Sisomicin: Stereochemistry and Attachment of the Unsaturated Sugar Moiety

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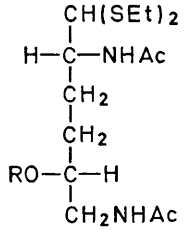
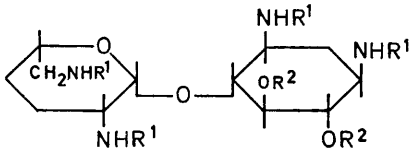
Summary Sisomicin has been shown to contain a 4-*O*-(2,6-diamino-2,3,4,6-tetradeoxy-α-D-*glycero*-hex-4-enopyranosyl)-2-deoxy-D-streptamine moiety.

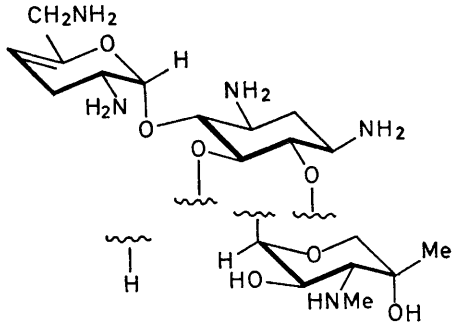
SISOMICIN, a new aminoglycoside antibiotic isolated from *Micromonospora inyoensis*[1] was recently assigned a gross tentative structure.[2] The following evidence permits assignment of the stereochemistry and point of attachment of the unsaturated sugar moiety in sisomicin.



(2) R = H
(3) R = Ac



(4) $R^1 = R^2 = H$
(5) $R^1 = R^2 = Ac$
(6) $R^1 = Ac$, $R^2 = H$



(7)
(1) when no Δ^4

Catalytic hydrogenation of sisomicin afforded dihydrosisomicin (**1**) [dihydro (**7**)], isomeric with gentamicin C_{1a},[3,5] as the major product. Compound (**1**) was isolated as a resin, $[\alpha]_D^{26}$ +145° (H_2O), *M* + 1 450, *m/e* 129 (100%) (diaminotetradeoxy hexose moiety), and 160 (83%) (garosamine moiety[4]). The n.m.r. (D_2O; 60 MHz) spectrum showed doublets at δ 5·10 (*J* 4·0 Hz) and 4·78 p.p.m. (*J* 1·7 Hz) for two anomeric protons; there was no vinyl proton signal as there was for the starting material. In comparison, gentamicin C_{1a} shows two anomeric proton doublets at δ 5·20 (*J* 4·0 Hz) and 5·08 p.p.m. (*J* 4·3 Hz)[5] while those for sisomicin are at δ 5·35 (*J* 2·0 Hz) and 5·04 p.p.m. (*J* 4·0 Hz).[2] The doublet near δ 5·1 p.p.m. is ascribed to the garosamine anomeric proton in the three compounds. The chemical shifts and coupling constants of the other anomeric protons provide evidence that in the second sugar moiety these and the adjacent protons are *cis*-oriented (*ax–eq* coupling), and that upon hydrogenation an inversion of the sugar ring has taken place, affording an axial anomeric proton in the dihydro-compound *vs.* equatorial anomeric protons in sisomicin and in gentamicin C_{1a}. The inversion is explained by an excessive 1,3-diaxial interaction in the hydrogenated product.

Acetylation of dihydrosisomicin (**1**) in methanol afforded the penta-*N*-acetyl derivative, m.p. 192—200°, $[\alpha]_D^{26}$ +98° (EtOH), which on treatment with EtSH–HCl followed by re-*N*-acetylation and chromatography gave the diethyl dithioacetal (**2**) of 2,6-diacetamido-2,3,4,6-tetradeoxy-L-*threo*-hexose, m.p. 81—84°; $[\alpha]_D^{26}$ +32° (MeOH). The n.m.r. spectrum of (**2**) in [$^2H_5$]pyridine supported the assigned structure. The stereochemistry was established by comparison (chromatography and n.m.r. spectrum) with an authentic sample of the D-*threo*-enantiomer,[6] $[\alpha]_D^{26}$ −30° (MeOH).† Acetylation of (**2**) gave the *NN'O*-triacetyl

† We thank Dr. Guthrie for a sample of authentic D-*threo* compound.

derivative (**3**) as a syrup, $[\alpha]_D$ +21·6 (MeOH) [the D-*threo* enantiomer[6] had $[\alpha]_D^{26}$ −19° (MeOH)].

In order to determine the position of attachment of the diamino-sugar to the deoxystreptamine moiety, dihydrosisomicin was treated with methanol to yield the pseudodisaccharide (**4**) which was characterized as the tetrahydrochloride monohydrate, m.p. 270—275° (decomp.), $[\alpha]_D^{26}$ +24·5° (H_2O). The compound was converted into the base, $[\alpha]_D^{26}$ +31° (H_2O), with IR-45 anion exchange resin and acetylated in pyridine to the hexa-acetate (**5**), which crystallized as a monohydrate acetone solvate, m.p. 161—164°; $[\alpha]_D^{26}$ +8° (H_2O). Saponification of (**5**) with sodium in methanol afforded the tetra-*N*-acetate (**6**), m.p. 250—260° (decomp.).

The cuprammonium complex c.d. curve (in Cupra A solution) of compound (**6**)‡ showed a *positive* Cotton effect at about 575 nm, demonstrating the vicinal nature as well as the negative dihedral angle (*k* conformation of the chelate) of the hydroxy-groups.[7] This result permits the assignment of the absolute stereochemistry of (**6**) as a 4-*O*-substituted-2-deoxy-D-streptamine derivative.

On the basis of the above data, structure (**7**), *O*-2,6-diamino-2,3,4,6-tetradeoxy-α-D-*glycero*-hex-4-enopyranosyl-(1 → 4)-*O*-[3-deoxy-4-*C*-methyl-3-methylamino-β-L-*arabino*-pyranosyl-(1 → 5) *or* (1 → 6)]-2-deoxy-D-streptamine, is assigned to sisomicin, with the only remaining point of uncertainty being the point of attachment (C-5 or C-6) of garosamine on the deoxystreptamine ring.

We thank Dr. M. Yudis and staff for the physical measurements.

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