Tetrahedron Letters No. 5, pp 379 - 382, 1976. Pergamon Press. Printed in Great Britain.

SYNTHESIS OF A HEXOSE-ANALOGUE OF PRUMYCIN (4-D-ALANYLAMINO-2-AMINO-2,4-DIDEOXY-D-GALACTOPYRANOSE)†

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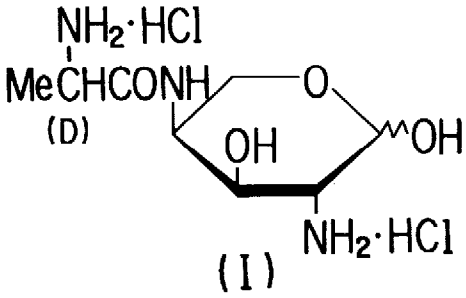
(Received in Japan 19 November 1975; received in UK for publication 23 December 1975)

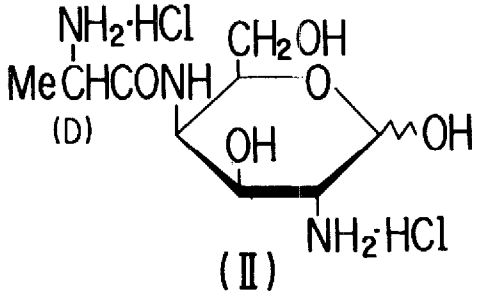
In the previous paper,[1] we have communicated the synthesis of a new antifungal antibiotic, Prumycin (dihydrochloride=I) consisting of 2,4-diamino-2,4-dideoxy-L-arabinopyranose and D-alanine residues. It is particularly interesting in the case of such a small molecule-antibiotic to examine the influence of structural modification on the biological activity. 2,4-Diamino-2,4-dideoxy-D-galactopyranose which has been prepared[2] from readily accessible 2-amino-2-deoxy-D-glucose has the same structure as the sugar moiety of I if its hydroxymethyl group at C-5 is disregarded. Therefore, we first chose 4-D-alanylamino-2-amino-2,4-dideoxy-D-galactopyranose (dihydrochloride=II) as a Prumycin analogue. This communication deals with the synthesis of II from 2-amino-2-deoxy-D-glucose <u>via</u> a new pathway that entails novel hydrolysis of a benzamido group and selective reduction of an azido group.

2-Phenyl-5',6'-O-isopropylidene-α-D-glucofurano-[2',1':4,5]-Δ^2-oxazoline (III) has been prepared[3] in two steps from 2-amino-2-deoxy-D-glucose and was treated in DMF with benzyl bromide, barium oxide, and barium hydroxide over night at room temperature, giving 3-O-benzyl derivative IV,[4] m.p. 82-3°; $[\alpha]^{21}_{365}$ -11° (c 0.690, $CHCl_3$), in 72% yield. Treatment of IV with dry HCl in benzyl alcohol (0.14 N) at room temperature gave a mixture of benzyl 2-benzoylamino-3-O-benzyl-2-deoxy-α-D-glucopyranoside (Va), m.p. 201-3°; $[\alpha]^{23}_{D}$ +158° (c 0.715, MeOH); ν^{KBr}_{max} 3450-3320 (NH, OH), 1635 (C=O), 1540 (NH), 851 (α glucoside) cm^{-1} and its β anomer (Vb), m.p. 219-21°; $[\alpha]^{23}_{D}$ +7° (c 0.689, MeOH); ν^{KBr}_{max} 3450-3310 (NH, OH), 1645 (C=O), 1540 (NH), 892 (β glucoside) cm^{-1},[5] in the ratio varying with the reaction time. (the α/β ratio was 1:3 after 4 hours, 3:1 after 3 days, and 20:1 after 2 weeks).

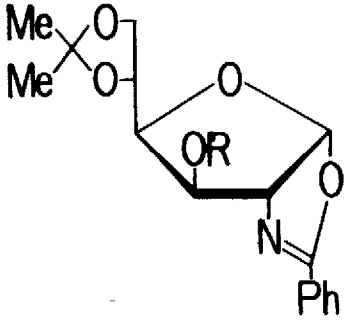
Since II includes an amide bond connecting the amino acid residue with the sugar and a labile free hemiacetal, the synthetic precursors of II must avoid keeping the benzamido group at C-2 of the sugar moiety. Although Va and Vb were heated with various bases for replacement of the benzoyl group with more easily



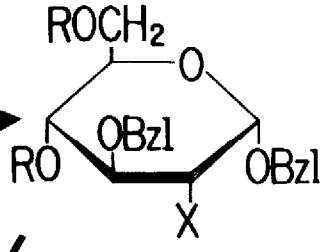
(I)

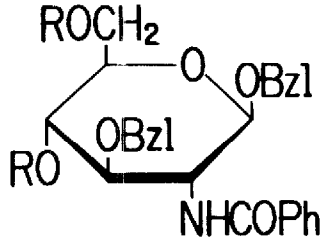


(II)

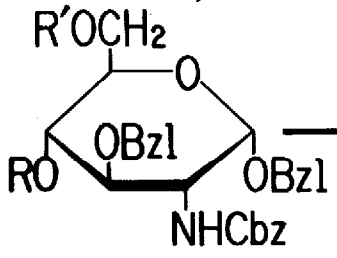


(III) R=H
(IV) R=Bzl

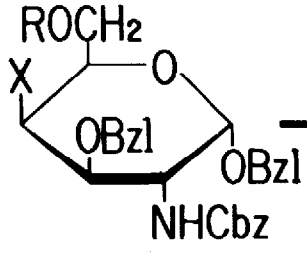


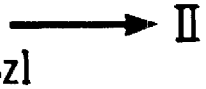


(Va) R=H, X=NHCOPh (Vb) R=H
(VIa) R=Ac, X=NHCOPh (VIb) R=Ac
(VII) R=Ac, X=NHCSPh
(VIII) R=Ac, X=$\overset{\oplus}{N}H=C(SMe)Ph$ $I^{\ominus}$



(IX) R=R′=Ac
(X) R=R′=H
(XI) R=H, R′=Tr
(XII) R=Ms, R′=Tr





(XIII) R=Tr, X=N_3
(XIV) R=H, X=N_3
(XV) R=H, X=NH_2
(XVI) R=H, X=MeCH(NHCbz)CONH

removable benzyloxycarbonyl group (Cbz), their benzamido group completely resisted alkaline hydrolysis. Therefore, our attention was turned towards hydrolysis under weakly acidic conditions that don't affect the glycosidic bond.

After treatment of Va,b with acetic anhydride-pyridine, the resulting diacetates, (VIa), m.p. 189-90°; $[\alpha]_D^{27}$ +117° (c 0.727, $CHCl_3$), and (VIb), m.p. 212-4°; $[\alpha]_D^{23}$ -9° (c 0.810, $CHCl_3$), were separately heated in toluene-pyridine (7:3, v/v) with phosphorus pentasulfide. In contrast to VIb which gave a complex mixture, VIa gave a glassy thioamide (VII), $[\alpha]_D^{24}$ +103° (c 1.03, $CHCl_3$), ν_{max}^{KBr} 3330 (NH), no absorption in the region of 1700-1600, 1530 (NH) cm^{-1}, in almost quantitative yield. Treatment of VII with methyl iodide at room temperature led to the thioimino ether VIII, which was not isolated but hydrolyzed in THF with dilute hydrochloric acid (2 N) for 15 minutes at room temperature after evaporation of methyl iodide.[6] After addition of large excess of aqueous sodium bicarbonate, the resulting mixture was treated with benzyloxycarbonyl chloride at 0° and eluted from silica gel (benzene-ether, 7:1 v/v) to give benzyl 4,6-di-O-acetyl-3-O-benzyl-2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranoside (IX), m.p. 130-2°; $[\alpha]_D^{23}$ +87° (c 0.673, $CHCl_3$); ν_{max}^{KBr} 3380 (NH), 1693 (C O of Cbz), 1540 (NH) cm^{-1}, in 84% yield based on VII. Acetyl group of IX was removed by sodium methoxide in methanol and the resulting X, m.p. 165-6°; $[\alpha]_D^{28}$ +103° (c 0.743, $CHCl_3$), was treated with trityl chloride in pyridine, giving glassy 6-O-trityl derivative XI, $[\alpha]_D^{24}$ +58° (c 0.750, $CHCl_3$). Compound XI was methanesulfonylated in the usual way and the resulting 4-O-mesylate XII, m.p. 140-2°; $[\alpha]_D^{26}$ +82° (c 0.977, $CHCl_3$); ν_{max}^{KBr} 1357, 1178 (SO_2) cm^{-1}, was treated in HMPA with NaN_3 at 120°, giving benzyl 4-azido-3-O-benzyl-2-benzyloxycarbonylamino-2,4-dideoxy-6-O-trityl-α-D-galactopyranoside (XIII), m.p. 150-2°; $[\alpha]_D^{24}$ +62° (c 0.293, $CHCl_3$), ν_{max}^{KBr} 2100 (N_3) cm^{-1}, δ ($CDCl_3$) 3.95 (1 proton, quartet, $J_{3,4}$=3.5, $J_{4,5}$= 1.5 Hz, H-4) ppm,[7] in 90% yield. The trityl group of XIII was removed on treatment with aqueous acetic acid (80% v/v) to afford XIV, m.p. 165-7°; $[\alpha]_D^{23}$ +92° (c 0.667, $CHCl_3$).

Reduction of the azido group of XIV without removal of the benzyloxycarbonyl and benzyl groups was the key step of this synthesis. This selective reduction was performed by careful catalytic hydrogenation at room temperature with Raney Ni. The catalyst was added in small portions several times through the reaction which was monitored by t.l.c.. In this way, 4-amino compound XV was obtained in more than 90% yield and used for the next coupling reaction without purification. Compound XV was treated in DMF with an equivalent amount of N-benzyloxycarbonyl-D-alanine p-nitrophenylester at room temperature and eluted from silica gel (benzene-acetone, 5:1 v/v), giving a coupled compound XVI, $[\alpha]_D^{23}$ +125° (c 0.983, $CHCl_3$), ν_{max}^{KBr} 3430, 3330 (NH, OH), 1720-1700 (C=O of Cbz), 1668 (C=O of amide), 1550-1515 (NH) cm^{-1}, in 83% yield. Finally, XVI was catalytically hydrogenated with Pd-C (10%) in the presence of acetic acid

in two steps, first in aqueous methanol and then in water. After filtration of the catalyst and addition of stoichiometric amount of hydrochloric acid, the mixture was lyophilized to give II, $[\alpha]_D^{23}$ +15° (c 0.880, H_2O, equilibrium); ν_{max}^{KBr} 3400-2980 (NH, OH, NH_3^+), 1675 (C=O), 1590, 1495 (NH_3^+), 1555 (NH) cm^{-1}, as homogeneous powder.

Conventional agar dilution assay indicated that II did not have any biological activity like I.

ACKNOWLEDGMENT

The authers express their gratitude to Prof. S. Ōmura of Kitasato University for the test of the biological activity. Also, they are indebted to Dr. T. Ogawa of this institute for valuable discussions.

REFERENCES AND NOTES

† A preliminary account of this work was first presented at the 19th Symposium on the Chemistry of Natural Products, October 27, 1975, Hiroshima. J. Yoshimura et al. of Tokyo Institute of Technology also presented the synthesis of II at the symposium.

1) H. Kuzuhara and S. Emoto, Tetrahedron Letters, 1975, 1853.

2) W. Meyer zu Reckendorf and N. Wassiliadou-Micheli, Chem. Ber. 105, 2998 (1972).

3) S. Konstas, I. Photaki, and L. Zervas, Chem. Ber. 92, 1288 (1959).

4) Sodium hydride and benzyl bromide in THF gave an unsatisfactory result in the synthesis of IV.

5) The n.m.r. spectrum of Va,b afforded no information concerning their anomeric configuration because their H-1, H-2 signals could not be assigned by interference with the methylene protons of benzyl groups. However, their anomeric configuration was unambiguously determined on the basis of their optical rotation and i.r. spectrum.

6) cf. H. Muxfeldt, G. Hardtmann, F. Kathawala, E. Vedejs, and J. B. Mooberry, J. Am. chem. Soc. 90, 6534 (1968).

7) Tetramethylsilane was used as internal standard.