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ERGOLINE DERIVATIVES—IX[1]

CONFIGURATION AND CONFORMATION OF 10-METHOXYDIHYDROLYSERGIC ACID DERIVATIVES

W. BARBIERI, L. BERNARDI, G. BOSISIO and A. TEMPERILLI

Istituto Ricerche Farmitalia—Milano, Italy

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Abstract—The preparation of the four isomeric methyl 10-methoxydihydrolysergates is reported. The configurations are assigned and the conformation of rings C and D is discussed. A mechanism for the formation of these 10-methoxy derivatives is suggested.

LYSERGIC acid and lysergic acid derivatives add, in the presence of light and in acid solution, a molecule of water across the double bond to give lumi derivatives,[2*] whose configurations have recently been elucidated in our laboratories.[3] In the course of this work we found that the esterification of lumilysergic acid in methanol–HCl afforded, besides the expected methyl ester, a less polar substance which was later shown by elementary analysis and methoxyl determination, to be the 10-methyl ether. The study of the configuration and conformation of this compound and of its isomers, is the object of the present paper.

When a solution of lumilysergic acid (I) in methanol containing 15% (v/v) H_2SO_4 was left overnight at room temperature a complete esterification and etherification was achieved and two compounds, IV and V, were formed in approximately 95:5 ratio. The same results were obtained when I was replaced by the lactone III[3] and when a solution of lysergic acid in methanol–H_2SO_4 was irradiated with a white light lamp. In order to clarify the configuration of compounds IV and V, these compounds were transformed stereospecifically† into the amides IV A and V A. It was expected to be able to differentiate between the two amides by means of their IR spectra since it has already been shown in the case of dihydrolysergamides,[1] that an axial amide group shows, in dichloromethane solution, an IR spectrum modified in the NH_2 stretching region,‡ owing to the presence of an intramolecular hydrogen bond between the amide group and the piperidine nitrogen atom of ring D. However, for reasons which will be discussed later, both amides§ showed the NH_2 stretching modes of a free NH_2 group, thus rendering any differentiation impossible.

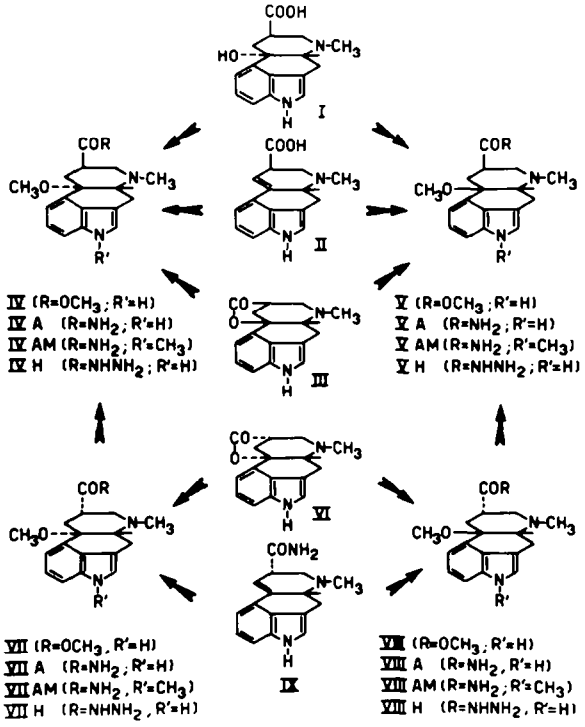
* All ergoline derivatives reported in this paper are optically active and belong to the D-lysergic acid stereochemical series. For the sake of simplicity prefix D has been omitted in all the formulae.

† It has been shown[4] that the hydrazinolysis of dihydrolysergic acid esters occurs stereospecifically and that the hydrazides yield the corresponding amides by treatment in ethanol with an excess of Raney nickel. The same reactions were used in this case and the isolation of four different hydrazides and amides, easily distinguishable by TLC, confirms the stereospecificity of the sequence.

‡ A narrow band at *ca.* 3480 cm^{-1} and a broad one at *ca.* 3200 cm^{-1} replace the usual[5] stretching modes at *ca.* 3510 cm^{-1} and 3400 cm^{-1}.

§ For solubility reasons and to avoid interference with the indole NH stretching mode, the amides IV A and V A, as well as VII A and VIII A were examined as their N_1 methyl derivatives (IV AM, V AM, VII AM, VIII AM), prepared strictly according to the procedure of Troxler and Hofmann[6] by methylation with CH_3I and KNH_2 in liq. NH_3.

The synthesis of the two 8α-isomers was next investigated and their relationship with IV and V determined. A solution of the lactone VI in methanol–H_2SO_4 gave VII and VIII in approximately 65:35 ratio;* moreover, in basic conditions VII and VIII were epimerized to give IV and V respectively† (Scheme 1). From VII and VIII the amides VII A and VIII A were obtained in the same way as IV A and V A and the IR spectra were examined.‡ In this case, the IR spectra clearly showed that the



SCHEME 1

amide group was intramolecularly bonded in VII A but not in VIII A. In VII A the amide group must therefore be axial and since it has the same configuration 8α, as the lactone VI or the isolysergamide IX, it follows that the C/D ring junction must be *trans* and the methoxyl group is consequently 10α. By exclusion, in VIII A, the methoxyl group must be 10β and the conformation of the amide group 8α, equatorial.

Since, in basic conditions, epimerization at C_8 occurs and VII and VIII afford IV viz. V, the configuration of these compounds are also determined, and are represented by the formulae in Scheme 1.

The fact that the amide group in V A is not hydrogen bonded can now be discussed. In V A the C/D ring junction is *cis* and therefore two conformations (*a* and *b*; Fig. 1) are possible: in the case of dihydrolysergic acid derivatives, conformation *a* (R = H)

* The same results were obtained when isolysergamide was irradiated in the usual methanol–H_2SO_4 solution. However, if the temperature was kept below 20° and the concentration of H_2SO_4 was reduced to *ca.* 1%, the amides VII A and VIII A could be isolated in fair yield.

† Since we were only interested in relating VII and VIII to IV and V, no attempt was made to obtain quantitative data.

‡ See footnote § on previous page.

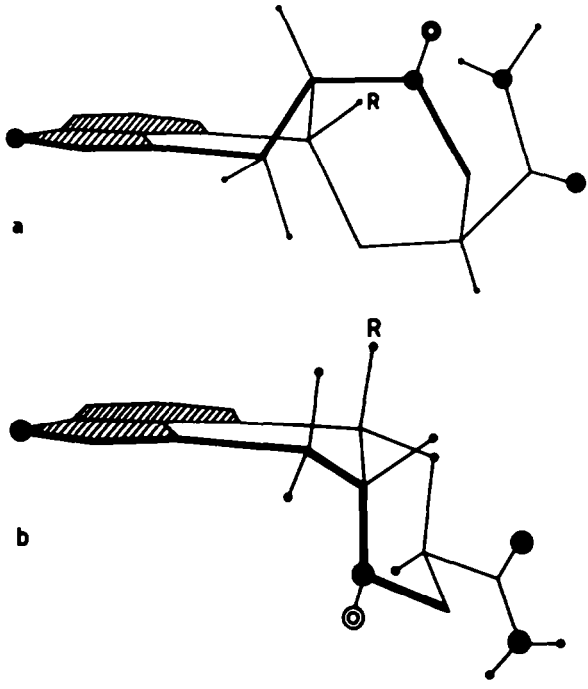
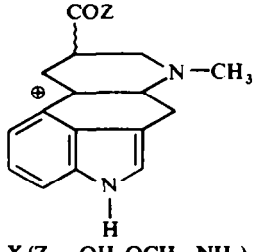


FIG. 1 10-β-Ergoline conformers *a* and *b*.

has been proposed by Barton and Cookson[7] and by Stoll[8] and confirmed by our group.[1] In the present case, the presence of a bulky group at C_{10} ($R = CH_3O$) introduces a strong 1,3-diaxial interaction which can, however, be relieved, if the molecule assumes conformation *b*. As a consequence, the conformation of the amide group becomes equatorial and no hydrogen bond with the N_6 nitrogen is possible.*

As far as the mechanism of formation of the reported 10-methoxyergoline derivatives is concerned, we assume that, as a first step, the stabilized carbonium ion X is formed by a proton attack on lactones III and VI, lumilysergic acid (I) or, by photoactivation, on lysergic acid and isolysergamide. Next, a nucleophilic attack by methanol gives the ether isomers by a thermodynamically controlled addition. To substantiate this argument, pure VII and VIII were dissolved overnight in methanol–



X (Z = OH, OCH_3, NH_2)

* The spectrum[1] of dihydrolysergamide-II (6-methyl-8β-carboxamid-10β-ergoline) shows that the amide group is not completely intramolecularly hydrogen bonded. In the light of the present data, we suggest now, that in the case of dihydrolysergamide-II both conformations, *a* (major) and *b* (minor) are probably present.

H_2SO_4. In each case a mixture of VII and VIII, in the ratio 65:35, was obtained; similarly V was largely (95%) isomerized into IV. These data are in accord with the expected greater stability of the *trans* ring junction.

In Table 1, the physical constants and the analytical data of the compounds synthesized in the present work, are summarized.

TABLE 1

Compound (Scheme 1)	m.p. (°)	$[\alpha]_D^{20}$ $c = 0{\cdot}5$ Py	Found (%)			Calc. (%)		
			C	H	N	C	H	N
IV	182–184	−22°	68·8	7·2	9·0	68·8	7·0	8·9
V	91–92	+58°	68·4	7·1	8·7	68·8	7·0	8·9
VII	254–255	−17°	68·7	7·2	8·9	68·8	7·0	8·9
VIII	228–230	+75°	68·5	7·1	8·8	68·8	7·0	8·9
IV H	249–250	−36°	64·7	7·2	17·6	64·9	7·0	17·8
V H	136–137	+16°	64·5	7·3	17·3	64·9	7·0	17·8
VII H	236–237	+34°	64·9	7·1	17·7	64·9	7·0	17·8
VIII H	260–262	+128°	64·5	7·1	18·0	64·9	7·0	17·8
IV A	254–255	−38°	67·9	7·0	14·1	68·2	7·1	14·0
V A	239–240	+23°	67·9	7·0	13·8	68·2	7·1	14·0
VII A	186–187	+65°	67·9	7·2	13·8	68·2	7·1	14·0
VIII A	252–253	+120°	68·1	7·1	14·1	68·2	7·1	14·0
IV AM	241–242	−32°	68·5	7·4	13·1	69·0	7·4	13·4
V AM	217–218	+15°	68·7	7·2	13·2	69·0	7·4	13·4
VII AM	114–115	+62°	68·8	7·7	13·0	69·0	7·4	13·4
VIII AM	229–230	+125°	68·7	7·3	13·3	69·0	7·4	13·4

EXPERIMENTAL

Methyl 10α-methoxydihydrolysergate (IV) *and methyl 10β-methoxydihydrolysergate* (V).

(a) Lysergic acid (II) (15 g) was dissolved in MeOH (375 ml) and H_2SO_4 (75 ml) and irradiated at 20°, in a Pyrex flask with a Philips-HPLR 250 W lamp for about 30 hr, until the absorption at 315 mμ completely disappeared. The solution was diluted with ice–water, basified with NH_4OH and extracted with $CHCl_3$. After evaporation of the solvent the residue was crystallized from Et_2O to give IV (10·6 g). The residue was chromatographed on silica gel and on elution with benzene–$CHCl_3$, V (0·2 g) was isolated from the initial fractions.

(b) The lactone of 10β-hydroxydihydrolysergic acid (III)[3] (1·5 g) was dissolved in MeOH (40 ml) and H_2SO_4 (8 ml): after 48 hr the solution was worked-up as in (a) and the same products IV and V were isolated. TLC estimation[9] showed the reaction product to contain 95 ± 2% of IV and 5 ± 2% of V. The same results were obtained when the lactone III was replaced by lumilysergic acid (I) or by V.

(c) By epimerization. MeOH (150 ml), liq. NH_3 (200 ml) and VII (0·6 g) were heated in a closed, stainless steel tube at 80° for 3 days. The solution was evaporated to dryness and the residue chromatographed: IV (0·1 g) was eluted first, followed by IV A (0·4 g).

Xilene (40 ml), NaH (0·4 g, 50% oil dispersion) and VIII (0·2 g) were refluxed for 2 hr. The solution was washed with water and evaporated. Preparative TLC of the residue afforded 30 mg of V.

Methyl 10α-methoxydihydroisolysergate (VII) *and methyl 10β-methoxydihydroisolysergate* (VIII)

(a) The lactone of 10α-hydroxydihydroisolysergic acid[3] (VI; 6 g) was dissolved in MeOH (150 ml) and H_2SO_4 (30 ml): after 24 hr the solution was diluted with ice–water, basified with NH_4OH and extracted with $CHCl_3$. After elimination of the solvent the residue was found, by TLC,[9] to consist of 65 ± 2% of VII and 35 ± 2% of VIII. It was chromatographed on silica gel and on elution with $CHCl_3$–MeOH 9:1, VIII (1·9 g) and next VII (2·2 g) were isolated. The same results were obtained when VI was replaced by either VII or VIII.

(b) Isolysergamide (IX; 5 g) was dissolved in MeOH (150 ml) and H_2SO_4 (30 ml) and irradiated at 25° in a Pyrex flask with a Philips-HPLR 250 W lamp for about 30 hr, until complete disappearance of the 315 mμ max was observed. The solution was allowed to stand overnight, diluted with ice–water, basified with NH_4OH and extracted with $CHCl_3$. After evaporation of the solvent, the residue was analysed and found to be identical with the one obtained according to (a).

10α-*Methoxydihydroisolysergylhydrazine* (VII H)

A suspension of VII (1·4 g) in 98% hydrazine hydrate (80 ml) was refluxed for 1 hr. The clear solution was concentrated and on cooling produced crystalline VII H (1·1 g). The other hydrazides reported in Table 1 were obtained similarly.

10α-*Methoxydihydroisolysergamide* (VII A)

A solution of VII H (0·3 g) in EtOH (150 ml) was refluxed for 20 min. in the presence of Raney nickel (6 g). After filtration the solution was concentrated and crystalline VII A (0·18 g) was obtained. The amides IV A, V A and VIII A were obtained similarly.

10α-*Methoxydihydroisolysergamide* (VII A) *and* 10β-*Methoxydihydroisolysergamide* (VIII A) *from isolysergamide* (IX)

Isolysergamide (IX; 2 g) was dissolved in MeOH (600 ml) containing H_2SO_4 (5 ml). The solution was irradiated at 15° in a Pyrex flask with a Philips-HPLR 250 W lamp until no further absorption at 315 mμ was observed (8 hr).

The solution was immediately basified with NH_3 and concentrated *in vacuo*. The residue was suspended in water and extracted with $CHCl_3$. Evaporation of the solvent left a residue which was chromatographed on silica gel. On elution with $CHCl_3$ and $CHCl_3$–MeOH (45:1) the following compounds were successively isolated: VIII (0·2 g), VII A (0·6 g) and VIII A (0·35 g).

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