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^{13}C-NMR SPECTRA OF LYSERGIC ACID DERIVATIVES—I

10-METHOXY-DIHYDROLYSERGIC ACID METHYL ESTERS

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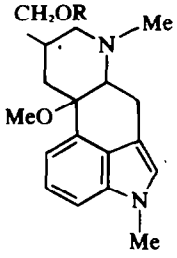
Abstract—The ^{13}C NMR spectra of the four stereoisomers of 10-methoxy dihydrolysergic acid methyl ester have been measured at 22·63 MHz and fully assigned on the basis of signal multiplicity, chemical shifts and single frequency proton decoupling. The ^{1}H NMR spectra were also measured at 270 MHz and completely analyzed; the result of this analysis provided a basis for some ^{13}C assignments and also evidence for conformations. Finally the ^{13}C shifts were correlated with steric effects determined from the prefered conformations.

The class of 10-methoxy-ergoline derivatives corresponding to the general formula 1 has been recently reported to possess a highly specific alpha adrenalergic blocking activity.[1] In view of the current chemical and pharmacological interest in this compounds, a spectroscopic study has been undertaken of their basic molecular skeleton by examining the methyl esters of the 10-methoxy dihydrolysergic acids 2. The four possible stereoisomers which have been previously synthesised and characterised[2] differ in the relative arrangements of the carbomethoxy and methoxy substituents in positions 8 and 10 respectively; they are 8α,10β; 8β,10β; 8α,10α; and 8β,10α.



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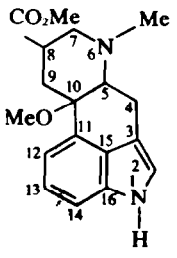

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In the present study use has been made of ^{1}H and ^{13}C NMR. In particular, the aim was to obtain from the proton spectrum detailed information about the conformation of the molecules in solution. In addition to this the assignments of the hydrogen signals should provide a basis for unambiguous assignments of the ^{13}C signals via heteronuclear decoupling {^{1}H}^{13}C. Finally the ^{13}C spectrum was analysed in view of the possibility of establishing a correlation between the ^{13}C chemical shifts and the previously determined geometry of the stereoisomeric molecules.

The interest in ^{13}C spectra is also due to the fact that while the proton spectra of the related lysergic acid dialkyl amides have recently been studied[3] there is no report available in the current literature on the ^{13}C spectra of this group of compounds.

EXPERIMENTAL

The ^{1}H spectra were recorded at 270 MHz, in frequency sweep mode, in 5 mm tubes. Signal positions were measured relative to TMS as an internal standard, 0·2 M solutions in $CDCl_3$ were employed. The ^{13}C spectra were obtained at 22·63 MHz in the pulsed FT mode with and without proton decoupling, lock was on $CDCl_3$. Average pulse width was 3 μsec using the single coil probe arrangement. The digital resolution of the transformed spectrum was 1·5 Hz/point in the standard spectra and 0·5 Hz/point in the expanded spectra. Exponential filtering with time constant 2/3 was used. Chemical shifts were measured from internal TMS at a temperature of 45°C, due to the irradiating power of the decoupler. Solutions were the same as for proton spectra.

DISCUSSION

Interpretation of spectra

(A) *Proton spectra.* The aromatic region consists of an ABX pattern due to the benzenoid ring protons and a triplet due to H-2, the latter was identified by irradiation of the pyrrolic NH group. The three methyl groups were distinguished because the NCH_3 group absorbs at higher field than the OCH_3 groups. The latter two were differentiated by comparison of the spectra of the methyl esters with those of the corresponding amides. To assign the aliphatic ring protons it was necessary to distinguish the 3 spin pattern (H-4a, H-4b, H-5) due to the C-4 and C-5 protons from the 5 spin pattern (H-7a, H-7b, H-8, H-9a, H-9b) due to the C-7, C-8 and C-9 protons. The labelling a and b of H-4, H-7 and H-9 is purely spectroscopic and has no steric meaning, because at this preliminary stage of the analysis it is not possible to distinguish between α and β protons. The procedure generally used was based on the following sequence of double resonance experiments, either in the decoupling or INDOR mode:

{NH} H-2; {H-2} H-4a; {H-4a} H-4b + H-5

In the 8α,10β isomer both H-4a and H-4b are coupled with H-2 as indicated by the signal sharpening during H-2 irradiation, so that this decoupling identifies simultaneously both H-4a and H-4b. However the absorption due to the C-2, C-4 and C-5 protons decoupled from the NH was readily analysed as an ABMX system.

The spectrum of isomer 8α,10α required a particular approach. Accidental identity of chemical shift between H-4a and H-4b was removed by using a mixture of deutero chloroform and deutero dimethylsulphoxide as solvent.

The remaining absorption due to the 5 spin system, was detected in each case as a well separated signal

corresponding to one proton at less than 2 ppm from TMS. This absorption was assigned to one of the H-9 protons because of its typical shift.[3] This signal preliminarly labelled H-9a was used as the starting point for another series of double resonance experiments:

{H-9a} H-9b + H-8; {H-9b} H-9a + H-8;

{H-7a} H-7b + H-8; {H-7b} H-7a + H-8

Assignment of H-7 was obtained by elimination and checked by the last two decouplings.

The spectrum of the C-7, -8 and -9 fragment was finally analyzed and computer simulated by using the LAOCN3 program.[4] For the $8\alpha,10\alpha$ isomer the coupling $J_{8,9b}$ could not be measured directly from absorptions of nuclei H-8 and H-9b because of their degeneracy. However this coupling was obtained from the spectrum of the chloroform–DMSO solution using INDOR double resonance. Monitoring each line of H-9a in turn it was possible to obtain four lines separated by a large splitting due to J_{gem} and a small splitting of about 2 Hz due to $J_{8,9b}$ (Fig. 1). Reciprocal INDOR experiments on each of the H-9b lines did not produce the usual pattern of a positive and a negative component in the INDOR spectrum of H-9a. Instead an overlap of 4 lines was obtained, two positive and two negative, the intensity ratio of the lines of same sign depended on the monitoring frequency (Fig. 2). This fact was exploited to measure the small $J_{8,9b}$ coupling, using the graphical method introduced by Kowaleski.[5] These values were checked by computer simulation of the spectrum measured in chloroform solution. In all cases the final spectral parameters were obtained for both the 3 and 5 spin systems by the least square fitting of calculated to observed spectra. The rms deviation of calculated from measured line positions was in each case less than 0·2 Hz.

(B) ^{13}C *Spectra.* The aromatic region consists of four singlets C-3, C-11, C-15, C-16 and four doublets C-2, C-12, C-13, C-14. The C-3 singlet was assigned by analogy with the upfield shift of the corresponding atom in 3-methyl indole,[6] while C-16 was identified being at lowest field. The shift of the latter, as in indole, is consistent with the α deshielding effect of nitrogen. The other two singlets due to C-11 and C-15 remained undifferentiated at this stage of the work. The C-2 doublet was recognised from the coupling constant J_{CH} = 180·7 Hz, which is characteristic[7] in the indole spectrum. In order to distinguish between C-12, C-13 and C-14 it was necessary to make use of the long range proton couplings. For example in the proton coupled ^{13}C spectrum of isomer $8\beta,10\alpha$ (Fig. 3), C-12 and C-14 show long range splittings with H-14 and H-12 respectively, while the doublet of C-13 does not have any

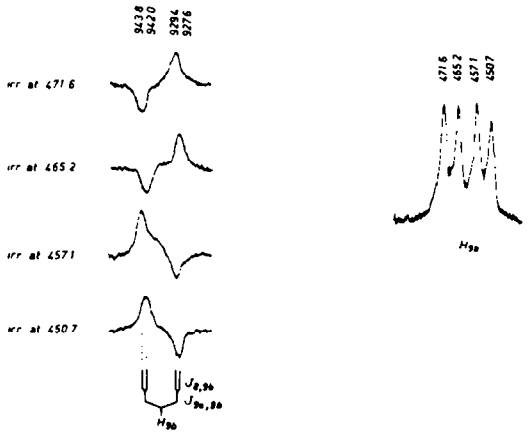


Fig. 1. INDOR spectrum of H-9b obtained from irradiation of H-9a transitions.

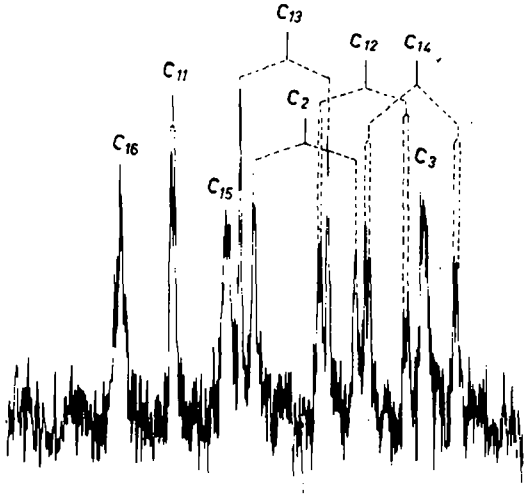


Fig. 3. Undecoupled ^{13}C-spectrum of aromatic region of $8\beta,10\alpha$ isomer.

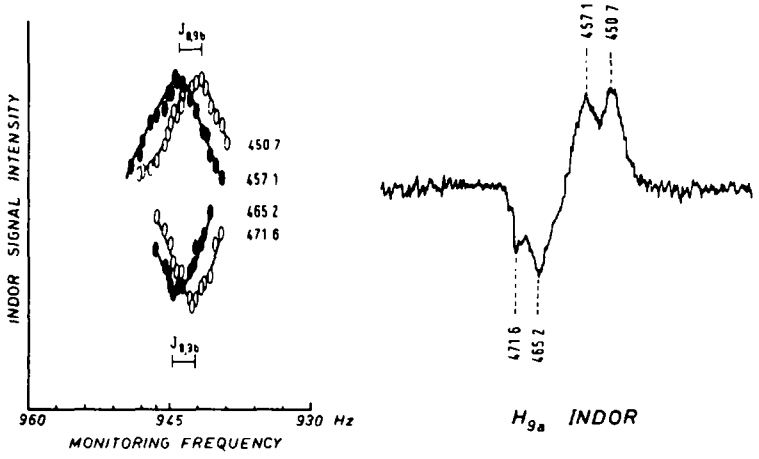


Fig. 2. Variation of H-9a INDOR spectrum right trace intensities versus monitoring frequency.

appreciable long range meta splitting. Moreover, by examination of the same high resolution spectrum it is possible to distinguish between C-11 and C-15. This is based on the fact that the former carbon can have only one long range interaction with H-13, while the latter shows a much higher multiplicity due to meta coupling with H-2, H-14, H-12 and the NH proton.

In conclusion only one ambiguity remains in the aromatic region, the assignment of C-12 and C-14, the latter can be assigned to the signal at higher field by analogy with indole, where C-14 is shifted upfield relative to C-12.

The aliphatic region of the spectrum consists of 3 quartets C-6', C-8', C-10', 3 triplets C-4, C-7, C-9, 2 doublets C-5, C-8 and one singlet C-10. Assignments inside each group of signals with the same multiplicity were obtained by the procedure outlined for isomer 8β,10β. The three methyl signals were differentiated by selective decoupling from the corresponding protons. The assignment of the two CH signals was simply based on the very different chemical shifts, due to the effect of the nitrogen atom which deshields C-5 relative to C-8. Finally the three methylene signals, the absorption at low field was assigned to C-7 because of the deshielding nitrogen effect, while C-4 and C-9 could not be differentiated by an argument based on shift. However selective decoupling from H-4 produced coalescence of the C-4 triplet at δ 20·3, the remaining triplet at δ 32·4 was by elimination assigned to C-9 (Fig. 4). As a check irradiation of H-9α or H-9β produced a partial decoupling of C-9, from triplet to doublet.

The proton spectra parameters are collected in Tables 1 and 2 with the probable errors obtained from the computer fitting. The ^{13}C chemical shifts are reported in

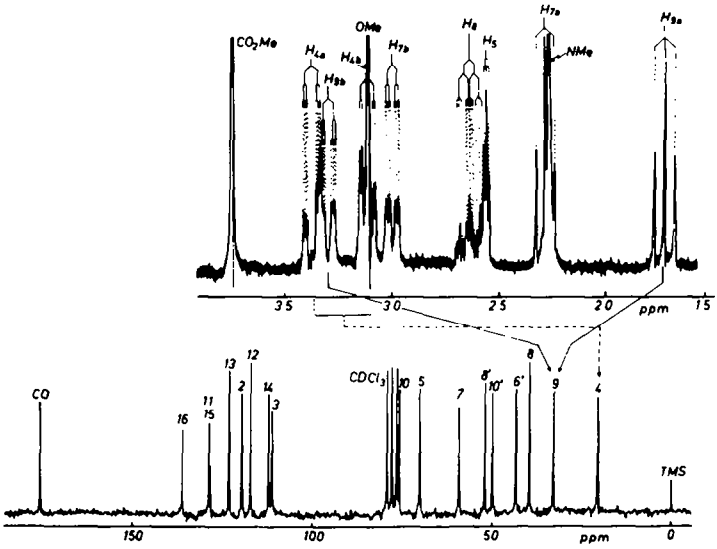


Fig. 4. Correlation of ^{1}H and ^{13}C assignments of 8β,10β isomer obtained from heteronuclear selective {^{1}H}^{13}C decoupling.

Table 1. Proton chemical shifts' of 10-methoxy dihydrolysergic acid methyl esters

PROTON	8 α10 β	8β 10β	8 α 10α	8 β 10α
7α	758 2(3)±0 05	805. 0(5)±0. 02	970. 0(9)±0 06	893 5(0)±0. 04
7β	800 6(4)±0 06	617. 4(3)±0 02	618 3(9)±0. 04	624. 3(5)±0. 04
8	910 2(1)±0 06	708 3(9)±0 02	717 4(2)±0. 04	845 4(7)±0 07
9α	503. 3(6)±0. 05	881 8	967 9(1)±0 06	876 0(1)±0. 09
9β	585 8(8)±0 05	468 4(7)±0 02	481. 8(9)±0. 04	446 5(2)±0 04
2	1861 8	1847. 4	1865. 3	1726 8
4α	829 3(5)±0. 15	834. 7(5)±0 05	787. 8(6)±0. 03	816. 5(2)±0 03
4β	841 3(6)±0 16	900. 0(6)±0. 05	840. 0(6)±0. 03	861. 0(9)±0 03
5	954. 9(3)±0 09	688. 6(8)±0. 05	608. 6(8)±0 03	633. 9(4)±0 02
12	1952. 9	1915. 8	1920. 8	1910. 4
13	1912. 3	1935. 2	1936. 6	1931. 5
14	1952. 9	1954. 8	1976. 9	1963. 2
CO_2Me	977 9	998. 1	1013. 1	1010. 1
OMe	859. 1	831. 0	761 6	804. 5
NMe	702. 7	612 4	664. 9	668. 2
NH	2161. 2	2145. 6	2208. 0	2173. 9

(+) Hz from internal TMS at 270 MHz.

Table 2. Proton coupling constants of 10-methoxy dihydrolysergic acid methyl esters

Coupling	8 α 10β	8β 10β	8α 10α	8β 10α
J 4α,4β	- 15.1(5)±0.15	- 16.3(6)±0.07	- 14.4(4)±0.04	- 14.4(9)±0.04
J 4α,5	11.6(0)±0.18	3.1(0)±0.07	11.4(6)±0.04	11.3(5)±0.03
J 4β,5	5.2(0)±0.21	2.5(7)±0.08	4.1(8)±0.04	4.4(5)±0.03
J 2,4α	n.d.	-	1.2(9)±0.06	1.6(9)±0.04
J 2,4β	n.d.	1.8(4)± 0.11	-	-
J 7α,7β	- 11.5(6)±0.07	- 11.2(9)±0.03	- 12.1(0)±0.07	- 11.6(3)±0.06
J 7α,8	11.6(8)±0.08	3.8(1)±0.03	1.8(3)±0.06	3.7(5)±0.07
J 7β,8	4.3(6)±0.08	11.4(9)±0.03	3.9(5)±0.05	11.8(4)±0.07
J 7α,9α	-	1.4(9)±0.04	1.7(3)±0.07	1.8(3)±0.07
J 7β,9β	0.6(4)±0.07	-	-	-
J 8,9α	12.9(2)±0.07	3.7(9)±0.05	1.9(0)±0.06	4.5(5)±0.11
J 8,9β	4.2(6)±0.07	12.8(1)±0.03	6.4(8)±0.05	13.2(6)±0.07
J 9α,9β	- 13.9(9)±0.07	- 12.7(5)±0.04	- 14.4(2)±0.07	- 14.0(5)±0.09

Table 3. ^{13}C chemical shifts* of 10-methoxy dihydrolysergic acid methyl esters

CARBON	8 α 10β	8β 10β	8α 10α	8β 10α	multiplicity
C_2	118.5	118.4	118.7	118.6	D
C_3	110.0	109.8	110.7	111.1	S
C_4	15.6	20.3	22.2	22.2	T
C_5	57.6	69.2	70.4	69.4	D
$C_{6'}$	42.9	43.0	43.8	43.6	Q
C_7	48.7	58.4	56.8	58.5	T
C_8	37.9	39.2	37.3	37.4	D
$C_{8'}$	51.5	51.5	51.8	51.7	Q
C_9	36.9	32.4	28.6	30.0	T
C_{10}	77.3	74.8	73.5	73.5	S
$C_{10'}$	50.0	49.3	50.9	49.5	Q
C_{11}	133.8 *	126.9 *	129.6	129.1	S
C_{12}	114.0	116.0	116.1	115.6	D
C_{13}	123.1	121.8	121.8	121.7	D
C_{14}	109.3	110.9	111.6	110.8	D
C_{15}	127.2	127.2 *	126.6	126.0	S
C_{16}	134.2 *	134.6	134.5	134.2	S
CO	174.8	173.8	173.8	174.6	S

(+) ppm from internal TMS
(*) uncertain assignments

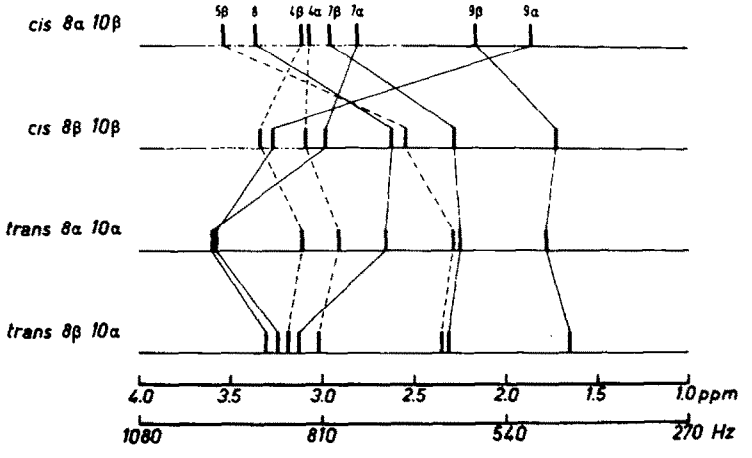
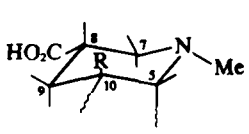


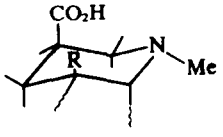
Fig. 5. Proton chemical shifts of aliphatic region of 10-methoxy-dihydrolysergic acid methyl esters.

Table 3 with the signal multiplicity. The proton and carbon assignments are represented by line spectra, Figs. 5 and 6.

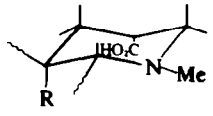
Conformation from proton spectra. The conformation of the piperidine ring D in the four dihydrolysergic acids has been assigned by Stoll[8] as indicated in formulae **3**, **4**, **5** and **6** (R = H).



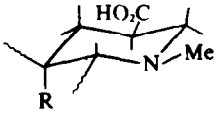
3
cis 8α,10β



4
cis 8β,10β

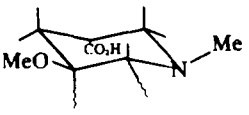


5
trans 8α,10α

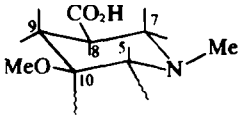


6
trans 8β,10α

Previously the conformation of the corresponding stereoisomeric amides of the 10-methoxy dihydrolysergic acids (R = OMe) has been studied by Bernardi *et al.* considering data obtained from infrared spectroscopy.[2] In particular the NH stretching frequency has been used as a probe for detecting the presence of intramolecular hydrogen bonding between the $CONH_2$ group in position 8 and the piperidine N atom. The absence of such a bond in isomers 8α,10β; 8β,10β and 8β,10α in contrast to its presence in isomer 8α,10α has been interpreted as evidence of axial orientation of $CONH_2$ in the latter isomer and of equatorial orientation in the remaining three isomers. Accordingly the alternative chair conformation **4a** has been proposed for isomer 8β,10β.



3a



4a

In the present paper the vicinal coupling constants between protons 7, 8 and 9 give direct evidence of the conformation of the piperidine ring D in the methyl esters of methoxy dihydro lysergic acids (R = OMe). Moreover, once the conformation is obtained, by considering the numerical value of the vicinal coupling constants and their relation with the dihedral angles, it is possible to assign the α and β protons of the CH_2 in position 7 and 9 as described below.

In the cis isomer 8α,10β **3** the observed vicinal coupling constants $J_{7a,8}$ = 11·7 Hz and $J_{8,9a}$ = 12·9 Hz are interpreted as $J_{ax,ax}$ while $J_{7b,8}$ = 4·3 Hz and $J_{8,9b}$ = 4·2 Hz are interpreted as $J_{eq,ax}$. The presence of a diaxial relationship of H-8 to both H-7 and H-9 rules out the alternative conformation **3a** and is clear evidence in favour of the normal conformation as represented by form **3**. Consequently assignment within the pairs H-7 and H-9 is as follows: H-7a = H-7α; H-7b = H-7β; H-9a = H-9α; H-9b = H-9β.

The other cis isomer, i.e. 8β,10β shows a very similar set of values for the above vicinal couplings of H-8 with H-7 and H-9. This immediately rules out form **4** since it does not justify the two observed diaxial couplings. However the alternative chair conformation **4a** is in complete agreement with the experimental *J* values as indicated by the following assignments:

$$J_{eq,ax}: \quad J_{7b,8} = 3{\cdot}8 \text{ Hz} \quad J_{9b,8} = 3{\cdot}8 \text{ Hz}$$

$$J_{ax,ax}: \quad J_{7a,8} = 11{\cdot}4 \text{ Hz} \quad J_{8,9a} = 12{\cdot}8 \text{ Hz}.$$

Accordingly the labeling of the protons in this isomer can be now transcribed into the conventional configuration nomenclature as follows: H-7a = H-7β; H-7b = H-7α; H-9a = H-9β; H-9b = H-9α.

The remaining two isomers both have a trans junction between rings C and D which automatically rules out the possibility of inverted conformations alternative to **5** and **6**. The previously observed coupling pattern is again found in the case of isomer 8β,10α. The interpretation in terms of the normal conformation **6** is straightforward and the assignment of the individual protons follows the criterion outlined before:

$$J_{eq,ax}: \begin{cases} J_{7b,8} = J_{7\alpha,8} = 3{\cdot}7 \text{ Hz}; \\ J_{9b,8} = J_{9\alpha,8} = 4{\cdot}5 \text{ Hz}; \end{cases}$$

$$J_{ax,ax}: \begin{cases} J_{7a,8} = J_{7\beta,8} = 11{\cdot}8 \text{ Hz}; \\ J_{8,9a} = J_{8,9\beta} = 13{\cdot}3 \text{ Hz}. \end{cases}$$

Finally the values of $J_{7,8}$ and $J_{8,9}$ measured in isomer 8α,10α are not fitted by perfect chair conformation **5**. The parameters which can reasonably be expected for the latter by consideration of suitable models are significantly different from those observed.

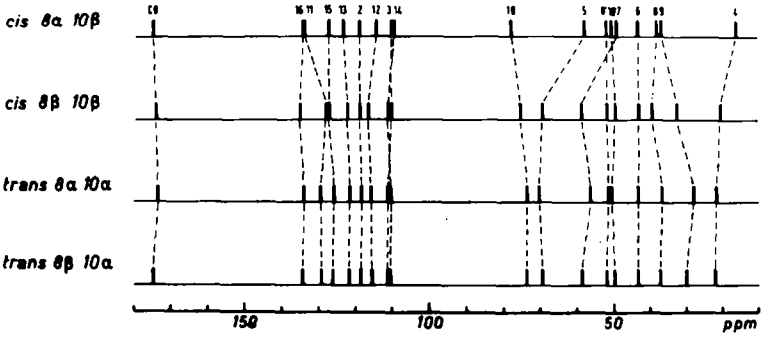
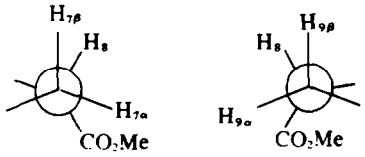


Fig. 6. ^{13}C chemical shifts of 10-methoxy-dihydrolysergic acid methyl esters.

	Observed	Predicted	Model
$J_{7b,8} = J_{7\alpha,8} = J_{eq,eq}$	1·8	2·5 Hz	$J_{2eq,3eq}$ in piperidines[9]
$J_{7a,8} = J_{7\beta,8} = J_{ax,eq}$	4·0	2·5 Hz	$J_{2ax,3eq}$ in piperidines[9]
$J_{8,9b} = J_{8,9\alpha} = J_{eq,eq}$	1·9	3 Hz	$J_{eq,eq}$ in cyclohexane[10]
$J_{8,9a} = J_{8,9\beta} = J_{eq,ax}$	6·5	4·2 Hz	$J_{8eq,9ax}$ in cis isomer $8\alpha,10\beta$

The relatively high value observed for the pair $J_{ax,eq}$ and $J_{eq,ax}$ together with the low values observed for $J_{eq,eq}$ suggests a distortion of ring D involving the following arrangements for bonds C-7–C-8 and C-9–C-8



Deviation of dihedral angles from perfect staggering accounts for both the increase of couplings $J_{7\beta,8}$ and $J_{8,9\beta}$ ($\theta < 60°$) and for the decrease of $J_{7\alpha,8}$ and $J_{8,9\alpha}$ ($\theta > 60°$).

In conclusion the examination of vicinal coupling constants in ring D clearly shows that while the normal chair conformations **3** and **4** are allowed for isomers $8\alpha,10\beta$ and $8\beta,10\alpha$ as indicated in Fig. 7, this is not the case for the remaining two isomers, $8\beta,10\beta$ adopts the alternative chair conformation and isomer $8\alpha,10\alpha$ appears to be in a distorted chair form. Further evidence on this matter is obtained by examining the values of the vicinal coupling constants in the CH_2–CH fragment of carbons C-4 and C-5. The assignment of the alternative chair conformation to isomer $8\beta,10\beta$ is confirmed by the small size (about 3 Hz) of both $J_{4\alpha,5}$ and $J_{4\beta,5}$ corresponding to a gauche relationship, as can be seen in the three dimensional representation of Fig. 7. However the large difference observed for the latter couplings in isomer $8\alpha,10\beta$ is in agreement with a normal chair conformation.

$\Delta J_{4a,5} = 11{\cdot}6$ corresponds to $J_{4\alpha,5}$

$J_{4b,5} = 5{\cdot}2$ corresponds to $J_{4\beta,5}$.

A similar difference is observed in the remaining two isomers where the trans junction between rings C and D produces the same steric arrangement of the CH_2CH fragment as in the previous isomer. The discrepancy between the J_8 value observed in the $8\beta,10\beta$ isomer and the average value of the remaining isomers might be due to a slight distortion of ring C.

Inspection of formulae in Fig. 7 shows that H-4a is to be assigned as H-4α in isomers $8\alpha,10\beta$; $8\alpha,10\alpha$ and $8\beta,10\alpha$ because of the large coupling with H-5 corresponding to a trans steric relationship. As a check the H-4b proton shows in the same isomers a value of $J_{4b,5}$ corresponding to J_8.

In isomer $8\beta,10\beta$ the assignment is reversed, i.e. H-4a = H-4β, this is based on the fact that this proton shows a dihedral angle of about 30° with respect to H-2, which accounts for the observed value of the allylic coupling $J_{4a,2} = 1{\cdot}8$ Hz. The same stereospecific coupling has been observed in isomers $8\alpha,10\alpha$ and $8\beta,10\alpha$ for proton H-4a.

The ^1H shifts of the aliphatic region show some systematic trends which reflect different steric situations in the four isomers. It is evident that the equatorial protons H-5, H-7β and H-9β in isomer $8\alpha,10\beta$ are shifted downfield 1·1, 0·6 and 0·4 ppm relative to the average absorption corresponding to the axial conformation in the other isomers (Fig. 5). Likewise H-9α which becomes axial in isomer $8\alpha,10\beta$ is shifted upfield by more than 1 ppm relative to the average δ value of 3·3 ppm.

^{13}C *chemical shifts.* The different chair conformation of the piperidine ring accounts for the observed differences of shift between isomers $8\alpha,10\beta$ and $8\beta,10\beta$ (Fig. 6). Thus in the $\beta\beta$ isomer C-11 becomes axial and moves upfield 6·9 ppm while C-4 becomes equatorial and moves downfield 4·7 ppm relative to the $\alpha\beta$ isomer. The strong deshielding effect observed on C-5 in the same isomer is in agreement with the change of orientation of the $-CH_2Ar$ substituent from axial to equatorial. Similar deshielding of C-7 can be explained by the relief of steric interaction of 1–3 axial type between H-7 and H-4 in the $8\beta,10\beta$ isomer. The interchange of orientation between the OMe group and the CH_2Ar produces a slight change of shift in C-9 and C-10. The conformation of the two trans isomers differ in the orientation of the substituent in position 8 and the distorsion suggested by the values of coupling constants in the $8\alpha,10\alpha$ isomer. In contrast with the pair of cis

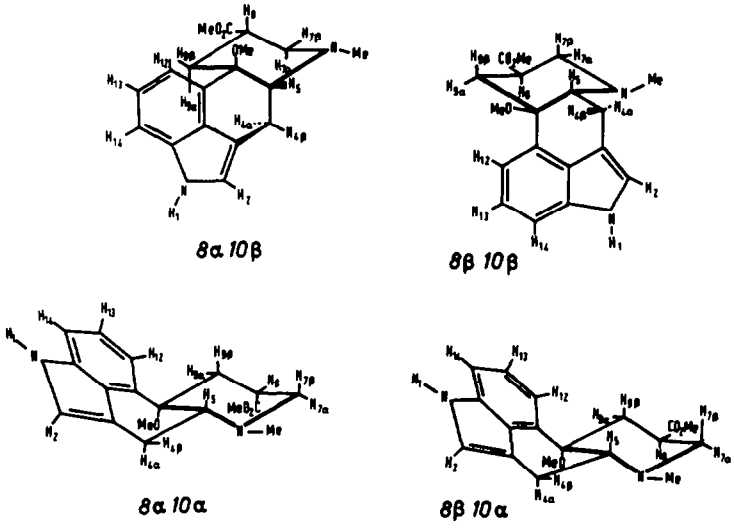


Fig. 7.

isomer the ^{13}C spectra do not show any large shift difference, indicating that the difference in steric interactions between isomer 8α,10α and 8β,10α is small.

The results of our work shows that the ^{13}C chemical shift can be used as a very sensitive parameter for characterising different steric isomers of complex molecules such the title compounds.

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