Short Communication

Synthesis and Stereochemistry of \((E)-5-(3,4,5,6\text{-Tetrahydropyrid-3-ylidenemethyl})-2\text{-furanmethanol, a Product of the Reaction between }\alpha\text{-Glucose and }\beta\text{-Lysine}\)

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The title compound (1) was recently identified as a product of the reaction between \(\alpha\)-glucose and \(\beta\)-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 \(\alpha\)-isomer of its trimer. The \((E)\)-configuration was assigned to 2 and 3 on the basis of the relatively strong allylic coupling (\(^\gamma_{\alpha\beta}\)) shown by the \(^1\)H NMR spectra.\(^5\)

Results and discussion

By analogy with previous work,\(^1\) 1 was prepared from 5-(hydroxymethyl)-2-furaldehyde (4) and a solution of 6, obtained from piperidine, \(N\)-chlorosuccinimide and potassium hydroxide.\(^6\) 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, \(J(\text{HC} = \text{NH}) = 8–9\) 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 “\(\text{Eu(fod)}_3\)”\(^7\); however, the results were far from conclusive and the crystal structure of 1 was
therefore investigated with the use of X-ray diffraction techniques. 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. 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. 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. 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 and monitored by TLC on silica gel (Riedel-de Haën, SIF). After the TLC plates had been inspected in UV light, phloroglucinol-hydrochloric acid was used as spray reagent.

Compound 1. Aldehyde 4 (630 mg, 5.0 mmol) was added to a solution (10 ml) of 6, freshly prepared from piperidine (860 mg, 10.0 mmol). 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.

Pircate. 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. C₉H₁₅N₄O₆: C, H, N.

Crystal structure. 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 MoKα radiation (λ = 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 ≥ 3σ(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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