Carbohydrate Research, 91 (1981) 159–164
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

REACTION OF MAGNESIUM DIBROMIDE ETHERATE WITH 2,3-ANHYDROALDOPYRANOSIDES

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(Received November 19th, 1980; accepted for publication, December 9th, 1980)

ABSTRACT

The reaction of some 2,3-anhydroaldo-hexo- and -pento-pyranoside derivatives with $MgBr_2$-etherate was found to afford bromodeoxy products in high yield. In the absence of any free hydroxyl group in the molecule, rigid bicyclic, and flexible monocyclic, 2,3-anhydro-α-D-aldopyranoside derivatives mainly yielded 3-bromo-3-deoxy products through an unusual, diequatorial opening of the oxirane ring. In contrast, similar 2,3-anhydro derivatives having a free hydroxyl group in the molecule underwent the usual, diaxial opening of the oxirane ring, affording the 2-bromo-2-deoxy product. However, methyl 2,3-anhydro-4-*O*-methyl-β-D-ribopyranoside, despite the absence of a free hydroxyl group, underwent *trans*-diaxial opening of the oxirane ring.

INTRODUCTION

In an early study, the reactions of an alkyl Grignard reagent with 2,3-anhydro-allo- and -manno-pyranosides were reported[1] to yield preponderantly the halogen-substituted hexoses, besides the *C*-alkyl derivatives. Richards and Wiggins[2] presumed that the methyl Grignard reagent gave rise to a magnesium halide which, in turn, effected opening of the oxirane ring, giving deoxyhalo derivatives. To substantiate this assumption of the formation of a halo (X) derivative, Richards *et al.*[3] studied the action of MgX_2 in ether on 2,3-anhydroaldopyranosides, and observed the formation of 2-deoxy-2-halo- and 3-deoxy-3-halo-hexosides. Although the halo derivatives were formed by the interaction of MgX_2 in ether with 2,3-anhydro-aldopyranosides, they were the position isomers of those obtained by the action of the methyl Grignard reagent on the same aldose oxiranes. It was thus evident that MgX_2 in ether (assumed to be MgX_2-etherate[2]) reacted with aldose oxiranes differently from what it did when generated *in situ* from the methyl Grignard reagent. The assumption by Richards and Wiggins[2] that MgX_2 in ether forms an etherate is untenable, as it could not rationalize their own results.

The present authors, however, assumed that MgX_2 produced *in situ* from the

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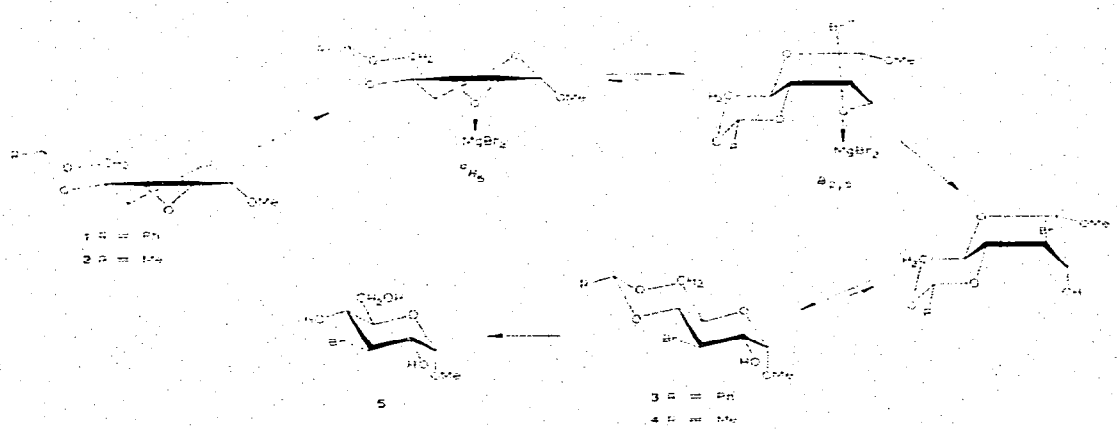
methyl Grignard reagent is present as an etherate that is not obtainable in a suspension of MgX_2 in ether. The $MgBr_2$-etherate used for the present study was prepared[4] through the interaction of the calculated amount of bromine with magnesium in absolute ether. It was expected that this etherate, having a bigger molecule, would react with the aldose oxiranes more stereospecifically than the suspension of $MgBr_2$ in ether.

In the present work, the action of $MgBr_2$-etherate on five different derivatives of 2,3-anhydroaldopyranosides having flexible monocyclic, and rigid bicyclic, skeletons was studied.

RESULTS AND DISCUSSION

When treated with $MgBr_2$-etherate, the aldose oxirane **1** yielded two products (t.l.c.) which were readily separated by chromatography. On comparison of the m.p. and optical rotation (m.p. 177°, $[\alpha]_D$ +4.8°), one of these compounds was identified as methyl 3-bromo-3-deoxy-4,6-*O*-benzylidene-α-D-glucopyranoside[5] **3**, and its subsequent debenzylidenation[6] afforded crystalline methyl 3-bromo-3-deoxy-α-D-glucopyranoside[5] (**5**). A comparison of the m.p. and rotation of the other product (m.p. 153°, $[\alpha]_D$ +90.0°) identified it as methyl 2-bromo-2-deoxy-α-D-altropyranoside (**8**). The formation of **8** resulted from the debenzylidenated aldose oxirane **1**, formed due to a trace of unreacted bromine present in the reaction mixture.

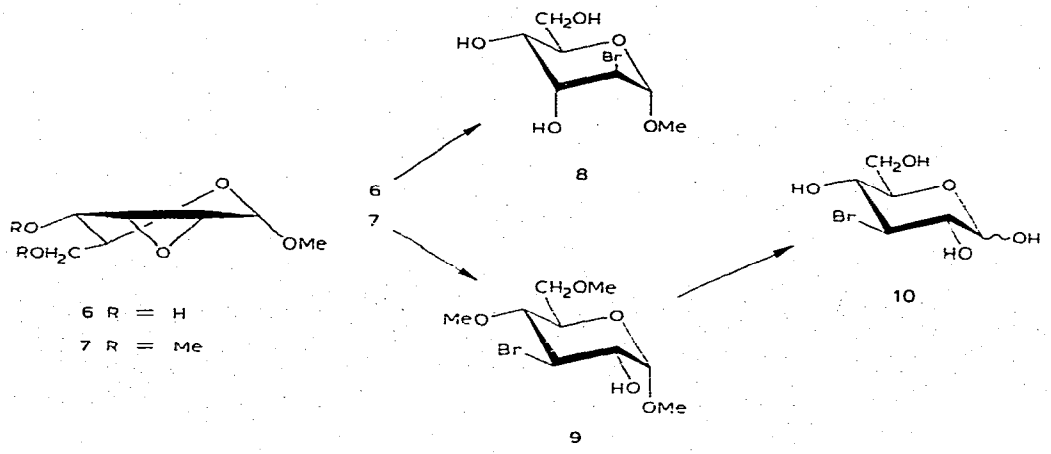
The behavior of the ethylidene derivative, which is not prone to hydrolysis in the presence of a trace of bromine, was also studied. When treated with $MgBr_2$-etherate, methyl 2,3-anhydro-4,6-*O*-ethylidene-α-D-allopyranoside (**2**) yielded a single product, namely, methyl 3-bromo-3-deoxy-4,6-*O*-ethylidene-α-D-glucopyranoside (**4**), m.p. 158°, $[\alpha]_D$ +66.4° (hitherto unreported). Mild hydrolysis of **4** with acid afforded the known 3-bromo-3-deoxy derivative **5**, m.p. 133°, identified by chromatographic comparison and by mixed m.p. with an authentic sample.



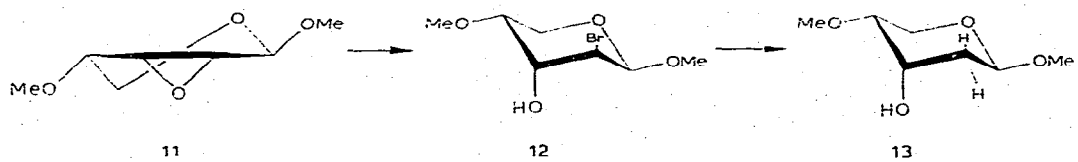
The study of the reactions of $MgBr_2$-etherate was also extended to compounds having a flexible, monocyclic skeleton, *viz.*, methyl 2,3-anhydro-4,6-di-*O*-methyl-α-

D-allopyranoside (**7**), methyl 2,3-anhydro-α-D-allopyranoside (**6**), and methyl 2,3-anhydro-4-*O*-methyl-β-D-ribopyranoside (**11**).

The bromo product, $C_9H_{17}BrO_5$, m.p. 102°, $[\alpha]_D$ +120°, obtained from **7** proved to be (the hitherto unreported) methyl 3-bromo-3-deoxy-4,6-di-*O*-methyl-α-D-glucopyranoside (**9**). Demethylation[7] of **9** afforded the known 3-bromo-3-deoxy-D-glucose (**10**), which was identified by p.c. and t.l.c. comparison with an authentic sample. The bromo product, m.p. 153°, $[\alpha]_D$ +90.0°, obtained from **6** was chromatographically identified as methyl 2-bromo-2-deoxy-α-D-altropyranoside (**8**).



Compound **11** reacted readily with $MgBr_2$-etherate, and yielded a new product, $C_7H_{13}BrO_4$ (**12**), m.p. 78°, $[\alpha]_D$ +34°. Its hydrogenation in the presence of Raney nickel yielded an amorphous deoxy-monosaccharide (**13**) which displayed a positive xanthydrol reaction characteristic for 2-deoxy sugars[8]. This led us to conclude that the bromo product **12** was a 2-bromo-2-deoxy-pentoside. From the formation of a 2-bromo-2-deoxy-pyranoside from **11**, it may be inferred that the product **12** is methyl 2-bromo-2-deoxy-4-*O*-methyl-β-D-arabinopyranoside.



In the reactions of compounds **1**, **2**, and **7**, a *trans*-diequatorial opening of the oxirane ring was observed which, according to the Fürst–Plattner rule, was unusual. This abnormal behavior may be explained on the basis of the assumption that the $MgBr_2$-etherate undergoes initial co-ordination with the oxirane oxygen atom, thereby producing a great steric strain, with the 1-*O*-methyl group *quasi*-axial (in the $^{\circ}H_5$(D) conformation). In order to escape this steric strain, the aldose oxirane undergoes a change in conformation, passing from the initial $^{\circ}H_5$ to the presumably

more favorable $B_{2,5}$(D) conformation. In such a conformation the polar, as well as the conformational, effects lead to exclusive, oxirane ring-opening at C-3, resulting in the formation of the *trans*-diaxial bromohydrin, which now undergoes a conformational change from $B_{2,5}$ to $^4C_1$(D). In fact, the oxirane ring-opening here, which appears to be *trans*-diequatorial, is achieved *via* the usual *trans*-diaxial opening of the oxirane ring, with a changed boat conformation as the reaction intermediate. This assumption is also supported by the oxirane ring-opening of the β anomer **11**, which gives the usual, *trans*-diaxial product.

The normal cleavage of the oxirane ring in the epoxide **6** is presumed to be due to the favored reaction of $MgBr_2$-etherate with its free hydroxyl groups; this results in the liberation of a high concentration of bromide ions which then lead to oxirane ring-opening of **6** (in its most-favored, $^4H_5$ conformation) according to the Fürst–Plattner rule, giving 2-bromohydrin **8**.

EXPERIMENTAL

All melting points are uncorrected. Optical rotations were measured at 26° with a Jasco DIP 180 automatic polarimeter. Far-infrared spectrograms (CsBr pellets) were recorded with a Perkin–Elmer 577 spectrophotometer. The mass spectra were recorded with a JEOL high-resolution J.M.S.-300 mass spectrometer.

Magnesium dibromide etherate. — Magnesium ribbon (1 mmol) and absolute ether (15 mL) were placed in a 25-mL flask, bromine (2 mmol) was added at room temperature, and the mixture was refluxed for 30 min, until all of the bromine had been consumed, and cooled. The colorless solution thus obtained contained $MgBr_2$-etherate, ready for the reactions.

Methyl 3-bromo-3-deoxy-4,6-O-benzylidene-α-D-glucopyranoside (**3**). — The oxirane **1** (100 mg) was treated with magnesium bromide-etherate solution (Mg, 15 mg) at the reflux temperature for 2 h (completion of the reaction; two products in t.l.c.). The ether was then evaporated, and the residue was decomposed with water, the mixture acidified with M HCl, and successively extracted with chloroform and 4:1 chloroform–methanol. The extracts were combined, successively washed with 10% $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated, to yield a syrup (110 mg) which was chromatographed on a column of silica gel with 19:1 benzene–ethyl acetate. First to be eluted was **3** (75 mg, 65%), which crystallized from ethanol, m.p. 177°, $[\alpha]_D^{26}$ +4.8°; lit.[5] m.p. 176°, $[\alpha]_D^{24}$ +12.0°; ν_{max}^{CsBr} 755 cm^{-1} (C–Br, equatorial).

Anal. Calc. for $C_{14}H_{17}BrO_5$: C, 48.7; H, 4.9; Br, 23.2. Found: C, 48.1; H, 4.8; Br, 23.7.

The second compound was methyl 2-bromo-2-deoxy-α-D-altropyranoside (**8**; 20 mg, 20%), m.p. 153°, $[\alpha]_D^{26}$ +90°; lit.[5] m.p. 153°, $[\alpha]_D^{24}$ +86.5°.

Anal. Calc. for $C_7H_{13}BrO_5$: C, 32.68; H, 5.06; Br, 31.1. Found: C, 32.80; H, 4.92; Br, 29.2.

Methyl 3-bromo-3-deoxy-α-D-glucopyranoside (**5**). — A mixture of the bromo

derivative **3** (20 mg) with M HCl (1 mL) was kept for 6 days at room temperature (single product in t.l.c.), and then shaken with ether (to remove liberated benzaldehyde). The acidic, aqueous solution was made neutral with 10% $NaHCO_3$, and evaporated to dryness under diminished pressure. The residue was exhaustively extracted with acetone, yielding an acetone-soluble product as a syrup that crystallized from acetone–ether; **5** (8 mg), m.p. 133°, $[\alpha]_D^{26}$ +104.0°; lit.[5] m.p. 133° $[\alpha]_D^{24}$ +109.0°.

Methyl 3-bromo-3-deoxy-4,6-O-ethylidene-α-D-glucopyranoside (**4**). — The oxirane **2** (80 mg) was treated with freshly prepared $MgBr_2$-etherate (Mg, 15 mg) for 2 h at the reflux temperature (single product in t.l.c.). After removal of the ether, the residue was decomposed with water, and the mixture acidified with M HCl, and extracted with chloroform. The extracts were combined, successively washed with 10% $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated to a syrup (100 mg) which, by purification on a column of silica gel (19 : 1 benzene–ethyl acetate) and crystallization from ethanol, yielded **4** (80 mg, 85%), m.p. 158°, $[\alpha]_D^{26}$ +66.4°.

Anal. Calc. for $C_9H_{15}BrO_5$: C, 38.2; H, 5.3; Br, 28.2. Found: C, 38.5; H, 5.1; Br, 27.5.

Methyl 3-bromo-3-deoxy-α-D-glucopyranoside (**5**). — The bromo derivative **4** (20 mg) was only partially hydrolyzed when it was mixed with M HCl, and kept for 24 h at 80°. The acidic solution was then made neutral with 10% $NaHCO_3$, and evaporated to dryness under diminished pressure. The residue was chromatographed on a column of silica gel with 1 : 1 benzene–ethyl acetate. First to be eluted was **4** (8 mg). The second compound obtained exhibited no depression in mixed m.p., and had the same mobility in t.l.c. (5 : 4 : 1 benzene–ethyl acetate–methanol), as an authentic specimen of 3-bromo-3-deoxy-α-D-glucopyranoside (**5**).

Methyl 3-bromo-3-deoxy-4,6-di-O-methyl-α-D-glucopyranoside (**9**). — A mixture of the oxirane **7** (80 mg) with $MgBr_2$-etherate (Mg, 15 mg) was boiled under reflux for 2 h, the ether was evaporated, and the product was isolated as for compound **3**, yielding a syrup (105 mg; single product in t.l.c.), purification of which through a column of silica gel (19 : 1 benzene–ethyl acetate) yielded compound **9** (85 mg, 90%), which crystallized from acetone–ether, m.p. 102°, $[\alpha]_D^{26}$ +120.0°; ν_{max}^{CsBr} 752 cm^{-1} (C–Br, equatorial); *m/z* 223 and 221 (0.7%, M — OCH_3 — CH_3OH), 209 and 207 (0.4%, M — CH_2OCH_3 — CH_3OH), 159 (0.14%, M — CH_2OCH_3 — HBr), and 141 (0.9%, M — OCH_3 — CH_3OH — HBr).

Anal. Calc. for $C_9H_{17}BrO_5$: C, 37.9; H, 5.95. Found: C, 38.0; H, 5.64.

3-Bromo-3-deoxy-D-glucose (**10**). — A solution of the methylated sugar **9** (5 mg) in 48% HBr (1 mL) was heated on a boiling-water bath for 20 min, cooled, and diluted with water (5 mL). HBr was removed with freshly prepared Ag_2CO_3, and the suspension was filtered. H_2S was passed through the filtrate to remove Ag^+ ions, the suspension was filtered, and the filtrate was evaporated to dryness under diminished pressure, yielding syrupy **10** (2 mg), which exhibited the same mobility in p.c. and in t.l.c. (5 : 4 : 1 benzene–ethyl acetate–methanol) as an authentic sample of 3-bromo-3-deoxy-D-glucose.

Methyl 2-bromo-2-deoxy-α-D-altropyranoside (**8**). — The oxirane **6** (50 mg)

was heated with $MgBr_2$-etherate (Mg, 12 mg) at reflux temperature for 1 h (single product in t.l.c.). The ether was evaporated, the residue was decomposed with water, and made neutral with M HCl, and the solution was evaporated to dryness under diminished pressure, yielding a syrupy residue. Trituration of this residue with acetone gave acetone-soluble, impure **8**, which was purified on a column of silica gel with 4:1 benzene–ethyl acetate; it crystallized from acetone–ether, giving pure **8** (55 mg, 90%), m.p. 153°, $[\alpha]_D^{26}$ +90° (lit.[5] m.p. 153°, $[\alpha]_D^{24}$ +86.5°); *m/z* 227 and 225 (3.0%, M − OCH_3), 209 and 207 (1.5%, M − OCH_3 − H_2O), 291 and 289 (1.8%, M − OCH_3 − 2 H_2O), which exhibited the same mobility in t.l.c. (5:4:1 benzene–ethyl acetate–methanol) as an authentic specimen of methyl 2-bromo-2-deoxy-α-D-altropyranoside.

Anal. Calc. for $C_7H_{13}BrO_5$: C, 32.68; H, 5.08; Br, 31.1. Found: C, 32.80; H, 4.92; Br, 29.2.

Methyl 2-bromo-2-deoxy-4-O-methyl-β-D-arabinopyranoside (**12**). — The oxirane **11** (50 mg) was mixed with $MgBr_2$-etherate (Mg, 12 mg), and the reaction was conducted and the product processed, as for compound **8**. The syrupy **12** crystallized from ethanol (55 mg, 90%), m.p. 78°, $[\alpha]_D^{26}$ +39.0°.

Anal. Calc. for $C_7H_{13}BrO_4$: C, 34.9; H, 5.39; Br, 33.19. Found: C, 34.5; H, 5.25; Br, 32.74.

Methyl 2-deoxy-4-O-methyl-β-D-arabinopyranoside (**13**). — The bromo derivative **12** (20 mg) in absolute ethanol (20 mL) was hydrogenated for 8 h with hydrogen at 70 lb.in.$^{-2}$ in the presence of Raney Ni (200 mg). The mixture was filtered, the solid washed with ethanol, and the filtrate evaporated under diminished pressure, yielding a syrup which was purified on a column of silica gel, affording **13** (5 mg) as a syrup that gave a pink coloration in the xanthydrol test, characteristic of a 2-deoxy sugar.

ACKNOWLEDGMENTS

Thanks are due Prof. L. Mester, Institut de Chimie des Substances Naturelles, Gif-sur-Yvette, France, for kindly providing the microanalytical data for bromine. One of us (S.K.D.) is grateful to the C.S.I.R., New Delhi, India, for the award of a research fellowship.

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