Short Communication

Synthesis and Stereochemistry of (*E*)-5-(3,4,5,6-Tetrahydropyrid-3-ylidenemethyl)-2-furanmethanol, a Product of the Reaction between D-Glucose and L-Lysine

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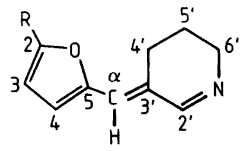
The title compound (**1**) was recently identified as a product of the reaction between D-glucose and L-lysine in slightly acidic aqueous solution.[1] The synthesis of **1** is reported here in order to support the proposed structure and formation mechanism and to make larger amounts of the compound available for metabolic and toxicological studies. The (*E*)-configuration of **1** has been established by X-ray diffraction techniques. Some preliminary results have been presented.[2]

Several compounds closely related to **1**, including **2** and **3**, have been prepared from the appropriate aldehyde, e.g. 2-furaldehyde (**5**) or benzaldehyde, and 2,3,4,5-tetrahydropyridine (**6**).[3] Compound **6** was generated from the initially isolated,[4] so-called α-isomer of its trimer. The (*E*)-configuration was assigned to **2** and **3** on the basis of the relatively strong allylic coupling ($^4J_{\alpha,4'}$) shown by the ^{1}H NMR spectra.[3]



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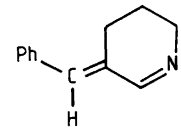
2: R = H



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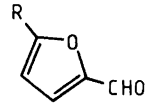

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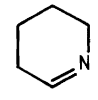

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Results and discussion

By analogy with previous work,[3] **1** was prepared from 5-(hydroxymethyl)-2-furaldehyde (**4**) and a solution of **6**, obtained from piperidine, *N*- chlorosuccinimide and potassium hydroxide.[5] Thus, the isolation of **6** or any of its oligomers was avoided. Compounds **2** and **3** were also prepared by this simplified procedure. The yields of **1–3** ranged from 52 to 64 %. The use of tin(II) fluoride as catalyst[6] did not increase the yields. Compounds **1–3** formed crystalline picrates.

Compound **1** was identical (MS, IR, ^{1}H NMR) with a sample obtained by the reaction between glucose and lysine.[1] On changing the solvent from chloroform-*d* to trifluoroacetic acid, all signals in the ^{1}H NMR spectra of **1–3** were shifted downfield, mainly owing to protonation of the nitrogen. For the same reason, the 2′-H signal split into a doublet, *J*(HC=NH) 8–9 Hz, and the 6′-H signal changed into a broad singlet (on standing, **1** was gradually converted to its *O*-trifluoroacetyl derivative).

In order to verify the (*E*)-configuration of **1–3** more rigorously, the ^{1}H NMR spectra of **2** and **3** were recorded in the presence of the shift reagent "Eu(fod)$_3$";[7] however, the results were far from conclusive and the crystal structure of **1** was

therefore investigated with the use of X-ray diffraction techniques.[8] Only the (*E*)-form is consistent with the X-ray data. These data also reveal that in the crystalline state, the conformation around the single bond joining carbons α and 5 is as shown by the formula (**1+2**).

Aldehyde **4** is a major degradation product of hexoses and was also identified in the glucose-lysine reaction mixture.[1] In the reaction between a sugar and an α-amino acid, the latter undergoes Strecker degradation. Several products identified in the glucose-lysine reaction mixture revealed such degradation of the lysine.[1] The expected degradation product, 5-aminopentanal, may cyclize to **6**. The formation from **4** and **6** was therefore suggested as one possible route to **1** in the glucose-lysine reaction.[1] The present facile synthesis of **1** from **4** and **6** indicates that this suggestion is reasonable.

Experimental

General. Column chromatography was performed by the "flash" technique[9] and monitored by TLC on silica gel (Riedel-de Haën, SIF). After the TLC plates had been inspected in UV light, phloroglucinol-hydrochloric acid[10] was used as spray reagent.

Compound **1**. Aldehyde **4**[11] (630 mg, 5.0 mmol) was added to a solution (10 ml) of **6**, freshly prepared from piperidine (860 mg, 10.0 mmol).[5] After 1 d, the solution was diluted with water (10 ml) and extracted with 1-butanol (2×20 ml). The extract was washed with water (10 ml) and evaporated. Column chromatography (EtOAc–95 % EtOH, 1:1 *v/v*) of the residue yielded **1** (610 mg, 64 % based on **4**). Physical data are given in Ref. 1.

Picrate. Picric acid (480 mg, 2.1 mmol) was dissolved in the minimum amount of 95 % ethanol and added slowly to a stirred solution of **1** (380 mg, 2.0 mmol) in 95 % ethanol (5 ml). After 15 min, the separated crystals were collected and recrystallized from 95 % ethanol. The picrate melted at 162–165.5 °C (cor.). Anal. $C_{17}H_{16}N_4O_9$: C, H, N.

Crystal structure.[8] Crystals of **1** were grown from toluene. The structure was determined from single crystal X-ray diffraction data measured at 22 °C. The space group is *Pbca* with the cell dimensions $a = 12.176$, $b = 8.790$ and $c = 18.922$ Å. The cell dimensions and intensity data were measured with a CAD4 diffractometer, using graphite-monochromated Mo*K*α radiation ($\lambda = 0.71073$ Å). The reflections were corrected for Lorentz and polarization effects. The structure was solved by direct methods. In the last cycle of least-squares refinement, the positions and anisotropic temperature parameters of 14 atoms were determined; 651 reflections with $I \geq 3\sigma(I)$ gave $R(F) = 0.12$.

Compounds **2** *and* **3**. These were prepared from the appropriate aldehydes and **6** as described above for **1**, but the reaction mixtures were extracted with ether rather than 1-butanol. The respective yields were 60 and 52 % (based on the aldehydes).

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References

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