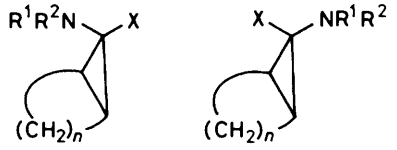
Assignment of Configuration of Larger Bicyclo[*n*.1.0]Alkylamines. The Use of a Lanthanide Shift Reagent

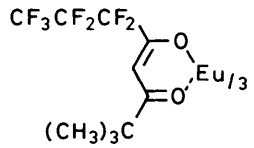
Elmar Vilsmaier,* Claus M. Klein, and Rainer Adam
Fachbereich Chemie, Universität Kaiserslautern, Erwin-Schrödinger-Strasse, D-6750 Kaiserslautern, West Germany

The detection of the *endo*- or *exo*-position for the amino-function in methylbicyclo[*n*.1.0]alkylmorpholines is accomplished by use of a lanthanide shift reagent. This method is particularly useful for larger [*n*.1.0]bicyclic systems because of the impossibility of establishing the configuration on the basis of the dynamics of the morpholino group. The differences in the chemical shifts caused by complexation of an *endo*- or an *exo*-amine are studied for the isomers of bicyclo[3.1.0]hexylmorpholine. A method for the preparation of sterically pure methylbicyclo[*n*.1.0]alkylmorpholines is described.

Until recently it was difficult to determine whether an amino-function in a disubstituted bicyclo[*n*.1.0]alkyl system (1) or (2) (X ≠ H) was in the *endo*- or the *exo*-position. With the results of two *X*-ray analyses as a basis, Koch and his group attempted to develop a method for distinguishing between the *endo*-isomer (1) and the *exo*-isomer (2) [1] using ^{15}N n.m.r. spectroscopy [Δδ between (1) and (2) *ca.* 12 p.p.m.; ^{15}N n.m.r. signal of (1) at higher field]. We have now developed a very simple method for differentiating between the *exo*- and *endo*-configurations (1) and (2) by observation of the dynamics of a nitrogen-heterocyclic function NR^1R^2.[2-12] ^1H N.m.r. spectra indicate that the dynamics of the heterocycle are more strongly hindered in (1) than in (2). In the simplest case this is detectable from the type of signal pattern of the heterocycle. Thus at room temperature morpholine, which we used most frequently, displays in the bicyclo[*n*.1.0]-hexane, -heptane, or -octane system an AA'XX' pattern in the *exo*-position (2) [*n* = 3—5; $R^1R^2 = (CH_2)_2O(CH_2)_2$] and an ABXY pattern in the *endo*-position (1) [*n* = 3—5, $R^1R^2 = (CH_2)_2O(CH_2)_2$].[2-10] In these compounds (1) the $\Delta G^{\ddagger}$ values for the dynamics of *endo*-morpholine amount to *ca.* 70—80 kJ mol^{-1}.[2-10] However, with a hydrogen atom as an *exo*-substituent (1; X = H) [11] or with the bicyclo[*n*.1.0]-undecane, -dodecane, or -pentadecane system (1) (*n* = 8, 9, or 12) [3,5,8,11,12] the hindrance of the morpholine dynamics decreases strongly. $\Delta G^{\ddagger}$ Values of only 50—60 kJ mol^{-1} result. Since for ring inversion of *N*-methylmorpholine $\Delta G^{\ddagger}$ is reported to be 48 kJ mol^{-1},[13] and the error limit for the determination of these quantities by the n.m.r. method is known to be in the range of ±1—2 kJ mol^{-1}, these values are no longer sufficient to distinguish between (1) and (2). For X = H this implies no restriction for the assignment of configuration; in this case (1) and (2) have quite different $^3J_{HH}$ coupling constants.[14-17] In the case of the larger ring systems, however, the application of a lanthanide shift reagent might be expected to allow the definite establishment of the configuration. In order to obtain exclusive complexation of the morpholine, we have studied this problem using methyl-substituted morpholinobicyclo[*n*.1.0]alkanes (6). Eu(fod)$_3$ (3) [18-21] was selected as the shift reagent. The different effects from complexation of an *endo*- or an *exo*-morpholine were investigated with the isomeric amines (11) and (12). A *trans*-bicyclic methyl derivative (9) was also included in these experiments, since it is expected to allow the study of the influence on *syn*- and *anti*-cyclopropane hydrogen atoms by the Eu(fod)$_3$–morpholine complex.



(1) (2)

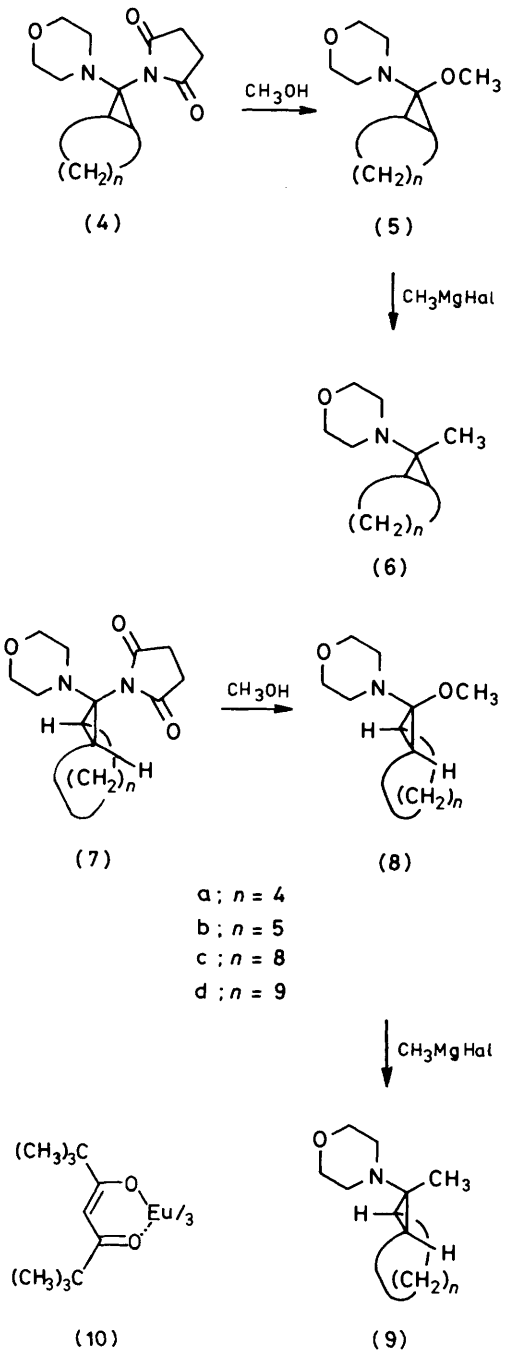


(3)

Results and Discussion

Synthesis of Methylbicyclo[n.1.0]*alkylmorpholines* (6) *and* (9).—In the field of middle–large ring systems, both *cis*- and *trans*-morpholino(succinimido)bicyclo[*n*.1.0]alkanes (4) and (7) are accessible with high stereoselectivity from enaminosulphonium salts.[3,22] Consequently (4) and (7) are suitable starting materials for synthesizing further [*n*.1.0]bicyclic compounds.[8,11,12,22] As shown for the bicyclo[4.1.0]heptane system, an alkyl substituent is introduced into the bicyclic system by reacting a methoxy-morpholino-derivative (5a) with Grignard reagents.[7] Therefore we investigated the preparation of the methoxy-compounds (5) and (8) from (4) and (7). This is achieved by heating (4b—d) or (7d) in methanol–methoxide causing substitution of the succinimide by a methoxy-group. The addition of methoxide should avoid *exo–endo* isomerization catalysed by protons; see *e.g.* ref. 2.

The reaction of (5) and (8), respectively, with methylmagnesium iodide leads to the expected methylbicyclo[*n*.1.0]alkylmorpholines (6) and (9). The compounds isolated from these reactions proved to be isomerically pure. Starting from the *cis*-succinimido-compound (4), the *cis*-derivatives (5) and (6) are obtained; similarly the *trans*-succinimido-compound (7d) leads to *trans*-derivatives (8d) and (9d). The *cis–trans* configuration of the bicyclic compounds is indicated by the ^{13}C n.m.r. data (Table 3). The *cis*-[*n*.1.0]bicyclic compounds (5) and (6) display a plane of symmetry. Therefore the *n* + 3 carbon atoms of a *cis*-[*n*.1.0]bicycle give either (*n*/2) + 2 signals (*n* = even) or (*n* + 1)/2 + 2 signals (*n* = odd). Consequently five signals are seen for (5b) and (6b), six signals for (5c) and (6c), and seven signals for (5d) and (6d); in every case the cyclopropane ring gives rise to one singlet and one doublet. On the other hand, the chirality of the *trans*-bicyclic derivatives produces for (8d) and (9d) three ^{13}C n.m.r. signals (2 doublets and 1 singlet) for the cyclopropane. The nine sig-



nals expected for the nonamethylene bridge are not totally resolved because of partial superposition.

In the ^{1}H n.m.r. spectra there are distinct differences between the *cis*- and *trans*-derivatives especially in the region of the cyclopropane protons (Table 1). In (5b) and (6b) morpholine appears in the ^{1}H n.m.r. spectrum at room temperature as an ABXY signal, which coalesces upon warming to 60—70 °C. From the known approximation formula,[23] a $\Delta G^{\ddagger}$ value of 68.7—69 kJ mol^{-1} results for the topomerization of the H_AH_B and H_XH_Y methylene hydrogen atoms, respectively. This establishes the *endo*-configuration of the morpholine in (5b) and (6b).

In (5c and d) and (6c and d) the ABXY pattern becomes visible only at lower temperatures (Table 1); the corresponding $\Delta G^{\ddagger}$ values vary from 48.9 to 56.6 kJ mol^{-1}. This order of magnitude for $\Delta G^{\ddagger}$ is expected for an *endo*-morpholine in the bicyclo[8.1.0]undecane and bicyclo[9.1.0]dodecane systems [*e.g.* $\Delta G^{\ddagger}$/kJ mol^{-1}: (4c) 54.9, 55.9 [3] (*X*-ray structural analysis[3]); (4d) 58.9, 60.3 [3]]. This is close to the energy required for the normal ring inversion of morpholine and therefore a definitive assignment of morpholine to the *endo*-position in (5c and d) and (6c and d) is not possible from a study of the dynamics. In the *trans*-derivatives (8d) and (9d) the low-temperature ^{1}H n.m.r. spectra show complex signal systems because of chirality; the $\Delta G^{\ddagger}$ values for the morpholine dynamics were not determined.

Lanthanide-induced Shift (LIS) *Experiments with Methylbicyclo*[n.1.0]*alkylmorpholines* (6) *and* (9).—Addition of 0.25, 0.5, 0.75, and 1 mol. equiv. Eu(fod)$_3$ (3) to a solution of the methylbicyclo[*n*.1.0]alkylmorpholines (6) in $CDCl_3$ leads to a large downfield shift of the morpholino signals. In an equimolar mixture of (6b—d) and (3), the OCH_2 signals are shifted to δ 15—18 and the NCH_2 signals appear in the region δ 8.5—9.5. This is in contrast to unsubstituted morpholine, for which the NCH_2 signals are found at lower field than the OCH_2 resonances in the presence of trisdipivaloylmethanatoeuropium (10).[24] But these differences may be due to steric effects, which have a large influence on the complexation properties of amines [chemical shift of the α-methylene group in a 1 : 1 complex with (10): piperidine δ 38.20; [25] *N*-methylpiperidine: δ 16.0 p.p.m.[25]).

For the establishment of the configuration of (6), the behaviour of the signals of the bicyclic system is important. The cyclopropane signal is not strongly affected by addition of Eu(fod)$_3$ (3). This signal with its characteristic splitting is observable for (6b and c) in all mixtures with (3); for (6d) it is recognized clearly only in the mixture with 0.25 and 0.5 equiv. of (3). In the mixture with 0.5 equiv. of (3) this signal is shifted by 1.2—1.1 δ units uniformly for (6b, c, and d) (Table 2). On the other hand, a strong influence on four hydrogen atoms of the bicyclic compound is observed by adding (3) to (6b and c) or (6d). With 1 equiv. Eu(fod)$_3$ they show a signal between δ 3.75 and 4.85. These four hydrogen atoms, most probably one hydrogen of each of the two by two methylene groups next to cyclopropane, should be on the *syn*-side of the carbon ring with respect to morpholine.

A slight shift of the cyclopropane hydrogen signals on the one hand and large shift of signals of the carbocyclic framework on the other allow the establishment of the *endo*-morpholino configuration for (6b—d). In the case of (6b) the correctness of this assignment is confirmed by the observation of the morpholino dynamics.

In order to obtain information about the influence of the morpholine–Eu(fod)$_3$ complex on *syn*- or *anti*-cyclopropane hydrogen atoms, we have studied the ^{1}H n.m.r. spectra of mixtures of (3) and the *trans*-compound (9d). In a 1 : 1 mixture of (3) and (9d), signals representing four hydrogen atoms are found between δ 4 and 5. It is to be expected that one of these signals corresponds to the *anti*-hydrogen atom on the cyclopropane ring. But it was not possible to trace the shift of the two different bridge head hydrogen atoms upon stepwise addition of Eu(fod)$_3$. Therefore (9d) is not suited to studying the shift effect of Eu(fod)$_3$ complexed to an *exo*-morpholino moiety.

LIS Experiments with the Bicyclo[3.1.0]*hexylmorpholine Isomers* (11) *and* (12).—The different effects of Eu(fod)$_3$ complexing an *endo*- or an *exo*-morpholine are demonstrated with the bicyclo[3.1.0]hexylmorpholines (11) and (12). As shown earlier, (11) and (12) are easily accessible from chloro-

Table 1. ^{1}H N.m.r. data (200 MHz; CD_2Cl_2; Me_4Si) and $\Delta G^{\ddagger}$ values for morpholinobicyclo[*n*.1.0]alkanes (5), (6), (8), and (9)

		Chemical shift (δ)					Characteristic coupling constants (Hz) [b]				
		NCH_2		OCH_2							$\Delta G^{\ddagger}$ [d]/
Compd.	T/°C	H_A	H_B	H_X	H_Y	Other signals [a]	J_{AB}	J_{XY}	J_{BX}	T_c [c]/°C	kJ mol^{-1}
(5b)	20	2.59	3.09	3.57	3.87	3.3 (s, 3 H), 1.0—2.2 (m, 12 H)	11.9	12.4	11.5	70 [e] 65 [f]	68.9 [e] 69.0 [f]
(5c)	−60	2.82	2.92	3.41	3.71	3.4 (s, 3 H), 1.15—1.9 (m, 16 H), 0.9—1.1 (m, 2 H)	11.5	10.4	10.5	−25 [e] −18 [f]	51.4 [e] 51.5 [f]
(5d)	−40	2.69	2.95	3.47	3.73	3.4 (s, 3 H), 1.15—1.9 (m, 18 H), 0.95—1.15 (m, 2 H)	11.6	10.4	11.3	5 [e] 2 [f]	56.6 [e] 56.0 [f]
(6b)	20	2.16	2.58	3.51	3.74	1.6—1.9 (m, 4 H), 1.0—1.5 (m, 6 H), 0.9 (s, 3 H), 0.4—0.6 (m, 2 H)	10.8	9.7		60 [e] 67 [f]	68.8 [e] 68.7 [f]
(6c)	−80	2.56 [g] (mc)		3.47	3.72	1.2—1.9 (m, 16 H), 1.0 (s, 3 H), 0.4—0.5 (m, 2 H)	*h*	10.7	*h*	−33 [f]	48.9 [f]
(6d)	−60	2.40	2.59	3.51	3.72	1.2—1.7 (m, 18 H), 1.0 (s, 3 H), 0.45—0.6 (m, 2 H)	11.2	10.9	11.0	−8 [e] −8 [f]	54.4 [e] 54.2 [f]
(8d)	20	2.85 [i]		3.60 [i]		3.4 (s, 3 H), 1.25—2.0 (m, 18 H), 0.5—1.25 (m, 2 H)				*i*	*i*
(9d)	20	2.54 [i]		3.59 [i]		1.2—1.9 (m, 16 H), 1.0 (s, 3 H), 0.65—0.95 (m, 2 H), 0.3—0.45 (m, 2 H)				*j*	*j*

[a] From the spectrum at 20 °C. [b] Further coupling constants: J_{AX}, J_{AY} *ca.* 0.2 Hz, J_{BY} *ca.* 2—3 Hz. [c] Coalescence temperature; (5b) and (6b) in $C_2D_2Cl_4$. [d] Calculated from ref. 23, limits of error ±1—2 kJ mol^{-1}. [e] AB System. [g] No separation of the signals. [h] Not detectable. [i] Typical morpholino AA'XX' pattern. [j] Chirality gives a complex spectrum at low temperatures.

Table 2. ^{1}H N.m.r. data (200 MHz; $CDCl_3$; Me_4Si; 20 °C) for mixtures of Eu(fod)$_3$ (3) and morpholinobicyclo[*n*.1.0]alkanes (6), (11), and (12)

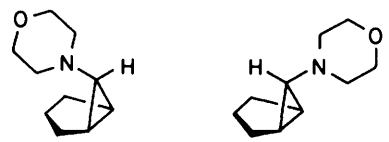
		Cyclopropane		Methyl group	
Compds.	Equivalents Eu(fod)$_3$ (3)	2 H	1 H (t) 6-H	(3 H, s)	$(CH_2)_n$ moiety in the presence of 1 equiv. Eu(fod)$_3$
(6b)	0	0.66		0.99	2.25—2.55 (m, 2 H),[a] 2.6—3.05 (m, 4 H), 3.75—3.9 (m, 2 H), 4.6—4.85 (m, 2 H)
	0.25	1.29		1.69	
	0.5	1.76		2.20	
	0.75	2.19		2.66	
	1	2.32		2.81	
(6c)	0	0.43		1.03	2.05—2.2 (m, 4 H),[a] 2.45—2.8 (m, 8 H), 4.25—4.4 (m, 4 H)
	0.25	1.09		1.74	
	0.5	1.63		2.34	
	0.75	1.83		2.56	
	1	2.11		2.86	
(6d)	0	0.50		1.00	1.95—2.83 (m, 14 H),[a] 4.14—4.36 (m, 2 H), 4.36—4.60 (m, 2 H)
	0.25	1.17		1.72	
	0.5	1.70		2.32	
	0.75	*b*		2.75	
	1	*b*		3.05	
(11)	0	1.33	1.53		3.52—3.73 (m, 3 H), 4.63—4.80 (m, 2 H), 5.57—5.82 (m, 1 H)
	0.25	2.33	3.32		
	0.5	2.87	4.39		
	0.75	3.16	4.86		
	1	3.35	5.22		
(12)	0	1.33	1.40		2.33—2.60 (m, 2 H), 2.85—3.40 (m, 4 H)
	0.25	2.64	2.85		
	0.5	3.62	3.86		
	0.75	4.25	4.52		
	1	4.75	5.06		

[a] Superposition with the cyclopropane signal; the resulting integral indicates the presence of two additional hydrogen atoms. [b] The position of the cyclopropane signal cannot be assigned clearly because of other similar adjacent and overlapping signal systems.

morpholinocyclohexene and $LiAlH_4$ followed by separation of the isomers by a buffer solution. Addition of 0.25, 0.5, 0.75, and 1 mol. equiv. Eu(fod)$_3$ (3) causes a smaller shift for the bridgehead hydrogen atoms in (11) and a stronger shift for the same protons in (12) [Δδ for the 1 : 1 mixture: (11) 2.02; (12) 3.42]. Furthermore, there is a strong and characteristic difference for the hydrogen atoms of the trimethylene group. In the 1 : 1 complex of (3) with (11) three hydrogen atoms show resonances at lower field (δ 4.7, 5.7); in (12) a maximal shifting up to Δδ 3.4 of the $(CH_2)_3$ signals is observed (Table 2). The ^{1}H n.m.r. spectra of the carbon ring in (11) and (12), respectively without and with 0.5 equiv. of Eu(fod)$_3$, are shown in the Figure. Within the limit of error the morpholino signals and the signal for 6-H in (11) and (12) are

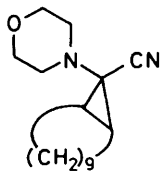
influenced equally by $Eu(fod)_3$ (3) in the 1 : 1 complex [1 : 1 complexes: NCH_2 (11) δ 10.5, (12) δ 10.3; OCH_2 (11) δ 21.6, (12) δ 20.4; 6-H (11) δ 3.69, (12) δ 3.66].

LIS experiments with (11) and (12) confirm the correct assignment of the *endo*-morpholino configuration in (6b—d) by means of $Eu(fod)_3$ (3). At the same time they demonstrate the characteristic rules for differentiation of an *endo*- from an *exo*-morpholine in a bicyclo[*n*.1.0]alkane using $Eu(fod)_3$ (3).



(11)

(12)



(13)

In the bicyclic systems studied so far, complexation could take place only between the $Eu(fod)_3$ (3) and the morpholino-moiety. This turned out to be an essential prerequisite for establishing the configuration by this method. Though a cyano-function displays only little tendency towards complexation [25] for (3) with respect to an ether or an amino-group, the configuration of (13) cannot be established by addition of $Eu(fod)_3$. Three signals, situated very close to each other, are shifted downfield in the presence of $Eu(fod)_3$. With 1 equiv. (3) they appear between δ 4 and 5, corresponding to six hydrogen atoms. In contrast to (6d), two more hydrogen atoms are influenced by the $Eu(fod)_3$, most probably the bridgehead hydrogen atoms. In this case their subsequent shift cannot be observed because of superposition with other signals. Altogether there is a change of the complexation properties between $Eu(fod)_3$ and the morpholino-moiety caused by the cyano-group which prohibits information about the configuration of (13) from being gained. A similar state of affairs was observed for the methoxy-morpholino-compound (5d). Therefore the establishment of configuration by means of $Eu(fod)_3$ becomes difficult with [*n*.1.0]bicyclic systems which contain another substituent with complexing ability for $Eu(fod)_3$ (3) in addition to the morpholino-group. As shown elsewhere,[26] for this type of compound assignment of the configuration is possible by replacing the morpholino-group with a hexahydroazepine moiety, followed by a study of the dynamic properties of the latter species.

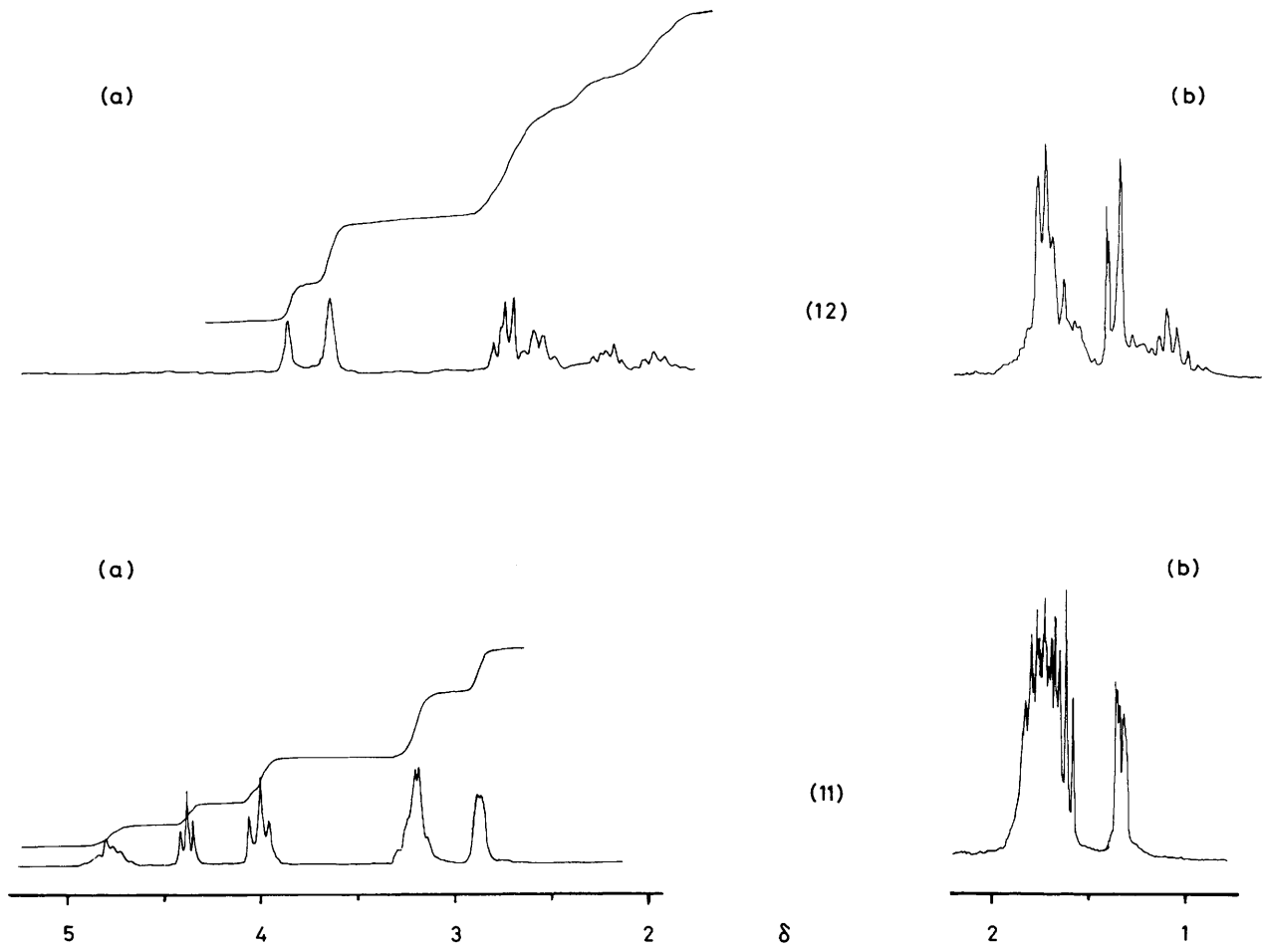


Figure 1. ^1H N.m.r. signals of the carbocyclic systems of (11) and (12) (b) without and (a) with 0.5 equiv. $Eu(fod)_3$ (200 MHz; $CDCl_3$; Me_4Si; 20 °C)

Table 3. ^{13}C Chemical shifts (50.28 MHz; $CDCl_3$; Me_4Si) of the morpholinobicyclo[*n*.1.0]alkanes (5), (6), (8), and (9)

	Chemical shift δ			
		Carbocycle		
	Morpholine [a]	Cyclopropane	Polymethylene bridge [a]	MeO or Me substituent
(5b)	67.7, 50.1	86.5 (s), 30.6 (d)	32.9, 29.6, 25.8	57.1 (q)
(5c)	67.8, 50.4	80.2 (s), 29.1 (d)	28.5, 26.7, 22.3, 20.6	56.7 (q)
(5d)	67.7, 50.1	82.9 (s), 29.8 (d)	26.6, 25.9, 23.2, 22.9, 22.2	56.7 (q)
(6b)	67.6, 49.8	47.8 (s), 31.0 (d)	32.9, 29.9, 24.4	16.5 (q)
(6c)	67.6, 50.3	41.6 (s), 29.1 (d)	29.0, 26.8, 22.5, 20.2	17.1 (q)
(6d)	67.7, 49.9	44.2 (s), 30.0 (d)	26.7, 26.4, 23.3, 22.9, 21.6	16.9 (q)
(8d)	67.8, 49.9	84.5 (s), 22.5 (d), 32.9 (d)	27.5, 27.3, 26.5, 26.3,[b] 26.1, 25.9, 22.8	58.1 (q)
(9d)	67.6, 49.4	46.2 (s), 34.7 (d), 32.0 (d)	26.9,[b] 26.4, 26.2, 25.3, 23.3	11.0 (q)

[a] All triplets. [b] Superposition of 2 or more signals.

Experimental

M.p.s and b.p.s are uncorrected. M.p.s were measured with a Mettler FP 5 apparatus. ^1H and ^{13}C n.m.r. spectra were recorded with a Bruker WP 200 spectrometer and chemical shifts are reported in δ units from internal tetramethylsilane. The reactions of the aminobicycloalkane derivatives with the LIS experiments were carried out under nitrogen to exclude moisture. Mass spectra were measured at 70 eV with a Varian MAT 311 instrument. Microanalyses were performed with a Perkin-Elmer 240 elemental analyser.

General Procedure for the Preparation of Aminomethoxybicyclo[n.1.0]*alkanes* (5) *and* (8).—The morpholinosuccinimidobicyclo[*n*.1.0]alkanes (4) and (7) were added to metallic sodium (0.24 g, 10 mmol) and dry methanol (20 ml) [(4b)[3] 2.82 g; (4c)[3] 3.34 g; (4d),[3] (7d)[3] 3.48 g; each 10 mmol]. After refluxing for 12 h (4b—d)[3] and 3 days (7d), the methanol was evaporated and the residue extracted with pentane (3 × 30 ml). Removing the solvent from the pentane extracts *in vacuo* gave colourless crystals of (5b—d) and (8d). 8-exo-*Methoxy*-8-*morpholino*-cis-*bicyclo*[5.1.0]*octane* (5b) (1.7 g, 76%) had m.p. 51.6 °C (Found: C, 69.0; H, 10.15; N, 6.1. $C_{13}H_{23}NO_2$ requires C, 69.3; H, 10.3; N, 6.2%); *m*/*z* 225 (M^+, 12%). 11-exo-*Methoxy*-11-*morpholino*-cis-*bicyclo*[8.1.0]*undecane* (5c). (1.94 g, 72%) had m.p. 44 °C (Found: C, 71.5; H, 10.75; N, 5.0. $C_{16}H_{29}NO_2$ requires C, 71.85; H, 10.95; N, 5.25%); *m*/*z* 267 (M^+, 10%). 12-exo-*Methoxy*-12-*morpholino*-cis-*bicyclo*-[9.1.0]*dodecane* (5d) (2.46 g, 87%) had m.p. 53 °C (Found: C, 72.6; H, 11.2; N, 4.9. $C_{17}H_{31}NO_2$ requires C, 72.55; H, 11.1; N, 5.0%); *m*/*z* 281 (M^+, 18%). 12-*Methoxy*-12-*morpholino*-trans-*bicyclo*[9.1.0]*dodecane* (8d) (1.13 g, 60%) had m.p. 90 °C (Found: C, 72.3; H, 11.0; N, 4.8. $C_{17}H_{31}NO_2$ requires C, 72.55; H, 11.1; N, 5.0%); *m*/*z* 281 (M^+, 10%).

N-(*Methylbicyclo*[n.1.0]*alkyl*)*morpholines* (6) *and* (9).—According to a published[7] procedure a mixture of methylmagnesium iodide in diethyl ether (0.2M, 35 ml, 7 mmol) and the methoxymorpholinobicyclo[*n*.1.0]alkanes (5) and (8) [(5b) 1.13 g; (5c) 1.34 g; (5d) and (8d) 1.41 g; each 5 mmol] was refluxed for 12 h. Work-up by addition of water (40 ml), extraction with pentane (3 × 30 ml), drying the pentane solution (Na_2SO_4) and removing the pentane gave (6) and (9). Compounds (6b—d) form crystals, which may be recrystallized from acetonitrile. Compound (9d), an oil, was distilled in a Kugelrohr apparatus. N-(8-exo-*Methyl*-cis-*bicyclo*[5.1.0]-*octyl*)*morpholine* (6b) (0.79 g, 76%) had m.p. 71 °C (Found: C, 74.5; H, 10.8; N, 6.5. $C_{13}H_{23}NO$ requires C, 74.6; H, 11.2; N, 6.7%); *m*/*z* 209 (M^+, 23%). N-(11-exo-*Methyl*-cis-*bicyclo*-[8.1.0]*undecyl*)*morpholine* (6c) (1.05 g, 84%) had m.p. 86 °C (Found: C, 76.1; H, 11.3; N, 5.4. $C_{16}H_{29}NO$ requires C, 76.45; H, 11.65; N, 5.55%); *m*/*z* 251 (M^+, 11%). N-(12-exo-*Methyl*-cis-*bicyclo*[9.1.0]*dodecyl*)*morpholine* (6d) (1.20 g, 91%) had m.p. 90 °C (Found: C, 76.9; H, 11.55; N, 5.2. $C_{17}H_{31}NO$ requires C, 76.9; H, 11.75; N, 5.3%); *m*/*z* 265 (M^+, 9%). N-(12-exo-*Methyl*-trans-*bicyclo*[9.1.0]*dodecyl*)*morpholine* (9d) (1.0 g, 75%) had b.p. 115—118 °C at 0.05 Torr (Found: C, 76.6; H, 11.65; N, 5.1. $C_{17}H_{31}NO$ requires C, 76.9; H, 11.75; N, 5.3%); *m*/*z* 265 (M^+, 12%).

LIS Experiments with Bicyclo[n.1.0]*alkylmorpholines* (5), (6), (9), and (11)—(13).—$Eu(fod)_3$ (3) (1.06 g, 1.02 mmol) was dissolved in a few ml of dry $CDCl_3$; the solution made up to 10 ml with $CDCl_3$ containing 1.02×10^{-2} mmol substrate per 0.1 ml solvent. From the bicyclo[*n*.1.0]alkylmorpholines (5), (6), (9), and (11)—(13) solutions were also prepared in dry $CDCl_3$; 0.1 ml of these solutions contained 4.08×10^{-2} mmol (5), (6), (9), and (11)—(13) [amounts for 1 ml solution: (6b) 85.4 mg; (6c) 102.6 mg; (6d), (9d) 108.3 mg; (11), (12) 68.3 mg; (5d) 114.8 mg, (13) 112.8 mg; each 0.408 mmol]. With exclusion of moisture under nitrogen the $Eu(fod)_3$ solution (0, 0.1, 0.2, 0.3, and 0.4 ml) and $CDCl_3$ (0.4, 0.3, 0.2, 0.1, and 0 ml) was added to the bicycloalkylmorpholine solutions (0.1 ml). ^1H N.m.r. spectra were run for each of the mixtures (0.5 ml).

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for support. We also thank Professor W. D. Sheldrick, Kaiserslautern, for checking our English.

References

1 R. C. Haltiwanger, J. M. Burns, G. C. Crockett, and T. H. Koch, *J. Am. Chem. Soc.*, 1978, **100**, 5110.
2 E. Vilsmaier and W. Tröger, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 798; E. Vilsmaier, W. Tröger, and G. Haag, *Chem. Ber.*, 1981, **114**, 67.
3 E. Vilsmaier and C. M. Klein, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 800; E. Vilsmaier, C. M. Klein, D. Dausmann, and G. Maas, *Chem. Ber.*, 1982, **115**, 1209.
4 E. Vilsmaier and W. Tröger, *Synthesis*, 1980, 463; 1981, 207, 721; *Chem. Ber.*, 1982, **115**, 1644.
5 E. Vilsmaier and L. Scheiber, *Synthesis*, 1980, 465.
6 E. Vilsmaier, W. Tröger, and M. Gewehr, *Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 273.
7 E. Vilsmaier and C. M. Klein, *Synthesis*, 1981, 206.
8 E. Vilsmaier, C. M. Klein, W. Tröger, and D. Dausmann, *Synthesis*, 1981, 724.
9 E. Vilsmaier and G. Kristen, *Chem. Ber.*, 1982, **115**, 1224.
10 E. Vilsmaier, B. Penth, and W. Tröger, *Tetrahedron Lett.*, 1982, **23**, 3475.
11 E. Vilsmaier, C. M. Klein, and W. Tröger, *Chem. Ber.*, 1982, **115**, 2795.

12 E. Vilsmaier, C. M. Klein, and D. Dausmann, *Synthesis*, 1981, 726.
13 R. K. Harris and R. A. Spragg, *J. Chem. Soc. B*, 1968, 684.
14 W. Kirmse and F. Scheidt, *Chem. Ber.*, 1970, **103**, 3711.
15 W. Kirmse and H. Jendralla, *Chem. Ber.*, 1978, **111**, 1857.
16 J. Szmuszkovicz, E. Cerda, M. F. Grostic, and J. F. Zieserl jr., *Tetrahedron Lett.*, 1967, 3969.
17 J. C. Blazejewski, D. Cantacuzene, and C. Wakselman, *Tetrahedron*, 1973, **29**, 4233.
18 D. H. Williams, *Pure Appl. Chem.*, 1974, **40**, 25.
19 O. Hofer, *Top. Stereochem.*, 1976, **9**, 111.
20 W. De W. Horrocks jr., in ' NMR of Paramagnetic Molecules,' eds. G. N. La Mar, N. De W. Horrocks jr., and R. H. Holm, Academic Press, New York, 1973, p. 479.
21 J. Reuben, *Prog. Nucl. Magn. Reson. Spectrosc.*, 1975, **9**, 1.
22 E. Vilsmaier, in ' Organic Sulfur Chemistry,' eds. R. Kh. Freidlina and A. E. Skorova, Pergamon Press, Oxford, 1981, p. 219.
23 H. Günther, ' NMR-Spektroskopie,' G. Thieme Verlag, Stuttgart, 1973, pp. 248 and 255.
24 H. Hart and G. M. Love, *Tetrahedron Lett.*, 1971, 625.
25 R. B. Lewis and E. Wenkert, in ' Nuclear Magnetic Resonance Shift Reagents,' ed. R. E. Sievers, Academic Press, New York and London, 1973, p. 99.
26 E. Vilsmaier, B. Schwaben, and K. Joerg, *Chem. Ber.*, in the press.

Received 17*th February* 1983; *Paper* 3/244