Monatshefte für Chemie 124, 71–75 (1993)

Monatshefte für Chemie
Chemical Monthly

^{17}O-NMR-Spectroscopy as a Tool for Stereochemical Analysis – Application to a Diterpene-Derivative

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Summary. Treatment of abietic acid methylester with $Hg(OAc)_2/MeOH$ produces a dimethoxy derivative. The determination of the configuration at C-7 of this product by means of 1D- and 2D-NMR-spectroscopic methods is described. The results are verified by application of ^{17}O-NMR spectroscopy and comparison with well-established stereochemical dependencies of ^{17}O chemical shifts.

Keywords. NMR, ^{17}O; Diterpene.

^{17}O-NMR-Spectroskopie zur stereochemischen Analyse. Anwendung auf ein Diterpen-Derivat

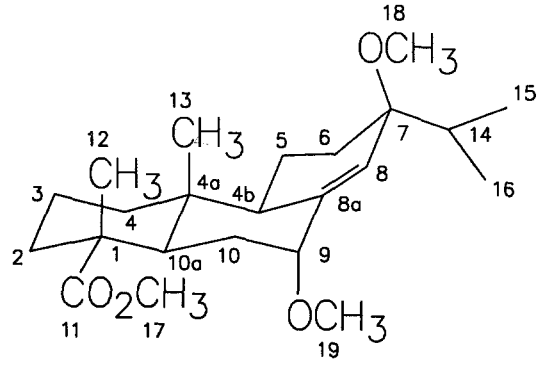
Zusammenfassung. Umsetzung von Abietinsäuremethylester mit $Hg(OAc)_2/MeOH$ führt zu einem Dimethoxyderivat. Die Bestimmung der Konfiguration am Zentrum C-7 erfolgt durch Anwendung von 1D- und 2D-NMR-Methoden. Die Resultate konnten durch ^{17}O-NMR-Spektroskopie aufgrund der bekannten stereochemischen Verschiebungsabhängigkeit bestätigt werden.

Introduction

^{17}O-NMR spectroscopy is now a well-established method among other NMR-techniques. The availability of high-field NMR instrumentation has driven ^{17}O-measurements, despite the problems connected with this low-abundant, low-frequency spin-5/2 isotope, into a routine task during the last few years. The number of published reference data is growing very rapidly [1]. The total shift range of oxygen-containing functionalities is known to be some 1500 ppm allowing good insight into stereochemical and electronic behaviour of organic compounds. Several investigations [2–4] deal with stereochemical dependencies of ^{17}O chemical shift values of six-membered ring system-derived alcohols and the corresponding ethers. Because of several problems caused by the properties of this nucleus, measurements were usually restricted to low molecular weight compounds (MW < 200 amu). During this investigation we will focus on the stereochemical assignment of a diterpen-derivative having a molecular weight of 378 amu and compare traditional NMR-techniques with ^{17}O-NMR spectroscopic results.

Results and Discussion

The reaction of abietic acid methylester with $Hg(OAc)_2$ in methanol [5] gives compound **1** in a yield of 85%.



1,2,3,4,4a,4b,5,6,7,9,10,10a–Dodecahydro–7,9–dimethoxy–1,4a–dimethyl–7(1–methylethyl)–1–phenanthrenecarboxylicacidmethylester [1R–(1α,4aβ,4bα,7β,9α,10aα)]

The structure elucidation of this compound was performed using 1D- and 2D-NMR techniques. The chemical shift values are summarized in Table 1. A comparison of the ^{13}C-NMR data of compound **1** with those of abietic acid methylester [6] shows a nearly unaffected A-ring and a severe change of chemical shift values within the B/C-ring systems. Only one double bond can be found and two signals at 81.51/D and 75.53/S appear in the spectrum indicating together with the ^{1}H-NMR data a CH_3–O–CH–C=CH–C–O–CH_3 fragment. The assignment of proton- and carbon chemical shift values can be done in a straightforward manner using the HH-COSY and HC-COSY spectra, leading to the assignment as given in Table 1. The assignment of the two OCH_3 signals can be performed by application of a COLOC-experiment; a cross-peak between the protons at 3.15 ppm and the carbon resonance at 75.5 ppm can be found.

The stereochemical assignment at the center C-9 utilizes the coupling pattern of H-9 showing two small and very similar couplings of 3.4 Hz and 2.7 Hz, respectively, leading to the conclusion of an axial OCH_3 group at C-9. The configurational assignment at C-7 can be done by NOE-measurements, but this is much more difficult to perform because the effects observed are very small. The NOE-difference spectrum recorded by disturbing the OCH_3 group located at C-7 shows NOE-effects at H-14 and the CH_3-group at C-4a; the control experiment starting from the methyl-group at C-4a gives NOE's at CH_3-12 and H-10ax, but no effect can be observed at OCH_3-18. In order to maximize the NOE buildup, transient NOE measurements were performed by inverting the CH_3-13 group using a purged half-gaussian pulse and after a mixing time of 300 ms the resulting 1D-NOESY spectrum [7] shows an effect at the OCH_3 at position C-7. From these observations the axial position of the OCH_3-18 can be deduced. The above mentioned experiments are a very time-consuming and tedious task, therefore an alternative, more simple NMR-

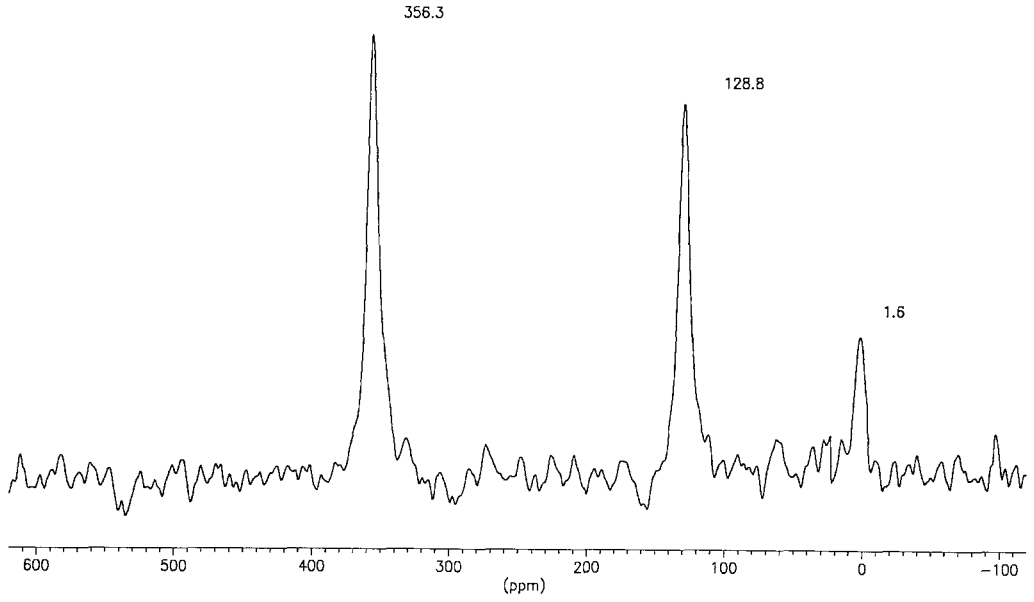


Fig. 1. ^{17}O-NMR spectrum of compound **1** recorded at 363 K in toluene-d_8 ($\delta_{H_2O} = 0$ ppm)

Table 1. ^{1}H/^{13}C-NMR spectroscopic data of **1** ($CDCl_3$, 300 K)

	$\delta(^1H)$/ppm	J(HH)/Hz	$\delta(^{13}C)$/ppm
1			47.03/s
2	1.81/m, 1.59/m		36.73/t
3	1.54/m, 1.54/m		18.05/t
4	1.66/m, 1.66/m		37.64/t
4a			38.39/s
4b	2.07/dd	7.1, 1.9	46.75/d
5	1.17/m, 1.60/m		16.61/t
6	1.28/m, 1.63/m		26.34/t
7			75.53/s
8	5.56/m		130.49/d
8a			142.17/s
9	3.55/d	3.4, 2.7	81.51/d
10	1.68/ddd (ax)	13.0, 14.1, 3.4	30.88/t
	1.47/ddd (equ)	2.7, 14.1, 2.7	
10a	2.36/dd	2.7, 13.0	42.81/d
11			178.91/s
12	1.18/s		16.80/q
13	0.80/s		13.88/q
14	2.04/qq	6.9	31.97/d
15	0.91/d	6.9	16.19/q
16	0.86/d	6.9	17.69/q
17	3.68/s		51.90/q
18	3.15/s		49.22/q
19	3.12/s		55.40/q

Table 2. ^{17}O-NMR spectroscopic data of **1**

	$\delta(^{17}O)$/ppm	Line width (Hz)
C=O	356.3	520
17-O*Me*	128.8	490
18-O*Me*	1.6	660
19-O*Me*	1.6	660

technique should be considered. A comparison of ^{17}O-NMR data taken from the literature [4] revealed that the stereochemical influence on methoxy-groups is of significant size. The difference between axial and equatorial methoxy-groups in 4-*tert.*butyl cyclohexane derived model compounds is around 13 ppm; the equatorial methoxy-group is found at 5.9 ppm, whereas the axial one is at −6.9 ppm, respectively. Further substitution at the carbon, where the OCH_3 is located increases the difference to more than 20 ppm with values of 25.1 ppm (equ-OCH_3) and 3.8 ppm (ax-OCH_3). This fragment corresponds to the situation found at C-7 in compound **1** described here having a shift value of 1.6 ppm leading to the conclusion that the methoxygroup is located in the axial position. The deviation between our measurements and the reference data taken from the literature can be attributed to the ring distortion introduced by the double bond.

Conclusion

^{17}O-NMR spectroscopic measurements are a valuable tool for stereochemical assignment of methoxy-groups located at quaternary carbons in a diterpene derivative. The example presented here shows that ^{17}O-NMR spectroscopy is a useful alternative to NOE-measurements, which might cause problems during data interpretation because of small or even vanishing effects in medium-sized molecules. Despite the problems concerned with ^{17}O-measurements, this technique has been shown to contribute valuable information to the solution of sophisticated stereochemical questions.

Experimental Part

The preparation of compound **1** was performed according to the Ref. [5]. NMR-spectroscopic investigations were performed on a BRUKER AM-400WB spectrometer connected to a X-32/3 workstation. Spectral parameters used are as follows:

DQF-COSY: SW1 = SW2 = 3400 Hz, 2 K × 512 data points, zero-filling to 2 K × 2 K.
HC-COSY: proton-detected, GARP-1 ^{13}C-decoupling, 4 K × 256, SW1 = 12500 Hz, SW2 = 3200 Hz, zero-filling to 4 K × 1 K.
1D-NOESY: purged half-gaussian pulse (90°-softpulse: 125 ms, 90°-hardpulse: 6.1 μs, mixing time: 300 ms.
^{17}O-measurements: 54.22 MHz, 10 mm tubes, solvent = toluene-d_8, concentration: 0.25 *M*, temperature = 363 K, SW = 45000 Hz, 4 K data field, 90°-pulse = 18 μs, NS = 150000, 90 μs pre-scan delay, baseline-correction by backward linear prediction of the first 16 datapoints using the next 256 datapoints with 128 coefficients followed by exponential weighting (LB = 100 Hz) and Fourier trans-

formation. All calculations were performed on the X-32 workstation using the Bruker standard-software package.

Acknowledgement

The NMR-spectrometer was made available by the Fonds zur Förderung der wissenschaftlichen Forschung in Österreich (Project-6537C).

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Received March 20, 1992. Accepted April 9, 1992