CCCXXVIII.—*The Development of a Novel Form of Stereoisomerism in the Sugar Series. Part I. The Third Variety of Triacetyl Methylrhamnoside.*

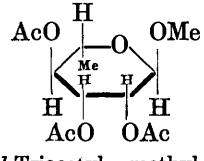
By WALTER NORMAN HAWORTH, EDMUND LANGLEY HIRST, and ERNEST JOHN MILLER.

FOR some time it has been recognised that there exist three varieties of triacetyl methylrhamnoside. Two of these, the α- and β-forms, possess normal properties and their specific rotations indicate their relationship with α- and β-rhamnopyranose. The third variety has been described as the "γ"-form, and to this E. Fischer, Bergmann, and Rabe (*Ber.*, 1920, **53**, 2362) allocated a different ring system. It has hitherto been accepted that this third form is a derivative of γ-rhamnose. The characteristic feature of the supposed triacetyl "γ"-methylrhamnoside is that only two of the three acetyl groups can be eliminated with hot alkali, and from this treatment a monoacetyl methylrhamnoside is isolated. On the other hand, the elimination of all three acetyl groups in both the α- and the β-variety of triacetyl methylrhamnoside proceeds smoothly and normally, and leads to the formation of α- and β-methylrhamnosides.

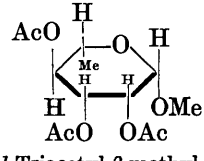
The pyranose structure of α-methylrhamnoside has already been established by earlier observations (Hirst and Macbeth, J., 1926, 22; see also preceding paper by Avery and Hirst). A direct proof of

the structure of the crystalline β-methylrhamnoside which is obtainable from triacetyl β-methylrhamnoside has not been developed, but that the substance is of the pyranose type may be inferred by comparing its properties with those of the crystalline trimethyl β-methylrhamnopyranoside isolated in the course of the present experiments. The question is, however, placed beyond reasonable doubt as the result of a parallel series of experiments which we have conducted on the β-form of the closely related tetra-acetyl methylmannoside. The α-, β-, and γ-varieties of tetra-acetyl methylmannoside (Dale, *J. Amer. Chem. Soc.*, 1924, **46**, 1046) offer such striking resemblances, both in physical and in chemical properties, to the α-, β-, and γ-forms of triacetyl methylrhamnoside as to render it almost inconceivable that the corresponding members of each group should differ in structure. In a subsequent paper it will be shown that the β-variety of tetra-acetyl methylmannoside has the pyranose structure and it follows therefore that a similar structure must be ascribed to triacetyl β-methylrhamnoside.

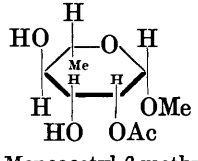
We have now investigated the ring system which is present in the third or supposed γ-variety of triacetyl methylrhamnoside, and our experiments disclose the fact that this also is a pyranoside having the same ring system as is present in the α- and β-forms. We are confronted, therefore, with the existence of three stereoisomeric modifications of this compound, all of them crystalline and structurally identical. On the accepted principles of stereoisomerism it is possible to accommodate two of these varieties, namely, the α- and β-forms in which the methoxyl residues at the first carbon atom in the ring are on opposite sides. The properties of the third variety are, moreover, distinctive in that one of the acetyl residues is stable to alcoholic ammonia and to aqueous alkali, and this group is, therefore, singled out as being in some way connected with the *raison d'être* of this variety. We have succeeded in showing that the position occupied by this recalcitrant group is at carbon atom 2 of the ring, where it encounters a second acetoxy-residue at the neighbouring position 3 on the same side of the ring. This congestion is increased by the presence of the methoxyl residue at position 1 when this is also at the same side.



l-Triacetyl α-methyl-rhamnoside.



l-Triacetyl β-methyl-rhamnoside.
(Occurs in two forms.)



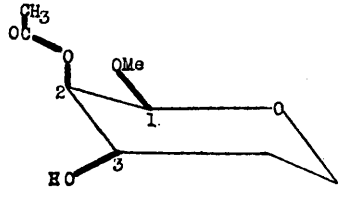
l-Monoacetyl β-methyl-rhamnoside.

Inspection of a model of β-methylrhamnoside serves to illustrate the effect introduced by the propinquity of acetylated residues at positions 2 and 3. There is interference of the free rotation of the addenda at these points of the ring and obstruction may easily be set up. Since this is the case, it follows that there may exist two stereoisomeric forms of triacetyl β-methylrhamnoside. Such an interlocking of groups has been envisaged in the obstacle theory for the existence of stereoisomerism in the diphenyl series, namely, the nitro- and chloro-diphenic acids which are substituted at positions 2 and 6 (Christie and Kenner, J., 1922, **121**, 614; Turner and Le Fèvre, *Chem. and Ind.*, 1926, **45**, 831; Bell and Kenyon, *ibid.*, p. 864; Mills, *ibid.*, p. 883; Mills and Elliott, J., 1928, 1291). The present anomaly may possibly be explained also on the view of the co-ordination of one of the acetoxyl residues with a neighbouring group, but in the present examples this hypothesis appears to be another and a less general way of expressing the obstacle theory. What is clearly evident is that there is restricted movement of the groups attached to carbon atoms 1, 2, and 3 in the triacetyl methylrhamnoside.

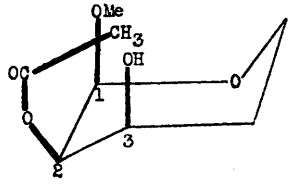
The occurrence of an anomalous behaviour in the mannose–rhamnose series has already been commented on (Haworth and Hirst, J., 1928, 1221), and other evidence in our possession shows that the methylated δ-lactones in this series display also an anomalous behaviour. These facts have revealed to us that the example illustrated in the case of rhamnose is by no means unique, and that it represents a phenomenon of which full account must be taken in a consideration of general principles of stereoisomerism. It is doubtful whether the presence of co-ordinate linkings alone can explain these facts in view of the other examples which have been quoted, and we are forced to adopt a working hypothesis which suggests the vibration of the constituent atoms of the sugar-ring, accompanied by the occurrence of phases representing the existence of strainless forms of rings. The free rotation of the addenda would be facilitated during certain of these phases and obstructed by others, with the result that, under selected experimental conditions, the occurrence of three stereoisomeric forms in the case of rhamnose and mannose is possible. It has been explained (" Constitution of Sugars," Haworth, 1929) that for each series, *d* and *l*, eight strainless forms of a pyranose ring are conceivable. It is the mean of these forms which has ordinarily been investigated in a sugar such as glucose in solution, which exhibits no obvious anomalies, and in which the spatial distribution of the addenda offers little opportunity for the interlocking of groups.

In the third variety of triacetyl methylrhamnoside the inter-

locking effect of adjacent groups persists even on removal of two of the three acetyl residues. The one remaining acetyl group is stabilised or obstructed, as is suggested in diagram B, whilst the easily hydrolysable type of grouping is illustrated in diagram A.



A
Unobstructed form.



B
Interlocked form.

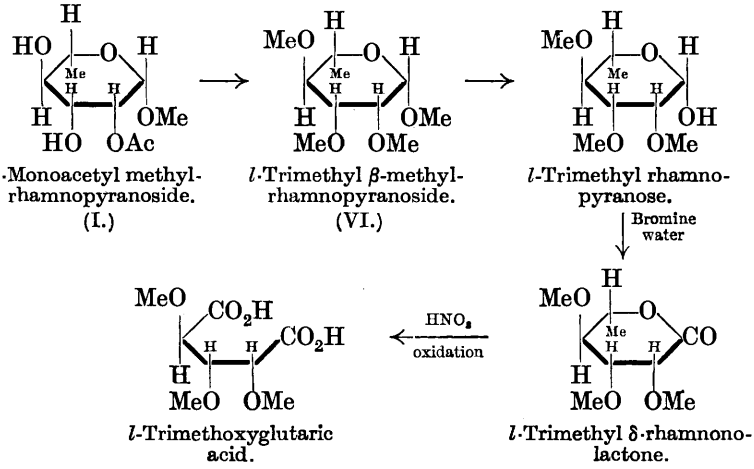
In one form of strainless ring (B) the valency directions at carbon atoms 1 and 3 are nearly vertical, whereas in the alternative form (A) they are extended outwards in an almost horizontal direction. The diagrams illustrate the two strainless ring forms of the *trans* or zig-zag type, but, alternatively, the same conditions arise if one utilises certain of the *cis* or boat-shaped forms of strainless rings.

The members of the mannose, lyxose, ribose, allose, and glucoheptose series may also, on this view, present similar anomalies among their glucosidic forms, and we are at present engaged in the study of certain of these cases. The wider implications of these hypotheses are being investigated and will be the subject of subsequent papers.

Discussion of Results.

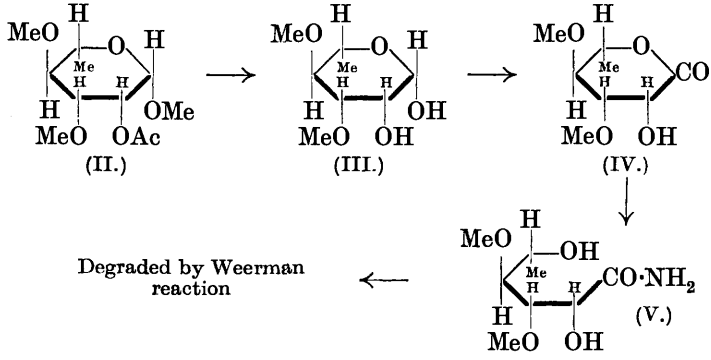
The stabilised acetyl group in monoacetyl methylrhamnoside is not eliminated either by alcoholic ammonia or by hot aqueous alkali. Digestion with dilute acid removes the glucosidic group and the acetyl residue simultaneously. Our problem was to discover a reagent which would effect the deacetylation without disturbing the glucosidic residue and would thus leave the ring structure intact. The desired conditions were developed from the accidental observation that " activated " silver oxide, prepared by precipitating silver oxide in the presence of sodium hydroxide, was effective, when used with methyl iodide, in bringing about simultaneous deacetylation and methylation of the methylrhamnoside. We therefore submitted monoacetyl methylrhamnoside to the action of methyl iodide and silver oxide containing an added quantity of solid sodium hydroxide and obtained a crystalline *trimethyl β-methylrhamnoside*. This substance gave on hydrolysis trimethyl rhamnose which, when oxidised with bromine water, was

transformed into the crystalline 2 : 3 : 4-trimethyl δ-rhamnonolactone. This lactone was identical with the specimen prepared by Avery and Hirst (see preceding paper), and its constitution is determined by the fact that it is degraded by oxidation with nitric acid to *l*-trimethoxyglutaric acid.



The next step was to determine the orientation of the acetyl group which is represented in the above formula (I) at position 2. That this position is correctly assigned is shown by the following series of transformations. The above monoacetyl β-methyl-rhamnopyranoside (I) gave rise on methylation with methyl iodide and silver oxide (prepared by precipitation with barium hydroxide) to a *monoacetyl dimethyl* β-*methylrhamnoside* (II) which was also crystalline. This substance was very sensitive to mineral acids, and was readily hydrolysed to the crystalline *dimethyl rhamnose* (III). The latter was converted by methylation into 2 : 3 : 4-*trimethyl* β-*methylrhamnoside* (VI), and also gave on oxidation with bromine water the crystalline *dimethyl* δ-*rhamnonolactone* (IV). The conclusion is therefore reached that the ring system of monoacetyl methylrhamnoside is of the six-atom type, and that this is an obstructed form of monoacetyl β-methylrhamnopyranoside. From the compound (IV) crystalline *dimethyl rhamnonamide* (V) was readily obtained, and this was submitted to the process of degradation which is known as the Weerman reaction (*Rec. trav. chim.*, 1917, **37**, 16). Under accurately controlled conditions this reaction is unfailing in the detection of a free hydroxyl group at position 2 in a sugar chain, and from the detailed account given in the experimental section it is evident that the dimethyl rhamnose must be unsubstituted at position 2. This must therefore have been the

position previously occupied by the acetyl residue in the monoacetyl dimethyl methylrhamnoside (II) and also in the monoacetyl methyl rhamnoside (I). Since the ring junctions of the pyranoside are at positions 1 and 5, the substituent methoxyl groups in the dimethyl derivative could only have been at positions 3 and 4.



It follows from these results that the three acetyl residues in the supposed triacetyl "γ"-methylrhamnoside occupy positions 2, 3, and 4 in the pyranose ring. The possibility of a change in ring structure during the series of transformations from the triacetyl to the trimethyl derivative has been considered and rejected in view of confirmative data which will be communicated later.

EXPERIMENTAL.

Rhamnose tetra-acetate was prepared by the action of pyridine and acetic anhydride on rhamnose according to Fischer, Bergmann, and Rabe (*loc. cit.*). By a slight modification of the method of extraction, the yield was increased to 80—85% of the theoretical. This was obtained by dissolving in chloroform the crude acetate which is precipitated when the product is poured into water, and shaking the chloroform solution in succession with dilute sulphuric acid, potassium bicarbonate solution, and water. The resulting acetate was a colourless viscid syrup. It was converted into aceto-bromorhamnose by the following modification of the process described by the above authors. Rhamnose tetra-acetate (50 g.) was dissolved in glacial acetic acid (25 c.c.) and treated at 0° with glacial acetic acid (100 c.c.) saturated with hydrogen bromide. After the solution had been kept for 90 minutes at 15°, chloroform (200 c.c.) was added and the solution was shaken with $N/2$-potassium bicarbonate until neutral to Congo-red, then with water, and dried over magnesium sulphate. Removal of the solvent under diminished pressure left acetobromorhamnose, which was obtained pure afte

one crystallisation from ether and ligroin (yield, 85% of the theoretical). The acetobromorhamnose was then treated with methyl alcohol in the presence of quinoline, giving "γ"-triacetyl methylrhamnoside, m. p. 83°, $[\alpha]_D^{21°}$ + 35° in absolute alcohol (c = 1), $[\alpha]_D^{21°}$ + 35° in chloroform (c = 1·0) (yield, variable up to 50% but usually about 20%).

Finally, "γ"-monoacetyl methylrhamnoside, m. p. 140—141°, was prepared by the action of methyl-alcoholic ammonia on the triacetyl derivative (yield, 95%) (compare Fischer, Bergmann, and Rabe, *loc. cit.*). For the monoacetyl derivative the value $[\alpha]_D^{21°}$ + 10° in absolute alcohol (c = 1·0) was recorded.

2-*Monoacetyl* 3 : 4-*Dimethyl Methylrhamnoside.*—A solution of "γ"-monoacetyl methylrhamnoside (8·3 g.) in a mixture of methyl iodide (20 c.c.) and dry methyl alcohol (25 c.c.) was heated at 45° for several hours with dry silver oxide (24 g.). It was necessary to use silver oxide which had been prepared by means of baryta (not sodium hydroxide). The product was extracted with dry methyl alcohol and immediately remethylated by the action of methyl iodide (34 c.c.) and silver oxide (21 g.) at 45°. After one further treatment under similar conditions the product crystallised spontaneously, giving 2-*monoacetyl* 3 : 4-*dimethyl methylrhamnoside* in long colourless needles, m. p. 67°. This substance was so soluble in all solvents that recrystallisation could not be effected, and it was purified by draining on porous tile. The crystals obtained were crisp and completely free from adhering syrup. B. p. about 90°/0·1 mm., $n_D^{17°}$ 1·4510 (supercooled liquid), $[\alpha]_D^{20°}$ + 36° in water (c = 1·02) (Found : C, 53·0; H, 8·2; OMe, 36·3. $C_{11}H_{20}O_6$ requires C, 53·2; H, 8·1; OMe, 37·45%). The pure substance did not reduce Fehling's solution and was very readily hydrolysed by dilute acids.

3 : 4-*Dimethyl Rhamnose.*—Monoacetyl dimethyl methylrhamnoside (3·2 g.) was heated with 2% aqueous hydrochloric acid (150 c.c.) until the rotation became constant ($[\alpha]_D^{20°}$ + 18° approximately). The acid was neutralised with lead carbonate, the water removed by evaporation under diminished pressure, and the product extracted from the solid residue by chloroform. Removal of the chloroform left a pale yellow syrup which soon crystallised (yield, 96%). Recrystallisation from ether–light petroleum gave *dimethyl rhamnose* in colourless needles, m. p. 91—92°. An aqueous solution (c = 1·5) of dimethyl rhamnose showed rapid mutarotation : $[\alpha]_D^{20°}$ 0° (3 mins. after dissolution), +5·9° (5 mins.), 7·3° (6 mins.), 9·9° (8 mins.), 13·3° (12 mins.), 15·3° (16 mins.), 16·6° (20 mins.), 17·9° (27 mins.), 18·6° (constant equilibrium value). From these figures the initial value of the specific rotation was calculated to be $[\alpha]_D^{20°}$ − 10°

(Found: C, 50·0; H, 8·7; OMe, 31·8. $C_8H_{16}O_5$ requires C, 50·0; H, 8·4; OMe, 32·3%). When dimethyl rhamnose was treated with phenylhydrazine or with *p*-bromophenylhydrazine, oily products were obtained which were insoluble in water. Their insolubility indicated that they were osazones, but they were intractable and could not be purified for analysis.

2 : 3 : 4-*Trimethyl* β-*Methylrhamnoside.*—Dimethyl rhamnose (4·9 g.) was heated with methyl iodide (34 c.c.) and silver oxide (17 g.) for 8 hours at 45—50°. The operation was repeated twice and the product then crystallised spontaneously (yield, 5·0 g.). The trimethyl methylrhamnoside obtained could not be recrystallised owing to its excessive solubility, but after thorough draining on a porous tile the long prismatic crystals were crisp and free from syrup; m. p. 53—54°, $[\alpha]_D^{21°}$ + 106° in water (c = 1·02). The substance was stable towards alkali and towards boiling Fehling's solution but was easily hydrolysed by acids. Titration with hot sodium hydroxide showed that no oxidation products were present (Found: C, 54·3; H, 8·9; OMe, 54·9. $C_{10}H_{20}O_5$ requires C, 54·5; H, 9·2; OMe, 56·3%).

2 : 3 : 4-*Trimethyl Rhamnose.*—Trimethyl methylrhamnoside (4·1 g.) was hydrolysed by heating at 95° with 0·5% aqueous hydrochloric acid. The specific rotation calculated on the weight of trimethyl rhamnose decreased steadily to a constant value $[\alpha]_D^{23°}$ + 29° at the end of 6 hours. The solution was neutralised with barium carbonate and then extracted with chloroform. Removal of the chloroform left trimethyl rhamnose as a pale yellow, uncrystallisable syrup, $n_D^{17°}$ 1·4570, $[\alpha]_D^{21°}$ + 27° in water (c = 1). It was proved to be identical with the trimethyl rhamnose obtainable by methylating α-methylrhamnoside (Purdie and Young, *loc. cit.*; Hirst and Macbeth, *loc. cit.*) by converting it into the corresponding trimethyl δ-rhamnonolactone. Trimethyl rhamnose (2·5 g.), dissolved in water (40 c.c.), was treated with bromine at room temperature until the reducing action had ceased (3 days). The bromine was removed by aeration, and the solution neutralised with silver oxide. The dissolved silver was removed by titration with dilute hydrochloric acid and after filtration the solution of the lactone was evaporated to dryness under diminished pressure. The solid residue was dissolved in chloroform, and the solution filtered and evaporated. The residue was distilled, giving trimethyl δ-rhamnonolactone, b. p. 120°/0·3 mm. (yield, 1·6 g.). The distillate rapidly crystallised and, after draining on porous tile, showed m. p. 40°, with slight softening from 36°, alone and when mixed with an authentic specimen. Further proof of the identity of this substance was forthcoming from a study of its hydrolysis in aqueous solution. The initial

value, $[\alpha]_D^{20°}$ — 127°, decreased regularly in the course of 100 hours to the constant value $[\alpha]_D^{20°}$ — 78°, these figures being in excellent agreement with those already rendered for trimethyl δ-rhamnonolactone (see previous paper).

3 : 4-*Dimethyl* δ-*Rhamnonolactone*.—Dimethyl rhamnose (1·9 g.), dissolved in water (28 c.c.), was treated at 40° with an excess of bromine until the reducing action had disappeared (30 hours). The product was isolated by the method described above, with the exception that distillation was in this case unnecessary. *Dimethyl rhamnonolactone* crystallised spontaneously after lactonisation had been completed by heating at 60° for 1 hour, and when recrystallised from ether–light petroleum gave long needles, m. p. 66—68°, $[\alpha]_D^{26°}$ — 153°, initial value in water (c = 1·05) (Found : C, 50·3; H, 7·9; OMe, 31·5. $C_8H_{14}O_5$ requires C, 50·5; H, 7·4; OMe, 32·6%).

Hydrolysis of 3 : 4-*Dimethyl Rhamnonolactone*.—The hydrolysis of the lactone and the lactonisation of dimethyl rhamnonic acid in aqueous solution were followed polarimetrically. From the initial values for the lactone ($[\alpha]_D^{20°}$ — 153°) and for the acid ($[\alpha]_D^{20°}$ — 15·9°, calculated as lactone) the proportion of lactone present at equilibrium was calculated to be 75%. The rotation of the acid was determined in the usual manner (see previous papers). Equilibrium was reached in about 100 hours, this figure being in close agreement with the corresponding periods for δ-lactones of the mannose, rhamnose, and lyxose series.

Lactone to acid (c = 1·05).			Acid to lactone.		
Time (hrs.).	$[\alpha]_D^{22°}$.	% Lactone.	Time (hrs.).	$[\alpha]_D^{21°}$.	% Lactone.
0	−153°	100	0	−15·9°	0
14·7	132	84·7	0·92	28·1	91
20·7	126	80·5	2·6	44·7	79
38·7	123	78·4	4	59	69
86·5	119	75·3	6	75	57
150	119	75·3	26	109	68
			96	118·1	75
			150	118·1	75

3 : 4-*Dimethyl Rhamnonamide*.—Dimethyl rhamnonolactone (0·2 g.) was dissolved in dry methyl alcohol (10 c.c.) saturated at 0° with ammonia. After 15 hours at room temperature the solvent was evaporated in a vacuum desiccator containing sulphuric acid. The solid residue of *dimethyl rhamnonamide* was recrystallised from ethyl alcohol and light petroleum, giving colourless needles, m. p. 152—155°, soluble in water, methyl alcohol or ethyl alcohol but insoluble in light petroleum (Found : C, 46·4; H, 8·4; N, 6·4; OMe, 29·2. $C_8H_{17}O_5N$ requires C, 46·4; H, 8·3; N, 6·8; OMe, 29·9%).

The presence of an α-hydroxy-group in this amide was proved by

applying Weerman's test (*loc. cit.*). Special precautions were taken to ensure the purity of the reagents used, and control experiments were performed simultaneously, both with amides containing α-hydroxy-groups and with amides containing α-methoxy-groups (compare Avery, Haworth, and Hirst, J., 1927, 2308). Positive results were uniformly obtained with the former, and negative results with the latter. It was proved that the presence of an excess of sodium hypochlorite did not invalidate the method, the trustworthiness of which was further substantiated by a series of blank experiments which in no case gave any trace of benzaldehyde-semicarbazone or hydrazodicarbonamide.

When dimethyl rhamnonamide (0·04 g.), dissolved in water (0·4 c.c.), was treated at 0° with the standard sodium hypochlorite solution (0·25 c.c.), the reaction was complete in about 40 minutes and the solution no longer gave a coloration with starch–iodide paper. Hydrazine sulphate (0·03 g. in 1 c.c. of water) was then added, the solution neutralised with sodium carbonate, and benzaldehyde (0·2 c.c.) added. After 3 hours the precipitate was collected and washed with ether to remove the soluble benzaldehyde-hydrazone, leaving a residue of benzaldehydesemicarbazone, m. p. 221°. In another experiment dimethyl rhamnonamide (0·04 g.) was treated as before with sodium hypochlorite; after 60 minutes, 0·5 c.c. of a saturated solution of sodium acetate was added, followed by the same volume of a saturated solution of semicarbazide hydrochloride. Within a few minutes a copious precipitate of hydrazodicarbonamide, m. p. 258°, was obtained, the presence of an α-hydroxy-group being thus proved.

Simultaneous Deacetylation and Methylation of "γ"-Monoacetyl Methylrhamnoside.—Methylation proceeded normally to give the crystalline monoacetyl dimethyl methylrhamnoside when "γ"-monoacetyl methylrhamnoside was treated in the ordinary way with methyl iodide and silver oxide which had been prepared by the aid of baryta and well washed. If, however, "activated" silver oxide, prepared by using sodium hydroxide, was employed, the acetyl group was to some extent replaced by methoxyl. For instance, in one series of experiments in which the "activated" oxide was used, only a small amount of 2-acetyl 3 : 4-dimethyl β-methylrhamnoside, m. p. 67°, was obtained after four methylations, and the main product was an uncrystallisable liquid, b. p. 73°/0·09 mm., $n_D^{21°}$ 1·4439, $[\alpha]_D^{25°}$ + 52° in water (c = 1·2) (Found: OMe, 43·9%). Nucleation with monoacetyl dimethyl methylrhamnoside (OMe, 37·5%) was unavailing. Two further methylations with ordinary silver oxide failed to raise the methoxyl content, but when the substance was treated with silver oxide

to which had been added 10% by weight of solid sodium hydroxide, two methylations sufficed to give a good yield (60%) of crystalline trimethyl β-methylrhamnoside, m. p. 52—54° alone or in admixture with a specimen prepared by methylating dimethyl rhamnose (see above). $[\alpha]_D^{23^\circ}$ + 106·9° in water (c = 0·6). Complete replacement of acetoxyl by methoxyl had thus been effected.

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