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EPOXIDE RING-OPENING REACTIONS OF METHYL 2,3-ANHYDRO-HEXOPYRANOSIDES AND A NEW SYNTHESIS OF 2,3-EPISULPHIDES*

WIESŁAWA KUDELSKA, MARIA MICHALSKA, AND ANNA ŚWIĄTEK
Department of Organic Chemistry, Faculty of Pharmacy, Medical Academy, 90-145 Łodz, Narutowicza 120A (Poland)

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ABSTRACT

Treatment of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**1**) with 2-mercapto-5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinane (**3**) gave methyl 4,6-*O*-benzylidene-3-(5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinanylthio)-α-D-altropyranoside (**4**) in high yield. The action of **3** on methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside (**2**) gave methyl 2-(5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinanylthio)-α-D-altropyranoside (**9**) and methyl 4,6-*O*-benzylidene-3-(5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinanylthio)-α-D-glucopyranoside (**8**). The formation of **9** is due to selective debenzylidenation of the *trans*-diaxial adduct **7**, whose presence was proved by ^{31}P-n.m.r. spectroscopy. Compound **8** is stable under these reaction conditions. Debenzylidenation of **4** to give methyl 3-(5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinanylthio)-α-D-altropyranoside (**6**) occurred when the time of the reaction of **1** with **3** was prolonged. The reaction of methyl 2,3-anhydro-α-D-mannopyranoside (**5**) with **3** also gave **6**. The epoxides **1** and **2** react with the triethylammonium salt of **3** to give the 2,3-episulphides **10** and **11**, respectively, in which the thi-irane ring is of opposite configuration to that of the starting epoxides.

INTRODUCTION

O,O-Dialkylphosphoro-thioic and -dithioic acids react with 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose under mild conditions to give 6-(dialkoxyphosphinylthio)-α-D-glucofuranoses, whereas the dialkylammonium salts effect quantitative transformation into the corresponding episulphide having the β-L-*ido* configuration. We now report extensions of these reactions to methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside[2] (**1**) and -allopyranoside[3] (**2**). The reactions of the epoxide rings in **1** and **2** with nucleophiles is well-documented[4].

Rigid, pyranoid epoxides usually follow the Fürst–Plattner rule of diaxial ring-opening[5,6]. However, there are some exceptions to this generalisation. Di-

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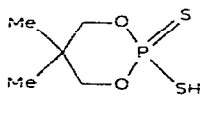
equatorial products preponderate when ring opening of epoxides is effected with acidic reagents[7]. These reagents removed the ring-stabilising 4,6-*O*-benzylidene group probably prior to opening of the epoxide ring, so that the steric course of the reactions is not so easily predictable. Another exception to the Fürst–Plattner rule in the sugar-epoxide series is ring opening in the presence of iodine[8]. It was suggested that S_N1-type reaction occurred, involving initial formation of a complex between iodine and the epoxide oxygen atom.

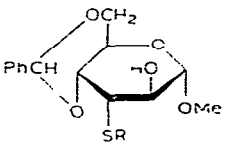
The cleavage of epoxide rings using an organophosphorus reagent can be monitored by using ^{31}P-n.m.r. spectroscopy, and the proportions of the adducts formed can be determined prior to their isolation from the crude reaction mixture. Previous quantitative evaluations of such reactions have been based on the yields of the isolated products.

RESULTS AND DISCUSSION

The reactions of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**1**) and -allopyranoside (**2**) with 2-mercapto-5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinane[9] (**3**) were performed under mild conditions, at room temperature, and in



3 δ ^{31}P +76.5



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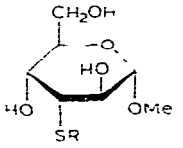

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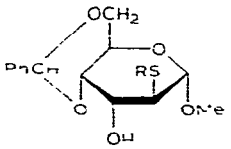

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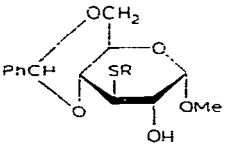

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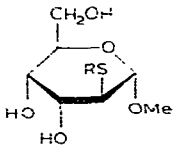

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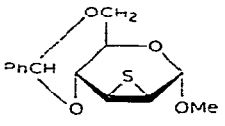

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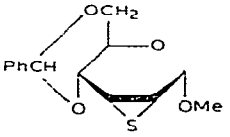

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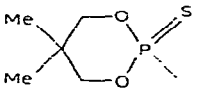
R = 

inert solvents. The reaction times were established on the basis of the disappearance of the ^{31}P-n.m.r. signal (δ ^{31}P +76.5) for the starting *O,O*-dialkylphosphorodithioic acid.

When the *manno*-epoxide **1** was treated with **3**, one product (**4**) was formed in quantitative yield, in which a 2,3-diaxial configuration was established on the basis of the low $J_{1,2}$ value ($\sim$1 Hz). It was concluded also that the nucleophile attacked at position 3. Thus, **4** was methyl 4,6-*O*-benzylidene-3-(5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinanylthio)-α-D-altropyranoside and its formation accords with the Fürst–Plattner rule.

Under similar reaction conditions, methyl 2,3-anhydro-α-D-mannopyranoside[10] (**5**) gave a single product (**6**) in quantitative yield, for which the *altro* configuration was indicated by the low value ($\sim$1 Hz) of $J_{1,2}$. Thus, in spite of the enhanced ring-flexibility of **5**, no 2,3-diequatorial product was formed, possibly because equatorial attack at C-2 by the large phosphorinanylthio group was sterically hindered by the axial MeO-1 group.

The reaction between the *allo*-epoxide **2** and **3** did not show the same stereo- and regio-specificity as the reactions of the anhydrides **1** and **5**. The diaxial, 2-substituted adduct **9** and the diequatorial, 3-substituted adduct **8** were isolated in the ratio 2:1.

During the reaction, selective debenzylidenation of the 2-substituted, *trans*-diaxial adduct **7** occurred to give **9**, whereas the 4,6-*O*-benzylidene derivative **8** was stable. The *trans*-diaxial and *trans*-diequatorial structures of **9** and **8**, respectively, were proved by the $J_{1,2}$ values, namely, 3 Hz for **8** and $\sim$1 Hz for **9**. The presence of **7** (δ ^{31}P + 87) at the beginning of the reaction was confirmed by ^{31}P-n.m.r. spectroscopy.

It may be concluded that **4** is also susceptible to debenzylidenation, although not as readily as **7**. Application of ^{31}P-n.m.r. spectroscopy demonstrated the formation of the debenzylidenated product **6** when the reaction of **1** and **3** was allowed to continue for 3 days at room temperature. The above results indicate that the rate of debenzylidenation diminishes in the series **7** > **4** > **8**. Similar results were obtained by Kovar and Jary[11] in their work on the solvolysis in acidic media of methyl 4,6-*O*-benzylidene-α- and -β-hexopyranosides substituted at positions 2 and 3. These effects cannot be rationalised at present.

The reactions of the *manno*-epoxide **1** and *allo*-epoxide **2** with the triethylammonium salt of **3** (δ ^{31}P +108.0) was investigated next, in relation to the synthesis of methyl 4,6-*O*-benzylidene-2,3-dideoxy-2,3-epithio-α-D-allo- and -manno-pyranosides. In sugar chemistry, sulphur derivatives are important starting materials for the introduction of other functional groups[12] and as models for enzyme reactions.

The transformation of the "rigid" epoxides into episulphides requires reaction conditions that are more drastic than those[1] necessary for 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose. When a solution of **2** in acetonitrile was boiled under reflux for several hours with equimolar amounts of **3** and triethylamine, 85% of the known[13] methyl 4,6-*O*-benzylidene-2,3-dideoxy-2,3-epithio-α-D-mannopyranoside

(**10**) was obtained. Application of ^{31}P-n.m.r. spectroscopy revealed unreacted triethylammonium salt of **3** together with monothioic acid.

The *manno*-epoxide **1** reacted more slowly, and only 60% of the 2,3-*allo*-episulphide[14] (**11**) had been formed after 60 h.

As previously suggested[1], the formation of the intermediate adducts in the epoxide–episulphide transformation under the influence of dialkylphosphorodithioic acid salts is unavoidable. Inspection of Dreiding models suggests that the configuration of the 2,3-substituents most advantageous for the formation of the pentacovalent phosphorus intermediate is the *trans*-diequatorial. However, our recent results show that the *trans*-diaxial adducts **4** and **7** are formed from the epoxides **1** and **2**, respectively. A *trans*-diequatorial configuration occurs only in the adduct **8**.

Under the conditions of the epoxide–episulphide transformation, it is probable that the pyranoside ring in **4** and **7** adopts a boat conformation in which the distances between the negatively charged oxygen atom and the thiophosphoryl group are such as to allow phosphorus migration and episulphide formation. The lower rate of reaction and yield of episulphide from the *manno*-epoxide can be explained by steric hindrance of formation of the boat conformation.

A quantitative yield of the *allo*-episulphide **11** was obtained when **4** reacted with a methanolic solution of an equimolar amount of sodium methoxide at 0°.

Under the reaction conditions described herein, polymerisation of the episulphides was not observed.

EXPERIMENTAL

Methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside[2] (**1**), methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside[3] (**2**), methyl 2,3-anhydro-α-D-mannopyranoside[10] (**5**), and 5,5-dimethyl-2-mercapto-2-thioxo-1,3,2-dioxaphosphorinane[9] were prepared by literature procedures.

Melting points (Kofler) are uncorrected. ^{1}H-N.m.r. spectra were recorded for solutions in $CDCl_3$ and C_6D_6 (external Me_4Si) with a Varian 60-MHz instrument. ^{31}P-N.m.r. spectra were recorded for solutions in $CHCl_3$ (external 85% H_3PO_4) with a Jeol 60-MHz FT instrument. Optical rotations were determined on solutions in $CHCl_3$ with a Polamat polarimeter. Analyses were performed at the Microanalytical Laboratories of the Centre of Molecular and Micromolecular Studies (Lodz).

The yields of the products (adducts and episulphides) were determined on the basis of ^{31}P-n.m.r. spectroscopy, and were not optimised.

Methyl 4,6-O-benzylidene-3-(5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinanylthio)-α-D-altropyranoside (**4**). — Solutions of **1** (1.3 g) in benzene (30 ml) and **3** (0.99 g) in benzene (10 ml) were mixed at 0–5° and then stirred at room temperature for 24 h. The crystalline, colourless product which precipitated was **4** (1.5 g, 66%), m.p. 201–202°, $[\alpha]_D^{22}$ +102° (*c* 2), ν_{max}^{KBr} 690 (P=S) and 3400 cm^{-1} (OH). N.m.r. data: δ ^{31}P +89.2.

The filtrate was washed with aqueous 5% $KHCO_3$ until neutral, dried ($MgSO_4$), and concentrated *in vacuo*, to give more **4** (0.3 g, 13.2%), m.p. 201–202°. Recrystallisation from benzene did not change the m.p.

Anal. Calc. for $C_{19}H_{27}O_7PS_2$: C, 49.33; H, 5.88; P, 6.69; S, 13.86. Found: C, 49.58; H, 6.22; P, 7.10; S, 13.77.

Methyl 3-(5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinanylthio)-α-D-altropyranoside (**6**). — A suspension of **5** (1 g) in benzene (50 ml) and a solution of **3** (1.1 g) in benzene (10 ml) were mixed at 0–5°, stirred for 9 h at room temperature, and left thereat for 24 h. The colourless needles of **6** (2 g, 94.3%), when collected, had m.p. 150–151°. Recrystallisation from chloroform gave material (1 g, 47%) having m.p. 151–152°, $[\alpha]_D^{25}$ +7° (*c* 0.8), ν_{max}^{KBr} 690 (P=S) and 3400 cm^{-1} (OH). N.m.r. data: δ ^{31}P +92.7.

Anal. Calc. for $C_{12}H_{23}O_7PS_2$: C, 38.49; H, 6.19; P, 8.27. Found: C, 38.67; H, 6.58; P, 8.50.

Reaction of methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside (**2**) *with* **3**. — Solutions of **2** (1 g) in benzene (20 ml) and **3** (0.75 g) in benzene (10 ml) were mixed at 0–5°, and then stirred at room temperature for 6 days. The product (0.7 g, 53.2%) was collected, and recrystallised from chloroform, to afford white needles of methyl 2-(5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinanylthio)-α-D-altropyranoside (**9**), m.p. 155–156°, $[\alpha]_D^{25}$ +14° (*c* 2), ν_{max}^{KBr} 690 (P=S) and 3400 cm^{-1} (OH). N.m.r. data: δ ^{31}P +85.

Anal. Calc. for $C_{12}H_{23}O_7PS_2$: C, 38.49; H, 6.19; P, 8.27; S, 17.12. Found: C, 38.50; H, 6.36; P, 8.06; S, 17.06.

The filtrate was washed with aqueous 5% $KHCO_3$ until neutral, dried ($MgSO_4$), and concentrated *in vacuo*. The colourless, syrupy residue (0.7 g) was crystallised from ether, to give methyl 4,6-*O*-benzylidene-3-(5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinanylthio)-α-D-glucopyranoside (**8**: 0.5 g, 28.7%), m.p. 177–180°. Recrystallisation from chloroform–ether gave colourless needles (0.4 g), m.p. 180–181°, $[\alpha]_D^{20}$ +54° (*c* 1.9), ν_{max}^{KBr} 690 (P=S) and 3500 cm^{-1} (OH). N.m.r. data: δ ^{31}P +83.8.

Anal. Calc. for $C_{19}H_{27}O_7PS_2$: C, 49.33; H, 5.88; P, 6.69; S, 13.86. Found: C, 49.45; H, 6.10; P, 7.04; S, 14.06.

Methyl 4,6-O-benzylidene-2,3-dideoxy-2,3-epithio-α-D-allopyranoside[14] (**11**). — Solutions of equimolar amounts of **1** (1 g), **3** (0.75 g), and triethylamine (0.38 g, 0.54 ml) in acetonitrile (30 ml) were heated under reflux for 60 h. The mixture was diluted with water (30 ml), chloroform (30 ml) was added, and the organic layer was separated. The aqueous layer was repeatedly extracted with chloroform (30 ml). The chloroform extracts were dried ($MgSO_4$), and concentrated *in vacuo*. The residue was recrystallised from 2-propanol, to give **11** (0.5 g, 47.2%) as colourless needles, m.p. 169–171°; lit.[14] m.p. 166–167°. The yield of **11**, determined by ^{31}P-n.m.r. spectroscopy, was 60%, based on the anion of 2-mercapto-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane formed (δ ^{31}P +53).

To a solution (3.9 ml) of methanolic sodium methoxide (from 0.01 g of sodium) was added **4** (0.2 g). The mixture was left at 0–5° for 45 min, chloroform was then

added, and the mixture was washed with water, dried ($MgSO_4$), and concentrated *in vacuo*, to give **11** (0.12 g), m.p. 168–169°.

Methyl 4,6-O-benzylidene-2,3-dideoxy-2,3-epithio-α-D-mannopyranoside[13] (**10**). — Solutions of equimolar amounts of **2** (1 g), **3** (0.75 g), and triethylamine (0.38 g) in acetonitrile (30 ml) were heated under reflux for 34 h. Work-up as described for **11** gave a crude product **10** (0.9 g, 84.9%) which, after recrystallisation from ethanol, had m.p. 153–154°; lit.[13] m.p. 155–156°.

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