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Synthesis and structure of derivatives of P(OCH2CH2)3N and structure-toxicity relationships of some bicyclic phosphorus esters

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SYNTHESIS AND STRUCTURE OF DERIVATIVES OF $P(OCH_2CH_2)_3N$ AND STRUCTURE-TOXICITY RELATIONSHIPS OF SOME BICYCLIC PHOSPHORUS ESTERS.

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Synthesis and structure of derivatives of $P(OCH_2CH_2)_3N$ and structure-toxicity relationships of some bicyclic phosphorus esters

by

Dean Stanford Milbrath

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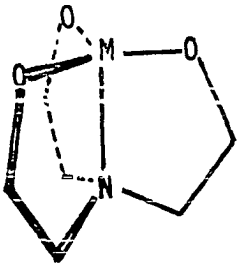
PART I: SYNTHESIS AND CHARACTERIZATION OF $P(OCH_2CH_2)_3N$ AND ITS DERIVATIVES

INTRODUCTION

The report of the synthesis of triethanol amine borate, $B(OCH_2CH_2)_3N$, 1, by Rojahn[1] in 1933 instigated the study of a unique class of caged compounds of the general formula $M(OCH_2CH_2)_3N$ where M = boron,[1-11] silicon,[12-35] tin,[36-40] germanium,[41-43] aluminum,[35,44-47] vanadium,[48-50] samarium,[51] bismuth,[52] titanium,[35,49,53-56] zirconium,[55] hafnium,[56] iron,[57] molybdenum[58,59] and zinc.[60] Tables 1, 2 and 3 list the known compounds for these elements.

The unique feature common to these systems is an internal N-M transannular coordinate bond which appears to account for an array of extraordinary properties. The



three five-member rings sharing a common side account for the frequent reference to these molecules as triptych[2] structures. Voronkov,[16] however, suggested that all triptych compounds could be unified under the name "atrane" with an appropriate prefix for the various bridgehead atoms (e.g., M=B, boratrane; M=Al, alumatrane; and M=SiH, silatrane). Comparison of the lengths of the Voronkov and IUPAC names

Table 1. Boratranes (1-bora-5-aza-2,8,9-trioxatricyclo-[3.3.3.0]undecanes

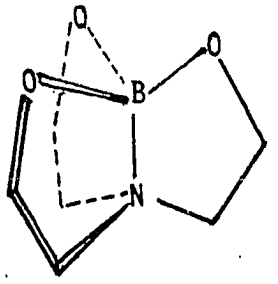
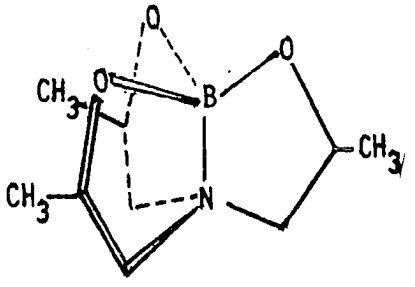
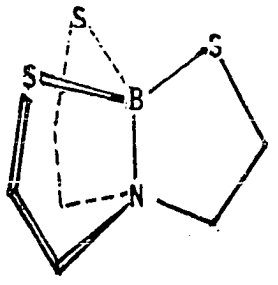
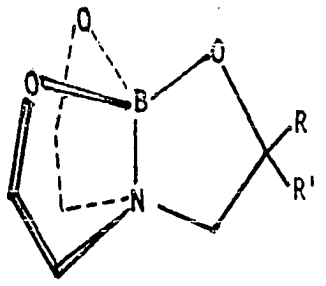
Compound				Reference
1				1-4
2				5,11,14
3				6
4		R=H	R'=CH_3	7,14

Table 1. (Continued)

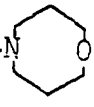
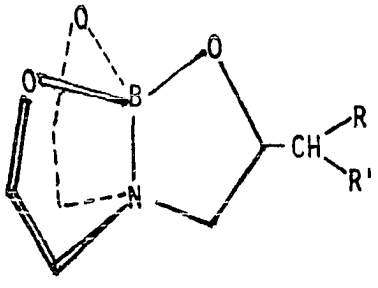
Compound			Reference
5	H	C_2H_5	7
6	H	$CH{=}CH_2$	7
7	H	C_6H_5	7
8	CH_3	CH_3	7
9	H	CH_2- 	7
10	H	CH_2- 	7
11		R=H	R'=OCH_3	7

Table 1. (Continued)

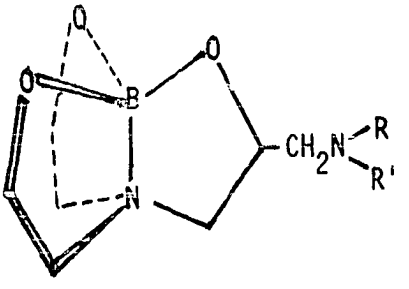
Compound			Reference
12	H	OC_2H_5	7
13	H	OC_6H_5	7,11
14	H	$OCH_2C_6H_5$	7
15	H	$OCH_2CH=CH_2$	7
16	H	$O_2C(CH_2)_{16}CH_3$	11
17	OC_2H_5	OC_2H_5	7
18		R=CH_3	R'=CH_3	7

Table 1. (Continued)

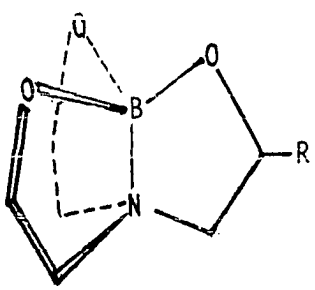
Compound			Reference
19	C_2H_5	C_2H_5	7
20	$n\text{-}C_3H_7$	$n\text{-}C_3H_7$	7
21	$n\text{-}C_4H_9$	$n\text{-}C_4H_9$	7
22	CH_3	C_6H_5	7
23		$R=CH_2Cl$	7
24	CH_2OH		7
25	CH_2NH_2		7

Table 1. (Continued)

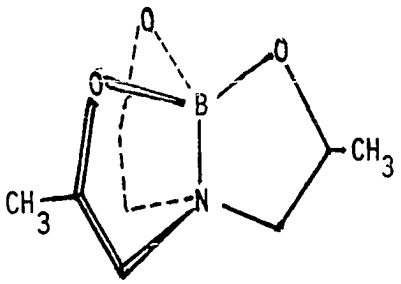
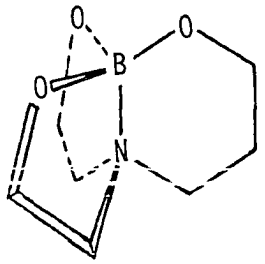
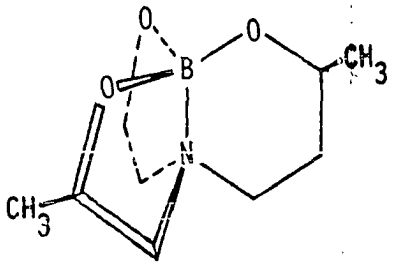
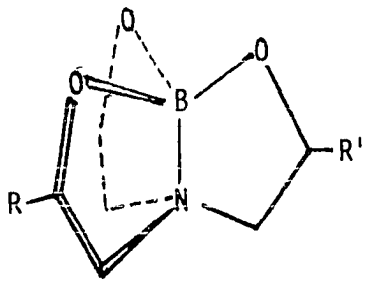
Compound		Reference
26	CH_2CN	7
27	$CH_2NHCO_2CH_2C_6H_5$	7
28		8,14
29		8
30		8
31	 R=$CH_2OC_6H_5$ R'=CH_3	11

Table 1. (Continued)

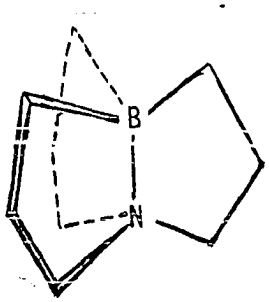
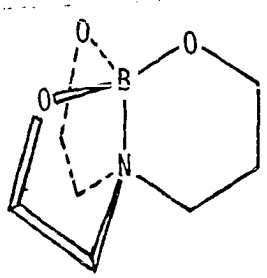
Compound			Reference
32	CH_3	C_6H_5	11
33	C_6H_5	CH_3	11
34	H	$CH_2O_2C(CH_2)_{16}CH_3$	11
35	CH_3	$CH_2O_2C(CH_2)_{16}CH_3$	11
36			9
37			10

Table 1. (Continued)

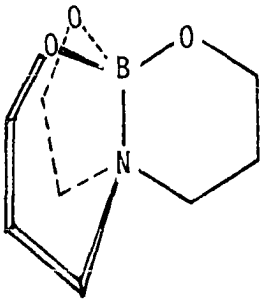
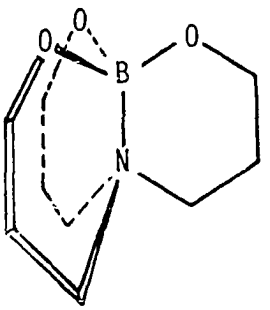
Compound	Reference
38 	10
39 	10

Table 2. Silatranes (1-sila-5-aza-2,8,9-trioxatricyclo-[3.3.3.0]undecanes)

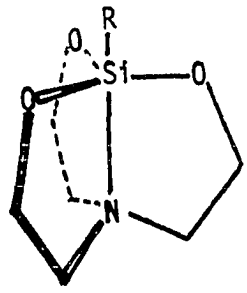
Compound			Reference
40		R=H	13-16
41		CH_3	12,13,16
42		C_2H_5	16,25
43		i-C_3H_7	16
44		n-C_5H_{11}	25
45		n-$C_{18}H_{37}$	13
46		C_6H_5	12,13,16,24
47		$CH_2C_6H_5$	22
48		$\begin{matrix} CHC_6H_5 \\ \vert \\ CH_3 \end{matrix}$	13

Table 2. (Continued)

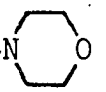
Compound		Reference
49	F	15
50	$CH_2=CH_2$	13,16,25
51	CH_2CH_2CN	24
52	CH_2Cl	20
53	$CH_2N(C_2H_5)_2$	19
54	$(CH_2)_3Cl$	20
55	$(CH_2)_3NH_2$	18,25
56	$(CH_2)_3N(C_2H_5)_2$	19
57	$(CH_2)_2NHCH_2CH_2NH_2$	18
58		19
59		19

Table 2. (Continued)

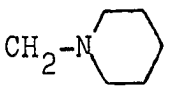
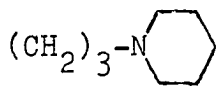
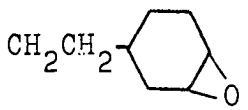
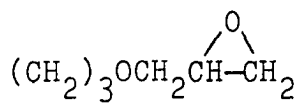
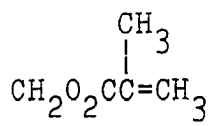
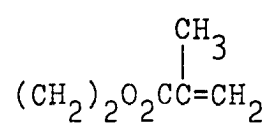
Compound		Reference
60		19
61		19
62	$CH_2SCH_2CH_2OH$	21
63		24
64		24
65	$CH_2O_2CCH=CH_2$	17
66		17
67	$(CH_2)_2O_2CCH=CH_2$	17
68		17
69	$(CH_2)_3O_2CCH=CH_2$	17

Table 2. (Continued)

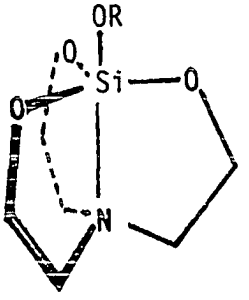
Compound		Reference
70	$(CH_2)_3O_2CC(CH_3)=CH_2$	17,24
71	$(CH_2)_4O_2CCH=CH_2$	17
72	$(CH_2)_4O_2CC(CH_3)=CH_2$	
73	$m\text{-}C_6H_4NO_2$	15
74	$m\text{-}C_6H_4Cl$	16
75	$p\text{-}C_6H_4Cl$	23
76	$CH_2\text{-}p\text{-}C_6H_4F$	22
77	$CH_2\text{-}m\text{-}C_6H_4F$	22
78	 R=H	15

Table 2. (Continued)

Compound			Reference
79		CH_3	16,27
80	C_2H_5		12,13,16,27,29
81	n-C_3H_7		16,27
82	i-C_3H_7		16,27
83	n-C_4H_9		16,27
84	s-C_4H_9		16,27
85	i-C_4H_9		16,27
86	t-C_4H_9		16,27
87	n-C_5H_{11}		16,27
88	i-C_5H_{11}		16,27
89	neo-C_5H_{11}		16,27

Table 2. (Continued)

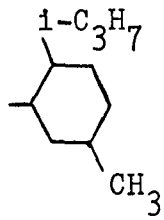
Compound		Reference
90	$n\text{-}C_6H_{13}$	16,27
91	$n\text{-}C_{14}H_{39}$	16,27
92	C_6H_{11}	16,27
93		13
94	C_6H_5	16,28
95	C_6F_5	26
96	$p\text{-}CH_3OC_6H_4$	26
97	$p\text{-}t\text{-}BuC_6H_4$	16,28
98	$p\text{-}ClC_6H_4$	16,28
99	$o\text{-}CH_3C_6H_4$	16,28

Table 2. (Continued)

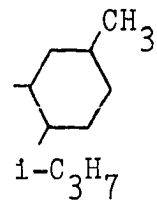
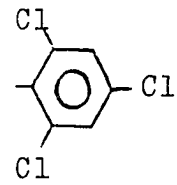
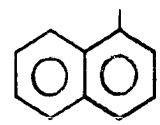
Compound		Reference
100	m-$CH_3C_6H_4$	16,28
101	p-$CH_3C_6H_4$	16,28
102	$CH_2C_6H_5$	16,27
103	o-$NO_2C_6H_4$	16,28
104	m-$NO_2C_6H_4$	16,28
105	p-$NO_2C_6H_4$	16,28
106		16,28
107		16,28
108		16,28

Table 2. (Continued)

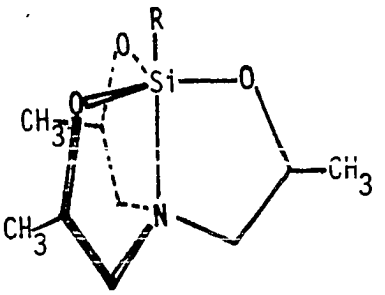
Compound			Reference
109		$C(O)CH_3$	15
110		$C(O)C_6H_5$	15
111		$Si(CH_3)_3$	15
112		$Si(C_6H_5)_3$	15
113		$Si(OCH_2CH_2)_3N$	15
114		R=H	14,15
115		CH_3	13
116		C_6H_5	13,16,22
117		Cl	15
118		Br	15

Table 2. (Continued)

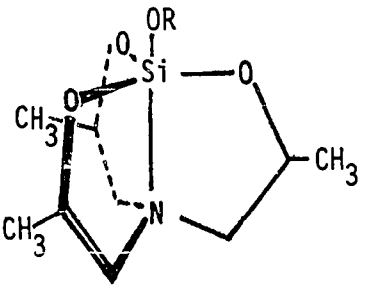
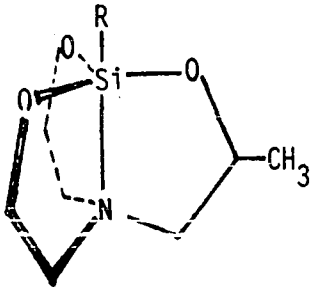
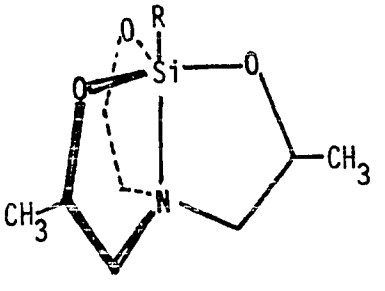
Compound		Reference
119	F	15
120	 R=C_2H_5	15
121	$Si(OCHCH_2)_3N$ (CH$_3$ on CH)	15,30
122	 R=H	14,31
123	C_6H_5	15
124	 R=H	14

Table 2. (Continued)

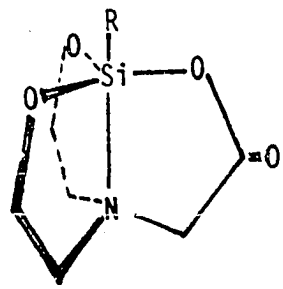
Compound			Reference
125		C_6H_5	15
126		R=CH_3	32
127		C_2H_5	32
128		n-C_3H_7	32
129		n-C_4H_9	32
130		$CH=CH_2$	32
131		C_6H_5	32
132		m-ClC_6H_4	32
133		p-ClC_6H_4	32
134		p-FC_6H_4	32

Table 2. (Continued)

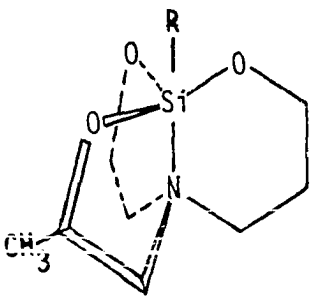
Compound		Reference
135	$m\text{-}CH_3C_6H_4$	32
136	$m\text{-}CF_3C_6H_4$	32
137	$CH_2C_6H_5$	32
138	$CH_2\text{-}p\text{-}ClC_6H_4$	32
139		$R=CH_3$ 33
140		$CH=CH_2$ 33
141		C_6H_5 33
142		$m\text{-}ClC_6H_4$ 33
143		$p\text{-}ClC_6H_4$ 33
144		$p\text{-}BrC_6H_4$ 33

Table 2. (Continued)

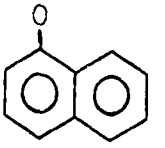
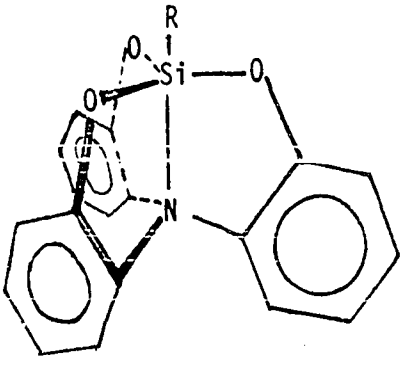
Compound		Reference
145	OCH_3	33
146	OC_2H_5	33
147	OC_6H_5	33
148		33
149		34
150	$CH=CH_2$	34
151	Cl	34
152	C_6H_5	34
153	OCH_3	34

Table 2. (Continued)

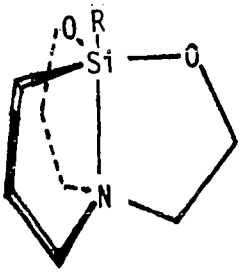
Compound			Reference
154		$OC(O)_2CH_3$	34
155		$R=C_6H_5$	35

Table 3. Metalatranes (1-M-5-aza-2,8,9-trioxatricyclo-[3.3.3.0]undecanes

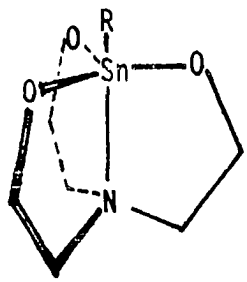
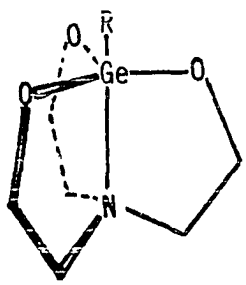
Compound			Reference
156		$R=CH_3$	37,39,40
157		C_2H_5	37,39,40
158		$n\text{-}C_4H_9$	37,39,40
159		C_6H_5	37,39,40
160		OCH_3	36
161		$O\text{-}i\text{-}C_3H_7$	38
162		$O\text{-}n\text{-}C_4H_9$	38
163		$R=CH_3$	41,42
164		C_2H_5	38,41,42

Table 3. (Continued)

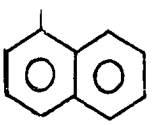
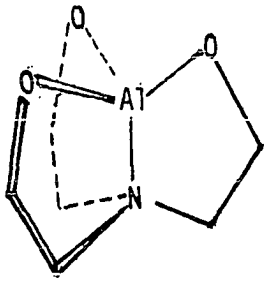
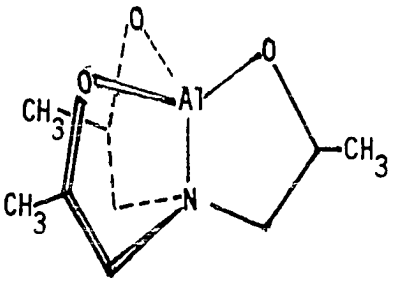
Compound		Reference
165	C_6H_5	42
166		42
167	OC_2H_5	43
168	O-n-C_4H_9	43
169	O-s-C_4H_9	43
170	O-t-C_4H_9	43
171		44,45,46,47
172		47

Table 3. (Continued)

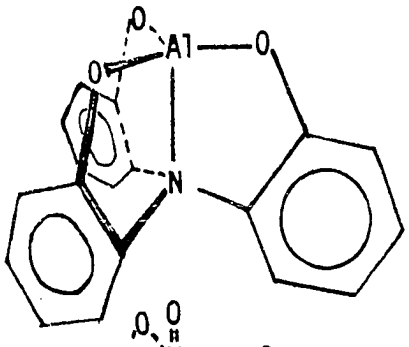
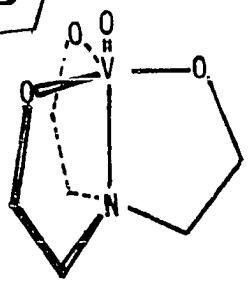
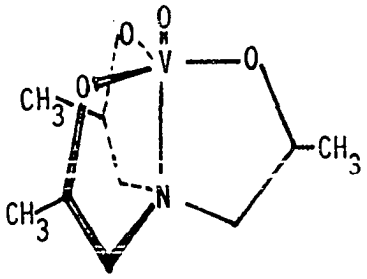
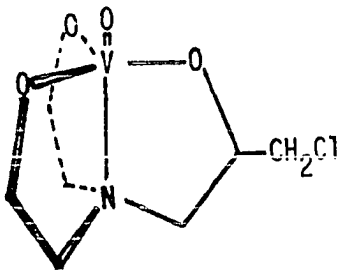
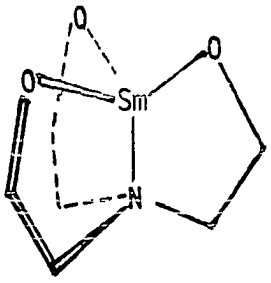
Compound		Reference
173		34
174		48,49,50
175		50
176		50
177		51

Table 3. (Continued)

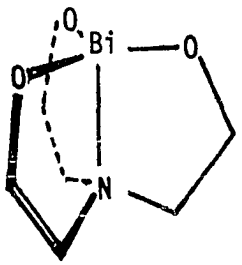
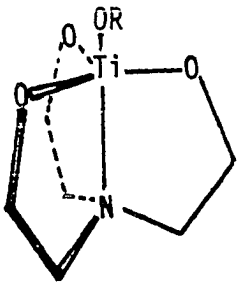
Compound			Reference
178			52
179		$R=C_6H_5$	53
180		$o\text{-}CH_3C_6H_4$	53
181		$m\text{-}CH_3C_6H_4$	49,53
182		$o\text{-}CH_3OC_6H_4$	49,53
183		$p\text{-}i\text{-}C_4H_7C_6H_4$	49,53
184		$p\text{-}t\text{-}C_4H_9C_6H_4$	49,53
185		$p\text{-}ClC_6H_4$	49,53

Table 3. (Continued)

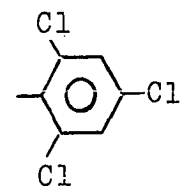
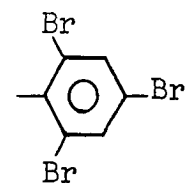
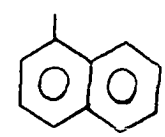
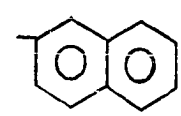
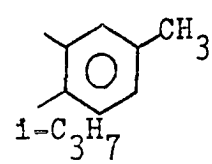
Compound		Reference
186	m-$NO_2C_6H_4$	49,53
187	p-$NO_2C_6H_4$	49,53
188		49,53
189		49,53
190		49,53
191		49,53
192		53

Table 3. (Continued)

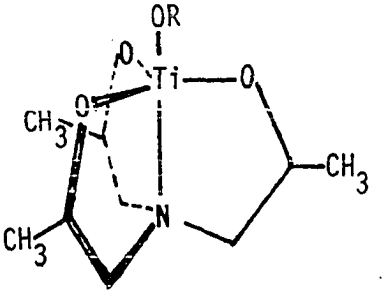
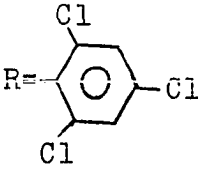
Compound		Reference
193	$Si(C_6H_5)_3$	55,56
194	$Si(CH_2C_6H_5)_3$	55,56
195	$Si(n\text{-}C_6H_{13})_3$	56
196	$Si(C_6H_5)_2CH_3$	55,56
197	$Sn(C_6H_5)_3$	54,56
198	$Sn(n\text{-}C_4H_9)_3$	54,56
199	$Sn(n\text{-}C_4H_9)_2$i-Pr	56
200		 53

Table 3. (Continued)

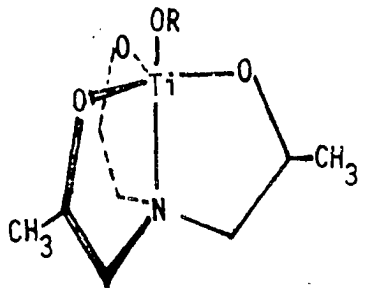
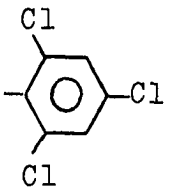
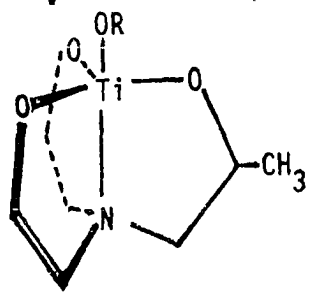
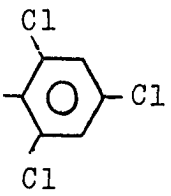
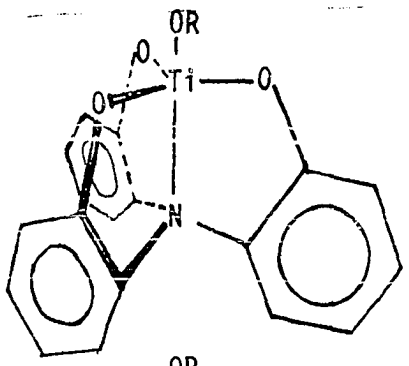
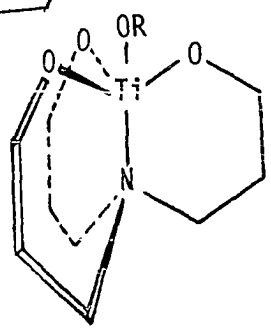
Compound		Reference
201	 R = 	53
202	 R = 	53
203	 R = i-C_3H_7	34
204	 R = $Sn(C_6H_5)_3$	56
205	$Si(CH_2C_6H_5)_3$	56

Table 3. (Continued)

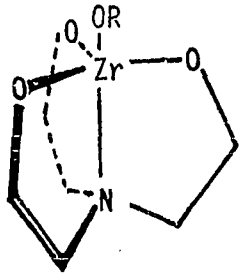
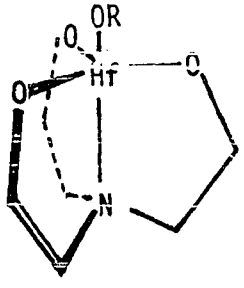
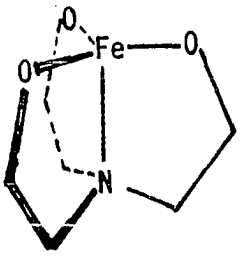
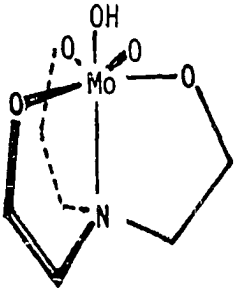
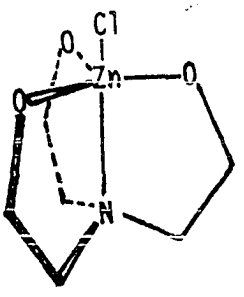
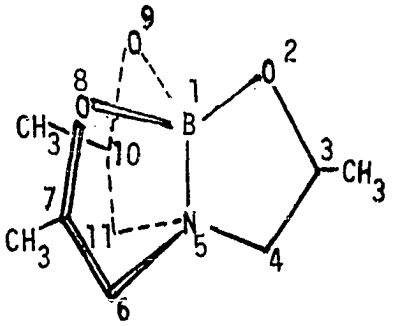
Compound		Reference
206	 R = $Sn(C_6H_5)_3$	56
207	$Si(C_6H_5)_3$	56
208	 R = $Sn(C_6H_5)_3$	56
209	$Si(C_6H_5)_3$	56

Table 3. (Continued)

Compound		Reference
210		57
211		58,59
212		60

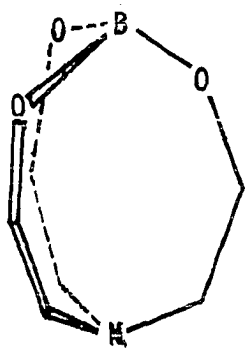
for 2 (3,7,10-trimethylboratrane versus 3,7,10-trimethyl-1-bora-5-aza-2,8,9-trioxatricyclo[3.3.3.0]undecane) points up an obvious advantage to the Voronkov system. For the



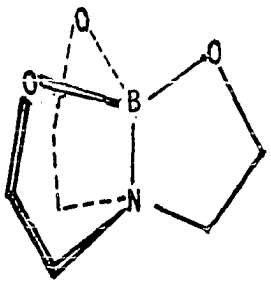
2

remainder of this dissertation the "atrane" terminology will be used.

Boratranes[1,2] are probably the most studied atranes and the known derivatives are listed in Table 1. The triptych structure was favored by Brown and Fletcher[2] over the bicyclic one because of the low chemical reactivity of 1. Rates of reaction for quaternization of nitrogen by methyl



Bicyclic



Triptych

iodide and protonation of nitrogen by strong acids[2] compared with the nitrogen of triethanol amine, tripropylamine, and

quinuclidine ($N(C_2H_4)_3CH$) showed that the nitrogen lone pair of 1 was not readily available.[2] It was also found that 1 and 2 were orders of magnitude more stable to hydrolysis than acyclic alkyl borates $B(OR)_3$.[61-64] This evidence was taken to be consistent with a triptych structure.

The lack of any examples of amine adducts of alkyl borates[9] raised some objections to this conclusion. The B-N transannular bond required by the tricyclic structure would not only involve such an adduct but also a rehybridization and subsequent loss of $p\pi$-$p\pi$ overlap of oxygen lone pairs with an empty p-orbital of boron. These considerations favored a bicyclic structure.

The equilibrium established in water solution for these two geometries reported by Lucchesi and DeFord[65] would have allowed the rationalization of the low chemical reactivity of 1 and 2. However, the assumption made by these authors that a mixture of triethanol amine and boric acid in water quantitatively forms boratrane is faulty. Experiments with a mixture of these materials has shown no infrared band characteristic of νB-N (1090 cm^{-1}) in 1.[9] Moreover, boratrane itself would have hydrolyzed[61] to these materials in the time allowed in their experiment.

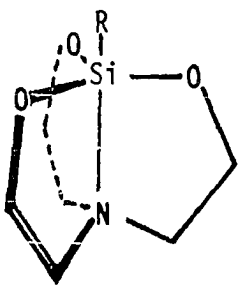
The measured dipole moment for 1 and 2 (8.8 and 6.9 Debye, respectively) is much larger than that calculated[66] using known bond moments and a bicyclic geometry. The

triptych framework with B-N and O-B bond moments aligned along the molecular axis fits this data better than the bicyclic structure.

Any remaining doubts about 1 and 2 having internal B-N coordination and a triptych structure were dismissed by the five reported crystal structure determinations.[67-71] Values of the B-N bond length range from 1.65 - 1.69 Å which is slightly greater than the sum of the covalent radii (1.65 Å[72]) and both nitrogen and boron are surrounded by a distorted tetrahedron of atoms.

This triptych geometry appears to be the major factor contributing to the stability of boratranes as evidenced by their ready formation, which in some cases is exothermic,[3] and the formation of a weak internal amine-borate adduct. This rather rigid geometry presents a steric barrier to electrophilic reaction at nitrogen and nucleophilic attack at boron owing to the presence of a B-N interaction. The steric barrier arises from the configuration of the NCH_2 protons blocking access to nitrogen. In contrast, hydrolysis of the tetrahedral borate moiety is inhibited compared to the planar boron geometry in $B(OR)_3$ by virtue of boron's four-coordination. The B-N interaction further protects boratrane from reaction by partially filling the empty p-orbital of boron and raising the ionization energy of the nitrogen lone pair.[73]

The silatranes (M=Si-R) listed in Table 2 have been extensively studied because of the unusual pentacoordinate stereochemistry of silicon. Intermediates in many organo-



silicon reactions are thought to be pentacoordinate,[74] but none are stable enough to isolate. Silatranes by contrast are quite stable, melting in the range 100 to 350°,[15,16] and they can be recovered from acidic aqueous solution.[15]

Frye et al.[15] noted that the νSiH band in the infrared spectrum of 40 was shifted to a lower frequency than that expected for an organosilicon compound with an $HSiO_3$ grouping, indicating an increase in the electron density on silicon. Voronkov[16] found that ^1H nmr chemical shifts of the nitrogen methylene hydrogens in 40-43, 46, 50, 79-86 and 102 to be 0.10 - 0.31 ppm down field from the value in triethanol amine due to a decrease in electron density at nitrogen. The dipole moments measured for 41, 43, 46, 50, 80 and 94[16] (larger than those calculated on the basis of a bicyclic structure and larger than those measured for

acyclic organotriethoxysilanes, $RSi(OC_2H_5)_3$) indicate a group moment of 5.2 ± 0.2 D for $-Si(OCH_2CH_2)_3N$. The binding energy of the nitrogen lone pair was found to be greater in the UPS spectra of 40, 41 and 80 than that of triethanol amine.[73] These results also favor the triptych structure.

Crystal structure determinations of 46, 73, 152 and 155[75-78] confirmed this conclusion for the solid state. The Si-N bond length varied (2.19, 2.12, 2.34, and 2.34 Å, respectively) due to the variable electron-withdrawing ability of the substituent on silicon[75,76] and the steric constraints of the fused benzene rings, 152.[77] It is possible that this bond length exceeds the sum of the covalent radii (1.93 Å[72]) because of the steric requirements of this geometry.[75] Silicon is pentacoordinate in a trigonal bipyramidal configuration while nitrogen is in a tetrahedral one.

The factors which presumably decrease the reactivity of silatranes as given by Frye et al.[15] are 1) the bridgehead coordination of silicon in an essentially strain free system precludes backside attack and reduces the likelihood of flank attack; 2) peripheral groups (alkyl substituents on ring carbon atoms) tend to impede the approach of an attacking nucleophile; and 3) the increased electron density from the Si-N dative bond partially fills silicon's 3d orbitals and makes them less available for incoming nucleophiles. Each factor is a result of the triptych geometry.

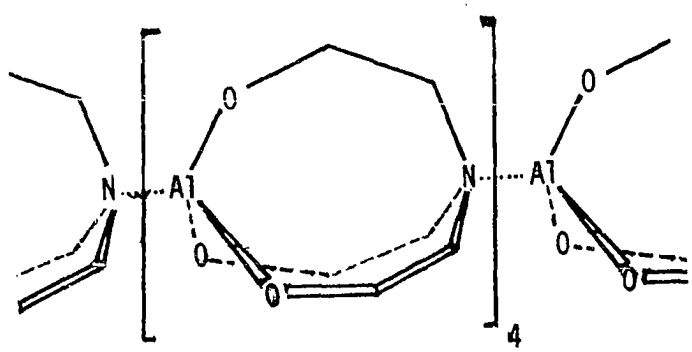
The remaining known atranes are listed in Table 3. These compounds have not been as extensively studied as the boratranes and silatranes, but the evidence for a triptych structure predominates. While only the synthesis procedure has been reported for a few compounds,[51,52,56] they are thought to have the atrane structure.

The work of Tzschach and Pönicke[37] and Tzschach et al.[40] has established that stannatranes 156-159 are tricyclic with Sn-N coordinate bonds. The nitrogen methylene hydrogens were observed at lower field than those of triethanol amine or other alkyl amines as observed for silatranes.[16] The increase in the tin-hydrogen coupling constant, $^{2}J_{SnH}$, indicates an increase in the coordination number of tin to five.[79] The measured dipole moment of 156 is also consistent with a triptych structure and trigonal bipyramidal coordination of tin. It is interesting that Mössbauer spectral measurements were not found to be useful for determining the geometry of stannatranes[39] because of little or no difference between the isomer shifts of acyclic and triptych compounds.

Germatranes were studied primarily by Voronkov et al.[42] but the literature available in English does not contain a great many details of their investigation. Crystal structure determinations are available, however, for 164 and 166.[80,81] These establish the triptych structure for germatranes with trigonal bipyramidal germanium coordination

and a Ge-N bond of 2.25 and 2.26 Å, respectively (sum of the covalent radii is 1.97 Å).[72]

Alumatrane exhibits polymer-like properties in solution. A molecular-weight determination produced a value six times the one expected.[44] Hein and Albert[45] have suggested a polymer structure with external Al-N



coordination. A polymer structure similar to that suggested by Hein and Albert was proposed for the monohydrate of ferratrane[57] in which hydrogen bonding to a water molecule linked adjacent molecules. This behavior can be attributed to dipolar interactions of polar triptych molecules much as was seen in concentrated solutions of boratrane.[82]

The vanadyl (V=O) band in the infrared spectra[83] of vanadatranes 174-176 was shifted to lower frequencies by increased electron density on vanadium. Large dipole moments (about 10 D)[83] also show that these compounds have colinear V=O and N-V bond moments which is consistent with a triptych geometry.

Voronkov and Faitel'son,[53] Peive *et al.*,[58] and Voronkov and Lapsin[59] used the ^{1}H nmr chemical shift parameter of the methylene hydrogens adjacent to nitrogen and dipole moment measurements to establish transannular N-M coordination for titanatranes 179-202, 204 and 205, zirconatranes 206 and 207, halfnatranes 208 and 209 and molybdatrane 211. Follner's[60] crystal structure determination of zincatrane, 212 (Zn-N distance of 2.15 Å compared to the sum of covalent radii of 2.0 Å),[72] and a distorted trigonal bipyramidal coordination geometry around zinc added this compound to the atrane class.

The large number of nitrilotriacetic acid (NTA) complexes[84] precluded their inclusion in the present list of atranes. NTA generally functions as a quadridentate ligand which is used extensively for the analytical determination and separation of metals. The one crystal structure reported for an NTA complex, $K_3Zr(NTA)_2$,[85] exhibits a triptych geometry with a Zr-N distance of 2.44 Å.

The strength of the M-N transannular bond in atranes depends upon the electronegativity of the M atom, its ability to accept added electron density (empty orbitals) and on the distance between M and N in the triptych structure.[86] Despite the greater electronegativity of phosphorus, P>B>Si,[87] and the availability of d-orbitals (like silicon) phosphatrane has hitherto not been

synthesized. The only example of M with more than two p-valence electrons is the reported synthesis of bismatrane, 178.[52] However, only the synthesis and no details of the characterization of 178, were included by the authors.

The goal of the research reported here was the synthesis of phosphatrane, $P(OCH_2CH_2)_3N$ (213), and the determination of whether the triptych structure was maintained in the presence of a lone pair of electrons on each bridgehead atom. Also of interest was the chemical reactivity of phosphatrane, since the possible donation of nitrogen's lone pair to phosphorus would presumably render phosphatrane a strong Lewis base.

EXPERIMENTAL

Materials

Solvents and materials unless specifically noted otherwise were all of reagent grade or better. Methylene chloride and chloroform were dried over 4A Molecular Sieves while acetonitrile was dried by refluxing with and distillation from calcium hydride onto 4A Molecular Sieves. Aromatic solvents were purified by shaking with concentrated sulfuric acid, neutralized with saturated sodium bicarbonate solution and dried by distilling off the water azeotrope before collecting over 4A Molecular Sieves.

Tris(dimethylamino)phosphine (TDP) and the borane adduct of tetrahydrofuran (H_3B:THF) were obtained from Aldrich Chemical Co. The 90% TDP, as supplied, was distilled under vacuum, Bp. 55-6° at 10 mm, before use. Triethanol amine (Fisher) was azeotropically dried with benzene and distilled, Bp. 172-3° at 0.5 mm, before use. Potassium superoxide (KO_2) and the hexacarbonyls of molybdenum and tungsten were used as supplied from Alfa and Pressure Chemical Co., respectively.

Nmr Spectra

All ^1H nmr spectra were obtained in 5-15% solutions using either a Varian A-60 or a Hitachi Perkin-Elmer R20-B spectrometer operating at 60 megahertz (MHz). Chemical

shifts are given in ppm (δ), a positive shift indicating a reasonance at lower magnetic field than the internal standard, tetramethylsilane. Coupling constants are reported in cycles per second (Hz).

A Bruker HX-90 spectrometer was used to obtain ^{13}C and ^{31}P nmr spectra operating at 22.63 and 36.44 MHz, respectively. The spectrometer was operated in the Fourier Transform (FT) mode using the "block averaging" technique to improve the signal to noise ratio. Carbon chemical shifts are reported in ppm relative to internal tetramethyl silane while phosphorus chemical shifts are reported in ppm relative to external 85% ortho phosphoric acid. The carbon spectra were white-noise proton decoupled while the phosphorus spectra were obtained with and without proton decoupling.

Infrared Spectra

A Beckman 4250 spectrometer was used to obtain infrared spectra of samples in solution (0.05 - 0.01 M) and in KBr pellets. The spectra were calibrated with polystyrene.

Mass Spectra

Mass spectra were obtained from an AEI MS-902 high resolution spectrometer. Exact masses were determined by peak matching with standards. Elemental analyses were performed by the Spang Microanalytical Laboratory.

Preparations

As a general precaution against moisture, a nitrogen atmosphere was maintained insofar as possible throughout the following preparations.

Triethyloxonium tetrafluoroborate

This compound was prepared by the literature procedure of Meerwein.[88]

Trimethyloxonium tetrafluoroborate

This compound was prepared by the procedure of Meerwein.[89]

Triphenylmethyl (trityl) tetrafluoroborate

This compound was prepared by the literature method[90] from triphenylcarbonol and fluoroboric acid in acetic anhydride.

18-Crown-6 ether

The procedure of Gokel and Cram[91] was found preferable to that of Greene[92] for preparation of this material since the product was more easily purified.

Tetraethylammonium bromopentacarbonyltungstate

The bromo tungsten carbonyl species, $[(OC)_5WBr]^-$, was prepared by refluxing the hexacarbonyl, 88 g (0.25 moles) with tetraethylammonium bromide, 42 g (0.20 moles) in 300 ml of diglyme.[93]

Acetonitrilopentacarbonyltungsten

The acetonitrile complex of tungsten hexacarbonyl was prepared from the bromide complex above and acetonitrile in the presence of a Lewis acid.[94]

1-Phospha-5-aza-2,8,9-trioxabicyclo[2.2.2]undecane (213)

The compound was prepared by the reaction of dilute solutions of triethanol amine and TDP in a three-neck round-bottom flask fitted with two needle-valve pressure equalizing addition funnels and a reflux condenser and flushed continuously with a stream of nitrogen. A solution of 7.5 g (50 mmoles) of $N(CH_2CH_2OH)_3$ in 30 ml chloroform diluted to 200 ml with dry toluene and a solution of 9.0 g (55 mmoles) of $P(N(CH_3)_2)_3$ in 200 ml of dry toluene, were simultaneously added dropwise over a two hour period to 250 ml of refluxing toluene in the flask. The presence of dimethyl amine in the exit stream of nitrogen indicated that reaction was taking place. The mixture was refluxed for two hours after the additions were complete. It was found that allowing the reaction to continue for a longer time made product separation more difficult and did not significantly increase the yield.

Isolation of the product (213) has not been successful using a variety of techniques including chromatography (column, thin layer and high pressure liquid), sublimation, distillation and crystallization. Each method resulted in

decomposition and/or no substantial increase in purity. However, the derivatives described below have been made and characterized.

1-Thio-1-phospha-5-aza-2,8,9-trioxabicyclo[3.3.3]undecane (214)

The reaction mixture of 213 was cooled to about 50-60° and sublimed sulfur (1.8 g, 56 mmoles) was added. The mixture was then slowly heated (one-half hour) to reflux and allowed to cool to room temperature. The mixture was filtered to remove any precipitated material (polymer as judged by its general insolubility in a variety of organic solvents). The filtrate was then evaporated to dryness on the vacuum line. (Use of a water aspirator for a vacuum source was found to be unsatisfactory.) After taking up the sticky solid in a minimum of methylene chloride, dropwise addition of Skelly B resulted in the precipitation of a white solid which upon settling appeared to have a rubbery, polymer-like texture. The mixture was filtered through a layer of Celite on a porous glass frit. This precipitation-filtration process was repeated with the filtrate until the precipitate formed remained as a finely divided solid. After several such cycles the filtrate became too dilute for efficient elimination of polymeric impurities and it was evaporated to dryness under vacuum and redissolved in a minimum of methylene chloride before the next addition of Skelly B.

The resulting white solid could be crystallized from a methylene chloride-hexane,[1] acetonitrile-ethyl ether[1] or toluene solution cooled to -78° or sublimed at 120-130° at 0.1 mm. Mp. 218-20° decomp., m/e 209.0276±0.0011 (calcd. 209.0276 for $C_6H_{12}NO_3PS$), ir νP=S, 881 and 612 cm^{-1} ($CHCl_3$). The yield of the reaction calculated on the basis of starting materials was 6% for product which is >95% pure as judged from nmr spectra. Higher purity material has been obtained after several recrystallizations reducing the yield to less than 1%.

1-Oxo-1-phospha-5-aza-2,8,9-trioxabicyclo[3.3.3]undecane (215)

The reaction mixture of 213 was cooled to 45-50° and a four-fold molar excess of finely ground potassium superoxide, KO_2, 14.2 g (200 mmoles), and a catalytic amount of 18-Crown-6, 0.2 g (0.75 mmoles), was added and the mixture was heated carefully to 90-100°C. As the reaction proceeds, gas is evolved. If heated too rapidly, a foam forms which will overflow the flask. Heating is continued for about one hour after the gas evolution stops.

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[1]Recrystallization was carried out using a concentrated solution of the compound in the first solvent and adding the second solvent dropwise with stirring to the cloud point. The mixture was then cooled to -78° until crystallization took place.

The mixture was then allowed to cool, filtered and the filtrate evaporated to dryness on the vacuum line. Purification was accomplished by the same procedure described for 214. The white powder which results from this tedious procedure was recrystallizable from methylene chloride-hexane (see footnote on preceding page) or chloroform solution cooled to -78° and sublimable at 120°, 0.1 mm. (A significant amount of material decomposes during sublimation). Mp. 208-12° decomp., m/e 193.0504±0.001 (calcd. 193.0489 for $C_6H_{12}NO_4P$), ir νP=O 1276 cm^{-1} ($CHCl_3$). The overall yield for this product was 3% and is substantially reduced to 0.5% when higher purity material is desired.

1-Seleno-1-phospha-5-aza-2,8,9-trioxabicyclo[3.3.3]undecane (216)

Red selenium,[95] 7.9 g (100 mmoles), was added to a cooled reaction mixture of 213 and the mixture heated to 75-80° for two hours. The temperature of the mixture should not rise above 80° since the more reactive red selenium reverts to the gray allotrope above 80°.

The isolation procedure was that described for the other chalconide derivatives, 214 and 215. Again, the white solid produced was recrystallizable from methylene chloride-hexane (see footnote on preceding page) solution cooled to -78°. Mp. 208-10° decomp., m/e 256.9648±0.001 (calcd.

256.9720 for $C_6H_{12}NO_3PSe$), ir νP-Se 580 cm^{-1} ($CHCl_3$). The overall yield again is low (4%).

1-H-1-phospha-5-aza-2,8,9-trioxatricyclo[3.3.3.0]undecane fluoroborate (217)

This derivative was the product of the reaction of triethyloxonium or trimethyloxonium fluoroborate (60 mmoles) with the reaction mixture of 213. The Meerwein reagent was added dropwise in acetonitrile solution (100 ml) at room temperature. The majority of the white solid which formed was precipitated polymer along with the reaction product. The solid was filtered and extracted with two 25 ml portions of hot acetonitrile. The solvent was removed *in vacuo* and the residue extracted with 25-30 ml of acetone. The nmr of the remaining solid showed it to be about 80% product.

Further purification was accomplished by the precipitation-filtration procedure already noted for 214 utilizing a concentrated acetonitrile solution and dropwise addition of ethyl ether to remove polymeric impurities. Eventually the product precipitated and was collected as a white powder which could be recrystallized in 8% overall yield from hot acetonitrile solution. Mp. 210-212°, *m/e* 177.0553±0.0009 (calcd. 177.0555 for $C_6H_{12}O_3P$). Calcd. C, 27.31; H, 4.86; N, 5.29; and F, 28.80. Found: C, 27.70; H, 4.95; N, 5.29; and F, 28.68, ir νP-H 2240, 2286 cm^{-1} (KBr), conductivity 1:1 electrolyte in DMSO.

1-Triphenylmethyl-1-phospha-5-aza-2,8,9-trioxatricyclo-[3.3.3.0]undecane fluoroborate (218)

An acetonitrile solution (100 ml) of triphenylmethyl (trityl) fluoroborate, 16 g (50 mmoles), was added dropwise to a reaction mixture of 213 at room temperature. After stirring for two hours the solvents were removed in vacuo. When the residue was extracted with 100 ml of chloroform a finely divided solid product remained. This solid was collected by filtration through Celite and extracted into acetonitrile solution.

The crude product in acetonitrile solution was purified by the procedure described for 217. It was necessary to repeat this process several times. Mp. 204-6° with decomposition, conductivity 1:1 electrolyte in acetonitrile. The overall yield was 8%.

1-Borano-1-phospha-5-aza-2,8,9-trioxatricyclo[3.3.3.0]-undecane (219)

Two equivalents (100 ml 1M THF solution) of the borane adduct of tetrahydrofuran ($H_3B \cdot THF$) was added dropwise to the reaction mixture of 213 at room temperature. After one hour of stirring the mixture was evaporated to dryness under vacuum and the residue was extracted with dry ethyl ether in a Soxhlet extractor for eight hours. Stripping off the ether and sublimation of the residue at 80-100°, yielded crude 219. Further purification was accomplished by repeated

sublimation. Due to substantial losses of product by repeated sublimation, recrystallization would probably be a better method of purification. Unfortunately, the compound is only soluble in DMSO and cannot be satisfactorily recrystallized from that medium. Mp. 175-8°, m/e 189.0847±0.001 (calcd. 189.0841 for $C_6H_{14}BNO_3PO$, ir νBH 2395, 2351 cm^{-1} (KBr)). Yields for this preparation are about 4%.

1-Pentacarbonyltungsten-1-phospha-5-aza-2,8,9-trioxabicyclo-[3.3.3]undecane (220)

A toluene solution of the acetonitrile complex of tungsten carbonyl, $(OC)_5WNCCH_3$, 19 g (52 mmoles), was added at room temperature to a reaction mixture of 213 which was then heated to 90° and held there for two hours. The yellow solution gradually precipitated a yellow solid and became dark brown in color. The mixture was filtered and the filtrate evaporated to a dark brown tar. The tar was dissolved in 50 ml of chloroform and absorbed on 50 g of silica gel by evaporating the mixture to dryness. After grinding the residue to a free-flowing powder it was added to the top of a silica gel column prepared with 350 g of silica gel and a 5:1 ratio of Skelly B/ethyl acetate in a 3 x 120 cm column. The column was eluted with 1 ℓ of 5:1 Skelly B/ethyl acetate, 2 ℓ of 3:1 Skelly B/ ethyl acetate and finally 500 ml of ethyl acetate. The middle fractions (3:1 Skelly B/ethyl acetate) contained 220. Solvents were

stripped from these fractions and the pale yellow residue was recrystallized from ethylacetate-hexane (see footnote on page 46) solution cooled to -78°. Mp. 139-40, m/e 498.9683±0.001 (calcd. 498.9783 for $C_{11}H_{12}NO_8PW$), ir νCO 2078, 1956, 1948 (cyclohexane). Yields of 13% for this species are the best achieved for any derivative of 213.

1-Pentacarbonylmolybdenum-1-phospha-1-aza-2,8,9-trioxa-bicyclo[3.3.3]undecane (221)

Molybdenum hexacarbonyl, 13.2 g (50 mmoles), was added to a reaction mixture of 213 and heated until carbon monoxide evolution had ceased (about two hours). After cooling, the mixture was filtered and evaporated to dryness under vacuum.

As with 220, the product was isolated by column chromatography on silica gel except that the elutions were carried out with 1 ℓ 5:1 Skelly B/ethyl acetate, 2.5 ℓ 3:1 Skelly B/ethyl acetate and 500 ml ethyl acetate. The product fractions (3:1 Skelly B/ethyl acetate) were evaporated and the combined residues were recrystallized from ethyl acetate-hexane (see footnote on page 46) (1:15) cooled to -78°. Mp. 122-4° with decomposition, m/e 408.9284±0.001 (calcd. 408.9363 for $C_{11}H_{12}NO_8PMo$), ir νCO 2078, 1956 (cyclohexane). The yield of this product was 9%.

1-Pentacarbonyltungsten-1-phospa-5-aza-5-methyl-2,8,9-trioxabicyclo[3.3.3]undecane fluoroborate (222)

Trimethyloxonium fluoroborate, 0.290 g (2 mmoles), and 0.761 g (1.5 mmoles) of 220, were placed in a 50 ml round bottom flask and dissolved in 25 ml of dry acetonitrile. The mixture was stirred at room temperature for four hours before anhydrous ether was added to the cloud point. The flask was then cooled (-78°) whereupon the product crystallized. It was collected and dried under vacuum. Mp. 255-8° decomp., yield 92%, ir νCO 2079, 1959 cm^{-1} (KBr).

1-Pentacarbonylmolybdenum-1-phospha-5-aza-5-methyl-2,8,9-trioxabicyclo[3.3.3]undecane fluoroborate (223)

This compound was prepared from 0.19 g (1.3 mmoles) of trimethyloxonium fluoroborate and 0.426 g (1 mmole) of 221 by the procedure described for 222. The molybdenum species appeared to oxidize slightly during the reaction, turning a pale green color. It was necessary to recrystallize the product twice to eliminate the green coloration. Mp. 165-8° decomp., yield 83%, ir νCO 2080, 1959 cm^{-1} (KBr).

1-Oxo-1-phospha-5-aza-5-methyl-2,8,9-trioxabicyclo[3.3.3]-undecane iodide (224)

The nitrogen atom of 215 was quaternized by reaction with methyl iodide in acetonitrile solution. Methyl iodide (0.24 g, 1.6 mmoles) was added to 0.076 g (0.4 mmoles) of 215 in a 4 ml of acetonitrile. The mixture was heated to 40°

for 10 hours, by which time a solid had formed in the flask. This white solid was collected by filtration and dried under vacuum. Mp. 201-2° decomp. The yield was virtually quantitative.

1-Thio-1-phospha-5-aza-5-methyl-2,8,9-trioxabicyclo[3.3.3]-undecane iodide (225)

This compound was prepared by the procedure described for 224. Mp. 178-80° decomp. The yield was virtually quantitative.

1-Seleno-1-phospha-5-aza-5-methyl-2,8,9-trioxabicyclo-[3.3.3]undecane iodide (226)

This compound was prepared by the procedure described for 224. Mp. 180-2° decomp. The yield was virtually quantitative.

X-Ray Crystal Structure Determinations

These experiments were carried out in collaboration with Dr. J. C. Clardy and Dr. J. P. Springer.

1-H-1-phospha-5-aza-2,8,9-trioxabicyclo[3.3.3]undecane fluoroborate (217)

Crystals of 217 were grown from an acetonitrile solution cooled to -10° for five days. A single crystal, 0.35 x 0.18 x 0.42 mm, was selected for study and mounted in a Lindeman capillary to protect it from atmospheric moisture.

Preliminary examination of 217 showed that the crystals belonged to the orthorhombic crystal class with $\underline{a}$ = 12.784(6), $\underline{b}$ = 9.320(4) and $\underline{c}$ = 8,988(3) Å and four molecular units of $[HP(OCH_2CH_2)_3N]BF_4$ per unit cell. Unfortunately, the assignment of a space group was not unambiguous since the systematic extinctions (0kℓ absent if k+ℓ = 2n+1, kOℓ absent if k = 2n+1) were consistent with both $Pna2_1$ and Pnam. The latter space group requires there to be a molecular mirror plane in the absence of disorder.

A total of 873 unique reflections using a variable ω-scan technique (minimum 1°/min) were measured ($2\theta \leq 114°$) with a Syntex $P2_1$ computer-controlled four-circle diffractometer and Cu K_α radiation (1.5418 Å). During data collection three standard reflections, (312), (223) and (014), were monitored. The intensities of these reflections were seen to remain the same throughout the data collection, making any correction for decomposition unnecessary. After correction for Lorentz, polarization and background effects, 615 reflections were judged to be observed ($F_o \geq 3\sigma(F_o)$). Intensity statistics did not prove to be helpful in determining which space group was correct since they were intermediate between centrosymmetric (Pnam) and noncentrosymmetric ($Pna2_1$), in value. The presence of a heavy atom could easily have been responsible for this result.

Solution of the crystal structure was begun by routine application of direct methods *via* a multiple solution weighted tangent formula scheme[96] in the noncentrosymmetric space group $Pna2_1$. The positions of the fluoroborate anion and phosphorus were located in the resulting electron density calculation. After three cycles of least squares refinement[97] of those positions, the conventional agreement factors R and ωR were 0.452 and 0.507, respectively. The phased electron density synthesis[97] revealed the positions of the rest of the nonhydrogen atoms which refined to R = 0.219 and ωR = 0.223. Variation of isotropic temperature factors, followed by the anisotropic factors in succeeding refinements resulted in agreement factors of 0.095 and 0.087 for R and ωR, respectively. All hydrogen atoms were located in subsequent F syntheses[97] and full matrix least squares refinement for the 615 observed reflections and 183 variables produced final crystallographic residuals of 0.062 and 0.062. The geometry of this model was very poorly behaved with chemically identical bonds differing by five standard deviations.

Refinement was then attempted in the alternate space group Pnam (an alternate setting of the standard Pnma). After the first cycles of isotropic refinement it was apparent that a model in which the molecule resided on a mirror plane would not refine and models in which the carbon atoms bonded to nitrogen, C(3) and C(4), were disordered

were tried. These refined satisfactorily to isotropic values of R = 0.186 and ωR = 0.199 and anisotropic residuals of R = 0.085 and ωR = 0.088. Inclusion of the hydrogen atoms resulted in final R and ωR of 0.065 and 0.067, respectively, for the 135 variables used in the refinement. The molecular geometry was much better behaved for this model. The atomic scattering factors used in these refinements were those of Hanson et al.[98] Corrections,[99] real or imaginary, for anomalous dispersion of phosphorus were also used in the calculations.

Statistical comparison[100] of these models showed them to be of the same level of significance. Despite the better R value (6.2%) for the $Pna2_1$ refinement of 183 variables, the Pnam R value (6.5%) was accomplished with 135 variables. Since the second treatment of the data is chemically more acceptable, those values of the positional and thermal parameters and the observed and calculated structure factors are listed in Tables 4, 5 and 6.

1-Thio-1-phospha-5-aza-2,8,9-trioxabicyclo[3.3.3]undecane (214)

Crystals of 214 were grown by slow evaporation of a methylene chloride solution or vapor diffusion of hexane into a methylene chloride solution in a closed container. A crystal fragment 0.34 x 0.22 x 0.40 mm was selected and

Table 4. Fractional coordinates of the unique atoms of $[HP(OCH_2CH_2)_3N]BP_4$

Atom	x/a	y/b	z/c
P	0.2386(1)	0.1965(2)	0.2500
O(1)	0.3454(4)	0.1110(5)	0.2500
O(2)	0.1894(3)	0.2489(4)	0.4014(4)
N	0.3236(4)	0.3748(6)	0.2500
C(1)	0.4447(6)	0.1804(10)	0.2500
C(2)	0.2198(6)	0.3834(7)	0.4694(8)
C(3)[a]	0.4275(9)	0.3338(13)	0.1858(2)
C(4)	0.3290(14)	0.4218(16)	0.4055(15)
C(4)*[b]	0.2630(15)	0.4757(15)	0.3494(17)
B	0.0258(7)	0.7334(10)	0.2500
F(1)	0.0790(6)	0.7615(11)	0.2500
F(2)	0.0782(10)	0.8560(10)	0.2500
F(3)	0.0443(5)	0.6510(6)	0.3732(5)
H(1)[c]	0.484(6)	0.151(8)	0.340(8)
H(2A)	0.248(6)	0.363(8)	0.557(12)
H(2B)	0.158(7)	0.443(9)	0.490(10)
H(3A)*	0.422(10)	0.342(10)	0.072(20)
H(3B)*	0.482(8)	0.393(11)	0.217(13)
H(4A)*	0.353(10)	0.540(12)	0.405(12)
H(4B)*	0.379(12)	0.370(16)	0.456(16)
H(4*A)*	0.312(17)	0.517(18)	0.110(17)
H(4*B)*	0.206(9)	0.515(12)	0.212(14)
H(P)*	0.188(6)	0.071(9)	0.267(15)

[a]Atom is disordered and was refined with an occupancy factor of 0.50.

[b]An asterisk (*) denotes a disordered atom which was refined with an occupancy factor of 0.50.

[c]Hydrogen atoms are labelled with the number of the carbon atom to which they are bonded. Where more than one hydrogen is bonded to a carbon atom, the hydrogens are labelled with a number and letter.

Table 5. Thermal parameters[a] for $[H\text{-}P(OCH_2CH_2)_3N]BF_4$

Atom[b]	β_{11}[c]	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
P	4.9(14)	5.98(21)	9.71(27)	0.54(13)	0.0	0.0
O(1)	5.75(35)	6.15(57)	20.62(94)	0.74(34)	0.0	0.0
O(2)	7.79(28)	11.36(45)	11.46(51)	-1.73(28)	2.86(30)	-0.60(42)
N	4.86(40)	6.95(63)	8.76(80)	-0.50(41)	0.0	0.0
C(1)	5.35(59)	10.8(12)	21.2(17)	0.60(66)	0.0	0.0
C(2)	9.40(53)	12.19(76)	11.48(93)	-0.19(54)	2.16(60)	-3.60(72)
C(4)	8.3(12)	7.6(13)	15.8(22)	-0.3(14)	-1.0(15)	5.2(17)
C(5)	7.9(11)	9.7(17)	12.6(19)	-0.8(12)	-0.3(13)	-1.4(15)
C(6)	4.93(72)	11.7(17)	16.7(23)	0.16(85)	1.27(84)	-0.0(12)
B	6.43(64)	9.1(12)	11.0(12)	1.79(65)	0.0	0.0
F(1)	11.71(59)	32.1(16)	38.1(18)	6.00(74)	0.0	0.0
F(2)	19.99(56)	21.29(79)	18.56(75)	4.09(50)	-2.62(50)	4.74(58)
F(3)	24.3(11)	21.2(13)	43.7(23)	-12.1(10)	0.0	0.0

[a]The anisotropic thermal ellipsoid is of the form $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}\ell^2 + 2\beta_{12}hk + 2\beta_{13}h\ell + 2\beta_{23}k\ell)]$.

[b]Numbering of the atoms corresponds to that in Figure 5.

[c]All β values are $\beta \times 10^3$.

Table 6. Observed and calculated structure factors for 1

H = 0			
K	L	FO	FC
0	4	41	45
0	6	62	-67
0	8	39	40
1	3	5	4
1	5	54	-49
1	7	20	19
1	9	6	-7
2	2	65	69
2	4	20	-22
2	6	42	44
2	8	20	-19
3	1	17	-13
3	3	37	36
3	5	21	-21
3	7	11	-13
3	9	5	-5
4	0	40	-42
4	2	9	9
4	4	26	-24
4	6	11	-10
5	1	7	-7
5	3	59	-59
5	5	27	27
5	7	8	9
6	2	22	-22
6	4	6	6
6	6	10	10
7	1	7	-5
7	3	32	32
8	0	14	13
8	2	11	11
8	4	7	-7
8	6	6	5
9	1	18	17
9	3	21	-21
10	0	7	8

H = 1			
K	L	FO	FC
1	0	10	-14
1	1	16	15
1	2	11	-11
1	3	51	52
1	4	13	15
1	5	12	-12
1	7	10	10
1	8	5	-5
2	0	26	28
2	1	11	-12
2	2	58	60
2	3	43	-47
2	5	25	26
2	6	14	14
2	7	6	5
2	8	10	-9
3	0	25	27
3	1	43	44
3	2	13	13
3	3	36	-38
3	4	28	-29
3	5	18	17
3	7	18	-17
3	8	9	8
3	9	6	6
4	0	54	53
4	1	5	6
4	2	19	-18
4	3	15	15
4	4	13	13
4	5	8	-7
4	6	20	-21
4	8	14	14
5	1	24	-24
5	3	15	14
5	5	32	-32
5	6	5	6
5	7	13	13
6	0	36	-35
6	2	15	15
6	3	8	8
6	4	33	-33
6	5	6	-8
6	6	16	17
7	1	20	21
7	2	8	-7
7	3	16	-17
7	4	11	11
7	5	11	11
7	7	5	-6
8	0	14	14
8	1	3	-2
8	2	18	-18
8	3	6	-5
8	4	9	9
8	5	4	5
9	1	3	-2
10	0	8	7

H = 2			
K	L	FO	FC
0	0	57	-65
0	1	25	27
0	2	40	-38
0	3	60	-65
0	4	37	-34
0	5	22	20
0	6	32	28
0	8	11	-11
1	0	41	36
1	2	54	-50
1	3	2	-5
1	4	16	12
1	5	35	39
1	6	3	2
1	7	36	-37
1	9	18	17
2	0	21	-17
2	1	25	17
2	2	13	12
2	3	41	43
2	4	9	5
2	5	5	-4
2	6	22	-20
2	7	14	-15
2	8	6	6
3	0	74	84
3	1	15	-15
3	2	34	-38
3	3	10	10
3	5	10	-12

Table 6. (Continued)

3	6	23	-22
3	7	19	19
3	8	8	8
4	0	32	-32
4	1	24	-18
4	2	10	8
4	4	43	45
4	5	12	-12
4	7	13	14
5	0	60	-63
5	2	24	26
5	3	10	7
5	6	10	10
5	8	5	-4
6	0	24	22
6	1	3	-5
6	2	17	18
6	3	8	10
6	4	22	-22
6	7	4	1
7	0	7	8
7	1	5	-4
7	2	11	11
7	3	10	-10
7	4	13	-13
7	5	4	-4
8	0	3	2
8	2	20	-20
8	3	15	-15
8	4	10	10
8	5	5	5
9	2	8	-8
9	3	15	15
9	4	7	7
10	0	17	-17

H = 3

K	L	FO	FC
1	0	25	-27
1	1	3	-3
1	2	8	7
1	3	2	3
1	4	23	26
1	5	6	-6
1	6	8	8
1	7	10	-9
1	8	7	-6
2	0	23	-22
2	2	46	-46
2	3	19	-20
2	4	24	24
2	5	7	9
2	6	13	-13
2	7	6	-7
3	0	23	27
3	1	46	-45
3	2	17	-16
3	3	3	-3
3	5	7	6
3	6	10	-9
3	7	13	13
3	8	8	8
3	9	6	-7
4	0	30	-31
4	1	2	-1
4	2	27	27
4	3	20	20
4	4	26	-25
4	5	9	-10
4	6	14	13
4	8	6	-6
5	0	21	-20
5	1	35	34
5	2	10	12
5	3	21	-20
5	4	16	-16
5	5	27	28
5	6	5	5
5	7	12	-12
6	0	25	25
6	1	8	10
6	2	7	-7
6	3	4	2
6	4	19	19
6	6	10	-10
7	0	4	2
7	1	20	-20
7	3	22	21
7	4	6	5
7	5	16	-16
7	6	4	-3
8	0	8	-7
8	2	4	4
8	3	7	-6
8	5	4	3
9	0	4	5
9	3	4	-4

H = 4

K	L	FO	FC
0	0	63	64
0	3	13	11
0	4	8	10
0	5	17	17
0	6	9	-10
0	7	6	7
0	8	15	15
0	9	5	-5
1	0	88	100
1	1	25	-25
1	2	13	12
1	3	33	30
1	4	30	-29
1	5	29	-25
1	6	9	-9
1	7	5	5
1	8	6	6
1	9	9	-8
2	0	25	-24
2	1	57	-54
2	2	16	17
2	3	9	-8
2	4	22	-24
2	5	10	-10
2	6	24	24
2	7	13	14
2	8	11	-11
2	9	3	3
3	0	36	-35
3	1	37	34
3	2	8	8
3	3	25	-23
3	4	11	11
3	5	14	14
3	6	27	27
3	7	14	-14
3	8	8	-9

Table 6. (Continued)

4	0	5	9
4	1	58	57
4	2	28	-31
4	4	10	12
4	5	6	5
4	6	12	-12
4	7	22	-22
4	8	3	2
5	0	13	-15
5	1	10	-5
5	2	10	10
5	3	6	-8
5	5	7	6
5	6	11	-13
6	0	17	15
6	2	13	-10
6	3	23	-24
6	5	6	6
6	6	5	-5
7	0	5	7
7	1	26	-27
7	2	22	-23
7	3	21	22
7	4	14	14
7	5	8	-9
7	6	5	-3
8	0	11	-11
8	1	14	-13
8	2	22	21
8	3	26	27
8	4	15	-15
8	5	6	-7
9	0	6	5
9	1	15	14
9	2	9	9
9	3	15	-16

H = 5

K	L	FO	FC
1	0	5	-8
1	1	7	7
1	2	14	-14
1	3	13	13
1	4	4	-3
1	5	16	-17
1	6	6	-7
1	7	9	10
1	8	3	4
2	0	26	-27
2	1	23	-26
2	2	18	19
2	3	22	20
2	4	7	7
2	5	9	-7
2	6	19	17
2	7	19	18
2	8	14	-13
3	0	16	18
3	1	18	16
3	2	11	10
3	3	37	-36
3	4	7	-8
3	5	22	23
3	6	8	9
3	7	11	-12
3	8	4	-4
4	0	50	52
4	1	9	10
4	2	37	-38
4	3	14	-14
4	4	22	22
4	5	14	14
4	6	21	-20
4	7	7	-6
4	8	16	16
5	0	10	10
5	1	22	-21
5	2	4	5
5	3	25	25
5	5	22	-22
5	7	10	10
6	0	31	-31
6	1	7	-6
6	2	23	22
6	4	29	-30
6	5	7	-7
6	6	15	16
7	0	10	-11
7	1	15	15
8	0	7	7
8	2	6	-6
9	1	3	2
9	2	4	-4

H = 6

K	L	FO	FC
0	0	19	-23
0	1	31	-37
0	2	32	33
0	3	27	-24
0	4	33	-30
0	5	15	-14
0	6	6	-7
0	7	12	11
1	0	16	-10
1	1	11	-13
1	2	16	-17
1	3	19	-19
1	4	7	-8
1	5	10	10
1	6	8	9
2	0	28	29
2	1	17	21
2	2	36	-37
2	3	17	15
2	4	34	33
2	5	5	4
2	6	12	-12
2	7	14	-14
2	8	6	6
3	0	24	19
3	1	21	-19
3	2	7	-5
3	3	35	34
3	4	17	-16
3	5	21	-20
3	6	7	-8
3	7	10	9
4	0	7	-7
4	2	27	27
4	3	3	3
4	4	16	-16
4	5	7	-6
4	6	7	7
4	7	11	11
5	0	18	-17
5	3	13	-13
5	4	15	14
5	6	4	5

Table 6. (Continued)

6	0	36	-36
6	1	9	10
6	2	15	15
6	5	4	5
6	6	9	10
7	0	10	11
7	1	31	31
7	2	11	11
7	3	15	-15
7	4	6	-7
7	5	11	11
8	0	23	23
8	1	6	-5
8	2	21	-21
8	3	6	-6
8	4	11	12
9	0	4	4
9	1	14	-15

H = 7

K	L	FO	FC
1	0	10	-10
1	1	14	15
1	2	24	23
1	4	4	-4
1	5	8	7
1	6	5	5
1	7	11	-10
2	0	3	-3
2	1	15	13
2	2	13	-13
2	3	10	-10
2	4	15	15
2	5	5	-5
2	6	13	-14
2	7	6	-6
3	0	12	13
3	1	32	-33
3	2	23	-23
3	3	15	14
3	4	10	10
3	5	11	-10
3	6	8	-9
3	7	14	13
4	0	7	-5
4	1	8	-7
4	2	16	15
4	4	15	-16
4	6	5	5
5	0	14	-14
5	1	15	15
5	3	18	-18
5	4	5	-5
5	5	15	15
6	0	13	11
6	1	7	5
6	2	5	-4
6	4	5	6
6	5	6	5
6	6	3	-4
7	0	7	6
7	1	8	-8
7	3	5	6
7	4	5	6
7	5	6	-6
8	0	9	-10
8	3	6	6

H = 8

K	L	FO	FC
0	0	32	-31
0	1	18	18
0	2	3	-3
0	3	15	-15
0	4	20	20
0	5	26	27
0	6	4	3
0	7	3	-5
1	0	47	49
1	2	21	-21
1	3	25	25
1	4	24	23
1	5	6	-6
1	6	19	-18
2	0	14	15
2	2	12	10
2	4	21	-21
2	6	4	4
3	0	4	4
3	2	10	9
3	3	20	-21
3	4	7	-4
3	5	10	11
3	6	6	4
4	0	5	2
4	1	15	-15
4	2	16	-17
4	3	12	12
4	4	11	11
4	5	12	-10
5	1	4	2
5	2	5	-3
5	3	12	13
5	4	4	1
5	6	3	-2
6	0	11	11
6	3	12	-12
6	5	3	3
7	0	14	-13
7	1	12	-12
7	2	3	1
7	4	3	-3
8	0	14	-14
8	1	6	-4
8	2	9	9

H = 9

K	L	FO	FC
1	1	9	-10
1	2	11	-10
1	3	9	10
1	5	10	-10
2	0	32	-29
2	1	6	-6
2	2	21	21
2	3	17	17
2	4	12	-12
2	5	4	-5
2	6	11	10
2	7	5	6
3	0	8	-7
3	1	19	20
3	2	11	11
3	3	16	-16
3	4	4	-3
3	5	9	10
3	6	9	9
4	0	20	20
4	1	11	11
4	2	16	-17
4	3	8	-9

Table 6. (Continued)

4	4	11	11
4	5	11	13
4	6	7	-7
5	0	20	20
5	1	9	-7
5	2	7	-5
5	3	9	8
5	4	8	8
5	5	4	-5
6	1	13	-13
6	2	4	5
6	3	6	7
6	4	7	-8
7	0	6	-7
7	1	6	5
7	2	7	6
7	3	4	-4

H = 10

K	L	FO	FC
0	0	21	-20
0	1	30	-30
0	2	28	27
0	3	25	24
0	4	16	-17
0	5	23	-23
0	6	5	6
1	0	11	-12
1	1	14	15
1	2	10	10
1	3	29	-29
1	4	17	-17
1	5	12	12
2	1	16	15
2	2	13	-13
2	3	22	-21
2	4	13	14
2	5	10	9
2	6	3	-3
3	0	16	-16
3	3	10	10
3	5	4	-3
3	6	4	4
4	0	9	10
4	1	4	5
4	3	10	9
5	0	18	18
5	1	4	-5
5	2	9	-8
5	4	5	5
6	0	11	-12
6	2	4	3
7	0	6	-5

H = 11

K	L	FO	FC
1	0	7	7
1	1	6	4
1	3	6	-6
1	5	7	7
2	0	6	7
2	2	6	-8
2	4	10	11
3	0	5	-3
3	1	10	-10
3	2	3	-3
3	3	8	9
3	4	3	3
3	5	9	-9
4	0	8	-8
4	1	7	-8
4	2	7	8
4	3	4	4
4	4	6	-7
5	0	15	-15
5	1	4	4
5	2	7	8
5	3	7	-7
6	0	4	3
6	1	10	11

H = 12

K	L	FO	FC
0	0	15	16
0	2	18	-17
0	3	8	-7
0	4	9	8
1	1	11	-12
1	2	7	-8
1	3	8	9
1	4	13	14
2	0	5	-4
2	2	7	7
2	3	8	8
2	4	5	-5
3	2	10	11
3	4	7	-8
4	2	3	3
4	3	5	-6
5	0	3	-2
5	1	3	3

H = 13

K	L	FO	FC
1	0	3	1
3	0	7	-7
3	1	3	2

mounted in the Lindeman capillary as a precaution against atmospheric moisture.

The crystals were found to belong to the orthorhombic crystal class with $\underline{a}$ = 12.231(2), $\underline{b}$ = 6.590(1) and $\underline{c}$ = 11.284(2) Å and four molecular units of $SP(OCH_2CH_2)_3N$ per unit cell. Systematic extinctions (hOℓ absent if h = 2n+1, Okℓ absent if ℓ = 2n+1) allowed assignment of the space group of $Pca2_1$.

A Syntex $P2_1$ computer-controlled four circle diffractometer was used to measure 755 unique reflection intensities inside a 2θ sphere of 114° with Cu K_α radiation (1.5418 Å). During the data collection three reflections, (341), (142) and (023), were observed. No significant change in them was noted. Of the reflections measured 631 were judged observed after correction for Lorentz, polarization and background effects ($F_o \geq 3\sigma(F_o)$).

Routine application of direct methods (MULTAN)[96] resulted in location of the positional parameters for sulfur, phosphorus and the three oxygens in the first phased E synthesis. These positional parameters were refined[97] to conventional agreement factor values of 0.302 and 0.321, R and ωR, respectively. The rest of the nonhydrogen atoms were located in subsequent electron density calculations[97] and reduced the R and ωR to 0.139 and 0.178. Isotropic (R = 0.108 and ωR = 0.130) then anisotropic thermal parameters (R = 0.068 and ωR = 0.076) were included in the

model. All of the hydrogen positions were found in difference F syntheses.[97] Final full matrix least-squares refinements led to crystallographic residuals, R and ωR, of 0.057 and 0.063, respectively. Fractional coordinates, thermal parameters and observed and calculated structure factors for this model are listed in Tables 7, 8 and 9. The atomic scattering factors used in the refinement were those of Hanson et al.[98] Corrections,[99] real and imaginary, for anomalous dispersion of phosphorus and sulfur were also used in the calculations.

Table 7. Fractional coordinates of $S{=}P(OCH_2CH_2)_3N$

Atom[a]	x/a[b]	y/b	z/b
S	0.2623(2)	0.1344(3)	0.0565(3)
P	0.1828(1)	-0.0621(2)	0.1478
O(1)	0.2604(5)	-0.2284(10)	0.1953(7)
O(2)	0.0957(6)	-0.1748(10)	0.0676(7)
O(3)	0.1223(6)	0.0380(9)	0.2502(7)
N	0.0510(6)	-0.3838(11)	0.2938(7)
C(1)	0.2517(8)	-0.3189(13)	0.3111(9)
C(2)	0.1581(9)	-0.4539(15)	0.3297(10)
C(3)	0.0655(8)	-0.3823(15)	0.0759(8)
C(4)	0.0079(9)	-0.4457(13)	0.1832(9)
C(5)	0.0187(9)	-0.0120(14)	0.2948(11)
C(6)	0.0090(10)	-0.2098(16)	0.3560(12)
H(1)	0.248(7)	-0.148(11)	0.344(8)
H(1A)	0.333(7)	-0.379(15)	0.331(9)
H(2)	0.166(8)	-0.597(16)	0.255(10)
H(2A)	0.163(6)	-0.528(12)	0.436(8)
H(3)	0.155(7)	-0.470(15)	0.093(9)
H(3A)	0.029(6)	-0.405(12)	0.007(7)
H(4)	-0.006(6)	-0.569(12)	0.179(7)
H(4A)	-0.070(8)	-0.364(15)	0.159(11)
H(5)	-0.032(6)	-0.030(12)	0.199(7)
H(5A)	-0.007(8)	0.085(15)	0.350(10)
H(6)	0.070(9)	-0.215(20)	0.457(12)
H(6A)	-0.064(6)	-0.209(13)	0.381(7)

[a]Numbering of the atoms corresponds to that in Figure 7.

[b]Standard deviations are given in parentheses.

Table 8. Anisotropic thermal parameters[a] for $S=P(OCH_2CH_2)_3N$

Atom[b]	β_{11}[c]	β_{22}	β_{33}	$\beta_{1,2}$	β_{13}	$\beta_{2,3}$
S	7.9(2)	20.9(5)	7.2(2)	-3.6(2)	0.5(2)	1.6(3)
P	5.2(1)	13.1(4)	4.3	-0.6(2)	0.0	0.0
O(1)	6.6(4)	28.6(16)	10.0(6)	0.3(7)	-0.6(4)	4.2(9)
O(2)	11.7(6)	27.0(17)	6.4(5)	-7.7(8)	-1.5(5)	2.2(9)
O(3)	11.3(6)	17.7(14)	10.3(6)	-0.1(8)	4.1(6)	1.2(8)
N	8.5(6)	19.9(17)	7.1(6)	-0.3(9)	1.4(5)	3.0(10)
C(1)	8.4(6)	27.3(21)	5.2(6)	2.5(13)	-0.7(6)	3.0(12)
C(2)	10.3(9)	26.6(27)	8.8(9)	0.0(12)	-1.5(7)	6.6(13)
C(3)	9.6(7)	25.2(24)	5.4(8)	-7.0(12)	-1.6(6)	-3.1(11)
C(4)	8.8(7)	19.3(22)	10.7(10)	-4.7(11)	-2.0(7)	2.7(11)
C(5)	9.8(8)	17.6(19)	10.3(9)	3.6(11)	3.9(8)	1.3(13)
C(6)	13.2(10)	25.5(27)	12.1(11)	0.1(15)	8.5(10)	3.0(14)

[a]The anisotropic thermal ellipsoid is of the form $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}\ell^2 + 2\beta_{12}hk + 2\beta_{13}h\ell + 2\beta_{2,3}k\ell)]$.

[b]Numbering of the atoms corresponds to that in Figure 7.

[c]All β values are $\beta \times 10^3$.

Table 9. Calculated and observed structure factors for $S{=}P(OCH_2CH_2)_3N$

H = 0			1-11	6	5	5 -6	13	12	2 -7	18	18
K L	FO	FC	1-10	9	10	5 -5	19	19	2 -6	10	10
0-12	25	27	1 -9	10	10	5 -4	18	17	2 -5	18	17
0-10	30	30	1 -8	4	3	5 -3	9	10	2 -4	27	28
0 -8	47	47	1 -7	11	12	5 -2	32	31	2 -3	23	23
0 -6	15	16	1 -6	27	33	5 -1	4	4	2 -2	30	31
0 -4	76	83	1 -5	16	16	5 0	34	33	2 -1	52	51
1-12	18	18	1 -4	25	30	6 -6	5	5	2 0	25	23
1-10	35	33	1 -3	39	40	6 -5	8	8	3-10	5	4
1 -8	30	29	1 -2	51	54	6 -4	8	8	3 -9	8	8
1 -6	13	13	1 -1	58	59	6 -3	7	7	3 -8	15	16
1 -4	2	4	1 0	54	51	6 -2	26	26	3 -7	11	12
1 -2	62	63	2-11	8	7	6 -1	4	5	3 -6	23	22
1 0	69	69	2-10	3	4	6 0	23	23	3 -4	33	34
2-10	14	13	2 -9	10	10	7 -2	5	6	3 -3	19	18
2 -8	29	28	2 -8	28	26	7 0	7	7	3 -2	14	16
2 -6	36	37	2 -6	29	30				3 -1	18	15
2 -4	16	12	2 -5	9	9	H = 2			3 0	26	23
2 -2	48	46	2 -4	63	69	K L	FO	FC	4-10	13	11
2 0	40	39	2 -3	27	28	0-12	18	19	4 -9	4	5
3-10	11	11	2 -2	29	29	0-11	18	17	4 -8	9	8
3 -8	21	23	2 -1	20	18	0-10	28	26	4 -6	12	12
3 -7	3	0	2 0	40	37	0 -9	14	13	4 -5	3	3
3 -6	44	46	3-11	3	2	0 -8	19	21	4 -4	20	21
3 -4	17	17	3-10	9	8	0 -7	12	13	4 -3	4	5
3 -2	56	58	3 -9	7	8	0 -6	15	18	4 -2	16	18
3 0	11	11	3 -8	21	19	0 -5	28	32	4 -1	4	4
4-10	10	10	3 -7	15	14	0 -4	8	8	4 0	15	14
4 -8	13	15	3 -6	39	40	0 -3	13	11	5 -8	9	10
4 -6	18	19	3 -5	13	13	0 -2	57	67	5 -7	7	8
4 -4	36	37	3 -4	35	38	0 0	32	35	5 -6	3	4
4 -2	40	42	3 -3	12	13	1-12	11	10	5 -5	13	14
4 0	15	16	3 -2	11	9	1-11	11	11	5 -4	19	19
5 -8	8	9	3 -1	29	32	1-10	21	19	5 -3	11	11
5 -6	8	9	3 0	4	4	1 -9	22	22	5 -2	2	1
5 -4	7	8	4-10	11	11	1 -8	21	21	5 -1	6	6
5 -2	17	17	4 -9	7	5	1 -7	21	21	5 0	34	32
5 0	11	11	4 -8	16	18	1 -6	10	11	6 -6	7	8
6 -6	13	14	4 -7	15	16	1 -5	11	10	6 -5	9	10
6 -4	21	22	4 -6	24	24	1 -4	13	15	6 -4	10	10
6 -2	14	13	4 -5	11	11	1 -3	42	42	6 -3	8	8
6 0	5	4	4 -4	24	24	1 -2	78	85	6 -2	8	8
7 -2	11	10	4 -3	14	15	1 -1	32	34	6 -1	5	5
7 0	3	3	4 -2	21	21	1 0	63	63	6 0	5	4
			4 -1	15	14	2-11	8	8	7 -1	9	10
H = 1			4 0	12	13	2-10	19	17			
K L	FO	FC	5 -8	12	12	2 -9	11	11			
1-12	4	3	5 -7	9	10	2 -8	21	20			

Table 9. (Continued)

H = 3		
K	L	FO	FC
1	-11	11	11
1	-10	17	17
1	-9	9	8
1	-8	17	15
1	-7	5	6
1	-6	34	37
1	-5	4	4
1	-4	53	59
1	-3	25	25
1	-2	66	73
1	-1	28	29
1	0	27	29
2	-11	10	9
2	-10	10	9
2	-9	14	13
2	-8	21	21
2	-7	17	17
2	-6	27	28
2	-5	11	10
2	-4	33	35
2	-3	25	28
2	-2	50	50
2	-1	46	45
2	0	13	16
3	-10	6	6
3	-9	17	17
3	-8	21	21
3	-7	12	12
3	-6	15	15
3	-5	30	32
3	-4	21	21
3	-3	27	28
3	-2	10	10
3	-1	19	18
3	0	30	29
4	-9	14	14
4	-8	5	6
4	-7	16	17
4	-6	5	6
4	-5	27	28
4	-4	15	17
4	-3	31	31
4	-2	13	12
4	-1	26	23
4	0	35	35
5	-8	11	10
5	-7	14	13
5	-6	13	13
5	-5	21	21
5	-4	11	12
5	-3	15	15
5	-2	24	24
5	-1	11	10
5	0	36	35
6	-6	9	9
6	-5	14	13
6	-4	2	3
6	-3	21	21
6	-2	14	13
6	-1	7	8
6	0	15	15

H = 4		
K	L	FO	FC
0	-11	16	14
0	-10	5	6
0	-9	31	29
0	-8	31	31
0	-7	34	35
0	-6	28	31
0	-5	50	57
0	-4	16	15
0	-3	41	48
0	-2	12	11
0	-1	11	10
0	0	73	76
1	-11	9	7
1	-10	4	4
1	-9	17	16
1	-8	13	13
1	-7	30	29
1	-6	11	12
1	-5	28	30
1	-4	32	33
1	-3	30	36
1	-2	30	33
1	-1	28	32
1	0	10	7
2	-11	11	10
2	-10	6	6
2	-9	13	11
2	-8	7	7
2	-7	11	11
2	-6	7	6
2	-5	18	19
2	-4	2	0
2	-3	22	25
2	-2	23	23
2	-1	25	29
2	0	34	33
3	-10	15	13
3	-9	11	11
3	-8	4	1
3	-6	23	25
3	-5	7	7
3	-4	8	8
3	-3	25	25
3	-2	20	21
3	-1	20	21
3	0	21	19
4	-9	7	7
4	-8	8	7
4	-7	5	5
4	-6	14	14
4	-5	16	16
4	-4	22	22
4	-3	17	15
4	-2	18	19
4	-1	14	14
4	0	16	15
5	-7	5	7
5	-6	7	7
5	-5	8	9
5	-4	10	10
5	-3	4	3
5	-2	13	14
5	-1	14	13
6	-5	9	9
6	-4	9	9
6	-3	10	10
6	-1	12	12
6	0	4	4

H = 5		
K	L	FO	FC
1	-11	5	5
1	-10	18	17
1	-9	13	11
1	-8	8	7
1	-7	8	8
1	-6	11	11
1	-5	13	14
1	-4	13	13
1	-3	2	2
1	-2	42	41
1	-1	12	11
1	0	13	15
2	-10	9	9
2	-9	15	14
2	-8	24	23
2	-7	10	10
2	-6	5	3
2	-5	9	9
2	-4	31	31
2	-3	10	10
2	-2	30	30
2	-1	25	23
2	0	50	50
3	-10	11	12
3	-9	13	13
3	-8	7	6
3	-7	15	15
3	-6	18	18
3	-5	8	8
3	-4	17	16
3	-3	23	23
3	-2	19	18
3	-1	39	39
3	0	22	22
4	-9	13	12
4	-8	11	11
4	-7	11	11
4	-6	8	7
4	-5	7	7
4	-4	22	23
4	-3	18	18
4	-2	16	16
4	-1	29	28
4	0	3	2
5	-7	10	10
5	-6	19	19
5	-5	12	12
5	-4	12	13
5	-3	13	13
5	-2	9	9
5	-1	22	22
6	-4	17	17
6	-3	8	7
6	-2	5	4
6	-1	8	8

Table 9. (Continued)

6	0	13	12	4	-7	6	5	3	0	46	48	3	-8	7	7
				4	-6	8	7	4	-7	3	3	3	-7	6	7
H =		6		4	-4	27	27	4	-6	9	9	3	-6	10	10
K	L	FO	FC	4	-3	10	9	4	-5	8	8	3	-5	6	7
0	-10	11	10	4	-2	13	14	4	-4	16	17	3	-4	9	9
0	-9	4	3	4	-1	8	8	4	-3	4	3	3	-3	2	1
0	-8	31	32	4	0	27	25	4	-2	23	23	3	-2	22	22
0	-7	27	26	5	-6	3	3	4	-1	9	9	3	0	21	20
0	-6	48	49	5	-5	8	7	4	0	17	17	4	-7	2	3
0	-5	34	33	5	-4	8	8	5	-5	3	3	4	-6	7	6
0	-4	44	48	5	-3	11	12	5	-4	15	17	4	-5	7	8
0	-3	12	10	5	-2	10	10	5	-3	6	7	4	-4	3	4
0	-2	32	38	5	0	2	1	5	-2	14	14	4	-3	5	6
0	-1	10	9	6	-3	5	6	5	-1	10	8	4	-2	14	14
0	0	14	14	6	-2	11	10	5	0	8	7	4	-1	6	7
1	-10	4	2	6	-1	4	5	6	-1	3	4	4	0	3	4
1	-9	8	8	6	0	14	13	6	0	3	3	5	-4	9	9
1	-8	21	21									5	-3	8	7
1	-7	15	15	H =		7		H =		8		5	-2	6	7
1	-6	35	35	K	L	FO	FC	K	L	FO	FC	5	-1	9	9
1	-5	32	32	0	-3	1	0	0	-9	6	7	5	0	3	3
1	-4	20	21	1	-10	13	12	0	-8	17	19				
1	-3	18	18	1	-9	7	8	0	-7	11	10	H =		9	
1	-2	17	19	1	-8	12	12	0	-6	33	32	K	L	FO	FC
1	-1	9	10	1	-5	18	18	0	-5	5	5	1	-8	6	6
1	0	3	2	1	-4	11	11	0	-4	34	32	1	-7	10	9
2	-10	3	3	1	-2	15	16	0	-3	6	5	1	-6	6	6
2	-9	5	4	1	-1	13	15	0	-2	12	12	1	-5	8	8
2	-8	14	15	1	0	13	13	0	-1	23	24	1	-4	10	10
2	-7	13	13	2	-9	7	6	0	0	16	16	1	-3	12	13
2	-6	15	15	2	-8	15	14	1	-9	7	7	1	-2	22	23
2	-5	13	14	2	-7	6	5	1	-8	11	12	1	-1	7	8
2	-4	8	10	2	-6	6	4	1	-6	26	27	1	0	6	7
2	-3	14	13	2	-5	7	6	1	-5	2	2	2	-8	12	11
2	-2	28	29	2	-4	9	8	1	-4	38	38	2	-7	13	12
2	-1	16	15	2	-3	10	10	1	-3	8	7	2	-6	2	3
2	0	50	54	2	-2	22	23	1	-2	18	19	2	-5	18	18
3	-9	7	7	2	-1	15	15	1	-1	8	9	2	-4	11	11
3	-8	10	10	2	0	24	26	1	0	2	3	2	-3	21	22
3	-7	10	9	3	-9	6	6	2	-8	4	5	2	-2	17	17
3	-6	14	13	3	-8	14	13	2	-7	8	8	2	-1	6	6
3	-5	10	11	3	-7	3	3	2	-6	14	13	2	0	30	29
3	-4	9	9	3	-6	13	12	2	-5	8	9	3	-7	11	9
3	-3	14	15	3	-5	9	9	2	-4	17	17	3	-6	4	3
3	-2	32	32	3	-4	9	8	2	-3	5	6	3	-5	13	13
3	-1	17	15	3	-3	9	9	2	-2	15	16	3	-4	8	8
3	0	23	22	3	-2	26	28	2	-1	7	6	3	-3	3	3
4	-8	12	12	3	-1	18	18	2	0	22	21	3	-2	17	17

Table 9. (Continued)

3	-1	7	8
3	0	23	23
4	-5	5	6
4	-4	17	17
4	-3	10	10
4	-2	12	12
4	-1	12	12
4	0	7	8
5	-2	9	9
5	-1	11	10

H = 10

K	L	FO	FC
0	-8	12	11
0	-7	11	10
0	-6	8	7
0	-5	7	6
0	-4	19	19
0	-3	24	22
0	-2	7	8
0	-1	27	28
0	0	10	9
1	-7	9	8
1	-6	13	12
1	-5	10	10
1	-4	7	6
1	-3	21	20
1	-2	8	9
1	-1	19	19
1	0	9	9
2	-7	6	5
2	-6	2	2
2	-5	12	10
2	-4	5	7
2	-3	12	12
2	-2	11	11
2	-1	4	5
2	0	12	11
3	-6	3	5
3	-5	12	12
3	-4	2	1
3	-3	9	9
3	-2	6	7
3	-1	3	2
3	0	4	4
4	-4	10	10
4	-3	9	9
4	-2	3	4
4	-1	9	9
4	0	7	8

H = 11

K	L	FO	FC
0	0	2	0
1	-6	6	5
1	-5	10	10
1	-4	3	3
1	-3	10	10
1	-2	10	10
1	-1	5	6
2	-5	12	13
2	-4	10	11
2	-3	8	9
2	-2	6	6
2	-1	9	9
2	0	11	11
3	-4	3	4
3	-3	14	14
3	-2	4	3
3	-1	6	6
3	0	2	1
4	0	4	4

H = 12

K	L	FO	FC
0	-5	4	5
0	-4	6	5
0	-3	13	13
0	-2	9	8
0	-1	21	22
0	0	18	17
1	-5	7	6
1	-4	3	3
1	-3	8	9
1	-2	7	7
1	-1	17	18
1	0	4	3
2	-4	5	5
2	-3	6	6
2	-1	6	6
2	0	2	1
3	-1	4	4
3	0	7	7

H = 13

K	L	FO	FC
1	-1	2	2
1	0	4	3

RESULTS AND DISCUSSION

Synthesis and Reactions of Phosphatrane

The goals of this study, namely, the synthesis of phosphatrane, 213, and the determination of its structure, have been reached by a somewhat indirect route. Phosphatrane 213 was prepared by Reaction 1, but the major product is a

$$P(N(CH_3)_2)_3 + N(CH_2CH_2OH)_3 \xrightarrow[\Delta]{C_6H_5CH_3} P(OCH_2CH_2)_3N + HN(CH_3)_2 + \text{"polymer"} \quad (1)$$

a polymer of unknown structure. The yield was increased by high dilution conditions to a maximum of 15% (estimated). This was achieved with the procedure described in the Experimental section. Longer reaction times, slower additions or higher dilutions did not increase yields beyond this level.

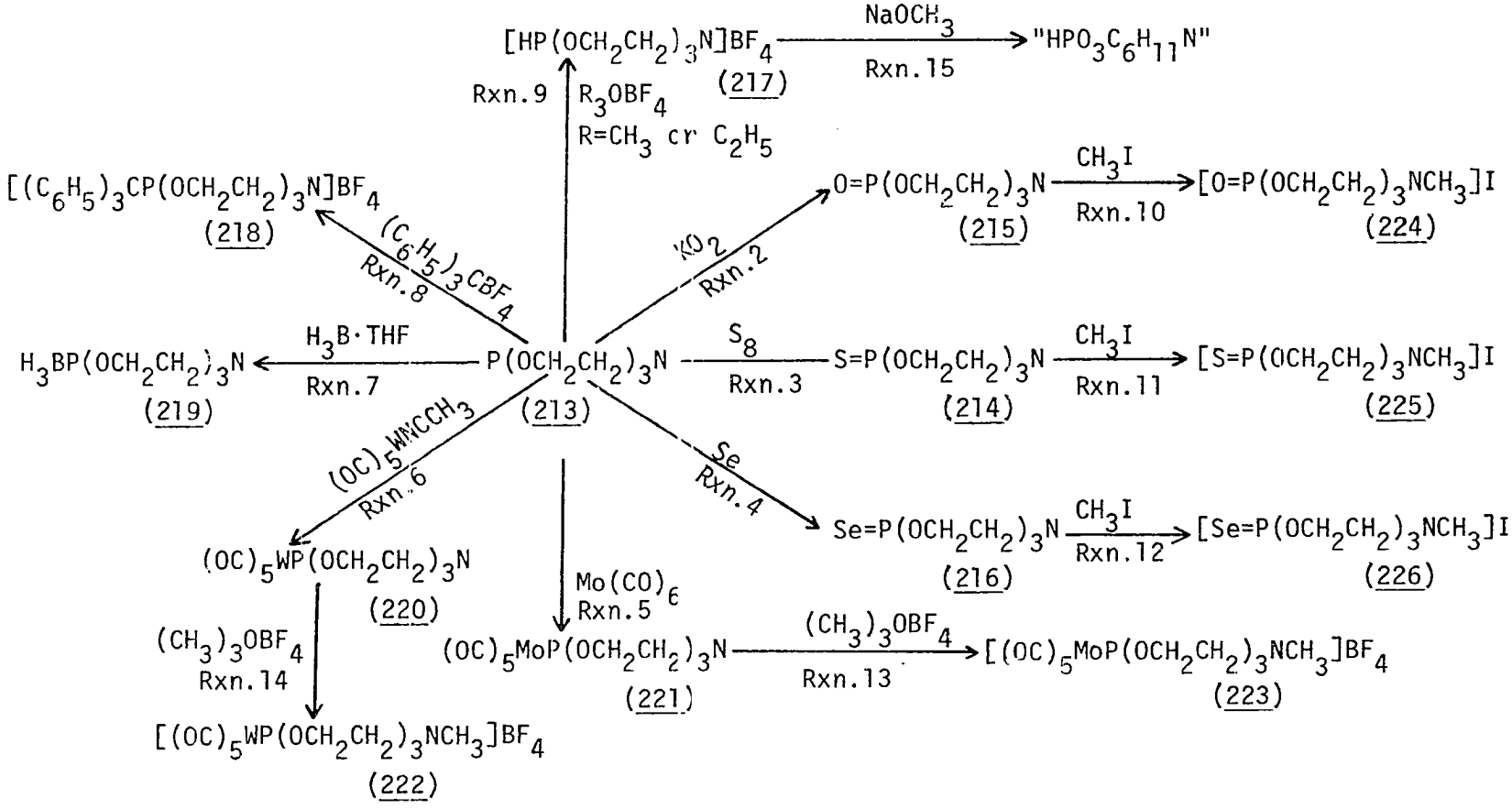
The small amount of 213 present in the reaction mixture relative to the large quantity of polymer would not have constituted an insurmountable separation problem were it not for the observation that concentration of the dilute reaction mixture or allowing the mixture to stand for a day or more resulted in further polymerization. Problems caused by the polymerization and the apparent facile hydrolysis of

213 during elution prevented isolation by chromatography. Residues from the evaporation of toluene from the reaction mixture could not be successfully recrystallized and were explosively pyrolyzed before the product sublimed or distilled.

While the reactivity of 213 seriously hampered purification attempts, it facilitated the formation of derivatives. The reactions shown in Figure 1 produced the stable compounds 214-226. It was hoped that the parent compound could be regenerated from one or more of these materials once they were purified. Failing this, it was hoped that spectroscopic examination of these derivatives might reveal important structural features of 213. Isolation of 214-226 was a laborious procedure consisting of repeated precipitation-filtration cycles to remove the polymer until crystallization took place.

The product of Reaction 9 (Figure 1) was 217 rather than the expected $[R\text{-}P(OCH_2CH_2)_3N]BF_4$, R = CH_3 or C_2H_5.[101] Although this reaction is not presently understood, the source of the proton is thought to be either the Meerwein reagent or water in the reaction mixture. Phosphatrane, 213, may deprotonate an ethyl or methyl group of R_3OBF_4, R = C_2H_5 or CH_3, releasing an olefin into the reaction mixtures. Reaction 8 (Figure 1) takes place as expected since there is no proton available for deprotonation in $(C_6H_5)_3CBF_4$. Water

Figure 1. The reactions which phosphatrane, 213, was observed to undergo


[HP(OCH2CH2)3N]BF4
(217)
NaOCH3
Rxn.15
"HPO3C6H11N"
Rxn.9
R3OBF4
R=CH3 or C2H5
[(C6H5)3CP(OCH2CH2)3N]BF4
(218)
(C6H5)3CBF4
Rxn.8
KO2
Rxn.2
O=P(OCH2CH2)3N
(215)
CH3I
Rxn.10
[O=P(OCH2CH2)3NCH3]I
(224)
H3B·THF
Rxn.7
H3BP(OCH2CH2)3N
(219)
P(OCH2CH2)3N
(213)
S8
Rxn.3
S=P(OCH2CH2)3N
(214)
CH3I
Rxn.11
[S=P(OCH2CH2)3NCH3]I
(225)
(OC)5WNCCH3
Rxn.6
Se
Rxn.4
Se=P(OCH2CH2)3N
(216)
CH3I
Rxn.12
[Se=P(OCH2CH2)3NCH3]I
(226)
(OC)5WP(OCH2CH2)3N
(220)
Mo(CO)6
Rxn.5
(CH3)3OBF4
Rxn.14
(OC)5MoP(OCH2CH2)3N
(221)
(CH3)3OBF4
Rxn.13
[(OC)5MoP(OCH2CH2)3NCH3]BF4
(223)
[(OC)5WP(OCH2CH2)3NCH3]BF4
(222)

in the reaction mixture, despite precautions to exclude it, produces fluoroboric acid, HBF_4, by decomposition of the Meerwein reagent, which could be deprotonated by 213. Presumably, water contamination also accounts for the observation of $[H\text{-}P(OCH_2CH_2)_3N]^+$ in the products of N_2O_4 oxidation of 213, since N_2O_4 forms a mixture of nitrous and nitric acids upon reaction with water.

A large number of reagents were employed to oxidize 213, but only potassium superoxide, KO_2, produced the isolable product 215. Benzoyl peroxide, m-chloroperbenzoic acid, trimethylamine oxide, potassium peroxydisulfate, ozone, singlet oxygen (formed photolytically) and dinitrogen tetroxide produced some reaction, but the product was not successfully separated from the resulting mixture or it was found not to be the desired material. The other reactions in Figure 1 proceeded to the expected products.

Nmr Data

The ^1H nmr spectra of 213-223, recorded in Table 10, consist of a doublet of triplets for the oxygen methylene group, OCH_2, and a triplet for the nitrogen methylene group, CH_2N, except in the spectra of 217 and 218 wherein the CH_2N resonances are an apparent quartet and a triplet of doublets, respectively. These splittings, due to phosphorus-hydrogen and hydrogen-hydrogen couplings, are similar for all of the

Table 10. ^{1}H nmr[a] data for phosphatrane derivatives

Compound	δCH_2O[b]	$^{3}J_{PH}$[c]	$^{3}J_{HH}$	δCH_2N	δ other H groups
213[d]	3.68dt	10.5	5.6	2.60t	
214	4.10dt	16.5	6.2	3.01t	
215	4.05dt	16.1	5.8	3.02t	
216	4.17dt	16.5	5.3	3.06t	
217[e]	4.16dt	14.1	6.2	3.43q ($^{4}J_{PH}$ = 6.2)	δPH, 6.01d ($^{1}J_{PH}$ = 794)
218[e]	4.23dt	16.8	6.0	3.30td ($^{4}J_{PH}$ = 3.0)	δC_6H_5, 6.79m
219[f]	3.96dt	14.1	5.1	2.97t	

[a]Spectra were recorded in d_1-chloroform unless otherwise noted.

[b]Chemical shifts are accurate to ±0.05 ppm.

[c]Coupling constants are accurate to ±0.5 Hz.

[d]The spectrum was recorded in benzene.

[e]The spectrum was recorded in d_3-acetonitrile.

[f]The spectrum was recorded in d_5-dimethylsulfoxide.

Table 10. (Continued)

Compound	δCH_2O	$^3J_{PH}$	$^3J_{HH}$	δCH_2N	δ other H groups
220	3.94dt	13.8	5.0	2.96t	
221	3.98dt	13.0	5.6	2.97t	
222[e]	4.45dt	14.0	4.0	3.71t	δCH_3, 3.18s
223[e]	4.38dt	15.0	5.0	3.80t	δCH_3, 3.18s
224[f]	4.66dt	16.0	4.0	4.11t	
$N(CH_2CH_2OH)_3$	3.67t		5.0	2.62t	

compounds listed ($^3J_{PH}$ = 13.0-16.5 Hz and $^3J_{HH}$ = 4.0-6.2 Hz). The appearance of $^4J_{PH}$ = 5.8 and 3.0 Hz in 217 and 218, respectively, is responsible for the different CH_2N splitting patterns in those compounds.

The chemical shift of the nitrogen methylene hydrogens of 214-216 and 219-221 are 0.35-0.41 ppm downfield from those of triethanol amine, while in 217 and 218 they are 0.82 and 0.69 ppm downfield, respectively. The positive charge on 217 and 218 may account for their larger shifts, but these values are not as great as the ones recorded for 222 (1.10 ppm) and 223 (1.19 ppm) which are also positively charged species. Voronkov,[16] Pestunovich et al.[86] and Tzschach et al.[40] attributed similar changes in δ $\underline{CH_2}N$ of silatranes (0.10-0.31 ppm) and stannatranes (0.25-0.34 ppm) to a reduced electron density on nitrogen as a result of participation in a transannular Si-N or Sn-N bond.

The ^{13}C nmr data in Table 11 show that the chemical shifts of the OCH_2 carbon and the phosphorus-carbon coupling constants, $^2J_{PC}$, in the phosphatrane compounds are similar to the values found for tri-n-butylphosphate. The chemical shifts of the CH_2N carbon of 214-220 are 3.5-6.4 ppm upfield with respect to triethanol amine while the δ $\underline{CH_2}N$ values of 222 and 224 are 7.9 and 8.4 ppm, respectively, downfield from triethanol amine. The different shift directions are not due to the positive charge on the quaternized nitrogen

Table 11. ^{13}C nmr data for phosphatrane derivatives

Compound[a]	$\delta CH_2(O)$[b]	$^2J_{PC}$[c]	$\delta CH_2(N)$	$^3J_{PC}$
214	67.7	11.8	50.9	---
215	65.9	8.9	49.0	---
216	67.6	12.8	50.7	---
217[d]	60.0	10.8	48.5	12.8
218[e]	63.2	12.8	48.0	9.8
219[e]	64.9	10.8	49.4	2.0
220	63.3	10.8	49.0	---
222[d]	60.2	10.8	62.3[f]	---
224[e]	64.3	6.9	63.1[f]	---
$N(CH_2CH_2OH)_3$	56.8		54.4	
$P(O\text{-}n\text{-}C_4H_9)_3$	66.0	5.9		

[a]Nmr were taken in d_6-acetone unless otherwise noted at a sweek width of 8000 Hz.

[b]Chemical shifts are accurate to ± 0.1 ppm.

[c]Coupling constants are accurate to ±0.5 Hz. Coupling that was not resolved is shown by a dash, ---.

[d]The spectrum was recorded in d_3-acetonitrile.

[e]The spectrum was recorded in d_6-dimethysulfoxide.

[f]The nitrogen methyl group has a coincident chemical shift.

of 222 and 224 since the cationic compounds, 217 and 218, have the largest upfield shifts, 5.9 and 6.4 ppm, respectively. Three-bond phosphorus-carbon couplings, $^{3}J_{PC}$, are observed in the spectra of 217-219 while this coupling is too small to be resolved for any of the other compounds, 214-216, 220, 222 and 224. As will be seen in later discussion, these observations are indicative of certain structural features in phosphatrane systems.

The ^{31}P nmr chemical shift parameters recorded in Table 12 for 214-216 are not very different from those of the bicyclic phosphorus compounds $Y\text{-}P(OCH_2)_3CCH_3$ where Y = S, O and Se (-57.4 ppm[102], 8.0 ppm[102] and -60.5 ppm,[103] respectively). The phosphorus-selenium coupling constant of 216 (973.2 Hz) is also close to that measured for $Se{=}P(OCH_2)_3CCH_3$ (1052.0 Hz).[103] The phosphorus-metal coupling constants in 220-223 are similar to those for acyclic and bicyclic phosphites in pentacarbonyltungsten complexes, $(OC)_5WL$ where L = $P(OCH_3)_3$ ($^{1}J_{WP}$ = 398) and L = $P(OCH_2)_3CC_5H_{11}$ ($^{1}J_{WP}$ = 393)[104,105] and in pentacarbonylmolybdenum complexes, $(OC)_5ML$ where L = $P(OCH_3)_3$ ($^{1}J_{MoP}$ = 216 Hz) and L = $P(OCH_2)_3CCH_3$ ($^{1}J_{MoP}$ = 226 Hz) (see Appendix). The nmr active isotopes of tungsten (^{183}W, 14.4%) and molybdenum ($^{95,97}Mo$, 15.7 and 9.5%) split the major ^{31}P resonances into a doublet for ^{183}W (I = 1/2) and a sextet for $^{95,97}Mo$ (I = 5/2). The sextet for 221 is reproduced in

Figure 2. These data are consistent with a tetrahedral geometry for the phosphorus atom in 214-216 and 220-224.

However, the δ ^{31}P values of 217-219 are unlike those of analogous compounds. The chemical shift of 217 (20.9 ppm) is over 40 ppm upfield from the shift for $[HP(OCH_2)_3CCH_3]^+$ (-32.2 ppm)[106] and $[HP(OCH_3)_3]^+$ (-24.4 ppm).[107] The spectrum of 217 contains coupling to both CH_2 groups' hydrogens ($^3J_{PH}$ and $^4J_{PH}$) and the proton bonded directly to phosphorus ($^1J_{PH}$) (Figure 3). The phosphorus-hydrogen coupling constant of 217 ($^1J_{PH}$ = 779.2 Hz) is distinctly smaller than that of either $[HP(OCH_2)_3CCH_3]^+$ (899 Hz)[106] and $HP(OCH_3)_3]$ (826 Hz).[107] While the ^{31}P chemical shift of 218 is considerably upfield from $[(C_6H_5)_3CP(OCH_2)_3CCH_3]^+$ (-51.3 ppm) and $[(C_6H_5)_3CP(OC_2H_5)_3]^+$ (-25.7 ppm), the phosphorus-carbon coupling constants, $^1J_{PC}$, are very similar (Table 12). The chemical shifts of 219 (-98.3 ppm) and $H_3B\text{-}P(OCH_2)_3CCH_3$ (-97.6) are nearly the same, but the phosphorus-boron couplings, $^1J_{PB}$, are markedly different (120.3 Hz and 91.0 Hz, respectively). A tetrahedral geometry for phosphorus in 217-219 is not consistent with these parameters.

Triptych Structures

A triptych structure for compound 217 requires a five-coordinate phosphorus atom with the ester oxygens equatorial and the hydrogen and nitrogen axial in a trigonal bipyramidal

Figure 2. The ^{31}P nmr spectrum of pentacarbonylmolybdenum phosphatrane, 221, shows a sextet (1:1:1:1:1:1) of satellite peaks due to $^{95,97}Mo$-^{31}P coupling

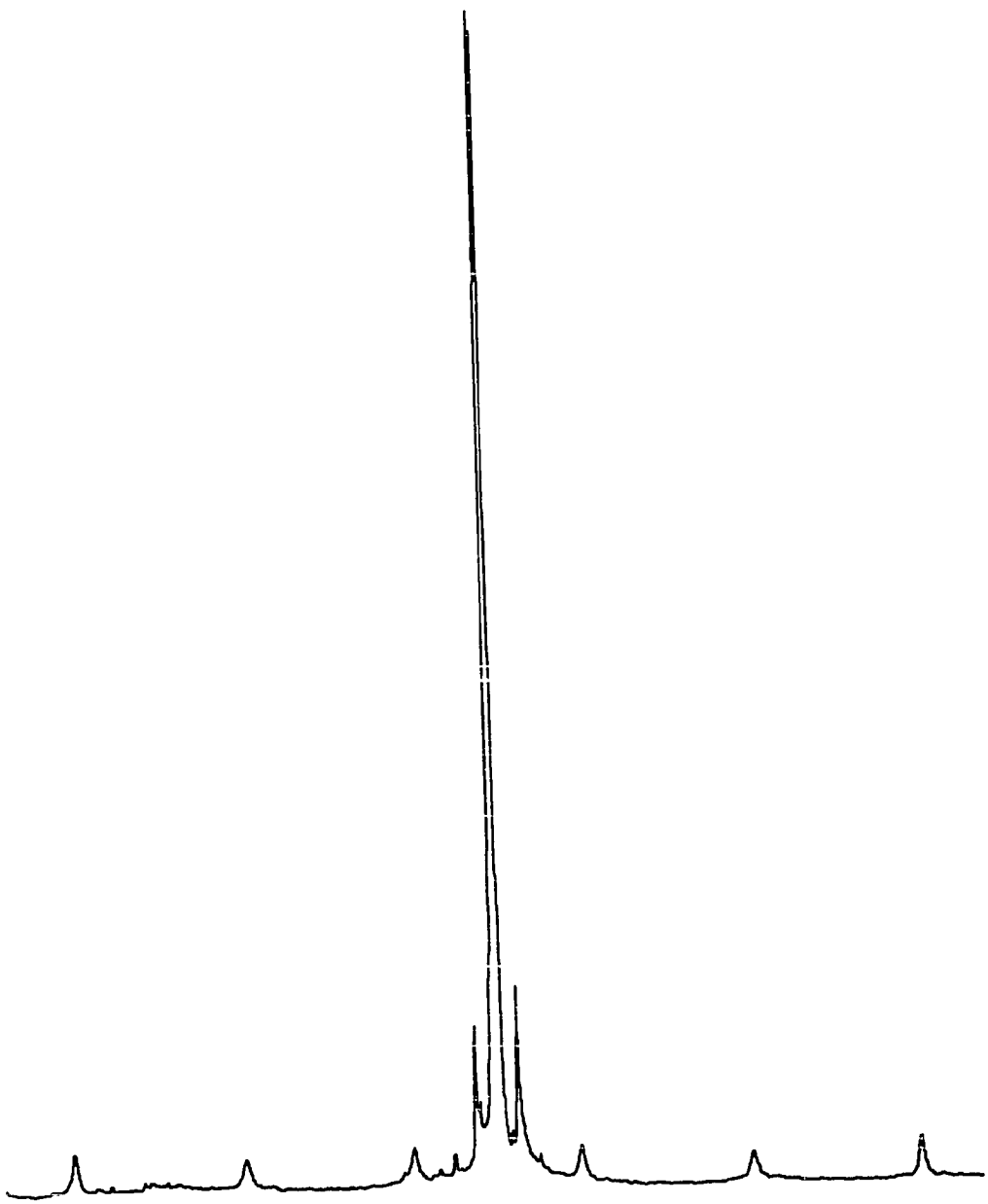


Figure 3. The ^{31}P nmr spectrum of 217 consists of a doublet of multiplet due to ^{1}H-^{31}P coupling. Eight of the expected fourteen peaks of each multiplet can be seen. The large singlet peak is the external standard, 85% H_3PO_4

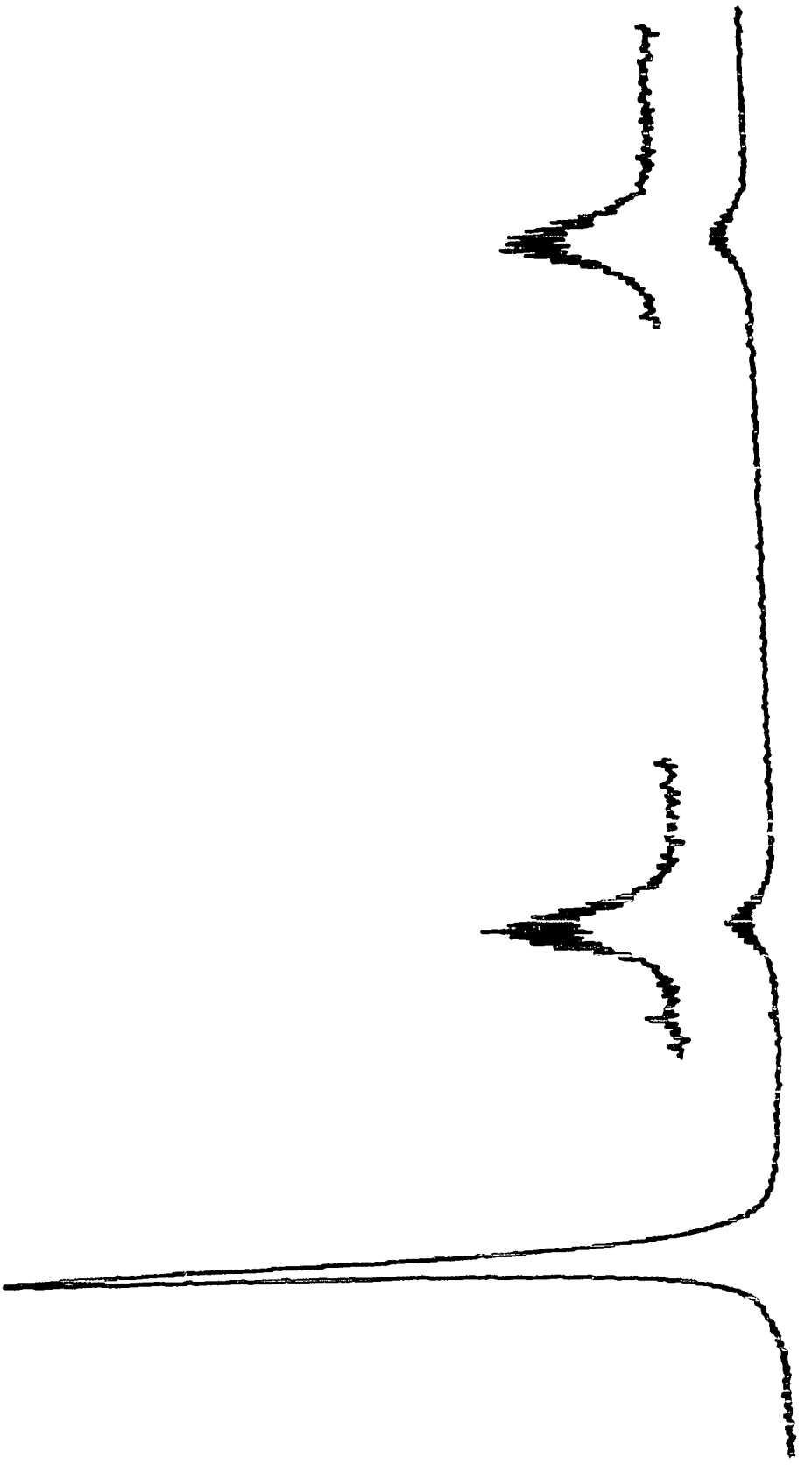


Table 12. ^{31}P nmr data for phosphatrane derivatives

Compound[a]	δ[b]	$^3J_{PH}$[c]	Miscellaneous Couplings
213[d]	-115.2	10.0	
214	-60.9	16.6	
215	6.6	15.8	
216	-58.0	16.6	$^1J_{PSe}$ = 973.2
217[e]	20.9	---	$^1J_{PH}$ = 779.6
218[f]	-5.9	16.1	$^1J_{PC}$ = 5.9
219[f]	-98.3	---	$^1J_{PB}$ = 120.3
220	-119.2	14.4	$^1J_{WP}$ = 403.6
221	-143.7	14.1	$^1J_{MoP}$ = 229.0

[a]Spectra were recorded in d_1-chloroform unless otherwise noted at a sweep width of 9000 Hz.

[b]Chemical shifts are accurate to ±0.1 ppm.

[c]Coupling constants are accurate to ±0.5 Hz. Coupling that was not resolved is shown by a dash, ---.

[d]The spectrum was recorded in benzene.

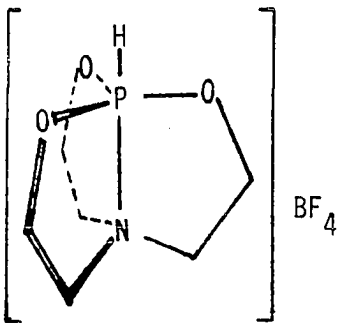
[e]The spectrum was recorded in d_3-acetonitrile.

[f]The spectrum was recorded in d_6-dimethylsulfoxide.

Table 12. (Continued)

Compound	δ	$^3J_{PH}$	Miscellaneous Couplings
222[e]	-122.5	14.0	$^1J_{WP}$ = 416.2
223[e]	-146.4	15.0	$^1J_{MoP}$ = 235.7
224[e]	7.2	16.1	
$[(C_6H_5)_3CP(OCH_2)_3CCH_3]^+$	-51.3	---	$^1J_{PC}$ = 5.9
$[(C_6H_5)_3CP(OCH_3)_3]^+$	-25.7	---	$^1J_{PC}$ = 6.0

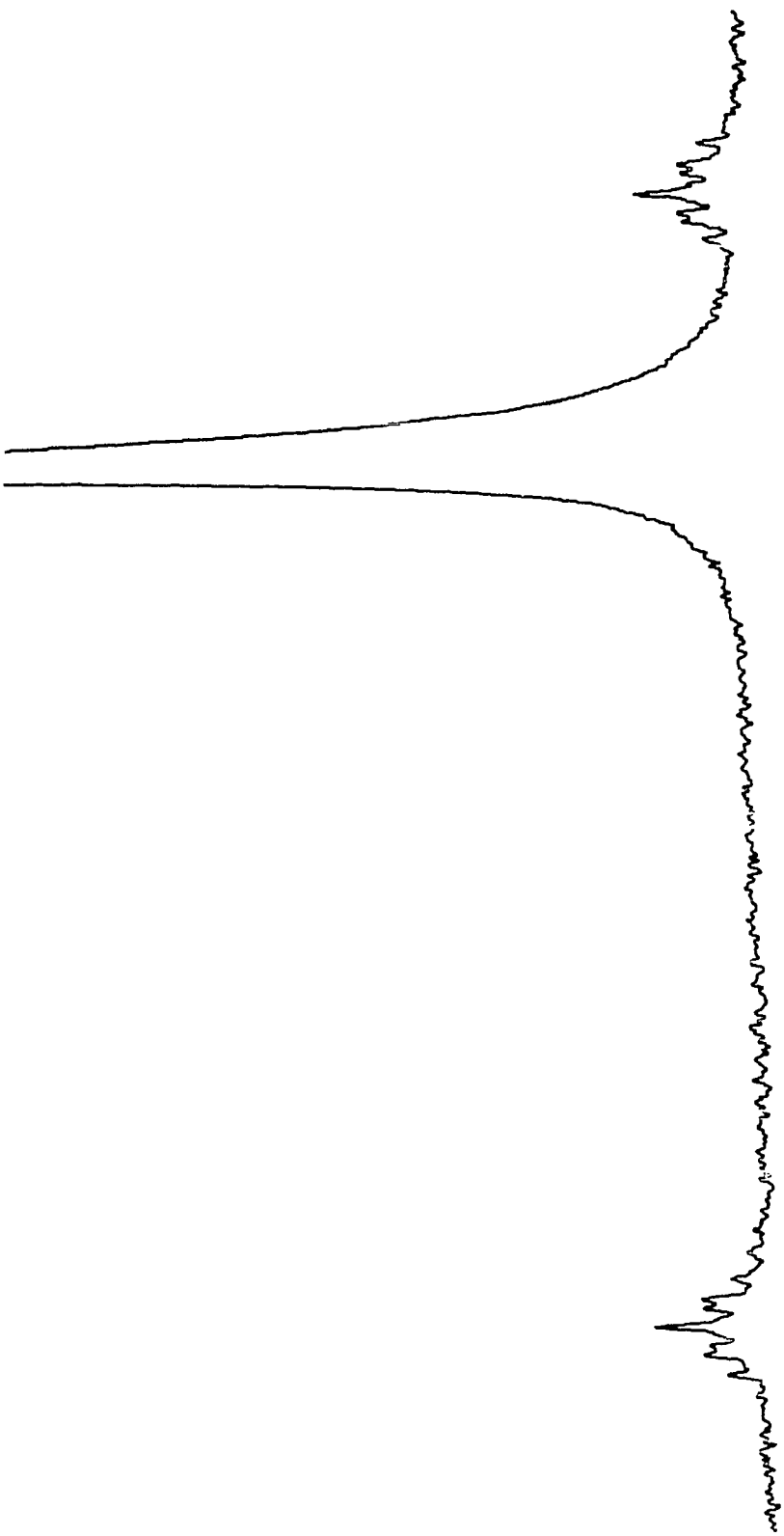
geometry. The P-N transannular bond would add electron



217

density to phosphorus increasing the base properties of the compound. This enhanced basicity is consistent with the unprecedented stability of 217. With the exception of 217, all protonated phosphite esters are formed only at low temperature in strongly acidic media.[106-108] The hydrogen bonded to phosphorus in 217 cannot be removed by ordinary bases. Four equivalents of 1,8-bis(dimethylamino)naphthalene (Proton Sponge) or two equivalents of sodium methoxide (Reaction 15 in Figure 1) do not deprotonate phosphorus, but rather appear to remove a hydrogen from a methylene group. The ^{31}P nmr spectrum of this product (Figure 4) shows a decidedly different multiplet with a chemical shift and $^{1}J_{PH}$ of 10.0 ppm and 726.9 Hz compared to 20.9 ppm and 779.6 Hz for 217. Although this product has not been isolated or further characterized, the symmetrical second order multiplets in Figure 4 are consistent with removal of a proton

Figure 4. The ^{31}P nmr spectrum of the product of Reaction 15 (Figure 1) is a double of multiplets. The large singlet is the external standard, 85% H_3PO_4



from one of the methylene groups of 217. Furthermore, under strongly acidic conditions, $HSO_3F \cdot SbF_5$ in liquid SO_2 at -50°, the ^{31}P spectrum of 217 remained unchanged, indicating that the nitrogen bridgehead was not protonated.

Vande Griend and Verkade[107] demonstrated a correlation between phosphite basicity and $^1J_{PH}$ for protonated phosphites. Phosphorus-hydrogen coupling has also been shown to mirror the effective nuclear charge parameter better than the percent s character parameter of the Fermi contact term in such systems wherein phosphorus is tetravalent.[109] The $^1J_{PH}$ value of 217 may be small because the electron density from nitrogen keeps the effective charge on phosphorus low. Moreover, the detection of this coupling in the absence of a protonating solvent demonstrates the strongly basic character of the parent compound 213.

A triptych structure was confirmed by an X-ray crystal structure determination in the case of 217.[110] The bond distances and bond angles are listed in Table 13 and computer drawings[97] are shown in Figures 5 and 6. The P-N transannular bond of 1.986 Å is greater than the sum of the covalent radii (1.85 Å).[72] This distance is about the same as the Si-N distances found in 46 and 73,[75,76] if the difference in atomic radii of silicon and phosphorus is taken into account. The P-N bond length is also comparable to the phosphorus-nitrogen distances in the six-coordinate

Table 13. Bond distances and angles for $[H\text{-}P(OCH_2CH_2)_3N]BF_4$

Atoms[a,b]	Distances (Å)	Atoms[c]	Angles (°)
P-H(P)	1.349(71)	P-O(1)-C(1)	122.7(4)
P-N	1.986(5)	P-O(2)-C(2)	121.7(3)
P-O(1)	1.577(3)	P-N-C(3)	106.0(4)
P-O(2)	1.581(4)	P-N-C(4)	105.7(5)
C(1)-O(1)	1.425(9)	P-N-C(4)*	103.9(5)
C(2)-O(2)	1.447(6)	O(1)-P-O(2)	120.0(1)
C(1)-C(3)	1.557(13)	O(1)-P-O(2)	120.0(1)
C(2)-C(4)	1.552(13)	O(2)-P-O(2)'	119.3(3)
C(2)-C(4)*	1.486(14)	N-C(3)-C(1)	105.1(7)
N-C(3)	1.498(11)	N-C(4)-C(2)	103.9(7)
N-C(4)	1.467(10)	N-C(4)*-C(2)	102.5(7)
N-C(4)*	1.510(10)	F(1)-B-F(2)	106.1(5)
B-F(1)	1.366(10)	F(1)-B-F(3)	109.3(8)
B-F(2)	1.368(6)	F(1)-B-F(3)'	106.1(5)
B-F(3)	1.324(11)	F(2)-B-F(3)	108.0(6)
		F(2)-B-F(3)'	113.4(5)
		F(3)-B-F(3)'	113.4(5)
		N-P-O(1)	87.1(2)
		N-P-O(2)	87.6(1)

[a]Numbering of the atoms corresponds to that in Figure 5.

[b]Primed atoms have been generated by the mirror plane.

[c]An asterisk (*) denotes a disordered atom.

Table 13. (Continued)

Atoms	Distances (Å)	Atoms	Angles (°)
		N-P-O(2)'	87.6(1)
		H-P-O(1)	88.8(29)
		H-P-O(2)	88.7(48)
		H-P-O(2)'	100.2(48)
		H-P-N	172.2(48)
		O(1)-C(1)-C(3)	106.6(5)
		O(2)-C(2)-C(4)	107.1(6)
		O(2)'-C(2)'-C(4)*	106.9(6)
		C(3)-N-C(4)	113.8(8)
		C(4)-N-C(4)*	112.6(7)
		C(3)-N-C(4)*	113.6(7)

Figure 5. The computer drawing shows the molecular structure of the cation of 217. Only the hydrogen bonded to phosphorus is shown for clarity

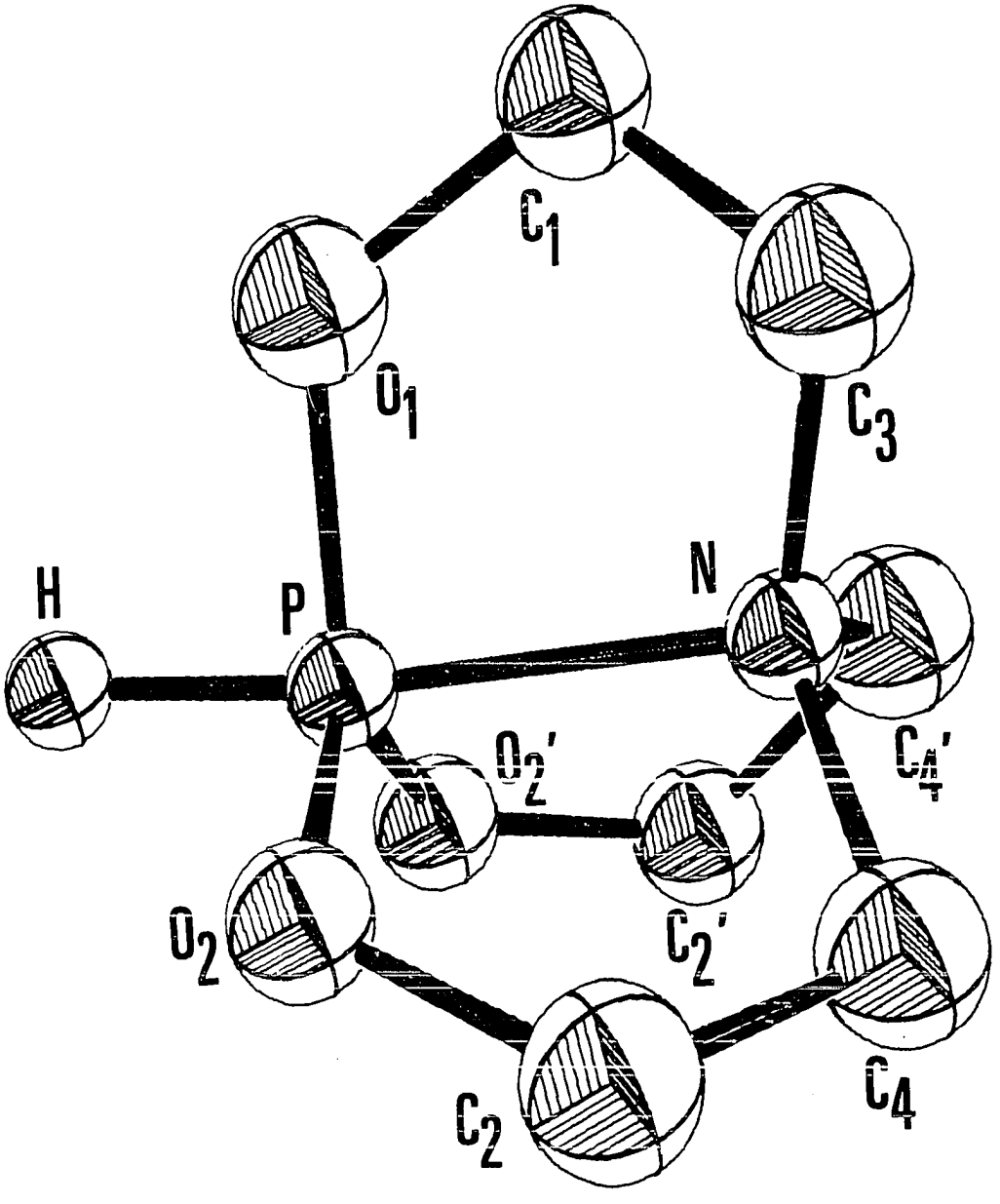
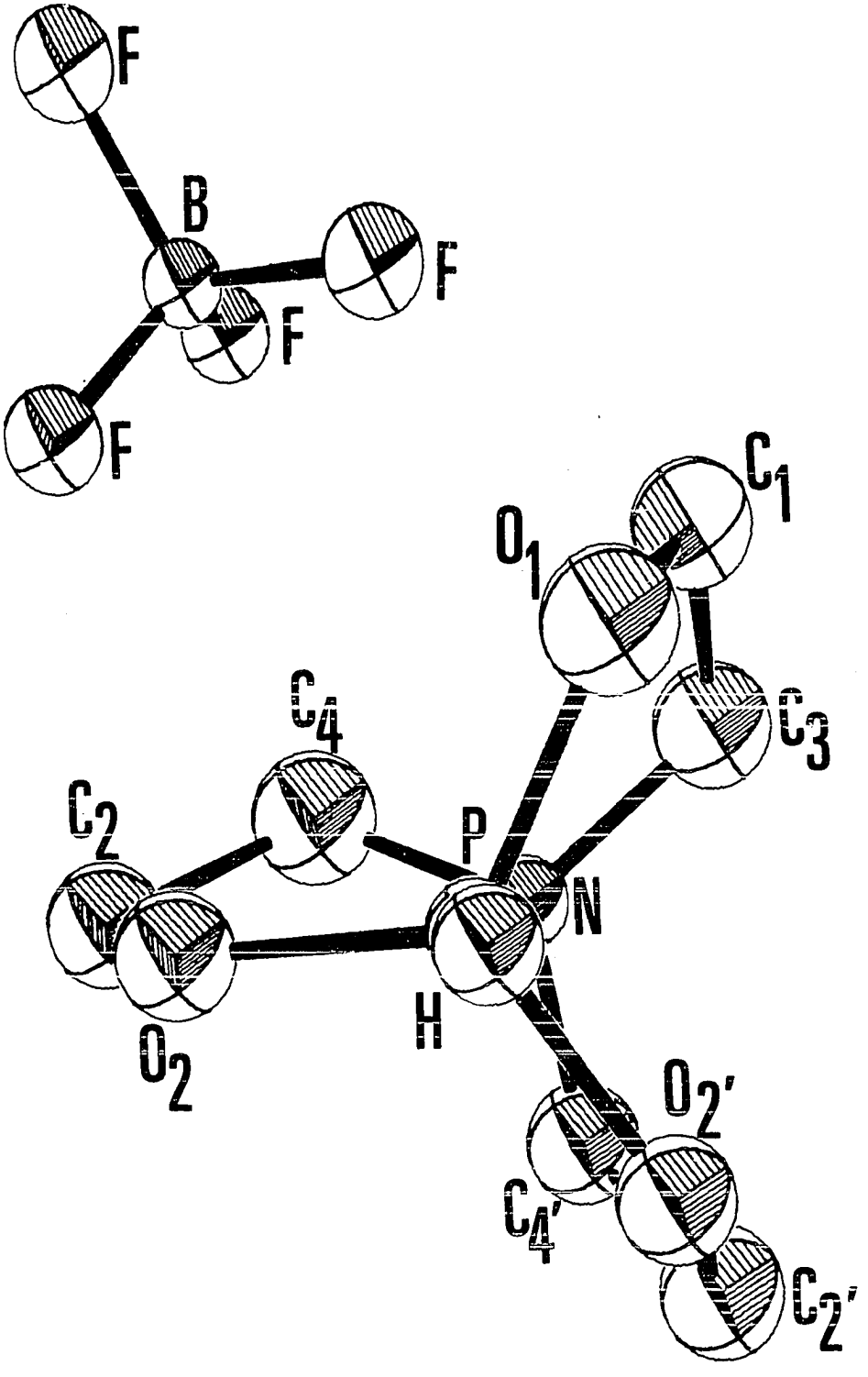
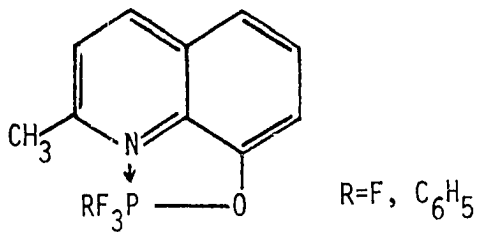

C1
O1
C3
H
P
N
O2'
C4'
O2
C2'
C2
C4

Figure 6. The computer drawing of the molecular structure of 217 is viewed down the H-P-N axis. Only the hydrogen bonded to phosphorus is shown for clarity


F
B
F
F
F
C1
O1
C3
C4
C2
P
N
H
O2
O2'
C4'
C2'

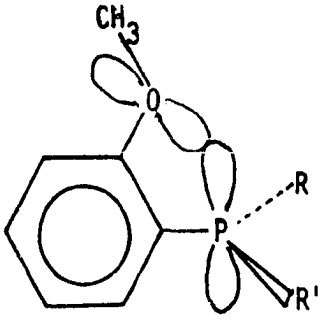
systems below (1.91-1.98 Å). The electronegative fluorines



on the six-coordinate phosphorane group are effective in making the phosphorus acidic enough to attract the nitrogen lone pair.[111]

The phosphorus coordination geometry is trigonal bipyramidal in 217 with O-P-O and O-P-N angles averaging 119.8 and 87.4°, respectively, and a H-P-N angle of 172.2(5)°. This slightly distorted trigonal bipyramidal geometry of the five electron pairs around the phosphorus atom in 217 contrasts the relative instability of this electron pair configuration in $:PX_3 \leftarrow NR_3$ adducts[112] and intermediates involved in certain reactions of trivalent phosphorus compounds.[113] The P-H bond distance in 217 (1.35 Å) is about 0.1 Å shorter than the 1.41 to 1.45 Å found in several phosphines and PH_4^+ [114] and is also slightly shorter than the sum of the covalent radii (1.38 Å).[72] The rest of the bond angles and distances of the tricyclic 217 are typical for this geometry.[75-77]

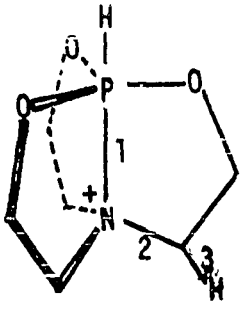
McEwen et al.[115] have proposed that a p-d interaction between the methoxy oxygen and phosphorus of o-anisyldiarylphosphines, as depicted below, lowers the transition state energy of quaternization reactions of these phosphines.

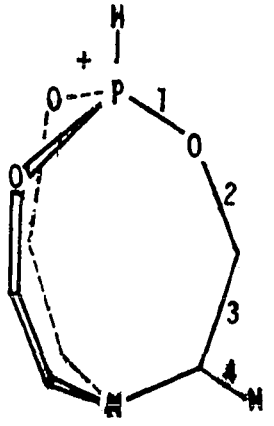


The increased electron density in the d-orbitals of phosphorus from such an interaction is believed to result in a marked acceleration of this reaction compared with triaryl phosphines lacking ortho-oxygens. The P-N p-d interaction of 217, which greatly enhances its stability and the base strength of the parent compound, lends some support to the rationale of McEwen et al.[115] It should be pointed out, however, that the ring size in 217 is larger than that in the proposed transition state shown above.

The triptych structure provides a rationalization for the observation of the $^{4}J_{PH}$ and $^{3}J_{PC}$ couplings in the nmr spectra of 217. Thus, the four-bond phosphorus-hydrogen coupling is reduced to a three-bond interaction by the P-N

transannular bond. Similarly, the phosphorus-carbon coupling



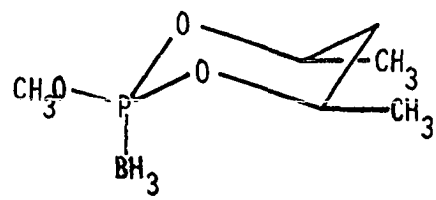


becomes a two-bond coupling. The fact that phosphorus does not couple to the nitrogen methylene groups of 214-216, 220 and 221 may be an indication of a bicyclic geometry for these compounds and hence the lack of a P-N bond. Since the ^{1}H and ^{13}C nmr spectra of 218 and 219 are similarly split by phosphorus, the triptych geometry must be considered likely for these compounds, too.

Compound 218 is far more stable than $[(C_6H_5)_3CP(OCH_2)_3CCH_3]^+$ or $[(C_6H_5)_3CP(OCH_3)_3]^+$ which decompose on standing. The ^{31}P chemical shift of 218 is about 20 ppm upfield from the resonances of the latter compounds. These observations coupled with the electron withdrawing property of the trityl group, $(C_6H_5)_3C^+$, and the above-mentioned phosphorus couplings indicate that the structure of 218 is probably also triptych.

The ^{1}H and ^{13}C nmr data of 219 are of little assistance in determining its structure since a $^{3}J_{PC}$ coupling is resolved

while a $^{4}J_{PH}$ splitting is not. The $^{1}J_{PB}$ value (120.3 Hz) observed in the ^{31}P spectrum of 219 is unusually large when compared with the largest value of this coupling in phosphite-borane adducts, 108.0 Hz for $(CH_3O)(H_3B)P(OCHCH_3)_2CH_2$ (227).



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It is tempting to attribute the large $^{1}J_{PB}$ value of 219 to an enhanced basicity of 213, but studies[116,117] have shown such conclusions to be tenuous. In smoothly varying series such as $H_3P\text{-}BH_3$, $F_2HP\text{-}BH_3$ and $F_3P\text{-}BH_3$ the $^{1}J_{PB}$ value quantitatively mirrors basicity; however, a comparison of $^{1}J_{PB}$ values of similar magnitude for compounds of very different composition or structure is not valid.[117] In light of this caution the phosphorus-boron coupling constant only indicates that there appears to be a change in phosphorus geometry and/or donor properties.

Exchange studies of solutions of 219 and a series of Lewis bases, however, do imply that the large $^{1}J_{PB}$ value is consistent with an increased base strength. No borane

exchange was evident in solutions of 219 and trimethylphosphite, triphenylphosphine, triethylamine and pyridine in Reaction 16 even when equilibrated for two months. The reverse exchange does take place (Reaction 17).

$$\underline{219} + \text{Base} \longrightarrow \text{N.R.} \qquad (16)$$

Base = $P(OCH_3)_3$, $P(C_6H_5)_3$, $N(C_2H_5)_3$ or 

$$\underline{213} + H_3BP(OCH_3)_3 \xrightarrow[DMSO]{} \underline{219} + P(OCH_3)_3 \qquad (17)$$

Application of Bent's isovalent hybridization rule[118] to the B-H bond and assuming that B-H and C-H stretching frequencies behave similarly in their dependence upon the carbon hybridization,[119] allows use of the νB-H frequencies of borane adducts as a measure of base strength. The hybridization of boron's valence orbitals and νB-H will vary with the amount of electron density donated by the base. A decrease in νB-H corresponds to less s character in the B-H bond and an increase in basicity. The νB-H frequencies in the infrared spectrum of 219 (2385, 2347 cm^{-1}) are lower than those of $H_3BP(OCH_2)_3CCH_3$ (2421, 2363 cm^{-1}) or 227 (2392, 2342 cm^{-1}). This evidence for the enhanced basicity of 219 coupled with the high polarity of the adduct as evidenced by its insolubility in all but the most polar solvents, reinforces the assignment of a tricyclic structure for 219.

Bicyclic Structures

The structure of the chalconide derivatives, 214-216, and zero-valent metal carbonyl complexes of phosphatranes, 220 and 221, are not easily deduced from the available spectroscopic data. Nmr data reflecting the phosphorus stereochemistry are consistent with a normal tetrahedral geometry, while those associated with the nitrogen bridgehead stereochemistry are rather ambiguous. The similarity of the ^{31}P chemical shifts of 214-216 and the ^{31}P-Se, $^{31}P^{183}W$ and $^{31}P^{95,97}Mo$ coupling constants in 216, 220 and 221, respectively, to known compounds, as previously noted, suggests a normal tetrahedral geometry at phosphorus. The infrared spectra of 214-216 also show no unusual $\nu P{=}S$, $\nu P{=}O$, or $\nu P{=}Se$ frequencies (881 and 614 cm^{-1}, 2176 cm^{-1} and 580 cm^{-1}, respectively), according to the ranges set by Thomas.[120]

The reactivity of the nitrogen bridgehead of 214-216 is greatly reduced. A reaction time of nearly 10 hours is needed to quaternize the nitrogen in 214-216 and methyl iodide at 40° in acetonitrile (Reactions 10-12 in Figure 1) while triethanol amine reacts completely in 30 minutes under the same conditions. Reactions 13 and 14 in Figure 1 quaternize the nitrogen of 220 and 221 after 4 hours, but trimethyloxonium fluoroborate does not methylate the nitrogen of 214-216 during the same time.

Neither a bicyclic nor a triptych structure accounts for this low reactivity. A bicyclic geometry would seem to require the nitrogen to be at least as reactive as triethanol amine. While a tricyclic structure severely decreases the availability of nitrogen for reaction, it also requires a pentacoordinate phosphorus which is inconsistent with the nmr evidence.

The chemical shifts of the nitrogen methylene group in the ^{1}H and ^{13}C nmr spectra of 214-216, 220 and 221, as discussed earlier in this section, are not consistent with a tetrahedral nitrogen. The values of the ^{13}C nmr parameters are nearly the same as those for 217-219, but no electronic interaction with phosphorus is indicated. Dipole moment measurements may have helped to decide which structure is correct, but these compounds were not sufficiently soluble in the solvents tried.

The dilemma was resolved by the crystal structure determination of 214.[121] The bond distances and bond angles for 214 are listed in Table 14. The phosphorus coordination geometry is tetrahedral with S-P-O and O-P-O angles averaging 110.8° and 108.1°. However, the nitrogen is nearly trigonal planar with C-N-C angles averaging 119.2°. This is readily seen in the computer drawings[97] of 214 in Figures 7 and 8. The nitrogen is 0.13 Å out of the plane formed by the carbons bonded to nitrogen. The P-N distance

Table 14. Intramolecular bond distances and angles for $S{=}P(OCH_2CH_2)_3N$

Atoms[a]	Distances (Å)	Atoms	Angles (°)
P-S	1.933(3)	S-P-O(1)	110.7(3)
P-O(1)	1.568(7)	S-P-O(2)	110.6(3)
P-O(2)	1.609(7)	S-P-O(3)	111.2(2)
P-O(3)	1.548(7)	O(1)-P-O(2)	106.2(4)
O(1)-C(1)	1.528(12)	O(1)-P-O(3)	110.0(4)
O(2)-C(3)	1.513(11)	O(2)-P-O(3)	108.0(4)
O(3)-C(5)	1.492(12)	O(1)-C(1)-C)2)	116.0(8)
C(1)-C(2)	1.537(14)	O(2)-C(3)-C(4)	116.6(8)
C(3)-C(4)	1.538(14)	O(3)-C(5)-C(6)	117.1(8)
C(5)-C(6)	1.589(14)	P-N-C(2)	84.1(5)
C(2)-N	1.460(14)	P-N-C(4)	85.6(5)
C(4)-N	1.424(14)	P-N-C(6)	84.3(5)
C(6)-N	1.466(14)	P-O(1)-C(1)	124.3(6)
		P-O(2)-C(3)	126.1(6)
		P-O(3)-C(5)	127.6(7)
		N-C(2)-C(1)	118.3(8)
		N-C(4)-C(3)	117.9(7)
		N-C(6)-C(5)	116.5(8)
		C(2)-N-C(4)	119.5(8)
		C(2)-N-C(6)	116.2(9)
		C(4)-N-C(6)	121.8(9)
		S-P-N	179.2(4)

[a]Numbering of the atom corresponds to that in Figure 7.

Figure 7. The computer drawing shows the molecular structure of 214. The hydrogen atoms have been omitted for clarity

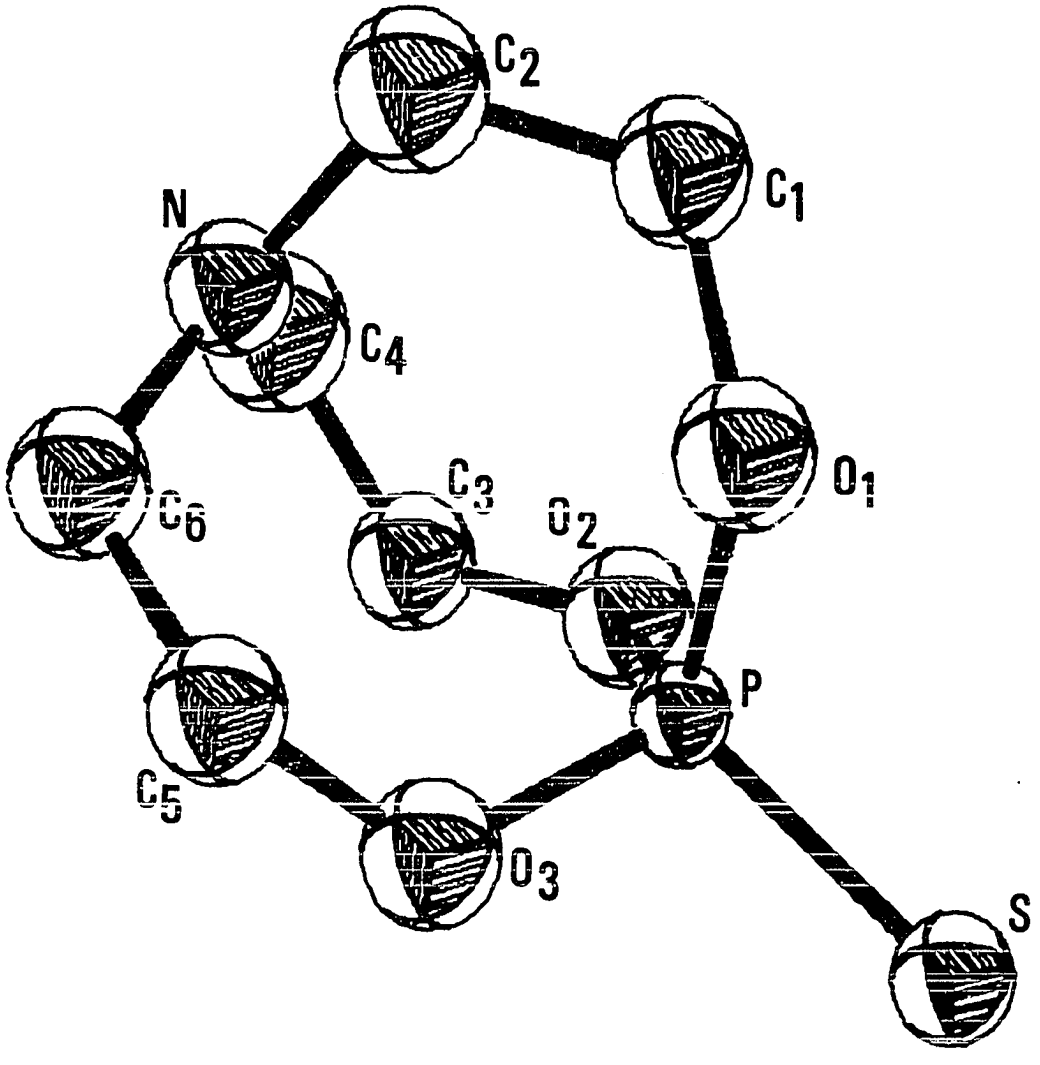
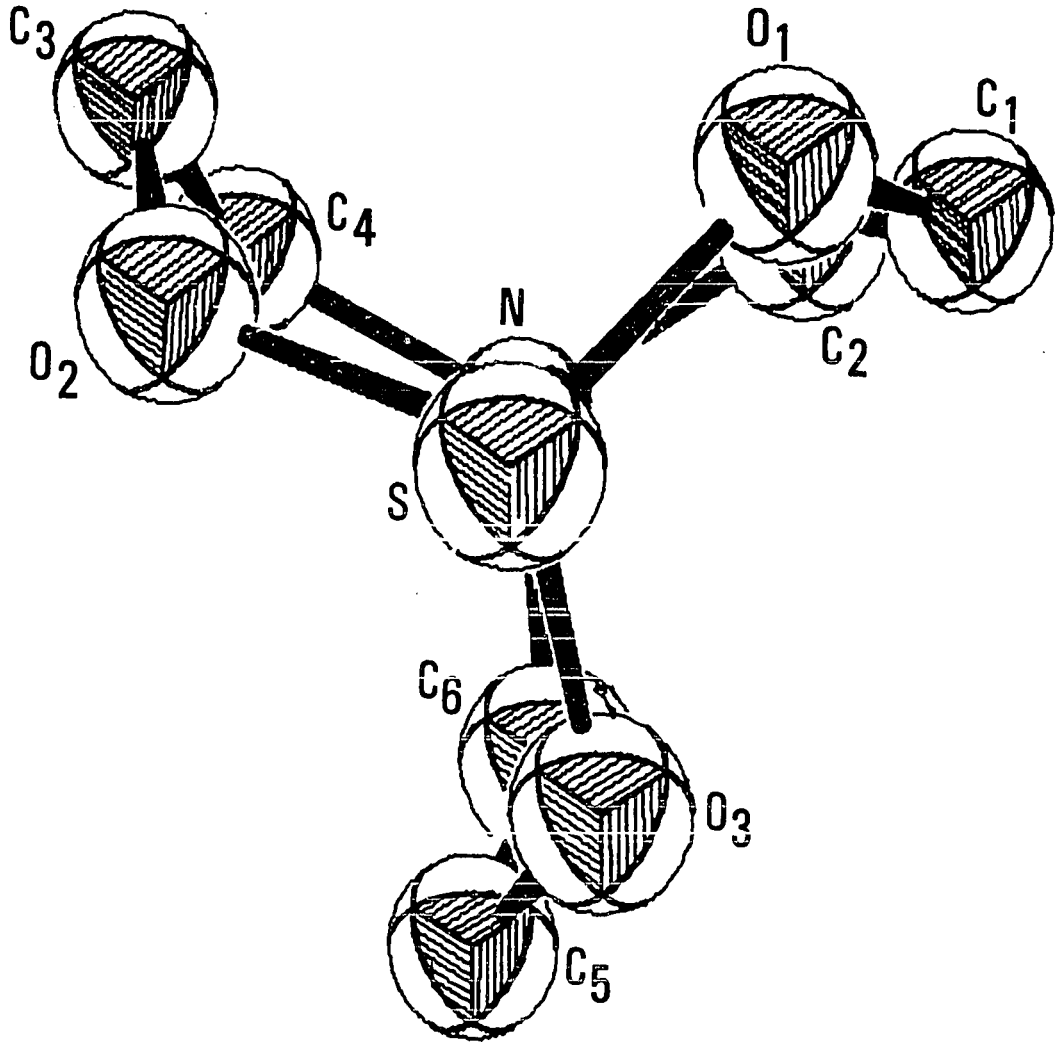
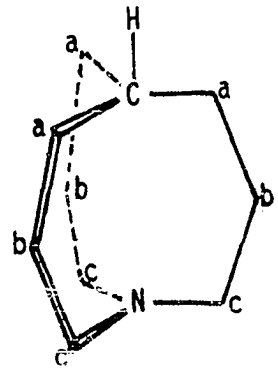

C2
C1
N
C4
C6
C3
O2
O1
P
C5
O3
S

Figure 8. The computer drawing shows the molecular structure of 214 viewed down the S-P-N axis. The hydrogens have been omitted for clarity


C3
O1
C1
C4
N
O2
C2
S
C6
O3
C5

(3.132 Å) arising as a consequence of the geometry appears to preclude any transannular P-N interaction. The P=S bond distance (1.933 Å) is slightly longer than the average bond length of thiophosphoryl groups (1.91±0.06 Å),[122] but within the range of known values (1.85-1.98 Å).[123]

The planar nitrogen in 214 is probably more steric in origin than electronic. The chemical and spectroscopic studies of manxine 228 have concluded that the nitrogen and



methine bridgeheads are substantially flattened to relieve 1,5 hydrogen-hydrogen interactions.[124-126] These interactions involve the hydrogens on carbons a and c and carbon b of different bridge arms of the cage. The best evidence for this flattening is the structure of manxine hydrochloride[127] whose C-N-C angles are opened to 115.5° and whose ring angles, N-C-C (117.4°) and C-C-C (113.9°-119.7°), deviate substantially from the tetrahedral value (109.5°). In 214 the absence of hydrogens on the three oxygens along

with the flexibility of oxygen in organophosphorus compounds[128] allows phosphorus to retain the normal angles. However, the hydrogen interactions from carbons b and c still cause ring strain (N-C-C, 117.6° and C-C-O, 116.6°) and flatten the nitrogen bridgehead.

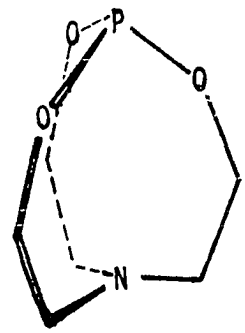
By analogy to 214 the structures of 215, 216, 220 and 221 may well have a tetrahedral phosphorus and a trigonal planar nitrogen. The reduced reactivity of nitrogen in these compounds may be the result of steric hindrance of the methylene hydrogens as in 228[124] which blocks approach to nitrogen lone pair. Strain produced in making nitrogen tetrahedral in the quaternization and/or a molecular dipole effect[129] may also be operative.

The values for the ^{1}H and ^{13}C chemical shifts of the nitrogen methylene group of manxine (2.85 and 50.1 ppm,[121] respectively) match the values in Tables 10 and 11 for compounds 214-221. These values are then more reasonably interpreted as indicative of a planar nitrogen rather than transannular bonding as proposed by Voronkov,[16] Pestunovich et al.,[86] and Tzschach et al.[40]

Structure of Phosphatrane

Phosphatrane, 213, can reasonably be assigned a structure in which phosphorus is tetrahedral and nitrogen is planar by analogy to the structures of the derivatives

214-221 already discussed. The geometries of the reaction



213

products of phosphatrane may be either triptych or may retain this bicyclic structure depending upon whether or not enough electron density is removed from phosphorus for it to accept the nitrogen lone pair. On the basis of the available data, phosphorus substituents which remove a large amount of electron density (H^+, $(C_6H_5)_3C^+$ and probably H_3B) result in a triptych configuration while those which do not (chalconides and zero-valent metal carbonyls) remain in the phosphatrane sulfide (214) structure.

SUMMARY

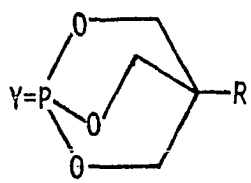
Phosphatrane, 213, which can be synthesized from triethanol amine and tris(dimethylamino)phosphine in toluene solution probably has a pyramidal phosphorus and a trigonal planar nitrogen. In reactions with chalconides and zero valent metal carbonyls, it appears to retain this geometry while in reactions with strong electron withdrawing groups such as H^+, $(C_6H_5)_3C^+$ and probably H_3B the phosphorus accepts electron density from the nitrogen lone pair forming the transannular P-N bond in the triptych geometry. These tricyclic products exhibit properties consistent with the consequent enhancement of the phosphorus Lewis basicity.

The [3.3.3] bicyclic structure in general forces both bridgehead atoms toward planarity in order to relieve hydrogen-hydrogen interactions. Thus, atrane compounds tend to have a trigonal planar nitrogen for steric rather than electronic reasons. In the presence of a sufficiently electronegative second bridgehead atom which also has an empty orbital, the nitrogen lone pair electrons form a transannular M-N bond in a triptych geometry.

PART II: STRUCTURE-TOXICITY RELATIONSHIPS OF BICYCLO[2.2.2]OCTANES

INTRODUCTION

The discovery of the high toxicity level of 4-alkyl-1-phospha-2,6,7-trioxabicyclo[2.2.2]octanes, $Y\text{-}P(OCH_2)_3C\text{-}R$, and their 1-oxo and 1-thio derivatives, Y = O,S was reported

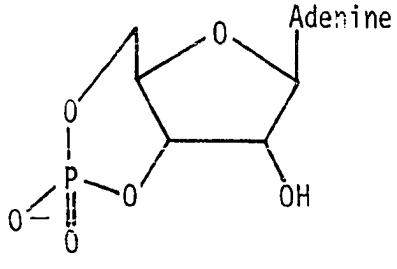


within the past three years by Bellet and Casida.[130] These compounds are approximately 30 times more toxic than the pesticide parathion, $(S)P(OC_2H_5)_2(OC_6H_4NO_2)$, or the central nervous system poison diisopropylfluorophosphate, $(O)PF(O\text{-}i\text{-}C_3H_7)_2$. This disclosure caused a great deal of concern for workers in many areas of the chemical community due to the use of these compounds in coordination and spectroscopic studies[131] and their patented properties as flame retardants,[132] stabilizers[133] and anti-oxidants[134] in polymer products.

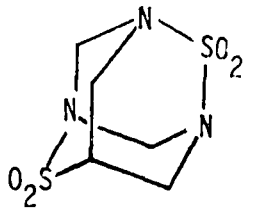
Intraperitoneal administration to mice in doses as low as 0.2 milligrams per kilogram of body weight of these compounds produce convulsive seizures and death within a few minutes. The ethyl compound, $P(OCH_2)_3C\text{-}C_2H_5$, was found to be fatal to rats in inhalation studies[135] (exposures of about

twelve hours at 5 ppm). Also, the small amounts of $O{=}P(OCH_2)_3CC_2H_5$ present in the combustion products of polyurethane foam containing trimethylol propane, $C_2H_5C(CH_2OH)_3$, as a plasticizer and flame retarded by organophosphorus compounds produced tonic-clonic seizures and death in rats.[136]

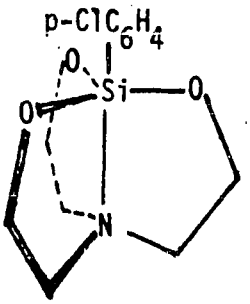
Studies which have indicated that the toxicity of these compounds is not due to acetylcholinesterase inhibition[130,137] (unlike other toxic organophosphorus compounds) have heightened the concern of those who work with these phosphorus esters while at the same time rendering these systems of keen interest to investigate with regard to their mode of action. Fortunately, barbiturates have been found to be useful antidotes and the toxicity is apparently not cumulative.[130] Bellet and Casida[130] speculated that the similar toxicities of the phosphite, phosphate and phosphorothionate forms of a given cage compound $Y{=}P(OCH_2)_3C{-}R$ (Y = lp, S or O) were probably due to prior <u>in vivo</u> oxidation of the phosphite and phosphorothionate to the phosphate. It was also felt that a structural similarity of the bicyclic phosphates to cyclic adenosine monophosphate (c-AMP) might be relevant.



Two other polycyclic compounds are known to act at similar dosage levels to produce severe convulsions and death in rats and mice, namely 2,6-dithio-1,3,5,7-tetrazatricyclo-[3.3.1.1]decane-2,2,6,6-tetraoxide (tetramethylenedisulfotetramine)[138,139] and 1-(p-chlorophenyl)-1-sila-5-aza-2,8,9-trioxatricyclo[3.3.3.0]undecane(p-chlorophenyl silatrane).[140,141] The similarity of the symptoms caused by



Tetramethylenedisulfotetramine



p-Chlorophenyl silatrane

these compounds and their dissimilarity in chemical composition and structure obscures any simple structure-toxicity relationships. The study presented here was designed to relate structure and composition features of bicyclic compounds of the type listed in Table 15 to toxicity as well as to look for indications of the mode of action.

EXPERIMENTAL

Materials

Materials not specifically noted and solvents were of reagent grade or better. In most instances solvents were dried and stored over Linde 4A Molecular Sieves. Anhydrous ether and tetrahydrofuran were obtained by refluxing over and distillation from lithium aluminum hydride on to Molecular Sieves under nitrogen. Phosphorus trichloride and trimethyl phosphite were obtained from Aldrich Chemical Company and carefully distilled before use. Pentaerythritol, 2-hydroxymethyl-2-methyl-1,3-propanediol, 2-hydroxymethyl-2-ethyl-1,3-propanediol, 2-hydroxymethyl-2-propyl-1,3-propanediol, triethylorthoformate, triethylorthoacetate, and trimethyl orthovalerate were also purchased from Aldrich and were used without further purification.

Nmr Spectra

All ^{1}H spectra were obtained in 15-20% chloroform-d_1 solution (except where noted) using either a Varian A-60 or Hitachi Perkin-Elmer R20-B spectrometer operating at 60 MHz. Chemical shifts are given in ppm (δ) relative to internal tetramethylsilane, with a positive shift indicating a resonance at an applied magnetic field less than that of the standard.

Infrared Spectra

Infrared spectra were obtained on a Beckman model 12 or a Beckman 4250 spectrometer. Both solids and liquids were run as 0.05 M - 0.01 M solutions in chloroform in demountable cells (Barnes Engineering Company) with sodium chloride windows and 0.1 mm spacers. All spectra were recorded in the double beam mode with solvent in the reference beam and were calibrated with polystyrene.

Mass Spectra

Routine mass spectra were obtained using an Atlas CH-4 mass spectrometer. All compounds, whether liquid or solid, were run as liquids due to their high volatility.

Preparations

For the purposes of this study compounds 278, 279 and 280 in Table 15 were obtained from Borg-Warner Chemicals and compounds 287, 291 and 292 were provided by Chemical Samples Company, M&T Chemicals Inc. and the Fish and Wildlife Service, United States Department of the Interior, respective respectively. Casida et al.[142] prepared compounds 247, 248, 250-252 and 286 and Ebel prepared compounds 281 and 282.[143] The preparations of the remaining compounds in this study are described below.

1,2,4-Butanetriol

The technical grade material from Aldrich Chemical Company was found to give poor results. Purification of the triol was accomplished by repeated washings with an equal volume of acetone. After vigorously shaking the mixture the triol would separate as a viscous layer with the acetone layer carrying away much of the yellow coloration and odor of the impure triol. Purification in this manner improved the yields of reactions greatly.

2-Hydroxymethyl-2-isopropyl-1,3-propanediol

This triol was prepared by three different literature methods.[144,145,146] The best procedure[146] involved the use of sodium hydroxide instead of calcium oxide or hydroxide and less formalin solution which results in less difficulty in the isolation of the product.

2-Hydroxymethyl-2-butyl-1,3-propanediol

This triol was prepared following the preceding method.[146]

2-Hydroxymethyl-2-hexyl-1,3-propanediol

This triol was prepared following the preceding procedure.[146]

2-Hydroxymethyl-2-pentyl-1,3-propanediol

This triol was prepared following the preceding method.[146]

2-Hydroxymethyl-2-phenyl-1,3-propanediol

This triol was prepared by a literature method.[144]

2-Hydroxymethyl-2-bromomethyl-1,3-propanediol

Monobromopentaarythritol was prepared by a literature procedure.[147]

Trimethylorthobutyrate

This orthoester was prepared following a literature procedure.[148]

Trimethylorthoisobutyrate

This orthoester was prepared by a literature procedure.[148]

4-Butyl-1-phospha-2,6,7-trioxabicyclo[2.2.2]octane

The cage phosphite was prepared by the reaction of the triol, $C_4H_9C(CH_2OH)_3$, with phosphorus trichloride as described by Rix et al.[149] This procedure was found to be preferable to the transesterification method[150] for long chain alkyl groups in the 4-position. The product was sublimed at 50° and .1 mm. Mp. 35-6°, yield 54%, ^1H nmr CH_2 (d, 3.93 $^3J_{PH}$ = 3 Hz), C_4H_9 (m, 112), m/e 190 (M^+).

4-Butyl-1-oxo-1-phospha-2,6,7-trioxabicyclo[2.2.2]octane (240)

The phosphite was oxidized using 30% hydrogen peroxide in absolute ethanol following the literature procedure for

oxidation of $P(OCH_2)_3C\text{-}CH_3$.[151] Mp. 197-8°, yield 78%, ^1H nmr CH_2 (d, 34.57 $^3J_{PH}$ = 6.4 Hz), C_4H_9 (m, 1.01), m/e 206 (M^+).

4-Pentyl-1-oxo-1-phospha-2,6,7-trioxabicyclo[2.2.2]octane (241)

The phosphate cage was prepared by the reported method.[152]

4-Hexyl-1-phospha-2,6,7-trioxabicyclo[2.2.2]octane

The phosphite was prepared by the literature procedure.[149]

4-Hexyl-1-oxo-1-phospha-2,6,7-trioxabicyclo[2.2.2]octane (242)

The phosphite was oxidized by the method noted for 240. Mp. 62-3°, yield 95%, ^1H nmr CH_2 (d, 4.50 $^3J_{PH}$ = 7 Hz), C_6H_{13} (m, 1.25), m/e 234 (M^+).

4-Phenyl-1-phospha-2,6,7-trioxabicyclo[2.2.2]octane

The compound was prepared by the method reported previously.[153]

4-Phenyl-1-oxo-1-phospha-2,6,7-trioxabicyclo[2.2.2]octane (243)

This phosphite was oxidized by the procedure described for 240. Mp. 87-8°, yield 90%, ^1H nmr CH_2 (d, 4.82 $^3J_{PH}$ = 6.5 Hz), C_6H_5 (m, 7.28), m/e 226 (M^+).

4-Methyl-2,6,7-trioxabicyclo[2.2.2]octane (253)

The procedure used to prepare compound 253 is the same as those used for compounds 254 to 277 and will only be described in detail for compound 253.

A mixture of 5.0 g (0.042 moles) of triol, $CH_3C(CH_2OH)_3$, 6.5 g (0.044 moles) of triethylorthoformate, $HC(OC_2H_5)_3$, and one drop of concentrated hydrochloric acid in a 50 ml round-bottom flask equipped with a magnetic stirring bar and a micro distillation apparatus was lowly heated to 80-90°. The ethanol produced by the transesterification reaction was collected as it distilled. After two hours, 90% of the theoretical amount of ethanol had been collected and the reaction flask was cooled. The syrupy reaction mixture was then vacuum distilled. All ortho esters boiled between 75 and 110° at 0.5 mm and most of the distillates crystallized upon cooling. These were further purified by sublimation at 50-60° and 0.5 mm while the liquids were redistilled. Mp. 103-4, yield 35%, ^1H nmr, CH_3 (s, 0.79), CH_2 (s, 379), HCO_3 (s, 5.31), m/e 130 (M^+), ir 2970s, 2880s, 1469m, 1392w, 1363m, 1258w, 1150s, 1126w, 1096w, 1066m, 1005vs, 970s, 959m, 912s, 855m, 850m. (The infrared spectra of the rest of the 2,6,7-trioxabicyclo[2.2.2]octanes prepared are very similar and will not be reported here.)

4-Ethyl-2,6,7-trioxabicyclo[2.2.2]octane (254)

This compound was prepared by the procedure described for compound 253. Mp. 58-60, yield 43%, ^{1}H nmr C_2H_5 (q, 1.20, t, 0.80), CH_2 (3.88), HCO_3 (5.46), m/e 144 (M^+).

4-Propyl-2,6,7-trioxabicyclo[2.2.2]octane (255)

This compound was prepared by the procedure described for compound 253. Mp. 57-8, yield 63%, ^{1}H nmr C_3H_7 (m, 0.94, 1.16), CH_2 (s, 390), HCO_3 (s, 5.49), m/e 158 (M^+).

4-Isopropyl-2,6,7-trioxabicyclo[2.2.2]octane (256)

This compound was prepared by the procedure described for compound 253. Mp. 58-60, yield 67%, ^{1}H nmr C_3H_7 (m, 1.45, 0.94), CH_2 (s, 3.94), HCO_3 (s, 5.46), m/e 158 (M^+).

4-Butyl-2,6,7-trioxabicyclo[2.2.2]octane (257)

This compound was prepared by the procedure described for compound 253. Bp. 95-8 (1 mm), yield 57%, ^{1}H nmr C_4H_9 (m, 0.89, 1.16), CH_2 (3.91), HCO_3 (5.52), m/e 172 (M^+).

1,4-Dimethyl-2,6,7-trioxabicyclo[2.2.2]octane (258)

This compound was prepared by the procedure described for compound 253. Mp. 105-6, yield 40%, ^{1}H nmr CH_3 (s, 0.81), CH_2 (s, 3.88), CH_3CO_3 (s, 1.43), m/e 144 (M^+).

4-Hexyl-1-methyl-2,6,7-trioxabicyclo[2.2.2]octane (259)

This compound was prepared by the procedure described for compound 253. Mp. 38-40, yield 87%, ^{1}H nmr C_2H_5 (m, 0.83, 1.18), CH_2 (3.90), CH_3CO_3 (1.40), m/e 158 (M^+).

4-Propyl-1-methyl-2,6,7-trioxabicyclo[2.2.2]octane (260)

This compound was prepared by the procedure described for compound 253. Mp. 38-9, yield 74%, ^{1}H nmr C_3H_7 (m, 0.94, 1.16), CH_2 (3.91), CH_3CO_3 (1.44), m/e 172 (M^+).

4-Isopropyl-1-methyl-2,6,7-trioxabicyclo[2.2.2]octane (261)

This compound was prepared by the procedure described for compound 253. Mp. 37-9, yield 83%, ^{1}H nmr C_3H_7 (d, 0.86, m, 1.44), CH_2 (s, 392), CH_3CO_3 (s, 1.41), m/e 172 (M^+).

4-Butyl-1-methyl-2,6,7-trioxabicyclo[2.2.2]octane (262)

This compound was prepared by the procedure described for compound 253. Bp. 100-5 (1 mm), yield 49%, ^{1}H nmr C_4H_9 (m, 0.94, 1.16), CH_2 (s, 3.92), CH_3CO_3 (s, 1.44), m/e 186 (M^+).

4-Hexyl-1-methyl-2,6,7-trioxabicyclo[2.2.2]octane (263)

This compound was prepared by the procedure described for compound 253. Bp. 105-7 (1 mm), yield 80%, ^{1}H nmr C_6H_{13} (m, 0.86, 1.19), CH_2 (s, 3.89), CH_3CO_3 (s, 1.42), m/e 214 (M^+).

4-Bromomethyl-1-methyl-2,6,7-trioxabicyclo[2.2.2]octane (264)

This compound was prepared by the procedure described for compound 253. Mp. 50-2, yield 89%, ^{1}H nmr $BrCH_2$ (s, 3.10), CH_2 (s, 3.98), CH_3CO_3 (s, 1.44), m/e 223 (M^+).

4-Methyl-1-ethyl-2,6,7-trioxabicyclo[2.2.2]octane (265)

This compound was prepared by the procedure described for compound 253. Bp. 104-5 (30 mm), yield 93%, ^{1}H nmr CH_3 (s, 0.81), CH_2 (s, 3.86), $C_2H_5CO_3$ (m, 0.90, 1.68), m/e 158 (M^+).

1,4-Diethyl-2,6,7-trioxabicyclo[2.2.2]octane (266)

This compound was prepared by the procedure described for compound 253. Bp. 114-6 (30 mm), yield 90%, ^{1}H nmr C_2H_5 (m, 0.94, 1.11), CH_2 (s, 3.90), $C_2H_5CO_3$ (m, 0.94, 1.67), m/e 172 (M^+).

4-Propyl-1-ethyl-2,6,7-trioxabicyclo[2.2.2]octane (267)

This compound was prepared by the procedure described for compound 253. Bp. 90-4 (2 mm), yield 85%, ^{1}H nmr C_3H_7 (m, 1.16), CH_2 (s, 3.91), $C_2H_5CO_3$ (m, 0.95, 1.66), m/e 186 (M^+).

4-Methyl-1-propyl-2,6,7-trioxabicyclo[2.2.2]octane (268)

This compound was prepared by the procedure described for compound 253. Mp. 40-1, yield 74%, ^{1}H nmr CH_3 (s, 0.80), CH_2 (s, 3.88), $C_3H_7CO_3$ (m, 0.95, 1.59), m/e 172 (M^+).

4-Ethyl-1-propyl-2,6,7-trioxabicyclo[2.2.2]octane (269)

This compound was prepared by the procedure described for compound 253. Mp. 99-105, yield 82%, ^{1}H nmr C_2H_5 (m, 0.82, 1.13), CH_2 (s, 3.88), $C_3H_7CO_3$ (m, 0.92, 1.57), m/e 186 (M^+).

1,4-Dipropyl-2,6,7-trioxabicyclo[2.2.2]octane (270)

This compound was prepared by the procedure described for compound 253. Mp. 71-2, yield 80%, ^{1}H nmr C_3H_7 (m, 0.90, 1.59), CH_2 (s, 3.90), $C_3H_7CO_3$ (m, 1.15, 1.59), m/e 200 (M^+).

4-Methyl-1-isopropyl-2,6,7-trioxabicyclo[2.2.2]octane (271)

This compound was prepared by the procedure described for compound 253. Mp. 37-8, yield 70%, ^{1}H nmr CH_3 (s, 0.78), CH_2 (s, 3.86), $C_3H_7CO_3$ (m, 0.95, 1.85), m/e 172 (M^+).

4-Ethyl-1-isopropyl-2,6,7-trioxabicyclo[2.2.2]octane (272)

This compound was prepared by the procedure described for compound 253. Mp. 30-1, yield 86%, ^{1}H nmr C_2H_5 (m, 0.90, 1.05), CH_2 (s, 3.88), $C_3H_7CO_3$ (m, 0.95, 1.85), m/e 186 (M^+).

4-Propyl-1-isopropyl-2,6,7-trioxabicyclo[2.2.2]octane (273)

This compound was prepared by the procedure described for compound 253. Mp. 34-5, yield 86%, ^{1}H nmr C_3H_7 (m, 1.13), CH_2 (s, 3.88), $C_3H_7CO_3$ (m, 0.96, 1.75), m/e 200 (M^+).

1,4-Diisopropyl-2,6,7-trioxabicyclo[2.2.2]octane (274)

This compound was prepared by the procedure described for compound 253. Mp. 64-5, yield 81%, ^{1}H nmr C_3H_7 (m, 0.85, 1.64), CH_2 (s, 3.93), $C_3H_7CO_3$ (m, 0.95, 1.75), m/e 200 (M^+).

4-Methyl-1-butyl-2,6,7-trioxabicyclo[2.2.2]octane (275)

This compound was prepared by the procedure described for compound 253. Mp. 33-4, yield 81%, ^{1}H nmr CH_3 (s, 0.79), CH_2 (s, 3.87), $C_4H_9CO_3$ (m, 1.40), m/e 186 (M^+).

4-Ethyl-1-butyl-2,6,7-trioxabicyclo[2.2.2]octane (276)

This compound was prepared by the procedure described for compound 253. Bp. 78-80 (0.2 mm), yield 94%, ^{1}H nmr C_2H_5 (m, 1.10), CH_2 (s, 3.82), $C_4H_9CO_3$ (m, 1.10), m/e 200 (M^+).

1-Tris(chloromethyl)methyl-4-methyl-2,6,7-trioxabicyclo-[2.2.2]octane (277)

This compound was prepared by the direct esterification of $(ClCH_2)_3CCO_2H$[154] by $CH_3C(CH_2OH)_3$, in xylene solution as described in the literature.[155]

1-Thio-1-phospha-5-aza-2,8,9-trioxabicyclo[3.3.3]undecane (214)

This compound was prepared as described in a previous part of this dissertation (p. 45).

1-Protio-1-phospha-5-aza-2,8,9-trioxatricyclo[3.3.3.0]-undecane tetrafluoroborate (217)

This compound was prepared by the procedure described in an earlier part of this dissertation (p. 48).

1-Triphenylmethyl-1-phospha-5-aza-2,8,9-trioxatricyclo-[3.3.3.0]undecane tetrafluoroborate (218)

This compound was prepared by the procedure described in an earlier portion of this dissertation (p. 49).

1-Oxo-1-phospha-2,8,9-trioxaadamantane (288)

This compound was prepared as described in the literature.[156]

1,3,9-Trioxaadamantane (289)

This compound was prepared by the procedure described in the literature.[157]

1-Methyl-2,7,8-trioxabicyclo[1.2.3]octane (290)

This compound was prepared by the procedure described for compound 253 from purified 1,2,4-butanetriol and triethylorthoacetate. Mp. 81-4°, yield 65%, ^{1}H nmr CH_2 (m, 2.20), OCH_2 (m, 3.98), OCH (m, 4.64), CH_3CO_3 (s, 1.56), m/e 130 (M^+).

Toxicity Studies

This portion of the study was carried out by Dr. J. E. Casida's research group at the University of California, Berkeley. Only the essential details of that work are included here. (A more detailed description can be obtained from reference 142.)

LD_{50} values (lethal dose 50% effective) were determined for male albino Swiss Webster mice 24 hours after ip (intraperitoneal) administration of the bicyclic compounds. Thirty or more mice were used to determine each LD_{50} value except 248 and 286 where only four mice were used because of a limited amount of compound.

Subacute toxicity tests with mice involved daily or bi-daily administration of the compounds.

Studies with other species were also made. The following animals were tested for sensitivity to the bicyclic compounds: mature white leghorn hens, one week old white leghorn chicks, fertile white leghorn eggs, leopard frogs (*Rana pipiens*), and adult male American cockroaches (*Periplaneta americana*). Other insects (adult milkweed bugs, adult German cockroaches, adult houseflies, larval and adult yellow mealworms, lepidopterous larvae of 4 species, bean aphids and two-spotted mites) were tested by standard contact, topical, spray or dip procedures.

Miscellaneous Biological Tests

The response of muscle and nerve tissue was tested with the diaphragm of mice and the abdominal nerve cord of the American cockroach and the crayfish (Cambarus. sp.).

The metabolism of 231, 232 and 233 by mouse liver microsomes with and without reduced nicotinamide adenine dinucleotide phosphate (NADPH) was investigated by biochemical techniques.

The effect of bicyclic compounds on the beef heart c-AMP phosphodiesterase enzyme was also checked to test the possible involvement of c-AMP in the mode of action.

RESULTS

Structure-Mouse Acute Toxicity

For the purposes of clarity and discussion, the compounds used in this study have been divided into three categories. The first includes 1-phospha-2,6,7-trioxabicyclo[2.2.2]-octanes, Y-P$(OCH_2)_3$C-R (229-252), while the second contains 2,6,7-trioxabicyclo[2.2.2]octanes, R'-C$(OCH_2)_3$C-R (253-277), and the last collects the remaining bicyclic compounds, 214, 217, 218 and 278-292. The results of the toxicity studies are summarized in Table 15.

There is a remarkable similarity within the first grouping of the potency of the corresponding phosphites, phosphates, and phosphorothionates (where R = CH_3, C_2H_5, n-C_3H_7, i-C_3H_7 and CH_2OH, compounds 229-239 and 244-246). In the R = n-alkyl series, 229-236 and 240-242, optimal toxicity appears with the n-propyl group, but two- to three-fold greater toxicity is found with the i-propyl group, 237-239. A phenyl substituent, 243, is about the equivalent of an n-butyl moiety, 240, in toxicity. Compounds containing a hydroxymethyl group, 244-246, are inactive (500 mg/kg) while the aceto compounds, 247, and the tertiary alcohol, 248, are moderately toxic. Nitrogen-containing R-groups vary greatly in toxicity from essentially nontoxic, 250 and 252, to moderately toxic, 249 and 251.

Table 15. Mouse intraperitoneal LD_{50} values for bicyclooctanes

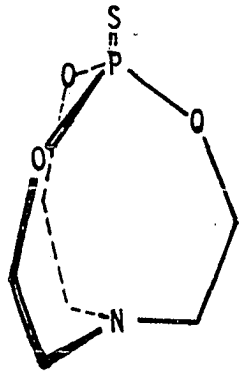
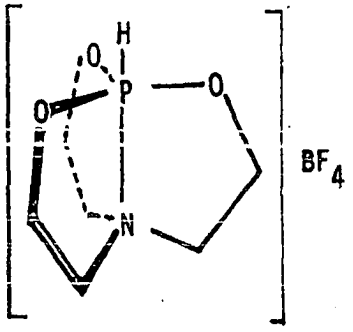
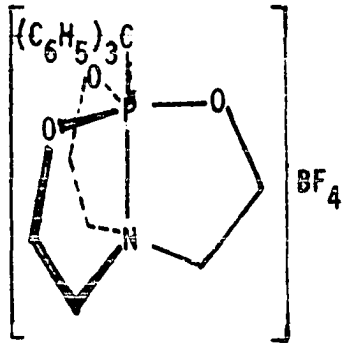
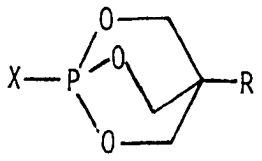
Compound		Ip LD_{50} (mg/kg)
214		260
217		270
218		28

Table 15. (Continued)

Compound				Ip LD_{50} (mg/kg)
229		X = O	R = CH_3	32[a]
230		S	CH_3	34[a]
231		&p	C_2H_5	1.1[a]
232		O	C_2H_5	1.0[a]
233		S	C_2H_5	1.1[a]
234		&p	n-C_3H_7	0.39[a]
235		O	n-C_3H_7	0.38[a]
236		S	n-C_3H_7	0.79[a]
237		&p	i-C_3H_7	0.22[a]
238		O	i-C_3H_7	0.18[a]
239		S	i-C_3H_7	0.26[a]
240		O	n-C_4H_9	1.5
241		O	n-C_5H_{11}	37

[a]These values were determined in reference 130.

Table 15. (Continued)

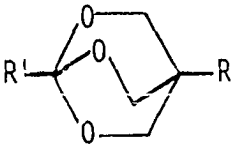
Compound				Ip LD_{50} (mg/kg)
242		O	$n\text{-}C_6H_{13}$	500
243		O	C_6H_5	1.5
244		ℓp	CH_2OH	>500[a]
245		O	CH_2OH	>500[a]
246		S	CH_2OH	>500[a]
247		O	$C(O)CH_3$	51
248		O	$C(OH)(CH_3)_2$	25-50
249		O	NO_2	9.5[a]
250		O	NH_2	>500
251		O	$N(CH_3)_2$	3.0
252		O	$N(CH_3)_3Cl$	>500
253		R' = H	R = CH_3	>500
254		H	C_2H_5	95

Table 15. (Continued)

Compound			Ip LD_{50} (mg/kg)
255	H	$n\text{-}C_3H_7$	23
256	H	$i\text{-}C_3H_7$	12
257	H	$n\text{-}C_4H_9$	220
258	CH_3	CH_3	>500
259	CH_3	C_2H_5	>500
260	CH_3	$n\text{-}C_3H_7$	85
261	CH_3	$i\text{-}C_3H_7$	42
262	CH_3	$n\text{-}C_4H_9$	250
263	CH_3	$n\text{-}C_6H_{13}$	>500
264	CH_3	CH_2Br	390
265	C_2H_5	CH_3	>500
266	C_2H_5	CH_3	500
267	C_2H_5	$n\text{-}C_3H_7$	>500
268	$n\text{-}C_3H_7$	CH_3	>500
269	$n\text{-}C_3H_7$	C_2H_5	420
270	$n\text{-}C_3H_7$	$n\text{-}C_3H_7$	29
271	$i\text{-}C_3H_7$	CH_3	>500

Table 15. (Continued)

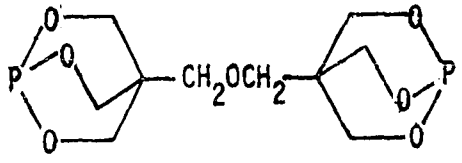
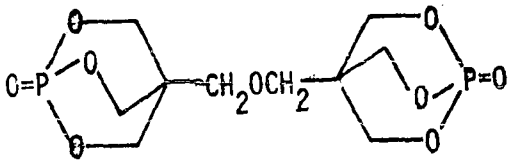
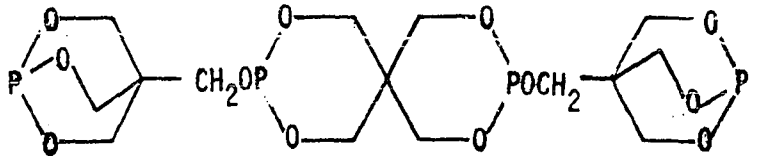
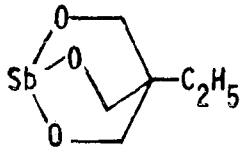
Compound			Ip LD_{50} (mg/kg)
272	$i\text{-}C_3H_7$	C_2H_5	350
273	$i\text{-}C_3H_7$	$n\text{-}C_3H_7$	>500
274	$i\text{-}C_3H_7$	$i\text{-}C_3H_7$	>500
275	$n\text{-}C_4H_9$	CH_3	295
276	$n\text{-}C_4H_9$	C_2H_5	22
277	$(ClCH_2)_3C$	CH_3	525
278			>500
279			>500
280			>500
281			>500

Table 15. (Continued)

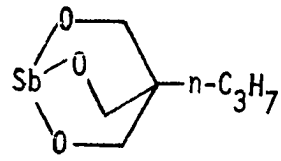
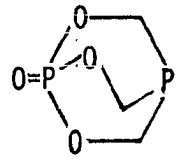
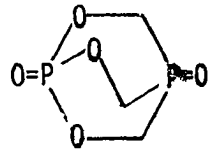
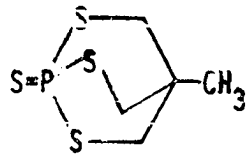
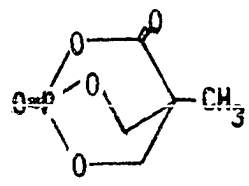
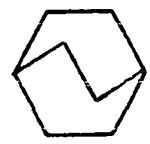
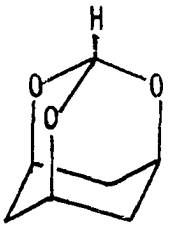
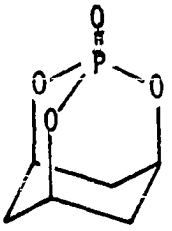
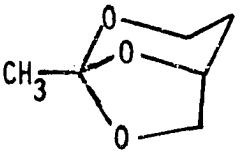
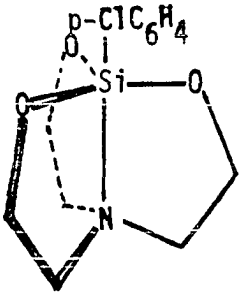
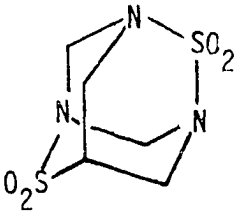
Compound		Ip LD_{50} (mg/kg)
282		250 mg
283		174[a]
284		189[a]
285		95[a]
286		>500
287		250-500

Table 15. (Continued)

Compound		Ip LD_{50} (mg/kg)
288		510
289		>500
290		>500
291		0.22
292		0.24

It is evident that the mouse toxicity of $Y\text{-}P(OCH_2)_3C\text{-}R$ compounds is greatly influenced by the size of the R-substituent. Sufficient data are available in the $O{=}P(OCH_2)_3C\text{-}R$ series for structure-toxicity regression analysis, using those compounds with well-defined LD_{50} values. The toxicity (log $1/LD_{50}$) correlates well with the van der Waals volume of the R-group, provided it is hydrophobic in nature such as the alkyl, phenyl and nitro groups. This relationship is shown in Figure 9 where $Vr = V_R/V_{CH_3}$ and V_R and V_{CH_3} are the van der Waals volumes[158] of the substituent and methyl group, respectively. However, the results for compounds with hydrophilic groups such as acetyl, hydroxymethyl, amino, or dimethylamino groups deviate significantly from the plot in Figure 9. The use of the Hausch-Fujita hydrophobicity parameter,[159] π, with the van der Waals volume did not yield a satisfactory correlation. This may be due to the fact that the π of hydrophobic groups is directly related to their volume while that of hydrophilic groups is not. For this reason the specific hydrophobicity factor, $\pi s = \pi/Vr$, was introduced. With this factor satisfactory correlation with both hydrophilic and hydrophobic groups was achieved as can be seen from Table 16. These results indicate that the optimal size (van der Waals volume) of the R-group is 33.97 cm^3/mole (Vr = 2.48).

Figure 9. Correlation of mouse toxicity (log $1/LD_{50}$) with selected properties of the R substituent in $O=P(OCH_2)_3C-R$ compounds

○ = Hydrophobic group

● = Hydrophilic group

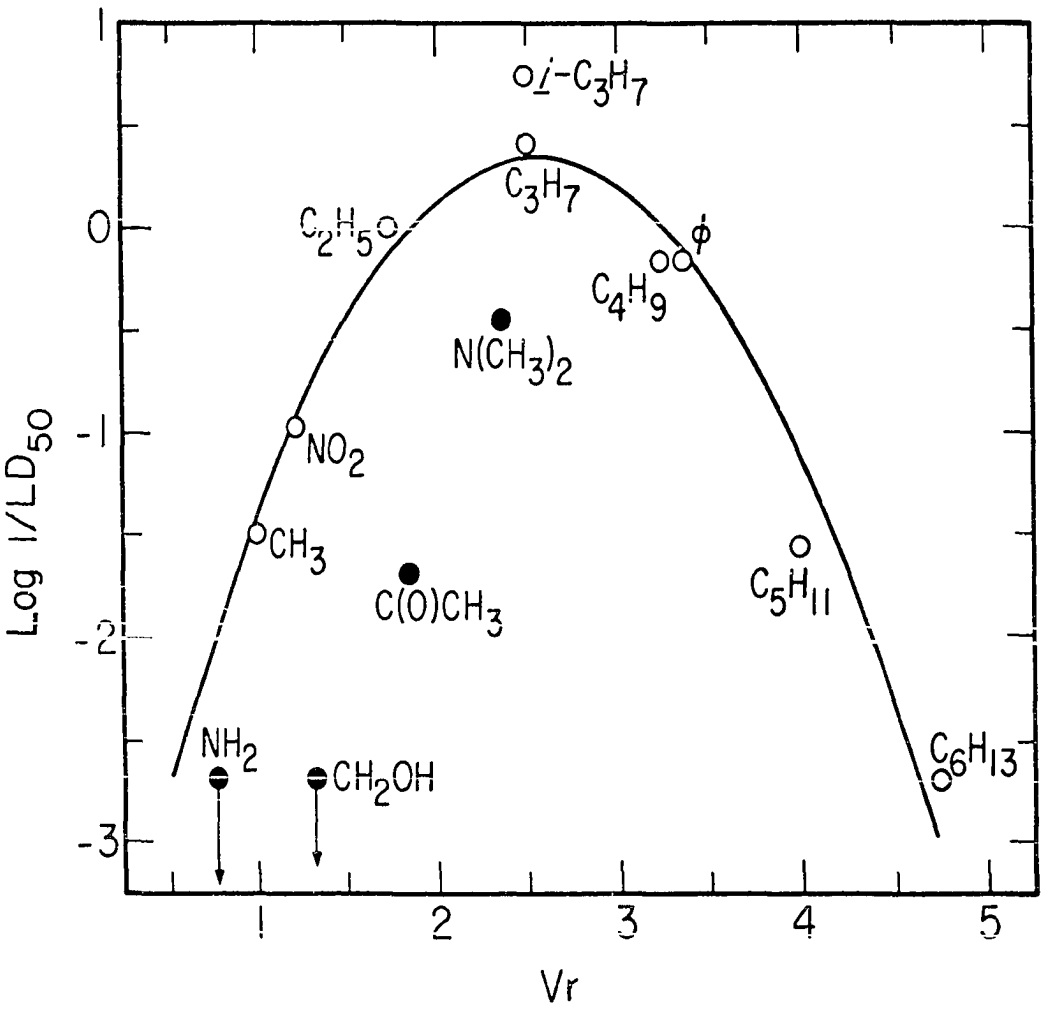

Log 1/LD50
Vr
1
0
-1
-2
-3
1
2
3
4
5
o-i-C3H7
C3H7
C2H5
ϕ
C4H9
N(CH3)2
NO2
CH3
C(O)CH3
C5H11
C6H13
NH2
CH2OH

Table 16. Regression analysis of structure-mouse toxicity relationship for $OP(OCH_2)_3C$-Z compounds

Compound	Z	Vr[a]	πs[b]	log 1/LD_{50}	
				Obs.	Calcd.
229	CH_3	1.00	0.52	-1.51	-1.15
232	C_2H_5	1.75	0.55	0.00	0.02
235	n-C_3H_7	2.50	0.57	0.42	0.42
238	i-C_3H_7	2.50	0.56	0.74	0.40
240	n-C_4H_9	3.23	0.59	-0.18	0.09
241	n-C_5H_{11}	3.99	0.54	-1.57	-1.15
242	n-C_6H_{13}	4.74	0.53	-2.70	-3.04
243	C_6H_5	3.35	0.56	-0.18	-0.10
247	$C(O)CH_3$	1.86	-0.20	-1.71	-1.49
249	NO_2	1.23	0.20	-0.98	-1.41
251	$N(CH_3)_2$	2.32	0.043	-0.48	-0.73

[a]Relative volume of Z calculated as $Vr = V_Z/V_{CH_3}$ where V_Z and V_{CH_3} are the van der Waals volumes of Z and CH_3, respectively.

[b]Specific hydrophobicity parameter calculated as $\pi s = \pi/Vr$.

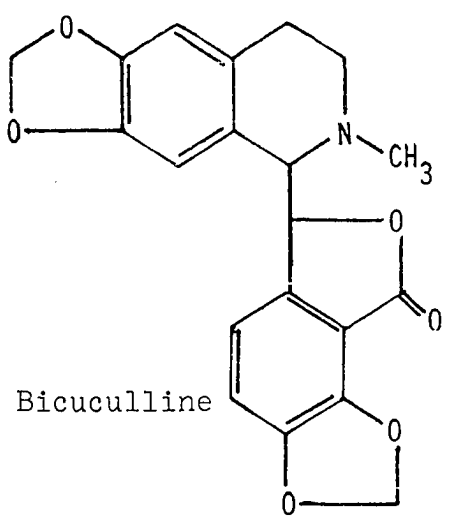
Replacement of phosphorus with carbon at the bridgehead of the bicyclic system in the second group of compounds, 253-277, always yields compounds of greatly reduced toxicity. The optimal R-substituent again appears to be the isopropyl group for orthoformates and orthoacetates, $H\text{-}C(OCH_2)_3C\text{-}R$ and $CH_3\text{-}C(OCH_2)_3C\text{-}R$. Toxicity was found to decrease in the order $H > CH_3 > C_2H_5$ for the R' substituent. This trend is not entirely clear because of the relatively high toxicity found for R' = R = n-propyl, 270, and R' = n-butyl, R = ethyl, 276. More compounds may be needed to explain this discrepancy.

The last grouping of test compounds (214, 217, 218 and 278-292) include many differing structural shapes and chemical compositions. The parent hydrocarbon, 287, of the bicyclics tested is of only moderate toxicity as are the phosphatrane derivatives, 214, 217 and 218. None of these caused the characteristic symptoms (see below) of the more toxic substances. Bicyclic compounds of nearly the same size but different shape, 288-290, were essentially inactive as were the polybicyclic compounds 278-280. Changing the phosphorus atom to an antimony atom, 281 and 282, resulted in detoxification (these compounds were administered as subspensions rather than solutions). Moderate toxicity was found for the diphospha cage compounds, 283 and 284. Replacement of all oxygens with sulfurs, 285, also reduces the toxicity. The unstable acyl bicyclic phosphate, 286,

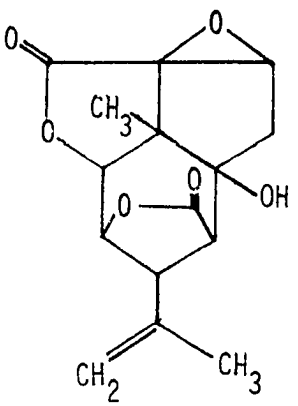
is not toxic. Two compounds, 291 and 292, known to be toxic were also tested for comparison purposes.

Symptoms of Poisoned Mice

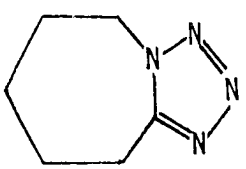
The symptoms of poisoning by all compounds with mouse ip LD_{50} values below 100 mg/kg shown in Table 15 (except compound 218) appear to be similar, if not identical to each other. Thus, a dose at least twice that of the LD_{50} typically yields alternate contraction and relaxation of muscles with severe flexion jerks of the hind legs initiated one to five minutes after injection. The convulsions appear with increasing intensity until generalized motor seizure occurs, culminating in death in three minutes to one hour. Death occurs more rapidly at higher doses. Petajan et al.[136] reported that the electroencephalogram of a poisoned rat showed high amplitude spike discharges well before any visible muscular flexions. Postmortem examination showed no gross pathology in all organs except for the lungs in which scattered hemorrhaging was evident.[136,138] Similar symptomology is evident for mice treated intraperitoneally with lethal doses of bicuculline, picrotoxin and pentylenetetrazol, but not with strychnine.



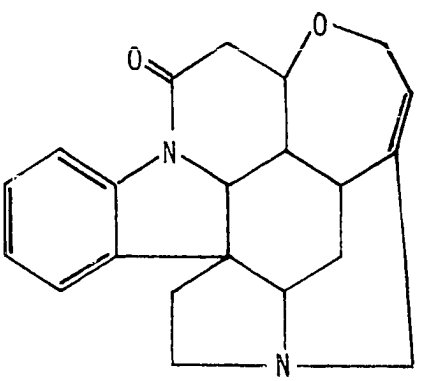
Bicuculline



Picrotoxin

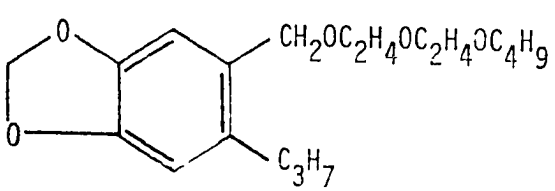


Pentylenetetrazol

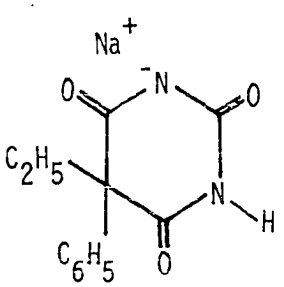


Strychnine

Pretreatment of mice with either of two agents was found to decrease the toxicity of the convulsants. The effect was los in magnitude and compound dependent with piperonyl butoxide but quite dramatic for all compounds with sodium phenobarbitol. Other compounds commonly used to combat

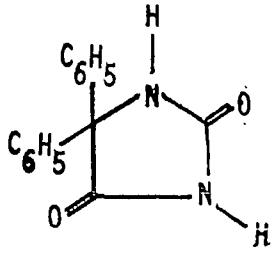


Piperonyl butoxide

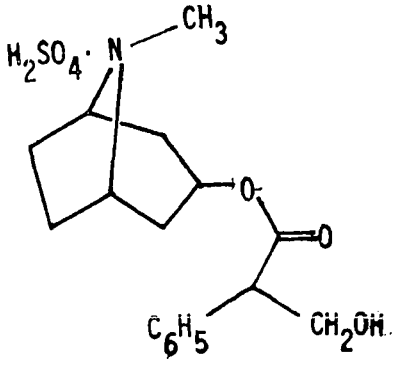


Sodium phenobarbitol

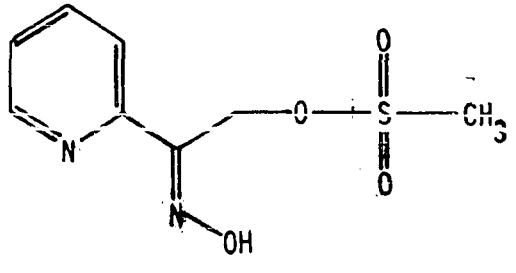
central nervous system poisoning, 5,5-diphenylhydantoin, atropine sulfate and 2-pyridinealoxime methyl methanesulfonate, were ineffective as antidotes.



5,5-Diphenylhydantoin



Atropine sulfate



2-Pyridinealoxime methylmethanesulfonate

Acute Toxicity with Other Species

The toxic effects of only the more toxic compounds studied were investigated with other species. With either hens or chicks, the acute ip LD_{50} values were 1.0 and 0.2 mg/kg, respectively, for 232 and 238. Three orthocarboxylic acid esters (260, 261 and 276) administered to chicks at

their mouse ip LD_{50} doses produced severe convulsive seizures, but the chicks recovered completely within three hours and showed no delayed effects.

Frogs injected with 238 or 292 produced convulsions and death in one to two hours (LD_{50} for both was 0.3 mg/kg).

A survey of various insects and mites revealed no species sensitive to 232. The American cockroach, however, gave an LD_{50} of ∿100 µg/g.

Subacute Toxic Effects

Subacute toxicity studies with mice showed no mortality or significant weight differences compared with control animals using 232 or 238. At the end of these observations the mice were normal in respect to their susceptibility to an LD_{50} dose of the test compound. Their weights and the gross appearance of their organs (brain, kidney, liver and spleen) were also normal.

Subacute toxicity studies with mature hens showed neither accumulative nor delayed effects with either 232 or 238.

Embryos of chicken eggs injected with 238 developed normally, but on hatching the weight of the chicks was reduced and there was a 33-100% incidence of fusion of leg joints from which the chicks did not recover during the observation period. Higher doses of these compounds

markedly reduced the hatch and produced 100% incidence of leg defects in the chicks. Other bicyclic compounds, 245, 249 and 258, failed to manifest this syndrome.

Action on Muscle and Nerve Tissue

Beef heart cyclic AMP phosphodiesterase is not sensitive to inhibition or stimulation by compounds 232, 238, 245 or 249.

Isolated mouse diaphram muscle tissue was induced to twitch rapidly on exposure to 238. Compound 292 also caused twitching while twenty-four other compounds were inactive, 229-233, 235, 239, 249, 254, 259-261, 264, 276, 282-285, 289, 291, bicuculline, picrotoxin and strychnine.

American cockroaches responded with an increase in spike frequency of the abdominal nerve when injected with an LD_{50} dose of 238. Sectioning of the motor neurons innervating the legs completely abolished the compound-induced twitching activity. Symptoms were observed to be undiminished if the animals were decapitated and sectioned, providing that the ganglionic innervation of the limb muscles was left intact.

The isolated abdominal nerve cord of the crayfish responds to 238 with an increase in spike frequency and the appearance of large intensity spikes. Solutions of 232 produced a similar but smaller response.

Metabolism of Bicyclic Phosphorus Compounds

Incubation of compounds 231, 232 and 233 with mouse liver microsomes and the oxidase cofactor NADPH did not cause any change in the phosphate and phosphorothionate. The result was no different without NADPH. The phosphite, though, was more than 50% metabolized in one hour to the phosphate. This oxidation did not occur without both the microsomes and NADPH present.

DISCUSSION

Three features appear to contribute to the high toxicity demonstrated by the compounds examined in this study. For optimal activity the compound must have a highly symmetrical cage structure (bicyclo[2.2.2]octane in this study), a hydrophobic substituent of critical size and shape at the relatively positive end of the dipolar molecule and strong molecular dipole moment.

Variations of the bicyclo[2.2.2]octane shape, demonstrated by compounds 288-290 resulted in the disappearance of nearly all activity while the parent hydrocarbon, 287, by contrast, is more toxic than would be expected for a pure hydrocarbon. The low LD_{50} values for compounds 291 and 292 indicate that the "football" shape of the bicyclo[2.2.2]-octanes is not a necessary structure if it assumed that these compounds act at the same site. However, the high degree of symmetry found in each of these cage compounds appears to be a requirement for toxicity.

Regression analysis of the structure-toxicity data for $O{=}P(OCH_2)_3C\text{-}R$ compounds showed the optimal size of the R-group to be about 34 cm^3/mole (about the van der Waals volume of a propyl group). The higher toxicities of alkyl groups also indicate that the R group should have hydrophobic character. Similar trends are evident for $Y\text{-}P(OCH_2)_3C\text{-}R$,

Y = lp or S, and R'-C$(OCH_2)_3$C-R, but there were insufficient data for regression analysis.

Changing the chemical composition of compound 238 by replacing phosphorus with carbon (253-277) or antimony (281-282), replacing the oxygens with sulfurs (285), or adding another phosphorus atom (283, 284) resulted in a decrease in activity. A common factor in each of these variations is a decrease in the overall dipole moment of the molecule. Caged hydrocarbon substituted orthoesters (2.7-3.2 D), phosphites (3.8-4.1 D), phosphates and phosphorothionates of the bicyclo[2.2.2]octane-type possess dipole moments roughly twice as large as their acyclic analogs. (This is due to the constraint of the bond moments and lone pair vector moments so that they lie along the axis of the cage.)[160-162]

These features apply only partially to the other cage compounds, 214, 217, 218 and 291-292, studied. The shape requirements mentioned above apply to these substances while the desired alkyl substituent is not present. The molecular dipole factor appears to be included in these compounds, however. The assumption that all of the compounds studied act at the same site may not be valid since the structurally very different bicuculline, picrotoxin, and pentylenetetrazol also produce the same symptoms of poisoning at the equivalent dosages.[163]

Previous speculation[130] about metabolic activation of the phosphorus compounds prior to poisoning has been proven partially wrong. Only the oxidation of the phosphite form to the phosphate form appears to take place. The phosphorothionate form remains unchanged as does the phosphate form. The expected microsomal oxidation[164] of the 4-alkyl substituent to a 4-C(O)-R or 4-CH(O)H)-R substituent was not observed. Since these oxidized derivatives, for example 247 and 248, are much less toxic than the parent compounds, such an oxidation would constitute a detoxification rather than an activation mechanism. Another metabolic pathway would be the oxidation of the cage methylene group, OCH_2, to the cyclic anhydride, OC(O), but again this derivative, 58, was not toxic, acting instead as an acylating agent.

The subacute toxicity studies indicate that there are no accumulative or delayed effects; the compounds being detoxified by some presently unknown metabolic process. Also, there were no tolerances to the toxicants built up during the studies.

The possible involvement of c-AMP in the mode of action for these compounds[130] appears to be ruled out by the lack of any activity of the phosphorus cages toward c-AMP phosphodiesterase. The toxicity of the bicyclic orthoesters provides even stronger evidence against this hypothesis since there is no phosphorus present in these compounds.

Ion trapping by the cage compounds as a mode of action must also be ruled out. These bicyclic structures do not possess a large enough cavity to trap Ca^{++}, K^{+} or Na^{+} ions. Although the phosphorus compounds have important metal ligating properties,[131] the noncoordinating orthoesters produce the same symptoms of poisoning.

The trioxabicyclo[2.2.2]octanes appear to act in the central nervous system (CNS) of vertebrates, primarily in the brain and possibly in the brain stem. Several other CNS stimulants, bicuculline, picrotoxin and pentylenetetrazol, produce similar poisoning symptoms and have similar interaction with barbiturates.[163] These natural product toxins are thought to antagonize the inhibitory neuronal function of the amino acids, glycine, γ-aminobutyric acid (GABA), and taurine.[165]

Interestingly, shortly after this present work was published,[142] a group of British scientists presented evidence[166] that the bicyclic phosphorus esters were involved in GABA antagonism. This included GABA's depressant action on single neurons in the rat brain and its depolarising action on isolated rat superior cervical ganglion. Also reported was a close correspondence of the LD_{50} values with the concentrations which both bicuculline and 238 and picrotoxin and 232 antagonized GABA, further supporting this mode of action as probably being the correct one.

SUMMARY

Several 2,6,7-trioxabicyclo[2.2.2]octanes have been screened for toxicity and mouse LD_{50} values range from greater than 500 mg/kg to a low of 0.2 mg/kg. The most toxic members of this series suggested that three factors were important for toxicity, the symmetrical shape of bicyclo[2.2.2]octanes, a substituent at the 4-position of the cage about the size of an isopropyl or propyl group and a substantial dipole moment for the molecule.

The compounds were central nervous system stimulants which cause tonic-clonic seizures in lethal doses. There were no accumulative actions or delayed effects observed. The mode of action appears to be much like that of bicuculline and picrotoxin which antagonize inhibitory neuronal mechanisms. The use of this type of compound should be undertaken with caution.

REFERENCES

1. C. A. Rojahn, Ger. Offn. 582,149 [Chem. Abstr. 27, 5153 (1933)].

2. H. C. Brown and E. A. Fletcher, J. Amer. Chem. Soc. 73, 2808 (1951).

3. R. C. Mehrotra and G. Srivastava, J. Indian Chem. Soc. 39, 521 (1962).

4. M. G. Voronkov and G. Zelcans, Metody, Poluch. Khim. Reactivov Prep. No. 14, 24 (1966) [Chem. Abstr. 67, 64321 (1967)].

5. H. Steinberg and D. L. Hunter, Ind. Eng. Chem. 49, 174 (1957).

6. I. I. Solomennikova, G. Zelcans, and E. Lukevics, Latv. PSR Zinat. Akad. Vestis, Khim. Ser. 491 (1975) [Chem. Abstr. 83, 193248g (1975)].

7. A. A. Schleppnik and C. D. Gutsche, J. Org. Chem. 25, 1378 (1960).

8. E. Lukevics, I. I. Solomennikova, G. Zelcans, I. Jankovska, I. Mazeika, and E. Liepins, Latv. PSR Zinat. Akad. Vestis, Khim. Ser. 483 (1975) [Chem. Abstr. 83, 193247f (1975)].

9. N. N. Greenwood, J. H. Morris, and J. C. Wright, J. Chem. Soc. 4753 (1964).

10. T. P. Onak, R. E. Williams, and R. Swidler, J. Phys. Chem. 67, 1741 (1963).

11. J. H. Ludwig and K. Witsken, Ger. Offn. 1,908,844 [Chem. Abstr. 72, 4052c (1970)].

12. A. B. Finestone (Westinghouse Electric) Ger. Offn. 1,731,681 [Chem. Abstr. 58, 4598h (1963)].

13. C. L. Frye, G. E. Vogel, and J. A. Hall, J. Amer. Chem. Soc. 83, 996 (1961).

14. G. I. Zeleans and M. G. Voronkov, Khim. Geterotsikl. Soedin. 371 (1967) [Chem. Abstr. 67, 108112k (1967)].

15. C. L. Frye, G. A. Vincent, and W. A. Finzel, J. Amer. Chem. Soc. 93, 6805 (1971).

16. M. G. Voronkov, Pure Appl. Chem. 13, 35 (1966).

17. S. Koristek and J. Stepanek, Czech. Pat. 128,408 [Chem. Abstr. 70, 115878e (1969)].

18. J. Lukasiak, A. Radecki, and Z. Jamrogiewicz, Rocz. Chem. 47, 1975 (1973).

19. E. Lukevics, L. Liberts, and M. G. Voronkov, Latv. PSR Zinat. Akad. Vestis, Khim. Ser. 451 (1972) [Chem. Abstr. 77, 152270r (1972)].

20. M. G. Voronkov, V. M. D'yakov, and V. P. Baryshok, Zh. Obshch. Khim. 43, 444 (1973) [Chem. Abstr. 79, 5384u (1973)].

21. M. G. Voronkov, M. S. Sorokin, V. M. D'yakov, M. V. Sigalov, and V. A. Pestunovich, Zh. Obshch. Khim. 44, 456 (1974) [Chem. Abstr. 80, 121049h (1974)].

22. A. Danehead, C. Eaborn, and D.R.M. Walton, J. Organomet. Chem. 85, 35 (1975).

23. C. B. Beiter, M. Schwarcz, and G. Crabtree, Soap Chem. Specialt. 46, 38 (1970); M. Schwarcz, C. B. Beiter, S. Kaplan, Jr., O. E. Loeffler, M. E. Martino, and S. Damle, Ger. Offn. 2,009,964 [Chem. Abstr. 73, 120748d (1970)].

24. K. H. Grundy, J. D. Crabtree, and A. E. Johnson (Fiberglass Ltd.), S. Africa Pat. 6,806,969 [Chem. Abstr. 73, 121219u (1970)].

25. C. M. Samour (Kendall Co.), U.S. Pat. 3,118,921 [Chem. Abstr. 60, 10716a (1964)].

26. M. G. Voronkov and G. Zelcans, Khim. Geterotsikl. Soedin. 43 (1969) [Chem. Abstr. 71, 3363x (1969)].

27. M. G. Voronkov and G. Zelcans, Khim. Geterotsikl. Soedin. 210 (1965) [Chem. Abstr. 63, 9936b (1965)].

28. M. G. Voronkov and G. Zelcans, Khim. Geterotsikl. Soedin. 511 (1966) [Chem. Abstr. 64, 85780g (1966)].

29. M. G. Voronkov and G. Zelcans, Metody Poluch. Khim. Reaktivov Prep. No. 14, 149 (1966) [Chem. Abstr. 67, 32275t (1967)].

30. C. L. Frye (Dow Corning Corp.), Ger. Offn. 2,004,837 [Chem. Abstr. 73, 131126a (1970)].

31. M. G. Voronkov and G. Zelcans, USSR Pat. 192,209 [Chem. Abstr. 68, 105348b (1968)].

32. E. Popowski, M. Michalik, and H. Kelling, J. Organomet. Chem. 88, 157 (1975).

33. E. Lukevics, I. I. Solomennikova, and G. Zelcans, Zh. Obshch. Khim. 46, 134 (1976) [Chem. Abstr. 84, 150696e (1976)].

34. C. L. Frye, G. A. Vincent, and G. L. Hanschildt, J. Amer. Chem. Soc. 88, 2727 (1966).

35. E. L. Morehouse, U.S. Pat. 3,032,576 [Chem. Abstr. 57, 9981h (1962)].

36. R. G. Kostyanovskii, A. K. Prokof'ev, V. I. Gol'danskii, V. V. Khrapov, and V. Ya. Rochev, Izv. Akad. Nauk SSSR, Ser. Khim. 270 (1968) [Chem. Abstr. 69, 92517z (1968)].

37. A. Tzschach and K. Pönicke, Z. Anorg. Allg. Chem. 413, 136 (1975).

38. R. C. Mehrotra and V. D. Grupta, Ind. J. Chem. 5, 643 (1967).

39. A. Zschunke, A. Tzschach, and K. Pönicke, J. Organomet. Chem. 51, 197 (1973).

40. A. Tzschach, K. Pönicke, L. Korec, and K. Burger, J. Organomet. Chem. 59, 199 (1973).

41. M. G. Voronkov, G. Zelcans, and V. F. Mironov, USSR Pat. 190,897 [Chem. Abstr. 68, 69128 u (1968)].

42. M. G. Voronkov, G. Zelcans, V. F. Mironov, J. Bleidelis, and A. Kemme, Khim. Geterotsikl. Soedin. 227 (1968) [Chem. Abstr. 69, 87129v (1968)].

43. R. C. Mehrotra and G. Chandra, Ind. J. Chem. 3, 497 (1965).

44. R. C. Mehrotra and R. K. Mehrotra, J. Ind. Chem. Soc. 39, 677 (1962).

45. Fr. Hein and P. W. Albert, Z. Anorg. Allg. Chem. 269, 67 (1952).

46. I. N. Elbling and A. B. Finestone (Westinghouse Electric Co.), Ger. Offn. 1,162,439 [Chem. Abstr. 60, 14705a (1964)].

47. J. M. Icken and E. J. Jahren (Internat. Latex Corp.), Belg. Pat. 619,940 [Chem. Abstr. 60, 2768b (1964)].

48. R. K. Mittal, Z. Anorg. Allg. Chem. 351, 309 (1967).

49. M. G. Voronkov and A. F. Lapsin, USSR Pat. 187,792, USSR Pat. 187,793 [Chem. Abstr. 67, 4452, 4453 (1967)].

50. M. G. Voronkov and A. Lapsina, Khim. Geterotsikl. Soedin. 357 (1966) [Chem. Abstr. 65, 8915f (1966)].

51. B. S. Sankhla and R. N. Kapoor, Bull. Chem. Soc. Japan 40, 1381 (1967).

52. W. T. Miller, J. Amer. Chem. Soc. 62, 2707 (1940).

53. M. G. Voronkov and F. D. Faitel'son, Khim. Geterotsikl. Soedin. 39 (1967) [Chem. Abstr. 67, 64321w (1967)].

54. H. J. Cohen, J. Organomet. Chem. 9, 177 (1967).

55. H. J. Cohen, J. Organomet. Chem. 5, 413 (1966).

56. H. J. Cohen (Glidden Co.) U.S. Pat. 3,334,119 [Chem. Abstr. 69, 77511z (1968)].

57. K. Starke, J. Inorg. Nucl. Chem. 6, 130 (1958); K. Starke, J. Inorg. Nucl. Chem. 11, 37 (1959).

58. J. Peive, M. G. Voronkov, N. N. Ivanova, M. G. Shirinskaya, P. N. Kubrovo, and A. Lapsina, Dokl. Akad. Nauk SSSR 174, 986 (1967) [Chem. Abstr. 67, 63364a (1967)].

59. M. G. Voronkov and A. F. Lapsin, USSR Pat. 187,795 [Chem. Abstr. 67, 4451 (1967)].

60. H. Follner, Acta Crystallogr. B 28, 157 (1972).

61. H. Steinberg and D. L. Hunter, Ind. Eng. Chem. 49, 174 (1957).

62. H. Steinberg and D. L. Hunter, J. Amer. Chem. Soc. 82, 853 (1960).

63. H. K. Zimmerman, Jr. and H. Weidmann, Justus Liebigs Ann. Chem. 628, 37 (1959).

64. R. K. Stump, H. K. Zimmerman, Jr., A. A. Schleppnik, and C. D. Gutsche, Ann. 667, 18 (1963).

65. C. A. Lucchesi and D. D. DeFord, J. Inorg. Nucl. Chem. 14, 290 (1960).

66. H. C. Fu, T. Psarros, H. Weidmann, and H. K. Zimmerman, Jr., Justus Liebigs Ann. Chem. 641, 116 (1961); J. M. Pugh and R. H. Stokes, Aust. J. Chem. 16, 204 (1963).

67. B. D. Sharma, Diss. Abstr. 22, 1427 (1961).

68. Z. Taira and K. Osaki, Inorg. Nucl. Chem. Let. 7, 509 (1971).

69. A. Kemme and J. Bleidelis, Latv. PSR Zurat. Akad. Vestis, Khim. Ser. 621 (1971) [Chem. Abstr. 76, 64773f (1972)].

70. R. Mattes, D. Fenske, and K. F. Tebbe, Chem. Ber. 105, 2089 (1972).

71. H. Follner, Monatsh. Chem. 104, 477 (1973).

72. J. E. Huheey in Inorganic Chemistry (Harper and Row, New York, 1972) p. 184.

73. S. Cradock, E.A.V. Ebsworth, and Irene Muiry, J. Chem. Soc., Dalt. 25 (1975).

74. J. R. Chippenfield and R. M. Prince, J. Chem. Soc. A 3567 (1963).

75. J. W. Turley and F. P. Boer, J. Amer. Chem. Soc. 90, 4026 (1968).

76. J. W. Turley and F. P. Boer, J. Amer. Chem. Soc. 91, 4129 (1969).

77. F. P. Boer, J. W. Turley, and J. J. Flynn, J. Amer. Chem. Soc. 90, 5102 (1968).

78. F. P. Boer and J. W. Turley, J. Amer. Chem. Soc. 91, 4134 (1969).

79. N. A. Matwiyoff and R. S. Drago, Inorg. Chem. 3, 337 (1964); M. L. Maddox, N. Flitcroft, and H. D. Kaesz, J. Organomet. Chem. 4, 50 (1965).

80. J. Bleidelis, A. Kemme, L. O. Atovneyan, and R. P. Shibaeva, Khim. Geterotsikl. Soedin. 184 (1968) [Chem. Abstr. 69, 100650e (1968)].

81. A. Kemme, J. Bleidelis, R. P. Shibaeva, and L. O. Atovmyan, Khim. Geterotsikl. Soedin. 1145 (1970) [Chem. Abstr. 74, 581586 (1970)].

82. J. M. Pugh and R. H. Stokes, Aust. J. Chem. 16, 211 (1963).

83. M. G. Voronkov, O. A. Osipov, V. A. Kogan, V. A. Chetverikova and A. F. Lapin, Khim. Geterotsikl. Soedin. 35 (1967) [Chem. Abstr. 67, 64320v (1967)].

84. J. Bjerrum, G. Schwarzenbach, and L. G. Siller in Stability Constants (The Chemical Society, London, 1957) Part I Organic Ligands p. 3.

85. J. L. Hoard, E. W. Silverton, and J. V. Silverton, J. Amer. Chem. Soc. 90, 2300 (1968).

86. V. A. Pestunovich, M. G. Voronkov, G. Zelcans, A. Lapsins, E. Lukevics, and L. Liberts, Khim. Geterotsikl. Soedin. 348 (1970) [Chem. Abstr. 72, 107403a (1970)].

87. J. E. Huheey in Inorganic Chemistry (Harper and Row, New York, 1972) p. 160.

88. I. H. Meerwein in Organic Synthesis edited by E. J. Corey (J. Wiley & Sons, New York, 1966) Vol. 46, p. 113.

89. I. H. Meerwein in Organic Synthesis edited by E. J. Corey (J. Wiley & Sons, New York, 1966) Vol. 46, p. 120.

90. H. J. Dauben, Jr., L. R. Honnen, and K. M. Harman, J. Org. Chem. 25, 1442 (1960).

91. G. W. Gokel and D. J. Cram, J. Org. Chem. 39, 2445 (1974).

92. R. N. Greene, Tetra. Let. 1793 (1972).

93. E. W. Abel, I. S. Butler, and J. G. Reid, J. Chem. Soc. 2068 (1963).

94. J. A. Connors, E. M. Jones, and G. K. McEwen, J. Organomet. Chem. 43, 357 (1972).

95. T. W. Campbell and J. D. McCullough, J. Amer. Chem. Soc. 67, 1965 (1945).

96. G. Germain, P. Main, and M. M. Woolfson, Acta Crystallogr., Sect. B, 24, 274 (1970).

97. The following library of crystallographic programs was used: C. R. Hubbard, C. O. Quicksall, and R. A. Jacobson, "The Fast Fourier Algorithm and the Programs ALFF, ALFFDP, ALFFT and FRIEDEL", USAEC Report IS-2625, Iowa State University-Institute for Atomic Research, Ames, Iowa, 1971; W. R. Busing, K. O. Martin, and H. A. Levy, "A Fortran Crystallographic Least Squares Program", USAEC Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965; C. Johnson, "ORTEP, A Fortran Thermal-Ellipsoid Plot Program", U.S. Atomic Energy Commission Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965.

98. H. P. Hanson, F. Herman, J. D. Lea, and S. Skillman, Acta Crystallogr. 17, 1040 (1964).

99. International Tables for X-Ray Crystallography (Kynoch Press, Birmingham, England, 1962) Vol. III, p. 214.

100. W. C. Hamilton, Acta Crystallogr. 18, 502 (1965).

101. K. Dimroth and A. Nurrenbach, Chem. Ber. 93, 1649 (1960); J. G. Verkade, T. J. Huttemann, M. K. Fung, and R. W. King, Inorg. Chem. 4, 83 (1965).

102. M. M. Crutchfield, C. H. Dungan, J. H. Letcher, J. R. VanWazer, and V. Mark, Top. Phosphorus Chem. 5, 227 (1967).

103. R. D. Kroshefsky and J. G. Verkade, in preparation.

104. S. O. Grim, P. R. McAllister, and R. M. Singer, J. Chem. Soc. D 38 (1969).

105. E. O. Fischer, L. Knauss, R. L. Keiter, and J. G. Verkade, J. Organomet. Chem. 37, C7 (1972); R. L. Keiter and J. G. Verkade, Inorg. Chem. 8, 2115 (1969).

106. W. McFarlane and R.F.M. White, Chem. Comm. 744 (1969); G. A. Olah and C. W. McFarland, J. Org. Chem. 36, 1374 (1971).

107. L. J. Vande Griend and J. G. Verkade, Phosphorus 3, 13 (1973).

108. J. G. Verkade, R. W. King, and C. W. Heitsch, Inorg. Chem. 3, 884 (1964).

109. L. J. Vande Griend, J. G. Verkade, J.F.M. Pennings, and H. M. Buck, J. Amer. Chem. Soc., in press.

110. J. C. Clardy, D. S. Milbrath, J. P. Springer, and J. G. Verkade, J. Amer. Chem. Soc. 98, 623 (1976).

111. K. P. John, R. Schmutzler, and W. S. Sheldrick, J. Chem. Soc. Dalt. 1841, 2466 (1974).

112. R. R. Holmes and R. P. Wagner, Inorg. Chem. 2, 384 (1963); and references therein.

113.. W. E. McEwen, Top. Phosphorus Chem. 2, 5 (1965); D. Denney and R. Dileone, J. Amer. Chem. Soc. 84, 4737 (1962).

114. D.E.C. Corbridge, Top. Phosphorus Chem. 3, 91 (1966).

115. W. E. McEwen, J. E. Fountaine, D. N. Schulz, and W. I. Shiou, J. Org. Chem. 41, 1684 (1976); W. E. McEwen, W. I. Shiou, Y. I. Yeh, D. N. Schulz, R. U. Pagilagau, J. B. Levy, C. Symmes, Jr., G. O. Nelson, and I. Granoth, J. Amer. Chem. Soc. 97, 1787 (1975); E. W. McEwen, V. L. Kyllingstad, D. N. Schulz, and Y. I. Yen, Phosphorus 1, 145 (1971).

116. A. H. Cowley and M. C. Damasco, J. Amer. Chem. Soc. 93, 6815 (1971).

117. R. W. Rudolph and C. W. Schultz, J. Amer. Chem. Soc. 93, 6821 (1971).

118. H. A. Bent, Chem. Rev. 61, 275 (1961).

119. J. Bellamy, The Infrared Spectra of Complex Molecules (Methuen and Co., Ltd., London, 1958).

120. L. C. Thomas in Interpretation of the Infrared Spectra of Organophosphorus Compounds (Heyden and Son, Ltd., London, 1974) Chapt. 2, 12 and 14.

121. D. S. Milbrath, J. C. Clardy, and J. G. Verkade, J. Amer. Chem. Soc., submitted.

122. D.E.C. Corbridge, Top. Phosphorus Chem. 3, 293 (1966).

123. L. S. Khaikin and L. V. Vilkov, Russ. Chem. Rev. 41, 1060 (1972); J. D. Lee and G. W. Goodacre, Acta Crystallogr. B 26, 507 (1970) and references therein.

124. J. C. Coll, D. R. Crist, M.C.G. Barrio and N. J. Leonard, J. Amer. Chem. Soc. 94, 7092 (1972).

125. D. H. Aue, H. M. Webb, and M. T. Bowers, J. Amer. Chem. Soc. 97, 4136 (1975).

126. A. Halpern, J. Amer. Chem. Soc. 96, 7655 (1974).

127. H. J. Wang, R. J. Missavage, S. R. Byrn, and I. C. Paul, J. Amer. Chem. Soc. 94, 7100 (1972).

128. J. G. Verkade, Bioinorg. Chem. 3, 165 (1974); J. C. Clardy, D. S. Milbrath, J. P. Springer, and J. G. Verkade, J. Amer. Chem. Soc. 98, 5493 (1976).

129. D. A. Allison and J. G. Verkade, Phosphorus 2, 257 (1973).

130. E. M. Bellet and J. E. Casida, Science 182, 1135 (1973).

131. J. G. Verkade, Coord. Chem. Rev. 9, 1 (1972).

132. W. A. Hills (FMC Corp.), U.S. Pat. 3,849,522 [Chem. Abstr. 82, 112704g (1975)]; J. S. Clovis and F. R. Sullivan (Rohm & Haas), U.S. Pat. 3,755,270 [Chem. Abstr. 80, 27846u (1974)].

133. H. Brunetti (Ciba-Geigg), Swiss 544,776 [Chem. Abstr. 80, 96031m (1974)]; S. L. Giolita and W. Stamm (Stauffer Chemical Co.), U.S. Pat. 3,607,990 [Chem. Abstr. 76, 15338j (1972)].

134. H. Brunetti (Ciba-Geigg), Swiss 552,629 [Chem. Abstr. 81, 120255f (1974)]; I. Kibayashi and B. Ryutani, Japan Kokai 73 55,229 [Chem. Abstr. 80,28543e (1974)].

135. J. C. Gage, Brit. J. Indust. Med. 27, 1 (1970).

136. J. H. Petajan, K. J. Voorhees, S. C. Packham, R. C. Baldwin, I. N. Einhorn, M. L. Grunnet, B. G. Dinger, and M. M. Birky, Science 187, 742 (1975).

137. R. D. O'Brien and J. G. Verkade, unpublished results.

138. J. Hagen, Deut. Med. Wschr. 75, 183 (1950).

139. A. R. Haskell and E. Voss, J. Amer. Pharm. Assoc. 46, 239 (1957).

140. C. B. Beiter, M. Schwarcz, and G. Crabtree, Soap and Chem. Specialties 46, 38 (1970).

141. M. G. Voronkov, Pure Appl. Chem. 13, 35 (1966).

142. J. E. Casida, M. Eto, A. D. Moscioni, J. L. Engel, D. S. Milbrath, and J. G. Verkade, Tox. Appl. Pharm. 36, 261 (1976).

143. M. Worsley, B. N. Wilson, B. O. Schoepfle, U.S. Pat. 3,109,853 [Chem. Abstr. 60, 2768f (1964)].

144. O. C. Dermer and P. W. Solomon, J. Amer. Chem. Soc. 76, 1697 (1954).

145. W. E. Conrad, L. A. Levasseur, R. F. Murphy, N. L. Hare, and H. M. Conrad, J. Org. Chem. 27, 2227 (1962).

146. M. M. Ketslakh, D. M. Rudkovskii, and F. A. Eppel, Oksosinteg Poluchemie Metodom Oksosintega Al'degidov Spirtov i Horichnykh Produktov na ikh Osnove, Vses. Nauchn.-Issled., Inst. Neftikhim. Protsessov, 151, 156 (1963) [Chem. Abstr. 60, 9133h (1963)].

147. S. Wawzonek, A. Matar, and C. H. Issidorides, in Organic Synthesis, edited by J. C. Sheehan (J. Wiley and Sons, New York, 1958) Vol. 38, p. 68.

148. S. M. McElvain and C. L. Aldridge, J. Amer. Chem. Soc. 75, 3987 (1953).

149. C. J. Rix, G. K. McEwen, M. F. Traynor, and J. G. Verkade, Inorg. Chem. 13, 2800 (1974).

150. W. S. Wadsworth, Jr. and W. D. Emmons, J. Amer. Chem. Soc. 84, 610 (1962).

151. J. G. Verkade and L. T. Reynolds, J. Org. Chem. 25, 663 (1960).

152. S. C. Goodman and J. G. Verkade, Inorg. Chem. 5, 498 (1966).

153. E. M. Hyde, P. Meakin, J. R. Swain, and J. G. Verkade, J. Chem. Soc., Dalt. in press.

154. A. Mooradian and J. B. Cloke, J. Amer. Chem. Soc. 67, 942 (1945).

155. R. A. Barnes, G. Doyle, and J. A. Hoffman, J. Org. Chem. 27, 90 (1962); Celanese Corp. Amer., Neth. Appl. 6,412,636 [Chem. Abstr. 63, 16370d (1965)].

156. H. Stetter and K. Steinaucker, Chem. Ber. 85, 451 (1952).

157. E. J. Boros, K. J. Coskran, R. W. King, and J. G. Verkade, J. Amer. Chem. Soc. 88, 1140 (1966).

158. A. Bondi, J. Phys. Chem. 68, 441 (1964).

159. T. Fujita, J. Iwasa, and C. Hausch, J. Amer. Chem. Soc. 86, 5175 (1964).

160. T. L. Brown, J. G. Verkade, and T. S. Piper, J. Phys. Chem. 65, 2051 (1961).

161. R. D. Bertrand, R. D. Compton, and J. G. Verkade, J. Amer. Chem. Soc. 92, 2702 (1970).

162. A. C. Vandenbroucke, Jr., E. J. Boros, and J. G. Verkade, Inorg. Chem. 7, 1469 (1968).

163. L. S. Goodman and A. Gilman, The Pharmacological Basis of Therapeutics (Macmillan, New York, 1975).

164. M. Eto, Organophosphorus Pesticides: Organic and Biological Chemistry (CRC Press, Cleveland, 1974).

165. D. R. Curtis and G.A.R. Johnston, Ergebn. Physiol. 69, 97 (1974).

166. N. G. Bowery, J. F. Collins, and R. G. Hill, Nature 261, 601 (1976).

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APPENDIX[1]

The only nuclei which have been reported to couple to $^{95,98}Mo$ are ^{19}F in MoF_6[2] and ^{17}O in molybdate ion.[3] In neither case were the two isotopic couplings resolved. In the Table are listed the first reported examples of $^{1}J^{95,97}Mo^{31}P$ couplings for ten $(OC)_5MoL$ complexes. Because I = 5/2 for each of these molybdenum isotopes and both are of comparable abundance (^{95}Mo, 15.72% and ^{97}Mo, 9.46%, respectively), the ^{31}P nmr spectrum decoupled from other nmr-active nuclei should consist of a main singlet with two sets of satellites, each set being composed of six peaks of equal intensity. Although the resolution of such sets of satellites has been reported for $^{1}J^{63,65}Cu^{31}P$ in $\{Cu[P(OMe)_3]_4\}ClO_4$,[4] $^{1}J^{111,113}Cd^{31}P$ in $\{CdI_2[P(\underline{n}\text{-}Bu)_3]_2\}$,[5] and $^{1}J^{117,119}Sn^{31}P$ in $\{SnCl_4[P(\underline{n}\text{-}Bu)_3]_2\}$,[5] for example, the closeness of the magnetic moments for ^{95}Mo (-0.9099) and ^{97}Mo (-0.9290), and the breadth of the satellite peaks (20 Hz at half height in the best cases) preclude resolution of the satellite sets which are expected to differ in J value by only 3 to 6 Hz in this coupling range. In the Figure is shown a ^{31}P spectrum of $(OC)_5MoPF_3$ which shows a quartet of satellite sets owing to ^{19}F-^{31}P coupling.

It has been observed with other metals such as ^{183}W,[6,7] ^{199}Hg,[4] and ^{195}Pt[8] that the absolute values of the metal-^{31}P couplings rise with the electronegativity of the phosphorus

substituents of the coordinated anionic ligands. As was found earlier by us for $^{1}J^{183}W^{31}P$ in $(OC)_5WL$ complexes using a similar set of ligands[6,7] $^{1}J^{95,97}Mo^{31}P$ rises linearly (correlation coefficient > 0.98) with the phosphorus substituent atom electronegativity using the Allred-Rochow, Sanderson or Pauling scales.

A few years ago it was determined that the sign of $^{1}J^{183}W^{31}P$ is positive in $(OC)_5WPMe_2Ph$[9] thus making it probable that this coupling is positive in all such complexes. Because of the similar trend of $^{1}J^{95,97}Mo^{31}P$ and $^{1}J^{183}W^{31}P$ with electronegativity, it is likely that the former coupling is negative since the magnetogyric ratios of $^{95,97}Mo$ and ^{183}W are of opposite sign. The larger reduced ^{183}W-^{31}P couplings for a given ligand can be attributed to the increased magnitude of the valence s orbital expected with rising atomic number of the acceptor atom.[10] The ^{183}W-^{31}P spin-spin interaction also appears to be somewhat more sensitive to the electronegativity of the phosphorus ligand since the slopes of these plots (1.63 to 1.98 x 10^2) are larger than those for the $^{96,97}Mo$-^{31}P couplings (0.99 to 1.11 x 10^2).

The complexes were made by literature methods (L = PF_3;[11] $P(C_6H_5)_3$ and $P(C_6H_5)(CH_3)_2$[12] and the remaining ligands[13]). ^{31}P nmr spectra were obtained on a Bruker HX-90 spectrometer operating at 36.434 MHz in the FT mode with white noise

proton decoupling in all cases except where L = PF_3. Typically 6000-8000 scans were required to observe the $^{95,97}Mo$ satellites with a sample of 200-300 mg. Except where indicated, the spectra were obtained in d_1-chloroform.

Table 1. ^{31}P nmr data for $(OC)_5MoL$ complexes

L	$\delta^{31}P$ (±0.1 ppm)	$^1J^{95,97}Mo^{31}P$ (Hz)[a]
PF_3[b]	-147.2	284(2)
$P(OPh)_3$	-154.3	231(2)
$P(OCH_2)_3CEt$	-137.3	226(1)
$P(OMe)_3$[c]	-161.1	216(1)
$P(OEt)_3$[c]	-155.9	214(1)
$PPh(OMe)_2$	-176.6	183(2)
$PPh_2(OMe)$[d]	-145.6	142(10)
PPh_3[d]	- 37.5	124(10)
$P(NMe_2)_3$	-145.4	173(1)
$PPhMe_2$	- 15.4	133(4)

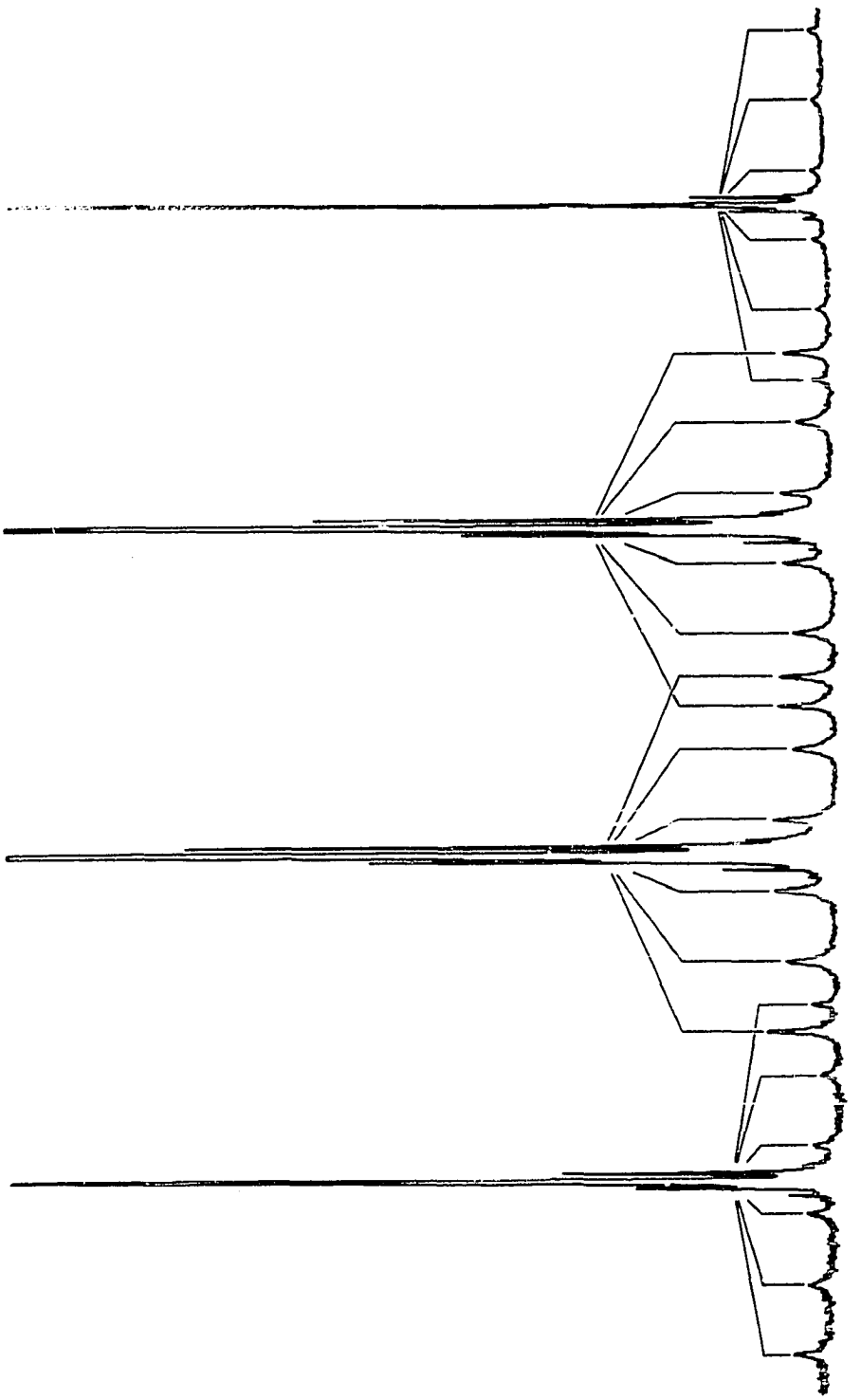
[a]Estimated uncertainties appear in parentheses.

[b]Taken in d^6-benzene.

[c]Taken on neat liquid using d^6-acetone as an internal lock.

[d]The relatively large uncertainty is due to overlap of the satellite members.

Figure 1. ^{31}P nmr spectrum of $(OC)_5MoPF_3$ showing the satellite peaks due to $^{95,97}Mo$ isotopes



REFERENCES

1. D. S. Milbrath, J. G. Verkade, and R. J. Clark, Inorg. Nucl. Chem. Lett., in press.

2. J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy", Permagon Press, New York, 1966, Vol. 2, p. 881.

3. R. R. Vold and R. L. Vold, J. Chem. Phys., 61, 4360 (1974).

4. R. W. King, T. J. Hutteman, and J. G. Verkade, Chem. Comm., 561 (1965).

5. A. Yamasaki and E. Fluck, Z. Anorg. Allg. Chem., 396, 297 (1973).

6. E. O. Fischer, L. Knauss, R. L. Keiter, and J. G. Verkade, J. Organometal. Chem., 37, C7 (1972).

7. R. L. Keiter and J. G. Verkade, Inorg. Chem., 8, 2115 (1969).

8. G. G. Mather, G. J. N. Parsey, and A. Pidcock, Inorg. Nucl. Chem. Lett., 9, 567 (1973).

9. W. McFarlane and D. S. Rycroft, Chem. Comm., 336 (1973).

10. J. F. Nixon and A. Pidcock in "Ann. Rev. NMR Spectroscopy," E. F. Mooney, Ed., Academic Press, London, 1969, Vol. 2, p. 356.

11. R. J. Clark and P. I. Hoberman, Inorg. Chem., 4, 1771 (1965).

12. G. Booth in Organic Phosphorus Compounds, ed. by G. M. Kosolapoff and L. Maier [J. Wiley and Sons, New York, 1972] Chapt. 3A.

13. K. J. Coskran and J. G. Verkade in Organic Phosphorus Compounds, ed. by G. M. Kosolapoff and L. Maier [J. Wiley and Sons, New York, 1972] Chapt. 3B.