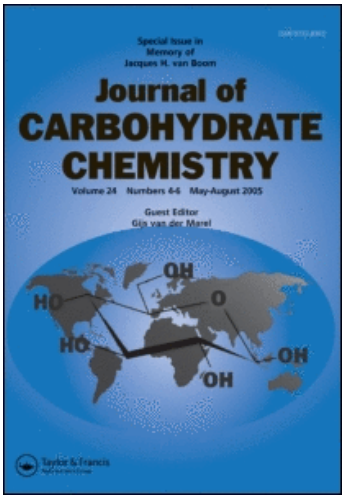

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A NOVEL OXAZOLIDINE DERIVATIVE FROM XYLOSE AND UREA

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ABSTRACT

Reaction of equimolecular amounts of xylose and urea in D_2O at 68 °C, monitored by ^{13}C NMR, gave a six carbon xylofuranosyl derivative as the major product. No intermediate in the formation of this monomeric compound was detected. The xylofuranosyl derivative was subsequently isolated and purified from a six week 0.1 molar reaction of xylose and urea in H_2O. Its structure, α-D-xylo-furano[1,2-d]oxazolidin-2-one 1, was confirmed by elemental analysis, ^1H coupled and decoupled ^{13}C NMR, ^1H NMR, IR and DCI-MS. The ^1H NMR and GC-MS (EI, DCI) of the N-acetyl-di-O-acetyl derivative 2 were in agreement with structure 1.

INTRODUCTION

Previous studies[1,2] on the interaction of carbohydrates with amino compounds (Maillard reaction) have shown that this reaction may be important in the formation of humic substances. In this study, the reaction of D-xylose, a prevalent carbohydrate in soils,[3] and urea, a commonly used fertilizer, are now reported.

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Numerous articles[4-10] and reviews[11,12] have been published on the condensation of carbohydrates and urea. In the case of pentoses, the acid catalyzed condensation of ribose with urea has been examined in depth.[8,9] Schoorl,[13] on the basis of a decrease in optical rotation concluded that a glycosyl ureide was formed by reaction of xylose with urea, while Johnson and Bergman[10] and Helferich and Kosche[5] reported the formation of 1,3-di-D-xylosyl urea from this reaction. A detailed examination of the reaction of xylose with urea, however, has not been reported.

RESULTS AND DISCUSSION

In the present study, xylose and urea were reacted in aqueous solution at a temperature of 68 °C. This temperature, although high by soil standards, was chosen in order to obtain products in a reasonable time.

Since the course of the reaction was unknown, and as the dark colored solution prevented us from following the reaction by thin layer chromatography, the reaction was monitored by ^{13}C NMR. A 0.001 molar solution of D-xylose and urea in D_2O was kept at 68 °C; at different time intervals ^{13}C NMR spectra were taken. After one week one major product was detected and its relative amount increased with time until after three weeks it surpassed the xylose content. At the end of six weeks the ^{13}C NMR spectrum of the reaction mixture showed the presence of one major product, some unreacted urea, small amounts of by-products, but no xylose (Fig. 1). Based on these results, equimolecular amounts of xylose and urea in water were reacted under sterile conditions at 68 °C. After six weeks, the solution was passed down a column of H^+ resin to remove the remaining urea, as well as most of the dark colored material. Thin layer chromatography (TLC) of the

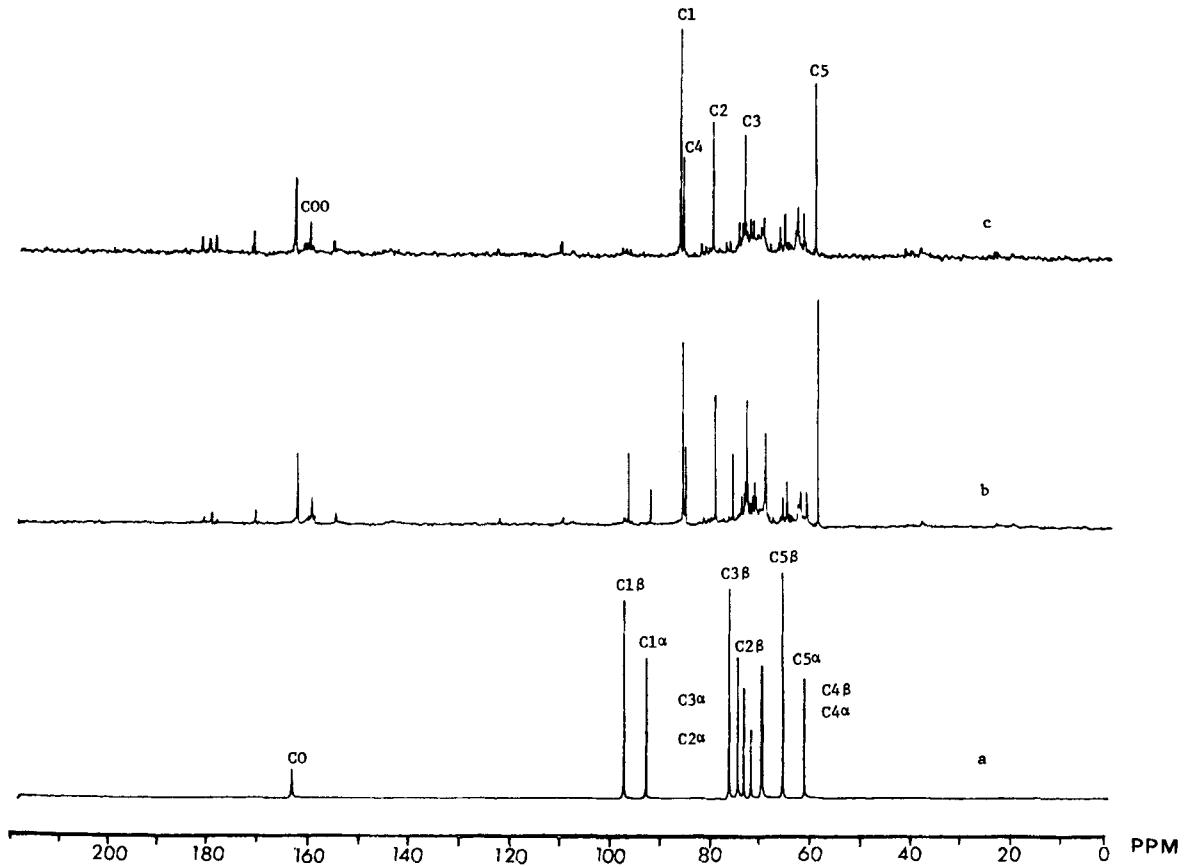
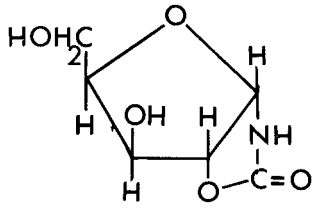


Fig. 1. ^{13}C NMR spectra of 0.001 M. solution of xylose and urea. Reaction times (weeks) a, 0; b, 3; c, 6.

product showed three components, two of which had similar R_f values. A further purification by preparative TLC was attempted. However, this purification step failed to separate the major component from the by product with a very similar R_f. A second passage through cation exchange column (H^+ form) gave a pure colorless syrup 1 which failed to crystallize. The ^{13}C NMR spectrum of 1 showed six carbons, one at a chemical shift of 159.98 ppm, attributed to a β-lactam or α,β-unsaturated ester or amide carbonyl. No C=N absorption band at 260 nm in the UV spectrum or a stretching band at 1620 cm^{-1} in the IR spectrum could be detected, thus eliminating the latter two possibilities. The IR spectrum showed a strong absorbance at 1760 cm^{-1} indicative of an ester or β-lactam carbonyl. The mass spectrum (DCI) gave a peak at m/z = 176 (M+1), suggesting a compound with a molecular weight of 175. This excludes the possibility of a dimer previously reported in the acid catalyzed condensation of xylose with urea.[5,10] The elemental analysis showed that 1 contained only one nitrogen atom eliminating glycosyl urea[9,4,8] as a possible structure for 1. The absence in the IR of a double peak at 1585 and 1685 cm^{-1} indicative of a urea derivative corroborated these results.

The ^{13}C chemical shifts of the five carbons at 85.98, 84.42, 79.53, 73.11 and 59.15 are consistent with a furanoside structure.[14] The furanoside configuration is confirmed by the presence in the IR spectrum[15] of absorption bands at 825 and 875 cm^{-1} and by the ^1H NMR spectrum. In the latter the chemical shifts and coupling constants (e.g. $J_{H-1,\ H-2}$ = 5.4 Hz, see experimental details) are those of an α furanoside structure. Based on the above data, compound 1 was assigned the structure α-D-xylo-furano[1,2-d]oxazolidin-2-one.

A final proof of the structure was obtained by derivatization. Acetylation of 1 in acetic anhydride with sodium acetate as catalyst, gave a product 2, which on a fused silica



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SE-54 capillary column gave one peak with a retention time RT=0.84 $RT_{myo\text{-}inositol}$. The acetyl derivative 2 gave mass spectra (EI and DCI) consistent with a triacetyl structure (see experimental details). The ^{1}H spectrum showed 9 acetyl protons: 2 OAc at 2.03 and 2.11 and an NAc at 2.52 ppm. In addition to the 9 acetyl protons, six other protons appear in the NMR spectrum of 2. H-1 as expected, appears at a lower chemical shift (6.30 ppm) relative to the underivatized compound 1 (5.69 ppm), due to the formation of NAc; H-2 is not affected, while H-3, H-4, H-5, H-5' are shifted slightly downfield. Proton assignments were based on chemical shifts and coupling constants comparable to those of the underivatized material 1. The formation of α-D-xylo-furano[1,2-d] oxazolidin-2-one 1 can be explained by the formation of xylosyl urea followed by immediate nucleophilic displacement of NH_2. No intermediate was detected in the reaction mixture by ^{13}C NMR. The stereochemistry of compound 1 is such as to facilitate the formation of an oxazolidine ring. In addition to compound 1, and the minor amounts of monomeric by-products, the reaction yielded a small quantity of dark brown colored polymer whose structure is presently being investigated.

EXPERIMENTAL

General Methods. The ^{13}C and ^{1}H NMR spectra were recorded on a Brucker WM 250 spectrometer. The ^{1}H spectra were recorded

in 5 mm tubes, SI:16K, SW:3000Hz, pulse delay: 5 sec. with HOD (6.4 ppm) peak as the reference for compound 1 and TMS (0 ppm) as internal standard for compound 2. The ^{13}C NMR spectra were recorded in D_2O in 10 mm tubes, SI: 16K, SW: 25000, pulse delay 10 sec. with TMS as external standard. ^{13}C coupled spectra were obtained without NOE enhancement. The IR spectrum was obtained using a Beckman 4250 spectrometer. The Gas Chromatographic analysis was done on a Hewlett-Packard 5880 A GC coupled with a 5880 A GC terminal using a 25 m fused silica SE-54 capillary column, a flame ionization detector, and helium as carrier gas. Operating conditions: injection temperature 220 °C, detector temperature 250 °C, column temperature 200 °C, split ratio 80/1, column flow, 0.67 mL/min. GC and GC-MS data were obtained on a Finnigan MAT 312 spectrometer. For the acetylated product 2, the column used was an OV-3 (6 ft) in a temperature programmed run from 170 to 250 °C at 3 °C/min. The electron impact (EI-MS) was obtained using an electron energy of 70 eV. The mass spectrometric operating conditions for the desorption chemical ionization (DCI-MS), with methane as reactant gas (0.4 mbar), were as follows: accelerating voltage: 3000 V, electron multiplier 2000 V, electron energy 250 eV, emission current 0.2 mA. Thin layer chromatography was carried out on silica gel 60 precoated TLC and PLC plates. (E. Merck, Darmstadt). The solvent used was n-butanol-acetic acid-water (5-2-1). Compounds were detected with 30% sulfuric acid in ethanol. Solutions were concentrated under reduced pressure at 38 °C. The cation exchange resin used was the H^+ form of AG 50W-X8, 200-400 mesh (Bio-Rad Laboratories).

Reaction of D-xylose with urea. A D_2O solution (2 mL) containing D-xylose (0.300 g) and urea (0.120 g) was kept at 68 °C in a 10 mm NMR tube. At different time intervals a ^{13}C NMR spectrum was run. At the end of six weeks, the spectrum showed no xylose and the presence of one major monomeric compound; ^{13}C NMR: δ (ppm) 159.90, 85.98. 85.42, 79.53, 73.11, 59.15.

α-D-xylo-furano[1,2-d]oxazolidin-2-one (1). A solution of D-xylose (15 g) and urea (6 g) in double distilled water (100 mL) was kept under sterile conditions for six weeks at 68 °C. A ^{13}C NMR spectrum in D_2O of an evaporated and dried fraction of this reaction mixture gave a spectrum similar to the one obtained in the D_2O reaction. An aliquot (20 mL) of the reaction mixture was passed down a column of AG 50W-X8 (75 x 2 cm). The column was eluted with two successive volumes of water, 20 and 340 mL. The first dark colored 20 mL were discarded. The 340 mL were evaporated under reduced pressure and dried over P_2O_5; yield: 1.22 g. A ^{13}C NMR spectrum of the mixture showed the presence of one major monomeric component with less than 10% by-products. TLC showed one major component with an R_f of 0.66 and two minor products with R_f of 0.61 and 0.44. Purification of the syrup was done by preparative TLC. The band containing the desired product was extracted with water and the solution obtained after filtration was evaporated to dryness. TLC still showed the presence of a small amount of by-product R_f 0.61. Further purification of 66 mg of this product was done on an AG 50W-X8 (H^+ form) cation exchange resin (95 x 1 cm). The compound, dissolved in water (0.2 mL), was added to the column which was eluted with water and 0.6 mL fractions were collected. All fractions containing the desired material were pooled, evaporated and dried over P_2O_5 yielding a syrup. IR(KBr) 3400 (OH,NH), 1760 (β-Lactam C=O); ^{13}C NMR (D_2O), ^1H decoupled, δ (ppm): 159.98 (C=O), 85.98 (C-1), 85.42 (C-4), 79.53 (C-2), 73.11 (C-3), 59.15 (C-5). ^{13}C NMR (D_2O), ^1H coupled, δ (ppm): 159.98 (s, C=O), 85.98 (d, C-1, 180 Hz), 85.42 (d, C-4, 168 Hz), 79.53 (d, C-2, 143 Hz), 73.11 (d, C-3, 157 Hz), 59.15 (dd, C-5, 148, 141 Hz). ^1H NMR (D_2O, 250 MHz) δ 5.69 (d, 1, H-1 $J_{H-1,\ H-2}$ = 5.4 Hz), 4.82 (d, 1, H-2 $J_{H-2,\ H-3}$ = 5.4 Hz), 4.21 (d, 1, H-3 $J_{H-3,\ H-4}$ = 2.7 Hz), 3.91 (m, 1, H-4), 3.66 (m, 2, H-5, H-5'). MS-DCI, 216 (M+41), 204 (M+29), 176 (M+1), 133, 115, 103, 91, 86, 75, 61.

Anal. Calcd for $C_6H_9NO_5$ (175.14): C, 41.14; H, 5.18; N, 7.99. Found: C, 41.43: H, 5.57; N, 7.68.

N-acetyl-di-O-acetyl-α-D-xylo-furano[1,2-d]oxazolidin-2-one (2). Compound 1 (20 mg) was acetylated in acetic anhydride (10 mL) with sodium acetate as catalyst at 120 °C. After two hours the reaction mixture was evaporated to dryness under vacuum in a dessicator over KOH. The N-acetyl-di-O-acetyl derivative was dissolved in chloroform, the chloroform extract was dried over Na_2SO_4 (anhydrous), and evaporated to dryness yielding a syrup. ^{1}H NMR ($CDCl_3$, 250 MHz) 6.30 (d, 1, H-1 $J_{H-1,\ H-2}$ = 5.4 Hz), 5.44 (d, 1, H-3 $J_{H-3,\ H-4}$ = 2.6 Hz), 4.83 (d, 1, H-2 $J_{H-2,\ H-1}$ = 5.4 Hz), 4.30 (m, 3, H-4, H-5, H-5'), 2.52 (s, 3, NAc), 2.11 (s, 3, OAc), 2.03 (s, 3, OAc). GC-MS (EI), 241 (0.78, M-AcOH), 228 (21.17, M-CH_2OA_c), 199 (10.61, M-AcOH-CH_2=C=O), 186 (25.65, M-CH_2OAc-CH_2=C=O), 168 (5.75, M-CH_2OAc-AcOH), 157 (27.00), 145 (37.17), 139 (13.89), 126 (59.44), 103 (29.89), 96 (12.72), 86 (14.69), 43 (100.00). GC-MS (DCI), 342 (M+41), 330 (M+29), 302 (M+1), 258, 242, 61.

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