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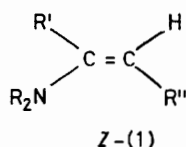
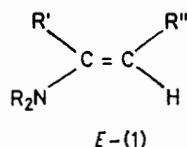
PERKIN TRANSACTIONS I Organic and Bio-organic Chemistry

Enamines. Part 40.¹ Carbon-13 Nuclear Magnetic Resonance Spectroscopy in the Determination of Aliphatic Enamine Configurations

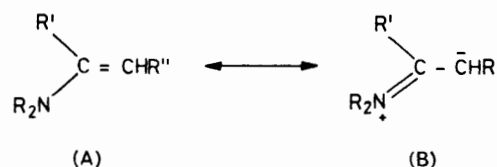
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The configurations of several enamines have been studied by ¹³C n.m.r. spectroscopy. The results obtained show that the chemical shift of the β-carbon atom is very sensitive to steric influence, an effect which can be correlated with the enamine configuration.

It has previously been reported^{2,3} that the n.m.r. spectra of the *E*- and *Z*-isomers of the enamines (1) show



that of the *Z*-isomer prevents the amine residue from taking up a conformation favourable to *p*-π overlap. Accordingly, a *Z*-configuration was assigned to the



a high degree of differential shielding for their ethylenic protons. This may be explained on the basis of the enamine mesomerism (A) ↔ (B) where the R'' sub-

stituent of the *Z*-isomer prevents the amine residue from taking up a conformation favourable to *p*-π overlap. Conversely, in the *E*-isomer (B) steric inhibition being

TABLE I

Compound	R ₂ N	Enamine Structure		Configuration *	C _α	C _β	Ref.
		R'	R''				
(3)	Morpholino	Ph	Me	<i>E</i> 98% <i>Z</i> 2%	154.2 <i>a</i>	103.4 114.5	3
(4)	Piperidino	Ph	Me	<i>E</i> 95% <i>Z</i> 5%	151.3 <i>a</i>	99.4 109.8	4
(5)	Diethylamino	Ph	Me	<i>E</i> 90% <i>Z</i> 10%	147.7 <i>a</i>	100.0 113.1	3
(6)	Diethylamino	Et	Me	<i>E</i> 86% <i>Z</i> 14%	148.9 <i>a</i>	98.4 115.4	2
(7)	Morpholino	Thienyl	Me	<i>E</i> 96% <i>Z</i> 4%	143.9 <i>a</i>	102.9 112.3	3
(8)	Morpholino	Ph	Ph	<i>E</i> 88% <i>Z</i> 12%	150.9 149.6	106.1 112.1	5
(9)	Morpholino	PhCH ₂	Ph	<i>E</i> 95% <i>Z</i> 5%	147.2 148.1	106.0 112.3	6
(10)	Morpholino	Me	Ph	<i>E</i> 97% <i>Z</i> 3%	146.2 <i>a</i>	104.7 111.3	6

* *E/Z* Ratios were measured from ¹H n.m.r. at 39 °C in CDCl₃ as solvent. *a* Too small to be detectable.

¹ Part 39, D. Pocar, R. Stradi, and P. Trimarco, *Tetrahedron*, 1975, **31**, 2427.

² R. Stradi and D. Pocar, *Chimica e Industria*, 1971, **53**, 265.

³ R. Stradi, D. Pocar, and C. Cassio, *J. Chem. Soc. Perkin I*, 1974, 2671.

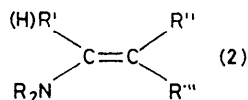
⁴ P. Y. Sollenberger and R. B. Martin, *J. Amer. Chem. Soc.*, 1970, **92**, 4261.

⁵ M. E. Munk and Y. K. Kim, *J. Org. Chem.*, 1965, **30**, 3705.

⁶ D. Pocar, G. Bianchetti, and P. Dalla Croce, *Gazzetta*, 1965, **95**, 1220.

absent, there is greater shielding of the olefinic proton and the signal is to higher field.

We now report the results obtained for the ^{13}C n.m.r. spectra of the enamines (2) which have been studied in

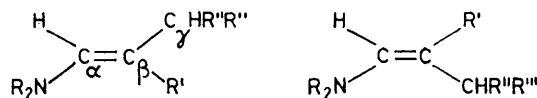


order to evaluate the potential of this technique in distinguishing between *Z*- and *E*-isomers.

RESULTS

In Tables 1 and 2 the ^{13}C chemical shifts of the relevant carbon atoms of the *E*- and *Z*-isomers of enamines derived from ketones (Table 1) and aldehydes (Table 2) are listed.

TABLE 2



Compound	R ₂ N	R'	R''	R'''	Configuration *	C _α	C _β	C _γ	Ref.
(11)	Morpholino	H	H	H	<i>E</i> pure form	141.0	95.7	15.4	7
					<i>Z</i> pure form	140.0	107.4	12.4	
(12)	Morpholino	Ph	H	H	<i>E</i> 85%	138.5	123.7—129.2	15.5	8
					<i>Z</i> 15%	136.4	123.7—129.2	22.8	
(13)	Morpholino	Ph	H	Me	<i>E</i> 60%	138.3	131.2	22.1	8
					<i>Z</i> 40%	135.7	120.8	30.3	
(14)	Morpholino	Ph	Me	Me	<i>E</i> 20%	138.8	124.9—129.9	28.7	<i>a</i>
					<i>Z</i> 80%	134.7	124.9—129.9	35.2	
(15)	Piperidino	Ph	H	H	<i>E</i> 88%	134.4	121.6	15.5	<i>a</i>
					<i>Z</i> 12%	137.7	112.9	22.8	
(16)	Pyrrolidinyl	Ph	H	H	<i>E</i> 80%	137.4	110.1	15.7	<i>a</i>
					<i>Z</i> 20%	135.6	106.7	22.9	
(17)	Pyrrolidinyl	Ph	H	Me	<i>E</i> 65%	136.7	117.3	22.2	<i>a</i>
					<i>Z</i> 35%	134.2	113.5	30.4	

* The *E/Z* ratios were measured from the ^1H n.m.r. spectra recorded on the equilibrium mixture at 39 °C in CDCl_3 for all enamines except for (11) where the two isomers were independently prepared. *a* See the Experimental section.

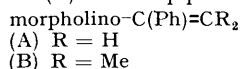
All the enamines are mixtures of the *E*- and *Z*-isomers, the molecular ratios for which have been determined by ^1H n.m.r. spectroscopy.^{2,3,8}

DISCUSSION

Table 1 shows that in the enamines derived from ketones the β -olefinic carbon atoms of the *Z*-isomers always resonate at lower field compared with those for the corresponding *E*-isomers.

This is clearly due to the reduced degree of p - π overlap consequent on the steric hindrance exercised by the R'' substituent in the *Z*-configuration.* Essentially, this agrees with the differences in the chemical shifts of the

* The importance of steric hindrance on the chemical shifts of the β -carbon atoms is well evidenced by the values found for (A) ⁹ 91.2 p.p.m., and (B) ¹⁰ 122.7 p.p.m. This large difference



(31.5 p.p.m.) cannot be explained simply by the substitution effect on the β -carbon atom and shows how the p - π overlap, easy for (A) and prevented for (B), play a very important role.

† For the enamine (9) the β - ^1H values of the chemical shift are even reversed. This probably occurs because of the shielding effect of the benzylic phenyl group on the olefinic proton in the *Z*-enamine. This sterical situation is clearly evidenced by molecular models.

olefinic protons of the *E-Z* pairs observed by ^1H n.m.r. spectroscopy. However, the differences in the chemical shifts of the olefinic protons are generally not very large. Moreover, an overlap of the ranges is often observed,[†] whereas the ^{13}C chemical shifts values generally are widely different, the ranges never overlapping. This fact is clearly evidenced from Figure 1 in which the shifts of β - ^{13}C and β - ^1H of the enamines (3)—(10) are reported.

This better separation occurs since the influence of the anisotropic groups is relatively insignificant in carbon magnetic resonance because of the far larger range of the ^{13}C chemical shifts in comparison with ^1H shifts. In fact, the anisotropic term remains essentially constant for ^{13}C and ^1H .¹¹

The enamines derived from aldehydes can be divided into two types. First, for compounds where a hydrogen

atom is bound to the β -carbon atom the spectroscopic behaviour parallels that for the enamines derived from ketones. Thus in 1-morpholinopropene (11) the difference between the chemical shifts for the β -carbon atoms in the *E*- and *Z*-forms is 11.7 p.p.m., the upfield signal being associated with the *E*-isomer.

When the β -carbon atom bears two substituents, as it does in the enamines (12)—(17), its chemical shift increases; this arises as a result both of the double substitution and the reduced degree of p - π overlap. This decreased delocalisation exists in the *E*- and *Z*-isomers, both having a *cis*-substituent to the amino-group. In the case of the morpholino-enamines (12)—(14) the β -carbon atom of the isomer pairs resonates between 120 and 132 p.p.m., that is in the range of the benzene carbons.

⁷ J. Sauer and H. Prah, *Chem. Ber.*, 1969, **102**, 1917.

⁸ L. Duhamel, P. Duhamel, S. Combrisson, and P. Siret, *Tetrahedron Letters*, 1972, 3603.

⁹ S. Bradamante, S. Maiorana, and G. Pagani, *J. Chem. Soc. Perkin I*, 1972, 282.

¹⁰ P. Dalla Croce and R. Stradi, *Tetrahedron*, 1977, **33**, 865.

¹¹ J. B. Stothers, 'Carbon-13 NMR Spectroscopy,' Academic Press, New York, 1972, p. 102.

However, when the amine residue is 'more basic' as in the pyrrolidino- and piperidinyl-enamines (15)—(17) the increased shielding on the β -carbon atoms shifts the related signals upfield and thus allowing their unequivocal assignment. In these enamines the β -carbon

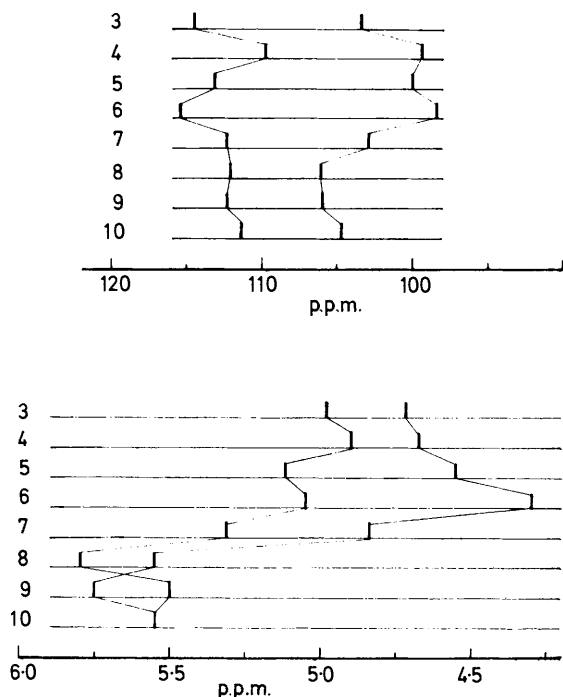


FIGURE 1 The chemical shifts of the β -carbon atom (upper diagram) and of the β -hydrogen atom (lower diagram) in the enamines (3)—(10)

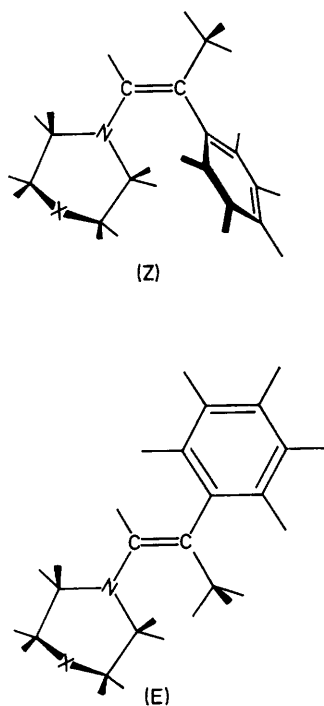
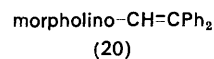


FIGURE 2 The probably preferred conformation of the phenyl group in the *Z*- and *E*-isomers of the enamines (12), (15), and (16)

signals of the *Z*-isomers were found at higher field than the corresponding signals of the *E*-isomers. These reversed values can be explained only by a difference in the steric inhibition of the β -substituent on the amine residue. As shown by molecular models, in these enamines participation of the phenyl group in the delocalisation is very different for the two isomers (Figure 2). In the *Z*-isomer since the phenyl group is strongly hindered towards taking a coplanar conformation to the double bond, the delocalisation of the nitrogen lone-pair on the aromatic ring is inhibited. This limitation is absent in the *E*-isomer. The more extended delocalisation decreases the electron density on the β -carbon which, accordingly, resonates at lower fields.

This conclusion is strongly supported by the fact that the spectrum of the enamine (20)¹² shows the β -carbon signals at 117.0 p.p.m., that is markedly at higher field with respect to the enamine *E*- and *Z*-(12).



Indeed, the delocalisation is strongly hindered in (20) owing to the mutual steric hindrance of the two phenyl groups.

A further point of interest with respect to the enamines listed in Table 2 is the large difference between the chemical shifts on the allylic carbons of the isomeric pairs. Steric interactions are known to give rise to upfield shifts for carbon resonances. Thus, in the enamines (12)—(17) the chemical shifts of the allylic carbon are separated by 6.5—8.2 p.p.m. Clearly, in line with the described steric compression effect, the upfield shifts are associated with the *E*-isomers in which the allylic carbon is perturbed by the proximity of the amino-group. In the cases examined this difference is independent of the type of amino-group of the enamine.

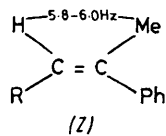
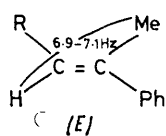
Conclusions.—¹³C N.m.r. spectrometry can be used to distinguish between the *E*- and *Z*-configurations of aliphatic enamines since the amount of p - π overlap present is dependent upon their configuration and the ¹³C spectra reflect this.

The results obtained agree with previous ¹H n.m.r. studies;^{2,3,5,7} moreover, the minor influence of the anisotropic effects in ¹³C magnetic resonance makes easier the interpretation of the spectra, chiefly in the enamines derived from ketones. For the enamines (12)—(17) the ¹H n.m.r. spectra of the isomeric pairs are very similar and, therefore, it is difficult to assign their configuration. However, Duhamel *et al*⁸ examined a number of enamines, including (12) and (13), and were able to differentiate the *E*- and *Z*-isomers by the ¹H n.o.e. effect.

In addition to the chemical-shift differences for the allylic and β -carbon atoms differences were noted for the coupling constants between the α -hydrogen and allylic carbon atoms. In fact, recently it has been

¹² G. P. Hager and K. H. Stahl, *J. Amer. Pharm. Assoc.*, 1953, **42**, 72.

shown¹³ that in vicinally disubstituted olefins, the magnitude of the vicinal ^{13}C - ^1H coupling constant changes with configuration and can be used to distinguish the *Z*- from the *E*-isomer. The examples studied always showed $J_{trans} > J_{cis}$. This difference seems to



- (12) R = morpholino
 (15) R = piperidino
 (16) R = pyrrolidinyl

be true for enamines too: *e.g.* the undecoupled spectra of the enamines (12), (15), and (16) show J (^{13}C - $^1\text{H}_{(trans)}$) = 6.9–7.1 Hz and J (^{13}C - $^1\text{H}_{(cis)}$) = 5.8–6.0 Hz in line with the published results.

¹³ J. E. Anderson, *Tetrahedron Letters*, 1975, 4080; A. W. Douglas, *Org. Magnetic Res.*, 1977, 9, 69.

¹⁴ D. J. Cram, F. A. Abd Elhafez, and H. L. Nyquist, *J. Amer. Chem. Soc.*, 1954, 76, 22.

EXPERIMENTAL

The ^{13}C n.m.r. spectra were recorded at 30 °C with a Varian CFT-20 spectrometer (20 MHz, 8 mm probe) in C_6D_6 solution (25–30% w/v) with tetramethylsilane as internal reference. The spectra were recorded both in the broad-band proton decoupling and in the single frequency off-resonance decoupling mode.

The enamines (14), b.p. (1 Torr) 135–145 °C (Found: C, 77.95; H, 9.1; N, 6.15. Calc. for C, H, N: C, 77.88; H, 9.08; N, 6.05%); (15), b.p. (1 Torr) 122–130 °C (Found: C, 83.25; H, 9.63; N, 6.79. Calc. for C, H, N: C, 83.53; H, 9.51; N, 6.96%); (16), b.p. (1 Torr) 115–125 °C (Found: C, 83.6; H, 9.4; N, 6.9. Calc. for C, H, N: C, 83.53; H, 9.51; N, 6.96%); (17), b.p. (1 Torr) 125–130 °C (Found: C, 83.5; H, 9.3; N, 7.6. Calc. for C, H, N; C, 83.37; H, 9.15; N, 7.48%) are new compounds and were obtained from the appropriate aldehyde¹⁴ and amine by azeotropic distillation of reaction water with benzene.

The authors thank Mrs. E. Gandini for technical assistance in recording ^{13}C n.m.r. spectra.

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