Tetrahedron Vol. 46, No. 16, pp. 5617-5620, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00
Pergamon Press plc

FORMATION OF 4,5-DIHYDROXY-2-α-D-GLUCOPYRANOSYLOXY-5-METHYL-2-CYCLOPENTEN-1-ONE IN THE MAILLARD REACTION OF MALTOSE

Sabine Estendorfer, Franz Ledl*, and Theodor Severin*

Institut für Pharmazie und Lebensmittelchemie der Universität,
Sophienstr. 10, 8000 München 2 (S.E. and T.S.)
Institut für Lebensmittelchemie und Analytische Chemie der Universität,
Pfaffenwaldring 55, 7000 Stuttgart 80 (F.L.)

(*Received in Germany* 9 *April* 1990)

Abstract - Among other products, 4,5-dihydroxy-2-α-D-glucopyranosyloxy-5-methyl-2-cyclopenten-1-one is formed in warming an aqueous solution of piperidinomaltulose.

INTRODUCTION

The term "Maillard reaction" subsumes transformational interactions between reducing sugars and amino acids or proteins. The Maillard reaction has major importance in foods, in which aroma substances, browning products, reductones, toxic compounds etc. are formed[1]. It has been known for some years that reactions between glucose and proteins also occur in the human body. It could be shown that there is a correlation between the extent of the Maillard reaction and processes of aging. Pathological lesions in diabetics are attributed to reactions between sugars and proteins[2].

The initial phase of the Maillard reaction has already been investigated in detail. Reducing sugars react with primary amines (e.g. the lysine side chain in the protein) or secondary ones to form amino sugars, which are readily converted into deoxyosones with cleavage of the amine component[3]. In the further course, a multitude of products is obtained. Only a small proportion of these could be isolated and identified up to now.

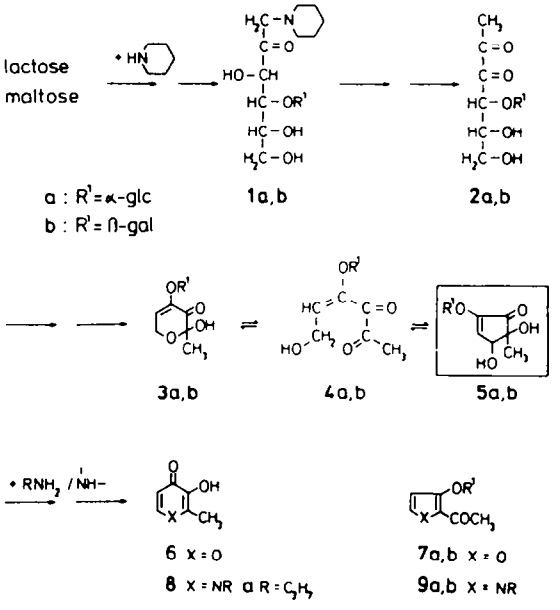
RESULTS AND DISCUSSION

With primary and secondary amines, maltose and lactose initially form glycosylamines, which are converted into compounds of type **1** by Amadori rearrangement. Among other products, maltol (**6**) and glucosyl or galactosyl isomaltol (**7a,b**) could be demonstrated as decomposition products of these amino sugars[4]. Relatively large amounts of pyridones with the structure **8** are formed with primary amines[5]. As a by-product the galactosyl pyrrole **9b** has been detected in lactose reaction mixtures[6]. It has recently become possible to isolate and identify the ß-pyranone **3b** from a lactose-glycine reaction mixture[6]. Compound **3b** can already be detected in milk which has been heated for a short time. The glucosyl derivative **3a** has been found in

red ginseng[7]. We were able to prove the existence of the deoxyosone **2** formed as an intermediate product by a trapping reaction with o phenylenediamine[8].

As a disaccharide reaction product which has not been known up to now, w isolated the cyclopentenone derivative **5**. 1-Deoxy-1-piperidino-maltulos **1a** slowly decomposes in aqueous solution at room temperature. Thi decomposition takes place more rapidly under heating, various product being formed. We were able to isolate a relatively large amount of th cyclopentenone derivative **5a** in a pure form by careful chromatographi separation. The structure results from the spectral data of th underivatized as well as of the acetylated substance. If an aqueou solution of **5a** is warmed in the presence of a secondary amin (piperidine), maltol (**6**) and glucosylisomaltol (**7a**) are obtained as th main products. With a primary amine **5a** is transformed into the pyridone **8** and the glucosyl pyrrole **9a** (R = propyl) among other products.

With consideration of these results, a sequence of reactions is suggeste in the formula scheme. The intermediate product **5** can evidently b transformed into the open-chain form **4** by retroaldol reaction, and thus b converted into the heterocycles **6**, **7**, **8** and **9**.



EXPERIMENTAL SECTION

General

Melting points were determined on a Büchi 510 apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra (internal Me_4Si) were recorded with a Jeol 400 spectrometer. IR spectra were measured with a Perkin Elmer 197 spectrometer. Thin-layer chromatography (TLC) was performed using glas plates coated with 0.5 mm thickness of Merck silica gel 60 F-254.

Isolation of **5a**

An aqueous solution (20 mL, buffered to pH 7) of 1-deoxy-1-piperidino-maltulose[9] (4 g, 10 mmol) was stored for 5 d at 37°C (or 2 h at 60°C). After removal of the solvent under reduced pressure the residue was dissolved in methanol, filtered and fractionated (TLC, 2.5:1 ethyl acetate-methanol). From a band with R_f 0.35 (red spot with alkaline triphenyltetrazolium chloride) compound **5a** was eluated with hot methanol (yield 0.2 %).

^{1}H-NMR of the sirupy residue (MeOD) δ 1.28 (s, 3H; CH_3), 3.45-3.89 (m, 6H; α-glc), 4.68 and 4.69 (2d, J=2.57, 1H; HC-CH=C), 5.54 and 5.61 (2d, J=3.42, 1H; anomeric H), 6.78 and 6.79 (2d, J=2.57, 1H; C=CH-CH).

Compound **5a** (10mg) was acetylated (acetic acid anhydride/pyridine at room temperature over night) and purified by TLC (70:130:2 hexane-ethyl acetate-triethyl amine). From a band with R_f 0.6 (red spot with alkaline TTC) **5a** (**acetylated**) was obtained with hot ethyl acetate as a mixture of the diastereomeric compounds A and B (2:3), mp 67°C; ^{1}H-NMR ($CDCl_3$) of A: δ 1.32 (s, 3H; CH_3), 2.03, 2.04, 2.08, 2.09, 2.10, 2.15 (6s, 18H; CH_3-C=O), 3.99 (m, 1H; H-5), 4.07, 4.25 (2dd, J=12.5, 1.8Hz; J=12.5, 4.4Hz, 2H; H-6), 5.02 (dd, J=10.3, 3.7Hz, 1H; H-2), 5.12 (t, J=9.9Hz, 1H; H-4), 5.63 (t, J=9.9Hz, 1H; H-3), 5.77 (d, J=3.7Hz, 1H; H-1), 5.95 (d, J=2.6Hz, 1H; HC-CH=C); 6.45 (d, J=2.6Hz, 1H; HC=C).

^{1}H-NMR of B: δ 1.33 (s, 3H; CH_3), 2.03, 2.04, 2.08, 2.09, 210, 2.15 (6s, 18H; CH_3-C=O, identical with A), 3.99 (m, 1H; H-5, identical with A), 4.09, 4.22 (2dd, J=10.5, 2.2Hz; J=10.5, 5.1Hz, 2H; H-6), 5.06 (dd, J=10.3, 3.7, 1H; H-2), 5.12 (t, J=9.9Hz, 1H; H-4, identical with A), 5.61 (t, 9.9Hz, 1H; H-3), 5.70 (d, J=3.7Hz, 1H; H-1), 5.97 (d, J=2.6Hz, 1H; HC-CH=C), 6.45 (d, J=2.6Hz, 1H; HC=C, identical with A).

^{13}C-NMR of A: δ 18.62 (CH_3), 20.40, 20.49, 20.55, 20.61 (CH_3C=O), 61.24 (C-6), 67.69 (C-4), 68.59 (C-5), 69.52 (C-5), 69.92 (C-2), 73.49 (HC-CH=C), 81.04 (CH_3-C-OAc), 94.26 (C-1), 125.52 (HC=C), 151.80 (HC=C), 169.92-170.45 (CH_3-C=O), 193.93 (C=O).

^{13}C-NMR of B: δ 18.94 (CH_3), 20.40, 20.49, 20.55, 20.61 (CH_3C=O), 61.57 (C-6), 68.02 (C-4), 68.51 (C-5), 69.56 (C-3), 69.92 (C-2), 73.64 (HC-CH=C), 81.42 (CH_3-C-OAc), 94.72 (C-1), 125.48 (HC=C), 151.15 (HC=C), 169.46-170.45 (CH_3-C=O), 193.93 (C=O).

IR(KBr): [cm^{-1}] 2965, 1755, 1632, 1438, 1164, 1120, 967, 929,897, 700. UV(EtOH): λ_{max}[nm] (ϵ) 242 (6000). Anal.Calc. for $C_{24}H_{30}O_{15}$: C, 51.61;H, 5.38. Found: C, 51.63;H, 5.54.

Degradation reactions of **5a**

a) Formation of maltol (**6**)

64 mg (0.2 mmol) of **5a** and 15 mg of piperidinium acetate were heated in 5 mL water (bufferded to pH 7) for 4 h in a sealed tube at 120°C. The solution was extracted with methylene chloride. The residue of the organic layer was identical with maltol (comparision of the spectral data with those of a commercial available substance).

Formation of glucosylisomaltol **6a**

30 mg (1 mmol) of **5a** were heated in the presence of 0.3 mmol of piperidinium acetate for 2 h at 80°C. After removal of the water the residue was dissolved in methanol, filtered and concentrated to give an oil. The ^{1}H-NMR spectra was identical with that of glucosylisomaltol **6a** prepared as described in ref.4b.

Formation of pyridone **8a**

50 mg (0.16 mmol) of **5a** were heated with an excess of propylammonium acetate (0.4 mmol) in 5 mL water (buffered to pH 7) for 2 h at 80°C. Extraction with methylene chloride led after removal of the organic solvent to a compound which was identical with **8a**. The reference substance was prepared from galactosylisomaltol[9] **6b** and propylamine.

Formation of glucosyl-acetyl-pyrrole **9a** (R=propyl)

60 mg (0.2 mmol) of **5a** were heated in a buffered (pH 7) aqueous solution with propylammonium acetate (0.4 mmol) for 2 h at 80°C. Compound **8a** was extracted with methylene chloride. The residue of the aqueous solution was purified by TLC (3:2 ethyl acetate-methanol, R_f 0.7). ^{1}H-NMR (MeOD) of the colorless solid: δ 0.94 (t, J=7.27Hz, 3H; $C\underline{H}_3$-CH_2), 1.65 (m, J=7.27Hz, 2H; $CH\underline{_2}$-CH_3), 2.50 (s, 3H; $C\underline{H}_3$-C=O), 3.42-3.85 (m, 6H; α-glc), 4.17 (t, J=7.27Hz, 2H; CH_2-N), 5,47 (d, J=3.42Hz; anomeric H), 6.07 (d, J=3.0Hz, 1H; pyrrole), 6.88 (d, J=3.0Hz, 1H; pyrrole). MS(CI): m/z 498 ($M+CH_3CO^+$).

REFERENCES

1. Ledl, F.; Schleicher, E. *Angew Chem* **1990**, in press.
2. Baynes, J.W.; Monnier, V.M.,Eds.;"The Maillard Reaction in Aging, Diabetes and Nutrition";*Prog Clin Biol Res* 304, New York 1989.
3. Paulsen, H.; Pflughaupt, K.W. In "Glycosylamines"; Pigman,W.; Horton,D., Eds.; Carbohydrates IB,Academic Press, New York, London, Toronto, Sydney, San Francisco, 1980;p 881.
4. a) Brand, *J. Chem. Ber.* **1894**, 37, 807. b) Patton, S. *J. Biol. Chem.* **1950**, 184, 131. c) Hodge, J.E.; Nelson, E.C. *Cereal Chem.* **1961**, 38, 207. d) Goodwin,J.C. *Carbohydr. Res.* **1983**, 115, 281.
5. Severin,T.; Loidl,A. *Z. Lebensm. Unters. Forsch.* **1976**, 161, 119.
6. Ledl,F.; Ellrich,G.;Klostermeyer,H. *Z. Lebensm. Unters. Forsch.* **1986**, 182, 19.
7. Matsuura, H.; Hirao,Y.; Yoshida, S.; Kunihiro, K.; Fuwa, T.; Kasai, R.; Tanaka, O. *Chem. Pharm. Bull.* **1984**, 32, 4674.
8. Beck, J.; Ledl, F.; Severin, T. *Z. Lebensm. Unters. Forsch.* **1989**, 188, 118.
9. Ledl, F.; Osiander, H.; Pachmayr, O.; Severin, T. *Z. Lebensm.Unters. Forsch.* **1989**, 188, 207.