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THE CRYSTAL AND MOLECULAR STRUCTURE OF STREPTOMYCIN OXIME SELENATE

S. Neidle, D. Rogers, M.B. Hursthouse*

Chemical Crystallography Laboratory,

Imperial College, London, S.W.7.

(*Now at Chemistry Department, Queen Mary College, London, E.1.)

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Extensive chemical work (1) has shown that streptomycin contains three fragments, N-methyl-L-glucosamine, L-streptose, and streptidine, linked together as in I. The absolute configuration of each fragment was derived by chemical and optical correlations (2). There has been some dispute about the nature of the glycosidic link between the streptose and streptidine rings. The original (1947) assignment was α-L-(2b) (3) based on rotational arguments on polyacetyl derivatives. This was reversed in 1954 (4) to β-L, thus making the two glycosidic links in I cis, but recent chemical and n.m.r. evidence (2,5) agrees with the original α-L assignment. An X-ray study of the structure of streptomycin oxime selenate has confirmed all the configurational details (relative and absolute) of structure I. In particular it has vindicated the original trans assignment of the ether linkages, and has incidentally validated the three independent correlation routes (with all their consequential implications) by which the absolute configurations of the three rings were deduced. It has also confirmed that the L-streptose fragment, which has never been isolated as a degradation product, is 5-deoxy-3-C-formyl-L-lyxose.

N.m.r. spectra of streptomycin and its salts show no sign of a free aldehyde group in solution (5,6), and it is characteristic in our experience that all derivatives of streptomycin (both α- and β- (7)) are exceptionally poorly crystalline unless the aldehyde group has been altered, as in dihydrostreptomycin, various Schiff's bases or the oxime. Aronson et al (6) have sought to explain the n.m.r. observations in terms of a link between the aldehyde and N-Me groups, but a link with a guanyl group might also be possible. Their explanation takes no cognisance of similar n.m.r. observations for the β-streptomycin salts (5).

Though it is unable to elucidate these latter points, the oxime selenate was studied as it was the first, suitable, well-crystalline derivative to become available. $C_{21}H_{40}N_8O_{12}[1\frac{1}{2}H_2SeO_4]$, $4H_2O$ crystallizes from aqueous methanol as monoclinic needles, space group C2, a = 17.10, b = 14.36, c = 16.13Å, β = 108°, D_m = 1.54 g.cm^{-3}, D_c = 1.55 g.cm^{-3} for 4 formula units per cell. 3236 independent reflections were recorded photographically with CuKα radiation, and their intensities measured visually. The elucidation of the structure following standard heavy-atom procedures has been slow, but relatively straightforward. R now stands at 0.121, but refinement continues. The absolute configuration of the molecule (shown in the figure) was deduced from the anomalous scattering of CuKα radiation by the selenium atoms (8): 26 Bijvoet pairs confirmed the earlier assignment. The crystal structure is held together by an elaborate system of hydrogen-bonding and ionic forces in which the water molecules and the selenate ions figure prominently. These numerous interactions are no doubt responsible for making the rather ill-disciplined streptomycin molecule form this crystalline derivative.

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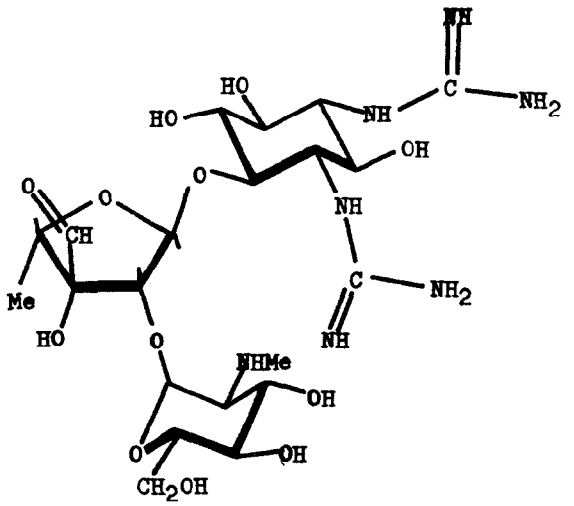

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