Use of Carbohydrate Derivatives for Studies of Phosphorus Stereochemistry. Part III.[1] Stereochemical Course of Nucleophilic Displacements of 2-Substituents in 1,3,2-Dioxaphosphorinan-2-ones and Related Compounds

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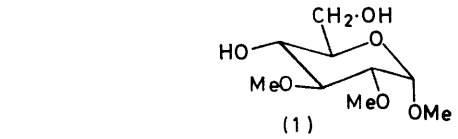
The stereochemistry of displacement of 2-substituents from 1,3,2-dioxaphosphorinan-2-ones, 1,3,2-oxathiaphosphorinan-2-ones, and 1,3,2-dioxaphosphorinan-2-thiones has been shown to depend on the nature of both the entering and the leaving group. Inversion of configuration has been observed for reactions involving good leaving groups and weak nucleophiles whereas with less good leaving groups and stronger nucleophiles the displacement reactions proceed with retention of configuration.

It has usually been assumed by analogy with acyclic systems, and evidence has been provided, that the normal stereochemical course of displacement of chloride from 2-chloro-1,3,2-dioxaphosphorinan-2-ones involves inversion of configuration [2-4] and that special reasons must be invoked in cases where retention of configuration is observed.[5] However, in recent reports [6,7] it is demonstrated that inversion and retention of configuration both occur and that the stereochemical courses of the displacement reactions are finely balanced, depending not only on the nature of the nucleophile but also on the nature of the leaving group. One possible explanation of these results is that whereas in some instances the transition intermediate approaches a trigonal bipyramid in which the entering and leaving groups occupy apical positions, in others the six-membered ring spans apical–basal positions and initial attack on phosphorus occurs in the apical position *trans* to the ring oxygen. In this latter case the leaving group leaves with retention of configuration either from a basal position, or from an apical position following pseudorotation. Other explanations are possible.[6] In view of the possible mechanistic implications of the effect of a six-membered ring on the stereochemistry of nucleophilic displacement reactions at phosphorus, we have studied the displacement of groups such as Cl, F, *p*-$O_2N{\cdot}C_6H_4{\cdot}O$, and SR from 2-oxo- and 2-thioxo-1,3,2-dioxaphosphorinans and 1,3,2-oxathiaphosphorinan-2-ones which form part of a *trans*-fused bicyclic system.

The phosphorochloridate (2) was prepared from the diol (1) and phosphoryl chloride. After purification over silica and crystallisation from di-isopropyl ether, the phosphorochloridate (2) could be stored at room temperature for about 1 month before decomposition was observable. Its n.m.r. spectrum was consistent with the presence of only one isomer. On the basis of the known preference [7] for an axial orientation of electronegative substituents in 1,3,2-dioxaphosphorinan-2-ones, and because of the stereochemistry of the preponderant products of those reactions of (2) which appear always to proceed with inversion of configuration at phosphorus (*e.g.* reaction with amines [4,6]), it is reasonable to assume that the chlorine atom in (2) is axially oriented.

Treatment of (2) with a variety of nucleophiles usually resulted in the formation of pairs of compounds which



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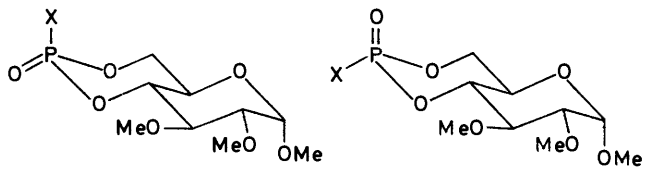


(2) X = Cl
(3*ax*) X = OEt
(4*ax*) X = NMe_2
(5*ax*) X = SPr
(6*ax*) X = *p*-$O_2N{\cdot}C_6H_4{\cdot}O$
(7*ax*) X = Me
(8) X = F

(3*eq*) X = OEt
(4*eq*) X = NMe_2
(5*eq*) X = SPr
(6*eq*) X = *p*-$O_2N{\cdot}C_6H_4{\cdot}O$
(7*eq*) X = Me

were isomeric at phosphorus, with one isomer preponderating. The configurations at phosphorus in these compounds were assigned on the basis that in any epimeric pair the isomer with the axial substituent on phosphorus displays a P=O i.r. stretching band at higher wavenumber and has a ^{31}P n.m.r. chemical shift at higher field than the isomer with the equatorial substituent on phosphorus [1,8] (see Experimental section). The results of the displacement reactions are summarised in the Table. In ethanol or ethanol–triethylamine reaction with inversion of configuration occurred, and (2) afforded preponderantly (3*eq*). Other reactions of (2) which proceeded preponderantly with inversion of configuration were with dimethylamine, sodium nitrophenoxide (1 mol. equiv.), and sodium propanethiolate from which (4*eq*), (6*eq*), and (5*eq*), respectively, were obtained. It has also been shown previously

[1] Part II, D. B. Cooper, J. M. Harrison, T. D. Inch, and G. J. Lewis, preceding paper.
[2] T. R. Fukoto and R. L. Metcalf, *J. Medicin. Chem.*, 1965, **8**, 759.
[3] W. Stec and A. Lopusinski, *Tetrahedron*, 1973, **29**, 547.
[4] W. Stec and M. Mikolajcyzk, *Tetrahedron*, 1973, **29**, 539.
[5] T. D. Inch and G. J. Lewis, *Tetrahedron Letters*, 1973, 2187.
[6] W. S. Wadsworth, S. Larsen, and H. L. Horten, *J. Org. Chem.*, 1973, **38**, 256.
[7] C. L. Bodkin and P. Simpson, *J.C.S. Perkin II*, 1973, 676.
[8] D. B. Cooper, T. D. Inch, and G. J. Lewis, *J.C.S. Perkin I*, 1974, 1043.

that displacements of Cl from 1,3,2-dioxaphosphorinan-2-ones by sodium thiolates and nitrophenoxide proceed with inversion of configuration.[6]

In contrast to the foregoing reactions, treatment of (2) with sodium ethoxide in ethanol afforded preponderantly (3*ax*), *i.e.* the reaction proceeded preponderantly with retention of configuration. [No equilibration, (3*ax*) ⇌ (3*eq*), occurred under the reaction conditions used and, when (3*ax*) and (3*eq*) were treated with an excess of sodium ethoxide, ring opening was observed.] Similarly, treatment of (2) with methylmagnesium iodide afforded mainly (7*ax*).

Retention of configuration was observed when both propylthio-isomers (5*ax* and *eq*) and both nitrophenoxy-isomers (6*ax* and *eq*) were treated with sodium ethoxide in ethanol, showing that the stereochemistry of the reaction is independent of the initial stereochemistry. These latter effects probably preclude the conformational argument that was used to explain why the reaction of (2) with methylmagnesium iodide proceeded with preponderant retention of configuration.[5]

The phosphorofluoridate (8) was prepared by treatment of (2) with antimony trifluoride. Only one isomer of (8) was detected irrespective of reaction times or whether a large excess of antimony trifluoride was used. It was therefore concluded that (8) was the isomer in which fluorine was oriented axially. The phosphorofluoridate (8) was also prepared when (1) was treated with dimethylamidophosphoric difluoride in dichloromethane in the presence of triethylamine. (It has been shown previously that dimethylamidophosphoric difluorides react with alcohols under weak basic conditions with initial cleavage of the P–N bond.[9] Evidence to support this observation has been obtained in this laboratory.) In the presence of strong base a mixture of (4*ax*) and (4*eq*) was formed from (1) and dimethylamidophosphoric difluoride. Treatment of (8) with methylmagnesium iodide in boiling benzene–ether gave preponderantly (7*ax*) but yields were very low. With sodium ethoxide in ethanol the preponderant reaction of (8) also occurred with retention of configuration. In contrast to (2), however, which underwent triethylamine-promoted ethanolysis with preponderant inversion of configuration, (8) reacted with preponderant retention of configuration under similar conditions. Although with methylamine (8), like (2), gave (4*eq*) (*i.e.* inversion of configuration) as the major product, the degree of stereoselectivity was low. It is of interest that in the presence of a trace of alcohol, alcoholysis preceded aminolysis when (8) was treated with dimethylamine. In contrast, (2) underwent aminolysis in preference to alcoholysis even when treated with 1 equiv. of dimethylamine in the presence of ethanol.

Nucleophilic displacement reactions on 1,3,2-dioxaphosphorinan-2-ones

Compound	Leaving group	Nucleophile	Products (%) Inversion	Retention
(2)	Cl	EtOH	(3*eq*) (93)	(3*ax*) (4)
(2)	Cl	EtOH–Et_3N	(3*eq*) (81)	(3*ax*) (trace)
(2)	Cl	EtOH–EtONa	(3*eq*) (42)	(3*ax*) (54)
(2)	Cl	Me_2NH–PhH	(4*eq*) (87)	(4*ax*) (8·7)
(2)	Cl	PrSNa–PhH	(5*eq*) (47)	(5*ax*) (4·4)
(2)	Cl	*p*-$O_2N{\cdot}C_6H_4{\cdot}ONa$ (1 mol. equiv)	(6*eq*) (60)	(6*ax*) (trace)
(2)	Cl	*p*-$O_2N{\cdot}C_6H_4{\cdot}ONa$ (3 mol. equiv.) in MeCN	(6*eq*) (trace)	(6*ax*) (75)
(2)	Cl	MeMgI–Et_2O–PhH	(7*eq*) (6·4)	(7*ax*) (32)
(5*ax*)	SPr	EtOH–NaOEt	(3*eq*) (trace)	(3*ax*) (77)
(5*eq*)	SPr	EtOH–NaOEt	(3*ax*) (trace)	(3*eq*) (67)
(6*ax*)	*p*-$O_2N{\cdot}C_6H_4{\cdot}O$	EtOH–NaOEt	(3*eq*) (trace)	(3*ax*) (88)
(6*eq*)	*p*-$O_2N{\cdot}C_6H_4{\cdot}O$	EtOH–NaOEt	(3*ax*) (15)	(3*eq*) (75)
(8)	F	MeMgI–Et_2O–PhH	(7*eq*) (3·5)	(7*ax*) (14)
(8)	F	EtOH–NaOEt	(3*ax*) (16)	(3*ax*) (46)
(8)	F	Me_2NH–PhH	(4*eq*) (53)	(4*ax*) (30)
(4*ax*)	Me_2N	EtOH–H^+	(3*eq*) (>95)	
(4*eq*)	Me_2N	EtOH–H^+	(3*ax*) (>95)	

These results substantiate the fact that oxygen nucleophiles promote P–F cleavage more readily than nitrogen nucleophiles, whereas the reverse is true for P–Cl cleavage.[10]

Acid-catalysed ethanolysis of (4*ax*) and (4*eq*) proceeded with inversion of configuration, affording (3*eq*) and (3*ax*), respectively. This result is to be expected because of the good leaving group ability conferred on the NMe_2 group by protonation. No isomerisation of (4*ax*) to (4*eq*) was observed, in contrast to a preliminary observation [11] which appeared to indicate that under acidic conditions equatorial P–NMe_2 groups epimerise to axial P–NMe_2 groups.

In addition to the foregoing studies in the 1,3,2-dioxaphosphorinan-2-one series, some experiments were also performed on the 1,3,2-oxathiaphosphorinan-2-one system.

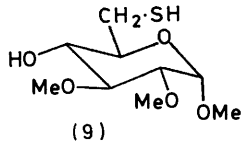
The chloridate (10), was prepared from (9) [1] and phosphoryl chloride, and was a highly crystalline solid which was chromatographically and spectroscopically homogeneous. On treatment with dimethylamine in

[9] BIOS Final Report No. 714, 'The Development of New Insecticides and Chemical Warfare Agents,' H. M. Stationery Office, London, 1947, p. 86.

[10] R. Greenhalgh, R. M. Heggie, and M. A. Weinberger, *Canad. J. Chem.*, 1970, **48**, 1351; R. F. Hudson and R. Greenhalgh, *J. Chem. Soc.* (*B*), 1969, 325.

[11] J. A. Mosbo and J. G. Verkade, *J. Amer. Chem. Soc.*, 1972, **94**, 8224.

benzene, (10) afforded (11) as essentially the only isomer. The dimethylamino-substituent was assigned the equatorial orientation in (11) because on treatment with



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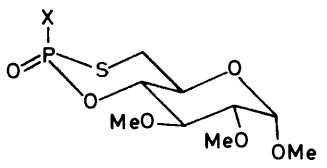
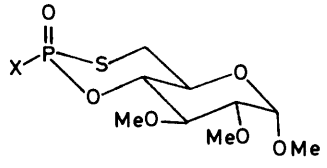


(10) X = Cl
(12*ax*) X = OEt
(13*ax*) X = *p*-$O_2N{\cdot}C_6H_4{\cdot}O$
(14*ax*) X = Me



(11) X = Me_2N
(12*eq*) X = OEt
(13*eq*) X = *p*-$O_2N{\cdot}C_6H_4{\cdot}O$
(14*eq*) X = Me

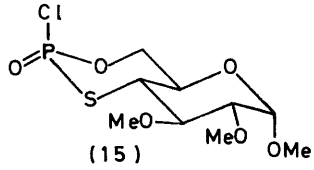
ethanolic hydrogen chloride (11) underwent conversion into (12*ax*), a reaction expected to proceed with inversion of configuration. Further, the n.m.r. spectrum of (11) showed strong similarities to the spectrum of (14*eq*),[1] showing characteristic deshielding (by the 2,4-diaxial interaction with P=O) of H-4, and no similarity to the spectrum of (14*ax*).

On treatment with warm ethanol (10) afforded only (12*eq*), whereas with ethanol–triethylamine or with 1 equiv. of sodium ethoxide in ethanol (12*ax*) was the only product. On the reasonable assumption, based on previous work described in this paper and elsewhere, that phosphorochloridates react with dimethylamine and with ethanol alone with inversion of configuration, it is clear that in (10) the chlorine atom is situated axially and that with sodium ethoxide displacement of chlorine occurred with retention of configuration.

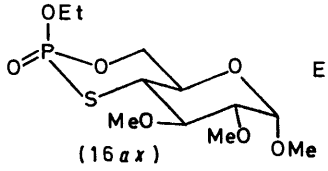
The reaction of (10) with sodium nitrophenoxide paralleled that of (2) in that with 1 equiv. of nitrophenoxide inversion of configuration occurred to afford (13*eq*); with an excess of nitrophenoxide (13*ax*) was the final product.

The chloridates (15) and (17) underwent reactions with ethanol alone with preponderant inversion of configuration affording (16*eq*) and (18*eq*), respectively. As with the chloridates (2) and (10), the chloridates (15) and (17) were converted with preponderant retention of configuration into the ethoxy-derivatives (16*ax*) and (18*ax*), respectively, when treated with sodium ethoxide in ethanol. The precise nature of the six-membered ring system therefore appears to have little influence on the stereochemistry of the displacement reactions.

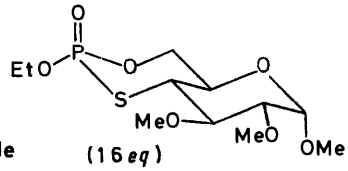
In displacement reactions at phosphorus in 1,3,2-dioxaphosphorinan-2-ones and related compounds, two types of trigonal bipyramid intermediate may be envisaged. In one instance, the entering and leaving groups occupy apical positions and the six-membered ring spans basal positions. Reactions *via* such an intermediate take place with inversion of configuration and it is this type of intermediate which is usually invoked for displacements of halogen by ethanol and by amines from 1,3,2-dioxaphosphorinans. In the second instance the incoming nucleophile and a ring oxygen atom occupy apical positions and the six-membered ring spans basal and apical positions. In this case the leaving group departs directly from a basal position or from an apical position following pseudorotation, and retention of configuration is observed. If the first type of intermediate is formed easily it is difficult to envisage why all displacement reactions of exocyclic substituents at phosphorus in 1,3,2-dioxaphorinans do not proceed with inversion of configuration. However, although it has been demonstrated that in pentaco-ordinate phosphorus compounds, six-membered rings can span basal–basal or basal–apical positions [12] it is possible that in pentaco-ordinate intermediates the basal–basal ring is energetically much less favoured than the basal–apical ring and consequently that trigonal bipyramids of the latter type will be preferred. Accordingly, and because reactions with inversion



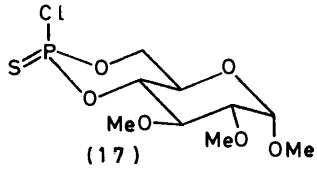
(15)



(16*ax*)



(16*eq*)



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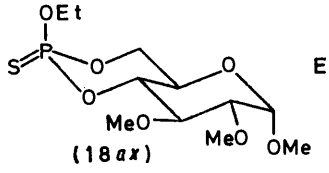
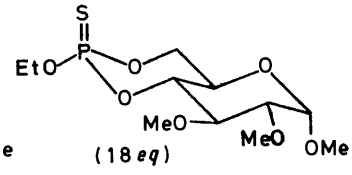


(18*ax*)



(18*eq*)

of configuration are observed only when good leaving groups and poor nucleophiles are involved, it is reasonable to suggest that in such reactions that proceed with inversion of configuration, bond breakage precedes bond

[12] B. C. Chang, W. E. Conrad, D. B. Denney, D. Z. Denney, R. Edelman, R. L. Powell, and D. W. White, *J. Amer. Chem. Soc.*, 1971, **93**, 4004.

formation, and that a formal trigonal bipyramid intermediate is not formed. A trigonal bipyramid intermediate need be invoked *only* for those reactions which take place with retention of configuration.

Other explanations have been proposed recently to account for the effects of solvents and added salts on the stereochemistry of similar displacement reactions.[13]

EXPERIMENTAL

The general experimental procedures used have been described elsewhere.[8]

Methyl 2,3-Di-O-methyl-α-D-glucopyranoside (S)-4,6-Phosphorochloridate (2).—A solution of phosphoryl chloride (2·2 g) in ether was added dropwise to a solution of methyl 2,3-di-*O*-methyl-α-D-glucopyranoside (1) (3 g) and triethylamine (2·8 g) in ether The reaction, monitored by t.l.c. in benzene–acetone (7 : 4) [R_F values: (1) 0·2; (2) 0·7] was complete after 30 min. The mixture was filtered, the residue was washed with chloroform, and the filtrate and washings were concentrated. The product, after chromatography over silica in benzene–acetone (7 : 3), was crystallised from di-isopropyl ether to afford pure *phosphorochloridate* (2) (2·4 g, 59%), m.p. 127—129°, $[\alpha]_D$ +114·5° (*c* 1·8) (Found: C, 35·6; H, 5·3. $C_9H_{16}ClO_7P$ requires C, 35·7; H, 5·3%).

Nucleophilic Displacement Reactions of the Phosphorochloridate (2).—(i) *With ethanol.* A solution of (2) (0·25 g) in ethanol (10 ml) was stored at room temperature for 5 h, then concentrated, and (3*ax*) (0·01 g, 4%) and (3*eq*) (0·24 g, 93%) were separated as described previously.[8]

(ii) *With ethanol containing triethylamine.* A solution of (2) (0·25 g) in ethanol (10 ml) and triethylamine (0·3 ml) was stored at room temperature for 3 h. The ethoxy-compounds (3*ax*) (trace) and (3*eq*) (0·21 g, 81%) were isolated.

(iii) *With ethanolic sodium ethoxide.* A solution of (2) (0·25 g) and sodium ethoxide (0·06 g) in ethanol (10 ml) was stored at room temperature for 1 h, neutralised with carbon dioxide, and concentrated; compounds (3*ax*) (0·14 g, 54%) and (3*eq*) (0·11 g, 42%) were separated chromatographically.

(iv) *With dimethylamine.* Treatment of (2) (0·5 g) with an excess of dimethylamine in benzene resulted in the immediate disappearance of (2) (t.l.c. in benzene–acetone, 2 : 1). The solution was concentrated and the product crystallised from di-isopropyl ether to afford *methyl 2,3-di-O-methyl-α-D-glucopyranoside (S)-4,6-dimethylphosphoramidate* (4*eq*) (0·45 g, 87%), m.p. 145—147°, $[\alpha]_D$ +105° (*c* 1·6), $\nu_{P=O}$ 1250 (KBr) or 1240 ($CDCl_3$) cm^{-1} (Found: C, 42·7; H, 7·1; N, 4·5. $C_{11}H_{22}NO_7P$ requires C, 42·3; H, 7·1; N, 4·5%), δ_H 2·76 (NMe_2, J_{P-N-CH_3} 10 Hz). The mother liquors were concentrated and residual (4*eq*) (R_F 0·16) was separated from (4*ax*) (R_F 0·13) over silica in benzene–ethanol (9 : 1). After crystallisation from di-isopropyl ether, *methyl 2,3-di-O-methyl-α-D-glucopyranoside* (R)-4,6-*dimethylphosphoramidate* (4*ax*) (0·045 g, 8·7%) had m.p. 105—110°, $[\alpha]_D$ +83° (*c* 1·1), $\nu_{P=O}$, 1263 (KBr) or 1252 ($CDCl_3$) cm^{-1} (Found: C, 42·4; H, 7·1; N, 4·4%), δ_H 2·75 (NMe_2, J_{P-N-CH_3} 11·3 Hz).

(v) *With sodium propane-1-thiolate.* A solution of (2) (3 g) and sodium propanethiolate (2 g) in benzene was stored at room temperature for 30 min; no (2) then remained (t.l.c. in benzene–acetone, 7 : 2). The solution was separated from the sodium salts by decantation and concentrated, and the residue was separated over silica in benzene–acetone (7 : 2) to afford the propyl thiophosphates (5*ax*) (0·15 g, 4·4%), $[\alpha]_D$ +29° (*c* 0·5), R_F 0·4, $\nu_{P=O}$ (CCl_4) 1285 cm^{-1}, δ (^{31}P) −24 p.p.m.; and (5*eq*) (1·6 g, 47%), $[\alpha]_D$ +53° (*c* 2), R_F 0·35, $\nu_{P=O}$ (CCl_4) 1255 cm^{-1}, δ (^{31}P) −29·2 p.p.m.

(vi) *With methylmagnesium iodide.* A solution of (2) (1 g) and methylmagnesium iodide (1·3 equiv.) in benzene–ether was boiled under reflux for 2 h. The products (7*eq*) (0·06 g, 6·4%) and (7*ax*) (0·3 g, 32%) were separated as described previously.[8]

(vii) *With 1 equiv. of sodium p-nitrophenoxide.* A solution of (2) (0·5 g) and sodium nitrophenoxide (0·32 g) in acetonitrile was stored overnight at room temperature. The solution was diluted with chloroform, washed with water, dried, and concentrated. The major product (R_F 0·45 in benzene–acetone, 7 : 1) was purified over silica and crystallised from di-isopropyl ether to afford methyl 2,3-di-*O*-methyl-α-D-glucopyranoside (*S*)-4,6-(*p*-nitrophenyl phosphate) (6*eq*) (0·4 g, 60%), m.p. 112—115°, $[\alpha]_D$ +43° (*c* 1·1), $\nu_{P=O}$ (KBr) 1287 cm^{-1}.

(viii) *With an excess of sodium p-nitrophenoxide.* A solution of (2) (0·5 g) and sodium nitrophenoxide (0·8 g) in acetonitrile was stirred at room temperature overnight. The major product (R_F 0·5 in benzene–acetone, 7 : 1) was isolated as in (vii) to afford the (*R*)-4,6-(*p*-nitrophenyl phosphate) (6*ax*) (0·5 g, 75%), m.p. 91—93°, $[\alpha]_D$ +80° (*c* 1·3), $\nu_{P=O}$ (KBr) 1295 cm^{-1}.

Treatment of the Propyl Thiophosphates (5) *with Sodium Ethoxide.*—(i) A solution of (5*eq*) (0·1 g) in ethanol containing a catalytic quantity of sodium ethoxide was stored at room temperature for 15 min, neutralised with carbon dioxide, concentrated, and chromatographed over silica in benzene–acetone (7 : 3) to afford (3*eq*) (0·6 g, 67%) and a trace of (3*ax*).

(ii) Similar treatment of (5*ax*) (0·1 g) afforded (3*ax*) (0·7 g, 77%) and plus a trace of (3*eq*).

Treatment of the Nitrophenyl Phosphates (6) *with Sodium Ethoxide.*—(i) A solution of (6*ax*) (0·1 g) in ethanol (5 ml) containing sodium ethoxide (0·03 g) was stored at room temperature for 1 h, diluted with chloroform, washed with water, dried, and concentrated. The ethyl phosphates (3*ax*) (0·62 g, 88%) and (3*eq*) (trace) were separated over silica in the usual way.

(ii) Similar treatment of (6*eq*) afforded (3*ax*) (0·012 g, 15%) and (3*eq*) (0·055 g, 75%).

Methyl 2,3-Di-O-methyl-α-D-glucopyranoside (S)-4,6-*Phosphorofluoridate* (8).—(*a*) A solution of (1) (5 g), triethylamine (10 ml), and dimethylamidophosphoric difluoride (2·5 g) in dichloromethane (50 ml) was stored at room temperature for 6 h, washed with water, dried, and concentrated. The residue was chromatographed over silica in benzene–acetone (7 : 3) to afford as the major product the (S)-*phosphorofluoridate* (8), R_F 0·8 (3 g, 47%), m.p. 126° (from di-isopropyl ether), $[\alpha]_D$ +88° (*c* 1·3 in $CHCl_3$) (Found: C, 38·0; H, 5·7. $C_9H_{16}FO_7P$ requires C, 37·8; H, 5·6%). No trace of methyl 2,3-di-*O*-methyl-α-D-glucopyranoside 4,6-dimethylamidophosphates (4) were detected, although spectroscopic indications of methyl 2,3-di-*O*-methyl-α-D-glucopyranoside 4- or 6-dimethylamidophosphorofluoridates were obtained.

(*b*) A mixture of (2) (3 g), antimony trifluoride (7 g), and a few drops of antimony pentachloride in benzene

[13] W. S. Wadsworth, jun., *J. Org. Chem.*, 1973, **38**, 2921.

(50 ml) was boiled under reflux for 24 h. The conversion of the chloridate (2) into the fluoridate (8) was monitored by double development of microchromatoplates in benzene–acetone (7 : 1) [(2), R_F 0·8; (8), R_F 0·75]. The solution was filtered, diluted with chloroform, washed with dilute aqueous sodium hydrogen carbonate, dried, and concentrated. After purification over silica in benzene–acetone (7 : 3), compound (8) (2 g, 70%) was recrystallised from di-isopropyl ether and was spectroscopically indistinguishable from the sample obtained in (*a*). Different samples prepared by either procedure (*a*) or (*b*) sometimes showed variation in m.p. from 95 to 125°. However, all samples had similar spectroscopic properties.

Nucleophilic Displacement Reactions of the Phosphorofluoridate (8).—(i) *With methylmagnesium iodide.* Treatment of (8) (0·3 g) with methylmagnesium iodide (0·3 g) in boiling ether–benzene for 5 h followed by conventional processing afforded unchanged (8) (0·02 g), (7*eq*) (0·01 g, 3·5%), and (7*ax*) (0·04 g, 14%).

(ii) *With sodium ethoxide.* The ethyl phosphates (3*ax*) (0·06 g, 46%) and (3*eq*) (0·02 g, 16%) were isolated from a solution of (8) (0·12 g) and sodium ethoxide (0·04 g) in ethanol stored for 1 h at room temperature.

(iii) A solution of (8) (0·12 g) and an excess of methylamine in ethanol-free dichloromethane was stored at room temperature overnight. The solution was concentrated and (4*eq*) (0·07 g, 53%) and (4*ax*) (0·04 g, 30%) were separated over silica in benzene–ethanol (20 : 1).

Methyl 2,3-*Di*-O-*methyl*-6-*thio*-α-D-*glucopyranoside* (S)-4,6-*Phosphorochloridothioate* (10).—A solution of the 6-thioglucopyranoside (9) (1·4 g), phosphoryl chloride (1·2 g), and triethylamine (2 ml) in ether was stored at room temperature for 1 h, filtered, concentrated, and passed over silica in benzene–acetone (7 : 1). The first major product eluted was the *phosphorochloridothioate* (10) (1·1 g, 59%), m.p. 129—131° (from di-isopropyl ether), $[\alpha]_D$ +206° (*c* 1·7) (Found: C, 34·3; H, 4·9. $C_9H_{16}ClO_6PS$ requires C, 33·9; H, 5·0%).

Nucleophilic Displacement Reactions of the Phosphorochloridothioate (10).—(i) *With dimethylamine.* A solution of the chloridate (10) (0·2 g) and an excess of dimethylamine in benzene was stored at room temperature for 10 min, diluted with chloroform, washed with water, dried, and concentrated, to give *methyl* 2,3-*di*-O-*methyl*-6-*thio*-α-D-*glucopyranoside* (S)-4,6-*phosphoramidothioate* (11) (0·18 g, 86%), m.p. 124° (from di-isopropyl ether), $[\alpha]_D$ +117° (*c* 0·9) (Found: C, 40·3; H, 6·8; N, 4·3. $C_{11}H_{22}NO_6PS$ requires C, 40·4; H, 6·7; N, 4·3%).

(ii) *With ethanol.* A solution of (10) (0·1 g) in ethanol was boiled under reflux for 5 h, and concentrated to afford (12*eq*) (0·08 g, 78%).

(iii) *With ethanolic sodium ethoxide.* A solution of (10) (0·16 g) and sodium ethoxide (1 mol. equiv.) in ethanol (10 ml.) was stored at room temperature for 1 h, neutralised with carbon dioxide, concentrated, and chromatographed over silica in benzene–acetone (7 : 1) to afford (12*ax*) [1] (0·1 g, 60%). With an excess of sodium ethoxide ring opening occurred.[13]

(iv) *With sodium* p-*nitrophenoxide.* (a) 1 *mol. equiv.* A solution of (10) (0·2 g) and sodium nitrophenoxide (1 mol. equiv.) in acetonitrile was stirred at room temperature for 3 h, diluted with chloroform, washed with water, and chromatographed over silica in benzene–acetone (7 : 1) to afford (13*eq*) (0·15 g, 53%) as a chromatographically (R_F 0·5 in benzene–acetone, 7 : 1) homogeneous syrup, $[\alpha]_D$ +45° (*c* 0·7), $\nu_{P=O}$ ($CDCl_3$) 1262 cm^{-1}.

(b) 3 *mol. equiv.* A solution of (10) (0·25 g) and sodium nitrophenoxide (3 mol. equiv.) in acetonitrile was stirred at room temperature for 4 h, diluted with chloroform, washed with water, dried, and concentrated. The residue crystallised (m.p. 165—168°) from di-isopropyl ether to give (13*ax*) (0·27 g, 77%), $[\alpha]_D$ +23° (*c* 1·1), R_F 0·6 in benzene–acetone (7 : 1), $\nu_{P=O}$ ($CDCl_3$) 1275 cm^{-1}.

Conversion of the Phosphoramide (11) *into the Ethyl Phosphate* (12*ax*).—A solution of (11) (0·1 g) in ethanolic hydrogen chloride was stored at room temperature for 24 h. The only product isolated was (12*ax*) (0·05 g).

Methyl 2,3-*Di*-O-*methyl*-4-*thio*-α-D-*glucopyranoside* (R)-4,6-*Phosphorochloridothioate* (15).—A solution of methyl 2,3-di-*O*-methyl-4-thio-α-D-glucopyranoside (1 g), and triethylamine (1 g) in dry ether (20 ml) was treated dropwise with a solution of phosphoryl chloride (0·65 g) in ether (5 ml) and stored overnight at room temperature. The solution was washed with water, dried, and concentrated and the residue passed over silica in benzene–ether (1 : 1) to afford the *chloridate* (15) (0·17 g, 12%), m.p. 127° (from di-isopropyl ether) $[\alpha]_D$ +41° (*c* 0·4) (Found: C, 34·2; H, 4·9. $C_9H_{16}ClO_6PS$ requires C, 33·9; H, 5·1%).

A solution of (15) (0·07 g) in ethanol containing sodium ethoxide (1 equiv.), worked up in the usual way, afforded (16*ax*) (0·02 g, 28%) after chromatography over silica in benzene–ether (1 : 1).

A solution of (15), boiled under reflux in ethanol afforded only (16*eq*).

Methyl 2,3-*Di*-O-*methyl*-α-D-*glucopyranoside* (S)-4,6-*Phosphorochloridothioate* (17).—A solution of (1) (2·2 g), thiophosphoryl chloride (1·9 g), and triethylamine (2·5 g) in benzene (30 ml) was boiled under reflux for 2 h, cooled, poured onto silica, and eluted with ethyl acetate–light petroleum (1 : 1), to afford the *product* (17) (2·7 g, 84%), m.p. 71—74° (from ether–light petroleum), $[\alpha]_D$ +96° (*c* 0·8) (Found: C, 34·4; H, 5·0. $C_9H_{16}ClO_6PS$ requires C, 34·4; H, 5·2%).

Nucleophilic Displacement Reactions of the Chloridate (17).—(i) *With ethanol.* A solution of (17) (0·3 g) in ethanol (10 ml) was boiled under reflux for 5 h, cooled, neutralised with sodium hydrogencarbonate, diluted with chloroform, washed with water, dried, and concentrated to afford (18*eq*) [1] (0·25 g, 81%), m.p. 81—82° (from cyclohexane–ethyl acetate).

(ii) *With sodium ethoxide in ethanol.* A solution of (17) (0·3 g) in ethanol (10 ml) containing sodium ethoxide (1 mol. equiv.) was stored at room temperature for 15 min. Further sodium ethoxide (0·04 g) was added and the solution was neutralised and processed as in (i). Chromatography in ethyl acetate–light petroleum (2 : 3) afforded (18*eq*) (0·095 g, 31%), m.p. 81—82° and (18*ax*) [1] (0·2 g, 65%), m.p. 140—141° (from light petroleum–ethyl acetate).

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