483. *The Action of Grignard Reagents on Anhydro-sugars of Ethylene Oxide Type. Part I. The Behaviour of Derivatives of α-Methyl-2 : 3-anhydroalloside towards Methylmagnesium Iodide.*

By F. H. Newth, G. N. Richards, and L. F. Wiggins.

4 : 6-Benzylidene α-methyl-2 : 3-anhydroalloside and methylmagnesium iodide give only 4 : 6-benzylidene α-methyl-3-iodo-3-deoxyglucoside, the structure of which is proved by conversion into the known 4 : 6-benzylidene 2-methyl α-methyl-3-deoxyglucoside. However, 4 : 6-dimethyl α-methyl-2 : 3-anhydroalloside gives 4 : 6-dimethyl α-methyl-2-iodo-2-deoxy-altroside, 4 : 6-dimethyl α-methyl-3-iodo-3-deoxyglucoside, and 4 : 6-dimethyl α-methyl-3-methyl-3-deoxyglucoside. The structure of the last compound is only tentatively assigned; those of the other two are proved—that of the iodoglucose derivative by synthesis of its acetyl derivative from 4 : 6-benzylidene α-methyl-3-iodo-3-deoxyglucoside, and that of the iodoaltrose isomer by conversion into 3 : 4 : 6-trimethyl α-methyl-2-deoxy-alloside and synthesis of this material. The proportion in which the three products from 4 : 6-dimethyl α-methyl-2 : 3-anhydroalloside and methylmagnesium iodide are formed varies with the reaction temperature.

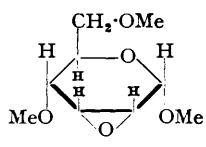
Reactions between compounds of ethylene oxide type and Grignard reagents have long been known and at first it was accepted that the normal reaction was that in which opening of the ring by RMgX occurred to yield compounds of the type R'·CHR·CH(OH)·R''. Thus, Henry (*Compt. rend.*, 1907, **145**, 453) found that propylene oxide and ethylmagnesium bromide yielded pentan-2-ol. It soon became apparent, however, that certain reactions which were at first regarded as abnormal were in fact quite common. These resolved themselves into two classes : (i) the formation of halogenohydrin derivatives, and (ii) rearrangement of the epoxy-compound to a ketone or aldehyde which then reacted with the reagent in the usual way. Blaise (*Compt. rend.*, 1902, **134**, 551) first noted that ethylene oxide and ethylmagnesium bromide formed ethylene bromohydrin, and Grignard (*Bull. Soc. chim.*, 1903, [iii], **29**, 946) then showed that,

by conducting the reaction at −15° and removing the solvent ether by distillation before hydrolysis, *n*-butyl alcohol was obtained. More recently Wiggins and Wood (*J.*, 1950, 1566) have found that the action of methylmagnesium iodide on 1 : 2-5 : 6-diepoxyhexane leads to dihydroxy-1 : 6-di-iodohexanes and that similar treatment of 3 : 4-*iso*propylidene 1 : 2-5 : 6-dianhydromannitol gives 3 : 4-*iso*propylidene 1 : 6-di-iodo-1 : 6-deoxymannitol. In fact it becomes increasingly likely that this type of reaction is the more common. The rearrangement type of reaction described for 2 : 3-epoxy-*n*-butane and 1 : 2-epoxy*iso*butane by Henry (*Compt. rend.*, 1907, **145**, 406) and for styrene oxide by Tiffeneau and Fournier (*Compt. rend.*, 1908, **146**, 697) seems at the moment to be of less importance in the field under consideration.

In view of these early results it appeared probable that the reaction between methylmagnesium iodide and an anhydro-sugar of ethylene oxide type would yield either a *C*-alkyl sugar or an iodo-sugar derivative. Moreover, if ring scission with the Grignard reagent followed the usual course (see Peat, *Adv. in Carbohydrate Chem.*, 1946, **2**, 37), two isomers of each type should be isolable. Thus, provided that ring scission of the oxide ring does in fact take place in the same way as that effected by means of acids and alkalis (Peat and Wiggins, *J.*, 1938, 1810; Newth, Overend, and Wiggins, *J.*, 1947, 18), we should expect to obtain, from 4 : 6-dimethyl α-methyl-2 : 3-anhydroalloside (I) and methylmagnesium iodide, any or all of the following compounds: 4 : 6-dimethyl α-methyl-3-methyl-3-deoxyglucoside (II), 4 : 6-dimethyl α-methyl-2-methyl-2-deoxyaltroside (III), 4 : 6-dimethy α-methyl-3-iodo-3-deoxyglucoside (IV), and 4 : 6-dimethyl α-methyl-2-iodo-2-deoxyaltroside (V). Both types of reaction will doubtless prove of value in synthetic carbohydrate chemistry.

The action of methylmagnesium iodide on two derivatives of α-methyl-2 : 3-anhydroalloside has now been investigated.

4 : 6-Benzylidene α-methyl-2 : 3-anhydroalloside (VI) and methylmagnesium iodide in boiling tetrahydropyran gave only (80%) a 4 : 6-benzylidene α-methyl-iododeoxyhexoside, characterized as the crystalline 2-toluene-*p*-sulphonate; no *C*-methyl sugar was found. That the iodo-sugar was either 4 : 6-benzylidene α-methyl-3-iodo-3-deoxyglucoside (VII) or 4 : 6-benzylidene α-methyl-2-iodo-2-deoxyaltroside (VIII) was shown by its alkaline hydrolysis to the anhydroalloside (VI) in excellent yield, this behaviour paralleling that of α-methyl-3-chloro-3-deoxyglucoside and α-methyl-2-chloro-2-deoxyaltroside (Newth, Overend, and Wiggins, *loc. cit.*). Aqueous oxalic acid removed the benzylidene group from the iodo-derivative, and a crystalline methyl-iodohexoside, which was either α-methyl-3-iodo-3-deoxyglucoside (IX) or α-methyl-2-iodo-2-deoxyaltroside (X), was obtained. Evidence in favour of (IX) was that the compound did not react with acetone and sulphuric acid; a compound (X) would have formed the 3 : 4-*iso*propylidene derivative, as does the 2-chloro-analogue (Newth, Overend, and Wiggins, *loc. cit.*). Final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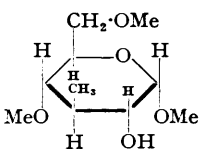
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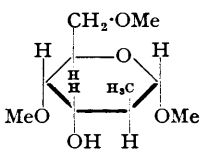
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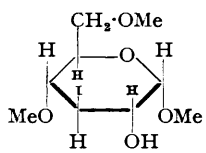
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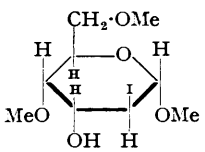
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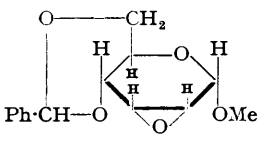
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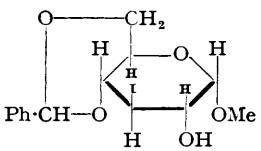
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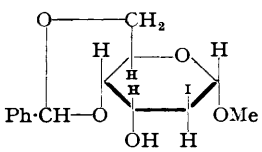
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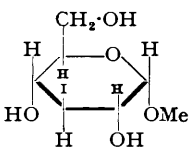
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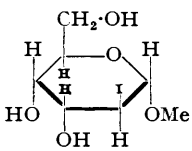
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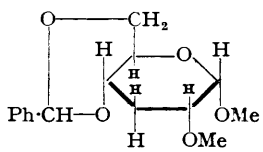

(XI.)

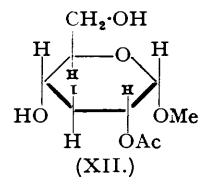
proof was obtained by methylation of the 4 : 6-benzylidene α-methyliododeoxyhexoside with silver oxide and methyl iodide to give a monomethyl derivative from which the iodine atom

was removed by hydrogenation, the product being 4 : 6-benzylidene 2-methyl α-methyl-3-deoxyglucoside (XI) (Prins, *Helv. Chim. Acta*, 1946, **29**, 1). Hence the product of the action of methylmagnesium iodide on 4 : 6-benzylidene α-methyl-2 : 3-anhydroalloside is (VII) and its acid hydrolysis product is (IX). Although the reaction of the Grignard reagent on the alloside was conducted under various conditions only the iodo-glucoside was obtained.

In view of these results, only one product, namely 4 : 6-dimethyl α-methyl-3-iodo-3-deoxyglucoside (IV), was expected to be formed from 4 : 6-dimethyl α-methyl-2 : 3-anhydroalloside (I) and methylmagnesium iodide, but in fact a complex mixture was obtained. It was only possible to isolate the individual constituents in rather poor yields. When the reaction was conducted at 35° a crystalline and two liquid products were isolated; of the liquid substances, one contained iodine and the other did not.

The crystalline material was 4 : 6-dimethyl α-methyliododeoxyhexoside which theoretically must be either 4 : 6-dimethyl α-methyl-3-iodo-3-deoxyglucoside (IV) or 4 : 6-dimethyl α-methyl-2-iodo-2-deoxyaltroside (V). It afforded the original anhydroalloside (I) on alkaline hydrolysis. Its structure was finally settled as (IV) because the acetyl derivative was identical with that synthesized as follows from the known deoxyglucoside (VII). (VII) was acetylated and then hydrolysed with dilute oxalic acid, with the formation of 2-acetyl α-methyl-3-iodo-3-deoxyglucoside (XII) which on careful methylation furnished 2-acetyl 4 : 6-dimethyl α-methyl-3-iodo-3-deoxyglucoside (XIII).

The liquid products were separated by the fractional distillation of their acetyl derivatives. Ultimate analysis showed the higher-boiling substance to be an acetyl dimethyl methyliododeoxyhexoside which on alkaline hydrolysis gave 4 : 6-dimethyl α-methyl-2 : 3-anhydroalloside in good yield and was clearly different from the crystalline 2-acetyl 4 : 6-dimethyl α-methyl-3-iodo-3-deoxyglucoside, so that it is assigned the structure (XIV). The iodine atom was readily removed from this by reduction with sodium amalgam in buffered solution, which also hydrolysed the acetyl group and furnished 4 : 6-dimethyl α-methyl-2-deoxyalloside (XV). Methylation gave 3 : 4 : 6-trimethyl α-methyl-2-deoxyalloside (XVI) (sample 1). Proof of the structure of this and hence of the 4 : 6-dimethyl α-methyl-2-iodo-2-deoxyaltroside precursor was furnished by a synthetic procedure. 4 : 6-Benzylidene α-methyl-2 : 3-anhydroalloside with ethanethiol in the presence of an equivalent amount of sodium methoxide gave liquid 4 : 6-benzylidene α-methyl-2-ethylthio-2-deoxyaltroside (XVII) [Jeanloz, Prins, and Reichstein (*Helv. Chim. Acta*, 1946, **29**, 371), from methanethiol and the same anhydro-sugar, obtained the amorphous 4 : 6-benzylidene α-methyl-2-methylthio-2-deoxyaltroside and proved its structure]. Methylation of the 2-ethylthio-derivative (XVII) with methyl iodide and silver oxide gave crystalline 4 : 6-benzylidene 3-methyl α-methyl-2-ethylthio-2-deoxyaltroside (XVIII), from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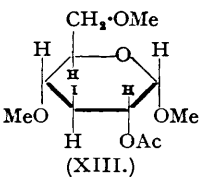
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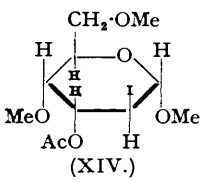
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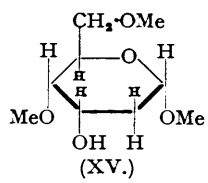
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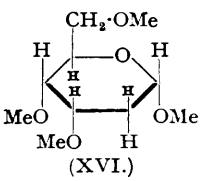
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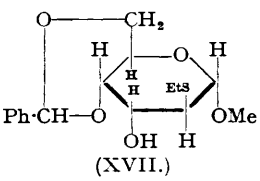
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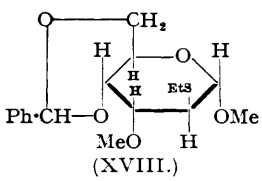
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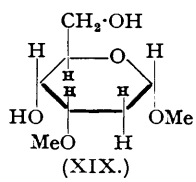
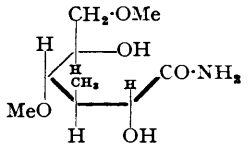

(XIX.)

which Bougault, Cattelain, and Chabrier's procedure (*Bull. Soc. chim.*, 1940, [v], **7**, 781) removed both the ethylthio- and the benzylidene group, affording 3-methyl α-methyl-2-deoxyalloside (XIX). When this was fully methylated, 3 : 4 : 6-trimethyl α-methyl-2-deoxyalloside (XVI) (sample 2) was isolated, identical in respect to specific rotation, refractive index, boiling point, and rate of hydrolysis with sample 1.

The halogen-free liquid product from the action of methylmagnesium iodide on 4 : 6-dimethyl α-methyl-2 : 3-anhydroalloside was shown by ultimate analysis to be a trimethyl methyldeoxyhexoside—theoretically 4 : 6-dimethyl α-methyl-3-methyl-3-deoxyglucoside (II) or 4 : 6-dimethyl α-methyl-2-methyl-2-deoxyaltroside (III). Its identity has not yet been definitely established but evidence is presented that it at least contains the glucoside (II). The main

difficulty has been failure to obtain crystalline derivatives (it formed a liquid toluene-*p*-sulphonate derivative, and after acidic hydrolysis gave a non-crystalline trimethyl deoxyhexose). Oxidation of the free sugar with bromine water gave a carboxylic acid lactone, but



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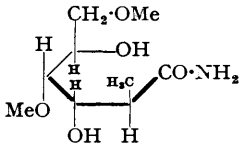
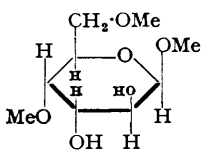


(XXI.)

neither this nor its amide was solid. Whether this amide is (XX) or (XXI) depends on whether the glycoside precursor is a derivative of glucose (II) or altrose (III). The amide (XX), possessing a hydroxyl group adjacent to the carbamyl group, should give a positive Weerman test; the altronamide (XXI) is not an α-hydroxy-amide. The syrupy amide isolated did in fact respond to the Weerman reaction and hence must at least contain the gluconamide (XX).

When methylmagnesium iodide and 4 : 6-dimethyl α-methyl-2 : 3-anhydroalloside reacted in ether at 35°, only 5·8% of the crystalline product, 4 : 6-dimethyl α-methyl-3-iodo-3-deoxyglucoside, was obtained, but at −15° the yield of this was 36·8%. At 86° in boiling tetrahydropyran, a still higher yield of 42% was obtained. The low yield of iodo-glucoside at 35° was not fortuitous since similar results were obtained when the experiment was repeatedly carried out.

Discussion.—Scission of an ethylene oxide ring asymmetrically situated in a sugar molecule has been shown to take place in both possible directions, invariably with Walden inversion, whether the reagent is alkaline or acidic. Thus, 4 : 6-dimethyl β-methyl-2 : 3-anhydroalloside and hot sodium hydroxide solution gave both 4 : 6-dimethyl β-methylaltroside (XXII) and 4 : 6-dimethyl β-methylglucoside (XXIII) (Peat and Wiggins, *J.*, 1938, 1810). Similarly treatment of 4 : 6-benzylidene α-methyl-2 : 3-anhydroalloside with hydrochloric acid in aqueous acetone effected hydrolysis of the benzylidene residue and scission of the anhydro-ring with the formation of α-methyl-3-chloro-3-deoxyglucoside (XXIV) and α-methyl-2-chloro-2-deoxyaltroside (XXV) (Newth, Overend, and Wiggins, *loc. cit.*).



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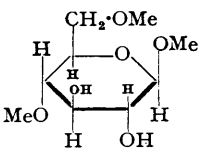

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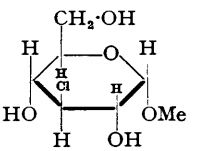

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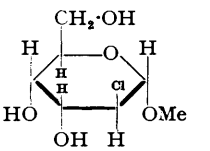


(XXV.)

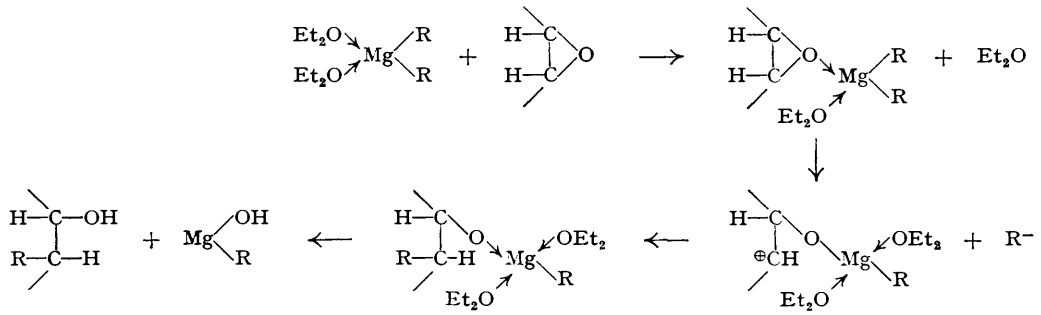
When a Grignard reagent attacks the oxide ring the mode of reaction must be essentially the same as that occurring with acid or alkaline reagents, irrespective of the way in which the Grignard reagent itself behaves. The Grignard reagent, however, may ionise two ways:

$$2RMgX \rightleftharpoons \begin{bmatrix} RMg^+ & + & X^- \\ R^- & + & MgX^+ \end{bmatrix} \rightleftharpoons R_2Mg + MgX_2$$

and any of the ions produced may attack the carbonium cation transiently formed at either of the two carbon atoms involved in the oxide ring.

There will assuredly be a competition between the two reagents R^- and X^-. Attack on the carbonium cation by R^- will lead to *C*-alkyl-sugar derivatives, whereas that by X^- will result in the formation of halogeno-derivatives. The ions R^- and X^- may arise, however, on the decomposition of a complex of the ethylene oxide ring with MgR_2 or with MgX_2. This complex may arise from that of the type proposed by Meisenheimer and Casper (*Ber.*, 1921, **54**, 1655) for a Grignard reagent and ether, by the substitution of one of the ether molecules with the ethylene oxide compound; it may be formed by the anhydro-sugar and either the dialkylmagnesium or the magnesium dihalide. Its hydrolysis would be expected to lead to the formation of R^- or X^- together with a carbonium cation liable to attack (accompanied by Walden inversion) by these ions. The following scheme represents a possible course for the

reaction of the ethylene oxide with dialkylmagnesium and may equally be applied to that involving magnesium dihalides:



Since experiments have demonstrated that the reaction of a Grignard reagent with 4 : 6-dimethyl and 4 : 6-benzylidene α-methyl-2 : 3-anhydroalloside leads primarily to the iodo-sugar derivatives the main attack on the oxide ring is by the iodide ion, probably produced from the decomposition of an intermediate complex. This being the case, it would be expected that magnesium iodide itself could effect ring scission of the ethylene oxide ring. When this reagent was heated in ethereal solution with either 4 : 6-benzylidene or 4 : 6-dimethyl α-methyl-2 : 3-anhydroalloside, 4 : 6-benzylidene and 4 : 6-dimethyl α-methyl-3-iodo-3-deoxyglucoside respectively were obtained. The action of other magnesium halides on anhydro-sugars of ethylene oxide type is being studied and it appears that this reaction provides a convenient and apparently a general method of preparing halogeno-sugars. Also, since in certain cases these halogen atoms may be replaced by hydrogen, the procedure leads to the synthesis of deoxy-sugars. The formation of halohydrins from non-sugar ethylene oxides and magnesium halides has been observed by Ribas and Tapia (*Anal. Fís. Quím.*, 1930, **28**, 636) who isolated 1-bromo-1-chloropropan-2-ol after treating epichlorohydrin with magnesium bromide in ether and obtained 1 : 3-dichloropropan-2-ol when epichlorohydrin was treated with zinc chloride in ether.

The formation of the more interesting *C*-alkyl sugars will doubtless involve the reaction of dialkylmagnesium or other similar organometallic derivative with the ethylene oxide compound. It has already been mentioned that these substances may be formed through the isomerisation of the ethylene oxide to a ketone and the subsequent action of the Grignard reagent thereon. The mode of formation of the *C*-alkyl sugars is however at present under investigation and we prefer to make no definite statement about the mechanism now.

In the reaction of the benzylidene anhydroalloside (VI) with methylmagnesium iodide, only 4 : 6-benzylidene α-methyl-3-iodo-3-deoxyglucoside (VII) was obtained and that in 80% yield. It is noteworthy that when the same anhydro-compound was treated with sodium methoxide or ammonia (*J.*, 1938, 1810) the main product, obtained in approximately 90% yield, was respectively a 2-methyl- or 2-amino-altrose derivative, the 3-methyl- or 3-amino-glucose derivative being obtained in, at most, 10% yield. Thus, in this particular case the relative proportions of ring scission products were reversed when the reagent used was magnesium iodide. The altrose isomer was also a minor constituent amongst the products of the more complex reaction of methylmagnesium iodide with 4 : 6-dimethyl α-methyl-2 : 3-anhydroalloside.

Experimental.

Treatment of 4 : 6-*Benzylidene* α-*Methyl*-2 : 3-*anhydroalloside with Methylmagnesium Iodide.*—The alloside (7·0 g.) (Richtmyer and Hudson, *J. Amer. Chem. Soc.*, 1941, **63**, 1727), m. p. 199—200°, dissolved in warm dry tetrahydropyran (200 c.c.), was added to a Grignard reagent prepared by warming methyl iodide (5·0 g.) in dry tetrahydropyran with magnesium turnings (0·9 g.) for 2 hours. An exothermic reaction took place and a white solid separated. The mixture was boiled for 2 hours, cooled, and treated with powdered ice, followed by dilute hydrochloric acid until all the solid had dissolved. The tetrahydropyran layer was separated and the aqueous layer extracted with a further quantity of solvent. The combined extracts were washed with dilute sodium carbonate solution and with water, dried ($MgSO_4$), filtered, and evaporated. Crystalline 4 : 6-*benzylidene* α-*methyl*-3-*iodo*-3-*deoxyglucoside* (13·6 g., 80%) remained. This, after being recrystallised from alcohol, had m. p. 195—196° and $[\alpha]_D^{19}$ −8·0° (*c*, 1·00 in chloroform) (Found: C, 42·8; H, 4·3; OMe, 8·3. $C_{14}H_{17}O_5I$ requires C, 42·9; H, 4·4; OMe, 7·9%). No other product was isolated.

4 : 6-*Benzylidene* 2-*Toluene*-p-*sulphonyl* α-*Methyl*-3-*iodo*-3-*deoxyglucoside.*—The above compound (0·2 g.) was treated in dry pyridine with toluene-*p*-sulphonyl chloride (0·15 g.) at room temperature.

After being kept overnight the solution was poured into water and the white precipitate was collected, washed with water, and recrystallised from alcohol. The *2-toluene-p-sulphonate* formed colourless crystals (0·19 g.), m. p. 137·5—138·5°, $[\alpha]_D^{21}$ −4·3° (*c*, 0·527, in chloroform) (Found: C, 46·5; H, 4·3. $C_{21}H_{23}O_7IS$ requires C, 46·1; H, 4·2%).

Treatment of 4 : 6-*Benzylidene* α-*Methyl*-3-*iodo*-3-*deoxyglucoside with Sodium Methoxide.*—The glucoside (0·156 g.) was dissolved in chloroform (1·5 c.c.) and a solution of sodium (0·12 g.) in dry methanol (6 c.c.) added at 0°. After 1 hour at room temperature needle-shaped crystals began to separate. On the next day these (0·102 g.) were collected, recrystallised from alcohol, and had m. p. 199—200° alone or on admixture with an authentic specimen of 4 : 6-benzylidene α-methyl-2 : 3-anhydroalloside.

Hydrolysis of 4 : 6-*Benzylidene* α-*Methyl*-3-*iodo*-3-*deoxyglucoside with Oxalic Acid.*—The glucoside (5·0 g.) was dissolved in acetone (225 c.c.), and a solution of oxalic acid (7·5 g. of the hydrate in 25 c.c. of water) was added. The solution was boiled for 100 hours, the specific rotation becoming constant after 85 hours. The acid was neutralised with barium carbonate, the solids were removed by filtration, and the solution was evaporated to dryness under reduced pressure. The residue of *α-methyl-3-iodo-3-deoxyglucoside* (2·9 g.), recrystallised from ethyl acetate, had m.p. 165° and $[\alpha]_D^{15}$ +136° (*c*, 1·00 in dioxan) (Found: C, 27·7; H, 4·3; OMe, 10·2. $C_7H_{13}O_5I$ requires C, 27·6; H, 4·3; OMe, 10·2%).

Attempted Condensation of α-*Methyl*-3-*iodo*-3-*deoxyglucoside with Acetone.*—The compound (0·201 g.) and concentrated sulphuric acid (0·13 c.c.) in dry acetone (15 c.c.) were kept overnight. Thereafter, the mixture was neutralised with anhydrous sodium carbonate, filtered, and evaporated. The residue, recrystallised from ethyl acetate, had m.p. 165° alone or on admixture with the original material.

Methylation of 4 : 6-*Benzylidene* α-*Methyl*-3-*iodo*-3-*deoxyglucoside.*—The glucoside (0·634 g.) was treated thrice with silver oxide and methyl iodide in the usual way, the product being extracted with chloroform. After the third methylation treatment, evaporation of the chloroform extract furnished 4 : 6-*benzylidene* 2-*methyl* α-*methyl*-3-*iodo*-3-*deoxyglucoside* as feathery needles which, recrystallised from chloroform–ether, had m. p. 193°, $[\alpha]_D^{15}$ −23·2° (*c*, 0·5 in chloroform) (Found: C, 44·0; H, 4·9. $C_{15}H_{19}O_5I$ requires C, 44·3; H, 4·7%).

Hydrogenation of 4 : 6-*Benzylidene* 2-*Methyl* α-*Methyl*-3-*iodo*-3-*deoxyglucoside.*—The above methylated glucoside (0·324 g.) was dissolved in a mixture of ether (30 c.c.) and methanol (30 c.c.). Potassium hydroxide (1 g.) and 10% palladised charcoal (0·2 g.) were added and the mixture hydrogenated at slightly elevated pressure, there being a steady absorption of hydrogen during 1 hour. Thereafter the solution was filtered, the charcoal was washed with ether, and the combined filtrates were evaporated to dryness. The residue was extracted with chloroform, and the extract filtered and then evaporated. The residual syrup completely crystallised and, recrystallised from aqueous ethanol, had m.p. 78° alone or on admixture with the 4 : 6-benzylidene 2-methyl α-methyl-3-deoxyglucoside of Newth, Overend, and Wiggins (*loc. cit.*).

Reaction of 4 : 6-*Dimethyl* α-*Methyl*-2 : 3-*anhydroalloside and Methylmagnesium Iodide.*—(a) *At* 35°. To a solution of methyl iodide (12·7 g.) in ether (50 c.c.) were added magnesium turnings (2·14 g.) and the mixture was warmed until reaction commenced. Thereafter the mixture was heated under reflux until all the metal had dissolved. The solution was then cooled and an ethereal solution of 4 : 6-dimethyl α-methyl-2 : 3-anhydroalloside (14·5 g.) added to a cooled solution from methyl iodide (12·7 g.) and magnesium (2·14 g.) in dry ether (50 c.c.). An immediate exothermic reaction occurred, accompanied by precipitation of a white solid. The mixture was heated under reflux for 2 hours, cooled, and treated with powdered ice, followed by dilute hydrochloric acid. The ethereal layer was separated, the aqueous portion extracted with more ether, and the extracts combined; after being washed with sodium hydrogen carbonate solution and water, the extract was dried ($MgSO_4$) and concentrated. Crystals of 4 : 6-*dimethyl* α-*methyl*-3-*iodo*-3-*deoxyglucoside* (0·82 g.) separated. These were collected and the mother-liquors kept. The aqueous layer was exactly neutralized with 5N-sodium hydroxide and evaporated to dryness. The residue was extracted several times with boiling chloroform, and the extracts were combined with the above ethereal mother-liquors and evaporated. The yellow syrup obtained was kept for several days, whereupon a further quantity of 4 : 6-dimethyl α-methyl-3-iodo-3-deoxyglucoside separated. This, recrystallised from ether, had m. p. 112·5—113° and $[\alpha]_D^{17}$ +119·9° (*c*, 1·031 in chloroform) (Found: C, 32·9; H, 5·2; I, 39·0. $C_9H_{17}O_5I$ requires C, 32·5; H, 5·2; I, 38·25%). The total yield of the 3-iodo-compound was 1·38 g. (5·8%). A mixture of the residual brown syrup (12·5 g.) and acetic anhydride (25 c.c.) in dry pyridine (60 c.c.) was kept overnight at room temperature and then poured into water, and the solution extracted with chloroform. The extract was washed with water, dried ($CaCl_2$), filtered, and evaporated. The syrup obtained (13·5 g.) was then fractionally distilled, giving pure (?) *2-acetyl* 4 : 6-*dimethyl* α-*methyl*-3-*methyl*-3-*deoxyglucoside*, b. p. 110° (bath-temp.)/0·02 mm., n_D^{18} 1·4593, $[\alpha]_D^{20}$ +108·5° (*c*, 1·087 in chloroform) (2·45 g., 15·9%) (Found: C, 54·6; H, 8·2; OMe, 35·0. $C_{12}H_{22}O_6$ requires C, 54·9; H, 8·5; OMe, 35·5%). All the material which distilled above 110°/0·02 mm. contained iodine and appeared to be a mixture of isomeric dimethyl methyliodohexosides. It was passed in light petroleum (b.p. 60—80°) through a column of alumina. Elution with light petroleum (b.p. 60—80°) gave a first fraction which was again purified by passage through alumina, whereupon *3-acetyl* 4 : 6-*dimethyl* α-*methyl*-2-*iodo*-2-*deoxyaltroside* was obtained as a pale yellow syrup. After being dried at 60°/0·2 mm. for 2 hours it showed n_D^{21} 1·4948, $[\alpha]_D^{22}$ +70·0° (*c*, 0·957 in chloroform) (Found: C, 36·0; H, 5·4. $C_{11}H_{19}O_6I$ requires C, 35·3; H, 5·1%) (total yield, 1·8 g., 6·8%).

(b) *At* −15°. The Grignard reagent from methyl iodide (1·5 g.), magnesium (0·255 g.), and ether (10 c.c.) was cooled to −15° (ice–salt) and a saturated solution of 4 : 6-dimethyl α-methyl-2 : 3-anhydroalloside (2 g.) in ether (50 c.c.), also at −15°, was slowly added with stirring. A white solid separated. The mixture was allowed to attain room temperature while stirring was continued overnight. Thereafter, the ether was removed by distillation at atmospheric pressure. Ice was added to the residue,

followed by chloroform (10 c.c.) and dilute hydrochloric acid sufficient to dissolve the magnesium hydroxide. The chloroform layer was separated and the aqueous portion extracted several times with chloroform. The extracts were combined, washed with dilute sodium hydrogen carbonate solution and with water, dried ($CaCl_2$), and evaporated. The syrup obtained crystallised on trituration with ether and, recrystallised from ether, gave colourless needles of 4 : 6-dimethyl α-methyl-3-iodo-3-deoxyglucoside (1·2 g., 37%), m. p. 111—112° alone or on admixture with authentic material. The mother-liquors yielded no other crystalline material except unchanged anhydroalloside (0·1 g.).

(c) *At* 86°. To a boiling Grignard reagent prepared from methyl iodide (0·76 g.) and magnesium (0·13 g.) in tetrahydropyran (10 c.c.), a solution of 4 : 6-dimethyl α-methyl-2 : 3-anhydroalloside was added dropwise. After 1 hour's heating a fine white granular precipitate separated. The solution was then cooled and ice added, followed by hydrochloric acid. The tetrahydropyran layer was separated and washed with dilute sodium hydrogen carbonate and sodium thiosulphate solutions and with water. After being dried ($MgSO_4$) the solution was evaporated to dryness. The partly crystalline residue, recrystallised from ether, afforded 4 : 6-dimethyl α-methyl-3-iodo-3-deoxyglucoside (0·546 g., 33·1%), m.p. 111·5—112·5° alone or on admixture with an authentic specimen. The aqueous layer from the reaction mixture was extracted exhaustively with chloroform. The extracts were washed as before and combined with the ethereal mother-liquors, and the mixture was evaporated to dryness. The residue was a liquid which distilled in two fractions: (i) b. p. 103—110° (bath-temp.)/0·05 mm. (45 mg.), n_D^{19} 1·4653, $[\alpha]_D^{19}$ +74·0° (*c*, 0·423 in chloroform), and (ii) b. p. 130—135° (bath-temp.)/0·045 mm. (0·30 g.). The syrup (ii) partly crystallised and when recrystallised afforded 4 : 6-dimethyl α-methyl-3-iodo-3-deoxyglucoside (0·15 g., 9·2%). The residual syrup (0·10 g.), n_D^{21} 1·5005, $[\alpha]_D^{16}$ +96·2° (*c*, 1·68 in chloroform), was not investigated further. Fraction (i) probably contained 4 : 6-dimethyl α-methyl-3-methyl-3-deoxyglucoside.

Reaction between Magnesium Iodide and 4 : 6-*Dimethyl* α-*Methyl*-2 : 3-*anhydroalloside*.—A solution of the alloside (0·491 g.) in absolute ether (20 c.c.) was added slowly to a well stirred suspension of anhydrous magnesium iodide (1·3 g., 2 mols.) in the same solvent (20 c.c.) at room temperature. No change in the appearance of the mixture occurred and no appreciable heat was evolved. The mixture was heated under reflux and stirring continued for 2½ hours. After the mixture had cooled, water (20 c.c.) was added; the aqueous layer was now alkaline and a small excess of hydrochloric acid was added. The ethereal layer was separated, washed with sodium hydrogen carbonate and thiosulphate solutions, then with water, and finally dried (Na_2SO_4). On evaporation, a white solid residue (0·240 g., 30·0%) was obtained which, recrystallised from light petroleum (b.p. 60—80°), had m. p. 112—113° alone or on admixture with authentic 4 : 6-dimethyl α-methyl-3-iodo-3-deoxyglucoside.

The aqueous layer from the reaction mixture was neutralised with sodium hydrogen carbonate and evaporated to dryness. The dry residue was extracted with boiling chloroform and the extracts evaporated to a yellow syrup (0·290 g.) which partly crystallised. The crystalline material was separated by filtration through sintered glass and was 4 : 6-dimethyl α-methyl-3-iodo-3-deoxyglucoside (0·124 g., 15·5%), m. p. 112—113°. The remaining yellow syrup (0·15 g., 18·8%) contained iodine and showed n_D^{23} 1·5168; it probably contained 4 : 6-dimethyl α-methyl-2-iodo-2-deoxyaltroside.

Acetylation of 4 : 6-*Dimethyl* α-*Methyl*-3-*iodo*-3-*deoxyglucoside*.—The glucoside (1·58 g.), treated in dry pyridine (10 c.c.) at 0° with acetic anhydride (2 c.c.), was kept at room temperature overnight and then poured into ice–water. The mixture was extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), filtered, and evaporated. The syrupy 2-*acetyl* derivative (sample 1) (1·69 g.), crystallised and recrystallised from light petroleum, had m. p. 66·5—67° and $[\alpha]_D^{19}$ +115° (*c*, 1·021 in chloroform) (Found: C, 35·7; H, 4·9. $C_{11}H_{19}O_6I$ requires C, 35·3; H, 5·1%).

2-*Acetyl* 4 : 6-*Benzylidene* α-*Methyl*-3-*iodo*-3-*deoxyglucoside*.—4 : 6-Benzylidene α-methyl-3-iodo-3-deoxyglucoside (1·25 g.) was treated in dry pyridine (10 c.c.) at 0° with acetic anhydride (2 c.c.). After being kept overnight at room temperature the mixture was poured on ice. The *acetyl* derivative which separated was collected and recrystallised from alcohol, forming prisms, m. p. 163—164°, $[\alpha]_D^{15}$ −16·4° (*c*, 1·016 in chloroform) (Found: C, 44·5; H, 4·4. $C_{16}H_{19}O_6I$ requires C, 44·2; H, 4·4%).

2-*Acetyl* α-*Methyl*-3-*iodo*-3-*deoxyglucoside*.—The foregoing acetyl derivative (1·16 g.) in acetone (40 c.c.), mixed with oxalic acid hydrate (1·7 g.) in water (7 c.c.), was boiled under reflux, and the reaction followed polarimetrically, the following data being obtained: $[\alpha]_D$ −9·7° (5 mins.), −2·4° (1 hr.), +47° (10 hrs.), +90° (30 hrs.). Thereafter the solution was cooled and neutralised with barium carbonate, the solids were filtered off, and the acetone was removed from the filtrate by evaporation. A small amount of unchanged starting material separated at this stage. Benzaldehyde present in the solution was removed by extraction with ether, the aqueous phase being evaporated to dryness. The residue crystallised and after extraction with alcohol and recrystallisation from alcohol–ether yielded 2-*acetyl* α-*methyl*-3-*iodo*-3-*deoxyglucoside* (0·79 g.), m. p. 132—132·5°, $[\alpha]_D^{16}$ +146·0° (*c*, 0·513 in ethyl alcohol). The substance softened at 127° and did not finally melt until 150°, but, after cooling, remelted sharply at 132—132·5° (Found: C, 30·8; H, 4·4; OMe, 8·9. $C_9H_{15}O_6I$ requires C, 31·2; H, 4·4; OMe, 9·0%).

2-*Acetyl* 4 : 6-*Dimethyl* α-*Methyl*-3-*iodo*-3-*deoxyglucoside* (Sample 2).—The above compound (0·7 g.) was methylated by three successive treatments with silver oxide and methyl iodide, the product of each treatment being extracted with boiling chloroform. The final product was distilled in two fractions: (i) b.p. 115—120° (bath-temp.)/0·007 mm. (0·25 g.), which was a mixture and appeared to contain anhydro-sugar derivatives; and (ii) b. p. 115° (bath-temp.)/0·007 mm. (0·10 g.). Fraction (ii) crystallised spontaneously and, recrystallised from light petroleum, had m. p. 66·5—67° alone or on admixture with sample 1 of the 2-acetyl derivative described above.

Alkaline Hydrolysis of 4 : 6-*Dimethyl* α-*Methyl*-3-*iodo*-3-*deoxyglucoside*.—The glucoside (0·126 g.), dissolved in methyl alcohol (5 c.c.), was treated with a solution of sodium (0·1 g.) in methyl alcohol

(5 c.c.). After being kept overnight at room temperature the solution was neutralised with solid carbon dioxide, water was added, and the solution extracted with chloroform. The extract was dried ($CaCl_2$) and evaporated to a syrup which rapidly crystallised. Recrystallised from light petroleum it formed 4 : 6-dimethyl α-methyl-2 : 3-anhydroalloside, long needles, m. p. 60—62° alone or on admixture with an authentic specimen.

Alkaline Hydrolysis of 3-*Acetyl* 4 : 6-*Dimethyl* α-*Methyl*-2-*iodo*-2-*deoxyaltroside*.—To the altroside (0·125 g.) in chloroform (2 c.c.), a solution of sodium (0·1 g.) in methyl alcohol (5 c.c.) was added at 0°. The solution was kept overnight but no change in optical rotation was observed; after it had been kept for 8 days at room temperature sodium iodide had separated. The solution was then neutralised with solid carbon dioxide and the mixture treated as described above. The syrup eventually obtained (50 mg.) crystallised and, after being recrystallised from light petroleum, the 4 : 6-dimethyl α-methyl-2 : 3-anhydroalloside showed m.p. 60—61° alone or on admixture with an authentic specimen.

Reduction of 3-*Acetyl* 4 : 6-*Dimethyl* α-*Methyl*-2-*iodo*-2-*deoxyaltroside*.—The altroside (1·27 g.) was dissolved in methyl alcohol (100 c.c.) and water (25 c.c.), a few drops of phenolphthalein were added, and the solution was saturated with carbon dioxide. Sodium amalgam (60 g.; 3%) was added while carbon dioxide was passed through the solution and the mixture stirred. When the amalgam had all decomposed the solution was decanted and evaporated to dryness, hydrochloric acid being added from time to time to remove alkalinity. The dry residue was extracted with ethyl acetate and the extract evaporated to a syrup (0·312 g.). In order to ensure that no acetyl groups remained in the product it was treated with sodium (0·05 g.) in dry methyl alcohol (50 c.c.). After being kept overnight, the solution showed $[\alpha]_D^{17}$ +175° and was evaporated to a pale yellow syrup (0·28 g., 40%). This was purified by chromatography on alumina from benzene solution. The product, 4 : 6-*dimethyl* α-*methyl*-2-*deoxyalloside*, was a syrup (0·17 g.) which, after being dried at 40°/0·5 mm. for 1 hr., showed n_D^{24} 1·4602 and $[\alpha]_D^{23}$ +180° (*c*, 0·194 in chloroform) (Found: C, 53·0; H, 8·7. $C_9H_{18}O_5$ requires C, 52·4; H, 8·8%).

3 : 4 : 6-*Trimethyl* α-*Methyl*-2-*deoxyalloside*.—The foregoing deoxyalloside (150 mg.) was methylated by three successive treatments with methyl iodide and silver oxide under the usual conditions. The *trimethyl* derivative (sample 1) (155 mg.) distilled at 110° (bath-temp.)/0·7 mm. and showed n_D^{24} 1·4505 and $[\alpha]_D^{24}$ +184° (*c*, 1·131 in chloroform) (Found: C, 54·2; H, 8·7. $C_{10}H_{20}O_5$ requires C, 54·5; H, 9·2%).

Synthesis of 3 : 4 : 6-*Trimethyl* α-*Methyl*-2-*deoxyalloside. The Reaction between Ethanethiol and* 4 : 6-*Dimethyl* α-*Methyl*-2 : 3-*anhydroalloside*.—The alloside (2 g.) was added to a solution of sodium (0·7 g.) and ethanethiol (2 g.) in dry methyl alcohol (20 c.c.), and the mixture boiled for 2 hours. Complete dissolution was effected within 10 minutes. After being cooled, the solution was evaporated to half its bulk. Water (3 c.c.) was then added and the rest of the methyl alcohol removed. The resulting oily suspension was extracted several times with ether (total, 50 c.c.), and the extract washed with water and dried (Na_2SO_4). Evaporation yielded a colourless syrup (2·245 g., 91%). Part of the product (0·95 g.) was purified by chromatography on an alumina column (8″ × ¾″) from benzene solution, the product being eluted with the same solvent. 4 : 6-*Benzylidene* α-*methyl*-2-*ethylthio*-2-*deoxyaltroside* recovered from the early fractions (0·648 g.) showed n_D^{18} 1·5485 and $[\alpha]_D^{19}$ +79·2° (*c*, 1·022 in chloroform) after being dried at 60°/0·04 mm. for 1 hour (Found: C, 59·0; H, 6·7. $C_{16}H_{22}O_5S$ requires C, 58·9; H, 6·8%). The material was distilled with slight decomposition but the distillate had the characteristics shown above. The *acetate*, prepared by treating the syrup (0·27 g.) in dry pyridine (2 c.c.) with acetic anhydride (0·5 c.c.) at 0° for 24 hours, separated as an oil when the mixture was poured into ice–water. It was extracted with chloroform, the extracts being washed with water and dried ($MgSO_4$), and obtained as a syrup, b.p. 190—200° (bath-temp.)/0·4 mm., n_D^{22} 1·5337, $[\alpha]_D^{20}$ +83·6 (*c*, 1·315 in chloroform) (Found: C, 58·2; H, 6·7. $C_{18}H_{34}O_6S$ requires C, 58·7; H, 6·6%).

4 : 6-*Benzylidene* 3-*Methyl* α-*Methyl*-2-*ethylthio*-2-*deoxyaltroside*.—The 2-ethylthio-derivative obtained as above (0·249 g.) was methylated by three successive treatments with methyl iodide and silver oxide in the usual way, the product being extracted with chloroform. The final extracts were evaporated to a yellow liquid which, after distillation at 190—200° (bath-temp.)/0·1 mm., crystallised spontaneously and recrystallised from ether. 4 : 6-*Benzylidene* 3-*methyl* α-*methyl*-2-*ethylthio*-2-*deoxyaltroside* formed fine white needles, m. p. 96—97° (0·23 g., 88%), $[\alpha]_D^{21}$ +74·7° (*c*, 1·112 in chloroform) (Found: C, 59·5; H, 7·1. $C_{17}H_{24}O_5S$ requires C, 59·9; H, 7·1%).

Reduction of 4 : 6-*Benzylidene* 3-*Methyl* α-*Methyl*-2-*ethylthio*-2-*deoxyaltroside with Alkaline Raney Nickel*.—The altroside (1·31 g.) was dissolved in ethyl alcohol (60 c.c.), Raney nickel (*ca.* 25 g.; freshly prepared and washed with water until the washings showed pH 10, then with alcohol until the washings showed pH 9) was added, followed by water (20 c.c.), and the mixture was heated under reflux for 2 hours. The nickel was then filtered off and washed with water. The odour of toluene was detectable in the filtrate. This was evaporated to dryness under reduced pressure and the syrupy residue dissolved in water (10 c.c.) and shaken with chloroform to remove unchanged starting material. The aqueous layer was saturated with hydrogen sulphide in the presence of ammonia and filtered. The filtrate was evaporated to dryness and the residue dried thoroughly by evaporation with benzene. The residue was extracted with chloroform to remove still further amounts of inorganic material. The final product obtained on evaporation of the chloroform was a colourless syrup (0·68 g., 91%) which distilled at 105—110° (bath-temp.)/0·3 mm. as an oil, n_D^{18} 1·4772, $[\alpha]_D^{20}$ +201° (*c*, 0·609 in chloroform) (Found: C, 49·8; H, 8·6. Calc. for $C_8H_{16}O_5$: C, 50·0; H, 8·4%). It was 3-methyl α-methyl-2-deoxyalloside. Reichstein *et al.* (*loc. cit.*) give $[\alpha]_D^{13}$ +196·5° for this substance.

Methylation of 3-*Methyl* α-*Methyl*-2-*deoxyalloside*.—The above alloside (0·587 g.) was methylated by three successive treatments with methyl iodide and silver oxide at 45° for 12 hours in the usual way, the product being extracted after each treatment with boiling chloroform. Evaporation of the final extract gave a liquid 3 : 4 : 6-trimethyl ether (0·559 g.) which distilled at 70—75° (bath-temp.)/0·2 mm.,

as a colourless mobile oil (0·43 g.), n_D^{23} 1·4510, $[\alpha]_D^{25}$ +185·0° (*c*, 1·298 in chloroform) (Found : C, 54·2; H, 9·0. Calc. for $C_{10}H_{20}O_5$: C, 54·5; H, 9·2%). It was identical with sample 1 recorded above.

Hydrolysis of 3 : 4 : 6-*Trimethyl* α-*Methyl-2-deoxyalloside* (*Samples* 1 *and* 2).—The trimethyl alloside (sample 2) (0·176 g.) was dissolved in ethyl alcohol (7·5 c.c.) at room temperature and 16% hydrochloric acid (0·5 c.c.) added. The mixture was kept at room temperature and the hydrolysis followed polarimetrically : $[\alpha]_D^{26}$ +190° (3 mins.); +150° (62 mins.); +122·6° (112 mins.); + 81·0° (4 hrs.); +63·5° (6 hrs.); +51° (24 hrs., constant). Similarly sample 1 (0·043 g.) in alcohol (3·75 c.c.) was treated with 16% hydrochloric acid (0·25 c.c.) at room temperature. The changes in specific rotation were : $[\alpha]_D^{24}$ +198° (4 mins.); +157·4° (57 mins.); +120·4° (2½ hrs.); +86·2° (4 hrs.); +66·6° (6½ hrs.); +51·8° (25 hrs., constant).

4 : 6-*Dimethyl* α-*Methyl-3-methyl-3-deoxyglucoside*.—2-Acetyl 4 : 6-dimethyl α-methyl-3-methyl-3-deoxyglucoside (2·23 g.), obtained by the action of methylmagnesium iodide on 4 : 6-dimethyl α-methyl-2 : 3-anhydroalloside at 35°, was deactylated by dissolving it in dry methyl alcohol, adding a small piece of sodium, and keeping the solution at room temperature. The following changes in specific rotation were observed : $[\alpha]_D$ +63·5° (20 mins.); +57·6° (4 hrs.); +54·0° (24 hrs.). Thereafter, the solution was evaporated to a syrup which distilled at 80° (bath-temp.)/0·02 mm. The colourless distillate (1·25 g., 67%), n_D^{22} 1·4640, $[\alpha]_D^{23}$ +73·5° (*c*, 1·305, in chloroform), was probably 4 : 6-dimethyl α-methyl-3-methyl-3-deoxyglucoside (Found : C, 54·8; H, 8·7. Calc. for $C_{10}H_{20}O_5$: C, 54·5; H, 9·2%). Treatment with toluene-*p*-sulphonyl chloride in pyridine gave a syrup, $[\alpha]_D^{18}$ +47·9° (*c*, 1·92, in chloroform) (Found : C, 54·7; H, 6·7. Calc. for $C_{17}H_{16}O_7S$: C, 54·5; H, 7·0%).

Hydrolysis of 4 : 6-*Dimethyl* α-*Methyl-3-methyl-3-deoxyglucoside*.—The glucoside (1·40 g.) was heated at 100° with 5% hydrochloric acid (25 c.c.) and the reaction followed polarimetrically : $[\alpha]_D$ +35·5° (initial); −29·6° (5 mins.); −29·4° (10 mins., constant). Thereafter the solution was neutralised with barium carbonate, filtered, and evaporated. The dry residue was extracted several times with boiling chloroform, and the extracts were evaporated to a viscous syrup (1·147 g.), which distilled (with some difficulty) at 130° (bath-temp.)/0·06 mm. and showed n_D^{19} 1·4840 and $[\alpha]_D^{21}$ −24·4° (*c*, 0·858 in water). It was probably 4 : 6-dimethyl 3-methyl-3-deoxyglucose (Found : C, 51·6; H, 8·0. Calc. for $C_9H_{18}O_5$: C, 52·4; H, 8·8%).

Formation of Hydrazodicarboxyamide from 4 : 6-*Dimethyl-3-methyl-3-deoxyglucose*.—The glucose derivative (0·223 g.) was dissolved in water (10 c.c.), bromine (0·5 c.c.) added, and the mixture kept in a stoppered flask at 35° for 20 hours. Excess of bromine was then removed by aeration and the solution neutralised with silver carbonate. The solids were filtered off and washed with water, and the filtrate was saturated with hydrogen sulphide. After the precipitated silver sulphide had been removed by filtration, the clear liquid was evaporated to a yellow syrup (0·104 g.). This was heated at 50°/0·2 mm. for a hour over phosphoric oxide to effect lactonisation and then dissolved in dry methyl alcohol (5 c.c.), and the solution was saturated with ammonia at 0°. After being kept at 15° for 40 hours under pressure the mixture was filtered and evaporated in a vacuum. A yellow amorphous solid (0·073 g.) was obtained which could not be crystallised. This was dissolved in water (1 c.c.), cooled to 0°, and treated with 1·5N-sodium hypochlorite (0·5 c.c.) for 30 minutes. Excess of hypochlorite was removed by the careful addition of sodium thiosulphate (starch–iodide), and solid sodium acetate (0·5 g.) was added. The solution was then filtered and treated with semicarbazide hydrochloride (0·075 g.). Hydrazodicarboxyamide separated rapidly as a fine white crystalline precipitate which was removed by centrifuging and washed with water; it (5 mg.) had m. p. 252° (decomp.), not depressed on admixture with an authentic specimen (m. p. 258°).

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