264. *Carbohydrate Components of Antibiotics. Part II.*[1] *Alkaline Degradation of Mycaminose and Synthesis of* 3,6-*Dideoxy*-3-*dimethylamino*-L-*altrose and Some Derivatives Therefrom.*

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A qualitative examination of the alkaline degradation of mycaminose indicates that the configuration at $C_{(4)}$–$C_{(5)}$ is *erythro*. Syntheses, from L-rhamnose, of 3,6-dideoxy-3-dimethylamino-L-altrose and 3,6-dideoxy-3-dimethylamino-L-altritol and its tetra-*O*-methyl derivative are described. These compounds differ from mycaminose and mycaminitol and its tetramethyl ether, respectively. Mycaminose does not have the *altro*-configuration.

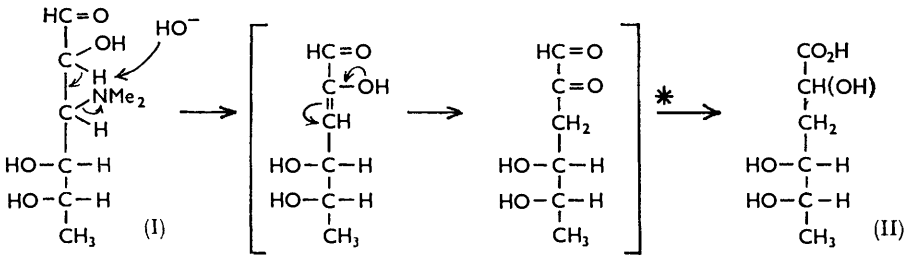
Mycaminose, a component of the macrolide antibiotics magnamycin [2] (carbomycin) and the members of the spiromycin group [3] (foromacidins) has been identified [4] as a 3,6-dideoxy-3-dimethylaminohexose. The deduction [5] that the substituents on $C_{(2)}$, $C_{(3)}$, and $C_{(4)}$ in mycaminose have the *arabino*-configuration implies a total *altro*- or *galacto*-configuration. We now report evidence that the configuration at positions 4 and 5 of mycaminose is *erythro* and also syntheses which show that the total configuration is not *altro*.

Although the mechanism (I) ⟶ (II) has been postulated [5] for the alkaline degradation of mycaminose, the identity of the carbohydrate product has apparently not been established. Desosamine, a 3,4,6-trideoxy-3-dimethylaminohexose, which is closely

[1] Part I, Bolton, Foster, Stacey, and Webber, *J.*, 1961, 4831.
[2] Wagner, Hochstein, Murai, Messina, and Regna, *J. Amer. Chem. Soc.*, 1953, **75**, 4684.
[3] Pinnert-Sindico, Ninet, Preud'homme, and Cosar, *Antibiotics Annual*, 1954—1955, 724; Paul and Tchelitcheff, *Bull. Soc. chim. France*, 1957, 443, 734, 1059.
[4] Hochstein and Regna, *J. Amer. Chem. Soc.*, 1955, **77**, 3353; Hochstein and Murai, *ibid.*, 1954, **76**, 5080.
[5] Woodward, *Angew. Chem.*, 1957, **69**, 50.

related structurally to mycaminose, is degraded [1] by alkali principally by the mechanism shown in (I) ⟶ (II). When a 0·7% solution of mycaminose hydrochloride in N-sodium hydroxide was kept at 50°, 65% of the theoretical amount of dimethylamine was evolved during 12 hr. Lactonization of the acidic carbohydrate product and then reduction [6] with sodium borohydride gave two reducing sugars which had paper chromatographic and ionophoretic properties indistinguishable from those of ascarylose (3,6-dideoxy-L-*arabino*-hexose), and paratose (3,6-dideoxy-D-*ribo*-hexose) and different from those of abequose (3,6-dideoxy-D-*xylo*-hexose); [7] 3,6-dideoxy-D- and -L-*lyxo*-hexose are unknown. This is strong evidence that the configuration at positions 4 and 5 in mycaminose is *erythro* since only the 2-centre should be racemized in the postulated alkaline degradation (I) ⟶ (II). Thus, the total configuration must be *gluco*, *manno*, *allo*, or *altro*. In view of the predicted [5] partial configuration of mycaminose a synthesis of 3,6-dideoxy-3-dimethylamino-L-altrose was undertaken.

The methanesulphonate of methyl 2,5-di-*O*-methyl-α-L-rhamnofuranoside (III), the structure of which has been established,[8] gave, with ethanolic dimethylamine at 180°, methyl 3,6-dideoxy-3-dimethylamino-2,5-di-*O*-methyl-α-L-altrofuranoside (IV). The structure of the compound (IV) followed by analogy with several substantiated examples [9] of the nucleophilic displacement by amines of carbohydrate secondary toluene-*p*-sulphonates with concomitant Walden inversion. Acidic hydrolysis of the glycoside (IV) gave 3,6-dideoxy-3-dimethylamino-2,5-di-*O*-methyl-L-altrose which was only partly demethylated by boron trichloride. In addition to the product with the properties expected for 3,6-dideoxy-3-dimethylamino-L-altrose (detected by paper chromatography) a monomethyl ether resistant to demethylation was formed in major amount. The location of the remaining methoxyl group was not determined and it is possible that the resistance involved a steric effect of the boron trichloride adduct with the dimethylamino-group. This view was supported by the observation that 3,6-dideoxy-3-dimethylamino-2,5-di-*O*-methyl-L-altritol, obtained by reduction of the altrose derivative with sodium borohydride and having relatively free rotation about the bonds in the carbon chain, was readily demethylated with boron trichloride to 3,6-dideoxy-3-dimethylamino-L-altritol. Several



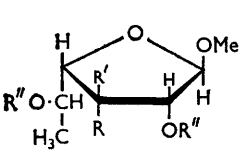
* " Benzilic acid rearrangement."

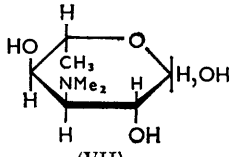
examples of the demethylation of sugar methyl ethers (including 2-amino-2-deoxy-3-*O*-methyl-D-glucose hydrochloride [10]) without change of configuration have been recorded.[11] The stability of the dimethylamino-group in the above compounds towards boron trichloride accords with the findings of other workers.[12]

[6] Wolfrom and Wood, *J. Amer. Chem. Soc.*, 1951, **73**, 2933.
[7] Davies, *Adv. Carbohydrate Chem.*, 1960, **15**, 286.
[8] Foster, Lehmann, and Stacey, *J.*, 1961, 4649.
[9] Lemieux and Chu, *J. Amer. Chem. Soc.*, 1958, **80**, 4745; Wolfrom and Yosizawa, *ibid.*, 1959, **81**, 3474, 3477; Wolfrom, Shafizadeh, and Armstrong, *ibid.*, 1958, **80**, 4885; Wolfrom, Shafizadeh, Armstrong, and Shen, *ibid.*, 1959, **81**, 3716.
[10] Foster, Horton, Salim, Stacey, and Webber, *J.*, 1960, 2587.
[11] Allen, Bonner, Bourne, and Saville, *Chem. and Ind.*, 1958, 630; Bonner, Bourne, and McNally, *J.*, 1960, 2929.
[12] For a review see Gerrard and Lappert, *Chem. Rev.*, 1958, **58**, 1081.

3,6-Dideoxy-3-dimethylamino-L-altritol gave a hydrochloride with an optical rotation (+13° in H_2O) different from that (+8°) for mycaminitol hydrochloride and, unlike the latter compound, it was not crystalline. Further, the two hydrochlorides had different R_F values on paper chromatography. Methylation of 3,6-dideoxy-3-dimethylamino-2,5-di-*O*-methyl-L-altritol gave a tetramethyl ether which had an optical rotation and infrared spectrum different from those of tetra-*O*-methylmycaminitol. In addition, only the former tetramethyl ether gave a crystalline methiodide. Thus mycaminose cannot have the *altro*-configuration. Syntheses of compounds with the *gluco*-, *manno*-, and *allo*-configurations are in progress.*

(III: R = Me·SO_3, R′ = H, R″ = Me)
(IV: R = H, R′ = NMe_2, R″ = Me)
(V: R = OH, R′ = H, R″ = Ph·CH_2)
(VI: R = H, R′ = NMe_2, R″ = Ph·CH_2)





(VII)

Reaction of 3,4-*O*-isopropylidene-L-rhamnose diethyl dithioacetal [8] with benzyl bromide and potassium hydroxide gave the 2,5-dibenzyl ether which, with methanolic mercuric chloride, gave methyl 2,5-di-*O*-benzyl-α-L-rhamnofuranoside (V) characterized as the toluene-*p*-sulphonate. The parallel sequence of reactions with the 2,5-di-*O*-methyl compounds has been studied in detail.[8] Treatment of the above toluene-*p*-sulphonate with ethanolic dimethylamine at 180° gave methyl 2,5-di-*O*-benzyl-3,6-dideoxy-3-dimethylamino-α-L-altrofuranoside (VI). Vigorous hydrolysis of the altroside with hydrochloric acid cleaved the glycosidic group and both the benzyl ether residues, affording 3,6-dideoxy-3-dimethylamino-L-altrose (VII). The amino-sugar appeared to be homogeneous on paper chromatography but its hydrochloride was not obtained crystalline. Mycaminose hydrochloride crystallizes easily. The synthetic amino-sugar also had an R_F value different from that of mycaminose and showed markedly different behaviour on detection with aniline hydrogen phthalate and silver nitrate.

The cleavage of the 5-benzyl group on treatment of the glycoside (VI) with acid is noteworthy since secondary benzyl ethers are generally considered to be fairly stable.[13] Primary benzyl ethers [13] and secondary groups adjacent to a glycosidic centre [14] are easily hydrolysed with acid.

Acidic hydrolysis of glycosides of aminodeoxy-sugars is retarded owing to electrostatic shielding of the glycosidic centre by attack from hydrions by the protonated amino-group. The amount of retardation is affected by the distance of the amino-group from the glycosidic centre: for instance, methyl 2-amino-2-deoxy-D-glucopyranosides are stable towards acid,[15] and the 3-deoxy-3-dimethylaminohexofuranosides described in this paper (and also the pyranoside analogues [16]) require acid conditions for hydrolysis (6N-acid at 100° for 4 hr.) somewhat more drastic than those necessary for neutral glucopyranosides (2N-acid at 100° for 3 hr.).

Experimental

Paper and cellulose-column chromatography was performed on Whatman No. 1 paper by downward irrigation with the organic phase of a butanol–ethanol–water (4 : 1 : 5) system. Optical rotations at 5461 Å were determined by using a type 143A Ericsson automatic polarimeter with a path length of 1 cm.

* *Added in proof* (February 2nd, 1962). The D-*gluco*-configuration has now been established for mycaminose (Richardson, *Proc. Chem. Soc.*, 1961, 255; Foster, Inch, Lehmann, Stacey, and Webber, *Chem. and Ind.*, 1962, 142.

[13] McCloskey, *Adv. Carbohydrate Chem.*, 1957, **12**, 137.
[14] Schwarz and MacDougall, *J.*, 1956, 3065.
[15] Foster, Horton, and Stacey, *J.*, 1957, 81.
[16] Foster, Inch, Lehmann, Stacey, and Webber, unpublished results.

Alkaline Degradation of Mycaminose Hydrochloride.—A solution of mycaminose hydrochloride [4] (2·1 g.) in N-sodium hydroxide (300 ml.) was kept at 50° for 12 hr. The dimethylamine evolved (65%) was swept into standard acid by a stream of carbon dioxide. Cations were removed from the solution on Amberlite IR-120 (H^+ form) resin; the filtrate afforded a residue (1·8 g.) on concentration. Fractionation of this product on a column of powdered cellulose (44 × 5 cm.) gave purified material (1 g.) which was homogeneous on paper chromatography and presumably was 3,6-dideoxy-*ribo*- and -*arabino*-hexonolactone.

A solution of the lactone mixture (0·2 g.) in ice–water (5 ml.) was treated [6] dropwise and simultaneously with sodium borohydride (0·2 g.) in water (10 ml.) and 0·1N-sulphuric acid so that a pH of 3—5 was maintained. After a further hour the solution was deionized by Amberlite resins IR-120 (H^+ form) and IRA-45 (HO^- form) and concentrated to yield 3,6-dideoxy-*ribo*- and -*arabino*-hexose (0·17 g.). Paper chromatography and detection with aniline hydrogen phthalate [17] revealed two components appearing as an elongated zone with R_{Rh} value (Rh = rhamnose) 1·72. The R_{Rh} values for 3,6-dideoxy-D-*ribo*-hexose (paratose), -L-*arabino*-hexose (ascarylose) and -D-*xylo*-hexose (abequose) are 1·68, 1·77, and 1·53, respectively. In paper ionophoresis [enclosed strip technique [18] with a borate buffer (pH 10)] the borohydride reduction product showed two components with M_G values [19] severally 1·48 and 1·66. The M_G values of abequose, ascarylose, and paratose are 1·22, 1·48, and 1·66, respectively.

Methyl 3,6-*Dideoxy*-3-*dimethylamino*-2,5-*di*-O-*methyl*-L-*altrofuranoside.*—A solution of methyl 3-*O*-methanesulphonyl-2,5-di-*O*-methyl-α-L-rhamnofuranoside [8] (1·5 g.) in 33% ethanolic dimethylamine (20 ml.) was heated at 180—185° in a sealed tube for 24 hr. The mixture was evaporated and a solution of the residue in chloroform was extracted thrice with water (total volume 210 ml.). The dried ($MgSO_4$) chloroform solution was concentrated, and a solution of the residue in 0·1N-hydrochloric acid was extracted thrice with chloroform (total volume 200 ml.). The aqueous solution was then basified with 30% aqueous sodium hydroxide and extracted five times with chloroform (total volume 300 ml.). The last chloroform extracts were combined, washed with water, dried ($MgSO_4$), and evaporated, and the residue was distilled, yielding the *product*, (0·62 g., 50%) b. p. 65—68°/0·5 mm., $[\alpha]_D^{20}$ −85° (*c* 1·5 in H_2O), $[M]_D$ +198° (Found: C, 56·9; H, 10·2; N, 6·2. $C_{11}H_{23}NO_4$ requires C, 56·7; H, 9·9; N, 6·0%). The *methiodide* had m. p. 134—135° (from acetone–ether) (Found: C, 38·4; H, 7·0; N, 4·0; I, 33·55. $C_{12}H_{26}INO_4$ requires C, 38·4; H, 6·9; N, 3·7; I, 33·9%).

3,6-*Dideoxy*-3-*dimethylamino*-2,5-*di*-O-*methyl*-L-*altritol.*—A solution of the foregoing glycoside (1 g.) in 6N-hydrochloric acid (25 ml.) was boiled under reflux for 4 hr. and then evaporated at *ca.* 40°/~12 mm. A solution of the residue in water (10 ml.) was added dropwise to a solution of sodium borohydride (0·7 g.) in water (20 ml.). After 5 hr. the excess of reductant was destroyed by adjusting the pH to 6·5—7 with acetic acid, and the solution was basified with 30% aqueous sodium hydroxide and continuously extracted with chloroform for 12 hr. The extract was washed with water, dried ($MgSO_4$), and concentrated, and the residue distilled to yield the *alcohol* (0·7 g., 75%), b. p. 90—92°/0·3 mm., $[\alpha]_D$ +44° (*c* 1·9 in H_2O), $[M]_D$ +97° (Found: C, 54·0; H, 10·5; N, 6·3. $C_{10}H_{23}NO_4$ requires C, 54·3; H, 10·4; N, 6·3%). The methiodide was not obtained crystalline.

3,6-*Dideoxy*-3-*dimethylamino*-1,2,4,5-*tetra*-O-*methyl*-L-*altritol.*—A solution of 3,6-dideoxy-3-dimethylamino-2,5-di-*O*-methyl-L-altritol (1·8 g.) in acetone (25 ml.) was stirred vigorously in the presence of powdered sodium hydroxide (5·4 g.). The temperature was maintained at 45—48° whilst dimethyl sulphate (6·5 ml.) was added during 30 min., and was then raised to 55—60° during 30 min. and kept thereat for 3 hr. The cooled mixture was poured into water and extracted several times with chloroform. The combined extracts were evaporated, and a solution of the residue in 2N-hydrochloric acid was extracted with chloroform. The aqueous solution was then basified with sodium hydroxide and extracted several times with chloroform, and the combined extracts were washed with water, dried ($MgSO_4$), and evaporated. Distillation of the residue gave the *product* (0·95 g., 46%), b. p. 60—61°/0·2 mm., $[\alpha]_{5461}^{22}$ +4·6° (*c* 1·7 in $CHCl_3$), $[M]_{5461}$ +11° (Found: C, 57·4; H, 10·8; N, 5·5. $C_{12}H_{27}NO_4$ requires C, 57·8; H, 10·9; N, 5·6%). The *methiodide* had m. p. 179—180° (from acetone–ether) (Found: C, 39·6; H, 7·9; N, 3·8. $C_{13}H_{30}INO_4$ requires C, 39·9; H, 7·7; N, 3·6%).

[17] Partridge, *Nature*, 1949, **164**, 443.
[18] Foster, *Chem. and Ind.*, 1952, 1050.
[19] Foster, *J.*, 1953, 982.

By essentially the above method mycaminitol hydrochloride [3] (0·27 g.; m. p. 136—137°) was converted into 1,2,4,5-*tetra*-O-*methylmycaminitol* (0·18 g.), b. p. 62—70°/0·2 mm., $[\alpha]_{5461}^{22}$ −0·3° (*c* 1·9 in $CHCl_3$), $[M]_{5461}$ −0·7° (Found: C, 57·2; H, 10·5; N, 6·25. $C_{12}H_{27}NO_4$ requires C, 57·8; H, 10·9; N, 5·6%). The methiodide was not obtained crystalline.

Boron Trichloride Experiments.—(*a*) A solution of 3,6-dideoxy-3-dimethylamino-2,5-di-*O*-methyl-L-altritol (1·2 g.) in dichloromethane (5 ml.) was treated with boron trichloride (25 ml.) at *ca.* −70° for 30 min. The excess of reagent and the solvent were removed at 40°/~12 mm. and the residue was heated at 50—60° for 30 min. Methanol (20 ml.) was slowly added and the mixture was evaporated at 40°/~12 mm. Methanol was twice more distilled from the residue. The boron trichloride treatment was twice repeated and an aqueous solution of the final product was freed from anions by Amberlite IRA-400 (HO^- form), then evaporated, and the residue was distilled. Incompletely demethylated material was obtained at b. p. 90—110°/0·1 mm., followed by 3,6-*dideoxy*-3-*dimethylamino*-L-*altritol* (0·45 g., 43%), b. p. 156—162°/0·1 mm., $[\alpha]_D^{20}$ ±0° (*c* 0·7 in H_2O) (Found: C, 49·95; H, 9·8; N, 7·15. $C_8H_{19}NO_4$ requires C, 49·7; H, 9·8; N, 7·25%). The hydrochloride was not obtained crystalline but had $[\alpha]_D^{20}$ +13° (*c* 0·8 in H_2O), $[M]_D$ +25°, and an R_F value slightly lower than that of mycaminitol hydrochloride.

(*b*) When 3,6-dideoxy-3-dimethylamino-2,5-di-*O*-methyl-L-altrose hydrochloride (obtained by hydrolysis of methyl 3,6-dideoxy-2,5-di-*O*-methyl-α-L-altrofuranoside with boiling 6N-hydrochloric acid for 4 hr., followed by evaporation at 40°/~12 mm.) was treated once with boron trichloride as in (*a*), and the product examined by paper chromatography, detection with aniline hydrogen phthalate [17] showed unchanged di-*O*-methyl compound (R_{Rh} 1·30) with an approximately equal amount of mono-*O*-methyl (R_{Rh} 0·96) and a small amount of demethylated product (R_{Rh} 0·67). After the fourth and subsequent boron trichloride treatments the composition of the product mixture was not changed further and by visual inspection of the chromatograms appeared to contain the mono-*O*-methyl and demethylated products in an approximate ratio of 2 : 1.

Mycaminitol Hydrochloride.—A solution of mycaminose hydrochloride [4] {2·6 g.; m. p. 117—118°, $[\alpha]_D$ +30·5° (*c* 3·4 in H_2O)} in water (20 ml.) was added dropwise to a solution of sodium borohydride (2 g.) in water (10 ml.). After 6 hr. at room temperature the mixture was acidified with acetic acid, and cations were absorbed on Amberlite IR-120 (H^+ form). Elution of the resin with N-ammonia gave mycaminitol in the first fractions, which were concentrated. Dissolution of the residue in propan-2-ol containing a slight excess of concentrated hydrochloric acid afforded the hydrochloride (2·1 g., 81%), m. p. 135°, $[\alpha]_D$ +9° (*c* 0·9 in H_2O). Paul and Tchelitcheff [3] record m. p. 134°, $[\alpha]_D$ +8° (in H_2O), for the compound prepared by catalytic reduction of mycaminose over Raney nickel.

Methyl 2,5-*Di*-O-*benzyl*-3-*toluene*-p-*sulphonyl*-α-L-*rhamnofuranoside.*—A vigorously stirred solution of 3,4-*O*-isopropylidene-L-rhamnose diethyl dithioacetal [8] (4·5 g.) in xylene (50 mg.) containing suspended finely powdered potassium hydroxide (36 g.) was kept at 70—80° and treated dropwise with a solution of benzyl bromide (35 ml.) in xylene (50 ml.). The temperature was then raised to 95—100° and maintained thereat for 3 hr. The cooled mixture was poured into water (300 ml.) and steam-distilled under diminished pressure till all volatile material had been removed. The remaining aqueous solution was extracted with chloroform, the extract was dried ($MgSO_4$) and concentrated, and the residue distilled, to yield crude 2,5-di-*O*-benzyl-3,4-*O*-isopropylidene-L-rhamnose diethyl dithioacetal (6·0 g., 88%), b. p. 210—220°/0·2 mm., as a yellow oil. Slight decomposition occurred during distillations and the once distilled product was used for the next reaction.

A solution of the foregoing product (40 g.) in dry methanol (550 ml.) containing mercuric chloride (65 g.) was boiled under reflux for 4 hr. The cooled mixture was filtered, the filtrate was concentrated, and the residue was shaken with 10% aqueous sodium carbonate. The filtered mixture was extracted several times with chloroform, and the combined extracts were washed with water, dried ($MgSO_4$), and concentrated, and the residue distilled, to yield crude methyl 2,5-di-*O*-benzyl-α-L-rhamnofuranoside (15 g., 47%), b. p. 188—194°/0·1 mm. Slight decomposition occurred during distillations. Treatment of the product in the usual way with pyridine and toluene-*p*-sulphonyl chloride gave the 3-*toluene*-p-*sulphonate* (60%), m. p. 65°, $[\alpha]_D$ −45° (*c* 1·6 in $CHCl_3$), $[M]_D$ −230° (Found: C, 65·6; H, 6·4; S, 6·3. $C_{28}H_{32}O_7S$ requires C, 65·6; H, 6·25; S, 6·25%).

Methyl 2,5-*Di*-O-*benzyl*-3,6-*dideoxy*-3-*dimethylamino*-α-L-*altrofuranoside and its Acidic Hydrolysis.*—A solution of the foregoing toluene-*p*-sulphonate (0·8 g.) in 33% ethanolic

dimethylamine (30 ml.) was heated in a sealed tube at 180—185° for 24 hr.; the *product* (0·42 g., 70%), isolated as for the 2,5-di-*O*-methyl analogue, had b. p. 160—165°/0·1 mm., $[\alpha]_D^{20}$ −39° (*c* 0·8 in MeOH), $[M]_D$ −150° (Found: C, 72·6; H, 7·8. $C_{23}H_{31}NO_4$ requires C, 71·7; H, 8·05%).

Hydrolysis of the product with 6N-hydrochloric acid at *ca.* 100° for 6 hr. and evaporation of the solution gave 3,6-dideoxy-3-dimethylamino-L-altrose hydrochloride, $[\alpha]_D$ *ca.* +17° (*c* 0·6 in H_2O), which failed to crystallize. In paper chromatography the altrose derivative had a slightly higher R_F value, a more rapid response to aniline hydrogen phthalate,[17] and a weaker reaction to ammoniacal silver nitrate [1] than did mycaminose hydrochloride. In preparing the paper chromatograms, it was necessary to use a solution of the dimethylamino-sugar in dilute hydrochloric acid. Without this precaution crystalline mycaminose hydrochloride and the synthetic amino-sugar each gave double spots.

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