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SYNTHESIS OF 2-DEOXYSTREPTAMINE

M.Nakajima, A.Hasegawa, and N.Kurihara

Department of Agricultural Chemistry, College of Agriculture

Kyoto University, Kyoto, Japan

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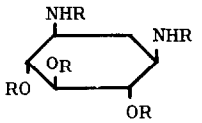
2-DEOXYSTREPTAMINE (2-deoxy-myo-inosadiamine-1,3*) (I) has been obtained from hydrolytic products of such antibiotics as kanamycins[1], neomycins[2], and paromomycins[3](zygomycins) and its N-methyl derivative also has been found in hygromycin B[4].

The configuration has been established as shown in the figure (I)[2,5]. Though some ambiguities[6] were pointed, studies[6,7] on NMR spectra of its derivatives have supported the conclusion.



I R = H
II R = Ac

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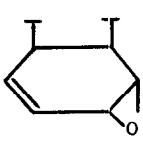
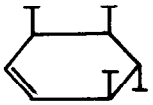
* In this paper, cyclitols are named and numbered according to the method proposed by H.G.Fletcher, Jr., L.Anderson, and H.A. Lardy, J.Org.Chem., 16, 1238 (1951). But, for tetrahydroxy-cyclohexenes and their derivatives, the conventional "fractional" system (cf. the above reference) was used together with the other conventional "conduritol" system. (cf. G.E.McCasland, and E.C. Horswill, J.Am.Chem.Soc., 75, 4020 (1953).)

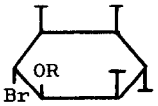
The authors synthesized I via a stereoselective route, and confirmed the configuration synthetically.



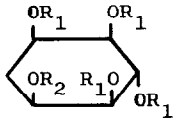
III⁻⁻



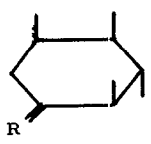
IV⁺



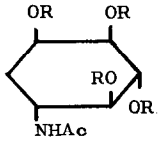
V⁺ R = H
VI R = Ac



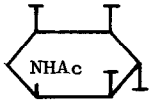
VII⁺ R_1= Ac, R_2= H
VIII R_1= R_2= Ac
IX R_1= R_2= H



X⁺ R = O
XI⁺ R = NOH



XII⁺ R = Ac
XIII⁺ R = H



XIV⁺

T = OAc
I = OH

\+ Racemic; only an arbitrarily chosen enantiomorph shown.

An isomer of tetraacetoxycyclohexene (rac-1,2,4/3*), i.e. tetra-O-acetylconduritol-F (IV)[8] was obtained in 72 % yield by hydrolysis and subsequent acetylation of the crystalline diacetate (III) of 1,2-anhydro-rac-1,2/3,4-tetrahydroxy-cyclohexene, i.e. 1,2-anhydroconduritol-E[9]. IV was mixed with bromine-water to give a tetra-O-acetyl-monobromodeoxyinositol (V) of m.p.168-9° in 65 % yield (Anal. Calcd. for $C_{14}H_{19}O_9Br$: C 40.89 H 4.66; Found: C 40.91 H 4.54).

Acetylation of V gave VI, identified with the authentic pentaacetate (VI)[10] of 3-bromo-3-deoxy-muco-inositol. Isolation of only one isomer in a high yield is explained by preferential diaxial addition.[11] Hydrogenolysis of V with Raney nickel W-2 gave a tetra-O-acetyl-monodeoxyinositol (VII) of m.p.161° in 82 % yield (Anal. Calcd. for $C_{14}H_{20}O_9$: C 50.60 H 6.07; Found: C 50.55 H 6.20). Acetylation gave VIII, identified with the authentic pentaacetate (VIII) of 3-deoxy-epi-inositol (IX).[10]

Ammonolysis gave free IX of m.p.95° quantitatively. Catalytic oxidation[12] of IX with oxygen in the presence of a platinum black gave a crystalline residue which should contain the ketone X resulted by oxidation of one of the two axial hydroxyl groups. The formation of the diketone has been empirically negligible.[12] Without further purification, hydroxylamine solution was added and the whole solution kept for 20 h. at room temperature. Oxime (XI), without isolation, was subjected to sodium amalgam reduction at pH 6 to 6.5 (with acetic acid). Removal of mercury, evaporation of water, acidification with conc.HCl with cooling, filtration of NaCl, removal of water and HCl, and acetylation of the residue gave XII of m.p.156° in 30 % yield. (Anal.Calcd. for $C_{16}H_{23}NO_9$: C 51.47 H 6.21 N 3.75; Found: C 51.41 H 6.25 N 3.79)

Another isomer (XIV) (m.p.201°) was also isolated in 6 % yield. (Anal. Calcd. for $C_{16}H_{23}NO_9$: C 51.47 H 6.21 N 3.75; Found: C 51.36 H 6.44 N 4.18). But no diaminocyclitol derivative was isolated in this stage. NMR examination established the each configuration (cf. ref.7) as shown in Table I.

TABLE I

Delta-value (ppm) of Acetyl Protons
(int.ref. Me_4Si)
(In parentheses are proton numbers)

XII 2.19 (3) (one axial OAc)
2.06 (3), 2.02 (3), 1.99 (3) (three equatorial OAc's)
1.91 (3) (one equatorial NHAc)

XIV 2.18 (3) (one axial OAc)
2.06 (3) (one equatorial OAc)
2.00 (9) (two equatorial OAc's and one axial NHAc)

Sodium amalgam reduction of a cyclitol keto-oxime has generally been giving the equatorial amine in higer yield than the axial one.[13] The present result coincides with this empirical rule. Ammonolysis of XII in absolute methanol at room temperature gave N-acetate XIII in 95 % yield (m.p.230°). XIII has one axial hydroxyl group left adjacent to the methylene.

Catalytic oxidation of XIII with oxygen and a platinum black was carried out. Oxime formation, sodium amalgam reduction, and acetylation followed in a similar way as described above. The resulted syrup was crystallized by adding ethanol, giving penta-O-acetyl-2-deoxystreptamine (II) in 49 % yield (m.p. over 270°). (Anal. Calcd. for $C_{16}H_{24}N_2O_8$: C 51.60 H 6.50; Found: C 51.39 H 6.63). It showed an infrared and an NMR spectrum identical with those of an authentic sample obtained from kanamycin monosulfate (6 n HCl hydrolysis and acetylation, cf. ref.1). Hydrolysis of II with 4 n HCl gave the dihydrochloride of I,

which was passed through a column of an anion exchanger to give the free base (I) of m.p.223°(dec.). Other derivatives were also prepared. Di-N,N'-carbobenzoxy-triol: m.p.240°(dec.) (Anal. Calcd. for $C_{22}H_{26}N_2O_7$: C 61.38 H 6.09 N 6.51; Found: C 61.56 H 6.22 N 6.30). Di-N,N'-carbobenzoxy-tri-O-acetate: m.p.197° (Anal. Calcd. for $C_{28}H_{32}N_2O_{10}$: C 60.42 H 5.80 N 5.03; Found: 60.39 H 5.76 N 5.18). Tri-O-acetyl dihydrochloride: m.p. over 250° (Anal. Calcd. for $C_{12}H_{22}N_2O_6Cl_2$: C 39.90 H 6.14 N 7.76; Found: C 39.87 H 6.14 N 7.96).

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13. cf. S.J.Angyal, and L.Anderson, Adv.in Carbohydr.Chem., 14, 135 (1959).