Use of Carbohydrate Derivatives for Studies of Phosphorus Stereochemistry. Part 8.[1] Preparation and Some Reactions of 1,3,2-Oxazaphospholidine-2-ones and -2-thiones derived from 2-Deoxy-3,4,6-tri-*O*-methyl-2-methylamino-D-glucopyranose

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The four cyclic phosphorus esters from the reaction of $MePSCl_2$ with 2-deoxy-3,4,6-tri-*O*-methyl-2-methylamino-D-glucopyranose (1) have been separated with difficulty, and structures assigned. Ring-opening of the isomers and subsequent detachment of the chiral phosphorus group from the carbohydrate moiety occurs in both acid and base, the nature of the products varying with reaction conditions and initial stereochemistry. In acid the P–N bond is broken first and then the C–O bond. In base P–N and P–O bonds are cleaved competitively; when the P–N bond is cleaved first subsequent detachment of the phosphorus group from the carbohydrate occurs by C–O and P–O bond cleavage depending on the anomeric configuration and on the concentration of the base. The P–N and P–O bond breaking reactions are highly stereoselective occurring with inversion of configuration. Reactions of (1) with $PhPSCl_2$, $MePOCl_2$, and $PhPOCl_2$ and ring-opening of the resultant esters are also described.

Tetrahydro-1,3,2-oxazaphosphorines derived from carbohydrates and 1,3,2-oxazaphospholidines from (−)-ephedrine are convenient and versatile intermediates for the synthesis of acyclic optically active phosphorus esters and related phosphorus derivatives.[2,3] The synthetic methods involve highly stereoselective ring-opening by cleavage of P–O or P–N bonds and then the detachment from phosphorus, also by highly stereoselective reactions, of the carbohydrate or ephedrine template. Under acid conditions ring-opening of the 1,3,2-oxazaphosphoro-system occurs by P–N bond cleavage with inversion of configuration and similarly where P–N bond cleavage occurs under basic conditions it is with inversion of configuration. However, whether P–N or P–O bond cleavage occurs in base or whether P–O bond cleavage occurs with inversion or retention depend on many factors including ring size, ring substituents, nature of nucleophile, and solvent *etc.* Although attempts have been made to rationalise some of the observations, the reasons for the variability of the ring-opening reactions in basic conditions are not well understood.[4,5] Consequently, as a continuation of these studies, a new group of 1,3,2-oxazaphospholidines has been prepared from 2-deoxy-3,4,6-tri-*O*-methyl-2-methylamino-D-glucopyranose (1) with the objective of exploring whether the additional reactivity at C-1 of the carbohydrate would introduce new features of synthetic advantage or might provide additional insight into the mechanisms of the ring-opening reactions.

2-Deoxy-3,4,6-tri-*O*-methyl-2-methylamino-D-glucopyranose (1) was prepared previously by sequential Kuhn methylation (MeI–Ag_2O–DMF) and hydrogenolysis of benzyl 2-(benzyloxycarbonyl)amino-2-deoxy-D-glucopyranoside.[6] In this laboratory, (1) was prepared more conveniently by permethylation of 2-acetamido-2-deoxy-D-glucose with MeI–NaH–DMF followed by acidic hydrolysis under conditions analogous to those reported for the preparation of 2-amino-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose from the corresponding acetamido glycoside.[7]

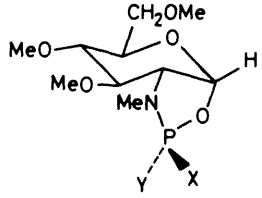
Treatment of (1) with methylthiophosphonic dichloride ($MePSCl_2$) in benzene in the presence of triethylamine afforded a mixture of the four isomers 1-*O*,2-*N*-[(*R*)-methyl(thio)phosphoryl]- (2β-*trans*) and 1-*O*,2-*N*-[(*S*)-methyl(thio)phosphoryl]-2-deoxy-3,4,6-tri-*O*-methyl-2-methylamino-β-D-glucopyranoside (2β-*cis*); and 1-*O*,2-*N*-[(*R*)-methyl(thio)phosphoryl-(2α-*trans*)- and *1*-*O*,2-*N*-[(*S*)-methyl(thio)phosphoryl]-2-deoxy-3,4,6-tri-*O*-methyl-2-methylamino-α-D-glucopyranoside (2α-*cis*). The α and β terms in the compound numbers indicate whether the compound is a derivative of α- or β-D-glucopyranose. With the C-2 proton of the sugar as reference point the *cis* and *trans* terms indicate the relative dispositions of the P=S group. A similar notation will be used for P=O derivatives.

Inspection of the ^{31}P n.m.r. (proton decoupled) spectrum of the reaction mixture indicated that the four isomers were formed in high yield and in approximately equal proportions. However, the difficulty of isomer separation was such that after multiple silica column chromatography the percentages isolated were: 15% (2β-*trans*), 3% (2β-*cis*), 7% (2α-*trans*), and 4% (2α-*cis*). The low yields of each isomer in a pure state imposed restrictions on subsequent comparative chemical studies. ^1H N.m.r. parameters of the four isomers of (2) are given in the Table. [^{31}P N.m.r. also clearly demonstrated that when triethylamine was added slowly to a mixture of (1) and $MePSCl_2$, four reaction intermediates, presumably the result of addition of $MePSCl_2$ to the sugar nitrogen (δ_P 73.7, 71.9, 71.2, 69.1), could be detected.]

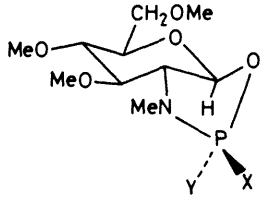
Treatment of (1) with phenylthiophosphonic dichloride afforded a similar mixture of four isomers which was not investigated further. However when (1) was treated with phenylphosphonic dichloride a 3 : 3 : 1 : 1 mixture (^{31}P n.m.r.) of isomers was obtained from which (3α-*trans*) (22%) and (3α-*cis*), (23%) were readily separated from the mixture of minor isomers and from each other by silica column chromatography. The minor isomers (3β-*trans*) and (3β-*cis*) were separated by h.p.l.c. Similar results were obtained on treatment of (1) with methylphosphonic dichloride, although in this case only the major isomers (4α-cis) and (4α-*trans*) were isolated in pure form. The ^1H n.m.r. parameters of the minor isomers (4β-*trans*) and (4β-*cis*) were obtained from the mixture.

Provisional structural assignments were made on the basis of ^1H n.m.r. data (which were subsequently confirmed by ring-opening and degradation experiments). The first problem was to decide which isomers were derivatives of α-D-glucopyranose and which were β-D-anomers. With D-glucopyranose in a chair conformation vicinal couplings for α- and β-

Table 1. N.m.r. data for some cyclic phosphate esters from compound (1)



α – series



β – series

Compound			Chemical shift (δ)				Coupling constant (Hz)		
	X	Y	NMe	PMe	1-H	P	$J_{1,2}$	$J_{1,P}$	$J_{P,NMe}$
2β-*trans*	Me	S	2.79	1.89	4.88	103.8	7.6	0	13.7
2β-*cis*	S	Me	2.67	1.94	4.79	109.6	7.7	0	16.8
2α-*trans*	Me	S	2.77	1.85	5.63	99.0	4.8	2.0	13.0
2α-*cis*	S	Me	2.83	2.05	5.87	102.0	4.5	4.5	12.9
3β-*trans*	Ph	O	2.58	—	5.15	32.1	7.0	0	11.0
3β-*cis*	O	Ph	2.79	—	4.85	35.3	6.5	0	12.0
3α-*trans*	Ph	O	2.71	—	5.84	30.0	5.0	5.0	
3α-*cis*	O	Ph	2.86	—	6.09	30.1	4.8	3.4	10.0
4β-*trans*	Me	O	2.74	1.59	4.93	40.0	7.0	0	11.9
4β-*cis*	O	Me	2.74	1.67	4.74		7.0	0	
4α-*trans*	Me	O	2.78	1.60	5.60	40.8	5.0	3.5	10.4
4α-*cis*	O	Me	2.81	1.67	5.88		4.5	4.5	10.0

anomers are in the ranges 2—5 Hz and 7—12 Hz, respectively. However, for α-D-glucopyranose derivatives with a five-membered ring fused to C-1 and C-2, the pyranoid ring does not retain a chair conformation.[8,9] There is no reason to suppose that β-D-glucopyranose derivatives should behave differently. Thus, the fact that the (2β), (3β), and (4β) isomers have larger $J_{1,2}$ couplings than the (2α), (3α), and (4α) isomers is not unequivocal proof of the anomeric configuration. Such proof was provided by treating the bicyclic derivatives with hydrogen chloride in ethanol, a reaction which cleaved the P–N bond affording glucopyranose 1-*O*-[ethyl methyl (or phenyl) phosphate] derivatives. In this way (2β-*trans*) afforded (5β*S*), with 1-H couplings of 10.1 and 8.1 Hz, (2β-*cis*) afforded (5β*R*) with 1-H couplings of 8.6 and 8.6 Hz, (2α-*trans*) afforded (5α*S*) with $J_{1,2}$ 3.3 Hz and $J_{1,P}$ 11.0 Hz, and (2α-*cis*) afforded (5α*R*) with $J_{1,2}$ 3.2 Hz and $J_{1,P}$ 11.4 Hz. The typical small couplings in (5α*S*) and (5α*R*) of 3.2—3.3 Hz and the typically large couplings in (5β*S*) and (5β*R*) confirmed that these isomers were derivatives of α-D- and β-D-glucopyranose, respectively. Similar results were obtained when the P–N bond in (3α-*cis*) and (3α-*trans*) was broken in acidic ethanol.

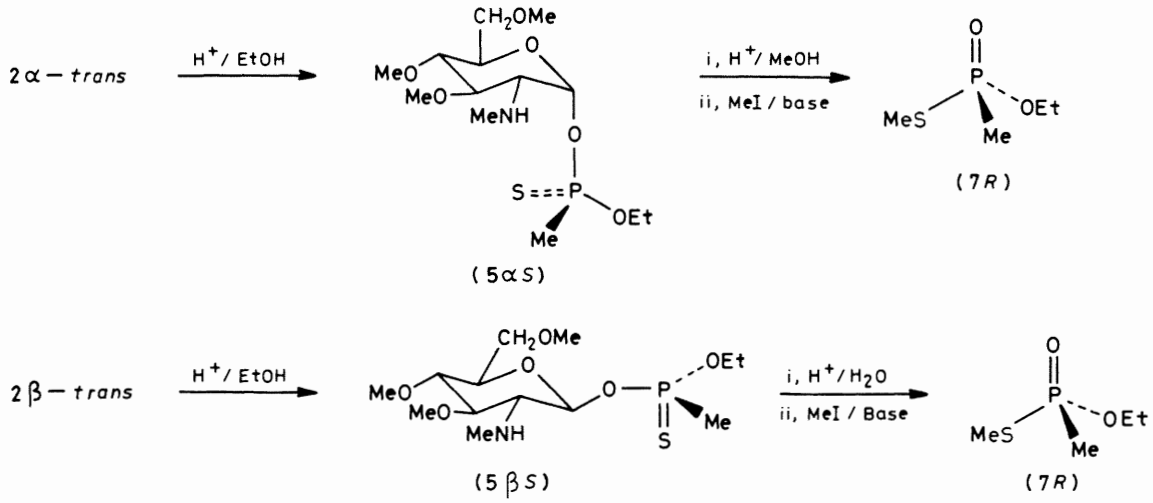
For the P=O derivatives (3) and (4), the configuration at phosphorus was assigned on the basis that the phosphoryl oxygen deshields *cis*-protons.[10] Thus in (4β-*trans*), 1-H (δ 4.93) is at lower field than 1-H (δ 4.74) in (4β-*cis*). Similar relations hold for (4α-*trans*) and (4α-*cis*), (3β-*trans*) and (3β-*cis*), and (3α-*trans*) and (3α-*cis*). Although the deshielding effect of P=S is less certain, the configuration of phosphorus in the pair of (2β) isomers and the pair of (2α) isomers was assigned on the same basis. In none of the isomers was 2-H visible in the ^{1}H n.m.r. spectrum (100 MHz).

Proof of the configuration at phosphorus for the four isomers of (2) was obtained by subjecting the products, (5β*S*) and (5α*S*), from P–N bond cleavage to more vigorous acidic hydrolysis and acidic methanolysis, respectively (Scheme 1). Following basification of the reaction mixtures and *S*-methylation of the product, (*R*)-(+)-ethyl *S*-methyl methylphosphonothioate (7*R*) was isolated from both reactions. Optical rotations of +82° and +85.9° respectively were recorded which by comparison with the rotations for the *R* and *S* isomers recorded elsewhere [2] (+85.5—87.5°) confirm that both the ring-opening reactions converting (2β-*trans*) into (5β*S*) and (2α-*trans*) into (5α*S*) and the reaction by which the phosphorus moiety is detached from the carbohydrate are essentially stereospecific. By analogy with many other acid-catalysed endocyclic P–N bond-breaking reactions,[2,3] the P–N bond cleavage in (2β-*trans*) and (2α-*trans*) must occur with inversion of configuration. Further, since (5α*S*), on treatment with acidic methanol, afforded ethyl methylphosphonothioic acid and not ethyl methyl methylphosphonothioate, it follows that the phosphorus moiety was detached from the carbohydrate by C–O bond cleavage and not by nucleophilic attack of methanol at phosphorus. Thus, detachment of the phosphorus from the carbohydrate occurs with retention of configuration and (2β-*trans*) and (2α-*trans*) (and also the other isomers) have the assigned structures.

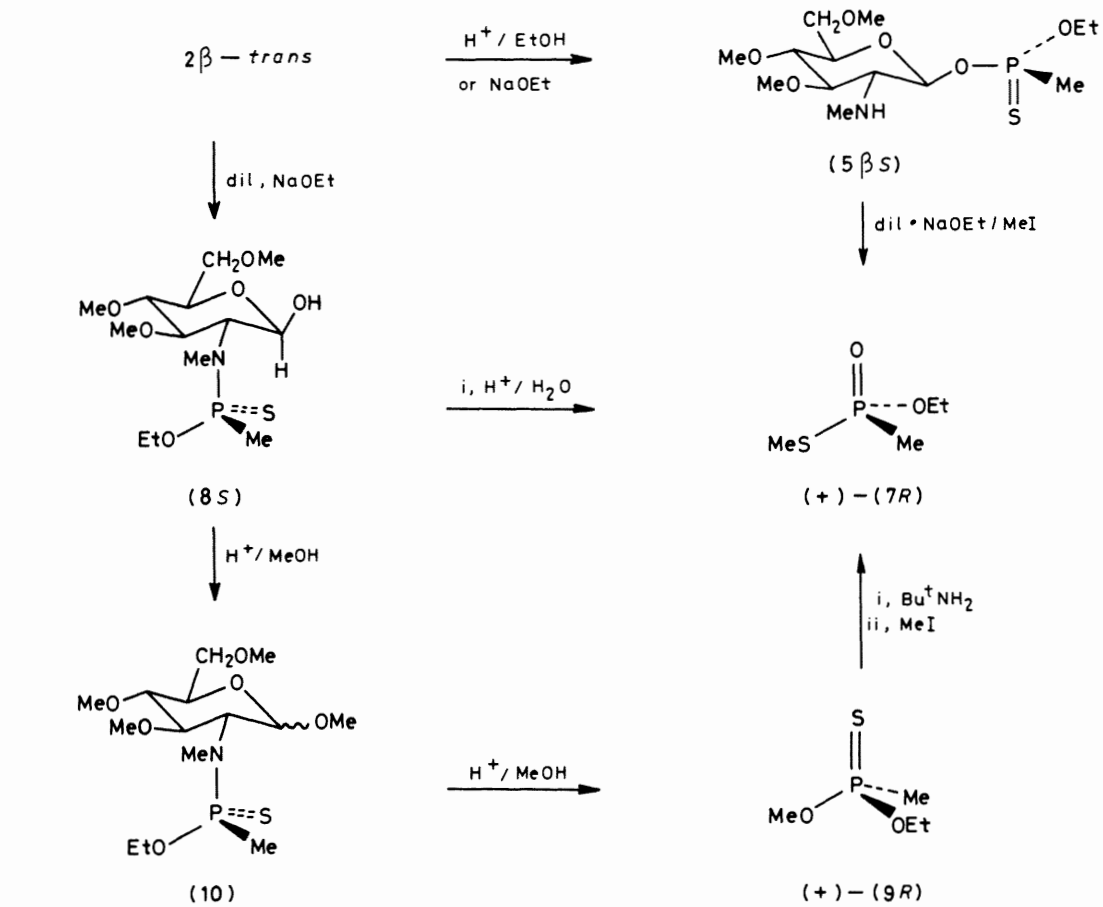
Further evidence for acid catalysed C–O bond cleavage in the 1-*O*-phosphonate sugar esters was provided when the products from acid catalysed ring-opening of (3α-*trans*) and (3α-*cis*) *viz* (6α*S*) and (6α*R*) were stored in deuteriomethanol for 24 h in the presence of trifluoromethylsulphonic acid. A ^{1}H n.m.r. spectrum of the solution showed the disappearance of the quartet for 1-H in the ester and the appearance of a doublet at δ 4.65 (*J* 8 Hz) consistent with the formation of the trideuteriomethyl 2-methylamino-3,4,6-tri-*O*-methyl-β-D-glucopyranoside.

Treatment of Cyclic Phosphorus Esters with Sodium Alkoxides.—The initial ring-opening reactions that take place when the cyclic phosphorus esters are treated with alkoxides, and the subsequent reactions of the ring-opened products are complex and depend on the concentration of the alkoxide and on the precise experimental conditions. Consequently the conditions chosen to allow isolation and identification of products were established by first monitoring the reactions by ^{31}P n.m.r. spectroscopy. Unless the alcohol used for preparation of the alkoxide and as the reaction solvent was dry, hydrolysis as well as alcoholysis products were formed.

(a) *Starting from the cyclic methyl(thio)phosphorylpyranoside*

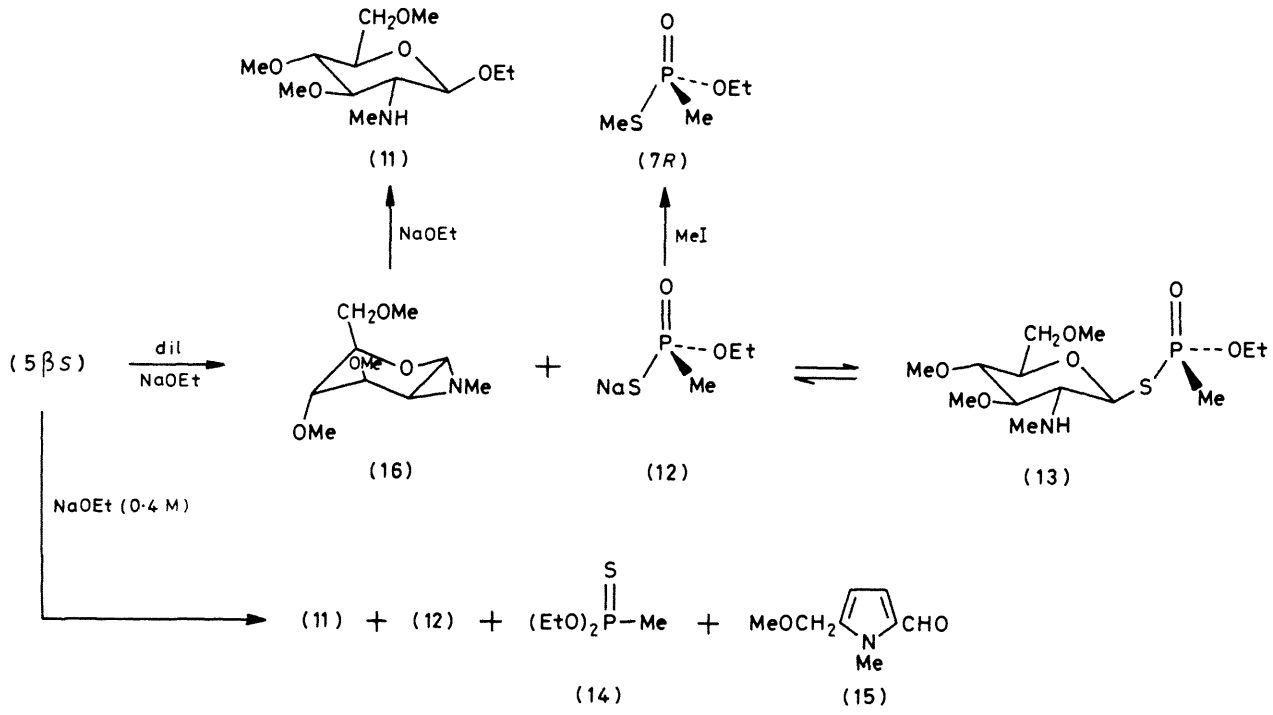


Scheme 1.



Scheme 2.

(2β-*trans*) (*Scheme* 2). Using an excess of ethanolic sodium ethoxide the only significant initial product was the 1-*O*-methylphosphonothioate (5β*S*), resulting from P–N bond cleavage. No product resulting from P–O bond cleavage was observed. However following dropwise addition of dilute ethanolic sodium ethoxide to a solution of (2β-*trans*) in ethanol a mixture of (5β*S*) and the thiophosphorylglucosamine (8*S*) was formed in the ratio 3 : 1. On storage in ethoxide, (5β*S*) undergoes further reactions and may be isolated more easily from reactions where the P–N bond in (2β-*trans*) is cleaved by acidic ethanol. Isolation of the thiophosphorylglucosamine (8*S*) was facilitated by storing a basic solution of the ring-opened mixture from (2β-*trans*) overnight thereby avoiding difficulties in the chromatographic separation of (5β*S*) and (8*S*). The thiophosphorylglucosamine (8*S*) was isolated following rapid silica column chromatography as



Scheme 3.

essentially the pure β-D-anomer which was stable in ethanol but which anomerised rapidly in chloroform.

The configuration at phosphorus in (8*S*) was established by sequential acidic hydrolysis and *S*-methylation to afford (*R*)-(+)-ethyl *S*-methyl methylphosphonothioate with $[\alpha]_D$ +83° (see above) but was essentially enantiomerically pure by the n.m.r. method.[2] Unless any participation by the C-1 hydroxy group occurred the P–N bond cleavage to give (7*R*) from (8*S*) would be with inversion of configuration. Consequently it follows that the ring-opening by P–O bond cleavage giving (8*S*) from (2β-*trans*) was also with inversion of configuration.

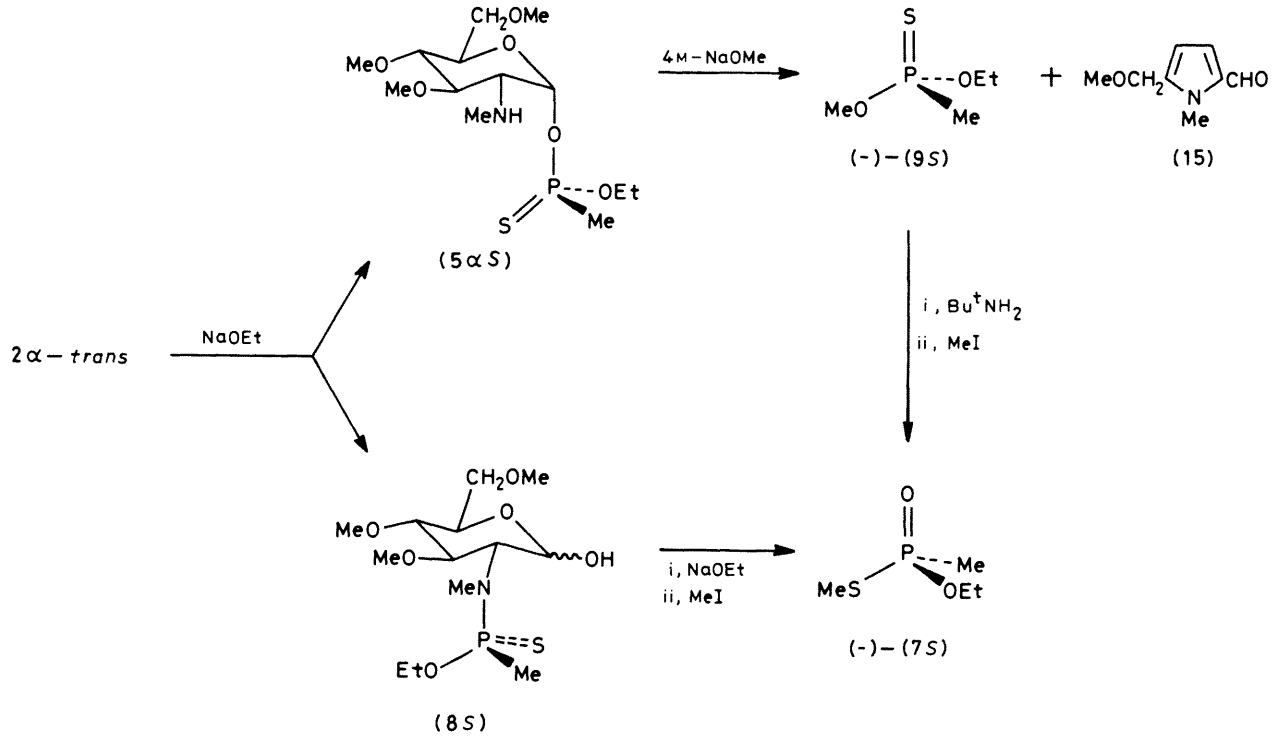
Any possibility of an error in the configurational assignment because of migration of phosphorus from nitrogen to the C-1 hydroxy group during the acid alcoholysis was precluded following an experiment where (8*S*) was treated with acidic methanol. The product was *R*-(+) ethyl methyl methylphosphonothioate (9*R*) which was converted into (7*R*) similarly to the conversion (9*S*) into (7*S*) (see later). P–N Cleavage must involve a direct displacement since in acidic methanol, glycoside formation preceded P–N bond cleavage at least to a significant extent since the anomeric mixture (10) was identified. If N to C-1 migration took place as a competitive reaction, the detachment of phosphorus from the carbohydrate would have been by C–O bond cleavage affording ethyl methylphosphonothioic acid as described previously. Participation by anomeric OMe is unlikely but cannot be completely ruled out.

The 1-*O*-phosphonothioate (5β*S*) formed from (2β-*trans*), underwent complex behaviour with sodium ethoxide (Scheme 3). When sodium ethoxide (0.4M) in ethanol was added dropwise to a solution of (5β*S*) in ethanol, with careful monitoring of the reaction by t.l.c. and with termination and conventional processing when no (5β*S*) remained, a high yield (77%) of (*R*)-(+)-ethyl *S*-methyl methylphosphonothioate (7*R*) was isolated [from (12)] that was essentially enantiomerically pure. Additionally ethyl 2-deoxy-2-methylamino-3,4,5-tri-*O*-methyl-β-D-glucopyranoside (11) was isolated in 55% yield. A minor product was the 1-*S*-methyl phosphonothioate (13) which on treatment with more ethoxide and *S*-methylation gave *R*-(+)-ethyl *S*-methyl methylphosphonothioate (7*R*). However, on treatment with excess of 0.4M ethanolic sodium ethoxide (5β*S*) gave in addition to (11) and (12), varying amounts of diethyl methylphosphonothioate (14) and the pyrrole (15).

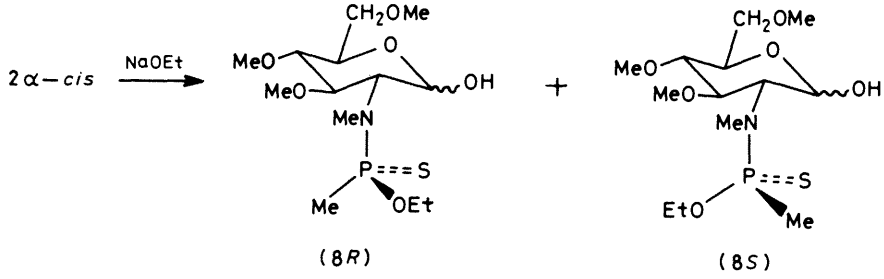
These results may be interpreted in the following way. In dilute ethoxide, intramolecular participation by the methylamino group occurs to displace the phosphate ester with formation of an aziridine (16). The aziridine is then subject to competitive attack by ethoxide to form the ethyl β-D-glucopyranoside (11) or by the sodium salt of the thioacid to form (13). This latter product is also prone to aziridine formation so that conversion of (13) into the ethyl β-D-glucopyranoside is to be expected. Alternatively a thiono ⟶ thiolo rearrangement of (5β*S*) to (13) may occur directly without the intermediacy of the aziridine, although previous results [11,12] may make this unlikely. Aziridine formation has been implicated in other situations where β-glucosides are formed.[13]

In strong alkoxide there is competition between intramolecular attack at C-1 by the methylamino group and direct attack by ethoxide at phosphorus forming diethyl methylphosphonothioate (14). The free amino sugar so produced undergoes various elimination reactions to afford the *N*-methylpyrrole (15).[14]

(b) *Reactions of* 2α-trans *with sodium ethoxide* (*Scheme* 4). On treatment with dilute sodium ethoxide in ethanol the cyclic methylphosphonothioate (2α-*trans*), afforded a mixture of the methylphosphonamidothioate (8*S*) (23%) and the 1-*O*-methylphosphonothioate (5α*S*) (66%). The product mixture was more stable than that from the (2β-*trans*) isomer because intramolecular participation of the methylamino group in subsequent reactions did not occur. The amidate (8*S*) was indistinguishable from that obtained from (2β-*trans*), once equilibration of the anomeric mixture had occurred. Thus ring-opening by P–O bond cleavage was with inversion of configuration.



Scheme 4.



Scheme 5.

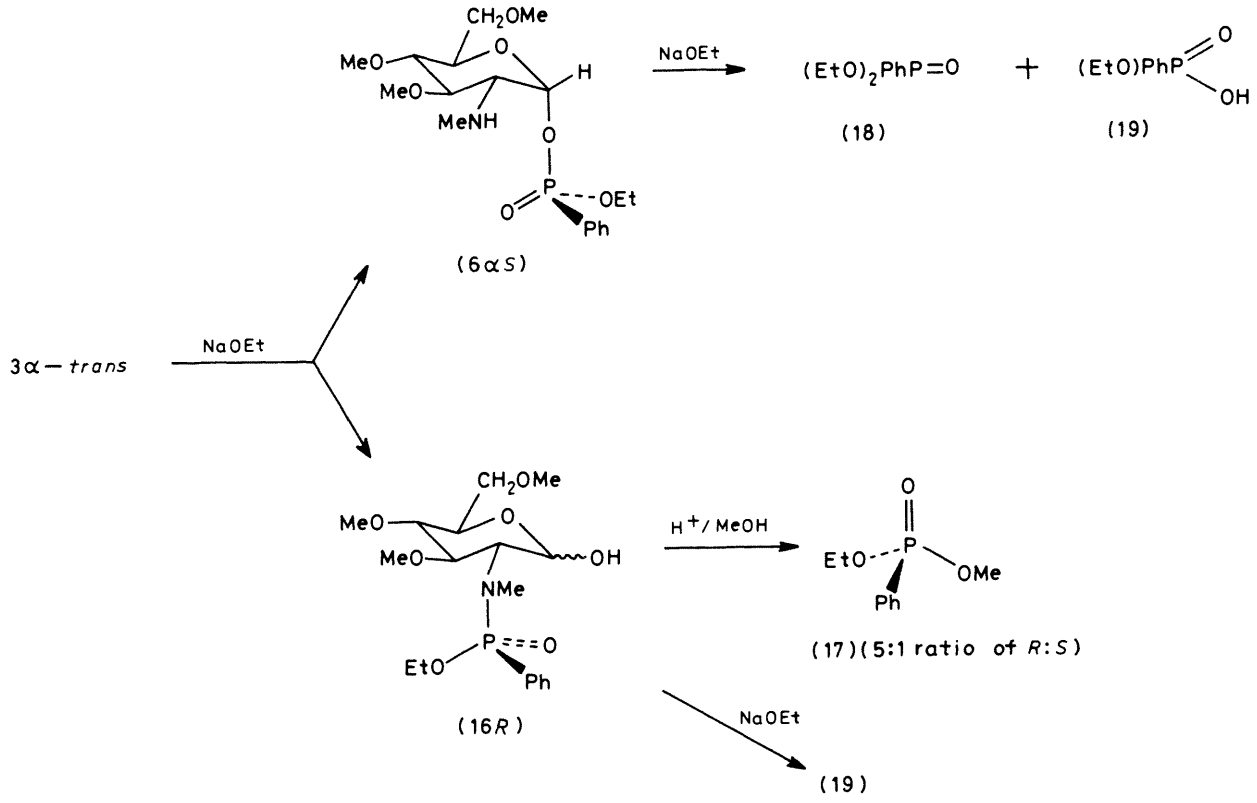
The 1-*O*-methylphosphonothioate (5α*S*), on treatment with 0.4M-sodium methoxide at 25 °C for two days afforded *S*-(−)-ethyl methyl methylphosphonothioate (9*S*) (88%) and the pyrrole (15) (71%). This result is consistent with nucleophilic attack of methoxide at phosphorus with displacement of carbohydrate (rather than ethoxy) with inversion of configuration.* Subsequent conversion of the free amino sugar into the pyrrole occurred under the basic conditions. The high yield of both isolated products showed little competition for attack by methoxide at C-1 as well as at phosphorus in contrast to reactions of the corresponding 1-*O*-(ethyl phenylphosphonates) (6α*S*) and (6α*R*) where attack at C-1 and phosphorus was clearly competitive (see later).

The common product from ring-opening of (2α-*trans*) and (2β-*trans*), *i.e.* the thiophosphorylglucosamine (8*S*) on storage in 0.4M sodium ethoxide at room temperature overnight, gave a product which on *S*-methylation was *S*-(−)-ethyl *S*-methyl methylphosphonothioate (the ^{1}H n.m.r. method showed a 5 : 1 excess of the *S* over the *R* enantiomer). This ester was isolated in 62% yield. A mechanism for the formation of (7*S*) from (8*S*) will be discussed in the following paper.[14]

(c) *Reactions of* (2α-cis) *with sodium ethoxide* (*Scheme* 5). The small amount of (2α-*cis*) available permitted only an n.m.r. investigation of the reaction with ethoxide. ^{31}P N.m.r. showed no P–N bond cleavage products (standards were available from acid-catalysed ring-openings). The only initial products were anomeric mixtures of the phosphonamidate (8*R*) and (8*S*), the former being found in yields of 80—90%. Thus, the ring-opening of (2α-*cis*) differs from the ring-openings of (2β-*trans*) and (2α-*trans*), firstly because P–N bond cleavage did not occur and secondly in that there was a significant amount (10—20%) of P–O bond cleavage with retention of configuration.

(d) *Reactions* (3α-trans) *with sodium ethoxide* (*Scheme* 6). The cyclic phenylphosphorylglucopyranoside (3α-*trans*) reacted rapidly with ethanolic sodium ethoxide (0.4M) to afford the thiophosphorylglucosamine (16*R*) (62%) resulting from P–O bond cleavage and the 1-*O*-phenylphosphonate (6α*S*) (6%) resulting from P–N bond cleavage. It was shown

* The (*S*)-ethyl methyl methylphosphonothioate had $[\alpha]_D$ −1.83°. On de-*O*-methylation and *S*-methylation the *S*-(−)-ethyl *S*-methyl methylphosphonothioate obtained had $[\alpha]_D$ −57° and by the n.m.r. method was a 5 : 1 ratio of *S* : *R* isomers.



Scheme 6.

by ^{31}P n.m.r. spectroscopy that only these products were present in the reaction mixture when all the (3α-*trans*) had disappeared. The 1-*O*-phenylphosphonate (6α*S*) was indistinguishable from the product obtained from (3α-trans) and acidic ethanol. Thus P–N bond cleavage occurred with inversion of configuration. Treatment of (16*R*) with acidic methanol gave a 5 : 1 ratio of *R* : *S* ethyl methyl phenylphosphonate (17). This result is consistent with P–O bond cleavage in (3α-*trans*) by ethoxide with preponderantly inversion of configuration. (The ethyl methyl phenylphosphonate (17) was not formed by initial migration to the anomeric hydroxy group since in acidic alcohol 1-phosphonates afford phosphonic acids by C–O bond cleavage as shown above).

On storage of the 1-*O*-phosphonate (6α*S*) in sodium ethoxide a mixture of diethyl phenylphosphonate (18) and ethyl phenylphosphonic acid (19) was obtained; the proportion of (18) increased as the concentration of the ethoxide increased. This result shows that the competition between attack at phosphorus and attack at C-1 favours attack at phosphorus as the concentration of ethoxide increases. Some ethyl 2-deoxy-2-methylamino-3,4,6-tri-*O*-methyl-β-D-glucopyranoside (11) could be detected in this reaction as well as the pyrrole (15).

Under carefully controlled conditions treatment of the thiophosphorylglucosamine (16*R*) with sodium ethoxide gave ethyl phenylphosphonic acid (19) as the only phosphorus-containing product. Under other conditions diethyl phenylphosphonate was also detected. These reactions and their mechanisms, like the conversion of (8) into (7), will be discussed in detail in the following paper.[14]

Sodium ethoxide reacted with (3α-*cis*) in similar fashion to the reaction with (3α-*trans*).

Discussion

The objectives of the work described in this paper were (*a*) to investigate the synthetic utility of cyclic phosphorus esters from (1), and (*b*) to use them for mechanistic studies. For the former objective the difficulties experienced in separating the isomers excluded any significant synthetic usefulness, although clearly the high stereoselectivity and mild reaction conditions both in acid and base might have been used to advantage. In particular, the ability to ring-open and to detach the phosphorus group from a chiral template using acid conditions for both reactions, or the ability to detach the phosphorus group from the chiral template under acid conditions could have been exploited in the synthesis of chiral phosphorus esters with base labile groups.

From the point of view of the mechanism of ring-opening a slightly different picture emerges compared with that for 1,3,2-oxazaphospholidines derived from ephedrine.[3] Treatment of ephedrine derivatives with ethoxide resulted in P–N bond cleavage with inversion of configuration. In the present work although P–N cleavage by ethoxide again occurs stereospecifically with inversion it is no longer the only, and often not the major reaction. The product distribution depends both on the concentration of the ethoxide and on the configuration at phosphorus in the substrate. The observed P–O bond cleavage is usually stereospecific with inversion of configuration but is not always so. This contrasts with the predominant retention of configuration when P–O is cleaved by hydroxide in ephedrine derivatives,[4] but is consistent with the results observed with other bicyclic 1,3,2-oxazaphospholidines derived from (−)-prolinol.[15] Possible reasons for the variability of results have been discussed previously and the results in this paper complement earlier studies of an extremely complex situation.

Experimental

^{1}H N.m.r. spectra were recorded at 100 MHz with deuteriochloroform as solvent and tetramethylsilane as internal standard. ^{31}P N.m.r. spectra were measured for the same solutions and shifts are quoted in p.p.m. downfield from phosphoric acid. Most reactions were first monitored by ^{31}P n.m.r. spectroscopy in the appropriate solvent then all significant products were isolated in preparative reactions as described below. Quoted yields represent the amount of pure compound isolated. In cases where total reported yields are low this is because of the difficulty of complete chromatographic separation of products rather than the formation of large amounts of by-products. Column chromatography was performed over Merck Kieselgel 60, particle size 0.040—0.063 mm, under a slight positive pressure. Optical rotations were measured in chloroform (path length 1 dm). All organic solutions of reaction products were dried over magnesium sulphate. Ether refers to diethyl ether.

2-Deoxy-2-methylamino-3,4,6-tri-O-methyl-α-D-glucopyranose Hydrochloride (1).—*N*-Acetyl-D-glucosamine (25 g) was added slowly as the solid to a suspension of sodium hydride (20 g) in dimethylformamide (850 ml). After 2 h the mixture was cooled and methyl iodide (125 g) was added slowly. The mixture was allowed to warm to room temperature and stored overnight. Excess of sodium hydride was destroyed by the careful addition of methanol, and the mixture was poured into water and extracted with chloroform. The extracts were concentrated and the residue dissolved in aqueous hydrochloric acid (3M; 750 ml) and heated on a steam-bath for 4 h. Concentration and crystallisation of the residue from methanol–ether gave the hydrochloride (1)[6] (26 g 80%), m.p. >210 °C (with decomp.), $[\alpha]_D$ +124° (*c* 0.1 in water, measured immediately), δ(D_2O) 2.76 (NMe), 3.39, 3.56, 3.64 (3 × OMe), 5.50 ($J_{1,2}$ 3.5 Hz, 1-H).

Storage of an aqueous solution of (1) for 1.5 h resulted in equilibration of the α- and β-anomers. The equilibrium mixture, $[\alpha]_D$ +117° (*c* 0.1 in water) contained *ca.* 10% of the β-anomer δ(D_2O) 2.81 (NMe), 5.00 ($J_{1,2}$ 8.2 Hz, 1-H).

Reaction of 2-Deoxy-2-methylamino-3,4,6-tri-O-methyl-α,β,D-glucopyranose Hydrochloride (1) *with Methyl Thiophosphonic Dichloride.*—A solution of methyl thiophosphonic dichloride (8.6 g) in benzene (50 ml) was added slowly to a suspension of (1) (15 g) in benzene (500 ml) and triethylamine (36.5 ml). After being stirred for 6 h the mixture was filtered and the filtrate was washed with water. Concentration of the benzene layer gave a crude product (14 g, 86%) which ^{1}H n.m.r. suggested was an approximately equal mixture of the isomers (2β-*trans*), (2β-*cis*), (2α-*trans*), and (2α-*cis*). Multiple chromatography with benzene–acetone (39 : 1) as eluant and crystallisation gave 1-O,2-N-[(R)-*methyl(thio)phosphoryl*]-2-*deoxy*-2-*methylamino*-3,4,6-*tri*-O-*methyl*-β-D-*glucopyranoside* (2β-*trans*) (2.5 g, 15%), m.p. 120—122 °C (from light petroleum), $[\alpha]_D$ +18.3° (*c* 0.4), δ_P 103.8 (Found: M^+, 311.0954. $C_{11}H_{22}NO_5PS$ requires *M*, 311.0956), 1-O,2-N-[(S)-*methyl(thio)phosphoryl*]-2-*deoxy*-2-*methylamino*-3,4,6-*tri*-O-*methyl*-β-D-*glucopyranoside* (2β-*cis*) (0.5 g, 3%), $[\alpha]_D$ +9.1° (*c* 1.0), δ_P 109.6 (Found: M^+, 311.0956. $C_{11}H_{22}NO_5PS$ requires *M*, 311.0956), 1-O,2-N-[(R)-*methyl-(thio)phosphoryl*-]-2-*deoxy*-2-*methylamino*-3,4,6-*tri*-O-*methyl*-α-D-*glucopyranoside* (2α-*trans*) (1.1 g, 7%), m.p. 119—120 °C (from light petroleum), $[\alpha]_D$ +83° (*c* 0.3), δ_P 99.0 (Found: M^+, 311.0952. $C_{11}H_{22}NO_5PS$ requires *M*, 311.0956) and 1-*O*,2-*N*-[(*S*)-methyl(thio)phosphoryl]-2-*deoxy*-2-methylamino-3,4,6-tri-O-methyl-α-D-glucopyranoside (2α-cis) (0.7 g, 4%), m.p. 89—90 °C (from light petroleum), $[\alpha]_D$ +93.4° (*c* 0.5), δ_P 102.0 (Found: M^+, 311.0954. $C_{11}H_{22}NO_5PS$ requires *M*, 311.0956).

A similar procedure to the above but substituting phenylthiophosphonic dichloride for its methyl analogue gave a crude product which ^{1}H n.m.r. spectroscopy suggested was an approximately equal mixture of four isomers: δ 4.84 (d, *J* 7.6 Hz, 1-H), 5.06 (d, *J* 7.0 Hz, 1-H), 5.86 (dd, *J* 4.9 and 3.5 Hz, 1-H), and 6.00 (dd, *J* 4.5 and 4.5 Hz, 1-H).

Reaction of 2-Deoxy-2-methylamino-3,4,6-tri-O-methyl-α,β-D-glucopyranose Hydrochloride with Phenylphosphonic Dichloride.—A solution of phenylphosphonic dichloride (3.4 g) in benzene (25 ml) was added slowly to a suspension of (1) (5 g) in benzene (100 ml) and triethylamine (10 ml). After being stirred for 2 h the mixture was filtered and the filtrate was washed with water. Concentration of the benzene layer gave a crude product (4 g, 62%) which ^{1}H n.m.r. spectroscopy indicated was a 3 : 3 : 1 : 1 mixture of four isomers. Conventional chromatography with benzene acetone (4 : 1) as eluant separated readily the two major components, 1-O,2-N-[(S)-*phenylphosphoryl*]-2-*deoxy*-2-*methylamino*-3,4,6-*tri*-O-*methyl*-α-D-*glucopyranoside* (3α-*trans*) (1.4 g, 22%) as a syrup R_F 0.5 (benzene–acetone–methanol, 7 : 3 : 1), $[\alpha]_D$ +63° (*c* 0.4), δ_P 30.0. (Found: M^+, 357.1348. $C_{16}H_{24}NO_6P$ requires *M*, 357.1341) and 1-O,2-N-[(R)-*phenylphosphoryl*]-2-*deoxy*-2-*methylamino*-3,4,6-*tri*-O-*methyl*-α-D-*glucopyranoside* (3α-*cis*) (1.5 g, 23%) as a syrup, R_F 0.4 (7 : 3 : 1), $[\alpha]_D$ +47° (*c* 0.6), δ_P 30.1 (Found: M^+, 357.1337. $C_{16}H_{24}NO_6P$ requires *M*, 357.1341). The minor components [R_F 0.55 (7 : 3 : 1)] were separated by h.p.l.c. using a LiChrosorb silica 60 (7 μm) column and with light petroleum–ether–isopropyl alcohol (20 : 20 : 1) as eluant; 1-*O*,2-*N*-[(*R*)-phenylphosphoryl]-2-deoxy-2-methylamino-3,4,6-tri-*O*-methyl-β-D-glucopyranoside (3β-*cis*) (0.3 g, 5%), m.p. 148 °C (decomp.) (from chloroform–light petroleum), $[\alpha]_D$ +35.3° (*c* 0.9), δ_P 35.3 and 1-*O*,2-*N*-[(*S*)-phenylphosphoryl]-2-deoxy-2-methylamino-3,4,6-tri-*O*-methyl-β-D-glucopyranoside (3β-*trans*) (0.2 g, 3%) as a syrup, $[\alpha]_D$ −4.8° (*c* 0.7), δ_P 32.1.

Reaction of 2-Deoxy-2-methylamino-3,4,6-tri-O-methyl-α,β-D-glucopyranose Hydrochloride (1) with *Methylphosphonic Dichloride.*—A solution of methylphosphonic dichloride (0.5 g) in benzene (20 ml) was added slowly to a suspension of (1) (1 g) in benzene (50 ml) and triethylamine (2.5 ml). After being stirred for 2 h the mixture was filtered and the filtrate was washed with water. Concentration of the benzene layer gave a crude product (0.8 g) which on chromatography, with benzene–acetone (4 : 1) as eluant yielded 1-O,2-N-[(R)-*methylphosphoryl*-2-*deoxy*-2-*methylamino*-3,4,6-*tri*-O-*methyl*-α-D-*glycopyranoside* (4α-*cis*) (0.18 g, 18%) as a syrup, $[\alpha]_D$ +50° (*c* 2.3), δ_P 40.0 (Found: M^+, 295.1195. $C_{11}H_{22}NO_6P$ requires *M*, 295.1185) and 1-O,2-N-[(S)-*methylphosphoryl*-2-*deoxy*-2-*methylamino*-3,4,6-*tri*-O-*methyl*-α-D-*glucopyranoside* (4α-*trans*) (0.51 g, 49%) as a syrup, $[\alpha]_D$ +62° (*c* 2.0), δ_P 40.8. (Found: M^+, 295.1180. $C_{11}H_{22}NO_6P$ requires *M*, 295.1185) and a mixture of the two β-D-glucopyranoside isomers (4β-*cis*) and (4β-*trans*) (0.1 g, 10%).

Acid-catalysed Ring Opening.—As an example, an anhydrous solution of hydrogen chloride in ethanol (2M; 3 ml) was added to a solution of (2α-*cis*) (0.1 g) in ethanol (5 ml). After 10 min the mixture was poured into dilute aqueous sodium carbonate and extracted with chloroform. Concentration of the chloroform extracts gave (5α*R*) (0.11 g, 96%) as a syrup, $[\alpha]_D$ +158° (*c* 0.6), δ_H 1.26 (CH_3CH_2O), 1.85 (*J* 16 Hz, PMe), 2.44 (NMe), 3.37, 3.52, and 3.60 (3 × OMe), and 5.97 (dd, *J* 11.4 and 3.2 Hz, 1-H); δ_P 95.7.

Likewise (2α-*trans*) gave (5α*S*), $[\alpha]_D$ +111° (*c* 0.7), δ_H 1.35 (CH_3CH_2O), 1.87 (*J* 15.9 Hz, PMe), 2.48 (NMe), 3.41, 3.56, and 3.64 (3 × OMe), and 5.93 (dd, *J* 11.0 and 3.3 Hz, 1-H);

δ_P 97.1; (2β-*cis*) gave (5β*R*, as the hydrochloride salt), $[\alpha]_D$ +26.3° (*c* 0.8); δ_H 1.30 (CH_3CH_2O), 1.91 (*J* 16 Hz, PMe), 2.88 (NMe), 3.38, 3.51, 3.77 (3 × OMe), and 5.59 (dd, *J* 8.6 and 8.6 Hz); (2β-*trans*) gave (5β*S*) $[\alpha]_D$ +10.9° (*c* 0.9, as the hydrochloride salt); δ_H 1.28 (CH_3CH_2O), 1.85 (d, *J* 15.8 Hz, PMe), 2.48 (NMe), 3.37, 3.51, 3.62 (3 × OMe), and 5.13 (dd, *J* 10.1 and 8.1 Hz, 1-H); δ_P 95.2.

Similarly, treatment of (3α-*trans*) with just sufficient HCl–ethanol to ensure acidity followed by just sufficient sodium carbonate to bring about neutralisation gave (6α*S*), $[\alpha]_D$ +118° (*c* 1.5); δ_H 1.37 (CH_3CH_2O), 2.48 (NMe), 3.30, 3.50, 3.63 (3 × OMe), 4.25 (2 H, m), 5.91 (dd, *J* 7.2 and 3.3 Hz, 1-H); δ_P 18.8 and (3α-*cis*) gave (6α*R*), $[\alpha]_D$ +110° (*c* 1.0), δ_H 1.33 (CH_3CH_2O), 2.37 (NMe), 3.37, 3.52, and 3.56 (3 × OMe), 4.17 (2 H, dq), and 5.92 (dd, *J* 7.0 and 3.1 Hz, 1-H); δ_P 18.2.

Acid Hydrolysis of Glucosamine-1-phosphonothioates (*Scheme* 1).—A solution of the glucosamine-1-phosphonothioate (5β*S*) (0.18 g) in 4M-hydrochloric acid–acetone (1 : 1; 20 ml) was boiled under reflux for 4 h and then poured into dilute sodium carbonate. The solution was washed with chloroform and then treated with an excess of methyl iodide and sufficient methanol as to ensure its dissolution. After 0·5 h conventional processing gave (*R*)-(+)-ethyl *S*-methyl methylphosphonothioate (7*R*) (0.04 g, 57%), $[\alpha]_D$ +82°.

Similarly a solution of the glucosamine-1-phosphonothioate (5α*S*) (0.2 g) in methanolic hydrogen chloride (4M) was boiled under reflux for 4 days (with occasional addition of further HCl). Conventional processing gave (*R*)-(+)-ethyl *S*-methyl methylphosphonothioate (7*R*) (0.04 g, 51%), $[\alpha]_D$ +85.9°.

Treatment of the Bicyclic Phosphoramidothioate (2β-trans) *with Sodium Ethoxide*.—All experiments were monitored by ^{31}P n.m.r. spectroscopy. The product distribution depended on both the strength of the ethoxide used and the rate of addition. Dilute ethoxide produced an initial ratio of *ca.* 3 : 1, (5β*S*) : (8*S*). On storage overnight (5β*S*) broke down as described elsewhere; (8*S*) was readily isolated. Thus, an ethanolic solution of sodium ethoxide (0.4M; 4 ml) was added dropwise during 2 h to a solution of (2β-*trans*) (2 g) in ethanol (100 ml). The mixture was stored overnight and then poured into water and extracted with ether. Concentration of the organic layer and chromatography of the residue (benzene–acetone–methanol, 8 : 1 : 1) gave (8*S*) (0.35 g, 15%) as the pure β-anomer, which epimerised rapidly (1 h) in chloroform but was stable for several days in ethanol in the absence of base.

^{31}P N.m.r. spectroscopy demonstrated that when (2β-*trans*) was dissolved in an excess of ethanolic sodium ethoxide solution (0.4M) (5β*S*) was the only significant product; no (8*S*) was observed.

Acid-catalysed P–N *Cleavage in the* 2-N-[(S)-*Thiophosphoryl*]*glucosamine* (8S).—A solution of (8*S*) (0.3 g) in acetone (5 ml) and hydrochloric acid (4M; 5 ml) was boiled under reflux for 2 h and then poured into dilute aqueous sodium carbonate. The aqueous solution was washed with chloroform and then treated with an excess of methyl iodide and sufficient methanol to ensure its dissolution. Conventional processing gave (*R*)-(+)-*O*-ethyl *S*-methyl methylphosphonothioate (7*R*) (0.06 g, 47%), $[\alpha]_D$ +83° (*c* 0.4). ^1H N.m.r. spectroscopy in the presence of $Eu(hfc)_3$ confirmed that this sample was essentially enantiomerically pure.

Similarly a solution of (8*S*) (0.4 g) in methanol (3.0 ml) and trifluoromethylsulphonic acid (0.5 ml) was boiled under reflux for 12 h and then poured into water and extracted with chloroform. Concentration of the organic layer and chromatography of the residue (light petroleum–ethyl acetate, 9 : 1) gave (*R*)-(+)-*O*-ethyl *O*-methyl methylphosphonothioate (9*R*) (0.075 g, 44%), $[\alpha]_D$ +1.7°.

In a further reaction, work-up after only 1 h of reflux enabled isolation of the methyl α,β-D-glucopyranosides (10α), (8%) δ 1.28 (CH_3CH_2O), 1.74 (PMe), 2.72 (NMe), 3.31, 3.40, 3.52 (4 × OMe), 4.62 (d, *J* 3.8 Hz, 1-H); and (10β), (16%) δ 1.26 (CH_3CH_2O), 1.77 (PMe), 2.68 (NMe), 3.41, 3.46, 3.53, 3.56 (4 × OMe), 4.39 (d, *J* 7.3 Hz, 1-H).

Treatment of the Glucosamine-1-phosphonothioate (5βS) *with Sodium Ethoxide*.—A dilute solution of ethanolic sodium ethoxide (0.4M) was added in small portions to a solution of (5β*S*) (0.5 g) in ethanol (25 ml) at such a speed as to ensure that the mixture had attained neutrality before each addition. When no (5β*S*) remained in solution (t.l.c.) the mixture was poured into water and extracted repeatedly with chloroform.

The aqueous layer was treated with an excess of methyl iodide and sufficient methanol to assure dissolution. Conventional processing yielded (*R*)-(+)-*O*-ethyl *S*-methyl methylphosphonothioate (7*R*) (0.19 g, 77%), $[\alpha]_D$ +82° (*c* 0.4). ^1H N.m.r. spectroscopy in the presence of $Eu(hfc)_3$ confirmed that (7*R*) was essentially enantiomerically pure.

The combined chloroform extracts were concentrated and rapidly chromatographed (benzene–acetone–methanol, 8 : 1 : 1), to give (13) (0.06, 10%) (^{31}P n.m.r. of the crude product before work-up suggests that this product is initially *ca.* 25% of the phosphorus content) as a clear unstable oil which could not be completely purified, δ_H 1.36 (CH_3CH_2O), 1.90 (d, *J* 16.6 Hz, PMe), 2.50 (NMe), 3.41, 3.55, and 3.67 (3 × OMe), 4.93 (dd, *J* 10.0 and 8.8 Hz, 1-H); δ_P 53.1 and the ethyl β-D-glucopyranoside derivative (11) (0.23 g, 55%).

Addition of further portions of dilute ethoxide to the crude reaction product above, resulted in a single phosphorus-containing product (^{31}P) which on alkylation with methyl iodide gave (*R*)-(+)-(7*R*).

Treatment of (5β*S*) directly with an excess of ethoxide gave in addition to (11) and (12) varying amounts of *O,O*-diethyl methylphosphonothioate (14) and the pyrrole (15). Increasing ethoxide concentration favoured (14) and (15). When (5β*S*) was dissolved in 0.4M-ethanolic sodium ethoxide (14) accounted for 15% of the phosphorus-containing product.

Treatment of the Bicyclic Methyl(thio)phosphorylglucopyranoside (2α-trans) *with Sodium Ethoxide*.—A solution of sodium ethoxide in ethanol (0.4M; 1 ml) was added dropwise to a solution of (2α-*trans*) (0.5 g) in ethanol (30 ml). The mixture was stored for 5 h and then poured into dilute aqueous acid and extracted with ether. Concentration of the ether extracts and chromatography of the residue, benzene–acetone–methanol (8 : 1 : 1) gave (8*S*) as a mixture of anomers (0.13 g, 23%), δ_H 1.18 (CH_3CH_2O), 1.74 (d, *J* 15.0 Hz, PMe), 2.78 (d, *J* 10.0 Hz, NMe), and 5.11 (d, *J* 3.6 Hz, 1-H); δ_P 93.2 and δ_H 1.18 (CH_3CN_2O), 1.76 (d, *J* 15.2 Hz, PMe), 2.65 (d, *J* 9.4 Hz, NMe), and 4.63 (d, *J* 8.4 Hz, 1-H); δ_P 93.8. $[\alpha]_D$ (equilibrium mixture) +8.1° (*c* 1.1). Basification of the aqueous layer and extraction with chloroform gave (5α*S*) (0.38 g, 66%).

Treatment of the Glucosamine-1-phosphonothioate (5αS) *with Sodium Methoxide*.—A solution of (5α*S*) (0.41 g) in methanolic sodium methoxide (0.4M; 20 ml) was stored at room temperature for 2 days and then poured into water and extracted with chloroform. Concentration of the organic layer and chromatography of the residue (light petroleum–

ethyl acetate, 9 : 1) gave (*S*)-(−)-*O*-ethyl *O*-methyl methylphosphonothioate (9*S*) (0.16 g, 88%), $[\alpha]_D$ −1.83° (*c* 1.5), δ_H 1.30 (CH_3CH_2O), 1.78 (d, *J* 15.2 Hz, PMe), 3.69 (d, *J* 13.4 Hz, POMe), 4.10 (CH_3CH_2O), and the pyrrole (15) (0.12 g, 71%).

A solution of the phosphonothioate (9*S*) (0.16 g) in t-butylamine (20 ml) was boiled under reflux for 18 h and then concentrated. The residue was dissolved in water and the solution was washed with chloroform. The aqueous layer was treated with an excess of methyl iodide and sufficient methanol to assure homogeneous dissolution. Conventional processing yielded (*S*)-(−)-*O*-ethyl *S*-methyl methylphosphonothioate (7*S*) (0.13 g, 81%), $[\alpha]_D$ −57° (*c* 0.3). ^{1}H N.m.r. spectroscopy in the presence of Eu(hfc)$_3$ confirmed that (7) was *ca.* a 5 : 1 ratio of the (−)-(*S*) and (+)-(*R*) isomers.

Base-catalysed P–N *Cleavage in the* 2-N-[(S)-*Thiophosphoryl*]*glucosamine* (8S).—A solution of (8*S*) (0.3 g) in ethanolic sodium ethoxide (0.4M; 20 ml) was stored at room temperature overnight and then poured into water. The aqueous solution was washed with chloroform and then treated with an excess of methyl iodide and sufficient methanol to assure dissolution. Conventional processing yielded (*S*)-(−)-*O*-ethyl *S*-methyl methylphosphonothioate (7*S*) (0.08 g, 62%), $[\alpha]_D$ −58° (*c* 0.8). ^{1}H N.m.r. spectroscopy in the presence of Eu(hfc)$_3$ confirmed that the (−)-(*S*) and (+)-(*R*) isomers of (7) were in a *ca.* 5 : 1 ratio.

Treatment of the Bicyclic Phosphonamidate (3α-trans) *with Sodium Ethoxide*.—An ethanolic solution of sodium ethoxide (0.4M) was added a few drops at a time to a solution of (3α-*trans*) (1 g) in ethanol (10 ml) until t.l.c. revealed that no (3α-*trans*) remained (1 h). The mixture was then poured into water and extracted with chloroform. Concentration of the organic layer and chromatography of the residue (benzene–acetone–methanol, 16 : 3 : 1) gave (16*R*) as a mixture of anomers (0.7 g, 62%), δ_H 1.38 (CH_3CH_2O), 2.60 (d, *J* 9.8Hz, NMe), 2.69 (d, *J* 9.8 Hz, NMe), 3.32, 3.39, and 3.53 (2 × 3 OMe), 4.70br (s, 1-H), and 5.16br (s, 1-H), δ_P 25.3 and 24.7; and (6α*S*) (0.07 g, 6%). ^{31}P N.m.r. spectroscopy demonstrated that the crude reaction product contained only (16*R*) and (6α*S*).

Storage of a solution of (6α*S*) in ethanolic sodium ethoxide (0.4M) for 2 h resulted in a 2 : 1 mixture of ethyl phenylphosphonic acid and diethyl phenylphosphonate as revealed by ^{31}P n.m.r. spectroscopy and the addition of authentic compounds. An increase in the ethoxide concentration resulted in a greater percentage of diethyl phenylphosphonate in the mixture. No intermediates were observed.

Acid-catalysed P–N *Cleavage in the* 2-N-[(S)-*Thiophosphoryl*]*glucosamine* (16R).—A solution of (16*R*) (0.85 g) in anhydrous hydrogen chloride–methanol (4M; 50 ml) was stored for 10 days then poured into water and extracted with chloroform. Concentration of the organic phase and chromatography of the residue (benzene–acetone–methanol, 34 : 7 : 1) gave (*R*)-(−)-ethyl methyl phenylphosphonate (17) (0.09 g, 21%), $[\alpha]_D$ −1.8° (*c* 0.9).[16] ^{1}H n.m.r. in the presence of (*R*)-(+)-t-butylphenylphosphinothioic acid [17] confirmed that (17) was a 5 : 1 mixture of *R* : *S* enantiomers.

A similar procedure, using the 2-*N*-[(*R*)-thiophosphoryl]-glucosamine (16*S*) derived from (3α-*cis*) by treatment with sodium ethoxide, gave (*S*)-(+)-ethyl methyl phenylphosphonate (32%), $[\alpha]_D$ +1.7° (*c* 1.6) again as a 5 : 1 mixture of enantiomers.

^{31}P N.m.r. spectroscopy demonstrated that storage of the glucosamine-1-phosphonate (6α*S*) in ethanolic hydrogen chloride resulted in ethyl phenylphosphonic acid (19) as the only phosphorus-containing product.

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