Ungernia ALKALOIDS

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The review is devoted to the study of the alkaloids of plants of the genus *Ungernia* (Amaryllidaceae). It gives their characteristic reactions and information on the determination of their structures and stereochemistry and on the dynamics of the accumulation of alkaloids in the plants of the genus *Ungernia*. A dependence of the physiological activity of the alkaloids on their structure is shown.

Plants of the genus *Ungernia* Bge., family Amaryllidaceae, are widely distributed on the territory of the Soviet Union and are represented by eight species [1-8]; *U. severzovii* (Rgl.) B. Fedtsch., *U. victoris* Vved. (growing in Uzbekistan) [3], *U. ferganica* Vved., *U. minor* Vved. (in Kirghizia) [5], *U. tadshikorum* Vved. (in Tadzhikistan) [6], *U. trisphaera* Bge., *U. spiralis* Proskor. (in Turkmenia) [7], and *U. vvedenskyi* S. Khamidkh (in Kazakhstan) [18].

A chemical study of the plants of the genus *Ungernia* was begun in 1936 by Orekhov and Norkina [9, 10]. From dried bulbs of *U. severzovii* they isolated for the first time the crystalline alkaloid ungernine, from which a number of salts and derivatives were obtained and of which the products of the Hofmann and alkaline decompositions were studied. It was found that in composition and properties ungernine was very similar to tazettine, which had been found by Späth and Kahovec [11] in the bulbs of *Narcissus tazetta* L. Ungernine also possessed similarity with the base VIII isolated by Kondo et al., [12] from the bulbs of *Lycoris radiata* growing in Japan.

In 1936, Späth, Kondo, and Huffner [13] reported the identity of base VIII and tazettine. Somewhat later, Kahovec and Spath [14] confirmed the identity of ungernine with tazettine and decided to retain the first name, tazettine, which had taken root for all three alkaloids.

The next alkaloid, lycorine, was isolated in 1938 by Yurashevskii [15] from bulbs of *U. tadshikorum* Vved.

Yunusov and Abduazimov continued the investigation of plants of the genus *Ungernia* in 1949. The necessity for a detailed and systematic investigation of new plants and those that have been studied previously was due to the fact that numerous chemical investigations of alkaloid-bearing plants of Central Asia [17-21] performed during the vegetation period with respect to each plant organ and each growth site had revealed a number of general laws. It was established that the alkaloid composition changes both qualitatively and quantitatively, and in the period of vigorous growth the maximum amount of alkaloids is laid down in the epigeal part of the plant and the minimum amount in the hypergeal part.

In 1953 the total alkaloids were isolated from *U. severzovii* [16], amounting to 0.7% of the weight of the dry bulbs, which is ten times greater than the combined alkaloids obtained by Orekhov and Norkina [9, 10].

At the present time, in a study of the plants of the genus *Ungernia*, depending on the growth site and the vegetation period it has been possible to isolate 20 alkaloids (Table 1). In the structure of their skeleton, the alkaloids belong to the lycorine, crinine, lycorenine, galanthamine, and tazettine groups.

Lycorine Group. The first representative of the alkaloids of this series — lycorine, $C_{16}H_{17}NO_4$ — was first isolated in 1877 by Gerrard from the bulbs of the plant *Narcissus*

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TABLE 1. *Ungernia* Alkaloids

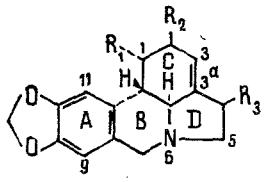
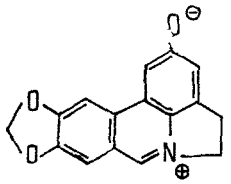
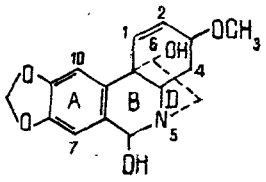
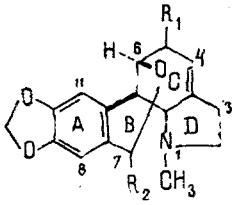
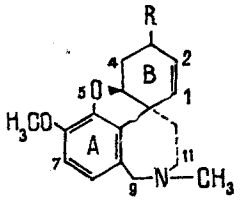
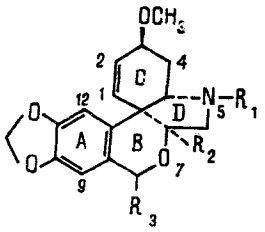
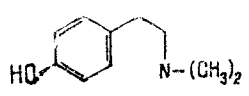
Alkaloid	Structural formula	Literature citation
Indophenanthridine derivatives or the lycorine group		
		
I. Lycorine, $C_{16}H_{17}NO_4$, mp 265-266°C (decomp., methanol), $[\alpha]_D$ −120° (pyr.)	$R_{1,2}$=OH R_3=H	15, 16, 19 22—27, 45
II. dl-Ungminorine, $C_{17}H_{19}NO_5$, mp 208-210°C (acetone), $[\alpha]_D \pm 0°$	$R_{1,3}$=OH R_2=OCH_3	45
III. l-Ungminorine, $C_{17}H_{19}NO_5$, mp 206-208°C (decomp., acetone), $[\alpha]_D$ − 28.8°	$R_{1,3}$=OH R_2=OCH_3	27—31 45
IV. Ungminoridine, $C_{16}H_{19}NO_4$, mp 193-194°C (methanol), $[\alpha]_D \pm 0°$	$R_{1,2}$=OH R_3=H C_3—C_{3a} = (dihydro)	27, 32, 45
V. Ungerimine, $C_{16}H_{11}NO_3$, mp 270-271°C (decomp., methanol) $[\alpha]_D \pm 0°$		32
Ethanophenanthridine derivatives, or the crinine group		
VI. Pancratine (luteine, hemanthidine) $C_{17}H_{19}NO_5$. mp 186-187°C (ethanol) $[\alpha]_D$−34.5° (chloroform)		29, 31 33—36
Lycorenine group		
		
VII. Hippeastrine (trisphaeridine), $C_{17}H_{17}NO_5$, mp 214-215°C (methanol), $[\alpha]_D$ +156° (chloroform)	R_1=OH R_2=O	23, 27, 31 37—39
VIII. Ungerine, $C_{18}H_{19}NO_5$, mp 135-136°C (70% ethanol), $[\alpha]_D$ +116.95° (chloroform)	R_1=OCH_3 R_2=O	26, 40
IX. Unsevine, $C_{18}H_{21}NO_5$, mp 173-174° (acetone), $[\alpha]_D$ +169.8° (chloroform)	R_1=OCH_3 R_2=OH	29, 30

TABLE 1 (continued)

Alkaloid	Structural formula	Literature citation
Galanthamine group		
X. Galanthamine, $C_{17}H_{21}NO_3$, mp 127-128°C (benzene) $[\alpha]_D$ −188.8° (ethanol)	R=OH	22, 26, 27 31, 35 39, 40, 45
XI. dl-Narwedine, $C_{17}H_{19}NO_3$, mp 186-137°C (methanol) $[\alpha]_D \pm 0°$	R=O	27, 30, 39
XII. l-Narwedine, $C_{17}H_{19}NO_3$, mp 184-185°C (benzene) $[\alpha]_D$ −34.7° (chloroform)	R=O	30
XIII. d-Narwedine, $C_{17}H_{19}NO_3$, mp 185-186°C (acetone), $[\alpha]_D$ + 310° (chloroform)	R=O	30
Tazettine group		
XIV. Tazettine (ungernine), $C_{18}H_{21}NO_5$, mp 210-211°C (methanol), $[\alpha]_D$ + 148.2° (chloroform)	R_1=CH_3 R_2=OH R_3=H	9, 10, 24, 27 29, 31, 35, 39, 40, 45
XV. Ungwedine, $C_{19}H_{23}NO_5$, mp 148-150°C (methanol) $[\alpha]_D$ + 12.5° (chloroform)	R_1=CH_3 R_2=OCH_3 R_3=H C_1—C_2= (dihydro)	46
XVI. Epimacronine, $C_{18}H_{19}NO_5$, mp 104-105°C (methanol), $[\alpha]_D$ + 10.9° (chloroform)	R_1=CH_3 R_2=H R_3=O	41
XVII. Dihydroepimacronine, $C_{18}H_{21}NO_5$, mp 98-99°C (methanol), $[\alpha]_D$ + 10.7° (chloroform)	R_1=CH_3 R_2=H R_3=O C_1—C_2= (dihydro)	42
XVIII. Ungspiroline, $C_{17}H_{17}NO_5$, mp 148-149°C (methanol), $[\alpha]_D$ + 105° (chloroform)	$R_{1,2}$=H R_3=O	43
XIX. Ungspirolidine, $C_{17}H_{19}NO_5$, mp 142-143°C (methanol), $[\alpha]_D$ + 11° (chloroform)	$R_{1,2}$=H R_3=O C_1—C_2= (dihydro)	43
XX. Hordenine, $C_{10}H_{15}NO$, mp 118-119° (acetone), $[\alpha]_D \pm 0°$		38

pseudo-narcissus L. [47], and is found in all species of *Ungernia*. Lycorine and related alkaloids are methylenated and methylated derivatives of tri-, tetra-, and pentahydroxyphenanthridines.

Gorter [48] was the first to obtain hydrastic acid by the oxidation of lycorine. Kondo et al. [49] performed the Hofmann degradation of lycorine and the dehydro product of the latter (XXI) was shown to be identical with synthetic 1-ethyl-10-methyl-6,7-methylenedioxydihydrophenanthridine [50].

On being heated with $POCl_3$, lycorine forms anhydrolycorine chloride, the oxidation of which gave the phenanthridone (XXII) [51]. Lycorine was also oxidized with periodic acid and its O-acetyl derivatives were obtained.

On the basis of the facts given above, structure (I), explaining all its chemical transformations, was established for lycorine. At the present time, the structures of all the other transformation products of lycorine have been established.

The elucidation of the structure of the alkaloid lycorine, and also the study of its chemistry, played a great part in determining the structure of the bases related to it, of which 29 are now known [52-54].

Three alkaloids of the lycorine type have been isolated from *U. minor* Vved. — ungminorine (II), ungminoridine (IV), and ungeremine (V).

The reduction of ungminorine with metallic sodium in n-amyl alcohol formed lycorene (XXIII) and caranine (XXIV) [28, 32]. Base (II) unlike lycorine, is not oxidized by periodic acid. This means that the hydroxy groups in it are not adjacent, and in the NMR spectrum the signals of the protons of the methoxyl are found at τ 6.65 ppm. It follows from this that ungminorine has the structural formula (II).

The second alkaloid — ungminoridine (IV) — is a saturated base not undergoing catalytic reduction. When its properties and developed formula were compared with those of lycorine, it was found that (IV) differs by two hydrogen atoms and is a derivative of indophenanthridine. A study of IR and NMR spectra established the presence in the molecule of two hydroxy groups and a methylenedioxy group and there were well-defined signals from the aromatic protons in the form of singlets at τ 3.08 and 3.40 ppm.

Thus, ungminoridine has the structural formula (IV) and is possibly a racemate of zephyranthine [55].

The composition, developed formula, and all the physicochemical parameters of ungeremine, including its UV and IR spectra, are similar to those of a substance known in the literature — a phenolobetaine obtained from lycorine [32]. Hence it follows that ungeremine has the structural formula (V).

The stereochemistry of the alkaloids of the indiphenanthridine group has been studied widely [56-58]. It has been established that the hydroxy groups of lycorine (I) have the trans and diaxial configuration.

The alkaloids of this group possess common and characteristic properties. They are reduced by sodium in the n-amyl alcohol, and this reaction is used to determine the main skeleton. It is interesting to note that in this reaction, in the majority of cases, free or substituted 1-, 9-, and 10-hydroxy groups remain unaffected, that on C-1 being particularly stable [59], while substituting groups present in positions 2, 4, 8, and 11 undergo hydrogenolysis.

In the establishment of structures, in addition to the Hofmann degradation [49, 65] the Emde degradation has also been used with success [53, 64]. It must be mentioned that ring A is always aromatic and the others are partially or completely hydrogenated. In all alkaloids of this type, substituents in the aromatic ring A occupy positions 8, 9, and 10. The oxidation of these bases forms the corresponding substituted phthalic acids [41, 60-64].

In ring C, the double bond occupies the 3-3a position. The presence of this double bond promotes the aromatization of the tetrahydrobenzene ring C during Hofmann degradation, during which substituting hydroxy or methoxy groups in ring C are split out in the form of water or methanol [63, 65]. In those alkaloids in which ring C is completely hydrogenated no aromatization is observed [49].

Characteristic is the capacity of the dihydro products [dihydrolycorine (XXV)] for forming a lactam group on oxidation (XXVI), which imparts a neutral character to the substance. Under the action of methyl iodide, the alkaloids of this group form well-crystallizing methiodides [66, 67] but some of them (**lycorine**, caranine) give two diastereoisomeric α- and β-methiodides [49, 65].

The structural similarity of the alkaloids of the lycorenine group can be seen from their UV and IR spectra.

In the mass spectra of the indophenanthridine alkaloids the value of the diagnostic ion depends on the number and nature of the substituting group in the aromatic and five-membered nitrogen-containing rings. Thus, if there is only a methylenedioxy group in ring A, as in lycorine and caranine, peaks are observed with m/e 227 and 226 [68], while in the case of a methoxy substituent of ring A peaks with m/e 243 and 242 are characteristic. For ungminorine and narcissidine, in which ring D contains substituents, the distinguishing peaks have m/e 259 and 258 [68].

Thus, the mass spectra of the alkaloids of this group are characteristic and can be used for solving structural problems.

Crinine Group. The group of alkaloids with the crinine skeleton numbers 23 bases [52-54]. The first representative of this series — crinine — was first found in the plant *Crinum moorei* [59, 69]. It is interesting that in all species of *Ungernia* so far only one alkaloid of this group has been found — pancratine — first isolated from *Pancratium maritimum* L. [70], and also found in many plants of the family Amaryllidaceae and known under the name of hemanthidine [71, 72].

Pancratine (VI) was identified by direct conversion into tazettine (XIV) [39, 73-75].

In contrast to the lycorine type, the alkaloids of this group do not aromatize when subjected to the Hofmann degradation and on oxidation with potassium permanganate they do not form a lactam conjugated with the aromatic ring as, for example, O-acetyldihydrocrinine, which, at the same time, is stable to the action of selenium dioxide. This indicates that crinine and related alkaloids do not have an indophenanthridine ring system but are methylated and methylenated derivatives of tetra- or pentahydroxy-5, 10b-ethanophenanthridine.

As in the alkaloids of the lycorine group, the methylenedioxy group is located in the aromatic part of the molecule, and the methoxy groups may be present either in the aromatic part or in the hydrogenated rings.

In contrast to the other groups of alkaloids of this family, in the crinine group there is only a single alkaloid of phenolic nature — amaryllicine [76] — together with alkaloids containing an epoxy group, i.e., flexinine, merbowdine, and undulatine [67, 72, 73].

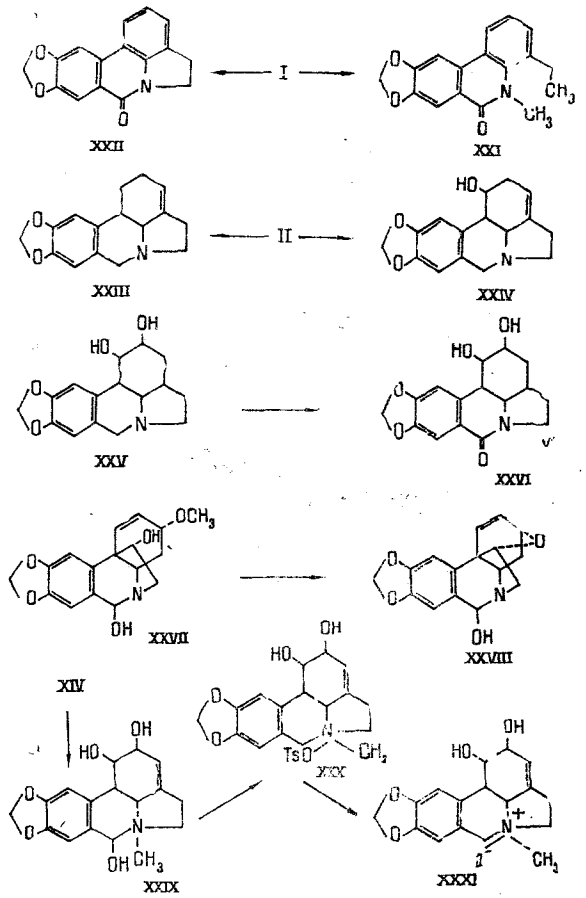
On reduction with sodium in n-amyl alcohol, the aromatic methoxy groups are split out [72].

It is characteristic that alcoholic groups in ring C are readily methylated in an alkaline medium by methyl p-toluenesulfonate, and the methoxy group is readily saponified under the action of dilute acids [78].

Rings C and D and the substituting methoxy and hydroxy groups in them are in the cis configuration with respect to one another and favor the formation of apo compounds. Thus, in hydroxycrinamine (XXVII) under the action of hydrochloric acid the methoxy group is readily saponified and a cyclic ether [apohemanthinine (XXVIII)] is readily formed. Hydroxy groups present in ring D are not oxidized by chromium trioxide to oxo compounds.

The lycorenine group contains 24 alkaloids isolated from plants of various genera of the family Amaryllidaceae [52-54]. The first representatives of this genus, lycorenine and homolycorenine, were found by Kondo and Tomimura in 1929 [12, 79] in the bulbs of the plant *Lycoris radiata*. This group of alkaloids is represented in plants [83, 84] by three compounds: hippeastrine (VII), ungerine (VIII), and usevine (IX).

Hippeastrine was first isolated from *Hippeastrum vittatum* [80]. The diol (XXIX) obtained on the reduction of hippeastrine by lithium tetrahydroaluminate was converted by treatment with p-toluenesulfonyl chloride in pyridine into lycorine tosylate (XXX), from which passage was made to lycorine methiodide (XXXIc) with the aid of hydrogen iodide [81].

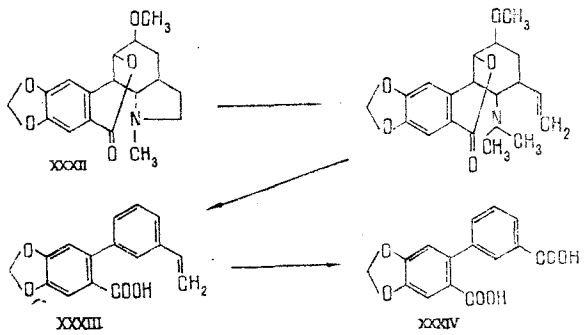


The UV spectrum of ungerine (VIII) has three absorption maxima, at 227, 268, and 306 nm (log ε 4.36, 3.72, 3.76), which are characteristic for alkaloids of the lycorenine group [85]. Its IR spectra has bands at 1725 cm^{-1} (τ-lactam group) and 1255, 1035, 935 cm^{-1}(aromatic ring). In the NMR spectrum of (VIII) [86], there are signals of protons in the following regions (τ, ppm): ss 2.60 and 3.09 (aromatic, 2 H), s 3.98 (methylenedioxy, 2 H), s 6.62 (methoxy, 3 H), s 8.04 (N-methyl, 3 H), d 4.40 (olefinic, 1 H).

Oxidation of (VIII) with potassium permanganate leads to hydrastic acid [82].

A study of the Hofmann cleavage of dihydroungerine (XXXII) showed that in the second stage a nitrogen-free substance (XXXIII) was formed which was oxidized to an acid identified as 4,5-methylenedioxybiphenyl-2,3'-dicarboxylic acid (XXXIV), also obtained by the oxidation of the nitrogen-free product from hippeastrine [44, 102].

The structure of ungerine was definitively established by passage from it to the known alkaloid hippeastrine [87], and from dihydroungerine to dihydrohippeastrine [88]



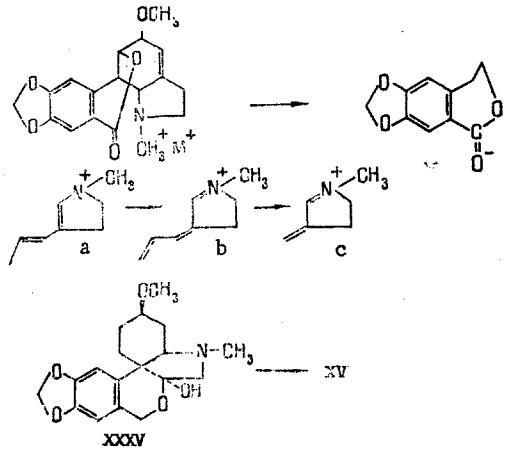
Unsevine (IX) shows two absorption maxima in the UV spectrum at 238 and 288 nm (log 3.76 and 3.64), demonstrating the presence of a substituted benzene ring in the alkaloid.

The IR spectrum (IX) revealed the absorption bands of bonds of the following groups: hydroxy at 3590 cm^{-1}, methoxy at 2832 cm^{-1}, and methylenedioxy at 1040 and 935 cm^{-1}

In a study of the Hofmann degradation and reduction (IX) it was established that at the position of the δ-lactone group in ungerine there is a hemiacetal group. This was confirmed by the formation of ungerine in the oxidation of unsevine with chromic acid.

The structure of ungerine and unsevine are also confirmed by their mass spectra [89]. Characteristic fragments in the spectra of the alkaloids ungerine and unsevine are the intense ions *a* (m/e 139), b (m/e 124), and c (m/e 96) (Scheme 1).

Scheme 1



XXXV

Information on the stereochemistry of the lycorenine alkaloids was obtained by effecting a transmission from this group to the indophenanthridine group of alkaloids with a known configuration [104].

Thus, the alkaloids of the lycorine group can be divided into two subgroups: with a hemiacetal ring and with a δ-lactone ring. This difference is clearly expressed in the ultraviolet spectra. In alkaloids with a hemiacetal group there is only one chromophore — a benzene ring with two or three substituents — which gives two absorption maxima in the 233-240 and 283-290 nm regions with the corresponding intensities [78, 90].

In the alkaloids with a δ-lactone ring there are two chromophores, i.e., in addition to the benzene ring with substituents there is a keto group conjugated with the benzene ring. Accordingly, the UV spectrum changes sharply: Three absorption maxima appear, in the 227-229, 268, and 303-308 nm regions, with different intensities [85].

The spectroscopic properties of the lycorenine alkaloids considerably facilitate their identification.

The basic skeleton of the alkaloids of the lycorenine type has been shown by Hofmann degradation [38, 44, 79] and confirmed by passage from the lycorenine to the lycorine alkaloids [81, 92, 83], and also by broad investigation using physical methods of analysis.

On the performance of the Hofmann degradation of many alkaloids of the family **Amaryllidaceae** [94, 95], the following characteristic appears: If in the six-membered nonaromatic ring C there is a substituting group (—OCH_3, —OH) and a double bond, then, after the first stage of degradation it is aromatized, as a rule, but if the ring does not contain a double bond no aromatization takes place.

Hippeastrine (VII), in ring C of which there is a hydroxyl and a double bond, is an exception: After the first stage of Hofmann degradation, no aromatization takes place in it. In the case of ungerine (VIII), however, which has one substitutent and a double bond, aromatization does take place; the influence of the substituting groups obviously has an effect.

The oxidation of hemiacetals to lactones is a widely used reaction [96]. It is, as it were, a bridge with the aid of which a passage is made from the hemiacetal alkaloids to the δ-lactone alkaloids. Other general reactions of such alkaloids are also interesting: the saponification of the lactone group by alkalis and cyclization of the hydroxy amino acids obtained back to the initial alkaloids, some lactones (δ-) opening readily and others (γ-) with

more difficulty [96]. Also characteristic is the reduction of these alkaloids with lithium tetrahydroaluminate [44, 87], which takes place in such a way as not to affect the double bond.

Hemiacetals and acetals hydrolyze readily when there are adjacent aromatic rings [97].

All the lycorenine alkaloids, with the exception of clivonine, which contains one ethylenic bond, are quantitatively reducible by hydrogen in the presence of platinum or palladium [98].

Oxidation of potassium permanganate has also been used as a method for proving the structure of alkaloids with two substituents in the benzene ring. The dicarboxylic acids so produced show that in the alkaloids the substituents occupy the 9,10 position [11, 64, 100-103]. However, there are representatives of this group in which the benzene ring bears three substitutents. They occupy the 9,10,11 or the 8,9,10 positions. It is impossible to determine positions of the substituent in these alkaloids by the oxidation method, since identical reaction products — trisubstituted phthalic acids — are formed in the two cases [99].

To prove the structure of such alkaloids use is made of the rate of formation of methiodides, since an investigation of models has shown that the approach of the reagents to the nitrogen atom is hindered by a substituent at C_8. It follows from this that the rate of formation of methiodide is greater for alkaloids without a substituent in position 8.

The difference in the localizations of the functional substituents in the benzene ring is also reflected in the IR and NMR spectra [99]. Thus, for example, in the IR spectrum of a compound in which the benzene ring has substituents in the 8,9,10 positions absorption is observed in the 1618 cm^{-1} region, while when the substituents are in the 9,10,11 positions it is in the form of a doublet at 1613 and 1592 cm^{-1}.

Very characteristic for alkaloids with a δ-lactone ring is the intense absorption of the bonds of the ester carbonyl at 1708-1735 cm^{-1} [118].

The Galanthamine Group. This comprises ten alkaloids [52, 53, 91]. The first representative of it — galanthamine — was first isolated in 1952 by Proskurnina and Yakovleva from the bulbs of *Galanthus woronowii* Losinsk. [105, 106], and then in 1953 by Uyeo et al. from *Lycoris radiata* [107]. In plants of the genus *Ungernia*, of alkaloids of this group galanthamine (X) and narwedine (XI) and its racemic form have been detected [23, 27, 39].

The saponification of galanthamine forms apogalanthamine and the methyl ether of apogalanthamine [108]. Oxidation of the des-base of galanthamine yielded 2,3-dimethoxybiphenyl-2',6-dicarboxylic acid [109]. The complete synthesis of galanthamine was effected for the first time in 1960 [110, 111].

The oxidation of galanthamine with manganese dioxide gives racemic narwedine [39]. Uyeo has established that racemic narwedine is readily formed from optically active narwedine [114].

A characteristic reaction for alkaloids of the galanthamine group is the opening of the bridge oxygen and the saponification of the methoxy group under the action of hydrochloric and hydrobromic acids. The other substituting group present in the partially hydrogenated ring is split out simultaneously; in this process the aromatization of this ring takes place [115]. If there is no double bond in ring B, no cleavage of the bridge oxygen under the action of mineral acids takes place: The methoxy group is saponified and the hydroxyl is replaced by halogen [116].

The results of a study of the spin—spin coupling constants of the protons with the aid of the NMR spectra of galanthamine, epigalanthamine, and their acetyl derivatives has confirmed that the hydroxy group in galanthamine is quasi-axial and that the hydroxy group in epigalanthamine is quasi-equatorial, while ring B has the half-chair conformation and a cis linkage with ring C [112, 113].

In the mass spectra of the alkaloids of the galanthamine group, the maximum peaks are those of the molecular ions [117].

The Tazettine Group. This group of alkaloids is represented in plants for the family Amaryllidaceae by 12 compounds [52, 54], six of them having been isolated from plants of *Ungernia* species (see Table 1). The parent of this group of alkaloids and of the subgroup with a hemiacetal grouping is tazettine (XIV), which was isolated from *Narcissus tazetta* by Späth and Kahovech in 1934 [11]. The same authors [11, 13, 14] obtained phenanthridine by

distilling (IV) with zinc dust. The oxidation of tazettine with potassium permanganate gave hydrastic acid. Two repetitions of the Hofmann degradation of the methiodide of (XIV) led to a nitrogen-free substance which was shown to be identical with synthetic 6-phenylpiperonyl alcohol tazettine. Kondo et al., in the course of a study of the structure of (XIV), established that on Hofmann degradation of dihydrotazettine methiodide the partially hydrogenated ring C, containing a methoxy group, remained unaromatized [116, 119]. The presence of a hemiacetal grouping in (XIV) was shown by the reduction of tazettine and dihydrotazettine to tazettadiol and dihydrotazettadiol [120-122]. The proposed structural formula of tazettine satisfactorily explains all the chemical reactions of this compound that have been described.

The alkaloid ungvedine (XV) has been isolated from *U. vvedenskyi*. Characteristic for its UV spectrum is the appearance of an inflection in the 235 nm region together with the two maxima common for this group of alkaloids, in this case 206 and 295 nm [46]. In the mass spectrum of (XV) there are the peaks of ions with m/e 347, 332, 316, 301, 272, 260, 247, 150, and 77, which are characteristic for tazettine [25]. The NMR spectrum ($CDCl_3$, τ scale) exhibits two one-proton singlets at 2.78 and 3.63 ppm relating to aromatic protons. A methylenedioxy group appears in the form of a two-proton singlet at 4.17 ppm, methoxy groups in the form of two three-proton singlets at 6.73 and 6.67 ppm, and a N-methyl group at 7.71 ppm.

A comparison of the spectral characteristics of tazettine and ungvedine showed that the latter is a methylation product of dihydrotazettine. In fact, the methylation of dihydrotazettine (XXXV) gave a substance identical with (XV).

It must be mentioned that a compound of this group — macronine [123] — is a representative of the subgroup of alkaloids containing a lactone grouping [26, 124].

In the UV spectra of such alkaloids as ungspiroline (XVIII) and ungspirolidine (XIX) there are three absorption bands, at 228-232, 268-270, and 307-310 cm^{-1} which are characteristic for alkaloids of the macronine subgroup [123].

The IR spectra of (XVIII) and (XIX) show absorption bands at 3040 cm^{-1} (>NH), 1710 cm^{-1} (carbonyl), and 1620, 1510, 1480 cm^{-1} (aromatic ring).

In the NMR spectra of (XVIII) and (XIX) there are singlet signals at 2.49 and 3.17 ppm (aromatic protons at C_9 and C_{12}), 4.02 ppm (2H, $-O,CH_2O-$), and 6.60 ppm (3H, $-OCH_3$). In the spectrum of (XVII), the signals of the olefinic protons at C_1 and C_2 appear in the form of two one-proton doublets at 3.65 and 4.55 ppm.

The Hess methylation of the bases (XVIII) and (XIX) led to their transformation into the known alkaloids epimacronine (XVI) and dihydroepimacronine (XVII), thereby confirming the structures proposed for them.

Thus, the alkaloids of the tazettine group are characterized by certain common and individual properties which facilitate their identification. On catalytic hydrogenation only the double bond is reduced, and the hemiacetal group remains unaffected, in contrast to the lycorenine group. Of all the Amaryllidaceae alkaloids, only the alkaloids of the lycorenine group and of the macronine subgroup have three maxima in the UV spectrum, which serves as a diagnostic characteristic, since in addition to a benzene ring bearing substituent they contain a carbonyl group conjugated with the aromatic ring.

A study of the mass spectra of tazettine and its isomer criwelline, differing by the configuration of the methoxy group at C_3, has shown that in the signal of tazettine the ion with the maximum intensity was that having a mass of 247 (M — 48), and in the spectrum of crivelline ions with masses of 70 and 71.

In the NMR spectra of the alkaloids of the tazettine, galanthamine, and lycorenine groups [126] the presence of signals from the protons of the methylimide group in the form of singlets at τ 7.63-9.77 permits them to be distinguished from other groups of alkaloids.

In tazettine and crinine the methylenedioxy groups are revealed in the form of singlets τ 4.09 and 4.18 ppm, respectively, and in lycorinine at 3.90-3.97 ppm. By studying NMR spectra it is possible to determine not only the positions of the substituents but also the absolute configurations of the alkaloids [99, 127-129].

Dynamics of the Accumulation of the Alkaloids and Their Mutual Transitions

A consideration of all the groups of Amaryllidaceae alkaloids from various species of *Ungernia* shows their diversity. A number of alkaloids — for example, galanthamine [130-134] and lycorine [135, 136] — possess valuable pharmacological properties.

The search for new sources of galanthamine and lycorine, and also the possibility of finding all the groups of Amaryllidaceae alkaloids in one species of plant and their mutual transitions has led to the beginning of an all-sized and systematic study of the dynamics of the accumulation of the alkaloids according to the vegetation periods and growth sites. In this it has been found that a full-value raw material for obtaining galanthamine and lycorine is not only the bulbs but also the leaves of the plants.

As can be seen from Table 2, to obtain these alkaloids the leaves of *U. victoris* and *U. trisphaera* must be gathered in the early spring (March), but at this time the leaves are only 1-5 cm long. For industrial purposes it is more desirable to gather the raw material in April, when the leaves are 15-25 cm long.

In the period of the complete withering of the plant [20, 38, 39], its shrivelled epigeal part contains no alkaloids, since they accumulate in the bulbs and roots (Table 3).

Such migration of the alkaloids at the end of the vegetation period once more confirms their special significance in the vital activity of the plant organism.

The accumulation of alkaloids largely depends not only on the species of plant but also on the climatic and soil conditions [137, 138]. Table 4 gives the dynamics of the accumulations of alkaloids and galanthamine in *U. victoris* growing on various sites of the Surkhandar'ya province of the Uzbek SSR.

In actual fact, as can be seen from Table 4, the content of total alkaloids, including galanthamine, varies sharply according to the growth site. The amount of total alkaloids in all the organs of the plants gathered in the mountains proved to be considerably smaller than in those gathered in the foothills [30], which is explained by the great diversity of the nutritional elements in the soils of the foothills as compared with the mountain soils [69].

The mechanism of the formation of Amaryllidaceae alkaloids in the plant organism has been studied widely [111, 139-144].

In an investigation of amino acid composition, it was found that the epigeal parts of *U. victoris* and *U. ferganica* contain not less than 12 amino acids, including phenylalanine and tyrosine, and it was shown that these amino acids are some of the components in the synthesis of the alkaloids [145, 146].

The alkaloid hordenine — a phenylethylamine derivative — has been isolated from the epigeal part of plants of the genus *Ungernia* [31, 34]. Its main precursor is tyrosine. An intermediate product, tyramine has been isolated from *Crinum* sp. (family Amaryllidaceae) [147].

A more detailed study of the alkaloids of all species of *Ungernia* according to vegetation periods has provided the possibility of isolating alkaloids similar in structure (see Table 1).

In a study of the alkaloids of *Ungernia severtzovii* (Rgl.) in the early vegetation period it was found that the amount of pancratine (hemanthidine) in the leaves was greater than that of tazettine. In a later period, the amount of pancratine decreased and that of tazettine increased. Similar results were obtained in an investigation of the alkaloids of the plant *Sternbergia lutea* (L.) Ker.-Gawl. of the same family [148].

With the aid of labeled hemanthamine and hemanthidine, their conversion to tazettine has been studied in *Sprekalia formosissima*. It has also been possible to isolate an enzyme (o-methylpherase) catalyzing the methylation of pancratine [149].

TABLE 2

Date of gathering of U. victoris	Percentage of the weight of the air-dry leaves		Date of gathering U. trisphaera	Percentage of the weight of the air-dry leaves	
	total alkaloids	galanthamine		total alkaloids	galanthamine
3/5	1.0	0.21	3/25	1,3	0.61
4/9	0,54	0,17	4/8	1,25	0,55
4/16	0,52	0,15	4/15	1,09	0,52
4/20	0,51	0,14	4/21	1,0	0,5
4/25	0,50	0,13	5/15	0 77	0,45
5/9	0,45	0,09	5/5	0,30	0,1
5/25	0,43	0,06	6/5	0,15	0,02

TABLE 3

Date of gathering	Plant organs	Percentage of the weight of the air-dry plant		
		total alkaloids	galanthamine	lycorine
	Ungernia victoris			
4/8	Leaves	0,53	0,14	0,052
	Bulbs	0 75	0,20	0,25
	Roots with tips	1 67	0 28	0,69
7/5	Leaves, naturally withered	—	—	—
	Bulbs	0,96	0,21	0,28
	Roots with tips	2,02	0,42	0,92
	Ungernia tadshicorum			
3/11	Leaves	0,12	0,01	0,01
	Bulbs	0 31	0,03	0,03
	Roots with tips	1,54	0,05	0,08
7/27	Leaves, naturally withered	—	—	—
	Bulbs	0,47	0,04	0,21
	Roots with tips	1,93	0,58	1,05

Using *U. trisphaera* (Bge.) as an example, it is possible to trace how the amount of lycorine in the leaves gradually falls and that of hipeastrine rises during the development of the plants. The opposite phenomenon is observed in the bulbs — towards the end of the vegetation period the amount of lycorine rises and that of hippeastrine falls. It is likely that in the leaves hippeastrine is formed from lycorine, and conversely in the bulbs. The passage from lycorine to hippeastrine has been effected under laboratory conditions [150], Japanese chemists have performed the reverse transition from hippeastine to lycorine under mild laboratory conditions [81]. These neutral transitions show the interrelationship of the lycorenine and lycorine alkaloids, and also the possibility of the passage of alkaloids into one another in the plant organism according to the period of vegetation in the presence of biocatalysts. Authors who have considered the biogenesis of the Amaryllidaceae alkaloids [151, 152] have suggested a scheme for the synthesis of the alkaloids of the various groups and a link between them [153-155].

Dependence of the Physiological Activity of the Molecule on Its Structure

One of the methods of seeking new drugs is the modification of alkaloids.

A rational method for the search for new synthetic drugs appears to be the creation in a single chemical class of compounds which would possess different types of pharmacological activity. The addition of various radicals to the alkaloid galanthamine and the changing of the position of a given radical in it enables us to obtain substances with different activities in the qualitative and quantitative respects. With this aim we have synthesized a number of derivatives of galanthamine.

In a determination of the anticholinesterase activities of the galanthamine derivatives it was found that this activity changed profoundly as the results of a modification of the alkyl radical attached to the nitrogen atom.

It is known that the introduction of a charge into a molecule increases its anticholinesterase activity. A similar relationship was also observed among the quaternary hydroxyalkyl derivatives of galanthamine. For example, galanthamine methohydroxide has an anticholinesterase activity more than 20 times stronger than that of galanthamine hydrobromide [156-158] (Scheme 2).

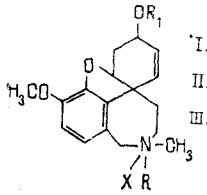
Dihydrogalanthamine (XL) and epigalanthamine (XXXVI) possess weak anticholinesterase properties (Scheme 3). And the cleavage of the oxygen bridge in galanthamine followed by the conversion of the seven-membered nitrogen-containing ring into an eight-membered ring leads to a marked fall in its anticholinesterase action with an activity approximately 12-15 times smaller than that of galanthamine hydrobromide. Des-N-methylgalanthamine obtained from galanthamine by Hofmann degradation exhibits no anticholinesterase properties.

It follows from this that the anticholinesterase activity of galanthamine probably depends on the bond and the distance between the hydroxyl-bearing carbon and nitrogen in the molecule.

TABLE 4

Alkaloids	Shar-gun'	Amanal-sai	Sangar-dak	Obiza-rang	Guliob	Shirkent	Sina
			1960				
	4/25	4/29	4/11	4/11	4/12	4/15	4/27
Total alkaloids	0,5	0,4	0,27	0,33	0,46	0,36	0,16
Galanthamine	0,13	0,08	0,025	0,09	0,07	0,04	Tr.
			1962				
	4/8	4/8	4/8	4/9	4/9	4/10	4/10
Total alkaloids	0,53	0,5	0,41	0,49	0,54	0,43	0,35
Galanthamine	0,14	0,11	0,08	0,12	0,09	0,085	0,04
			1970				
	4/23	4/24	4/24	4/23	4/24	4/24	
Total alkaloids	0,41	0,39	0,32	0,36	0,38	0,33	—
Galanthamine	0,1	0,075	0,04	0,08	0,07	0,065	—
			1975				
	4/21	4/21	4/21	4/22	4/22	4/23	
Total alkaloids	0,39	0,34	0,29	0,32	0,35	0,31	—
Galanthamine	0,09	0,046	0,03	0,03	0,045	0,041	—

Scheme 2

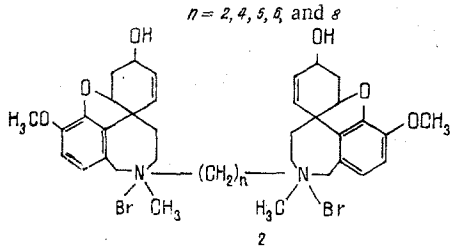


I. R= from CH_3 to C_9H_{19}; R_1=H; X= I, Br

II. R=H; R_1=CH_3–C(=O); C_6H_5–C(=O); X= J, Br, NO_3

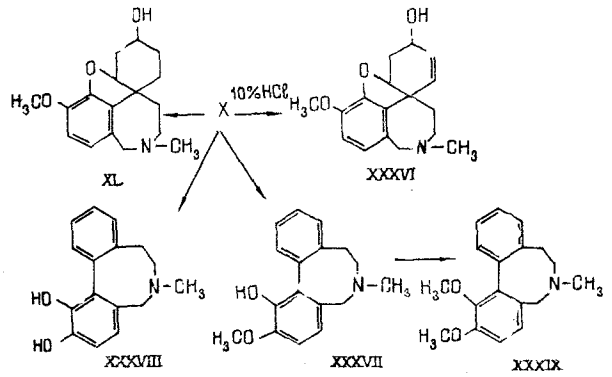
III. R= from CH_3 to C_4H_9; R_1=CH_3–C(=O); C_6H_5–C(=O); X= J, Br.

I – N-alkyl halide derivatives of galanthamine
II – esters of galanthamine
III – N-alkyl halides of esters of galanthamine
IV – N,N'-alkylenedigalanthamine dibromides



2

Scheme 3



As we have already mentioned, the passage from the seven-membered nitrogen-containing ring in galanthamine to an eight-membered ring leads to a decrease in its anitcholinesterase activity and to the appearance of a new pharmacological property. Pharmacologists have found that the preparation methylapogalanthamine (XXXVII) in doses of 0.5-1 mg/kg reduces the arterial pressure by 30-60%, and the effect lasts for 2-4 h.

A further increase in the dose of methylapogalanthamine hydrochloride leads to an intensification and prolongation of the hypotensive effect [159-160].

On passing from apogalanthamine (XXXVIII) to methylapogalanthamine (XXXVII) and from methylapogalanthamine to dimethylapogalanthamine (XXXIX), the hypotensive activity increases. This is apparently connected, in the first place, with the increase in the weight of the apogalanthamine molecule and, in the second place, with the participation of the hydroxy group in the enzyme systems of the organism.

The products of the Hofmann degradation of methylapogalanthamine do not possess hypotensive activity [161, 162].

This means that the hypotensive activity of methylapogalanthamine is due mainly to the presence of the eight-membered nitrogen-containing ring.

The oxygen of galanthamine (X) forms narwedine (XI), and the appearance of a keto group in the latter leads to a fall in its anticholinesterase activity, while a marked stimulation of respiration is observed in intact and anesthetized animals [163, 164].

The alkaloids lycorine (I), tazettine (XIV), and galanthamine (X) possess a pronounced hypotensive action.

A lengthening of the tazettine molecule by the introduction of various >N-alkyl radicals leads to an increase in its hypotensive activity. Among the >N-alkyl derivatives the most active has proved to be tazettine methohydroxide [165].

Japanese pharmacologists established that lycorine also possesses emetic properties. Later, Altymyshev [135] observed new medicinal properties of lycorine which permitted it to be used in medical practice in the treatment of acute and chronic bronchitis, etc. The hydrogenation of the double bond of lycorine forms dihydrolycorine in which the emetic effect has disappeared and a new pharmacological property has arisen — an antiarrhythmic effect.

Thus, by modifying the structure of the alkaloids galanthamine, narwedine, lycorine, tazettine, and others, it has been possible to elucidate the dependence of the physiological activity of the molecule on its structure, as a result of which highly effective drugs have been found: methylapogalanthamine hydrochloride, dihydrolycorine hydrochloride, diacetyldihydrolycorine hydrochloride, tazettine methohydroxide, apogalanthamine hydrobromide, galanthamine methohydroxide, narwedine hydrobromide, lycorine hydrochloride, and others.

The methods developed for preparing galanthamine, methylapogalanthamine hydrochloride, and lycorine [166, 167] have been introduced into the Tashkent Pharmaceutical Chemicals Factory.

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