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Direct Syntheses of Methyl 2-Deoxy-2-alkoxycarbonylamino-D-glucopyranoside from 2-Amino-2-deoxy-D-glucose

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Synopsis. Methyl 2-deoxy-2-methoxycarbonylamino- and methyl 2-deoxy-2-ethoxycarbonylamino-D-glucopyranosides were synthesized by the reaction of 2-amino-2-deoxy-D-glucose with alkyl chlorocarbonate and sodium carbonate in methanol by a one-step process.

This note deals with the direct syntheses of methyl 2-deoxy-2-methoxycarbonylamino-α- (MI-α), methyl 2-deoxy-2-methoxycarbonylamino-β- (MI-β), methyl 2-deoxy-2-ethoxycarbonylamino-α- (MII-α) and methyl 2-deoxy-2-ethoxycarbonylamino-β-D-glucopyranoside (MII-β) starting from 2-amino-2-deoxy-D-glucose hydrochloride.

MI-β and MII-β were synthesized in two steps with 15—28% yield,[1,2] the first step being the formation of 2-deoxy-2-methoxycarbonylamino- (I) and 2-deoxy-2-ethoxycarbonylamino-D-glucose (II) by the reaction of 2-amino-2-deoxy-D-glucose with a half equivalent of methyl and ethyl chlorocarbonate respectively in methanol, and the second step the glycosidation with methanolic hydrogen chloride. Recently, MI-α has been synthesized in 78% yield[3] by the reaction of 2-amino-2-deoxy-D-glucose with an equivalent of methyl chlorocarbonate and sodium carbonate in aqueous acetone, followed by evaporation to dryness and the glycosidation with methanolic hydrogen chloride without isolation of I. The author has found that 2-amino-2-deoxy-D-glucose reacts with excess methyl or ethyl chlorocarbonate in methanol to give the main product MI-α, MI-β, MII-α, or MII-β in a good yield. The reaction might be utilized as a convenient procedure for the syntheses.

2-Amino-2-deoxy-D-glucose hydrochloride was dissolved in methanol containing an equivalent of sodium. After the addition of finely powdered anhydrous sodium carbonate, excess methyl or ethyl chlorocarbonate was added under stirring. The components of the reaction products were detected by thin-layer chromatography with silica gel and *n*-propanol–concd ammonia water–water (6:2:1). It was confirmed that, after the formation of I or II, β-glycoside appeared, gradually changing into α-glycoside. Separation of the components was carried out by column chromatography using silicic acid and ethyl acetate–methanol (9:1). Evaporation of the elution and crystallization gave the pure products. At refluxing temperature overnight, the thermodynamically stable α-glycoside was the major product in 83% yield accompanied by a small amount of the kinetically favorable β-glycoside in 9—10% yield. After being stirred at room temperature for three days, the β-glycoside was found to be the main product in 65—66% yield, in addition to a considerable amount of the α-glycoside as a by-product in 29% yield.

The α- and β-glycoside were identified by elementary analysis and the physical constant measurements.[1,2] The melting point of MI-α differed from that of the reference,[3] MII-α being an unknown compound. In the NMR spectrum of MI-α in deuterium oxide the protons OCH_3 (singlet, τ 6.60), $NHCOOC\underline{H}_3$ (singlet, τ 6.32) and H-2,3,4,5,6,6′ (multiplet, τ 6.1—6.6) were identical with those of the reference.[3] However, the proton of H-1, reported[3] to appear at τ 5.18 (doublet, J=2 Hz), could not be detected because of the overlapping with HOD signal (τ 5.15—5.4). The data are in good agreement with the NMR spectrum of MI-β except the protons OCH_3 and H-1. In the NMR spectrum of MII-α in deuterium oxide, protons $NHCOOCH_2C\underline{H}_3$ (triplet, τ 8.78), $NHCOOC\underline{H}_2CH_3$ (quartet, τ 5.91) and H-2,3,4,5,6,6′ (multiplet, τ 6.1—6.6) were essentially identical with those of MII-β, and protons OCH_3 (singlet, τ 6.62) were in good agreement with those of MI-α, differing from those of MI-β (τ 6.50) and MII-β (τ 6.52). As in the case of MI-α the proton of H-1 of MII-α could not be detected at τ 5.2. Therefore, by measuring the NMR spectra in acetic acid-d_4, protons of H-1 of MI-α and MII-α were detected at τ 5.26 (doublet, J=1.8 Hz) and at τ 5.27 (doublet, J=1.7 Hz), respectively. These NMR data were compatible with those of the α-glycoside.

The reaction mechanism is considered to consist of the formation of I or II and the subsequent methyl glycosidation catalyzed with hydrogen chloride liberated by the decomposition of alkoxy chlorocarbonate.

Experimental

All melting points were taken in capillaries with a Yamato melting point apparatus model MP-21. NMR spectra were measured with a JEOL PS-100 spectrometer. Sodium 4,4-dimethyl-4-silapentane-1-sulfonate (for the solution of deuterium oxide) and tetramethyl silane (for the solution of acetic acid-d_4) were used as an internal standard. Thin-layer chromatography (tlc) was carried out on precoated plates of silica gel G (E. Merck) with the solvent (*n*-propanol–concd ammonia water–water (6:2:1)), and the spots were visualized with iodine vapor. Column chromatography was carried out with silicic acid (AR 100 mesh, Mallincrodt).

Reaction at Refluxing Temperature in Methanolic Solution. 2-Amino-2-deoxy-D-glucose hydrochloride (2 g) was dissolved in methanol (50 ml) containing sodium (0.23 g). After the addition of finely powdered anhydrous sodium carbonate (1 g), methyl chlorocarbonate (6 ml) was added dropwise to the mixture under stirring. When the mixture was refluxed overnight, tlc showed two spots corresponding to MI-α (R_f

0.65, major spot) and **MI-β** (R_f 0.57, minor spot). The mixture was neutralized with lead carbonate and filtered. The clear solution was evaporated to a crystalline residue, which was chromatographed on a column of silicic acid (65×4.5 cm) with ethyl acetate–methanol (9: 1). The two components were obtained as needles after evaporation of the elution. MI-α was recrystallized from methanol–ether; 1.85 g (83%), mp 150—151 °C, $[\alpha]_D^{32}$ +137° (*c* 2, methanol); (lit,[3] mp 126—128 °C, $[\alpha]_D^{22}$ +135° (*c* 2, methanol)).

Found: C, 42.75; H, 7.00; N, 5.49%. Calcd for $C_9H_{17}NO_7$: C, 43.02; H, 6.82; N, 5.58%.

NMR (in D_2O): τ 6.61 (3H, s, OCH_3), 6.32 (3H, s, $NHCOOCH_3$), 6.1—6.6 (6H, m, H-2,3,4,5,6,6′). (in CD_3COOD): 6.63 (3H, s, OCH_3), 6.33 (3H, s, $NHCOOCH_3$), 6.0—6.5 (6H, m, H-2,3,4,5,6,6′), 5.26 (1H, d, J=1.8 Hz, H-1).

MI-β was recrystallized from methanol: 0.21 g (9%), mp 197—198 °C, $[\alpha]_D^{22}$ −35° (*c* 1, water); (lit,[1] mp 196—197 °C, $[\alpha]_D^{18}$ −33.8° (water)). (Found: C, 42.86; H, 6.82; N, 5.53%).

NMR (in D_2O): τ 6.50 (3H, s, OCH_3), 6.32 (3H, s, $NHCOOCH_3$), 6.1—6.7 (6H, m, H-2,3,4,5,6,6′), 5.58 (1H, d, J=8 Hz, H-1).

When ethyl chlorocarbonate (6 ml) was used, the reaction gave MII-α (R_f 0.70, major product) and MII-β (R_f 0.61, minor product) on tlc. MII-α was recrystallized from methanol–ether; 2.05 g (83%); mp 113—115 °C, $[\alpha]_D^{31}$ +114° (*c* 1, water), +127° (*c* 1, methanol).

Found: C, 45.46; H, 7.26; N, 5.37%. Calcd for $C_{10}H_{19}NO_7$: C, 45.27; H, 7.22; N, 5.28%.

NMR (in D_2O): τ 8.78 (3H, t, $NHCOOCH_2C\underline{H}_3$), 6.62 (3H, s, OCH_3), 6.1—6.6 (6H, m, H-2,3,4,5,6,6′), 5.89 (2H, q, $NHCOOC\underline{H}_2CH_3$). (in CD_3COOD): 8.78 (3H, t, $NHCOOCH_2C\underline{H}_3$), 6.64 (3H, s, OCH_3), 6.05—6.5 (6H m, H-2,3,4,5,6,6′), 5.91 (2H, q, $NHCOOC\underline{H}_2CH_3$), 5.27 (1H, d, J=1.7 Hz, H-1).

MII-β was recrystallized from methanol; 0.24 g (10%), mp 188—189 °C, $[\alpha]_D^{22}$ −30° (*c* 1, water); (lit,[2] mp 188—189 °C, $[\alpha]_D^{15}$ −31° (*c* 3.2, water). (Found: C, 45.05; H, 7.24; N, 5.30%).

NMR (in D_2O): τ 8.78 (3H, t, $NHCOOCH_2C\underline{H}_3$), 6.52 (3H, s, OCH_3), 6.1—6.8 (6H, m, H-2,3,4,5,6,6′), 5.91 (2H, q, $NHCOOC\underline{H}_2CH_3$), 5.62 (1H, d, J=8 Hz, H-1).

Reaction at Room Temperature. 2-Amino-2-deoxy-D-glucose hydrochloride (2 g) was dissolved in methanol (50 ml) containing sodium (0.23 g). After addition of finely powdered anhydrous sodium carbonate (1 g) methyl chlorocarbonate (4 ml) was added dropwise to the mixture under stirring. When the mixture was stirred for 3 days at room temperature, tlc showed MI-β (major product) and MI-α (minor product). The same treatment gave the two components which yielded on crystallization; 1.53 g (66%) of MI-β and 0.68 g (29%) of MI-α.

When ethyl chlorocarbonate (4 ml) was used, the reaction gave MII-β yielding 1.60 g (65%) and MII-α yielding 0.72 g (29%).

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