Enamine Chemistry. Part 25.[1] Preparation and Carbon-13 Nuclear Magnetic Resonance Spectra of *N*-Alkyl-morpholines and -pyrrolidines. Comparison with the Carbon-13 Spectra of the Corresponding Acyclic Enamines

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The preparation and ^{13}C chemical shifts of a series of *N*-alkyl-morpholines and -pyrrolidines are reported. The α- and β-effects of the amine moieties have been evaluated and compared with those operating in the corresponding enamines and with the α- and β-effects of an isopropyl group. The factors affecting the relative magnitude of these effects are discussed.

We have recently studied [2] the ^{13}C spectra of a series of acyclic enamines derived from morpholine and pyrrolidine. In an attempt to isolate the effects of the conjugated π-electron system on the ^{13}C chemical shifts we have now determined the ^{13}C spectra of the corresponding amines derived by borohydride reduction of the iminium salts obtained by C-2 protonation of the enamines. In particular, we were interested in evaluating the factors which affect the magnitude of the α-effect of the amine function on the chemical shift of C-1 since in the enamine series we had found [2] this to be not appreciably larger than the α-effect of an isopropyl group. Accordingly, a number of other amines have also been prepared, either by *N*-alkylation of morpholine or pyrrolidine, or by reaction of a Grignard reagent with an iminium salt.

The chemical shifts of the *N*-alkylmorpholines are recorded in Table 1 and those of the *N*-alkylpyrrolidines in Table 2. Where possible the chemical shifts were determined for the neat liquids, as had been the case for the enamines.[2] Otherwise solutions in chloroform were used since, as shown by the two sets of values obtained for compound (8a) (Table 1), there was no significant difference in the chemical shifts under these conditions. The assignments were made from proton noise decoupled and off-resonance decoupled spectra, and the relative intensities of the signals. These assignments are mostly straightforward and unambiguous, except for

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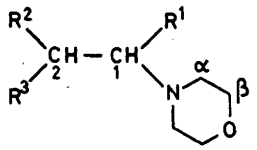
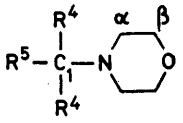
[2] M. G. Ahmed and P. W. Hickmott, *J.C.S. Perkin II*, 1977, 838.

TABLE 1

^{13}C Chemical shifts of *N*-alkylmorpholines *



(I)



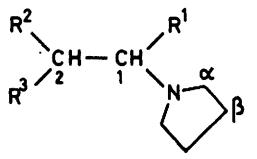
(II)

Compound						^{13}C Chemical shifts								
No.	R^1	R^2	R^3	R^4	R^5	C-1	C-2	R^1	R^2	R^3	R^4	R^5	α-CH_2	β-CH_2
(1a)				H	H	46.5							55.9	66.8
(2a)	H	H	H			52.8	12.0						53.8	67.0
(3a)	Me	H	H			54.9	18.55	18.55					49.7	67.4
(4a)				Me	Me	53.3					25.8	25.8	46.8	67.8
(5a)				H	Bu^t	71.1						33.2(C) 28.0(CH_3)	56.6	67.2
(6a)	H	Me	H			61.1	20.1		11.9				54.3	67.0
(7a)	H	Et	H			59.0	29.2		20.8(CH_2) 14.15(CH_3)				54.3	67.0
(8a)	H	Me	Me			67.6	25.3		20.8	20.8			54.5	66.9
						67.6 †	25.2 †		20.8 †	20.8 †			54.5 †	67.0 †
(9a)	Me	Me	H			61.2	26.45	13.9	11.1				49.5	67.5
(10a)	Et	Me	H			68.1	22.4	22.4(CH_2) 11.7(CH_3)	11.7				49.4	67.6
(11a)	Pr^i	Me	Me			75.85	28.8	28.8(CH) 21.3(CH_3) 20.9(CH_3)	21.3	20.9			52.1	67.8
(12a)	Et	Me	Me			72.5	29.9	20.2(CH_2) 13.5(CH_3)	21.1	20.2			50.5	67.6
(13a)				Et	Me	57.8 †					27.95 †(CH_2) 8.2 †(CH_3)	19.5 †	45.9 †	68.1 †
(14a)				Et	Et	59.8 †					26.6 †(CH_2) 8.95 †(CH_3)	26.6 †(CH_2) 8.95 †(CH_3)	47.15 †	68.4 †

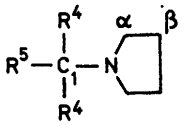
* As neat liquids relative to tetramethylsilane. † In $CHCl_3$ solution.

TABLE 2

^{13}C Chemical shifts of *N*-alkylpyrrolidines *



(I)



(II)

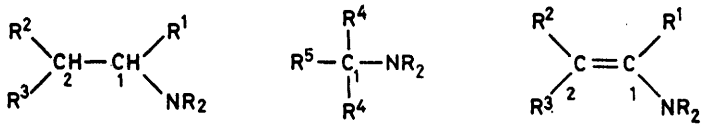
Compound						^{13}C Chemical shifts								
No.	R^1	R^2	R^3	R^4	R^5	C-1	C-2	R^1	R^2	R^3	R^4	R^5	α-CH_2	β-CH_2
(1b)				H	H	42.1							56.5	24.7
(2b)	H	H	H			50.3	14.4						54.0	24.0
(3b)	Me	H	H			54.8	22.2	22.2					51.8	24.0
(4b)				Me	Me	51.9					26.3	26.3	46.0	24.6
(5b)				H	Bu^t	69.0						32.9(C) 28.4(CH_3)	56.9	24.4
(6b)	H	Me	H			58.5	22.65		12.1				54.3	24.0
(7b)	H	Et	H			56.2	31.7		21.0(CH_2) 14.2(CH_3)				54.3	23.9
(8b)	H	Me	Me			65.1	27.9		21.1	21.1			54.5	23.9
(10b)	Et	Me	H			65.35	23.55	23.55(CH_2) 10.0(CH_3)	10.0				50.6	24.0
(11b)	Pr^i	Me	Me			70.5	29.6	29.6(CH) 21.3(CH_3) 20.1(CH_3)	21.3	20.1			51.25	24.8
(12b)	Et	Me	Me			69.1	31.3	21.5(CH_2) 13.6(CH_3)	20.4	18.7			50.4	24.1

* As neat liquids relative to tetramethylsilane.

compounds (9a) and (12a). In assigning the signals of (9a) use was made of the parameters introduced by Beierbeck and Saunders [3] to confirm the assignment of the R^1 and R^2 methyl groups. In general it is difficult to apply this technique to acyclic amines owing to uncertainties as regards the conformational isomer distribution and to steric interactions which may cause poor rotational averaging of alkyl groups and hence result in chemical shifts which deviate from the expected value. the methyl carbons of the isopropyl group. This nonequivalence was readily discernible in (12b), the R^1 methylene and the R^2 and R^3 methyl signals being well resolved. In (12a) the R^2 and R^3 methyl groups appeared to be equivalent at first since the signal at 20.2 p.p.m. was clearly due to two carbons. However, expansion of this region and examination of the fully proton coupled spectrum clearly demonstrated that this signal consisted of a triplet superimposed on a quartet in

TABLE 3

Contributions ($\Delta\delta c$) * of the amine moiety to the ^{13}C chemical shift in amines (I) and (II) and the corresponding enamines (III) †



(I) (II) (III)

a; R_2N = morpholino

b; R_2N = pyrrolidino

	Compound					Morpholine derivatives (a)				Pyrrolidine derivatives (b)			
						ΔδC-1		ΔδC-2		ΔδC-1		ΔδC-2	
No.	R^1	R^2	R^3	R^4	R^5	Amine	Enamine	Amine	Enamine	Amine	Enamine	Amine	Enamine
1				H	H	+48.8 (+26.4)				+44.4			
2	H	H	H			+47.1 (+25.9)		+6.3 (+5.8)		+44.6		+8.7	
3	Me	H	H			+39.0 (+18.1)		+3.15 (+3.8)		+38.9		+6.8	
4				Me	Me	+28.3 (+7.7)		+1.7 (+2.9)		+26.9		+2.2	
5				H	Bu^t	+39.5 (+21.7)		+5.2 (+2.9)		+37.4		+4.9	
6	H	Me	H			+45.7 (+26.5)	+25.6 (+23.1)	+4.2 (+4.9)	−40.1 (−14.6)	+43.1	+21.2	+6.75	−43.4
							+24.6 ‡ (+22.6)		−28.2 ‡ (−14.9)		+22.2 ‡		−38.6 ‡
7	H	Et	H			+46.0 (+25.9)	+26.7 (+23.7)	+4.4 (+4.9)	−36.7 (−11.0)	+43.2	+22.4	+6.9	−39.6
8	H	Me	Me			+43.5 (+24.9)	+26.1 (+23.4)	+0.3 (+0.7)	−17.7 (−12.6)	+41.0	+25.2	+2.9	−26.4
9	Me	Me	H			+36.4 (+15.8)	+21.6 (+17.3)	+1.65 +0.9 (+2.0)	−25.7 (−8.0)				
10	Et	Me	H			+34.0 (+13.5)	+18.5 (+15.7)	+0.2 (+0.4)	−25.1 (−6.8)	+31.25	+15.0	+1.35	−32.3
11	Pr^i	Me	Me			+26.85	+14.0	+3.1	−3.4	+21.5	+11.4	+3.9	−5.1
12	Et	Me	Me			+30.6	+18.5	+2.0 +0.3	−8.5	+27.2	+14.2	+3.4 +0.7	−12.6
13				Et	Me	+21.0		−1.45 +0.8					
14				Et	Et	+17.4		+1.4					

* Difference in chemical shift between the corresponding alkane [4a,8] and amine or alkene [7b] and enamine,[2] in which a hydrogen of the alkane or alkene is replaced by NR_2 [*i.e.* $\Delta\delta c = \delta(R{-}NR_2) - \delta(R{-}H)$]. Negative values indicate high field shifts. † Figures in parentheses indicate the corresponding α- or β-shifts caused by an isopropyl group in an alkane or alkene [*i.e.* $\delta(R{-}CHMe_2) - \delta(R{-}H)$], calculated from values reported in refs. 4*a*, 7*b*, 8, and 24. ‡ Values for the *cis*-enamines.

In (9a) we assumed that the rotamer having only two *gauche*-butane interactions about the C-1–N bond was populated to a predominant extent. In systems having equivalent C-1–N rotamers [*i.e.* (1) and (4)] these parameters yielded quite accurate predictions of the chemical shifts. Compounds (12a and b) contain an asymmetric centre which engendered magnetic nonequivalence [4] in the proton coupled spectrum and could therefore be assigned to the R^1 methylene group and the R^3 methyl group. The methyl carbons of the isopropyl groups in (11a and b) are diastereotopic and also give rise to two well resolved signals.

Introduction of substituents at C-2 [*i.e.* R^2 and R^3 in

[3] H. Beierbeck and J. K. Saunders, *Canad. J. Chem.*, 1976, **54**, 632.

[4] (*a*) J. I. Kroschwitz, M. Winokur, H. J. Reich, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1969, **91**, 5927; (*b*) L. P. Lindeman and J. Q. Adams, *Analyt. Chem.*, 1971, **43**, 1245.

(I)] results in weak deshielding of the α-methylene carbons of the amine moiety (δ-interaction [5]) [compare (6)—(8) with (2); Tables 1 and 2]. A similar deshielding occurs in enamines [2] except that the effect is much greater when the δ-substituent is *cis*-orientated to the amine moiety than when *trans*. Conversely, introduction of substituents at C-1 [*i.e.* R^1 in (I), R^4 and R^5 in (II)] results in marked shielding of the α-methylene carbons (γ-interaction [6]) [compare (2) and (4) with (I); (3) with (2); (9), (10), (13), and (14) with (6); and (11) and (12) with (8); Tables 1 and 2]. The only exception is the introduction of a t-butyl group at C-1 which surprisingly causes weak deshielding of the α-methylene carbons [compare (5) with (I)]. Similar effects of an R^1 substituent are discernible in the enamine series.[2]

The contribution ($\Delta\delta c$) of the amine moiety to the chemical shift of C-1 and -2 has been derived from the expression $\Delta\delta c = \delta(\text{amine}) - \delta(\text{alkane})$. These results are summarised in Table 3, together with the values previously obtained [2] for the corresponding enamines, and clearly demonstrate that the α-effect of the amine moiety (ΔδC-1) is considerably greater in the amine series than in the enamine series [compounds (6)—(12)]. In both series the *apparent* α-effect (*i.e.* assuming the the α- and β-effects of other substituents are not affected by the steric perturbations caused by the introduction of a bulky amine moiety, which of course is not the case) decreases with increasing substitution at C-1 and, in the case of the amines, to a lesser extent with substitution at C-2. The values range from +48.8 in (1a) to +17.4 p.p.m. in the most sterically hindered system we have prepared [(14a)]. Interestingly, the ratio ΔδC-1 (enamine) : ΔδC-1(amine) is roughly constant and averages to 0.55 for morpholine and 0.52 for pyrrolidine. The reduction in the ΔδC-1 values with increasing substitution can obviously be attributed to steric perturbations resulting in possible bond elongation, angle distortion, or hybridization changes.[7,8] Since the isopropyl group is roughly sterically equivalent to the morpholine moiety, and the β- and γ-effects of the methyl groups should therefore be similar to those of the α-methylene groups of the amine ring, we have evaluated the effect of an isopropyl group on the ^{13}C chemical shift of C-1 and -2 in alkanes and alkenes [*i.e.* $\Delta\delta c = \delta(R{-}CHMe_2) - \delta(R{-}H)$]. These values have been included in parentheses in Table 3 for comparison purposes.

There are several interesting features about these results. First the α-effect (ΔδC-1 value) of an isopropyl group in an alkane, while varying with the degree of substitution, shows little difference to its value in an alkene. This rules out the difference in electronegativity of sp^2 compared to sp^3 hybridised carbon as a reason for the large change in the ΔδC-1 values of the amine moiety. Secondly the β-effect (ΔδC-2 value) of an isopropyl group, although also varying with the degree of substitution, shows a striking similarity to the β-effect of the morpholine moiety. This confirms the view [9] that the β-effects of substituents are not a manifestation of inductive electron withdrawal. Finally, as we have noted previously,[2] the α-effects of the morpholine and pyrrolidine rings are similar to that of an isopropyl group when attached to a carbon–carbon double bond despite the electronegativity differences of the substituent atom and the fact that the β-effect of methyl or methylene groups are independent of the atom through which the effect is transmitted.[7b]

The reduction in the α-effect (ΔδC-1 value) of an amine moiety in an enamine compared to the correspondingly substituted amine is a significant phenomenon which does not appear to have received attention before, despite the fact that the phenomenon is not confined to enamines. A similar reduction in the deshielding ΔδC-1 contribution of an ethoxy-group occurs in enol ethers [*i.e.* CH_3CH_2OEt(ΔδC-1 + 60.5*); $CH_2{=}CHOEt$ [10] (ΔδC-1 + 30.7)] and of halogens in vinyl halides [CH_3CH_2X [11] (X = Cl, ΔδC-1 + 33.5; X = Br, ΔδC-1 + 22.5); $CH_2{=}CHX$ [12] (X = Cl, ΔδC-1 + 2.6; X = Br, ΔδC-1 − 7.9)].† Several effects could be responsible for this reduction in the deshielding contribution of substituents attached to a carbon–carbon double bond, the relative importance of which will depend upon the nature of the substituent being considered. Changes in the hybridization of the X atom and C-1–X bond length relative to that in the corresponding alkane derivative will alter the anisotropic contribution of the X atom (or C–X bonds) to the C-1 chemical shift, but in the case of nitrogen this would not be expected to be large.[11] Seidman and Maciel [14] have emphasized the importance of changes in electron distributions, resulting from different orbital electron populations without necessarily different net electron densities, in causing substantial changes in chemical shifts. In enamines the σ-electron withdrawal (I_s) by the nitrogen will be attenuated by the π-electron repulsion (I_π effect) of the nitrogen lone pair, thus resulting in a decreased σ-electron deficiency at C-1 in an enamine compared to C-1 in an amine. However, in terms of the Karplus–Pople

* Diethyl ether: δc (neat liquid) 66.2 (α-CH_2), 15.5 (β-CH_2)

† A reduced α-effect has been noted [13] in geminal dichloroethylenes and attributed to the mutual interaction of the geminal substituents, an explanation which is not applicable here.

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[6] D. M. Grant and B. V. Cheney, *J. Amer. Chem. Soc.*, 1967, **89**, 5315.

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[14] K. Seidman and G. E. Maciel, *J. Amer. Chem. Soc.*, 1977, **99**, 659.

theory of ^{13}C shifts,[15] the loss of π-electron density at C-1 would result in contraction of the $2p$ orbital at this position and a higher $\langle r^{-3}\rangle_{2p}$ value with consequent *increased* deshielding (*i.e.* a larger ΔδC-1 value). This is contrary to observations, possibly because π-electron deficiency at C-1 can be compensated for by mesomeric electron donation from the nitrogen.[2] A more attractive possibility is that there is an increase in the effective excitation energy (ΔE), since it is known that the introduction of an electron donating substituent into an alkene raises the energy of the LUMO relative to that of the unsubstituted alkene.[16] This would cause a reduction in the local paramagnetic contribution to the shielding and therefore a reduction in the ΔδC-1 value. Recent estimates [17] of the excitation energy show that there is a wide range of variation in ΔE even in a related series of compounds, but that the introduction of a methyl substituent lowers the ΔE value at the position of substitution (α) and increases the ΔE value at the β-position. If an amine substituent behaved in the same way this again would result in an increased ΔδC-1 value, contrary to observation. Finally, there is the possibility of reduction in the bond-order term which would also result in decreased deshielding and a lower ΔδC-1 value.

Clearly the situation is complex and it is not possible at present to designate the factors primarily responsible for the reduced ΔδC-1 values which we have observed.

EXPERIMENTAL

N-Methylpyrrolidine, *N*-methylmorpholine, and *N*-ethylmorpholine were obtained commercially. *N*-Ethyl- and *N*-propyl-pyrrolidine were prepared in an analogous manner to a reported method for the preparation of *N*-allylmorpholine.[18] *N*-Propylmorpholine, *N*-isopropylmorpholine, *N*-isopropylpyrrolidine, *N*-t-butylmorpholine, and *N*-t-butylpyrrolidine were prepared by literature methods.[19-21] The remaining amines were prepared by the following general methods.

Method A. Neopentyl tosylate (70%, m.p. 38°) was prepared in an analogous manner to isopropyl tosylate.[22] A mixture of the amine (0.1 mol) and neopentyl tosylate (0.033 mol) was heated under reflux for 24—70 h. The two layers which formed were separated and the top layer dried (K_2CO_3) and distilled under reduced pressure to give the product.

Method B.[23] Glacial acetic acid (90 ml) was added dropwise over 1—1.5 h to a mixture of the enamine (3.0 g) and sodium borohydride (6 g) in dry tetrahydrofuran (150 ml) at room temperature under nitrogen. The mixture was then heated under reflux for 1 h, cooled, and basified with 10% aqueous sodium hydroxide solution. The mixture was extracted with ether and the extracts dried ($MgSO_4$) and concentrated to give the crude product which was purified by distillation.

Method C. A solution of 3-*N*-morpholinopent-2-ene (4 g, 0.025 mol) in dry benzene (100 ml) was saturated with hydrogen chloride gas at 5° over a period of 1.5 h. The solvent was removed *in vacuo* at room temperature and the residual iminium salt was suspended in dry ether (60 ml). The suspension was heated under reflux and a solution of the Grignard reagent, prepared from methyl or ethyl iodide (0.037 5 mol) and magnesium (0.9 g) in dry ether (20 ml), was added dropwise with efficient stirring. The mixture was then heated under reflux for 2 h, cooled, and water (60 ml) added. The mixture was heated under reflux for a further 1 h, cooled, and the ether layer separated off. The aqueous layer was extracted with ether and the combined ether layer and extracts were extracted with 2N-hydrochloric acid (5 × 5 ml). The acid extracts were basified with concentrated sodium hydroxide solution and extracted with ether. The ether extracts were dried ($MgSO_4$) and evaporated to give the pure products.

Preparative data for the amines obtained by Methods A—C are summarised in Table 4.

TABLE 4

N-Alkyl-morphilines and -pyrrolidines *

Compound	Method	Yield (%)	B.p. [°C(*p*/mmHg)]
(5a)	A	45	62—63(14)
(5b)	A	64	51(18)
(7a)	B	75	77—78(22)
(7b)	B	60	55—56(22)
(8a)	B	30	67(22)
(8b)	B	60	45—46(22)
(9a)	B	43	76—78(24)
(10a)	B	50	95—96(22)
(10b)	B	45	76—77(27)
(11a)	B	80	54—55(0.2)
(11b)	B	50	93—94(22)
(12a)	B	50	93—94(14)
(12b)	B	50	76—78(16)
(13a)	C	19	
(14a)	C	30	

* Details of the ^1H n.m.r. spectra can be obtained from the authors on request.

The ^{13}C n.m.r. spectra were recorded at 20 MHz with a Varian CFT-20 spectrometer for neat liquids unless stated otherwise, and the ^1H n.m.r. spectra were recorded at 60 MHz with a Varian EM 360 spectrometer for chloroform solutions. All chemical shifts are given in p.p.m. relative to internal Me_4Si. Accurate mass measurements were determined with an A.E.I. MS 9 mass spectrometer operating at 70 eV. The structures were confirmed by mass spectrometry (including accurate mass measurement of the molecular ions) and ^1H n.m.r. spectroscopy.

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