The Synthesis of 3,6-Anhydro-5-*O*-methyl-D-galactose

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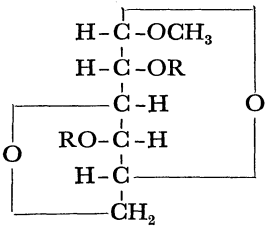
3,6-Anhydro-5-*O*-methyl-D-galactose has been synthesized for the first time through a series of reactions composed of blocking the hydroxyl groups at C_2 and C_4 of methyl 3,6-anhydro-α-D-galactopyranoside with the phenylcarbamoyl groups, converting the resulting derivative of the methyl glycoside into the corresponding dimethyl acetal, methylating the newly formed hydroxyl group at C_5, removing the blocking substituents, and finally hydrolysing the dimethyl acetal. The partially methylated anhydro-sugar obtained was uncrystallizable, and was characterized by its crystalline dimethyl acetal and crystalline aldonamide.

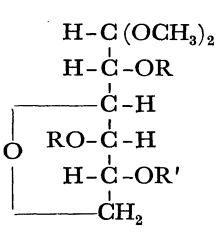
3,6-Anhydro-D- and -L-galactoses occur in a variety of red seaweed polysaccharides as their component sugars.[1] In a course of our structural investigation on some of these polysaccharides, 3,6-anhydro-5-*O*-methyl-D-galactose has been needed as a reference compound. This partially methylated anhydro-sugar has never appeared in literatures, although its isomeric 2-*O*-methyl[2,3] and 4-*O*-methyl[4] derivatives have been described. Its synthesis has been carried out for the first time through the route described below.

Methyl 3,6-anhydro-α-D-galactopyranoside(I) has been used as a starting compound. Its hydroxyl groups at C_2 and C_4 were blocked with the phenylcarbamoyl groups. The resulting phenylcarbamoylated methyl glycoside(II) was converted into the corresponding dimethyl acetal(III) with the open chain structure by an action of boiling methanolic hydrogen chloride. This opening of the pyranose ring has been reported to be an unusual property of 3,6-anhydro-galactosides.[5,6] The newly formed hydroxyl group at C_5 was then methylated(III→IV). Reductive removal of the blocking substituents[7] from IV gave crystalline 3,6-anhydro-5-*O*-methyl-D-galactose dimethyl acetal(V), which was further characterized by its crystalline *p*-nitrobenzoate. Three isomers are possible for 3,6-anhydro-mono-*O*-methyl-D-galactose dimethyl acetal in respect to the position of the *O*-methyl group. As the dimethyl acetal obtained above was distinguished in properties from the 2-*O*-methyl and 4-*O*-methyl isomers, the *O*-methyl group of the dimethyl acetal should exist on C_5 as expected. Mild hydrolysis of the dimethyl acetal(V) afforded 3,6-anhydro-5-*O*-methyl-D-galactose, which was uncrystallizable. Any other reducing derivatives of the anhydro-sugar as well as the anhydro-sugar itself have never been crystallized.

The partially methylated anhydro-sugar obtained above showed a ketose reaction, reduced a Fehling's solution at room temperature, and restored the color to a Schiff's reagent. These properties are in agreement with those of the parent anhydro-sugar.[5] When oxidized with bromine, the partially methylated anhydro-sugar gave 3,6-anhydro-5-*O*-methyl-D-galactonic acid, which was characterized by its crystalline amide. This amide was again distinguishable from the 2-*O*-methyl and 4-*O*-methyl isomers.



(I) R=H
(II) R=CONHC$_6$H$_5$



(III) {R=CONHC$_6$H$_5$, R'=H}
(IV) {R=CON(CH$_3$)C$_6$H$_5$, R'=CH$_3$}
(V) {R=H, R'=CH$_3$}

Experimental

General Methods. Solutions were concentrated under reduced pressure below 40°C with a rotary evaporator. Melting points were determined on a micro hot stage with Yanagimoto apparatus Model MP-S2. Paper chromatography was carried out on Toyo filter paper No. 51 with, unless otherwise stated, 1-butanol - acetic acid - water(4 : 1 : 2 v/v) as a solvent. Spots were located with an *o*-aminophenol reagent.[8]

*Methyl 3,6-Anhydro-2,4-di-*O*-phenylcarbamoyl-α-D-galactopyranoside(II).* To a solution of methyl 3,6-anhydro-α-D-galactopyranoside(I)[9] (2.0 g) in dry pyridine(20 m*l*) was added phenylisocyanate(3.5 g) and the mixture was heated at 100°C for 2 hr. A small amount of methanol was added to destroy the excess of the reagent, the mixture concentrated, and the residual syrup was dissolved in methanol(20 m*l*). Diphenylurea, which crystallized on standing, was removed by filtration and the filtrate was concentrated to a glass (4.7 g); $[\alpha]_D^{25}$ +50.8° (*c* 1.24 in methanol), $[\alpha]_D^{25}$ +44.6° (*c* 1.04 in chloroform), (Found: N, 6.95; OCH_3, 7.18%. Calcd for $C_{21}H_{22}O_7N_2$: N, 6.76; OCH_3, 7.49%).

*3,6-Anhydro-2,4-di-*O*-phenylcarbamoyl-D-galactose Dimethyl Acetal(III).* A solution of II(4.7 g) in 1% methanolic hydrogen chloride(50 m*l*) was refluxed for 1.5 hr, when the optical rotation of the solution reached a constant value

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TABLE 1. PROPERTIES OF THE DERIVATIVES OF 3,6-ANHYDRO-MONO-*O*-METHYL-D-GALACTOSES

Derivative	Properties	2-*O*-Methyl[a]	4-*O*-Methyl[4]	5-*O*-Methyl
Dimethyl acetal	Mp (°C)	liquid	liquid	53—54
	$[\alpha]_D$ (°) (H_2O)	−31.1	+33.9	+45.3 (*c* 0.93, 25°C)
	R_f[b]	0.61	0.68	0.53
	Retention time (min)[c]	5.5	3.0	4.4
Aldonamide	Mp (°C)	171—172	111	47—48 (monohydrate)
	$[\alpha]_D$ (°) (H_2O)	−75.4	+82.66	+65.5 (*c* 1.80, 25°C)

a) The values reported for L-compounds[2] are cited herein, as the corresponding D-compounds have not been reported so far.
b) Paper chromatograms were irrigated with cyclohexanol saturated with water.[2]
c) Gas liquid chromatography was carried out on a column (1 m) packed with 3% ECNSS-M on Chromosorb-W at 160 °C. Xylitol pentaacetate, added as an internal marker, showed the retention time 9.2 min.

($[\alpha]_D$ +51°→39°). The solution was neutralized with silver carbonate, filtered, and concentrated to a colorless thick syrup(4.7 g); $[\alpha]_D^{25}$ +30.0° (*c* 0.40 in methanol), $[\alpha]_D^{25}$ +53.4° (*c* 0.88 in chloroform). The slightly lower value of the methoxyl content indicated that the product was contaminated with a small amount of II and its β-isomer, which had been in equilibrium with III during the reaction. (Found: N, 6.40; OCH_3, 13.10%. Calcd for $C_{22}H_{26}O_8N_2$: N, 6.28; OCH_3, 13.90%).

3,6-Anhydro-5-O-methyl-2,4-di-O-(N-methylphenylcarbamoyl)-D-galactose Dimethyl Acetal (IV). The syrup (4.6 g) obtained above, was methylated twice with iodomethane (10 m*l*) and silver oxide(10 g) in *N,N*-dimethylformamide (40 m*l*) according to the method of Kuhn and his coworkers.[10] The product(IV) was obtained as a slightly colored syrup (5.0 g); $[\alpha]_D^{25}$ +34.5° (*c* 1.51 in methanol), $[\alpha]_D^{25}$ +28.4° (*c* 0.81 in chloroform). (Found: OCH_3, 18.51%. Calcd for $C_{25}H_{32}O_8N_2$: OCH_3 19.06%).

3,6-Anhydro-5-O-methyl-D-galactose Dimethyl Acetal(V). Accroding to the procedure of Bouveng,[7] IV(5.0 g) was treated with lithium aluminum hydride (2.0 g) in boiling tetrahydrofuran(100 m*l*) for 3 hr. The crude product obtained was purified by dissolution in water(20 m*l*) and extraction with hexane to remove an oily by-product. Evaporation of the aqueous solution gave a colorless syrup(1.8 g). Paper chromatographic examination of this syrup showed the presence of a small amount of methyl 3,6-anhydro-galactosides (R_f 0.68) in addition to V(R_f 0.75). The mixture was separated on a charcoal-Celite column(4.6×33 cm), which was eluted first with 2% ethanol(4.7 *l*) and then 5% ethanol (15 *l*). The methyl glycosides together with a small amount of V were eluted with the former eluant. Concentration of the effluent containing V gave a syrup, which was further purified by solution in acetone, filtration and re-concentration. V was obtained as a colorless syrup, which crystallized on standing for several months; yield 1.2 g (48% based on I). It was recrystallized twice from ethyl acetate-benzene-hexane(1 : 1 : 2). Its mp, specific optical rotation, R_f value in paper chromatography, and retention time in gas liquid chromatography are recorded in Table 1. These properties are distinguishable from those of 2-*O*-methyl and 4-*O*-methyl isomers, as compared in the same table.

Found: C, 48.46; H, 8.17; OCH_3, 41.60%. Calcd for $C_9H_{18}O_6$: C, 48.64; H, 8.16; OCH_3, 41.90%.

3,6-Anhydro-5-O-methyl-D-galactose Dimethyl Acetal 2,4-Di-p-nitrobenzoate. A mixture of V(0.10 g), *p*-nitrobenzoyl chloride(0.50 g), and dry pyridine(5 m*l*) was allowed to stand at room temperature for 24 hr. Water (0.5 m*l*) was added to hydrolyse the excess of the reagent, and a saturated sodium bicarbonate solution(50 m*l*) was then added with strirring. The *p*-nitrobenzoate(0.24 g), which was precipitated, was recrystallized twice from ethanol; mp 145—146°C, $[\alpha]_D^{27}$ +69.7° (*c* 0.76 in chloroform).

Found: C, 52.89; H, 4.61; N, 5.31%. Calcd for $C_{23}H_{24}O_{12}N_2$: C, 53.08; H, 4.65; N, 5.38%.

3,6-Anhydro-5-O-methyl-D-galactose. The dimethyl acetal(V) (0.80 g) was hydrolysed with 0.02 N sulfuric acid (30 m*l*) at 100°C for 1.5 hr. The product, isolated in the usual manner, was further purified by dissolution in methanol, filtration and concentration to give the reducing sugar as a colorless syrup(0.60 g). It showed a Seliwanoff's ketose reaction, reduced a Fehling's solution at room temperature and restored the color to a Schiff's reagent; $[\alpha]_D^{28}$ +23.2°→+26.8° (*c* 0.56 in water). (Found: OCH_3, 17.26%. Calcd for $C_7H_{12}O_5$: OCH_3, 17.61%).

3,6-Anhydro-5-O-methyl-D-galactonamide. The reducing sugar (0.58 g) obtained above was oxidized with bromine (0.40 m*l*) in water(10 m*l*) in the dark at room temperature for 24 hr. The excess of the oxidant was removed by aeration, and the solution was neutralized with silver carbonate and filtered. The filtrate was passed through a column of Amberlite IR-120(H^+ form)(10 m*l*), and then neutralized with a barium hydroxide solution. Concentration of the solution gave the barium salt, which was purified by dissolution in ethanol, filtration, and precipitation with acetone. The salt was then dissolved in water and treated with Amberlite IR-120(H^+ form) (10 m*l*). Evaporation of the solution gave 3,6-anhydro-5-*O*-methyl-D-galactonic acid as a colorless syrup (0.50 g); $[\alpha]_D^{25}$ +25.4° (*c* 0.63 in water). Crystallization was unsuccessful. This acid was converted into the methyl ester by reaction with boiling 3% methanolic hydrogen chloride(5 m*l*) for 4 hr. The product was purified by dissolution in ethyl acetate, filtration, and concentration. The ester was obtained as a colorless syrup(0.40 g); $[\alpha]_D^{25}$ +22.7° (*c* 0.66 in water). Crystallization was again unsuccessful.

The methyl ester obtained above was dissolved in cold methanol(8 m*l*) saturated with dry ammonia, and the mixture was left to stand in a refrigerator for 24 hr. Concentration of the reaction solution gave a syrup, which crystallized on addition of a drop of water. Solids were collected on a porous plate, and recrystallized twice by dissolving in 2-propanol(0.5 m*l*) and adding ethyl acetate saturated with water(2.0 m*l*). The amide was obtained as tetragonal monohydrate. The physical constants are recorded in Table 1, and compared with those of 2-*O*-methyl and 4-*O*-methyl isomers.

Found: C, 40.05; H, 7.49; N, 6.82%. Calcd for $C_7H_{13}O_5N\cdot H_2O$: C, 40.19; H, 7.23; N, 6.70%.

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