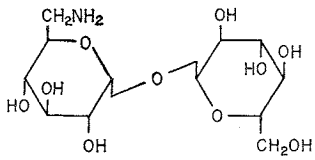
SYNTHESIS OF 6-AMINO-6-DEOXY-α,α-TREHALOSE: A POSITIONAL ISOMER OF TREHALOSAMINE

Sir:

Since its discovery, little has been reported on the chemical modification and the synthesis of analogs of the antitubercular antibiotic, trehalosamine[1]. The synthesis of this substance which can be considered as one of the structurally simplest aminoglycoside antibiotics[2], was reported by S. UMEZAWA and coworkers[3].

We now report on the synthesis of 6-amino-6-deoxy-α,α-trehalose (6-trehalosamine) which is an analog of trehalosamine.



6-Trehalosamine

Monobromination[4] of anhydrous α,α-trehalose with a mixture of triphenylphosphine and N-bromosuccinimide (two molar equivalents each) in DMF at room temperature for 43 hours, followed by acetylation with acetic anhydride in pyridine, afforded a crystalline product which showed the presence of three components by t.l.c. (dichloromethane - ethyl acetate, 4 : 1). Separation by chromatography on silica gel using the above solvent, gave 6, 6'-dibromo-6, 6'-dideoxy-α,α-trehalose hexaacetate, mp 166~167°C (18 %)*; 6-bromo-6-deoxy-α,α-trehalose heptaacetate, mp 119~120°C (chloroform hexane); $[\alpha]_D$ 142° (*c* 0.53, chloroform) (37 %) and a small amount of trehalose octaacetate[6]**. The dibromo compound could be obtained in over 60 % yield by using a larger excess of brominating agent and triphenylphosphine. The structure of the brominated products were firmly established by reduction to the acetylated 6-deoxy[5] and 6,6'-dideoxy[6] derivatives, mp 88.5~90°C and mp 195~196°C respectively.

Treatment of 6-bromo-6-deoxy-α,α-trehalose heptaacetate with an excess of sodium azide in DMF at 95°C during 27 hours afforded the highly crystalline 6-azido-6-deoxy-α,α-trehalose heptaacetate in 75 % yield, mp 119~120.5°C; $[\alpha]_D$ 166.8° (*c* 2.02, chloroform). Deacetylation of this product with sodium methoxide in methanol at 0°C afforded 6-azido-6-deoxy-α,α-trehalose as an amorphous powder, $[\alpha]_D$ 178° (*c* 0.19, methanol) which was chromatographically homogeneous (chloroform - methanol - hexane, 10 : 4 : 1). Catalytic reduction of the 6-azido derivative with 20 % Pd-C in methanol afforded 6-amino-6-deoxy-α,α-trehalose as a colorless solid in quantitative yield. The ninhydrin-positive product was homogeneous when chromatographed on paper and on cellulose plates using several solvent systems: R_{Gm} 0.51 (*n*-BuOH - pyridine - AcOH - H_2O, 5 : 5 : 3 : 1)[7]; authentic trehalosamine*** had R_{Gm} 0.83 in the same solvent system. Further chemical proof for the structure of the product was provided by the results of hydrolysis studies. Thus, treatment of 6-amino-6-deoxy-α,α-trehalose with aqueous 2 N sulfuric acid at 100°C liberated D-glucose and an amino sugar which was identified as 6-amino-6-deoxy-D-glucose (R_{Gm} 0.68) by chromatographic comparison with an authentic sample obtained by acid hydrolysis of kanamycin A and of methyl 6-acetamido-6-deoxy-α-D-glucopyranoside.

Treatment of 6-amino-6-deoxy-α,α-trehalose with 1-fluorodinitrobenzene in aqueous ethanol containing sodium hydrogen carbonate followed by acetylation and chromatographic purification on silica gel gave 6-deoxy-6-dinitroanilino-α,α-trehalose, heptaacetate, mp 100~102°C (from ether); $[\alpha]_D$ 130° (*c* 0.5, chloroform).

* All crystalline compounds reported herein gave correct analyses and had spectral characteristics (n.m.r., mass) expected of their structures. Melting points are uncorrected. Mass spectra were obtained with MS 902 high resolution and Hitachi medium resolution mass spectrometers. N.m.r. spectra were recorded on Jeol 100 MHz and 60 MHz spectrometers. Optical rotations were measured with a Perkin Elmer model 141 automatic spectropolarimeter.

** The quoted yields are not optimal. They represent pure fractions obtained by chromatographic separation.

*** A sample of trehalosamine was obtained by courtesy of Dr. F. ARCAMONE, Milan, Italy.

The synthetic 6-amino-6-deoxy-α,α-trehalose was inactive against *Mycobacterium tuberculosis* at a dose of 200 μg/ml, while trehalosamine itself was active at 6.2 μg/ml*. Further chemical manipulation are in progress in this series and will be reported in due course.

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* Testing performed by courtesy of Farmitalia, Milan, Italy.