Tetrahedron, 1965, Vol. 21, pp. 2539 to 2551. Pergamon Press Ltd. Printed in Northern Ireland

# ERGOLINE DERIVATIVES—VIII*

## CONFIGURATION AND CONFORMATION OF LYSERGAMIDES AND DIHYDROLYSERGAMIDES

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(*Received* 29 *December* 1964; *in revised form* 20 *April* 1965)

**Abstract**—The NH region of the IR spectra of lysergamides and dihydrolysergamides are reported, discussed and the bands assigned. Axial and equatorial amides are clearly distinguishable, the former present between the amide hydrogen and the tertiary nitrogen atom an intramolecular hydrogen bond which can vary in strength. The CO stretching region has been examined and a good agreement between configuration and CO-frequency found. The configuration and the conformation of lysergamide and isolysergamide has been discussed on the basis of the IR spectra. The *pK* values of various amides have been determined and the results discussed in the light of the spectroscopic data.

Equilibration of lysergamides and dihydrolysergamides in alkaline solution have been shown to be solvent-dependent. The equilibrium shifts toward the axial isomer in aprotic solvents. The reasons for such behaviour are given.

THE available evidence concerning the stereochemistry of dihydrolysergic acids is not completely unequivocal and the accepted configuration of lysergic and isolysergic acid[1] is based on indirect evidence. According to Stoll[2] the reduced basicity of lysergic acid monoalkylamides (in comparison with the dialkylamides) and the relative preponderance[3] at equilibrium of isolysergic acid monoalkylamides can be explained by assuming the existence of an intramolecular hydrogen bond between the secondary amide group of isolysergamides and the piperidine nitrogen of ring D. The stereochemistry of isolysergamides was based on the only one of the $C_8$ configurations which allows such an intramolecular bond.

We have previously shown[4,5] that certain derivatives of dihydrolysergic acid I and II[6] and among them notably the amides, can be epimerized into the corresponding derivatives of dihydrolysergic acid-I and -II and *vice versa*. The equilibrium constant[7] is the same in either the primary and secondary amides or esters and, therefore, we concluded that the intramolecular hydrogen bond (if present) plays a negligible role in stabilizing the epimer for which an internal bond could be present on steric grounds.

* Part VII: L. Bernardi, G. Bosisio, O. Goffredo and B. Patelli *Gazz. Chim. Ital.* **95**, 384 (1965).

[1] R. F. Manske and J. E. Sexton, *The alkaloids* Vol. VII; pp. 12, 14. Academic Press, New York (1960).

[2] A. Stoll, Th. Petrzilka, J. Rutschmann, A. Hofmann and H. Gunthard, *Helv. Chim. Acta* **37**, 2039 (1954).

[3] Equilibration experiments performed at 25° in EtOH containing NaOH as a catalyst.

[4] Part II. L. Bernardi and O. Goffredo, *Gazz. Chim. Ital.* **94**, 947 (1964).

[5] Part VI. L. Bernardi and W. Barbieri, *Gazz. Chim. Ital.* **95**, 375 (1965).

[6] According to Stoll class I compounds present a *trans* C/D ring junction; class II compounds a *cis* C/D ring junction. All ergoline derivatives reported on this paper are optically active and belong to the D-lysergic acid stereochemical series. For the sake of simplicity prefix D has been omitted in all the formulae.

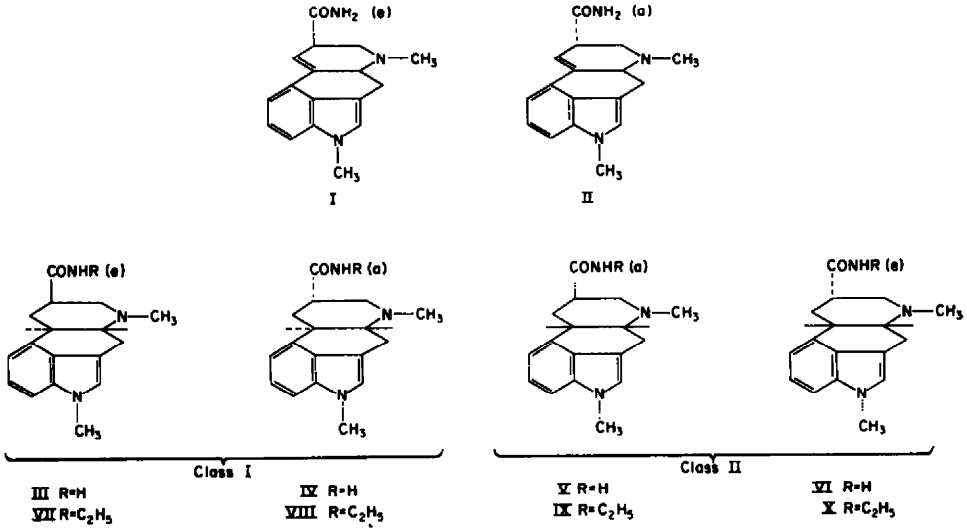
[7] The isomerization experiments were performed at 80° in t-butanol solution containing potassium t-butoxide as a catalyst. An average of 30% content of the less stable (axial) epimer was found to be present at equilibrium.

In order to demonstrate the existence of an intramolecular hydrogen bond in some (sterically) suitable cases, a spectroscopic study of the NH stretching mode was undertaken since it is known that hydrogen bonding lowers the frequencies of the NH vibrations.[8,9]

Consequently, the configurations previously assigned to lysergamides and dihydrolysergamides have been confirmed and the conformations of these compounds partially clarified.

*The IR spectra of dihydrolysergamides—the* NH *modes*

The spectra (NH stretching region) of several 1-methyllysergamides and 1-methyldihydrolysergamides[10] (I to X), in chloroform and dichloromethane solutions are reported in Figs. 1–4. Owing to the presence of both an amide group and a basic centre many compounds had to be investigated before certain features of these spectra could be interpreted.[11]




Compounds III and VI show in dichloromethane (Fig. 1) the asymmetric and symmetric NH stretching modes of a primary free amide group[13]; in chloroform solution (Fig. 2) the same compounds are still mainly in the associated form as shown

[8] See, L. J. Bellamy. *The infrared spectra of complex molecules* p. 204. Methuen, London (1958).

[9] Other less direct approaches (*pK*; equilibrium shift) were also considered and the results are reported here.

[10] We have examined 1-methyl derivatives to eliminate interferences due to the indolic hydrogen. Besides these compounds are appreciably soluble in apolar solvents and fairly concentrated solutions can be obtained: the unmethylated amides are too insoluble to be of any use.

[11] For a complete and detailed discussion about the association bands in the spectra of basic amides we refer to the next paper,[12] where ample evidence is reported to support the following conclusions:
(a) Contrary to simple amides, basic amides present, in chloroform, strong bands due to intermolecular N—H . . . N hydrogen bonds: these bands are affected by dilution only in a limited way, but they are no longer present in dichloromethane, a better dissociating solvent.
(b) Basic amides that can be, owing to favourable steric conditions, intramolecularly hydrogen bonded, present even in dichloromethane a strong broad band at about 3220 $cm^{-1}$, unaffected by dilution.

[12] W. Barbieri and L. Bernardi, *Tetrahedron* **21**, 2447 (1965).

[13] Ref. 8 p. 206.

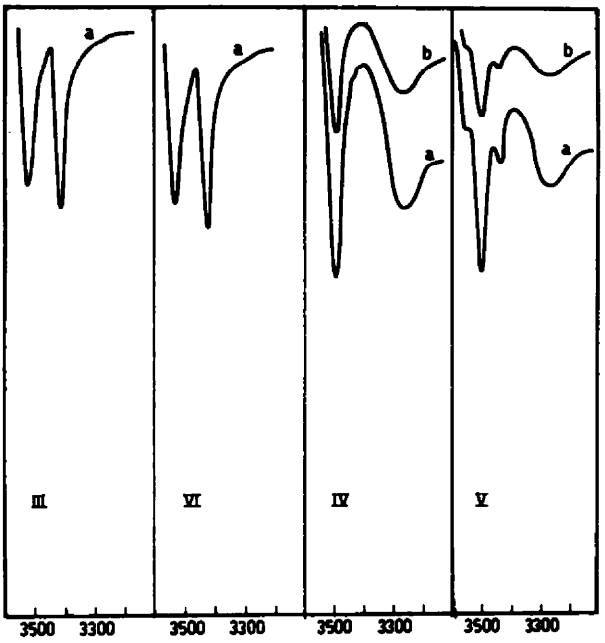



FIG. 1. Spectra of 1-methyldihydrolysergamide-I (III); 1-methyldihydroisolysergamide-I (IV); 1-methyldihydrolysergamide-II (V); 1-methyl-dihydroisolysergamide-II (VI) in dichloromethane.
*a* = 0·03 molar solution; *b* = 0·015 molar solution.

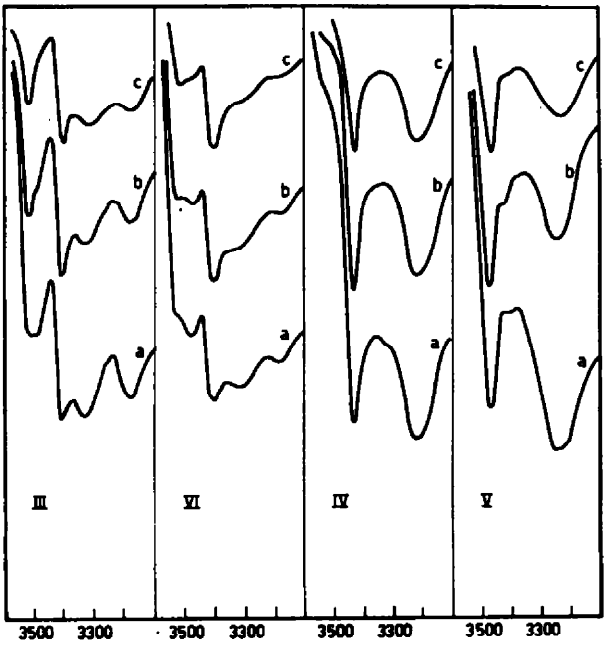



FIG. 2. Spectra of 1-methyldihydrolysergamide-I (III); 1-methyldihydroisolysergamide-I (IV); 1-methyldihydrolysergamide-II (V); 1-methyldihydroisolysergamide-II (VI) in chloroform.
*a* = 0·06 molar solution; *b* = 0·03 molar solution; *c* = 0·015 molar solution

by the presence of the concentration-dependent absorption bands at 3480 $cm^{-1}$, 3330 $cm^{-1}$ and 3180 $cm^{-1}$. The homologues VII and X present in dichloromethane (Fig. 3) only the 3460 $cm^{-1}$ band normally assigned to the NH stretching mode of a free secondary amide[14] whereas in chloroform (Fig. 4) a second strong band at 3330 $cm^{-1}$ is evident. This band, solvent dependent but little affected by dilution, is to be ascribed on the account of what is reported in the following paper, to a strong N—H . . . N intermolecular[15] hydrogen bond.

The spectra of the amides IV and V show both in chloroform and in dichloromethane (Figs. 1 and 2) two bands at about 3450 $cm^{-1}$ and 3220 $cm^{-1}$. This latter band, strong and very broad is of the shape usually ascribed to the associated NH or OH stretching modes. And since it is not concentration dependent and is little affected by changes in solvent, we assigned this band to a N—H . . . N intramolecular bond. This is confirmed by the spectra of the monoethylamides VIII and IX (Figs. 3 and 4) which present, instead of the expected 3460 $cm^{-1}$ band,[14] a similar broad band at about 3220 $cm^{-1}$.

The strong, sharp, concentration-independent 3450 $cm^{-1}$ band present in the spectra of the primary amides (IV and V) is due, in our opinion, to the NH mode of the remaining amidic nitrogen not involved in the intramolecular bond.[16]

On this basis a closer examination of the spectra of IV, V, VIII and IX reveals that whereas the spectrum of VIII presents a single band at 3220 $cm^{-1}$ in both chloroform and dichloromethane, the spectrum of IX shows a second band at about 3450 $cm^{-1}$ due to the NH stretching mode of the free (secondary) amide and, therefore, in IX, the internal hydrogen bonding is incomplete. Similarly, V is also intramolecularly only partially bonded since the spectrum shows the 3510 $cm^{-1}$ and 3400 $cm^{-1}$ bands due to a free $NH_2$ group[17,18] (Fig. 1).

The spectral data reveal the following conclusions: Ring D has a stable, chair conformation[20] and the amide group is either equatorial as in III, VI, VII and X (no

[14] Ref. 8, p. 207.

[15] The bond is considered intermolecular on the basis of the frequency of the associated absorption band and moreover because it is not present in dichloromethane solution.

[16] A primary bonded amide behaves as a secondary amide because in both cases the electronegativity of the amidic nitrogen is increased. The CO stretching mode is likewise influenced (v.i.)

[17] These same bands cannot be seen in the spectrum reported in Fig. 2 because in chloroform solution bands due to intermolecular bonds are also present. As a consequence the association band is partly concentration-dependent.

[18] We think that the different behaviour of the two groups of amides can be best understood when taking into consideration the strain induced on ring C by the indolic moiety. Such strain will be transferred to ring D in different ways depending on whether the ring junction is *cis* or *trans*. Recently Bucourt[19] has shown that when a source of strain (e.g. a double bond) is applied on one decalin ring the conformation of the other ring becomes modified thus changing the usual pattern of the 1,3-diaxial interactions; if the junction is *cis* certain interactions will increase, while the same interactions will be reduced when the junction is *trans*. In our case we cannot calculate the strain induced by the indolic group, but we are bound to expect that it will alter in one isomer (*trans*) both the bond angles and the distances in a way favourable to the formation of an intramolecular hydrogen bond; the same strain will work the opposite way on the other isomer (*cis*) thus reducing the chances of internal bond.

[19] R. Bucourt, *Bull. Soc. Chim. Fr.* 1262 (1963).

[20] It will be shown in the next note[13] that the intramolecular hydrogen bond can partly stabilize an otherwise improbable conformation: the absence of a detectable intramolecular bond in the spectra of equatorial amides shows that the free-energy difference between the boat and the chair conformation of the piperidine ring D is greater than the energy of the hydrogen bond.

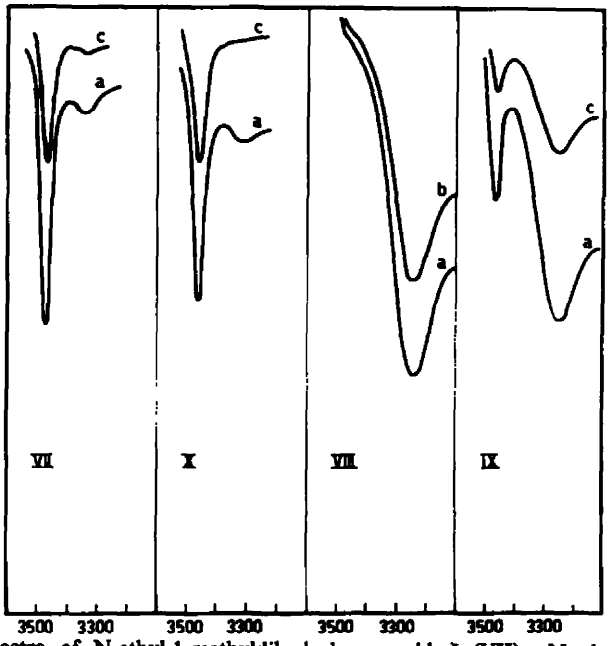



FIG. 3. Spectra of N-ethyl-1-methyldihydrolysergamide-I (VII); N-ethyl-1-methyldihydroisolysergamide-I (VIII); N-ethyl-1-methyldihydrolysergamide-II (IX); N-ethyl-1-methyldihydroisolysergamide-II (X) in dichloromethane.
*a* = 0·06 molar solution; *b* = 0·03 molar solution; *c* = 0·015 molar solution

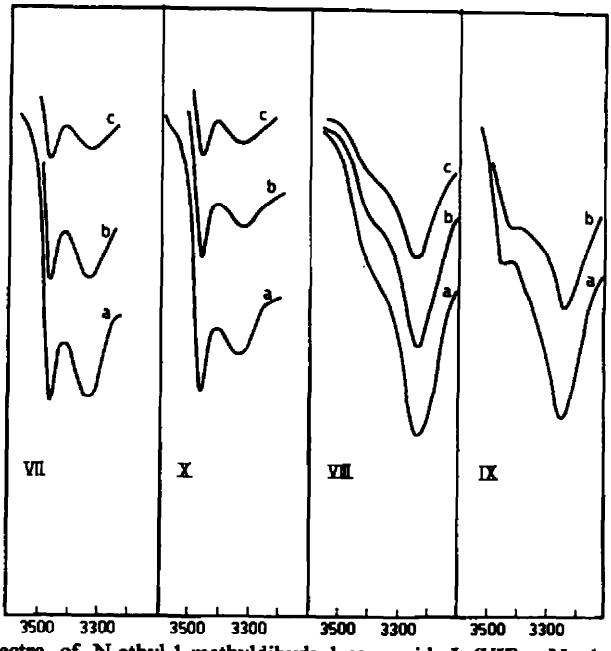



FIG. 4. Spectra of N-ethyl-1-methyldihydrolysergamide-I (VII); N-ethyl-1-methyldihydroisolysergamide-I (VIII); N-ethyl-1-methyldihydrolysergamide-II (IX); N-ethyl-1-methyldihydroisolysergamide-II (X) in chloroform.
*a* = 0·06 molar solution; *b* = 0·03 molar solution; *c* = 0·015 molar solution.

intramolecular bond feasible) or axial as in IV, V VIII and IX (intramolecularly bonded).[21]

The conformation of the amide groups in compounds III to X, formerly assigned by Stroll,[2] on the grounds of indirect evidence is, therefore, substantiated by direct proof.

*The IR spectra of dihydrolysergamides—the* CO *mode*

Since a strong N—H . . . N bond can modify the carbonyl absorption, the amide I band of compounds III to X have been examined in the solid state and in dilute solution. As in the solid state the formation of a number of hydrogen bonds is likely (N—H . . . N both inter- and intramolecular beside the usual CO . . . H—N) only[23] the spectra in dilute solutions should be taken into consideration since only intramolecular bonds are present under these conditions. When the hydrogen atoms of the amides are bonded, the amide nitrogen becomes more electronegative and the ionic forms are favoured; the CO bond is weakened and the carbonyl band shifts towards lower frequencies.[24] The position of the CO stretching band indicates, therefore, whether the amide group is bonded or not.

TABLE 1. CARBONYL ABSORPTION BAND ($cm^{-1}$) (0·015 MOLAR SOLUTIONS)

| Compound | Conformation | KBr pellet | $CHCl_3$ soln | $\Delta\nu$ | Dioxan soln | $\Delta\nu$ |
|---|---|---|---|---|---|---|
| I | e | 1645 | 1670 | +25 | | |
| II | a | 1675 | 1648 | −27 | | |
| III | e | 1635 | 1675 | +40 | | |
| VI | e | 1625 | 1675 | +50 | | |
| IV | a | 1660 | 1660 | — | | |
| V | a | 1650 | 1660 | +10 | | |
| VII | e | 1635 | 1660 | +25 | 1675 | +40 |
| X | e | 1642 | 1655 | +13 | 1673 | +31 |
| VIII | a | 1660 | 1645 | −15 | 1665 | +5 |
| IX | a | 1642 | 1640 | −2 | 1665 | −23 |

[21] In the case of the C/D *cis* ring junction (compounds V, VI, IX and X) two chair conformations are possible[22] (proton at $C_8$ is $\beta$, $C_8$ can be either above or below the plane of ring C) of which the one having the large aromatic group equatorial (i.e., $C_8$ above the plane of ring C) is usually preferred[22]; conversion of one form into the other would however render equatorial, an axial substituent and *vice versa*. The spectra of V and IX show, as we have already seen, an incompletely bonded amide group and this could well mean that the strain due to the axial substituent is relieved by changing into the other conformation ($C_8$ below the plane). The free-energy difference between the two conformations should therefore be small and we do not see why an equatorial amide should not acquire analogously a partial axial conformation, which is stabilized by the intramolecular hydrogen bond. Since the spectra of VI and X do not present any appreciable band due to an intramolecular hydrogen bond, we believe that the interconversion of these two chair conformations is rather unlikely and we favour the former[18] interpretation of the spectra of V and IX.

[22] D. H. R. Barton and R. C. Cookson, *Quart. Rev.* **10**, 74 (1956).

[23] Ref. 8, p. 210.

[24] The same bathochromic shift is experienced when passing from a primary amide to a tertiary amide and it is likewise due to an increase of electronegativity of the nitrogen atom.

Examination of Table 1 clearly shows that compounds IV and V, VIII and IX absorb at lower frequencies than III and VI, VII and X.[25]

This confirms the axial conformation of their amide groups. On the other hand, compounds III, VI, VII and X, to which an equatorial conformation had been assigned, present the normal large shift of the carbonyl frequency following a change of state.[27]

*Dissociation constants of lysergamides and dihydrolysergamides*

In order to check the results obtained from the IR spectra, the ionization constants of a number of amides were determined since the value of such data in determining the configuration of these compounds is known.[2] Since ionization constants are determined in highly polar protic solvents where solvation and polar forms play a primary role, whilst IR spectra are determined in far less polar solvents, complete uniformity between the two methods was not expected.

TABLE 2

| Parent acid | amide $pK^a$ | diethylamide $pK^a$ | methyl esters[a] $pK^a$ |
|---|---|---|---|
| Dihydrolysergic acid-I | 6·7 | 6·7[b] | 6·20 |
| Dihydroisolysergic acid-I | 7·5 | 8·87[c] | 6·40 |
| Dihydroisolysergic acid-II | 6·9 | 7·1 | 6·42 |
| Dihydrolysergic acid-II | 7·8 | 7·8 | 6·86 |
| Lysergic acid | 6·25 | 6·37[c] | |
| Isolysergic acid | 6·55 | 7·52[c] | |

[a] determined by titration of a 0·005 molar solution in 50% EtOH.
[b] the reported value[2] in EtOH–methylcellosolve is 6·79.
[c] reported values[2] in 80% EtOH.

From the data[28] reported in Table 2 it is evident that axial amides are more basic than the equatorial amides and this must be due to the stabilization of the protonated piperidine nitrogen through a hydrogen bond with the (axial) amide group.[29]

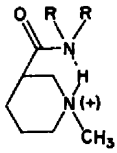
[25] On looking for a better hydrogen-bond breaking solvent we have examined some of our amides in dioxan solution and we wish to take the occasion for pointing out a wrong interpretation of Richards and Thompson[26] on a former report. These authors observed in the CO region, in dilute dioxan solution, beside the 1690 $cm^{-1}$ band, a broad band at 1605–1620 $cm^{-1}$ of variable intensity and they assigned this band to the C=N stretching motion of the enolic form of the amide group. We also obtained repeatedly the same kind of band, but since the intensity was variable and the results did not fit in a clear pattern we re-examined the whole experimental procedure and we can now conclusively affirm that such bands *are due to water*, easily taken up from the atmosphere. If special care was taken to avoid absorption of moisture when preparing the solutions and cell filling, no spurious band was present.

[26] R. E. Richards and H. W. Thompson, *J. Chem. Soc.* 1248 (1947).

[27] The reasons why the CO frequency of some axial amides can be higher in the solid state than in solution are not clear.

[28] The measurements were made at least in duplicate. Owing to differences of solvents, the general trend more than the absolute values should be considered when comparing the data of different authors.

[29] In our opinion the bond is N—H . . . N rather than N—H . . . O since in the case of esters the corresponding increase in basicity is of limited entity.



The strength of this bond, or in other words the basicity of the axial derivatives, is consequently influenced by steric conditions and one would expect that axial ergoline carboxamides of class I would be more basic than the isomers of class II. In fact the IR spectra have revealed that the axial amides of class II are only partly bonded owing to unfavourable steric conditions; these very conditions would contrast the stabilization of the protonated molecule and would therefore weaken basicity. Accordingly, N,N-diethyldihydrolysergamide-II is less basic than N,N-diethyldihydroisolysergamide-I.

In primary axial amides, the amide group can stabilize, via an intramolecular hydrogen bond, either the basic molecule (the bond, N . . . H—N—CO, reduces the basicity) or its salts (the bond, (+)N—H . . . N—CO, increases the basicity). The experimental data show that axial primary amides are always more basic than equatorial amides, but the enhancement of basicity is greater in dihydrolysergamide-II than in dihydroisolysergamide-I.

This means that dihydroisolysergamide-I, rather than its salts is stabilized by the intramolecular hydrogen bond and in effect the IR spectra confirm the existence of such strong bond. The less bonded, dihydrolysergamide-II is accordingly more basic.[30]

This agreement between the *pK* values and IR spectra suggests that even in a highly solvating protic solvent, intramolecular hydrogen bonding is still effective.

*The configuration and the conformation of lysergamides and dihydrolysergamides*

The evidence presented, both direct and indirect, concerns the conformation of the amide groups in compounds III to X, but their configuration and, therefore, the configuration of lysergamides is still based on indirect proof reported by Stoll.[2] Slow reduction of isolysergamides affords dihydro derivatives of both class I and II, whereas fast reduction gives preponderantly class II dihydro derivatives, which should, therefore, be the less stable isomers, or, in other words, the C/D ring junction in class II compounds must be *cis*.

Examination of Dreiding models shows that the $N_6$ nitrogen lone pair interacts with two ($C_8$ and $C_{10}$) hydrogen atoms in compounds having a C/D *cis* ring junction and interacts with three ($C_4$, $C_8$ and $C_{10}$) hydrogen atoms in compounds having a C/D *trans* ring junction. It follows that compounds having a C/D *cis* ring junction should be more basic, more strongly adsorbed on alumina[34] and the ease of

[30] 3-Aminoalcohols such as lysergol,[31] dihydrolysergol and tropine[32] behave in a similar way, to say in these compounds intramolecular hydrogen bonding, when feasible, reduced the basicity. On the contrary in the case of 2-aminoalcohols[33] hydrogen bonding enhances the basicity. We suggest that this different behaviour is related to the size of the ring (5 or 6 member ring) formed by the intramolecular bond and we think that such a question should warrant further investigation.

[31] A. Hofmann, R. Brunner, H. Kobel and A. Brack, *Helv. Chim. Acta* **40**, 1358 (1957).

[32] G. Fodor and K. Nador, *J. Chem. Soc.* 721 (1953).

[33] T. A. Geissmann, B. D. Wilson and R. B. Medz, *J. Amer. Chem. Soc.* **76**, 4182 (1954).

[34] For instance *cis* decahydroquinoline is more strongly adsorbed on alumina than the *trans* isomer.[35]

[35] E. A. Mistryukov, *J. Chromat.* **9**, 314 (1962).

quaternarization should also be greater, than in the corresponding isomers having a C/D *trans* ring junction.

The *pK* data reported in Table 2 clearly show that all the compounds of class II are more basic than the corresponding isomers belonging to class I (except for axial diethylamides, already discussed). In the nor-series[2] the same phenomenon is present. According to Stoll[36,37] and our own experience, the derivatives of dihydroisolysergic acid-II (equatorial) are more strongly adsorbed on alumina than the corresponding derivatives of dihydrolysergic acid-I (equatorial). Accordingly, these results strongly suggest that in compounds of class II, the C/D ring junction is *cis*.

The rates of ethobromide formation[38] for ethyl dihydrolysergate-I and ethyl dihydroisolysergate-II (in both compounds the ester group is equatorial and it should not interfere), using the technique employed by Shamma[39] for heteroyohimbine alkaloids, gave the following half-lives:

ethyl dihydrolysergate-I $t_{0.5} = 285 \pm 20$ minutes

ethyl dihydroisolysergate-II $t_{0.5} = 155 \pm 20$ minutes

It is evident that the $N_6$ nitrogen is less hindered in class II compounds and therefore supports the former evidence. A *cis* configuration can be assigned to the C/D ring junction in these compounds.

The configuration and the conformation of the four dihydrolysergamides can therefore, be assigned as follows:

III (and VII) 8$\beta$,10$\alpha$; junction *trans*. The amide group is equatorial and 8$\beta$.

IV (and VIII) 8$\alpha$,10$\alpha$; junction *trans*. The amide group is axial and 8$\alpha$.

V (and IX) 8$\beta$,10$\beta$; junction *cis*. The amide group is axial and 8$\beta$; $C_5$ is above the plane of ring C.[21]

VI (and X) 8$\alpha$,10$\beta$; junction *cis*. The amide group is equatorial and 8$\alpha$; $C_5$ is above the plane of ring C.[21]

The configuration of lysergamide (8$\beta$) and isolysergamide (8$\alpha$) follows directly from the configuration of the dihydrolysergamides; while the conformation of ring D is revealed by IR spectral examination.

The IR spectrum of 1-methylisolysergamide (II) (Fig. 5) conforms to the pattern previously exhibited by intramolecularly bonded axial amides, whereas the spectrum of 1-methyllysergamide (I) (Fig. 5) is more complex and can be explained only by assuming that both intramolecular and intermolecular bonds are present.[40]

Examination of Dreiding models of lysergamide (and isolysergamide) shows that ring D can exist in two almost equivalent twisted forms[41] with $C_5$, $C_8$, $C_9$ and $C_{10}$ in

[36] A. Stoll and J. Rutschmann, *Helv. Chim. Acta* **33**, 67 (1950).

[37] A. Stoll, Th. Petrzilka and J. Rutschmann, *Helv. Chim. Acta* **35**, 1249 (1952).

[38] Ethyl bromide was used instead of the customary methyl iodide because with the later reagent the reaction was too fast.

[39] M. Shamma and J. B. Moss, *J. Amer. Chem. Soc.* **83**, 5038 (1961).

[40] Note the strong 3480 $cm^{-1}$ and 3220 $cm^{-1}$ bands present in dichloromethane solution.

[41] Cookson[42] has postulated a boat conformation to explain the exclusive reduction of lysergic acid derivatives to dihydrolysergic acid-I derivatives. Such boat conformation is however improbable because it will not allow an intramolecular bond of the kind we observed.

[42] R. C. Cookson, *Chem. & Ind.* 337 (1953).

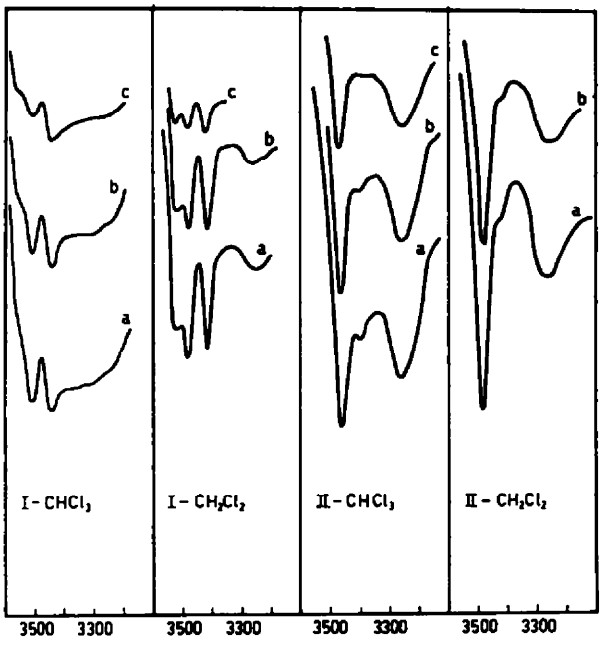



FIG. 5. Spectra of 1-methyllysergamide (I) and 1-methylisolysergamide (II) in chloroform and in dichloromethane.
$a$ = 0·06 molar solution; $b$ = 0·03 molar solution; $c$ = 0·015 molar solution.

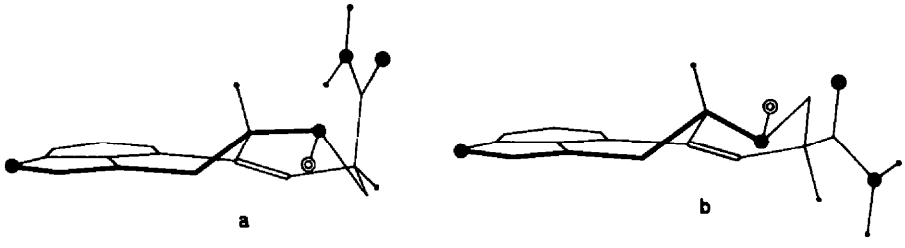



FIG. 6. Lysergamide conformers *a* and *b*.

one plane and, in order, $N_6$ and $C_7$ above and below the plane (Fig. 6*a*) or below and above (Fig. 6*b*). In conformation *a* ($N_6$ up, $C_7$ down) the amide group (8$\beta$) of lysergamide is *quasi*-axial and an intramolecular bond is feasible; in conformation *b* ($N_6$ down, $C_7$ up) the amide group (8$\beta$) is *quasi*-equatorial.

The IR spectra of lysergamide and isolysergamide show that conformation *b* ($N_6$ down, $C_7$ up) is the more stable but the free-energy difference between *a* and *b* is not great. In fact isolysergamide is completely hydrogen bonded (Fig. 5) and therefore the D ring has the more stable conformation, $N_6$ down $C_7$ up, since this conformation only allows an intramolecular bond between the 8$\alpha$ amide group and the $N_6$ nitrogen atom.

On the other hand lysergamide (I) (Fig. 5) is partly unbonded ($N_6$ down-$C_7$ up; amide group 8$\beta$, equatorial Fig. 6*b*) and partly bonded: to allow an intramolecular

bond the ring D must assume the conformation shown in Fig. 6*a* ($N_6$ up-$C_7$ down; amide group 8$\beta$, axial).[43] In lysergamide both conformations (*a* and *b*) are therefore present.

*Axial-equatorial equilibrium shift*

Since intramolecular bonds are present in compounds II, IV, V, VIII and IX it was necessary to determine whether the equilibrium constant of the epimerization

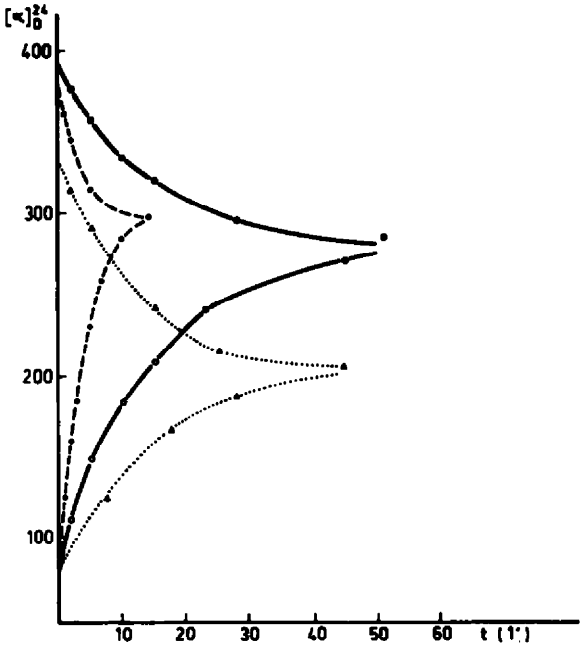



FIG. 7. Alkaline epimerization of lysergamide and isolysergamide
▲ ..... ▲ in methanol
○ ——— ○ in methanol-benzene 1/1
● - - - - ● in methanol-benzene 1/3

reaction is influenced by the formation of an intramolecular hydrogen bond between the axial amide group and the tertiary nitrogen atom.

As the experimental conditions previously employed[5] minimized the effect of hydrogen-bonding, it was decided to carry out the isomerization reactions in an aprotic solvent where hydrogen bonds are stronger. The epimerization of lysergamide (I) and isolysergamide (II) in various solvents is recorded in Fig. 7 which summarizes the results of various runs, performed at 24°, with 0·005 M solution of I and II in

[43] The intramolecular hydrogen bond, whose energy has been found to be about 1 kcal/mole, compensates in part the extra energy requirements of form *a*, which becomes stabilized. In a similar way a N . . . H—O bond was found to be able to stabilize the boat conformation of cyclohexane.[44]

[44] M. Svodoba, M. Tichy, J. Fajkos and J. Sicher, *Tetrahedron Letters* No. 16, 717 (1962).

methanol and in methanol–benzene mixtures containing 10 equivalents of potassium methoxide. At equilibrium the content of axial amide[45] was calculated:

| | |
|---|---|
| in methanol | 50% |
| in methanol–benzene 1:1 | 63% |
| in methanol–benzene 1:3 | 69% |
| in methanol–dioxane 1:19[46] | 63% |

Under similar conditions, various solutions of methyl lysergate showed that the equilibrium is practically unaffected by a change of solvent—the axial isomer averaged $25 \pm 3\%$.[47,49]

The increase in the proportion of the axial isomer observed when primary *amides* are epimerized in less and less protic solvents, clearly demonstrates the effect of the intramolecular hydrogen bond on the equilibrium constant of the epimerization reaction.

In order to determine whether a similar effect is present on dihydrolysergamides, 0·015 M solutions of VII and X were treated at 80° for 10 hr in benzene–*t*-butanol in the presence of 0·6 equivalents of potassium *t*-butoxide. The equilibrium mixtures were subsequently analysed by TLC as previously described[5] and it was found that the ratio VII:VIII was 45:55 and the ratio X:IX was 52:48 instead of the customary 70:30 obtained in *t*-butanol solution.[5]

It is interesting to note that not only does an aprotic solvent shift the equilibrium constant in favour of the axial isomer, but, as expected, the shift is greater when the (formed) axial isomer amide shows the strongest hydrogen bond in the IR spectra.

## EXPERIMENTAL

The IR spectra were recorded on a Perkin–Elmer M 21 spectrometer fitted with NaCl optics and checked with a Perkin–Elmer M 237 double grating spectrometer.

Samples were prepared as solutions in different solvents ($CHCl_3$, $CH_2Cl_2$, $C_2H_4Cl_2$, $CHBr_3$, dioxan) and examined in 1 mm cells with NaCl windows and as dispersions in pressed KBr discs.

*Equilibration of lysergamides.* About 7 mg of I or II were dissolved in 4·75 ml MeOH or dioxan or benzene–MeOH mixtures and 0·25 ml of a stock solution of MeOK (1 g K in 25 ml MeOH) was added. The optical rotations were read on an automatic polarimeter (Perkin–Elmer M 141) at suitable intervals. The following $[\alpha]_D^{20°}$ were determined in MeOH, MeOH–benzene 1:1, MeOH–benzene 1/3, MeOH–dioxan 1/19 solutions: lysergamide (I) 80°, 75°, 70°, 30°; isolysergamide (II) 330°, 395°, 395°, 385°; equilibrium mixtures 205°, 275°, 295°, 255°. From the data the equilibrium constants are easily calculated.

*Equilibration of methyl lysergate.* About 20 mg methyl lysergate was dissolved in MeOH, iMeOH–benzene 1:1 or benzene (9·5 ml) and 0·5 ml of stock solution of MeOK (1 g K in 25 ml of MeOH) was added. After 3 min, 3 ml of MeOH–acetic acid mixture (2 ml of AcOH in 100 ml of MeOH) were added and the solution evaporated *in vacuo* at room temp. The residue was dissolved in 5 ml $CHCl_3$ and the optical rotation of the (filtered) solution determined: $[\alpha]_D^{20°} = 110° \pm 4$ (6 different

[45] The optical rotations of I and II in the different solvents were separately determined to avoid extrapolation errors.

[46] In this solvent the reaction is exceedingly fast. We limited ourselves to the determination of the final rotation.

[47] A small change of the equilibrium constant had been expected since it is known that the steric requirements of a nitrogen lone pair, and consequently its interactions with the (axial) ester group, are larger in protic solvents.[48] Within the limits previously reported, no such change was observed.

[48] K. Brown, A. R. Katritzky and A. J. Woring, *Proc. Chem. Soc.* 257 (1964).

[49] Methyldihydrolysergate was previously[5] found to isomerize (at 80°) to a mixture having $30 \pm 2\%$ content of axial isomer.

determinations). Since the optical rotation of the isomers are known (methyl lysergate $[\alpha]_D^{20°} = +82°$ ($CHCl_3$)[50]; methyl isolysergate $[\alpha]_D^{20°} = +200°$ ($CHCl_3$)[51] the equilibrium constant is easily calculated: K = 3·3.

*Synthesis.* The amides I and II were prepared according to Troxler[52] and beside having the expected physical constants, were found pure by TLC (ethyl acetate–dimethylformamide–n-butanol–pyridine 4:1:3:1). The synthesis of compounds III to X has already been reported.

*Rates of ethobromide formation.* A 50 mg sample of ester was dissolved in 10 ml of acetonitrile and 1 ml of ethyl bromide was added. The resistance was measured with a conventional cell, at 25°, employing a Metrohm Mod. E 114 apparatus[53] (readings were taken after 1, 2, 3, 5, 7 and 24 hr). Half-lives were found graphically by determining the time which corresponds to a conductivity value of $\Lambda/2$ ($\Lambda$ is the conductivity at $t = \infty$).

*Acknowledgments*—We wish to thank Prof. Bruno Camerino, Director of these Laboratories for his sustained interest and Prof. Luigi Panizzi for his kind suggestions. The friendly help of Adriano Alemanni of our microanalytical laboratory in securing the *pK* data is gratefully acknowledged.

[50] S. Smith and G. Timmis, *J. Chem. Soc.* 1440 (1936).
[51] A. Stoll, H. Hofmann and W. Schlientz, *Helv. Chim. Acta* **32**, 1947 (1949).
[52] F. Troxler and A. Hofmann, *Helv. Chim. Acta* **40**, 1721 (1957).
[53] We thank Mr. L. Valentini for carrying out these measurements.