# PHOTOCHEMICAL ISOMERS OF TROPOLONE ALKALOIDS

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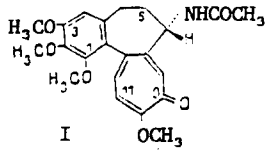
This review, which covers the literature up to 1989, generalizes advances in the field of the study of the photochemical isomers of colchicine and tropolone alkaloids related to it. Information is given on their natural sources, methods of isolation, structure, and configuration, and photochemical and thermal interconversions. Characteristics distinguishing them from the topolone alkaloids in their UV, IR, mass, and $^{1}H$ and $^{13}C$ NMR spectra of the photochemical isomers are pointed out.

The tropolone alkaloids colchicine and its accompanying alkaloids produced by plants of the genus Colchicum L. and many other genera of the family Liliaceae, readily undergo various rearrangement reactions under the effect of light and a number of chemical agents [1]. The most interesting and widespread among the products of these reactions are photochemical isomers obtained by the irradiation of the tropolone alkaloids, which have also been isolated from numerous colchicine-containing species of plants. At the present time, photochemical isomers of almost all tropolone alkaloids are known, and they form a large group of plant substances. However, in spite of the considerable number of publications, including a monograph by Kuhn et al. [2] and a number of publications of review nature [3-6], information on this interesting class of colchicine alkaloids requires generalization.

As is well known, the main representatives of the tropolone alkaloids, colchicine and colchamine, are powerful antimitotic substances and find use in biology and medicine. Colchicine mitosis is due to the disorganizing action of colchicine on the microtubules of the mitotic apparatus of the cell because of interaction with the protein tubulin and inhibition of the formation of microtubules [7-9]. In contrast to colchicine, lumicolchicine does not affect mitosis and does not stimulate the formation of polyploid nuclei [10, 11], since it does not bind with the protein microtubules and does not interfere with them, but it does inhibit the transport of thymidine and uridine [12].




I

The change in colchicine (I) under the action of light was known long before the complete determination of its structure [13]. However, it was only in 1946 that Grewe [14] first succeeded in isolating and characterizing the product of the transformation of colchicine by irradiating its aqueous solution with a powerful source of UV light. This gave a small amount of a new crystalline substance with a different melting point and UV spectrum. It was called lumicolchicine.

In 1951, Šantavý [15], by irradiating crystals of colchicine with sunlight for five years isolated lumicolchicine-I with a 20% yield. When, however, a solution of colchicine was irradiated with UV light as was done by Grewe, he obtained lumicolchicine-I (20%) and the previously unknown lumicolchicine-II in very low yield (1%). In these experiments the bulk of the colchicine did not change. Almost simultaneously, both these photochemical products of colchicine were isolated by Šantavý from the autumn crocus (Colchicum autumnale L.) [16, 17].

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TABLE 1. Physical Constants of the Lumicolchicines

| Compound | mp, °C | $[\alpha]_D$ in $CHCl_3$, deg | mp °C | $[\alpha]_D$ in $CHCl_3$, deg | Rf in $SiO_2$ |
|---|---|---|---|---|---|
| | from [18] | | from [2] | | |
| Colchicine | 155 | −120 | 150—151 | −153 | 0,18 |
| α-Lumicolchicine | | | | | |
| in the hydrated form | 164 | +81 | 164 | +95 | 0,35 |
| anhydrous | 206 | +105 | (209—210) | +98 | 0,35 |
| β-Lumicolchicine | | | | | |
| in stable form | 183 | +304 | 186 | +341 | 0,60 |
| γ-Lumicolchicine | 206 | +309 | 209—210 | +341 | |
| | 268 | −445 | 276—279 | −447 | 0,45 |

Šantavý [16] showed differences in the chemical properties of colchicine and the lumicolchicines. He established that the carbonyl group in a lumicolchicine, in contrast to that in colchicine, readily forms functional derivatives (oxime) and is more difficult to reduce polarographically. The photochemical isomers do not change under the action of reagents causing a rearrangement of the tropolone ring. They do not give a positive Oberlin-Zeisel reaction for the presence of a tropolone ring.

At the same time, Grewe and Wulf [18], by irradiating a dilute aqueous solution of colchicine with sunlight, converted it completely into photochemical isomers and isolated compounds which they called α-, β-, and γ-lumicolchicines. In its physical constants, β-lumicolchicine corresponded to lumicolchicine-I, and γ-lumicolchicine to lumicolchicine II that had been isolated by Santavý.

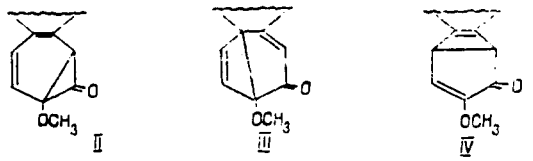
All three photochemical products had the same empirical formula as the initial colchicine ($S_{22}H_{25}O_6N$) but differed greatly in their physical constants (Table 1).

The lumicolchicine and the photochemical isomers of other tropolone alkaloids isolated later are colorless well-crystallizing substances. The melting points of the majority of them, particularly those of the γ-series, are considerably higher than those of the tropolone alkaloids corresponding to them. Furthermore, these compounds differ strongly in their specific rotations. Because of features of their configuration, the β- and γ-series of compounds differ with respect to both the sign and the value of the specific rotation. The dextrorotatory isomers belong to the β-series and the levorotatory isomers to the γ-series of the lumicolchicines [2-4]. The great change in their specific rotation relative to the initial compound is explained by the appearance in the molecule of new asymmetric centers at C-8 and C-12.

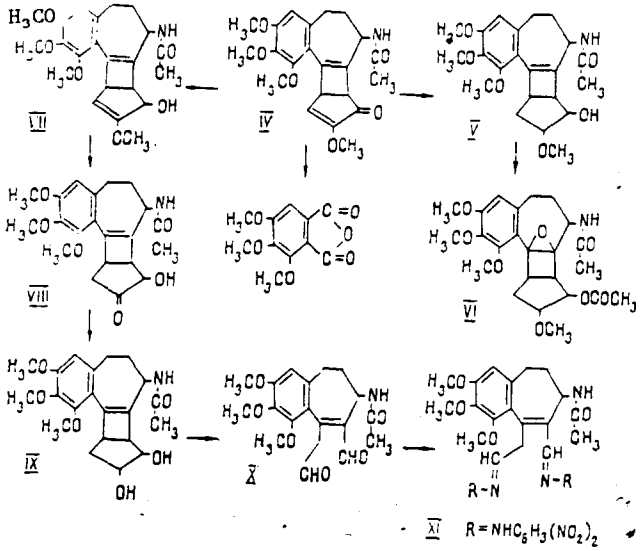
On catalytic hydrogenation in the presence of platinum oxide the β- and γ-lumicolchicines formed tetrahydro derivatives [18] while colchicine added three molecules of hydrogen, being converted into a hexahydro derivative [19, 20]. On titration with perbenzoic acid, the tetrahydro-β- and tetrahydro-γ-lumicolchicines each added one atom of oxygen, being converted into epoxy compounds, which showed the retention in their molecule, as in hexahydrocolchicine, of one ethylenic double bond. These results showed the tetracyclic structure of the lumicolchicine, i.e., the appearance of a new ring as the result of a rearrangement of the tropolone of colchicine in the process of photochemical isomerization.

After investigations by Forbes, the tetrahydrolumicolchicines and their epoxy derivatives obtained by Grewe and Wulf [18] can be represented by the general formulas (V) and (VI) (Scheme 1).

Considering three possible variants of the rearrangement of the tropoline ring of colchicine — (II), (III), and (IV) — using IR spectra and chemical transformations of the lumicolchicines, Forbes [21] came to the conclusion that the last of the structures with coupled cyclobutene and cyclopentene rings was preferable. Their absorption spectrum contained the absorption band of a carbonyl group in a five-membered ring, while the dihydrolumicolchicines are readily hydrolyzed in dilute acids, which shows the presence of a methyl enol ether grouping in them.



On the basis of the facts given above, the great similarity of the UV and IR spectra of the β- and γ-lumicolchicines, and chemical transformations (see Scheme 1), Forbes [21] came to the conclusion that these compounds do not differ structurally but only stereochemically. β-Lumicolchicine was reduced with sodium tetrahydroborate to the dihydro derivative (VII) the product of the hydrolysis of which – the ketoalcohol demethyldihydro-β-lumicolchicine (VIII) – on reduction with sodium tetrahydroborate formed the diol (IX). This diol was oxidized with sodium hypoiodite to the dialdehyde (X). The latter, in contrast to the dialdehyde formed in the oxidation of hexahydrocolchicine [22] did not undergo the aldol condensation; the C-8–C-12 bridge bond excludes the possibility of such condensation.

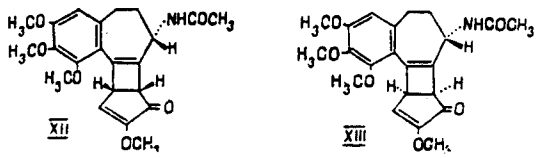


Scheme 1

In these reactions, γ-lumicolchicine showed complete analogy with β-lumicolchicine forming only configurationally differing derivatives. The periodate oxidation of the corresponding diols (IX) led to one and the same dialdehyde (X), which was identified in the form of the bis-2,4-dinitrophenylhydrazone (XI) [21]. Possible differences in the stereochemistry of these two photochemical isomers of colchicine have also been discussed.

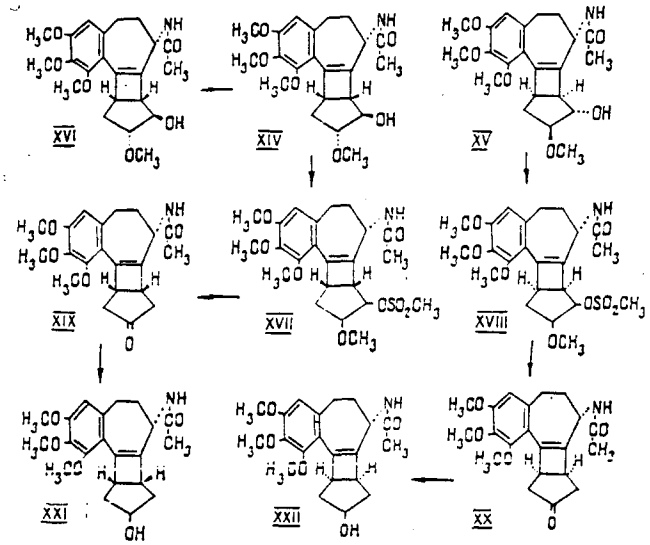
The retention of the pentasubstituted benzene ring in β- and γ-lumicolchicines was confirmed by their oxidation to 1,2,3-trimethoxyphthalic acid, and the retention of the acetamide group by their IR spectrum (1642 $cm^{-1}$) [21]. It was also established that β- and γ-lumicolchicines, in contrast to colchicine, do not change under the action of dilute acids, alkalis and sodium alcoholates. From β-lumicolchicine, in addition to the oxime, a dioxime and a 2,4-dinitrophenylosazone were obtained, these being formed after demethylation in the C-10 position [21].

Gardner et al. [23] confirmed the structure of (IV) proposed for the lumicolchicines by a UV spectroscopic study. They showed that existence of a bathochromic shift of the absorption maximum in the UV spectra of tetrahydro-β- and tetrahydro-γ-lumicolchicines due to the presence of the cyclobutene fragment in their molecules. In addition, it was established that the coefficient of molar absorption in nonpolar solvents changed to a greater extent with an increase in the concentration in the case of tetrahydro-γ-lumicolchicine than in that of tetrahydro-β-lumicolchicine. On this basis it was concluded that an intermolecular bond was present in tetrahydro-β-lumicolchicine and an intramolecular one in its γ-isomer. Structure (XII) with the cis arrangement of the acetamide group and ring D was put forward for β-lumicolchicine and structure (XIII) with the trans arrangement for γ-lumicolchicine.



Correspondingly, their tetrahydro derivatives have structures (XIV) and (XV) (scheme 2). A consideration of their structures on models also showed that with the cis configuration of the acetamide group and ring D the existence of an intermolecular hydrogen bond between the hydroxy group at C-9 and the amide carbonyl is possible. This is excluded in the case of the trans configuration.

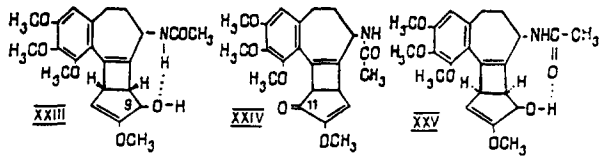
The base-catalyzed isomerization of β-lumicolchicine into γ-lumicolchicine in boiling methanolic solution was performed, which confirmed the stereoisomeric relationships between them.



Scheme 2

Gardner et al. [23] also made an attempt to pass from the lumicolchicines back to troponoid compounds. With this aim, from tetrahydro-β- and tetrahydro-γ-lumicolchicines they obtained the corresponding methanesulfonates (XVII) and (XVIII) which were converted by solvolysis into the ketones (XIX) and (XX). The latter were reduced with sodium tetrahydroborate to the corresponding alcohols (XXI) and (XXII). As a result, substances with an unchanged tetracyclic structure were obtained.

Chapman et al. [24] in a study of β- and γ-lumicolchicines and their dihydro derivatives by PMR spectroscopy found that in both dihydro-β- and dihydro-γ-lumicolchicine the signal of the NH group was greatly shifted downfield and appeared at 8.60 ppm, while in the spectrum of dihydro-β-lumicolchicine the signal of its proton had a chemical shift of 6.46 ppm. This shows the participation of the amide group in the formation of a hydrogen bond with the alcoholic hydroxyl at C-9. Such a hydrogen bond is possible between the acetamide and hydroxyl groups only if they are located on the same side of the molecule in the cis configuration (XXIII).

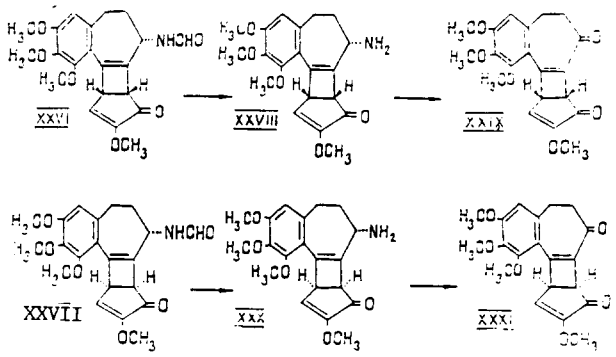


The facts mentioned confirmed the position of the carbonyl group at C-9 in the lumicochicines, excluding the other possible position, C-11 (XXIV).

In dihydro-γ-lumicolchicine the signal of the amide proton (6.68 ppm) is shifted downfield to a smaller extent in relation to the corresponding proton in γ-lumicolchicine (5.70

ppm). In addition to this, the proton of the alcoholic hydroxyl resonates in a weaker field (5.40 ppm) than the corresponding proton of dihydro-β-lumicolchicine (4.47 ppm). This showed the participation of the hydroxy group in the formation of an intramolecular hydrogen bond (XXV).

Thus, it has been shown that an intramolecular hydrogen bond arises in dihydro-β-lumicolchicine between the hydrogen of the amino group and the oxygen of the hydroxyl in ring D, while in dihydro-γ-lumicolchicine it arises between the hydrogen of the hydroxyl of ring D and the oxygen of the acetamide group. Furthermore, on comparing the integral intensities and chemical shifts of the protons of the methylene and methine groups in the lumicolchicines and colchicine, Chapman et al. [24] came to the conclusion that ring B of colchicine remains unaffected during photochemical isomerization.

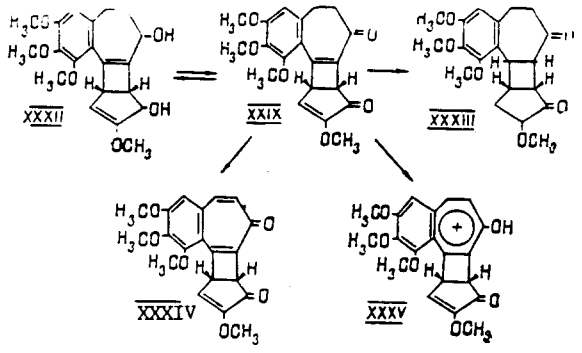


Scheme 3

A direct proof of the diastereomeric relationships of structures (XII) and (XIII) for β- and γ-lumicolchicine was provided by Canonica et al. [25], starting from N-formyl-N-deacetyl-β- and N-formyl-N-deacetyl-γ-lumicolchicines ((XXVI) and (XXVII), Scheme 3). By the action of 1 N hydrogen chloride in methanol, (XXVI) was hydrolyzed to N-deacetyl-β-lumicolchicine (XXVIII), which was then oxidized by ninhydrin to β-lumicolchicone (XXIX).

In a similar way, γ-lumicolchicone (XXXI) was obtained from (XXVII). The lumicolchicones isolated (XXIX) and (XXXI) proved to be identical with respect to melting points (195°C) and spectral characteristics but had opposite signs of their optical rotations (+346° and −342°, respectively).

β-Lumicolchicone was also isolated by Canonica et al. [26] from the plant Malabar glory lily (Gloriosa superba L.) and its structure was completely demonstrated (Scheme 4).



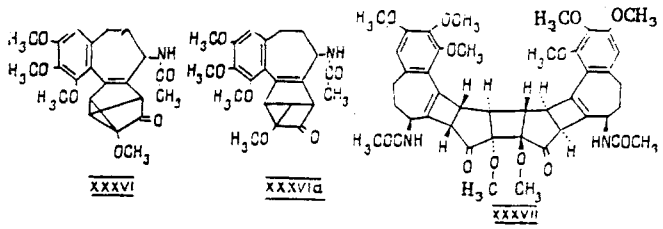
Scheme 4

The reduction of (XXIX) with sodium tetrahydroborate gives the diol (XXXII) and its catalytic hydrogenation with palladium on calcium carbonate the tetrahydro derivative (XXXIII). The IR spectrum of the latter retains the absorption band of the carbonyl groups in seven-membered and saturated five-membered rings (1742 and 1701 $cm^{-1}$, respectively). The dehydrogenation of (XXIX) with selenium dioxide gives the dehydro derivative (XXXIV), in the PMR spectrum of which the signals of olefinic protons appear at 7.35 and 6.80 ppm with the spin-spin coupling constant J = 13 Hz. In trifluoroacetic acid, β-lumicolchicone forms the tropylium cation (XXXV).

The structure of α-lumicolchicine was studied by Schenck et al. [27] and by Chapman et al. [28, 29]. They established that this compound differed considerably in structure and properties from β- and γ-lumicolchicines. Its PMR spectrum lacked the signal of an olefinic proton in ring D, and the number of aliphatic protons was once more. The UV spectrum showed the presence of only a trimethoxystyryl chromophore, and the IR spectrum showed the absence of an enol group.

Investigations by the above-mentioned authors showed that α-lumicolchicine, unlike β- and γ-lumicolchicines does not form functional derivatives of the carbonyl group, although the presence of this group was established from the IR spectrum. A feature distinguishing α-lumicolchicine from β- and γ-lumicolchicines is the absence from it and its dihydro derivative, formed by tetrahydroborate reduction, of a double bond capable of being hydrogenated catalytically; nevertheless, the presence of a double bond in it was shown, as in the case of β- and γ-lumicolchicines, with the aid of reactions with per-acids and bromine water. Like the β- and γ-isomers, α-lumicolchicine does not change under the action of sodium methanolate, and all the methoxy groups in it and its dihydro derivative are stable in relation to mineral acids. From this followed the conclusion that the methoxy group of ring B in it is not present at a double bond and is aliphatic.

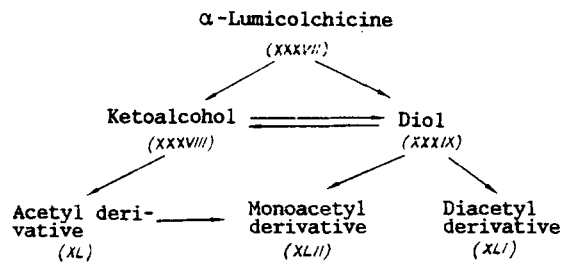
On the basis of the information given above, Schenck et al. [27] proposed for α-lumicolchicine the probable structure (XXXVI).



XXXVI XXXVIa XXXVII

Subsequently [2], structure (XXXVIa) as a variant of (XXXVI) was also considered for α-lumicolchicine. However, from the facts given above and from additional results, Chapman et al., drew a different conclusion, and for α-lumicolchicine they proposed the dimeric structure (XXXVII). In their opinion, in this compound the five-membered ring D is a saturated cyclopentanone ring, which can be explained only by the formation of a photodimer. As facts confirming this the authors adduced the ready thermal conversion of α-lumicolchicine into β-lumicolchicine and the formation of α-lumicolchicine when β-lumicolchicine was irradiated.

Dihydro-α-lumicolchicine – the ketoalcohol (XXXVIII) (scheme 5), obtained by the reduction of α-lumicolchicine (XXXVII) with one equivalent of sodium tetrahydroborate – is photochemically and thermally stable. On being heated above its melting point (284°C) it decomposes into β-lumicolchicine, dihydro-β-lumicolchicine, and other compounds, which have not been studied. On the reduction of α-lumicolchicine with an excess of sodium tetrahydroborate, the diol (XXXIX) was obtained. The oxidation of this ketoalcohol and this diol with chromium trioxide again led to β-lumicolchicine. From (XXXVIII) and (XXXIX) were obtained the corresponding mono- and diacetyl derivative ((XL) and (XLI)). The tetrahydroborate reduction of the acetyl derivative of the ketoalcohol (XL) led to a compound identical with the monoacetyl derivative of the diol (XLII). The reverse transition of these alcohols to the corresponding ketones by their oxidation with chromium trioxide was also performed.




Scheme 5

The molecular masses of the diol and its mono- and diacetyl derivatives and of the acetyl derivative of the ketoalcohol determined by the Rast method showed the dimeric structure of α-lumicolchicine [29].

In addition, Chapman et al. [29] directed their attention to the shift of the signal of the aliphatic methoxy group of ring D in the PMR spectrum into an unusually high field (3.02 ppm) and came to the conclusion that this is the result of the diamagnetic screening by an unsaturated group. In their opinion, this unsaturated group is the carbonyl group present in the other half of the dimeric structure and located fairly close to the methoxy group and, thanks to this, effectively screening it. On considering different variants of the dimerization of β-lumicolchicine molecule, the authors came to the conclusion that the diamagnetic screening of the methoxy group by the ketone group was possible only in the cases of a head-to-head dimeric structure with the trans-linkage of the two β-lumicolchicine molecules, which corresponds to structure (XXXVII).

In this structure, the aliphatic methoxy groups are located in such a way that, on rotation, each of them, passes directly above the carbonyl group in the other half of the molecule and thus intersects the region of maximum screening. When the carbonyl groups are reduced, the effect of the screening of the methoxy groups disappears.

The NMR spectra of α-lumicolchicine and its derivatives agree with the dimeric composition and spatial structure proposed for α-lumicolchicine. The presence of intermolecular and intramolecular hydrogen bonds in it has been established.

In spite of such voluminous information given by Chapman et al. to substantiate a dimeric structure for α-lumicolchicine, Kuhn et al. [2] were unable to obtain results unambiguously confirming a monomeric or dimeric structure. In a comparative determination by various methods of the molecular masses of α-, β-, and γ-lumicolchicine, a number of their derivatives, colchicine, colchicerine, and some other related compounds, they obtained ambiguous results, depending on the method and the solvent used. For example, by Singer's method double (dimeric) molecular masses were found for α- and dihydro-α-lumicolchicines in acetone, methanol, and chloroform. A double molecular mass was also found mass-spectrometrically for dihydro-α-lumicolchicine. Monomeric molecular masses were obtained for these compounds in dimethyl sulfoxide, naphthalene, and phenol, and so on. Thus, these results did not give a clear answer about molecular mass and, consequently, the monomeric or dimeric nature of the structure of the α-lumicolchicine.

Assuming that reduction by one mole of sodium tetrahydroborate of two carbonyl groups in one molecule of the compound (dimer) was more probable than that of one carbonyl group in separate molecules (monomers), Kuhn et al. [2] carried out the reduction of α-lumicolchicine as a "dimer." They recovered part of the α-lumicolchicine in unchanged form, which appeared to be evidence in favor of its monomeric structure. At the same time, the results of some experiments performed by Chapman et al. could not be reproduced by these authors. Furthermore, Kuhn et al., report that if the dimerization of β-lumicolchicine into α-lumicolchicine takes place on irradiation, it remains incomprehensible why on illumination cycloadducts consisting of two molecules of γ-lumicolchicine, β- and γ-lumicolchicines, or β-lumicolchicine and 10-demethyl-β-lumicolchicine (lumicolchiceine B) are not obtained.

On considering the structure of lumicolchiceine A — a compound analogous to α-lumicolchicine — Kuhn et al. [2] also report that the results of a chemical study and of a determination of its molecular mass did not make it possible to answer the question of whether it was a monomeric valence isomer formed on oligomeric associate or a dimeric adduct in which a new ring had been formed.

The structure of α-lumicolchicine and lumicolchiceine A as monomeric or dimeric compounds remains unelucidated. At the same time, the conclusion of Kuhn et al. in favor of a monomeric structure for these compounds based on the absence of similar dimerization in other cases can be disputed on the basis of the assumption that dimerization does not take place in them because of different spatial conditions, different local charge states of the molecules, or the photolability of the dimers formed.

The yields and quantitative ratios of the products of the photoisomerization of colchicine depended on the source of light, the solvent, the concentration of the substance, the duration of the reaction, and some other factors [2, 15, 18, 27, 29]. The yields of the individual isomers (Table 2) are connected to a certain degree with their capacity for undergoing further photochemical interconversion, and this also explains the divergences in the results of the authors mentioned.

TABLE 2. Yields of Lumicolchicines in Photochemical Reactions (%)

| Authors and references | Lumicolchicines | | | Colchicine (recovery) |
|---|---|---|---|---|
| | α | β | γ | |
| Šantavý [15] | — | 20 | 1 | 61 |
| Grewe and Wulf [18] | 31 | 23 | 15 | — |
| Forbes [21] | 5,2 | 79 | 6,5 | — |
| Chapman et al. [29] | — | 25 | 3,8 | — |
| Schenck et al. [27] | 52 | 22 | 5 | — |
| Kuhn et al. [2] | 57,6 | — | — | |
| " | 46,0 | 19,5 | 19,9 | — |
| " | 5,6 | 45 6 | 15,3 | — |
| " | — | 46,0 | 19,5 | — |

According to some reports [18, 29], α-lumicolchicine is not formed on the irradiation of colchicine by sunlight, while according to others [2] it is formed in very low yield as an impurity in the β- and γ-isomers. Thus, the irradiation of 2.0 g of colchicine in 500 ml of water with sunlight by Kuhn et al. yielded 1.36 g (67.9%) of β-lumicolchicine, 0.11 g (5.5%) of γ-lumicolchicine, 0.69 g (34.4%) of a decomposition product, and only 0.015 g (0.75%) of α-lumicolchicine.

Kuhn et al. [2, 27] have carried out fundamental work on the reactions involved in the photochemical isomerization of colchicine and the interconversions of the lumicolchicines using the sources of UV light under very different conditions. The yields and ratios of the photochemical isomers in the reaction products varied greatly.

On irradiation of dilute ($10^{-3}$ M) solutions, β- and γ-lumicolchicines are isomerized reversibly. The irradiation of β-lumicolchicine in chloroform or methanol leads to a sucessive fall in the magnitude of the positive rotation of the solution and then to change in sign to the opposite. This is explained by the conversion of part of it into the γ- isomer which has a negative specific rotation. The process is completed by the formation of a mixture of equal amounts of these substances showing in combination a negative rotation $[\alpha]_D$ −48°. On the irradiation of γ-lumicolchicine under the same conditions the opposite process takes place (its conversion into the β-isomer, but only with a decrease in the value of the negative rotation of the solution).

The ratio of β- and γ-isomers in solutions, i.e., the course of the photochemical isomerization reaction, was monitored polarometrically and by thin-layer chromatography [2].

On irradiation in saturated ($5 \cdot 10^{-3}$ M) solutions β-lumicolchicine is converted into α-lumicolchicine (yield about 38%). In contrast to this, on irradiation in solutions ($10^{-4}$ M) and in the solid state, α-lumicolchicine is converted quantitatively into β-lumicolchicine. At the beginning of irradiation the value of the positive rotation of the solution increases to a maximum corresponding to β-lumicolchicine. Then it decreases, passing into the region of negative values and settles at the equilibrium value mentioned, corresponding to a mixture of equal amounts of β- and γ-lumicolchicines. This shows that the formation of γ-lumicolchicines begins only after the complete conversion of the α-lumicolchicine into β-lumicolchicine. α-Lumicolchicine is converted photochemically only into β-lumicolchicine, and α- and γ-lumicolchicines are not converted into one another.

By using irradiation corresponding to the absorption maximum of colchicine, Schenck et al. [27] succeeded in avoiding the reverse conversion of α-lumicolchicine into colchicine. When colchicine was irradiated with light having $\lambda > 334$ nm they obtained α-lumicolchicine with a yield of about 52%.

It follows from what has been said above that the first period of the photoisomerization of colchicine is β-lumicolchicine, and then the photoisomers are reversibly converted to one another [2].

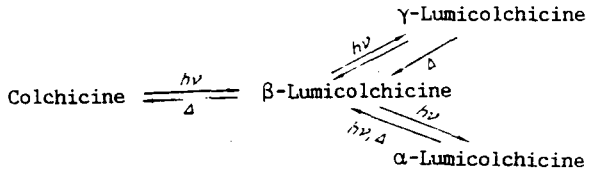
α-Lumicolchicine is less stable, both photochemically and thermochemically, than β-lumicolchicine. On being heated above 100°C in the solid state and in solutions it is converted quantitatively into β-lumicolchicine with mp 209-210°C (see Table 1). Because of this, α-lumicolchicine does not lower the melting point of β-lumicolchicine. When α-lumicolchicine is heated to the melting point (164°C), this transition takes place

instantaneously. The thermal conversion of α-lumicolchicine into β-lumicolchicine has been performed by a number of authors [2, 27-29].

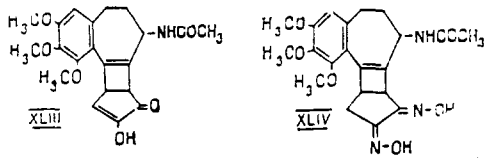
β-Lumicolchicine is also formed thermally, but in low yield. As also for simple tropolones [30, 31], rearrangements in the reverse direction – to a tropolone structure from a lumi- structure – have been performed for the lumicolchicines, but under different conditions. For example, on being heated to the melting point or on sublimation (300°C), β-lumicolchicine isomerizes into α-colchicine with a 12.3% yield. Heating γ-lumicolchicine to 290°C also gives a small amount of colchicine, together with β-lumicolchicine [2].

The thermal isomerization of β- and γ-lumicolchicines into α-colchicine shows that the centers of symmetry present in the colchicine molecule [32] and in ring B [33] do not change during photochemical isomerization. Furthermore, these transformations confirm that the isomeric structures (XII) and (XIII) proposed by Gardner [23] are possible for β- and γ-lumicolchicines and they exclude structure (XXIV) discussed by Chapman et al. [21].

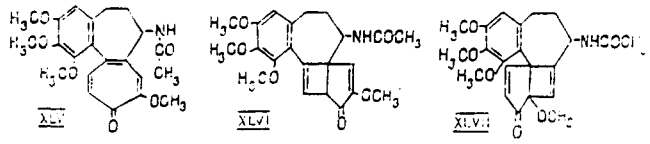
Gardner et al. [2] have generalized the photochemical and thermal interconversion of colchicine and the lumicolchicines by the following scheme:




The products of the irradiation with UV light of two very close derivatives of colchicine – colchiceine and isocolchicine have been studied. Schank et al., on irradiating colchiceine, obtained compounds which they called lumicolchiceine A and lumicolchiceine B. Their structures were elucidated by chemical transformations and a spectral study. The structure of the first of the compounds, with mp 236-240°C and $[\alpha]_D$ −236°, as 10-demethyl-α-lumicolchicine (α-lumicolchiceine) was confirmed by methylation with diazomethane to α-lumicolchicine. The second compound proved to be β-lumicolchiceine (XLIII), as was confirmed by the identity of its dioxime with the dioxime (XLIV) obtained from demethyl-β-lumicolchicine [21].

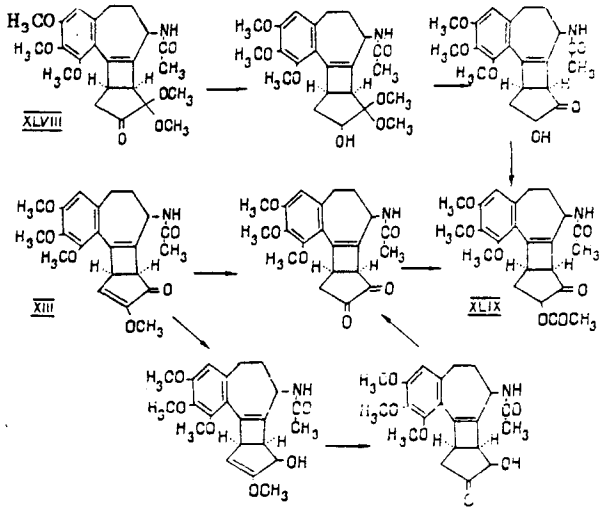



The photochemical isomerization of isocolchicine (XLV) was studied by Dauben and Cox [34] and by Chapman et al. [35]. They isolated two new compounds. After their study in comparison with the products of the photochemical isomerization of the methyl ether of α-tropolone [36] and of β- and γ-lumicolchicines and on the basis of IR-spectral characteristics, the probable structures (XLVI) and XLVII) were proposed for one of them. The results of UV and PMR spectroscopy and chemical transformations confirmed structure (XLVI) for lumiisocolchicine.




The second, similar, compound from the photochemical reaction of isocolchicine proved to be a product of the addition of the solvent, methanol, to ring D of reaction product (XLVIII) (Scheme 6). According to the scheme proposed by the authors, in the reaction the addition of a methanol molecule to the initial comopund first takes place and then a structure corresponding to lumicolchicine arises. A somewhat different mechanism for this reaction has also been suggested [5]. On the basis of the identity of the enol acetates (XLIX) obtained from this compound and from γ-lumicolchicine (XIII) it was established that the

adduct formed belongs to the γ-lumicolchicine series, and its structure was determined. Later, the authors prepared this adduct from γ-lumicolchicine.



Scheme 6

Kuhn et al. [2] also studied the photochemical reactions of colchiceine and isocolchicine and the chemical, photochemical, and thermal interconversions of lumicolchiceines A and B. In addition, they investigated the photochemical isomerization of colchamine, N-acetylcolchamine, oxycolchicine, the adduct of colchicine with maleic anhydride, allocolchicine, allocolchiceine, and colchicinol methyl ether. In view of the absence of a tropolone ring from them, the last three compounds did not form similar photochemical isomers [2, 15]. Other authors [5] have obtained photochemical isomers of colchicamide (Table 3) and of isocolchicamide, mp 198-199°C, $[\alpha]_D$ −158°.

The influence of the elements of the structure of the tropolone alkaloids on the course and result of photoisomerization has been considered in [5, 35, 37]. It has been found that the trimethoxystyryl grouping directs the formation of a new bond between the C-8a and C-11 atoms and not between C-9 and C-12a as should be expected by analogy with the methyl ether of α-tropolone [36]. It has also been found that the course of the reaction is affected by the presence of a hexadiene ring [37]. Other authors [35] have found that isocolchicine exhibits greater stability than colchicine in the photoisomerization reaction.

However, the dependence of the yields of photochemical derivatives of tropolone alkaloids on their structure has remained almost unstudied. It is possible to give only a few indirect facts relating to this question. In the epigeal part of Kesselring's autumn crocus (Colchicum kesselringii Rgl.) the fraction of alkaloids with a phenolic nature consists mainly of 3-demethylcolchicine (alkaloid C) and 2-demthyl-β-lumicolchicine (alkaloid D). The 3-demethyl-β-lumicolchicine (alkaloid K-12) and 2-demethylcolchicine (alkaloid E) corresponding to them were not detected in this plant [38]. A considerable noncorrespondence between the amounts of 2- and 3-demethylcolchicines and their photochemical isomers has also been observed in some other plants studied by us [39, 40]. From this the hypothesis followed that the tropolone alkaloids containing a hydroxy group in the aromatic ring, especially in the C-2 position, undergo the photochemical reaction considerably more readily than the completely methylated compounds (colchicine, etc.).

Other examples are known of the fact that different tropolone alkaloids are not converted into their photochemical isomers to the same degree in plants. β-Lumicolchicine has been isolated from all colchicine-containing plants, while β-lumicolchamine has been detected only in certain species. Colchamine is obviously less subject to photochemical isomerization than colchicine. We have also observed an acceleration of the photoreaction with an increase in the volume of the substituent attached to the nitrogen in the case of speciosine and speciosamine.

From the observations reported above it is possible to make the assumption that substituents both in the trimethoxystyryl grouping and in the cyclohexadiene ring exert a definite influence on the rate and direction of the photochemical reaction.

TABLE 3. Photochemical Isomers of the β-Series

| Compound | Designation | No. | Composition | mp, °C | $[\alpha]_D$, deg | Photochemical partial synthesis | First isolated from the following plants |
|---|---|---|---|---|---|---|---|
| 1. β-Lumicolchicine | I | XII | $C_{22}H_{25}O_6N$ | 183—185 | +304 | 14, 15, 18 | Colchicum autumnale [16, 17, 53] |
| 2. 2-Demethyl-β-lumicolchicine | D | L | $C_{21}H_{23}O_6N$ | 235-237 | +294 | 15, 54 | . |
| 3. 3-Demethyl-β-lumicolchicine | $S_2$, K-12 | LI | $C_{21}H_{23}O_6N$ | 202—203 | +337 | 55 | Gloriosa superba, Colchicum kesselringii [55, 56] |
| 4. β-Lumicolchiceine (lumicolchiceine B) | — | XLIII | $C_{21}H_{23}O_6N$ | 146—147 | +189 | 27 | — |
| 5. Acetyl-2-demethyl-β-lumicolchicine | — | LII | $C_{23}H_{25}O_7N$ | 228 | | 54 | — |
| 6. β-Lumicolchicoside | — | LIII | $C_{27}H_{33}O_{11}N$ | 185 | +82 | 57 | — |
| 7. β-Lumicornigerine | CC-16 | LIV | $C_{21}H_{21}O_6N$ | 262 | +339 | 54 | Colchicum cornigerum [58] |
| 8. N-Formyl-N-deacetyl-β-lumicolchicine | $S_4$ | LV | $C_{21}H_{23}O_6N$ | 214—215 | +340 | 54, 55 | Gloriosa superba [55] |
| 9. 3-Demethyl-N-formyl-N-deacetyl-β-lumicolchicine | $S_1$ | LVI | $C_{20}H_{21}O_6N$ | 248—249 | +362 | 55 | Gloriosa superba [55] |
| 10. β-Lumicolchamine | | LVII | $C_{21}H_{25}O_5N$ | 185 | +306 | 59 | Colchicum autumnale [60] |
| 11. 2-Demethyl-β-lumicolchamine | | LVIII | $C_{20}H_{23}O_5N$ | 190 | | 54 | — |
| 12. 3-Demethyl-β-lumicolchamine | | LIX | $C_{20}H_{23}O_5N$ | 148 | | 54 | — |
| 13. N-Methyl-β-lumicolchamine | | LX | $C_{22}H_{27}O_5N$ | Amorph. | | 54 | Colchicum speciosum |
| 14. N-Acetyl-β-lumicolchamine | | LXI | $C_{23}H_{27}O_6N$ | 132—133 | +410 | 54, 59 | Colchicum speciosum |
| 15. N-Formyl-β-lumicolchamine | | LXII | $C_{22}H_{25}O_6N$ | 188 | +432 | 54 | — |
| 16. β-Lumicolchicamide | | LXIII | $C_{21}H_{24}O_5N$ | 208—209 | | 5 | — |
| 17. β-Lumispeciosine | | LXIV | $C_{28}H_{31}O_6N$ | 174—176 | | | Colchicum speciosum |

An influence of substituents in the aromatic ring on the photochemical reaction, although of somewhat different nature, has also been observed in the homoproaporphine bases that accompany the tropolone alkaloids in Central Asian species of autumn crocus. It has been established that a base with aphenolic hydroxy group in the C-2 position (luteine, kesselringine) [41-44] undergoes photochemical oxidation considerably more readily than a compound with the methoxy group in the C-1 position (jolantamine, luteidine) [45, 46] and, particularly, relative to completely methylated substances (regeline, regelidine) [47, 48].

The influence of various solvents on the quantum yield of the products of the photoisomerization of colchicine has been studied [49].

The facts given above are an example of how photochemical reactions cause deep structural changes in plant substances the investigation of which may throw light on some role of the alkaloids in metabolic processes. It may be assumed that the photochemical isomers of alkaloids are formed as the result of definite biochemical processes in the plant accompanied by the absorption or evolution of a certain amount of energy. Hypotheses have been put forward on the possibility of the formation of lumicolchicines from colchicine in the plant in vivo without the action of light [50].

Because the photochemical reactions of the tropolone alkaloids may take place under the direct action of sunlight and without it, in some cases doubt may arise as to the native nature of individual photochemical compounds of plants. This is all the more the case since the majority of lumi- derivatives isolated from plants are isomers of the tropolone alkaloids present simultaneously in them.

TABLE 4. Photochemical Isomers of the γ-Series

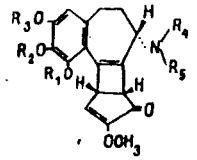
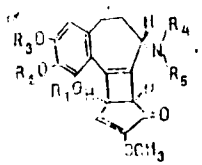
| | Compound | Designation | No. | Composition | mp, °C | $[\alpha]_D$, deg | Photochemical partial synthesis | First isolated from the following plants |
|---|---|---|---|---|---|---|---|---|
| 1. | γ-Lumicolchicine | | XIII | $C_{22}H_{25}O_6N$ | 272—274 | —445 | 15, 18 | Colchicum autumnale [53] |
| 2. | 2-Demethyl-γ-lumicolchicine | L-6 | LXV | $C_{21}H_{23}O_6N$ | 291—293 | —440 | 54 | Colchicum luteum [61] |
| 3. | 3-Demethyl-γ-lumicolchicine | K-13 | LXVI | $C_{21}H_{23}O_6N$ | 287—288 | —420 | — | Colchicum kesselringii [62] |
| 4. | Acetyl-2-demethyl-γ-lumicolchicine | | LXVII | $C_{23}H_{25}O_7N$ | 289 | —447 | 54 | — |
| 5. | 2-Demethyl-N-methyl-γ-lumicolchicine, glucoside | M | LXVIII | $C_{28}H_{35}O_{11}N$ | 310—314 | —310 | — | Colchicum autumnale [63] |
| 6. | γ-Lumicolchicoside | | LXIX | $C_{27}H_{33}O_{11}N$ | 250—252 | —320 | 57 | — |
| 7. | γ-Lumicornigerine | CC-8 | LXX | $C_{21}H_{21}O_6N$ | 330 | —550 | 54 | Colchicum cornigerum [58] |
| 8. | N-Formyl-N-deacetyl-γ-lumicolchicine | | LXXI | $C_{21}H_{23}O_6N$ | 255—257 | —580 | 54, 55 | Gloriosa superba [55] |
| 9. | 2-Demethyl-γ-lumicolchamine | | LXXII | $C_{20}H_{23}O_5N$ | 235 | | 54 | — |
| 10. | 3-Demethyl-γ-lumicolchamine | CC-9 | LXXIII | $C_{20}H_{23}O_5N$ | 250 | —430 | 54 | Colchicum cornigerum [58, 64] |
| 11. | N-Methyl-γ-lumicolchicamine | | LXXIV | $C_{22}H_{27}O_5N$ | Amorph. | | 54 | — |
| 12. | N-Formyl-γ-lumicolchamine | | LXXV | $C_{22}H_{25}O_6N$ | 200 | —570 | 54 | — |
| 13. | γ-Lumicolchamine | | LXXVI | $C_{21}H_{25}O_5N$ | 248 | —555 | 59 | Colchicum autumnale, Colchicum latifolium [65, 66] |
| 14. | N-Deacetyl-N-demethyl-γ-lumicornigine | AM-3 | LXXVII | $C_{21}H_{23}O_5N$ | 245—247 | —391 | | Androcymbium melanthioides [67] |

The photochemical isomers are considered as secondary plant substances and final products of transformations in the biogenetic scheme of the tropolone alkaloids in autumn crocuses and plants related to them [13, 51, 52]. They form two large groups of compounds the β- (cis-) and γ- (trans-) series which are given in Tables 3 and 4 (for the tropolone compounds corresponding to them, see [1]). The structures of plant photochemical compounds are shown in Table 5. Three compounds — β-lumispeciosine, N-methyl-β-lumicolchicamine, and N-acetyl-β-lumicolchamine, and N-acetyl- β-lumicolchamine have been discovered by us for the first time in plants, and information on them is being prepared for publication.

Because of the considerable change in their structure, the photochemical isomers differ greatly in their spectral characteristics from compounds with a tropolone ring. However, β- and γ-lumicolchicines, while differing sharply with respect to their melting points and specific rotations, have very similar spectra. In their UV spectra a slight difference is observed in the extinction of the absorption maximum in the long wave region. Thus, to β- and γ-lumicolchicines correspond maxima at 225, 266, and 340 nm with log ε 4.46, 4.36, and 3.29 for the former and with log ε 4.46, 4.35, and 4.32 for the latter of these compounds [2, 13, 15, 18, 29, 72, 73]. Correspondingly, the other compounds of these series have similar spectra. Characteristic for α-lumicolchicine are absorption maxima at 215, 230, and 282 nm (log ε 4.69, 4.65, and 4.64) [18, 29].

Šantavý et al. [74, 75] have studied the optical rotation, optical rotatory dispersion, and circular dichroism of the colchicine alkaloids, including the β- and γ-lumi- derivatives, which show the properties of diastereomers.

TABLE 5. Structures of the Photochemical Isomers of Tropolone Alkaloids of Plant Origin

| Alkaloid | Structure | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | Literature |
|---|---|---|---|---|---|---|---|
| **Compounds of the β-series** | | | | | | | |
| 1. β-Lumicolchicine (XII) |  | $CH_3$ | $CH_3$ | $CH_3$ | H | $COCH_3$ | 15, 23 |
| 2. 2-Demethyl-β-lumicolchicine (L) | | $CH_3$ | H | $CH_3$ | H | $COCH_3$ | 15 |
| 3. 3-Demethyl-β-lumicolchicine (LI) | | $CH_3$ | $CH_3$ | H | H | $COCH_3$ | 55, 56 |
| 4. β-Lumicornigerine (LIV) | | $-CH_2-$ | | $CH_3$ | H | $COCH_3$ | 54, 58 |
| 5. N-Formyldeacetyl-β-lumicolchicine (LV) | | $CH_3$ | $CH_3$ | $CH_3$ | H | CHO | 55 |
| 6. 3-Demethyl-N-formyldeacetyl-β-lumicolchicine (LVI) | | $CH_3$ | $CH_3$ | H | H | CHO | 55 |
| 7. β-Lumicolchamine (LVII) | | $CH_3$ | $CH_3$ | $CH_3$ | H | $CH_3$ | 59, 60 |
| 8. N-Methyl-β-lumicolchamine (LX) | | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | |
| 9. N-Acetyl-β-lumicolchamine (LXI) | | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | $COCH_3$ | |
| 10. β-Lumispeciosine (LXIV) | | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | $-CH_2-$  | |
| **Compounds of the γ-series** | | | | | | | |
| 1. γ-Lumicolchicine (XIII) |  | $CH_3$ | $CH_3$ | $CH_3$ | H | $COCH_3$ | 15, 23 |
| 2. 2-Demethyl-γ-lumicolchicine (LXV) | | $CH_3$ | H | $CH_3$ | H | $COCH_3$ | 68, 69 |
| 3. 3-Demethyl-γ-lumicolchicine (LXVI) | | $CH_3$ | $CH_3$ | H | H | $COCH_3$ | 62 |
| 4. γ-Lumicornigerine (LXX) | | $-CH_2-$ | | $CH_3$ | H | $COCH_3$ | 54, 58 |
| 5. 3-Demethyl-γ-lumicolchamine (LXXIII) | | $CH_3$ | $CH_3$ | H | H | $CH_3$ | 58 |
| 6. N-Methyl-γ-lumicolchamine (LXXIV) | | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | |
| 7. N-Formyldeacetyl-γ-lumicolchicine (LXXI) | | $CH_3$ | $CH_3$ | $CH_3$ | H | CHO | 55 |
| 8. 2-Demethyl-N-methyl-γ-lumicolchicine glucoside (LXVIII) | | $CH_3$ | $C_6H_{11}O_5$ | $CH_3$ | $CH_3$ | $COCH_3$ | 70 |
| 9. γ-Lumicolchamine (LXXVI) | | $CH_3$ | $CH_3$ | $CH_3$ | H | $CH_3$ | 65, 66 |
| 10. N-Deacetyl-N-dimethyl-γ-lumicornigerine (LXXVII) | | $CH_3$ | $-CH_2-$ | | $CH_3$ | $CH_3$ | 71 |

Unlike those of the tropolone alkaloids, the IR spectra of β- and γ-lumicolchicines exhibit absorption bands at 1550-1710 $cm^{-1}$ due to the presence of cyclobutene and cyclopentene rings. An absorption band at 1710-1715 $cm^{-1}$ corresponds to a carbonyl group in a cyclopentene ring, a band at 1675 $cm^{-1}$ to an amide group, bands at 2835, 2935, and 3010 $cm^{-1}$ to methoxy groups, and band at 1570-1620 $cm^{-1}$ to a conjugated ring system. The IR spectra of the β- and γ-lumicolchicines differ only with respect to the frequency of 1295 $cm^{-1}$ that is observed in γ-lumicolchicine [72].

With respect to their PMR spectra, the photochemical isomers differ from the tropolone alkaloids mainly by the positions of the signals of the "bridge" protons H-8 and H-12, which show a pronounced upfield shift [55, 72, 76-78]. They appear, respectively, at 3.63 and 4.12 ppm, while in the spectrum of colchicine they have chemical shifts of 7.63 and 7.37 ppm [76]. The signals of some other protons, particularly those of the methoxy groups in the C-1 and C-10 positions, have also undergone considerable changes. These methoxy groups give signals in the colchicine spectrum at 3.67 and 4.03 ppm and in the lumicolchicine spectrum at 3.98 and 3.68 ppm, changing places, as it were. The chemical shifts of the protons of all the methoxy groups were determined unambiguously from the intranuclear Overhauser effect [78].

The spectra of γ-lumicolchicine and its analogs are close to those of the compounds of the β-series. They differ mainly by the resonance frequencies of the amide proton (NH 6.36 ppm in β-lumicolchicine and 5.70 ppm in γ-lumicolchicine) [21]. As already mentioned, this is explained by the difference in the configurations of the photochemical isomers.

$^{13}C$ NMR spectra have been used to establish the structures of the number of tropolone alkaloids and their photochemical isomers. In addition, special investigations have been devoted to them [78-84]. The main difference between the spectra of β- and γ-lumicolchicines and that of colchicine relates to the signals of the C-8 and C-12 atoms, which have a strong upfield shift in the photochemical isomers. The signals of the C-1a, C-7a, and C-10 atoms are also shifted upfield to some extent. Counterbalancing this, the signals of the C-9, C-11, and C-12a atoms are shifted downfield [78].

In the mass spectrum of each of the β- and γ-lumicolchicines a very intense peak of an ion with m/z 356 $(M - 43)^+$ and weak peaks with m/z 399 $(M^+)$, 340 and 326 are observed. It has been suggested [85] that the main ion, with m/z 356, is formed either as the result of the elimination of an acetyl group from the acetamide group or of carbon monoxide and a methyl group from the cyclobutene ring as the result of its breakdown.

It was established by an investigation of the mass spectra of β- and γ-lumicolchicines and their analogs with hydroxy groups in the C-2 or C-3 positions that these compounds undergo decomposition mainly in the most strained part of the molecule – in rings C and D – with the elimination of carbon monoxide and a methyl radical. Subsequently, an acetamide group is eliminated from this main fragment, with the formation of an ion with m/z 297. The latter, in its turn, by splitting out the next molecule of carbon monoxide, is converted into an ion with m/z 269. Another route of the fragmentation of the ion with m/z 356 – through the successive ejection of CO and $NH_2COCH_3$ – leads to the same ion.

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