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STUDIES CONCERNING LYSERGIC AND DIHYDRO-LYSERGIC ACID α-HYDROXYETHYLAMIDES

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Abstract—Lysergic and dihydrolysergic acid α-hydroxyethylamides (Ia and IIa) undergo acid catalysed solvolytic substitutions at the asymmetric carbon atom in the side chain, resulting in the formation of epimeric compounds. The mutarotation of IIa has been studied, and shown to take place by an A-1 mechanism. The hemiacetalic character of the side chain hydroxyl, and other lines of evidence, confirm the structure Ia previously assigned to the metabolite of *Claviceps paspali* Stevens and Hall.

LYSERGIC acid[3] α-hydroxyethylamide is a metabolite of *Claviceps paspali* Stevens and Hall.[4] Structure Ia has been assigned to this alkaloid on the basis of its cleavage to lysergic acid amide and acetaldehyde under mild conditions.[5] We wish now to report the results of an investigation on the behaviour of the novel α-hydroxyethylamide derivatives Ia and IIa in acidic medium.

The natural compound Ia—as obtained from the fermentation media, carefully avoiding any acid treatment during the extraction process—and its dihydroderivative IIa are readily converted, by aqueous acids, to equilibrium mixtures, each consisting of two epimers having opposite configurations at the asymmetric carbon in the side

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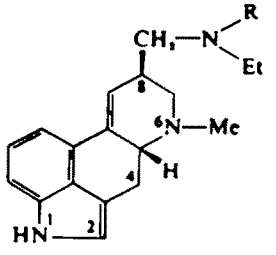
[3] Throughout this paper "lysergic acid" indicates D-lysergic acid, and "dihydrolysergic acid" indicates D-dihydrolysergic acid—I [A Stoll, Th. Petrzilka, J. Rutschmann, A. Hofmann and Hs. H. Günthard, *Helv. Chim. Acta* 37, 2039 (1954)].

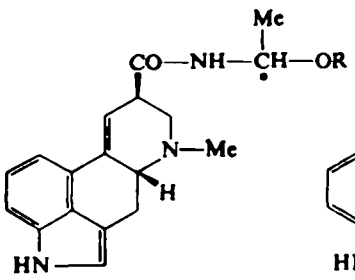
[4] F. Arcamone, E. B. Chain, F.R.S., A. Ferretti, A. Minghetti, P. Pennella, A. Tonolo and L. Vero, *Proc. Roy. Soc.* 155B 26 (1961;) P. Bianchi, E. B. Chain, F.R.S., P. G. Mantle and A. Tonolo *Nature Lond.* 202, 312 (1964).

[5] The attachment of the two-carbon fragment to the amide nitrogen has been confirmed by reduction of Ia with LAH to 6-methyl-8-ethylaminomethyl-Δ^9-ergolene (i, R = H), which in turn was converted to the corresponding N-acetate (i, R = $COCH_3$). The identity of the latter compounds was

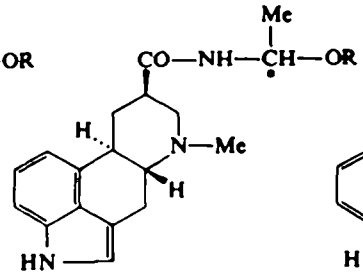


i

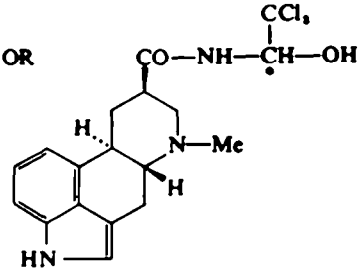
proved by their independent synthesis starting from lysergic acid monoethylamide [A. Stoll and A. Hofmann, *Helv. Chim. Acta* 38, 421 (1955)] by the same procedure.



Ia: R = H
Ib: R = Me
Ic: R = Et



IIa: R = H
IIb: R = Me
IIc: R = Et
IId: R = CH_2—CH_2OH
IIe: R = CH_2—CH_2—NH—CO—Me



III

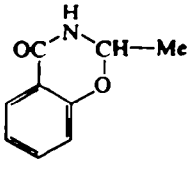
chain. In the case of Ia, formation of the strongly dextrorotatory isolysergic acid derivative[4] does not occur; therefore, the isomerization of Ia observed under these conditions does not involve a variation of configuration at C-8. The two isomeric dihydrolysergic acid α-hydroxyethylamides (IIa) are readily cleaved to dihydrolysergic acid amide and acetaldehyde, thus proving that they are epimeric compounds which differ only in the spatial arrangement of the substituents around the asymmetric carbon in the side chain.[6] A similar reversible isomerization to "aci-compounds" in acid medium has been described for the alkaloids of the ergotamine type, the reaction taking place in the peptide part of the molecule.[7]

When the α-hydroxyethylamides Ia or IIa are treated with alcohols in the presence of a weak acid, the reaction results in the formation of O-alkyl derivatives (Ib,c or IIb–IIe) which are easily cleaved to lysergic or dihydrolysergic acid amide by heating in either acid or alkaline aqueous solution.[6] Compounds IIb–IIe are obtained as mixtures of two diastereoisomers having opposite configurations at the asymmetric carbon in the side chain. By heating each individual isomer in the appropriate alcohol, and in the presence of weak acids, the mixtures of both epimers results. If, on the other hand, the reaction is carried out in another alcohol (R'OH, where R' ≠ R in

[4] The natural form of Ia—and the corresponding dihydroderivative—will be referred to as "epimer A"; the novel isomers will be indicated as "epimers B".

[7] W. Schlientz, R. Brunner, F. Thudium and A. Hofmann, *Experientia* 17, 108 (1961).

[6] A similar degradation in weakly alkaline soln is known to occur with certain peptide ergot alkaloids, for instance ergotamine, which also contains a substituted α-hydroxyalkylamide group [A. Stoll and A. Hofmann, *Helv. Chim. Acta* 33, 1705 (1950).] Analogously, 2H-2-methyl-1,3-benzoxazin-4-one (ii) is cleaved into salicylamide and acetaldehyde when heated with



ii

aqueous alkalis [W. L. Hicks, *J. Chem. Soc.* 97, 1032 (1910)].

the starting material) the epimeric mixture of the corresponding new O-alkyl derivative arises.

Although it seems reasonable to expect that the α-alkoxyethyl-amides Ib,c—resulting from the O-alkylation of Ia under identical conditions—also consist of epimeric mixtures, confirmatory evidence for such a case was not available: the products had a sharp m.p., appeared chromatographically homogeneous, and fractional crystallization failed to effect any separation. In absence of evidence to the contrary, we assume that compounds Ib,c were indeed mixtures of diastereoisomers.

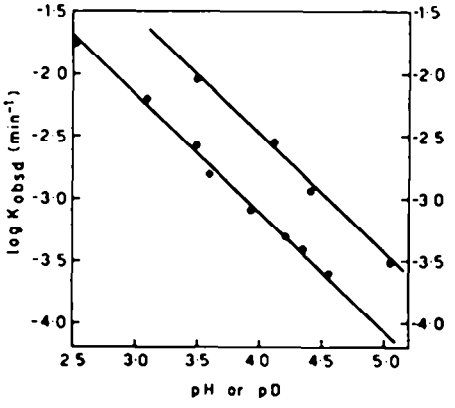
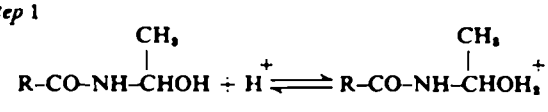


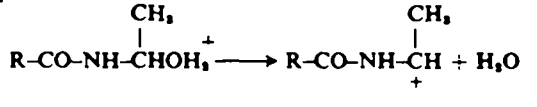
FIG. 1. Epimerization of IIa—Logarithm of the first order rate constants in H_2O as a function of pH ○, and in D_2O as a function of pD ●, at 24° and constant ionic strength 0·50.

The epimerization of IIa in water has been studied polarimetrically in order to gain information about its mechanism. The equilibrium mixture contains equal amounts of the two epimers, the final rotation being the mean value between the initial rotations of the two optically pure forms.[9] The reaction shows specific proton catalysis, the rate constant being directly proportional to the hydrogen-ion concentration (Fig. 1), but independent from the buffer concentration (Fig. 2).[10] The observed rate is faster in D_2O by a factor of 4 (Fig. 1). This result is consistent with a fast pre-equilibrium protonation of the substrate (Step 1), followed by a unimolecular rate determining step (Step 2).[11]

Step 1



Step 2



[9] For instance, epimer A (footnote 6) of IIa mutarotates in pH 4·0 acetate buffer from $[\alpha]_{644}^{24}$ −270° (*c* 0·5) to −200°; epimer B mutarotates from $[\alpha]_{644}^{24}$ −130° to −200°.

[10] A similar behaviour has been observed in the hydrolysis of simple acetals. See for instance C. K. Ingold, *Structure and Mechanism in Organic Chemistry* p. 334. Cornell University Press (1953); F. A. Long and M. A. Paul, *Chem. Revs.* **57**, 965 (1957).

[11] F. A. Long, *Ann. N.Y. Acad. Sci.* **84**, 596 (1960).

The magnitude of the entropy of activation ΔS^* is often used as a criterion to distinguish between an A-1 or A-2 mechanism.[18] The activation energy calculated from the temperature dependence of K_{obsd} (Fig. 3) is 18·15 Kcals mole^{-1}. Thus the ΔS^* value calculated for the mutarotation of IIa is $-5{\cdot}3$ cals deg^{-1} mole^{-1}. This value suggests an A-1 mechanism involving a slow rate-determining heterolysis to leave a planar carbonium ion (Step 2), the latter being then solvolysed to give the mixture of epimers (reverse of step 2), in agreement with the D_2O solvent isotope effect. The fact that the reaction does not proceed with III (in which the electron-donating methyl is replaced by the electron-withdrawing trichloromethyl group) is consistent with the proposed mechanism involving formation of the intermediate carbonium ion which, in the case of III, would be destabilized by inductive effect.

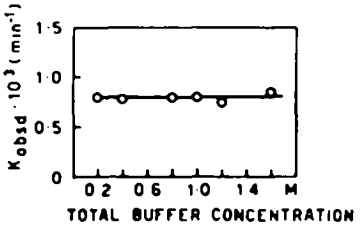


FIG. 2. Epimerization of IIa—Plot of first order rate constants against the total concentration of pH 4·0 acetate buffer at 24°; ionic strength maintained at 0·50 by addition of KCl.

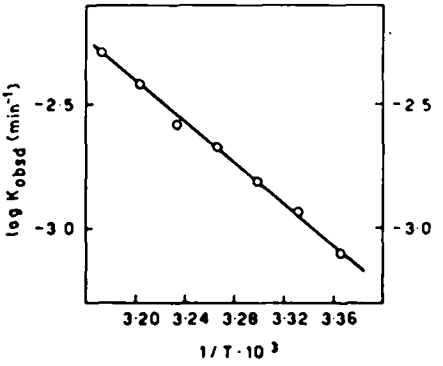


FIG. 3. Epimerization of IIa—Temperature dependence of K_{obsd} at pH 3·91 (0·8M acetate buffer); ionic strength maintained at 0·50 by addition of KCl.

EXPERIMENTAL

TLC on Kieselgel G Merk was employed for identification purposes and homogeneity tests, solvent system: AcOEt dimethylformamide, n-butanol, pyridine (60:45:45:15). All m.ps are uncorrected and, unless otherwise specified, were determined in capillary tubes. Rotations were measured at 20 ± 3°, unless otherwise stated, with a Perkin–Elmer 145 Polarimeter. IR spectra: KBr, Perkin–Elmer 21.

6-Methyl-8-ethylaminomethyl-Δ⁹-ergolene (*i*, R = H) *and 6-methyl-8-(N-ethyl-N-acetyl)aminomethyl-Δ⁹-ergolene* (i, R = Ac) *from natural lysergic acid α-hydroxyethylamide* (Ia) *and from lysergic acid ethylamide*

Compound Ia (2 g) was treated with LAH (2 g) in THF (60 ml). The mixture was refluxed 1 hr, then AcOEt and ice were added, and the resulting suspension centrifuged. The precipitate was washed with ether, and the combined supernatant and washings were dried over Na_2SO_4 and treated with an ethereal soln of maleic acid (2 g). The resulting oily precipitate was dissolved in a mixture of MeOH and ether from which the maleate of i (R = H) separated in crystalline form, yield 835 mg, m.p. 177–80° (dec), $[\alpha]_D$ +56° (*c* 0·8, water). (Found: C, 60·29; H, 6·40; N, 7·94. $C_{16}H_{22}N_2{\cdot}2C_4H_4O_4$ requires: C, 60·81; H, 6·08; N, 8·18%.) This compound (550 mg), dissolved in 5% Na_2CO_3aq (50 ml), was treated, under stirring, with Ac_2O (3 ml) at room temp. After 30 min, more Na_2CO_3aq (30 ml) and Ac_2O (1·5 ml) were added, and stirring continued for 1 hr. The reaction mixture was then

[18] F. A. Long, J. G. Pritchard and F. E. Stafford, *J. Amer. Chem. Soc.* 79, 2362 (1957); P. M. Collins, *Tetrahedron* 21, 1809 (1965), and references cited therein.

made strongly alkaline with Na_2CO_3, cooled and filtered. The solid precipitate (210 mg) was extracted with boiling benzene, and the extract evaporated to dryness *in vacuo*. The residue was recrystallized from EtOH (6 ml), yield 48 mg, m.p. 213–215°, $[\alpha]_D$ +93° (*c* 0·43 EtOH 95%). (Found: C, 74·37; H, 7·98; N, 12·77. $C_{36}H_{44}ON_4$ requires: C, 74·27; H, 7·79; N, 12·99%.)

Lysergic acid ethylamide (2·6 g), prepared from the mixed anhydride of lysergic acid and sulfuric acid,[13] was reduced with LAH as described above. The yield of the maleate of i (R = H) was 0·5 g, m.p. 175–177°. Acetylation of the whole sample yielded 45 mg of i(R = Ac), m.p. 213–215°, $[\alpha]_D$ +96° (*c* 0·5, EtOH). Both compounds showed IR spectra and chromatographic behaviour identical with those of the corresponding products prepared starting from the natural alkaloid.

Epimerization of lysergic acid α-hydroxyethylamide (Ia)

A soln of the natural Ia (epimer A, 2 g) in 2% aqueous maleic acid (100 ml) was allowed to stand 2 hr at room temp, then treated with excess solid $NaHCO_3$ and extracted with chf. The solid material (800 mg) which separated at the interface was collected, and after crystallization from acetone (19 ml) yielded 600 mg of starting material, m.p. 196–198° (dec), $[\alpha]_D$ +0·6° (*c* 1·0, pyridine), and +44° (*c* 1·0 EtOH). (Found: C, 69·66; H, 6·92; N, 13·59. $C_{18}H_{21}O_2N_3$ requires: C, 69·43; H, 6·80; N, 13·50%). The chf extract was evaporated *in vacuo* and the residue (800 mg), after crystallization from acetone (9 ml), yielded 700 mg of epimer B, m.p. 201–202 (dec), $[\alpha]_D$ −17° (*c* 1·0, pyridine) and +68° (*c* 1·0, EtOH). (Found: C, 69·39; H, 7·14; N, 13·39%.) The latter epimer, when treated with aqueous maleic acid as above, yielded starting material and epimer A. The IR spectrum of the natural epimer A shows the amide I and amide II band at 1665 and 1520 cm^{-1} respectively; the novel epimer B shows the same absorptions at 1640 and 1550 cm^{-1}.

Dihydrolysergic acid α-hydroxyethylamides (IIa) *from lysergic acid α-hydroxyethylamides* (Ia)

Compound Ia (2 g), as obtained from the fermentation broths of *Claviceps paspali* (epimer A), was hydrogenated at 50° and 50 atm in dioxane (100 ml) in the presence of 10% PdC (1 g). The yield of IIa (epimer A) was 1·4 g (from acetone), m.p. 260–263° (dec). IR spectrum: 1705 (acetone), 1640 (amide I) and 1525 (amide II band). (Found: C, 66·49; H, 7·88; N, 12·01. $C_{18}H_{23}O_2N_3 \cdot \frac{1}{2}CH_3COCH_3 \cdot \frac{1}{2}H_2O$ requires: C, 66·64, H, 7·74; N, 11·96%.) $[\alpha]_D$ −108° (*c* 1·0, pyridine), −98° (*c* 1·0, EtOH), and −71° (*c* 1·33, 1% maleic acid), the values of $[\alpha]_D$ being calculated for the dry substance. The observed value $E^{1cm}_{1\%}$ = 184 (at 281 mμ) corresponds to 88% dry wt (calc. 89%). At the Kofler hot stage this dihydro derivative appears as prismatic crystals which lose solvent at *ca.* 100°, undergo a transformation (chemical?) at 160°, begin to darken at 210–220° and decompose extensively at ca. 260°.

When 0·7 g of epimer B of Ia was hydrogenated as described above, there was obtained 0·25 g of the corresponding dihydro derivative, m.p. 260° (dec), $[\alpha]_D$ −57° (*c* 1·0, EtOH), identical with the compound obtained by epimerization of the dihydro derivative of natural Ia (see below).

Epimerization of dihydrolysergic acid α-hydroxyethylamide (IIa)

A soln of IIa (epimer A, 1 g) in 2% aqueous tartaric acid (50 ml) was left to stand 2 hr at room temp, then extracted with chf after addition of an excess of solid $NaHCO_3$. Starting material separated at the interface and was crystallized from acetone; yield 300 mg, $[\alpha]_D$ −98° (*c* 0·8, EtOH), and −71·5° (*c* 1·0, water containing 1% maleic acid). The chf extract was concentrated *in vacuo* to allow crystallization of epimer B, which was recrystallized from acetone; yield 220 mg, m.p. 260° (dec). (Found: C, 69·10; H, 7·47. $C_{18}H_{23}O_2N_3$ requires: C, 68·98; H, 7·40%); $[\alpha]_D$ −54° (*c* 1·15, EtOH) and −71·6° (*c* 1·0 water containing 1% maleic acid). At the Kofler hot stage epimer B appears as elongated rectangular plates which turn opaque at 160°, yield a sublimate at 230°, and undergo extensive dec at ca. 258°.[14]

Both epimers A and B, when heated for 20 min in 60% aqueous alcohol on a hot water bath, yielded acetaldehyde and dihydrolysergic acid amide. The former was isolated and identified as the

[13] W. A. Garbrecht, *J. Org. Chem.* **24**, 368 (1959).

[14] When 50 mg of this epimer was sublimed *in vacuo* at 226° it yielded 42 mg of thin crystals, showing $[\alpha]_D$ −133° (*c* 0·2 pyridine) and identical IR spectrum and chromatographic behaviour as dihydrolysergic acid amide.

2,4-dinitrophenylhydrazone (90% yield); the latter was identified by its elemental analysis and comparison of its m.p., $[\alpha]_D$, IR spectrum and chromatographic behaviour with those of an authentic specimen.

Dihydrolysergic acid α-hydroxy-β-trichloroethylamide (III)

A mixture of dihydrolysergic acid amide (10 g) and anhydrous chloral (26·2 g) in dioxane (220 ml) was stirred 60 hr at room temp. The resulting precipitate, essentially consisting of the less soluble epimer, was collected by filtration and crystallized from acetone, yield 4·3 g; m.p. 195° (dec), $[\alpha]_D$ −100° (*c* 1·0, pyridine). (Found: C, 52·13; H, 5·08; Cl, 25·39%.) The filtered soln, containing the more soluble epimer, was evaporated *in vacuo*, the residue washed with MeOH and ether, and crystallized twice from MeOH yield 2·2 g, m.p. 167° (dec) $[\alpha]_D$ −80° (*c* 1·0 pyridine). (Found: C, 52·19; H, 5·17; O, 7·51; N, 9·88; Cl, 24·62. $C_{18}H_{20}O_2N_2Cl_3$ requires: C, 51·88; H, 4·84; O, 7·68; N, 10·08; Cl, 25·52%.) The R_f values (TLC) of the two epimers were 0·7 and 0·9 respectively. Both isomers showed spectroscopic properties in agreement with the assigned structure. They did not show mutarotation even in 1M perchloric acid.

Lysergic acid α-alkoxyethylamides (Ib, c)

Lysergic acid α-methoxyethylamide (Ib). A soln of Ia(1 g) and maleic acid (0·4 g) in MeOH (30 ml) was refluxed for 30 min. On cooling the product precipitated as the maleate (0·99 g) which was recrystallized from MeOH; $[\alpha]_D$ +50° (*c* 1·85, dimethylformamide) and ill defined m.p. (Found [maleate]: C, 62·37; H, 6·06; N, 9·25. $C_{19}H_{23}O_2N_3 \cdot C_4H_4O_4$ requires: C, 62·57; H, 6·16; N, 9·52%.) The free base was isolated by treatment of an aqueous acetone soln of the maleate with Dowex 1-X4 resin (50–100 mesh, OH form), followed by filtration, removal of most of the acetone *in vacuo*, and extraction with chf. The residue obtained on evaporation of chf was crystallized from acetone, and yielded Ib (76% recovery); m.p. 166–167° (dec), $[\alpha]_D$ +50° (*c* 0·56, EtOH 95%).

Lysergic acid α-ethoxyethylamide (Ic). This was prepared in similar manner, yield 77%; m.p. 176–177° (dec), $[\alpha]_D$ +62° (*c* 1·0, EtOH). (Found [free base]: C, 70·68; H, 7·74. $C_{20}H_{25}O_2N_3$ requires: C, 70·77; H, 7·43%.)

Dihydrolysergic acid α-alkoxyethylamides (IIb-IIe)

General procedure. A soln. of IIa (1 mM) and maleic acid (1–1·5 mM) in the appropriate alcohol was heated at 70° for 2 hr. The crude IId and IIe (mixtures of isomers) were recovered as free bases by using Dowex-1-X4 resin as described above; comps IIb and IIc, instead, were removed from the reaction mixture by extraction with chf, after addition of an excess of solid $NaHCO_3$ and evaporation to near dryness. In all cases, repeated fractional crystallization of the crude materials from AcOEt allowed the separation of the two epimers.

α-Methoxyethylamide (IIb)

Less soluble epimer. Yield 36%; m.p. 224–225° (Kofler), $[\alpha]_D$ −68° (*c* 0·25, EtOH). (Found: C, 69·50; H, 8·10; N, 12·72. $C_{19}H_{24}O_2N_3$ requires: C, 69·70; H, 7·70; O, 9·77; N, 12·84%.) *More soluble epimer.* Yield 12%; m.p. 217–218° (Kofler), $[\alpha]_D$ −68° (*c* 0·25, EtOH). (Found: C, 69·42; H, 7·82; O, 9·94%.)

α-Ethoxyethylamide (IIc)

Less soluble epimer. Yield 24%; m.p. 213–214° (dec, Kofler), $[\alpha]_D$ −90° (*c* 0·2, EtOH). (Found: C, 70·36; H, 8·06; O, 9·46. $C_{20}H_{27}O_2N_3$ requires: C, 70·35; H, 7·97; O, 9·37, N, 12·31%.) *More soluble epimer.* Yield 23%; m.p. 198–199° (dec, Kofler), $[\alpha]_D$ −95° (*c* 0·2, EtOH). (Found: C, 70·30; H, 7·98; N, 12·52%.)

α-(2-Hydroxyethoxy)ethylamide (IId)

Less soluble epimer. Yield 28%; m.p. 231–232° $[\alpha]_D$ −75° (*c* 1·0 EtOH). (Found: C, 67·11; H, 7·58. $C_{20}H_{27}O_3N_3$ requires: C, 67·20; H, 7·61%); IR spectrum: primary alcohol absorption at 3600 and 1050 cm [1]

More soluble epimer. Yield 12% ; m.p. 209–212°, $[\alpha]_D$ −48° (*c* 1·0, EtOH). (Found: C, 64·35; H, 7·98. $C_{20}H_{27}O_3N_3 \cdot CH_3CO_2C_2H_5$ requires: C, 64·69; H, 7·92%.) IR spectrum: 1740 and 1240 (AcOEt); 1045 (CO) and a very broad O–H band (bonded).

α-(2-*Acetamidoethoxy)ethylamide* (IIe)

Less soluble epimer. Yield 24%; m.p. 228–230°, $[\alpha]_D$ −55° (*c*, 1·0 EtOH). (Found: C, 66·13; H, 7·77; O, 12·28; N, 13·70. $C_{18}H_{30}O_3N_4$ requires: C, 66·31; H, 7·59; O, 12·05; N, 14·06%.)

More soluble epimer. Yield 27%; m.p. 204–206° $[\alpha]_D$ −70° (*c* 1·0, EtOH). (Found: C, 66·31; H, 7·57.)

The members of each epimeric pair mentioned above showed—in addition to a different solubility—different chromatographic behaviour and IR spectrum. In particular, the solubility ratio of the two epimeric α-methoxyethylamides (IIb) was 2 to 1; these epimers were undistinguishable by TLC, but they showed two quite distinct spots when chromatographed on paper impregnated with pH 7 phosphate buffer and with chf as the solvent.[15]

When any epimer was treated with the parent alcohol and maleic acid under the conditions described above, the mixture of the two epimers resulted. In addition, when IIc (less soluble epimer), 0·5 g, was heated with 1,2-ethanediol and maleic acid, the mixture of the two epimeric IId was obtained. From the reaction mixture 0·166 g of the less soluble epimer and 0·103 g of the more soluble one could be isolated.

Cleavage of lysergic and dihydrolysergic acid α-ethoxyethylamides (Ic and IIc)

(a) *In acid solution.* A soln of Ic maleate (61 mg) in 1M phosphoric acid (3 ml) was heated on a steam bath while a vigorous stream of N was bubbled through. The outgoing gas was passed through two tubes each containing a saturated soln of 2,4-dinitrophenylhydrazine (25 ml) in 2N HCl. All acetaldehyde evolved was collected in the first tube as the 2,4-dinitrophenylhydrazone (24 mg, 80% of theory).

(b) *In alkaline solution.* Compound Ic (500 mg) was suspended in 125 ml of 66% aqueous EtOH and treated with 50 ml 1N NaOH. The mixture was heated under reflux for 1 hr, concentrated *in vacuo* and chilled. The precipitate, upon crystallization, yielded 80 mg lysergic acid amide and 50 mg isolysergic acid amide. TLC of the mother liquors of crystallization showed also presence of traces of starting material.

Compound IIc (100 mg) was suspended in 25 mg of 66% aqueous EtOH, and treated with 5 ml of 1N NaOH. The mixture, after heating under reflux for 1 hr, concentration *in vacuo* and chilling, yielded 70 mg of dihydrolysergic acid amide, $[\alpha]_D$ −130° (*c* 0·5 pyridine). Its IR spectrum and chromatographic behaviour was identical with those of an authentic sample.

Epimerization of dihydrolysergic acid α-hydroxyethylamide (IIa). *Kinetic measurements*

Kinetic studies were carried out in water and D_2O. Acetate and formate buffers were employed in the range 0·2 to 1·6M, the ionic strength being maintained at 0·50 all the times by addition of KCl. Measurements of pH were made with a glass electrode and a Metrohm E388 pH-meter. The pD was determined by the glass electrode correction formula of Fife and Bruice.[16] The rates of epimerization were measured by following the variation of optical rotation at 364 and 426 mμ. Temp was kept constant (±0·1°) by the use of jacketed polarimetric tubes. The buffer solutions were equilibrated in a thermostat before use. Compd IIa (epimer A or B) were weighed in 10 ml volumetric flasks which were then filled to mark with the proper buffer soln. Readings were taken beginning 5 min after the addition of buffer to the sample, and continued at intervals until the epimerization had proceeded to

[15] In addition, the less soluble epimer was found to show less than one tenth the activity of the more soluble one in antagonizing the action of epinephrine on the isolated guinea pig seminal vescicle. A similar trend was also observed in the series of the 1-methyl derivatives of compounds IIb–IIe (British Pat. 980,016, May 15, 1965; Canadian Pat. 724,185, Dec. 12, 1965); namely the *in vivo* and *in vitro* biological activity of the 1-methyl derivatives of the more soluble epimers was found to be constantly greater than that displayed by the analogous derivatives of the corresponding less soluble epimers. Specifically, in the case of the pair of epimeric α-methoxyethylamides IIb, the 1-methyl derivative of the more soluble isomer showed an anti-5-hydroxy-tryptamine activity on the rat paw oedema equal to 250, while that displayed by the 1-methyl derivative of the less soluble isomer was 75, the activity of lysergic diethylamide having been made equal to 100 (A. Glässer, personal communication).

[16] T. H. Fife and T. G. Bruice, *J. Phys. Chem.* 65, 1079 (1961).

completion. The final reading α_∞ was taken after a time interval equal to 5–10 half-lives. The results of each run were plotted on semi-logarithmic graph paper as $\alpha - \alpha_\infty$ vs. time, the value of $\alpha_\infty - \alpha_\infty$ being obtained by extrapolation at zero time. The epimerization reaction was treated as a unimolecular racemization $A \underset{K'}{\overset{K}{\rightleftharpoons}} B$ where $K = K'$. The first order rate constants ($K_{obsd} = K + K' = 2K$) were obtained from the slopes of plots of log $(\alpha_\infty - \alpha_0/\alpha - \alpha_\infty)$ against time. Precise first order plots were invariably obtained. All recorded values of K_{obsd} are mean values from two or three experiments, each experiment being carried out in duplicate runs with different concentrations of the solute (from 0·005 to 0·02 M). The values of K_{obsd} were reproducible to within $\pm 5\%$ and the results did not necessitate a statistical treatment. Values of the Arrhenius energy of activation (E) were obtained in the usual fashion from the gradient of the plot of K_{obsd} vs. the reciprocal of the absolute temperature. Values of $\Delta S^\ddagger$ were calculated from the Eyring equation (1), where $K_{H^+} = K/[H^+]$.

$$\ln K_{H^+} = \ln (ekT/h) + \Delta S^\ddagger/R - E/RT \quad (1)$$

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