCUSSION

The final atomic positions for all thirty-two atoms are listed in Table 22, and the thermal parameters for all non-hydrogen atoms are given in Table 23 according to the numbering system illustrated in Figures 11 and 12. Table 24 lists the values of F_o and F_c for the 1601 reflections above background.

The ring exists in a chair conformation flattened at the phosphorus end by 18.5° from that of a perfect chair. Flattening at phosphorus has also been reported for all structural investigations of 1,3,2-dioxaphosphorinanes (33, 34, 38, 55, 63-65). The configuration at phosphorus being axial phosphoryl oxygen and equatorial substituent is the same in the solid state as the preferred solution geometry of the dimethylamino compound 51 described in Part I, and opposite to all reported solid state structures of 1,3,2-dioxaphosphorinanes. The equatorial substituent orientation is probably due at least in part to the sterically induced instability of the opposite phosphorus configuration (see Part I).

The atom N(1) is within experimental error of lying within the plane defined by C(2), C(4), and P(1) with the sum of the angles equal to 360.1 $\pm$ 0.6° (bond angles are listed in Table 25). Near planarity of nitrogens is common in solid state structures of amino-phosphorus compounds (128, 154, 179) where steric factors are absent (157). The phosphorus-nitrogen pi bonding implied by the planar geometry is also indicated in

Table 22. Final atomic positions

Atom	x/a	y/b	z/c
Cl(1)	-0.2882(6)	0.5995(1)	-0.021(1)
Cl(2)	0.1812(1)	1.1194(1)	0.2465(1)
P(1)	0.2582(1)	0.7914(1)	0.5376(4)
O(1)	0.3486(1)	0.8841(4)	0.7157(5)
O(2)	0.1501(1)	0.6951(4)	0.630(1)
O(3)	0.553(1)	0.8912(7)	0.1546(3)
N(1)	0.126(2)	0.8198(8)	0.3482(2)
N(2)	0.3673(1)	0.7379(7)	0.3963(8)
C(1)	-0.1579(3)	0.7027(7)	0.202(5)
C(2)	0.0144(3)	0.740(1)	0.1575(5)
C(3)	0.221(2)	0.9945(2)	0.2331(6)
C(4)	0.1078(1)	0.9271(5)	0.3625(9)
C(5)	0.230(1)	0.6232(1)	0.732(4)
C(6)	0.3036(3)	0.5741(6)	0.5538(4)
C(7)	0.4333(9)	0.6550(8)	0.4798(1)
H(1)	0.4375	0.7875	0.3281
H(2)	0.3411	1.0060	0.3092
H(3)	0.2187	0.9766	0.0781
H(4)	0.1562	0.9687	0.5312
H(5)	-0.0312	0.9062	0.2812
H(6)	-0.1562	0.6767	0.3281
H(7)	-0.1875	0.7656	0.2031
H(8)	0.0625	0.6875	0.1406
H(9)	0.0091	0.7701	0.0127
H(10)	0.1435	0.5647	0.7823
H(11)	0.3281	0.6719	0.8906
H(12)	0.2129	0.5355	0.4168
H(13)	0.3750	0.5312	0.6562
H(14)	0.4687	0.6328	0.2969
H(15)	0.5301	0.7109	0.6133
H(16)	0.4687	0.8750	0.0312
H(17)	0.5937	0.9531	0.1875

[a]The estimated standard deviations as given by the inverse least-squares matrix appear in parentheses and apply to the last digit in each case. No deviations were determined for hydrogen atomic positions which were not refined.

Table 23. Final thermal parameters[a]

Atom	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Cl(1)	0.02768(1)	0.006728(1)	0.048654(1)	-0.000125(4)	-0.007475(1)	0.002744(1)
Cl(2)	0.024573(4)	0.005228(4)	0.04889(1)	0.004438(3)	0.009050(8)	0.007231(3)
P(1)	0.015363(4)	0.004344(2)	0.021181(5)	0.003267(1)	0.005241(2)	0.003094(1)
O(1)	0.01975(2)	0.005948(7)	0.02734(4)	0.003700(6)	-0.00053(5)	0.001198(7)
O(2)	0.020429(7)	0.006486(4)	0.035183(3)	0.004644(7)	0.01328(2)	0.005565(1)
O(3)	0.025897(3)	0.006897(8)	0.03218(1)	0.003782(1)	0.009626(3)	0.005197(7)
N(1)	0.01393(1)	0.003968(1)	0.02904(1)	0.002835(2)	0.003219(5)	0.000044(3)
N(2)	0.015743(5)	0.005903(6)	0.028151(8)	0.004663(1)	0.006402(1)	0.00330(1)
C(1)	0.01730(5)	0.00663(3)	0.03271(1)	-0.00043(1)	0.00318(2)	0.001984(1)
C(2)	0.01554(4)	0.00593(1)	0.03218(3)	0.00361(3)	0.00281(2)	0.00031(3)
C(3)	0.01948(2)	0.004286(8)	0.04295(4)	0.004637(5)	0.01334(1)	0.00740(1)
C(4)	0.01806(5)	0.003977(1)	0.03555(1)	0.004543(5)	0.01217(4)	0.006148(2)
C(5)	0.03232(5)	0.00761(1)	0.03966(5)	0.00919(3)	0.01434(5)	0.01135(3)
C(6)	0.022334(7)	0.005450(6)	0.05109(4)	0.004788(3)	0.01090(1)	0.06871(2)
C(7)	0.01828(3)	0.006170(3)	0.05088(1)	0.005884(5)	0.00951(3)	0.008207(8)

[a]The estimated standard deviations as given by the inverse least-squares matrix appear in parentheses and apply to the last digit in each case. Hydrogen atom parameters do not appear in this table because they were not allowed to vary. The form of the anisotropic temperature factor is $\exp(-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{33}kl))$.

Table 24. Observed and calculated F's for cyclophosphamide (206)

Figure 11. Computer drawing of cyclophosphamide excluding hydrogen atoms

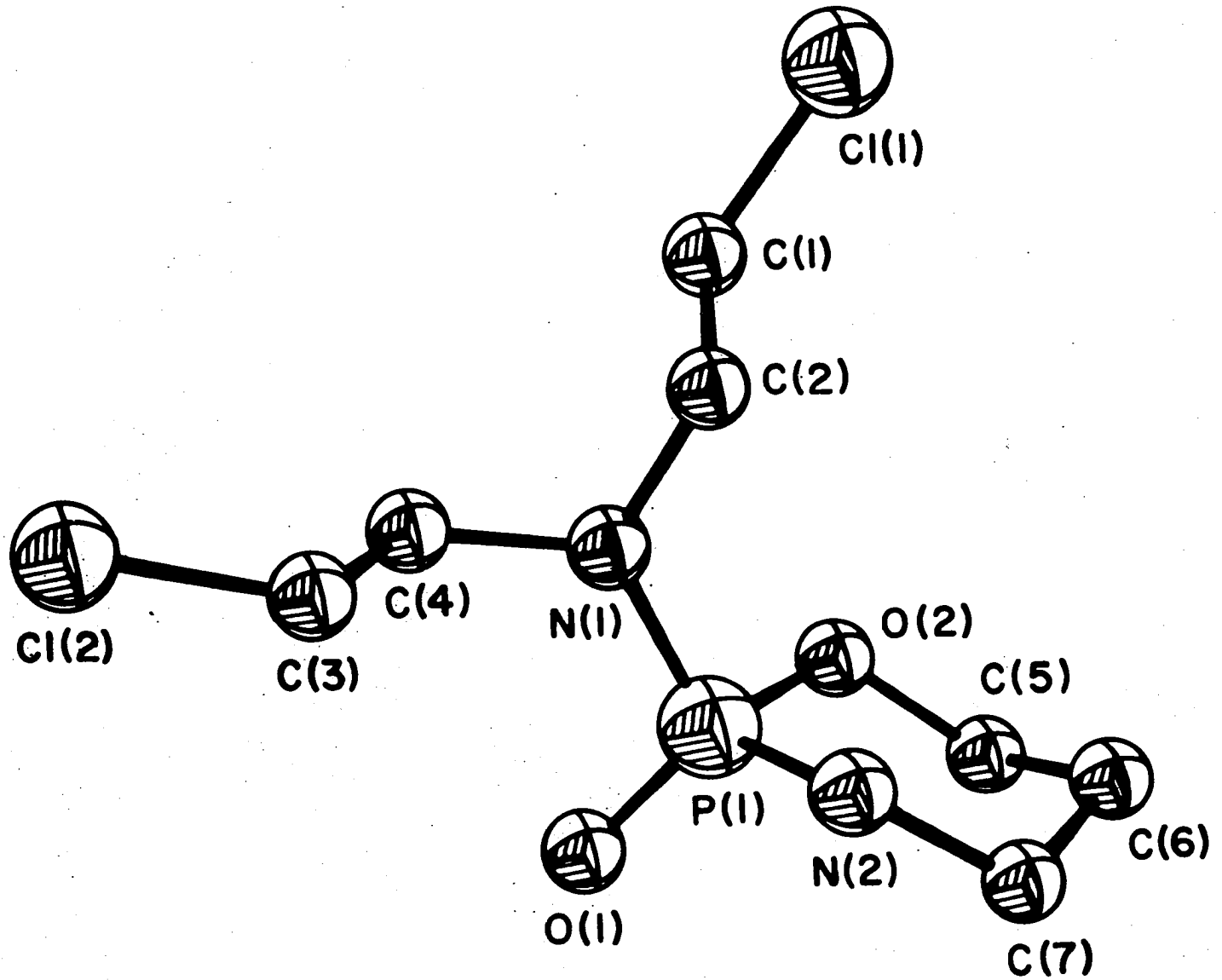

Cl(1)
C(1)
C(2)
Cl(2)
C(3)
C(4)
N(1)
O(2)
C(5)
P(1)
N(2)
C(6)
O(1)
C(7)

Figure 12. Drawing of cyclophosphamide including hydrogen atoms

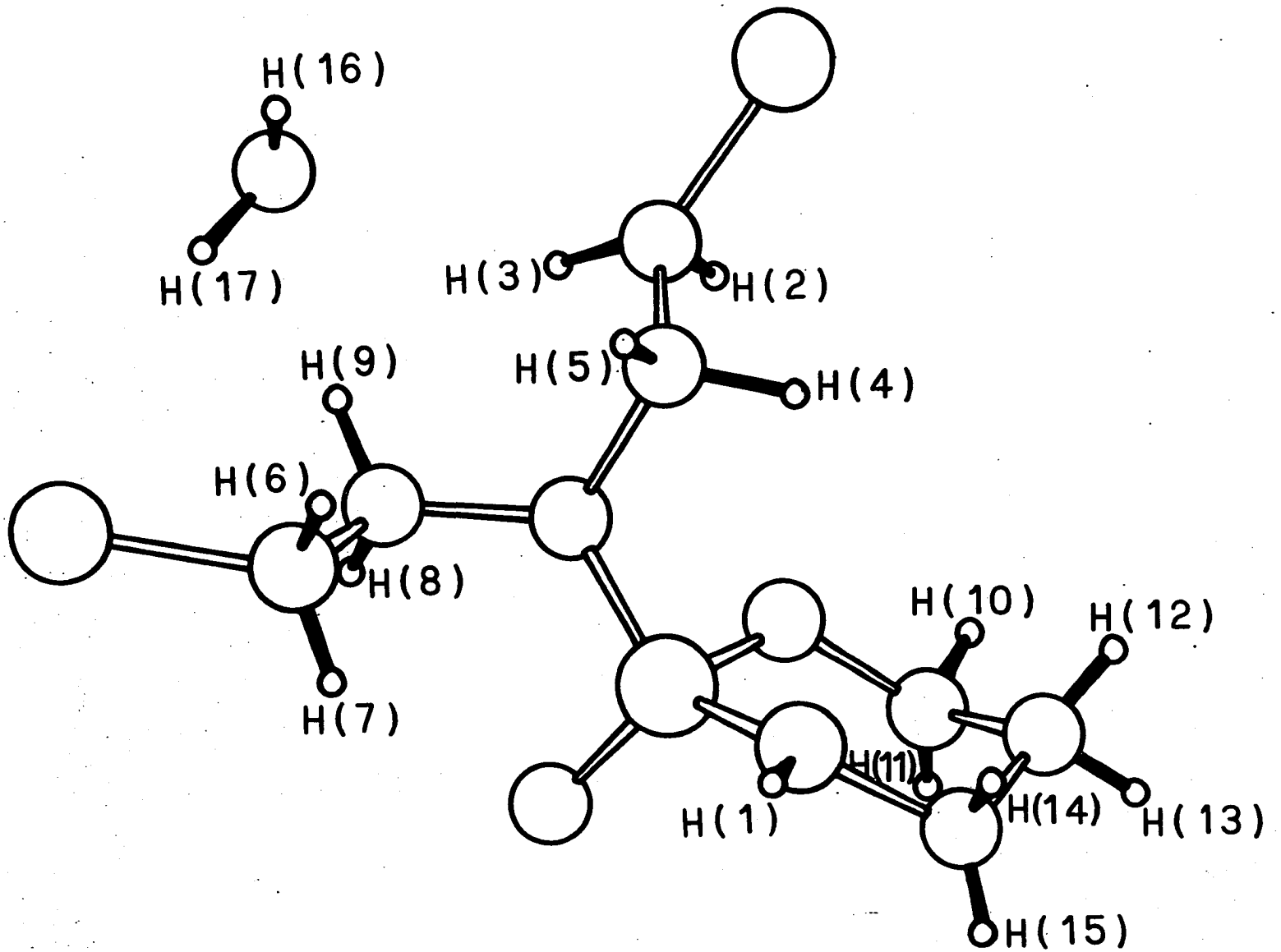

H(16)
H(17)
H(3)
H(2)
H(9)
H(5)
H(4)
H(6)
H(8)
H(7)
H(10)
H(12)
H(11)
H(1)
H(14)
H(13)
H(15)

Table 25. Bond angles[a]

Atoms	Angle, degrees	Atoms	Angle, degrees
Cl(1)-C(1)-H(2)	106.6(5)	P(1)-N(2)-C(7)	121.5(4)
Cl(1)-C(1)-H(3)	112.7(5)	P(1)-N(2)-H(1)	112.1(4)
Cl(1)-C(1)-C(2)	110.3(5)	H(1)-N(2)-C(7)	115.8(5)
H(2)-C(1)-H(3)	115.6(7)		
H(2)-C(1)-C(2)	110.6(6)	N(1)-P(1)-O(1)	110.4(2)
H(3)-C(1)-C(2)	101.0(5)	N(1)-P(1)-O(2)	104.4(2)
C(1)-C(2)-H(4)	114.0(6)	N(1)-P(1)-N(2)	106.7(2)
C(1)-C(2)-H(5)	108.9(5)	O(1)-P(1)-O(2)	113.8(2)
H(4)-C(2)-H(5)	107.1(6)	O(1)-P(1)-N(2)	117.3(3)
C(1)-C(2)-N(1)	110.6(5)	O(2)-P(1)-N(2)	103.1(2)
H(4)-C(2)-N(1)	105.9(5)		
H(5)-C(2)-N(1)	110.2(5)	O(2)-C(5)-H(10)	109.6(6)
Cl(2)-C(3)-H(6)	109.8(4)	O(2)-C(5)-H(11)	107.2(5)
Cl(2)-C(3)-H(7)	102.7(4)	O(2)-C(5)-C(6)	108.9(5)
Cl(2)-C(3)-C(4)	107.2(4)	H(10)-C(5)-C(6)	109.8(6)
H(6)-C(3)-H(7)	102.6(5)	H(11)-C(5)-C(6)	112.4(6)
H(6)-C(3)-C(4)	109.6(5)	C(5)-C(6)-H(12)	108.7(6)
H(7)-C(3)-C(4)	124.3(6)	C(5)-C(6)-H(13)	102.4(6)
C(3)-C(4)-H(8)	101.4(5)	C(5)-C(6)-C(7)	112.1(6)
C(3)-C(4)-H(9)	114.1(5)	H(12)-C(6)-H(13)	120.9(6)
H(8)-C(4)-H(9)	120.3(5)	H(12)-C(6)-C(7)	109.1(6)
C(3)-C(4)-N(1)	110.7(4)	H(13)-C(6)-C(7)	103.5(6)
H(8)-C(4)-N(1)	110.0(5)	C(6)-C(7)-H(14)	118.6(6)
H(9)-C(4)-N(1)	100.5(4)	C(6)-C(7)-H(15)	117.2(6)
		C(6)-C(7)-N(2)	110.5(5)
C(4)-N(1)-C(2)	116.3(5)	H(14)-C(7)-H(15)	117.3(5)
C(4)-N(1)-P(1)	122.1(4)	H(14)-C(7)-N(2)	92.1(4)
C(2)-N(1)-P(1)	121.7(4)	H(15)-C(7)-N(2)	93.4(5)
		H(16)-O(3)-H(17)	109.6(6)
P(1)-O(2)-C(5)	118.8(4)		

[a]The estimated standard deviations as given by the inverse least-squares matrix appear in parentheses and apply to the last significant digit in each case. Angles involving hydrogen are probably of dubious value since atomic positions of those atoms were not allowed to vary.

the bond length (Table 26) of 1.623 Å which is substantially shorter than the generally accepted single bond distance of 1.769 Å in $Na[H_3NPO_3]$ (180). Shortening of the P(1)-N(2) bond is also evident (1.634 Å) whereas the remaining bond lengths are within accepted values (181). The dihedral angle of the C(2)-N(1)-C(4) plane to the N(2)-P(1)-O(2) plane, 92.1 ± 0.5°, is 2.1° from bisecting the N(2)-P(1)-O(2) bond angle. This orientation of the planar nigrogen has been found for Me_2NPF_2 (151, 152), Me_2NPCl_2 (153), and H_2NPF_2 (154) and the observed phosphorus configuration of 206 is consistent with these results. If the phosphorus atom were to be in the opposite configuration (axial substituent and equatorial phosphoryl oxygen) with the plane of the nitrogen group bisecting the O(2)-P(1)-N(2) angle, there would be severe steric interactions of the axial hydrogen atoms H(11) and H(15) with hydrogen atoms on the two β-chloroethyl groups. One means of alleviating the interaction would be formation of an unstable half-chair as observed for 179 (33, 34) while another alternative would be a 90° rotation about the P(1)-N(1) bond resulting in what is an apparently unstable nitrogen orientation. (See the Results and Discussion section of Part I for a discussion of these conformations.) By adopting the axial phosphoryl oxygen-equatorial substituent orientation, both the stable chair conformation and the stable nitrogen orientation are preserved. However, since the preferred phosphorus

Table 26. Bond lengths[a]

Atoms	Distance, Å	Atoms	Distance, Å
Cl(1)-C(1)	1.769(6)	N(1)-C(4)	1.483(6)
Cl(2)-C(3)	1.798(5)	N(2)-C(7)	1.481(7)
P(1)-O(1)	1.466(4)	C(1)-C(2)	1.512(8)
P(1)-O(2)	1.580(4)	C(3)-C(4)	1.513(7)
P(1)-N(1)	1.623(5)	C(5)-C(6)	1.52(1)
P(1)-N(2)	1.634(5)	C(6)-C(7)	1.488(8)
O(2)-C(5)	1.460(7)	O(1)-H(16)	1.979(3)[b]
N(1)-C(2)	1.457(7)	O(3)-H(1)	2.028(4)[b]

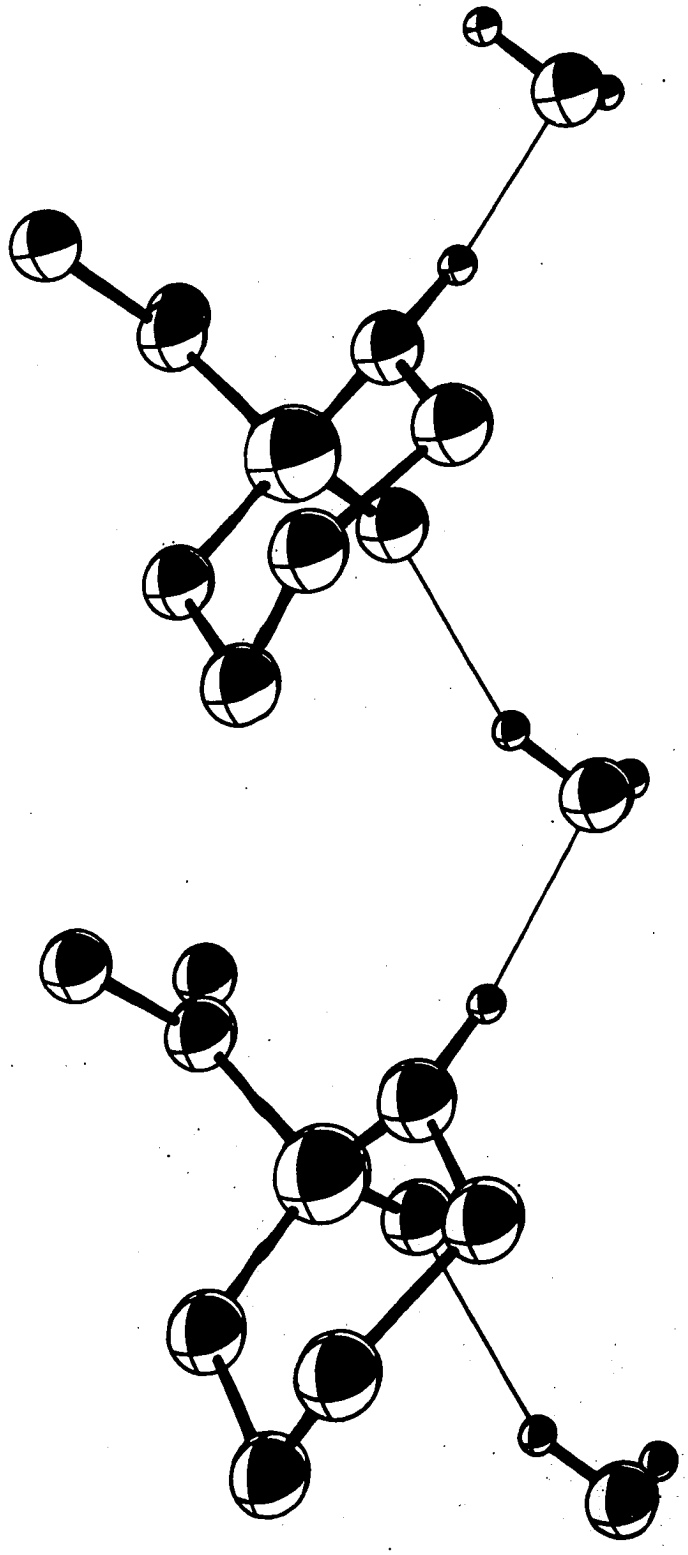
[a]The estimated standard deviations as given by the least-squares matrix appear in parentheses and apply to the last significant digit in each case. Bond distances involving hydrogen, being of questionable value since the positions of these atoms were not allowed to vary, have been omitted from the table with the exception of the hydrogen-bonds labelled by b.

[b]Hydrogen bonds.

configuration of 1,3,2-azaoxaphosphorinanes have not been reported, that of 206 may in fact represent the stable configuration for any phosphorus substituent. That this is possible is indicated by evidence, albeit tenuous, for preferred equatorial substituent geometries in 1,3,2-diazaphosphorinanes (127) (see Introduction to Part I).

Intermolecular hydrogen bonding is depicted in Figure 13 where the chloromethyl moieties of the β-chloroethyl groups

Figure 13. Computer drawing of the hydrogen bonding of the water of hydration to cyclophosphamide. The chloromethyl groups of the bis-(β-chloroethyl) groups and the hydrogen atoms of cyclophosphamide not involved in hydrogen bonding are omitted for clarity

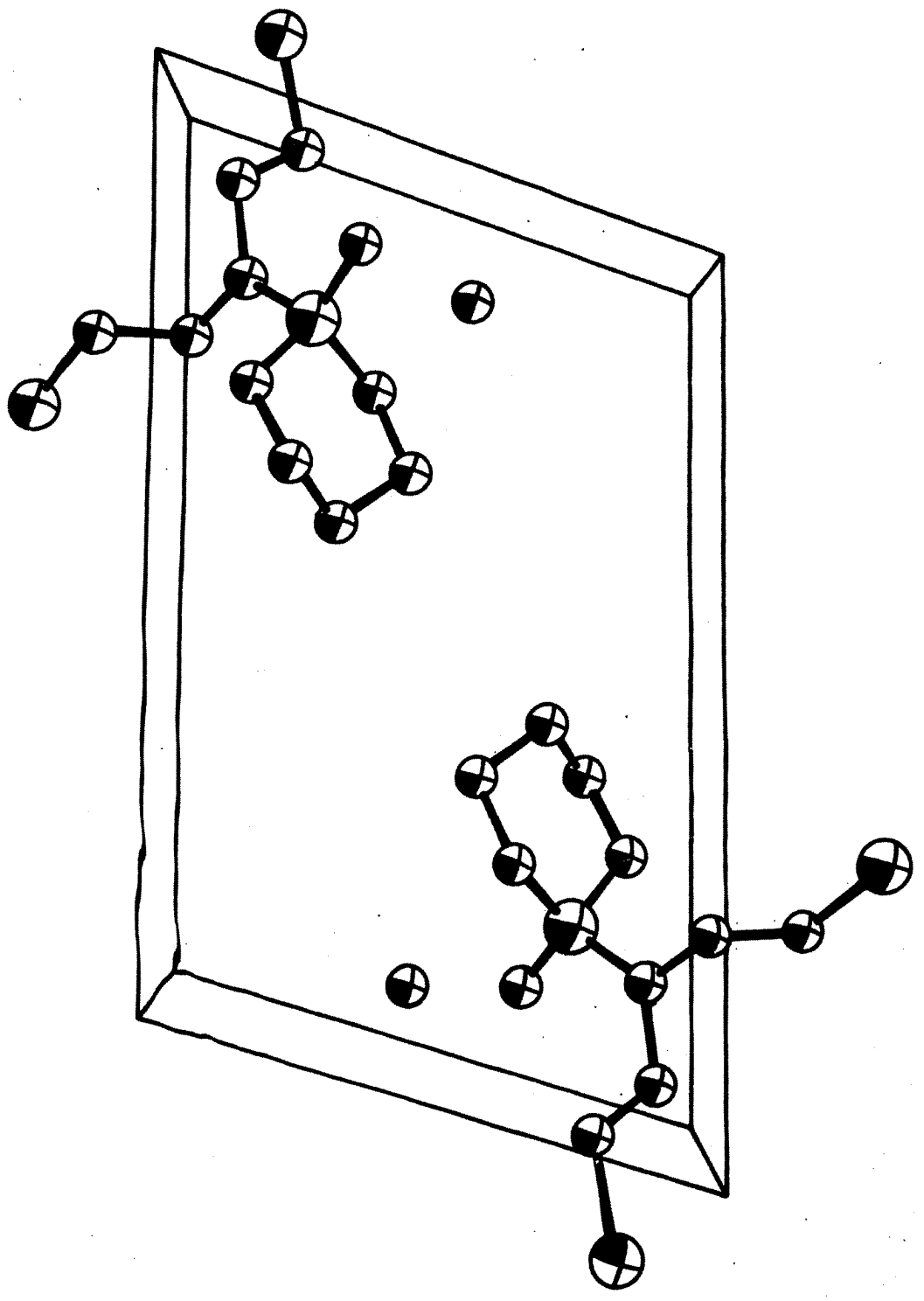


have been omitted for clarity. The H(1)-O(6) and H(31)-O(4) bonds are 1.979 ± 0.003 and 2.028 ± 0.004 Å, respectively, (Table 26) where one water molecule spans two molecules of cyclophosphamide.

Figure 14 represents a unit cell containing two molecules of cyclophosphamide and two of water. There are no unusually small intermolecular or intramolecular distances other than those incurred in the hydrogen bonding described above.

The structural determination indicates that the assumptions of a planar exocyclic nitrogen and the proclivity of that plane to bisect the O-P-O ring bond angle in phosphoramidates 51, 160a and b, and 175a and b are valid.

Figure 14. Computer drawing of unit cell of cyclophosphamide including two water molecules. Hydrogen atoms are omitted



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