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Elucidation of the Constitution of a Heterocyclic Rearrangement Product by Means of ^{17}O-NMR-Spectroscopy

Johannes Fröhlich[1],*, **Reinhard Ilk**[1], **Hanspeter Kählig**[2], and **Wolfgang Robien**[2]

[1] Institute of Organic Chemistry, Technical University Vienna, Getreidemarkt 9, A-1060 Wien, Austria

[2] Institute of Organic Chemistry, Vienna University, Währinger Straße 38, A-1090 Wien, Austria

Summary. In the course of an attempted elimination reaction starting from an isothiochromane derivative substituted with an amino-alcohol moiety, a benzo[c]thiophene derivative formed via a rearrangement reaction was isolated unexpectedly. Its constitution was confirmed unambiguously via ^{17}O-NMR-spectroscopy.

Keywords. Spiro compounds; Heterocycles; Rearrangement; ^{17}O-NMR.

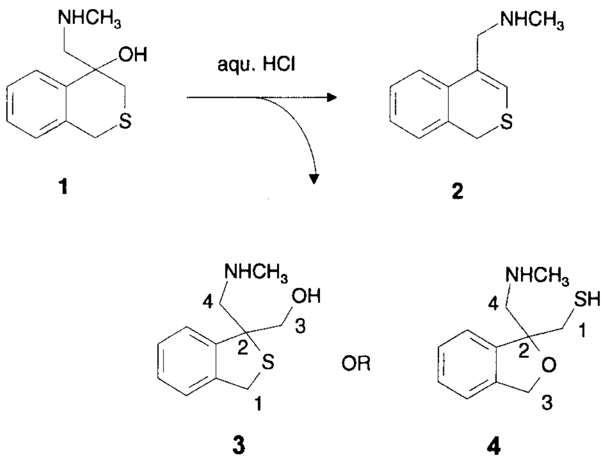
Konstitutionsaufklärung eines heterozyklischen Umlagerungsproduktes mittels ^{17}O-NMR-Spektroskopie

Zusammenfassung. Im Verlauf einer versuchten Eliminierungsreaktion wurde ausgehend von einem Aminoalkoholderivat eines Isothiochromansystems unerwarteterweise ein Benzo[c]thiophen-derivat isoliert. Die Konstitution des Umlagerungsproduktes wurde eindeutig durch ^{17}O-NMR-Spektroskopie bestätigt.

Introduction

Within our investigations of the syntheses and reactions of heterocyclic small-ring spiro systems [1] the intermediate product **1** – an amino alcohol derivative of an iso-thiochromane – was reacted in 3*n* HCl at reflux temperature for 2 hours to approach the eliminated compound **2** (Scheme 1) [2].

Instead of one expected target compound a 1:1 mixture of two products was obtained: separation was possible via flash chromatography on SiO_2 (eluent: petrol–ether/ethyl acetate/triethylamine = 5:4:1). Product **2** ($Rf = 0.32$) could be identified easily via its olefinic proton by ^{1}H-NMR spectroscopy ($\delta = 6.45$ ppm), the structure of the by-product ($Rf = 0.14$) was elucidated by a combination of ^{1}H, ^{13}C and ^{17}O-NMR spectroscopy.



Scheme 1

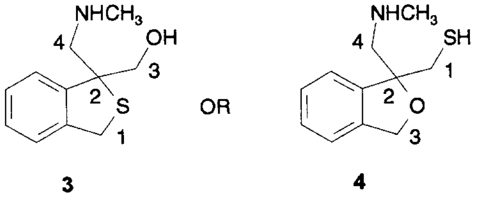
Methods

On the basis of the ^{1}H-NMR spectrum (exhibiting no olefinic proton, but similar to the starting compound three diastereotopic methylene groups with geminal coupling) formulae **3** and **4** were proposed. A third possible isomer with an iso-indole parent system could be excluded due to comparison with analogous reactions [2]: similar by-products are formed from even tertiary ethanolamines.

Neither ^{1}H- nor ^{13}C-NMR spectra exhibited unequivocal information to distinguish between structure **3** and **4**: by changing the positions of the hetero atoms sulphur and oxygen the adjacent methylene carbon atoms C-1, C-3 merely "swap" their ^{13}C-shifts, whereas C-4 practically remains unchanged as can be demonstrated by calculations [3, 13].

The quarternary centre (C-2) is influenced by such a large number of parameters (steric, conformative) that a reliable estimation is impossible (see Table 1).

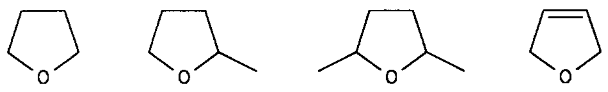
Table 1. ^{13}C-NMR incrementation of the aliphatic carbons in compounds **3** and **4**



Observed centre (multiplicity)		C-1 (t)	C-2 (s)	C-3 (t)	C-4 (t)
Calculated shifts of compounds [3]	**3**	33.1	50.1	70.8	49.0
	4	33.1	89.9	68.8	50.3
Estimation from data base [13]	**3**	35.2	70.1	65.2	46.1
	4	39.2	86.8	61.8	46.1
Observed values (multiplicity)		34.95 (t)	67.83 (s)	70.22 (t)	60.25 (t)

Therefore the compound in question was studied by ^{17}O-NMR spectroscopy, a method that is highly sensitive to steric as well as electronic influence [4]. Following considerations led to an unambiguous decision:

The chemical shift of *THF* (**5**) is about 15 ppm [5–7], its methyl-β-increment derived from **6** and **7** is about 30 ppm [7]. Unsaturation on the c-edge (as present in **4**) decreases the intrinsic chemical shift of *THF* **5** by 22 ppm [6], (Scheme 2).

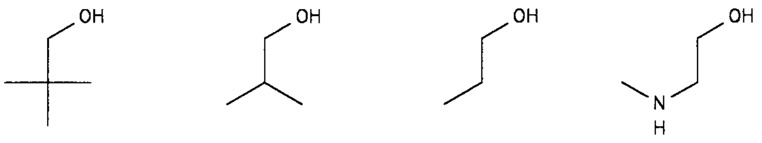


	5	**6**	**7**	**8**
^{17}O-shift (ppm):	14.0 [6] / 16.2 [7]	43.9	66.7 (cis) 74.5 (trans)	-7.0

Scheme 2

Via estimation from these data and additionally taking into account the γ-increments of sulphur (less than 5 ppm [8]) and of nitrogen (about -4 ppm [9]) an approximate chemical shift of 40–50 ppm is to be expected for compound **4**.

On the other hand, the ^{17}O-NMR-shifts of β-mono-, di- and trisubstituted ethanols (Scheme 3), which can be seen as adequate substructures of **3**, are present within a very narrow range of 0 to -7 ppm [9–10], which fits the observed value (1.8 ppm) quite well.



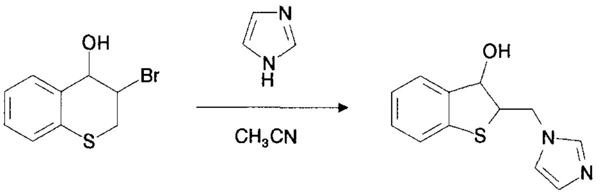
	9	**10**	**11**	**12**
^{17}O-shift (ppm):	-6.8	-2.0	-0.5	-5.3

Scheme 3

This significant difference between the chemical shifts of alcohol- and ether-type oxygens made the decision clear for structure **3**.

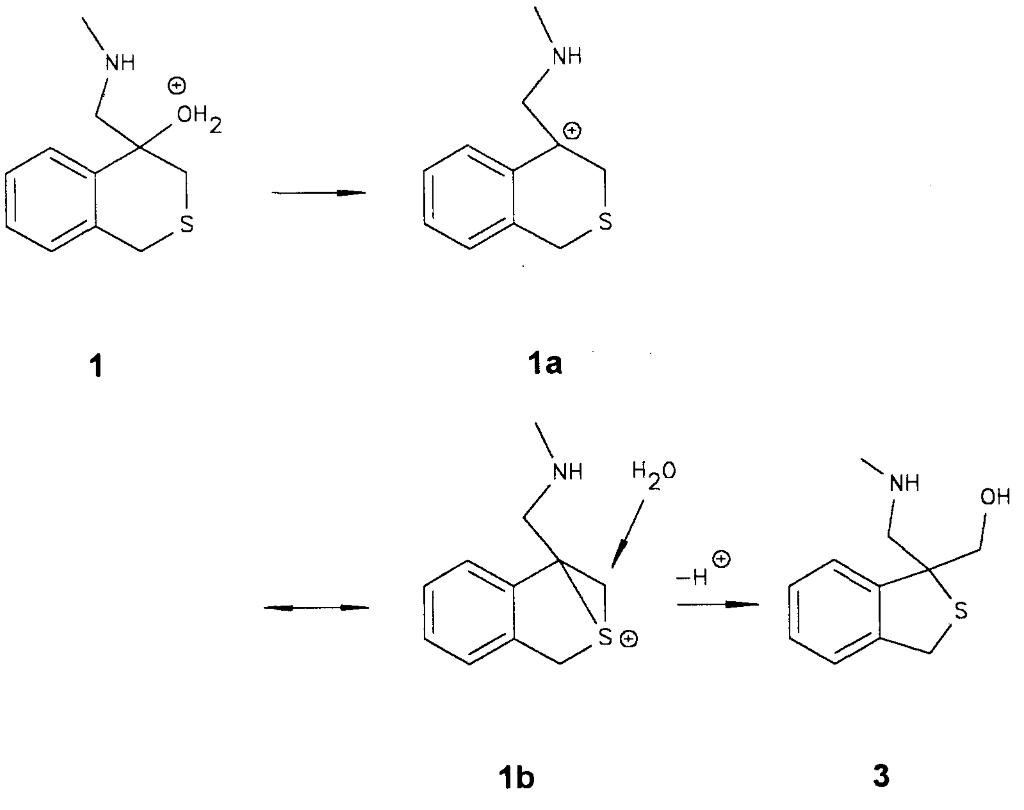
Results and Discussion

The observed reaction is a new example of a proton catalyzed ring-contraction leading from an iso-thiochromane system to a substituted benzo[c]thiophen derivative. A similar type of reaction is described in the literature [11–12]: on attempted nucleophilic substitution at a thiochromane-system a benzo[b]thiophene parent was formed (Scheme 4). Quite in contrast to our example the presence of a nucleophile is essential to initiate the reaction.



Scheme 4

The formation of the title compound **3** can be explained by following mechanistic suggestions (Scheme 5): on loss of H_2O the protonated starting amino alcohol **1** suffers ring contraction via attack of sulphur at the carbenium ion **1a** and ring-opening reaction of the thiirane **1b** by H_2O. After deprotonation the benzo[c]-thiophene **3** is released.



Scheme 5

Several efforts were undertaken to influence the ratio of eliminated and rearranged product. It turned out that on refluxing the starting compound **1** for 40 minutes in excess of conc. HCl (12 n) only eliminated product **2** was formed and could be isolated as a hydrochloride with a yield of 92%. Decreasing the $[H^+]$-concentration in the reaction mixture favoured the ring-contraction reaction: in 3*n*-HCl (3 h, reflux) a 1 : 1-mixture, in 0.3 *n* HCl (20 d, reflux) a 9 : 1-mixture of **3** : **2** was obtained. The ratios were determined from the ^{1}H-NMR spectra upon integration of the CH_2–S-signals for the olefin **2** ($\delta = 3.75$ ppm) and the benzo[c]thiophene **3** ($\delta = 4.19$ ppm). Longer reaction times under less acidic conditions were necessary for complete conversion of starting compound **1**. Under influence of acid is was by no means possible to isolate only ring-contracted compound. Therefore the stability of **2** and **3** was studied: both compounds were stable under alkaline conditions (10% aqu. NaOH), whereas in acids only the eliminated product **2** remained unchanged. When exhibiting the thiophene-derivative **3** to acidic aqueous media, formation of eliminated compound **2** was observed, e.g. heating pure **3** (obtained from "flash"-chromatography) in 3*n*-HCl for 5 h led to a ca. 1:1 mixture of **2** and **3**. This behaviour proves the reversibility of the ring-contraction under influence of acids (initiated by protonation at the methanol-moiety – see Scheme 5, reversed reaction – and loss of H^+ from **1a**) and gives an explanation for the exclusive formation of the obviously most stable elimination product in conc. HCl.

Experimental Part

The melting points given were determined on a Kofler melting point apparatus and are uncorrected. Microelementary Analyses were performed at the Microanalytical Laboratory, Institute of Physical Chemistry, University of Vienna (Mag. J. Theiner). TLC: TLC-layers with SiO_2 60 F_{254}, Merck Art.-Nr. 5554; eluents: petroleum ether (*PE*)/ethyl-acetate (*EA*)/triethylamine (*TA*) = 5:4:1. "Flash"-chromatography: SiO_2 60 F_{254}, Merck Art.-Nr. 9385, particle size: 0.040–0.063 mm, pressure: 1 bar; 50 g SiO_2 in 450 × 25 mm glass columns. ^{13}C- and ^{1}H-NMR-spectra: Bruker AC 200 (^{1}H: 200.13 MHz, ^{13}C: 50.47 MHz), 5 mm dual ^{1}H/^{13}C-VT-probe head at 300 K; solvent: *DMSO-d$_6$* and $CDCl_3$, respectively; δ-values are given ppm, internal standard *TMS* ($\delta = 0$ ppm).

N-Methyl-1H-4-Isothiochromanemethanamine (2) *and 1,3-Dihydro-1-(N-methyl-amino-methyl)-1-benzo[c]thiophenemethanol* (3)

1.0 g (4.78 mmol) amino-alcohol **1** [2] was reacted according to the reaction parameters given in Table 2 (in experiment c a few drops of ethanol had to be added to afford a clear solution). Prior to work-up the cooled reaction mixture was extracted with diethyl ether, then made alkaline (*pH* = 10) with conc. aqu. NaOH-solution and exhaustively extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$ and evaporated to dryness. In case of mixtures the remaining yellowish oil was resolved by "flash" chromatography.

2: Colorless oil, $C_{11}H_{13}NS$ (191.30); *Rf* = 0.32, eluent: *PE-EA-TA* = 5:4:1. ^{1}H-NMR ($CHCl_3$): 7.45–7.25 (m, 4H), 6.45 (m, 1H), 3.75 (s, 2H, $-CH_2S-$), 3.68 (d, 2H, $J = 1.0$ Hz, $-CH_2N\langle$), 2.45 (s, 3H, N–CH_3), 1.24 (sb, 1H, NH). ^{13}C-NMR ($CDCl_3$): 133.28 (s), 132.69 (s), 129.22 (s), 127.54 (d), 127.11 (d), 126.57 (d), 122.72 (d), 120.66 (d), 54.13 (t), 35.49 (q), 30.50 (t). $C_{11}H_{13}NS$. HCl (227.76): calc. C 58.01, H 6.20, N 6.15; found C 58.11, H 6.24, N 6.36.

Table 2. Reaction parameters for **2**/**3**

Reaction conditions	Time	Ratio **2**:**3**	Yield: g (%)
(a) 30 ml 12*n* HCl	40 min	1:0	1.07 (92)
(b) 30 ml 3*n* HCl	2 h	1:1	0.79
(c) 30 ml 0.3*n* HCl	20 d	1:9	0.70

3: Colorless oil, $C_{11}H_{15}NOS$ (209.31); *Rf* = 0.14, eluent: *PE-EA-TA* = 5:4:1. ^{1}H-NMR ($CDCl_3$): 7.25–7.20 (m, 4H), 4.19 (s, 2H, $-CH_2S-$), 4.14 (d, 1H, J_{AB} = 11.2 Hz, CH_2O-), 3.77 (d, 1H, J_{AB} = 11.2 Hz, CH_2O-), 3.2 (sb, 2H, NH and OH), 3.08 (s, 2H, $-CH_2N<$), 2.43 (s, 3H, $N-CH_3$). ^{13}C-NMR ($CDCl_3$): 142.93 (s), 140.44 (s), 127.16 (d), 126.35 (d), 124.51 (d) 123.10 (d), 70.22 (t, CH_2O-), 67.83 (s), 60.25 (t, $CH_2N<$), 36.25 (q, $N-CH_3$), 34.95 (t, CH_2S-). $C_{11}H_{15}NOS$. HCl (245.77): calc. C 53.89, H 6.52, N 5.78; found C 53.76, H 6.56, N 5.70.

^{17}O-NMR-Measurement

The ^{17}O-NMR-measurement was performed on a BRUKER AM 400 WB NMR-Spectrometer equipped with a tuneable 10 mm probehead at 54.244 MHz. The acquisition parameters used are 4 K datapoints, 18 µs 90° pulse and 90 µs prescan delay. All the processing was done on a BRUKER X32/3 datastation using the UXNMR standard software. The first 16 datapoints of the FID, distorted due to acoustic ringing, were corrected by backward linear prediction using the 128 following datapoints and twice the number of coefficients. The chemical shift relative to H_2O of compound **3** in $CDCl_3$ at 313 K is 1.8 ppm (linewidth of 1000 Hz).

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