406. *Carbohydrate Components of Antibiotics. Part III.*[1] *Synthesis of 3,6-Dideoxy-3-dimethylamino-β-D-glucose Hydrochloride Monohydrate:*[2] *the Absolute Configuration of Mycaminose.*

By A. B. Foster, T. D. Inch, J. Lehmann, M. Stacey, and J. M. Webber.

3,6-Dideoxy-3-dimethylamino-β-D-glucose hydrochloride monohydrate, a synthesis of which from methyl 2,3-anhydro-α-D-allopyranoside is described, is identical with the dimethylamino-sugar derivative obtained by degradation of magnamycin.

Mycaminose, a component of the macrolide antibiotic magnamycin[3] and of members of the spiromycin group,[4] has been identified[5] as a 3,6-dideoxy-3-dimethylaminohexose. Alkaline degradation of mycaminose and partial reduction of the product with sodium borohydride gave[1] a mixture of 3,6-dideoxy-*arabino*- and -*ribo*-hexitose, indicating an *erythro*-configuration for positions 4, 5 in the dimethylamino-sugar and a total configuration *gluco*, *manno*, *allo*, or *altro*. The deduction[6] that the configuration at positions 2, 3, 4 of mycaminose is *arabino* implies a total *altro*- or *galacto*-configuration. However, 3,6-dideoxy-3-dimethylamino-L-altrose is neither enantiomorphous nor identical with mycaminose.[1] We have found that 3,6-dideoxy-3-dimethylamino-D-glucose hydrochloride monohydrate, a synthesis of which is now reported, is identical with mycaminose hydrochloride monohydrate.

Using a different synthetic approach Richardson[7] has also established that mycaminose has the D-*gluco*-configuration.

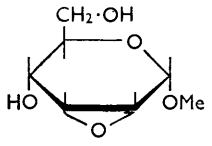
Treatment of methyl 2,3-anhydro-α-D-allopyranoside (I) with ethanolic dimethylamine at *ca.* 170° for 18 hr. gave a product which consumed ~0·5 mol. of periodate in 1·5 hr. and thereafter a further amount relatively slowly. Such behaviour would be expected for an approximately equimolar mixture of methyl 3-deoxy-3-dimethylamino-α-D-glucopyranoside (II) and methyl 2-deoxy-2-dimethylamino-α-D-altropyranoside (III) since only the latter contains a vicinal diol grouping. The subsequent slow consumption of periodate was probably due to cleavage of ·CH(OH)·CH(NMe_2)·; *trans*-2-dimethylaminocyclohexanol is slowly attacked by periodate[8] (0·28 mol. of oxidant was consumed in 47 hr.). The mixture of methyl 3-deoxy-3-dimethylamino-α-D-glucoside (II) and the periodate-oxidised methyl 2-deoxy-2-dimethylamino-α-D-altroside (III) was readily separated since the latter component by virtue of its aldehyde groups was absorbed by an anion-exchange resin.[9] Methyl 3-deoxy-3-dimethylamino-α-D-glucopyranoside (II) was thus obtained and characterised as the hydrochloride.

By analogy with the reactions of many other sugar epoxides[10] methyl 2,3-anhydro-α-D-allopyranoside would be expected to yield a mixture of the glucose and altrose derivatives (II) and (III). The equimolar composition of the mixture reflects the flexibility of the anhydroalloside (I) which permits attack[10] by dimethylamine equally at positions 2 and 3. It is established[11] that, when the flexibility of the alloside compound (I) is diminished, for example, in the 4,6-*O*-benzylidene derivative, the epoxide ring

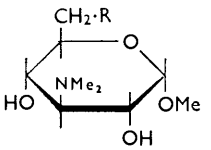
[1] Part II, *J.*, 1962, 1396.
[2] For a preliminary publication see Foster, Inch, Lehmann, Stacey, and Webber, *Chem. and Ind.*, 1962, 142.
[3] Wagner, Hochstein, Murai, Messina, and Regna, *J. Amer. Chem. Soc.*, 1953, **75**, 4684.
[4] Paul and Tchelitcheff, *Bull. Soc. chim. France*, 1957, 443, 734, 1059.
[5] Hochstein and Murai, *J. Amer. Chem. Soc.*, 1954, **76**, 5080; Hochstein and Regna, *ibid.*, 1955, **77**, 3353.
[6] Woodward, *Angew. Chem.*, 1957, **69**, 50.
[7] Richardson, *Proc. Chem. Soc.*, 1961, 430.
[8] Bolton, Ph.D. Thesis, Birmingham, 1961.
[9] Roseman, Abeles, and Dorfman, *Arch. Biochem. Biophys.*, 1952, **36**, 232.
[10] Overend and Vaughan, *Chem. and Ind.*, 1955, 995.
[11] Newth, *Quart. Rev.*, 1959, **13**, 30.

tends to open to give products of the *altro*-configuration in accordance with the Fürst–Plattner rule.[12] It is also of interest to contrast the behaviour of methyl 2,3-anhydro-α-D-allopyranoside with ethanolic dimethylamine and with aqueous sodium hydroxide: in the latter case an intramolecular reaction occurs and the main product is methyl 3,6-anhydro-α-D-glucopyranoside.[13]

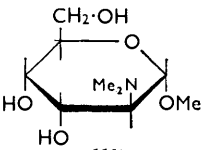
Treatment of methyl 3-deoxy-3-dimethylamino-α-D-glucopyranoside (II) with an excess of toluene-*p*-sulphonyl chloride in pyridine failed to yield a crystalline product, but reduction of the gummy ester with lithium aluminium hydride in boiling tetrahydrofuran afforded crystalline methyl 3,6-dideoxy-3-dimethylamino-α-D-glucopyranoside (IV) in moderate yield. Hydrolysis of this glycoside with 6N-hydrochloric acid at 95—100° for



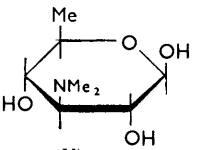
(I)



(II : R = OH)
(IV : R = H)



(III)



(V)

4 hr. gave 3,6-dideoxy-3-dimethylamino-β-D-glucose (V), isolated as the hydrochloride monohydrate. Comparison of physical properties established the identity of the synthetic product and mycaminose hydrochloride monohydrate. The β-configuration is assigned on the basis of the mutarotation in water: +11° (10 min.) ⟶ +31° (equilibrium).

Most of the hexosamine derivatives isolated from antibiotics and of established configuration have been found to have the *gluco*-configuration. In addition to mycaminose, there are *N*-methyl-L-glucosamine [14] (streptomycin), 3-amino-3-deoxy- and 6-amino-6-deoxy-D-glucose [15] (kanamycin), and 2,6-diamino-2,6-dideoxy-D-glucose [16] (neomycin C). Desosamine, a 3,4,6-trideoxy-3-dimethylamino-hexose which is a component of several macrolide antibiotics, belongs to the D-series [17] and probably [18] has the D-*xylo*-configuration and hence may be regarded as a derivative of 4-deoxy-D-glucose. A known [19] exception to this pattern is mycosamine, the 3-amino-3,6-dideoxyhexose present in nystatin.

Experimental

Methyl 3-Deoxy-3-dimethylamino-α-D-glucopyranoside Hydrochloride.—A solution of methyl 2,3-anhydro-α-D-allopyranoside [12] (2 g.) in 33% ethanolic dimethylamine (20 ml.) was heated in a sealed tube at 170° ± 10° for 18 hr. The oily residue, which contained methyl 3-deoxy-3-dimethylamino-α-D-glucopyranoside and methyl 2-deoxy-2-dimethylamino-α-D-altropyranoside, obtained by evaporation of the reaction solution was dissolved in a solution of sodium metaperiodate (4 g.) in water (*ca.* 100 ml.). After storage at room temperature for 2·5—3 hr. the solution was filtered and then passed through a column (60 × 5 cm.) of Amberlite IRA-400 (HO^- form). The column was washed with water until the eluate was optically inactive, the eluate was then concentrated at ~65°/14 mm. to *ca.* 75 ml., then continuously extracted with chloroform overnight. Concentration of the chloroform solution and distillation of the residue gave methyl 3-deoxy-3-dimethylamino-α-D-glucopyranoside (0·7 g.), b. p. ~170° (bath)/0·3 mm., m. p. 107—108° (from ethanol–ether). When a solution of the free base (100 mg.) in dry methanol (3 ml.) was treated with dry hydrogen chloride the *hydrochloride* (65 mg.) separated,

[12] Fürst and Plattner, Abs. 12th Internat. Congr. Pure Appl. Chem., 1951, p. 409.
[13] Foster, Stacey, and Vardheim, *Acta Chem. Scand.*, 1958, **12**, 1819.
[14] Lemieux and Wolfrom, *Adv. Carbohydrate Chem.*, 1948, **3**, 337.
[15] Cron, Fardig, Johnson, Whitehead, Hooper, and Lemieux, *J. Amer. Chem. Soc.*, 1958, **80**, 2342.
[16] Rinehart, Hichens, Striegler, Rover, Culbertson, Tatsuoka, Horii, Yamaguchi, Hitomi, and Miyake, *J. Amer. Chem. Soc.*, 1961, **83**, 2964; Wiedmann and Zimmerman, Abs. Papers Amer. Chem. Soc. Meeting, St. Louis, March 1961, p. 3D.
[17] Bolton, Foster, Stacey, and Webber, *J.*, 1961, 4831.
[18] Bolton, Foster, Stacey, and Webber, unpublished results.
[19] Richardson, *Proc. Chem. Soc.*, 1961, 255.

with m. p. 194° (from acetone–methanol), $[\alpha]_D$ +112° (*c* 0·3 in H_2O), $[M]_D$ +288° (Found: C, 41·8; H, 7·9; N, 5·8; Cl, 13·75. $C_9H_{19}NO_5$,HCl requires C, 41·7; H, 7·8; N, 5·4; Cl, 13·8%).

Periodate Oxidations (Dr. C. H. BOLTON).—A solution (50 ml.) of the glucoside–altroside mixture (54·5 mg.), from the above reaction, in 0·25M-sodium metaperiodate consumed oxidant as follows at room temperature.

Time (hr.)	0·1	0·3	1·0	1·5	2·0	4·0	6·0
Oxidant consumed (mol.)	0·33	0·39	0·485	0·50	0·515	0·56	0·59

A similar solution containing *trans*-2-dimethylaminocyclohexanol (40 mg.) consumed periodate as follows:

Time (hr.)	3	7	21·5	47	70	166	336
Oxidant consumed (mol.)	0·05	0·075	0·17	0·28	0·41	0·60	0·765

The periodate uptake was followed by a standard method.[20]

Methyl 3,6-Dideoxy-3-dimethylamino-α-D-glucopyranoside.—A solution of methyl 3-deoxy-3-dimethylamino-α-D-glucopyranoside (4 g.) in pyridine (30 ml.) was treated with toluene-*p*-sulphonyl chloride (14 g.) in pyridine (30 ml.). After storage overnight at 40° the mixture was poured into ice–water (200 ml.), basified with sodium carbonate, and extracted with chloroform. The chloroform solution was washed with water, dried (Na_2SO_4), and concentrated at 40°/0·2 mm., to yield the product (8·5 g.) that failed to crystallise but presumably was the 2,4,6-tri-*O*-toluene-*p*-sulphonate.

Lithium aluminium hydride (*ca.* 2 g.) was added to a suspension of the foregoing product (8·5 g.) in tetrahydrofuran which was then stirred vigorously and boiled under reflux for 1 week. The excess of reductant was destroyed with ethyl acetate, and alkoxides with water. Insoluble material was collected and washed with 2N-sodium hydroxide. The volume of the combined filtrate and washings was adjusted to 200 ml. with 2N-sodium hydroxide, and the solution was then concentrated to *ca.* 80 ml. at 80°/14 mm. and continuously extracted overnight with chloroform. Evaporation of the dried (Na_2SO_4) extract and distillation of the residue gave *methyl 3,6-dideoxy-3-dimethylamino-α-D-glucopyranoside* (1·2 g., 33%), b. p. 80°/0·25 mm., m. p. 81—82° [from isopentyl alcohol–light petroleum (b. p. 40—60°); by sublimation at 110°/0·2 mm.], $[\alpha]_D$ +123° (*c* 0·43 in H_2O), $[M]_D$ +252° (Found: C, 52·65; H, 9·1; N, 6·8. $C_9H_{19}NO_4$ requires C, 52·7; H, 9·3; N, 6·8%).

3,6-Dideoxy-3-dimethylamino-D-glucose Hydrochloride Monohydrate.—A solution of the foregoing glycoside (0·24 g.) in 6N-hydrochloric acid (8 ml.) was kept at 95—100° for 4 hr., then evaporated at 30°/14 mm. Examination of the crystalline residue by paper chromatography with the organic phase of butanol–ethanol–water (4 : 1 : 5) and detection with aniline hydrogen phthalate [21] revealed a single major component with R_F identical with that of mycaminose hydrochloride. Two recrystallisations of the residue from moist isopropyl alcohol gave 3,6-dideoxy-3-dimethylamino-D-glucose hydrochloride monohydrate (0·15 g.), m. p. 114—116° alone or in admixture with the dimethylamino-sugar obtained [5] from magnamycin, $[\alpha]_D$ +31° (equilibrium) (*c* 0·96 in H_2O), $[M]_D$ +76°. Mycaminose hydrochloride monohydrate has $[\alpha]_D$ +32° (equilibrium) (*c* 1·42 in H_2O). The infrared spectra (KCl discs) of the natural and the synthetic compound were indistinguishable and had $\nu_{max.}$ 1650 cm.$^{-1}$ characteristic [22] of water of crystallisation.

The authors thank Pfizer Ltd. for generous gifts of magnamycin and Imperial Chemical Industries Limited for a Fellowship (to J. L.).

CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15. [*Received, December 20th*, 1961.]

[20] Jackson, *Org. Reactions*, 1944, **2**, 341.
[21] Partridge, *Nature*, 1949, **164**, 443.
[22] Barker, Bourne, and Whiffen, in "Methods of Biochemical Analysis," Interscience Publ. Inc., New York, 1956, Vol. III, p. 224.