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NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY OF SOME DIHYDROLYSERGIC ACID DERIVATIVES

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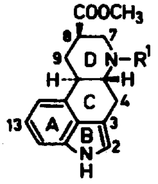
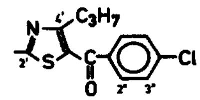
Abstract - Due to the interest in the conformation[1,2] of the ergot alkaloids the ^{1}H-NMR spectra of 1, 3 and the ^{13}C-NMR spectra of 1, 2, 4, 5 were recorded and the conformations determined. The synthesis of 1, 2 and 3 was described[3,4] elsewhere.

RESULTS AND DISCUSSION

Interpretation of the NMR spectra of D-6-(5-p-chlorobenzoyl-4-n-propyl-thiazol-2-yl)-8β-methoxycarbonyl-ergoline-I (1), D-6-(5-p-bromobenzoyl-4-ethyl-thiazol-2-yl)-8β-methoxycarbonyl-ergoline-I (2), D-8β-methoxycarbonyl-6-(6-methyl-4H-1,3-thiazin-4-on-2-yl)-ergoline-I (3) and 6-nor-9,10-dihydrolysergic acid methylester (4) leads to the following results: In contrast to the normal ring D chair conformation of the 9,10-dihydrolysergic acid derivatives compound 1 shows a twist-boat (75 %) and a chair form (25 %) in solution. The preferred conformation of 6-thiazinylergoline 3 is the twist-boat form. The dynamic behaviour of 3 was studied and is interpreted as a hindered rotation of the thiazine moiety around the N-6/C-2'-bond.



1 R^1=



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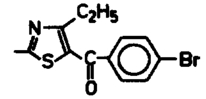
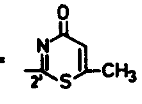
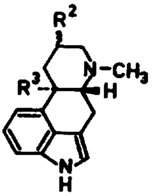


3 R^1=



4 R^1= H

5 R^1= CH_3



6 R^2= β-$COOCH_3$
R^3= CH_3O

7 R^2= β-CH_3
R^3= H

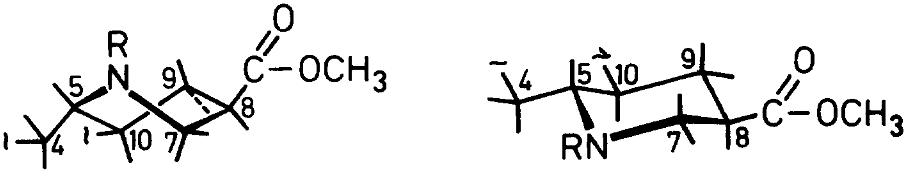
8 R^2= α-$COOCH_3$
R^3= CH_3O

^{1}H-NMR. The C- and D-ring protons were assigned by means of decoupling experiments for H-7, H-8, H-9 and two dimensional shift-correlated ^{1}H-NMR spectroscopy (2D-COSY). The long range coupling constants $^{4}J_{4\alpha-2}$ and $^{4}J_{10\alpha-12}$ were obtained by spin decoupling.

The axial/equatorial position of the hydrogens can be identified by the $^{3}J_{\text{axial-axial}}$ coupling constants; $^{3}J_{a-a} > 10$ Hz for the 6 spin system H-4α, H-4β, H-5β, H-9α, H-9β, H-10α (Table 2).

The configuration at C-8 can only be determined in connection with a conformational analysis owing to the lack of the $^{3}J_{a-a}$ for the spin systems H-7/H-8 and H-9/H-8. An equatorial H-8β of a normal chair conformation can be excluded (Table 3). The measured and expected coupling constants of 3 are in good agreement with a H-8α configuration of the twist-boat conformer of the type I (Table 3).

The H-7/H-8 and H-9/H-8 coupling constants of 1 can be interpreted in terms of an assumed conformational equilibrium of the twist-boat (I, 75 %) and the chair (II, 25 %) form (Fig. 1).



(I) . (II)

Fig. 1 Twist-boat (I) and chair (II) conformation of ring-D of compounds 1 and 3

The 6-thiazinylergoline 3 exists as the nearly pure twist-boat conformer, yielding the contributions J^{I}, while the pure chair conformer 10α-methoxy-9,10-dihydrolysergic acid methylester[5] (6) gives the coupling constants J^{II} with $\bar{J} = \sum_{i} p_i J_i$. The calculated and measured coupling constants of compound 1 are the following:

	calculated	measured
$\bar{J}$ (7α-8α)	5.7 Hz	5.9 Hz
$\bar{J}$ (7β-8α)	3.6 Hz	4.1 Hz
$\bar{J}$ (9α-8α)	7.9 Hz	8.1 Hz
$\bar{J}$ (9β-8α)	9.9 Hz	9.7 Hz

On the basis of these populations the difference between the normal values of the free enthalpy of the twist-boat and the chair conformer can be calculated.

1: ΔG chair, twist-boat $\approx 2.7 \pm 0.5$ kJ · mol^{-1}
3: ΔG chair, twist-boat $\gtrsim 5.7$ kJ · mol^{-1}

In accord with these data, the chemical shifts of H-7α/H-7β (Table 1 and Fig. 2) for 3 at axial and equatorial positions show the expected large difference $\Delta\delta\alpha/\beta \geq 1.35$ ppm whilst the value of this difference for 1 is only 0.56 ppm due to the alteration of H-7 axial to H-7 equatorial and vice versa in the conformational equilibrium I $\rightleftarrows$ II.

The sequence of chemical shifts of H-7α/H-7β of 3 is reversed compared to 6 and festuclavine[6] (7) (Fig. 2). The 6-thiazolylergoline 1 displays a smaller $\Delta\delta$axial/equatorial but the same chemical shift order for the protons at C-7 as in 3. These data are also in accord with the determined ratio of conformers of 1.

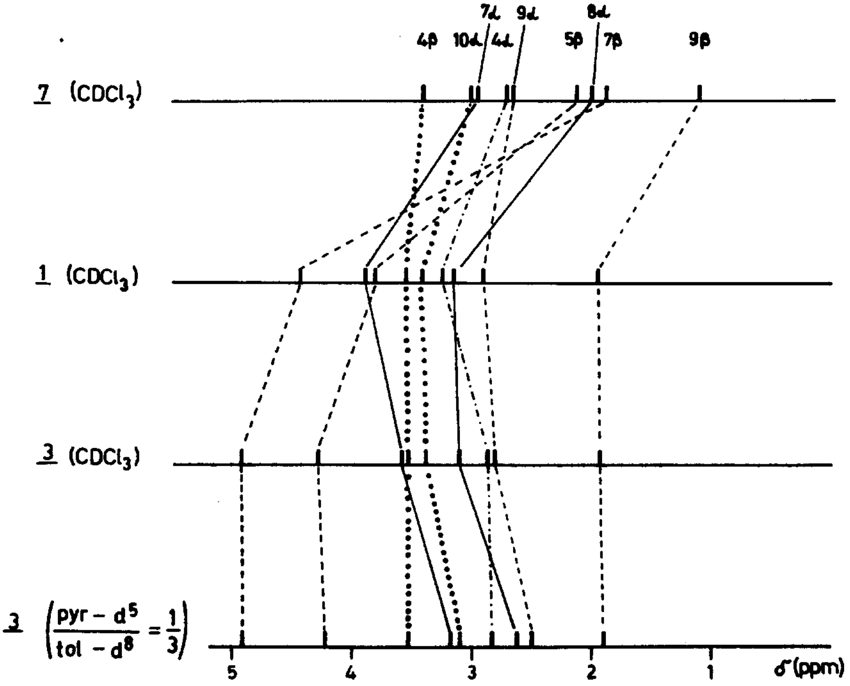


Fig. 2 ^{1}H chemical shifts of the aliphatic region of 1, 3 and 7

From the determined configurations of the hydrogens H-5β, H-10α, H-8α, the configuration of the $COOCH_3$ substituent is 8β, and the C/D ring fusion is trans.

The assumption of a conformational change is supported by a comparison of the chemical shifts H-7/H-5 of 1 and 3 with festuclavine[6] (7); $\Delta\delta$1-7: H-7α = 0.93 ppm, H-7β = 2.57 ppm, H-5β = 1.71 ppm. $\Delta\delta$3-7: H-7α = 0.63 ppm, H-7β = 3.06 ppm, H-5β = 2.18 ppm. In addition to the conformational change these downfield shifts also indicate the influence of the 8-CO_2CH_3 group of 1 and 3 on H-7α/H-7β and H-5β compared to the 8-CH_3 moiety of festuclavine. This influence can be estimated by comparison of 7 with 10α-methoxy-9,10-dihydrolysergic acid methylester (6); $\Delta\delta$6-7: H-7α ≈ 0.36 ppm, H-7β ≈ 0.44 ppm, H-5β ≈ 0.25 ppm. The thiazole and the thiazine moiety of 1 and 3 is not responsible for these large downfield shifts since the H-4β proton has a similar steric relation to the thiazole or the thiazine ring; $\Delta\delta$ 1-7: H-4β = 0.16 ppm, $\Delta\delta$ 3-7: H-4β = 0.14 ppm. It is obvious that the chemical shifts of H-7β and H-5β of 1 and 3 represent changes in the anisotropic influences associated with the conformational change of the D ring from the normal chair to the twist-boat conformation.

One explanation for the existence of the unexpected twist-boat conformer of 1 and 3 arises from the increasing sp^2 hybrid character of the bonding orbitals of the nitrogen N-6. Thus the greater planarity of this ring part is explained and as a result the twist-boat conformation is energetically favoured. Further evidence for this assumption is given by the low temperature ^{1}H-NMR spectra and the mass spectral data of 1 and 3. The fragmentation pattern of 1 and 3 is characterized by the splitting of C-7/N-6 and C-5/N-6 bonds and in the case of compound 3 a 2-aminothiazine-ion can be detected by collision induced dissociation (CID) mass spectrometry[7]. This is in agreement with the increased double bond charater of the N-6/C-2'-bond corresponding to a mesomeric stabilization of the charge in both the thiazole and the thiazine moieties.

Dynamic behaviour of compound 3.

In contrast to the ^{1}H-NMR spectrum of 1, which shows no striking changes in the temperature range of 300 K - 183 K, the spectrum of 3 exhibits a strong temperature dependence. On lowering the temperature all signals display linewidth broadening. They coalesce at different temperatures and at $T \leq 200$ K the signals are smaller and doubled. Due to the complexity of the spectrum in the aromatic and aliphatic region only the signals of H-7β and H-1 which also exhibit the largest low temperature splittings ($\Delta\delta \approx 1$ ppm) can be analysed. Both resonances show in $CD_2Cl_2/CDCl_3$ 3:1 at about 233 K coalescence and at 193 K a splitting of the bands with an intensity ratio 1:2, $\Delta\delta$(H-1) = 1.13 ppm and $\Delta\delta$(H-7β) = 1.01 ppm. A further interpretable signal doubling, in the same intensity ratio, is observed for the CO_2CH_3 group with $\Delta\delta$ = 0.09 ppm and a coalescence temperature of about 210 K.

Table 1. Proton chemical shifts of 1 and 3 in ppm referred to $\delta(CHCl_3)$ = 7.26 ppm $\delta(C_6D_5CHD_2)$ = 2.09 ppm, T = 297 K

Proton	1	3		
	$CDCl_3$	$CDCl_3$	toluene-d_8/pyridine-d_5	
			1:1	3:1
4α	3.25	2.85	2.87	2.82
4β	3.55	3.53	3.55	3.53
5β	3.81	4.28	4.24	4.21
7α	3.88	3.58	3.38	3.19
7β	4.44	4.93$^{+)}$	4.92	4.92$^{+)}$

Proton	1	3		
	$CDCl_3$	$CDCl_3$	toluene-d_8/pyridine-d_5	
			1:1	3:1
8α	3.10	3.08	2.82	2.67
9α	2.92	2.83	2.63	2.52
9β	1.94	1.91	1.90	1.90
10α	3.44	3.39	3.26	3.10
1	8.00	8.53+)		11.28
2	6.95	6.90		6.88
12	6.94	6.81		6.77
13	7.19	7.09		7.12
14	7.24	7.19		7.28
CO_2CH_3	3.72	3.76+)		3.62+)

+) Proton chemical shifts of 3 in ppm at low temperatures

	$CD_2Cl_2/CDCl_3$ 3:1		toluene-d_8/pyridine-d_5 3:1	
	T = 193 K		T = 204 K	
H-7β	4.34	5.35	5.50	4.75
H-1	9.93	8.80	12.50	12.35
CO_2CH_3	3.76	3.67	3.86	3.48

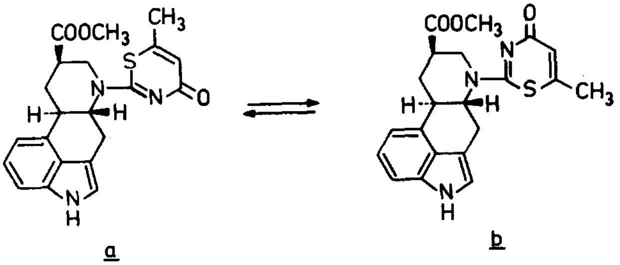


Fig. 3 Rotamers of 3 showing hindered rotation around the N-6/C-2'-bond

Table 2. Proton coupling constants of 1 and 3 in Hz (Δ J = ± 0.15 Hz), T = 297 K

J_{H-H}	1	3	
	$CDCl_3$	$CDCl_3$	toluene-d_8/pyridine-d_5 3:1
4α - 4β	14.7	14.1	14.4
4α - 5β	11.0	11.0	11.2
4β - 5β	4.3	3.7	3.8
4α - 2	1.6		1.6
5β - 10α	11.0	11.0	11.0
7α - 7β	14.2	14.5	14.3
7β - 8α	4.1	≤1	≤1

	<u>1</u>	<u>3</u>	
J_{H-H}	$CDCl_3$	$CDCl_3$	toluene-d_8/pyridine-d_5 3:1
7α - 8α	5.9	6.3	6.6
9α - 9β	13.3	13.7	13.3
9α - 8α	8.1	≳9	9.7
9α - 10α	3.2	3.4	2.7
9β - 8α	9.7	8.8	8.6
9β - 10α	13.2	13.7	13.3
10α - 12		~1.5	~1.5
12 - 13	7.0	6.6	7.0
13 - 14	8.3	8.3	8.2

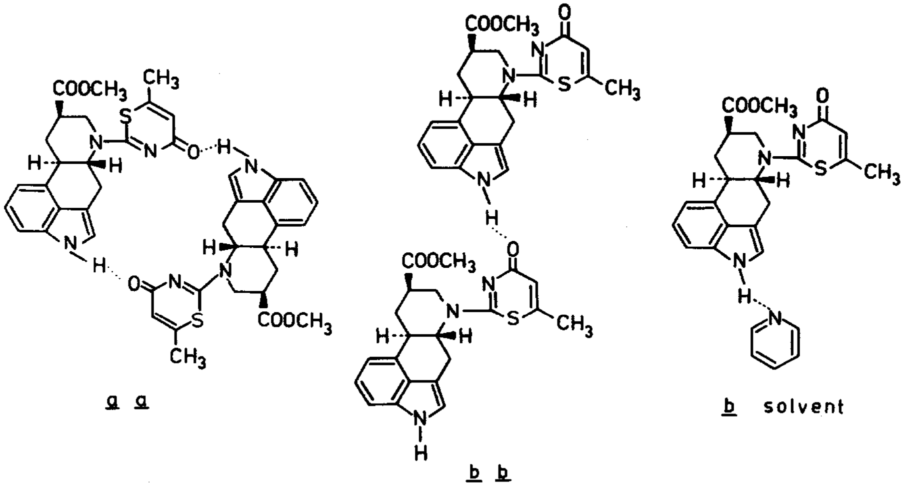
Table 3. Vicinal proton coupling constants of <u>1</u> and <u>3</u> in Hz, solvent $CDCl_3$, T = 297 K, respectively for the distorted chair conformation of <u>8</u> (H-8β) and the normal chair conformation of <u>6</u> (H-8α) according to ref. 5 and for the twist-boat form I expected according to Karplus, dihedral angles φ from Dreiding models.

	measured		expected					
			chair		twist-boat			
$^3J_{H-H}$	<u>1</u>	<u>3</u>	H-8β	H-8α	H-8β	φ [°]	H-8α	φ [°]
7α - 8	5.9	6.3	1.8	3.7	7-10	150	5- 8	30
7β - 8	4.1	≤1	3.9	11.8	5- 8	30	0	90
9α - 8	8.1	≳9	1.9	4.5	0	90	5- 8	30
9β - 8	9.7	8.8	6.4	13.2	5- 8	30	7-10	150

In toluene-d_8/pyridine-d_5 3:1 other coalescence temperatures T_c appear especially for H-7α, H-8α, H-9α, H-10α in addition to the toluene induced ASIS (aromatic solvent induced shifts) effects (Tab. 1), and an inversion of the intensity relation of the split H7β-signals is observed.

compound <u>3</u> in	H	H-1	H-7β	CO_2CH_3
toluene-d_8/ pyridine-d_5 3:1	T_c [K]	~216	~230	~224

A ring inversion process (in this case only as a partial ring inversion I⇄II due to the trans C/D ring fusion) can be excluded, to some extent, as responsible for the observed dynamic behaviour. A proof is that <u>3</u>, which strongly dominated by the twist-boat conformer, shows the dynamic behaviour and not <u>1</u>, which displays significant populations for both the chair and the twist-boat conformers. If I⇄II interconversion were responsible for the low temperature splitting of signals of <u>3</u>, this effect should be even stronger for <u>1</u>, which is not the observation. In agreement with the dynamic behaviour of <u>3</u> is the proposal of hindered rotation of the thiazine moiety around the N-6/C-2'-bond (Fig. 3) which should exhibit partial double bond character. Association effects of dimers (<u>a</u> <u>a</u>) (<u>b</u> <u>b</u>) (Fig. 4) as synergetic effects can induce the observed strong solvent dependence and also explain a high entropy contribution ΔS^0.



a a b b b solvent

Fig. 4 Possible associates of the rotamers of 3

^{13}C-NMR. ^{13}C-NMR spectra of 1, 2, 4 and 5 were recorded (Table 4, Fig. 5). The signals were assigned by means of off-resonance ^{1}H decoupled spectra and compared with 9,10-dihydrolysergic acid methylester[6] (5). The C/D ring juncture (H-5β, H-10α) established by ^{1}H-NMR spectra of 1 and 3 is also confirmed from the ^{13}C-NMR data of 1 and 2.

The data of 10α-methoxy-9,10-dihydrolysergic acid methylester[5] (6) are in agreement with those of the closely related 5 with respect to the effects of the 10-OCH_3 group.

$\Delta\delta = \delta_6 - \delta_5$: $\Delta\delta\alpha$ (C-10) = 31.9 ppm, $\Delta\delta\beta a$ (C-5) = 2.6 ppm, $\Delta\delta\beta a$ (C-9) = -0.7 ppm, $\Delta\delta\gamma a$ (C-4) = -4.8 ppm, $\Delta\delta\gamma a$ (C-8) = -2.8 ppm.

The small βa-effect of the 10-OCH_3 group with opposite sign for C-5 and C-9 and the relatively small γ_a-effect on C-8 are remarkable. Substitution of the N-6-CH_3 group by H of 5 in 4, yields β- and γ-effects of the N-CH_3 moiety.

$\Delta\delta = \delta_5 - \delta_4$: $\Delta\delta\beta$ (C-5) = 7.2 ppm, $\Delta\delta\beta$ (C-7) = 10.2 ppm, $\Delta\delta\gamma$(C-8) = -1.2 ppm, $\Delta\delta\gamma$(C-10) = -1.7 ppm, $\Delta\delta\gamma_g$ (C-4) = -2.8 ppm.

Table 4. ^{13}C-chemical shifts of 1, 2, 4, 5 and 6

Carbon	1 $CDCl_3$	2 $CDCl_3$	4 $CDCl_3$	5 $CDCl_3$	6[5] $CDCl_3$	multiplicity
2	118.6	118.4	117.6	117.8	118.6	D
3	111.3	111.0	111.9	111.8	111.1	S
4	25.9	25.9	29.8	27.0	22.2	T
5	64.2	64.0	59.6	66.8	69.4	D

Carbon	1 $CDCl_3$	2 $CDCl_3$	4 $CDCl_3$	5 $CDCl_3$	6[5] $CDCl_3$	multiplicity
7	47.2	46.8	48.6	58.8	58.5	T
8	37.3	37.1	41.4	40.2	37.4	D
9	26.2	25.9	30.7	30.7	30.0	T
10	39.9	39.7	43.3	41.6	73.5 S	D
11	131.7	130.9	132.6	132.7	129.1	S
12	113.2	112.9	113.1	113.4	115.6	D
13	123.0	122.8	123.1	123.2	121.7	D
14	109.3	109.1	108.7	108.7	110.8	D
15	133.5	134.0	133.6	133.4	134.2	S
16	126.0	125.9	126.5	126.2	126.0	S
17	174.1	173.9	174.5	174.3	174.6	S
CO_2CH_3	52.2	52.0	51.7	51.8	51.7	Q
6-CH_3				43.0	43.6	Q
2'	165.3	166.2				S
4'	139.6	139.8				S
5'	128.2	129.5				S
4'-alkyl						
CH_2	43.0					T
CH_2	22.3	25.3				T
CH_3	14.0	13.0				
5'-p-Br-(Cl)-benzoyl						
1''	130.9	131.5				S
2''	129.5	131.2				D
3''	128.4	131.2				D
4''	137.4	125.6				S
5''	128.4	131.2				D
6''	129.5	131.2				D
7''	171.9	171.8				S

Substitution of the H-6 of 4 by the thiazole moiety of 1, 2 leads to a usual ß-effect at C-5 ($\Delta\delta_{\beta} = \delta_1 - \delta_4$ = 4.6 ppm for 1 and $\Delta\delta_{\beta} = \delta_2 - \delta_4$ = 4.4 ppm for 2) and at C-7 to an upfield shift ($\Delta\delta_{\beta}$ = -1.4 ppm for 1 and -1.8 ppm for 2) which are easily explained by a conformational change of the D ring. The β_e-effect of the axial like arranged CO_2CH_3 group of the dominating twist-boat conformer is observed at C-9 ($\Delta\delta\beta_e = \delta_1 - \delta_4$ = -4.5 ppm for 1 and $\Delta\delta\beta_e = \delta_2 - \delta_4$ = -4.8 ppm for 2). This β_e-effect and the ß-effect of the thiazole moiety act at C-7 and in such a way that a small upfield shift of C-7 is found.

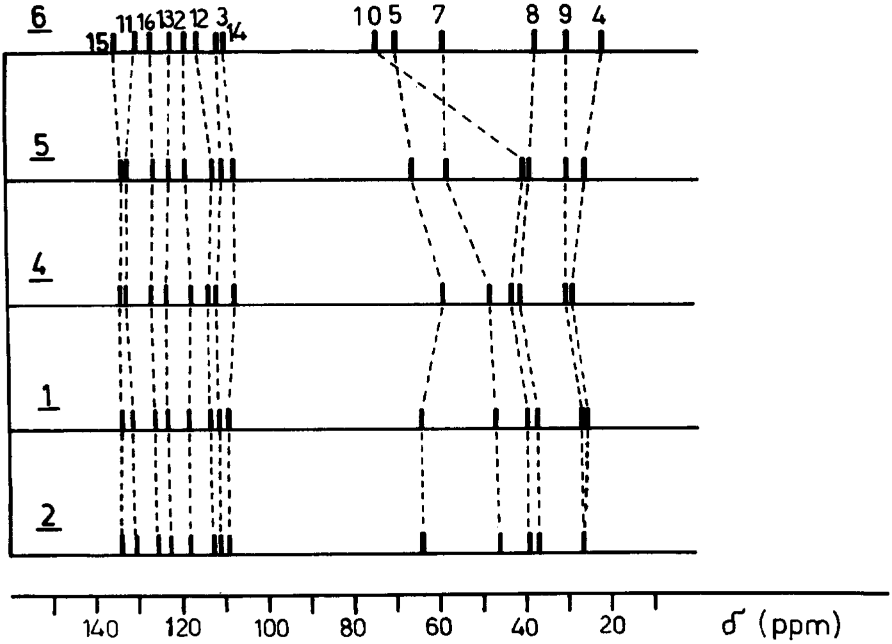


Fig. 5 ^{13}C chemical shifts of 1, 2, 4, 5 and 6

EXPERIMENTAL

The NMR spectra were recorded on a Bruker WP200 spectrometer at 200.132 MHz (^1H) and 50.327 MHz (^{13}C) in $CDCl_3$, $CD_2Cl_2/CDCl_3$ 3:1, toluene-d_8/pyridine-d_5 1:1 and 3:1. Chemical shifts are the normal positive downfield shifts from reference TMS referred to the standard values of the solvent signals; ^1H: $\delta(CHCl_3) = 7.26$ ppm, $\delta(C_6D_5CHD_2) = 2.09$ ppm; ^{13}C: δ $(CDCl_3) = 77.0$ ppm. The assignments in ^{13}C-NMR based on off-resonance- and APT (attached proton test) - ^{13}C-NMR spectra.

The two-dimensional COSY-NMR spectra were measured by means of the 2D-NMR program version 810515.6 included in the software of the Aspect 2000 computer of the WP 200 in a 128 x 128 point data matrix (2.7 Hz/point digital resolution) and transformed with a $\pi/6$-shifted sine bell window function. The representation was in the absolute value mode of a contour diagram.

The temperatures are the uncorrected values of the built-in thermocouple but corrected within ± 1 degree at room temperature and ± 5 degrees at 193 K.

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