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METHYL SIBIROSAMINIDE, A NOVEL BRANCHED-CHAIN AMINOHEXOPYRANOSIDE FROM THE ANTIBIOTIC SIBIROMYCIN.

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Sibiromycin, an antitumor antibiotic possessing pronounced activity against a number of transplantable tumors of animals, has been isolated from the culture filtrate of actinomycete Streptosporangium sibiricum /I,2/.

Methanolysis of sibiromycin in refluxing 9% methanolic HCl afforded a mixture of the anomeric methyl glycosides of an aminomonosaccharide, named sibirosamine. Methyl sibirosaminides were isolated from methanolysis mixture neutralized with Dowex Ix2 (HCO_3^-) by chromatography on Dowex 50x8 (NH_4^+) with Iν NH_4OH used as an eluent. An oily product obtained after evaporation of the solvent in vacuo below 35° was applied to a column of silica gel. Both anomers of methyl sibirosaminide were readily separated by the use of the solvent system benzene-acetone(I:I). One anomer accounting for 90% of the mixture was obtained as a crystalline hydrochloride, m.p. I84-I87°, $[\alpha]_D^{20}$ -50° (2%,water). The second anomer was obtained as an amorphous hydrochloride, m.p. I78-I79°, $[\alpha]_D^{20}$ +75° (I%,water). On the basis of elemental analysis and molecular weight determination (mass-spectrometry) molecular formula of methyl sibirosaminide was calculated to be $C_9H_{19}NO_4$ (M^+ 205) /3/.

Acetylation of the laevorotary anomer of methyl sibirosaminide with acetic anhydride in methanol yields crystalline methyl N-acetyl-sibirosaminide, $C_{11}H_{21}NO_5$ (M^+ 247), m.p. 125-126°, $[\alpha]_D^{20}$ -121° (0.3%,methanol), ν_{max} ($CHCl_3$) 1635 (N-Ac) and 3450 (OH) cm^{-1}, δ 1.96 (3H singlet; N-$COCH_3$). Acetylation of the same anomer with acetic anhydride in pyridine affords crystalline N,O-diacetate, $C_{13}H_{23}NO_6$ (M^+ 289), m.p. 135-136°, $[\alpha]_D^{20}$ -70° (0.4%,methanol), ν_{max} ($CHCl_3$) 1635 (N-Ac), 1748 (O-Ac) and 3450 (OH) cm^{-1}, δ 2.15 (6H singlet; N,O-Ac). The additional acetylation of N,O-diacetate with acetic anhydride in triethylamine in the presence of 4-dimethylamino-pyridine /4/ affords crystalline N,O-triacetate, $C_{15}H_{25}NO_7$ (M^+ 331), m.p. 127-128°, $[\alpha]_D^{20}$ -25° (0.3%,methanol), ν_{max} ($CHCl_3$) 1635 and 1748 cm^{-1}, δ 1.95 , 2.05 and 2.26 (three 3H singlets).

Oxidation of methyl sibirosaminide with periodate resulted in the consumption of two moles of oxidant. Among the products of oxidation there were no volatile carbonyl compounds (negative reaction with the 2,4-dinitrophenylhydrazine), but there was found methylamine (isolated as the 3,5-dinitrobenzoate). Oxidation of N-acetyl-sibirosaminide resulted in the uptake of one mole of periodate; di- and triacetates consumed no periodate. These data show that in the molecule of methyl sibirosaminide there is the fragment -C(OH)-C(OH)-C(NRMe)-. The ready cleavage of the sugar from the parent antibiotic precludes the presence of an amino function at C-2, thus C-2 must carry a OH-substituent.

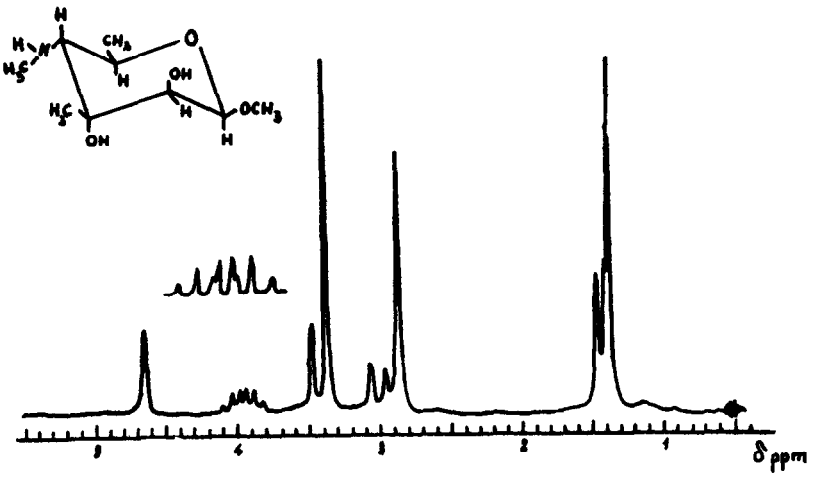

Figure I. ^{1}H nmr spectrum ($CDCl_3$; 100 MHz) of methyl 4-methylamino-4,6-dideoxy-3-C-methyl-β-D-altropyranoside.

The ^{1}H nmr spectrum of the glycoside hydrochloride with $[\alpha]_D^{20}$ -50° is presented in Figure I. Observed signals are as follows: 1.37 (3-CH_3,s); 1.41 (5-CH_3,d, $J_{CH_3,5}$ = 6.2 Hz); 2.86 (N-CH_3, s); 2.98 (H-4, d, $J_{4,5}$ = 10.0 Hz); 3.38 (O-CH_3, s); 3.45 (H-2, d, $J_{2,1}$ = 1.7 Hz); 3.94 (H-5, dq , $J_{5,4}$ =10.0 Hz; J_{5,CH_3} = 6.2 Hz); 4.65 (H-1, d, $J_{1,2}$ = 1.7 Hz). The splitting patterns and magnitudes of the coupling constants established the relative stereochemistry at C-4 and C-5. The large value of $J_{4,5}$ (10.0 Hz) requires H-4 and H-5 to be trans-diaxial. The dublets observed for H-2 and H-4 show that C-3 must be disubstituted, a fact confirmed by the uncoupled 3-CH_3 signal and by the formation of triacetate of methyl sibirosaminide.

The evidence for the absolute stereochemistry at C-5 and C-I was obtained from periodate oxidation of the sibirosaminide with $[\alpha]_D^{20}$-50°. We succeeded in isolating from the oxidation mixture the known D'-methoxy-D-methyldiglycolic aldehyde with $[\alpha]_D^{20}$ -89° (0.3%,water) /5/. This result proved that C-5 had "D" configuration and that the laevorotary methyl sibirosaminide is "β" anomer. The small value of the coupling constant $J_{I,2}$ (I.7 Hz) requires H-2 to be equatorial. The measurements of the change of the molecular rotation upon complexing in tetraaminecopper(II) sulfate solution /6/, specific for the adjacent NH and OH groups, gave the value $\Delta[M]_{436}$ =-3000°. The large negative rotational shift together with all above-mentioned considerations allow us to propose for the methyl sibirosaminide the structure and absolute stereochemistry of methyl 4-methylamino-4,6-dideoxy-3-C-methyl--β-D-altropyranoside.

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