On the Photo-transformation of Ergot Alkaloids

II. Lumilysergic Acids

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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, pK_a -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 C_8 and C_{10} ^{1,2}. Stoll and Schlientz¹ have described the preparation of lumilysergic acid I, and — as preliminarily reported³ — 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 lumiergometrins². 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 R_F -values, and in the ammoniacal method the difference between the R_F -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 $\rightarrow$ A + C (traces)*Isolysergic acid* $\rightarrow$ B + A (small quantity) + C (small quantity) + D (traces).*Hydrolysis* (KOH in 50 % ethanol, boiling 1 1/2 h)Lumi ergocristine I $\rightarrow$ A + BLumi ergocristinine II $\rightarrow$ 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 C₁₀-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 lumi ergocristine I and lumi ergocristinine 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 C₈. According to Stoll *et al.*⁴ 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 C₈ 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 C₈, 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 *lumiisolysergic 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 *lumiisolysergic acid* II.

The connections thus made probable are corroborated by a comparison of the *R_F*-values obtained by the acidic methods for lumialkaloids in the first paper of this series² and for lumiacids in this paper (Table 1). Using the same provisional nomenclature as in Ref.² * 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 C₈.

Table 1. Paper chromatography of lumilysergic acids (see experimental part).

	R_F	
	Acidic method	Ammoniacal method
Lumilysergic acid I (= substance A)	0.39	0.16
Lumiisolysergic acid I (= substance B)	0.32	0.41
Lumilysergic acid II (= substance C)	0.32	0.06
Lumiisolysergic acid II (= substance D)	0.48	0.18

α -lumi-ine = lumi-ine II; lumilys.acid II = α -lumilys.acid.

β -lumi-ine = lumi-ine I; lumilys.acid I = β -lumilys.acid.

α -lumi-inine = lumi-inine I; lumiisolys.acid I = α -lumiisolys.acid

β -lumi-inine = lumi-inine II; lumiisolys.acid II = β -lumiisolys.acid

Also a glance at those lumialkaloid and lumiacid pairs which are supposed here to be sterically similar at C₁₀ reveals a corresponding regularity, possibly with one weak point, viz. the lumiergometrine I and the lumiergometrinine 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)

Table 2. Summary of appearance and some physical properties of the lumilysergic acids (constants corrected to dry basis).

	Appearance	Heating on Kofler block	Optical rotation $[\alpha]_D^{20}$ $c = 0.5$ in 0.5 M HCl	Light Absorption E (1 %, 1 cm) in 0.1 M HCl
Lumilysergic acid I (substance A)	From water: Short pillars From methanol: Long needles, breaking up to short rods	Decomposition at 240°C	+ 38°	224 at 283 m μ (max.)
Lumitsolysergic acid I (substance B)	From water: Conglomerate of thin plates	Melting and decomp. 185°–190°C	+ 47°	230 at 283 m μ (max.)
Lumilysergic acid II (substance C)	From water: Rectangular plates	Melting and decomp. ca. 190°C	+ 10°	228 at 284 m μ (max.)
Lumitsolysergic acid II (substance D)	From methanol: Conglomerate of small apparently irregular crystals	Decomposition at 210°C	– 13°	205 at 281 m μ (max.)

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 $C_{18}H_{18}O_3N_2$ (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 ($[\alpha]_D^{20}$ 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 CO_2 -atmosphere under reduced pres-

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

	pK_1	pK_2
Lysergic acid *	3.22	7.93
Isolysergic acid *	3.12	8.57
Lumilysergic acid I	3.38	9.00
Lumitsolysergic acid I	3.94	9.17
Lumilysergic acid II	3.42	8.33
Lumitsolvsergic acid II	3.38	9.20

* Ref.⁵ reports the following figures (24°C): Lysergic acid $pK_1 = 3.19$, 3.44; $pK_2 = 7.96$, 7.68. Isolysergic acid $pK_1 = 3.21$, 3.44; $pK_2 = 8.31$, 8.61.

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, lumisolysergic acid I (substance B) came out as the second peak. After changing the elutrient 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 lumilysergic acid I (substance A) and from the second a few mg of lumilysergic acid II (substance C) were isolated. Lumisolysergic acid II (substance D) was identified paper-chromatographically in the liquid fraction containing lumilysergic acid I.

The main fraction, containing lumisolysergic 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 lumisolysergic 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 C₁₈H₁₈O₃N₂ (286.34): C 67.12; H 6.34; N 9.78; O 16.76).

Hydrolysis of lumiergocristine I. A solution of 1 g of crystallized lumiergocristine I ($[\alpha]_D^{20} = +17^\circ$; $c = 1$ 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 elutrient being changed after lumisolysergic acid I (*v. supra*). The second and the third fractions were dominating and contained lumisolysergic acid I (substance B) and lumilysergic acid I (substance A), respectively. After the removal of the solvent the residues were treated as described under the headlines "irradiation of isolysergic acid" and "irradiation of lysergic acid". The yields of crude crystalline material were 50 mg of lumisolysergic acid I and 95 mg of lumilysergic acid I. 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 lumiergocristinine II. 0.45 g of lumiergocristinine II (pure according to the criteria given in Part I of this series; Ref.²) was hydrolyzed as described for lumiergocristine 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 lumisolysergic acid II (substance D) and the second lumilysergic acid II (substance C). The fractions were evaporated to dryness.

The residue containing lumilysergic 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 C₁₈H₁₈O₃N₂ (286.34): C 67.12; H 6.34; N 9.78; O 16.76).

The residue containing lumisolysergic acid II having been dissolved in a few ml of methanol, the substance crystallized. The yield was 55 mg. After recrystallization from methanol lumisolysergic 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 C₁₈H₁₈O₃N₂ (286.34): C 67.12; H 6.34; N 9.78; O 16.76).

C. Determination of protolytic 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 pK_a -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. pK_a -values for the lysergic acids in aqueous solution have been determined by Craig *et al.*⁵ Their figures, which do not seem to be very accurate, are not inconsistent with ours.

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