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THE STEREOCHEMISTRY AND SYNTHESIS OF FOROSAMINE: A DEOXY-AMINO SUGAR MOIETY OF THE SPIRAMYCIN ANTIBIOTICS

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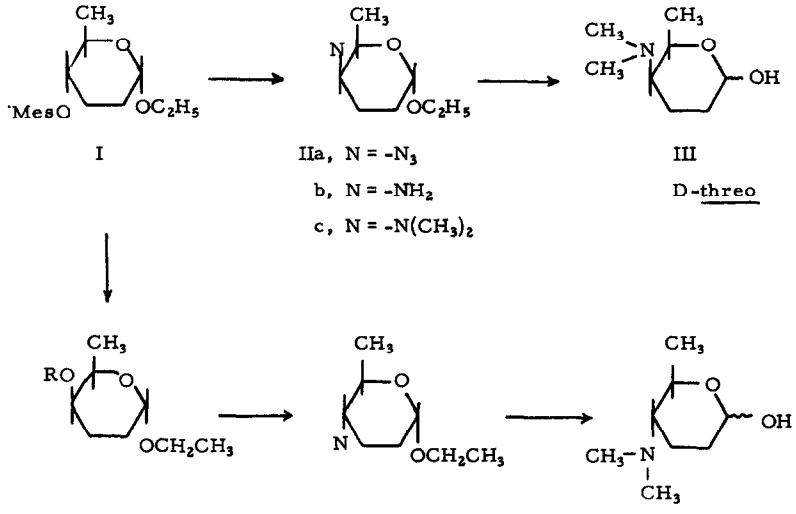
Recent experimental evidence[1] has led to the revision of structures representing the spiramycin antibiotics (foromacidines), isolated from Streptomyces.[2,3] Earlier studies[4] of the spiramycins A, B, and C had established that each member of this family of macrolide antibiotics yielded, in addition to other fragments, a basic fragment, forosamine, (VI) upon vigorous acid hydrolysis. The gross structure of this fragment has been established.[4] We now wish to report the synthesis and determination of the stereochemistry of forosamine.

The structure of forosamine[4] afforded four stereochemical possibilities: the D-threo (III), D-erythro (VI), and their corresponding L-enantiomers. Comparison of the rotations of 2,3,6-trideoxy-D-erythro and threo-aldohexose[5] (4-hydroxy analogs of forosamine) with that of forosamine indicated perhaps a D-erythro configuration for that natural product. However, the uncertainties associated with extending such an analogy warranted the synthesis of both diastereomers (D series) of the forosamine gross structure.

The synthetic route to both aminosugars started from the known



ethyl 2,3,6-trideoxy-4-O-methanesulfonyl-α-D-erythro-hexopyranoside (I), obtained in seven steps from α,β-D-glucose pentaacetate by a modification of the procedure of Foster, et al.[6] Entry into the threo series was accomplished by inversion at C4 with azide ion in refluxing DMF affording the 4-azido compound IIa in 84 % yield; $n_D^{25.5^\circ} = 1.4590$; $[\alpha]_D^{24} = +52.9^\circ$ (c, 1.9 in CH_3OH). Reduction of IIa with sodium borohydride in 2-propanol yielded 85% of the 4-amino derivative (IIb), most easily isolated and handled as its p-toluenesulfonate salt, m.p. 147°; $[\alpha]_D^{26^\circ} = +81.0^\circ$ (c, 1.1 in CH_3OH). Reductive dimethylation of the tosylate salt of IIb cleanly afforded the tosylate salt of IIc, m.p. 128-9°.

$[\alpha]_D^{26^\circ} = +53.0^\circ$ (c, 0.9 in CH_3OH).

Acidic hydrolysis (sulfuric acid, pH4, 80°) of this tosyl salt gave the threo product III in 55-60% yield as a heavy, colorless syrup after distillation in vacuo (60°/0.01 mm.); $[\alpha]_D^{26^\circ} = -2.46^\circ$ (c, 1.1 in CH_3OH); -31.2° (c, 1.10 in H_2O).* The picrate and methiodide derivatives of III had m.p. 171-172°; $[\alpha]_D^{27^\circ} = -1.4^\circ$ (c, 1.0 in CH_3OH) and m.p. 162-163°, $[\alpha]_D^{27^\circ} = +3.67^\circ$ (c, 1.0 in CH_3OH) respectively. These physical constants were widely different from those reported for the natural product's derivatives,[4] thereby eliminating the D- and L-threo isomers as stereochemical possibilities.

The erythro amines were prepared in the following way. Treatment of I with acetate ion in dimethylsulfoxide afforded acetate IVa as a liquid which could be purified to a satisfactory extent by low temperature crystallization. With only cursory characterization IVa was saponified to the known[5,6] IVb and tosylated at room temperature in pyridine to give the crystalline threo tosylate IVc, m.p. 79-80.5°, $[\alpha]_D^{25}$ +63.7° (c, 1.1 in $CHCl_3$). The yield of IVc from I was 30%. The nmr of IVc showed the C1 proton as an unresolved multiplet (half-width 5 cps) at δ 4.82 and the equatorial C4 proton as another unresolved multiplet (half-width 6 cps) at δ 4.50. When contrasted with the spectrum of erythro mesylate I (C4 proton (axial) moved upfield to δ 4.25), the spectrum of IVc was

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* Interestingly, III exhibited significant aldehyde carbonyl absorption (1725 cm^{-1}) in its infrared spectrum indicative of the open chain form of III. This was confirmed by its nmr spectrum which revealed absorption at 9.5 (0.25 H) for an aldehyde hydrogen. By way of contrast, VI was devoid of carbonyl absorption in its infrared spectrum.

consistent with the threo configuration. Reaction of IVc with sodium azide in dimethylsulfoxide (125°) gave azide Va as an oil, infrared 2130 cm^{-1}, which was homogeneous by vpc* after alumina chromatography. Catalytic hydrogenation (platinum) of the purified Va gave amine Vb isolated and characterized as its tosylate salt, m.p. 131-2°, $[\alpha]_D^{25°}$ +76.2° (c, 1.0 in CH_3OH). The yield of Vb from IVc was 50%. Reductive dimethylation of Vb-tosylate gave Vc-tosylate as an extremely hygroscopic crystalline solid, m.p. 90-92°, $[\alpha]_D^{27°}$ + 92° (c, 0.75 in CH_3OH). Sulfuric acid hydrolysis of Vc gave VI as a crystalline solid (30 %) after distillation; m.p. 60°, $[\alpha]_D^{27°}$ + 88° (c, 1.1 in CH_3OH); +61° (c, 1.0 in H_2O); picrate, m.p. 160-1°; methiodide, m.p. 180-182°. Reported for natural VI,[4] m.p. 60° (after distillation); $[\alpha]_D$ +84° (c, 1.0 in CH_3OH); 62.6° (c, 1.0 in H_2O); picrate, m.p. 160°; methiodide, m.p. 182-3°. Thus, forosamine is identified as VI.

All new crystalline compounds gave satisfactory elemental analyses, as did VI.

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* A 3% carbowax-20M (on chromosorb W) column was used isothermally at 85°.

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