496. *The Action of Grignard Reagents on Anhydro-sugars of Ethylene Oxide Type. Part II.* The Behaviour of* 4 : 6-*Benzylidene* 2 : 3-*Anhydro-α-methyl-*D*-alloside towards Ethyl- and Phenyl-magnesium halides.*

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When 4 : 6-benzylidene 2 : 3-anhydro-β-methyl-D-allopyranoside is treated with methylmagnesium iodide 4 : 6-benzylidene 3-deoxy-3-iodo-α-methyl-D-glucopyranoside is the only product isolable (see Part I). With ethylmagnesium bromide or iodide the anhydro-sugar furnishes the corresponding 2-bromo- or 2-iodo-altrosides and no glucose isomer is obtained. The structure of the 2-bromo-2-deoxyaltroside is proved by its conversion into the known 2-bromo-2-deoxy-α-methyl-D-altroside and that of the 2-deoxy-2-iodoaltroside by its transformation into the crystalline 2-deoxy-α-methyl-D-alloside which is also obtained from the 2-bromo-2-deoxyaltroside. With phenylmagnesium bromide also, the 2 : 3-anhydroalloside yields 4 : 6-benzylidene 2-bromo-2-deoxy-α-methylaltroside but with zinc methyl iodide 4 : 6-benzylidene 3-deoxy-3-iodo-α-methyl-D-glucoside is obtained.

In Part I * it was shown that 4 : 6-benzylidene 2 : 3-anhydro-α-methyl-D-allopyranoside (I) and methylmagnesium iodide yield 4 : 6-benzylidene 3-deoxy-3-iodo-α-methyl-D-glucopyranoside (II; R = I) only, the structure of which was proved by conversion into the known 4 : 6-benzylidene 3-deoxy-2-methyl-α-methyl-D-glucoside. The halogenoglucoside obtained from the anhydro-sugar arose from the cleavage of the oxide ring and the addition of the halide ion derived from the Grignard reagent and the authors suggested a mechanism for the reaction. According to the accepted ideas on the cleavage of αβ-anhydro-sugars by ionic reagents which have been summarized by Peat (*Adv. Carbohydrate Chem.*, 1946, **2**, 37), it would have been expected that both 4 : 6-benzylidene 2-deoxy-2-halogeno-α-methylaltroside and the corresponding 3-deoxy-3-halogenoglucoside would have been produced. However, only the latter could be isolated.

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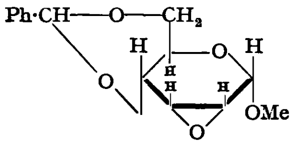
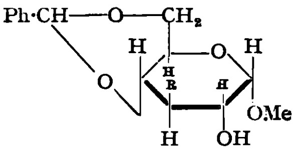
* Part I, *J.*, 1950, 2356.

The opening of oxide rings by neutral reagents is related to the present work and in this field the anhydroalloside has been treated with lithium aluminium hydride (Prins, *J. Amer. Chem. Soc.*, 1948, **70**, 3956) and with Raney nickel in an atmosphere of hydrogen (Prins, *Helv. Chim. Acta*, 1946, **29**, 1). The only product isolated from the first reaction was 4 : 6-benzylidene 2-deoxy-α-methylalloside, while in the second reaction the anhydroalloside was almost entirely converted into 3-deoxy-α-methylglucoside. This reversal of the direction of scission may be compared with the behaviour of the anhydroalloside towards methyl- and ethyl-magnesium iodides and serves further to emphasize the danger of attempting to predict the direction of scission of a given ethylene oxide ring by a given type of reagent.

In the present work the reaction of 4 : 6-benzylidene 2 : 3-anhydro-α-methylalloside (I) with ethylmagnesium iodide and bromide and with phenylmagnesium bromide has been examined. When the alloside (I) was treated with ethylmagnesium iodide in tetrahydropyran solution, only one of the isomeric 4 : 6-benzylidene deoxyiodo-α-methylhexosides was isolated (50% of the theoretical yield). This must be either 4 : 6-benzylidene 3-deoxy-3-iodo-α-methyl-D-glucoside (II; R = I) or 4 : 6-benzylidene 2-deoxy-2-iodo-α-methylaltroside (III; R = I), and it would be expected that the action of sodium methoxide on the deoxyiodohexoside would furnish the original alloside (I). This transformation was also accomplished when an attempt was made to methylate the 4 : 6-benzylidene deoxyiodo-α-methylhexoside under anhydrous conditions. This eliminates structures other than (II; R = I) or (III; R = I) for the deoxyiodohexoside. Since the compound possessed physical constants different from those of the known (II; R = I) it must be the isomeric altroside (III; R = I). This was verified by its transformation into crystalline 2-deoxy-α-methyl-D-allopyranoside (IV; R = H) by treatment with Raney nickel, according to the procedure described by Bougault, Cattelain, and Chabier (*Bull. Soc. chim.*, 1940, **7**, 781) for reductive desulphurization of thio-compounds. This compound was evidently identical with the amorphous 2-deoxy-α-methylalloside which Jeanloz, Prins, and Reichstein (*Helv. Chim. Acta*, 1946, **29**, 371) prepared by the reductive desulphurization of 4 : 6-benzylidene 2-deoxy-2-methylthio-α-methylaltroside (III; R = SMe). Nevertheless, an independent synthesis is described later.



(I)



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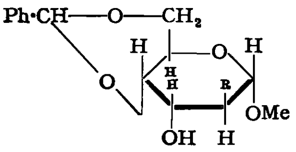

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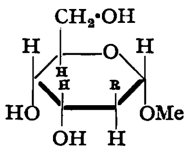

(IV)

When the reaction of the alloside (I) with ethylmagnesium bromide was studied, it was found that the only product isolated was an altroside derivative, namely, 4 : 6-benzylidene 2-bromo-2-deoxy-α-methyl-D-altropyranoside (III; R = Br), the structure of which was demonstrated by hydrolysis with oxalic acid in aqueous acetone; the benzylidene residue was removed and a crystalline product was obtained which rapidly consumed one mol. of lead tetra-acetate and was identical with the 2-bromo-2-deoxy-α-methylaltroside (IV; R = Br) of Newth, Overend, and Wiggins (*J.*, 1947, 10). Furthermore, alkaline hydrolysis of the 4 : 6-benzylidene 2-bromo-2-deoxy-α-methylaltroside (III; R = Br) afforded 4 : 6-benzylidene 2 : 3-anhydro-α-methylalloside (I). Hence the representation of the product of the reaction of ethylmagnesium bromide with the alloside (I) as (III; R = Br) must be correct.

When this compound was treated with Raney nickel in boiling ethyl alcohol, both the benzylidene and the bromine residue were removed and a deoxyhexoside was isolated, which, from the mode of synthesis must be 2-deoxy-α-methylalloside. This was identical with the compound derived from the product of the action of ethylmagnesium iodide on the alloside (I) and hence provides proof of the structure of that compound.

4 : 6-Benzylidene 2 : 3-anhydro-α-methylalloside (I) and phenylmagnesium bromide gave the same 2-bromo-2-deoxyaltroside (III; R = Br) as was obtained with ethylmagnesium bromide, although the product was more complex and the yield of altroside only 38%.

It is therefore evident that when the ethylene oxide ring of 4 : 6-benzylidene 2 : 3-anhydro-α-methylalloside is cleaved by ethylmagnesium bromide or iodide or by phenylmagnesium bromide, the only substance isolated was the 2-deoxy-2-halogenoaltroside, whereas methylmagnesium iodide gave, as main product, the alternative isomer, namely, a 3-deoxy-3-iodoglucoside. It is remarkable that replacement of methyl by ethyl in the Grignard reagent should have changed the direction of fission, but, since phenyl has the same effect as ethyl, the result may possibly be due to the size of the group in the Grignard complex. It was of interest that when the anhydroalloside was treated with methylzinc iodide, a substance closely similar to the Grignard reagent yet containing the larger metal ion, the reaction was similar to that with methylmagnesium iodide.

EXPERIMENTAL

Reaction of 4 : 6-*Benzylidene* 2 : 3-*Anhydro-α-methyl-*D-*alloside with Ethylmagnesium Iodide.*—The Grignard reagent was prepared in the usual manner from ethyl iodide (1·62 g.; freshly distilled), magnesium turnings (0·25 g.), and dry tetrahydropyran (10 c.c.). To this was added, at room temperature, a solution of the alloside (2·5 g.) in warm tetrahydropyran (150 c.c.), at <20°. A heavy white granular precipitate was formed and the colour deepened to dark orange. On boiling, the precipitate dissolved and after 1 hr.' refluxing the colour faded and a very fine, white precipitate was deposited. After cooling to room temperature, ice was added, followed by dilute hydrochloric acid. The tetrahydropyran layer was immediately washed with sodium hydrogen carbonate and sodium thiosulphate solutions and with water, dried (Na_2SO_4), and evaporated to dryness. The residue was fractionated as described for a similar experiment with ethylmagnesium bromide (see below); 0·876 g. of starting material was recovered unchanged, together with well-formed cubic crystals of 4 : 6-*benzylidene* 2-*deoxy*-2-*iodo-α-methyl-*D-*altroside*, which on recrystallisation from ethyl alcohol had m. p. 105—106°, $[\alpha]_D^{20}$ +39·0° in $CHCl_3$ (*c*, 1·333) (1·681 g., 47%) (Found : C, 43·1; H, 4·4. $C_{14}H_{17}O_5I$ requires C, 42·8; H, 4·3%).

Acetylation of 4 : 6-*Benzylidene* 2-*Deoxy*-2-*iodo-α-methyl-*D-*altroside.*—The altroside (1·075 g.) when treated and acetic anhydride (2 c.c.) in pyridine (10 c.c.) at 30° (18 hr.) gave an amorphous solid (1·185 g.), isolated by means of chloroform. This was dissolved in ether–acetone, filtered, and again evaporated to dryness, giving 3-*acetyl* 4 : 6-*benzylidene* 2-*deoxy*-2-*iodo-α-methylaltroside*, which after being dried at 50°/0·2 mm. showed $[\alpha]_D^{17}$ +12·8° in $CHCl_3$ (*c*, 1·56) (Found : C, 44·4; H, 4·5. $C_{16}H_{19}O_6I$ requires C, 44·2; H, 4·4%).

4 : 6-*Benzylidene* 3-*Toluene*-p-*sulphonyl* 2-*Deoxy*-2-*iodo-α-methyl-*D-*altroside.*—4 : 6-Benzylidene 2-deoxy-2-iodo-α-methylaltroside (0·150 g.) and toluene-*p*-sulphonyl chloride (0·2 g.) in pyridine (5 c.c.) at 30° (18 hr.) gave a syrupy product which solidified under water overnight. The 3-*toluene*-p-*sulphonate* (0·115 g.) was then collected, washed with water, and recrystallized from aqueous ethyl alcohol. It had m. p. 114·5—115° (decomp.), $[\alpha]_D^{18}$ −15·6° in $CHCl_3$ (*c*, 0·769) (Found : C, 45·6; H, 3·95. $C_{21}H_{23}O_7IS$ requires C, 46·1; H, 4·2%).

Reduction of 4 : 6-*Benzylidene* 2-*Deoxy*-2-*iodo-α-methylaltroside with Raney Nickel.*—To a solution of the altroside (0·43 g.) in ethyl alcohol (20 c.c.) was added barium carbonate (2 g.), followed by Raney nickel (*ca.* 7 g.; Mozingo, *J. Amer. Chem. Soc.*, 1943, **65**, 1013), suspended in the same solvent (*ca.* 10 c.c.). After the addition of water (7 c.c.) the mixture was warmed under reflux for 1½ hr., cooled, and filtered, the residual solids being washed several times with hot water. The combined filtrates were evaporated under reduced pressure and the residue was redissolved in water (5 c.c.), extracted several times with chloroform to remove unchanged starting material, and again evaporated to dryness. The residue was then extracted with ethyl acetate, filtered to remove barium iodide, and once more evaporated. The dried residue, crystallized from ether–ethyl alcohol–light petroleum (b. p. 60—80°), had m. p. 91—93° alone or in admixture with 2-deoxy-α-methylalloside prepared from 4 : 6-benzylidene 2-bromo-2-deoxy-α-methylaltroside (see below). The yield was 0·158 g. (81%).

Alkaline Hydrolysis of 4 : 6-*Benzylidene* 2-*Deoxy*-2-*iodo*-α-*methylaltroside*.—A solution of the altroside (0·120 g.) in chloroform (1 c.c.) was treated with a solution of sodium (0·1 g.) in absolute methyl alcohol (5 c.c.) at 0°. The needle-shaped crystals formed (0·065 g., 80%) were removed by filtration and washed with ether; they had m. p. 199—200·5° alone or in admixture with authentic 4 : 6-benzylidene 2 : 3-anhydro-α-methylalloside.

Attempted Methylation of 4 : 6-*Benzylidene* 2-*Deoxy*-2-*iodo*-α-*methylaltroside*.—The altroside (1·209 g.) was heated under reflux with dry methyl iodide (10 g.) and dry silver oxide (*ca.* 5 g.). White needles began to separate after several hours and, after refluxing had continued overnight, the solution was filtered and the residual solids were washed several times with boiling chloroform. The combined filtrates were evaporated under reduced pressure. The colourless solid residue (0·811 g.), when recrystallized from ethyl alcohol, showed m. p. 199—200° alone or in admixture with authentic 4 : 6-benzylidene 2 : 3-anhydro-α-methylalloside.

Action of Ethylmagnesium Bromide on 4 : 6-*Benzylidene* 2 : 3-*Anhydro*-α-*methylalloside*.—To the Grignard reagent prepared from ethyl bromide (1·13 g.), magnesium turnings (0·249 g.), and dry tetrahydropyran (10 c.c.), at room temperature, was added slowly the alloside (2·453 g.) in warm tetrahydropyran (150 c.c.). A very fine colourless precipitate separated. After 2 hr.' refluxing, ice was added, followed by a slight excess of dilute hydrochloric acid. The ethereal layer was washed with sodium hydrogen carbonate solution and with water, dried (Na_2SO_4), and evaporated. The semi-solid residue was extracted with ethyl alcohol (100 c.c.) at room temperature. An insoluble portion (0·522 g.) had m. p. 196—199° and was of unchanged starting material. The alcoholic solution was evaporated and the crystalline residue fractionally recrystallized from ethyl alcohol–ether, giving a further 0·335 g. of unchanged starting material (total, 35%) together with 4 : 6-*benzylidene* 2-*bromo*-2-*deoxy*-α-*methylaltroside*, which crystallized from ethyl alcohol–ether as cubes m. p. 117·5—118·5°, $[\alpha]_D^{19}$ +58·0° in $CHCl_3$ (*c*, 2·478) (1·635 g., 51%) (Found: C, 48·7; H, 5·1. $C_{15}H_{17}O_5Br$ requires C, 48·7; H, 4·9%).

Treatment of 4 : 6-*Benzylidene* 2-*Bromo*-2-*deoxy*-α-*methylaltroside with Toluene*-p-*sulphonyl Chloride*.—The altroside (0·246 g.) was treated in dry pyridine (5 c.c.) with toluene-*p*-sulphonyl chloride (0·3 g.) at room temperature for 24 hr. The solution was then poured into water, giving a yellow solid. This was collected and washed with water. Recrystallized from ethyl alcohol, 4 : 6-*benzylidene* 2-*toluene*-p-*sulphonyl* 2-*bromo*-2-*deoxy*-α-*methylaltroside* formed needles (0·142 g.), m. p. 159·5—160°, $[\alpha]_D^{19}$ +36·9° in $CHCl_3$ (*c*, 2·770) (Found: C, 50·3; H, 4·3. $C_{21}H_{23}O_7BrS$ requires C, 50·5; H, 4·6%).

Hydrolysis of 4 : 6-*Benzylidene* 2-*Bromo*-2-*deoxy*-α-*methylaltroside with Oxalic Acid*.—To the altroside (0·406 g.) in acetone (22·5 c.c.) oxalic acid (0·75 g. of the dihydrate in 2·5 c.c. of water) was added. The solution was heated under reflux for 24 hr. and thereafter neutralized with barium carbonate. The barium salts were removed and washed with hot water, the combined filtrates being evaporated to dryness under reduced pressure. The residue was distilled with steam until the odour of benzaldehyde was no longer detected and then dissolved in water, and the solution washed several times with chloroform to remove any unchanged starting material, filtered, and evaporated to dryness. The residue, recrystallized from ethyl alcohol, formed cubes of 2-bromo-2-deoxy-α-methylaltroside, m. p. 152—153·5° alone or in admixture with an authentic specimen prepared by Newth, Overend, and Wiggins (*loc. cit.*).

Alkaline Hydrolysis of 4 : 6-*Benzylidene* 2-*Bromo*-2-*deoxy*-α-*methylaltroside*.—The altroside (46 mg.) was dissolved in ethyl alcohol (1·2 c.c.), and 5N-sodium hydroxide (0·1 c.c.) added at room temperature. A colourless solid separated and after being kept at room temperature for 3 hr. this was collected, washed with water, and dried under reduced pressure over phosphoric oxide. It (35 mg.) had m. p. 198—200° alone or in admixture with 4 : 6-benzylidene 2 : 3-anhydro-α-methylalloside.

Reduction of 4 : 6-*Benzylidene* 2-*Bromo*-2-*deoxy*-α-*methylaltroside with Raney Nickel*.—To a solution of the altroside (0·96 g.) in ethyl alcohol (40 c.c.) was added barium carbonate (4 g.) followed by Raney nickel (*ca.* 15 g.; cf. above) suspended in the same solvent (*ca.* 20 c.c.). Water (15 c.c.) was added and the mixture warmed under reflux for 1½ hr. Bromide ion was detected in the solution after a few minutes and the odour of toluene was noted. The cooled solution was filtered, the residual solid was washed with hot water, and the combined filtrates were evaporated under reduced pressure. The residue was dissolved in water (10 c.c.), extracted several times with chloroform, and again evaporated to dryness. When the syrupy residue was dried at 50° at 0·2 mm. over phosphoric oxide, crystallization was induced and was completed by trituration with ether. Recrystallized from ether–ethyl alcohol–light petroleum, 2-deoxy-α-methylalloside (altroside) formed very hygroscopic cubes (0·412 g., 83%), m. p. 91—93° (rapid heating), $[\alpha]_D^{19}$ +144·0° in $CHCl_3$ (*c*, 0·376) (Found : C, 46·8; H, 7·75. Calc. for $C_7H_{14}O_5$: C, 47·2; H, 7·9%). Jeanloz, Prins, and Reichstein (*loc. cit.*) give $[\alpha]_D^{13}$ +143·1° ± 2° in $CHCl_3$ (*c*, 0·978).

Oxidation of 2-*Bromo*-2-*deoxy*-α-*methylaltroside with Lead Tetra-acetate*.—The bromoaltroside ($2·12 \times 10^{-4}$ mole) consumed the following amounts of lead tetra-acetate under conditions prescribed by Hockett and McClenahan (*J. Amer. Chem. Soc.*, 1939, **61**, 1667) : 0·621 g.-atom of O (5 min.), 0·818 (10 min.), 0·953 (20 min.), 0·99 (30 min.), and 0·98 (60 min.).

Reaction of 4 : 6-*Benzylidene* 2 : 3-*Anhydro*-α-*methylalloside with Phenylmagnesium Bromide*.—To a solution of the Grignard reagent [from bromobenzene (1·64 g.) and magnesium turnings (0·25 g.) in tetrahydropyran (15 c.c.)], kept at <20°, was added the anhydroalloside (2·45 g.) in warm tetrahydropyran (150 c.c.). After 1 hr. heating, during which a fine colourless granular precipitate separated, the solution was allowed to cool to room temperature, and ice and a slight excess of 5N-hydrochloric acid were added. The ethereal layer was washed with sodium hydrogen carbonate solution and with water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was fractionated as described for the reaction with ethylmagnesium bromide; unchanged starting material (0·96 g., 39·2%) was isolated, together with 4 : 6-benzylidene 2-bromo-2-deoxy-α-methylaltroside (1·299 g., 38·3%), m.p. 117—118·5° alone or in admixture with the compound obtained from the reaction with ethylmagnesium bromide. The mother-liquors yielded on evaporation a colourless syrup (0·898 g.) having a characteristic sweet odour. Distillation of this product occurred in two fractions: (i), b. p. 90—95° (bath-temp.)/0·04 mm., a colourless, mobile liquid (0·177 g.), n_D^{13} 1·4978, α ±0°, contained bromine but was not identified (Found: C, 65·8; H, 8·3%); (ii) b. p. at 145—150° (bath-temp.)/0·035 mm., a colourless, viscous liquid (0·104 g.), n_D^{19} 1·4930, $[\alpha]_D^{22}$ +11·7° in $CHCl_3$ (*c*, 1·88), contained bromine, but was not identified (Found: C, 65·85; H, 9·1%). The remainder of the product decomposed without further distillation below 165° at the same pressure.

Treatment of 4 : 6-*Benzylidene* 2 : 3-*Anhydro*-α-*methylalloside with Methylzinc Iodide*.—The reagent was prepared essentially by Blaise's method (*Bull. Soc. chim.*, 1911, **4**, 9). The final reaction mixture was then made faintly acid with dilute hydrochloric acid, and the toluene layer separated, washed with sodium hydrogen carbonate and sodium thiosulphate solutions and with water, dried (Na_2SO_4), and evaporated under reduced pressure. The colourless solid residue, recrystallized from chloroform–light petroleum (b. p. 60—80°), had m. p. 194—195° alone or in admixture with 4 : 6-benzylidene 3-deoxy-3-iodo-α-methylglucoside (yield, 2·0 g., 45%).

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