Use of Carbohydrate Derivatives for Studies of Phosphorus Stereochemistry. Part V.[1] Preparation and Some Reactions of Tetrahydro-1,3,2-oxazaphosphorine-2-ones and -2-thiones

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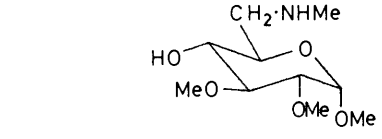
The configurations at phosphorus in pairs of tetrahydro-1,3,2-oxazaphosphorines, epimeric at phosphorus and prepared by treatment of methyl 6-deoxy-2,3-di-*O*-methyl-6-methylamino-α-D-glucopyranoside (1) with phosphonic dihalides, have been established by spectroscopic methods. Treatment of the glucopyranoside derivative (1) with phosphoric or phosphorothioic trichloride afforded 2-chlorotetrahydro-1,3,2-oxazaphosphorine derivatives which on treatment with sodium alkoxides (aryloxides) under mild conditions were converted, with inversion of configuration at phosphorus, into the corresponding 2-alkoxy- (aryloxy-) derivatives. All displacement reactions of the exocyclic substituent at phosphorus occurred with inversion of configuration. With sodium alkoxides under more vigorous conditions the tetrahydro-1,3,2-oxazaphosphorines underwent endocyclic P–N fission as well as P–O fission, both reactions occurring with inversion of configuration. Acid-catalysed endocyclic fission reactions also occurred with inversion of configuration at phosphorus. Methyl 2,3-di-*O*-methyl-α-D-glucopyranoside cyclic (*R*)-4(*O*),6(*N*)-*NP*-dimethylphosphonamidothioate was degraded to (*R*)-ethyl methylphosphonothioic acid by successive treatment with sodium ethoxide and dilute hydrochloric acid.

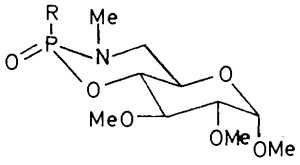
In previous papers[1-4] it was shown that the stereochemistry of reactions at phosphorus may be studied conveniently within the framework of carbohydrate derivatives of 1,3,2-dioxa- (and oxathia-) phosphorinans. In this paper attention is focused on the preparation and reactions of some tetrahydro-1,3,2-oxazaphosphorine carbohydrate derivatives, with particular reference to the stereochemistry at phosphorus in the cyclic products and to the stereochemical course of endocyclic P–N and P–O cleavage reactions and exocyclic P–X cleavage reactions. The reactions and stereochemistry of tetrahydro-1,3,2-oxazaphosphorine derivatives have hitherto been little studied although recently this ring system has received some attention in connection with analogues of cyclic adenosine monophosphate.[5]

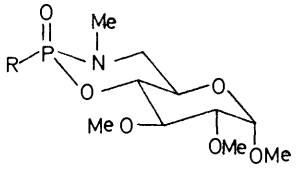
Preparation of Tetrahydro-1,3,2-oxazaphosphorines.—Methyl 6-deoxy-2,3-di-*O*-methyl-6-methylamino-α-D-glucopyranoside (1) was prepared in 80% yield from methyl 2,3-di-*O*-methyl-α-D-glucopyranoside by successive treatment with toluene-*p*-sulphonyl chloride and methylamine.

The glucopyranoside (*R*)-4(*O*),6(*N*)-*NP*-dimethylphosphonamidate (2*ax*) was obtained as the major product when the amino-sugar (1) was treated with methylphosphonic dichloride and triethylamine in dichloromethane at room temperature for a short period. Small quantities of the isomer (2*eq*) were also formed and n.m.r. studies of crude products showed that the proportion of (2*eq*) increased with the time of the reaction.†



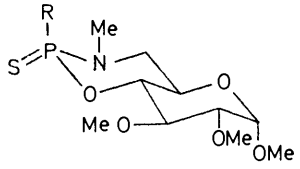
(1)

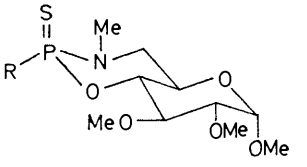




(2 *ax*) R = Me
(3 *ax*) R = Ph
(5) R = Cl
(7 *ax*) R = OMe
(8 *ax*) R = OEt
(12 *ax*) R = 4·NO_2·C_6H_4·O

(2 *eq*) R = Me
(3 *eq*) R = Ph
(7 *eq*) R = OMe
(8 *eq*) R = OEt
(9 *eq*) R = O^{n}Pr
(12 *eq*) R = 4·NO_2·C_6H_4O





(4 *ax*) R = Me
(6) R = Cl

(4 *eq*) R = Me
(10 *eq*) R = OMe
(11 *eq*) R = OPr^n

For example when the reaction of (1) with $MePOCl_2$ was carried out under intermittent reflux in benzene

† In contrast to the reaction of (1) with $MePOCl_2$, the reaction with $MePOF_2$ proceeded very slowly and afforded only (2*eq*). The difference in rates may arise because of difference in reaction intermediates. The first formed product from the $MePOCl_2$ reaction is presumably the 6-methylphosphoramidochloridate, whereas the 4-methylphosphonofluoridate is presumably the first formed product from the $MePOF_2$ reaction since P–Cl and P–F displacements occur preferentially with N and O nucleophiles, respectively.[4,6] The formation of only (2*eq*), which is the product of thermodynamic control, may be a consequence of a situation where the equilibration of (2*ax*) to (2*eq*) is faster than the formation of (2*ax*). It is unlikely that the direction of ring closure will affect the stereochemistry of the product directly. Experimental evidence has now been obtained to validate a previous suggestion[2] that the product of kinetic control in reactions between $MePOCl_2$ of $MePOF_2$ and methyl 2,3-di-*O*-methyl-α-D-glucopyranoside has the P–Me group orientated axially irrespective of whether the glucopyranoside 4-methylphosphonofluoridate of the glucopyranoside 6-methylphosphonofluoridate is the intermediate.

[1] Part IV, D. B. Cooper, J. M. Harrison, T. D. Inch, and G. J. Lewis, *J.C.S. Perkin I*, 1974, 1058.
[2] D. B. Cooper, T. D. Inch, and G. J. Lewis, *J.C.S. Perkin I*, 1974, 1043.
[3] D. B. Cooper, J. M. Harrison, T. D. Inch, and G. J. Lewis, *J.C.S. Perkin I*, 1974, 1049.
[4] J. M. Harrison, T. D. Inch, G. J. Lewis, *J.C.S. Perkin I*, 1974, 1053.
[5] A. Murayama, B. Jastorff, F. Cramer, and H. Hettler, *J. Org. Chem.*, 1971, **36**, 3029; B. Jastorff and T. Krebs, *Chem. Ber.*, 1972, **105**, 3192.
[6] R. F. Hudson and R. Greenhalgh, *J. Chem. Soc.* (*B*), 1969, 325; R. Greenhalgh, R. M. Heggie, and M. A. Weinberger, *Canad. J. Chem.*, 1970, **48**, 1351.

for 14 days the (2*ax*) : (2*eq*) ratio was 1.3 : 1. This result is consistent with the results of previous studies [2] in which it was shown that in 1,3,2-dioxaphosphorinan-2-ones the isomer with an axial P–Me group is kinetically favoured whereas that with an equatorial P–Me group is thermodynamically preferred. The isomers (2*ax*) and (2*eq*) were not separable chromatographically but the crystalline (2*ax*) was easily obtained pure by crystallisation. The isomer (2*eq*) did not crystallise.

The glucopyranoside (*R*)- and (*S*)-4(*O*),6(*N*)-*N*-methyl phenylphosphonamidates (3*ax*) (33%) and (3*eq*) (25%) respectively were prepared by treatment of the methylamino-sugar (1) with phenylphosphonic dichloride and the glucopyranoside (*R*)- and (*S*)-4(*O*),6(*N*)-*NP*-dimethylphosphonamidothioates (4*ax*) (63%) and (4*eq*) (13%), respectively, were prepared by treatment of (1) with methylphosphonothioic dichloride. In each reaction the products were separated by chromatography over silica. No attempt was made to adjust the reaction conditions to obtain optimum yields of either the axial or the equatorial isomer.

The chloridates (5) and (6) were prepared in good yield as the only tetrahydro-1,3,2-oxazaphosphorine products by treatment of (1) with phosphoric and phosphorothioic trichloride, respectively.

Attempts to prepare pairs of 2-alkoxytetrahydro-1,3,2-oxazaphosphorine isomers by treatment of the methylamino-sugar (1) with appropriate alkoxyphosphoric dichlorides resulted only in the formation of complex mixtures. Only in one instance, the EtO·$POCl_2$ reaction, were small quantities of the required axial (8*ax*) and equatorial (8*eq*) isomers isolated. The equatorial isomers (7*eq*), (8*eq*), and (9*eq*) were prepared conveniently as essentially the only products when the chloridate (5) was treated at room temperature with NaOMe–MeOH, NaOEt–EtOH, and $NaOPr^n$–Pr^nOH, respectively. Similarly the phosphoramidothioates (10*eq*) and (11*eq*) were prepared from the phosphoramidothioic chloride (6).

The 4-nitrophenyl phosphoramidate derivative (12*eq*) was formed in good yield as essentially the only product when a solution of the chloridate (5) and sodium 4-nitrophenoxide in acetonitrile was stirred at room temperature for 5 h. The epimeric 4-nitrophenyl phosphoramidate (12*ax*) was formed by heating a solution of (12*eq*) and an excess of sodium 4-nitrophenoxide in acetonitrile under reflux for 8 h. With sodium methoxide in methanol at room temperature (12*ax*) afforded essentially only (7*eq*), whereas (12*eq*) afforded (7*eq*) (9%) as well as the preponderant product (7*ax*) (67%). The formation of the axially substituted alkyl phosphoramidate from (12*eq*) probably represents a general synthetic route since chromatographic experiments also indicated that with sodium ethoxide (12*eq*) afforded (8*ax*) as the preponderant product.

Configuration at Phosphorus in 2-Substituted Tetrahydro-1,3,2-oxazaphosphorines.—It has been shown [2,3,7] that the configuration at phosphorus in 1,3,2-dioxaphosphorinan-2-ones, 1,3,2-oxathiaphosphorinan-2-ones, and related compounds may be assigned on the basis of n.m.r. and i.r. data provided that the isomer with the P=O group equatorial and that with the P=O group axial are both available. Where the P=O group is equatorial the P=O stretching band is at a higher wavenumber and the ^{31}P chemical shift is at higher field than where the P=O group is axial. Where the P=O group is axial, any protons in a 2,4-diaxial relation on the six-membered ring are deshielded and resonate at lower field than the equivalent protons where the P=O group is equatorial. Also for specific compounds other parameters may be distinctive of the configuration at phosphorus. For example $J_{P,Me}$ in methylphosphono-derivatives is larger when the P–Me group is equatorial than when it is axial, and for phenylphosphono-derivatives the pattern of aromatic proton signals appears to be related to the orientation of the phenyl substituent.

Configurational assignments to the axial–equatorial pairs of phosphono-derivatives (2)—(4) could be made with some confidence on the basis of combinations of the features outlined above. For example, on the basis of the n.m.r. data the equatorial methylphosphono-derivative (2*eq*) [δ (H-4) 4.1; δ (^{31}P) −35.5 p.p.m.; $J_{P,Me}$ 16.5 Hz] was easily distinguished from the axial isomer (2*ax*) [δ (H-4) 3.9; δ (^{31}P) −30.6 p.p.m.; $J_{P,Me}$ 15.5 Hz]. On the basis of n.m.r. and i.r. data the equatorial phenylphosphono-derivative (3*eq*) [δ (H-4) 4.25; $\nu_{P=O}$ 1 249 (benzene); $\nu_{P=O}$ 1 247 ($CDCl_3$) cm^{-1}] was easily distinguished from the axial isomer (3*ax*) [δ (H-4) 4.0; $\nu_{P=O}$ 1 270 (benzene); $\nu_{P=O}$ 1 258 ($CDCl_3$) cm^{-1}]. Also the n.m.r. spectrum of (3*eq*) contained an aromatic proton pattern (*i.e.* separate two- and three-proton multiplets) which was shown previously [3] to be characteristic of a phenyl group in an equatorial orientation. The configurations of the thioates (4*eq*) and (4*ax*) were assigned on the basis of n.m.r. data (see Experimental section) and because (4*eq*) and (4*ax*) were converted into (2*eq*) and (2*ax*), respectively, on oxidation with 4-chloroperbenzoic acid under conditions which give retention of configuration for P=S to P=O transformations.[8]

The n.m.r. and i.r. data for the pairs of phosphoro-derivatives (7), (8), and (12) did not permit configurational assignments to be made with any degree of confidence because the expected differences in the diagnostic parameters were small or non-existent. For example although (8*ax*) [δ (H-4) 3.85; $\nu_{P=O}$ 1 266 ($CDCl_3$); $\nu_{P=O}$ 1 290 (benzene) cm^{-1}] could be distinguished from (8*eq*) [δ (H-4) 4.1; $\nu_{P=O}$ 1 253 ($CDCl_3$); $\nu_{P=O}$ 1 275 (benzene) cm^{-1}] on the basis of H-4 chemical shift and i.r. values the ^{31}P chemical shift values (−5.9 p.p.m.) were the same for both isomers. Similar results were obtained with the methyl phosphoro-derivatives (7*ax*) and (7*eq*). The spectroscopic data were even less helpful for the isomeric nitrophenyl derivatives (12*ax*)

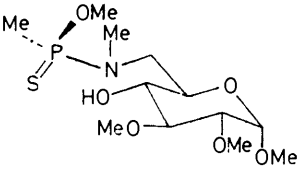
[7] J. P. Majoral and J. Navech, *Bull. Soc. chim. France*, 1971, **95**, 1331, 2609.
[8] A. W. Herriott, *J. Amer. Chem. Soc.*, 1971, **93**, 3304.

and (12*eq*) (which were easily separable by chromatography over silica). For these isomers there was only a very small difference in the wavenumber of the P=O i.r. band [1 304 and 1 300 cm^{-1} for (12*ax*) and (12*eq*), respectively]. There was no significant difference in the ^{31}P chemical shift and the ^{1}H n.m.r. spectra were too complex to permit assignment of even tentative values of the H-4 chemical shifts. These results with 2-alkoxy- or 2-aryloxy-tetrahydro-1,3,2-oxazaphosphorin-2-ones are the first in our experience from which it was not possible to make confident configurational assignments.

Configurational assignments to all the phosphoro-derivatives described in this paper were eventually made on the assumption that the chloro-substituent in (5) and (6) is located in an axial orientation and the further assumption that all displacement reactions of the exocyclic 2-substituent in tetrahydro-1,3,2-oxazaphosphorines take place with inversion of configuration. The former assumption follows from the many observations that electronegative substituents in phosphorus-containing [4,9] and other heterocyclic systems [10] prefer to occupy an axial orientation. Arguments and experimental data to support the latter assumption will be provided later in this paper.

Ring-opening Reactions of Tetrahydro-1,3,2-oxazaphosphorines.—By analogy with alkaline hydrolyses [11] of dialkyl phosphoramidates it was expected that treatment with sodium alkoxides of tetrahydro-1,3,2-oxazaphosphorines derived from methyl 6-deoxy-2,3-di-*O*-methyl-6-methylamino-α-D-glucopyranoside (1) would result in breakage of the endocyclic P–O bond, and not the P–N bond. Accordingly, when the methylphosphonoamidothioate (4*ax*) was heated under reflux with an excess of N-sodium methoxide, ethoxide, or isopropoxide in the corresponding alcohol until it was shown by t.l.c. that all the (4*ax*) had reacted, the result that compounds (13)—(15) could be isolated in good yield (56—76%) was consistent with expectation. However when the crude product from the reaction of (4*ax*) with NaOMe was acetylated before isolation of (13), the diacetate of the amino-sugar (1) was isolated in 16% yield as well as the 4-acetate of (13) (49%). No other products were found. Since acyclic P–NR_2 (R = alkyl) bonds are resistant to alkaline hydrolysis it was probable that the intermediate leading to (1) was the methylphosphonothioate derivative (16) [which can be derived from (4*ax*) by P–N cleavage with sodium methoxide] and not the methylphosphonamidothioate derivative (13). Evidence to support this contention was obtained when (16) was isolated in low yield from the reaction mixture obtained by treatment of (4*ax*) with 0.5N-sodium methoxide in boiling methanol for 1.5 h. After this reaction time, (4*ax*), (13), and (1), in addition to (16), were all present in the reaction mixture (t.l.c. evidence only) but were not isolated. Compound (16) was rapidly (5—10 min) converted into (1) when treated with an excess of N-sodium methoxide in hot methanol.

The direction of ring opening, that is whether the P–O or the P–N bond is broken, is easily established from the n.m.r. spectra of the products. Where the



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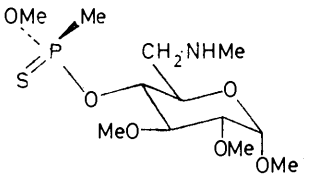

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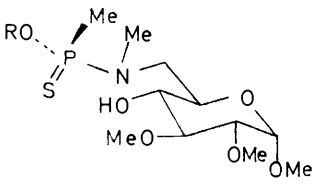
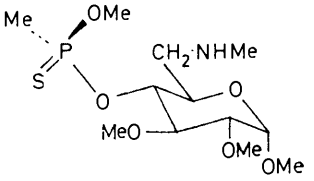


(13) R = Me
(14) R = Et
(15) R = Pr^{i}



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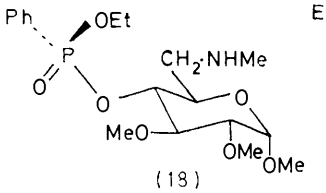

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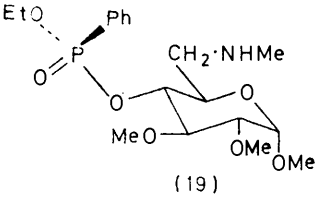

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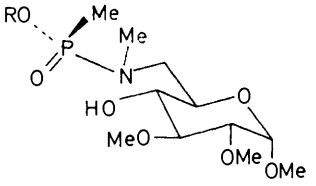


(21) R = Me
(22) R = Et
(23) R = Pr^{i}

P–O bond is broken the NMe signal remains as a phosphorus-coupled doublet; the NMe signal is a singlet where the P–N bond is broken. Acetylation of the products causes a downfield shift of the H-4 signal in the P–O-cleaved products; the *N*-acetyl derivatives from the P–N-cleaved products have complex spectra at room temperature but simple spectra at higher temperatures diagnostic of restricted rotation of the amide group.

Evidence to show that both P–O and P–N bonds are broken with inversion of configuration at phosphorus has been obtained. Although no direct proof of the configuration at phosphorus in (13)—(15) is available,

[9] For references see reference 2 in reference 2.

[10] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, in 'Conformational Analysis,' Interscience, New York, 1966, p. 376.

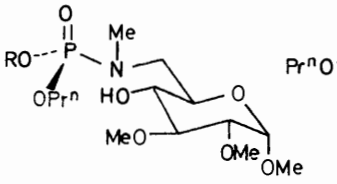
[11] M. A. H. Fahmy, A. Khasawinah, and T. R. Fukuto, *J. Org. Chem.*, 1972, **37**, 617; N. K. Hamer and R. D. Tack, *J.C.S. Perkin II*, 1974, 1184.

indirect proof was provided by the acid-catalysed hydrolysis of (14) to ethyl methylphosphonothioic acid, isolated as the dextrorotatory dicyclohexylamine salt ($[\alpha]_D$ +7.9°) which is known to have the *R*-configuration.[12] Since acid-catalysed cleavage of P–N bonds proceeds with inversion of configuration,[13] it follows that the base-promoted conversion of (4*ax*) into (14) also proceeded with inversion and that (14) has the *S*-configuration at phosphorus.

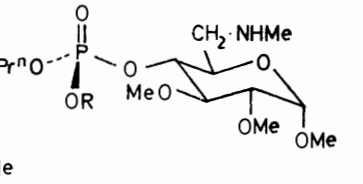
The stereochemistry of the methylphosphonothioate derivative (16), formed by base-promoted P–N cleavage in (4*ax*), was investigated in the following way. Treatment of (4*ax*) with methanolic hydrogen chloride and conversion of the product into the free base gave material which had an n.m.r. spectrum indistinguishable from that of (16). However treatment of (4*eq*) with methanolic hydrogen chloride and conversion of the product into the free base gave a compound (17) with an n.m.r. spectrum consistent with a P–N-cleaved product but distinct from the spectrum of (16). These experiments show clearly that P–N bonds in 2-methyltetrahydro-1,3,2-oxazaphosphorine-2-thiones are broken by $^-$OMe or by MeOH–HCl with the same overall stereochemistry. Evidence to support the mechanistically reasonable assumption that acid-catalysed cleavage of endocyclic P–N bonds occurs with inversion of configuration at phosphorus was obtained when with ethanolic hydrogen chloride the phenylphosphono-derivatives (3*ax*) and (3*eq*) were converted into (18) and (19), respectively. Whereas in (19) all the methoxy-groups resonated at similar field (δ 3.41, 3.52, and 3.61), in (18) one of the three methoxy-groups resonated at much higher field (2.84) than the other two (3.44). By analogy with other methyl 2,3-di-*O*-methyl-α-D-glucopyranoside 4-*O*-phenylphosphonate derivatives,[1,2] the distinctive upfield position of one of the methoxy-resonances in (18) is consistent with the depicted *S*-configuration at phosphorus.

The equatorial methylphosphonamidothioate isomer (4*eq*) behaved similarly to (4*ax*) when treated with hot methanolic sodium methoxide; the product (20) resulting from P–O cleavage was isolated in 73% yield. Similarly the glucopyranoside 6-*N*-methylphosphonamidate derivatives (21)—(23) were formed in good yields when (2*ax*) was treated with sodium methoxide in methanol, sodium ethoxide in ethanol, and sodium isopropoxide in propan-2-ol, respectively.

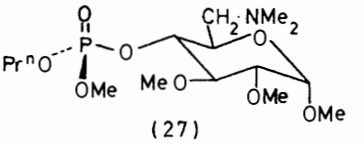
In contrast to reactions of the 2-alkyltetrahydro-1,3,2-oxazaphosphorines with alkoxides from which it was possible to isolate good yields of ring-opened products resulting from P–O cleavage, the yield (45%) of the glucopyranoside 6-*N*-(methyl n-propyl phosphoramidate) derivative (24) isolated from the reaction between the 2-n-propyloxytetrahydro-1,3,2-oxazaphosphorin-2-one (9*eq*) and sodium methoxide was less good, and other similar reactions with phosphoroamidates and phosphoroamidothioates gave very poor yields of P–O-cleaved products. As with the methylphosphonamido-derivative–sodium alkoxide reactions, under suitable conditions it was also possible to isolate the product (25) which resulted from P–N cleavage as well as the amino-sugar (1) from the reaction between (9*eq*) and sodium methoxide. The n-propyl phosphate (25) had an n.m.r. spectrum indistinguishable from that of the basic compound liberated from the product of the reaction between (9*eq*) and methanolic hydrogen chloride. Attempts to establish whether this spectrum differed



(24) R = Me
(26) R = Et



(25) R = Me
(28) R = Et



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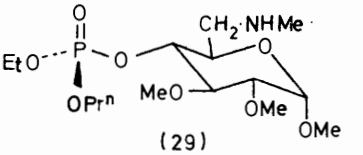

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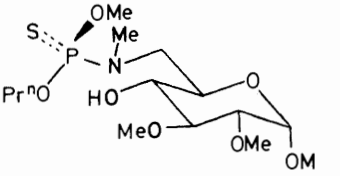


(33)

from that of the product (following conversion into the free base) of the reaction between (7*eq*) and propan-1-ol–HCl (and thus to establish conclusively that base- and acid-promoted P–N cleavage occurred with the same overall stereochemistry) were inconclusive because variable amounts of the dimethylamino-derivative (27) were formed during reactions with the methyl phosphoro-derivatives. Presumably (27) was formed as a result of intermolecular nucleophilic attack of –NHMe at the methyl group of the methyl phosphate ester.

Proof that in the phosphoro-derivatives as well as in the phosphono-derivatives P–N cleavage by alkoxides occurs with inversion of configuration was obtained when it was demonstrated that the n.m.r. spectrum of the product (28) formed with inversion of configuration by the reaction of (9*eq*) with EtOH–HCl was indistinguishable from the spectrum from the P–N-cleaved product from the reaction of (9*eq*) with NaOEt. The diastereoisomeric product (29) from the reaction of (8*eq*) with Pr^nOH–HCl had a slightly different n.m.r. spectrum. In these reactions there were no dimethylamino-by-products, presumably reflecting the established differences in rates of nucleophilic attack on carbon in methyl and ethyl phosphate esters.[14]

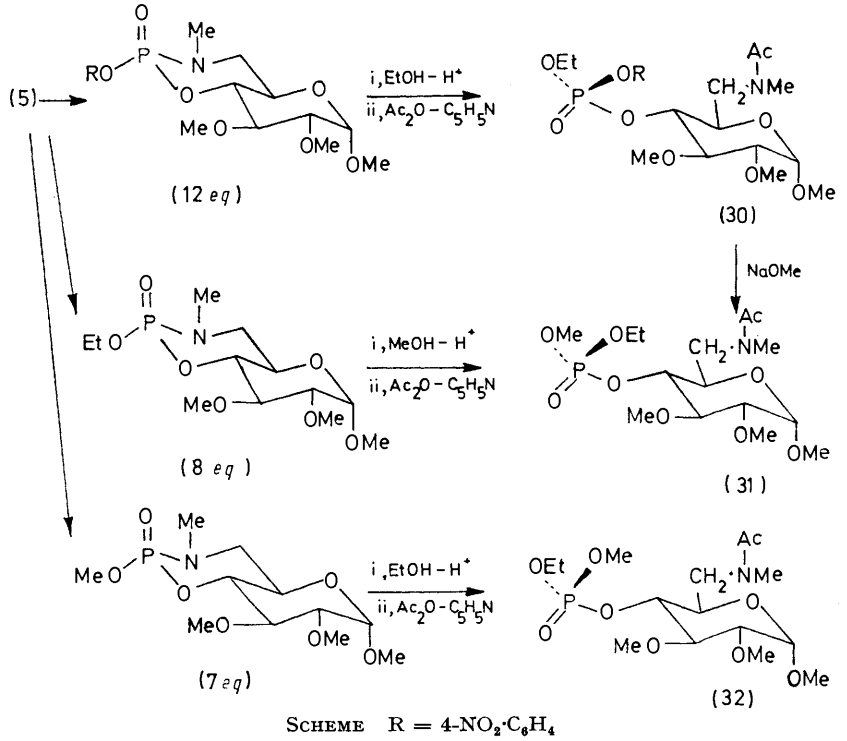
[12] M. Mikolajczyk, J. Omelánczuk, and M. Para, *Tetrahedron*, 1972, **28**, 3855.

[13] D. A. Tyssee, L. P. Bausher, and P. Haake, *J. Amer. Chem. Soc.*, 1973, **95**, 8066.

[14] J. Adamson and T. D. Inch, Proceedings 7th British Insecticide and Fungicide Conference, 1973, p. 65.

In later acid-catalysed ring-opening experiments such as those indicated in the Scheme (see later) interference by the liberated -NHMe group was avoided by acetylation before isolation of the P–N-cleaved product. Thus no problems were encountered during the isolation of (30)—(32).

Although the phosphoramidothioate derivatives [*e.g.* (10*eq*) and (11*eq*)] required more vigorous conditions for their ring opening than the compounds previously described, the pattern of reaction was the same. Thus the conversion of (11*eq*) into (33) only proceeded within a reasonable time (2 h) when (11*eq*) was boiled under reflux with 4N-sodium methoxide. A poor yield (14%) of (33) was obtained and the major product was the amino-sugar (1).



SCHEME R = 4-NO_2·C_6H_4

In the base-promoted ring-opening experiments described in this section no attempt has been made to estimate the relative extent of P–O and P–N breaking reactions since the ring-opening reactions may be reversible and the rapid conversion of P–N-cleaved products into methyl 6-deoxy-2,3-di-*O*-methyl-6-methylamino-α-D-glucopyranoside (1) will obviously affect the observed ratio of products. It is clear however, that the six-membered-ring tetrahydro-1,3,2-oxazaphosphorines contain P–N bonds whose stability towards base is intermediate between those in the base-stable acyclic phosphoramidates and those in the exceedingly base-labile 1,3,2-oxazaphospholidines.[15] It is possible that a detailed kinetic study of similar ring-opening reactions in which the nature of the groups about phosphorus and nitrogen is varied systematically might provide insight into the relative importance of stereochemical and electronic factors with regard to the stability of P–N bonds. At present only theoretical[16] and limited experimental[17] data are available and these are difficult to equate with the effect of ring size on the stability of the P–N bond towards base.

Stereochemistry of Reactions involving Replacement of Exocyclic P-*Substituents in Tetrahydro*-1,3,2-*oxazaphosphorin*-2-*ones*.—As already mentioned the spectroscopic data which are usually so useful for assigning the configuration at phosphorus in 1,3,2-phosphorinan-2-ones and -2-thiones could only be applied with confidence to phosphono-derivatives of tetrahydro-1,3,2-oxazaphosphorines; the spectroscopic data for the phosphoro-derivatives at best only permitted tentative assignments. However, on the basis of one justifiable assumption and a number of correlative sequences it was possible to make reasonably definite stereochemical assignments which provided a self-consistent pattern.

The necessary assumption, supported by a great deal of experimental data from other heterocyclic systems,[9,10] was that electronegative 2-substituents in tetrahydro-1,3,2-oxazaphosphorine-2-ones and -2-thiones prefer to be located in an axial orientation when the six-membered ring is in a chair conformation. On this basis the chloro-substituent must be axial in both (5) and (6). Also the thermodynamically preferred nitrophenyl derivative (12*ax*) must have an axial nitrophenyl group and the kinetically preferred derivative (12*eq*) must have an equatorial nitrophenyl group. Further, the initial

[15] D. B. Cooper, J. M. Harrison, and T. D. Inch, *Tetrahedron Letters*, 1974, 2697.

[16] R. Hoffmann, J. M. Howell, and E. L. Muetterties, *J. Amer. Chem. Soc.*, 1972, **94**, 3047.

[17] S. Trippett and P. J. Whittle, *J.C.S. Perkin I*, 1973, 2302.

displacement of chloride in (5) by sodium nitrophenoxide to afford (12*eq*) proceeded with inversion of configuration. Since it is demonstrated here that acid-catalysed alcoholysis of endocyclic P–N bonds occurs with inversion of configuration, and since it is known that displacement of a nitrophenyl group by alkoxides proceeds with inversion of configuration in acyclic derivatives,[18] the correlative sequence in the Scheme shows that the conversion of (5) into (8*eq*) on treatment with sodium ethoxide proceeded with inversion of configuration. [The ethyl methyl phosphates (31) and (32) were easily distinguishable by their n.m.r. spectra. Although many of the common groups in the two isomers had indistinguishable chemical shifts, the quartet for P–OMe (*i.e.* the usual doublet appearing as a quartet because of restricted rotation of the amide group) was quite different in the spectra of the two isomers (see Experimental section).] It follows that there is a high probability that all displacement reactions of chloride by alkoxide from (5) and (6) occur with inversion, thereby permitting the assignment of an equatorial configuration to the 2-substituents in (7*eq*), (9*eq*), (10*eq*), and (11*eq*).

Treatment of the nitrophenyl derivative (12*eq*) with sodium methoxide gave principally the inversion product (7*ax*), and similar treatment of (12*ax*) also resulted in a product (7*eq*) formed with inversion.

A further reaction which occurred with inversion was observed when (5) afforded preponderantly the 2-phenylphosphono-derivative (3*eq*) on treatment with phenylmagnesium bromide in benzene–ether. Similarly, treatment of (6) with methylmagnesium iodide provided an indication that (4*eq*) was formed preferentially to (4*ax*). However, in the Grignard reactions yields were low, presumably because of the formation of ring-opened products which were not further investigated.

It is therefore clear that all the exocyclic reactions we have observed in the tetrahydro-1,3,2-oxazaphosphorines proceed with *inversion* of configuration at phosphorus. This result contrasts sharply with results from previous experiments[4] in the 1,3,2-dioxa- and 1,3,2-oxathia-phosphorinans in which the exocyclic displacement reactions proceeded either with *inversion* or *retention* of configuration, depending on the natures of the nucleophiles and leaving groups. For example, treatment of methyl 2,3-di-*O*-methyl-α-D-glucopyranoside (*S*)-4,6-phosphorochloridate gave products formed with preponderantly *inversion* of configuration on treatment with ethanol or sodium nitrophenoxide but products formed with preponderantly *retention* of configuration on treatment with sodium ethoxide or methylmagnesium iodide.

Although, as previously,[4] it is tempting to speculate about the factors which control the stereochemical sequence during displacement reactions from phosphorus in tetrahydro-1,3,2-oxazaphosphines, it is clear that these factors are so delicately balanced and change so easily as new variables are introduced, that comprehensive generalisation is still not possible. However, although retention of configuration, which presumably indicates the presence of pseudorotation, has not been observed in reactions of the six-membered-ring tetrahydro-1,3,2-oxazaphosphorines, the presence of a P–N bond alone is not sufficient to prevent pseudorotation since displacement reactions with retention of configuration have been observed in five-membered-ring 1,3,2-oxazaphospholidines.[15]

EXPERIMENTAL

T.l.c. was performed by upward irrigation (with multiple irrigation where necessary) on microscope slides coated with Merck silica gel G, and column chromatography was performed with Merck silica gel of particle size 0.05—0.2 mm in the same solvent as used for t.l.c.

^{1}H N.m.r. spectra were measured with a JEOL JNM-4-H-100 spectrometer at 100 MHz with deuteriochloroform as solvent (unless stated otherwise) and tetramethylsilane as internal standard. ^{31}P N.m.r. spectra were measured at 40 MHz and chemical shifts are quoted in p.p.m. from 85% H_3PO_4 (low field negative). Although only selected n.m.r. data are reported, all compounds had n.m.r. spectra consistent with the assigned structures and the reported data allow distinction between isomers epimeric at phosphorus.

Solvents were dried over $MgSO_4$ and light petroleum refers to the fraction of b.p. 60—80°. Optical rotations were measured in chloroform (path length 0.5 or 1 dm).

Methyl 6-Deoxy-2,3-di-O-methyl-6-methylamino-α-D-glucopyranoside (1).—A solution of toluene-*p*-sulphonyl chloride (40 g) in pyridine (100 ml) was added dropwise to a solution of methyl 2,3-di-*O*-methyl-α-D-glucopyranoside (40 g) in pyridine (100 ml). The mixture was stored at room temperature for 6 h, poured into water, and extracted with ether. The extract was dried and concentrated and residual pyridine was removed by codistillation with toluene. The product crystallised slowly on trituration with light petroleum to afford methyl 2,3-di-*O*-methyl-6-*O*-*p*-tolylsulphonyl-α-D-glucopyranoside (55 g) as an off-white crystalline solid (R_F 0.3 in benzene–ether, 1 : 1) contaminated with a trace of the 4,6-di-*p*-tolylsulphonyl derivative (R_F 0.5). A solution of the crude 6-*O*-*p*-tolylsulphonyl derivative (55 g) in ethanol (500 ml) containing 33% (w/v) of methylamine was boiled under reflux for 6 h. The solution was concentrated, aqueous 3% sodium hydroxide (200 ml) was added, and the solution was continuously extracted with chloroform. Concentration of the dried extract afforded the crude *amino-sugar* (1) (34 g, 80%) as a pale yellow solid which was used without further purification for subsequent reactions. A sample purified by crystallisation from di-isopropyl ether had m.p. 92—95°, $[\alpha]_D$ +127° (*c* 1) (Found: C, 51.4; H, 8.9; N, 5.9. $C_{10}H_{21}NO_5$ requires C, 51.1; H, 9.0; N, 5.9%).

Methyl 2,3-Di-O-methyl-α-D-glucopyranoside Cyclic (R)- *and* (S)-4(O),6(N)-NP-*Dimethylphosphonamidates* [(2*ax*) *and* (2*eq*)].—(a) *By reaction with methylphosphoric dichloride.* A solution of the amino-sugar (1) (6 g), methylphosphonic dichloride (4 g), and triethylamine (10 g) in dichloromethane (150 ml) was stirred at room temperature for 2 h, washed with water, dried, and concentrated. The product was passed over silica in benzene–acetone–methanol (7 : 3 : 1). The major component (R_F 0.6) was recrystallised from di-isopropyl ether–acetone to give the *phosphonamidate* (2*ax*) (4 g, 53%), m.p. 173—176°, $[\alpha]_D$ +96° (*c* 2)

[18] H. P. Benschop, G. R. Van Den Berg, and H. L. Boter, *Rec. Trav. chim.*, 1968, **87**, 387.

(Found: C, 44.9; H, 7.4; N, 4.5. $C_{11}H_{22}NO_6P$ requires C, 44.7; H, 7.5; N, 4.7%), δ_H 3.90 (H-4), 1.51 (PMe, $J_{P,Me}$ 15.5 Hz), and 2.72 (NMe, J_{P-N-Me} 11—12 Hz), δ_P −30.6 p.p.m. The mother liquors from (*2ax*) contained (*2eq*), which was a syrup, δ_H 4.1 (H-4), 1.55 (PMe, $J_{P,Me}$ 16.5 Hz), and 2.68 (NMe, J_{P-N-Me} 11—12 Hz), δ_P −35.5 p.p.m. Compounds (*2ax*) and (*2eq*) were not separated chromatographically and the proportion of (*2eq*) depended on the conditions of the experiment. In one experiment when the mixture was boiled under reflux intermittently for 14 days, the (*2ax*) : (*2eq*) ratio obtained by integration of the P–Me n.m.r. signals was 1.3 : 1.

(b) *By reaction with methylphosphonic difluoride.* A solution of (1) (1 g), methylphosphonic difluoride (0.6 g), and triethylamine (3 g) was boiled under reflux for 3 days. The formation of (*2ax*) or (*2eq*) was monitored by t.l.c. [benzene–acetone–methanol (7 : 3 : 1)] and found to be very slow. The mixture was processed in the usual manner and following chromatography over silica only (*2eq*) (0.1 g, 8%) was isolated.

(c) *By oxidation of the phosphonothioates* (*4ax*) *and* (*4eq*). A solution of (*4eq*) (0.1 g) and 4-chloroperbenzoic acid (0.086 g) in methylene chloride (30 ml) was stored at 0 °C. After 5 min t.l.c. (benzene–acetone, 9 : 1) indicated the absence of (*4eq*). The solution was poured into aqueous sodium carbonate, and the dichloromethane layer was separated, dried, and concentrated. The product (0.08 g), after chromatography over silica in benzene–acetone–methanol (8 : 1 : 1) had an n.m.r. spectrum indistinguishable from that of (*2eq*).

Compound (*4ax*) was similarly oxidised to (*2ax*).

Methyl 2,3-Di-O-methyl-α-D-glucopyranoside Cyclic (R)- *and* (S)-4(O),6(N)-N-*Methylphenylphosphonamidate* [(*3ax*) *and* (*3eq*)].—A solution of (1) (0.8 g), triethylamine (1.4 g), and phenylphosphonic dichloride (0.7 g) in benzene was stored for 3 h at 60 °C. The mixture was processed in the usual manner and the crude product passed over silica in chloroform to afford, in order of elution, (*a*) the *phosphonamidate* (*3ax*) (0.4 g, 33%), m.p. 101—103° [from light petroleum (b.p. 80—100°)], $[\alpha]_D$ +73° (*c* 2) (Found: C, 53.3; H, 6.6; N, 3.7. $C_{16}H_{24}NO_8P$ requires C, 53.8; H, 6.8; N, 3.9%), $\nu_{P=O}$ 1 270 (benzene); $\nu_{P=O}$ 1 258 ($CDCl_3$) cm^{-1}, δ_H 2.86 (NMe, J_{P-N-Me} 9 Hz), 4.0 (H-4), 4.78 (H-1, $J_{1,2}$ 3.5 Hz), and 3.43, 3.48, and 3.58 (3 OMe); (*b*) (*3eq*) (0.3 g, 25%) as a syrup, $[\alpha]_D$ +50° (*c* 1.5), $\nu_{P=O}$ 1 249 (benzene), $\nu_{P=O}$ 1 247 ($CDCl_3$) cm^{-1}, δ_H 2.56 (NMe, J_{P-N-Me} 11 Hz), 4.25 (H-4), 4.87 (H-1, $J_{1,2}$ 3.5 Hz), 3.48, 3.52, and 3.54 (3 OMe), and 7.3—8.1 (Ph as separate two- and three-proton multiplets).

Methyl 2,3-Di-O-methyl-α-D-glucopyranoside Cyclic (R)- *and* (S)-4(O),6(N)-NP-*Dimethylphosphonamidothioate* (*4ax*) *and* (*4eq*).—Methylphosphonothioic dichloride (3.4 g) was added to a stirred suspension of (1) (4.6 g) and triethylamine (10 g) in benzene and the mixture was boiled under reflux for 5 h. Following conventional processing the products were separated by chromatography over silica in benzene–acetone (9 : 1). The first product eluted was the *phosphonamidothioate* (*4 eq*) (0.8 g, 13%), m.p. 123° (from light petroleum), $[\alpha]_D$ + 142° (*c* 1.2) (Found: C, 42.7; H, 7.0; N, 4.4. $C_{11}H_{22}NO_5PS$ requires C, 42.4; H, 7.1; N, 4.5%), δ_H 1.93 (PMe, J_{P-Me} 15.5 Hz), 2.46 (NMe, J_{P-N-Me} 17 Hz), 4.25 (H-4, $J_{3,4} = J_{4,5} = 9.5$ Hz, $J_{P,4}$ 5 Hz), and 4.82 (H-1), δ_P −98.1 p.p.m. The second product eluted was the *phosphonamidothioate* (*4ax*) (3.9 g, 63%), m.p. 181—183° [from light petroleum (b.p. 80—100°)], $[\alpha]_D$ +57° (*c* 1.8) (Found: C, 42.6; H, 7.1; N, 4.6%), δ_H 1.83 (PMe, J_{P-Me} 13 Hz), 2.28 (NMe, J_{P-N-Me} 12 Hz), and 4.81 (H-1, $J_{1,2}$ 3.5 Hz) (with the exception of H-1 there were no proton signals below δ 4.0), δ_P −90.6 p.p.m.

Methyl 2,3-Di-O-methyl-α-D-glucopyranoside Cyclic (S)-4(O),6(N)-N-*Methylphosphoramidochloridate* (*5*).—A solution of phosphoryl chloride (0.8 g) in dichloromethane was added to a stirred solution of (1) (1.2 g) and triethylamine (2.5 g) in dichloromethane at room temperature. After 2 h, the solution was washed with water, dried, and concentrated and the product crystallised from light petroleum to afford the *phosphoramidochloridate* (*5*), m.p. 123—125° (1.16 g, 73%), $[\alpha]_D$ +86° (*c* 1.5) (Found: C, 38.4; H, 6.1; N, 4.5. $C_{10}H_{19}ClNO_6P$ requires C, 38.1; H, 6.1; N, 4.4%).

Methyl 2,3-Di-O-methyl-α-D-glucopyranoside Cyclic (S)-4(O),6(N)-N-*Methylphosphoramidochloridothioate* (*6*).—A solution of (1) (1.2 g), thiophosphoryl chloride (0.9 g), and triethylamine (2.5 g) in dichloromethane (25 ml) was stored overnight at room temperature. T.l.c. (benzene–acetone, 9 : 1) indicated only one product. The solution was washed with water, dried, and concentrated and the product crystallised from light petroleum to afford the *phosphoramidochloridothioate* (*6*) (1.3 g, 90%), m.p. 123—127°, $[\alpha]_D$ +57° (*c* 1.2) (Found: C, 36.5; H, 5.6; N, 4.2. $C_{10}H_{19}NClO_5PS$ requires C, 36.2; H, 5.8; N, 4.2%).

Treatment of the Phosphoroamidochloridate (*5*) *with Sodium Alkoxides.*—A solution of (*5*) (1—2 g) in the appropriate alcohol (20 ml) was treated with the corresponding N-sodium alkoxide (10 ml) at room temperature. The reaction was monitored by t.l.c. (benzene–acetone–methanol, 8 : 1 : 1). In each case no starting material remained after *ca.* 30 min and essentially only one product, which has a lower R_F value than (*5*), was indicated. The solution was neutralised with CO_2, diluted with chloroform, washed with water, dried, and concentrated. N.m.r. spectra were obtained following chromatography over silica to remove trace impurities. The following compounds were prepared in 80—90% yield as syrups: (*a*) methyl 2,3-di-*O*-methyl-α-D-glucopyranoside cyclic (*R*)-4(*O*),6(*N*)-(methyl *N*-methylphosphoramidate) (*7eq*), $[\alpha]_D$ +80° (*c* 4), δ_H 2.73 (NMe, J_{P-N-Me} 10 Hz), 3.41, 3.53, and 3.61 (3 OMe), 3.73 (POMe, J_{P-O-Me} 12 Hz), 3.9—4.2 (H-4, m), and 4.82 (H-1, $J_{1,2}$ 3.5 Hz), $\nu_{P=O}$ 1 265 ($CDCl_3$) cm^{-1}; (*b*) the (*R*)-4,6-(ethyl *N*-methylphosphoramidate) (*8eq*), $[\alpha]_D$ +67°, δ_H 1.33 ($CH_3{\cdot}CH_2$), 2.72 (NMe, J_{P-N-Me} 11 Hz), 3.45, 3.54, and 3.60 (3 OMe), 4.1 (3 H, m, $CH_3{\cdot}CH_2$ and H-4), and 4.82 (H-1), $J_{1,2}$ 3.5 Hz), δ_P −5.9 p.p.m., $\nu_{P=O}$ 1 253 ($CDCl_3$), $\nu_{P=O}$ 1 275 (benzene) cm^{-1}, R_F 0.4 in benzene–acetone–methanol (8 : 1 : 1); (*c*) the (*R*)-4,6-(n-propyl *N*-methylphosphoramidate) (*9eq*), $[\alpha]_D$ + 71° (*c* 2), δ_H 0.96 ($CH_3{\cdot}CH_2{\cdot}CH_2$), 1.68 ($CH_3{\cdot}CH_2{\cdot}CH_2$), 2.71 (NMe, J_{P-N-Me} 10.5 Hz), 3.44, 3.53, and 3.59 (3 OMe), and 4.79 (H-1, $J_{1,2}$ 3.5 Hz).

Treatment of the Amino-sugar (*1*) *with Ethyl Phosphorodichloridate.*—A solution of (1) (1.5 g), $EtOPOCl_2$ (1 g), and an excess of triethylamine in dichloromethane was stored overnight at room temperature, washed with water, dried, and concentrated. T.l.c. (benzene–acetone–methanol, 8 : 1 : 1) showed that the product was a multi-component mixture. The product was chromatographed over silica to afford, in addition to unidentified compounds and mixtures of compounds, a small quantity (0.1 g) of the (*S*)-4,6-(ethyl *N*-methylphosphoramidate) (*8ax*), R_F 0.45, $[\alpha]_D$ +53° (*c* 0.5), δ_H 1.37 ($CH_3{\cdot}CH_2$), 2.73 (NMe, J_{P-N-Me} 11 Hz), 3.46, 3.55, and 3.64 (3 OMe), 3.85 (H-4, m), 4.14 ($CH_3{\cdot}CH_2$), and 4.82 (H-1, $J_{1,2}$ 3.5 Hz), δ_P −5.9 p.p.m.,

$\nu_{P=O}$ 1 266 ($CDCl_3$), $\nu_{P=O}$ 1 290 (benzene) cm^{-1}. A small quantity of (8*eq*) (R_F 0.4) was also isolated.

Treatment of the Phosphorochloridothioate (6) *with Sodium Alkoxides.*—(*a*) A solution of the phosphorochloridothioate (6) (0.35 g) in N-sodium methoxide in methanol (10 ml) was stored overnight at room temperature. Conventional processing and chromatography of the product over silica in benzene–acetone (9 : 1) afforded *methyl* 2,3-*di*-O-*methyl*-α-D-*glucopyranoside cyclic* (R)-4(O),6(N)-(*methyl* N-*methylphosphoramidothioate*) (10*eq*) (0.3 g, 87%), m.p. 70—73° (from light petroleum), $[\alpha]_D$ +155° (*c* 1) (Found: C, 40.0; H, 6.8; N, 4.2. $C_{11}H_{22}NPS$ requires C, 40.3; H, 6.8; N, 4.3%), δ_H 2.53 (NMe, J_{P-N-Me} 15 Hz), 3.46, 3.53, and 3.58 (3 OMe), and 3.79 (POMe, J_{POMe} 14 Hz).

(*b*) Similarly (6) (0.3 g), on treatment with N-sodium propoxide in propan-1-ol, afforded the (*R*)-4,6-(n-propyl *N*-methylphosphoramidothioate) (11*eq*) as a syrup (0.25 g, 78%), $[\alpha]_D$ +145° (*c* 1.2), δ_H 0.97 ($CH_3{\cdot}CH_2{\cdot}CH_2$), 1.71 ($CH_3{\cdot}CH_2{\cdot}CH_2$), 2.52 (NMe, J_{P-N-Me} 15 Hz), and 3.45, 3.54, and 3.58 (3 OMe). In all t.l.c. solvent systems studied, (6) and (11*eq*) had the same R_F values.

Preparation of the 4-*Nitrophenyl Phosphoramidates* (12*eq*) *and* (12*ax*).—(i) A solution of (5) (0.4 g) and sodium 4-nitrophenoxide (0.25 g) in acetonitrile was stirred at room temperature for 3 h, diluted with chloroform, washed with water, dried, and concentrated, and the residue (R_F 0.5 in acetone–light petroleum, 2 : 3) was recrystallised from di-isopropyl ether to afford the *nitrophenyl phosphoramidate* (12*eq*) (0.3 g, 56%), m.p. 98—101°, $[\alpha]_D$ +59° (*c* 1), $\nu_{P=O}$ 1 300 (benzene) cm^{-1}, δ_H 2.87 (NMe, J_{P-N-Me} 11 Hz), 3.93, 3.52, and 3.57 (3 OMe), and 3.9—4.3 (2 H, m, H-4 and -5), δ_P +0.6 p.p.m. (Found: C, 46.1; H, 5.6; N, 6.7. $C_{16}H_{23}N_2O_9P$ requires C, 45.9; H, 5.5; N, 6.7%).

(ii) A solution of (12*eq*) (0.4 g) [or (5)] and sodium 4-nitrophenoxide (1 g) in acetonitrile was boiled under reflux for 6 h. After this time the conversion of (12*eq*) into (12*ax*) was essentially complete [(12*ax*) had R_F 0.6 in acetone–light petroleum, 2 : 3]. The solution was cooled, diluted with chloroform, washed with water, dried, and concentrated, and the residue was passed over silica in light petroleum–acetone (3 : 2) and crystallised from di-isopropyl ether to afford the *nitrophenyl phosphoramidate* (12*ax*) (0.26 g, 48%), m.p. 120—124°, $[\alpha]_D$ +102° (*c* 0.8), $\nu_{P=O}$ 1 304 (benzene) cm^{-1}, δ_H 2.89 (NMe, J_{P-N-Me} 11 Hz), 3.51, 3.56, and 3.61 (3 OMe), and 4.0—4.15 (2 H, m, H-4 and -5), δ_P +0.6 p.p.m. (Found: C, 46.1; H, 5.4; N, 6.6%).

Treatment of the Nitrophenyl Phosphoramidates (12*ax*) *and* (12*eq*) *with Sodium Methoxide in Methanol.*—(i) A solution of (12*eq*) (0.3 g) in N-sodium methoxide in methanol was stored at room temperature for 2 h. T.l.c. (benzene–acetone, 7 : 3) showed complete conversion into (7*ax*) (R_F 0.5) and (7*eq*) (R_F 0.3). The solution was neutralised with CO_2, diluted with chloroform, washed with water, dried, and concentrated and the residue was passed over silica in benzene–acetone (7 : 3) to afford (*a*) the *methyl phosphoramidate* (7*ax*) (0.15 g, 67%), m.p. 110—120° (from di-isopropyl ether), $[\alpha]_D$ +45° (*c* 0.7), $\nu_{P=O}$ 1 275 ($CDCl_3$) cm^{-1} (Found: C, 42.9; H, 6.9; N, 4.6. $C_{11}H_{21}NO_7P$ requires C, 42.6; H, 6.8; N, 4.5%), δ_H 2.75 (NMe, J_{P-N-Me} 11 Hz), 3.45, 3.55, and 3.64 (3 OMe), and 3.76 (POMe, J_{POMe} 12 Hz) (no signals below δ 3.95), and (*b*) (7*eq*) (0.02 g, 9%).

(ii) A solution of (12*ax*) (0.2 g) in N-sodium methoxide in methanol was stored at room temperature for 4 h. Normal processing afforded (7*eq*) (0.1 g, 68%).

Treatment of the (R)-*Methylphosphonamidothioate* (4*ax*) *with Alkoxides.*—(i) *With sodium methoxide in methanol.* A solution of (4*ax*) (0.9 g) in N-sodium methoxide in methanol (15 ml) was boiled under reflux for 3 h. Only traces of (4*ax*) then remained (t.l.c. in benzene–acetone, 4 : 1). The solution was neutralised with CO_2, diluted with chloroform, washed with water, dried, and concentrated. The residue was passed over silica in benzene–acetone to give *methyl* 2,3-*di*-O-*methyl*-α-D-*glucopyranoside* 6(N)-(*methyl* NP-*dimethyl phosphonamidothioate*) (13) as a chromatographically pure syrup (0.75 g, 76%) which slowly crystallised. Recrystallisation from cyclohexane–ethyl acetate gave material of m.p. 78—79°, $[\alpha]_D$ +134° (*c* 0.47) (Found: C, 42.3; H, 7.3; N, 4.1. $C_{12}H_{26}NO_6PS$ requires C, 42.0; H, 7.6; N, 4.1%), δ_H 1.83 (PMe, $J_{P,Me}$ 15 Hz), 2.83 (NMe, J_{P-N-Me} 11 Hz), 3.42, 3.52, and 3.65 (3 OMe), 3.54 (POMe, J_{P-O-Me} 13 Hz), and 4.82 (H-1, $J_{1,2}$ 3.5 Hz).

In a second experiment the reaction mixture from 0.3 g of (4*ax*) was concentrated following treatment with CO_2 and acetylated with acetic anhydride in pyridine overnight at room temperature. The solution was diluted with chloroform, washed with water, dried, and concentrated, and residual pyridine and acetic anhydride were removed by coevaporation with toluene. The residue was chromatographed over silica in benzene–acetone (8 : 1), to afford the 4-*O*-acetyl derivative of (13) (0.18 g, 49%), δ_H 2.13 (OAc), 2.82 (NMe, J_{P-N-Me} 11 Hz), and 4.71 (H-4, $J_{3,4} = J_{4,5} = 10$ Hz), and the diacetate of (1) (0.05 g, 16%).

In a third experiment a solution of (4*ax*) (0.4 g) in 0.5N-sodium methoxide in methanol (10 ml) was heated under reflux for 1.5 h. The mixture was processed in the usual manner and the product passed over silica in chloroform–methanol (9 : 1) to give, in order of elution, (*a*) a mixture of (4*ax*) and (13) (R_F 0.9 and 0.8, respectively) and (*b*) (16) (R_F 0.3), which had an n.m.r. spectrum indistinguishable from that of the product obtained by treatment of (4*ax*) with methanolic hydrogen chloride (for details see below).

(ii) *With sodium ethoxide in ethanol.* A solution of (4*ax*) (1.8 g) in N-sodium ethoxide in ethanol (20 ml) was boiled under reflux for 3 h. Usual processing and chromatography over silica in benzene–acetone (9 : 1) afforded (14) as a chromatographically homogeneous syrup (1.12 g, 56%), $[\alpha]_D$ +143° (*c* 1.1), δ_H 1.26 ($CH_3{\cdot}CH_2$), 1.82 (PMe, $J_{P,Me}$ 15 Hz), 2.82 (NMe, J_{P-N-Me} 10 Hz), and 3.41, 3.51, and 3.64 (3 OMe).

(iii) *With sodium isopropoxide in propan-2-ol.* A solution of (4*ax*) (0.9 g) in N-sodium isopropoxide in propan-2-ol (25 ml) was boiled under reflux for 8 h. The reaction was monitored by t.l.c. [double irrigation in benzene–acetone (4 : 1)]. Normal processing and chromatography over silica afforded (15) as a chromatographically homogeneous syrup (0.71 g, 70%), $[\alpha]_D$ +127° (*c* 0.7), δ_H 1.25 (Me_2CH), 1.83 (PMe, $J_{P,Me}$ 15 Hz), 2.82 (NMe, J_{P-N-Me} 11 Hz), 3.42, 3.52, and 3.65 (3 OMe), 4.6 (Me_2CH), and 4.79 (H-1, $J_{1,2}$ 3.5 Hz).

Treatment of the Phosphonamidothioates (4*ax*) *and* (4*eq*) *with Methanolic Hydrogen Chloride.*—(i) A solution of (4*ax*) (0.1 g) in methanolic hydrogen chloride was stored at room temperature for 10 min. No starting material then remained (t.l.c. in $CHCl_3$–MeOH, 9 : 1.) The solution was poured into dilute aqueous sodium hydroxide and extracted with chloroform, and the extract was dried and concentrated. The product (16) (0.95 g, 86%) had $[\alpha]_D$ +122° (*c* 1), δ_H 1.88 (PMe, $J_{P,Me}$ 16 Hz), 2.48 (NMe), 3.45, 3.51, and 3.55 (3 OMe), 3.72 (POMe, J_{P-O-Me} 14 Hz), 4.28 (H-4,

$J_{3,4} = J_{4,5} = 10$ Hz, $J_{P,4}$ 14 Hz), and 4.85 (H-1, $J_{1,2}$, 3.5 Hz). The *N*-acetyl derivative of (16) had $[\alpha]_D$ +100° (*c* 0.8), δ_H [$(CD_3)_2SO$ at 77 °C] 1.83 (PMe, $J_{P,Me}$ 16 Hz), 1.96 (NAc), 2.97 (NMe), 3.27, 3.38, and 3.45 (3 OMe), 3.72 (POMe, J_{P-OMe} 15 Hz), and 4.84 (H-1, $J_{1,2}$ 3.5 Hz).

(ii) Treatment of (*4eq*) (0.2 g) with methanolic hydrogen chloride as above afforded (17) (0.18 g, 82%), $[\alpha]_D$ +140° (*c* 1.5), δ_H 1.82 (PMe, $J_{P,Me}$ 15 Hz), 2.46 (NMe), 3.44, 3.51, and 3.55 (3 OMe), 3.76 (POMe, J_{P-O-Me} 14 Hz), 4.37 (H-4, $J_{3,4} \simeq J_{4,5} \simeq 10$ Hz, $J_{P,4}$ 14 Hz), and 4.84 (H-1, $J_{1,2}$ 3.5 Hz). The *N*-acetyl derivative of (17) had $[\alpha]_D$ +124° (*c* 1.2), δ_H [$(CD_3)_2SO$ at 77 °C], 1.86 (PMe, $J_{P,Me}$ 16 Hz), 1.98 (NAc), 2.95 (NMe), 3.47, 3.42, and 3.30 (OMe), 3.70 (POMe, J_{P-O-Me} 15 Hz), 4.22 (H-4, $J_{3,4} \simeq J_{4,5} \simeq 9.5$ Hz, $J_{P,H-4}$ 13 Hz), and 4.83 (H-1, $J_{1,2}$ 3.5 Hz).

Treatment of the Phenylphosphonamidates (*3ax*) *and* (*3eq*) *with Ethanolic Hydrogen Chloride.*—(i) A solution of (*3ax*) (0.2 g) in ethanolic hydrogen chloride was stored at room temperature. All the (*3ax*) had reacted in 10 min [t.l.c. in $CHCl_3$–MeOH (9 : 1)]. The solution was diluted with chloroform, washed with dilute aqueous sodium hydroxide and water, dried, and concentrated to afford chromatographically homogeneous (18) (0.15 g, 67%), $[\alpha]_D$ +110° (*c* 1.2), δ_H 1.33 (CH_3·CH_2), 2.52 (NMe), 2.84 and 3.44 (×2) (3 OMe), and 4.80 (H-1, $J_{1,2}$ 3.5 Hz). The *N*-acetyl derivative of (18) had δ_H 2.10 and 2.14 (NAc), 2.75 and 2.82 (NMe), 3.00 and 3.13 (OMe), 3.34 and 3.35 (OMe), 3.41 and 3.42 (OMe), and 3.71 and 3.86 (POMe) (doubled resonances because of restricted amide rotation).

(ii) Compound (*3eq*) (0.4 g) under conditions essentially as above was converted into (19) (0.32 g, 71%), $[\alpha]_D$ +88° (*c* 1.8), δ_H 1.33 (CH_3·CH_2), 2.30 (NMe), 3.41, 3.52, and 3.61 (3 OMe), and 4.82 (H-1, $J_{1,2}$ 3.5 Hz). The *N*-acetyl derivative of (19) had δ_H 1.79 and 1.96 (NAc), 2.74 and 2.94 (NMe), 3.25 (OMe), 3.46 and 3.48 (OMe), 3.52 and 3.55 (OMe), and 3.72 (POMe) (some resonances doubled because of restricted amide rotation).

Treatment of the (S)-*Methylphosphonamidothioate* (*4eq*) *with Sodium Methoxide.*—A solution of (*4eq*) (0.15 g) in N-sodium methoxide in methanol (2 ml) was boiled under reflux for 2.5 h. At this time t.l.c. (benzene–acetone, 4 : 1) showed spots corresponding to (*4eq*) (trace), (20) (major), and (1) (trace). The solution was processed in the usual manner and the product chromatographed over silica to give (20) as a homogeneous syrup (0.12 g, 73%), $[\alpha]_D$ +58° (*c* 0.5), δ_H 1.77 (P–Me, $J_{P,Me}$ 15 Hz), 2.83 (NMe, J_{P-N-Me} 11 Hz), 3.41, 3.52, and 3.64 (3 OMe), and 3.62 (POMe, J_{P-OMe} 14 Hz).

In a similar experiment the reaction mixture from (*4eq*) (0.2 g) was processed and acetylated before chromatography over silica in benzene–acetone (4 : 1) to give the 4-acetate of (20) (0.17 g, 70%), δ_H 1.78 (PMe, $J_{P,Me}$ 15 Hz), 2.14 (OAc), 2.85 (NMe, J_{P-N-Me} 11 Hz), 3.43, 3.52, and 3.58 (3 OMe), and 4.68 (H-4, $J_{3,4} \simeq J_{4,5} \simeq 10$ Hz), and the diacetate of (1) (0.03 g, 21%).

Preparation of (R)-*Dicyclohexylammonium Ethyl Methylphosphonothioate.*—A solution of (14) (1.1 g) in 2N-hydrochloric acid (10 ml) was stirred at room temperature for 1.75 h, saturated with sodium chloride, and extracted thoroughly (6×) with chloroform. The extract was dried and concentrated. The product was distilled (b.p. 80° at 0.1 mmHg) to give ethyl methylphosphonothioic acid (0.4 g, 66%), which was treated with dicyclohexylamine (0.45 g) in ether. The product, recrystallised from light petroleum–di-isopropyl ether, had m.p. 127°, $[\alpha]_D$ +7.9° (*c* 3 in MeOH) (lit.,[19] +8.4°; lit.,[20] +7.0°).

Treatment of the (R)-*Methylphosphonamidate* (*2ax*) *with Alkoxides.*—(a) *Sodium methoxide in methanol.* A solution of (*2ax*) (0.15 g) was boiled under reflux in 0.5N-sodium methoxide in methanol (2 ml) for 1.5 h. The mixture was processed in the usual way and the product passed over silica in benzene–acetone–methanol (7 : 3 : 1) to afford (21) (0.13 g, 78%), $[\alpha]_D$ +110° (*c* 0.9), δ_H 1.50 (PMe), 2.72 (NMe), 3.41, 3.52, and 3.65 (3 OMe), and 3.58 (POMe).

(b) *Sodium ethoxide in ethanol.* A solution of (*2ax*) (1.0 g) was boiled under reflux in N-sodium ethoxide in ethanol (15 ml). Following normal processing and chromatography, *methyl* 2,3-*di*-O-*methyl*-α-D-*glucopyranoside* 6(N)-(*ethyl* NP-*dimethylphosphonamidate*) (22) (0.7 g, 60%) was isolated as crystals, m.p. 85—88° (from di-isopropyl ether), $[\alpha]_D$ +115° (*c* 1.3) (Found: C, 46.2; H, 8.3; N, 4.25. $C_{13}H_{28}NO_7P$ requires C, 45.8; H, 8.3; N, 4.1%), δ_H 1.28 (CH_3·CH_2), 1.52 (PMe), 2.72 (NMe), and 3.42, 3.53, and 3.67 (3 OMe).

(c) *Sodium isopropoxide in propan-2-ol.* A solution of (*2ax*) (1.0 g) following treatment with N-sodium isopropoxide in propan-2-ol (15 ml) as described in (b) afforded the *isopropyl phosphonamidate* (23) (0.73 g, 63%), m.p. 118—119° (from di-isopropyl ether–acetone), $[\alpha]_D$ +116° (*c* 1.09) (Found: C, 47.4; H, 8.5; N, 3.9. $C_{14}H_{30}NO_7P$ requires C, 47.3; H, 8.5; N, 3.9%), δ_H 1.28 (Me_2CH), 1.49 (PMe), 2.71 (NMe), 3.41, 3.52, and 3.66 (3 × OMe), and 4.50 (Me_2CH).

Treatment of the n-Propyl Phosphoramidate (*9eq*) *with Sodium Methoxide.*—(i) A solution of (*9eq*) (3 g) in 2N-sodium methoxide in methanol (60 ml) was boiled under reflux for 30 min, neutralised with carbon dioxide, diluted with chloroform, dried, and concentrated. The residue was passed over silica in benzene–acetone–methanol (7 : 3 : 1) to afford the methyl n-propyl phosphoramidate (24) (1.5 g, 45%) as a chromatographically homogeneous syrup, $[\alpha]_D$ +77° (*c* 0.42), δ_H 0.94 (CH_3·CH_2·CH_2), 1.68 (CH_3·CH_2·CH_2), 2.75 (NMe, J_{P-N-Me} 10 Hz), 3.40, 3.52, and 3.65 (3 OMe), and 3.74 (POMe, J_{P-O-Me} 11.3 Hz).

(ii) In a second experiment on (*9eq*) (0.25 g) as described above, after neutralisation with carbon dioxide the solution was concentrated and acetic anhydride (1 ml) and pyridine (1 ml) were added. The solution was stored overnight at room temperature and concentrated, and the residue was passed over silica in benzene–acetone–methanol (8 : 1 : 1) to give, in order of elution, (*a*) the 4-acetate of (24) as a chromatographically homogeneous syrup (0.1 g, 24%), $[\alpha]_D$ +82° (*c* 0.87), δ_H 0.96 (CH_3·CH_2·CH_2), 1.68 (CH_3·CH_2·CH_2), 2.12 (OAc), 2.75 (NMe, J_{P-N-Me} 10 Hz), 3.45, 3.49, and 3.51 (3 OMe), 3.68 (POMe, J_{POMe} 12 Hz), and 4.70 (H-4, $J_{3,4} \simeq J_{4,5} \simeq 10$ Hz); and (*b*) the 4-*O*-acetyl-6-*N*-acetyl derivative of (1) (0.08 g, 34%) as a syrup.

(iii) A solution of (*9eq*) (0.45 g) in N-sodium methoxide methanol (6 ml) was boiled under reflux for 30 min. T.l.c. in chloroform–methanol (4 : 1) showed unchanged (*9eq*), the phosphoramidate (24), and a product with R_F 0.5. The reaction mixture was poured into aqueous sodium chloride and extracted with chloroform, and the extract was dried and concentrated. The residue was passed over silica in chloroform–methanol (4 : 1) to give, in order of

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[20] H. S. Aaron, J. Braun, T. M. Shryne, H. F. Frack, G. E. Smith, R. T. Uyeda, and J. I. Miller, *J. Amer. Chem. Soc.*, 1960, **82**, 596.

elution, (*a*) a mixture of (9*eq*) and (24), and (*b*) the glucopyranoside 4-(methyl n-propyl phosphate) (25) (0.06 g) as a chromatographically homogeneous syrup, δ_H 0.96 ($CH_3{\cdot}CH_2{\cdot}CH_2$), 1.72 ($CH_3{\cdot}CH_2{\cdot}CH_2$), 2.49 (NMe), 3.44, 3.51, and 3.58 (3 OMe), and 3.81 (POMe, J_{POMe} 11 Hz).

Treatment of the n-Propyl Phosphoramidate (9*eq*) *with Methanolic Hydrogen Chloride.*—A solution of (9*eq*) (0.25 g) was stored at room temperature for 10 min, diluted with chloroform, washed with aqueous sodium hydroxide, dried, and concentrated to afford (25) as a syrup contaminated with a trace of a product with a slightly higher R_F value than (25) in chloroform–methanol (10 : 1). [In other experiments isolation of this contaminant was possible and the n.m.r. spectrum was consistent with that of the dimethylamino-derivative (27): δ_H 0.97 ($CH_3{\cdot}CH_2{\cdot}CH_2$), 1.72 ($CH_3{\cdot}CH_2{\cdot}CH_2$), 2.29 ($NMe_2$), 3.48, 3.52, and 3.58 (3 OMe), and 3.77 (POMe, J_{POMe} 11 Hz).] Acetylation of the product with acetic anhydride in pyridine and conventional processing, followed by chromatography over silica, afforded the *N*-acetyl derivative of (25) (0.27 g, 89%), $[\alpha]_D$ +95° (*c* 2.2), δ_H [$(CD_3)_2SO$ at 77 °C] 0.93 ($CH_3{\cdot}CH_2{\cdot}CH_2$), 1.68 ($CH_3{\cdot}CH_2{\cdot}CH_2$), 1.98 (NAc), 2.92 (NMe), 3.29, 3.41, and 3.48 (3 OMe), 3.72 (POMe, J_{P-O-Me} 11 Hz), and 4.82 (H-1, $J_{1,2}$ 3.5 Hz).

Treatment of the n-Propyl Phosphoramidate (9*eq*) *with Ethanolic Hydrogen Chloride.*—A solution of (9*eq*) (1 g) in ethanolic hydrogen chloride was stored at room temperature for 15 min. The solution was rendered alkaline with sodium ethoxide, diluted with chloroform, washed with water, dried, and concentrated and the residue was passed over silica in chloroform–methanol (10 : 1) to afford the ethyl n-propyl phosphate (28) as a chromatographically homogeneous syrup (0.6 g, 53%), $[\alpha]_D$ +107° (*c* 3), δ_H 0.98 ($CH_3{\cdot}CH_2{\cdot}CH_2$), 1.37 ($CH_3{\cdot}CH_2$), 1.73 ($CH_3{\cdot}CH_2{\cdot}CH_2$), 2.46 (NMe), 3.44, 3.53, and 3.59 (3 OMe), and 3.99, 4.06, 4.11, and 4.25 (main peaks from $CH_3{\cdot}CH_2{\cdot}CH_2$, $CH_3{\cdot}CH_2$, and H-4 multiplet).

Treatment of the Ethyl Phosphoramidate (8*eq*) *with Hydrogen Chloride in Propan-1-ol.*—A solution of (8*eq*) (1 g) in hydrogen chloride in propan-1-ol was stored at room temperature for 15 min, rendered alkaline with sodium n-propoxide, diluted with chloroform, washed with water, dried, and concentrated. The residue was passed over silica in chloroform–methanol (10 : 1) to afford the ethyl n-propyl phosphate (29) as a chromatographically homogeneous syrup (0.8 g, 66%), $[\alpha]_D$ +105° (*c* 2.2), δ_H 0.98 ($CH_3{\cdot}CH_2{\cdot}CH_2$), 1.37 ($CH_3{\cdot}CH_2$), 1.73 ($CH_3{\cdot}CH_2{\cdot}CH_2$), 2.46 (NMe), 3.44, 3.52, and 3.59 (3 OMe), and 4.03, 4.10, 4.15, and 4.22 (main peaks from $CH_3{\cdot}CH_2{\cdot}CH_2$, $CH_3{\cdot}CH_2$, and H-4 multiplet).

Treatment of the n-Propyl Phosphoramidate Derivative (9*eq*) *with Sodium Ethoxide.*—A solution of (9*eq*) (1.4 g) in N-sodium ethoxide in ethanol (20 ml) was stored at room temperature overnight. The solution was heated at 50 °C for 30 min, cooled, neutralised with carbon dioxide, diluted with chloroform, dried, and concentrated. The residue was chromatographed over silica in chloroform–methanol (10 : 1) to afford unchanged (9*eq*) (0.6 g), a mixture of (9*eq*) and presumably the P–O ring-opened product (26), and finally (28), which was indistinguishable from (28) prepared by treatment of (9*eq*) with ethanolic hydrogen chloride (above).

Treatment of the Chloridate (5) *with Phenylmagnesium Bromide.*—A solution of (5) (0.3 g) in benzene to which phenylmagnesium bromide (0.45 g) in ether (1.5 ml) had been added was boiled under reflux for 30 min. The mixture was diluted with aqueous ammonium chloride and extracted with ether. The extract was dried and concentrated and the residue passed over silica in benzene–acetone (7 : 3) to afford, in order of elution, (*a*) (5) (trace), (*b*) (3*ax*) (0.015 g, 4.4%), and (*c*) (3*eq*) (0.16 g, 46%).

Treatment of the Chloridate (6) *with Methylmagnesium Iodide.*—A solution of (6) (0.3 g) in benzene to which methylmagnesium iodide (0.3 g) in ether (2 ml) had been added was boiled under reflux. The reaction was monitored by t.l.c. [benzene–ether (1 : 1)]. Spots corresponding to (6) (R_F 0.7), (4*eq*) (R_F 0.6), and (4*ax*) (R_F 0.5) were evident. The intensity of the spot corresponding to (4*eq*) was always greater than that of the spot corresponding to (4*ax*). After all the chloridate (6) had reacted, conventional work-up and chromatography afforded only a trace of (4*eq*) together with a more polar material which was presumably a ring-opened product and which was not further investigated.

Preparation of the 4-Phosphates (30)—(32) (*Scheme*).—(a) (30) *from* (12*eq*). A solution of (12*eq*) (0.6 g) in ethanol containing hydrogen chloride (sufficient to keep the solution just acidic and to promote P–N cleavage as measured by t.l.c. in ethyl acetate–light petroleum, 1 : 2) was stored at room temperature for 15 min. The solution was concentrated and the residue treated with acetic anhydride in pyridine overnight at room temperature. The resulting solution was concentrated and the product passed over silica in chloroform–methanol (9 : 1) to afford (30) as a chromatographically homogeneous syrup (0.5 g, 69%), $[\alpha]_D$ +72° (*c* 1.5), δ_H (60 MHz) 1.39 ($CH_3{\cdot}CH_2$), 2.09 (NAc), 2.90 and 3.10 (NMe), and 3.38, 3.52, and 3.59 (OMe).

(b) (31) *from* (30). A solution of (30) (0.5 g) in N-sodium methoxide in methanol was kept at room temperature for 15 min, treated with carbon dioxide, diluted with chloroform, washed with water, dried, and concentrated. The product was passed over silica in chloroform–methanol (9 : 1) to afford (31) (0.2 g, 51%) as a chromatographically homogeneous syrup, $[\alpha]_D$ +90° (*c* 1), δ_H 1.37 ($CH_3{\cdot}CH_2$), 2.10 and 2.14 (NAc), 2.98 and 3.14 (NMe), 3.34 and 3.36 (OMe), 3.53 (OMe), 3.58 and 3.61 (OMe), and 3.76, 3.79, 3.87, and 3.90 (POMe, J_{POMe} 11 Hz).

(c) (31) *from* (8*eq*). A solution of the ethyl phosphoramidate (8*eq*) (0.3 g) in methanolic hydrogen chloride was stored at room temperature for 15 min, concentrated, treated with acetic anhydride in pyridine at room temperature, and processed as for (30), to afford (31) (0.25 g, 68%) following chromatography over silica in chloroform–methanol (9 : 1).

(d) (32 *from* (7*eq*). A solution of (7 *eq*) (0.4 g) was stored in ethanolic hydrogen chloride for 10 min, then treated with acetic anhydride in pyridine and processed as above to afford (32) (0.35 g, 68%) as a chromatographically homogeneous syrup, [α] + 82° (*c* 2), δ_H 1.37 ($CH_3{\cdot}CH_2$) 2.09 and 2.13 (NAc), 2.98 and 3.12 (NMe), 3.34 and 3.36 (OMe), 3.52 (OMe), 3.58 and 3.61 (OMe), and 3.75, 3.81, 3.86, and 3.92 (POMe, J_{POMe} 11 Hz).

Treatment of the n-Propyl Phosphoramidothioate (11*eq*) *with Sodium Methoxide.*—A solution of (11*eq*) (1.6 g) in 4N-sodium methoxide in methanol (60 ml) was boiled under reflux for 2 h. The reaction was monitored by t.l.c. in benzene–acetone–methanol (7 : 1 : 1). (The reaction proceeded exceedingly slowly if more dilute solutions of sodium methoxide were used.) The solution was treated with carbon dioxide, diluted with chloroform, washed with

water, dried, and concentrated. The product was passed over silica in benzene–acetone–methanol (7 : 1 : 1) to afford methyl 2,3-di-*O*-methyl-α-D-glucopyranoside (*S*)-6(*N*)-(methyl n-propyl *N*-methylphosphoramidothioate) (**33**) (0.25 g, 14%), $[\alpha]_D$ +180° (*c* 2), δ_H 0.95 ($CH_3 \cdot CH_2 \cdot CH_2$), 1.78 ($CH_3 \cdot CH_2 \cdot CH_2$), 2.82 (NMe, J_{P-N-Me} 10 Hz), 3.41, 3.49, and 3.62 (3 OMe), and 3.68 (POMe). In a similar experiment the reaction mixture was concentrated and treated with acetic anhydride in pyridine immediately after the CO_2 treatment. The major product isolated was the diacetate of (1).

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