SYNTHESIS OF D- AND L-GLUCOSAMINE EMPLOYING THE UGI REACTION

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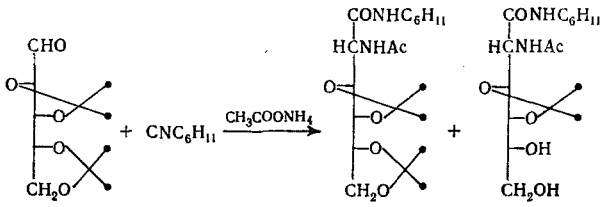
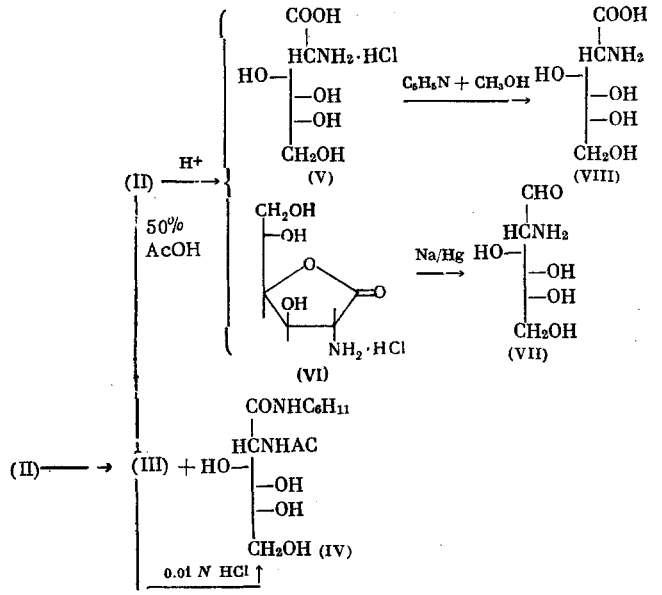
Previously it was shown that the Ugi reaction can be used to synthesize the amides of 2-amino-2-desoxyaldonic acids [1]. The structure and some of the properties of the condensation products of 2,3,4,5-di-O-isopropylideneal-D-arabinose (I) with cyclohexyl isocyanide in the presence of $AcONH_4$ were studied in the present paper.



(I) (II) (III)

Two products (II) and (III) were obtained as a reaction result, which were isolated in the pure state by chromatography. The structure of amides (II) and (III) was confirmed by the elemental analysis, IR, and NMR spectral data.

A study of the reaction products and the reaction mixture by NMR spectroscopy testifies to the high stereospecificity of the Ugi reaction for the isopropylidene derivatives of al-arabinose. One signal at δ 1.9 ppm corresponds to the acetamide protons of products (II) and (III) in the NMR spectrum, which testifies to the formation of one epimer at C_2 [2]. Based on the Levene empirical rule [3], as applied to (IV), product



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(II) can be assigned the D-configuration at C_2, while the molecule as a whole can be assigned the gluco-configuration. A more rigorous proof of the structure of amide (II) is based on its conversion to the previously described [4,5]D-glucosaminic acid (VIII) and D-glucosamine (VII) (in respective yields of 69 and 37%).

Besides the factors that determine the stereochemistry of the iminonitrile synthesis in carbohydrates, the stereospecificity of the reaction can also be caused by the reaction of the immonium ion, which is formed in the first step of the reaction, with the oxygen at C_4 (I). Apparently, the partial hydrolysis of the isopropylidene protection at C_4–C_5 is a consequence of this. It was shown separately that (I) is not affected by NH_4OAc under the experimental conditions.

Analogous results were obtained with 2,3,4,5-di-O-isopropylidene-L-arabinose.

EXPERIMENTAL METHOD

The IR spectra were taken on a UR-10 instrument as KBr pellets, the NMR spectra were taken on a Tesla BS487B instrument at 20°C using HMDS as the internal standard, while the optical activity was measured on a Jena polarimeter.

Cyclohexylamide of 2-Acetamido-2-desoxy-D-gluconic Acid (IV). A solution of 0.2 g of amide (II) in 5 ml of 50% aqueous AcOH was kept at 20° for 16 h, and then evaporated in vacuo to dryness. Based on the paper chromatography (PC) data the residue contains two components with R_f 0.88 (III) and 0.77 (IV). The components were separated by chromatographing on a cellulose column, and then recrystallized from methanol. We isolated 1.135 g (87%) of amide (III), mp 238-240°, $[\alpha]_D^{20}$ + 60° (C 1.9, EtOH). Infrared spectrum (ν, cm^{-1}): 1645, 1560 (NHCO), 3280 (OH). NMR spectrum (δ, ppm, in CD_3OD): 7.0 (amide protons), 3.62-4.62 (protons at C_2–C_6), 1.63 (cyclohexyl protons), 2.25 (protons of methyl groups), 1.9 (acetamido protons). We also obtained 0.03 g (2.3%) of product (IV), mp 195-196°, $[\alpha]_D^{20}$ + 33° (C 0.5, EtOH $-H_2O$, 1:1).

A solution of 0.16 g of (III) in 5 ml of 0.01 N HCl solution was kept at 100° for 1 h. The hydrolyzate was evaporated in vacuo, and the residue was recrystallized from methanol; the yield of (IV) was 0.14 g (83%), mp 195-196°, $[\alpha]_D^{20}$ + 33 (C 0.5 EtOH $-H_2O$, 1:1). Infrared spectrum (ν, cm^{-1}): 1640, 1556 (CONH), 3280 (NH), 3400 (OH). Found: C 52.8; H 7.89; N 8.82%. $C_{14}H_{26}N_2O_6$. Calculated: C 52.8; H 8.1; N 8.8%.

D-Glucosaminic Acid Hydrochloride (V). A suspension of 0.6 g of amide (II) in 5 ml of 4 N HCl solution was heated at 100° for 45 min. The solution was decolorized with active carbon, filtered, and evaporated in vacuo at 50°. The residue [yield 0.29 g (86%)], which represented a mixture of products with R_f 0.06 (V) and 0.15 (VI), was dissolved in 7 ml of water-saturated n-butanol and chromatographed on a column containing 30 g of cellulose. We obtained 0.2 g (69%) of acid (V). Infrared spectrum (ν, cm^{-1}): 1745, 2940 (CO), 3130, 1500, 1630 (NH_3^+), 3400 (OH). Compound (V) was treated twice with 5 ml of a 9:1 MeOH–C_5H_5N mixture, and the precipitate was filtered, washed with methanol, and recrystallized from ethanol. We obtained 0.17 g of (VIII), mp 250° (decompn.), $[\alpha]_D^{20}$ 0 (C 1.8, H_2O), $[\alpha]_D^{20}$ −16.5 → −12° (C 1.16, 2.5% HCl solution); cf. [4]. Found: N 7.2%. $C_6H_{13}O_6N$. Calculated: N 7.2%.

The fractions containing (V) and (VI) were combined and evaporated. We obtained 0.05 g of a mixture. All of the frequencies given above for (V) and an intense band at 1785 cm^{-1} (γ-lactone) are present in the IR spectrum.

D-Glucosamine Hydrochloride. D-Glucosamine hydrochloride was obtained as described in [5] from 0.32 g of a mixture of (V) and (VI), rich in (V); yield 37%, $[\alpha]_D^{22}$ + 97 → +70.5° (C 1.2; H_2O); cf. [6].

N-Acetyl-D-glucosamine. N-Acetyl-D-glucosamine was obtained as described in [7], mp 186-188°, $[\alpha]_D^{20}$ (final) + 40° (C 0.96, H_2O); cf. [8].

L-Glucosaminic Acid. L-Glucosaminic acid was obtained as described above for D-glucosaminic acid in 70% yield. Its IR spectrum resembles that of D-glucosaminic acid, mp 250° (decompn.), $[\alpha]_D^{20}$ + 14° (C 1.5, 2.5% HCl); cf. [9].

L-Glucosamine Hydrochloride. L-Glucosamine hydrochloride was obtained as described above in 32% yield, $[\alpha]_D^{20}$ (final) −71.8° (C 1.86; H_2O); cf. [10].

CONCLUSIONS

It was shown that the Ugi reaction can be applied to the synthesis of D- and L-glucosamine. It was found that the reaction has a high stereochemical directivity.

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