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Preliminary communication

The reaction of 3-deoxy-D-*glycero*-pentos-2-ulose ("3-deoxyxylosone") with aminoguanidine*

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The occurrence of Maillard reactions *in vivo* is now a well-established fact[1]. Under physiological conditions, reducing sugars react with protein amino groups to give Amadori compounds (1-amino-1-deoxy-2-ketoses, "glycated proteins"), with subsequent protein modifications such as crosslinking and the production of fluorescent compounds. Recently, aminoguanidine (guanylhydrazine) has been shown to inhibit Maillard reactions under physiological conditions[2], but the mechanism as to how this is accomplished is unclear. It has been suggested that aminoguanidine functions by reacting directly with Amadori compounds while these are attached to the protein[3]. During the degradation of Amadori compounds, one of the initially produced intermediates is a deoxy-dicarbonyl compound. 3-Deoxy-D-*erythro*-hexos-2-ulose[4] ("3-deoxyglucosone") and 1-deoxy-D-*erythro*-2,3-hexodiulose[5] ("1-deoxyglucosone") represent the primary degradation products that arise during the decomposition of an Amadori compound, and L-ascorbic acid is known to give rise to pentose analogs during its degradation[6]. For the case of 3-deoxyglucosone, it has been shown that it causes crosslinking *in vitro* of protein[7,8] and that aminoguanidine inhibits this reaction, in terms of the extent of crosslinking observed[9].

We wish to report a study of the interaction of aminoguanidine with dicarbonyl sugar derivatives using 3-deoxy-D-*glycero*-pentos-2-ulose[6] (**1**) as a model compound. In an earlier report, Wolfrom and co-workers[10] reported that aminoguanidine reacts with several dicarbonyl sugar derivatives to give amido-osazone (bishydrazone) derivatives, and that these reactions required extensive heating in order to form. The findings reported herein show that under physiological conditions the major products of this reaction are substituted 3-aminotriazine derivatives and that they are rapidly formed in the reaction solution. The relevant structures are shown in Scheme 1.

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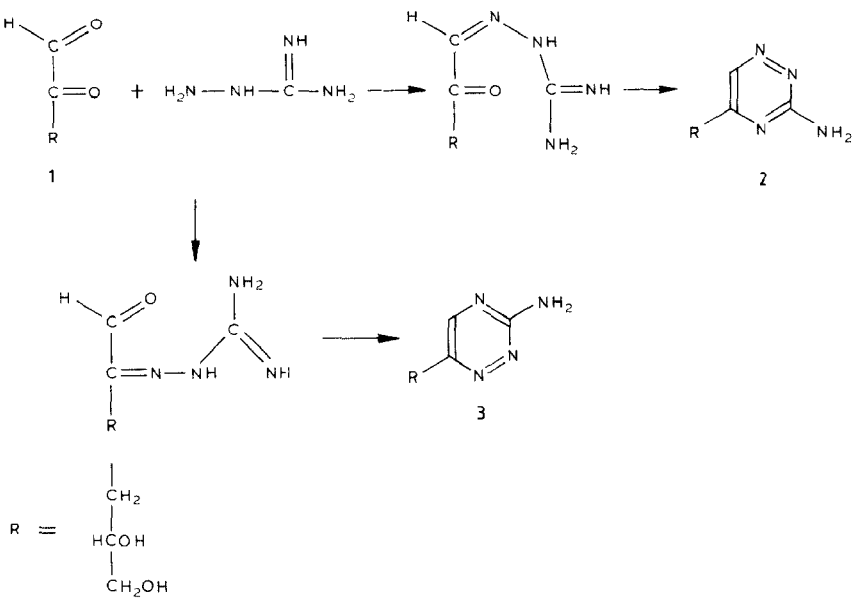

Scheme 1

In a typical experiment, aminoguanidine, bicarbonate salt (630 mg, 4.63 mmol) was reacted with **1** (500 mg, 3.79 mmol) in phosphate buffer (25 mL) at pH 7.0 at 37°. T.l.c. (Whatman K5F silica gel) using 7:3:0.3 chloroform–methanol–water as the irrigant showed that **1** had completely reacted within five min. to give two different reaction products (R_F = 0.65 and 0.60) in a ratio of 1:2. Detection was effected by charring the plates with 5% sulfuric acid in ethanol and also with u.v. light. The reaction products were separated on a silica gel column (100 g, 200–400 mesh) using 5:1 chloroform–methanol as irrigant and were obtained as crystalline materials.

The faster moving component (40 mg, 6,2%), m.p. 139–140° (ethanol), $[\alpha]_D$ −77.3° (*c* 0.87, H_2O), was identified as 3-amino-5-[(2S)-2,3-dihydroxypropyl)]-1,2,4-triazine (**2**) from its ^{1}H-, ^{13}C-n.m.r., and m.s. spectra.

^{1}H-N.m.r. data* (500 MHz, D_2O): δ 2.66 (dd, 1 H, $J_{1a,1b}$ 14.39 Hz, $J_{1b,2}$ 9.21 Hz, H-1′$_b$), 2.79 (dd, 1 H, $J_{1a,2}$ 4.03 Hz, H-1′$_a$), 3.47 (dd, 1 H, $J_{3a,3b}$ 11.76 Hz, $J_{3b,2}$ 6.38 Hz, H-3′$_b$), 3.56 (dd, 1 H, $J_{3a,2}$ 4.2 Hz, H-3′$_a$), 4.04 (m, 1 H, H-2′), 8.43 (s, 1 H, H-6); ^{13}C-n.m.r. data (125 MHz, ^{1}H-decoupled, confirmed by DEPT editing, D_2O): δ 38.7 (C-1′), 65.2 (C-3′), 70.4 (C-2′), 141.6 (C-6), 163.6 (C-3), 162.4 (C-5); m.s. data (collected using a Kratos model MS25 instrument with a DS-55 data system, direct probe, 70eV, with a source temperature of 200°): *m/z* 170 (M), 152 (M − H_2O), 139 (M − CH_2OH), 123 (M − CH_2OH − NH_2), and 110 (M − CH_2OH − CHOH + H^+).

Anal. Calc. for $C_6H_{10}N_4O_2$: C, 42.35: H, 5.92; N, 32.92. Found: C, 42.46; H, 6.03; N, 32.08.

*Unprimed Nos. refer to the triazine rings, while primed nos. refer to the side chain (see scheme 1).

The slower moving compound (75 mg, 11,6%), m.p. 72–74° (acetonitrile), $[\alpha]_D$ −23,1° (*c* 1.0, H_2O), was identified as 3-amino-6-[(2S)-2,3-dihydroxypropyl]-1,2,4-triazine (**3**) from its ^1H, ^{13}C-n.m.r., and m.s. spectra.

^1H-N.m.r. data (500 MHz, D_2O): δ 2.84 (dd, 1 H, $J_{1a,1b}$ 14.5 Hz, $J_{1b,2}$ 8.88 Hz, H 1′$_b$, 2.99 (dd, 1 H, $J_{1a,2}$ 4.37 Hz, H-1′$_a$, 3.54 (dd, 1 H, $J_{3a,3b}$ 11.75 Hz, $J_{3b,2}$ 6.54 Hz, H-3′$_b$), 3.65 (dd, 1 H, $J_{3a,2}$ 4.1 Hz, H-3′$_a$), 4.01 (m, 1 H, H-2′), 8.30 (s, 1 H, H-5); ^{13}C-n.m.r. data (125 MHz, ^1H-decoupled, D_2O): δ 35.7 (C-1′, 65.1 (C-3′), 71.2 (C-2′), 149.9 (C-6), 153.4 (C-5), m.s. data: *m/z* 171 ($M + H^+$), 152 ($M - H_2O$), 139 ($M - CH_2OH$), 123 ($M - CH_2OH - NH_2$) and 110 ($M - CH_2OH - CHOH + H^+$).

Anal. Calc. for $C_6H_{10}N_4O_2$: C, 42.35; H, 5.92; N, 32.92. Found: C, 42.18; H, 5.94; N, 31.60.

The structural assignments for **2** and **3** are based on published[11] ^{13}C-n.m.r. data for 3-amino-1,2,4-triazine, which assigns signals at 153.3 and 141.0 p.p.m. to C-5 and C-6, respectively. The substituted C-5 carbon (for **2**) and C-6 carbon (for **3**) signals are shifted to 162.4 and to 149.9 p.p.m., respectively, consistent with the methylene substituents shown. It is noteworthy that both **2** and **3** showed u.v. absorption maxima at 322 nm (H_2O).

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