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THE STRUCTURE OF SULTONE FORMED IN REYCHLER´S REACTION

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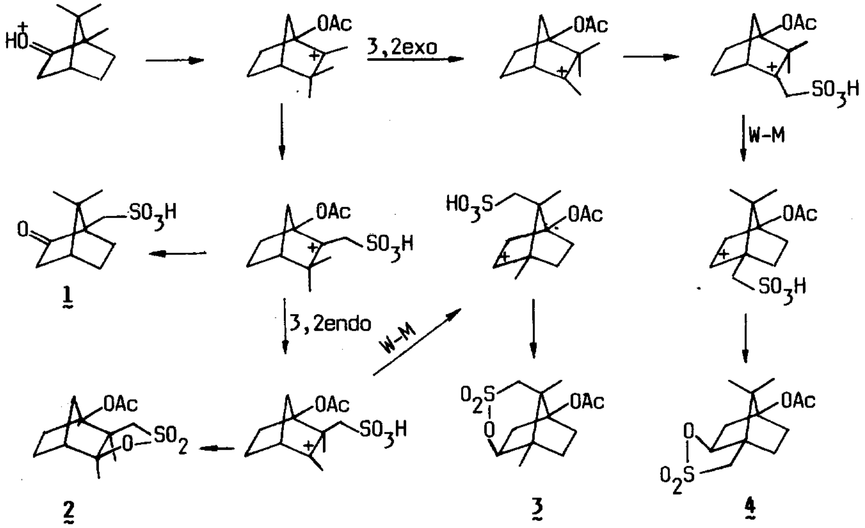
Abstract: The structure of 4-acetoxy-2-exo-hydroxybornane-10-sulfonic acid sultone was established on the grounds of extensive NMR studies employing a variety of different techniques. The final determination of the connectivities between all carbon atoms in the molecule was achieved by 1D- and 2D-INADEQUATE NMR spectra. To differentiate both the geminal methyl groups the investigated sulton was synthesized also using camphor-8-D as the labelled starting material.

The application by Reychler[1/] of acetic anhydride as a reaction medium in camphor sulfonation made it possible to develop a stereospecyfic synthesis of (+)-10-camphorosulfonic acid (1). Almost 90 years later the structure of the minor product of this reaction has still not been determined. The product was separated for the first time by Frerejacque[2/] who assumed it to be a hydrogensulfate. Later, Asachina[3/] suggested that it might have the structure of an acetoxy sulton (2); this, however, was not confirmed by his further synthetic investigations[4/]. The situation being such, we decided to apply NMR methods to solve this problem. We hoped that the information obtained may increase our knowledge on the mechanism of the transformations occurring in the camphor molecule upon sulfonation, and in particular, of the role of acetic anhydride applied as the reaction medium.

The sulfonation of (+)-camphor performed according to a widely accepted procedure[5/], led to the neutral product being isolated in 5% yield showing the elemental composition $C_{12}H_{18}O_5S$, melting point 155-156°C, and $[\alpha]_D=-22°$. The presence of one-proton doublet of doublets in the ^{1}H-NMR spectrum at 4.45 ppm pointed to a vicinal position of two hydrogen atoms with respect to the observed methine proton attached to the carbon bearing the sulfonyloxy oxygen. Such an observation completely rules out the structure 2 for this product; however, it allows to propose structure 3 or 4 for it. Both of them could be the product of ring closure of carbocationic intermediates, the presence of which in the mechanism of camphor racemization induced by strong acids was suggested by Nishikawa[6] and Finch[7]. The optical activity of the product suggests a limited number of carbocation transformations on the way to racemization before the sulfonation and sulton ring closure occurs.



Scheme 1.

As follows from the analysis of the coupling constants of the proton absorbing at 4.45 ppm ($J_{endo,endo}$=8.2, $J_{endo,exo}$=3.6 Hz) with protons attached to C-3 (2.96 and 2.20 ppm), the H-2 proton is located in the endo position. The exo position of the H-3 proton absorbing at 2.20 ppm is indicated by the long-range coupling (J=3.8 Hz) with H-5-exo (1.76 ppm). This coupling can be easily recognized also in the 2D COSY spectrum (Fig.1).

Contrary to the observations done by Flautt and Erman[8] as well as by Vederas[9] on the other bornane derivatives we found that the signals of $H\text{-}3_{endo}$ and $H\text{-}5_{endo}$ of the investigated sulton appeared at a lower field ($\Delta\delta$ =0.76 and 0.6 ppm respectively) than those of $H\text{-}3_{exo}$ and $H\text{-}5_{exo}$. This probably results from the deshielding effect caused by the acetoxy group attached to C-4. Such an influence is not observed in the case of considerably remote protons attached to C-6, of which H_{exo} absorbs at a lower field than H_{endo} by 0.47 ppm. The analysis of the coupling constants also revealed that the formation of an additional sulton ring in the molecule caused some deformation of the bornane skeleton. Such a conclusion follows from the increased coupling constant between H-5$_{exo}$ and H-6$_{exo}$ to 12 Hz in comparison with the usually observed$^{10/}$ value of 10 Hz.

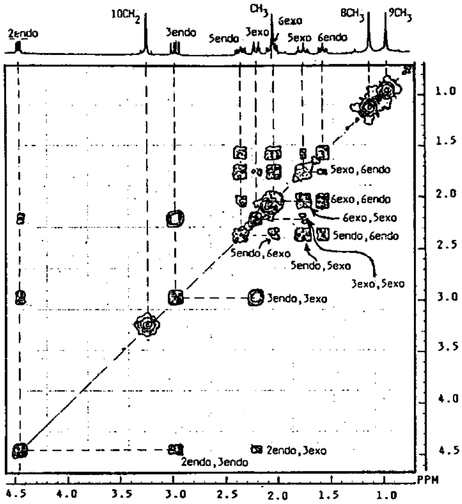


Figure 1. ^{1}H-^{1}H COSY spectrum of sultone **4**. Approx. 20 mg in 0.5 ml of CDCl$_3$ at 297°K. Spectral width 2.2 KHz, ω_2 domain: size 1K, number of data points 1K, ω_1 128 data points zero-filled to 512W, sine multiplication was used prior to 2D-FT transformation, spectrum was symmetrized about diagonal.

The results of the analysis of ^{13}C NMR spectrum, the DEPT spectrum and the ^{1}H-^{13}C chemical shift correlation (Fig.2) led to an unambiguous assignment of the observed signals to most of the carbon atoms present in the molecule. However, we still were not able to distinguish between the two quaternary carbon atoms (51.94 ppm and 48.56 ppm) which could be either C-1 or C-7, and the two primary carbon atoms of the methyl groups.

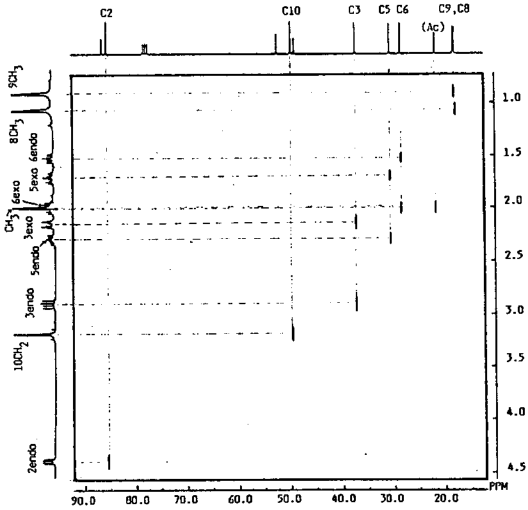


Figure 2. ^{1}H-^{13}C chemical shift correlation NMR spectrum for sultone **4**. Spectral parameters: ω_2 - spectral width 6 KHz, size 4K, number of data points 4K, polarization transfer 3.6 ms, number of scans 64, ω_1, spectral width 2.3 KHz, size 512W, number of data points 256; total acquisition time 12h, 2D FID was processed using sine multiplication in ω_2 and Gaussian multiplication in ω_1, LB=-2, GB=0.2.

We have made an attempt to differentiate between C-1 and C-7 by the 1D ^{13}C-^{13}C INADEQUATE experiment. The expanded fragments (A, B, C, D and E) of such spectrum showing the absorption of the carbon atoms for which the same value of ^{13}C-^{13}C coupling constant were determined on the basis of the satellite patterns, are presented in Figure 3. The spectrum of quaternary carbon atom absorbing at 51.94 ppm (trace A) shows four pairs of satellites with coupling constants J=37.4, J=34.3, J= =33.4 and J=29.3 Hz. These values of coupling constance also are observed in resonance patterns of all carbons bound to C-1 in structure 4 (traces B to E). In spite of the observation of all four ^{13}C-^{13}C couplings to one quaternary carbon (assigned to C-1, trace A) and two couplings to the other one (C-7, trace E), the key evidence allowing to distinquish between structure 3 and 4 beyond doubts was still not achieved. Such conclusion follows from the rather large estimated experimental error in the coupling constant determination due to limited digital resolution in the INADEQUATE spectrum (±0.2) and often line overlap. Therefore the value of 37.4 Hz assumed to be the C_{10}-C_1 coupling could fit also to the coupling pattern of secondary carbon C-10 to the quaternary carbon resonating at 48.7 ppm (C-7, see Table 1).

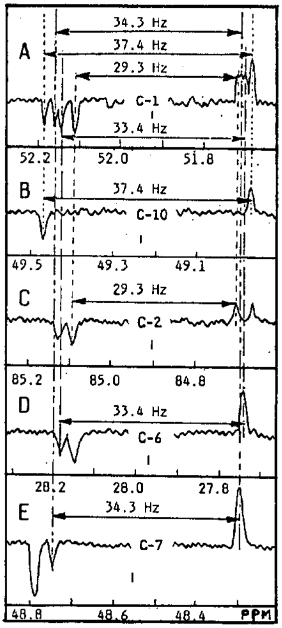


Figure 3. Some fragments of the ID-INADEQUATE spectrum of 4.

A final proof of the connection of $-CH_2SO_2$ group to C-1 atom was provided by the 2D-INADEQUATE spectrum (Fig.4). It appeared that the diagonal line is made of lines related to chemical shifts of C-4, C-1, C-7 and carbons of three methyl groups, whereas the pairs of off-diagonal peaks coming from the coupled carbon atoms point to the following bondings: C_2-C_1, C_4-C_3, C_2-C_3, C_4-C_5, C_1-C_{10}, C_1-C_6, 2x C_7-CH_3, C_5-C_6.

The most important evidence given by this two dimensional experiment is that C-1 atom is bonded to C-10 of the CH_2-SO_2 group and C-7 atom to C-8 and C-9 of both CH_3 groups (the chemical shifts and coupling constants are listed in table). This observation proves beyond doubt that the sulton under investigation has the structure 4.

In order to assign the signals arising from C-8 and C-9 atoms of methyl groups, we have carried out the Reychler synthesis using camphor specifical-

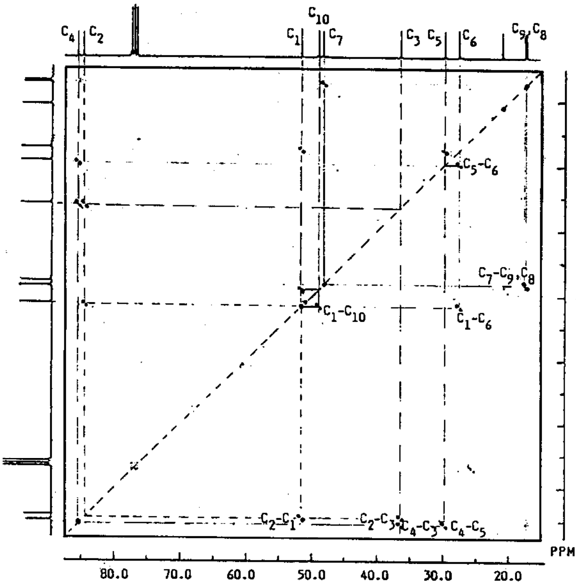
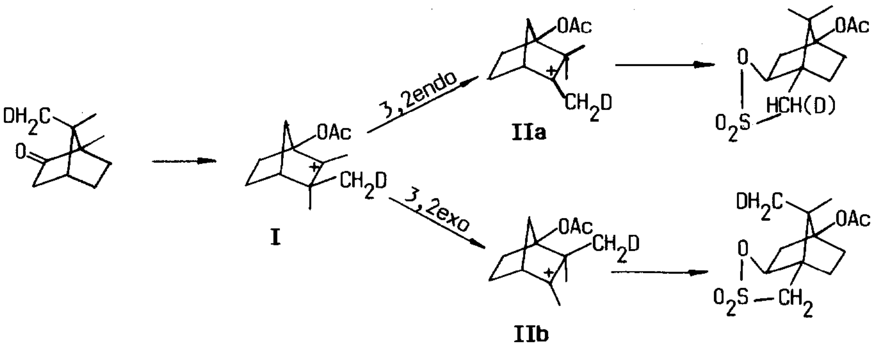


Figure 4. 75.47 MHz ^{13}C-^{13}C 2D-INADEQUATE NMR spectrum of sultone 4 with COSY-like representation. Connectivities within the sixmembered ring are shown as dashed lines and those of C1-C10 and C7-C8 (C9) as solid lines. Spectral parameters: sweep width 5.3 KHz, 35 Hz ^{13}C-^{13}C coupling constant was assumed to calculate the delay for generation of double-quantum coherence, ^{13}C signals were considered to be weakly coupled; spectrum size: 512 2Kwords spectra each consisting of 128 scans were acquired during 24 h; 2D FID was worked up using Gaussian multiplication with $LB(LB_1)=-2$ and $GB(GB_1)=0.15$ (0.1). The spectrum was symmetrized about diagonal. The connectivities between quaternary carbon atoms were not observed.

ly labelled with deuterium at C-8 position. The labelled camphor was obtained by deuterogenolysis of (+)-8-bromocamphor[11]. Assuming that in the process of transformation of carbocation I into carbocation II (Scheme 2) the exo or endo migration of methyl group might occur, the deuterium label should be



Scheme 2.

expected to appear at C-8 or C-10 position, respectively.

The proton spectrum of the labelled sulton has shown that the signal of 10-CH_2 group retained its integrated intensity and multiplicity (AB system, $^2J=13.9$ Hz) as compared to the unlabelled sulton. On the other hand, a two-proton absorption appeared at 1.12 ppm instead of a three-proton singlet.

Table 1. ^{1}H and ^{13}C NMR chemical shifts and coupling constants of 4 in CDCl$_3$

^{13}C NMR			^{1}H NMR			
position C	[ppm]	^{13}C-^{13}C coupling [Hz]	position H	δ [ppm]	$\Delta\delta$ [ppm]	^{1}H-^{1}H coupling [Hz]
C=0	170.4					
C_4	85.8	C4-C3=C4-C5=C4-C7=37.0				
C_2	84.9	C2-C1=29.3 C2-C3=35.0	H2 endo	4.45		$J_{2endo-3endo}=8.2$ $J_{2endo-3exo}=3.6$
C_1	51.9	C1-C10=37.4 C1-C2 =29.3 C1-C7 =34.3 C1-C6 =33.4				
C_{10}	49.3	C10-C1=37.4	10-CH_2	3.25 and 3.21		$J_{gem}=13.9$
C_7	48.6	C7-C1 =34.3 C7-C4 =37.0				
C_3	36.8	C3-C2 =35.0 C3-C4 =37.0	H_{3exo}	2.2	0.76	$J_{gem}=13.7$, $J_{3exo,5exo}=3.8$ $J_{3exo,2endo}=3.6$
			H_{3endo}	2.96		$J_{gem}=13.7$, $J_{3,2endo}=8.2$
C_5	30.1	C5-C4 =37.0 C5-C6 =30.8	H_{5exo}	1.76	0.6	$J_{gem}=13.0$ $J_{5exo,6exo}=12.3$ $J_{5exo,6endo}=3.8$ $J_{5exo,3exo}=3.8$
			H_{5endo}	2.36		$J_{gem}=13.0$,$J_{5endo,6endo}=9.3$ $J_{5endo,6exo}=4.8$
C_6	27.99	C6-C1 =33.4 C6-C5 =30.8	H_{6exo}	2.04	0.47	$J_{gem}=12.5$, $J_{6exo,5exo}=12.3$ $J_{6exo,5endo}=4.8$
			H_{6endo}	1.57		$J_{gem}=12.5$,$J_{6endo,5endo}=9.3$ $J_{6endo,5exo}=3.8$
CH_3(Ac)	21.14			2.05		
C_9	17.7	C9-C7 =37.2	9CH_3	0.95		
C_8	17.5	C8-C7 =36.6	8CH_3	1.12		

Hence, it is concluded that the deuterium label has migrated together with the 8-CH_2D group (exo shift) to the 8-position (cis to C-2) of the obtained sulton. Thus, taking also into account the ^1H-^{13}C correlation (Figure 2), we conclude that the signal at 17.5 ppm (^{13}C-NMR) corresponding to the proton resonance at 1.12 ppm, arises from C-8 atom, whereas the other one at 17.7 ppm (0.95 ppm) from C-9.

Our results have also confirmed Finch's[7/] observation concerning the preference of exo [3,2] methyl migration in the norbornyl cationic intermediate (e.g. I, Scheme 2) with no substituent present at C-7.

EXPERIMENTAL

All NMR spectra of the sultone **4** were recorded in chloroform-d solution with Bruker MSL-300 spectrometer operating at 300.13 MHz and 75.47 MHz for ^1H and ^{13}C, respectively. Chemical shifts were referenced to external TMS. The conditions were as follows: temperature 300°K, 5(^1H) or 10(^{13}C)mm sample tube, concentration ca. 20% in $CDCl_3$, which was used as an internal lock, 90° flip angle /10µs (^1H), 11µs (^{13}C), scan repetition time 2s. The assignment of resonances in ^1H NMR spectra were aided by ^1H-^1H chemical shift correlation (Figure 1), and the assignment of lines in ^{13}C spectra were based on DEPT technique and ^1H-^{13}C correlation (Figure 2). Through-bond connectivities were obtained by ^{13}C-^{13}C 1D- and 2D-INADEQUATE experiments (Figure 3 and 4).

4-Acetoxy-2-exo-hydroxybornane-10-sulfonic acid sultone (4)

Sulfonation of D-camphor ($[\alpha]_D$=+44°, 10g) in Ac_2O was carried out according to Bartlett, Knox[5/] procedure at room temperature for two weeks. Next, the filtrate after camphor-10--sulfonic acid (7.5g) separation was concentrated under diminished pressure, and the residue extracted with Et_2O-hexane (4:1). The organic layer was washed with water and dilute NaOH aq, dried and the solvent removed under vacuum. The resulted colourless solid (3.1g) was kept at 80°/1mm Hg to sublime off the unreacted camphor $[\alpha]_D$=+43° and the residue (0.9g) was chromatographed on SiO_2 in benzene and recrystallized from benzene-hexane (1:1) which yielded the pure product of m.p. 155-156° and $[\alpha]_D$=-22,3°($CHCl_3$) [lit.[3/]: m.p.156-8°C, $[\alpha]_D$=-25° (EtOH)]. MS (75eV, 15eV): m/e=232 (M^+ - CH_2=C=O), 210 (M^+ - SO_2), 194, 193, 152, 151, 150(100%); IR (KBr, cm^{-1}): 1739, 1369, 1349, 1276, 1182, 1083, 815. For NMR data see Table 1. For $C_{12}H_{18}O_5S$ (274.34) calcd.: 52.53% C, 6.61% H, 11.69% S, found: 52.49% C, 6.59% H, 11.68% S.

Sulfonation of 8-deuterocamphor

A stirred solution of 8-bromocamphor[11/] [1.23g, m.p.85-85.5°C, $[\alpha]_D$=+80.0° ($CDCl_3$)] in 10 ml of AcOD was treated slowly with zinc dust (3.5g), and next refluxed for 30 mins, diluted with 5 ml D_2O and left overnight at room temperature. The product was taken up into n-pentane, and the resulted solution washed with water, 10% $NaHCO_3$ aq, dried and concentrated afforded a residue (0.74g, 90.8%) which after sublimation showed m.p. 177--178°C, $[\alpha]_D$=+43.0° (c=1, $CDCl_3$); ^1H NMR, ^{13}C NMR and mass spectra of camphor-8-D were identical with those described in the literature[12/].

The so obtained 8-deuterocamphor (0.6g) was transformed into the suitable deuterosulton (60 mg) following the procedure described above for the unlabelled sulton preparation. The pure sulton-8-D was obtained as a colourless plates (benzene-hexane): m.p.156-157°C, $[\alpha]_D = -22.5°$ ($CHCl_3$), MS (75eV, 15eV): m/e=233 ($M^+ - CH_2=C=O$), 211 ($M^+ - SO_2$), 151 (100%). ^1H NMR ($CDCl_3$, ppm): 0.95 (s, 3H) 9-CH_3; 1.10 (t, 2H, J=1.8 Hz) 8-CH_2D.

ACKNOWLEDGEMENT

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    Our NMR results are in agreement with the data reported by Vederas (ref. 9), and indicate that some of the chemical shifts assignments to the corresponding atoms of camphor molecule recently done by Waterhouse (Magn.Reson.Chem. , 1989, **27**, 37), beside the misleading carbon and hydrogen numbering, are incorrect.