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UNEXPECTED FORMATION OF THE MOST STRAINED δ-LACTONE IN THE PYROLYSIS OF DIETHYL ESTER OF cis-4-HYDROXY-trans-5-METHOXY-trans-1,2-CYCLOHEXANEDICARBOXYLIC ACID

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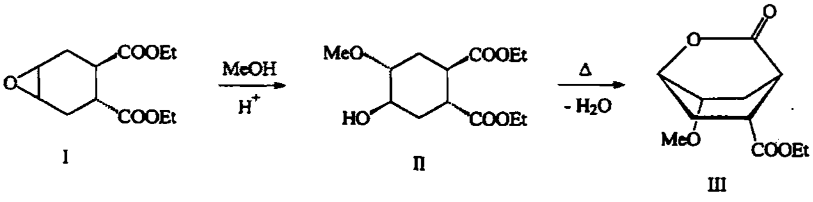
Vacuum distillation of diethyl ester of cis-4-hydroxy-trans-5-methoxy-trans-1,2-cyclohexanedicarboxylic acid gave a single compound, 5-ethoxycarbonyl-7-methoxy-2-oxa[2.2.2]bicyclooctan-3-one. The structure of this δ-lactone was demonstrated by data of NMR and IR spectroscopy. Calculations using the method of molecular mechanics showed that this structure has the highest steric strains of all possible stereoisomeric δ-lactones.

During a synthesis of cyclohexane derivatives, changing conformation with changing pH of the medium, from diethyl ester of 4,5-epoxy-trans-1,2-cyclohexanedicarboxylic acid (I), there was obtained diethyl ester of cis-4-hydroxy-trans-5-methoxy-trans-1,2-cyclohexanedicarboxylic acid (II) [1]. In attempting to purify compound II by vacuum distillation, we obtained only one compound, later characterized as δ-lactone III (the yield after two steps was 51%). Formation of a δ-lactone is unusual. Earlier, during lactonization of derivatives of trans-1,2-cyclohexan(en)dicarboxylic acid, formation of only or predominantly γ lactones was noted [2-5]. Isomerization of the more strained δ-lactone to the stable γ-lactone has also been described [4]. Therefore, a reliable determination of the structure of the lactonization product of compound II was of key importance for the present study.



I

II

III

Formation of precisely a six-membered lactone ring is indicated by the characteristic absorption frequency of the corresponding carbonyl group in the IR spectrum: 1765 cm^{-1} [2, 3]. A reliable confirmation of the δ-structure of the lactone and data on the spatial orientation of the substituents were obtained by NMR spectroscopy. The character of the ESR spectrum (see Fig. 1) suggests that the substance studied is a single isomer. This is indicated by the presence of a single signal of the methoxy group (3.27 ppm; 3H), one signal of the protons of the ethoxycarbonyl group (1.20 ppm; 3H, t, $\underline{CH_3}CH_2$; 4.12 ppm; 2H, q, $CH_3\underline{CH_2}$), as well as a group of well-resolved signals of cyclic protons: six multiplets (A, C, E, F, G, and J; Fig. 1, Scheme 1) with an intensity corresponding to one proton, and one signal of double intensity H and I protons. The key point for assigning the signals is the characteristic chemical shift of the A proton (4.63 ppm). The COSY experiment made it possible

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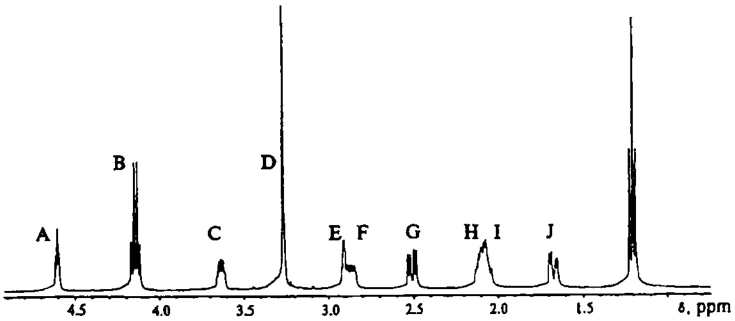


Fig. 1. ESR spectrum of δ-lactone III.

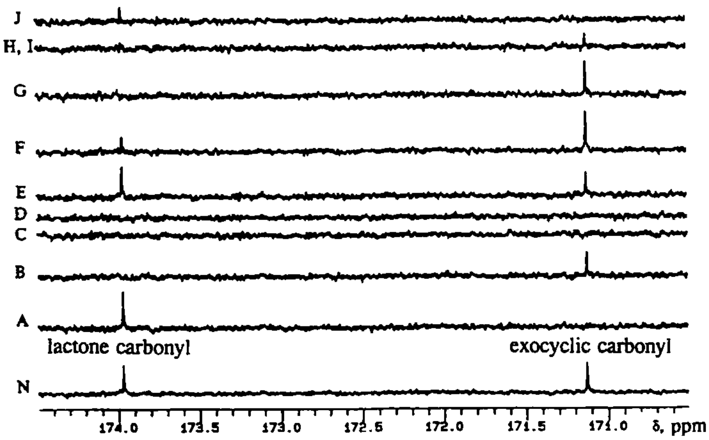
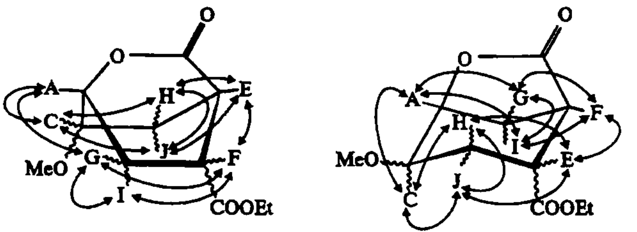


Fig. 2. Series of difference spectra of the spin echo with selective excitation (SESE) for the carbonyl region of δ-lactone III.

to follow the interaction of protons related to each other by the vicinal and geminal constants and to establish the sequence of arrangement of the cyclic protons. At the same time, however, it was found that the structure of the correlations of constants J_{HH} corresponds equally well to δ-lactone III and to γ-lactone IV.

Scheme 1



III

IV

The structure of the δ-lactone and γ-lactone differs fundamentally in the arrangement of the protons of methylene groups G, I, H and J relative to the carbonyl carbon atoms. Compound III is characterized by a vicinal arrangement of the G and I protons relative to the exocyclic carbonyl of the ester group COOEt, whereas in structure IV, the G and I protons have a vicinal arrangement relative to the lactone carbonyl. In structure III, the H and J protons are separated by three bonds from the carbon atom $C_{(3)}$, whereas in structure IV, these protons are located three bonds away from the carbon atom of the ethoxycarbonyl group. To make the final choice between a δ- and a γ-lactone, an SESE experiment was carried out, which we had used earlier to establish the structure of nitrogen heterocycles [6, 7].

Figure 2 shows the region of carbonyl groups for a series of difference spectra with successive excitation of nine resonance regions of the signals of A, B, C, D, E, F, G, G + I and J. The lower spectrum (with an H mark) corresponds to

TABLE 1. Experimental Chemical Shifts ^1H (δ, ppm) and SSCC J_{HH} (Hz) of 5-Ethoxycarbonyl-7-methoxy-2-oxa[2.2.2]bicyclooctan-3-one (solution in $CDCl_3$ at 300 K)[*]

Chemical shifts δ[†]		J_{HH}	
1-H (A)	4,631	1-H, 6-H$_a$	1,146 (0,006)
4-H (E)	2,952	1-H, 6-H$_e$	4,497 (0,014)
5-H (F)	2,889	1-H, 7-H	3,878 (0,005)
6-H$_a$ (G)	2,542	1-H, 8-H$_a$	0,486 (0,005)
6-H$_e$ (I)	2,104	4-H, 5-H	4,033 (0,007)
7-H (C)	3,660	4-H, 8-H$_a$	1,977 (0,004)
8-H$_a$ (J)	1,686	4-H, 8-H$_e$	3,992 (0,005)
8-H$_e$ (H)	2,126	5-H, 6-H$_a$	5,880 (0,005)
		5-H, 6-H$_e$	11,731 (0,008)
		5-H, 8-H$_e$	2,045 (0,005)
		6-H$_a$, 6-H$_e$	-14,655 (0,006)
		6-H$_e$, 7-H	1,609 (0,005)
		7-H, 8-H$_a$	4,577 (0,004)
		7-H, 8-H$_e$	9,658 (0,004)
		8-H$_a$, 8-H$_e$	-14,449 (0,004)

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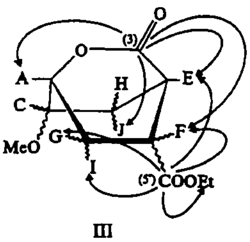
[*] The calculation is made in terms of the eight-spin system ACEFGHIJ; the standard deviation for 506 assigned theoretical transitions is 0.040 Hz. Given in parentheses are the standard deviations for SSCC. The table does not give the far SSCC, which do not exceed 0.05 Hz in absolute value (hypothetically).

[†] Given in parentheses is the assignment of the signals in the ESR spectrum; see Fig. 1.

a control spin echo experiment, in which both signals of the carbonyl groups are seen as being of approximately equal intensity. This experiment was optimized to a value of the constant $^{13}C-H$ of the order of 8 Hz. The signal in the difference spectrum is observed when the constant $^{13}C-H$ exists between the carbon atom and the proton being excited, and the response reaches its maximum if the constant is close to the specified value of 8 Hz (the amplitude of the maximum signal corresponds to twice the intensity of the control signal). The signal is not observed when the corresponding constant $^{13}C-H$ is close to zero. The spectra of series A and B permit a reliable assignment of the signals of the carbonyl groups. The spectra of series G and J permit one to make a definitive choice between the γ-lactone and δ-lactone. The observed correlations of the lactone carbonyl ($C_{(13)}$ atom) with the J proton and of the exocyclic carbonyl ($C_{(5')}$ atom) with the G proton are consistent only with the structure of the δ-lactone (Scheme 2). At this stage, however, the orientation of the exocyclic groups OMe and COOEt as well as of the protons of H and J, G, and I cannot be established.

Scheme 2



III

For a final determination of the conformation of compound III, we carried out a complete analysis of the ESR spectrum of exocyclic protons using the PAREMUS-LAOCOON program package [8, 9]. The spectrum was analyzed in terms of the ACEFGHIJ eight-spin system. In the initial stage, to increase the resolution, transformation of the Lorentzian line shape to the Gaussian was used. We isolated 100 spectral components by deconvolution. The initial values of the chemical shifts and SSCC were estimated by use of a series of double-resonance experiments on the assumption that the spectrum was close to first-order. In the calculation, we used data for 75 spectral components assigned to 506 theoretical transitions. All the vicinal constants

TABLE 2. Vicinal SSCC J_{HH} (Hz), Experimental and Calculated with PCMODEL 3.2 [11], for Alternative Structures III, V-VII

Experiment		Calculated $^3J_{HH}$			
protons	J_{HH}	III	V	VI	VII
1-H, 6-H_a	1,15	1,40	1,83	2,01	1,96
1-H, 6-H_e	4,50	5,30	4,57	4,23	4,31
1-H, 7-H	3,88	4,14	1,63	4,60	1,63
4-H, 5-H	4,03	2,19	3,04	1,28	1,29
4-H, 8-H_a	1,98	2,56	3,30	3,00	3,19
4-H, 8-H_e	3,99	4,00	3,17	3,44	3,20
5-H, 6-H_a	5,88	5,50	3,94	9,93	10,01
5-H, 6-H_e	11,73	10,18	10,38	6,35	6,18
7-H, 8-H_a	4,58	3,85	9,70	3,04	9,71
7-H, 8-H_e	9,66	9,71	4,43	9,57	4,34
SD*	—	0,27	0,82	0,76	1,04

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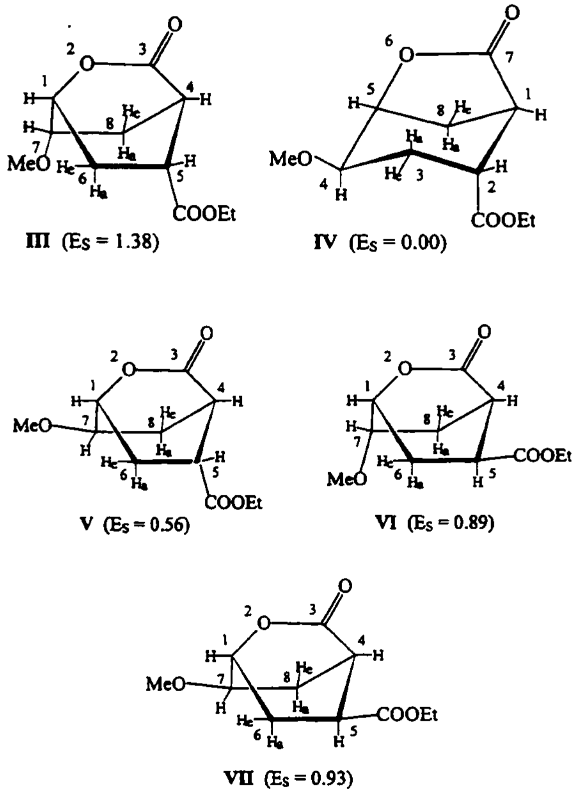
*Standard deviation of experimental and calculated values of vicinal constants in Hz.

were given a positive sign, and the geminal ones (J_{GI} and J_{JH}) were given a negative sign. We also assumed that constants J_{CG} and J_{EJ}, separated by four bonds and relatively large in absolute value were positive. The sign of the relatively small constant J_{AJ} (about 0.5 Hz) could be both positive and negative. We carried out two calculations for alternative sets of spectral parameters corresponding to two possible signs of J_{AJ}. For positive J_{AJ}, the agreement between the calculated spectrum and the experimental spectrum was significantly better. The corresponding standard deviations were 0.040 Hz and 0.054 Hz, and their difference is significant at a confidence level of 99.9% (the experimental value of the Fisher criterion F = 1.77 exceeds the tabular value F = 1.46 for a confidence coefficient α = 99.9% with 500 degrees of freedom [10]). Table 1 gives the final results of the analysis of the ESR spectrum.

Scheme 3



III (Es = 1.38)

IV (Es = 0.00)

V (Es = 0.56)

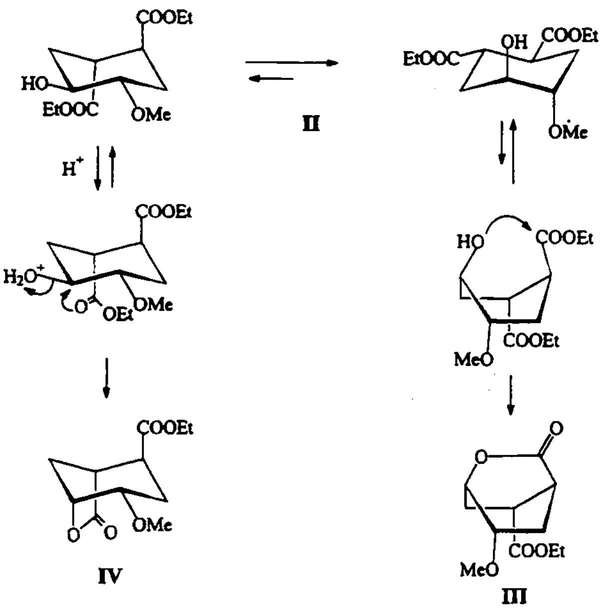
VI (Es = 0.89)

VII (Es = 0.93)

The calculations of the geometrical parameters and steric energy for all the stereoisomeric δ-lactones III, V-VII (Scheme 3) was carried out by use of the method of molecular mechanics MMC (PCMODEL 3.2 program [11]). The values of steric energy E_S are given in parentheses in the schemes (in kcal/mole relative to the energy of the γ-lactone IV). The same program made it possible to obtain calculated estimates of vicinal SSCC for the ESR spectra of compounds III, V-VII (Scheme 3) and to compare them with the experimental values (Table 2). Analysis of the values of vicinal constants given in Table 2 indicates good agreement only for δ-lactone III. The standard deviation between the calculated and experimental values of the vicinal constants is 0.27 Hz, which is within the limits of allowable errors of the approximation, used in this work, of constants J_{HH} by the Karplus equation [12, 13]. Thus, analysis of the ESR spectra in combination with the calculated data has permitted a unique solution of the problem of establishing the structure of bicyclic compound III.

It is interesting to note that, according to the calculated estimates of steric strains in molecules III-VII, the only isomer that we have isolated is the most unstable one even among δ-lactones (Scheme 3). It is obvious that its formation is controlled by kinetic factors. Examination of possible lactonization paths makes it possible to provide a rational explanation for this result (Scheme 4).

Scheme 4



The configuration of the hydroxyl group in molecule II is such that cyclization to γ-lactone IV is possible only via the intermediate formation of a carbocation or via a cationoid transition state. The detachment of the hydroxyl group in this case requires acid catalysis. Since the lactonization took place during vacuum distillation after the acid impurities were driven off, this requirement was not met. At the same time, formation of δ-lactone III can take place via intramolecular transesterification. Evidently, the activation energy of the second reaction is substantially lower than that of the first, and this accounted for the exclusive formation of the δ-lactone. The orientation of the substituents in lactone III is determined by their configuration in the initial compound II.

EXPERIMENTAL

The ESR and NMR ^{13}C spectra were recorded on a Varian VXR-400 spectrometer for solutions in deuterochloroform at 300 K. The SESE experiments involved the use of an SEL2DJ pulse sequence [14]. The chromato-mass spectrum was obtained on an NR5972A spectrometer. The ESR spectra were calculated by use of the PAREMUS-LAOCOON [8] program package on an IBM PC.

5-Ethoxycarbonyl-7-methoxy-2-oxa-[2.2.2]bicyclooctan-3-one (III). To a solution of 1.04 g (0.004 mole) of epoxide I in 15 ml of absolute methanol is added dropwise conc. H_2SO_4, and the solution is allowed to stand for two days at room temperature. The mixture is neutralized with calcium carbonate and filtered, and the solvent is driven off on a rotary evaporator. Compound II obtained is distilled at a reduced pressure of 22 Torr in a collar flask at a bath temperature of 225-245°C. After the distillation the product is purified by column chromatography on alumina (chloroform eluent), and 0.33 g of lactone III is obtained. In addition, 0.17 g of pure crystalline lactone is collected from the neck of the distillation flask. The total yield of lactone III is 0.50 g (51%). MP 83-84°C. For the data of NMR spectra, see the text and tables. IR spectrum (Vas. oil): 1731 (C=0), 1765 cm^{-1} (C=0). Mass spectrum, m/z (I, %): M^+ 228(13), 200 (34), 196(43), 183(48), 182(19), 170(69), 157(15), 156(83), 154(13), 152(63), 142(53), 141(100), 127(10), 126(27), 125(26), 124(76), 123(39), 114(85), 113(23), 110(32), 99(18), 98(13), 97(75), 96(61), 95(15), 86(15), 85(11), 84(17), 81(38), 79(75), 78(22), 77(31), 72(31), 71(41), 69(24), 68(20), 67(29), 65(11), 59(12), 58(73), 55(39), 53(19), 45(48), 43(21), 42(18).

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