Structural preferences for the double bond position in some unsaturated 3,3-diphenylpyrrolidines

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The reaction between 3,3-diphenyl-3-cyano-1-methylpropyl isocyanate and ethyl magnesium bromide leads to 2-ethyl-5-methyl-3,3-diphenyl-1-pyrroline rather than the isomeric 2-ethylidenepyrrolidine. The protonated *N*-methyl analogue (identical with a major metabolite of methadone) retains the 1-pyrroline structure, but the free base is a *cis–trans* mixture of the corresponding 2-ethylidenepyrrolidines; the *cis* Me/Ph isomer preponderates and is the sole product (obtained as a quaternary salt) when the mixture is treated with methyl iodide. 5-Methyl-2-methylene-3,3-diphenylpyrrolidine, a lower homologue of the methadone metabolite, isomerizes to a 1-pyrroline derivative when protonated or methylated. All structural conclusions are based on i.r. and p.m.r. spectroscopic evidence.

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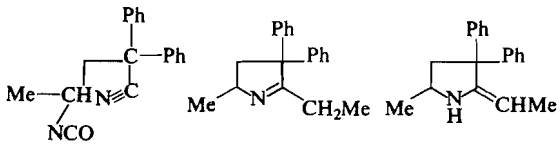
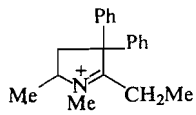
The base derived from the product of reaction between 3,3-diphenyl-3-cyano-1-methylpropyl isocyanate (**1**) and ethyl magnesium bromide



1 **2***a* **2***b*

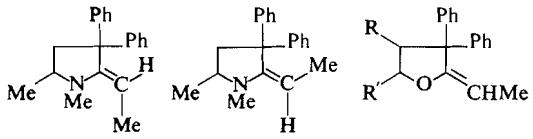
may be formulated either as a 1-pyrroline **2***a* or a pyrrolidine **2***b* since it gives reactions typical of both forms (1). We prepared this base in connection with work upon the metabolism of methadone (2), and report here its structural preference together with that of its derivatives on the basis of spectroscopic evidence.

The p.m.r. spectrum of the base **2** in $CDCl_3$ displays signals characteristic solely of the endocyclic alkene **2***a*, in particular a quartet and a triplet typical of an ethyl group (details in Experimental).[1] The i.r. spectrum of the base (film) shows bands at 1700 and 1630 cm^{-1} of medium intensity as seen in acyclic ketimines and attributed to C=N stretching (3), and spectroscopic features of the base hydrochloride establish that the *endo* structure is retained in the protonated form. Treatment of the pyrroline **2** with dimethylsulfate gives a tertiary base which may be isolated as a hydriodide. Evidence for the pyrroline structure **3** of this salt and its identity with a major



3

metabolite of methadone has been given elsewhere (2). The *N*-methyl base corresponding to **3** may also be obtained from 1,5-dimethyl-3,3-diphenylpyrrolid-2-one (2). A freshly distilled sample derived from this source had spectroscopic properties which showed it to be a *cis–trans* mixture of the exocyclic alkenes **4** and **5**. Thus its



4 *trans* Me/Ph

5 *cis* Me/Ph

6 *a* R = H; R′ = Me; *b* R = Me; R′ = H

p.m.r. spectrum displayed duplicate vinylic (quartets), vinylic methyl (doublets), 5-methyl (doublets) and *N*-methyl signals of similar, but not equal, intensities, while its i.r. spectrum showed an intense band at 1650 cm^{-1}. This i.r. band is assigned to $\nu_{C=C}$ and its high intensity is attributed to the polarizing influence of the adjacent nitrogen atom; the $\nu_{C=C}$ bands of the related tetrahydrofurans **6***a* and **6***b*, are similarly of high intensity (4). One of the four methyl doublets of the p.m.r. spectrum of the *t*-base mixture in various solvents appeared much lower field (δ 1.72) than the other three which formed an overlapping multiplet near δ 1.0, best resolved in benzene. Signal assignments were aided by the

[1]The p.m.r. evidence upon **2** and its analogues does not preclude the existence of minor components, but if other structural isomers are present in the various samples they must represent less than 10% of the total.

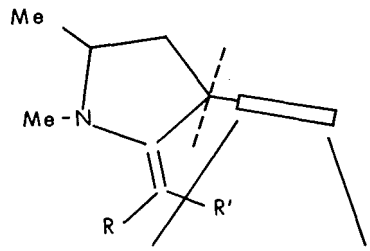
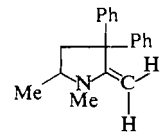


FIG. 1. Diagram of Dreiding model of *cis* and *trans* 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (**4** and **5**) viewed from above. The rectangle and dotted line represent the end on views of the two phenyl substituents at C-3.

fact that the vinylic methine protons exchanged for deuterium when the base in $CDCl_3$ was shaken with D_2O, with the result that their signals disappeared. The methyl doublets which simultaneously collapsed to singlets (δ 1.72 and 0.95) were thus identified as the vinylic methyl resonances.

A favored conformation for the exocyclic alkenes **4** and **5** is probably one in which the two 3-phenyl groups are orientated as in Fig. 1, the plane of one of the rings being almost at right angles to the mean plane of the pyrrolidine ring; in this arrangement non-bonded interactions are at a minimum (4, 5). This conformation removes the R vinylic substituent from the aromatic influence and its chemical shift should be in the normal range of a group attached to a carbon–carbon double bond; the R′ substituent, however, falls within the diamagnetic screening zone of the aromatic group and its p.m.r. signal should occur at an unusually high field position. On these grounds the vinylic methine signal at δ 4.33 (within normal range) (6) and the methyl signal at δ 0.95 (upfield of normal range) are assigned to the *cis* Me/Ph isomer **5**, and the signals at δ 3.72 (HC=, high field) and δ 1.72 (MeC=, normal) to the *trans* isomer **4**. The lower field vinylic signal was clearly the more intense, hence the *cis* form preponderates, and the more intense of the two *N*-methyl signals is therefore assigned to the same isomer. This assignment was corroborated by data upon the 2-methylene analogue **7**; the chemical shift of the *N*-methyl group of this derivative (δ 2.68) was closer to that of the major ethylidene isomer (δ 2.63) than that of the minor (δ 2.78). It is concluded that the vinylic methyl group in *trans* **4** has a small deshielding influence on the *N*-methyl protons.



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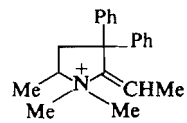
In **7**, the higher field vinylic signal is assigned to the methine proton *cis* to the 3-phenyl substituent, and the lower field signal to the *trans* proton from arguments already discussed. Vinylic chemical shifts calculated using these values and the geminal shielding parameter of methyl attached to a C=C double bond (σ_{gem} Me −0.44 p.p.m.) (7) agree closely with the observed shifts of vinylic protons in the ethylidene derivatives **4** and **5** (see Scheme 1); this result shows that vinylic protons suffer similar degrees of aromatic shielding in **7** and the isomers **4** and **5**.

The p.m.r. spectrum of the total product of reaction between the mixture of bases **4** and **5** and methyl iodide displayed a *single* 5-methyl and vinylic methyl doublet. This establishes that the *exo*-cyclic alkene salt, **8**, consists of only *one* of



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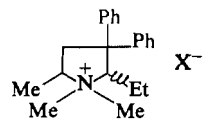
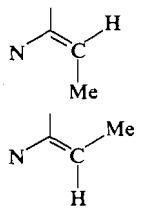


9

the two possible geometrical isomers. The lower field doublet (δ 1.67) in the spectrum of **8** is assigned to 5-methyl because of its broad nature (attributed to ^{14}NCCH coupling, known to amount to about 2 Hz in quaternary salts) (8) and by comparison of its chemical shift with that of 5-methyl in the saturated analogue **9** (δ 1.58). The upfield doublet (δ 1.21) is therefore due to the vinylic methyl group, and its high field position shows that the quaternary salt **8** has a *cis* Me/Ph configuration. The *trans* isomer is probably unfavored on steric grounds since models show that this structure entails interactions between vinylic methyl and *both* of the *N*-methyl groups. The $\nu_{C=C}$ band of the quaternary salt **8** was much weaker than that of the corresponding free base mixture **4** and **5**, and this results supports the argument of the intense absorption seen in the latter being due to the polarizing influence of the ring nitrogen atom; in the quaternary salt **8** the absence of a nitrogen



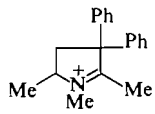
$\nu_{cis\text{-}H} = -3.25 - 0.44 = -3.69$; observed, 3.73 p.p.m. (δ)

$\nu_{trans\text{-}H} = -3.81 - 0.44 = -4.35$; observed, 4.35 p.p.m. (δ)

SCHEME 1

lone-pair of electrons precludes the resonance interaction $\dot{N}\overset{\curvearrowright}{}\!\!-C{=}C \leftrightarrow \overset{+}{N}{=}C{-}\bar{C}$.

The 2-methylene analogue of the bases **4** and **5** also had a preferred exocyclic alkene structure **7** since its p.m.r. spectrum showed two broad vinylic methine signals and its i.r. spectrum, an intense $\nu_{C=C}$ band at 1650 cm^{-1}. In the spectrum of a purified sample in $CDCl_3$, the vinylic resonances were considerably broadened (w_H 13 Hz), indicating their exchangeable nature. This conclusion was confirmed by the diminution of the signal intensities when D_2O was added. Pronounced broadening of these signals was not seen in the spectrum of the base **7** in DMSO-d_6, a solvent which presumably reduces the proton exchange rate by its hydrogen bonding properties. Protonation of **7** occurs at the exocyclic carbon atom of the methylene group rather than at nitrogen (giving **10**), as is clear from the



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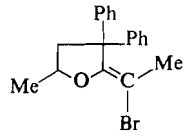
appearance of a broad 3-proton signal at δ 2.48 and the disappearance of the vinylic methine signals when trifluoroacetic acid is added to the base in $CDCl_3$. The signal at δ 2.48, assigned to vinylic methyl in **10**, was of greatly reduced intensity in the spectrum of the acidified base in $CDCl_3$—D_2O. Methylation of **7** also occurred at the same exocyclic carbon atom to yield the hydriodide of the methadone metabolite **3**.

This study shows that 1-pyrrolines of type **2** are more stable than corresponding pyrrolidines with an exocyclic alkene substituent at C-2; the latter structures are only favored in cases where pyrroline formation entails the cleavage of an N—C bond (**4**, **5**, and **7**) or the generation of severe non-bonded interactions (**8**). The governing influence of steric factors in determining preference for *cis–trans* Me/Ph geometry in the five-membered ethylidene derivatives **5** and **8** is also apparent in the tetrahydrofuran analogues **6***a*, **6***b*, and **11**.



11

In the first two the *trans* isomers are preferred as is evident by the normal resonance positions of their vinylic methyl [δ 1.66 (**6***a*), 1.63 (**6***b*)] and high field vinylic methine signals [δ 3.95 (**6***a*), 4.03 (**6***b*)] (4). In the bromo derivative **11** (9), however, the vinylic methyl chemical shift is very close to that of *cis* **5** (δ 0.95) after allowance is made for the deshielding influence of a geminal bromine atom ($\nu_{Me,\ corrected} = 1.53 - 0.56^2 =$ δ 0.97); hence **11** has a *cis* configuration as anticipated from the relative bulk of the bromo and methyl substituents.

Experimental

The p.m.r. spectra were recorded on a Varian A-60 spectrometer using $CDCl_3$ as solvent unless otherwise stated. Chemical shifts are expressed in δ units with TMS as internal standard; in most cases only signals diagnostic of endocyclic or exocyclic alkene structures are reported. The i.r. spectra of salts were recorded as Nujol mulls and bases as liquid films.

The p.m.r. spectrum of base **2**, b.p. 135–140°/0.3 mm (1, 2) showed a quartet at 2.13, *J* 6.5 Hz (2-CH_2Me) and a triplet at 1.08, *J* 6.5 Hz (2-CH_2Me). The spectrum of **2** hydrochloride, m.p. 160–162° (2) showed the same signals at 2.78 and 1.27 (*J* 7.5 Hz).

The mixture of bases **4** and **5** derived from the reaction of 1,5-dimethyl-3,3-diphenylpyrrolid-2-one with ethyl lithium (2) distilled at 131–133°/0.1 mm.

Anal. Calcd. for $C_{20}H_{23}N$: C, 86.6; H, 8.4. Found: C, 86.5; H, 8.4.

The mixture had the following p.m.r. characteristics:

[2]Calculated from ν_{Me} in propene (δ 1.72) and 2-bromopropene (δ 2.28) (10).

quartets at 4.33 (major) and 3.72, *J* 7 Hz (vinylic methine); singlets at 2.78 and 2.63 (major) (N—*Me*); doublets at 1.72 and 0.95, *J* 7 Hz (vinylic methyl), and at 1.12 and 1.07, *J* 5.6 Hz (5-*Me*). In benzene these signals had the chemical shifts: 4.38, 3.92, *J* 7 Hz (vinylic methine); 2.68, 2.50 (N—*Me*); 1.72, 1.17, *J* 7 Hz (vinylic methyl); 1.17, 1.02 *J* 6 Hz (5-*Me*).

1,5-Dimethyl-3,3-diphenyl-2-methylene Pyrrolidine (7)

Compound **7** (5 g) b.p. 120°/0.1 mm, was prepared by treating 1,5-dimethyl-3,3-diphenylpyrrolid-2-one (8.5 g) with methyl lithium obtained from lithium (0.9 g) and methyl iodide (6 g) in ether at −40 °C.

Anal. Calcd. for $C_{19}H_{21}N$: C, 86.6; H, 8.05. Found: C, 86.9; H, 8.4.

The undistilled base had the following p.m.r. characteristics: broad singlets at 3.8 and 3.25, width at half height (w_H) ~ 3 Hz (vinylic methines); singlet at 2.68 (N—Me); doublet at 1.1, *J* 6.5 Hz (5-*Me*). The vinylic methine singlets were at 3.73 and 3.13 ($w_H \sim 3$) in DMSO-d_6, and were replaced by a broad singlet at 148, $w_H \sim 4$ Hz of relative intensity 3 (vinylic methyl) in $CDCl_3$–TFA. The p.m.r. spectrum of the product of reaction between **7** and methyl iodide showed signals characteristic of **3** (2) namely; a multiplet at 5.15 (5-methine); a singlet at 4.03 (N—Me); a quartet near 3.0 (2-CH_2Me); and a triplet at 0.7, *J* 7 Hz (2-CH_2Me).

A mixture of **4** and **5** (4.2 g), dimethyl sulfate (1.4 ml), and benzene (25 ml) was heated under reflux for 1 h and cooled. The solid which separated was recrystallized from ethanol–ether to give **8** (X = $MeSO_4^-$) (3.5 g), m.p. 235–237°, lit. (1) 227–230°.

Anal. Calcd. for $C_{22}H_{29}NO_4S$: C, 65.5; H, 7.2; N, 3.5. Found: C, 65.6; H, 7.2; N, 3.3.

The methiodide **8** (X = I^-) m.p. 185–187°, was prepared similarly and crystallized as a hemihydrate, ν_{max} 3420 cm^{-1} (H_2O).

Anal. Calcd. for $C_{21}H_{26}IN$, 0.5 H_2O: C, 58.9; H, 6.35; N, 3.3. Found: C, 59.3; H, 6.1; N, 2.95.

Its p.m.r. spectrum showed singlets at 3.68 and 3.63 (N—*Me*); doublets at 1.27, *J* 6.5, (w_H of each doublet line ~ 3 Hz) (5-*Me*) and 1.21, *J* 7.5 (vinylic methyl). The quaternary salt **9** (X = $MeSO_4^-$), m.p. 68–70°, prepared from 1,5-dimethyl-3,3-diphenyl-2-ethylpyrrolidine (11) and dimethyl sulfate, also crystallized as a hemihydrate, ν_{max} 3500 cm^{-1} (H_2O).

Anal. Calcd. for $C_{22}H_{31}NO_4S$, 0.5 H_2O: C, 63.7; H, 7.8. Found: C, 63.9; H, 7.8.

Its p.m.r. spectrum showed a multiplet, centered at 4.6 (5-methine), singlets at 3.67 ($MeSO_4^-$), 3.42 and 2.98 (N—*Me*), a doublet at 1.58, *J* 6.5 Hz with broadened lines ($w_H \sim 2$ Hz) (5-Me), plus a deformed triplet with separations ~ 7 Hz at 1.0 (2-CH_2Me).

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Hydrophobic folding of maltose in aqueous solution

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The apparent specific thermal expansibilities of glucose, cellobiose, and maltose were compared to show that the maltose molecule folds in solution and undergoes intramolecular hydrophobic bonding.

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An examination of a molecular model of glucose reveals that certain surfaces are hydrophobic in character. Presumably, the net effect of glucose on the structure of liquid water is a sum of the effects of the hydrophilic —OH groups and the hydrophobic surfaces (1). If a dimer of glucose were able to rotate about its glycosidic linkage such that the hydrophobic surfaces were juxtaposed, these surfaces would bond intramolecularly (2) and thus increase the net hydrophilic character of the molecule. On the other hand, if such a conformational arrange-