Improved Method of Preparation of Glycosylmethylamines

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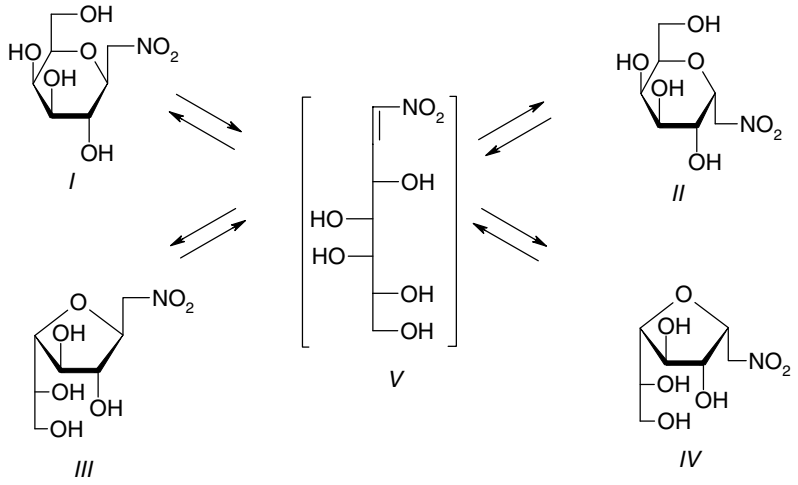
As shown especially for the transformation of the thermally rather unstable α-D-galactofuranosylnitromethane to α-D-galactofuranosylmethylamine, the electron-transfer reduction of glycosylnitromethanes with ferrous ions in aqueous ammonia at room temperature is a very mild and convenient alternative of the preparation of the corresponding glycosylmethylamines. Also β-L-rhamnopyranosylmethylamine, β-D-mannopyranosylmethylamine, β-D-galactopyranosylmethylamine, β-D-glucopyranosylmethylamine, and 2-acetamido-2-deoxy-β-D-glucopyranosylmethylamine were prepared by this improved method. Due to a simple isolation procedure the method gives 90—95 % yields of these interesting *C*-glycosyl compounds containing no isomeric products detectable by ^{1}H NMR spectroscopy. A preparation of β-L-rhamnopyranosylnitromethane is also described.

An electron-transfer reduction of glycosylnitromethanes to the corresponding glycosylmethylamines with ferrous ions in aqueous ammonia has been described in 1980's [1—3]. The reaction conditions of the reduction with ferrous ions, originally developed for preparation of aromatic amines, were completely applied, including increased temperature, also to the reduction of glycosylnitromethanes. Thus, a boiling aqueous solution of a glycosylnitromethane is mixed with a boiling aqueous solution of $FeSO_4$ under addition of concentrated aqueous ammonia to keep the mixture strongly alkaline. The method gives high yields of these interesting *C*-glycosyl compounds and has become an alternative method to the catalytic hydrogenation [4, 5] owing to a simple isolation procedure. From the final reaction mixture containing soluble glycosylmethylammonium and ammonium sulfates and insoluble $Fe_2O_3 \cdot xH_2O$, the iron compound is removed by filtration first. A following treatment of the filtrate with an excess of a strongly basic anion exchanger in the OH form placed in a rotatory evaporator under a diminished pressure removes both sulfate anions and ammonia leaving the free glycosylmethylamine in a final aqueous filtrate.

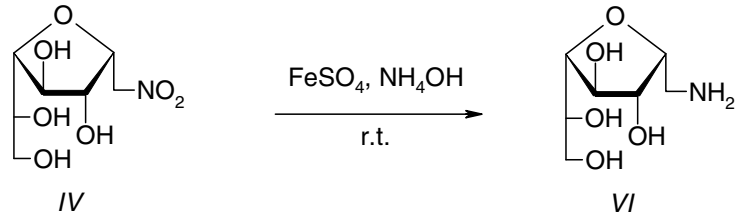
A closer investigation of the reduction has revealed that the increased temperature applied can lead to the formation of isomeric glycosylmethylamines. Namely, at increased temperatures, a thermodynamic equilibration of glycosylnitromethanes *via* a 1,2-dideoxy-1-nitroald-1-enitol, a process analogous to the mutarotation of aldoses, proceeds giving rise to isomeric glycopyranosyl and glycofuranosylnitromethanes [4, 6]. The process is here shown for the corresponding D-galactose derivatives *I*—*IV* that mutually interconvert *via* the corresponding 1,2-dideoxy-1-nitro-D-*galacto*-hept-1-enitol *V* (Scheme 1). Thus, the complementary isomeric glycosylnitromethanes possibly appearing under the reduction conditions can be cotransformed to the unwanted isomeric by-products and become a source of contamination.

To avoid the unwanted competitive reactions, proceeding in addition to the reduction of the nitro to amino group under the advantageous application of the ferrous hydroxide as the reduction agent, the influence of the reaction temperature to the reduction was examined. Surprisingly, the reduction proceeded comparably fast also at room temperature either with a freshly prepared $Fe(OH)_2$ or a commercial $FeSO_4 \cdot 7H_2O$ and ammonia. Apparently, the only reason why the temperature of boiling water was originally applied for the reduction of aromatic nitro to amino compounds [7] was to avoid a phase separation of the nitro aromatics in water.

The newly optimized conditions of the reduction were applied for a convenient transformation of some selected glycosylnitromethanes to the corresponding glycosylmethylamines. Thus, α-D-galactofuranosylmethylamine (*VI*) was prepared and isolated in a 93 % yield from the thermally rather unstable α-D-galactofuranosylnitromethane (*IV*, Scheme 2). Similar respective yields (90—95 %) of β-L-rhamnopyranosylmethylamine (*VII*), β-D-mannopyranosylmethylamine (*VIII*), β-D-galactopyranosylmethylamine (*IX*), β-D-glucopyranosylmethylamine (*X*), and 2-acetamido-2-deoxy-β-D-glucopyranosylmethylamine (*XI*) were obtained from the corresponding starting glycosylnitromethanes. Due to the manipulation simplicity, the method applying directly $FeSO_4 \cdot 7H_2O$, without intermediate isolation of the active species, $Fe(OH)_2$ that is extremely sensitive to the atmospheric oxygen, was



Scheme 1



Scheme 2

preferentially used for the preparation of the glycosylmethylamines.

According to the data of ^{1}H NMR spectroscopy, the glycosylmethylamines prepared were pure compounds not containing traces of the isomeric products (such isomers are usually detectable in mother liquors after crystallization of glycosylmethylamines obtained by the reduction of glycosylnitromethanes with ferrous hydroxide *in situ* in boiling aqueous solution). The NMR spectra of the newly prepared compounds confirm that, except of the expected reduction of the nitromethyl to the aminomethyl group, no other changes in the matrix structure of the glycosyl moiety occurred. The molecular structure of the newly prepared glycosylmethylamines was proved also by the mass spectrometry of their per-*N*,*O*-acetyl derivatives that provided the $(M + H)^+$ ions in their EI mass spectra.

Also the starting glycosylnitromethanes are simply available compounds obtainable in a two-step procedure from a parent glycose (aldose). The addition of nitromethane to the aldose in the first step provides a pair of acyclic 1-deoxy-1-nitroalditol epimers. These compounds easily, already by heating in aqueous solution, eliminate their β-hydroxy group *via* an elimination process initiated from their tautomeric *aci*-nitroforms, giving rise to the corresponding 1,2-dideoxy-1-nitroald-1-enitol, the structure analogical to that of *V* shown in Scheme 1. A spontaneous ring closure of the nitroaldenitol at such increased temperatures then results in the thermodynamic equilibrium mixture of four possible glycosylnitromethanes in which, due to the obvious stereochemical reasons, β-pyrano isomer highly prevails.

The application of this procedure to L-rhamnose enabled to obtain crystalline β-L-rhamnopyranosylnitromethane in a 55 % yield. The investigation of its final reaction mixture by NMR spectroscopy has revealed that the amount of the individual accompanying isomeric by-products did not exceed 5 %.

Thus, the glycosylmethylamines that conveniently mimic the glycosyl moiety of the parent aldoses are easily available *via* their nitro precursors. Unlike the intermediate glycosylnitromethanes, the glycosylmethylamines possess already a stable structure of their glycosyl moiety not susceptible to isomerization changes in a wide range of conditions. Therefore the compounds are of a high significance for further synthetic modifications and subsequent use in biochemical applications, such as *e.g.* a search for potent glycosidase inhibitors for combating civilization diseases [13, 14] or in other protein-affinity applications [15, 16].

EXPERIMENTAL

Specific rotations were measured on a Perkin—Elmer 141 polarimeter and the melting points were determined on a Kofler stage. Elemental analyses were done with a Fisons EA 1108 analyzer. NMR spectra

were recorded at 20 °C on a Bruker AVANCE DPX 300 spectrometer (300.13 MHz, internal standard sodium 3-(trimethylsilyl)propionate, $\delta = 0.00$ for ^{1}H and 75.47 MHz, internal standard methanol, $\delta = 50.15$ for ^{13}C). Homo and hetero nuclear correlation spectroscopy experiments were performed when indicated. EI mass spectra (70 eV) were recorded using a Finnigan MAT SSQ 710 spectrometer.

TLC was run on glass plates precoated with silica gel TLC (5—40 μm, Aldrich) and eluted with ethyl acetate—butan-1-ol—methanol—water (φ_r = 18:9:7:3). Detection was effected by spraying the chromatograms with a 10 % ethanolic sulfuric acid and charring them on a hot plate. For paper chromatography, Whatman No. 1 sheets, butan-1-ol—ethanol—water ($\varphi_r = 5:1:4$), and detection with alkaline silver nitrate spraying were used.

Ferrous hydroxide was prepared by precipitation of an aqueous 0.05 M-$FeSO_4$ solution with an equimolar amount of 1 M-NaOH and a repeated centrifugation and washing the sky-blue precipitate with water until a neutral supernatant was obtained. All the operations for preparation and use of ferrous hydroxide were performed with preboiled water and under argon. Individual glycosylmethylamine per-*N*,*O*-acetyl derivatives for mass spectrometry were prepared by a standard acetylation procedure with acetic anhydride—pyridine ($\varphi_r = 1:1$) at a temperature below 40 °C controlled by the rate of addition of a powdery glycosylmethylamine or its solution in methanol to the reaction mixture.

β-L-Rhamnopyranosylnitromethane (2,6-Anhydro-1,7-dideoxy-1-nitro-L-*glycero*-L-*galacto*-heptitol)

To a stirred solution of L-rhamnose (50 g) in methanol (300 cm^3), nitromethane (100 cm^3), a sodium methoxide solution (12.5 g of sodium dissolved in 350 cm^3 of methanol), and after 2 h butan-1-ol (250 cm^3) were added successively at room temperature. After 24 h at 5 °C, the mixture was filtered to collect crystalline product that after being washed with a cold mixture of methanol—butan-1-ol (φ_r= 1:1, 3 × 50 cm^3) was transferred to a stirred mixture of water (300 cm^3) and crushed solid carbon dioxide (dry ice, 100 g) that was kept for half an hour at a temperature slightly above 0 °C not to allow it to freeze. During this time, additional dry ice (100 g) was being gradually added to the mixture to keep its permanent presence there. Then, a cation-exchange resin in the H form (Amberlite IR-120, 37—75 μm, 200 g) was added and the mixture was stirred until dry ice completely disappeared and a neutral solution over the resin was obtained. Then the resin was filtered off, washed with water (3 × 50 cm^3) and the combined filtrate and washings were heated at 100 °C for 30 h. Finally, activated charcoal (3 g) was added to the hot solution, left to cool and filtered to a colourless filtrate. Its evaporation gave a raw sirupy β-L-rhamnopyranosylnitromethane (containing about 5 % of starting L-rhamnose) that gradually turned to crystals. Yield = 17.7 g (55 %). Chromatographically pure β-L-rhamnopyranosylnitromethane was obtained by a purification *via* its nitronate form with a strongly basic anion-exchange resin in the OH form (Dowex 1, X-4, 150—300 μm), washing the nitronate form of the resin with water and a subsequent release of the glycosylnitromethane from the resin by treatment with carbon dioxide. M.p. = 119—121 °C, [α] (D, 20 °C, water, ρ = 10.0 g dm^{-3}) = + 33.2°. For $C_7H_{13}O_6N$ ($M_r = 207.18$) w_i(calc.): 40.58 % C, 6.32 % H, 6.76 % N; w_i(found): 40.70 % C, 6.30 % H, 6.51 % N. ^{1}H NMR* (D_2O), δ: 4.80 (dd, 1H, H-1, $J_{1,2} = 2.9$ Hz, $J_{1,1'} = 13.7$ Hz), 4.71 (dd, 1H, $J_{1',2} = 9.3$ Hz, H-1′), 4.37 (dd, 1H, $J_{2,3} = 3.3$ Hz, H-2), 4.02 (d, 1H, $J_{3,4} = 3.3$ Hz, H-3), 3.66 (dd, 1H, $J_{4,5} = 9.0$ Hz, H-4), 3.35—3.46 (m, 2H, H-5, H-6), 1.28 (d, 3H, $J = 5.5$ Hz, H-7, H-7′, H-7″). ^{13}C NMR* (D_2O), δ: 77.65 (C-1), 77.17 (C-6), 75.75 (C-2), 74.32 (C-4), 73.03 (C-5), 70.38 (C-3), 17.87 (C-7).

Reduction of Glycosylnitromethanes with Freshly Prepared Ferrous Hydroxide (Method *A*)

A solution of a glycosylnitromethane (β-D-galactopyranosylnitromethane or β-D-glucopyranosylnitromethane [1], 1 g; 4.5 mmol) in preboiled water (10 cm^3) was added to an aqueous suspension of ferrous hydroxide (20 cm^3) freshly prepared from $FeSO_4 \cdot 7H_2O$ (10 g; 3.6 mmol) and left to stir at room temperature under argon for 30 min. Then, the precipitate was filtered off and washed with 5 % aqueous ammonia (5 × 10 cm^3). The collected filtrates were concentrated on a rotatory evaporator under reduced pressure, the residue was three times repeatedly dissolved in methanol and evaporated again. The residue was finally crystallized from methanol to obtain the pertinent glycosylmethylamine *IX* or *X*.

Reduction of Glycosylnitromethanes with Ferrous Sulfate and Ammonia (Method *B*)

A solution of a glycosylnitromethane (β-D-galactopyranosylnitromethane, 1 g; β-D-glucopyranosylnitromethane, 1 g; β-D-mannopyranosylnitromethane [8], 1 g; α-D-galactofuranosylnitromethane [9], 1 g; β-L-rhamnopyranosylnitromethane, 0.95 g; or 2-acetamido-2-deoxy-β-D-glucopyranosylnitromethane [3], 1.2 g; always 4.5 mmol) in preboiled water (10 cm^3) was mixed with a solution of $FeSO_4 \cdot 7H_2O$ (8.75 g; 31.5 mmol) in a similarly deoxygenated water (20 cm^3) and after addition of a 25 % aqueous ammonia (15

*Assignment of the NMR signals is referred to the alternative name of the compound in parentheses.

cm^3) the mixture was stirred at room temperature under argon for 10 min. The precipitate was filtered off and washed with 5 % aqueous ammonia (5 × 10 cm^3). The collected filtrates, mixed with Amberlite IRA 402 (400 cm^3) were concentrated on a rotatory evaporator under reduced pressure to a thick suspension and the procedure was repeated twice, always after addition of water (100 cm^3). Finally, the combined filtrates obtained after filtrating and washing the resin with water (4 × 50 cm^3) were concentrated on a rotatory evaporator under reduced pressure, the residue was three times repeatedly dissolved in methanol and evaporated again. The residue was crystallized from methanol or dried over sodium hydroxide pellets in vacuum to obtain the pertinent glycosylmethylamine *VI*—*XI*.

α-D-Galactofuranosylmethylamine (7-Amino-3,6-anhydro-7-deoxy-D-*glycero*-L-*galacto*-heptitol, *VI*)

Yield = 0.8 g (93 %), glassy foam, [α] (D, 20 °C, water, ρ = 10.0 g dm^{-3}) = −17.0°. For $C_7H_{15}NO_5$ (M_r = 193.19) w_i(calc.): 43.52 % C, 7.85 % H, 7.25 % N; w_i(found): 43.14 % C, 7.74 % H, 7.14 % N. ^{1}H NMR* (D_2O), δ: 4.16—4.27 (m, 2H, H-2, H-3), 4.13 (dd, 1H, $J_{3,4}$ = 2.2 Hz, $J_{4,5}$ = 4.5 Hz, H-4), 3.83 (m, 1H, H-6), 3.78 (dd, $J_{5,6}$ = 9.1 Hz, H-5), 3.68 (dd, $J_{1,2}$ = 4.4 Hz, $J_{1,1'}$ = 11.7 Hz, H-1), 3.63 (dd, $J_{1',2}$ = 6.9 Hz, H-1′), 3.24 (dd, $J_{6,7}$ = 3.6 Hz, $J_{7,7'}$ = 13.2 Hz, H-7), 3.19 (dd, $J_{6,7'}$ = 6.3 Hz, H-7′). ^{13}C NMR* (D_2O), δ: 85.05 (C-3), 79.11 (C-4), 78.21 (C-5), 77.78 (C-6), 71.96 (C-2), 63.57 (C-1), 40.16 (C-7). Mass spectrum (EI) of the per-*N*,*O*-acetyl derivative: m/z = 404 (M + H)$^+$.

β-L-Rhamnopyranosylmethylamine (1-Amino-2,6-anhydro-1,7-dideoxy-L-*glycero*-L-*galacto*-heptitol, *VII*)

Yield = 0.75 g (94 %), m.p. = 55—56 °C, [α] (D, 20 °C, water, ρ = 10.0 g dm^{-3}) = + 44.8°. For $C_7H_{15}NO_4$ (M_r = 177.20) w_i(calc.): 47.45 % C, 8.53 % H, 7.90 % N; w_i(found): 47.11 % C, 8.85 % H, 7.74 % N. ^{1}H NMR* (D_2O), δ: 3.93 (d, 1H, $J_{2,3}$ = $J_{3,4}$ = 3.1 Hz, H-3), 3.48—3.62 (m, 2H, H-2, H-4), 3.28—3.40 (m, 2H, H-5, H-6), 3.17 (dd, 1H, $J_{1,2}$ = 7.0 Hz, $J_{1,1'}$ = 13.7 Hz, H-1), 2.79 (dd, 1H, $J_{1,2}$ = 4.9 Hz, H-1′), 1.27 (d, 3H, J = 5.6 Hz, H-7, H-7′, H-7″). ^{13}C NMR* (D_2O), δ: 79.52 (C-2), 77.00 (C-6), 74.73 (C-4), 74.49 (C-5), 70.58 (C-3), 42.08 (C-1), 17.89 (C-7). Mass spectrum (EI) of the per-*N*,*O*-acetyl derivative: m/z = 346 (M + H)$^+$.

β-D-Mannopyranosylmethylamine (1-Amino-2,6-anhydro-1-deoxy-D-*glycero*-D-*galacto*-heptitol, *VIII*)

Yield = 0.82 g (95 %), m.p. = 166—167 °C, [α] (D, 20 °C, water, ρ = 10.0 g dm^{-3}) = −24.0°. For $C_7H_{15}NO_5$ (M_r = 193.19) w_i(calc.): 43.52 % C, 7.85 % H, 7.25 % N; w_i(found): 43.17 % C, 7.60 % H, 6.97 % N. ^{1}H NMR* (D_2O), δ: 3.88—3.95 (m, 2H, H-2, H-3), 3.68 (dd, 1H, $J_{6,7}$ = 7.0 Hz, $J_{7,7'}$ = 12.1 Hz, H-7), 3.57—3.66 (m, 2H, H-4, H-7′), 3.53 (t, 1H, $J_{4,5}$ = $J_{5,6}$ = 9.5 Hz, H-5), 3.35 (dtd, 1H, $J_{6,7'}$ = 2.2 Hz, H-6), 2.96 (dd, $J_{1,2}$ = 8.5 Hz, $J_{1,1'}$ = 13.4 Hz, H-1), 2.88 (dd, $J_{1',2}$ = 4.2 Hz, H-1′). ^{13}C NMR* (D_2O), δ: 80.93 (C-2), 78.42 (C-6), 74.91 (C-5), 70.59 (C-3), 68.25 (C-4), 62.39 (C-7), 42.13 (C-1). Mass spectrum (EI) of the per-*N*,*O*-acetyl derivative: m/z = 404 (M + H)$^+$.

β-D-Galactopyranosylmethylamine (7-Amino-2,6-anhydro-7-deoxy-L-*glycero*-L-*galacto*-heptitol, *IX*)

Method *A*, yield = 0.80 g (92 %), method *B*, yield = 0.81 g (94 %). M.p. = 192—193 °C, [α] (D, 20 °C, water, ρ = 10.0 g dm^{-3}) = + 29.2°; Ref. [10] gives m.p. = 191—192 °C, [α] (D, 20 °C, water, ρ = 16.1 g dm^{-3}) = + 30.0°; Ref. [11] gives m.p. = 194—195 °C, [α] (D, 20 °C, water, ρ = 10.0 g dm^{-3}) = + 29.5°.

β-D-Glucopyranosylmethylamine (1-Amino-2,6-anhydro-1-deoxy-D-*glycero*-D-*gulo*-heptitol, *X*)

Method *A*, yield = 0.78 g (90 %), method *B*, yield = 0.80 g (92 %). M.p. = 167—168 °C, [α] (D, 20 °C, water, ρ = 10.0 g dm^{-3}) = −6.4°; Ref. [12] gives m.p. = 164—165 °C, [α] (D, 20 °C, water, ρ = 16.1 g dm^{-3}) = −6.7°; Ref. [10] gives m.p. = 171.4—171.7 °C, [α] (D, 20 °C, water, ρ = 14.0 g dm^{-3}) = −6.4°.

2-Acetamido-2-deoxy-β-D-glucopyranosylmethylamine (3-Acetamido-1-amino-2,6-anhydro-1,3-dideoxy-D-*glycero*-D-*gulo*-heptitol, *XI*)

Yield = 1.0 g (94 %), m.p. = 203—205 °C, [α] (D, 20 °C, water, ρ = 10.0 g dm^{-3}) = −26.0°; Ref. [3] gives m.p. = 205—206 °C, [α] (D, 20 °C, water, ρ = 20.0 g dm^{-3}) = −26.3°.

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