Tetrahedron Letters No. 46, pp 4013 - 4016, 1974. Pergamon Press. Printed in Great Britain.

AMINOGLYCOSIDE ANTIBIOTICS: SYNTHESIS OF 6-O-(β-D-RIBOFURANOSYL) PAROMAMINE

Tomoya Ogawa, Tetsuyoshi Takamoto and Stephen Hanessian*
Department of Chemistry, University of Montreal
Montreal, Quebec, Canada

(Received in USA 23 July 1974; received in UK for publication 8 October 1974)

To date, all the known microbially-derived 4,5-linked aminoglycoside antibiotics contain a β-D-pentofuranosyl moiety attached to carbon-5 of the deoxystreptamine portion, as in the paromomycin-neomycin[1]-lividomycin[2], and ribostamycin[3]-butirosin[4] groups. In a general program directed toward the synthesis and chemical modification of aminoglycoside antibiotics[5], it was of interest to prepare the title compound, a positional isomer of a bioactive pseudotrisaccharide[6,7] and to study the biochemical consequences of the "unnatural" attachment of the D-ribofuranose moiety. Paromamine[8] was chosen as the aglycon because it lends itself to preferential functionalization. A further advantage is the structural versatility of the anticipated pseudotrisaccharide and its derivatives, since a conversion from the paromamine to the neamine-type can be easily achieved by novel procedures[9].

Benzoylation of the di-O-isopropylidene acetal of tri-N-benzyloxycarbonyl paromamine[5,10] followed by preferential cleavage of the acetal function (80% AcOH) gave the crystalline 3'-benzoate derivative[11] 1 in 95% overall yield m.p 247-248° (MeOH); $[\alpha]_D^{20}$ + 91.6 (DMF). Treatment of 1 with benzaldehyde in 98% formic acid (25°, 4.5 h), followed by neutralization, and usual processing gave the 4',6'-O-benzylidene acetal 2 as a chromatographically homogeneous amorphous solid (85%), m.p 315° (charring); $[\alpha]_D^{20}$ + 44.3° (dioxane). The glycosidation reaction between 2 and 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl chloride[12] 3 was effected in a 1:3 mixture of DMF and 1,2-dichloroethane in the presence of mercuric cyanide and calcium sulfate (50°, 18h). Convential processing afforded a crude product that consisted essentially of one component (t.l.c, CCl_4, acetone, 4:1 and toluene,

EtOAc, 3:2). Trituration with isopropyl ether and dichloromethane gave the pseudotrisaccharide derivative 4 as a white amorphous solid (96%) which could be further purified by filtration through a bed of silica gel (CCl_4, acetone, 4:1); m.p 278-279°; $[\alpha]_D^{20}$ + 26.8 (dioxane)[13a]. Removal of the acetal function (aq. AcOH-dioxane, 50°, 4d) followed by debenzoylation (NaOMe), MeOH, CH_2Cl_2) gave the tri-N-benzyloxycarbonyl analog 5 (62% overall), m.p 260-265° (dec); $[\alpha]_D^{20}$ + 41.4 (DMF), which was found to be different from the 5-O-substituted positional isomer[6], thus pinpointing the position of attachment of the D-ribofuranosyl moiety in the glycosidation reaction. Hydrogenolysis in the presence of 20% Pd-C in a mixture of methanol and dioxane containing 1N hydrochloric acid, followed by treatment of the product with Rexyn (OH^-) resin gave the pseudotrisaccharide 6 as a white solid (77%), m.p 174-175°; (sintering at 145°); $[\alpha]_D^{20}$ + 34.2° (H_2O)[13b]; t.l.c (silica gel, $CHCl_3$, MeOH, NH_4OH, 1:3:2, Rf 0.53; $R_{paromamine}$ 1.07); paper chromatography (n-PrOH-pyridine-H_2O-AcOH, 15:10:12:3; $R_{paromamine}$ 1.24). The structure of the product 6 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[14]; calcd. for a $C_{30}H_{63}O_{10}N_3Si_4$ fragment (deoxystreptamine, glucosamine portions), 737.3590; found 737.3586; calcd. for a $C_{27}H_{57}O_8N_2Si_4$ fragment (deoxystreptamine, ribose portion), 649.3192; found 649.3198.

It is noteworthy to mention that in the synthesis of ribostamycin, Ito and coworkers[15] effected a similar glycosidation reaction between the halide 3 and tri-N-benzyloxycarbonyl 3',4'-di-O-benzyl neamine, and reported the isolation of a major product in which the D-ribofuranosyl moiety was attached to the 5-position of the deoxystreptamine unit. It is somewhat surprising that glycosidation under essentially similar conditions, and of the same unit in the structurally related paromamine and neamine derivatives, respectively, leads to such widely divergent substitution patterns[16].

The pseudotrisaccharide 6 was much less active against bacteria, compared to its positional isomer described in the accompanying paper[6]. These results will be communicated at a later date.

Acknowledgments - Generous financial assistance from an NRCC-PRAI grant is gratefully acknowledged.

REFERENCES

1. S. Hanessian and T.H. Haskell, in "The Carbohydrates", W. Pigman and D. Horton ed., Academic Press, N.Y. vol. IIA, 139 (1970); K.L. Rinehart, Jr., "The Neomycins and Related Antibiotics", Wiley, New York 1964.

2. T. Oda, T. Mori, Y. Kyotani and M. Nakayama, J. Antibiotics (Japan), 24, 511 (1971).

3. E. Akita, T. Tsuruoka, N. Ezaki and T. Niida, J. Antibiotics (Japan), 23, 173 (1970).

4. P. W.K. Woo, H.W. Dion and Q.R. Bartz, Tetrahedron Lett., 2625 (1971).

5. S. Hanessian, R.F. Butterworth and T. Nakagawa, Carbohyd. Res., 26, 261 (1973).

6. T. Takamoto and S. Hanessian, Tetrahedron Lett., preceding paper.

7. H. Tuskiura, K. Saito, S. Kobaru, M. Konishi and H. Kawaguchi, J. Antibiotics (Japan), 29, 386 (1973).

8. T.H. Haskell, J.C. French and Q.R. Bartz, J. Amer. Chem. Soc., 81, 3480 (1959).

9. S. Hanessian, M.M. Ponpipom and P. Lavallée, Carbohyd. Res., 24, 45 (1972); S. Hanessian and P. Lavallée, J. Antibiotics (Japan) 25, 683 (1972).

10. S. Umezawa, K. Tatsuta and S. Koto, Bull. Chem. Soc. Japan, 42, 529 (1969).

11. Preliminary experiments to obtain this product were conducted by Dr. R.F. Butterworth in this laboratory.

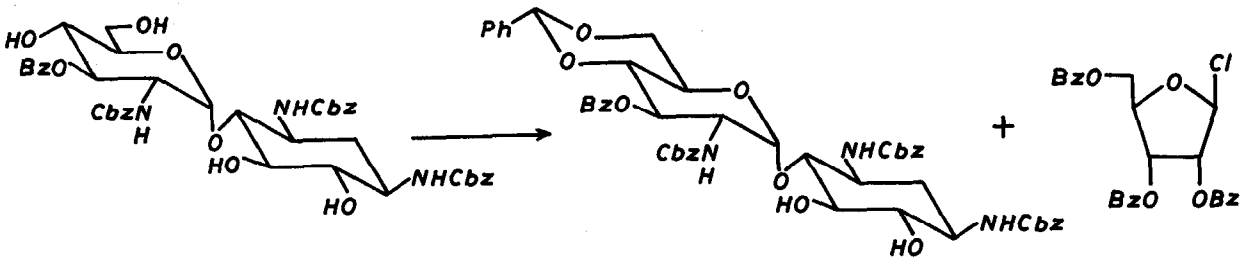
12. J.J. Fox and I. Wempen, Methods in Carbohydrate Chem., 2, 221 (1963).

13a Microanalytical data were in agreement with the proposed structures. b. Free aminoglycoside preparation contained variable amounts of carbonic acid depending on the periods of exposure to air.

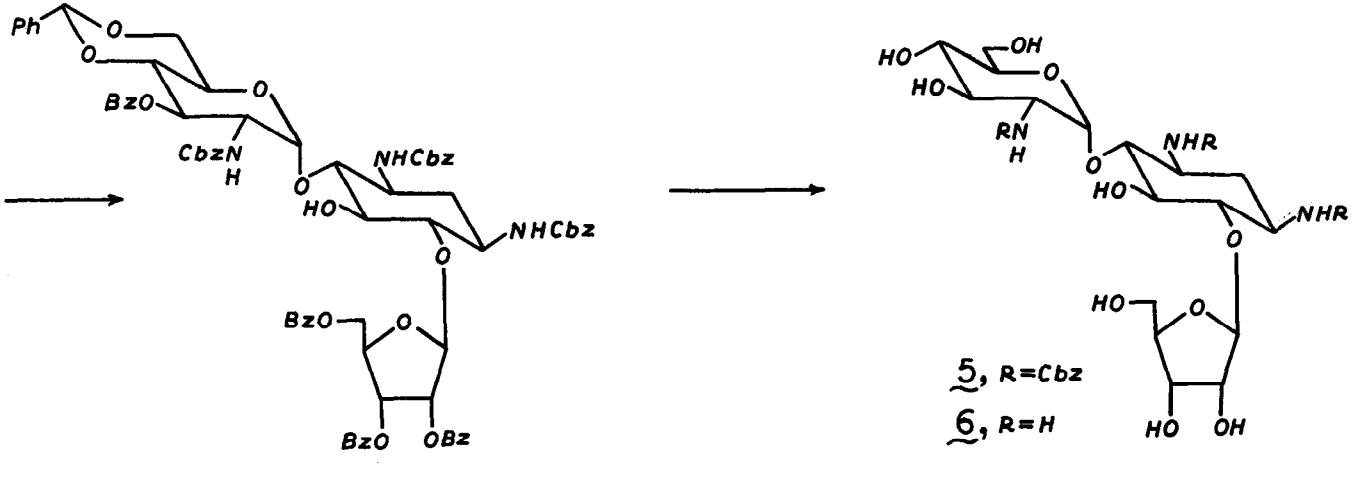
14. D.C. DeJongh, J.D. Hribar, S. Hanessian and P.W.K. Woo, J. Amer. Chem. Soc., 89, 1469 (1967); D.C. DeJongh, T. Radford, J.D. Hribar, S. Hanessian, M. Bieber, G. Dawson and C.C. Sweeley, J. Amer. Chem. Soc., 91, 1728 (1969).

15. T. Ito, E. Akita, T. Tsuruoka and T. Niida, Antimicrobial Agents and Chemotherapy, 33 (1970).

16. Similar results have been observed elsewhere, private communication, Dr. G. Cassinelli, Farmitalia, Milan.



1 2 3



4

5, R=Cbz

6, R=H