On the Photo-transformation of Ergot Alkaloids

II. Lumilysergic Acids

HANS HELLBERG

Chemical Department, State Pharmaceutical Laboratory, Stockholm, Sweden

The preparation of the four theoretically possible lumilysergic acids is here reported together with a description of the physical properties of these substances such as the appearance of crystals, optical rotation, light absorption, pKₐ-values. A scheme for the identification of the acids by paper chromatography has been elaborated. Finally the stereochemical connections between the lumiacids on one hand and the lumialkaloids and the dihydroalkaloids on the other have been discussed and established with rather great probability.

Several series of lumiergot alkaloids are known today and there are good reasons for assuming that all their members derive from the four theoretically possible lumilysergic acids, which differ stereochemically at the atoms C₈ and C₁₉. Stoll and Schlientz have described the preparation of lumilysergic acid I, and — as preliminarily reported — we have now succeeded in preparing all four acids.

Paper chromatography was used for the identification of the lumilysergic acids. The first method was taken over from our previous work on the lumigométrins. It works with an acetic acidic aqueous phase and is here called "the acidic method". The main feature of the second method is the ammoniacal water phase, and it is therefore referred to as "the ammoniacal method".

Already in experiments on a micro scale, the products being identified only by paper chromatography, did we find four lumilysergic acids (Table 1). For a logical discussion we may provisionally denote them as A, B, C and D. In the acidic method the acids B and C do not differ in Rₚ-values, and in the ammoniacal method the difference between the Rₚ-values for A and D is too small to be of use for the purpose of identification. But used in combination the two methods give a fairly reliable identification of the lumilysergic acids.

The preparation of the lumiacids took place both by irradiation of lysergic and isolysergic acids in acidic solution, and by alkaline hydrolysis of lumialkaloids. The products were separated by partition chromatography on kieselguhr (celite) with the solvents from the methods on paper but in somewhat changed proportions. Details are given in the experimental part, but the results may be summarized as follows: —
Irradiation (acidic solution)

Lysergic acid → A + C (traces)
Isolysergic acid → B + A (small quantity) + C (small quantity) + D (traces).

Hydrolysis (KOH in 50 % ethanol, boiling 1 1/2 h)

Lumiergocristine I → A + B
Lumiergocristinine II → C + D

Thus the irradiation of lysergic acid gave an almost pure lumiacid in conformity with the behaviour of the alkaloids derived from lysergic acid. However, also isolysergic acid gave one strongly dominating product, unlike its alkaloidal derivatives, which on irradiation give the two possible C₉-alternatives in measurable yields. The appearance here of the acids A + C in small quantities may at least partly be attributed to a transformation of isolysergic acid into lysergic acid in the strongly acidic solution which was irradiated.

At the alkaline hydrolysis of both lumiergocristine I and lumiergocristinine II two acids were obtained in yields of comparable magnitude. However, the treatment of pure lumiacids with ethanolic KOH under the conditions of hydrolysis used did not cause any transformation detectable even by paper chromatography, and so the transformation occurring during the hydrolysis of the lumialkaloids must be coupled with the hydrolytic cleavage. Very probably it is an epimerization at C₉. According to Stoll et al., the same treatment of the analogous dihydroalkaloids leads to only one acid in each case. In the main this could be confirmed by us on paper chromatograms for dihydroergotamine I and dihydroergocristine I. Thus there seems to be a distinct difference between lumialkaloids and dihydroalkaloids in their ability to epimerize at C₉ on alkaline hydrolysis.

The stereochemical connections of the lumilysergic acids to lumialkaloids and dihydroalkaloids can, to begin with, be discussed on the basis of the preparative experiments made. If we postulate that the hydrolytic decomposition leads to an epimerization at C₉, the lumiacids A and B must be denoted as I while C and D must be assigned the figure II. From the results of the irradiation of lysergic acid it may be concluded that A is lumilysergic acid I. Then B must be lumisoalysergic acid I, which is not contrary to the results of the irradiation of isolysergic acid. The appearance of C and D, respectively, at the irradiation of lysergic and isolysergic acid, respectively, indicates that C is lumilysergic acid II and D lumisoalysergic acid II.

The connections thus made probable are corroborated by a comparison of the Rₜ-values obtained by the acidic methods for lumialkaloids in the first paper of this series and for lumiacids in this paper (Table 1). Using the same provisional nomenclature as in Ref. the scheme given there may be extended as follows:

* α denotes the slower and β the faster component of a pair of substances, probably having the same steric configuration at C₉.

Acta Chem. Scand. 12 (1958) No. 4
Table 1. Paper chromatography of lumilysergic acids (see experimental part).

<table>
<thead>
<tr>
<th></th>
<th>Acidic method</th>
<th>Ammoniacal method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumilysergic acid I (= substance A)</td>
<td>0.39</td>
<td>0.16</td>
</tr>
<tr>
<td>Lumiselysergic acid I (= substance B)</td>
<td>0.32</td>
<td>0.41</td>
</tr>
<tr>
<td>Lumilysergic acid II (= substance C)</td>
<td>0.32</td>
<td>0.06</td>
</tr>
<tr>
<td>Lumiselysergic acid II (= substance D)</td>
<td>0.48</td>
<td>0.18</td>
</tr>
</tbody>
</table>

$\alpha$-lumi-ine $\equiv$ lumine II; lumilys.acid II $= \alpha$-lumilys.acid.
$\beta$-lumi-ine $\equiv$ lumine I; lumilys.acid I $= \beta$-lumilys.acid.
$\alpha$-lumi-ine $\equiv$ lumine I; lumiselyls.acid I $= \alpha$-lumiselyls.acid
$\beta$-lumi-ine $\equiv$ lumine II; lumiselyls.acid II $= \beta$-lumiselyls.acid

Also a glance at those lumialkaloid and lumiacid pairs which are supposed here to be sterically similar at C₁₉ reveals a corresponding regularity, possibly with one weak point, viz. the lumiergometrine I and the lumiergometrine I, which show approximately identical $R_F$-values.

Finally reference may be made to the tentative discussion of the same sterical connections which appeared in the former paper of this series², where from an argument entirely different from those of this paper the same allotment of configurations was obtained.

EXPERIMENTAL

A. Paper chromatography

The acetic acid method has been described in the first paper of this series². The ammoniacal method was performed in a very similar way, the main difference being that the acetic acid was exchanged for ammonia. The solvent mixture had the following definite composition: Benzene, butanol, 2 M ammonia (1:3:4).

In Table 1 there are collected the average $R_F$-values of the lumilysergic acids, obtained with both methods.

B. Preparation of the lumilysergic acids

Irradiation of lysergic acid. A solution of 0.75 g of crystallized lysergic acid ($[\alpha]_D^{20} = +43^\circ; c = 1$ in pyridine) in 30 ml of 0.2 M HCl, kept air-free by a stream of N₂, was irradiated in a quartz flask until transformation ceased. (Time: ca. 3 h with a Hanovia S-4 U.V.-lamp). The dark blue solution was made alkaline with 3 ml of 5 M ammonia and saturated with a stream of CO₂. Gradually a crystalline substance, corresponding paper-chromatographically to lumilysergic acid I (substance A) was precipitated. The crystallization was completed over-night in the refrigerator. The precipitate was redissolved in 50 ml of 0.2 M ammonia and precipitated again with CO₂. Yield: 0.25 g of a light grey substance. Before the determination of physical constants (Tables 1, 2 and 3)

Acta Chem. Scand. 12 (1958) No. 4
Table 2. Summary of appearance and some physical properties of the lumilysergic acids (constants corrected to dry basis).

<table>
<thead>
<tr>
<th></th>
<th>Appearance</th>
<th>Heating on Kofler block</th>
<th>Optical rotation [α]D (c = 0.5) in 0.5 M HCl</th>
<th>Light Absorption (E (1 %, 1 \text{ cm})) in 0.1 M HCl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumilysergic acid I (substance A)</td>
<td>From water: Short pillars. From methanol: Long needles, breaking up to short rods</td>
<td>Decomposition at 240°C</td>
<td>+ 38°</td>
<td>224 at 283 μ (max.)</td>
</tr>
<tr>
<td>Lumisolysergic acid I (substance B)</td>
<td>From water: Conglomerate of thin plates</td>
<td>Melting and decomp. 185°—190°C</td>
<td>+ 47°</td>
<td>230 at 283 μ (max.)</td>
</tr>
<tr>
<td>Lumilysergic acid II (substance C)</td>
<td>From water: Rectangular plates</td>
<td>Melting and decomp. ca. 190°C</td>
<td>+ 10°</td>
<td>228 at 284 μ (max.)</td>
</tr>
<tr>
<td>Lumisolysergic acid II (substance D)</td>
<td>From methanol: Conglomerate of small apparently irregular crystals</td>
<td>Decomposition at 210°C</td>
<td>− 13°</td>
<td>205 at 281 μ (max.)</td>
</tr>
</tbody>
</table>

and elementary composition the lumilysergic acid I was recrystallized from a great quantity of methanol. (Substance dried in a high vacuum at 140°C. Found: C 65.85; H 6.44; N 9.54; O 16.88. Calc. for C₉H₇O₃N₂ (286.34): C 67.12; H 6.34; N 9.78; O 16.76). In the mother liquor of the first crystallization lumilysergic acid II (substance C) was identified by paper chromatography.

**Irradiation of isolysergic acid.** 0.5 g of crystallized isolysergic acid ([α]D between +260° and +270°; c = 1 in pyridine) dissolved in 7.5 ml of acetic acid and 20 ml of water was treated as the solution of lysergic acid. The irradiated solution was neutralized to pH 7 with ammonia and evaporated to dryness in a CO₂-atmosphere under reduced press-

Table 3. Estimated pKₐ-values for lysergic and lumilysergic acids. Water Solution. 22°C. (See experimental part.)

<table>
<thead>
<tr>
<th></th>
<th>pKₐ</th>
<th>pKₐ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lysergic acid *</td>
<td>3.22</td>
<td>7.93</td>
</tr>
<tr>
<td>Isolysergic acid *</td>
<td>3.12</td>
<td>8.57</td>
</tr>
<tr>
<td>Lumilysergic acid I</td>
<td>4.38</td>
<td>9.00</td>
</tr>
<tr>
<td>Lumisolysergic acid I</td>
<td>3.94</td>
<td>9.17</td>
</tr>
<tr>
<td>Lumilysergic acid II</td>
<td>3.42</td>
<td>8.33</td>
</tr>
<tr>
<td>Lumisolysergic acid II</td>
<td>3.38</td>
<td>9.20</td>
</tr>
</tbody>
</table>

*Ref.⁴ reports the following figures (24°C): Lysergic acid pKₐ = 3.19, 3.44; pKₐ = 7.96, 7.68. Isolysergic acid pKₐ = 3.21, 3.44; pKₐ = 8.31, 8.61.

* Acta Chem. Scand. 12 (1958) No. 4
sure. The residue, freed from the ammonium salts by sublimation at 60°C in a high vacuum, was subjected to partition chromatography. Column: 38 × 3.4 cm; 120 g of celite. Solvent mixture at the start: benzene, butanol, 2 M ammonia (1:1:2). The dominating fraction, lumiserylsergic acid I (substance B) came out as the second peak. After changing the eluent to the organic phase of the mixture benzene, butanol, 2 M ammonia (1:3:4) there were obtained two more small fractions. From the first of these ca. 20 mg of lumiserylsergic acid I (substance A) and from the second a few mg of lumiserylsergic acid II (substance C) were isolated. Lumiserylsergic acid II (substance D) was identified paper-chromatographically in the liquid fraction containing lumiserylsergic acid I.

The main fraction, containing lumiserylsergic acid I was evaporated in a vacuum (N₂-atmosphere). The residue, dissolved in 20 ml of 0.4 M ammonia, was filtered, neutralized with CO₂ and evaporated in a CO₂-atmosphere to a volume of ca. 2 ml. The lumiserylsergic acid crystallized from the solution. The yield, 120 mg, was recrystallized once from water. Physical properties in Tables 1, 2 and 3. (Substance dried in a high vacuum at 80°C. Found: C; 67.00 H 6.44; N 9.83; O 16.52. Calc. for C₇₆H₈₆O₂N₄ (286.34): C 67.12; H 6.34; N 9.78; O 16.76).

Hydrolysis of lumisergocrinine I. A solution of 1 g of crystallized lumisergocrinine I ([α]₂⁰ = +17°; c = 1 in pyridine) in 16 ml of M KOH in 50 % ethanol was boiled under reflux in an N₂-atmosphere for 1 1/2 h. After cooling most of the ethanol was evaporated in an N₂-atmosphere, and then the solution was saturated with CO₂ and evaporated to dryness in a CO₂-atmosphere, both distillations being made under reduced pressure. The residue was chromatographed as described in the former section, the eluent being changed after lumiserylsergic acid I (v. supra). The second and the third fractions were dominating and contained lumiserylsergic acid I (substance B) and lumiserylsergic acid II (substance A), respectively. After the removal of the solvent the residues were treated as described under the headlines "irradiation of isoserylsergic acid" and "irradiation of lysergic acid". The yields of crude crystalline material were 50 mg of lumiserylsergic acid I and 95 mg of lumiserylsergic acid II. The recrystallized products were identified through the physical properties given in Tables 1, 2 and 3. They were not submitted to elementary analysis.

Hydrolysis of lumisergocrinine II. 0.45 g of lumisergocrinine II (pure according to the criteria given in Part I of this series; Ref. 3) was hydrolyzed as described for lumisergocrinine I. The reaction mixture was neutralized with CO₂ and evaporated under reduced pressure in a CO₂-atmosphere. The residue was extracted with 100 + 50 + 50 ml of absolute ethanol, the filtered extracts evaporated to dryness in an N₂-atmosphere under reduced pressure and submitted to partition chromatography. Column: 40 × 3.4 cm; 140 g of celite. Solvent mixture at the start: benzene, butanol and 20 % acetic acid (1:1:2). Two main fractions were obtained, the first one containing lumiserylsergic acid II (substance D) and the second lumiserylsergic acid II (substance C). The fractions were evaporated to dryness.

The residue containing lumiserylsergic acid II was dissolved in 20 ml of 0.4 M ammonia. The solution was filtered, neutralized with CO₂ and evaporated in a CO₂-atmosphere to ca. 2 ml. The substance crystallized from this solution in a yield of 45 mg, and after recrystallization from water the material had the physical properties given in Tables 1, 2 and 3. (Substance dried in a high vacuum at 100°C. Found: C 67.20; H 6.36; N 9.51; O 16.56. Calc. for C₇₆H₈₆O₂N₄ (286.34): C 67.12; H 6.34; N 9.78; O 16.76).

The residue containing lumiserylsergic acid II having been dissolved in a few ml of methanol, the substance crystallized. The yield was 35 mg. After recrystallization from methanol lumiserylsergic acid II showed the physical properties given in Tables 1, 2 and 3. (Substance dried in a high vacuum at 80°C. Found: C 66.63; H 6.59; N 9.90; O 16.90. Calc. for C₇₆H₈₆O₂N₄ (286.34): C 67.12; H 6.34; N 9.78; O 16.76).

C. Determination of proteolytic constants

About 6 mg of the substance, dissolved in ca. 5 ml of CO₂-free water by the addition of ca. 0.25 ml of 0.1 N hydrochloric or methanesulphonic acid, were titrated potentiometrically with 0.02 N CO₂-free sodium hydroxide. The measuring system used (glass-electrode, calomel electrode, Radiometer PHM 3) was constantly and carefully calibrated by means.
of pH-standards (M/20 potassium hydrogen phthalate and M/20 sodium borate). The temperature was 22°C. The first equivalence point of the acids could be fixed by a sufficient pH-change. From this value the volumes for half-neutralization in either direction were calculated, using the weight of substance taken, the molecular weight of the acids and the normality of the sodium hydroxide. Then the pKₐ-values were read from the titration curve without further correction. The individual results obtained did not as a rule differ more than ±0.05 pH-units from the averages given in Table 3. pKₐ-values for the lysergic acids in aqueous solution have been determined by Craig et al.² Their figures, which do not seem to be very accurate, are not inconsistent with ours.

Acknowledgements. The elementary analyses were performed by Dr. Alfred Bernhardt, Max-Planck-Institut für Kohlenforschung, Mühlheim (Ruhr), which is gratefully acknowledged. My thanks are also due to Statens Medicinska Forskningsråd for financial support, and to Mrs M. Spilsbury, who revised the English.

REFERENCES


Received February 10, 1958.

Acta Chem. Scand. 12 (1958) No. 4