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AMINOGLYCOSIDE ANTIBIOTICS: CHEMICAL TRANSFORMATION OF PAROMOMYCIN INTO A BIOACTIVE PSEUDOTRISACCHARIDE

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A number of aminoglycoside antibiotics have been isolated from fermentation sources in recent years, that bear a close structural resemblance to the paromomycin-neomycin group of aminoglycosides[1]. Ribostamycin[2] for example, differs from neomycin in the absence of the diaminohexose unit attached to the D-ribofuranose moiety. It is an important chemical precursor of butirosin B[3], in which the N-1 amino group is acylated with the L-haba (L-2-hydroxy-4-aminobutyric acid) unit. Like other representatives of this class of antibiotics, these novel types have an interesting biological profile, particularly against gram-negative organisms[4].

In this paper, we describe a chemical conversion of the readily available aminoglycoside antibiotic paromomycin[1,5], into a bioactive analog in which the diaminohexose unit has been preferentially removed by a unique β-elimination reaction.

Penta-N-benzyloxycarbonyl paromomycin, an amorphous solid, $[\alpha]_D^{20}$ + 22.6° (MeOH), was prepared from the parent antibiotic in the usual manner (92%). Treatment of the latter with benzaldehyde in 98% formic acid (1°, 25h), followed by neutralization and conventional processing gave the 4',6'-O-benzylidene derivative 1, as an essentially homogeneous amorphous solid (95%) (t.l.c, $CHCl_3$, EtOAc, MeOH, 10:2:1). A sample purified by preparative t.l.c showed $[\alpha]_D^{20}$ + 17.8° (MeOH). The preferentially protected derivative 1 was treated with periodic acid (1.5 equiv., 1°, 24h) in dry tetrahydrofuran containing 4A molecular seive. The solution was neutralized and processed in the usual manner to give a colorless solid which was triturated

with ether and dried (93%). The resulting essentially homogeneous (t.l.c, $CHCl_3$, EtOAc, MeOH, 20:4:3) dialdehyde derivative 2 could be detected on chromatograms with the aniline hydrogen phthalate spray[6] (orange-colored spot) and the ammonium molybdate spray[7] (blue-colored spot), and was suitable for use in the subsequent step. Treatment of 2 with triethylamine in methanol (25°, 4h), followed by evaporation of the solution and crystallization of the residue from ethanol, gave the pseudotrisaccharide derivative 3 (63%) as an essentially pure product, contaminated by traces of 1. Purification by silica gel chromatography (silica gel containing 2% boric acid, $CHCl_3$), followed by recrystallization from ethanol gave 3, m.p 221-222°; $[\alpha]_D^{20}$ + 35° (acetone); t.l.c ($CHCl_3$, EtOAc, MeOH, 20:5:3, Rf 0.42)[8a]. Preferential cleavage of the acetal function in 3 (80% AcOH, 25°, 30h) gave the crystalline tri-N-benzyloxycarbonyl derivative 4 (quant.), m.p 213-215° (MeOH); $[\alpha]_D^{20}$ + 31.7° (dioxane), t.l.c ($CHCl_3$, EtOAc, MeOH, 4:1:1, Rf 0.25; Rf 0.03 boric acid containing plate). Hydrogenolysis in the presence of 20% Pd-C in a 2:1 mixture of methanol and dioxane containing 1.2 equiv. of hydrochloric acid, followed by treatment of the resulting hydrochloride salt with Rexyn (OH^-) resin gave the pseudotrisaccharide 5 as a chromatographically homogeneous colorless, amorphous solid (94%). The product was further purified by dissolution in the minimum volume of water and precipitation with ethanol. The amorphous solid sintered between 165-170° and showed $[\alpha]_D^{20}$ + 41° (H_2O)[8b]; t.l.c (silica gel, $CHCl_3$, MeOH, NH_4OH, 1:3:2, Rf 0.42; $R_{paromamine}$ 0.85); paper chromatography (n-PrOH-pyridine-H_2O-AcOH, 15:10:12:3, $R_{paromamine}$ 1.25). The structure of 5 was further substantiated by high resolution mass spectral data on the corresponding tri-N-acetyl-O-trimethylsilyl derivative, which was prepared according to a standard procedure[9]; calcd. for a $C_{31}H_{64}N_3O_{11}Si_4$ fragment (deoxystreptamine, glucosamine, ^+CHOH), 766.3617; found, 766.3612; calcd. for a $C_{28}H_{59}N_2O_{10}Si_4$ fragment (deoxystreptamine, ribose, ^+CHOH), 695.3246; found, 695.3249.

It is of interest to note that the bioactive pseudotrisaccharide 5 has been recently obtained as the carbonate salt (m.p 168-170°; $[\alpha]_D$ + 42°, H_2O) from the alkaline hydrolysis of an antibiotic substance designated as

Bu 1709E_2[10], which differs from 5 in that the N-1 amino group has the L-haba side chain, as in the butirosin group of aminoglycosides. The pseudotrisaccharide 5, which can be considered as a 6'-hydroxy analog of ribostamycin, is thus readily available from the sequence described in this paper, and it is an important link in deciphering the structure-activity relationships of these closely related, yet subtly different group of antibiotics. The microbiological activity profile and other bio-data for compound 5 will be published elsewhere.

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H5IO6
THF
Et3N
R=CH2NHCbz
1
2
3
4, R=Cbz
5, R=H