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Note

A synthesis of 3-amino-2,3,6-trideoxy-D-*ribo*-hexose (D-ristosamine) hydrochloride*

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The antibiotic ristomycin, isolated[1] from *Proactinomyces fructiferi*, contains an amino sugar component[2], ristosamine, whose structural assignment[3] as 3-amino-2,3,6-trideoxy-L-*ribo*-hexose has been confirmed by syntheses of its hydrochloride[4] and *N*-benzoyl derivatives[5]. The synthesis of the hydrochloride, *N*-benzoyl, and some other derivatives of the D-enantiomer has also been described recently[6]. In continuation of our work on synthetic analogs[7–9] of natural aminopolydeoxy sugars, we now report an alternative synthesis of derivatives of 3-amino-2,3,6-trideoxy-D-*ribo*-hexose (D-ristosamine).

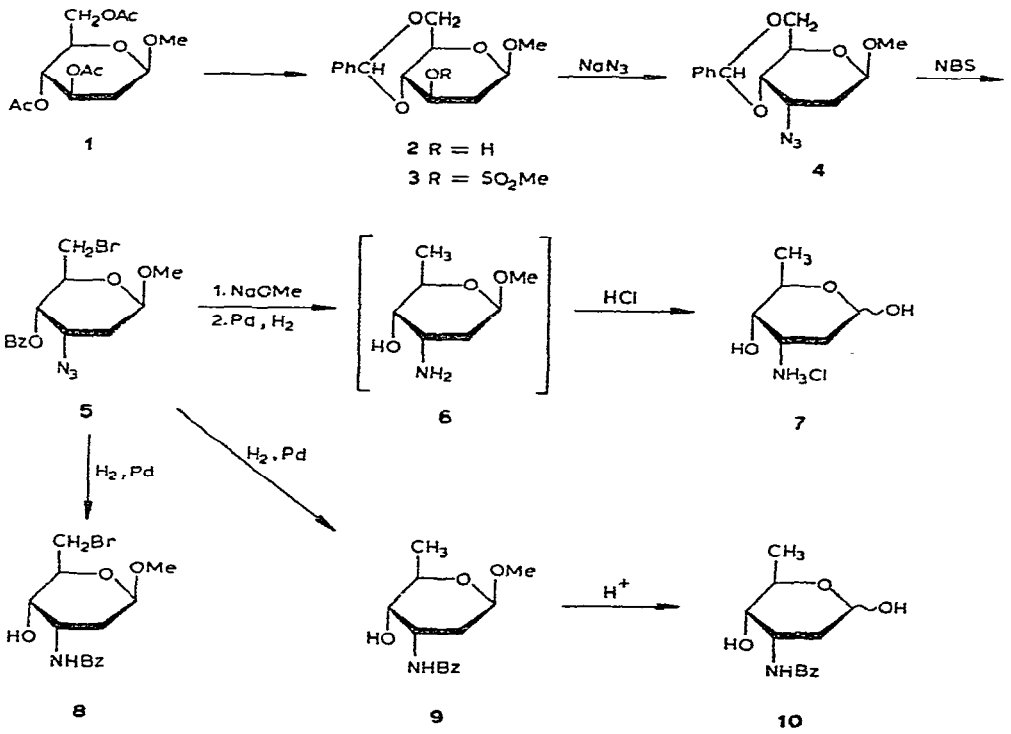
The point of departure was originally methyl 4,6-*O*-benzylidene-2-deoxy-β-D-*arabino*-hexopyranoside (**2**), first obtained[10] by reductive denitration of a nitro-sugar epoxide. As a more economical alternative, we chose to prepare **2** by *O*-deacetylation and *O*-benzylidenation of methyl 3,4,6-tri-*O*-acetyl-2-deoxy-β-D-*arabino*-hexopyranoside (**1**) which in turn is readily obtainable[11] from 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (tri-*O*-acetyl-D-glucal) by methoxymercuration and subsequent borohydride reduction. The yield of **2** prepared from **1** was 80%.

Compound **2** was mesylated (yield, 92%), and the sulfonate **3** subjected to displacement by sodium azide in *N*,*N*-dimethylformamide to give the azide **4** in 84% yield. Treatment of **4** with *N*-bromosuccinimide according to Hanessian[12] furnished a 69% yield of methyl 3-azido-4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-β-D-*ribo*-hexopyranoside (**5**). Compound **5** was sequentially *O*-debenzoylated with sodium methoxide and catalytically hydrogenated with palladium on carbon in the presence of barium carbonate. The syrupy product (**6**) was not characterized, but was hydrolyzed directly by hydrochloric acid to give crystalline (although very hygroscopic) 3-amino-2,3,6-trideoxy-β-D-*ribo*-hexose hydrochloride (**7**) in 57% yield (based on **5**). The synthetic D-ristosamine hydrochloride showed mutarotation:

*Dedicated to the memory of Professor J. K. N. Jones, F.R.S.

$[\alpha]_D$ +28.2° → +36.5° (in water); the absolute end-value agreed with the specific rotation reported for the natural enantiomer*.

Reduction of compound 5 without prior saponification of the benzoate group proceeded with some difficulty. When palladium on carbon and a hydrogen pressure of 15 lb. in.$^{-2}$. was used during 1 h, hydrogenation appeared to be largely confined to the azido group. A crystalline product was isolated in 50% yield after preparative t.l.c., and its i.r. and n.m.r.-spectroscopic data were compatible with the structure of methyl 3-benzamido-6-bromo-2,3,6-trideoxy-β-D-*ribo*-hexopyranoside (8). Evidently,



benzoyl migration from O-4 to the newly generated amino group at C-3 had occurred, and the bromo substituent was retained. Although the product had a sharp melting-point, microanalysis gave a carbon value somewhat too high, which suggested contamination by debrominated material. When the catalytic hydrogenation of 5 was performed more forcibly (3 h at 35 lb. in.$^{-2}$), the 3-proton doublet expected for a CH–CH_3 group appeared in the n.m.r. spectrum, indicating successful debromination.

*The value recorded[3] for L-7 is 34.3° (in water); the negative sign was omitted, presumably by an oversight. Lee and coworkers[4] have indeed found negative values for different samples of synthetic L-7. The cause of a discrepancy between these values and that reported[6] for synthetic 7 ($[\alpha]_D$ +85°, equil., water) is under investigation.

The product, presumed to be methyl 3-benzamido-2,3,6-trideoxy-β-D-*ribo*-hexopyranoside (**9**), was obtained as a syrup (yield, 75%) and was characterized only by physical data. Upon hydrolysis with 50% acetic acid, it furnished crystalline 3-benzamido-2,3,6-trideoxy-D-*ribo*-hexose (**10**), identified by comparison of its melting point and optical rotation with values published[6] for **10** and[3,5] the enantiomer.

EXPERIMENTAL

General methods. — Optical rotations were measured at room temperature in a Perkin–Elmer 141 automatic polarimeter. N.m.r. spectra were obtained at 100 MHz from solutions in chloroform-*d* and were internally standardized with tetramethylsilane. Column chromatography was performed with Silica Gel 60 (70–230 mesh ASTM), and t.l.c. with Silica Gel G (E. Merck AG, Darmstadt, Germany). Unless otherwise indicated, the chromatographic solvent was 1:2 ethyl acetate–petroleum ether, b.p. 30–60° (solvent A), or 5% methanol in chloroform (solvent B).

Methyl 4,6-O-benzylidene-2-deoxy-β-D-arabino-hexopyranoside (**2**). — Methyl 3,4,6-tri-*O*-acetyl-2-deoxy-β-D-*arabino*-hexopyranoside (**1**), m.p. 99–101°, $[\alpha]_D$ −23.6° (*c* 1, chloroform), was prepared[11] from commercial 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol via methyl 3,4,6-tri-*O*-acetyl-2-chloromercuri-2-deoxy-β-D-glucopyranoside, m.p. 175–176°, $[\alpha]_D$ +11.3° (*c* 1, chloroform). Solid sodium methoxide (200 mg) was added with stirring to a solution of **1** (1.70 g) in spectral-grade methanol (10 ml). After 2 h, t.l.c. indicated complete conversion of **1** into a more-slowly migrating product (solvent A), and the mixture was deionized by Amberlite IR-120(H^+) cation-exchange resin, filtered, and evaporated. The colorless syrup thus obtained was stirred with benzaldehyde (10 ml) and anhydrous zinc chloride (1 g) for 14 h. After addition of water (10 ml), the mixture was extracted with chloroform (20 ml). The extract was washed with water (10 ml) and evaporated. Portions of 1-propanol were repeatedly evaporated at 55° from the residue until the odor of benzaldehyde had waned. Recrystallized from ethyl acetate–petroleum ether, the product (**2**) weighed 1.20 g (80%); m.p. 156–157°, $[\alpha]_D$ −66.2° (*c* 1, chloroform). Lit.[10]: m.p. 155–156°, $[\alpha]_D$ −67°.

Methyl 4,6-O-benzylidene-2-deoxy-3-O-(methylsulfonyl)-β-D-arabino-hexopyranoside (**3**). — Methanesulfonyl chloride (0.9 ml, 3 mol. equiv.) was added with external cooling (15°) to a solution of **2** (1.0 g) in dry pyridine (10 ml). After 30 min, the mixture was evaporated, with periodic additions of 1-propanol (20 ml). The dry residue was washed with cold water, and then extracted into ether. Evaporation of the dried (calcium chloride) solution gave **3** (1.20 g, 92%), which was recrystallized from ethyl acetate–petroleum ether; m.p. 149° (dec.), $[\alpha]_D$ −61.8° (*c* 0.5, chloroform), ν_{max}^{Nujol} 1170 cm^{-1} (OMs); n.m.r. data: δ 7.38 (5H, Ph), 5.56 (s, 1H, *Ph*–CH), 4.77 (octet, $J_{2a,3}$ 12, $J_{2e,3}$ 5.5, $J_{3,4}$ 10 Hz, H-3), 4.55 (q, $J_{1,2a}$ 10, $J_{1,2e}$ 2.5 Hz, H-1), 4.37 (q, $J_{5,6e}$ 4.5, $J_{6a,6e}$ 10 Hz, H-6e), 3.82 (q, $J_{3,4}$ 10, $J_{4,5}$ 12 Hz, H-4), 3.73 (t, $J_{5,6a}$ 10 Hz, H-6a), 3.54 (s, 3H, OMe), 3.4-region (m, broad, H-5), 2.98 (s, 3H, OMs), 2.53 (octet, $J_{2a,2e}$ 13 Hz, H-2e), and 1.94 (octet, H-2a).

Anal. Calc. for $C_{15}H_{20}O_7S$ (344.4): C, 52.31; H, 5.85. Found: C, 52.49; H, 5.92.

*Methyl 3-azido-4,6-O-benzylidene-2,3-dideoxy-β-*D*-ribo-hexopyranoside* (**4**). — A solution of the 3-sulfonate **3** (1.40 g) in *N,N*-dimethylformamide (30 ml, dried over molecular sieves, type 4-A) containing sodium azide (0.80 g, 3 mol. equiv.) was stirred for 17 h at 120°. The cooled mixture was evaporated, with intermittent additions of 1-propanol (50 ml). The crystalline residue was extracted with ether. Evaporation of the extract and recrystallization of the residue from ethyl acetate–petroleum ether gave pure **4** (1.00 g, 84%); m.p. 93–94°, $[\alpha]_D$ −93.7° (*c* 0.4, chloroform), ν_{max}^{Nujol} 2100 cm^{-1} (N_3); n.m.r. data: δ 7.4-region (m, 5H, Ph), 5.56 (s, 1H, *Ph*–CH), 4.70 (q, $J_{1,2a}$ 9, $J_{1,2e}$ 2.5 Hz, H-1), 4.35 (q, *J* 3.5 and 9 Hz, probably H-4), 4.25–3.65 (m, 4H), 3.51 (s, 3H, OMe), 2.10 (octet, $J_{2a,2e}$ 13 Hz, H-2e), and 1.86 (octet, H-2a).

Anal. Calc. for $C_{14}H_{17}N_3O_4$ (291.3): C, 57.72; H, 5.88; N, 14.42. Found: C, 57.53; H, 5.87; N, 14.17.

*Methyl 3-azido-4-O-benzoyl-6-bromo-2,3,6-trideoxy-β-*D*-ribo-hexopyranoside* (**5**). — A stirred mixture of the benzylidene acetal **4** (0.80 g), *N*-bromosuccinimide (1.5 g, 3 mol. equiv.), and barium carbonate (2 g) in dry carbon tetrachloride (25 ml) was boiled for 2 h at reflux. The solution gradually became yellow and then red, and then faded to a pale yellow. The mixture was filtered while hot and the inorganic residue was washed with chloroform (10 ml). Evaporation of the filtrate gave a syrup whose ethereal solution was washed with water (10 ml), dried (sodium sulfate), and evaporated. T.l.c. with solvent A showed a faint, slow-moving spot in addition to the main product. Column chromatography on silica gel (20 g) with solvent A yielded **5** as a thick oil (0.70 g, 69%) that still contained a trace of the unidentified by-product. An analytical sample was further purified by preparative t.l.c. and it then showed $[\alpha]_D$ −81.2° (*c* 0.7, chloroform); ν_{max} (neat oil) 2100 (N_3) and 1715 cm^{-1} (ester CO); n.m.r. data: δ 8.07 and 7.5 (m, 2+3H, Ph–CO), 5.17 (q, $J_{1,2a}$ 9, $J_{1,2e}$ 3.5 Hz, H-1), 4.78 (q, $J_{3,4}$ 3, $J_{4,5}$ 9 Hz, H-4), 4.4–4.1 (m, 2H), 3.49 (s, 3H, OMe, superposed on m, 2H), and δ 2-region (m, 2H, H-2a,2e).

Anal. Calc. for $C_{14}H_{16}BrN_3O_4$ (370.2): C, 45.42; H, 4.35; Br, 21.58. Found: C, 45.57; H, 4.49; Br, 21.80.

*3-Amino-2,3,6-trideoxy-*D*-ribo-hexose hydrochloride* (*D-ristosamine hydrochloride*) (**7**). — A solution of compound **5** (550 mg) in methanol (17 ml) containing sodium methoxide (50 mg) was kept for 3 h at room temperature, after which time t.l.c. (solvent A) indicated complete conversion of **5** into a single, new product (presumably the *O*-debenzoylated bromo derivative). The solution was deionized with Amberlite IR-120(H^+) cation-exchange resin and then hydrogenated for 4 h at ambient temperature and pressure in the presence of palladium on carbon (600 mg) and barium carbonate (400 mg). Evaporation of the filtrate from the mixture gave a pale-yellow syrup that was extracted into ethyl acetate. The product (**6**), which could not be obtained crystalline, was recovered from the solvent and hydrolyzed by heating in 0.1M hydrochloric acid for 1 h at 90°. Evaporation of the hydrolyzate, with

periodic addition of several portions of aqueous, 40% ethanol, gave a brownish, semicrystalline mass. The material was treated with activated charcoal in ethanol, recovered by evaporation of the solvent, washed repeatedly by trituration with ethyl acetate, and finally crystallized from abs. ethanol by careful addition of dry ether and cooling. Compound **7** was obtained as extremely hygroscopic crystals (155 mg, 57%); $[\alpha]_D$ +28.2° (initial) → +36.5° (24 h, constant; *c* 0.5, water); lit.[3] for L-**7**, (−)34.3° and[6] for **7**, +85° (equil., water) (see footnote in the Discussion).

*Methyl 3-benzamido-6-bromo-2,3,6-trideoxy-β-*D-ribo-*hexopyranoside* (**8**). — Compound **5** (50 mg) in 99% ethanol (15 ml) was hydrogenated for 1 h at room temperature under pressure (15 lb. in.$^{-2}$) in the presence of 10% palladium on carbon (50 mg) and barium carbonate (30 mg). Evaporation of the filtrate gave a colorless syrup that was dissolved in a small amount of ethyl acetate. T.l.c. (solvent B) indicated total conversion of **5** into a main product (**8**) that was accompanied by a small proportion of a more-slowly migrating product (presumably **9**). Isolation of the main component by preparative t.l.c. (solvent B) gave **8** (23 mg, 50%) as colorless crystals, m.p. 146–147°, $[\alpha]_D$ −53.4° (*c* 0.3, chloroform); $\nu_{max}^{CHCl_3}$ 3400 (broad; OH, NH), 1650 (amide I), and 1510 cm^{-1} (amide II); n.m.r. data: δ 7.7 and 7.5 (m, 2+3H, PhCO), 4.74 (q, $J_{1,2a}$ 6 and $J_{1,2e}$ 3.5 Hz, H-1), 3.51 (s, 3H, OMe), and 2.1-region (broad m, 2H, H-2a,2e). Ring protons resonating in the δ 4.6–3.5 region (intensity 5H) gave ill-resolved signals; there were minor peaks near δ 1.3–1.4 due to contamination (C–Me of **9**?).

Anal. Calc. for $C_{14}H_{18}BrNO_4$ (344.2): C, 48.85; H, 5.27. Found: C, 50.35; H, 5.37.

*Methyl 3-benzamido-2,3,6-trideoxy-β-*D-ribo-*hexopyranoside* (**9**). — Compound **5** (50 mg) was hydrogenated as described for the preparation of **8**, except that the hydrogen pressure was 35 lb. in.$^{-2}$ and the reaction time, 3 h. Processing as for **8** furnished syrupy **9** (27 mg, 75%); $[\alpha]_D$ −31° (*c* 0.6, chloroform), $\nu_{max}^{CHCl_3}$ 3400 (broad; OH, NH), 1645 (amide I) and 1510 cm^{-1} (amide II); n.m.r. data: δ 7.7 and 7.4 (m, 2+3H, PhCO), 3.46 (s, 3H, OMe), 3.1 (1H, broad, removable by D_2O exchange), 2.0-region (broad m, 2H, H-2a,2e), and 1.40 (d, 3H, *J* 6 Hz, C–Me). Overlapping signals of ring protons in the δ 3.5–4.7 region were difficult to assign.

*3-Benzamido-2,3,6-trideoxy-*D-ribo-*hexose* (N-*benzoyl*-D-*ristosamine*) (**10**). — A sample of **9** (17 mg) was refluxed for 3 h in 50% aqueous acetic acid (2 ml). The residue obtained by evaporation was crystallized from ethyl acetate–ether to give **10** (13 mg, 81%); m.p. 135–137°, $[\alpha]_D$ +15.6° (initial) → +9.8° (15 min, constant; *c* 0.5, ethanol); lit.[3] for L-**10**: m.p. 131–133°, $[\alpha]_D$ −14° → −11° and[5] m.p. 126–128°, $[\alpha]_D$ −10° (ethanol); reported[6] for **10**, m.p. 128–129° and $[\alpha]_D$ +13.5° (equil. in ethanol).

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REFERENCES

1 G. F. GAUZE, E. S. KUDRINA, R. S. UKHOLINA, AND G. V. GAVRILINA, *Antibiotiki*, 8 (1963) 387–392; M. G. BRAZHNIKOVA, N. N. LOMAKINA, M. F. LAVROVA, I. V. TOLSTYKH, M. S. YURINA, AND L. M. KLYUEVA, *ibid.*, 8 (1963) 392–396.
2 N. N. LOMAKINA, I. A. SPIRIDONOVA, R. BOGNÁR, M. PUSKÁS, AND F. SZTARICSKAI, *Antibiotiki*, 13 (1968) 975–978.
3 R. BOGNÁR, F. SZTARICSKAI, M. E. MUNK, AND J. TAMAS, *J. Org. Chem.*, 39 (1974) 2971–2974.
4 W. W. LEE, H. Y. WU, J. J. MARSH, JR., C. W. MOSHER, E. M. ACTON, L. GOODMAN, AND D. W. HENRY, *J. Med. Chem.*, 18 (1975) 767–768.
5 F. SZTARICSKAI, I. PELYVÁS, R. BOGNÁR, AND G. BUJTÁS, *Tetrahedron Lett.*, (1975) 1111–1114.
6 D. HORTON AND W. WECKERLE, *Carbohydr. Res.*, 46 (1976) 227–235.
7 H. H. BAER, K. ČAPEK, AND M. C. COOK, *Can. J. Chem.*, 47 (1969) 89–97.
8 H. H. BAER AND C. W. CHIU, *Can. J. Chem.*, 52 (1974) 122–124.
9 H. H. BAER AND F. F. Z. GEORGES, *Can. J. Chem.*, 55 (1977) 1100–1103.
10 H. H. BAER AND W. RANK, Amer. Chem. Soc.–Chem. Inst. Canada Joint Conf., Toronto, Ontario, May 1970, Abstr. CARBO-12; H. H. BAER AND C. B. MADUMELU, *Carbohydr. Res.*, 39 (1975) C8–C11.
11 G. L. INGLIS, J. C. P. SCHWARZ, AND L. MCLAREN, *J. Chem. Soc.*, (1962) 1014–1019.
12 S. HANESSIAN, *Carbohydr. Res.*, 2 (1966) 86–88.