On the Photo-Transformation of Ergot Alkaloids

IV. Lumilysergic Amides

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An account is given of methods leading to the four possible lumilysergic amides. Three of the substances have been prepared in crystalline form. The physical and chemical properties of the amides are described, as well as their stereochemical relation to the four lumilysergic acids.

In attempts to produce lumilysergic acids on a preparative scale from commercially available mixtures of ergot alkaloids, the yields were very poor. When studying the causes of this drawback, it was observed that if the final alkaline hydrolysis of the lumi alkaloid mixtures was performed too cautiously, considerable quantities of a by-product were obtained, whose chromatographic properties resembled those of the lumiergometrine series. It appeared as a first fraction in partition-chromatographic separation of the expected acids on kieselguhr (celite), impregnated with an ammoniacal aqueous phase. The substance lay close to the front line on ammoniacal paper chromatograms, and separated into three spots, with R_F values ranging from 0.2 to 0.5, on acetic acid paper chromatograms (For methods: see Ref.² and Experimental).

As early as 1932, Smith and Timmis^{4,5} showed that ergot alkaloids, on moderate treatment with methanolic potassium hydroxide, gave rise to ergine. In their further studies of this substance they found that, on strong alkaline hydrolysis, it yielded lysergic acid⁶, but that it was actually the amide of isolysergic acid⁷. Stoll and Hofmann⁸ demonstrated that dihydroergotamine I, and corresponding dihydro compounds of other peptide alkaloids, yielded dihydrolysergic amide I on cautious treatment with alkali. They pointed out that a specific cleavage took place, due to the labile nature of the so-called peptide part of the alkaloids.

Consequently, it was reasonable to assume that the by-product obtained on hydrolysis of the lumi ergot alkaloids consisted of lumilysergic amides. In the course of the present work, four such substances appeared — in complete agreement with the theoretical considerations — and were initially denoted arbitrarily as A, B, C, and D.

Lumilysergic amides from lumi alkaloids. Paper-chromatographic analysis of the products of alkaline hydrolysis, under the standard conditions used earlier (1 M KOH in 50 % ethanol, boiling water bath), showed that lumiergocristine I and lumiergocristinine II disappeared already within 5 minutes, but that the yield of acids was poor after this short time. Instead, the amide fraction was large. Cleavage of lumiergocristinine I could not be kept in the amide stage, even by this brief treatment, but continued to acids. It was, however, possible to obtain an amide yield from this alkaloid as well by using 95 % ethanol as solvent, and lower temperature (60°C for 45 min). The conditions for amide cleavage of lumiergocristine II, which is relatively difficult to prepare, were not tested separately.

The amide cleavage of available lumiergocristines (described in detail under the heading of Experimental) can be summarized as follows:

A remarkable feature is that the amide produced from lumiergocristinine I is the same as that from lumiergocristine I. Despite the fact that disruption of the molecule takes place more than two atoms beyond C₈, epimerization can evidently occur at this carbon atom. This was confirmed by the results obtained with lumiergocristinine II.

Lumilysergic amides from ergine (isolysergic amide). Irradiation of ergine in 0.1 M HCl (in analogy with treatment of the ergometrine alkaloids in Ref.¹) resulted in only one amide, *i.e.*, substance A, instead of the expected two. When irradiation of ergine was performed in 5 % acetic acid instead, it yielded — in addition to A — a substance that could be presumed to be D. This was the only method which led to recovery of D, and the substance could not, unfortunately, be obtained in crystalline form. In attempts to purify it further, it was rapidly destroyed. This experience, as well as the results of the cleavage of lumi alkaloids, indicates that substance D is labile.

Place of the amides in the stereochemical system. In view of the appearance of substance C on cautious hydrolysis of lumiergocristine I and lumiergocristinine I, it is highly probable that it belongs to series I. Substances A and B

probably belong to series II, since they are obtained in a corresponding way from lumiergocristinine II. A and D, which occur on illumination of the isolysergic amide (ergine), seem likely for this reason to be lumi-isolysergic amides.

Thus, the methods of preparation already seem to afford good reason to use the following denotations:

- Substance C: lumilysergic amide I
- Substance D: lumi-isolysergic amide I
- Substance B: lumilysergic amide II
- Substance A: lumi-isolysergic amide II

Additional evidence in favour of this statement is given by the physical and chemical properties of the substances, summarized in Table I. Thus, decided support is provided by the results of strong alkaline hydrolysis of the amides A, B and C. Although D was an impure product, the results confirm that the substance does, at any rate, belong to series I.

The UV spectra proved, to some extent, to be typical of the various lumilysergic acids and their derivatives. The chief characteristics were the details of the structure around $283\text{ m}\mu$, and the exact position of the maximum close to this wave-length. Substance C showed the distinct maximum at $283\text{ m}\mu$, normal for derivatives in the I series, and an inflexion point at $290\text{ m}\mu$. Substance A had its maximum and inflexion point displaced 2–3 $\text{m}\mu$ towards shorter wave-lengths, which is normal for derivatives of lumi-isolysergic acid II. Substance B had a flattened peak with a maximum at $284\text{ m}\mu$, which is characteristic of derivatives of lumilysergic acid II.

The order of appearance on chromatograms does not, in view of its highly empirical nature, furnish particularly strong proof for arrangement of isomers in stereochemical systems. The aforementioned denotations are, however, in good agreement with the order of appearance of lumiergometrines on alumina¹, and with that of lumilysergic acids on paper (Ref.², acetic acid method). The agreement with the lumiergometrines on paper¹ is not, however, as good.

EXPERIMENTAL

As a rule, the experiments were first made on a micro scale under varying conditions, and the products were studied by paper chromatography, using the methods described earlier².

The amides were denoted as A, B, C, and D, according to the order in which they were produced. Amides and acids were identified in the course of the work by paper chromatography, using the solvents benzene, butanol and 20 % acetic acid (1 + 1 + 2), as described in a previous paper². The products obtained by the different procedures were further characterized by means of their crystalline appearance, melting point on the Kofler block, UV spectrum in 0.1 M HCl, and IR spectrum in a KBr plate. Most of these properties are listed in Table I.

Substances C (lumilysergic amide I) and A (lumi-isolysergic amide II) were produced in sufficient quantities to permit elementary analyses. The following results were obtained:

Lumilysergic amide I, dried in high vacuum at 140°C . Found: C 67.20; H 6.69; N 14.86; O 11.37. Calc. for $\text{C}_{16}\text{H}_{19}\text{O}_2\text{N}_3$ (285.34): C 67.34; H 6.71; N 14.73; O 11.21.

Lumi-isolysergic amide II, dried in high vacuum at 100°C . Found: C 66.86; H 6.76; N 14.89; O 11.14. Calc. for $\text{C}_{16}\text{H}_{19}\text{O}_2\text{N}_3$ (285.34): C 67.34; H 6.71; N 14.73; O 11.21.

Amides from a lumi alkaloid mixture. 5 g of "Secale Mischalkaloide, Anton v. Waldheim, Wien", containing more than 95 % of ergot alkaloids, was isomerized by boiling

Table 1. Physical and chemical properties of the lumilysergic amides.

	Appearance	Heating on Kofler block	Light absorption in 0.1 M HCl (dry basis)	Optical rotation $[\alpha]_D^{20} c = 1$ in 0.1 M HCl (dry basis)	Lumilysergic acids on strong alkaline hydrolysis (cf. Ref. ¹)	Paper chromatogram, HAc method (Ref. ¹) ** R_F
Lumilysergic amide I (Substance C)	From methanol: small pillars	Decomposition at 250°C	Max: 283 m μ $E(1\%, 1\text{ cm}) = 229$ Infl.pt. 290 m μ	+ 21°	I + small amt. iso I	~ 0.29
Lumi-isolysergic amide I * (Substance D)					I + iso I	~ 0.25
Lumilysergic amide II (Substance B)	From methanol: small prisms	Melting and decomposition at 155°C	Max: 284 m μ $E(1\%, 1\text{ cm}) = 199$ *** Flattened peak		II + minute amt. iso II	~ 0.21
Lumi-isolysergic amide II (Substance A)	From methanol: thick, usually broken pillars	Melting point: 153 – 154°C (decomp.)	Max: 281 m μ $E(1\%, 1\text{ cm}) = 231$ Infl. pt. 288 m μ	+ 22°	II + iso II	~ 0.39

* Impure amorphous product.

** R_F values not directly comparable with those in Ref.¹ and Ref.²

*** Calculated on undried substance.

with 50 ml of methanol in an N_2 atmosphere for 2 days. The precipitate was filtered off, and allowed to dry in the air. Yield: 3.5 g with high positive optic rotation ($[\alpha]_D$ about $+500^\circ$ in 1% $CHCl_3$ solution).

The precipitate was transformed into lumi alkaloids in portions of 0.35 g, which were dissolved in 5 ml of concentrated acetic acid, and diluted to 100 ml with water. Irradiation and extraction were performed as described for ergocristine in Ref.¹ The main part of the coloured material was removed from the product by extraction with ether, using the method given in Ref.³ Yield 1.4 g.

The lumi alkaloid mixture was boiled with 20 ml of 1 M KOH in 50% ethanol in a water bath for 15 min and then treated as described below for lumiergocristine I. The first fraction obtained in partition chromatography (column 50×3.5 cm) contained three amides, i.e., substances A, B and C. Later fractions contained small quantities of lumilysergic acids. The amide fraction was separated by chromatography on alumina (80×2 cm Al_2O_3 , according to Brockmann, Merck), using gradient elution with chloroform containing 0 to 10% ethanol. The content of lumilysergic acid derivatives was measured spectrophotometrically at $283 m\mu$ in the eluates. The three amides separated; A appeared first, followed by B and then by C. There was a large preponderance of A (lumi-isolysergic amide II), the yield being 100 mg, whereas B (lumilysergic amide II) and C (lumilysergic amide I) were obtained in quantities of only about 10 mg. All three were crystallized from methanol.

Amides from lumiergocristine I. 0.5 g of lumiergocristine I was boiled in a water bath for 8 min with 20 ml of 1 M KOH in 50% ethanol. After cooling, the mixture was saturated with CO_2 to pH 7, when 200 ml of absolute alcohol were added. Saturation with CO_2 was allowed to continue for a short time, after which the precipitate was centrifuged off. The solution was evaporated to dryness. The residue of the alcoholic solution was chromatographed on a kieselguhr (celite) column (50×2 cm) with benzene, butanol and 2 M ammonia (1 + 1 + 2). The first fraction contained substance C only, i.e., lumilysergic amide I. (Two additional, smaller fractions were obtained, containing lumi-isolysergic acid I and lumilysergic acid I, respectively). Lumilysergic amide I was crystallized from methanol. Yield 90 mg.

Amides from lumiergocristinine I. 0.1 g of lumiergocristinine I in 5 ml of 1 M KOH in 95% ethanol was heated in a water bath at $60^\circ C$ for 45 min under aeration with nitrogen. The ethanolic solution was worked up in the same way as in the case of lumiergocristine I. Two fractions were obtained. The first contained substance C, i.e., lumilysergic amide I, and the second lumi-isolysergic acid I. Paper-chromatographic analyses before and after chromatography on Al_2O_3 showed only an inappreciable quantity of lumilysergic acid I in addition to the aforementioned substances. No spot which could be interpreted as substance D (lumi-isolysergic amide I) was observed. Yield of lumilysergic amide I 9 mg.

Amides from lumiergocristinine II. 0.5 g of lumiergocristinine II was treated in the same way as lumiergocristinine I (see above). The residue after evaporation of the ethanolic solution was chromatographed directly on an Al_2O_3 column (80×2 cm) with chloroform containing 0–10% ethanol (gradient elution). An inappreciable fraction, identified by paper chromatography as substance B (lumilysergic amide II) appeared first, followed by the main fraction, consisting of substance A (lumi-isolysergic amide II). Lumi-isolysergic amide II was obtained by crystallization from a minute quantity of methanol. Yield 60 mg.

Photo-transformation of ergine in 0.1 M HCl. 0.25 g of ergine in 25 ml of 0.1 M HCl was irradiated with an UV lamp, under the conditions described in detail in Ref.¹ for ergocristine. 6.5 g of NaCl and 0.65 g of $Na_2HPO_4 \cdot 2 aq$ were added to the solution, as well as 2 M NaOH to pH 9. The mixture was extracted with 6×50 ml of $CHCl_3$. The chloroform phases were dried with anhydrous Na_2SO_4 , and evaporated to dryness *in vacuo*. The dry residue was transferred to a small quantity of washed sea sand, and placed on an Al_2O_3 column (80×2 cm, according to Brockmann, Merck). The column was eluted with chloroform containing 0–10% ethanol (gradient elution). Only one fraction of any appreciable size was obtained, and was found to consist of substance A (lumi-isolysergic amide II). Yield 15 mg. None of the small fractions obtained could be shown to contain any lumilysergic amide.

Photo-transformation of ergine in acetic acid solution. 0.25 g of ergine was dissolved in 2.5 ml of concentrated acetic acid, and diluted with 25 ml of water. The solution was

treated as in the preceding experiment. Two fractions were obtained, both containing more than one lysergic acid derivative. The main component of the first fraction was probably substance D. Unfortunately, it could not be obtained in crystalline form, since it was rapidly destroyed on attempts to purify it. The main component of the second fraction from Al_2O_3 chromatography was substance A (lumi-isolysergic amide II).

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