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# REACTION OF SUGAR EPOXIDES WITH PHOSPHOROTHIOIC ACIDS, EVIDENCE OF THE PENTACOORDINATE PHOSPHORUS INTERMEDIATE IN THE REACTION OF 5,6-ANHYDRO-1,2-O-ISOPROPYLIDENE-α-D-GLUCOFURANOSE WITH PHOSPHOROTHIOIC ACIDS

WIESŁAWA KUDELSKA AND MARIA MICHALSKA*

Laboratory of Organic Chemistry, Faculty of Pharmacy
Medical Academy, 90-151, Łódź, Muszyńskiego 1, POLAND

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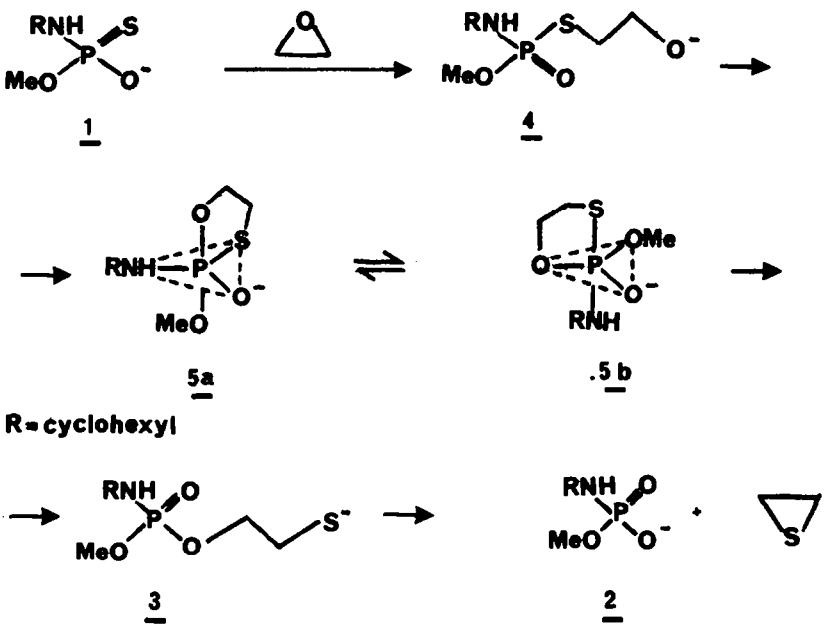
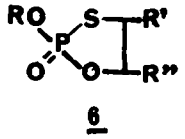
Abstract - The reaction of sugar epoxides with organic monothioacids of phosphorus provides a convenient procedure for synthesizing sugar thiophosphates and mercaptosugar phosphates. Based on detailed analysis of intermediates and factors influencing the reactivity of phosphorus monothioacids with sugar epoxides the reaction scheme is proposed involving pentacoordinate intermediate which undergoes endo or/and exocyclic elimination. It was found that the reaction of 5,6-anhydro-1,2-O-isopropylidene-α-D-glucofuranose 7 with phosphorothioic acids 8a and 8b yields three types of products in equilibrium: the thiophosphates 9a and 9b, the oxathiaphospholanes 11a and 11b and the mercaptophosphates 10a and 10b. Under more drastic conditions the phosphates 10a and 10b can be converted irreversibly into the episulphide 12 and phosphoric acids 13a and 13b, respectively. It is clearly possible that both compounds 10 and 11 can be formed from the same pentacoordinate intermediate, and the experimental evidence provides strong support for it.

Migration of the phosphoryl group bound to oxygen to the vicinal hydroxyl group in the 1,2-diol system, which occurs in many biological processes, has long been the subject of extensive studies.[1,2] A similar migration of the phosphoryl group from sulphur to oxygen has been observed in the reaction of oxiranes with monothioacids of phosphorus[3] and in the reactions of carbanions containing the thiophosphoryl group with carbonyl compounds[4] to give episulphides or olefines in the final stage. Analyzing the course of reaction between sodium methyl-N-cyclohexyl phosphoramidothioate 1 and ethylene oxide, in which the only characterized products were ethylene sulphide and sodium methyl-N-cyclohexyl phosphate 2, Hamer[5] made the assumption that this reaction must occur through the intermediate ester 3, which in turn is formed from the ester 4 (Scheme 1). This conversion 4 → 3, was explained by Hamer, according to Westheimer's principle[6], as the reaction involving V-coordinate intermediate 5a and 5b which were interconvertible through a pseudorotation process 5a → 5b. The author simultaneously assumed that the pseudorotation process is faster than the exocyclic elimination of the methanolate anion from the intermediate product 5a which would result in the




Scheme 1

cyclic compound 6. The transphosphorylation under discussion represents a particular case of nucleophilic substitution at tetracoordinate phosphorus atom. Products of type 3 and 4 were observed by Arbuzov and Nuretdinova[7] in the reaction of alkene oxides with monothioacids of phosphorus. These authors also observed the formation of cyclic products, oxathiaphospholanes of type 6 in the above reactions. In the case of aryloxy groups bound to phosphorus, 6 were final reaction products.



6

$\delta\,^{31}P = +40 - +45$ ppm

R=Ph

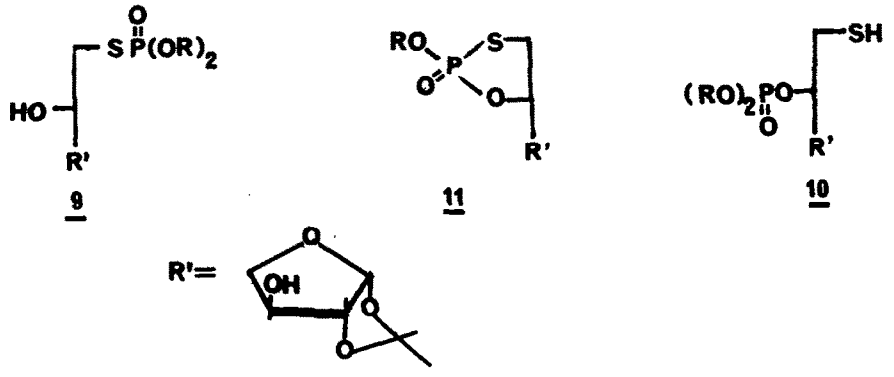
We observed the formation of products 3 in our work concerning the synthesis of unsaturated sugars through the reaction of sugar oxiranes with alkylammonium phosphoroselenoates.[8] On this basis a transphosphorylation mechanism of the phosphoryl group bound to selenium, to the vicinal hydroxyl group, analogous to that proposed by Hamer, was suggested. Recently, we have found that when the above reaction is carried out with O,O-di-t-butylphosphoroselenoate, it can be stopped at the stage of the product 4.[9]

Our present work is a continuation of the investigations devoted to the synthesis of sugar thiiranes.[10] We found that careful monitoring of the reaction of monothioacids of phosphorus with 5,6-anhydro-1,2-O-isopropylidene-α-D-glucofuranose 7 allows deeper insights into the mechanism of that reaction. It affords

new, convincing arguments for the participation of the pentacoordinate intermediate 14 in the transphosphorylation step 9 ⟶ 10.

## RESULTS AND DISCUSSION

Thorough investigations of the reaction of the model oxirane 7 with monothioacids of phosphorus 8 were performed on two model acids: O,O-diethylphosphorothioic acid 8a and O,O-diphenylphosphorothioic acid 8b. The reactions were carried out with free acids in inert solvents. The temperature ranges were adjusted so that the formation of intermediate products could be followed by $^{31}$P-NMR spectroscopy. The advantage of performing the reaction with free acids in non-aqueous solvents is that one can avoid complications connected with the hydrolytic process. In this way it was possible to demonstrate that intermediate products represented in Scheme 2 were formed.




Scheme 2

In the course of investigations which are not included in this paper, we have been able to isolate the product 9 when using the acid 8 (R=$^{t}$Bu)[9] and also products of type 10.[11]

The reaction of the oxirane 7 with the acid 8a (R=Et) was performed in toluene solution, at 18°C using stoichiometric amounts of reagents. The progress of the reaction in course of time, as viewed by $^{31}$P-NMR spectroscopy is represented in Figure 1.

The appearance of a signal characterized by chemical shift $\delta\ ^{31}P = +26.0$ ppm was observed after a few minutes. Twenty minutes later two new signals appeared, $\delta\ ^{31}P = +42.2$ and +41.2 ppm. During the next few hours the intensity of the signals at $\delta = +26.0$, +42.2 and +41.2 ppm increased, and after 3 hrs a new signal at −0.6 ppm appeared. The signals at +42.2 and +41.2 ppm showed maximum

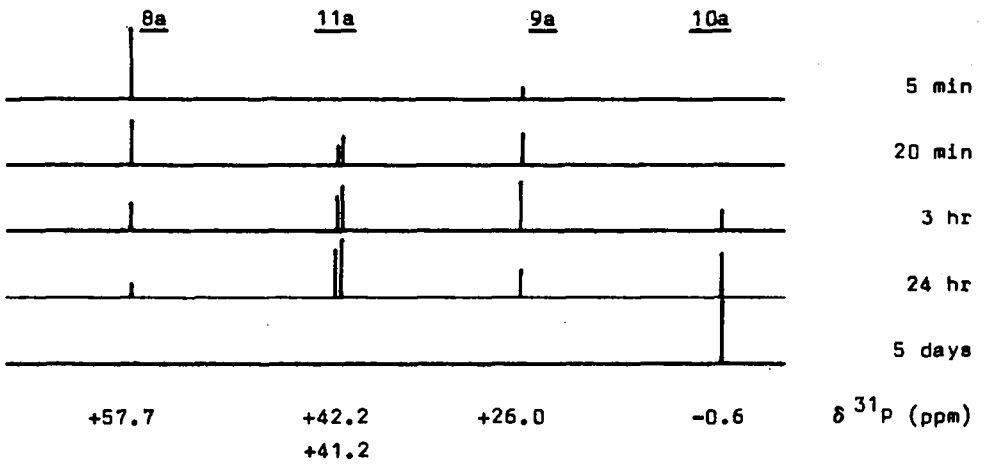



Figure 1

intensity after 24 hrs, during which time the signal at +26.0 ppm diminished and the signal at -0.6 ppm considerably increased. After 5 days all signals including the signal corresponding to the starting O,O-diethylphosphorothioic acid ( $\delta^{31}P$= +57.7 ppm) had disappeared and only the signal at -0.6 ppm was observed.

The signal at +26.0 ppm can be ascribed to the adduct 9a by comparison with the $\delta^{31}P$ value found for the product 9 (R=$^{t}$Bu)[9] as well as with the adducts described by Russian workers.[3] The signal at $\delta$ = -0.6 ppm corresponds to the isomerisation product 10a. This is confirmed by the IR spectra of the isolated product. The signals at +42.2 and +41.2 ppm occur in the region characteristic of chemical shifts ascribed to the oxathiaphospholanes.[3] Additional evidence for the structure 11 is the presence of two signals which correspond to two diastereoisomers.

The reaction of 7 with 8a can be steered towards the formation of the product 11a (R=Et) by removing ethyl alcohol from the reaction medium. Equimolar amounts of 8a and 7 were dissolved in toluene and allowed to react at room temperature until the signal corresponding to the starting thioacid 8a (R=Et) disappeared. During that time, ethyl alcohol formed was continuously removed under vacuum. It was found that under these conditions, the post-reaction mixture contained, besides diastereomeric oxathiophospholanes 11a ( $\delta^{31}P$= +42.2 and +41.2 ppm), only minute amounts of the mercaptophosphate 10 ( $\delta^{31}P$= -0.6 ppm).

In the same reaction carried out with excess ethyl alcohol, however, no oxathiaphospholanes were observed, at least in amounts detectable by the spectroscopic method used.

The reaction of 7 with O,O-diphenylphosphorothioic acid 8b proceeds with high selectivity towards diastereoisomeric oxathiaphospholanes 11b ( $\delta^{31}P$= +40.6 and 40.0 ppm) in 1:2 ratio, respectively (Figure 2).

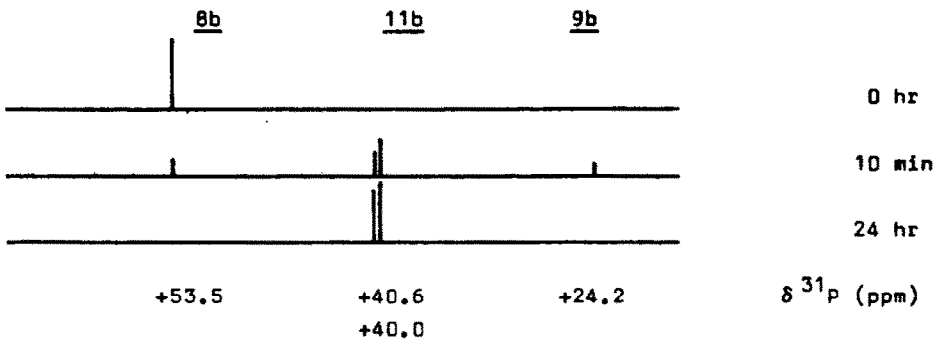
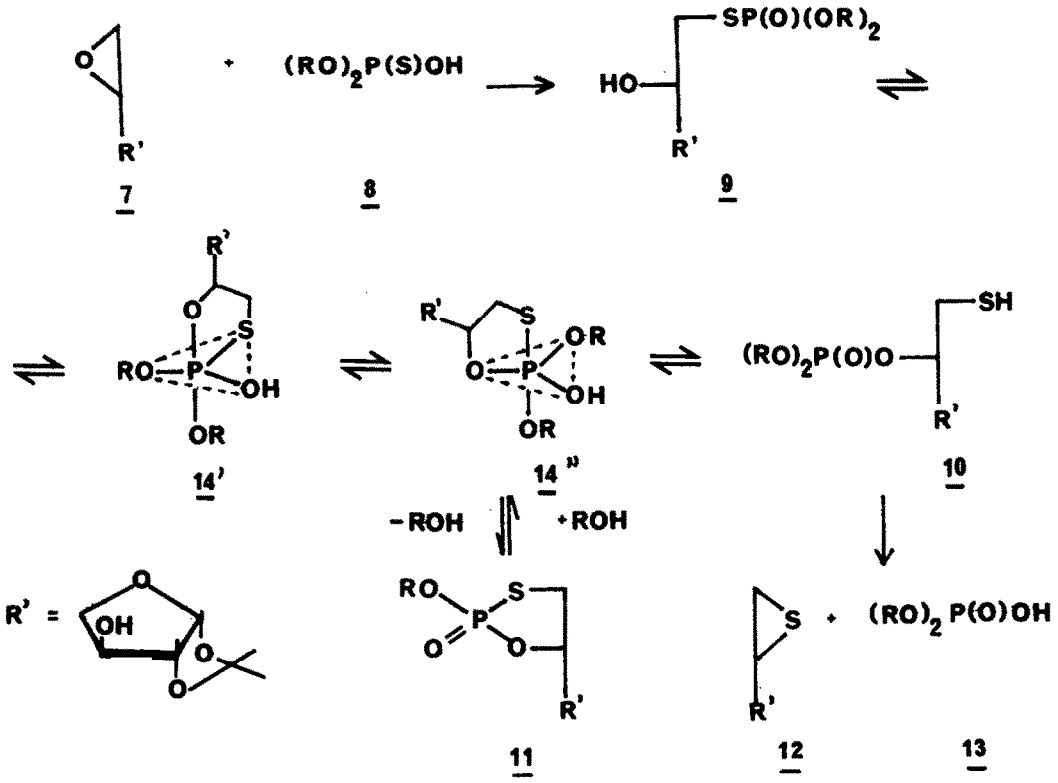



Figure 2

The question is, what role do the oxathiaphospholanes play in the mechanism of the reaction between alkene oxides and phosphorothioic acids? In other words, are the oxathiaphospholanes intermediate products in the isomerisation 9 ⟶ 10 or not? The fact that oxathiaphospholanes are formed on elimination of alcohol strongly suggests the existence of equilibria between 9, 10, and 11.

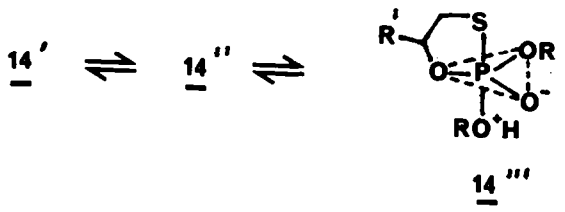
The intramolecular nucleophilic substitution at phosphorus results from the attack of the hydroxyl group on phosphorus in the phosphoryl group of compound 9 and leads to the formation of the pentacoordinate system 14 (Scheme 3).




Scheme 3

According to Westheimer, pentacoordinate compounds like 14 should be stabilized by the presence of the five-membered ring.

In order to fulfill the rule of apical entry and apical departure, the ligand re-arrangement 14′ ⟶ 14′′ is required, with the OH group as a pivot. The pentacovalent system exists in equilibrium with its protonated forms, e.g.: 14′′′.



Scheme 4

The proton source can be internal, from the OH group which on deprotonation increases its equatoriality, or external, from the monothiophosphoric acid. The V-coordinate phosphorus intermediate 14′′ or its protonated form 14′′′ can disintegrate in two ways: through rupture either of the P-O bond, or of the P-S bond. The first route leads to an oxathiaphospholane 11, the second to the product 10 containing a free thiolo group. The exocyclic elimination affording oxathiaphospholane is a reaction leading to a chiral system 11. The process of formation of compound 11 proceeds, according to the experimental data, with stereochemical selection.

In the case of R=phenyl, the equilibrium is shifted towards oxathiaphospholanes because phenoxide ion is a good leaving group. When R=Et, it is possible to shift the equilibrium towards the oxathiaphospholanes by removal of ethyl alcohol. It is obvious that in the case of further transformation of compound 10 into episulphide 12 the equilibrium is shifted towards 12 due to the irreversible character of the reaction.

Returning to the question of the role of compound 11 in the reaction under consideration, it should be emphasized that 11 cannot be the intermediate product in the isomerisation process 9 ⟶ 10. The pentacoordinate system 14 is the true intermediate product in this transformation. The oxathiaphospholanes 11 are formed through the same intermediate 14 in a parallel elimination reaction of alcohol or phenol. They are in equlibrium with the product 9 as well as with 10 through the pentacoordinate system 14. The formation of 11 seems to be kinetically controlled. When the eliminated alcohol is not removed, 11 undergoes transformation into 10 (which is thermodynamically the more stable product) or,

under more drastic conditions, into the final reaction product which has the episulphide structure 12. This final reaction step is accompanied by the elimination of the corresponding phosphoric acid 13. In this sense, it can be considered as the end of the oxygenation process of the starting phosphorothioic acid.

The ease of exocyclic elimination of alcohol or phenol from the pentacoordinate system 14 is worth emphasizing. In spite of the fact that the P-S bond in the apical position is likely to undergo an easier fission than the analogous P-O bond, the dominating factor in the reaction is the leaving group ability of the alkoxy or aryloxy group in its protonated form.

Our results provide strong support for mechanistic schemes proposed by other authors for the transphosphorylation reaction in 1,2-diol systems[1,2] and analogous systems containing sulphur[5], selenium[8] or tellurium[12]. They demonstrate the importance of pentacoordinate phosphorus intermediates in nucleophilic displacement at tetracoordinate phosphorus atom according to Westheimer's[6] conceptions.

## EXPERIMENTAL

$^{31}P$ NMR spectra were recorded with a Jeol 60 MHz/FT operating at 24.3 MHz ($CHCl_3$ as solvent and 85% $H_3PO_4$ as external reference). The chemical shifts are reported as $\delta$ values ($\pm$ 1 ppm).

5,6-Anhydro-1,2-O-isopropylidene-α-D-glucofuranose (7) was prepared according to Wiggins[13]; m.p. 133-134°C (benzene).

O,O-Diethylphosphorothioic acid (8a) was prepared by standard procedure consisting of addition of elemental sulphur to O,O-dialkylphosphite in the presence of sodium ethanolate followed by acidification of the sodium salt obtained, chloroform extraction, drying and distillation. Colorless oil, b.p. 107-109°C/2.5 mm Hg (lit.: b.p. 106-107°C/2.5 mm Hg[14]). NMR: +57.7 (one signal).

O,O-Diphenylphosphorothioic acid (8b) was prepared by addition of elemental sulphur to O,O-diphenylphosphite[15] (colorless oil, b.p.110-112°C/0.05 mm Hg ; lit.: b.p. 145-148°C/0.15 mm Hg[16] ; NMR: +0.2) in the presence of dicyclohexylamine. The dicyclohexylammonium salt of 8b, m.p. 193-195°C (ethanol/water 2:1); NMR: +46.7; Analysis $C_{24}H_{34}O_3NPS$ requires: C, 64.41; H, 7.66; P,6.92; S, 7.16; found: C, 64.64; H, 7.83; P, 6.85; S, 6.86. The dicyclohexylammonium salt was converted into the sodium salt which on acidification with HCl, chloroform extraction, drying and evaporation of the solvent gave 8b as colorless, thick oil. NMR: +53.5 (one signal). Attempted purification of 8b by high-vacuum distillation resulted in decomposition (several $^{31}P$ signals).

The reactions represented in Figure 1 and Figure 2 were performed in NMR tubes at 18°C using stoichiometric amounts of reagents.

Reaction of 7 with 8a

390 mg (1.93 mmol) 7, 330 mg (1.93 mmol) 8a were dissolved in toluene (2 ml).

Reaction of 7 with 8b

480 mg (2.4 mmol) 7, 640 mg (2.4 mmol) 8b were dissolved in benzene (2.5 ml). The course of experiments is described in Results and Discussion.

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REFERENCES

1. O. Bailly, Ann. Chim., 6, 96-154 (1916).
2. A. Pondaven and G. Sturz, Bull. Soc. Chim. Fr., 215-229 (1978); S.L. Buchwald, D.H. Pliura and J.R. Knowles, J. Am. Chem. Soc., 106, 4916-4922 (1984) and references therein.
3. O.N. Nuretdinova, F.F. Guseva and B.A. Arbuzov, Izv. A.N. SSSR, Ser. Khim., 2625-2627 (1976); O.N. Nuretdinova and F.F. Guseva, ibid., 2594 (1980).
4. K. Tanaka, N. Ono, Y. Kubo, and A. Kaji, 890 (1979); K. Tanaka, H. Unema, N. Ono and A. Kaji, Chem. Lett., 1039 (1979).
5. N.K. Hamer, J. Chem. Soc. Chem. Comm., 1399 (1968); D.C. Gay and N.K. Hamer, J. Chem. Soc. (B), 1123-1127 (1970).
6. F.H. Westheimer, Acc. Chem. Res., 1, 70-78 (1968).
7. O.N. Nuretdinova and B.A. Arbuzov, Izv. A.N. SSSR, Ser. Khim., 1130-1132 (1981) and references therein.
8. W. Kudelska and M. Michalska, Tetrahedron 37, 2989-2994 (1981).
9. P. Lipka and M. Michalska, unpublished results.
10. W. Kudelska and M. Michalska, Carbohydr. Res., 83, 43-49 (1980); W. Kudelska and M. Michalska, ibid., 90, 1-6 (1981).
11. In our previous paper ref. 10, 83, 43-49 (1980) the products of epoxide ring opening with monothioacids of phosphorus were erroneously ascribed structure 9; they were in fact mercaptophosphates 10.
12. D.L.J. Clive and S.M. Menchen, J. Chem. Soc., Chem. Comm., 658 (1977).
13. L.F. Wiggins, Methods in Carbohydrate Chemistry, Vol. 2, 190; Academic Press, 1963.
14. M.I. Kabachnik, C.T. Joffe and T.A. Mastryukova, Zh. Obshch. Khim. 25, 684 (1955).
15. A.E. Arbuzov and M.G. Imaev, Izv. A.N. SSSR, Ser. Khim., 171 (1959).
16. E.V. Kuznecov and R.K. Valetdinov, Trudy Kazansk. Khim. Tekhnol. Inst. S.M. Kirova, 23, 187-189 (1957); C.A., 52, 8940 d (1958).