Carbohydrate Research, 177 (1988) 240–243
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

Formation of 1-deoxy-D-*erythro*-2,3-hexodiulose from Amadori compounds

JAKOB BECK, FRANZ LEDL*, AND THEODOR SEVERIN

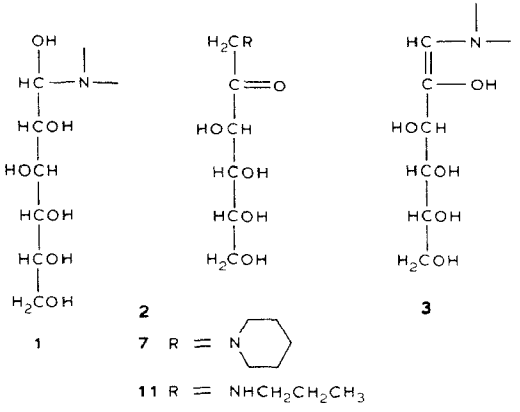
Institut für Pharmazie und Lebensmittelchemie der Universität München, Sophienstr. 10, D-8000 München 2 (F.R.G.)

(Received August 27th, 1987; accepted for publication, December 3rd, 1987)

Maillard reactions, *i.e.* the degradation of sugars in the presence of amino acids or proteins, are of importance when foods are to be heated or stored. In proteins, especially, the amino groups of the lysine side-chains react with sugars.

Primary or secondary amines combine with glucose, forming glycosylamines (**1**) which rearrange into the so-called Amadori compounds (1-amino-1-deoxy-fructoses, **2**) that are degraded by loss of the amino group. The 1-deoxy-2,3-hexodiulose **5** can be formed from the 2,3-endiol **4**, and the 3-deoxyhexos-2-ulose **6** can be derived from aminoenol **3** (formed from **2**). Apparently, most of the essential degradation pathways of glucose and fructose in the presence of amines lead to α-dicarbonyl compounds of the types **5** and **6** as intermediates[1]. In reality, compounds **1**–**6** exist as cyclic hemiacetals and the structures depicted are a simplification.

The 3-deoxyhexos-2-ulose **6** has been isolated from a hexosamine mixture[2] and the analogous pentose product has been identified[3]. Further degradation of **6**,



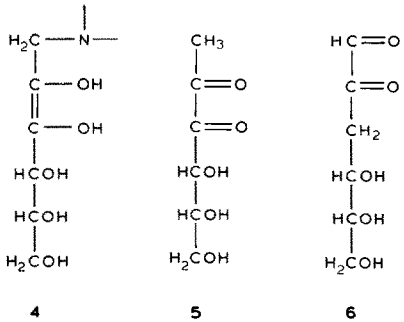
1 **2** **3**

7 R = N

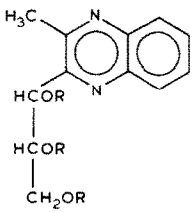
11 R = $NHCH_2CH_2CH_3$

*Author for correspondence.

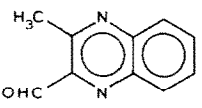
0008-6215/88/$ 03.50



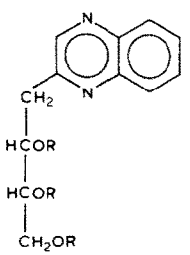
4 5 6



8 R = H
12 R = Ac



9



10 R = H
13 R = Ac

predominantly in acidic solution, leads to 5-hydroxymethylfurfural[2]. The 1-deoxy-2,3-hexodiulose **5** has not yet been detected and its formation as an intermediate has only been postulated. Attempts have been made to synthesise **5**. Starting with 3,6-anhydro-4,5-*O*-isopropylidene-D-mannitol, Fisher and co-workers[4] obtained crystalline 1-deoxy-4,5-*O*-isopropylidene-D-*erythro*-2,3-hexodiulose. After removing the protecting group under acidic conditions, **4** could not be isolated but its presence in solution was proved by the formation of a bis-hydrazone. Theander and co-workers[5] obtained the bis-phenylhydrazone of **5** from 1-deoxyfructose. This product was hydrolysed with nitric acid, and the formation of **5** was proved by the isolation of racemic saccharinic acid and erythronic acid after alkaline treatment.

It may be inferred from these results that **5** is easily degraded. An attempt was made therefore to trap **5** with *o*-phenylenediamine. We began with Amadori compounds of type **2** obtained from glucose and primary and secondary amines.

Morita and co-workers[6] have studied the degradation of glucose in alkaline media in the presence of excess of *o*-phenylenediamine and obtained quinoxaline derivatives of 3-deoxyhexos-2-ulose **6**, methylglyoxal, 4-hydroxy-2-oxobutanal, and 1-hydroxy-2,3-butanedione. The quinoxaline derived from 1-deoxy-2,3-hexodiulose **5** apparently is unknown.

On heating a solution of 1-deoxy-1-piperidino-D-fructose (**7**) and *o*-phenylenediamine in neutral phosphate buffer for 10 h under reflux, the quinoxaline **8** was obtained in high yield, indicating that most of **7** had been trans-

formed into **5**. The structure of **8** was proved by periodate oxidation, which gave the aldehyde **9**, and by acetylation.

Under similar conditions of reaction, considerable amounts of the quinoxaline **10** were obtained from 1-deoxy-1-propylamino-D-fructose (**11**). Thus, the main degradation products of the Amadori compound **11** are **5** and **6** (formed in the ratios of 20:1 at pH 7 and 8:5 at pH 4.5 based on the peak areas of **12** and **13** in g.l.c.). Both quinoxalines were found in reaction mixtures of glucose with propylamine and glycine. Further investigations are necessary in order to explain the ratio in which **5** and **6** are formed during the degradation of the Amadori compounds.

EXPERIMENTAL

General methods. — Melting points were determined with a Büchi 510 apparatus and are uncorrected. I.r. spectra were recorded for KBr discs with a Perkin–Elmer 197 spectrometer. N.m.r. spectra (internal Me_4Si) were recorded with a Varian A-60 spectrometer. Mass spectra were produced with a Varian MAT CH7 spectrometer equipped with a probe inlet. Silica Gel 60 F_{254} (Merck, 5554 and 5717) was used for t.l.c.

G.l.c. was performed with a Perkin–Elmer 8320 instrument equipped with a flame-ionisation detector and a quartz capillary column (25 m × 0.25 mm i.d., permaphase, Perkin–Elmer 698345) coated with dimethylsilicone; injection and detection ports at 280°; temperature programme 100°→260° at 6°/min.

2-Methyl-3-(1,2,3-trihydroxypropyl)quinoxaline (**8**). — A mixture of **7**[7] (1.24 g, 5 mmol) and *o*-phenylenediamine (1.1 g, 10 mmol) in phosphate buffer (pH 7, 10 mL) was heated for 10 h under reflux. T.l.c. then indicated that no **7** remained. The mixture was concentrated under diminished pressure to a syrup, a solution of which in methanol was filtered and concentrated under diminished pressure. Column chromatography (1:1 ethyl acetate–methanol) gave a fraction containing **8**, preparative t.l.c. (95:5 acetonitrile–water) of which gave a band with R_F 0.5–0.6 from which **8** was obtained by extration with methanol. Compound **8** (0.82 g, 70%) had m.p. 169–170°; ν_{max} 1595, 1550, 1470, 1000, 750 cm^{-1}. ^{1}H-N.m.r. data (CD_3OD): δ 2.92 (s, 3 H), 4.08 (m, 2 H), 4.26 (m, 1 H), 5.27 (d, 1 H, *J* 8 Hz), 8.03 (m, 4 H).

Anal. Calc. for $C_{12}H_{14}N_2O_3$: C, 61.5; H, 6.02; N, 12.0. Found: C, 61.4; H, 5.99; N, 11.9.

When a mixture of **7** and *o*-phenylenediamine was treated as above but at pH 4.5 (phosphate buffer), the main product was **8**. Conventional treatment of **8** (0.12 g, 0.5 mmol) with dry pyridine (2 mL) and acetic anhydride (1 mL) gave the triacetate **12** (0.17 g, 90%), b.p. 105°/0.1 Torr. Mass spectrum: *m/z* 360 (0.4%, M^+), 317 (0.5), 301 (6), 259 (9), 241 (17), 216 (40), 199 (46), 174 (96), 173 (16), 143 (16), 43 (100). ^{1}H-N.m.r. data ($CDCl_3$): δ 1.90 (s, 3 H), 2.03 (s, 3 H), 2.11 (s, 3 H), 2.90 (s, 3 H), 4.60 (m, 2 H), 5.63 (m, 1 H), 6.30 (d, 1 H, *J* 7 Hz), 7.87 (m, 4 H).

2-Formyl-3-methylquinoxaline (**9**). — A solution of **8** (65 mg, 0.27 mmol), sodium periodate (120 mg, 0.54 mmol), and sodium hydrogencarbonate (30 mg, 0.54 mmol) in water (10 mL) was stirred overnight at room temperature and then extracted with ether (3 × 20 mL). The combined extracts were concentrated under diminished pressure and the residue was distilled at 90–115°/0.1 Torr. Crystallisation of the product from ethyl acetate gave **9** (35 mg, 73%), m.p. 135°; ν_{max} 1675, 1578, 1437 cm^{-1}. Mass spectrum: *m/z* 172 (100%, M^+), 144 (98), 143 (97), 117 (42), 102 (98), 76 (83), 75 (83). ^{1}H-N.m.r. data ($CDCl_3$): δ 2.93 (s, 3 H), 7.92 (m, 4 H), 10.29 (s, 1 H).

Anal. Calc. for $C_{10}H_8N_2O$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.68; H, 4.62; N, 16.19.

*Reaction of 1-deoxy-1-propylamino-*D*-fructose* (**11**) *with o-phenylenediamine.* — A mixture of **11**[8] (oxalate; 0.27 g, 1 mmol) and *o*-phenylenediamine (0.22 g, 2 mmol) in phosphate buffer (pH 7 and pH 4.5, respectively; 10 mL) was heated for 10 h under reflux and then concentrated under diminished pressure. A solution of the syrupy residue in methanol was filtered and concentrated *in vacuo*, and the residue was treated conventionally with dry pyridine (1 mL) and acetic anhydride (0.5 mL). The quinoxalines **12** and **13** were separated by g.l.c. (*T* 25.85 and 27.11 min, respectively). Mass spectrum: **13**, *m/z* 360 (0.4%, M^+), 301 (11), 300 (13), 258 (16), 241 (32), 215 (23), 199 (38), 157 (42), 144 (100), 43 (87). Compound **10** was prepared from 3-deoxyhexos-2-ulose[9] and *o*-phenylenediamine, and acetylated to give **13**, the spectral data of which were identical with those published[6].

REFERENCES

1 H. Paulsen and K. W. Pflughaupt, in W. Pigman and D. Horton (Eds.), *The Carbohydrates: Chemistry and Biochemistry*, 2nd ed., Vol. 1B, Academic Press, New York, 1980, pp. 881–927.
2 E. F. L. J. Anet, *Aust. J. Chem.*, 13 (1960) 396–403.
3 H. Kato, *Agric. Biol. Chem.*, 26 (1962) 187–192.
4 B. E. Fisher, H. B. Sinclair, and J. C. Goodwin, *Carbohydr. Res.*, 116 (1983) 209–215.
5 A. Ishizu, B. Lindberg, and O. Theander, *Carbohydr. Res.*, 5 (1967) 329–334.
6 N. Morita, M. Mizutani, K. Hayashi, M. Kirihata, I. Ichimoto, H. Ueda, and M. Takagi, *Bull. Univ. Osaka Prefect., Ser. B*, 35 (1983) 59–70; *Chem. Abstr.*, 100 (1984) 6996j.
7 J. E. Hodge and B. E. Fisher, *Methods Carbohydr. Chem.*, 2 (1963) 99–107.
8 F. Micheel and G. Hagemann, *Chem. Ber.*, 92 (1959) 2836–2840.
9 H. El Khadem, D. Horton, M. H. Meshreki, and M. A. Nashed, *Carbohydr. Res.*, 17 (1971) 183–192.