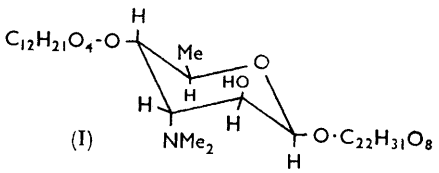
529. *The Synthesis of* D- *and* L-*Mycaminose Hydrochlorides.**

By A. C. Richardson.

Preparation of methyl 3-amino-3,6-dideoxy-α-D-glucoside from methyl 6-deoxy-α-D-glucoside by the Fischer nitromethane cyclisation reaction is described. Di-*N*-methylation with formic acid–formaldehyde afforded the dimethylamino-analogue which on acid hydrolysis yielded 3,6-dideoxy-3-dimethylamino-β-D-glucose, identical with mycaminose isolated from magnamycin. An analogous synthesis of the L-enantiomorph is described. Mycaminose probably exists in a boat conformation in magnamycin.

Mycaminose, which constitutes the basic portion of the magnamycins,[1] spiramycins,[2] and leucomycins,[3] is a 3,6-dideoxy-3-dimethylaminohexose.[4] In magnamycin it is linked glycosidically to a 17-membered lactone,[5] and a neutral sugar, mycarose, is linked by its glycosidic group to the 4-hydroxyl group of mycaminose, as in (I). The effect of *O*-substitution of mycaminose at positions 2 and 4 on the pK_a of the basic group was studied. Acetylation of the 2-hydroxyl group decreased the pK_a by 1·0, whereas acetylation at position 4 caused a greater decrease of 1·9. Even the weakly electron-attracting neutral sugar, mycarose, at position 4 (see I) caused a greater decrease (1·3) in basicity



than acetoxyl at position 2. It was evident from these results that the 4-hydroxyl group was closer to the basic group than that at position 2, so Woodward,[5] assuming a chair conformation, proposed a stereochemistry for mycaminose, which was compatible only with the β-D-*altro*-isomer (I).[2]

Hochstein and Murai[1] prepared two isomeric tri-*O*-acetates from mycaminose, the molecular rotations of which (+6020° and +30,100°) did not correspond to those of β- and α-D-altrose penta-acetate[6] (−17,200° and +24,500° respectively). These rotations, however, were in better agreement with those of 3-amino-3,6-dideoxy-β- and -α-D-glucose tetra-acetate[7] (+7450° and +36,800° respectively, calculated from the L-forms). It was thus of considerable interest to synthesise 3,6-dideoxy-3-dimethylamino-D-glucose for comparison with mycaminose.

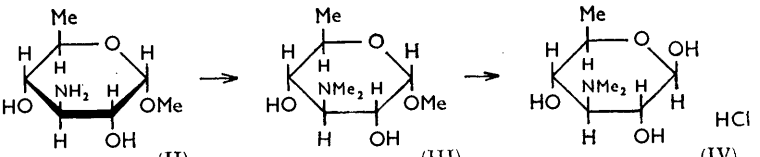
The preparation of methyl 3-amino-3,6-dideoxy-α-L-glucoside from methyl α-L-rhamnoside has been described.[7] The rhamnoside was oxidised with sodium metaperiodate and the resulting dialdehyde cyclised with nitromethane. Reduction of the resulting mixture of 3-nitro-pyranosides yielded the amino-glucoside in 25—31% yield. Application of the same reaction sequence to methyl 6-deoxy-α-D-glucoside afforded a 24% yield of methyl 3-amino-3,6-dideoxy-α-D-glucoside (II), with an infrared spectrum identical with that of the L-enantiomorph.

No general method for the conversion of amino-sugars into dimethylamino-sugars has been described, although fully *O*- and *N*-methylated derivatives of glucosamine have been

* Preliminary communication: Richardson, *Proc. Chem. Soc.*, 1961, 430.

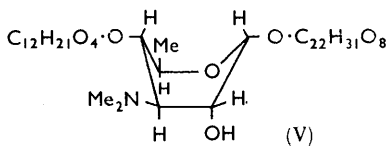
[1] Hochstein and Murai, *J. Amer. Chem. Soc.*, 1954, **76**, 5080.
[2] Paul and Tchelitcheff, *Bull. Soc. Chim. France*, 1960, 150.
[3] Watanabe, *Bull. Chem. Soc. Japan*, 1961, **34**, 15.
[4] Hochstein and Regna, *J. Amer. Chem. Soc.*, 1955, **77**, 3353.
[5] Woodward, Festschrift Prof. Dr. Arthur Stoll, Birkhauser, Basle, 1957, p. 524; *Angew. Chem.*, 1957, **69**, 50.
[6] Richtmyer and Hudson, *J. Amer. Chem. Soc.*, 1941, **63**, 1727.
[7] Richardson, *Proc. Chem. Soc.*, 1961, 255, and preceding paper.

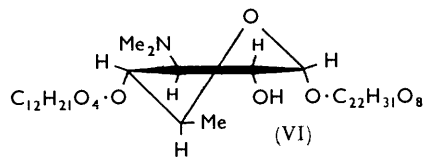
reported.[8] Freudenberg *et al.* prepared derivatives of 3-deoxy-3-dimethylamino-D-allose [9] and 6-deoxy-6-dimethylamino-D-galactose [10] by replacement of sulphonyloxy-groups with dimethylamine. Di-*N*-methylation of some aminopyranosides with a mixture of formic acid and formaldehyde [11] has been investigated and has led to good yields of several new dimethylamino-sugars.[12] In particular, application of this method to methyl 3-amino-3,6-dideoxy-α-D-glucoside (II) afforded a 72% yield of the dimethylamino-analogue (III), isolated as the formate salt. Likewise, the L-glucoside afforded an 88% yield of the



L-enantiomorph of (III). Subsequent hydrolysis with hydrochloric acid yielded 3,6-dideoxy-3-dimethylamino-β-D-glucose hydrochloride (IV) and its L-isomer. By melting points, mixed melting points, optical rotations, and infrared spectra the D-isomer (IV) was shown to be identical with the salt of mycaminose isolated from magnamycin.*

This result, although at variance with the conclusions of Woodward,[5] may be reconciled with his results (see above) if mycaminose exists in the boat conformation (V) in magnamycin. Although some doubt exists,[13] such a conformation is thought to be present in some of the repeating α-D-glucopyranose units of the 1,4-linked polysaccharide amylose [14] and the related Schardinger dextrans,[15] owing to steric strain in the normal C1 conformation. Mycaminose, which is 1,4-disubstituted in the antibiotic, is probably linked to the large nucleus by an α-glycosidic bond, which by analogy with the postulated boat form of amylose would hold the pyranose ring in the boat conformation (V), in which all groups apart from the 2-hydroxyl are equatorial. Woodward's results could be explained equally if the pyranose ring adopted the half-chair conformation (VI). How-





ever, in this case the large nucleus would be held in a quasi-axial position, and the mycarosyl residue would be quasi-equatorial. On account of this, the half-chair would be less favourable than the boat conformation.

Experimental

Evaporations were done *in vacuo*. Optical rotations were determined at 20°. pK_a's and molecular weights were determined by potentiometric titration.

* Since the preliminary announcement of this work Dr. A. B. Foster has informed me that he has achieved an alternative synthesis involving the ring opening of an epoxide with dimethylamine (see Foster, Inch, Lehmann, Stacey, and Webber, *Chem. and Ind.*, 1962, 142).

[8] Irvine and Hynd, *J.*, 1912, 1128; 1914, 698.
[9] Freudenberg, Burkhart, and Braun, *Ber.*, 1926, **59**, 714.
[10] Freudenberg and Smeykal, *Ber.*, 1926, **59**, 100.
[11] Clark, Gillespie, and Weisshaus, *J. Amer. Chem. Soc.*, 1933, **55**, 4576; Kaluszyner and Galun, *J. Org. Chem.*, 1961, **26**, 3536.
[12] Richardson, unpublished results.
[13] Greenwood and Rossotti, *J. Polymer. Sci.*, 1958, **27**, 481.
[14] Reeves, *J. Amer. Chem. Soc.*, 1954, **76**, 4595.
[15] Freudenberg and Cramer, *Chem. Ber.*, 1950, **83**, 296.

Methyl 3-*Amino*-3,6-*dideoxy*-α-D-*glucoside* (II).—This was prepared from methyl 6-deoxy-α-D-glucoside [16] (1·73 g.) in a way analogous to that described for the L-enantiomorph.[7] The resulting semi-crystalline mixture of amines was dissolved in hot ethanol, and ethyl acetate added, affording *methyl* 3-*amino*-3,6-*dideoxy*-α-D-*glucoside* (412 mg., 24%), m. p. 175—177°, $[\alpha]_D$ +148° (*c* 0·57 in H_2O) (Found: C, 47·2; H, 8·25; N, 7·75. $C_7H_{15}NO_4$ requires C, 47·47; H, 8·45; N, 7·9%). The infrared spectrum of this compound was identical with that of the L-enantiomorph.[7]

Methyl 3,6-*Dideoxy*-3-*dimethylamino*-α-D-*glucoside Formate* (cf. III) *and its* L-*Enantiomorph*.—A solution of methyl 3-amino-3,6-dideoxy-α-D-glucoside (376 mg.) in 98—100% formic acid (2 ml.) and 37—41% w/v aqueous formaldehyde (1 ml.) was heated under reflux 2½ hr., then evaporated to dryness. The syrup did not crystallise until seeded with the L-enantiomorph. Recrystallisation from ethanol–light petroleum (b. p. 40—60°) gave 379 mg. (72%) of *methyl* 3,6-*dideoxy*-3-*dimethylamino*-α-D-*glucoside formate*, m. p. 162—164°, $[\alpha]_D$ +105° (*c* 0·2 in H_2O) (Found: C, 47·55; H, 8·25; N, 5·5. $C_{10}H_{21}NO_6$ requires C, 47·9; H, 8·35; N, 5·6%).

The L-enantiomorph was prepared from methyl 3-amino-3,6-dideoxy-α-L-glucoside [7] (2 g.) in an analogous manner. The yield of the highly crystalline *dimethylaminoglucoside formate* was 2·52 g. (88%) after recrystallisation from ethanol–light petroleum (b. p. 40—60°); the amine had m. p. 164—166° and $[\alpha]_D$ −106° (*c* 5 in H_2O) (Found: C, 47·9; H, 8·3; N, 6·0%). The infrared spectra of the two glucosides were identical.

3,6-*Dideoxy*-3-*dimethylamino*-β-D-*glucose* (D-*Mycaminose*) *Hydrochloride* (cf. IV).—Methyl 3,6-dideoxy-3-dimethylamino-α-D-glucoside formate (346 mg.) in concentrated hydrochloric acid (10 ml.) was heated under reflux for 2 hr., then evaporated to dryness. The resulting syrup was repeatedly dissolved in water and re-evaporated to remove the last traces of acid, and finally dried *in vacuo* for 48 hr. over phosphorus pentoxide and potassium hydroxide. A part of the resulting syrup crystallised when its aqueous solution evaporated slowly. The bulk was dissolved in propan-2-ol (1 ml.), and water (0·025 ml.) was added. The solution was seeded and kept at −10° for 2 days. Filtration afforded 109 mg. (32%) of 3,6-*dideoxy*-3-*dimethylamino*-β-D-*glucose hydrochloride monohydrate*, which was washed with ice-cold propan-2-ol, acetone, and ether. The hydrochloride had m. p. 116—118° and $[\alpha]_D$ +11° (1½ min.) ⟶ +17° (3 min.) ⟶ +28° (45 min.) ⟶ +30° (3 hr.) ⟶ +31° (24 hr.) (*c* 1·08 in H_2O). The mother-liquors were allowed to evaporate slowly at room temperature, yielding a crystalline residue. Trituration with propan-2-ol afforded a further crop of the sugar (70 mg., 21%), m. p. 117—117·5°. The mixed m. p. with a sample of mycaminose isolated from magnamycin was 117° and the infrared spectra of the two samples were identical (Found: C, 38·9; H, 8·3; N, 5·8. $C_8H_{20}ClNO_5$ requires C, 39·1; H, 8·2; N, 5·7%).

Hochstein and Murai [1] report that mycaminose hydrochloride crystallises as the monohydrate, m. p. 115—116°, $[\alpha]_D$ +31° (in H_2O; 24 hr.).

3,6-*Dideoxy*-3-*dimethylamino*-β-L-*glucose* (L-*Mycaminose*) *Hydrochloride*.—Methyl 3,6-dideoxy-3-dimethylamino-α-L-glucoside formate (0·5 g.) was hydrolysed with 2N-hydrochloric acid (20 ml.) for 17 hr. at 100°. The colourless solution was then evaporated to a glass. Crystallisation from 96% aqueous propan-2-ol (2·5 ml.) afforded 3,6-*dideoxy*-3-*dimethylamino*-β-L-*glucose hydrochloride monohydrate* (99 mg., 22%), m. p. 116—117°, $[\alpha]_D$ −13° (1 min.) ⟶ −22° (30 min.) ⟶ −28° (90 min.) ⟶ −30° (24 hr.). A further 161 mg. (31%) of the sugar was obtained, as three crops, from the mother-liquors (Found: C, 39·5; H, 8·3; N, 5·6%; *M*, 240. $C_8H_{20}ClNO_5$ requires C, 39·1; H, 8·2; N, 5·7%; *M*, 245·5).

The amine had pK_a 8·6. On paper chromatograms, with butan-1-ol–pyridine–water (10 : 3 : 3 v/v), synthetic D- and L-mycaminose and the naturally occurring mycaminose (R_F 0·22) were indistinguishable. The sugars were detected with the *p*-anisidine hydrochloride spray as yellow-brown spots. The infrared spectra of these three samples were identical.

Heating an alkaline solution (pH 12) of L-mycaminose gave the odour of dimethylamine.

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THE UNIVERSITY, BRISTOL. [*Received, December* 21*st*, 1961.]

[16] Helferich, Klein, and Schäfer, *Ber.*, 1926, **59**, 79; *Annalen*, 1926, **447**, 19.