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THE ISOLATION AND SYNTHESIS OF OSSAMINE, THE AMINOSUGAR FRAGMENT FROM THE FUNGAL METABOLITE OSSAMYCIN

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Treatment of ossamycin (1), a fungal metabolite, with refluxing 4 N hydrochloric acid in 30% ethanol-water liberated an aminosugar hydrochloride (23 mg from 100 mg of ossamycin). The aminosugar was isolated by extraction of an aqueous acid solution with chloroform and butanol. Several recrystallizations from abs ethanol-acetone gave pure material having the formula $C_8H_{18}ClNO_2$*: mp 145-147°; $[\alpha]_D$ + 3° (c 3.4, EtOH); nmr (D_2O) δ2.8, 2.9, 3.1 [-N(CH_3)$_2$, split due to anomers and the open chain form], δ1.1, 1.2 (C-5-CH_3 doublet), and ca. δ5.1 (broad poorly resolved multiplet, $W_{1/2}$ 17 cps, C-1-H.)

The aminosugar hydrochloride was converted into a monoacetate hydrochloride by treatment with acetic anhydride in pyridine. Distillation of the free base gave a compound analyzing for $C_{10}H_{19}NO_3$: mol wt 201 (mass spectrum); picrate, mp 161-165°.

On the basis of this evidence, it was concluded that the aminosugar fragment of ossamycin was a tetradeoxy 3- or 4-N,N-dimethylaminohexose. The only naturally occurring aminosugar in this category which had been described was isomycamine (2).** A sample of this sugar, kindly supplied by Dr. R. Paul, gave a monoacetate picrate with mp 124-6°; quite different from the unknown N,N-dimethylaminosugar. At this juncture it was shown by synthesis (5) that isomycamine was 2,3,4,6-tetradeoxy-4-N,N-dimethylamino-D-erythro-hexopyranoside. Thus two possibilities remained; that ossamine was 2,3,4,6-tetradeoxy-4-N,N-dimethylamino-(D or L)-threo-hexopyranose (1), or a 3-N,N-dimethylaminohexose. That ossamine had structure 1 was confirmed by independent synthesis (5).

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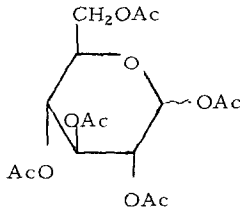
* All new compounds reported herein have correct elemental analyses.

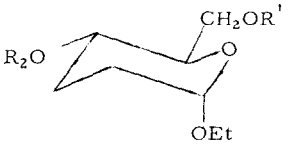
** Also called forosamine; see references 3, 4 and 5.

Ethyl 2,3-dideoxy-4,6-di-O-mesyl-α-D-erythro-hexopyranoside (3) was used as the starting material for the preparation of 1. Compound 3 was readily available via a seven step reaction sequence, similar to that employed previously (6, 7) from D-glucose penta-

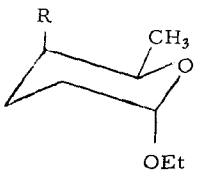


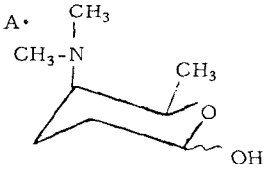
2

7 steps



3, $R^1 = R^2 =$ mesyl
4, $R^1 = I$; $R^2 =$ mesyl
5, $R^1 = H$, $R^2 =$ mesyl





6, R= N_3
7, R= NH_2 · p-toluenesulfonic acid
8, R= $N(CH_3)_2$ · p-toluenesulfonic acid

9, A= p-toluenesulfonic acid
10, A= HCl
11, A= picric acid
12, A= methyl iodide

acetate (2). Thus compound 3 was converted into ethyl 2,3,6-trideoxy-4-O-mesyl-α-D-erythro-hexopyranoside (5) by a selective potassium iodide displacement of the primary 6-O-mesyl group in the presence of the secondary 4-O-mesyl of 3 to give 4, followed by hydrogenolysis of the 6-iodo group in the presence of Raney Nickel catalyst. The physical constants of 5 were in agreement with those reported in the literature (6, 7).

Entry into the threo-series was achieved by inversion at C-4. Compound 5 afforded ethyl 4-azido-2,3,4,6-tetradeoxy-α-D-threo-hexopyranoside (6) in high yield on treatment with excess sodium azide in refluxing N,N-dimethylformamide.

Recent reports (8 - 13) have indicated that ring contraction may occur under conditions similar to those employed here. That the displacement leading to 6 had,

indeed, proceeded with inversion of configuration at C-4, without ring contraction, was shown by nmr and mass spectral data.

Compound 6 was converted into ossamine hydrochloride (1) via a five step sequence. Sodium borohydride reduction of 6, and tosylate salt formation, yielded ethyl 4-amino-2,3,4,6-tetradeoxy-D-threo-hexopyranoside tosylate salt (7): mp 147°; $[\alpha]_D^{26}$ 81° (c 1.1, CH_3OH). Reductive dimethylation of 7 gave 8: mp 128-129°; $[\alpha]_D^{26}$ 53° (c 0.9, CH_3OH). Acid hydrolysis of 8 and neutralization with Dowex 1 (OH^-) resin afforded the title compound, 2,3,4,6-tetradeoxy-4-N,N-dimethylamino-D-threo-aldohexose (1)*: bp 60° (bath temperature) (0.01 mm); $n_D^{25.5}$ -31.2° (c 1.0, H_2O). Tosylate salt 9 (mp 102-103°), hydrochloride salt 10 (mp 144-145°), picrate derivative 11 (mp 171-172°), and methiodide 12 (mp 162-163°) were prepared also from compound 1.

The structure of ossamine hydrochloride, the aminosugar fragment isolated from ossamycin, was established by a comparison with synthetic 10 by X-ray powder patterns, mixture mp determinations, rotations and infrared and nmr spectra. The samples were identical in all respects. Similarly, the mixture mp of the synthetic methiodide (12) with the methiodide prepared from ossamine was undepressed. Thus ossamine is 2,3,4,6-tetradeoxy-4-N,N-dimethylamino-D-threo-hexopyranoside (1).

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* Compound 1 exhibited significant aldehyde absorption (1725 cm^{-1}) in the infrared spectrum indicative of the open chain form of 1. The nmr spectrum revealed absorption at 9.5δ (0.25 H, -C(O)-H) to confirm this assignment.

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