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SYNTHESIS OF THREE STEREOISOMERS OF 2-DEOXYSTREPTAMINE

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Prompted by recent reports (1) on the synthesis of the antibiotics component, 2-deoxystreptamine (I, all-trans-1, 3-diamino-4, 5, 6-trihydroxycyclohexane), and of related diaminocyclitols we wish to communicate that catalytic hydrogenation of 4, 6-dinitropyrogallol (2) has furnished three stereoisomers of I, to which the configurational formulas II, III, and IV are tentatively assigned. In addition, products of hydrogenolysis were formed, two of which were found to be 1, 3-diamino-4, 6-dihydrocyclohexanes (V, VI). No 2-deoxystreptamine appeared to be produced.

Hydrogenation of 4, 6-dinitropyrogallol proceeded best with platinum in 50% aqueous acetic acid at 25° and atmospheric pressure. Similar results were obtained in 0.2 N sulfuric acid, whereas in 0.33 N hydrochloric acid the relative amount of split products (V, VI and others) was increased. Palladium catalysts proved unsuitable in the present case although on some previous occasions (3) palladium-catalysed reductions of aromatic compounds to the inositol stage have been successful.

Mixtures of II - VI were obtained in yields of 30 - 45% of the theory. Fractionation by multiple ion exchange chromatography on Dowex-50(H^+), Dowex-1-X2(OH^-) and Dowex-1-X2(borate form) gave uniform fractions, in yields of 2 - 8%, of crystalline dihydrochlorides of II - VI. These were characterized by their x-ray powder diagrams, NMR spectra, and paper chromatographic mobilities relative to I-dihydrochloride (R_{ds} - values). The R_{ds} - values on borax paper irrigated with n-butanol-ethanol-0.95% $Na_2B_4O_7$ in water (1:1:1, v/v) were 0.74 (II), 0.80 (III), 0.96 (IV), 1.15 (V), and 1.35 (VI).

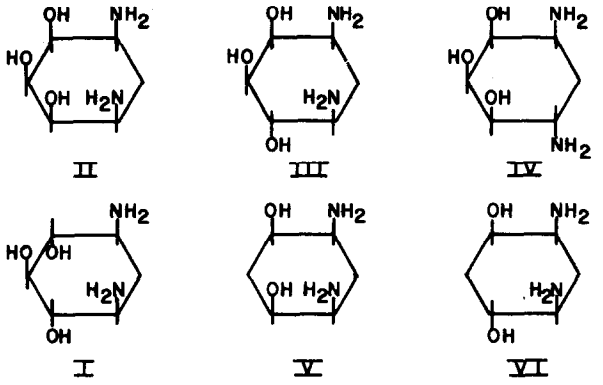
The NMR spectra of the dihydrochlorides of II, III, and IV were taken in deuterium oxide. Although the signals for most of the ring protons were not resolved well enough to permit interpretation, the signal that appeared at lowest field in each of the three spectra was a clear triplet. These triplets were assigned to hydrogens at C-4 and (or) C-6 since deshielding exerted by the neighboring, positively charged nitrogen was expected to cause a downfield shift (4). In II-dihydrochloride the triplet (5.67 τ)

had an intensity corresponding to two protons, whereas in III-dihydrochloride (5.76 τ) and in IV-dihydrochloride (5.79 τ) the intensities corresponded to one proton. This implied that in II the hydrogens at C-4 and C-6 had equal, and in III and IV unequal, chemical shifts and that consequently II should be a symmetrical molecule whereas III and IV must be (racemates of) unsymmetrical molecules. The splittings observed in the triplets were 2.6, 2.5, and 3.0 c.p.s. respectively, indicating the absence of di-axial arrangements among the protons that caused these splittings.

The pentaacetate of II exhibited substituent resonances at 7.73 τ (6 H), 7.94 τ (3 H), and 8.00 τ (6 H) which were assigned to two axial acetoxy groups, one equatorial acetoxy group, and two equatorial acetamido groups (5). The pentaacetate of III in deuterochloroform gave five acetyl signals of equal intensities at 7.83, 7.93, 7.95, 8.04 and 8.07 τ, which indicated one axial and two equatorial acetoxy groups, plus two acetamido groups, of which one was equatorial and the other probably equatorial but possibly axial. The pentaacetate of IV gave signals (5) at 7.70 τ (3 H), 7.87 τ (6 H), 7.93 τ (3 H), and 7.96 τ (3 H), likewise suggesting one axial and two equatorial acetoxy groups and at least one equatorial acetamido group.

The periodate oxidation rates at 3° of the N,N'-diacetates of II, III, and IV were compared under identical conditions with those of methyl α-D-mannopyranoside, which possesses a cis-trans triol grouping, and of methyl α-D-glucopyranoside and N,N'-diacetyl-2-deoxystreptamine, which possess trans-trans triol groupings. Consumption of the first mole of periodate in III-diacetate was about as fast as in the mannoside, while the II- and IV-diacetates reacted about twice as fast. The trans-trans triols were oxidized considerably more slowly. It therefore appeared reasonable to assume a cis-trans triol configuration in III, and cis-cis triol configurations in II and IV. Together with the NMR data this led to tentative configurational assignments for II, III, and IV as depicted in the formulas, although in III either amino group could possibly be inverted.

Upon N-acetylation the diols V and VI were stable against periodate, which proved their hydroxyl groups to be non-vicinal. The tetraacetate of V in deuterium oxide showed two NMR signals of equal intensities at 7.80 and 7.96 τ attributable to two axial acetoxy and two equatorial acetamido groups (5). The tetraacetate of VI in deuterochloroform gave signals at 7.83 τ (3 H), 7.96 τ (3 H), and 8.03 τ (6 H) which were assigned to one axial and one equatorial acetoxy group and 2 equatorial acetamido groups.



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5. The spectrum was measured in deuterium oxide because of poor solubility of the compound in deuterochloroform. In the latter solvent these substituent resonances appear approximately 0.06 p.p.m. to higher field than in the former. A similar though slightly smaller solvent effect has recently been reported by F. W. Lichtenthaler and H. P. Albrecht, Ber. 99, 575 (1966), and F. W. Lichtenthaler and H. Leinert, Ber. 99, 903 (1966), who also give references to some of the previous literature concerning configurational assignments based on acetoxy and acetamido resonances in the cyclitol series.