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USE OF CARBOHYDRATE DERIVATIVES FOR STUDIES OF PHOSPHORUS STEREOCHEMISTRY.

PART VI*. A STEREOCHEMICAL COMPARISON OF *S*-ALKYL ALKYLPHOSPHONOTHIOATE–SODIUM METHOXIDE AND *S*-ALKYL PHOSPHOROTHIOATE–SODIUM METHOXIDE REACTIONS†

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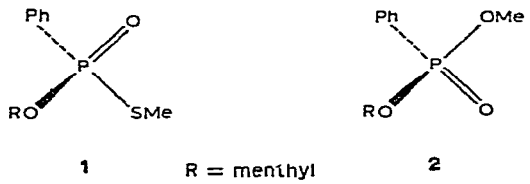
ABSTRACT

Cyclic phosphonamidothioate and cyclic phosphoramidothioate derivatives of carbohydrates are converted stereospecifically into acyclic *S*-methyl phosphonothioate and phosphorothioate carbohydrate derivatives. These derivatives are convenient substrates for studies of nucleophilic displacement reactions of phosphorus in acyclic phosphorus thioates. The *S*-methyl group is displaced by methoxide with *inversion* of configuration at phosphorus in the phosphonothioates and with *retention* of configuration in the phosphorothioates.

INTRODUCTION

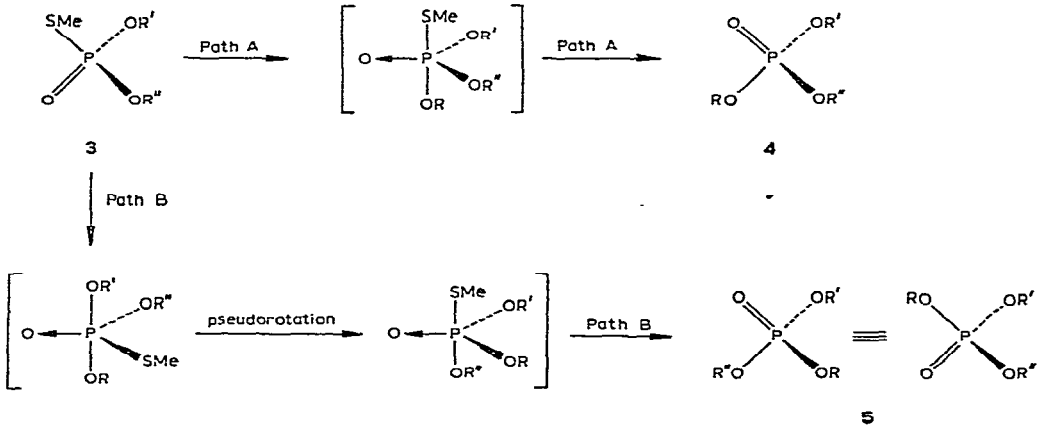
It was suggested by Westheimer[1] in 1966 that pseudorotation is less likely to occur in nucleophilic displacement reactions at phosphorus in those cyclic phosphorus esters that contain a direct carbon-to-phosphorus bond than in those esters which do not. In other words, nucleophilic substitutions at phosphorus are more likely to occur with retention of configuration in phosphoro derivatives (*i.e.*, compounds which do not contain a C–P bond) than in phosphono derivatives (*i.e.*, compounds which contain a C–P bond). Although Westheimer's experimental results with cyclic phosphorus esters have played a key role in the development of modern theories of phosphorus stereochemistry, it has not been possible to demonstrate that the same general conclusions are valid for acyclic phosphono and phosphoro esters. The reason for this is that whereas many optically active phosphono derivatives of established configuration have been prepared, until recently[2] no configurational assignments had been reported even for the very limited number of optically active phosphoro derivatives that have been described[3]. Thus, although it is well known that the phosphonothioate **1**, on treatment with sodium methoxide, affords the phosphonate **2**

*For Part V, see Ref. 5.
†Dedicated to the memory of Dr. Hewitt G. Fletcher, Jr.



1 R = menthyl 2

with inversion of configuration[4] at phosphorus, it has not been possible to determine whether substitutions in phosphorothioates such as **3** (Scheme 1) occur by direct displacement opposite sulphur with inversion of configuration (Path A) to give **4**, or by indirect displacement involving initial attack opposite oxygen followed by a pseudorotation process (Path B) to give **5**.

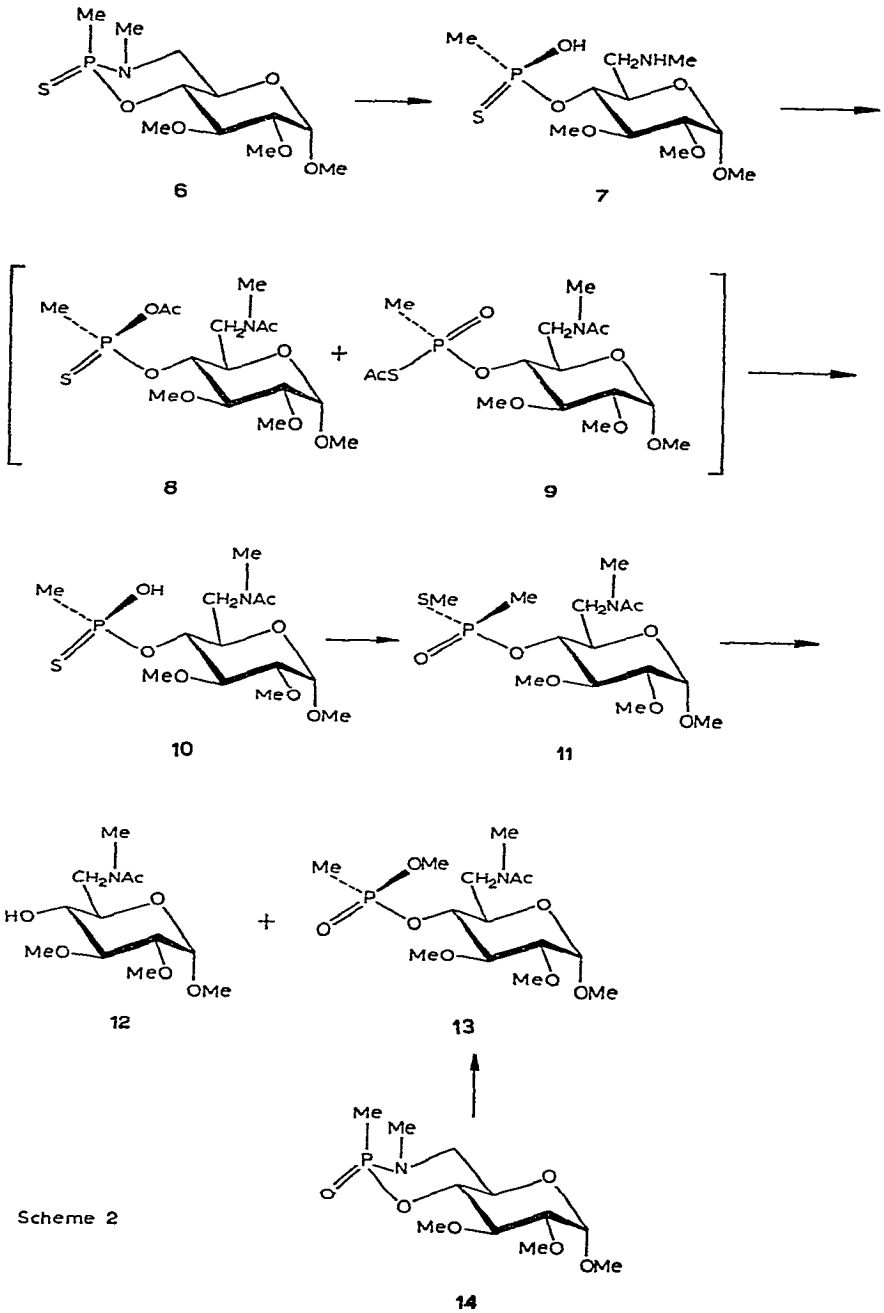


Scheme 1

We now demonstrate that by creating acyclic phosphorothioate and phophonothioate derivatives of defined absolute configuration within a carbohydrate framework, it is possible to make a direct comparison of nucleophilic substitutions in phosphoro and phosphono derivatives. This approach, using carbohydrates, circumvents the conventional difficulties (*i.e.*, difficulties in resolution, configuration assignment, and assessment of optical purity) normally associated with studies of optically active phosphorus compounds.

Preparation and reactions of acyclic phosphonothioates. — Methyl 6-deoxy-2,3-di-*O*-methyl-6-methylamino-α-D-glucopyranoside 4,6-(*R*)-methylphosphonamidothioate[5] (**6**) was converted into the acyclic *S*-methyl methylphosphonothioate derivative **11**, which has the *R* configuration at phosphorus, by the route illustrated in Scheme 2. Acidic hydrolysis of **6** gave **7** following P–N bond cleavage with inversion of configuration. Treatment of **7** with acetic anhydride in pyridine to acetylate the free methylamino group also resulted in the formation of the mixture of mixed anhydrides **8** and **9**. These were not isolated but were converted by mild hydrolysis

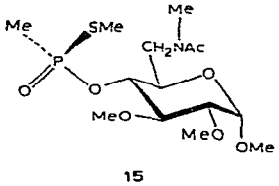
with aqueous alkali into the sodium salt of **10** which, on treatment with methyl iodide, was converted into **11**. It has been shown[6] that mixed anhydrides such as **8** and **9** are hydrolysed by nucleophilic attack at carbonyl carbon and not by attack at phosphorus. Thus, the formation of **11** from **7** involves no change of configuration at phosphorus.



Scheme 2

On treatment with sodium methoxide in methanol at room temperature, **11** afforded a mixture of methyl 6-deoxy-2,3-di-*O*-methyl-6-methylacetamido-α-D-glucopyranoside (**12**, 8%) and the methylphosphonate derivative **13** (52%), which had the *S* configuration at phosphorus. This configurational assignment, which confirmed that phosphonothioate–sodium methoxide reactions occur with inversion of configuration, followed from the result that **13** was also formed by treatment of methyl 6-deoxy-2,3-di-*O*-methyl-6-methylamino-α-D-glucopyranoside 4,6-(*R*)-methylphosphonamidate[5] (**14**) with methanolic hydrogen chloride and subsequent acetylation of the product. Acid-promoted cleavage of endocyclic P–N bonds has been shown to proceed with inversion of configuration[5].

The phosphorus epimer of **11**, *i.e.*, **15**, was prepared from methyl 6-deoxy-2,3-di-*O*-methyl-6-methylamino-α-D-glucopyranoside 4,6-(*S*)-methylphosphonamidothioate[5] (**16**) in a manner similar to that for the conversion of **6** into **11**. Treatment of **15** with sodium methoxide in methanol at room temperature afforded the glucopyranoside 4-[(*R*)-methyl methylphosphonate] derivative **17** (47%) and the phosphorus-free product **12** (26%).



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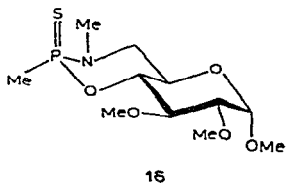

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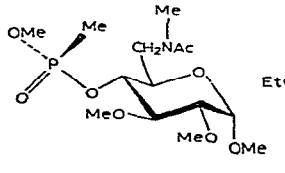

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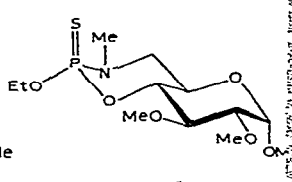

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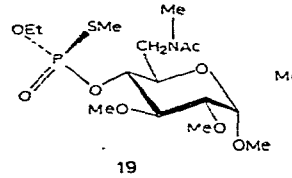

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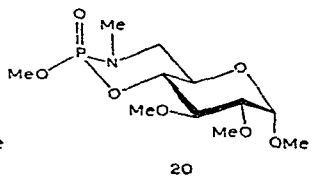

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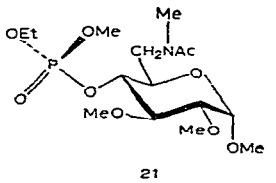

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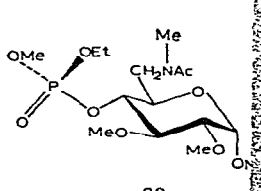

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The isomers **13** and **17**, although indistinguishable chromatographically, were conveniently distinguished by their n.m.r. spectra. Restricted rotation of the methylacetamido group caused doubling of some of the signals; notably, the P–Me and P–OMe signals in both isomers appeared as pairs of doublets. Whereas the shift in signals in **13** was small for the P–Me group (doublets centred at 1.57 and 1.60 p.p.m.) and larger for the P–OMe group (doublets centred at 3.77 and 3.87 p.p.m.), the reverse was true in **17** (P–Me, 1.52 and 1.62; P–OMe, 3.78 and 3.82 p.p.m.). As a consequence of the quite distinct signals, small (>5%) amounts of one isomer as an impurity in the other could be detected. With regard to the above limitation, both **13** prepared from **11** and **14**, and **17** prepared from **15**, were considered to be stereochemically pure on the basis of the n.m.r. evidence.

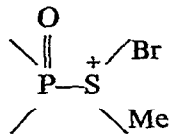
The above results show clearly that, in phosphonothioates, P–S bond-cleavage caused by nucleophilic attack by sodium methoxide takes place with inversion of configuration. Also, it is shown that the relative proportion of P–S and P–O bond-cleavage appears to depend very considerably on the stereochemical environment of the asymmetric phosphorus atom. Thus, from **11** the ratio of P–S to P–O bond-cleavage was 6.5:1, whereas from **15** the ratio was 1.8:1.

Preparation and reactions of an acyclic phosphorothioate. — The cyclic ethyl phosphoramidothioate derivative **18**[5] was converted into the ethyl *S*-methyl phosphorothioate derivative **19** by procedures similar to those used for forming **11** from **6**. Compound **19** has the *S* configuration at phosphorus. On treatment with sodium methoxide in methanol at room temperature, the *S*-methyl derivative **19** afforded the *O*-methyl derivative **21**. That **21** had the *R* configuration at phosphorus, *i.e.*, that the transformation of **19** into **21** proceeded with retention of configuration, was confirmed when **21** was also formed by sequential acid-catalysed methanolysis and acetylation of the (*R*)-methylphosphonamidate **20**. Compound **21**, $[\alpha]_D$ +82°, and the isomer **22**, $[\alpha]_D$ +90°, both of which have been described previously[5], are most-easily distinguished by comparison of their n.m.r. spectra. The P–OMe doublet, which appears as a double doublet due to restricted rotation of the *N*-methylacetamido group, has signals at 3.75, 3.81, 3.86, and 3.92 p.p.m. in **21**, and at 3.76, 3.79, 3.87, and 3.90 in **22**.

DISCUSSION

The above results, which show that alkylphosphonothioate–methoxide reactions occur with *inversion* of configuration at phosphorus (at least in respect of the P–S bond-breaking reaction) and that phosphorothioate–methoxide reactions occur with *retention* of configuration, are consistent, at least superficially, with the hypothesis that pseudorotation can take place more readily in the absence, than in the presence, of a C–P bond. Also, the finding that the relative proportions of P–O and P–S bond-cleavage in the phophonothioates **11** and **15** depend on the stereochemistry at phosphorus is consistent with previous observations[7,8] that the steric course of displacements from phosphorus carrying *O*-alkyl and *S*-alkyl ligands is very dependent on the nature of all the groups attached to phosphorus. However, perhaps in addition to previous results, these findings emphasise that steric as well as electronic effects can have a significant influence on the ratio of the P–O and P–S bond-breaking processes.

Although the main purpose of the work described in this paper was to compare the stereochemistry of P–S bond-breaking reactions with sodium methoxide in phosphonothioates and phosphorothioates, the presence of the carbohydrate moiety also enabled attention to be focused on the importance of stereochemical factors on another type of P–S bond-breaking reaction. When simple methylphosphonothioates, such as (*S*)-ethyl *S*-methyl methylphosphonothioate[9], are treated with bromine in methanol, (*R*)-ethylmethyl methylphosphonate is formed with inversion of configuration in a stereospecific reaction. In contrast, when **11** was treated with bromine

in methanol, **13** and **17** were formed in the ratio 1:4, *i.e.*, displacement of the S–Me group occurred mainly with retention of configuration. Similarly, when **15** was treated with bromine in methanol, the methanolysis again took place mainly with retention of configuration, affording **13** and **17** in the ratio 2:1. Since bromine in methanol does not cause racemisation of either **13** or **17** under the conditions used, the product ratio must be determined during the displacement process. Presuming that a group such as  is formed prior to the bond-breaking process, it may be that the steric course of the displacement is, in part, determined by the bulk of this group in relation to the carbohydrate moiety, thereby giving rise to a situation which does not exist in dialkyl alkylphosphonothioates.

It is not the purpose of this paper to suggest possible mechanisms for the various reactions described. At this stage, it appears that although the main factors which affect our knowledge of the stereochemistry of reactions at phosphorus may be already appreciated[10], the interdependence of these factors will only become apparent when more experimental data are available. The use of sugar derivatives for providing such data has obvious possibilities.

EXPERIMENTAL

Unless stated otherwise, p.m.r. spectra were measured in deuteriochloroform with a JEOL, JNM-4-H-100 n.m.r. spectrometer at 100 MHz. For most of the methylacetamido derivatives, many (but not all) of the signals were doubled because of restricted rotation of the methylacetamido group. Where signal-doubling was observed, values for both signals are reported.

*Methyl 6-deoxy-2,3-di-*O*-methyl-6-methylacetamido-α-*D*-glucopyranoside 4-[(R)-S-methyl methylphosphonothioate]* (**11**). — A solution of the cyclic methylphosphonamidothioate **6**[5] (1.9 g) in dilute, aqueous hydrochloric acid containing a little ethanol was stored at room temperature for 1 h and then concentrated. The residue was dried by repeated evaporation of toluene and treated overnight at room temperature with pyridine containing acetic anhydride, and the mixture was then concentrated. [A small portion of the residue was eluted from silica gel in benzene–acetone–methanol (7:2:1) and the major product (R_F 0.6) was examined by n.m.r. and i.r. spectroscopy; the spectra were consistent with a mixture of the mixed anhydrides **8** and **9**]. The residue was stored in dilute, aqueous, ethanolic sodium hydroxide for 2 h, methyl iodide was then added, and the solution was stored overnight at room temperature. The solution was extracted with chloroform, the extract was dried and concentrated, and the residue was eluted from silica gel with chloroform–methanol (9:1) to afford **11** (R_F 0.6; 1.4 g, 60%), $[\alpha]_D$ +93° (*c* 2, chloroform); δ_H (60 MHz) 1.83, 1.86 (PMe, $J_{P,Me}$ 16 Hz); 2.10, 2.13 (NAc); 2.40 (PSMe, $J_{P,Me}$ 14 Hz); 3.00, 3.14 (NMe); 3.39 (OMe), 3.52 (OMe), 3.59 (OMe).

*Methyl 6-deoxy-2,3-di-*O*-methyl-6-methylacetamido-α-*D*-glucopyranoside 4-[(S)-methyl methylphosphonate]* (**13**). — (*a*) A solution of **11** (0.5 g) in M sodium methoxide in methanol (10 ml) was stored at room temperature for 1 h. No **11** then remained, and both **12** and **13** were detected by t.l.c. in benzene–acetone–methanol (7:3:1) (triple irrigation, R_F values: **11**, 0.7; **12**, 0.75; **13**, 0.65). The solution was neutralised with carbon dioxide, diluted with water, and extracted with chloroform, and the extract was dried and concentrated. Following chromatography on silica gel, **12** (28 mg 8%) and **13** (0.25 g 52%), $[\alpha]_D$ +96° (*c* 1.8, chloroform), were obtained; δ_H (**13**) 1.57, 1.60 (PMe, $J_{P,Me}$ 18 Hz); 2.09, 2.15 (NAc); 2.99, 3.14 (NMe); 3.35, 3.37 (OMe); 3.52 (OMe), 3.57, 3.59 (OMe); 3.77, 3.87 (POMe, $J_{P,Me}$ 12 Hz).

(*b*) Compound **13** was also prepared from **14**. A solution of **14** (0.25 g) was stored for 15 min in methanolic hydrogen chloride at room temperature, and then concentrated. A solution of the residue in pyridine containing acetic anhydride was stored overnight at room temperature, and then concentrated. The residue was eluted from silica gel with benzene–acetone–methanol (7:3:1) to afford **13** (0.2 g, 64%), $[\alpha]_D$ +95° (*c* 2, chloroform), having the same n.m.r. parameters as those reported above.

*Methyl 6-deoxy-2,3-di-*O*-methyl-6-methylacetamido-α-*D*-glucopyranoside 4-[(S)-S-methyl methylphosphonothioate]* (**15**). — A solution of **16** (1.2 g) was converted into **15** (1.1 g, 74%) by essentially the procedure used for the conversion of **6** into **11**. Compound **15** had $[\alpha]_D$ +97° (*c* 1.6, chloroform); δ_H 1.85, 1.89 (PMe, $J_{P,Me}$ 16 Hz); 2.06, 2.12 (NAc); 2.37, 2.42 (PSMe, $J_{P,Me}$ 14 Hz); 2.96, 3.09 (NMe); 3.34 (OMe), 3.49 (OMe), 3.56 (OMe).

*Methyl 6-deoxy-2,3-di-*O*-methyl-6-methylacetamido-α-*D*-glucopyranoside 4-[(R)-methyl methylphosphonate]* (**17**). — A mixture of **17** (0.18 g, 47%) and **12** (75 mg, 26%) was obtained when **15** (0.4 g) was treated with sodium methoxide as described for the corresponding reaction of **11**. Compound **17** had $[\alpha]_D$ +115° (*c* 1.2, chloroform); δ_H 1.52, 1.62 (PMe, $J_{P,Me}$ 18 Hz); 2.08, 2.13 (NAc); 2.97, 3.11 (NMe); 3.35 (OMe), 3.52 (OMe), 3.58 (OMe); 3.78, 3.82 (POMe, $J_{P,Me}$ 11 Hz).

*Methyl 6-deoxy-2,3-di-*O*-methyl-6-methylacetamido-α-*D*-glucopyranoside 4-[(S)-ethyl S-methyl phosphorothioate]* (**19**). — A solution of the cyclic phosphoramidothioate derivative **18** (2.5 g) was converted into **19** (2.5 g, 85%) by essentially the same sequence of reactions as used to convert **6** into **11**. Compound **19** (R_F 0.7 in chloroform–methanol, 9:1) had $[\alpha]_D$ +70° (*c* 1.3, chloroform); δ_H 1.40 (CH_3CH_2–); 2.09, 2.14 (NAc); 2.35, 2.40 (SMe, $J_{P,Me}$ 16.5 Hz); 3.36 (OMe), 3.53 (OMe), 3.59 (OMe).

Treatment of **11** *and* **15** *with bromine in methanol.* — An excess (10 molar) of bromine was added dropwise to a solution of the sugar derivative (**11** or **15**, 0.3 to 0.5 g) in methanol (10 ml) for 0.5–1 h. The solution was diluted with chloroform, washed with aqueous sodium hydrogen carbonate, dried, and concentrated. The mixture of **13** and **17** was separated from minor products by chromatography on silica gel with benzene–acetone–methanol (7:2:1), and examined by n.m.r. spectroscopy.

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