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Note

Synthesis of *N*-substituted D-mannosylamines and 1-(benzylamino)-1-deoxyalditols for biological evaluation

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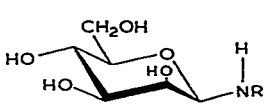
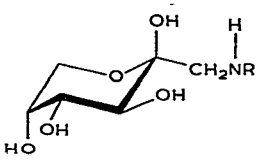
The finding of insulin-like activity associated with various amino-alkyl and -aryl glycosides[1–4] prompted us to investigate another class of compounds, namely, *N*-glycosyl compounds, in an effort to uncover more-potent, insulin-like agents. Glycosylamines are a well known class of compounds[5,6], and various glycosylated amino acids have received considerable attention, mainly because of their occurrence as junctures in glycoproteins and related substances[7,8]. *N*-Substituted glycosylamines, *e.g.*, *N*-(*p*-hydroxyphenyl)-D-mannopyranosylamine, are known to be inhibitors of hemagglutinins[9], and glycosylamines have been reported[10] to constitute a class of specific, and relatively potent, inhibitors of glycosidases. When acting on the β-D-glucosidase from yeast, D-glucosylamine has a K_I value of 2.2 μM, making it one of the most potent, competitive glycosidase inhibitors thus far reported[10]. The present article describes the synthesis of a number of *N*-substituted D-mannosylamines and 1-(benzylamino)-1-deoxyalditols for biological evaluation.

N-Benzyl-β-D-mannopyranosylamine (**1**) was prepared by condensation of molar equivalents of D-mannose and benzylamine in absolute ethanol. The crystalline material obtained exhibited a melting point (131–132°) significantly higher than that (80–82°) reported[11] in the literature. 1-(Benzylamino)-1-deoxy-D-fructopyranose[11] (**2**) and *N*-(*p*-nitrophenyl)-β-D-mannopyranosylamine[12] (**3**) were obtained by known procedures. In the preparation of **3**, 1-deoxy-1-(*p*-nitrophenyl)-D-fructopyranose (**4**) was, by fractional recrystallization, isolated as a coproduct of the reaction.



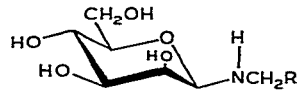
1 R = CH_2Ph
3 R = $C_6H_4NO_2$-*p*
5 R = C_5H_4OH-*p*



2 R = CH_2Ph
4 R = $C_6H_4NO_2$-*p*

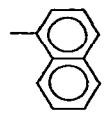
N-(*p*-Hydroxyphenyl)-β-D-mannopyranosylamine (**5**), previously mentioned in the literature[9] (without physical constants), has now been fully characterized.

Several classes of compounds have been reported to produce an insulin-like activity on rat adipocytes *in vitro*. Among these are the D-mannose-specific lectin concanavalin A (refs. 13–15), hydrogen peroxide[4,16,17] and its biochemical precursors, polyamines[18], and benzylamine. Several amino-alkyl and -aryl 1-thio-D-mannosides are effective at $\leqslant 100\mu M$ *in vitro*[1,2,4]. Compound **1** was also found[19] to exert insulin-like activity at $100\mu M$. It is not clear whether the activity of **1** derives from *in vitro* hydrolysis to benzylamine, and the possible contribution of the D-mannose moiety to binding to the insulin-receptor region also needs clarification.



1 R = Ph
6 R = C_6H_4OMe-*p*
7 R = C_6H_4F-*o*
8 R = C_6H_4CN-*p*

9 R =



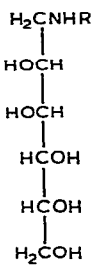
10 R =

11 R =

Following this observation, members of a group of *N*-substituted D-mannosylamines (**6–11**) were prepared for evaluation in various bioassays. Compounds **10** and **11** were also found to mimic the action of insulin on utilization of D-glucose by fat cells[19]. The Amadori compound **2** inhibited the ADP-induced aggregation of rabbit platelets *in vitro*[20] (total inhibition at 1 mg/mL). *N*-*p*-Hydroxyphenyl-β-D-mannopyranosylamine (**5**) was toxic to erythrocytes at 800 μg/mL, as determined by hemolysis. As, in a control experiment, *p*-aminophenol (*p*-hydroxyaniline) was also found to be toxic, the observed toxicity of **5** was probably due to *p*-aminophenol, produced by hydrolysis of **5** in the testing medium.

Glycosylamines are, in general, of limited medicinal interest, because of their hydrolytic instability, even at room temperature. The stability of glycosylamines in aqueous media is a function of the nature of the amine[21]; as an illustration, the *N*-*p*-hydroxyphenyl derivative **5** undergoes rapid hydrolysis, whereas the *N*-1-naphthylmethyl analog (**9**) is stable under the same conditions; ~15% of *N*-benzyl-β-D-

mannopyranosylamine (**1**) and 10% of the *N*-2-pyridylmethyl derivative (**11**) are hydrolyzed in 5 h at room temperature.



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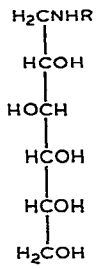

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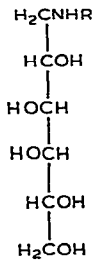

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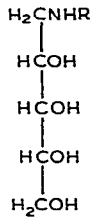

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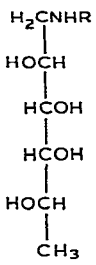

16

R = CH_2Ph

To circumvent this lability, the synthesis, for biological evaluation, of the isomeric, but stable, 1-benzylamino-1-deoxyalditols was investigated. This led to the preparation of **12–16**, which were obtained in crystalline form by following known procedures[22]. Compounds **14–16** exhibited moderate, insulin-antagonistic activity (~80% inhibition at 100 μg/mL)[19], but the nature of this activity is not yet clear.

EXPERIMENTAL

General methods. — Solutions were evaporated below 50° under diminished pressure. Melting points were determined with a Thomas–Hoover "Unimelt" apparatus and are uncorrected. Optical rotations were measured at 27° with a Zeiss polarimeter. N.m.r. spectra were recorded at 60 or 100 MHz with Varian T-60 and HA-100 n.m.r. spectrometers, respectively. Thin-layer chromatography (t.l.c.) was performed on 250-μm Silica Gel GF_{254} (Analtech) plates, and indication was effected with a ceric sulfate (1%)–sulfuric acid (10%) spray.

*N-Benzyl-β-*D*-mannopyranosylamine* (**1**). — D-Mannose (18 g, 0.1 mol) and benzylamine (10.9 mL, 0.1 mol) were dissolved in absolute ethanol (50 mL), and the solution was boiled under reflux for 5 min, cooled, and allowed to crystallize in the cold, to yield **1** (15.5 g, 58%), m.p. 131–132°, $[\alpha]_D^{27}$ −35.3° (*c* 1, methanol); lit.[11] m.p. 80–82°, $[\alpha]_D$ −38.9° (*c* 1, methanol).

Anal. Calc. for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.82; H, 7.23; N, 5.01.

*1-(Benzylamino)-1-deoxy-*D*-fructose* (**2**). — A solution of **1** (1.0 g) and anhydrous oxalic acid (0.5 g) in 10:3 1,4-dioxane–methanol (13 mL) was heated for 5 min at 80°, and the product was crystallized from 2-propanol. Recrystallization from 95% ethanol afforded the oxalate of **2** (90%), m.p. 157–159° (dec.), $[\alpha]_D^{27}$ −26.0 ±1.0° (*c* 1.02, water); lit.[11] m.p. 146–148°, $[\alpha]_D$ −51.3° (*c* 1.0, water).

Anal. Calc. for $C_{13}H_{19}NO_5 \cdot C_2H_2O_4$: C, 50.13; H, 5.89; N, 3.90. Found: C, 50.12; H, 6.16; N, 3.88.

N-(p-*Nitrophenyl*)-β-D-*mannopyranosylamine* (**3**). — Conc. hydrochloric acid (0.18 mL) was added to a solution of D-mannose (9 g) and *p*-nitroaniline (9 g) in methanol (200 mL), and the mixture was heated on a steam cone for 15 min. The products crystallized upon cooling. The solid was filtered off, and the two products were fractionated with boiling methanol. The alcohol-insoluble residue was recrystallized from water, to give **3**, m.p. 217° (dec.), $[\alpha]_D^{27}$ −329 ±0.5° (*c* 1.0, pyridine); lit.[12] m.p. 219°, $[\alpha]_D$ −406→−325° (*c* 0.16, pyridine).

Anal. Calc. for $C_{12}H_{16}N_2O_7$: C, 48.00; H, 5.36; N, 9.33. Found: C, 48.04; H, 5.45; N, 9.34.

1-Deoxy-1-(*p*-nitrophenyl)-D-fructose (**4**) was crystallized, and recrystallized, from methanol; m.p. 215–217° (dec.), $[\alpha]_D^{27}$ −335 ±0.5° (*c* 1.02, pyridine). The combined yield of **3** and **4** was 85%.

Anal. Calc. for $C_{12}H_{16}N_2O_7$: C, 48.00; H, 5.36; N, 9.33. Found: C, 47.66; H, 5.58; N, 9.07.

N-(p-*Hydroxyphenyl*)-β-D-*mannopyranosylamine*[9] (**5**). — D-Mannose (17 g) and *p*-aminophenol (10.4 g) were dissolved in methanol (40 mL) containing a catalytic amount of zinc chloride. The solution was boiled under reflux for 1 h, cooled, and allowed to crystallize in the cold. The solid was filtered off and recrystallized from methanol, to give **5** (15 g, 55%), m.p. 151–152°, $[\alpha]_D^{27}$ −79.8 ±0.5° (*c* 1.0, methanol).

Anal. Calc. for $C_{12}H_{17}NO_6$: C, 53.13; H, 6.31; N, 5.16. Found: C, 52.80; H, 6.50; N, 4.87.

N-(p-*Methoxybenzyl*)-β-D-*mannopyranosylamine* (**6**). — A solution of D-mannose (19 g) and *p*-methoxybenzylamine (13.7 g) in ethanol (50 mL) was boiled under reflux for 10 min, and cooled; the solution became a gel, which was warmed to dissolution and poured into ether. The solid was filtered off and crystallized from ethanol–ethyl acetate–ether, to give **6** (12 g, 40%), m.p. 90–91°, $[\alpha]_D^{27}$ −38.0 ±0.5° (*c* 1.0, methanol).

Anal. Calc. for $C_{14}H_{21}NO_6$: C, 56.17; H, 7.07; N, 4.68. Found: C, 56.23; H, 7.22; N, 4.36.

N-(o-*Fluorobenzyl*)-β-D-*mannopyranosylamine* (**7**). — A suspension of D-mannose (9.0 g) and *o*-fluorobenzylamine (6.25 g) in ethanol (30 mL) was heated under reflux until dissolution occurred. The solution was cooled, and allowed to crystallize. The solid was filtered off, and washed with cold ethanol–ethyl ether, to give **7** (8.8 g, 61%), m.p. 127–129°, $[\alpha]_D^{27}$ −34.6 ±0.5° (*c* 1.0, methanol).

Anal. Calc. for $C_{13}H_{18}FNO_5$: C, 54.35; H, 6.31; F, 6.61; N, 4.88. Found: C, 54.30; H, 6.35; F, 6.52; N, 4.77.

N-p-*Cyanobenzyl*-β-D-*mannopyranosylamine* (**8**). — This compound was prepared similarly to **7**. The crystals were washed with 2-propanol–ether; m.p. 132–133°, $[\alpha]_D^{27}$ −53.7 ±0.5° (*c* 1.0, methanol).

Anal. Calc. for $C_{14}H_{18}N_2O_5$: C, 57.13; H, 6.16; N, 9.52. Found: C, 56.90; H, 6.39; N, 9.27.

N-1-Naphthylmethyl-β-D-mannopyranosylamine (**9**). — A suspension of D-mannose (18 g) and (1-naphthylmethyl)amine (15.7 g) in ethanol (50 mL) containing a catalytic amount of zinc chloride was boiled under reflux for 30 min. The resulting solution was cooled, and allowed to crystallize. Recrystallization from methanol afforded pure **9**, m.p. 151–152°, $[\alpha]_D^{27}$ −42.4 ±0.5° (*c* 1.0, methanol).

Anal. Calc. for $C_{17}H_{21}NO_5$: C, 63.93; H, 6.63; N, 4.38. Found: C, 63.85; H, 6.49; N, 4.25.

N-2-Furanylmethyl-β-D-mannopyranosylamine (**10**). — This compound was prepared similarly to **9**. Recrystallization from ethanol afforded pure **10**, m.p. 78–84°, $[\alpha]_D^{27}$ −40.6 ±0.5° (*c* 1.0, methanol).

Anal. Calc. for $C_{11}H_{17}NO_6$: C, 50.95; H, 6.61; N, 5.40. Found: C, 50.76; H, 6.78; N, 5.16.

N-2-Pyridylmethyl-β-D-mannopyranosylamine (**11**). — This compound was prepared as for **9** in 80% yield; m.p. 120–121°, $[\alpha]_D^{27}$ −31.6 ±0.5° (*c* 1.0, methanol).

Anal. Calc. for $C_{12}H_{18}N_2O_5$: C, 53.32; H, 6.71; N, 10.37. Found: C, 53.03; H, 7.01; N, 9.99.

1-Benzylamino-1-deoxyalditols. — A suspension of benzylamine (0.1 mol) and an aldose (0.1 mol) in methanol (120 mL) was stirred, with brief heating if necessary, until dissolution occurred. Platinum oxide (0.5 g) was added, and the contents were hydrogenated at 40 lb.in.$^{-2}$ for 24 h at room temperature. The mixture was warmed, and filtered, and the solid was washed with methanol. The product usually crystallized on cooling the filtrate. Pure material was obtained upon recrystallization from the same solvent.

1-(Benzylamino)-1-deoxy-D-mannitol (**12**) was prepared in 67% yield, m.p. 162–165°, $[\alpha]_D^{27}$ −21.9 ±0.5° (*c* 0.99, pyridine); lit.[23] m.p. 164–165°, $[\alpha]_D^{22}$ +9.0° (*c* 1.0, water).

Anal. Calc. for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.14; H, 8.09; N, 4.88.

1-(Benzylamino)-1-deoxy-D-glucitol[22] (**13**) was obtained as a crystalline material, m.p. 140–141.5°, $[\alpha]_D^{27}$ −26.6 ±0.5° (*c* 1.03, pyridine).

Anal. Calc. for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.61; H, 7.56; N, 4.98.

1-(Benzylamino)-1-deoxy-D-galactitol (**14**) was obtained in 64% yield, m.p. 160–161°, $[\alpha]_D^{27}$ −12.1 ±0.5° (*c* 1.0, pyridine).

Anal. Calc. for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.40; H, 7.57; N, 5.08.

1-(Benzylamino)-1-deoxy-D-ribitol (**15**) was prepared in good yield, m.p. 101–102°, $[\alpha]_D^{27}$ −0.44 ±0.5° (*c* 1.0, pyridine); lit.[22] m.p. 99–102°.

Anal. Calc. for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.73; H, 7.74; N, 5.57.

1-(Benzylamino)-1-deoxy-L-fucitol (**16**) was isolated as a crystalline material, m.p. 150–153°, $[\alpha]_D^{27}$ −12.5 ±1.0° (*c* 1.04, pyridine).

Anal. Calc. for $C_{13}H_{21}NO_4$: C, 61.15; H, 8.29; N, 5.49. Found: C, 61.23; H, 8.02; N, 5.43.

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