[CONTRIBUTION FROM THE POLARIMETRY SECTION, BUREAU OF STANDARDS, U. S. DEPARTMENT OF COMMERCE]

RELATIONS BETWEEN ROTATORY POWER AND STRUCTURE IN THE SUGAR GROUP. XXX. THE ALPHA AND BETA METHYL-*d*-GALACTOSIDES AND THEIR TETRA-ACETATES[1]

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In 1918 the writers[2] prepared the crystalline tetra-acetate of α-methyl-*d*-galactoside for the first time and found its rotation to agree with the value that was predicted by the rules of isorotation. By an oversight the details of the preparation were not published and mention was not made that the substance was new; in consequence our record of the compound has been overlooked by later investigators, probably because it was not mentioned in recent reference books. Levene and Sobotka[3] attempted the preparation of this substance in 1926 but were unable to obtain it crystalline. They record $[\alpha]_D$ + 69.3 in chloroform for a sirup which had been distilled at 190° under 0.8-mm. pressure. Using this figure in their calculations they concluded that the molecular rotation difference for the acetylated methylgalactosides did not agree with the corresponding difference for the acetylated methylglucosides and hence that optical superposition or isorotation does not hold among the acetylated methylglycosides. This conclusion does not appear justified, however, because the specific rotation which they record for their sirupy α-tetra-acetylmethylgalactoside is certainly not the value for the pure substance. We used the value $[\alpha]_D^{20}$ +133 in our earlier article and now on repreparing this compound find this value to be correct for the pure substance, which we have obtained again in crystalline form without difficulty. We recorded a table in our 1918 article which clearly shows that isorotation holds closely for the alpha and beta acetates of methyl glucoside, xyloside and galactoside, all of which were prepared in pure crystalline condition. It has also been shown[4] that the rotations of the hepta-acetates of alpha and beta methylgentiobioside agree closely with values calculated from theory. The methylgalactosides and their acetates have now been carefully prepared again and the rotations have been found to agree closely with the previously published experimental values. The results are included in the following two tables, which are to be regarded as revisions and extensions of the two similar tables previously published.[2,5]

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[1] Publication authorized by the Director of the Bureau of Standards, U. S. Department of Commerce. No. XXIX was published in THIS JOURNAL, **52**, 2519 (1930).

[2] Hudson and Dale, *ibid.*, **40**, 997 (1918).

[3] Levene and Sobotka, *J. Biol. Chem.*, **67**, 759, 771 (1926).

[4] Hudson and Johnson, THIS JOURNAL, **39**, 1272 (1917); Hudson, *ibid.*, **47**, 872 (1925); Helferich, Klein and Schäfer, *Ann.*, **447**, 26 (1926).

[5] Hudson, THIS JOURNAL, **47**, 268 (1925).

Table I shows the specific rotation in water and molecular rotational difference for five pairs of methyl glycosides. The close agreement in the molecular rotational differences for the pairs is evidence that the rules of isorotation hold in first approximation, though not with mathematical exactness, for compounds of this type.

TABLE I

ROTATIONS IN WATER OF PURE METHYLGLYCOSIDES

Substance	Mol. wt.	$[\alpha]_D$	$[M]_D$	Difference
α-Methyl-*d*-glucoside[6]	194	158.9	30,830	37,460
β-Methyl-*d*-glucoside	194	−34.2	−6,630	
α-Methyl-*d*-galactoside	194	196.1	38,040	37,900
β-Methyl-*d*-galactoside	194	0.7	140	
α-Methyl-*d*-xyloside[5]	164	153.9	25,240	35,980
β-Methyl-*d*-xyloside	164	−65.5	−10,740	
α-Methyl-*l*-arabinoside[5]	164	17.3	2,840	−37,420
β-Methyl-*l*-arabinoside	164	245.5	40,260	
α-Methyl-gentiobioside[4]	356	65.5	23,300	36,100
β-Methyl-gentiobioside	356	−36	−12,800	

Table II shows the specific rotations in chloroform and molecular rotational differences for four pairs of acetylated glycosides. Here again there is a close agreement in the molecular rotational differences, leading to the conclusion that the rules of isorotation hold closely when applied to the completely acetylated glycosides. On the basis of these data we must disagree with Levene and Sobotka's conclusion that isorotation does not apply in the group of the known acetylated methylglycosides.

TABLE II

ROTATIONS IN CHLOROFORM OF ACETYLATED METHYLGLYCOSIDES

Substance	Mol. wt.	$[\alpha]_D$	$[M]_D$	Difference
α-Tri-acetyl-methyl-*d*-xyloside[2]	290	119.6	34,700	52,300
β-Tri-acetyl-methyl-*d*-xyloside	290	− 60.7	−17,600	
α-Tetra-acetyl-methyl-*d*-glucoside[2]	362	130.5	47,300	53,900
β-Tetra-acetyl-methyl-*d*-glucoside	362	−18.3	−6,600	
α-Tetra-acetyl-methyl-*d*-galactoside	362	133	48,400	53,460
β-Tetra-acetyl-methyl-*d*-galactoside	362	−14.0	−5,060	
α-Hepta-acetyl-methyl-gentiobioside[4]	650	64.5	41,900	54,250
β-Hepta-acetyl-methyl-gentiobioside	650	−19	−12,350	

Experimental Part

Preparation of Alpha and Beta Methyl-*d*-galactoside.—Fifty grams of *d*-galactose was refluxed on a steam-bath with 400 cc. of methanol containing 1% of hydrogen chloride until the rotation became constant, which required fourteen hours. A few pieces of porous plate in the flask insured steady boiling. After neutralizing the acid with silver carbonate and filtering, the filtrate was decolorized with active carbon and

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[6] Riiber, *Ber.*, **57**, 1797 (1924).

concentrated to a thick sirup under reduced pressure. This sirup was dissolved in 200 cc. of hot isopropyl alcohol, from which on cooling there crystallized 26 g. of α-methyl-*d*-galactoside monohydrate which showed $[\alpha]^{20}_{D}$ +175.5 in water. After one recrystallization from hot absolute alcohol the value was $[\alpha]^{20}_{D}$ +178.7 (0.7064 g. of substance in 25 cc. of aqueous solution rotated 10.1 to the right in a 2-dm. tube). The mother liquor was evaporated under reduced pressure until it crystallized spontaneously in the flask. The resulting mixture of sirup and crystals was dissolved in 100 cc. of hot isopropyl alcohol, from which on cooling there crystallized 9.2 g. of β-methyl-*d*-galactoside which showed $[\alpha]^{20}_{D}$ +1.2 in water. After recrystallization from hot absolute alcohol the value was $[\alpha]^{20}_{D}$ +0.61 in aqueous solution (1.0261 g. of substance in 25 cc. of aqueous solution rotated 0.05° to the right in a 2-dm. tube).

Preparation of Alpha Tetra-acetyl-methyl-*d*-galactoside.—This compound was readily prepared by dissolving 13.5 g. of α-methyl-*d*-galactoside in a mixture of 68 cc. of acetic anhydride and 88 cc. of pyridine which had previously been cooled in an ice-bath. The mixture was kept in the ice-bath for three hours and then in an ice chest for two days. The solution was then poured into a liter beaker filled with crushed ice and crystallization took place almost immediately. After the ice had melted the crystalline material was separated from the ice water by filtration. Dried at 35° there was obtained 20 g. of substance. It was purified by recrystallization from a mixture of equal parts of ethyl ether and petroleum ether followed by a second recrystallization from 50% alcohol. After the first recrystallization $[\alpha]^{20}_{D}$ = +132.5°. After the second recrystallization, $[\alpha]^{20}_{D}$ = +133.0 (0.7209 g. of substance in 25 cc. of chloroform[7] solution rotated 7.67 to the right in a 2-dm. tube). A check determination of the specific rotation was made in chloroform which had been purified by shaking with five successive portions of water and drying with calcium chloride. The value was +133.1°, which is not sensibly different from the previous measurement.

The compound melted sharply at 87° (corr.). It crystallized from water, ether or a mixture of alcohol and petroleum ether, in radiating prismatic needles. It was readily soluble in ether, alcohol, chloroform, acetone and hot water, but insoluble in petroleum ether. An acetyl determination was made by Kunz's[8] method; 0.2598 g. of substance was dissolved in 25 cc. of pure acetone and 40 cc. of 0.1 *N* sodium hydroxide was added. After standing all night in an ice box the solution was titrated with 0.1 *N* hydrochloric acid and it was found that 28.62 cc. of the 0.1 *N* alkali had been neutralized, indicating 66.09% of acetic acid; calcd., 66.30%.

De-acetylation of Alpha-Tetra-acetyl-methyl-*d*-galactoside.—Thirteen grams of the twice recrystallized tetra-acetate was dissolved in 125 cc. of methanol saturated with dry ammonia gas. The solution was kept in an ice box overnight and then evaporated under diminished pressure almost to dryness. The residue was extracted with several portions of warm ether to remove acetamide and then dissolved in a little hot absolute alcohol. On cooling, crystals separated which were filtered from the mother liquor and washed with absolute alcohol. After recrystallization from absolute alcohol and drying at 35° the $[\alpha]^{20}_{D}$ of this product was found to be +179.3 in aqueous solution (1.0052 g. of substance in 25 cc. of solution rotated 14.42 to the right in a 2-dm. tube). This agrees with the value, $[\alpha]^{20}_{D}$ +178.7, found for α-methyl-*d*-galactoside monohydrate made by direct methylation of *d*-galactose.

The water of crystallization was determined by drying a 1-g. sample in a weighing bottle to constant weight at 90° and 50 mm.; found: 8.47% of water; calculated for methylgalactoside monohydrate, 8.49%. This dried material was used for a direct

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[7] The specific rotation determinations of α- and β-tetra-acetyl-methylgalactoside were made in U. S. P. chloroform unless otherwise stated.

[8] Kunz and Hudson, THIS JOURNAL, **48**, 1982 (1926).

determination of the specific rotation of anhydrous α-methyl-*d*-galactoside. The dried product, amounting to 0.9153 g., when dissolved in water to a volume of 25 cc. read 14.36 to the right in a 2-dm. tube, hence $[\alpha]^{20}_{D}$ +196.1, which corresponds to $[\alpha]^{20}_{D}$ +179.4 for the monohydrate, in good agreement with the directly observed values.

Preparation of β-Tetra-acetyl-methyl-*d*-galactoside.—Seven grams of recrystallized β-methyl-*d*-galactoside was acetylated by heating for three hours on a steam-bath with 16 cc. of acetic anhydride and 2 g. of fused sodium acetate. The reaction mixture was then poured into ice water. The sirupy phase which separated crystallized on standing overnight in an ice box. A further portion was obtained by neutralizing the supernatant acid water with sodium bicarbonate and extracting with chloroform. The chloroform extract was dried with calcium chloride and evaporated to a thin sirup which on stirring with the addition of petroleum ether crystallized immediately. The two portions of impure β-tetra-acetyl-methyl-*d*-galactoside were combined and recrystallized from absolute alcohol. The yield of pure product was 8 g. or 61% of the theoretical. It showed $[\alpha]^{20}_{D}$ −14.05 in chloroform (0.5514 g. of substance in 25 cc. of chloroform solution rotated 0.62 to the left in a 2-dm. tube). After a second recrystallization from absolute alcohol the specific rotation was unchanged.

De-acetylation of β-Tetra-acetyl-methyl-*d*-galactoside.—As a check upon the specific rotation and purity of the β-methyl-*d*-galactoside that was obtained by the direct methylation of *d*-galactose, the substance was also prepared by de-acetylating the purified β-tetra-acetyl-methyl-*d*-galactoside described above. Four grams were dissolved in 40 cc. of methanol saturated with dry ammonia gas and the solution kept in an ice box overnight. It was then evaporated until on reaching the consistency of a thin sirup β-methylgalactoside crystallized in the flask. The crystalline mass was extracted with several portions of warm ether to remove acetamide and was then dissolved in hot absolute alcohol. On cooling β-methylgalactoside quickly crystallized. After filtering, washing with absolute alcohol and drying at 35°, there was obtained 2.0 g. or 93% of the theoretical. It showed $[\alpha]^{20}_{D}$ 0.73° in aqueous solution (1.0194 g. of substance in 25 cc. of aqueous solution rotated 0.06° to the right in a 2-dm. tube), in good agreement with the previous measurement.

Summary

The preparation and properties of pure crystalline α-methyl-*d*-galactoside tetra-acetate are described. The rotation of the substance was recorded by us in 1918 but the details of preparation were inadvertently omitted. These are now supplied and our earlier measurement of the rotation is confirmed. Using the best revised data for the rotations of the pure alpha and beta forms of methylxyloside, arabinoside, glucoside, galactoside and gentiobioside, and such of the fully acetylated derivatives of these substances as are known, it is shown by the data recorded in Tables I and II that the rules of isorotation hold closely in all these cases.

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