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Amino-deoxy- and Deoxy-sugars from Methyl 3-Oxo-β-D-glucopyranoside

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Methyl 3-oxo-β-D-glucopyranoside has been converted to the two corresponding 3-amino-3-deoxy-glucosides and to the 3-deoxy-glucoside.

Oxo-glucosides should be useful intermediates for syntheses in the carbohydrate field, where the recent isolation of a number of "non-classical" sugars from natural sources has created new synthetic problems. For example methyl β-D-glucopyranoside has been transformed into the D-alloside *via* the 3-oxo-derivative [1], thus proving the position of the oxo-group in the latter compound. A further example is the synthesis of a branched sugar, related to noviose by a sequence of reactions involving oxidation to an oxo-derivative followed by a Grignard reaction [2]. The present paper describes studies of some reaction routes, starting from methyl 3-oxo-β-D-glucopyranoside [3](I).

The oxo-glucoside (I) on treatment with hydroxylamine hydrochloride in aqueous solution was transformed into the oxime (II) in a yield of 95 % or better. The pH was kept at 4.0 by addition of sodium hydroxide, and this was also used to follow the oximation analytically [4]. The oxime proved to be quite labile and decomposed easily into the oxo-glucoside. Thus on paper chromatography in acid solvent systems or on attempted deionisation by carbon column chromatography, the oxo-glucoside was formed almost quantitatively. By careful concentration of the aqueous solution to dryness, after adjustment of the pH to 7.0, and extraction of the solid residue with butanol, the oxime was finally obtained reasonably pure, and this butanolic solution was used for further reactions.

Catalytic reduction of inososes [5] and oxo-glucopyranosides [6] with platinum catalysts is known to yield preferentially the isomer, in which the new hydroxyl is axial in the most stable chair form. Similar results have been obtained by catalytic reduction of oximes or hydrazones in the cyclohexane series [7,8]. Reduction with sodium amalgam, on the other hand, yields comparable amounts of equatorial and axial substituents or sometimes even higher proportions of the former, particularly in the case of oximes and hydrazones [8].

Catalytic reduction of the oxime (II) using Adams' catalyst, gave a crystalline compound, m.p. 199—200°, $[\alpha]_D$ —54° (water) in 85 % yield; this should be methyl 3-amino-3-deoxy-β-D-allopyranoside (III). A study of the optical rotations (Table 1) supports this conclusion. On reduction of II with sodium amalgam, a different compound, m.p. 205—207°, $[\alpha]_D$ —38° (water) was obtained in a yield of 45%. Peat and Wiggins [9] prepared methyl 3-amino-3-deoxy-β-D-glucopyranoside (IV) by another route and report the same m.p. but a lower optical rotation, —47°. The tetra-acetates of the two products, however, have identical constants, m.p. 159—160°, $[\alpha]_D$ —21.4° and —22°, resp. (chloroform). Our value for the optical rotation of the unacetylated product agrees somewhat better with the corresponding rotation for methyl β-D-glucopyranoside (—34°), which should be similar. The presence of the amino-alloside (III) in the mother liquors was demonstrated by paper chromatography and paper electrophoresis.

It is of interest that 3-amino-3-deoxy-D-glucose is identical with kanosamine, a component of the antibiotic kanamycin [10]. Lemieux and Chu [11] have recently demonstrated that some substances prepared by Freudenberg *et al.*[12] and claimed to be 3-amino-3-deoxy-D-glucose derivatives are actually the corresponding allose derivatives. The same seems to be true of some compounds recently prepared by Wolfrom *et al.*[13] by routes, analogous to those

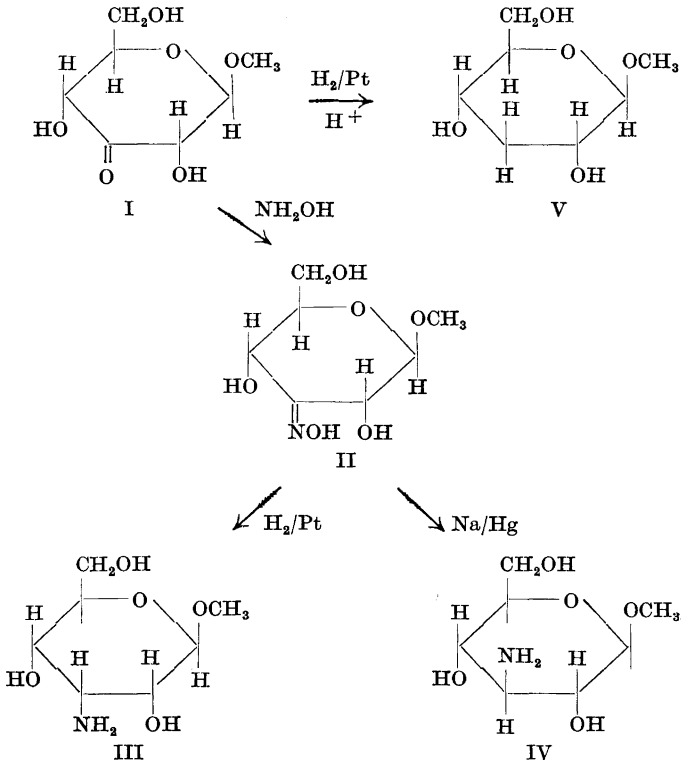

Table 1. Optical rotations of some methyl β-glycosides.

Substance		$[\alpha]_D$	$[M]_D$
Methyl β-D-glucopyranoside		−34°	6 600°
Methyl β-D-allopyranoside		−53°	10 300°
Methyl 3-amino-3-deoxy-β-D-glucopyranoside	(a)	−47°	9 100°
	(b)	−38°	7 300°
Methyl 3-amino-3-deoxy-β-D-allopyranoside		−54°	10 400°
Methyl 3-deoxy-β-D-glucopyranoside		−46°	8 200°
Methyl 3-oxo-β-D-glucopyranoside		−63°	12 100°

a. Ref.[9]
b. Present investigation.

used by Freudenberg *et al.* A new synthesis of 3-amino-sugars has recently been described by Baer and Fisher [14].

Posternak [15] has shown that the oxo-group in *myo*-inosose-2 is reduced to a methylene group on catalytic reduction with Adams' catalyst in acid solution. An analogous reduction of I yielded 59 % of methyl 3-deoxy-β-D-glucoside (V), m.p. 94—96°, $[\alpha]_D$—46° (water) together with smaller amounts of unchanged starting material and a mixture of methyl β-D-glucopyranoside and methyl β-D-allopyranoside. The glucoside was transformed into the β-tetraacetate of the free sugars, m.p. 130—131°, $[\alpha]_D$ −19° (chloroform). Richtmyer and Pratt [16] report m.p. 129—130°, $[\alpha]_D$ −14°, Černý and Pacák [17] m.p. 129—130°, $[\alpha]_D$ −20° for this substance. The free sugar, which was not isolated, had an electrophoretic mobility of 0.85, relative to glucose, in borate buffer. The corresponding value for 3-*O*-methyl-D-glucose is 0.76; close agreement between these values is to be expected [18].

Glycosides of deoxy-sugars hydrolyse faster than the corresponding glycosides of the parent sugars (*cf.* Ref.[19]). Thus Richards [20] reports rate constants of 1.7×10^{-2} and 2.3×10^{-3} for the hydrolysis of methyl 3-deoxy-α-D-glucopyranoside and methyl α-D-glucopyranoside, respectively, in N sulphuric acid at 100°. Under the same conditions, the values 6×10^{-2} and 7.8×10^{-3} (Briggs' logarithms, time in min) were now obtained for the corresponding β-glucosides. The first of these values is rather inaccurate, as the hydrolysis, which was followed polarimetrically, is accompanied by formation of the 1,6-anhydrosugar [16] and also because the reaction was inconveniently fast under the conditions used.

EXPERIMENTAL

Melting points are corrected. Solutions were concentrated under reduced pressure at a bath temp. of about 40°.

Paper chromatography was done on Whatman No. 1 and No. 3 MM filter papers using the solvent systems (v/v):

a. Ethyl acetate-acetic acid-water, 3:1:3 (upper phase)
b. Butanol-ethanol-water, 10:3:5

Table 2. Chromatographic and electrophoretic data for some methyl glycosides.

Substance	$R_{Glucose}$ (solvent a)	$M_{Glucose}$ (borate buffer)
Methyl β-D-glucopyranoside	1.94	0.16
Methyl β-D-allopyranoside	2.23	0.49
Methyl 3-deoxy-β-D-glucopyranoside	3.44	0.14
Methyl 3-oxo-β-D-glucopyranoside	3.57	0.60
Methyl 3-amino-3-deoxy-β-D-glucopyranoside	1.80	0.13
Methyl 3-amino-3-deoxy-β-D-allopyranoside	1.80	0.09

Paper electrophoreses were done on Whatman No. 1 filter paper in 0.1 M borate buffer of pH 10 and in 0.1 M acetate buffer at pH 4.

The following spray reagents were used: silver nitrate in acetone-ethanolic sodium hydroxide, *p*-anisidine hydrogen chloride in butanol, resorcinol-hydrochloric acid in ethanol and ninhydrin in ethanol-acetic acid. Chromatographic and electrophoretic data are summarised in Table 2.

Oximation of methyl 3-oxo-β-D-glucopyranoside (I). In a typical experiment, I (0.43 g) was dissolved in a solution of hydroxylamine hydrochloride (1.38 g) in water (40 ml) which had previously been adjusted to pH 4.0. The temperature was kept at 22° by external cooling and 0.1 N sodium hydroxide was added through an automatic titrator to keep the pH at 4.0. The reaction was followed by the consumption of sodium hydroxide; it was complete in about 8 h when the sodium hydroxide consumption corresponded to 97 % conversion. The aqueous solution was adjusted to pH 7, concentrated until the salts precipitated, and then further dried in a vacuum desiccator over silica gel. The solid residue was extracted with butanol (5 × 10 ml) and the filtered solution was concentrated to about 15 ml.

Methyl 3-amino-3-deoxy-β-D-allopyranoside. A solution of the oxime from 750 mg I in butanol (25 ml) was treated with hydrogen in the presence of Adams' catalyst (100 mg) for 20 h. The solution was filtered and concentrated to dryness. The crystalline residue on recrystallisation from ethanol gave pure III (435 mg), m. p. 199–200°, $[\alpha]_D^{20}$ −54° (water, c = 2). Fractionation of the material in the mother liquors on thick filter paper in solvent system a gave a further quantity of III (200 mg) together with smaller amounts of unidentified compounds, none of which seemed to be identical with IV. (Found: C 43.9; H 8.03; N 6.78. Calc. for $C_7H_{15}NO_5$: C 43.5; H 7.83; N 7.25.)

Acetylation with acetic anhydride in pyridine gave the tetraacetate, which was crystallised from butanone, m. p. 179–180°, $[\alpha]_D^{23}$ −43° (chloroform, c = 1). (Found: C 50.5; H 6.33. Calc. for $C_{15}H_{23}NO_9$: C 49.9; H 6·42.)

Methyl 3-amino-3-deoxy-β-D-glucopyranoside. A solution of the oxime from 450 mg I in butanol (15 ml) was diluted with ethanol (25 ml) and 2.5 % sodium amalgam (20 g) was added in portions with vigorous stirring over 4 h. The pH was kept at 6 by addition of 5 % aqueous acetic acid. The product was then put on a carbon-Celite column and the salts were eluted with water and the glycosides with 5 % aqueous acetic acid. The glycoside fraction was concentrated to dryness, dissolved in water, filtered through a column of Dowex 2 (OH^-) and concentrated to dryness. The crystalline residue (362 mg) on crystallisation from ethanol yielded almost pure IV (202 mg), m. p. 198–200°. After two further crystallisations the substance was pure, m. p. 205–207°, $[\alpha]_D^{20}$ −38 (in water, c = 2). The mother liquors contained IV, smaller amounts of III and minor amounts of other unknown substances.

Treatment of IV with acetic anhydride and pyridine yielded the tetraacetate, m. p. 159–160°, $[\alpha]_D^{2}$ −22° (chloroform, c = 2).

Methyl 3-deoxy-β-D-glucopyranoside (V). Hydrogen was bubbled through a solution of I (450 mg) in 5 % aqueous sulphuric acid (25 ml) containing Adams' catalyst (from

200 mg of platinum dioxide) for 4 h with the addition of a second portion of catalyst (100 mg) after 2 h. The catalyst was filtered off, the acid was neutralised with barium carbonate, the barium salts were filtered off and the solution was concentrated to a thick syrup (440 mg). The product on fractionation on a cellulose column (45 × 3.5 cm) using butanol saturated with water as eluent, yielded V (293 mg), unchanged starting material (27 mg) and a mixture of methyl β-D-glucopyranoside and -allopyranoside (92 mg). V crystallised from methyl ethyl ketone on standing and was recrystallised from the same solvent, m. p. 94—96°, $[\alpha]_D^{20}$ −46° (water, c = 2). (Found: OCH_3 16.6. Calc. for $C_7H_{14}O_5$: OCH_3 17.4.)

Part of the product was converted into the β-tetraacetate of 3-deoxy-D-glucose, m. p. 130—131°, $[\alpha]_D^{20}$ −19° (in chloroform, c = 2).

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