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5-ACETAMIDO-5,6-DIDEOXY-L-IDOSE

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ABSTRACT

Treatment of 6-azido-6-deoxy-1,2-*O*-isopropylidene-3,5-di-*O*-mesyl-α-D-glucofuranose (**1**) with hydrazine–Raney nickel formed an intermediate 5,6-epimine which immediately underwent reductive ring-opening to yield the salt of methanesulphonic acid and 5-amino-5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-mesyl-β-L-idofuranose (**3**). *N*-Acetylation of **3** gave 5-acetamido-5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-mesyl-β-L-idofuranose (**4**), which was prepared independently by selective substitution of 6-deoxy-1,2-*O*-isopropylidene-3,5-di-*O*-mesyl-α-D-glucofuranose (**6**) with azide, reduction, and *N*-acetylation. Hydrolysis of the sulphonate and isopropylidene groups gave 5-acetamido-5,6-dideoxy-L-idose, as a mixture of the isomeric furanose (**9**) and piperidinose (**10**) forms which were separated by column chromatography.

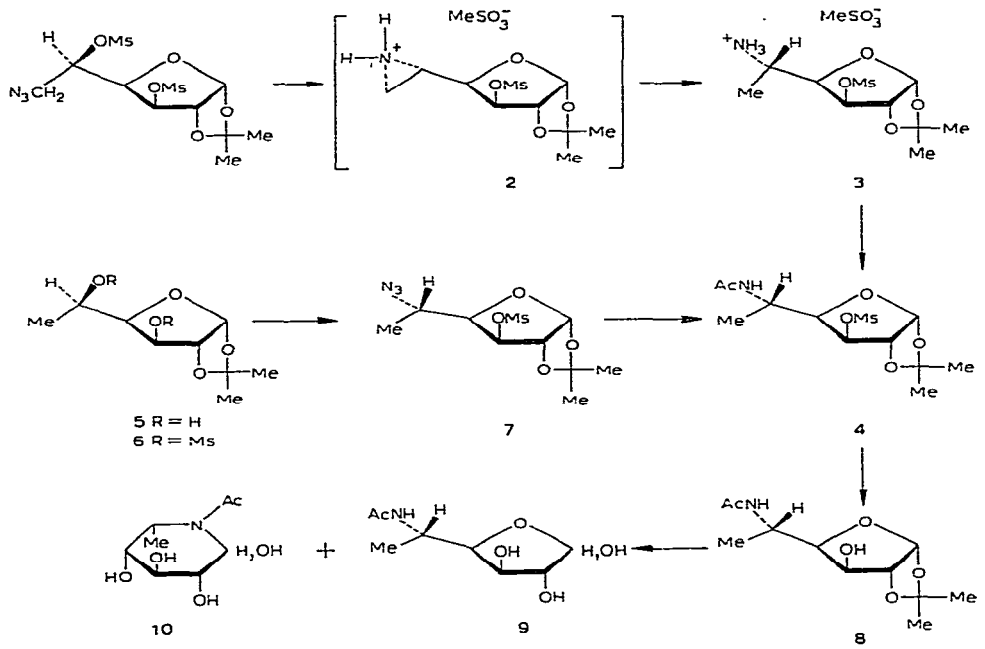
INTRODUCTION

5-Amino sugars are of interest in terms of both their chemistry and potential as antibiotics[1]. Thus, Saeki and Ohki[2] have prepared the antibiotic nojirimycin (5-amino-5-deoxy-D-glucopyranose) by ring opening of 3-*O*-benzyl-5,6-dideoxy-5,6-epimino-1,2-*O*-isopropylidene-α-D-glucofuranose to give 5-amino-5-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose. Protection of the hydroxy and amino functions of the latter with the trifluoroacetyl group directed ring closure of the free sugar to the piperidinose on subsequent hydrolysis of the isopropylidene groups. Saeki and Ohki[3] have also synthesised the corresponding 5,6-epimine derivatives of α-L-altrofuranose and β-L-idofuranose in a related study. Paulsen and Stoye[4] prepared an *N*-amino-5,6-epimine by the action of dry hydrazine on 3-*O*-benzyl-1,2-*O*-isopropylidene-5,6-di-*O*-mesyl-α-D-glucofuranose. Subsequent ring-opening with hydrazine–Raney nickel gave 5-amino-3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-idofuranose. 5-Acetamido-5,6-dideoxy-L-talofuranose was formed from the free sugar in greater preponderance than the pyranose form[5].

RESULTS AND DISCUSSION

In an attempt to prepare a 5,6-epimine (*e.g.* **2**), 6-azido-6-deoxy-1,2-*O*-isopropylidene-3,5-di-*O*-mesyl-α-D-glucofuranose (**1**) was treated with hydrazine and Raney

nickel[6]. However, the product, which was water-soluble, was not the methanesulphonic acid salt of the required epimine[7] (**2**), but the salt of a primary amine, giving a purple colour with ninhydrin. The derived amine was treated with acetic anhydride in ethanol to give a crystalline *N*-acetyl derivative (**4**). The infrared spectrum of **4** showed both amide I and amide II bands and a sharp band at 3,350 cm^{-1} (NH stretching), confirming that the precursor was a primary amine.



The absence of an hydroxyl group, as evidenced by the infrared spectrum, was confirmed by treatment with acetic anhydride in pyridine, when no change occurred. The n.m.r. spectrum of **4** showed the presence of a third methyl peak, split into a doublet overlapping the isopropylidene signals. This evidence, coupled with the elemental analysis, suggested that the acetylated product was a 5-acetamido-5,6-dideoxy derivative, and it follows that the original product was the methanesulphonate salt of a 5-amino-5,6-dideoxy derivative. This product would arise by initial formation of epimine **2** followed by reductive ring-opening, with a change of configuration at position 5, leading to the β-L-*ido* configuration. The salt and the *N*-acetyl derivative (**4**) were thus designated as derivatives of 5-amino-5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-mesyl-β-L-idofuranose (**3**). The structure was confirmed by an independent synthesis of **4** from 6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**5**). Mesylation of **5** gave the 3,5-di-*O*-mesyl derivative (**6**) which was subjected to selective azide replacement to give a mono-azido derivative. In the absence of participating groups, this reaction proceeds with inversion of configuration at position 5, giving 5-azido-5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-mesyl-β-L-idofuranose (**7**). Catalytic reduction,

followed by *N*-acetylation, yielded 5-acetamido-5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-mesyl-β-L-idofuranose (**4**), identical with that obtained above.

Removal of the mesyl group from **4** with sodium ethoxide gave the 3-hydroxy derivative (**8**) which, on acidic hydrolysis of the isopropylidene group, gave a syrupy mixture showing two spots, positive to *p*-anisidine, on a paper chromatogram. Separation by chromatography on a cellulose column yielded the faster component as crystalline 5-acetamido-5,6-dideoxy-L-idofuranose (**9**), and the slower component as syrupy 5-acetamido-5,6-dideoxy-L-idopyranose (**10**), in the ratio of ~2:1. The structures assigned to **9** and **10** were deduced from their infrared spectra, the former isomer showing both amide I and amide II bands, and the latter isomer showing amide I but no amide II band. The isomers were stable in neutral solution. In basic or acidic solution, an equilibrium mixture was formed in which the furanose form was preponderant; further reaction gave slow-moving compounds.

EXPERIMENTAL

General methods. — Melting points were determined on a Kofler microstage. Optical rotations were measured at 20° on a Perkin–Elmer 141 polarimeter. Concentrations were effected under diminished pressure. N.m.r. spectra were measured at 60 MHz on a Varian A-60 spectrometer with tetramethylsilane as internal reference. Paper chromatography was performed by the descending method on Whatman No. 1 paper, using 2:5:5 (v/v; top layer) pyridine–ethyl acetate–water as mobile phase. Thin-layer chromatography (t.l.c.) was performed on silica gel G (Merck) at room temperature.

6-Azido-6-deoxy-1,2-O-isopropylidene-3,5-di-O-mesyl-α-D-glucofuranose (**1**). — To a solution of 6-azido-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose[9] (0.52 g) in pyridine (10 ml) was added methanesulphonyl chloride (0.65 ml), and the mixture was kept for 18 h at room temperature. A little water was added to decompose the excess of methanesulphonyl chloride; the addition of more water caused crystallisation to take place. Filtration and recrystallisation from ethanol–water gave the the sulphonate **1** as needles (0.61 g; 72%), m.p. 99–100° (Found: C, 32.9; H, 5.0. $C_{11}H_{19}N_3O_9S_2$ calc.: C, 33.0; H, 4.8%).

5-Amino-5,6 dideoxy-1,2-O-isopropylidene-3-O-mesyl-β-L-idofuranose–methanesulphonic acid salt (**3**). — To a solution of 6-azido-6-deoxy-1,2-*O*-isopropylidene-3,5-di-*O*-mesyl-α-D-glucofuranose (1.8 g) in methanol (27 ml) was added hydrazine hydrate (1.3 ml) and Raney nickel (1 spatula). The mixture was refluxed for 5 h, during which time ammonia was evolved. The filtered solution was evaporated to a syrup, which crystallised on the addition of chloroform. The product (0.7 g; a second crop brought the total yield to 0.83 g, 50%) was recrystallised from isopropyl alcohol to give the salt **3**, m.p. 200–201°, $[\alpha]_D$ −14° (*c* 1.0, water) (Found: C, 34.7; H, 6.2; N, 3.8. $C_{11}H_{23}NO_9S_2$ calc.: C, 34.8; H, 6.1; N, 3.7%). The compound was soluble in water, weakly alkaline, and gave a purple colour with ninhydrin.

5-Acetamido-5,6-dideoxy-1,2-O-isopropylidene-3-O-mesyl-β-L-idofuranose (**4**). — The salt **3** (0.83 g) was dissolved in a little water, and an excess of saturated, aqueous sodium carbonate was added. This solution was thrice extracted with chloroform, and the combined extracts were dried (Na_2SO_4) and evaporated to a syrup. To a solution of this syrup in methanol (50 ml), acetic anhydride (2 ml) was added, and t.l.c. (chloroform–methanol, 4:1, v/v) indicated that complete reaction occurred within a few minutes. After 15 min, the solution was evaporated to a syrup, and remaining acetic anhydride was removed by coevaporation with toluene. The resulting syrup was crystallised from ethyl acetate–light petroleum to yield **4** (0.63 g, 89%), m.p. 133–135°, $[\alpha]_D$ −48° (*c* 2, chloroform) (Found: C, 44.4; H, 6.6; N, 4.3. $C_{12}H_{21}NO_7S$ calc.: C, 44.6; H, 6.5; N, 4.3%).

The i.r. spectrum showed peaks at 3350 (NH stretching), 1660 (amide I), and 1535 cm^{-1} (amide II). No band assignable to OH was present. After treatment with acetic anhydride in pyridine, only starting material was recovered, confirming the absence of an OH group. The n.m.r. spectrum showed a doublet of 3 protons at τ 8.75 (splitting, 7 Hz), indicating the presence of a third methyl group.

6-Deoxy-1,2-O-isopropylidene-3,5-di-O-mesyl-α-D-glucofuranose (**6**). — Syrupy 6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose[8] (**5**), derived from 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose (1.1 g) was dissolved in pyridine (10 ml) to which mesyl chloride (1.5 ml) was added. Crystallisation of pyridinium chloride commenced immediately, and the solution became warm. T.l.c. (chloroform–acetone, 4:1, v/v) indicated that reaction was complete in 1 h. The reaction mixture was poured into ice–water, when a syrup was deposited which partially crystallised on standing overnight at 0°. The crystalline disulphonate **6** was decanted off and collected, leaving a syrupy residue. This was partitioned between water and chloroform, and the chloroform layer was evaporated to a syrup. Crystallisation from isopropyl alcohol (seeding with the above crystals) gave **6** (total yield 470 mg, 24%). Recrystallisation from isopropyl alcohol gave needles (340 mg, 17%), m.p. 96–99°, $[\alpha]_D$ +32° (c 0.6, chloroform) (Found: C, 36.6; H, 5.6. $C_{11}H_{20}O_9S_2$ calc.: C, 36.5; H, 5.6%).

5-Azido-5,6-dideoxy-1,2-O-isopropylidene-3-O-mesyl-β-L-idofuranose (**7**). — To a solution of 6-deoxy-1,2-*O*-isopropylidene-3,5-di-*O*-mesyl-α-D-glucofuranose (400 mg) in a 1:1 mixture of *N,N*-dimethylformamide and butanone was added sodium azide (400 mg), and the solution was refluxed (bath temp., 130°) for 20 h. T.l.c. (chloroform–ether, 1:1, v/v) indicated that considerable starting material remained; consequently, the solution was refluxed for a further 20 h, when all of the starting material had reacted. The solution was evaporated to dryness, and the residue was partitioned between water and chloroform. The aqueous layer was further extracted with chloroform, and the combined chloroform solutions were washed with water and dried (Na_2SO_4). Evaporation afforded a syrup, which was co-concentrated with dry ethanol. The resulting syrup crystallised on trituration with isopropyl alcohol, and recrystallisation from this solvent yielded the 5-azido derivative **7** (131 mg, 39%), m.p. 113–114°, $[\alpha]_D$ −30° (*c* 1.4, chloroform) (Found: C, 39.8; H, 5.5; N, 13.7. $C_{10}H_{17}N_3O_6S$ calc.; C, 39.1; H, 5.5; N, 13.7%).

5-Acetamido-5,6-dideoxy-1,2-O-isopropylidene-3-O-mesyl-β-L-idofuranose (**4**). — The azido compound **7** (62 mg) in ethanol (10 ml) was hydrogenated for 20 h at atmospheric pressure in the presence of palladium-on-charcoal. T.l.c. (chloroform–ether, 1:1, v/v) indicated that reaction was then complete, yielding one product which gave a purple colour with ninhydrin. The catalyst was filtered off and washed with ethanol. To the combined filtrate and washings was added acetic anhydride (0.1 ml), the solution was stored for 1 h at room temperature and evaporated, and remaining acetic anhydride was removed by co-evaporation with toluene. The resulting syrup crystallised on scratching, and the product was triturated with ether and collected (32 mg, 49%), m.p. 132–135°. Recrystallisation from ethyl acetate–light petroleum gave the acetamido derivative **4**, m.p. 139–140°, which was identical (i.r. spectrum and mixed m.p.) with the product from the hydrazine–Raney nickel reaction.

5-Acetamido-5,6-dideoxy-L-idofuranose (**9**) *and -idopyranose* (**10**). — A solution of the sulphonate **4** (0.63 g) in 0.27M ethanolic sodium ethoxide (60 ml) was refluxed for 2 h. T.l.c. (chloroform–methanol, 4:1, v/v) then indicated almost complete reaction, giving a slower-moving product with some impurity near the starting line. The solution was poured on to a short, wide column of silica, and elution was continued with 4:1 (v/v) chloroform–methanol. The desulphonylated product **8**, freed of both the ionic material and the slow-moving impurity, was obtained as a syrup (0.4 g) on evaporation of the solvents. A solution of this syrup in dilute sulphuric acid (pH 1.5, 10 ml) was heated for 1 h at 95–100°, and then passed through Duolite A4(OH^-) resin and evaporated. Paper chromatography of the resultant syrup showed the presence of two major components (in the approximate ratio of 2:1) both stained by *p*-anisidine hydrochloride, as well as traces of one faster- and three slower-moving impurities that stained with ninhydrin. Chromatography on a column of cellulose, using butyl alcohol half-saturated with water, separated the two major components from the other impurities. Concentration of the solution containing the faster component yielded crystals of 5-acetamido-5,6-dideoxy-L-idofuranose (**9**) (32 mg), m.p. 162–165°. Concentration of the mother liquors at room temperature yielded impure **9** (27 mg), m.p. 150–159°, which, when recrystallised from isopropyl alcohol–acetone, gave colourless crystals of **9**, m.p. 164–166°, $[\alpha]_D$ −17° (*c* 0.5, water) (Found: C, 46.95; H, 7.3; N, 6.7. $C_8H_{15}NO_5$ calc.: C, 46.8; H, 7.4; N, 6.8%).

Concentration of the eluate containing the slower-moving component (**10**) yielded a syrup (27 mg), $[\alpha]_D$ +10.5° (*c* 0.8, methanol), which showed a single component on chromatograms but could not be obtained analytically pure. It is believed to be 5-acetamido-5,6-dideoxy-L-idopyranose (**10**), from the infrared spectrum which showed amide I but no amide II band, and from the fact that it equilibrated with the furanose form (**9**) (as shown by paper chromatography) when dissolved in dilute ammonium hydroxide or hydrochloric acid. The total yield of **9** and **10** was only 26%, presumably due to their acid lability and the formation of decomposition products.

Neither **9** nor **10** showed mutarotation in neutral, aqueous solution at room temperature.

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