Synthesis and 270 MHz Nmr Structural Studies of the Isomers of 2,3,5-Trimethyl- and 2,3,6-Trimethylmorpholine

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The four isomers of 2,3,5-trimethylmorpholine and those of 2,3,6-trimethylmorpholine have been synthesized from appropriately substituted ethanolamines and separated by means of preparative gas-liquid chromatography. The configuration of each isomer was determined from 270 MHz FT-nmr studies of the magnitudes of the methine-methine and methine-methylene proton coupling constants. The evaluated chemical shifts of axial methyl groups are discussed.

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Introduction.

One of the basic tenets of the analysis of conformational equilibria (1,2) is that axial substituents in six-membered ring compounds are less stable than equatorial ones. However, exceptions are known where dipolar interactions (3) or attractive steric effects (4) between substituents predominate, and thus the axially substituted conformer is more stable than the equatorially substituted analog. In our continuing study of the stereochemistry and conformational stability of methyl-substituted morpholines, we were interested in synthesizing derivatives in which at least one substituent is axial. In this paper, the syntheses and nmr spectroscopic studies of the isomers of 2,3,5- and 2,3,6-trimethylmorpholines are described. Of special interest in this work was an investigation of the nmr shifts of axial methyl groups.

Results and Discussion.

Syntheses.

The syntheses, starting from the pure *cis*- and *trans*-2,3-epoxybutanes and reacting them with the appropriately substituted ethanolamines (see synthetic scheme) gave mixtures of the expected appropriately substituted diethanolamines.

Unfortunately we have not yet been able to separate these intermediates into pure isomers on a preparative scale. The same routes and the same conditions as in our study of 2,3,5,6-tetramethylmorpholine (5) were used throughout the synthetic work to obtain the desired mor-

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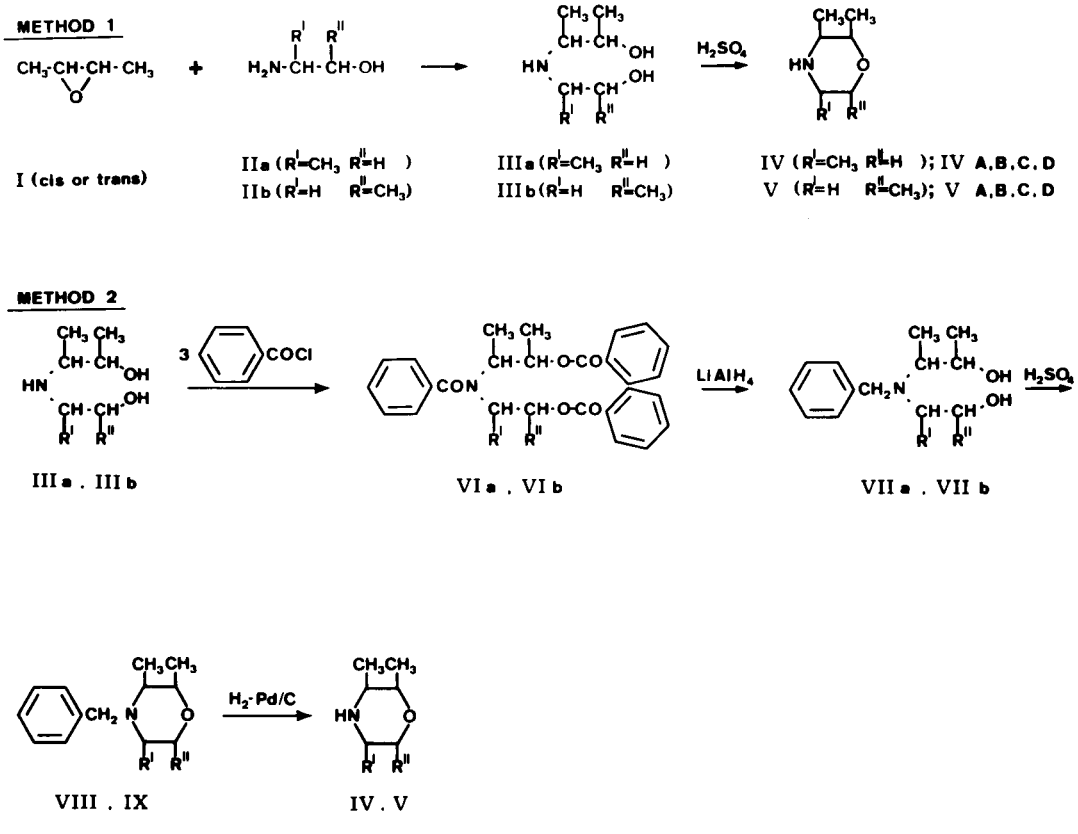

Table I

Yields of the Various Isomers of 2,3,5-Trimethyl- and 2,3,6-Trimethylmorpholines Obtained by Method 1 and 2

Starting material	Method (a)	Isomers % 2,3,5-Trimethylmorpholine IVA	IVB	IVC	IVD	2,3,6-Trimethylmorpholine VA	VB	VC	VD
cis-2,3-epoxybutane + DL-alaninol	1	37	27	24	12				
cis-2,3-epoxybutane + DL-alaninol	2	12	22	36	30				
trans-2,3-epoxybutane + DL-alaninol	1	43	36	15	6				
trans-2,3-epoxybutane + DL-alaninol	2	19	37	12	32				
cis-2,3-epoxybutane + DL-1-amino-2-propanol	1					64	26	7	3
cis-2,3-epoxybutane + DL-1-amino-2-propanol	2					27	28	36	9
trans-2,3-epoxybutane + DL-1-amino-2-propanol	1					22	10	41	27
trans-2,3-epoxybutane + DL-1-amino-2-propanol	2					2	10	52	36

(a) The synthetic routes are given in the Scheme.

Table II

Physical Data of 2,3,5- and 2,3,6-Trimethylmorpholines and their Hydrochlorides.

Isomer	R	R′	R″	n_D^{25}	M.p. °C	Analysis Calcd. Cl%	Found
IVA	H	CH_3	H	1.4407	liquid		
	H,HCl	CH_3	H		201-204	21.40	21.50
IVB	H	CH_3	H	1.4445	liquid		
	H,HCl	CH_3	H		190-192	21.40	21.54
IVC	H	CH_3	H	1.4453	liquid		
	H,HCl	CH_3	H		136-151 (b)	21.40	21.63
IVD	H	CH_3	H	1.4448	liquid		
	H,HCl	CH_3	H		236-238	21.40	21.38
VA	H	H	CH_3	1.4430	liquid		
	H,HCl	H	CH_3		(c)		
VB	H	H	CH_3	1.4451	liquid		
	H,HCl	H	CH_3		122-123	21.40	21.57
VC	H	H	CH_3	1.4464	liquid		
	H,HCl	H	CH_3		174-176	21.40	21.68
VD	H	H	CH_3	1.4460	liquid		
	H,HCl	H	CH_3		147-149	21.40	21.40

(a) The melting points are uncorrected. (b) The compound has unexpectedly a very unsharp melting point. The hydrobromide (R = H, HBr) melts at 115-118° (Br calcd. 38.03%, found 38.35%) and the picrate at 158-160°. (c) The hydrochloride is extremely hygroscopic and has not been isolated in pure form. The hydrobromide (R = H, HBr) melts at 129-130° (Br calcd. 38.03%, found 37.85%) and the picrate at 147-149°.

pholines. The isomers were separated by preparative glc. The yields are given in Table I and in the Experimental. The description of the glc separation of the isomers may be found in the Experimental.

The reproducibility (6) of the syntheses is extremely good. Furthermore the two isomers (IVD and VC) with all three methyl groups situated on the same side of the ring plane are obtained in surprisingly good yield under suitable experimental conditions (see Table I). Further studies to elucidate the reaction mechanisms by starting the syntheses from optically active appropriately substituted diethanolamines are in progress in our laboratory.

Simple derivatives have been prepared from all eight isomers. The physical data are collected in Table II.

Nmr Spectra.

At low ($\approx$ -110°) temperature the ring inversion in morpholine is slow on the nmr time scale (7). We would thus expect different conformations for each of the isomers of 2,3,5-trimethyl- and those of 2,3,6-trimethylmorpholine at slow interconversion rates. Low-temperature carbon-13 nmr studies (8) on the isomers have shown that the molecules exist mainly in one conformation, which indicates that the population of one of these is too low to be detected by this method. It is realistic to assume that an aee (or eae or eea) conformation in the trimethyl-substituted morpholines is more favourable than a conformation with two axial methyl groups. In the following we thus treat the isomers as rigid molecules in the preferred chair conformation with at most one axial methyl substituent.

The methylene and methine proton nmr spectra look quite complex at 60 MHz and 100 MHz but most of the groups of signals are nicely separated at 270 MHz. The effect on the nmr pattern of increasing the frequency can be seen in Figure 1 where spectra of one isomer have been recorded at three different resonance frequencies. Theoretically, the CH- and CH_2-proton spectrum of the isomers consists of one K_3AXK_3' and one $ABXK_3''$ spectrum at 270 MHz if couplings across the ring are neglected. Cross-coupling of this type between protons in the two different parts of the morpholine ring, which has been detected in *e.g.* 2,6-dimethylmorpholine (9), has not been found in our spectra.

A. Coupling Constants.

The magnitude of the spin-spin coupling constants and chemical shifts for the vicinal methine-methine proton pair (K_3AXK_3' spin system) were determined directly from expanded spectra. The corresponding values for the methylene-methine proton part of the molecule ($ABXK_3''$ spin system) were obtained from line frequencies and equations for transition energy differences valid for an ABX spectrum (10,11). In this simplification the AB part of an $ABXK_3''$ spectrum would in principal be invariant compared to an ABX spectrum if couplings between A (or B) and K'' can be ignored. This assumption appears to be valid for most of the spectra (see below). We have only utilized the AB part of the spectrum to extract coupling constants due to the complicated pattern of the X-spectrum.

In the assignment of the different C-H protons (in the vicinal methine-methine proton pair) we have assumed that protons next to the more electronegative oxygen appear at lowest field. This assumption is in good agreement with the methine proton shieldings found in the spectrum of *cis*-2,6- and *cis*-3,5-dimethylmorpholine, in which the assignment is evident.

The differentiation between a CH_3-CH-CH_2-methine proton (next to oxygen in 2,3,6-trimethyl- and next to nitrogen in 2,3,5-trimethylmorpholine) and a CH_3-CH-CH-CH_3-methine proton is simple due to the more complicated pattern of the X-part of an $ABXK_3''$ spectrum compared to the X-part of a first-order K_3AXK_3' spectrum (see Figure 1).

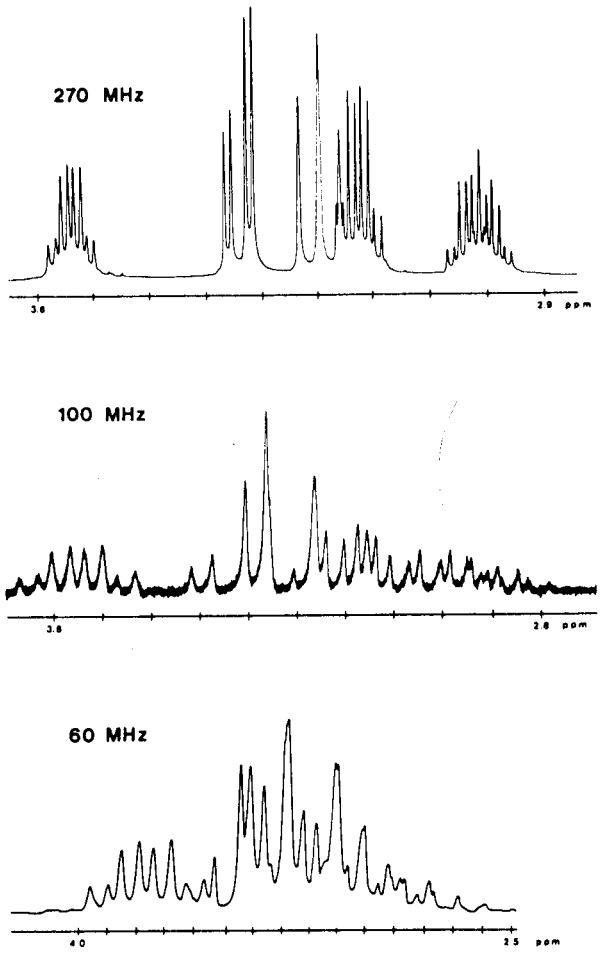

Figure 1. Methylene-methine part of ^{1}H-nmr spectra of compound IVD at three different frequencies.

Table III

Chemical Shifts (a) and Coupling Constants (a) of the Isomers of 2,3,5- and 2,3,6-Trimethylmorpholines at Ambient Temperature

Compound (b)	Chemical shift (ppm) CH_3	CH	CH_2 H_A H_B	NH (c)	Coupling constant (Hz) J (H,CH_3)	J (H-2,H-3)	J_{AB} (CH_2)	J (H,CH_2)
IVA	1.135 (2)	3.026 (2)			6.2			10.2
	1.002 (3)	2.552 (3)	3.749		6.5	8.6	10.7	2.8
	0.959 (5)	2.964 (5)	3.100	1.336	6.2			
IVB	1.158 (2)	3.059 (2)			6.2			3.4
	0.949 (3)	2.826 (3)	3.724		6.2	8.7	11.0	1.5
	1.304 (5)	3.042 (5)	3.618	1.483	7.0			
IVC	1.061 (2)	3.682 (2)			6.5			10.2
	1.181 (3)	2.865 (3)	3.767		6.7	2.8	11.6	1.9
	0.897 (5)	3.151 (5)	3.095	1.404	5.9			
IVD	1.190 (2)	3.746 (2)			6.7			10.8
	0.930 (3)	3.184 (3)	3.416		6.7	3.8	11.3	3.7
	0.960 (5)	2.952 (5)	3.265	1.608	6.2			
VA	1.147 (2)	3.141 (2)			6.4			10.3
	0.990 (3)	2.418 (3)	2.861	1.540	6.4	8.5	12.1	2.3
	1.126 (6)	3.569 (6)	2.560		6.0			
VB	1.092 (2)	3.442 (2)			6.4			4.1
	1.024 (3)	2.454 (3)	3.121		6.4	8.3	12.2	1.6
	1.330 (6)	3.977 (6)	2.689	1.512	6.7			
VC	1.069 (2)	3.785 (2)			6.4			10.5
	1.146 (3)	2.777 (3)	2.702		6.7	2.9	12.6	3.2
	1.128 (6)	3.578 (6)	2.562	1.766	6.4			
VD	1.220 (2)	3.80 (2)			6.7			10.2
	0.922 (3)	3.067 (3)	2.865		7.0	3.8	12.1	2.6
	1.056 (6)	3.813 (6)	2.532	1.425	6.4			

(a) Values determined from spectra run at 270 MHz (see Experimental). (b) Solid lines denote equatorial and dotted lines axial methyl groups. (c) The compounds are hygroscopic and were not specially dried before use. The accuracy in the chemical shift determination may thus be diminished.

The methyl and methine protons were identified by decoupling experiments at 100 MHz by sweeping the H_2-field stepwise through the signals in the methylene and methine proton region while the methyl proton spectrum was observed. In this way an assignment of the signals could be made, and rough values of the chemical shifts of the groups could be obtained. Accurate determinations were made from the 270 MHz spectra.

In Table III, chemical shifts and coupling constants determined at 270 MHz are summarized. The elucidated structures of the isomers are also included in this Table.

In analogy with results obtained from the isomers of 2,3,5,6-tetramethylmorpholine (12), it is possible to obtain information about the spatial orientation of the vicinal methine protons (and methyl groups) from the magnitude of the methine-methine proton coupling constants [J(H-2, H-3)]. The magnitude of an a_2a_3 coupling for the tetrasubstituted morpholines was found to be 8.7 Hz (12). Similarly, we have reported that an a_2e_3 coupling is smaller than an e_2a_3 spin-spin coupling, approximately 2.7 Hz and 3.9 Hz, respectively. Based on these observations it is evident from values in Table III that the 2- and 3-methyl groups of isomers IVA, IVB, VA and VB are in an equatorial-equatorial arrangement. The methine proton coupling constant in the 2,3,5-trimethyl-substituted isomer IVC [J(H-2,H-3) = 2.8 Hz] is smaller than that in isomer IVD [J(H-2,H-3) = 3.8 Hz]. It is thus most plausible that the methyl groups are arranged in the equatorial-axial (CH_3-2,e; CH_3-3,a) configuration in IVC and axial-equatorial (CH_3-2,a; CH_3-3,e) in isomer IVD. The same arguments can be used to stereochemically assign the 2- and 3-methyl groups in the 2,3,6-trimethyl-substituted isomers VC and VD (see structures given in Table III). It is interesting to note that the magnitudes of the various coupling constants are in excellent agreement with those extracted from spectra of the tetramethyl-substituted isomers (12).

The angular dependence of the vicinal coupling con-

stants shown in the spectra of the methylene-methine part of the molecules made it possible to obtain information about the stereochemistry of the 5-methyl-(2,3,5-isomers) and 6-methyl-(2,3,6-isomers) groups. The magnitudes of these coupling constants are given in Table III. It is evident that the six isomers with J (H,CH_2) values (J_{AX} or J_{BX} in the spin system) in the range 10.4 ± 0.4 Hz are equatorially methyl-substituted in the 5- and 6-position. The magnitudes correlate well with an axial-axial proton coupling (10.3 Hz) found in 2,6-dimethylmorpholine (9,13). The remaining compounds (IVB and VB) with lower values are most probably axially substituted. The spectrum of the 4-benzylsubstituted-2,3,5-trimethylmorpholine IVB confirms this suggestion by giving a typical AB-spectrum of the benzylic methylene protons (14).

In Table IV methylene-methine proton coupling constants for some methyl substituted morpholines are summarized. The coupling constants were derived from spectra run at ambient temperature (13,15).

Table IV

Averaged Vicinal CH_2-CH Spin-Spin Coupling Constants (a) in Methyl-Substituted Morpholines

Morpholine	J_{aa} (Hz)	J_{ae} (Hz)	J_{ea} (Hz)	J_{ee} (Hz)
2,6-di	10.3	2.1	4.3	0.9
trans-2,5-di	10.7 ± 0.4	2.2	2.9	
2,3,6-tri	10.3 ± 0.2	2.7 ± 0.5	4.1	1.6
2,3,5-tri	10.4 ± 0.4	3.4	2.8 ± 1.0	1.5

(a) Values extracted from spectra run at ambient temperature.

A comparison between the di- and tri-substituted isomers reveals that there is a good deal of scatter in the values of an a_6e_5 and an e_6a_5 coupling. The a_6a_5 coupling constants for the different compounds are, however, in good agreement. The scatter in the *cis*-coupling constants may probably be attributed to the difference in relative orientation of the methyl groups on the opposite side of the ring in the isomers of 2,3,5- and 2,3,6-trimethylmorpholine.

Long-range coupling between the low-field methylene proton and a vicinal axial methyl group in the 5 and 6 position has been detected for compounds IVB and VB. The couplings are only of the order of 0.5 Hz and do not disturb the simplified ABX-treatment of the other coupling constants.

B. Chemical Shifts.

It is known that hydrogen atoms which are subject to steric compression generally exhibit a shift to lower field. Cheney (16) has given an expression for the magnetic deshielding of protons in hydrocarbons. This equation alone can probably not describe the interaction between proximate protons in a system involving heteroatoms, α to the (carbon)-hydrogen atoms, but a general downfield shift of *e.g.* axial methyl groups in the morpholine derivatives is expected. If the chemical shift of the equatorial 5-methyl protons in compound IVA is compared to shifts of similar protons in compound IVB, we can see that the axial methyl protons in the latter compound are shifted to lower field (93.2 Hz downfield at 270 MHz). There are probably many atoms in the molecule that interact with the methyl group, but it is evident from values in Table III that the main interacting atoms are an axial 3-CH-proton (shifted 74.0 Hz downfield) and a 6-methylene proton (shifted 140.0 Hz to lower field).

A similar shift to lower field is found for the 6-methyl protons, an axial 2-methine proton and one of the 5-methylene protons in compound VB compared to VA. It is also interesting to note that the chemical shift of axial and equatorial methylene protons, which are not in "steric contact" with axial methyl protons are nearly constant from isomer to isomer.

From the values in Table III and the fact that methylene protons are shifted to lower field by steric compression, we suggest that the axial methylene proton in IV is most downfield (see IVB), whereas the opposite assignment is valid for protons next to nitrogen (in the 5-position in V).

Methyl protons in a vicinal *cis*-arrangement (*e.g.* in IVC, IVD, VC and VD) also give rise to a downfield shift of axial methyl protons if comparisons are made with similar protons in a *trans* configuration, whereas the equatorial methyl protons are found at somewhat higher field. This means that the vicinal methyl groups are sufficiently separated in space to be out of "steric contact" with each other. The downfield shift of the axial methyl protons is probably caused by van der Waals interactions with protons on the opposite side of the morpholine ring. Possible interacting proton-proton pairs are *e.g.*: [$3\text{-}CH_3{}^a$, 5-CH^a] in isomer IVC and [$2\text{-}CH_3{}^a$, 6-CH^a] in VD. Quite large shifts to lower field are observed for these protons (see Table III), but more data is probably needed to fully interpret these observations. We will expand the discussion further in connection with a forthcoming paper (8) on carbon-13 nmr chemical shifts of these compounds.

EXPERIMENTAL

Glc.

The preparative work was for the most part carried out as described earlier (5), but a few modifications were made. It was found convenient and time-saving to first separate the isomers of 2,3,5-trimethylmorpholine into two fractions (IVA + IVB and IVC + IVD, respectively) on a short column (4.5 m x 6.7 mm with 20% Carbowax 20M + 3% potassium hydroxide on Chromosorb A 60/80; temperature 130-140° and gas flow about 60 ml. of nitrogen/minute). The pure isomers were then obtained as described for 2,3,5,6-tetramethylmorpholine.

2,3,6-Trimethylmorpholine gave only three peaks on our preparative columns with Carbowax 20M as stationary phase. Analytical glc showed that one of the three isolated fractions was a mixture of isomer VB and VC. A preparative column (4.5 m x 6.2 mm) with Carbowax 1000 instead of Carbowax 20M gave a fairly good separation of these isomers.

Due to the small differences in retention time it was necessary to do the separation steps twice to obtain the isomers with a purity better than 99%.

Preparation of 1,1′,2-Trimethyldiethanolamine (IIIa).

One hundred g. (1.39 moles) of *trans*-2,3-epoxybutane (I), 105 g. (1.4 moles) of DL-alaninol (IIa) and 100 ml. of 96% ethanol were heated together in a stainless steel autoclave at 120° for 5 hours. The reaction mixture was distilled, which gave 187 g. (91%) of 1,1′,2-trimethyldiethanolamine (IIIa) (a mixture of two racemates: 1) 1S,2R; 1′S and 1R,2S; 1′R; 2) 1S,2R; 1′R and 1R,2S; 1′S); b.p. 112-123° (8 mm).

Preparation of 2,3,6-Trimethylmorpholine (V).

1,2,2′-Trimethyldiethanolamine (IIIb) (147 g., 1 mole) was added to 750 ml. of 70% sulfuric acid, with stirring and cooling. The mixture was kept in a glass autoclave at 140-150° for 15 hours. An excess of 20% sodium hydroxide solution was then added with stirring and efficient cooling. The product was extracted with diethyl ether, and the ether extract dried over sodium sulfate. Evaporation of the ether gave a crude product which was directly analyzed, and after distillation 2,3,6-trimethylmorpholine (V) (112 g., 87%), b.p. 145-160°, was obtained.

Preparation of *N*-Benzyl-2,3,5-trimethylmorpholine (VIII).

N-Benzyl-1,1′,2-trimethyldiethanolamine (VIIa) (119 g., 0.5 mole) was added to 350 ml. of 70% sulfuric acid with stirring and cooling. The mixture was kept in a glass autoclave at 140-150° for 15 hours. An excess of 20% sodium hydroxide solution was added with stirring and efficient cooling. The organic layer was separated and the residue extracted with diethyl ether. The combined organic phases were dried with sodium sulfate, filtered and evaporated. Distillation gave a fraction of 101 g. (92%) of *N*-benzyl-2,3,5-trimethylmorpholine (VIII), b.p. 86-90° (0.1 mm).

Nmr Spectra.

The compounds were dissolved in deuteriochloroform (containing a few drops of TMS) in concentrations of about 6 mole %. Spectra were run on a Varian T 60, a JEOL MH-100 nmr spectrometer and a Bruker 270 MHz FT-nmr instrument. All spectra were obtained at ambient temperature. Internal lock on either TMS (continuous wave spectra) or deuterated chloroform (FT spectra) was utilized. In the 270 MHz runs, 10-20 free induction decays were accumulated with a total delay time of 5 seconds between the pulses: 16 K points were sampled in a sweep range of 2200 Hz, which is equivalent to steps of 0.275 Hz. The resolution could be adjusted by optimizing the slope and height of the decay for each spectrum.

The decoupling experiments were performed at 100 MHz. The sweep rate and scale expansion in these experiments was 0.1 Hz/seonce and 3.0 Hz/cm, respectively. The beat from the H_2 field was stepwise (10-15 Hz each time) passed through the methylene and methine proton region while the methyl proton spectrum was observed. In this way approximate values for methine proton shifts could be obtained.

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(6) The largest deviation in the yields in Table I in 5 experiments of each synthesis is ± 3% units. The corresponding deviation in the syntheses of 2,3,5,6-tetramethylmorpholine was also ± 3% units; see Table I in reference (5).

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