[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

2-METHYL-*l*-RHAMNOSE AND 2-METHYL-*d*-FUCOSE AND THEIR BEARING ON THE CONFIGURATION OF DIGITALOSE

HAROLD B. MACPHILLAMY AND ROBERT C. ELDERFIELD

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INTRODUCTION

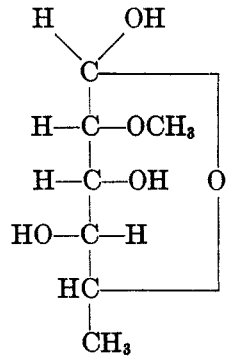
The chemistry of cardiac glycosides has interested investigators for a number of years. However, it has been only within the last few years that substantial progress has been made in the elucidation of their chemical structure[1]. Investigations in this field can be divided into two groups. The first, in which structural studies have been by far the more productive, is concerned with the non-carbohydrate or aglycone portion of the glycosides. The second, in which our knowledge is still comparatively meager, deals with the sugar components of the glycosides. It is to this latter group that the present investigation relates.

In addition to the relatively common sugars, such as glucose and rhamnose, a number of much rarer sugars, many of which are characterized by unusual structural features, are found as components of the cardiac glycosides[1]. The chemical structure and configuration of two of these sugars, digitoxose[2] and cymarose[3] have been established. Of the remaining sugars isolated from the hydrolytic products of the glycosides the configuration of digitalose and the structures and configurations of oleandrose and sarmentose, are still to be determined. The purpose of this research was to aid in establishing the configuration of digitalose.

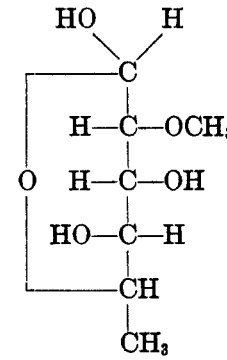
Digitalose was first obtained as a syrup by Kiliani[4] in 1892 from the products of hydrolysis of *Digitalinum verum*. On oxidation of the sugar with bromine water, he obtained a crystalline digitalonic lactone having the formula $C_7H_{12}O_5$. Hence the sugar itself must have the formula $C_7H_{14}O_5$. The seventh carbon atom was diagnosed as comprising a methyl ether group. On further oxidation with silver oxide Kiliani obtained acetic acid, thus indicating the presence of a terminal methyl group. Digitalonic lactone gave, on nitric acid oxidation, an α,β-dihydroxy-α'-

[1] ELDERFIELD, *Chem. Rev.*, **17**, 187 (1935).
[2] MICHEEL, *Ber.*, **63**, 347 (1930).
[3] ELDERFIELD, *J. Biol. Chem.*, **111**, 527 (1935).
[4] KILIANI, *Ber.*, **25**, 2116 (1892).

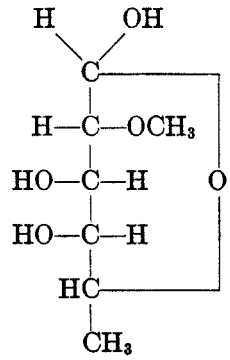
methoxyglutaric acid[5]. Kiliani also observed that digitalose formed a phenylhydrazone but not an osazone. This indicated that the methoxyl group was located on the second carbon atom of the hexose chain, thus blocking osazone formation. Later Schmidt and Zeiser[6] showed that the dihydroxymethoxyglutaric acid obtained by Kiliani, on complete methylation, gave *l*-arabotrimethoxyglutaric acid, thus establishing its steric configuration. From this evidence it follows that digitalose must therefore have one of the following formulas:



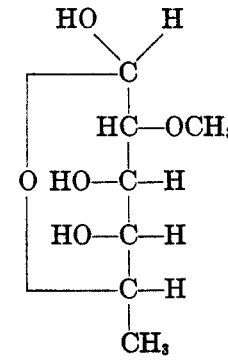
2-Methyl-
d-gulomethylose



2-Methyl-
l-rhamnose



2-Methyl-
d-fucose



2-Methyl-
l-altromethylose

More recently Lamb and Smith[7] have succeeded in obtaining the sugar in crystalline form by hydrolysis of a glycoside from *Strophanthus eminii* seeds.

[5] KILIANI, *ibid.*, **38**, 3621 (1905); **55**, 92 (1922); **64**, 2027 (1931).
[6] SCHMIDT AND ZEISER, *ibid.*, **67**, 2127 (1934).
[7] LAMB AND SMITH, *J. Chem. Soc.*, **1936**, 442.

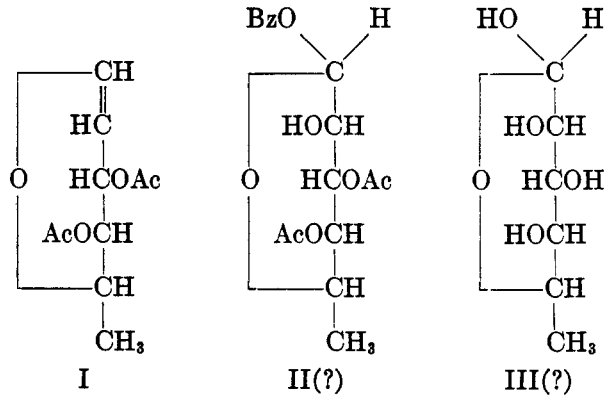
The simplest and most direct method of determining which of these configurations represents that of digitalose is to compare a completely methylated derivative of each sugar with the corresponding one of digitalose. However, since digitalose is so exceedingly difficult to obtain, this method of procedure was rejected in favor of direct synthesis.

The synthesis of two of the above four possibilities, namely *2-methyl*-l-*rhamnose* and *2-methyl*-d-*fucose*, has been accomplished. A comparison of the constants of these two sugars with those of digitalose, showed that neither was identical with digitalose. 2-Methyl-*l*-rhamnose as here obtained is a syrup, showing a final value of $[\alpha]_D$ of 31°; 2-methyl-*d*-fucose shows a variable melting point between 155° and 161° and a final value for $[\alpha]_D$ of 87°; digitalose[7] melts at 106° or 119° and shows a final value for $[\alpha]_D$ of 106°. Therefore, digitalose must be either 2-methyl-*d*-gulomethylose or 2-methyl-*l*-altromethylose. On the basis of biogenetic considerations, the latter alternative is much to be preferred.

A review of available methods for the preparation of 2-methyl sugars showed that one of the most promising was that of oxidizing the corresponding acetoglycal with perbenzoic acid according to the method of Bergmann and Schotte[8]. This procedure results in a sugar having an unsubstituted hydroxyl group only on the second carbon atom which could then be readily methylated by the Purdie and Irvine method. Final hydrolysis of the blocking groups would result in the desired 2-methyl sugar.

In discussing the structures of the sugars which are produced predominately by the perbenzoic acid oxidation of glycals, Levene and Tipson[9] made the following generalizations: when the hydroxyl group on carbon atom three is unsubstituted, the resulting hydroxyl group produced on carbon atom two, will be in the *cis* position to the one on carbon atom three. On the other hand, when the hydroxyl group on carbon atom three is substituted, the new hydroxyl group will be *trans* to it. If this is a general rule, it would be expected that if diacetylrhamnal (I) be similarly oxidized, the resulting substance would be a derivative of *epi*rhamnose instead of rhamnose. Bergmann and Schotte[8] report that, whereas rhamnal is oxidized by perbenzoic acid to give rhamnose, diacetylrhamnal is not oxidized in aqueous solution by this reagent. It has now been found that when the oxidation is carried out in chloroform, diacetylrhamnal yields a compound furnishing analytical figures for the expected 1-benzoyl-3, 4-diacetylhexomethylose (II). On subsequent hydrolysis of this substance without methylation, the sugar produced was not rhamnose. Definite identification of the latter as *epi*rhamnose (III) was not made, although it is presumably this sugar, thus confirming Levene and Tipson's rule.

[8] BERGMANN AND SCHOTTE, *Ber.*, **54**, 440, 1569 (1921).
[9] LEVENE AND TIPSON, *J. Biol. Chem.*, **93**, 631 (1931).



However, in the case of the oxidation of acetogalactal, a galactose derivative should be and is formed, as was shown by Levene and Tipson. This method then could be used for the preparation of 2-methylgalactose. But the long series of reactions necessary to convert this to 2-methyl-*d*-fucose, make it less attractive than two other methods.

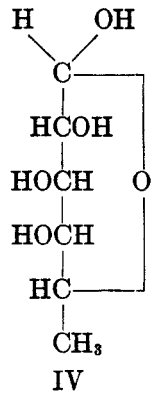
The first of these methods proceeds directly from *d*-fucose (IV), which was prepared from galactose according to the method of Freudenberg and Raschig[10]. Appropriate blocking of the hydroxyl groups was then accomplished by forming methyl-*d*-fucopyranoside. This on condensation with acetone resulted in 3,4-acetonemethyl-*d*-fucopyranoside (V) which after methylation with Purdie's reagents and hydrolysis gave the desired 2-methyl-*d*-fucose (VI).

In this series of reactions, the mixture of α- and β-methyl-*d*-fucopyranosides was used directly for the subsequent steps. However, in one experiment, the crystalline α-methyl-*d*-fucopyranoside was isolated. Votoček and Valentin[11] prepared α-methyl-*d*-fucopyranoside and gave $[\alpha]_D$ as 189.9° but did not report a melting point. Our material showed $[\alpha]_D^{25°}$ 190°, and melted at 155–156°.

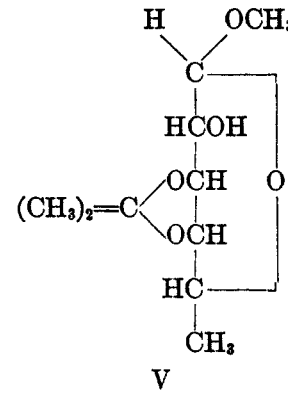
While this work was in progress a paper by Oldham and Bell[12], in which the preparation of 2-methyl- and 2,6-dimethyl-*d*-galactose was described, appeared. Their synthesis was similar to the above, except that the blocking group in position 6 was the nitrate group instead of the *p*-toluenesulfonyl group here used.

The second route to 2-methyl-*d*-fucose started with α-methyl-*d*-galactopyranoside. Upon unimolecular tosylation[13] the primary hydroxyl group was selectively tosylated, although in rather poor yield, to give 6-tosyl-

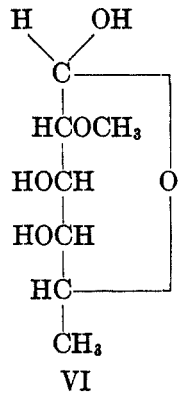
[10] FREUDENBERG AND RASCHIG, *Ber.*, **60**, 1633 (1927).
[11] VOTOČEK AND VALENTIN, *Coll. Czech. Chem. Com.*, **2**, 36 (1930).
[12] OLDHAM AND BELL, *J. Am. Chem. Soc.*, **60**, 323 (1938).
[13] LEVENE AND RAYMOND, *J. Biol. Chem.*, **102**, 317 (1933).



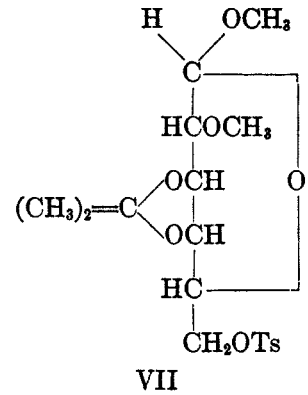
IV



V



VI



VII

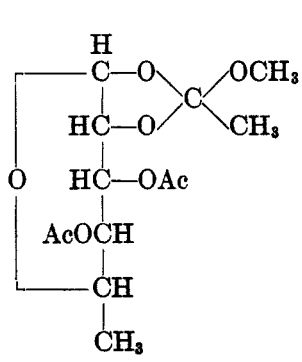
α-methyl-*d*-galactopyranoside, a compound prepared in a more indirect way by Ohle and Thiel[14]. Condensation with acetone produced 3,4-acetone-6-tosyl-α-methyl-*d*-galactopyranoside, in which all the hydroxyl groups but the one on the second carbon atom are blocked. Methylation with Purdie's reagents led to 2-methyl-3,4-acetone-6-tosyl-α-methyl-*d*-galactopyranoside (VII) which on heating with sodium iodide in acetone gave 2-methyl-3,4-acetone-6-iodo-α-methyl-*d*-galactopyranoside. Catalytic reduction of the latter with Raney nickel gave 2-methyl-3,4-acetone-α-methyl-*d*-fucopyranoside, from which the blocking groups were easily removed, yielding 2-methyl-*d*-fucose (VI).

The preparation of 2-methyl-*l*-rhamnose was not as simple. Due to the configuration of the hydroxyl groups it is not possible to block them selectively with acetone or other bridging reagents. The reactions finally used were based on a peculiar behavior of sugar 1,2-orthoacetates. These compounds are formed on treatment of acetobromo sugars with quinoline

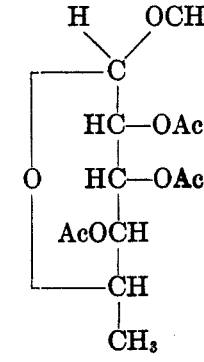
[14] OHLE AND THIEL, *Ber.*, **66**, 525 (1933).

or similar bases in methyl alcoholic solution and their structures have been definitely proved.[15]

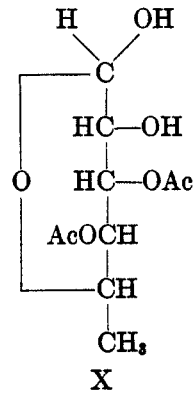
Isbell[16], in a study of the action of methyl alcoholic hydrogen chloride on heptaacetyl-4-glucosidomannose-1,2-orthoacetate, obtained hexaacetyl-4-glucosidomannose, presumably by selective hydrolysis of the orthoester group. However, beyond the facts that this substance contained no methoxyl and that it gave on acetylation the known octaacetyl-4-glucosidomannose, the position of the free hydroxyl groups was not further demonstrated. If the removal of the orthoester group was carried out in chloroform 1-chloroheptaacetyl glucosidomannose was obtained. In a later paper, Pigman and Isbell[17] advanced a general theory governing the configuration necessary for the formation of such orthoacetates. When the above reactions were applied to the corresponding rhamnose derivatives the analogous compounds were formed, and the correctness of Isbell's interpretation was shown.



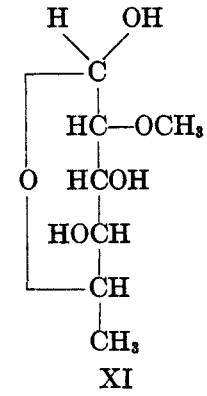
VIII



IX



X



XI

[15] HAWORTH, HIRST, AND SAMUELS, *J. Chem. Soc.*, **1931**, 2861.
[16] ISBELL, *Bur. Standards J. Research*, **7**, 1115 (1931).
[17] PIGMAN AND ISBELL, *ibid.*, **19**, 198 (1937).

3,4-Diacetyl-*l*-rhamnopyranose-1,2-orthoacetate (VIII) was prepared according to Haworth, Hirst, and Samuels.[15] This, on treatment with methyl alcoholic hydrogen chloride, gave the expected mixture of the previously known 2,3,4-triacetyl-β-methyl-*l*-rhamnopyranoside[18] (IX) and, presumably, 3,4-diacetyl-*l*-rhamnose (X). The former compound was easily isolated by crystallization from water. The latter, excessively soluble in water, could not be crystallized, and decomposed on attempted distillation. Therefore it was methylated directly, and the subsequent products were purified. In this way 2-methyl-3,4-diacetyl-methyl-*l*-rhamnopyranoside was obtained, which on deacetylation and hydrolysis of the glycosidic methyl group gave 2-methyl-*l*-rhamnose (XI). The location of the methyl group was shown by formation of *l*-rhamnose *p*-nitrophenyl osazone with loss of the methoxyl group. Such loss of a methyl group in the 2-position of a hexose is not without parallel. Brigl and Schinle[19] and Levene, Meyer, and Raymond[20] have noted a similar behavior of 2-methyl glucose, and Oldham and Bell[12] report that 2-methyl-, 2,3-dimethyl- and 2,6-dimethylgalactose give osazones with loss of the methyl group in position 2.

2-Methyl-*l*-rhamnose is not readily attacked by bromine water. This again parallels roughly the low reducing values obtained when 2-methyl-glucose derivatives are estimated by various copper methods[21]. No further study was made of this resistance to oxidation, it being felt that the whole question of the behavior of methylated sugars on oxidation warranted fuller investigation as a separate project, particularly in view of the fact that bromine water is not a general reagent. It is significant that digitalose on similar treatment yields digitalonic lactone[4,7].

EXPERIMENTS WITH *d*-GALACTOSE

*6-Tosyl-α-methyl-*d*-galactoside.*—α-Methyl-*d*-galactoside[22] was treated according to the directions of Levene and Raymond[13] for the monomolecular tosylation of monoacetone xylose. Thirty-seven grams of anhydrous α-methyl-*d*-galactoside was dissolved in 190 cc. of dry pyridine, and 40 g. of *p*-toluenesulfonyl chloride, dissolved in 75 cc. of chloroform, was added. The reaction mixture was kept at 0° for an hour and then allowed to stand at room temperature for 24 hours. It was then poured into a mixture of ice and dilute sulfuric acid with rapid stirring, when a white crystalline solid separated. This was filtered, washed with cold methanol, and finally recrystallized from methyl alcohol. It melted at 172° as stated by Ohle and Thiel[14]. The yield was 25 g., or about 40% of the theoretical. A small additional quantity was obtained by concentration of the chloroform solution.

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[18] HAWORTH, HIRST, AND MILLER, *J. Chem. Soc.*, **1929**, 2469.

[19] BRIGL AND SCHINLE, *Ber.*, **63**, 2884 (1930).

[20] LEVENE, MEYER, AND RAYMOND, *J. Biol. Chem.*, **91**, 497 (1931).

[21] SOBOTKA, *J. Biol. Chem.*, **69**, 267 (1926).

[22] MICHEEL AND LITTMANN, *Ann.*, **466**, 115 (1928).

6-Tosyl-3,4-acetone-α-methyl-d-*galactoside.*—6-Tosyl-α-methyl-*d*-galactoside was subjected to acetone condensation by a modification of the method of Ohle and Thiel[14]. Twenty-four grams of 6-tosyl-α-methyl-*d*-galactoside was added to a mixture of 120 g. of anhydrous copper sulphate, 3.6 g. of concentrated sulfuric acid, and a few drops of acetaldehyde with 1050 cc. of acetone. This mixture was shaken at room temperature for 48 hours. The copper sulfate was filtered off, 100 cc. of water was added, and the acid was neutralized by shaking with an excess of wet calcium hydroxide. After filtration, the acetone solution was concentrated *in vacuo* until crystalline material separated. Water was then added until all of the material had precipitated. The product was washed with water, dried, and recrystallized from benzene-petroleum ether. The melting point was 129°, in agreement with that reported by Ohle and Thiel[14]. The yield was 22 g. of recrystallized material, or about 82% of the theoretical.

2-Methyl-3,4-acetone-6-tosyl-α-methyl-d-*galactoside.*—Seventeen grams of 6-tosyl-3,4-acetone-α-methyl-*d*-galactoside was methylated with Purdie's reagents. The yield was 12 g. of material which crystallized on rubbing. It was recrystallized from ether-petroleum ether. The melting point was 86–87°; yield 70%.

Anal. Calc'd for $C_{18}H_{26}O_8S$: C, 53.7; H, 6.5; OCH_3, 15.4.
Found: C, 53.8; H, 6.8; OCH_3, 15.0.

2-Methyl-3,4-acetone-6-iodo-α-methyl-d-*galactoside.*—Nine grams of the preceding substance was dissolved in 30 cc. of acetone and heated with 9 g. of sodium iodide in bomb tubes at 140° for five hours. The acetone was removed under reduced pressure, and the residue taken up in chloroform. This was washed with dilute sodium thiosulfate and finally with water. The chloroform was removed, and 5 g. of yellow oil was obtained. Inasmuch as a suitable means of purification could not be found the material was reduced directly. The yield was about 50%.

2-Methyl-3,4-acetonemethyl-d-*fucoside.*—Four grams of crude 2-methyl-3,4-acetone-6-iodo-α-methyl-*d*-galactoside was reduced with Raney nickel catalyst in alkaline methyl alcohol solution according to Levene and Compton[23]. On distillation, 3 g. of material was obtained which boiled at 77–78° at 2 mm. pressure; yield about 60%.

Anal. Calc'd for $C_{11}H_{20}O_5$: C, 56.9; H, 8.7.
Found: C, 57.1; H, 8.8.

EXPERIMENTS WITH *d*-FUCOSE

d-*Fucose.*—This was prepared according to Freudenberg and Raschig[10] from *d*-galactose with the exception that 6-iododiacetone-*d*-galactose was reduced to diacetone-*d*-fucose catalytically with Raney nickel in alkaline methyl alcohol solution according to Levene and Compton[23]. The *d*-fucose obtained showed a final rotation of $[\alpha]_D^{20}$ 75.3°. Freudenberg and Raschig[10] report $[\alpha]_D^{19°}$ 76.3°.

α-Methyl-d-*fucopyranoside.*—Twenty grams of *d*-fucose was refluxed with 300 cc. of absolute methyl alcohol containing 4% of hydrogen chloride for 8 hours, when the solution no longer reduced Fehling's solution. After removal of the chloride ion with silver carbonate, the solution was boiled with Norite, filtered and concentrated to about 50 cc., when copious crystallization occurred. After 2 crystallizations from methyl alcohol the α-methyl-*d*-fucopyranoside melted constantly at 155–156°; $[\alpha]_D^{25°}$ 190.0° (*C* = 4.166 in water). Votoček and Valentin[11] report $[\alpha]_D$ 189.9°.

Anal. Calc'd for $C_7H_{14}O_5$: C, 47.2; H, 7.9.
Found: C, 47.4; H, 8.4.

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[23] LEVENE AND COMPTON, *J. Biol. Chem.*, **111**, 325 (1935).

3,4-Acetonemethyl-d-fucopyranoside.—Twenty grams of mixed α- and β-methyl fucopyranosides obtained as above was dissolved in 250 cc. of acetone containing 1.5% of hydrogen chloride and 5 drops of paraldehyde. After standing 20 minutes at room temperature, the solution was poured into 1300 cc. of dilute ammonia. The ammoniacal solution was extracted 10 times with chloroform. After drying and removal of the chloroform, 11 g. of a syrup remained, and was distilled at 0.2 mm. pressure. After a slight forerun the main fraction boiled at 88–92°. On standing over the summer this crystallized for the most part. After recrystallization from acetone-petroleum ether, the crystalline 3,4-acetone-methyl-*d*-fucopyranoside melted at 98–100° when air dried. On drying in an evacuated desiccator the material lost solvent and became syrupy. The syrup was analyzed:

Anal. Calc'd for $C_{10}H_{18}O_5$: C, 55.0; H, 8.3.
Found: C, 54.5; H, 8.4.

The aqueous ammoniacal solution after extraction with chloroform was concentrated to dryness, and the residual salts were thoroughly extracted with hot acetone. From the acetone extracts, 6 g. of α-methyl-*d*-fucopyranoside was recovered.

2-Methyl-3,4-acetonemethyl-d-fucopyranoside.—The material obtained in the preceding experiment was methylated with Purdie's reagents. After removal of the solvent, the residual syrup crystallized spontaneously. After recrystallization from petroleum ether, the crystalline 2-methyl-3,4-acetonemethyl-*d*-fucopyranoside melted at 100° after preliminary softening.

Anal. Calc'd for $C_{11}H_{20}O_5$: C, 56.9; H, 8.7; OCH_3, 26.7.
Found: C, 56.9; H, 8.8; OCH_3, 25.7.

2-Methyl-d-fucose.—2-Methyl-3,4-acetonemethyl-*d*-fucopyranoside was hydrolyzed by boiling with 4% sulfuric acid for 6 hours. After neutralization with barium carbonate, the solution was treated with Norite, and concentrated to dryness, leaving a crystalline mass. This was recrystallized from alcohol. 2-Methyl-*d*-fucose shows a somewhat variable melting point, different samples of the same purity melting from 155 to 161° depending on the rate of heating. The 2-methyl-*d*-fucose prepared by either route crystallized as leaflets indistinguishable in form, and a mixture of the substances prepared in both ways showed no depression in the melting point. The sugar from both sources showed the same optical behavior; $[\alpha]_D^{27°}$ 73° (10 minutes after preparing the solution), and becoming constant at 87° in twenty hours (C = 1.309 in water).

Anal. Calc'd for $C_7H_{14}O_5$: C, 47.2; H, 8.1; OCH_3, 17.4.
For the substance from fucose: Found: C, 47.0; H, 7.9; OCH_3, 16.8.
For the substance from galactose: Found: C, 47.4; H, 8.0; OCH_3, 17.0.

EXPERIMENTS WITH *l*-RHAMNOSE

Reaction of 3,4-diacetyl-l-rhamopyranoside-1,2-orthoacetate with methyl alcoholic hydrogen chloride.—Fifty-eight grams of 3,4-diacetylrhamnopyranoside-1,2-orthoacetate, prepared according to Haworth, Hirst and Samuels[15] was dissolved in 580 cc. of absolute methyl alcohol, and sufficient 6% methyl alcoholic hydrogen chloride solution was added to furnish 4 g. of hydrogen chloride. After standing for 10 minutes at room temperature the mixture was poured onto a paste of 116 g. of silver carbonate and 23 cc. of water and stirred mechanically until all of the chloride ion was removed. The filtrate from the silver salts was concentrated under reduced pressure to a syrup which was dissolved in hot water and treated with Norite. On

cooling, 9.2 g. of crystals separated. These were recrystallized from water to a constant melting point of 150–151°; $[\alpha]_D^{25}$ 46° (C = 1.674 in acetylene tetrachloride). Haworth, Hirst, and Miller[13] report 2,3,4-triacetyl-β-methyl-*l*-rhamnopyranoside melting at 151–152° and showing $[\alpha]_D^{18}$ 45.7°.

Anal. Calc'd for $C_{13}H_{20}O_8$: C, 51.3; H, 6.6.
Found: C, 51.5; H, 6.6.

The mother liquor from the above crystalline material was concentrated to a syrup, which was dried by repeated concentration with absolute alcohol and benzene. This material was strongly reducing toward Fehling's solution. By analogy with the substance prepared by Isbell[16] from heptaacetyl-4-glucosidomamnose-1,2-orthoacetate, this is predominately 3,4-diacetyl-*l*-rhamnose-1,2-orthoacetate. It could not be crystallized, and, on attempted distillation under high vacuum, it decomposed. Therefore it was methalated as such.

*2-Methyl-3,4-diacetylmethyl-*l*-rhamnopyranoside.*—The syrup (47 g.) obtained in the preceding experiment was methylated twice with Purdie's reagents. The material thus obtained was fractionally distilled at 0.2 mm. pressure, the fraction boiling at 110–130° being collected. This was dissolved in hot water, and, on cooling, the solution deposited crystalline material which was identified as more of the triacetylmethylrhamnopyranoside described above. The mother liquor was concentrated to dryness, and the residue was again distilled at 0.2 mm. The fraction boiling at 110–115° was a light oil, and consisted of higher methylation products apparently formed as the result of partial saponification of the acetyl groups during the methylation. The main fraction weighed 22 gms. and boiled at 115–120°. This was redistilled at 0.2 mm. and boiled constantly at 116–118°. It furnished analytical figures corresponding to 2-methyl-3,4-diacetylmethyl-*l*-rhamnopyranoside.

Anal. Calc'd for $C_{12}H_{20}O_7$: C, 52.2; H, 7.3; OCH_3, 22.5.
Found: C, 52.4; H, 7.4; OCH_3, 22.8.

*2-Methylmethyl-*l*-rhamnopyranoside.*—Ten grams of 2-methyl-3,4-diacetylmethyl-*l*-rhamnopyranoside was dissolved in 250 cc. of ice-cold absolute methyl alcohol; 17 cc. of 0.208 molar barium methylate solution was added, and the solution was placed in the refrigerator for 48 hours. After addition of 400 cc. of water and saturation with carbon dioxide, the solution was heated 1 hour on the steam bath and then chilled. The filtrate from the barium salts was concentrated under reduced pressure to a syrup which crystallized from a large volume of "Skelly-solve D". After six crystallizations the melting point was 139–140° and still rising. Inasmuch as the substance was probably still a mixture of α- and β-glycosides, further crystallization was not carried out.

Anal. Calc'd for $C_8H_{16}O_5$: C, 50.0; H, 8.4; OCH_3, 32.3.
Found: C, 50.3; H, 8.7; OCH_3, 29.9.

The material from the mother liquors of the above crystalline substance was a syrup and probably consisted of a mixture of stereoisomers.

*2-Methyl-*l*-rhamnose.*—2-Methylmethyl-*l*-rhamnopyranoside as previously obtained was hydrolyzed by heating on the steam bath with 3.7% hydrochloric acid for 6–7 hours. After removal of the inorganic ions in the usual manner, the solution was concentrated to a syrup under reduced pressure. This was dried by repeated concentration with absolute alcohol and benzene. All attempts at crystallization, both with and without seeding with digitalose*, failed. For analysis the syrup was

* We wish to express our appreciation to Dr. Sidney Smith of the Wellcome Chemical Works, Dartford, England, for a sample of crystalline digitalose.

further dried at 80° over calcium chloride and analyzed as such, although it was still impure. The material was strongly reducing toward Fehling's solution.

Anal. Calc'd for $C_7H_{14}O_5$: C, 47.2; H, 8.1; OCH_3, 17.4.
Found: C, 48.2; H, 7.9; OCH_3, 18.8.

$[\alpha]_D^{27}$ 31° (20 minutes after preparing the solution; no change after 24 hours) (C = 1.136 in water).

Attempted oxidation of 2-methylrhamnose with bromine water.—One-half gram of 2-methylrhamnose was allowed to stand for four days with 100 cc. of bromine water. After removal of the inorganic constituents in the usual manner, concentration left a syrup which was strongly reducing towards Fehling's solution.

*Oxidation of 2-methyl-*l*-rhamnose with nitric acid.*—Three-tenths gram of 2-methylrhamnose was dissolved in 10 cc. of 50% nitric acid, and the solution was allowed to stand for 3 days at room temperature. The nitric acid was removed by repeated concentration at reduced pressure with addition of water. A syrupy residue, which offered some difficulty in crystallization, remained. The acid was accordingly isolated as the di-*N*-methyl amide. The syrup was heated with 5 cc. of 3% absolute methyl alcoholic hydrogen chloride in a sealed tube at 100° for 6 hours. After removal of chloride ion by silver carbonate the solution was concentrated to a syrup. This was dissolved in 10 cc. of absolute methyl alcohol and saturated with dry methylamine. After standing for twenty-four hours at room temperature, the solvent was removed, and the residue was crystallized twice from ethyl acetate; m. p. 204–205°; $[\alpha]_D^{28}$ 71° (C = 0.453 in water). The analysis corresponded to that of the di-*N*-methyl amide of *l*-arabomonomethoxyglutaric acid. A free acid isomeric with the above was obtained as an oxidation product of digitalose by Kiliani[5].

Anal. Calc'd for $C_6H_{16}N_2O_5$: C, 43.6; H, 7.3; OCH_3, 14.1; N, 12.7.
Found: C, 43.1; H, 7.3; OCH_3, 13.0; N, 13.0.

*Action of methyl alcoholic hydrogen chloride on 2-methyl-*l*-rhamnose.*—Three-tenths gram of 2-methyl-*l*-rhamnose was boiled with 10 cc. of 4% absolute methyl alcoholic hydrogen chloride solution for 6 hours. After removal of the chloride ion as usual and concentration, a syrup remained which could not be crystallized. It no longer reduced Fehling's solution, thereby showing that glycoside formation had occurred.

*Rhamnose-*p*-nitrophenylosazone from 2-methyl-*l*-rhamnose.*—Three-tenths gram of 2-methyl-*l*-rhamnose was heated on the steam bath with 3 equivalents of *p*-nitrophenylhydrazine hydrochloride in 10 cc. of water containing 2 drops of concentrated hydrochloric acid for one hour. A copious red precipitate formed after five minutes. The precipitate was collected and washed well with dilute hydrochloric acid and water. After recrystallization from a large volume of alcohol, the substance melted with decomposition at 209–211°. Feist[24] reports *l*-rhamnose *p*-nitrophenylosazone as melting at 208° with decomposition.

Anal. Calc'd for $C_{18}H_{20}O_7N_6$: C, 50.0; H, 4.7.
Found: C, 50.0; H, 4.6.

The substance did not contain methoxyl.

Oxidation of diacetylrhamnal with perbenzoic acid.—Six and nine-tenths grams of diacetylrhamnal was dissolved in 220 cc. of an ice-cold chloroform solution of perbenzoic acid containing 0.0222 g. of perbenzoic acid per cc. After standing 4 days in the refrigerator the calculated amount of perbenzoic acid had been consumed. The solution was concentrated to dryness and the residual solid was repeatedly extracted with ligroïn for the removal of benzoic acid. The portion which was in-

[24] FEIST, *Ber.*, **33**, 2099 (1900).

soluble in ligroïn crystallized readily from absolute alcohol. It melted at 193°; $[\alpha]_D^{24}$ −15.2° (*C* = 1.220 in chloroform). The substance furnished analytical figures for 1-benzoyl-3,4-diacetylrhamnose or *epi*rhamnose.

Anal. Calc'd for $C_{17}H_{20}O_8$: C, 57.9; H, 5.7.
Found: C, 58.2; H, 5.7.

On catalytic removal of the benzoyl and acetyl groups, a reducing syrup was obtained which could not be seeded with rhamnose. Therefore the *epi*rhamnose configuration seems preferable.

The analyses here reported were made by Mr. Saul Gottlieb.

SUMMARY

2-Methyl-*l*-rhamnose and 2-methyl-*d*-fucose have been prepared and shown not to be identical with digitalose.

Digitalose is either 2-methyl-*d*-gulomethylose or 2-methyl-*l*-altromethylose.

A general method has been developed for the preparation of 2-methyl derivatives of sugars having the configuration demanded by the theory of Pigman and Isbell[17].

Diacetylrhamnal has been shown to be oxidized by perbenzoic acid, presumably with the formation of an *epi*rhamnose derivative.