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Note

The identification of *N*-substituted 1-amino-1-deoxyhexuloses by ^{13}C-n.m.r. spectroscopy of their oximes

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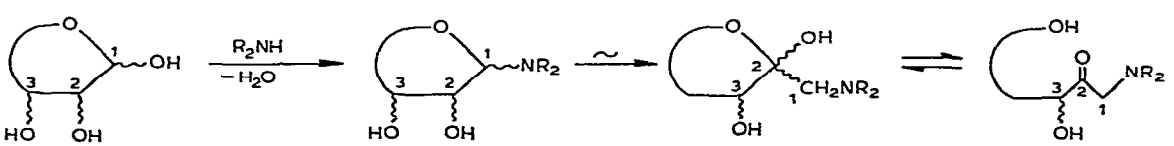
The Amadori rearrangement[1,2] is the isomerization of an *N*-substituted aldosylamine (**2**) to an *N*-substituted 1-amino-1-deoxyhexulose (**3**, **4**)

This reaction is of biochemical interest, and has often been described from a preparative[1,3,4] and mechanistic[2] point of view For instance, the Amadori rearrangement products **3** and **4** have long been recognized as key substances in the non-enzymic, browning (Maillard) reaction[1,5,6].

The identification of the products **3** and **4** is often difficult, because glycosylamines **2** may also be present in the reaction mixture[4]. and all the possible isomers of **2** and **3** may have similar chemical and spectroscopic properties[4,7] Only the open-chain structure **4** can be determined by i r spectroscopy[8], due to its C=O band near 1720 cm^{-1} With the help of ^{13}C-n m r spectroscopy, the constitution and configuration of the Amadori products **3** and **4** have been determined[9] If solutions of *N*-substituted 1-amino-1-deoxyhexuloses in pyridine were allowed to mutarotate, up to 29 ^{13}C-signals (all for the carbohydrate part of the molecule) appeared, most of these signals occurred in a very narrow range[10] This finding shows that all five possible isomers (**4**, two pyranoses **3**, and two furanoses **3**) were formed



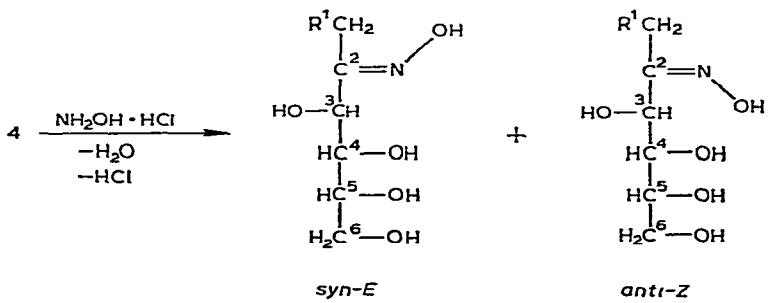
1 **2** **3** **4**

Addition of hydroxylamine hydrochloride in pyridine[11] to the mixture of the five isomers drastically simplified the ^{13}C-n m r. spectra. All of the products are converted quantitatively (>98%) into oximes within a few minutes at room temperature. As shown below, two isomers are formed, and hence a maximum of 12 ^{13}C-n.m r. signals for the carbohydrate part of the molecules can be observed Furthermore, the glycosylamines **2** do not give this reaction In the present paper, the following compounds have been investigated by ^{13}C-n m r spectroscopy 1-deoxy-1-(*N,N*-dibenzylamino)-D-fructose oxime (**5**), 1-deoxy-1-(*N*-methylanilino)-D-fructose oxime (**6**), 1-deoxy-1-piperidino-D-fructose oxime (**7**), 1-deoxy-1-morpholino-D-fructose oxime (**8**), and, as reference, D-fructose oxime (**9**)

The ^{13}C-spectra were obtained under conditions of proton-noise decoupling, and the data are given in Table I.

In all of the cases, only two products are present They can be assigned to the open-chain forms of the *syn-E* and *anti-Z* isomers This is made possible by comparison with aldoximes and ketoximes of simple products[12] and of some monosaccharide *O*-methyl oximes[13] investigated previously by ^{13}C-n m r spectroscopy. The C-1–C-6 signals of the D-fructose *O*-methyl oximes[13] are nearly identical with those of D-fructose oxime (**9**) In this paper, **9** is used as reference material, as it has the same constitution (apart from R) as the Amadori products **5–8**

As expected, the resonance of the sp^2-hybridized C-2 of **5–9** is seen between δ 153.6 and 161 3 So the ^{13}C-signals of the open-chain form of non-oximated products are shifted upfield by up to 58 p p m on oxime formation In all cases, the signal for *syn*-C-2, as compared to the *anti*-C-2, is shifted upfield by up to 2 p p m Only for **6** do the two C-2-resonances overlap The resonances of C-1 and C-3 also shift upfield on oxime formation[10,12] The shift of the signal for the carbon *cis* to the =N-OH group is larger than that for the carbon located *trans*, an effect noted earlier with *cis* and *trans* alkenes[14] The difference amounts to 5 2–7 6 p p m This effect is the basis for the assignments to the *syn* and *anti* forms



syn-E *anti-Z*

5 R = $NBzl_2$
6 R = N(Me)Ph
7 R = NC_5H_{10}
8 R = NC_4H_8O
9 R = OH

TABLE I

^{13}C-CHEMICAL SHIFTS[a] FOR THE OXIMES 5–9 IN PYRIDINE-d_5 AT 35°, AND THE *anti–syn* RATIO

Compound	5	6	7	8	9
syn *form*					
C-1	48 9	48 8	50 7	50 9	56 4
C-2	157 4	159 5	153 6	155 6	161 3
C-3	72 2	70 6	72 9	73 0	71 1
C-4[b]	74 8	73 9	76 3	76 0	73 8
C-5[b]	73 3	73 2	73 0	73 2	72 9
C-6	65 7	65 3	65 1	65 4	64 9
anti *form*					
C-1	54 8	54 5	58 3	58 4	61 6
C-2	158 1	159 5	155 6	156 5	161 9
C-3	68 6	68 3	68 3	68 1	67 8
C-4[b]	74 0	74 4	73 6	73 8	73 4
C-5[b]	73 3	73 5	72 9	73 2	72 7
C-6	65 5	65 4	65 3	65 4	64 8
R[c]	137 9	151 3	55 3	66 2	
	134 8	150 9	54 8	65 9	
	131 6	130 0	24 3	54 5	
	130 7	129 8	22 5	53 9	
	129 7	118 0			
	129 6	117 5			
	129 5	114 3			
	59 5	114 0			
	58 3	40 2			
		39 5			
anti–syn Ratio[d]	1 1	1 3	4 2	4 0	1 2

[a]Shifts are in p p m downfield from tetramethylsilane [b]Assignments uncertain [c]See formulae [d]The intensities for equivalent carbon atoms are compared

The variations in the positions of the ^{13}C-signals for C-1 are rationalized in terms of the different groups R The signals at δ ~65 0 and δ 72 7–76 0 have shifts typical of primary and secondary alcohols, respectively

The assignment to the *syn* and *anti* forms is supported by the relative intensities of the ^{13}C-signals In all cases, the major isomers are the *anti* forms (see Table I) The *anti–syn* ratio for **7** and **8** is exceptionally high, because of the steric hindrance imposed by the large, cyclic amino-group Such a steric influence was previously observed with simple ketoximes and some monosaccharide *O*-methyl oximes[12 13]

Apart from the pyridine-d_5 signals and the resonances of the groups R, which are not discussed here, there are no further signals in the ^{13}C-spectra proving the absence of cyclic oxime derivatives If present, their concentration must be below 3%, as the signal-to-noise ratio is quite high in all the spectra

Under the experimental conditions, the glycosylamines are not stable, but are quantitatively converted into D-glucose oximes (*syn* and *anti* forms) and the corre-

sponding amines This was observed with *N*-butyl-β-D-glucopyranosylamine monohydrate and *N*-(β-D-glucopyranosyl)piperidine. There is no difficulty in distinguishing the aldose oxime from the *N*-substituted 1-amino-1-deoxyketoxime, even in a mixture, because the signals, especially those of C-1–C-3, are well separated

EXPERIMENTAL

^{13}C-N m r. spectroscopy — The ^{13}C-spectra were obtained under conditions of proton-noise decoupling on a Bruker WH 270 instrument (67 8 MHz for ^{13}C, with an internal deuterium lock) operating in the Fourier-transform mode It was equipped with a Nicolet BNC 12 computer with a 32K data memory and a Diablo Disk-System. All measurements given in Table I were carried out at 35° on solutions in pyridine-d_5 (10-mm sample tubes) with a spinning rate of ~30 sec^{-1} Up to 20 000 scans with a pulse sequence of 10 sec and a pulse angle of 30° were used to record a spectrum Internal standards were tetramethylsilane or the highest pyridine-d_5 signal (δ 148 4 relative to that of Me_4Si)

Oximes — The Amadori rearrangement products 1-deoxy-1-(*N*,*N*-dibenzylamino)-D-fructose[15], 1-deoxy-1-(*N*-methylanilino)-D-fructose[15], 1-deoxy-1-piperidino-D-fructose[6], 1-deoxy-1-morpholino-D-fructose[15], the glycosylamines *N*-butyl-β-D-glucopyranosylamine monohydrate[9 16] and *N*-(β-D-glucopyranosyl)piperidine[17], and D-fructose (2 25 mmol) were dissolved in 1 5 ml of pyridine-d_5 together with hydroxylamine hydrochloride (4 5 mmol) All of the solution of each sample was used for the ^{13}C-n m r measurements The reaction was complete within a few minutes, and the mixture was stable for several days at room temperature

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