Use of Carbohydrate Derivatives for Studies of Phosphorus Stereochemistry. Part IV.[1] Ring-opening Reactions of 1,3,2-Dioxaphosphorinan-2-ones and Related Compounds with Grignard Reagents and with Sodium Methoxide

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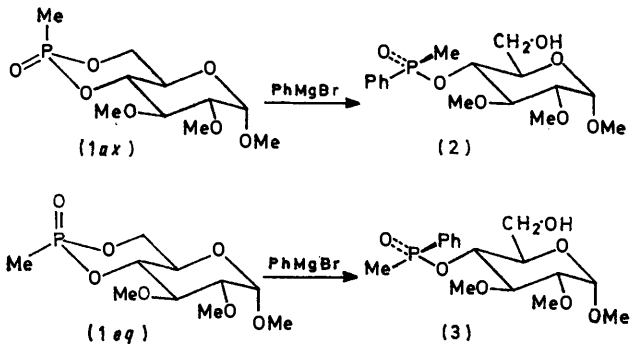
The 1,3,2-dioxaphosphorinan-2-one ring in methyl 2,3-di-*O*-methyl-α-D-glucopyranoside (*R*)- and (*S*)-4,6-alkyl-(or aryl-)phosphonates is opened by Grignard reagents by attack at phosphorus with inversion of configuration and with preponderant cleavage of the bond between phosphorus and O-6 of the glucopyranoside unit. By contrast, in the corresponding 1,3,2-dioxaphosphorinan-2-thiones the stereochemistry at phosphorus and the nature of the *P*-substituent determines whether the P–O(4) or the P–O(6) bond is cleaved preponderantly and whether the cleavage occurs with inversion or retention of configuration. Ring opening of the foregoing dioxaphosphorinans with sodium methoxide results first in the preponderant formation of glucopyranoside 4-[methyl alkyl-(or aryl-)phosphonates (phosphonothioates)]. Migration of the *P*-substituent from O-4 to O-6 then occurs. The stereochemistry of the ring-opening and migration reactions is discussed. The stereochemistry of the ring-opening reaction, with Grignard reagents, of the 1,3,2-oxathiaphosphorinan ring in methyl 2,3-*O*-methyl-6-thio-α-D-glucopyranoside (*S*)- and (*R*)-4,6-methylphosphonothioates and the corresponding ethyl phosphorothioates is also described. The 2-methyl-1,3,2-oxathiaphosphorinan-2-ones with sodium methoxide in methanol undergo P–O bond fission with inversion of configuration, in contrast to the corresponding 2-ethoxy-derivatives which undergo P–S cleavage with probable retention of configuration at phosphorus. On storage in methanol containing sodium methoxide methyl 2,3-di-*O*-methyl-6-thio-α-D-glucopyranoside 6-(methyl methylphosphonothioate) is converted with preponderant inversion of configuration into the corresponding 4-(methyl methylphosphonates).

It has been demonstrated that optically active phosphine oxides are formed from carbohydrate 1,3,2-dioxaphosphorinan-2-ones by a process in which the 1,3,2-dioxaphosphorinan-2-one ring is opened selectively by one Grignard reagent and the carbohydrate–phosphorus linkage is then cleaved by a second Grignard reagent.[2] In principle it should be possible to use similar procedures, in which an optically active phosphorus centre is created within a carbohydrate framework and then detached from that framework, as a general method for the synthesis of optically pure phosphorus derivatives. In practice the general utility of this type of process will depend on the stereochemical homogeneity and predictability of the reactions involved. In this paper studies of ring-opening reactions of 1,3,2-dioxaphosphorinan-2-ones, 1,3,2-dioxaphosphorinan-2-thiones, and 1,3,2-oxathiaphosphorinan-2-ones are described.



Scheme 1

Grignard Reagent–2-Methyl-1,3,2-dioxaphosphorinan-2-one Reactions.—It has been demonstrated[2] that the derivatives (1*ax*) and (1*eq*) (Scheme 1) undergo ring opening by Grignard reagents with preponderant if not exclusive cleavage of the P–O(6) bond and that the reactions occur with inversion of configuration to afford the 4-methylphenylphosphinates † (2) and (3) respectively. With regard to subsequent configurational assignments of 4-phenylphosphonate derivatives from other ring-opening reactions it is noteworthy that the n.m.r. spectrum of (3) shows one of the methoxy-groups to be strongly shielded (δ 3·07) whereas in (2) and in other compounds where the phenyl group is absent the normal range for methoxy-groups is δ 3·41—3·66.

Grignard Reagent–2-Methyl(and 2-Phenyl)-1,3,2-dioxaphosphorinan-2-thione Reactions (*Scheme* 2).—The reaction of phenylmagnesium bromide with the 2-methyl-2-thioxo-derivatives (4*ax*) and (4*eq*) [3] followed a different course to the corresponding reactions of (1*ax*) and (1*eq*). Thus although (4*eq*) underwent preponderant P–O(6) cleavage with phenylmagnesium bromide (no other product was isolated), the reaction occurred with retention of configuration at phosphorus to afford the (*S*)-4-methylphenylphosphinate (6). Compound (6) was also formed as the minor product (32%) from (4*ax*) with inversion of configuration at phosphorus. However, the PhMgBr–(4*ax*) reaction afforded preponderantly (43%) the 6-methylphenylphosphinate. This reaction is represented in Scheme 2 as occurring with inversion of configuration although there is no unequivocal evidence for this.

The reactions of the 2-phenyl-2-thioxo-derivatives (7*ax*) and (7*eq*) with methylmagnesium iodide were similar to the corresponding reactions of (4*ax*) and (4*eq*) with phenylmagnesium bromide in that the

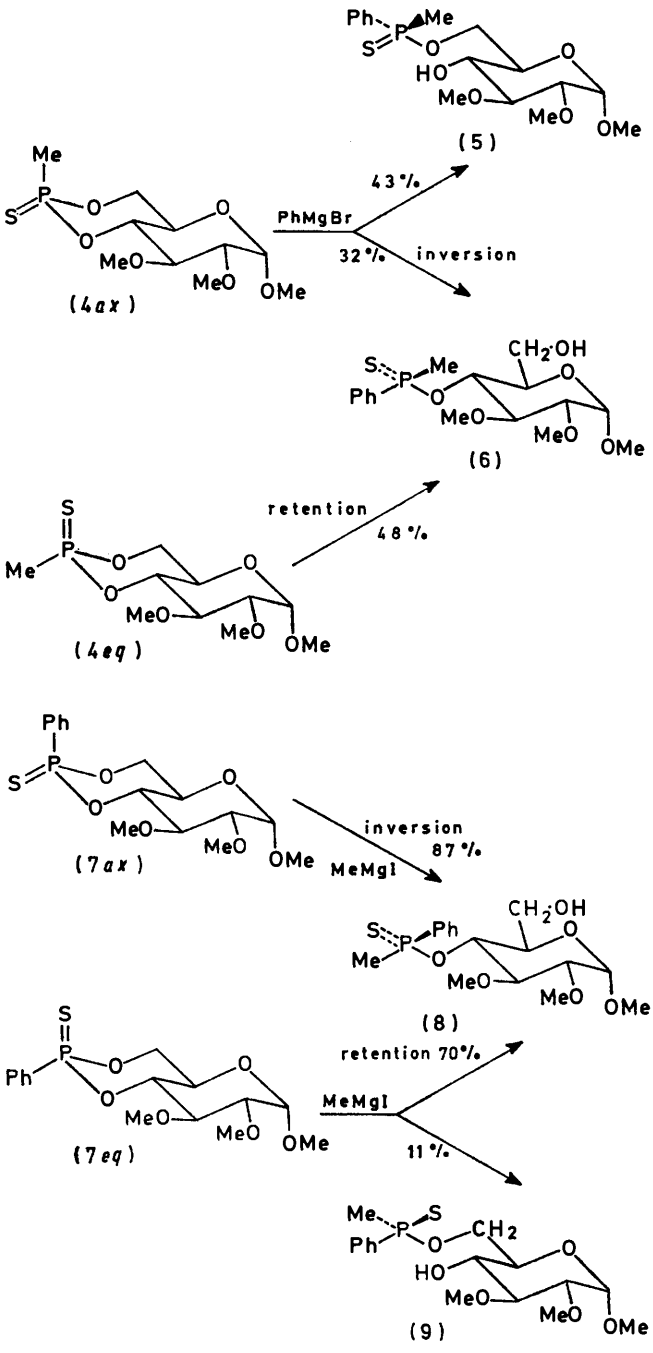
† *Nomenclature.* In this paper substituent numbers refer to the carbohydrate part of the molecule unless specific reference is made to the phosphorus-containing hereocycle.

[1] Part III, J. M. Harrison, T. D. Inch, and G. J. Lewis, preceding paper.

[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.

(*R*)-4-methylphenylphosphinate (8) was formed from (7*ax*) with inversion of configuration and from (7*eq*) with retention of configuration. However, whereas (8) was the only product from (7*ax*), the 6-methylphenylphosphinate (9) was also formed from (7*eq*).



SCHEME 2

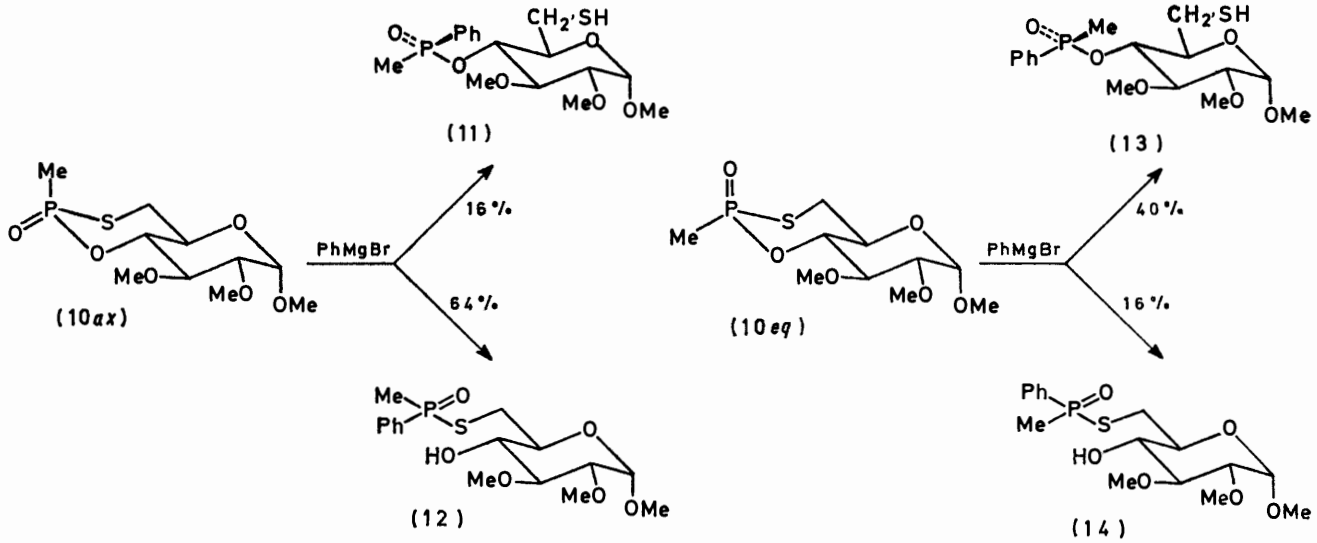
The direction of ring opening was evident from the n.m.r. spectra of the products. The 4-methylphenylphosphinates showed a clear one-proton pair of triplets for H-4 at δ 4·5—4·6 ($J_{3,4} = J_{4,5} = 9$—10, $J_{P,4}$ 15 Hz) whereas the 6-methylphenylphosphinates showed a complex two-proton multiplet for the 6-protons at 4·3—4·7. The assignment of stereochemistry to (6) and (8) follows from the observation that in the spectrum of (8) as in that of (3) one methoxy-resonance is at high field (δ 2·63) whereas in the spectrum of (6) as in that of (2) all the methoxy-resonances are in the same range (3·42—3·61).

Grignard Reagent–2-Methyl-1,3,2-oxathiaphosphorinan-2-one Reactions (*Scheme* 3).—Treatment of the oxathiaphosphorinan-2-one [3] (10*ax*) with phenylmagnesium bromide afforded the 4-*O*-substituted derivative (11) (16%) and the 6-*S*-substituted derivative (12) (64%). From the (10*eq*) [3]–Grignard reagent reaction however, the 4-methylphenylphosphinate (13) (40%) was the major product and the 6-methylphenylphosphinothioate (14) (16%) was the minor product. The direction of ring opening was apparent from the n.m.r. spectra of the products, (11) and (13) showing distinct SH and H-4 signals which were absent in the spectra of (12) and (14). No configurational assignments to (12) and (14) were possible but it is probable that the P–O(4) cleavage occurred with inversion of configuration at phosphorus. Compound (11) may be assigned the *R*-configuration at phosphorus by analogy with (3) and (8) since a high-field (δ 2·87) methoxy-signal (see Experimental section) was apparent which was lacking in the spectrum of (13). On this basis the P–S cleavage by phenylmagnesium bromide in both (10*ax*) and (10*eq*) occurred with retention of configuration. It has been shown [4] that acyclic phosphonothioates react with Grignard reagents with retention of configuration.

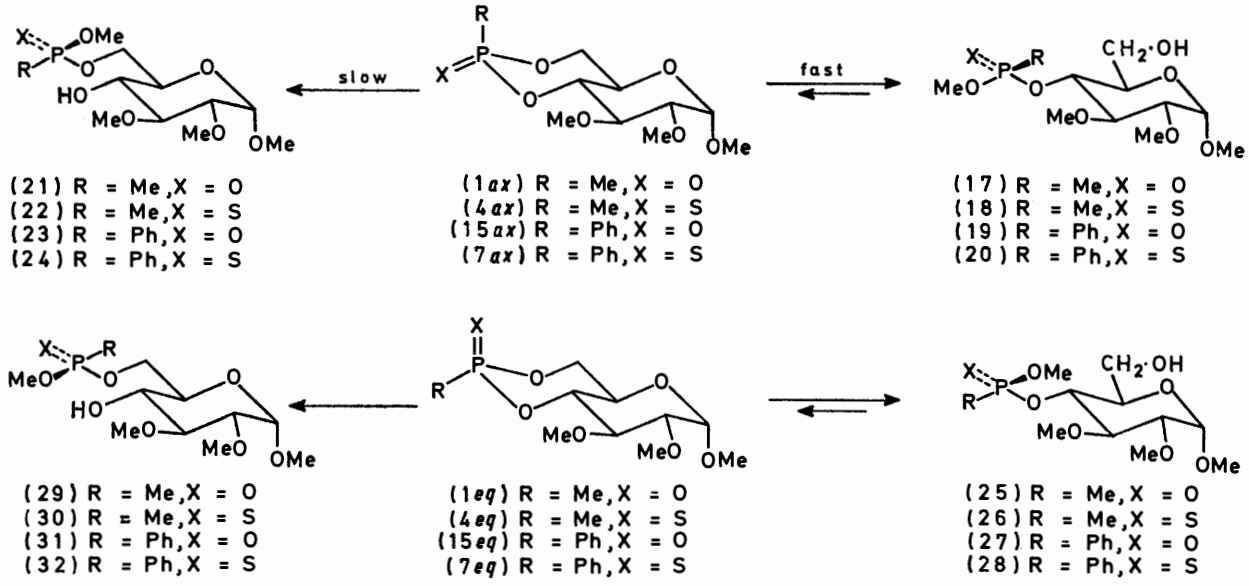
Sodium Methoxide–2-Alkyl(or Phenyl)-2-oxo(or thioxo)-1,3,2-dioxaphosphorinan Reactions (*Scheme* 4).—The 2-oxo(and thioxo)-1,3,2-dioxaphosphorinans carrying axial 2-substituents [(1*ax*), (4*ax*), (15*ax*), and (7*ax*)] and equatorial 2-substituents [(1*eq*), (4*eq*), (15*eq*), and (7*eq*)] were stored in methanol containing sodium methoxide at room temperature. The progress of the reactions was monitored by t.l.c. The axially substituted compounds reacted (*ca.* 2 h) to give initially the corresponding 4-substituted glucopyranose derivatives (17)—(20) and then on prolonged storage (18 h) at room temperature appreciable amounts of the 6-substituted derivatives (21)—(24) were formed. In contrast, the equatorially substituted compounds reacted more slowly and from the outset of the reactions both the 4-substituted (25)—(28) and the 6-substituted glucopyranose derivatives (29)—(32) were present. After storage overnight at room temperature only the 6-substituted derivatives were present.

As in the previously described 1,3,2-dioxaphosphorinan ring-opening reactions the direction of ring opening was clearly indicated by the absence or presence of the characteristic H-4 n.m.r. signal (Table 1). Further acetylation of the products with cold acetic anhydride–pyridine caused the expected downfield shifts of the

[4] J. Donohue, N. Mandel, W. B. Farnham, R. K. Murray, K. Mislow, and H. P. Benschap, *J. Amer. Chem. Soc.*, 1971, **93**, 3792.



SCHEME 3



SCHEME 4

TABLE 1

N.m.r. data of ring-opened products in Scheme 4

Compound	δ Values						J/Hz
	H-1	H-4	H-6	P·OMe	PMe	OMe	
(17)	4·90	4·21		3·77	1·60	3·45, 3·53, 3·60	$J_{3,4} = J_{4,5} = J_{P,4} = 9$—10
(18)	4·90	4·36		3·76	1·90	3·45, 3·52, 3·56	$J_{P,4}$ 13, $J_{3,4} = J_{4,5} = 9$—10
(19)	4·88	4·36		3·83		2·98, 3·46 (×2)	$J_{3,4} = J_{4,5} = J_{P,4} = 9$—10
(20)	4·88	4·55		3·78		2·71, 3·44 (×2)	$J_{P,4}$ 13, $J_{3,4} = J_{4,5} = 9$—10
(21)	4·86		4·2—4·6	3·75	1·51	3·42, 3·50, 3·60	
(22)	4·86		4·1—4·6	3·72	1·86	3·43, 3·51, 3·65	
(23)	4·83		4·1—4·6	3·78		3·39, 3·51, 3·65	
(24)							
(25)	4·87	4·38		3·83	1·53	3·42, 3·52, 3·60	$J_{3,4} = J_{4,5} = J_{P,4} = 9$—10
(26)	4·92	4·48		3·83	1·85	3·45, 3·54, 3·69	$J_{P,4}$ 13, $J_{3,4} = J_{4,5} = 9$—10
(27)	4·88	4·57		3·88		3·40, 3·55, 3·64	$J_{3,4} = J_{4,5} = J_{P,4} = 9$—10
(28)	4·90	4·68		3·87		3·41, 3·55, 3·64	$J_{P,4}$ 13·3, $J_{3,4} = J_{4,5} = 9$—10
(29)	4·86		4·28	3·77	1·51	3·43, 3·51, 3·66	Poorly resolved 2H, q for H-6
(30)	4·87		4·33	3·76	1·84	3·45, 3·52, 3·66	H-6: 2H, q with spacings 3·5 and 9
(31)	4·82		4·46	3·81		3·39, 3·50, 3·67	
(32)	4·80		4·46	3·78		3·38, 3·49, 3·64	

H-4, H-6, and H-6′ signals. Configurational assignment at phosphorus in the ring-opened products was not so easy. Since the 4-phenylphosphonates (19) and (20) both showed a characteristic high-field methoxy-signal which was absent in spectra of (27) and (28), it is probable, by analogy with other ring-opening reactions [*e.g.* (1*eq*) to (3), Scheme 1; (7*ax*) and (7*eq*) to (8), Scheme 2] that P–O(6) cleavage occurred with inversion of configuration. It is therefore reasonable to assume that the 4-substituted sugar methyl methylphosphonates and corresponding thioxo-derivatives [(17), (18), (25), and (26)] were also formed from their cyclic precursors with inversion of configuration at phosphorus.

There is no direct evidence for the configuration at phosphorus in the 6-substituted glucopyranose derivatives. The isomers in each of the pairs of derivatives (21) and (29), (22) and (30), and (23) and (31), had closely similar n.m.r. spectra (Table 1). However, usually there were some distinctive features. For example the shape of the signals for the 6-protons in (22) and (30) were different. Also (22) was converted into (21) and (30) was converted into (29) by peroxy-acid oxidation,[3] confirming the differences in the n.m.r. spectra of (21) and (29). In most cases the 6-substituted glucopyranose derivatives were stereochemically pure but the product from overnight storage of (15*ax*) with sodium methoxide in methanol contained (31) as well as (23). The (23) : (31) ratio was 5 : 1.

When the crystalline 4-substituted derivative (26) was dissolved in methanolic sodium methoxide, re-formation of a small amount of the cyclic derivative (4*eq*) as well as migration of phosphorus to position 6 in the glucopyranose derivative was observed by t.l.c. Chromatographic evidence for the re-formation of cyclic derivatives during O-4 to O-6 migration of the other examples given in Scheme 4 was obtained and was particularly noticeable in migration observed in simple 1,3,2-dioxaphosphorinan derivatives obtained from butane-1,3-diol.[5]

In Scheme 4 it is assumed that the 6-substituted glucopyranose derivatives are formed from their cyclic precursors with inversion of configuration at phosphorus. Reasons for this assumption are tentative and will be discussed subsequently in this paper.

Sodium Methoxide(or Phenoxide)–2-Methyl-1,3,2-oxathiaphosphorinan-2-one Reactions (*Scheme* 5).—The reactions of the cyclic methylphosphonothioates (10*ax*) and (10*eq*) with sodium methoxide in methanol were in sharp contrast with those of the corresponding acyclic derivatives: the initial reaction was rapid P–O fission rather than the expected P–S fission. Thus after storage in methanolic sodium methoxide for 10 min at room temperature (10*ax*) and (10*eq*) afforded (33) and (37), respectively. On further storage in methanolic sodium methoxide at room temperature (33) and (37) were converted in part into the thio-sugar (34), presumably with formation of dimethyl methylphosphonate. Additionally, (33) and (37) were converted in part into the 4-substituted sugar derivatives (35) and (36), Compound (35) was the preponderant isomer from (37) and compound (36) the preponderant product from (33). The position of phosphorus substitution on the sugar ring in all the products was apparent from their n.m.r. spectra (Table 2), which showed the presence or absence of SH and 4-substituents.

TABLE 2

N.m.r. chemical shift (δ) data for ring-opened products in Scheme 5

Compd.	H-1	H-4	H-6	P·OMe	PMe	SH
(33)	4·82			3·81	1·82	
(35)	4·87	4·25	2·8	3·81	1·52	*ca.* 2
(36)	4·87	4·15	2·8	3·74	1·57	*ca.* 2
(37)	4·83			3·77	1·84	
(38)	4·84		2·85	3·78	1·56	
(39)	4·84		2·85	3·78	1·53	
(40)	4·86	4·36	2·8		1·63	2·25
(41)	4·82	4·18	2·8		1·71	2·25

No direct evidence can be offered for the configuration at phosphorus in (33) and (37), so in the absence of evidence to the contrary the formation of these compounds is represented in Scheme 5 as occurring with the expected inversion of configuration.

A limited amount of chemical and n.m.r. evidence enables tentative configurational assignments for (35) and (36) to be made. Treatment of (10*eq*) with iodine in warm methanol afforded the disulphide (39), which was also the major product when the mixture of (35) and (36) prepared from (10*eq*) was treated with iodine and methanol. Similarly, treatment of (10*ax*) with iodine in methanol afforded the disulphide (38), which was also obtained as the major product by oxidising the mixture of (35) and (36) from (10*ax*) with iodine in methanol. On the reasonable assumption that iodine-promoted methanolyses of phosphonothioates involve charged species[6] that undergo displacements with inversion of configuration (since $^{+}$SR is a much better leaving group than SR) the preponderant sodium-methoxide-induced reactions leading to (36) from (10*ax*) and (35) from (10*eq*) must also proceed with inversion of configuration.

Evidence to support this conclusion was provided by a comparison of the P–Me, P–OMe and H-4 chemical shifts of (35) and (36) (Table 2) with those of (18) and (26) (Scheme 4; Table 1). Table 1 shows that the P–Me signal is at lower field and the P–OMe and H-4 signals are at higher field in compound (18) than in (26). Similarly, the P–Me signal is at lower field and the P–OMe and H-4 signals are at higher field in (36) than in (35). Since (18) and (26) were formed from (4*ax*) and (4*eq*), respectively, with inversion of configuration, it is reasonable to suppose that (36) and (35) were formed with inversion of configuration from (10*ax*) and (10*eq*), respectively.

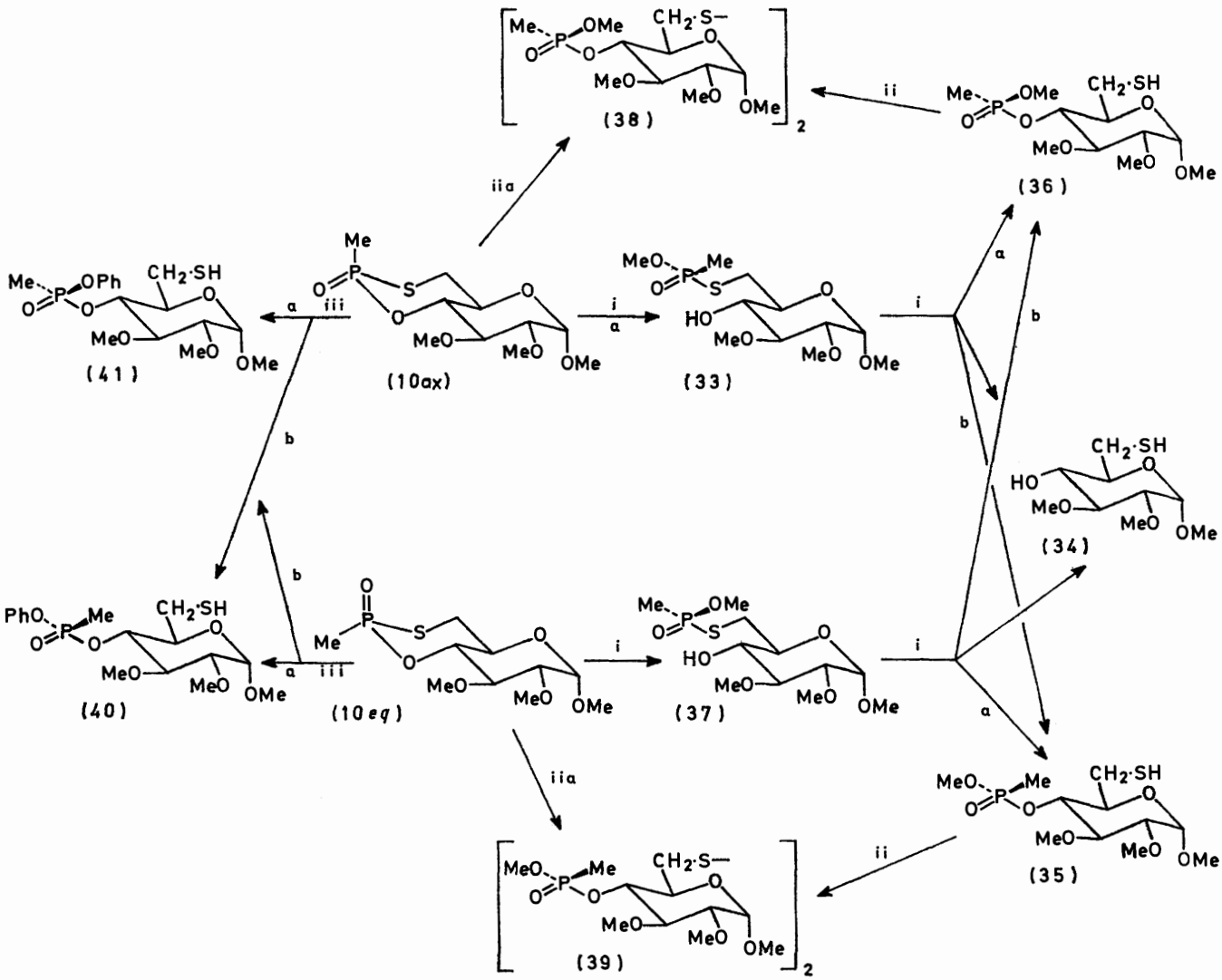
The reactions of methyl 2,3-di-*O*-methyl-4-thio-α-D-glucopyranoside (*R*)- and (*S*)-4,6-methylphosphonothioates with sodium methoxide in methanol followed

[5] J. M. Harrison and T. D. Inch, unpublished results.
[6] T. Wieland and R. Lambert, *Chem. Ber.*, 1956, **89**, 2476.

a similar pattern to the corresponding reactions of (10*ax*) and (10*eq*), with P–O bond cleavage preceding P–S cleavage. However, since the n.m.r. spectra of the final 6-substituted derivatives were indistinguishable and because the disulphides from iodine-promoted methanolysis could not be distinguished, no indications of the stereochemistry of these reactions were obtained.

benzene (10*ax*) and (10*eq*) both undergo direct P–S cleavage with inversion of configuration. With alkoxides, acyclic methylphosphonothioates have also been shown to undergo P–S bond cleavage with inversion of configuration.[7]

Sodium Alkoxide–2-Ethoxy-1,3,2-oxathiaphosphorinan-2-one Reactions (*Scheme* 6).—Treatment of methyl



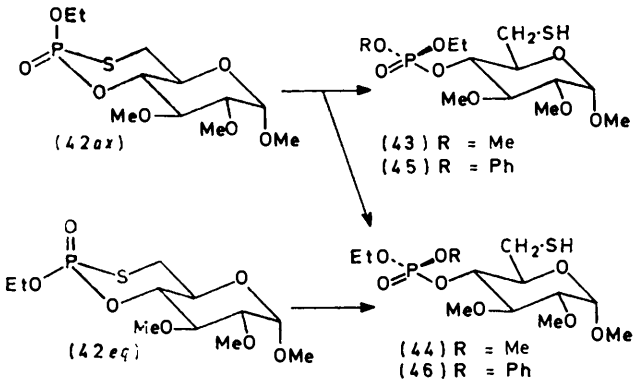
SCHEME 5 i, NaOMe–MeOH; ii, MeOH–I_2; iii, NaOPh–PhH. Stereochemistry: a, inversion; b, retention

Treatment of (10*ax*) and (10*eq*) with sodium phenoxide in warm benzene afforded only the isomers resulting from P–S cleavage. Compound (41) was the preponderant product from (10*ax*) [ratio (41) : (40) was 2 : 1] and (40) was the preponderant product from (10*eq*) [ratio of (40) : (41) was 2 : 1]. Configuration assignments to (40) and (41) were based on chemical shift comparisons of P–Me and H-4 similar to those already described. Thus with sodium phenoxide in

[7] W. B. Farnham, K. Mislow, N. Mandel, and J. Donohue, *J.C.S. Chem. Comm.*, 1972, 120.

2,3-di-*O*-methyl-6-thio-α-D-glucopyranoside (*R*)- and (*S*)-4,6-(ethyl phosphorothioates) [(42*ax*) and (42*eq*), respectively] with sodium methoxide in methanol afforded only (44) from (42*eq*) and a mixture of (43) and (44) from (42*ax*) [ratio (43) : (44) was 7 : 1]. Thus in contrast to the corresponding phosphonothioate reactions (Scheme 5) P–S cleavage and not P–O cleavage occurred as the first observable reaction. The direction of ring opening was apparent from the n.m.r. spectra of the products (Table 3). Similarly, P–S cleavage occurred when (42*ax*) and (42*eq*) were treated with

sodium phenoxide in benzene. Compound (42*ax*) afforded a mixture of (45) and (46) [ratio (45) : (46) was 3 : 1] and compound (42*eq*) afforded only (46).



SCHEME 6

The tentative configurational assignments to compounds (43)—(46) were based first on n.m.r. evidence. Table 2 shows that the P–OMe signal (δ 3·74) of (36), which was obtained from the axially substituted compound (10*ax*) with inversion of configuration, was at higher field than the P–OMe signal (3·81) of (35), which was obtained from (10*ax*) with retention of configuration. Data for the P–OMe signals in Table 1 show that the signals for (17) and (18), formed from the axially substituted (1*ax*) and (4*ax*) with inversion of configuration, were at higher field than the corresponding signals for (25) and (26), which were formed from the equatorially substituted (1*eq*) and (4*eq*) with inversion of configuration. Thus the fact that the P–OMe signal of (43) (δ 3·81) was at lower field than that of (44) (3·78) suggests that (43) and (44) were formed from (42*ax*) and (42*eq*), respectively, with retention of configuration.

TABLE 3

N.m.r. chemical shift (δ) data for ring-opened products in Scheme 6

Compd.	H-1	P·OMe	OMe	CH_2·S	O·CH_2·CH_3	SH
(43)	4·82	3·81	3·46, 3·52, 3·59	1·75—1·95	1·33	1·80
(44)	4·83	3·78	3·48, 3·54, 3·01	1·75—1·95	1·35	1·80
(45)	4·82		3·45, 3·46, 3·50	1·90—2·10	1·32	1·65
(46)	4·81		3·44, 3·51, 3·58	1·90—2·10	1·34	1·65

Similar comparative evidence was obtained for (45) and (46) and the phosphono-derivatives (40) and (41), all obtained in ring-opening reactions with sodium phenoxide. The major product (40) obtained with inversion of configuration from the axially substituted (10*ax*) had low field resonances for the sugar methyl substituents at δ 3·55 and 3·64. There were no signals at lower field than 3·53 in the spectrum of (41), which was formed from (10*ax*) with retention of configuration and from (10*eq*) with inversion. Presumably the shielding of the OMe groups in the two compounds depends on the orientation of the phenoxy-substituent, which will exhibit similar effects in (45) and (46). Thus since the lowest-field signals for (45) and (46) were observed in the spectrum of (46) (Table 3), (46) was presumably formed with retention of configuration from (42*eq*).

No direct evidence for the configuration at phosphorus in compounds (43)—(46) was obtained. Iodine-promoted methanolysis of (42*ax*) and (42*eq*) did not take place.

Sodium Alkoxide–2-Alkoxy-1,3,2-dioxaphosphorinan-2-thione Reactions (*Scheme* 7).—The reactions of the pair of isomers (47*ax*) and (47*eq*) with sodium methoxide in methanol and the reactions of (51*ax*) and (51*eq*) with sodium methoxide in methanol and with sodium ethoxide in ethanol were studied. The reactions were monitored by t.l.c. In most cases the separation of 4-substituted glucopyranose derivatives (which had higher R_F values than the 6-substituted derivatives) was accomplished only with difficulty. The ring-opening reactions of (47*eq*) and (51*eq*) proceeded more rapidly than the corresponding reactions of (47*ax*) and (51*ax*), and the 4-substituted derivatives were formed first and then rearranged to the 6-substituted derivatives. Although the ring-opening reactions of (47*ax*) and (51*ax*) were slower than the corresponding reactions of (47*eq*) and (51*eq*), their 4-substituted products were transformed into the 6-substituted products more rapidly than the corresponding 4-substituted products from (47*eq*) and (51*eq*). The products (48) and (49) which were expected to be formed with inversion of configuration from (47*ax*) and (47*eq*) respectively, had indistinguishable n.m.r. spectra (Table 4), which showed the P–OMe signals as pairs of doublets (J_{P-O-CH_3} 13 Hz). Apart from signals resulting from the presence of the ethoxy-group the spectra of (48) and (49) were indistinguishable from the spectrum of (52), which was prepared by treatment of (51*ax*) or (51*eq*) with sodium methoxide. 4-Substituted glucopyranose derivatives were not isolated from the reactions involving treatment of (51*ax*) and (51*eq*) with sodium ethoxide although they were observed by t.l.c. as being present during the reactions. The 6-substituted products represented as (50) had indistinguishable n.m.r. spectra whether formed with methoxide from (47*ax*) and (47*eq*) or with ethoxide from (51*ax*) and (51*eq*). All the spectra showed

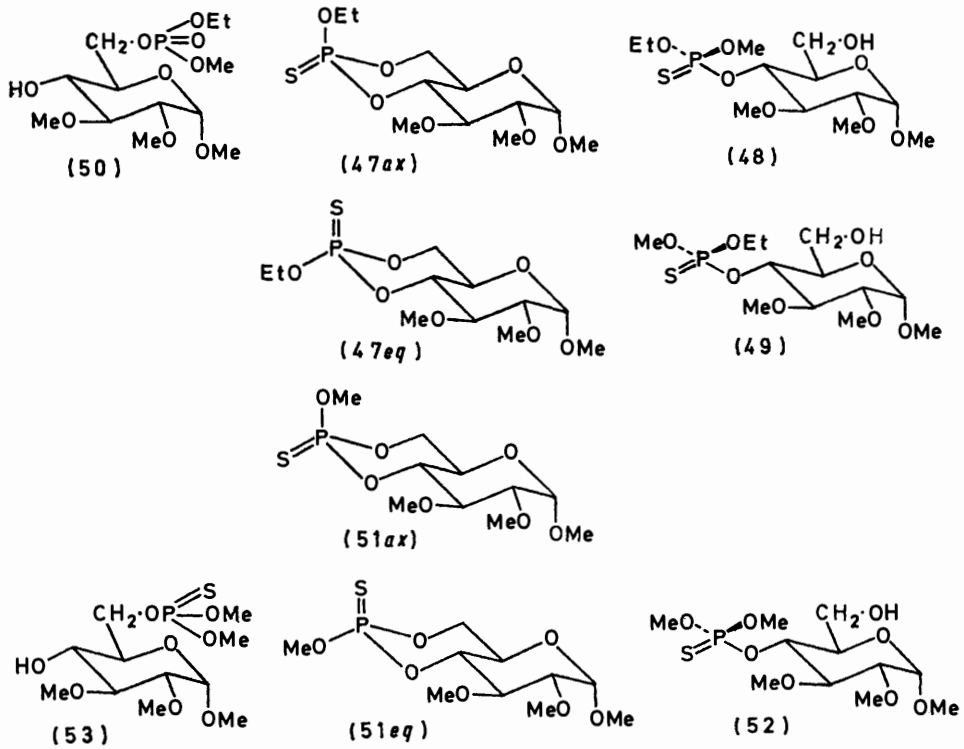
TABLE 4

N.m.r. chemical shift (δ) data for ring-opened products in Scheme 7

Compd.	H-1	H-4	H-6	P·OMe	OMe	O·CH_2·CH
(48)	4·85	4·45		3·82, 3·78	3·43, 3·52, 3·58	1·34
(49)	4·86	4·45		3·82, 3·78	3·43, 3·52, 3·58	1·34
(50)	4·87		4·2—4·4	3·76	3·43, 3·50, 3·64	1·38
(52)	4·88	4·4		3·82, 3·78	3·43, 3·52, 3·58	
(53)	4·88		4·25—4·4	3·77	3·44, 35·2, 3·66	

P·OMe and P·O·CH_2·CH_3 signals of equal intensity. The P·OMe signal was indistinguishable in shape from, but half the intensity of, the corresponding signal from (53).

The n.m.r. spectra of the products in Scheme 7 provided no evidence concerning the ring-opening and migration reactions. However, the observation that there was no appreciable exchange of methoxy- and ethoxy-groups during the migration reactions has mechanistic implications which will be discussed subsequently.



SCHEME 7

DISCUSSION

The studies described here were carried out primarily to obtain information about the stereochemical homogeneity of ring-opening reactions of carbohydrate 1,3,2-dioxaphosphorinans and related compounds in order to evaluate the potential utility of such optically active cyclic phosphorus compounds as substrates for the stereospecific synthesis of enantiomeric, acyclic, simple phosphorus esters. In this connection, on the credit side, the results show clearly that many of the ring-opening reactions are stereochemically homogeneous, *i.e.* they occur with either retention or inversion of configuration and not with racemisation. However, on the debit side, the direction of ring opening is not so well defined. With Grignard reagents, although 4-substituted glucopyranose derivatives are usually the preponderant products in some instances, 6-substituted glucopyranose derivatives are also formed. Further, the ring-opening reactions with sodium methoxide gave initially the kinetically preferred products, which were usually not the thermodynamically favoured products. For example, ring opening followed by migration of the phosphorus group from O-4 to O-6 or from S to O was observed. It is obvious therefore, that, for the type of cyclic phosphorus ester system described in this paper, the number of potential inter- and intra-molecular reactions is too great to permit the unambiguous stereospecific synthesis of optically pure phosphorus esters.

Although some of the stereochemical assignments are tentative, the results in Schemes 1—7 are of considerable interest since they provide novel information about the influence of stereochemical and other factors on nucleophilic displacement reactions at phosphorus. This information is of particular value since although in principle the geometrical permutations of reactions and pseudorotations involving pentaco-ordinate transition intermediates have been well documented,[8] practical evidence for these reactions is more difficult to obtain. Thus although it is recognised that whether or not a reaction proceeds with inversion or retention of

[8] I. Ugi and F. Ramirez, *Chem. in Britain*, 1972, 198; P. Gillespie, P. Hoffman, H. Klusacek, D. Marquarding, S. Pfohl, F. Ramirez, E. A. Tsolis, and I. Ugi, *Angew. Chem. Internat. Edn.*, 1971, **10**, 687; I. Ugi, D. Marquarding, H. Klusacek, P. Gillespie, and F. Ramirez, *Accounts Chem. Res.*, 1971, **4**, 288; F. Ramirez, *Bull. Soc. chim. France*, 1970, 3491; F. Ramirez, S. Pfohl, E. A. Tsolis, J. F. Pilot, C. P. Smith, I. Ugi, D. Marquarding, P. Gillespie, and P. Hoffman, *Phosphorus*, 1971, **1**, 1; K. Mislow, *Accounts Chem. Res.*, 1970, **3**, 321; P. C. Lauterbut and F. Ramirez, *J. Amer. Chem. Soc.*, 1968, **90**, 6722.

configuration may depend on the initial direction of attack by the nucleophile, the solvent, the relative apicophilicities of the *P*-substituents, and constraints to pseudorotation such as P–C bonds or ring systems,[8] the relative importance of these and other factors has not been elucidated.

The reactions summarised in Schemes 1, 2, and 4 show that 1,3,2-dioxaphosphorinans usually undergo nucleophilic attack at phosphorus with preferred cleavage of the P–O(6) bond, *i.e.* cleavage of the bond between phosphorus and the oxygen atom attached to a primary carbon atom. These results are consistent with previous reports[9] that aqueous alkaline hydrolyses of D-glucopyranose and D-galactopyranose 4,6-phosphates afford preponderantly the corresponding 4-phosphates. The direction of ring opening does not appear to be influenced significantly by the carbohydrate portion of the molecule; similar reactions of sodium methoxide with *cis*- and *trans*-2,4-dimethyl-1,3,2-dioxaphosphorinan-2-ones and the corresponding 2-thioxo-derivatives also proceed with preponderant initial cleavage of the bond between phosphorus and the oxygen atom attached to the primary carbon atom.[5] There is no obvious stereochemical explanation for these observations. The conclusion from previous hydrolysis experiments with dialkyl alkylphosphonates was that hydrolysis rates were dependent on the size rather than on the pK_a of the leaving group.[10] Unfortunately, no mixed esters were studied and it is therefore difficult to relate those data with the results of the present study. It is clear, however, that, although not obvious, stereochemical effects are important, since with sodium methoxide (Scheme 4) the ratio of the rates of P–O(6) cleavage and P–O(4) cleavage is much greater when the 2-substituent is axial than when it is equatorial (see later).

The P–O(6) cleavage of the 1,3,2-dioxaphosphorinan-2-ones with Grignard reagents (Scheme 1) and with methoxide (Scheme 4) and the P–O(6) cleavage of the corresponding 2-thioxo-derivatives with methoxide (Scheme 4) all proceed with inversion of configuration, irrespective of the initial stereochemistry of the *P*-substituent. However, ring opening with methoxide proceeded more rapidly where the alkyl or aryl *P*-substituent was oriented axially than where it was oriented equatorially. In contrast, 1,3,2-dioxaphosphorinans with equatorial 2-alkoxy-substituents underwent ring opening more readily than the corresponding axially substituted derivatives (Scheme 7). Further, with Grignard reagents, axially substituted 1,3,2-dioxaphosphorinan-2-thiones (Scheme 2) underwent ring opening with inversion of configuration, whereas the corresponding equatorially substituted derivatives reacted with retention of configuration. These results are consistent with the hypothesis that ring-breaking reactions, like ring-forming reactions,[2] take place most easily through intermediates which adopt non-chair conformations. Thus, whereas axially substituted 2-methyl and 2-phenyl derivatives can easily adopt energetically favoured non-chair conformations with the substituent on phosphorus, pseudoequatorial compounds with equatorial substituents on phosphorus give pseudoaxially substituted non-chair intermediates. The latter intermediates are energetically unfavourable when the substituent is methyl or phenyl but energetically favourable when the substituent is alkoxy.[2]

It appears probable that pseudorotation is a more favourable process with P=S derivatives than with P=O derivatives. Thus with Grignard reagents the energy required for pesudorotation with equatorially substituted P=S compounds (Scheme 2) is lower than that required for ring opening in a chair form and pseudorotation, which results when the subsequent formation of an energetically favourable non-chair intermediate precedes ring opening. With alkoxide, ring cleavage occurs without pseudorotation for P=S and P=O derivatives.

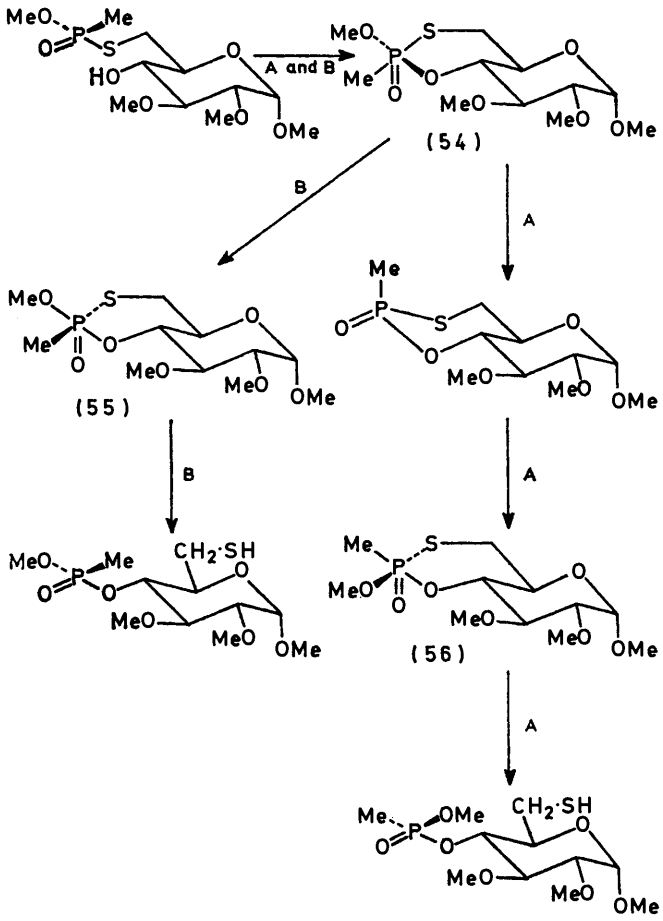
Further evidence for the intermediacy of non-chair intermediates in ring-opening reactions is provided by the experiments summarised in Scheme 3. Treatment of (10*ax*) with phenylmagnesium bromide afforded preponderantly the P–O cleavage product (12) which was formed probably with inversion of configuration. In contrast (10*eq*), which cannot readily adopt a non-chair conformation without a change of configuration at phosphorus, underwent ring opening with phenylmagnesium bromide with P–S cleavage and retention of configuration. It is reasonable to suppose that the difference in stereochemical course of the reactions of (10*ax*) and (10*eq*) is strongly influenced by the relative ease with which a non-chair intermediate is formed prior to the ring-opening reaction.

The experiments summarised in Scheme 5, in which treatment of cyclic methylphosphonothioates with sodium methoxide in methanol resulted in initial preferential P–O cleavage are in marked contrast to corresponding reactions of acyclic methylphosphonothioates, which result in P–S cleavage.[4] Presumably incorporation of a P–O bond into a ring increases its lability. On storage in methanolic sodium methoxide the acyclic 6-methylphosphonothioates (33) and (37) either underwent direct methanolysis to afford (34) or else migration of the phosphorus group from S to O-4 occurred. The two mechanisms illustrated in Scheme 8 can, in principle, account for the observed migration. In path A ring formation is the reverse of ring breaking, and migration, with inversion of configuration, takes place by attack of methoxide opposite sulphur [see (56)]. In path B ring formation occurs only to the stage of the trigonal bipyramid intermediate (54), and pseudorotation of this intermediate to (55) occurs prior to P–S bond cleavage with overall retention of configuration. The results in Scheme 5 show that the products from both (10*ax*) and (10*eq*) are formed with preponderant inversion of configuration, therefore indicating that path A is favoured. Similarly

[9] P. Szabo and L. Szabo, *J. Chem. Soc.*, 1960, 3758.
[10] R. F. Hudson and L. Keay, *J. Chem. Soc.*, 1956, 2463.

ring opening of (10*ax*) and (10*eq*) by sodium phenoxide in benzene proceeded with preponderant inversion of configuration although in these reactions only P–S cleavage and not the initial P–O cleavage was observed.

The foregoing results show that direct cleavage of P–S bonds by alkoxides in phosphonothioates is preferred even in a situation where P–S cleavage following



SCHEME 8

pseudorotation might be considered favourable. This result is consistent with early claims that pseudorotation of phosphonates is not energetically favourable.[11] This evidence has a strong influence on any conclusion concerning the stereochemistry of the O-4 to O-6 phosphonate migrations summarised in Scheme 4. Since, generally, the 6-substituted derivatives were stereochemically homogeneous and since clear evidence for the intermediacy of the original cyclic precursors was obtained, direct P–O(4) cleavage with inversion of configuration (a path analogous to path A, Scheme 8) seems probable.

The experiments on the ethyl phosphorothioate derivatives which are summarised in Scheme 6 contrast with the experiments with the phosphonothioate derivatives (Scheme 5). With sodium methoxide in methanol the phosphorothioate (42*eq*) underwent stereochemically homogeneous P–S bond cleavage to afford (44). The axial isomer (42*ax*) also underwent P–S bond cleavage, to afford (43), although some (44) was also present. Similar reactions [(42*eq*) to (46); (42*ax*) to (45) and (46)] were observed with sodium phenoxide in benzene. It has been pointed out previously that there is little direct evidence for the stereochemistry at phosphorus in compounds (43)—(46). However the preference for P–S cleavage with NaOMe–MeOH in the phosphorothioates as compared with the phosphonothioates, the high stereospecificity of the reactions of (42*ax*) with alkoxide compared with the moderately stereoselective corresponding reactions of (10*ax*), and other evidence that phosphonothioates undergo P–S cleavage with retention of configuration [4] present a pattern of results that is consistent with tentative n.m.r.-based conclusions that (42*ax*) and (42*eq*) undergo P–S cleavage with retention of configuration.

No conclusions about the stereochemistry of the 6-substituted or 4-substituted products illustrated in Scheme 7 were possible since the n.m.r. spectra of the products from different starting materials were indistinguishable. However, some insight into the mechanisms was provided by the observation that no exchange of methoxy for ethoxy, or ethoxy for methoxy could be detected during migration of the phosphorus substituent from O-4 to O-6. Ester exchange would be expected if migrations from O-4 to O-6 occurred to an appreciable extent, *via* 1,3,2-dioxaphosphorinan-2-ones (*i.e.* by paths analogous to path A, Scheme 8). Thus, migrations presumably proceed preponderantly by paths similar to path B (Scheme 8), *i.e. via* a pentacoordinate intermediate which breaks down to the 6-substituted glucopyranose derivatives after pseudorotation.

In conclusion, the foregoing results clearly illustrate the important influence of the absolute configuration and conformation of cyclic phosphorus esters on the stereochemical course of ring-opening reactions. Further, the results also indicate certain differences between cyclic phosphonic and phosphoric esters. Detailed kinetic studies are required to supplement the stereochemical studies before any firm conclusions regarding reaction mechanisms can be drawn.

EXPERIMENTAL

The routine procedures used and procedures for obtaining n.m.r. data are described elsewhere.[2]

Grignard Reactions.—These were carried out by adding the required quantity of Grignard reagent (1- to 3-fold excess) in ether to a solution of the sugar derivative in benzene and by boiling the mixture under reflux for as long as t.l.c. studies indicated to be necessary. The reaction was monitored by t.l.c. in the solvent system eventually used to separate the products by silica gel column chromatography. The reaction mixtures were processed by dilution with aqueous ammonium chloride, extraction with chloroform, and chromatography over silica of the dried and concentrated chloroform extracts.

[11] E. A. Dennis and F. H. Westheimer, *J. Amer. Chem. Soc.*, 1966, **88**, 3431, 3432.

Scheme 2.—(i) A solution of (4*ax*) (0·6 g) and phenylmagnesium bromide was boiled under reflux for 3 h. The products were separated over silica in benzene–ethanol (15 : 1) to give (*a*) (4*ax*) (0·1 g.), R_F 0·35; (*b*) methyl 2,3-di-*O*-methyl-α-D-glucopyranoside (*S*)-4-methylphenylphosphinothioate (6) (0·2 g, 32%), $[\alpha]_D$ +50° (*c* 0·9), R_F 0·3, δ_H 2·11 (PMe), 3·43, 3·55, and 3·65 (3 OMe), 4·92 (H-1), and 4·61 (H-4, $J_{3,4} = J_{4,5} = 9$—10, $J_{P,4}$ 15 Hz); and (*c*) methyl 2,3-di-*O*-methyl-α-D-glucopyranoside 6-methylphenylphosphinothioate (5) (0·28 g, 43%), $[\alpha]_D$ +75° (*c* 0·8), R_F 0·25, δ_H 2·01 (PMe), 3·42, 3·48, and 3·61 (3 OMe), and 4·85 (H-1).

(ii) A solution of (4*eq*) (0·6 g) and phenylmagnesium bromide was boiled under reflux for 8 h. The product (6) (0·12 g, 48%), R_F 0·3, was separated from unchanged (4*eq*) (0·4 g.), R_F 0·6, in light petroleum–acetone (4 : 1).

(iii) A solution of the 2-phenyl derivative (7*ax*) (0·25 g) and methylmagnesium bromide was boiled under reflux for 4 h. Starting material (7*ax*) (0·18 g), R_F 0·6, and product (R_F 0·4) were separated over silica in light petroleum–acetone (9 : 1). The product was methyl 2,3-di-*O*-methyl-α-D-glucopyranoside (*R*)-4-methylphenylphosphinothioate (8) (0·15 g, 87%), $[\alpha]_D$ +64° (*c* 1·5), δ_H 2·08 (PMe), 2·63, 3·40, and 3·44 (3 OMe), 4·87 (H-1), and 4·52 (H-4, $J_{3,4} = J_{4,5} = 10$, $J_{P,4}$ 15 Hz).

(iv) A solution of (7*eq*) (0·25 g) and methylmagnesium bromide was boiled under reflux for 6 h. The following compounds were obtained by chromatography over silica in light petroleum–acetone (8 : 1): (*a*) (7*eq*) (0·12 g); (*b*) compound (8) (0·095 g, 70%); (c) methyl 2,3-di-*O*-methyl-α-D-glucopyranoside 6-methylphenylphosphinothioate (9) (0·015 g, 11%), R_F 0·4, δ_H 2·11 (PMe), 3·42, 3·65, and 3·56 (3 OMe), and 4·92 (H-1).

Scheme 3.—(i) A solution of the oxathiaphosphorinan (10*ax*) (0·1 g) and phenylmagnesium bromide was boiled under reflux for 2 h. The products were passed over silica in benzene–acetone–methanol (14 : 6 : 1) to afford (*a*) the (*R*)-4-methylphenylphosphinate (11) (0·02 g, 16%), R_F 0·6, $[\alpha]_D$ +90° (*c* 0·4), δ_H 4·18 (H-4, $J_{3,4} = J_{4,5} = J_{P,4} =$ 9—10 Hz), 1·9 (SH), 1·70 (PMe), and 2·87, 3·41, and 3·47 (3 OMe); and (*b*) *methyl* 2,3-*di*-O-*methyl*-6-*thio*-α-D-*glucopyranoside* 6-*methylphenylphosphinothioate* (12) (0·08 g, 64%), m.p. 124—125° (from di-isopropyl ether), $[\alpha]_D$ +85° (*c* 1·6), R_F 0·4 (Found: C, 51·0; H, 6·7. $C_{16}H_{25}O_6PS$ requires C, 51·1; H, 6·7%), δ_H 1·98 (PMe) and 3·35, 3·51, and 3·66 (3 OMe).

(ii) A solution of the oxathiaphosphorinan (10*eq*) (0·1 g) and phenylmagnesium bromide was boiled under reflux for 2 h. The products were passed over silica in benzene–acetone–methanol (14 : 6 : 1) to afford (*a*) the (*S*)-4-methylphenylphosphinate (13) (0·5 g, 40%), $[\alpha]_D$ +86° (*c* 1), R_F 0·6, δ_H 4·3 (H-4, $J_{3,4} = J_{4,5} = J_{P,3} =$ 9—10 Hz), 2·75 (SH), 1·78 (PMe), and 3·46, 3·55, and 3·65 (3 OMe); and (*b*) the 6-methylphenylphosphinothioate (14) (0·02 g, 16%), $[\alpha]_D$ +129° (*c* 0·4), R_F 0·4, δ_H 2·03 (PMe) and 3·38, 3·48, and 3·63 (3 OMe).

Scheme 4.—*Reactions of* 2-*alkyl*(*or aryl*)-1,3,2-*dioxaphosphorinans with sodium methoxide.* A solution of the 1,3,2-dioxaphosphorinan (0·1—0·6 g) and sodium methoxide (0·1—1 ml of 3% w/v sodium methoxide in methanol) in methanol (10 ml) was stored at room temperature and the progress of the reaction was monitored by t.l.c. The solution was treated with carbon dioxide and diluted with chloroform, and the chloroform solution was washed with water, dried, and concentrated. The residue was resolved chromatographically, if possible, over silica in the same solvent as used for t.l.c.

(i) A methanolic solution of (1*ax*) (0·28 g) and sodium methoxide (0·1 ml) was stored at room temperature for 3 h. Chromatography [benzene–acetone–ethanol (14 : 2 : 1)] afforded (17) (0·24 g, 77%), R_F 0·4, $[\alpha]_D$ +100° (*c* 0·8); and (21) (0·04 g, 13%), R_F 0·35, $[\alpha]_D$ +93° (*c* 0·4).

Compound (1*ax*) (0·15 g) and sodium methoxide (1 ml) stored at room temperature for 8 h afforded (17) (0·045 g, 27%) and (21) (0·07 g, 42%).

(ii) A methanolic solution of (1*eq*) (0·28 g) and sodium methoxide (0·1 ml) was stored at room temperature for 2 h. Chromatography [benzene–acetone–ethanol (14 : 2 : 1)] afforded (25) (0·15 g, 48%), R_F 0·4, $[\alpha]_D$ +134° (*c* 1); and (29) (0·1 g, 32%), R_F 0·35; $[\alpha]_D$ +100° (*c* 0·5).

Compound (1*eq*) (0·15 g) and sodium methoxide (0·1 ml) stored at room temperature for 8 h afforded (25) (0·045 g) and (29) (0·08 g, 48%).

(iii) A methanolic solution of (4*ax*) (0·3 g) and sodium methoxide (0·1 ml) was stored at room temperature for 2 h [chromatography: benzene–ether (1 : 1)]. The major product, R_F 0·35, was (18) (0·2 g, 60%), $[\alpha]_D$ +95° (*c* 1). On storage overnight at room temperature with sodium methoxide (0·5 ml), (18) was converted mainly into (22) (R_F 0·32). In this experiment (4*ax*), (18), and (22) were separable only with difficulty by t.l.c. and column chromatography. By choosing appropriate reaction times essentially homogeneous samples were obtained for n.m.r. analysis.

(iv) Compound (4*eq*) (0·2 g) and sodium methoxide (0·1 ml) were stored at room temperature for 5 h [chromatography: light petroleum–acetone (4 : 1)]. The products were the 4-(*methyl methylphosphonothioates*) (26) (0·095 g, 43%), R_F 0·4, $[\alpha]_D$ +149° (*c* 0·5), m.p. 103—104° (from di-isopropyl ether) (Found: C, 40·1; H, 6·7. $C_{11}H_{23}O_7PS$ requires C, 40·0; H, 7·0%), and (30) (0·056 g, 25%), R_F 0·35, $[\alpha]_D$ +102° (*c* 0·4). From the start of the reaction the two products were always present. Storage of the reaction mixture or storage of (26) with sodium methoxide resulted in the formation of (30).

(v) The conversion of (15*ax*) into (19) occurred within 30 min, and on further storage at room temperature, (23) was formed preponderantly. Compounds (15*ax*), (19), and (23) were extremely difficult to separate chromatographically and no satisfactory solvent was found.

(vi) On storage at room temperature for 4 h with sodium methoxide (1 ml), compound (15*eq*) afforded (27) and (31), which were separated with difficulty by chromatography over silica in benzene–acetone (7 : 3).

Scheme 5.—*Reactions of* 2-*alkyl*-1,3,2-*oxathiaphosphorinan*-2-*ones with sodium methoxide and sodium phenoxide.* (i) A solution of (10*eq*) (0·2 g) in methanol (10 ml) and sodium methoxide (0·1 ml of 10% w/v NaOMe in methanol) was stored at room temperature for 10 min, neutralised with carbon dioxide, diluted with chloroform, washed with water, dried, and concentrated. T.l.c. [benzene–acetone–methanol (14 : 2 : 1)] showed that the major product was (37) (R_F 0·5), obtained along with traces of the thiols (34) (R_F 0·7) and (35) and (36) (R_F 0·6). *Methyl* 2,3-*di*-O-*methyl*-6-*thio*-α-D-*glucopyranoside* 6-(*methyl methylphosphonothioate*) (37) (0·13 g, 59%), m.p. 101° (from di-isopropyl ether), $[\alpha]_D$ +41° (*c* 1) (Found: C, 39·8; H, 7·0. $C_{11}H_{23}O_7PS$ requires C, 40·0; H, 7·0%), was isolated by chromatography over silica.

A solution of (37) (0·15 g) in methanol (10 ml) and sodium methoxide (0·5 ml of 3% w/v NaOMe in methanol) was

stored at room temperature for 2 h. The solution was processed in the usual way and the product chromatographed over silica to afford (*a*) the thiol (34) (0·05 g) and (*b*) a mixture (0·05 g) of the 4-(methyl methylphosphonates) (35) and (36) in the ratio 2 : 1.

A solution of (35) and (36) and iodine in methanol was stored at room temperature for 30 min, diluted with chloroform, washed with aqueous sodium thiosulphate, dried, and concentrated. The product partially crystallised and was shown by n.m.r. to be mainly the disulphide (39).

(ii) A solution of (10*ax*) was treated similarly; benzene–acetone–methanol (14 : 2 : 1) was used as t.l.c. solvent to monitor the reactions and to isolate products. The 6-(methyl methylphosphonothioate) (33) was a syrup, $[\alpha]_D$ +90° (*c* 2). The mixture of the 4-(methyl methylphosphonates) (35) and (36) was formed in the ratio 2 : 1 and on oxidation gave preponderantly the disulphide (38).

(iii) A solution of (10*ax*) and an excess (5-fold) of sodium phenoxide in benzene was warmed for 30 min. The major component (t.l.c. in benzene–acetone, 7 : 2), which had a higher R_F value than (10*ax*), was isolated in the usual way by column chromatography and was shown by n.m.r. to be a 2 : 1 mixture of (41) and (40) {$[\alpha]_D$ +100° (*c* 1)}.

(iv) When treated with sodium phenoxide under similar conditions, compound (10*eq*) afforded a 2 : 1 mixture of (40) and (41) {$[\alpha]_D$ +110° (*c* 1)}.

Treatment of the methylphosphonothioates (10) *with methanol and iodine.* (i) A solution of iodine and (10*eq*) (0·1 g) in methanol was boiled under reflux for 2 h, diluted with chloroform, washed with aqueous sodium thiosulphate, dried, and concentrated. The product was purified over silica in benzene–acetone–methanol (7 : 2 : 1) and crystallised from di-isopropyl ether to afford the *disulphide* (39) (0·05 g), m.p. 148—150° (Found: C, 39·8; H, 6·55. $C_{22}H_{44}O_{14}P_2S_2$ requires C, 40·0; H, 7·0%).

(ii) Treatment of (10*ax*) with iodine in methanol afforded a mixture of products from which a syrup with an n.m.r. spectrum consistent with the disulphide structute (38) was isolated in low yield.

Scheme 6.—*Reactions of* 2-*ethoxy*-1,3,2-*dioxaphosphorinan*-2-*ones with sodium methoxide and sodium phenoxide.* Products were identified on the basis of n.m.r. data recorded in Table 3.

(i) *With sodium methoxide.* (*a*) A solution of (42*ax*) (0·2 g) in methanol (10 ml) containing sodium methoxide (0·2 ml of 3% w/v sodium methoxide in methanol) was stored at room temperature for 10 min, neutralised with carbon dioxide, and processed in the usual way. T.l.c. (benzene–acetone, 7 : 2) showed preponderantly one product, which was purified over silica to give a mixture of (43) and (44) (0·04 g), $[\alpha]_D$ +113° (*c* 0·5), in the ratio 7 : 1 as shown by n.m.r. (ratio of P·OMe signals).

(*b*) Similar treatment of (42*eq*) (0·2 g) afforded only (44) (0·6 g), $[\alpha]_D$ +114° (*c* 0·6).

(ii) *With sodium phenoxide.* (*a*) A mixture of (42*ax*) (0·1 g) and sodium phenoxide (0·1 g) in benzene (10 ml) was warmed in benzene for 1 h. T.l.c. (benzene–acetone, 7 : 2) showed no (42*ax*) and only a product of higher R_F value. The solution was washed with water, dried, and concentrated to afford a mixture of (45) and (46) (0·16 g), $[\alpha]_D$ +90° (*c* 0·14), in the ratio 3 : 1 (from OMe n.m.r. signals).

(*b*) Similar treatment of (42*eq*) (0·1 g) afforded only (46) (0·03 g), $[\alpha]_D$ +113° (*c* 0·3).

Scheme 7.—*Reactions of* 2-*alkoxy*-1,3,2-*dioxaphosphorinan*-2-*thiones with sodium alkoxides.* A solution of the 2-alkoxy-1,3,2-dioxaphosphorinan (0·1 g) and sodium alkoxide (0·2 ml of 3% w/v sodium alkoxide in alcohol) in the appropriate alcohol (10 ml) was stored at room temperature. The reaction was monitored by t.l.c. in a solvent such as chloroform or benzene–acetone (7 : 2). Always the glucopyranose 4,6-(alkyl phosphates) had higher R_F values than the 4-(dialkyl phosphorothioates), which in turn had higher R_F values than the 6-(dialkyl phosphorothioates). The products were isolated by chromatography over silica, after the alcoholic solution had been neutralised with carbon dioxide, diluted with chloroform, washed with water, dried, and concentrated. The products were examined only by n.m.r. (see Table 4).

[3/2424 *Received*, 26*th November*, 1973]