# Preparation of 2-acetamido-2-deoxy-β-D-glucopyranosylmethylamine *via* nitromethane route

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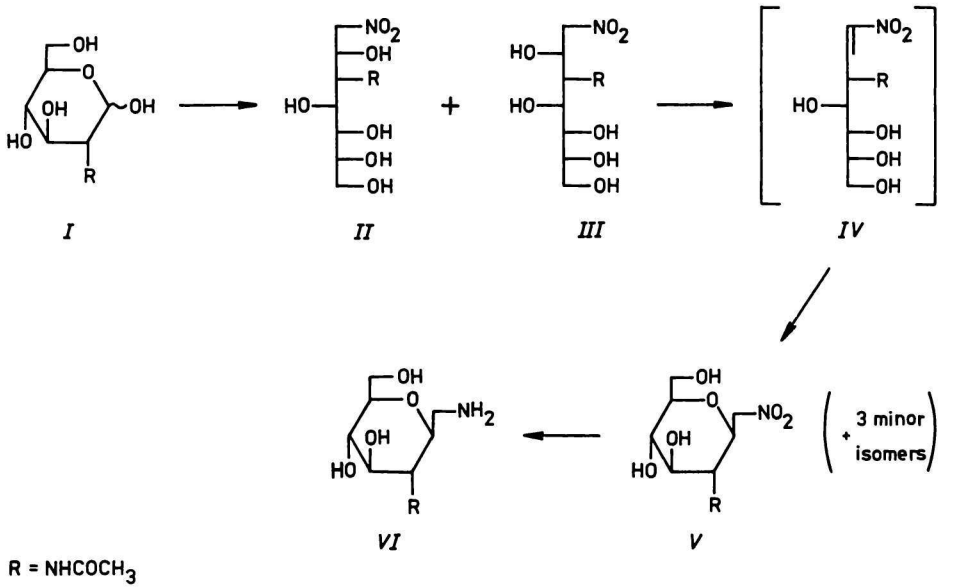
*Dedicated to Professor P. Hrnčiar, DrSc., in honour of his 60th birthday*

Epimeric 3-acetamido-1,3-dideoxy-1-nitroheptitols formed in the nitromethane synthesis with *N*-acetyl-D-glucosamine were converted to 2-acetamido-2-deoxy-β-D-glucopyranosylnitromethane by intramolecular cyclodehydration. The compound was isolated as a salt of a strongly basic anion-exchange resin in the OH form, from which it was liberated by carbon dioxide. Reduction of the nitro derivative with iron(II) hydroxide *in situ* afforded 2-acetamido-2-deoxy-β-D-glucopyranosylmethylamine. Its structure was proved by the $^{13}C$ NMR spectrometry.

Эпимерные 3-ацетамидо-1,3-дидезокси-1-нитрогептитолы, образуемые путем нитрометанового синтеза из *N*-ацетил-D-глюкозамина, были превращены в 2-ацетамидо-2-дезокси-β-D-глюкопиранозилнитрометан посредством внутримолекулярной циклодегидратации. Это соединение было выделено в виде соли сильно основной анионо-обменной смолы в OH-форме, из которой затем было изолировано с помощью двуокиси углерода. Восстановление нитропроизводного гидроокисью железа(II) *in situ* приводило к образованию 2-ацетамидо-2-дезокси-β-D-глюкопиранозилметиламина. Его структура была установлена с помощью $^{13}C$ ЯМР спектрометрии.

Glycosylmethylamines and glycosylnitromethanes are important derivatives of saccharides useful above all as synthetic precursors [1—7]. Recently we have described an advantageous method of preparation and isolation of glycosylnitromethanes, which enabled to synthesize the (1 → 4) disaccharidic derivatives [8] as well. Further, an efficient application of the iron(II) hydroxide reduction of glycosylnitromethanes leading to the corresponding glycosylmethylamines [9, 10] has been shown. In the present work, these procedures have been modified and utilized for the preparation of the glycosylmethylamine derivative from *N*-acetyl-D-glucosamine.

Nitromethane synthesis with *N*-acetyl-D-glucosamine (*I*, Scheme 1) in the presence of sodium methoxide afforded crystalline sodium salts of 3-acetamido-1,3-dideoxy-1-nitro-D-*glycero*-D-*gulo*-heptitol (*II*) and 5-acetamido-




*Scheme 1*

-5,7-dideoxy-7-nitro-D-*glycero*-L-*gulo*-heptitol (*III*). The compounds were deionized in an aqueous suspension of crushed solid carbon dioxide and a cation exchanger in its H-form. Carbonic acid brings about the neutralization of strongly basic anions of nitroalditols *II* and *III* immediately in homogeneous reaction mixture, and not only after their diffusion into the structure of the ion exchanger. If the deionization was carried out without the coeffect of carbon dioxide, the total yield of *II* and *III* was substantially decreased. The derivatives *II* and *III* ($R_{GANAc}$ = 1.38 and 1.58) were converted by heating in aqueous solution to a mixture of isomeric glycosylnitromethanes. 2-Acetamido-2-deoxy--$\beta$-D-glucopyranosylnitromethane (*V*) (3-acetamido-2,6-anhydro-1,3-dideoxy--1-nitro-D-*glycero*-D-*gulo*-heptitol) was the dominant product of the intramolecular cyclodehydration. Paper chromatography revealed a presence only of low amounts of other isomeric ($\alpha$-pyrano-, $\alpha$- and $\beta$-furano-) glycosylnitromethanes ($R_{GANAc}$ = 1.93, 2.44, and 2.59). At elevated temperatures, all these compounds are convertible to each other. The interconversion proceeds *via* a 1,2-unsaturated intermediate [1, 11], in our case apparently *via* the structure *IV*. The high preference of the derivative *V* in the equilibrium reaction mixture is due to the stability of its per-equatorially substituted pyranoid ring as well as a negligible influence of the anomeric effect of the nitromethyl group. The structure of *V* was proved on the basis of the determination of the chemical shift of its

$CH_2NO_2$ carbon atom ($\delta = 77.8$ ppm). This value was the same for analogical derivatives of D-glucose, D-galactose, maltose, cellobiose, and lactose as well [9], the structures of which have been confirmed by a CD method [8, 12].

The isolation of the derivative *V* (together with the minor isomers) from reaction mixture containing also starting material *I*, which rises during the cyclodehydration of *II* and *III* by their simultaneous retroaldol cleavage, was carried out by the ionic binding of *V* to a strongly basic anion exchanger in its OH form ($pK_a$ values of nitro derivatives of sugars vary in the range 8.8—9.2 [2]). If a higher amount than a sufficient one of the anex was used, an excess of nitromethane ($pK_a = 10.2$) had to be added to occupy all the free functional groups of the resin. Otherwise a strong, with water not extractable sorption of the starting aldose occurred ($pK_a$ of common reducing sugars is 12.0 to 12.4). After washing the anex with water to remove starting *I*, its recycling to the $HCO_3$ form by excess of carbon dioxide ($pK_{a1}$ of carbonic acid is 6.5) liberated *V* containing low admixtures of its other isomers in total 55 % yield.

Treatment of *V* in aqueous solution with iron(II) sulfate and ammonia at about 100 °C for 15 min afforded 2-acetamido-2-deoxy-β-D-glucopyranosylmethylamine (*VI*) (3-acetamido-1-amino-2,6-anhydro-1,3-dideoxy-D-*glycero*-D-*gulo*-heptitol), which was isolated by a very simple procedure in 95 % yield. $^{13}C$ NMR spectral measurement confirmed the structure of *VI*, *i.e.* neither any cleavage nor any migration of the secondary *N*-acetyl group occurred during the reduction and isolation steps.

## 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 an automatic Perkin—Elmer 240 analyzer. $^{13}C$ NMR spectra were recorded with a Bruker AM-300 spectrometer at room temperature using methanol as internal standard. Purity of compounds and composition of reaction mixtures were examined by chromatography on the Filtrak FN 1 paper (VEB Specialpapierfabrik, Niederschlag, GDR) in the elution system $S_1$ 1-butanol—ethanol—water, volume ratio = 5 : 1 : 4. Chromatographic mobilities of individual compounds are referred to the mobility of *N*-acetyl-D-glucosamine ($R_{GANAc} = 1.00$).

### *2-Acetamido-2-deoxy-β-D-glucopyranosylnitromethane (V)*

To a stirred solution of *N*-acetyl-D-glucosamine (5 g) in dimethyl sulfoxide (20 $cm^3$), nitromethane (8 $cm^3$), a sodium methoxide solution (1 g of sodium, 35 $cm^3$ of methanol), and, after 2 h, 1-butanol (150 $cm^3$) were added successively at room temperature. After 24 h at 0 °C, the mixture was filtered to collect the crystalline product which, after being

washed with cold methanol (2 × 20 $cm^3$), was transferred to a stirred mixture of water (50 $cm^3$), a cation exchanger in the H form (Dowex 50 W X-8, 75—150 μm, 20 g), and crushed solid carbon dioxide (15 g). 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. Decolourized filtrate (with 0.3 g of activated charcoal) was added to a strongly basic anion exchanger in the OH form (Dowex 1 X-4, 150—300 μm, 5 g) and left to stand under occasional stirring for 1 h. The anex was filtered off and thoroughly washed with water (250 $cm^3$). The residue after the evaporation of the filtrate and the washings was a regenerated portion of starting *N*-acetyl-D-glucosamine (1.7 g, 34 %).

The suspension of the washed anex in water (25 $cm^3$) was treated under stirring with crushed solid carbon dioxide (4 × 5 g) at 20 °C (to prevent freezing the mixture). The anex was finally filtered off, washed with water (3 × 30 $cm^3$), and the combined filtrates evaporated under reduced pressure to a crude *V*, yield = 3.5 g (55 %). Its crystallization afforded hydrate of *V*, yield = 2.2 g (35 %), m.p. = 202—203 °C (methanol), $[\alpha]$(D, 20 °C, $\varrho = 20$ g $dm^{-3}$, water) = −8.1°, $R_{GANAc} = 1.73$ ($S_1$). For $C_9H_{16}N_2O_7 \cdot H_2O$ ($M_r = 282.25$) $w_i$(calc.): 38.30 % C, 6.43 % H, 9.93 % N; $w_i$(found): 38.35 % C, 6.67 % H, 9.78 % N. $^{13}C$ NMR spectrum ($^2H_2O$), $\delta$/ppm: 175.9 (C=O), 80.8 (C-1), 77.8 ($CH_2NO_2$), 76.3, 76.0 (C-5, C-3), 71.0 (C-4), 61.9 (C-6), 53.8 (C-2), 23.3 ($CH_3$).

### *2-Acetamido-2-deoxy-β-D-glucopyranosylmethylamine (VI)*

A solution of *V* (2 g) in hot water (20 $cm^3$) was added to a stirred boiling solution of iron(II) sulfate heptahydrate (16.3 g) in water (35 $cm^3$). Concentrated aqueous solution of ammonia was then added portionwise (à 3 $cm^3$) under stirring until the reaction mixture had a strong alkaline reaction. After boiling for 10 min (the alkaline reaction was kept by addition of further ammonia), the precipitate was filtered and washed with 2 % aqueous solution of ammonia (50 $cm^3$). The filtrate was cooled, mixed with Dowex 1 X-4 ($OH^-$; 50 g) and the suspension was concentrated on a rotatory evaporator under diminished pressure to half of the original volume. After addition of water (100 $cm^3$), the operation was repeated twice more. Then the anex was filtered off and washed with water (3 × 50 $cm^3$). Concentration of the filtrate and washings afforded *VI*. Yield = 1.6 g (95 %), m.p. = 205—206 °C (methanol), $[\alpha]$(D, 20 °C, $\varrho = 20$ g $dm^{-3}$, water) = = −26.3°, $R_{GANAc} = 0.88$ ($S_1$). For $C_9H_{18}N_2O_5$ ($M_r = 234.25$) $w_i$(calc.): 46.15 % C, 7.74 % H, 11.96 % N; $w_i$(found): 45.98 % C, 7.80 % H, 12.18 % N. $^{13}C$ NMR spectrum ($^2H_2O$), $\delta$/ppm: 175.8 (C=O), 80.6, 80.3, 76.4 (C-1, C-5, C-3), 71.5 (C-4), 62.4 (C-6), 54.1 (C-2), 43.0 ($CH_2NH_2$), 23.3 ($CH_3$).

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