Formation of Heterocyclic Products in Michael Reactions of Ascorbic Acid with α,β-Unsaturated Compounds. 3rd Communication [1]. Structural Analysis of Michael Adducts of Ascorbic Acid by ^{13}C-nmr Spectroscopy in the Solid State

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Received February 24, 1992

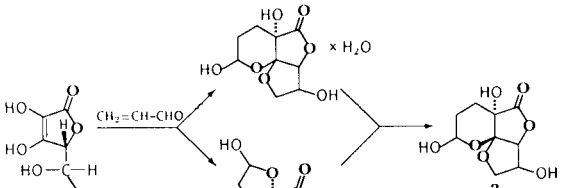
Dedicated to Prof. Dr. E. Bayer, University of Tübingen,
on the occasion of his 65th birthday.

The structure of the Michael adducts of ascorbic acid (AA) and AA-6-palmitate with acrolein can be unambiguously determined by using ^{13}C-nmr solid state spectroscopy.

J. Heterocyclic Chem., **29**, 1225 (1992).

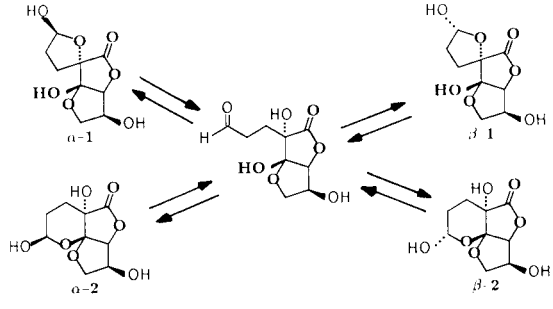
During the last three decades some attention was directed towards the derivatization of ascorbic acid [2]. Jackson and Jones [3] were the first to observe C2-alkylations besides the expected O3-benzylation in the reaction of ascorbic acid with benzyl chloride, which underlined the ambident character of the vitamin towards nucleophilic reagents. More recently Fodor *et al.* [4] reported the Michael reaction of α,β-unsaturated aldehydes and ketones to the C2-position of ascorbic acid. In the reaction with acrolein (Scheme 1) they obtained a single product and determined it to be the monohydrate of an 1:1 adduct of the aldehyde with the enole system of ascorbic acid. After removal of the water of crystallization the X-ray crystal-structure analysis clearly proved the formation of compound **2**. Since the ^{1}H- and the ^{13}C-nmr spectra of the monohydrate and **2** were identical (Figures 1a and b), Fodor assumed the same structure for both **1** and **2**. In

Scheme 1



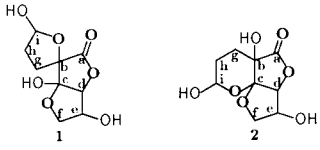
contrast, Eger and co-workers [5] were able to show that the monohydrate in fact was the tricyclic furanoid spiro compound **1**, which underwent rearrangement to the pyranoid **2** during the azeotropic distillation. Compounds **1** and **2** are transformed into one another in a complex solvent- and time-dependent equilibrium, in which **1** predominates (Scheme 2). The transformation of **2** into **1** could be monitored by time-dependent ^{1}H-nmr spectroscopy [6], but due to overlapping signals in the ^{1}H-nmr spectra the interpretation was not straightforward. Due to the long data acquisition time no difference between the two isomers, **1** and **2**, can be seen in the ^{13}C-nmr spectra (Figures 1a and b). The broadband decoupled spectra indicate a structural rearrangement in solution only by the appearance of "doublet signals". Fodor *et al.* interpreted the doublet signals as an indication of the mutarotational equilibrium between α-**2** and β-**2** *via* the open chain aldehyde (Scheme 2).

Scheme 2



We are now able to show that an unambiguous and solvent-independent characterization of both isomers can be achieved by ^{13}C-nmr spectroscopy in the solid state [7]. During the rearrangement (**1** ⇌ **2**) the positions **b**, **c** and **i** (Scheme 3) change their structural environment, and this should lead to obvious changes in the ^{13}C-chemical shifts for these atoms. Indeed, the transformation of the tertiary

Scheme 3



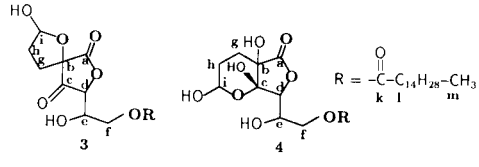
alcoholic carbon atom **2-b** into the spiro-ether **1-b** produces a signal shift of 16 ppm downfield; while **2-b** shows resonance at 72 ppm the signal for **1-b** appears at 88 ppm (Table 1, Figures 1c and d). The signal of the acetale carbon atom **2-i** (95 ppm) is only slightly shifted downfield by 6 ppm to 101 ppm in **1-i**, whereas **2-c** and **1-c** respectively are not influenced at all; they both show resonance at 107 ppm. The structural assignments from the ^{13}C-solid state nmr spectra allow to a certain extend an interpretation of the ^{13}C-nmr spectra of **1** and **2** in [D6]-DMSO solution (Figures 1a and b). In both spectra only the resonances of **1** give major peaks, both spectra are exactly identical. The minor resonances belong to **2** and the open chain isomers.

Table 1. Chemical shifts of **1** and **2** in the solid state and in solution

Atom-	Solid state spectra		Solutional spectrum ([D6]-DMSO)
index	1	2	mutarotated mixture
a	175.2	174.0	175.1
b	88.0	72.0	87.3 and 87.6
c	107.5	107.5	106.0 and 106.8
d	85.3	86.1	85.3
e	78.5	78.5	74.5
f	73.1	74.7	73.8
g	28.4	29.5	29.4 and 29.9
h	32.3	29.5	32.3
i	101.2	94.9	100.0 and 99.7

The same problem of structural assignment was faced by Eger *et al.* in the case of the Michael adduct of acrolein and ascorbic acid palmitate [6]. In analogy to the reaction given in Scheme 1 the adduct should exist in two isomeric forms, **3** and **4** (Scheme 4). The authors found that the

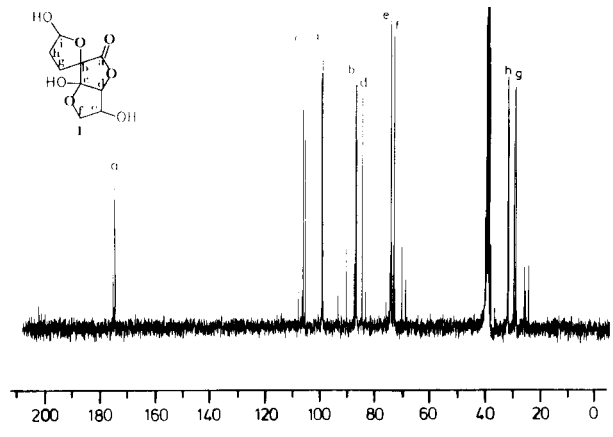
Scheme 4



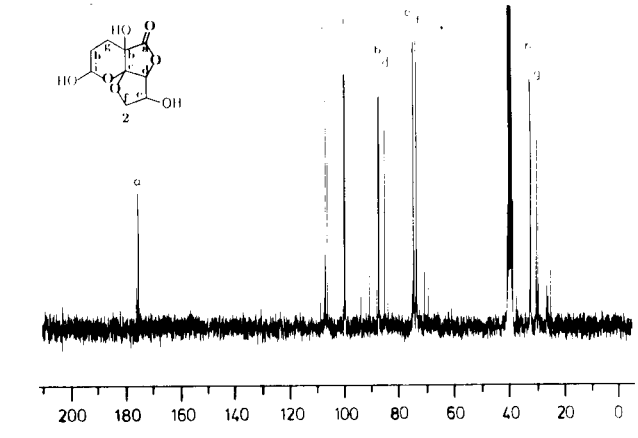
^{1}H-nmr spectrum of the reaction product was in accordance with structure **3**. As a further proof for the ketone moiety they prepared a dinitrophenylhydrazone derivative. New results now indicate that in absolute ethanol only **4** is formed. As shown above, solid state nmr spectroscopy provides a useful means for an unambiguous structure elucidation of the reaction product.

Figure 1. Broadband decoupled ^{13}C-nmr spectra of **1** and **2** in [D6]-DMSO solution and in the solid state

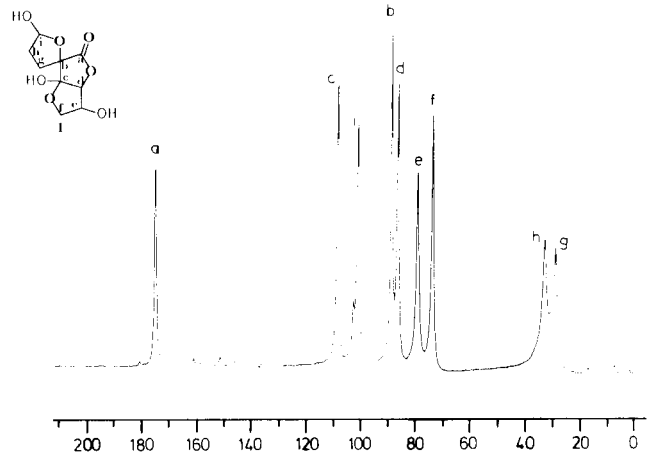
a) Spectrum of **1** in [D6]-DMSO solution



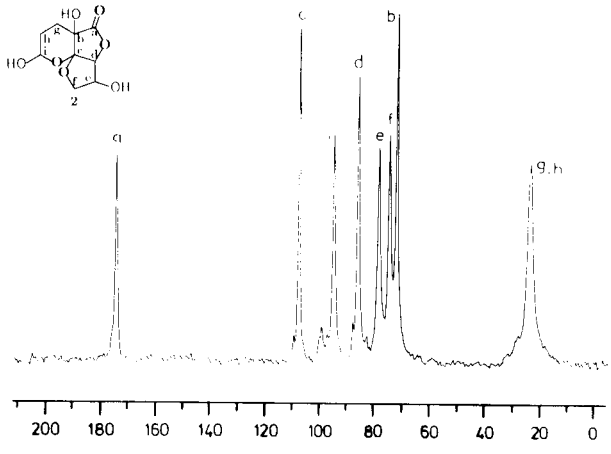
b) Figure 1, continued. Spectrum of **2** in [D6]-DMSO solution



c) Figure 1, continued. Spectrum of **1** in the solid state



d) Figure 1, continued. Spectrum of **2** in the solid state



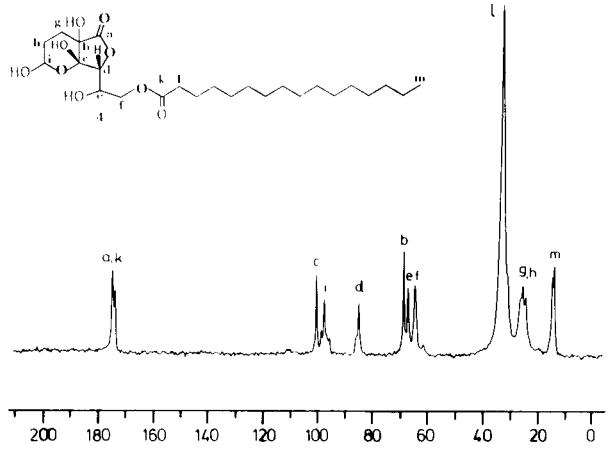
The ^{13}C-nmr solid state spectrum (Figure 2a) only shows signals of one compound, which can be identified as the pyranoid **4** by comparing the chemical shifts of carbon atom **4-b** (Scheme 4, Table 2) with those of **1-b** and **2-b** (Scheme 3) in the solid state spectra given in Figures 1c and 1d. In Figure 2a the signal of the tertiary alcoholic carbon atom **4-b** appears at 70 ppm (Table 2), which is perfectly consistent with the resonance of **2-b** at 72 ppm (Table 1). Even more important, the signal of **4-c** is shifted upfield to 101 ppm (compared to 107 ppm in **1-c** and **2-c**), while the resonance of **3-c** would be expected to appear above 200 ppm. Recording the ^{13}C-nmr spectrum at 62.5 and 20 MHz yields an indication for a possible rearrangement of **4** into **3** in [D6]-DMSO solution. The spectrum taken at 62.5 MHz (50 mg, 6000 scans) is very similar to the solid state spectrum (Figures 2a and b). Apart from a few minor peaks it contains only the structural information of **4**. Measured at 20 MHz (50 mg, 12000 scans), the

Table 2. Chemical shifts of **4** in the solid state and in solution

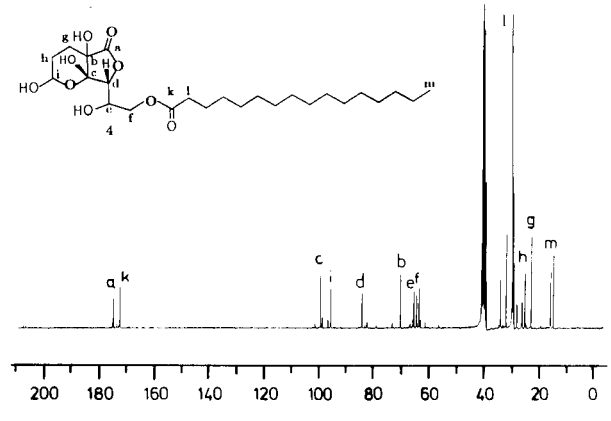
Atom-	Solid state spectrum	Spectrum in [D6]-DMSO solution	
index	**4**	**4** (62.5 MHz)	**3/4** (20 MHz)
a	175.3	175.6	174.9
b	69.5	69.9	78.9 and 69.9
c	101.3	101.4	207.2 and 101.4
d	85.8	84.1	82.4, 83.0 and 84.1
e	68.0	65.6	66.8 and 65.5
f	65.4	64.1 and 65.1	62.7 and 63.2
g	26.1	22.1	22.1
h	25.1	25.7	24.4 and 25.4
i	99.6	95.6	99.3 and 95.6
k	174.4	172.7	172.6
l	33.6	27.3 - 33.4 (m)	27.4 - 34.0 (m)
m	14.7	13.9 and 15.0	13.8 and 14.9

Figure 2. Solution and solid state spectra of **4**

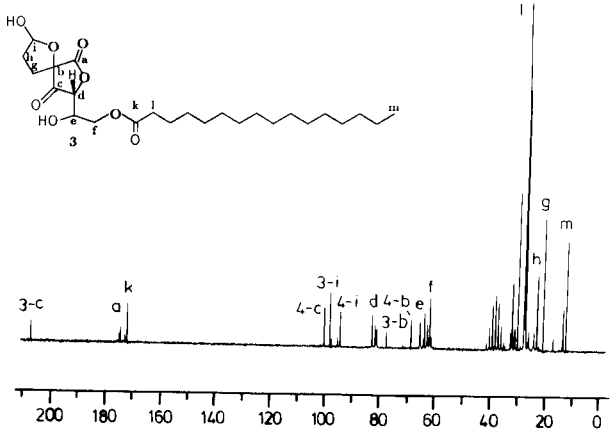
a) Spectrum of **4** in the solid state



b) Figure 2, continued. Spectrum of **4** in [D6] DMSO solution, recorded at 62.5 MHz



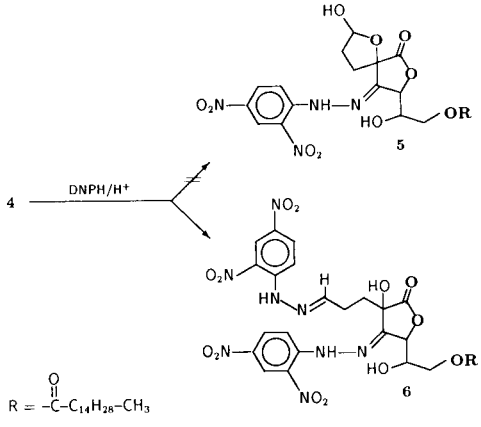
c) Figure 2, continued. Spectrum of **3** and **4**, recorded at 20 MHz



spectrum shows signals of both compounds **3** and **4** (Figure 2c). We identify the ketone resonance of **3-c** at 207 ppm, and the signal of **3-b** is shifted downfield to the expected value of a spiro ether, 79 ppm, whereas **4-b** shows

resonance at expected value of a spiro ether, 79 ppm, whereas **4-b** shows resonance at 70 ppm. In addition to the nmr results we repeated the above mentioned formation of a dinitrophenylhydrazone. We now believe the assumed structure **5** (Scheme 5), published in [6], was not formed under our experimental conditions. Instead, we obtain **6**, which is confirmed by spectral evidence.

Scheme 5



The ^{1}H-nmr spectrum of **6** shows two N-H signals and two sets of coupling paths for a dinitrophenylhydrazone group. Further confirmation comes from the ^{13}C-nmr spectrum (in solution), mass spectrum and elemental microanalysis.

EXPERIMENTAL

Apparatus.

Melting points were determined on a Büchi 510 melting point apparatus, and are uncorrected. The ir spectra (potassium bromide) were recorded on a Perkin Elmer 1710 FTIR spectrometer. The ^{1}H and ^{13}C-nmr spectra in solution were measured on a Bruker AC 200 spectrometer using tetramethylsilane as an internal standard, the spectrum of **3** was taken on a Bruker AC 80. For the resonance signals the following abbreviations are used: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; m, multiplet. The structural assignment derived from the ^{13}C-nmr spectra in solution was confirmed by the DEPT135 sequence and by literature data. Solid state ^{13}C magic-angle-spinning (MAS) spectra were obtained on a Bruker MSL 200 NMR spectrometer at 4.7 T. Quantities of 200-300 mg of powdered samples were packed into double bearing rotors of zirconium oxide which were spun at 3.6 kHz by a dry air gas drive. Solid state nmr experiments were performed by combination of Magic Angle Spinning (MAS), cross polarization (CP) and high power decoupling in order to obtain high resolution spectra [7,8]. The Hartmann-Hahn conditions for cross polarization was calibrated with glycine. Typically, CP/MAS spectra were recorded with a pulse length of 5 μs, a contact time of 1 ms, and a repetition time of 2 s. Chemical shifts were externally referenced to liquid tetramethylsilane. The mass spectrum was obtained by the Field Desorption method (FD) on a Finnigen MAT 711A spectrometer (modified by AMD Intectra GmbH) using a direct inlet system. It was recorded by the department Massenspektrometrie, Organisch-Chemisches Institut der Universität Tübingen. Elemental analysis was performed by the department Elementaranalyse, Anorganisch-Chemisches Institut der Universität Tübingen.

Synthesis of {(*S*)-2-[(2*R*)-3-(2,4-Dinitrophenylhydrazono)-4-[3-(2,4-dinitrophenylhydrazono)propyl]-4-hydroxy-5-oxo-2-furyl]-2-hydroxyethyl} Hexadecanoate (**6**).

2,4-Dinitrophenylhydrazine (0.4 g, 2 mmoles) was dissolved in 2 ml of concentrated sulphuric acid. The stirred mixture was carefully diluted with 3 ml of distilled water. To the warm solution 10 ml of ethanol were added. A suspension of 0.5 g (1 mmole) of **4** in 20 ml of ethanol was added to the stirred solution. The immediately formed precipitation was allowed to continue crystallization at 4° overnight. The amorphous mass was separated from the solution by suction and recrystallized from methanol. A dark red amorphous powder, yield 0.45 g (54%), mp 124° was obtained; ir (potassium bromide): ν 2925, 2853 (C-H, N-H), 1794, 1738 (lactone, ester), 1619, 1599, 1519, 1507, 1426, 1339, 1141, 923, 834, 764; ms: (m/z) 831.0 (M^+); ^{1}H-nmr ([D6]-DMSO, 250 MHz): δ (ppm) 1.20 and 1.55 (m, 31 H, fatty acid chain), 2.35 (m, 4 H, -C*H*$_2$-C*H*$_2$), 4.16 (m, 2 H, CHOH-C*H*$_2$-OR), 4.28 (m, 1 H, C*H*OH-CH$_2$OR), 5.44 (d, J = 1.8 Hz, 1 H, N=CR-C*H*OR-CHOH-), 7.67 and 7.76 (2x d, $J_{5',6'}$ = 9.6 Hz, 2x 1 H, phenyl-H-6'), 7.94 (t, J = 4.7 Hz, 2x 1 H, C*H*=N-N), 8.18 (dd, $J_{5',6'}$ = 9.6 Hz, $J_{5',3'}$ = 2.7 Hz, 1 H, phenyl-H-5'), 8.26 (dd, $J_{5',6'}$ = 9.6 Hz, $J_{3',5'}$ = 2.6 Hz, 1 H, phenyl-H-5'), 8.77 (d, $J_{3',5'}$ = 2.4 Hz, 1 H, phenyl-H-3'), 8.78 (d, $J_{3',5'}$ = 2.0 Hz, 1 H, phenyl-H-3'), 12.10 and 12.59 (s, 2x 1H, NH); ^{13}C-nmr ([D6]-DMSO, 62.5 MHz): δ (ppm) 13.8 (CH_3, fatty acid), 22.1, 24.4, 26.6, 28.6, 28.8, 29.1, 31.3, 32.4 and 33.4 (CH_2, fatty acid and propyl side chain), 64.0 (CHOH-*C*H$_2$-OR), 67.4 (*C*HOH-CH$_2$OR), 74.9 (CH$_2$-*C*ROH-CO), 78.3 (CO-O*C*R-CHOH), 115.7 and 116.1 (phenyl-C-6'), 122.7 (phenyl-C-3'), 128.6 and 129.6 (phenyl-C-5'), 136.5 (phenyl-C-2', 137.5 (phenyl-C-4'), 144.0 and 144.4 (phenyl-C-1'), 152.5 (CH=N-N), 153.0 (R_2 C=N-N), 172.7 and 173.6 (C=O, lactone and ester).

Anal. Calcd. for $C_{37}H_{50}N_8O_{14}$ (830.83): C, 53.48; H, 6.07; N, 13.49; O, 26.96. Found: C, 53.32; H, 6.26; N, 13.20; O, 27.22.

Acknowledgements.

K. E. wishes to thank the Deutsche Forschungsgemeinschaft (DFG) for financial support.

REFERENCES AND NOTES

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