Use of Carbohydrate Derivatives for Studies of Phosphorus Stereochemistry. Part 7.† Stereochemistry of Alkoxide-induced Ring-opening of 1,3,2-Dioxaphosphorinan-2-ones, and of Migration of Alkyl Alkyl Phosphoryl Groups between the 4- and 6-Positions of Glucose

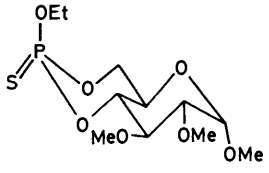
By **John M. Harrison** and **Thomas D. Inch,*** Chemical Defence Establishment, Porton Down, Salisbury, Wiltshire SP4 0JQ

Cyclic glucose 4,6-(ethyl phosphates) undergo ring-opening in dilute sodium methoxide to afford glucose 4-(ethyl methyl phosphates) as the kinetically favoured products. Ring-opening occurs with preponderant inversion of configuration. On storage in sodium methoxide glucose 4-(ethyl methyl phosphates) afford glucose 6-(ethyl methyl phosphates) with retention of configuration at phosphorus. The stereochemical results for the ring-opening and migration reactions are fully consistent with the intermediacy of trigonal bipyramidal intermediates, which break down by apical departure of the leaving group before pseudorotation or after simple pseudorotational sequences. The configurations at phosphorus of the glucose 4(*R*)- and 4(*S*)-, and 6(*R*)- and 6(*S*)-(ethyl methyl phosphates) are established by independent synthetic sequences.

THE fact that differences in hydrolytic reactions of five-membered cyclic phosphates and phosphonates can be explained in terms of the relative propensity to pseudorotation of trigonal bipyramidal (TBP) intermediates [1] has contributed significantly to current views on organophosphorus stereochemistry.[2] Surprisingly, although many additional studies of various types of five-membered cyclic phosphorus esters have been reported,[3] comparable studies with six-membered cyclic derivatives have received scant attention. Consequently, it was pertinent to follow up observations [4] that there were probable differences in the ring-opening reactions of some cyclic phosphate and phosphonate esters of methyl 2,3-di-*O*-methyl-α-D-glucopyranoside with the stereochemical studies reported in this paper.

RESULTS AND DISCUSSION

The observations which prompted the stereochemical studies can be summarised by the following examples. When the cyclic ethyl phosphorothioate (1) was treated with sodium methoxide, two products were formed; the kinetically-favoured 4-phosphorothioate ‡ (2), formed by cleavage of the P–O-6 bond, and the thermodynamically favoured 6-phosphorothioate (3). On storage in sodium methoxide or in sodium ethoxide, (2) was converted into (3). This result is consistent with migration of (2) to (3) *via* a TBP intermediate which undergoes pseudorotation and then breakage of the P–O-4 bond, but is not consistent with a migration that involves reformation of a cyclic phosphorothioate and ring reopening. This latter course would lead to significant exchange of alkoxy-groups, and this did not occur. In contrast, when the cyclic methylphosphonate (4) was treated with sodium methoxide a mixture of (5) and (6) was formed. Again the 4-phosphonate (5) was the kinetic product and the 6-phosphonate (6) was the thermodynamic product, and in sodium methoxide (5) was converted into (6). However, chromatographic evidence for the re-formation of (4) during the migration of (5) to (6) was obtained and in sodium ethoxide exchange of the methoxy-group for an ethoxy-group was observed.



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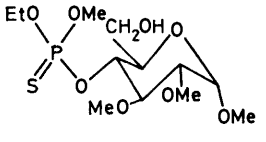

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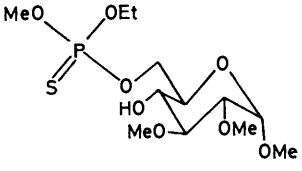

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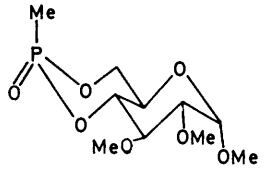

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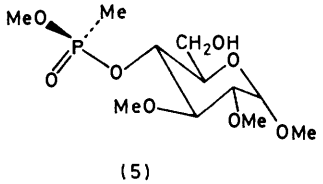

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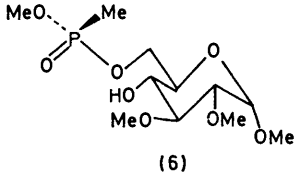


(6)

In the initial studies, other than commenting briefly on the differences between the cyclic phosphates and phosphonates, little attempt was made to establish the stereochemistry of the products, or to consider in any detail the possible pathways or intermediates that could be involved in the ring-opening and migration reactions. Some of the possible reaction pathways and intermediates are now considered, in the light of the stereochemical results obtained for the ring opening of the cyclic ethyl phosphates (7-ax) and (7-eq) with sodium methoxide, and the subsequent migrations of the initially formed products. (Reactions in which alcohols rather than water are the source of the nucleophile have

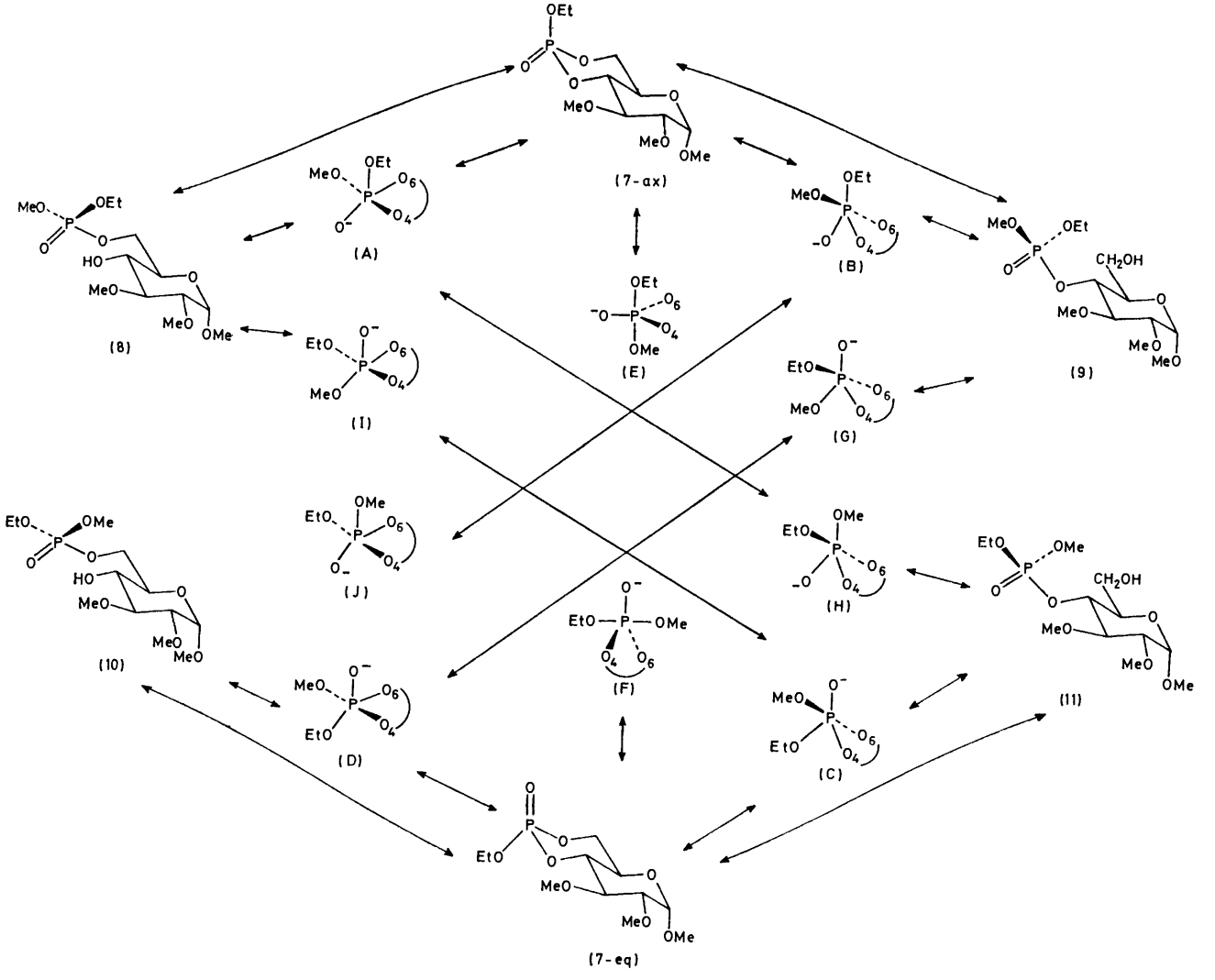
† Part 6, T. D. Inch and G. J. Lewis, *Carbohydrate Res.*, 1975, **45**, 65.

‡ For the convenience of abbreviation, substituent positions are numbered by carbohydrate convention.

the advantage that the stereochemistry of attack at phosphorus in P=O compounds can be determined).

The results obtained are most easily described and discussed by reference to Scheme 1 which was devised making the following assumptions. (*a*) TBP intermediates [*i.e.* (A)—(J)] were probable but not essential; hence direct S_N2P ring opening mechanisms are included. (For the present discussion S_N2P processes are placing the six-membered ring so that it spans apical positions.

The first requirement for considering Scheme 1 was to establish whether ring-opening reactions occurred with inversion or retention of configuration at phosphorus. Consequently the 4-phosphates (9) and (11) and the 6-phosphates (8) and (10) were synthesised by unambiguous routes (see later). Fortuitously the pairs of isomers had



SCHEME 1

those which proceed through a transition state rather than an intermediate). (*b*) No TBP intermediates in which the six-membered ring spans basal positions will make significant contributions to the overall reactions. Assumption (*b*) is based on the facts firstly that significant exchange of alkoxy-groups does not occur [amongst other things this precludes TBP intermediates such as (E) and (F)], and secondly that in strong base the phosphoryl oxygen will exist as $P–O^-$ in TBP intermediates, will have an overriding preference for a basal position, and will preclude pseudorotations which would necessitate distinctive ^1H n.m.r. spectra permitting facile characterisation of the products from the ring-opening reactions, and allowing reasonable estimates of the isomer proportions in mixtures to be made.

Characteristic ^1H n.m.r. data from (8), (9), (10), and (11) are given in Table 1.

The experimental approach adopted to provide the stereochemical data against which Scheme 1 was to be considered was to store the cyclic phosphates (7-ax) and (7-eq) in sodium methoxide in methanol, to remove aliquots with time, to separate starting materials and

TABLE 1

N.m.r. data for compounds in Scheme 2 *

Compound	P–NMe_2	P–OMe	P–OCH_2CH_3	Carbohydrate OMe	H-2	H-1	CH_2Ph	CH_2Ph
(14)	2.72 (d, 9.0)	3.67 (d, 12)		3.41 (s), 3.51 (s), 3.63 (s)	3.21 (dd, 4.10)	4.78 (d, 4)		
(15)	2.74 (d, 11)	3.77 (d, 12)		3.45 (s), 3.56 (s), 3.62 (s)	3.20 (dd, 4, 10)	4.88 (d, 4)		
(16)	2.72 (d, 10)		1.34 (dt, 1, 7)	3.41 (s), 3.51 (s), 3.66 (s)	3.24 (dd, 4, 9)	4.82 (d, 4)		
(17)	2.71 (d, 10.4)		1.37 (dt, 1.0, 6.8)	3.42 (s), 3.53 (s), 3.59 (s)	3.28 (dd, 3.6, 9.6)	4.85 (d, 3.6)		
(18)	2.69 (d, 12)	3.64 (d, 12)		3.40 (s), 3.51 (s), 3.63 (s)	3.35 (dd, 4.0, 10.0)	4.80 (d, 4.0)	4.68, 4.88 (q, 13.2)	7.32 (m)
(19)	2.60 (d, 12)	3.63 (d, 12)		3.47 (s), 3.60 (s), 3.58 (s)	3.28 (dd, 3.4, 10.0)	4.82 (d, 3.4)	4.52, 4.72 (q, 14.4)	7.32 (m)
(20)	2.64 (d, 10)		1.28 (dt, 0.5, 7.2)	3.38 (s), 3.52 (s), 3.62 (s)	3.22 (dd, 3.6, 9.2)	4.83 (d, 3.6)	4.70, 4.86 (q, 10.4)	7.32 (m)
(21)	2.60 (d, 10)		1.30 (dt, 0.8, 7.2)	3.42 (s), 3.50 (s), 3.58 (s)	3.28 (dd, 3.6, 9.6)	4.85 (d, 3.6)	4.56, 4.72 (q, 12.0)	7.35 (m)
(22)		3.72 (d, 11.2)	1.32 (dt, 0.9, 6.8)	3.40 (s), 3.52 (s), 3.64 (s)	3.22 (dd, 3.6, 9.2)	4.82 (d, 3.6)	4.66, 4.86 (q, 10.8)	7.34 (m)
(23)		3.63 (d, 11.0)	1.32 (dt, 1.2, 10.6)	3.41 (s), 3.49 (s), 3.58 (s)	3.30 (dd, 3.4, 9.6)	4.86 (d, 3.4)	4.56, 4.62 (q, 14.0)	7.30 (m)
(24)		3.72 (d, 11.2)	1.32 (dt, 1.0, 7.2)	3.40 (s), 3.50 (s), 3.62 (s)	3.22 (dd, 3.4, 9.2)	4.85 (d, 3.4)	4.66, 4.82 (q, 10.8)	7.34 (m)
(25)		3.78 (d, 11.2)	1.28 (dt, 1.2, 7.2)	3.47 (s), 3.54 (s), 3.61 (s)	3.30 (dd, 3.4, 9.6)	4.88 (d, 3.4)	4.58, 4.68 (q, 12)	7.36 (m)
(8)		3.80 (d, 11.2)	1.36 (dt, 1.1, 7.6)	3.44 (s), 3.52 (s), 3.66 (s)	3.23 (dd, 3.4, 10.4)	4.86 (d, 3.4)		
(9)		3.78 (d, 11.2)	1.36 (dt, 1.2, 7.2)	3.40 (s), 3.50 (s), 3.58 (s)	3.29 (dd, 3.6, 9.6)	4.85 (d, 3.6)		
(10)		3.84 (d, 11.0)	1.37 (dt, 1.0, 6.9)	3.43 (s), 3.51 (s), 3.65 (s)	3.24 (dd, 3.4, 10.0)	4.85 (d, 3.4)		
(11)		3.85 (d, 11.4)	1.36 (dt, 1.2, 7.0)	3.42 (s), 3.52 (s), 3.60 (s)	3.26 (dd, 3.6, 9.6)	4.86 (d, 3.6)		

* Chemical shifts in p.p.m., coupling constants in Hz; d = doublet, dt = double triplet, s = singlet, m = multiplet, dd = double doublet.

products by chromatography over silica, to determine approximate product ratios on a weight basis, and to determine isomeric compositions by ^1H n.m.r. Further data were obtained by following the migration of the 4-*O*-phosphate (11) and the 6-phosphate (10), induced by storage with NaOMe–MeOH. The base strengths in all experiments were selected to give experimentally convenient reaction times. Experiments [5] designed to provide kinetic data using ^{31}P n.m.r. spectroscopy have shown that the ring-opening and migration reactions were first order with respect to methoxide ion throughout the range of concentrations used.

In Table 2 results are summarised for the ring-opening reactions carried out with sodium methoxide in methanol for the cyclic ethyl phosphates (7-ax) and (7-eq). The most important result was that the preponderant products were those formed with inversion of configuration at phosphorus, *i.e.* (7-ax) afforded preponderantly the 4-phosphate (9) and the 6-phosphate (8), and (7-eq) afforded the 4-phosphate (11) and the 6-phosphate (10). To assist the interpretation of the results from these experiments, the pure 4-phosphate (11) and 6-phosphate (10) were separately treated with sodium methoxide in methanol and the results are summarised in Table 3.

Although the isomeric purity of the 4-phosphate (11) decreased on storage in 0.5M sodium methoxide, this decrease in purity occurred far too slowly to be by the same mechanism that gives mixtures of 4-phosphate isomers during the ring-opening of (7-ax) [or (7-eq)]. It should be noted that the concentration of sodium methoxide used for the migration experiments (Table 3) was much higher than that used for the ring-opening experiments (Table 2). The migration of the methyl ethyl phosphate group occurred readily from the 4- to 6-positions of glucose with retention of configuration at phosphorus, *i.e.* (11) afforded (8). The reverse migration

TABLE 2

Ring-opening reactions of (7-ax) and (7-eq) with sodium methoxide in methanol

Time (min)	% Unchanged	4-Phosphates % (9) + (11) (Ratio 9 : 11)	6-Phosphates % (8) + (10) (Ratio 8 : 10)
(1) Treatment of (7-ax) (1.7 g) in MeOH (17 ml) with 0.05N NaOMe–MeOH (10 ml)			
10	93	4 (84 : 16)	3 (100 : 0)
30	80.5	11.5 (85 : 15)	8 (100 : 0)
60	65	18 (83 : 17)	17 (>95 : <5)
(2) Treatment of (7-eq) (0.9 g) in MeOH (10 ml) with 0.05N NaOMe–MeOH (5 ml)			
8	93.5	6.5 (28 : 72)	
20	84.5	13.2 (30 : 70)	2.3 (10 : 90)
(3) Treatment of (7-eq) (0.52 g) in MeOH (10 ml) with 0.1N NaOMe–MeOH (5 ml)			
	Disappearance of (7-eq)	61.6 (29 : 71)	38.4 (37 : 63)

TABLE 3

Isomerisation of the 6-phosphate (10) and the 4-phosphate (11) with sodium methoxide in methanol

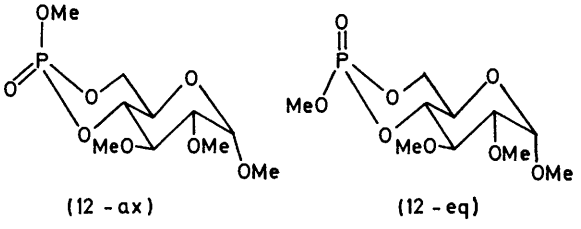
Time (min)	4-Phosphate % (9) + (11) (Ratio 9 : 11)	6-Phosphate % (8) + (10) (Ratio 8 : 10)
(1) Treatment of (10) (0.55 g) in MeOH (5 ml) with 1N NaOMe–MeOH (5 ml)		
0		100 (<5 : >95)
90	Detectable but not measurable	98 (<5 : >95)
210	3.6 (78 : 22)	96.4 (<5 : >95)
(2) Treatment of (11) (0.55 g) in MeOH (5 ml) with 1N NaOMe–MeOH (5 ml)		
0	100 (100 : 0)	
30	86 (>95 : <5)	14 (10 : 90)
60	71 (95 : 5)	29 (10 : 90)
90	71 (96 : 4)	29 (10 : 90)
135	54 (92 : 8)	46 (10 : 90)
175	47 (90 : 10)	53 (11 : 89)

from the 6- to the 4-position on glucose also occurred with preponderant retention of configuration at phosphorus [*i.e.* (10) afforded (9)] but this migration occurred too slowly to have any significant effect on the product distribution during the time scale of the ring-opening reactions.

One further experiment showed that an equal mixture of the 4-phosphate isomers (9) and (11) migrated to give 6-phosphates in such a way that at any time there was a 1 : 1 mixture of (9) and (11) and a 1 : 1 mixture of the 6-phosphates (8) and (10); *i.e.* the rate of migration from the 4- to 6-position of glucose appeared to be independent of the stereochemistry at phosphorus.

The above results may be interpreted in the following way by reference to Scheme 1. Attack by methoxide on the cyclic ethylphosphate (7-ax) occurred opposite both O-4 and O-6. When methoxide attack was opposite O-4 the TBP intermediate (A) was formed which broke down without pseudorotation to give the 6-phosphate (8) with inversion of configuration at phosphorus, or after pseudorotation through (H) to give the 4-phosphate (11) with retention of configuration. When attack by methoxide was opposite O-6 the 4-phosphate (9) was formed, probably through the TBP intermediate (B). In this case there was no evidence to support the production of (B) during ring-opening, since no 6-phosphate (10) [expected to be formed following pseudorotation of (B) to (J) and subsequent breakdown by P–O-4 bond cleavage] was detected in the early products from (7-eq). However, since there is such good evidence consistent with the formation of TBP intermediates for most of the product-forming reactions in Scheme 1, there is no reason to prefer an S_N2P process rather than a TBP intermediate mediated process for the formation of (9) from (7-ax).

There is little doubt that TBP intermediates such as (B), (G), (H), and (C) are fully consistent with the observed migrations of the methyl ethyl phosphate group from O-4 to O-6. The results, which show that the migrations occur preponderantly with retention of configuration, substantiate that the migrations do not occur (at least other than a very minor pathway) through a sequence which involves re-formation and ring re-opening of cyclic phosphates; such migrations would occur with inversion of configuration and with some exchange of methoxy- and ethoxy-groups. However, that a small amount of 1,3,2-dioxaphosphorinan-2-one formation occurs is probable, and could be one mechanism by which the slight loss of isomeric purity occurs during migrations. [Other mechanisms for loss of isomeric purity include more complex pseudorotational sequences.] Indeed, although in sodium methoxide evidence for the re-formation of (7-ax) and (7-eq) or the cyclic methyl phosphate [4] derivatives (12-ax) and (12-eq) during migration experiments is inconclusive, in other



(12 - ax) (12 - eq)

experiments in which migrations of *e.g.* (9) and (11) were promoted with sodium ethoxide, chromatographic and spectroscopic evidence for the re-formation of 1,3,2-dioxaphosphorinan-2-ones has been obtained.[6] This does not detract from the argument that the migrations described take place preponderantly *via* TBP intermediates but emphasises that this may not be a general conclusion, and that the choice of available routes will be a function of the substituents, and the solvent and base.

The results obtained are consistent with the hypothesis that TBP intermediates and pseudorotational sequences play as important part in reactions of six-membered cyclic phosphates as they do with five-membered cyclic phosphates. Experiments carried out recently on six-membered cyclic phosphonates confirmed that ring-opening reactions take place stereospecifically with inversion of configuration, and that migrations which also occur stereospecifically involve re-formation of the original cyclic phosphonates. It was not possible to establish whether the reactions were S_N2P or whether TBP intermediates were formed.

In the absence of precise kinetic data it is not possible to make any further detailed analysis of the events shown in Scheme 1. Some further comments may be of interest, however. For example, in the ring opening of (7-ax), the approximately equal amounts of 4-[(9) + (11)] and 6-phosphates [(8) + (10)], and the relatively small proportion of the minor 4-phosphate (11) in major 4-phosphate isomer (9), are consistent with the notion that methoxide attacks phosphorus opposite O-4 and O-6 with equal facility. With (7-eq), the situation is not grossly different, for although only 4-phosphates are present in the early stages of ring-opening, the fact that the ratio of (9) : (11) is 3 : 7 suggests a significant attack of methoxide opposite O-4. The mechanisms which determine that P–O-6 bond cleavage in (7-ax) is relatively facile compared with the similar bond cleaving in (7-eq), or that pseudorotation of (D) is much easier than of (A), are hard to define; it is possible that the answer may be provided from studies of the ring conformations preferred in six-membered rings containing pentaco-ordinate phosphorus. It has been shown previously that conformational effects in such intermediates can affect the stereochemistry of the 1,3,2-dioxaphosphorinan-2-ones derived from them.[7]

The results reported in this paper conflict on a number of points with generalisations creeping in to review literature. For example, it has been claimed that hydrolysis rates for six-membered cyclic phosphates are close to those of their acyclic analogues.[8] The results in this paper show that ring-opening reactions occur much faster than migration reactions, which in turn are much faster than the alcoholysis of the methyl ethyl glucose phosphates (to give for example dimethyl ethyl phosphate, trimethyl phosphate, *etc.*). Indeed, scrutiny of some of the original references quoted in support of the generalisations indicates that the reviewers have oversimplified and that neutral six-membered ring phosphate esters have been little studied.

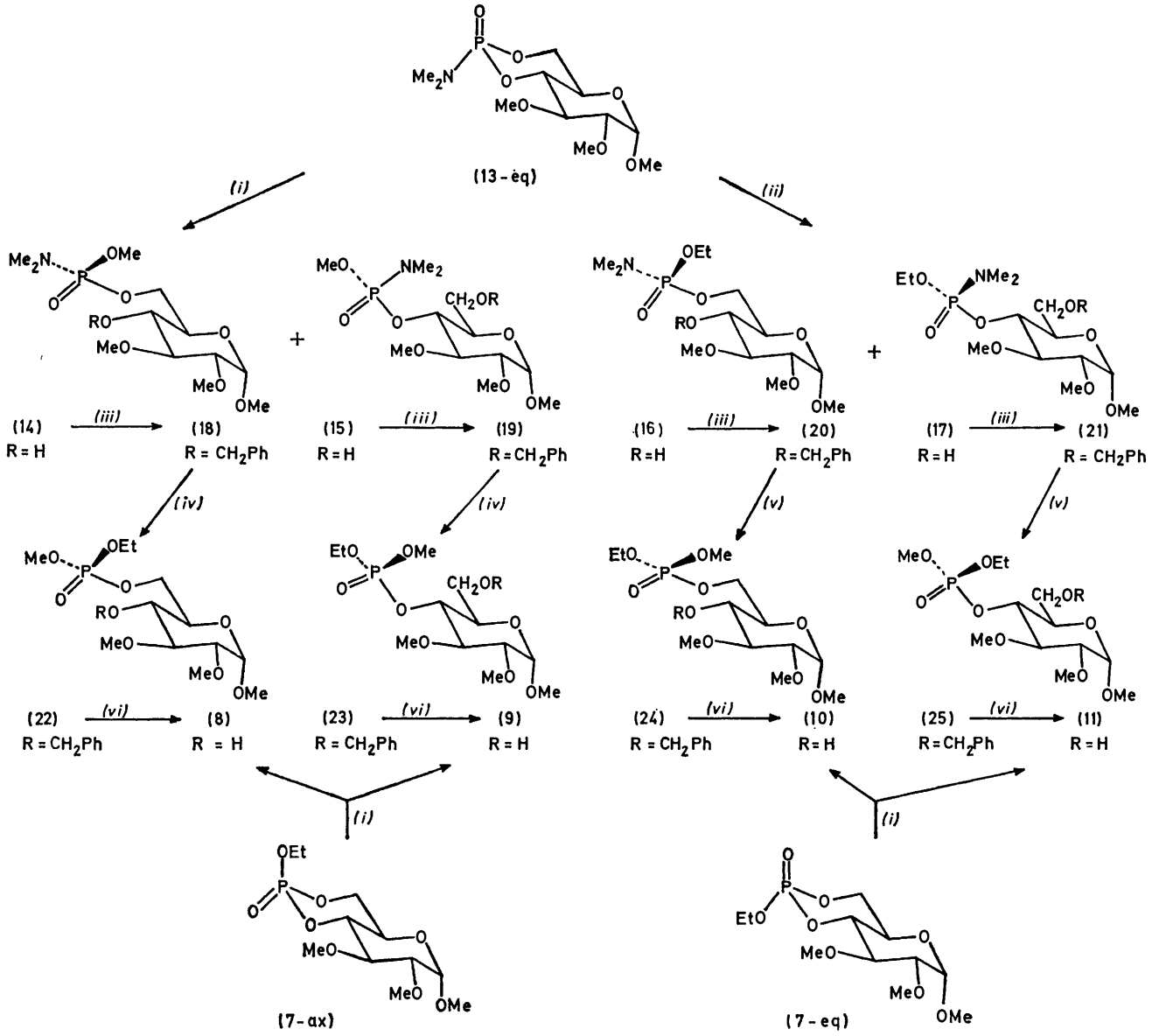
In an excellent and stimulating review [3] an attempt was made to interpret available data on the hydrolysis of phosphate esters in a series of summary rules. Two of these rules were that six-membered rings prefer to span basal positions in TBP intermediates, and that in the decomposition of pentaco-ordinate phosphorus the preference is for rings to be retained. Clearly the results presented in this paper are in direct contradiction of those rules (based mainly on results with phosphonium salts, not esters) since there is no evidence for direct displacements involving intermediates such as (E) and (F), and migrations do not involve re-formation of 1,3,2-dioxaphosphorinan-2-ones. Indeed, previous results [9] have also shown that even with good leaving groups there is a considerable barrier to the formation of intermediates in which the six-membered ring spans basal positions, with the consequence that displacement of the exocyclic group occurs with retention of configuration.

Preparation of the 6-*Phosphates* (8) *and* (10) *and the* 4-*Phosphates* (9) *and* (11), *and the Assignment of their Configurations*.—The four phosphates required to establish the stereochemical course of the ring-opening reactions of (7-ax) and (7-eq) were prepared as illustrated in Scheme 2 by reaction sequences which allowed their absolute configurations to be assigned. The key starting material, methyl 2,3-di-*O*-methyl-α-D-glucopyranoside (*S*)-4,6-dimethylphosphoramidate [9] (13-eq) was prepared by treatment of methyl 2,3-di-*O*-methyl-α-D-glucopyranoside (*S*)-4,6-phosphorochloridate with dimethylamine. The preponderant isomer was (13-eq) whose configuration has been previously assigned.[9] On treatment with sodium ethoxide in ethanol (13-eq) afforded approximately equal amounts of the 6-phosphate (16) and the 4-phosphate (17). The initial presumption that (16) and (17) were formed from (13-eq) with inversion of configuration at phosphorus was supported by subsequent experiments. Thus during attempts to convert (17) into (11) by treatment with methanolic hydrogen chloride the only product formed was the cyclic phosphate (7-ax). Similar treatment of (16) with methanolic hydrogen chloride afforded (7-ax) (42%) and (10) (55%). Since acid-catalysed P–N bond cleavage reactions in methanol usually occur stereospecifically with inversion of configuration,[10] and because the formation of (10) was stereospecific, it is reasonable to assume that the more facile intramolecular P–N bond cleaving reaction in the case of (17), or the equally facile intramolecular reaction in the case of (16), also proceed with inversion of configuration; double displacement reactions involving formation of intermediate chloridates followed by intramolecular displacement of chloride could not compete with direct methanolysis.[10] With ethanolic hydrogen chloride in comparative experiments the 4-substituted derivative (15) afforded only the cyclic methoxy-isomer (12-ax) (98%) whereas the 6-substituted (14) afforded a much lower yield, 63%, of (12-ax).

The above results, in addition to providing evidence to support the assumption that ring-opening of (13-eq) with alkoxides occurs with inversion of configuration, made it necessary to block the free hydroxy group in (14), (15), (16), and (17) before carrying out hydrogen chloride promoted alcoholyses of the P–N bond. Thus (14), (15), (16), and (17) were benzylated to afford (18), (19), (20), and (21) respectively. These benzylated derivatives were then treated with ethanolic or methanolic hydrogen chloride as appropriate to afford (22), (23), (24), and (25) respectively. The n.m.r. spectra of these derivatives were essentially consistent with the expected structures, but did show, in some cases, the presence of probable isomeric impurities. No attempt was made to estimate the proportions of these impurities at this stage, but instead the benzylated derivatives were hydrogenated over 10% palladium–charcoal in ethanol. The hydrogenated products were subjected to detailed n.m.r. analysis and chromatographic separation where possible, with the following results.

The sequence of reactions (21)→(25)→(11) was found to proceed stereospecifically, since hydrogenation of (25) afforded (11) in 97% yield, and no other product [including (9)] was detected.

Although the reaction sequence (20)→(24)→(10) proceeded much as expected with 91% of (10) being isolated as the 6-*O*-methyl ethyl phosphate isomer, a mixture of the 4-*O*-phosphates (9) and (11) were isolated in 4% yield. The stage at which this isomerisation occurs has not been established.



SCHEME 2 (*i*) NaOMe–MeOH; (*ii*) NaOEt–EtOH; (*iii*) $PhCH_2Br$–NaH; (*iv*) EtOH–HCl; (*v*) MeOH–HCl; (*vi*) H_2,Pd–C

The sequence (19)→(23)→(9) afforded preponderantly (9) in admixture with about 20% of the isomer (11), and the sequence (18)→(22)→(8) afforded preponderantly (8) in admixture with about 23% of the isomer (10). These results are in accord with expectation for hydrogen chloride promoted ethanolyses of P–N bonds.[10]

EXPERIMENTAL

^{1}H N.m.r. spectra were measured with a JEOL MH 100 spectrometer at 100 MHz in deuteriochloroform solution, with $SiMe_4$ as internal standard. The diastereoisomeric composition at phosphorus of mixtures of (8) and (9), and of (10) and (11), was estimated by measurement of the peak heights of P–OMe doublets in the n.m.r. spectrum, which were sufficiently well resolved for each pair of compounds. Column chromatography was performed with Merck silica gel of particle size 0.05—0.2 mm. All solvents were distilled prior to use. Solutions of methanolic or ethanolic hydrogen chloride were prepared by the addition of acetyl chloride to the alcohol to give a solution *ca.* 2N with respect to hydrogen chloride, and as a result also contained a few per cent of the corresponding acetate. Sodium hydride refers to the material supplied as an 80% dispersion in oil.

Methyl 2,3-Di-O-methyl-α-D-glucopyranoside (S)-4,6-NN-Dimethylphosphoramidate (13-eq).—Phosphoryl chloride (10.0 g, 0.065 mol) was added dropwise to a stirred solution of methyl 2,3-di-*O*-methyl-α-D-glucopyranoside (13.2 g.

0.06 mol) and triethylamine (13.0 g, 0.13 mol) in methylene chloride. Stirring was continued for 1 h and the mixture stored at room temperature overnight. The chloridate was not isolated but reacted directly with dimethylamine (8 ml, 5.4 g, 0.12 mol) in the presence of triethylamine (8 ml, 6.0 g, 0.06 mol). The mixture was stirred for 1 h at room temperature and then poured into water. The organic layer was washed with water, aqueous potassium carbonate solution, and water, dried, and concentrated. The brown residue was recrystallised from cyclohexane–ethyl acetate (2 : 1). Two recrystallisations afforded (13-eq) as colourless crystals (9.0 g, 48%) homogeneous by t.l.c. [benzene–petrol–ethanol (4 : 5 : 1)]. Further, (13-eq), together with the axial isomer, could be isolated by column chromatography of the mother-liquors. The use of longer reaction times (*i.e.* several hours) gave reaction mixtures in which the axial isomer preponderated.

Methyl 2,3-*Di*-O-*methyl*-α-D-*glucopyranoside* (R)-4- *and* (S)-6-(*Methyl* NN-*Dimethylphosphoramidate*), (15) *and* (14).—A solution of (13-eq) (3.0 g, 0.0096 mol) in *ca.* 1N sodium methoxide in methanol (40 ml) was refluxed for 1.5 h. The solution was concentrated to *ca.* 10 ml and poured into water. Conventional work-up gave a yellow syrup which was chromatographed [chloroform–methanol (19 : 1)] to afford, in order of elution; unchanged (1) (0.2 g); methyl 2,3-di-*O*-methyl-α-D-glucopyranoside (*R*)-4-(methyl *NN*-dimethylphosphoramidate) (15) (1.1 g, 33%); and methyl 2,3-di-*O*-methyl-α-D-glucopyranoside (*S*)-6-(methyl-*NN*-dimethylphosphoramidate) (14) (1.0 g, 30%), together with a mixture of (14) and (15) (0.7 g).

Methyl 2,3-*Di*-O-*methyl*-α-D-*glucopyranoside* (R)-4- *and* (S)-6-(*Ethyl* NN-*Dimethylphosphoramidate*), (17) *and* (16).—A solution of (13-eq) in *ca.* 1N sodium ethoxide in ethanol (40 ml) was stored at room temperature for 18 h, when t.l.c. [chloroform–methanol (38 : 1)] indicated approximately equal proportions of (13-eq), (16), and (17). The separation of this mixture was difficult and required repeated column chromatography [chloroform–methanol (76 : 1)] to afford unchanged (13-eq) (0.6 g), methyl 2,3-di-*O*-methyl-α-D-glucopyranoside (*R*)-4-(ethyl *NN*-dimethylphosphoramidate) (17) (1.1 g, 32%), and methyl 2,3-di-*O*-methyl-α-D-glucopyranoside (*S*)-6-(ethyl *NN*-dimethylphosphoramidate) (16) (1.0 g, 29%).

Methyl 2,3-*Di*-O-*methyl*-4-O-*benzyl*-α-D-*glucopyranoside* (S)-6-(*Methyl* NN-*Dimethylphosphoramidate*) (18).—Sodium hydride (0.5 g) was added to a stirred solution of (14) (0.96 g, 0.0002 8 mol) and benzyl bromide (1 ml) in ether (20 ml) cooled in an ice–water bath. After the addition, the cooling bath was removed and the mixture stirred at room temperature for 16 h when t.l.c. [benzene–acetone (7 : 3)] indicated no (14) to be present. The mixture was added to water and worked up in the usual way to afford, after column chromatography, (18) (0.85 g, 70%) as a pale yellow syrup.

Methyl 2,3-*Di*-O-*methyl*-6-O-*benzyl*-α-D-*glucopyranoside* (R)-4-(*Methyl* NN-*Dimethylphosphoramidate*) (19).—As described above, (15) (1.14 g, 0.003 3 mol) was treated with sodium hydride (0.5 g) and benzyl bromide (1 ml) in ether (20 ml) for 1.5 h to afford (19) 1.33 g, 93%) as a yellow syrup.

Methyl 2,3-*Di*-O-*methyl*-4-O-*benzyl*-α-D-*glucopyranoside* (S)-6-(*Ethyl* NN-*Dimethylphosphoramidate*) (20).—Sodium hydride (0.25 g) was added to a stirred solution of (16) (1.0 g, 0.002 8 mol) and benzyl bromide (1 ml) in dry dimethylformamide (10 ml) cooled in an ice–water bath. After 50 min, conventional processing and column chromatography [benzene–acetone (7 : 3)] of the crude product gave (20) (0.7 g, 56%). (It should be noted that the use of ether as reaction solvent gave complex reaction products.)

Methyl 2,3-*Di*-O-*methyl*-6-O-*benzyl*-α-D-*glucopyranoside* (R)-4-(*Ethyl* NN-*Dimethylphosphoramidate*) (21).—Sodium hydride (0.25 g) was added to (17) (1.5 g, 0.004 2 mol) and benzyl bromide (1.3 ml) in DMF (15 ml) as described above to afford, after chromatography [benzene–acetone (7 : 3)], (21) (1.4 g, 75%) as a syrup.

Methyl 2,3-*Di*-O-*methyl*-4-O-*benzyl*-α-D-*glucopyranoside* (R)-6-(*Methyl Ethyl Phosphate*) (22).–A solution of (18) (0.48 g, 0.001 1 mol) in *ca.* 2N hydrogen chloride in ethanol (10 ml) was stored at room temperature for 6 h. Work-up, by addition to an excess of 10% aqueous potassium carbonate solution and chromatography [benzene–acetone (7 : 3)] of the product afforded (22) (0.28 g, 58%).

Methyl 2-3-*Di*-O-*methyl*-α-D-*glucopyranoside* (R)-6-(*Methyl Ethyl Phosphate*) (8).—A solution of (22) (0.28 g, 0.000 6 mol) in ethanol (10 ml) was hydrogenated over 10% palladium–charcoal at room temperature and pressure. Removal of the catalyst by filtration and chromatography [chloroform–methanol (38 : 1)] afforded (8) (0.17 g, 82%) as a colourless syrup containing *ca.* 23% (10).

Methyl 2,3-*Di*-O-*methyl*-6-O-*benzyl*-α-D-*glucopyranoside* (S)-4-(*Methyl Ethyl Phosphate*) (23).—A solution of (19) (0.5 g, 0.0001 2 mol) in *ca.* 2N ethanolic hydrogen chloride was stored at room temperature for 28 h, when t.l.c. [benzene–acetone (7 : 3)] indicated an absence of starting material. Conventional work-up and chromatography afforded (23) (0.34 g, 65%) as a syrup.

Methyl 2,3-*Di*-O-*methyl*-α-D-*glucopyranoside* (S)-4-(*Methyl Ethyl Phosphate*) (9).—A solution of (23) (0.34 g, 0.000 8 mol) in ethanol (10 ml) was hydrogenated in the usual way to afford, after chromatography [chloroform–methanol (38 : 1)], (9) (0.24 g, 89%) containing *ca.* 20% of (11).

Methyl 2,3-*Di*-O-*methyl*-4-O-*benzyl*-α-D-*glucopyranoside* (S)-6-(*Methyl Ethyl Phosphate*) (24).—A solution of (20) (1.45 g, 0.003 2 mol) was stored in *ca.* 2N methanolic hydrogen chloride (25 ml) for 5 h. The usual work-up and chromatography [benzene–acetone (8 : 2)] gave (24) (1.28 g, 89%) as a syrup.

Methyl 2,3-*Di*-O-*methyl*-α-D-*glucopranoside* (S)-6-(*Methyl Ethyl Phosphate*) (10).—A solution of (24) (1.28 g, 0.002 9 mol) in ethanol (20 ml) was hydrogenated in the usual way to afford after chromatography [chloroform–methanol (38 : 1)], in order of elution, a mixture of (9) and (11) [0.045 g, 4%; (9) : (11) *ca.* 20 : 1]; and (10) (0.95 g, 91%) as a colourless syrup. Compound (6) could not be detected by ^{1}H n.m.r. analysis.

Methyl 2,3-*Di*-O-*methyl*-6-O-*benzyl*-α-D-*glucopyranoside* (R)-4-(*Methyl Ethyl Phosphate*) (25).—A solution of (21) (1.4 g, 0.003 1 mol) in *ca.* 2N methanolic hydrogen chloride was stored at room temperature for 21 h. Conventional processing and chromatography [benzene–acetone (7 : 3)] afforded (25) (1.18 g, 85%) as a syrup.

Methyl 2,3-*Di*-O-*methyl*-α-D-*glucopyranoside* (R)-4-(*Methyl Ethyl Phosphate*) (11).—A solution of (25) (1.18 g, 0.002 6 mol) in ethanol (30 ml) was hydrogenated in the usual way. Removal of the catalyst and chromatography [chloroform–methanol (38 : 1)] afforded (11) (0.90 g, 97%) as a colourless syrup; (9) was not detected in (11) by ^{1}H n.m.r. analysis.

Reaction of (15) *with Ethanolic Hydrogen Chloride.*—A solution of (15) (0.28 g, 0.000 82 mol) in *ca.* 2N ethanolic hydrogen chloride (4 ml) was stored at room temperature for 45 min. Conventional processing and chromatography [chloroform–methanol (38 : 1)] gave (12-ax) (0.24 g, 98%) as the sole product.

Reaction of (14) *with Ethanolic Hydrogen Chloride.*—A solution of (14) (0.11 g, 0.000 32 mol) in *ca.* 2N ethanolic hydrogen chloride was stored at room temperature for 90 min. Usual work-up and chromatography [chloroform–methanol (38 : 1)] gave as the preponderant product (12-ax) (0.06 g, 63%), together with a mixture of other glucose phosphates which were not further investigated.

Reaction of (16) *with Methanolic Hydrogen Chloride.*—A solution of (16) (0.1 g, 0.000 28 mol) in *ca.* 2N methanolic hydrogen chloride (2 ml) was stored at room temperature for 2 h. Conventional processing and chromatography [chloroform–methanol (38 : 1)] afforded in order of elution (7-ax) (0.037 g, 42%) and (10) (0.055 g, 55%).

Reaction of (17) *with Methanolic Hydrogen Chloride.*—A solution of (17) (0.1 g, 0.000 28 mol) in *ca.* 2N methanolic hydrogen chloride was stored at room temperature for 1 h. Chromatography [chloroform–methanol (38 : 1)] gave (7-ax) (0.085 g, 98%) as the sole product.

Ring-opening of (7-eq) *with Sodium Methoxide.*—A solution of *ca.* 0.05N sodium methoxide methanol (5 ml) was added to a solution of (7-eq) (0.9 g) in methanol (10 ml). After 8 min a 10-ml aliquot of the reaction mixture was withdrawn and worked up. The remainder of the mixture was worked-up after 20 min. Both samples were chromatographed [chloroform–methanol (38 : 1)] to separate unchanged (7-eq) and the products of ring-opening. The ratio of (8) : (10) and (9) : (11) was determined by ^{1}H n.m.r.

In another experiment, (7-eq) (0.52 g) in MeOH (10 ml) was treated with *ca.* 0.1N sodium methoxide in methanol (5 ml) until t.l.c. indicated the disappearance of starting material (*ca.* 3 h). Again the reaction product was chromatographed to separate the isomeric 4- and 6-phosphates and the ratios (8) : (10) and (9) : (11) were determined.

The results of both experiments are shown in Table 2.

Ring-opening of (7-ax) *with Sodium Methoxide.*—A solution of *ca.* 0.05N sodium methoxide in methanol (10 ml) was added to a solution of (7-ax) (1.7 g) in methanol (17 ml). After 10 min, a 15-ml aliquot was worked up, after 30 min a further 10-ml aliquot, and the remainder after 60 min. Unchanged (7-ax) was separated from the 4- and 6-phosphates by chromatography [chloroform–methanol (38 : 1)] and the ratio of (8) : (10) and (9) : (11) determined by ^{1}H n.m.r. The results are shown in Table 2.

Base-promoted Isomerisation of 4-*Phosphate* (11).—A solution of (11) (0.55 g) in methanol (5 ml) was treated with *ca.* 1N sodium methoxide in methanol (5 ml). 2-ml Aliquots were withdrawn after 30, 60, 90, 135, and 175 min, and the 4-phosphate separated from the 6-phosphate by column chromatography [chloroform–methanol (76 : 1)]. The ratio of (8) : (10) and (9) : (11) was determined by ^{1}H n.m.r. spectroscopy for each sample. The results are reported in Table 3.

Base Treatment of 6-*Phosphate* (10).—A solution of (10) (0.55 g) in methanol (5 ml) was treated with *ca.* 1N sodium methoxide in methanol (5 ml). Aliquots were withdrawn after 30, 60, and 210 min. The samples withdrawn after 30 and 60 min were essentially unchanged (10), although traces of 4-phosphate could be detected by t.l.c. The 210-min sample was chromatographed [chloroform–methanol (76 : 1)] to afford 4-phosphate [4 mg, (11) : (9) *ca.* 22 : 78] and 6-phosphate [105 mg, (10) : (8) *ca.* $>95 : <5$] (Table 3).

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REFERENCES

[1] F. H. Westheimer, *Accounts Chem. Res.*, 1968, **1**, 70; F. Covitz and F. H. Westheimer, *J. Amer. Chem. Soc.*, 1963, **85**, 1773; R. Kluger, F. Covitz, E. Dennis, L. D. Williams, and F. H. Westheimer, *J. Amer. Chem. Soc.*, 1969, **91**, 6066.

[2] R. Luckenbach, 'Dynamic Stereochemistry of Pentacoordinated Phosphorus and Related Elements,' Thième, Stuttgart, 1973.

[3] P. Gillespie, F. Ramirez, I. Ugi, and D. Marquarding, *Angew. Chem. Internat. Edn.*, 1973, **12**, 91.

[4] D. B. Cooper, J. M. Harrison, T. D. Inch, and G. J. Lewis, *J.C.S. Perkin I*, 1974, 1058.

[5] J. M. Harrison, T. D. Inch, R. P. Scott, P. Watts, and C. Brown, unpublished results.

[6] J. M. Harrison and T. D. Inch, unpublished results.

[7] D. B. Cooper, T. D. Inch, and G. J. Lewis, *J.C.S. Perkin I*, 1974, 1043.

[8] J. Emsley and D. Hall, 'The Chemistry of Phosphorus,' Harper and Row, London, 1976, p. 330.

[9] J. M. Harrison, T. D. Inch, and G. J. Lewis, *J.C.S. Perkin I*, 1974, 1053.

[10] C. R. Hall and T. D. Inch, *J.C.S. Perkin I*, 1979, 1646.