VI.—*The Structure of the Normal Monosaccharides. Part III. Rhamnose.*

By Edmund Langley Hirst and Alexander Killen Macbeth.

As earlier work led to the conclusion that normal derivatives of the pentose sugars xylose and arabinose have the amylene-oxidic structure (Hirst and Purves, J., 1923, **123**, 1352; Hirst and Robertson, J., 1925, **127**, 358), it was obviously of interest to determine the structure of normal derivatives of a typical methyl pentose. Evidence is now submitted showing that *l*-rhamnose and its stable derivatives also are amylene-oxidic. This view conflicts with the suggestion of Pringsheim ("Zuckerchemie," 1925, p. 102) that a butylene-oxidic structure for rhamnose follows from the apparently definite furoidal structure of rhamnal (Bergmann and Schotte, *Ber.*, 1921, **54**, 404). Fischer, Bergmann, and Rabe (*Ber.*, 1920, **53**, 2362) found, however, that during the conversion of aceto-

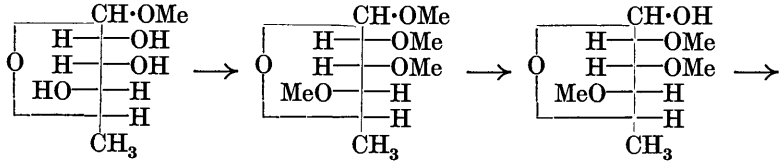
bromorhamnose into triacetyl methylrhamnoside a mixture of isomeric substances is formed by the wandering of acetyl groups accompanied by corresponding changes in the nature of the oxidic linkings. We are therefore of the opinion that it would be unsafe to base the structure of rhamnose derivatives on that of rhamnal, and, when considered in the light of the work now described, the presence of a γ-oxidic linking in triacetyl rhamnal is to be taken rather as evidence of the occurrence of an isomeric change during the reduction of acetobromorhamnose than as proof of the constitution of rhamnose itself.

The observations of Fischer, Bergmann, and Rabe led us to consider with special care the stability of the methoxyl groups in methylated rhamnose, for any wandering of the methyl groups would complicate very seriously the oxidation method we proposed to use in determining the structure of the compound. A wandering of a methyl group from position 6 to position 3 in the glucose molecule has been suggested (Ohle, *Ber.*, 1924, **57**, 403) to explain certain discordant observations in the chemistry of the acetone derivatives of the sugars, but, so far as we are aware, no case of such a transformation has been encountered during the oxidation of a methylated carbohydrate. Both γ- and normal derivatives oxidise to stable methoxy-acids without wandering of the methyl groups (compare, *e.g.*, Irvine, Fyfe, and Hogg, J., 1915, **107**, 539; Irvine and Oldham, J., 1921, **119**, 1744; Pryde, J., 1923, **123**, 1808; Levene, *J. Biol. Chem.*, 1924, **60**, 167; Haworth and Baker, J., 1925, **127**, 365; etc.). A study of methylated rhamnose and its oxidation has convinced us that the course of oxidation is normal in this case also, and that in consequence the structure of methylated rhamnose may be deduced when the nature of the oxidation products is known.

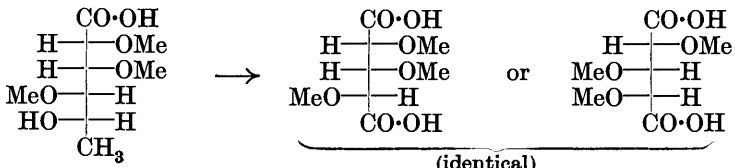
Rhamnose indeed, when methylated under various conditions, has shown a rather unusual capacity for yielding methyl derivatives of one structural form only. On methylation, either by preliminary formation of the crude mixture of α- and β-methylrhamnosides with acid methyl alcohol followed by use of the Purdie reagents, or by direct treatment with methyl sulphate, only the normal trimethyl rhamnose (Purdie and Young, J., 1906, **89**, 1194) was obtained, whereas in many cases mixtures containing both the amylene- and the butylene-oxide form of the methylated sugar are produced (Pryde, Hirst, and Humphreys, J., 1925, **127**, 348).

Oxidation of this trimethyl rhamnose by nitric acid not only showed that the compound was free from admixture with isomeric forms of different oxidic linking, but also gave a direct proof of its constitution. The oxidation product under the special conditions

adopted was *l*-arabotrimethoxyglutaric acid, which may also be obtained by oxidising trimethyl arabinose or by methylating *l*-trihydroxyglutaric acid. No methoxy-group was lost during the reaction, but the terminal methyl group was removed. These observations can be interpreted (assuming the stability of the methoxy-groups) only on the basis of an amylene-oxidic structure for normal trimethyl rhamnose, and from arguments which have been detailed previously this leads to the assigning of the amylene-oxidic formula to α- and β-methylrhamnosides and in all probability to rhamnose itself. A summary of the reactions involved is given in the accompanying scheme.



Methylrhamnoside. Trimethyl methylrhamnoside. Trimethyl rhamnose.



Trimethyl rhamnonic acid. (identical) Arabotrimethoxyglutaric acid.

The mechanism of the oxidation is in itself interesting. After the production of the intermediate trimethylrhamnonic acid, the action of nitric acid on the terminal $-CH(OH)\cdot CH_3$ group involves a quantitative transformation to $-CO\cdot OH$ and CO_2. This must proceed *via* the ketone $-CO\cdot CH_3$, and the present reaction (although not in accord with the usual behaviour of methyl ketones) is thus brought into line with certain other instances. For example, lævulic acid yields succinic acid on treatment with nitric acid (Tollens, *Annalen*, 1881, **206**, 257) and rhamnose itself gives *l*-trihydroxyglutaric acid (Will and Peters, *Ber.*, 1889, **22**, 1697). The simple nature of the change is here emphasised because of its contrast with the more complicated course of oxidation undergone by the allied group $-CH(OH)\cdot CH_2\cdot OMe$.

A study of the latter question has been completed by one of us in connexion with work on glucose, and details of this will be given in a future communication.

EXPERIMENTAL.

Methylation of Rhamnose.—A mixture of α- and β-methylrhamnosides (Fischer, *Ber.*, 1895, **28**, 1158) was methylated in the manner described by Purdie and Young (*loc. cit.*). The trimethyl α-methylrhamnoside so prepared showed the properties and physical constants given by these authors (b. p. 101°/9 mm.; $[\alpha]_D$ — 15° in water; $[\alpha]_D$ — 54° for $c = 2{\cdot}15$ in alcohol. The refractive index, hitherto unrecorded, was $n_D^{15°} = 1{\cdot}4415$).

In a second series of experiments rhamnose was treated in the usual way with methyl sulphate and caustic soda. Two such treatments followed by one with silver oxide and methyl iodide gave in good yield the fully methylated sugar as a colourless, uncrystallisable syrup, b. p. 100—101°/9 mm., $n_D^{18°}$ 1·4415 (Found: C, 54·5; H, 9·2; OMe, 55·2. Calc., C, 54·5; H, 9·1; OMe, 56·3%). It was stable to alkaline potassium permanganate solution and showed $[\alpha]_D$ — 11·3° in alcohol ($c = 1{\cdot}77$) and + 11·5° in water ($c = 2{\cdot}002$). It was therefore a mixture of the α- and β-forms of trimethyl methylrhamnoside. On hydrolysis with 8% aqueous hydrochloric acid at 90°, the specific rotation decreased regularly from the initial value of + 15·5° ($c = 1{\cdot}159$) to zero after 40 minutes and then rose gradually to a constant value, + 21·2° ($c = 1{\cdot}085$ as trimethyl rhamnose), after 200 minutes. On plotting the values against time, a curve is obtained which is characteristic of the hydrolysis of a mixture of the α- and β-forms of a methyl aldoside. Experiments on a larger scale gave a final value of + 19·5° ($c = 6{\cdot}4$) (compare Purdie and Young, *loc. cit.*). An improved method was employed to isolate the trimethyl rhamnose. After neutralisation of the acid with barium carbonate the hydrolysis product was extracted with chloroform and purified by distillation (yield 75%), being thus obtained as a colourless, viscous syrup, b. p. 141°/19 mm. (bath at 153°), $n_D^{15°}$ 1·4565 (Found: C, 52·3; H, 8·7; OMe, 44·7. Calc., C, 52·4; H, 8·7; OMe, 45·1%). $[\alpha]_D$ + 24·9° (in water, $c = 2{\cdot}53$), — 9° (in alcohol, $c = 1{\cdot}36$). It was obviously identical with the trimethyl rhamnose prepared by Purdie and Young.

Oxidation of Trimethyl Rhamnose.—A solution of 3·0 g. of trimethyl α-methylrhamnoside (prepared from α-methylrhamnoside; or trimethyl rhamnose may be used) in 70 c.c. of nitric acid (d 1·2) was heated slowly until oxidation commenced, at 85°. The reaction proceeded vigorously and was apparently complete after 4 hours. Heating was then renewed, and continued for a further 2½ hours. The oxidation product was freed from nitric acid, dried, and esterified with acid methyl alcohol by the method described in previous papers of this series. The ester (2·61 g. or 77% of the

theoretical yield) was purified by distillation and thus obtained as a colourless, uncrystallisable syrup [2·41 g.; b. p. 135°/9 mm. (bath at 150°); $n_D^{20°}$ 1·4350; $[\alpha]_D$ + 47·6° (in methyl alcohol, c = 1·706)]. It behaved as an ester on titration, and analysis and a comparison of its physical constants with those of an authentic sample prepared from arabinose showed it to be dimethyl *l*-arabotrimethoxyglutarate ($n_D^{21°}$ 1·4355; b. p. 143°/18 mm.; $[\alpha]_D$ + 47·3° for c = 1·842 in methyl alcohol) [Found : C, 47·8; H, 7·25; OMe, 60·2; CO_2Me (by hydrolysis), 46·3. Calc., C, 48·0; H, 7·2; OMe, 62·0; CO_2Me, 47·2%]. In view of the large difference in rotatory power between the acid and its fully methylated dimethyl ester (Hirst and Robertson, *loc. cit.*), it was of interest to examine the rotation of the sodium salt. A weighed quantity of the ester was hydrolysed with just more than the calculated quantity of caustic soda, and the solution was exactly neutralised with hydrochloric acid; $[\alpha]_D$ + 25° was thus found for the sodium salt (compare Purdie and Irvine, J., 1901, **79**, 962, for the rotations of dimethyl *d*-dimethoxysuccinate and the corresponding sodium salt).

When the ester was treated with methyl alcohol saturated with dry ammonia (0·36 g. in 3·6 c.c.), crystals of the diamide separated after 15 hours, and after 3 days 0·20 g. was collected (63% yield). The crystals were washed with cold methyl alcohol and ether and recrystallised once from methyl alcohol; they then had m. p. 230°, alone or mixed with an authentic specimen of *l*-arabotrimethoxyglutardiamide. The solubilities, the crystalline form, the behaviour on heating, and the specific rotation of this substance were in exact agreement with those previously recorded. $[\alpha]_D$ + 50·4° (c = 0·6942 in water) (Found : OMe, 41·6. Calc., OMe, 42·3%).

ARMSTRONG COLLEGE, NEWCASTLE UPON TYNE, AND DEPARTMENT OF SCIENCE, DURHAM,
UNIVERSITY OF DURHAM. [*Received, November 20th,* 1925.]