FOR THE 50th ANNIVERSARY OF THE LABORATORY OF ALKALOID CHEMISTRY, INSTITUTE OF THE CHEMISTRY OF PLANT SUBSTANCES OF THE UZBEKISTAN REPUBLIC ACADEMY OF SCIENCES

ADVANCES IN THE FIELD OF ALKALOID CHEMISTRY

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The present review gives the main advances made in the laboratory of alkaloid chemistry of the Institute of Plant Substances of the Usbekistan Republic Acacemy of Sciences [IKhRV AN RUz] (Tashkent) over 50 years in the field of the chemistry of diterpene, isoquinoline, quinoline, steroid, indole, spiropiperidine, sulfur-containing, tropane, pyrrolidine, quinazoline, quinolizidine, amaryllis, and pyrrolizidine bases and possible routes for the biosynthesis of some of these groups of alkaloids.

The main directions of investigations in the laboratory of alkaloid chemistry of IKhRV An RUz is the search for alkaloid-bearing plants, the development of methods of isolating and separating the alkaloids and establishing their structures, the study of their chemistry, and the dynamics of their accumulation in the plant, the elucidation of the dependence of physiological action on structure, the creation from alkaloids of medicinal preparations, the solution of questions of the biosynthesis and interrelationship of alkaloids, the use of information on the structure of these compounds for the chemosystematics of plants, the synthesis of alkaloids for confirming their structures, and the preparation of compounds valuable from the pharmacological point of view.

Chemical studies have been made of 266 species of plants belonging to 29 families, from which 913 alkaloids have been isolated. The structure of 518 new alkaloids belonging to the isoquinoline, diterpene, quinoline, steroid, quinolizidine, diterpene, quinoline, steroid, quinolizidine, indole, tropane, pyrrolizidine, quinazolone, sulfur-containing, amaryllis, and other groups have been established.

New alkaloid-bearing plants of the genera Nitraria, Dipthychocarpus, Haplophyllum have been found and other, new, types of alkaloids have been discovered, methods have been developed for establishing their structures, and routes for their biosynthesis in the plants have been suggested. These developments have served as the starting point for new promising directions in alkaloid chemistry and have openend up new routes for their use in medicine.

S. Yu. Yunusov's investigations on the dynamics of the accumulation of alkaloids in each organ of a plant according to the vegetation periods and the growth sites laid the foundations of this work [1].

These investigations have permitted alkaloid-bearing species to be determined more accurately, the maximum number of alkaloids to be isolated, and the laws of the dynamics of their accumulation in each organ of the plant during its development to be elucidated, which is particularly important for revealing the genesis and role of alkaloids in plants. As a result of these investigations, S. Yu. Yunusov drew the following conclusion: alkaloids play an active role in the vital activity of plants and fulfill diverse functions. Qualitative and quantitative changes in them take place throughout the vegetative period and, as a rule, they accumulate in those parts of the plant which are important and necessary for creating the following generation at this stage. With a change in the ecologogeographic conditions the alkaloids in a plant change more rapidly than its morphological characteristics. Consequently, one and the same species of plant may contain different alkaloids under different conditions [1, 2]. This methodological approach has been made the basis of the study of each alkaloid-bearing plant.

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Alkaloids are being widely used for the purposes of taxonomy. Thus, information on the combined presence of diterpene and isoquinoline alkaloids in plants of the genera Aconitum and Delphinimum [3, 4] has confirmed the view of botanists on the phylogenetic relationship of the Papaveraceae and Ranunculaceae families. The chemical analysis of close species of plants of the genus Nitraria has shown that they produce specific new alkaloids characteristic only of plants of this genus. N. sibirica contains alkaloids of the spiropiperidine type. N. komarovii those of the indole type, and N. schoberi representatives of both types. This feature of the alkaloid composition of species of the genus Nitraria makes it possible to use it in disputed questions for the chemosystematics of species of the Nitraria genus [5].

In cooperation with pharmacologists, investigations have been made to establish the dependence of pharmacological properties on structure in a series of diterpene, indole, quinoline, steroid, quinazoline, sulfur-containing, and other alkaloids, which has permitted the development of valuable medical preparations.

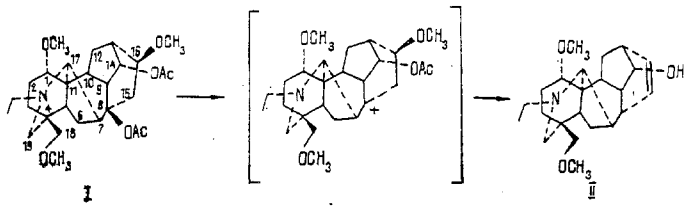
At the present time the pharmaceutical industry is producing the drugs lycorine, deoxypeganine, galanthamine, cytosine, and allapinin; the bioreagents bicuculine, aconitine, heliotrine and imperialine have been created and are being produced for medicobiological studies.

Investigations important in the practical respect include those on the causes of diseases of Man and animals that are sometimes widespread in Central Asia — Dzhelangarian encephalitis and toxic hepatitis with ascites. The cause of these diseases has proved to be pyrrolizidine alkaloids present in certain weed plants. These plants have been assigned to the quarantine type. Below we consider the main directions and the work of the laboratory of alkaloid chemistry.

DITERPENE ALKALOIDS

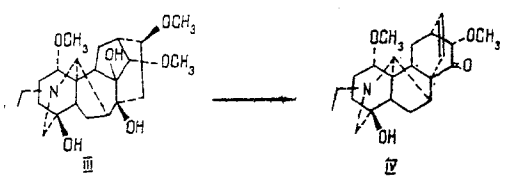
The sources of this group of alkaloids are plants of the genera Aconitum and Delphinimum that are widespread in Uzbekistan and other states of the former Union. At the present time, 44 plants of these genera have been investigated, and from these about 150 diterpene alkaloids have been isolated. The structure of 89 new compounds belonging to the C_{20}-, C_{19}-, and C_{18}-diterpene types have been established. It must be mentioned that the isolation and chemical investigation of the first representatives of the C_{18}-diterpene alkaloids [6, 7] was carried out in the laboratory of alkaloid chemistry.

Numerous investigations on the chemistry and analysis of the spectral characteristics of diterpene alkaloids have permitted the proposal of new methods for establishing their structures, revealing a number of relationships between structure and reactivity, drawing conclusions concerning the mechanism of certain reactions characteristic of the group of substances, finding new type of bases, and revealing the dependence of the pharmacological properties of the alkaloids on their structures. Thus, it has been established that the pyrolysis of diacetyltalatisamine (I) in glycerol forms compound (II). Consequently, in this reaction the elimination of a molecule of methanol, the saponification of the ester group at C-14, and the hydrogenolysis of the acetoxy group at C-8 take place



The acetoxy group undergoes hydrogenolysis as the result of an ionic hydrogenation reaction in which the source of the hydride ion is a molecule of glycerol [8].

The isomerization of lappaconine (III) to form compound (IV) of the denudatine type has proved to be a common one for alkaloids with a C-8—C-9 diol system and makes it possible to judge the nature of the substitution in ring D [9].

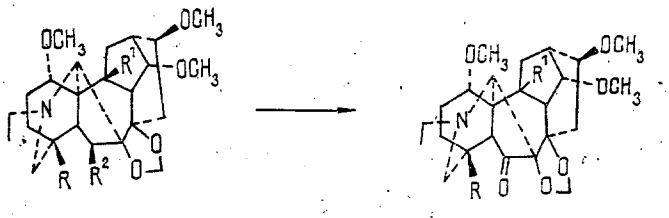


The possibility has been shown of the selective acylation and hydrolysis of lycoctonine alkaloids. In particular, it is most difficult to acylate the C-14 hydroxyl group and most difficult to saponify the ester group at C-1. The ease of its saponification when a hydroxy group, is present at C-10 is connected with intramolecular catalysis [10, 11].

The reaction of alkaloids of the lycoctonine group with acetic anhydride and p-toluenesulfonic acid, leading to the acetates at the 7,8-diol system and to anhydro compounds has been studied [12].

An unusual reaction – the formation of 6-keto derivatives (VIII, IX) on the interaction of the lycoctonine alkaloids eldeline (V), eldelidine (VI), and delcorine (VII) with sodium in liquid ammonia has been detected for the first time. It has been established that the conversion of a hydroxy group into a carbonyl group in the absence of a proton donor is characteristic only for 6-hydroxy or acetoxy derivatives [13].

Systematic investigations of the behavior of diterpene alkaloids under the conditions of mass spectrometry have shown the possibility of using this method for predicting structures and for determining the positions of functional groups. Thus, except for special cases [14], the maximum ion in the spectra of each alkaloid is that formed through splitting out of the substituent at C-1 [15]. Alkaloids of the aconitine type containing an acetoxy group at C-8 or such a group and, simultaneously, a benzoyl group at C-14 readily eliminate an acetic acid molecule and therefore the peak of the molecular ion is either absent or has a very low intensity [16]. For these compounds the maximum peak is that of the $(M - 91)^+$ ion formed by the ejection of acetic acid (C-8–OAc) and of a methoxy radical (C-1–OCH_3) [11].



V–VII

VIII, IX

V. R=Me, R^1=OH, R^2=Ac

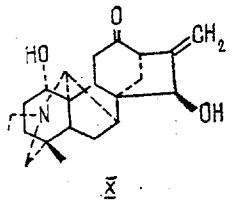
VI. R=Me, R^1=R^2=OH

VII. R=CH_2OMe, R^1=H, R^2=OH

VIII. R=Me, R^1=OH;

IX. R=CH_2OMe, R^1=H

It has also been found that the presence of a C-6(OCH_3)–C-7(OH)–C-8(OH) chain in the molecule of a C_{19}-diterpene alkaloid leads to a high intensity of the peak of the $(M - 15)^+$ ion through the loss of the methoxy group at C-6 [17]. The fragmentation of bases of this type has been studied for the first time using songorine and its derivatives as examples. Characteristic for these substances, in contrast to the lycoctonine type of alkaloids, is the appearance of a stable molecular ion and breakdown with the splitting out of the elements of rings A and D [18].

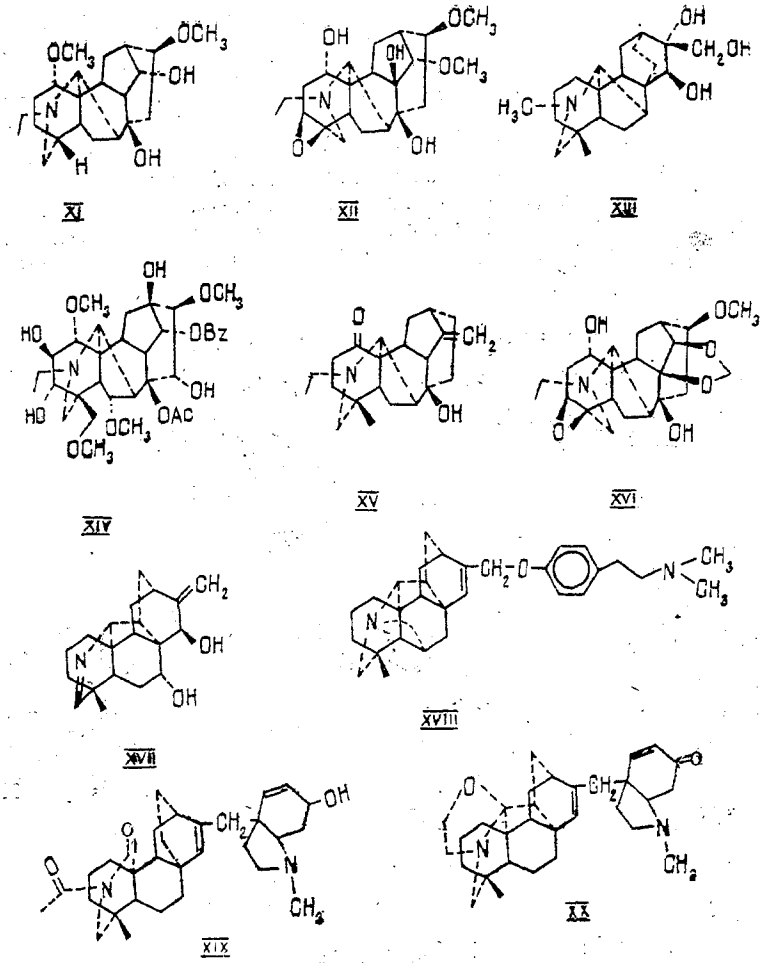


X

The ejection of an acrolein molecule with the formation of the $(M - 56)^+$ ion is characteristic for alkaloids that are internal esters of α-carbinolamines and contain a 1-α-hydroxy group [17, 18]. However, the intensity of this ion in the spectra of hydroxy and 1-α-hydroxy derivatives falls considerably if a C-6(OCH_3)–C-7(OH)–C-8(OH) chain is present in the alkaloids, and also on passing from anhydroxy bases to their nor-analogues [17].

Alkaloids of new types have been detected in the course of structural investigations. Thus, aconosine (XI), which has no substituent at C-4 [19], excelsine (XII), a C_{18}-diterpene alkaloid with an epoxy function at C-3, C-4 [20], dictysine (XIII), containing a C-15, C-16, C-17-triol system [21], altaconitine (XIV), having the greatest number of substituents and

being the only representative with a C-2, C-3-diol system [22], actaline (XV), a C_{20}-diterpene alkaloid with a lycoctonine skeleton and a exomethylene group at C-14 [23], akirine (XVI), with a methylenedioxy group at C-9, C-14 [24], talasamine (XVII), containing C-19—N double bond [25], zeraconine (XVIII), with a dimethylaminophenethyloxy substituent at C-17 [26], coryphidine (XIX) and coryphine (XX), both containing a hexahydro-N-methylinodole fragment at C-17, while XIX has an imide group in the diterpene skeleton [27] and XX an oxazolidine ring with a C-14, C-20 bridge [28], are unique from the structural point of view.



Among compounds of this group N-oxide forms have been found of the alkaloids songorine and zeraconine, and alkyl derivatives of 14-hydroxyhetisine and others [2, 29-32], and also a single base esterified by propionic acid (acoridine) [33].

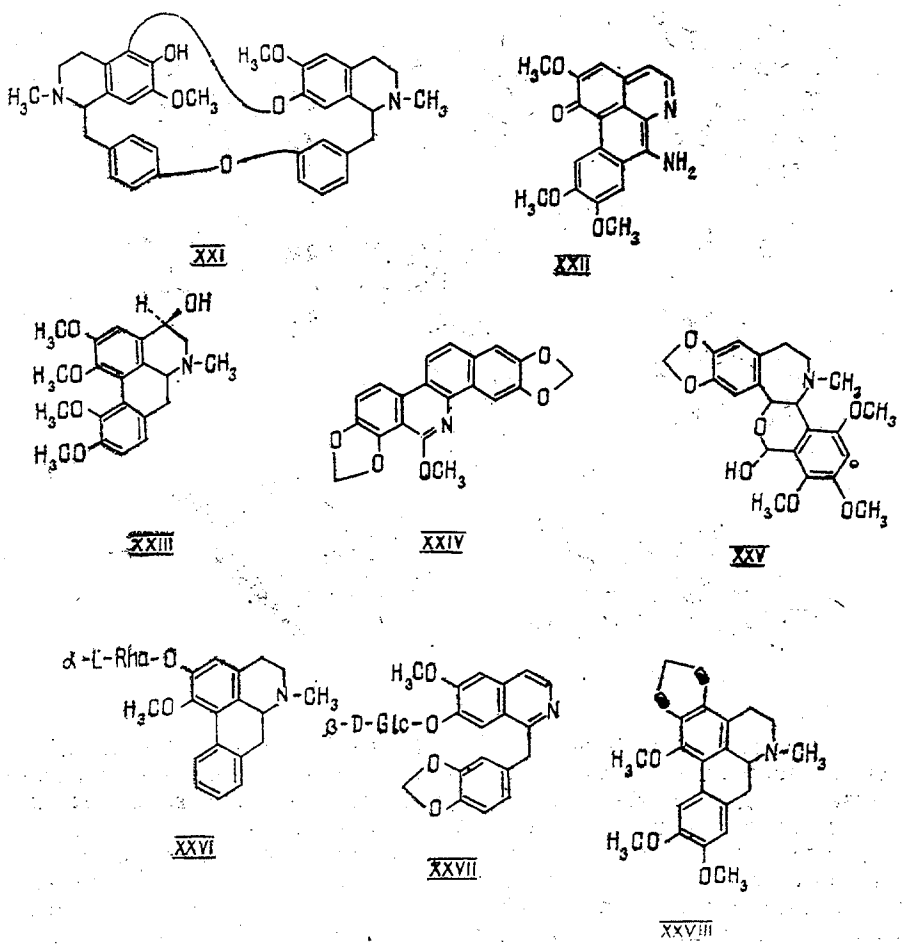
More than 150 diterpene alkaloids and their derivatives have been subjected to pharmacological investigation. As a result, information has been obtained about the dependence of pharmacological activity on structure. Compounds possessing pronounced antiarrhythmic, local anesthetic, spasmolytic, anti-inflammatory, gangliolytic, and curaremimetic and psychostimulating, arrhythmogenic, and antitoxic properties in relation to aconitine have been found [34]. Antiarrhythmic properties were first detected in the series of diterpene alkaloids. One of them, under the name allapinin is being used in medical practice and is being produced by the Chimkent and Tashkent Pharmaceutical Chemical Factories and the experimental production unit of the Institute of Plant Substances of AN RUz.

These investigations represent a new direction in the creation of antiarrhythmic drugs.

ISOQUINOLINE ALKALOIDS

This group of compounds is found in plants of the genus Papaver, Roemeria, Glaucium, Argemone, and Hylomecon (family Papaveraceae), Corydalis, Dicentra, Fumaria, and Hypecoum (family Fumariaceae), Thalictrum, Delphinium, and Aconitum (family Ranunculaceae), Liriodendron, and Magnolia (family Magnoliaceae), Ziziphus (family Rhamnaceae), and Leontice and Berberis (family Berberidaceae). About 200 bases belonging to various groups of isoquinoline

alkaloids have been isolated: protopine, spiroisoquinoline, naphthophenanthridine, tetrahydroisoquinoline, aporphine, diisoquinoline, rheadine, phthalidisoquinoline, morphinan, benzylisoquinoline, pavine and isopavine, and bisbenzyl- and aporphine-benzylisoquinoline dimeric bases. The structures of more than 70 new alkaloids have been established. Many of the bases isolated have original structures. For example, the bisbenzoisoquinoline alkaloid thalmine (XXI) [35] with a 21-membered dioxide ring, forming the foundation of the new thalmine type of bisbenzylisoquinoline alkaloids, has been isolated from Thalictrum minus. 1-Oxo-substituted (pancorydine, pancorynine (XXII) [36]), and 1,2,4,10,11-pentasubstituted (glaufidine, epiglaufidine (XXIII) [37]) aporphinoids, pancorine (XXIV) [38] – a norbenzophenanthridine alkaloid with a substituent at C-8, zangezurine (XXV) [39] – a pentasubstituted representative of the rheadine type, and 7,8-substituted benzyltetrahydroisoquinoline derivatives (gortchacoine, juziphine, and norjuziphine and their N-oxides) have been assigned to new types [2]. The new aporphine glycoalkaloid floropavidine (XXVI) has been isolated from Papaver floribundum and P. bracteatum [40], and glycomarine (XXVII) from P. orenarium [41].



In formula XXIII there should be OH at C-1 instead of OCH_3.

To confirm the structure of baicaline (XXVIII) – a pentasubstituted aporphine alkaloid with a methylenedioxy group in the 2,3 position [2] its complete synthesis has been achieved [42].

In an investigation of the aporphine alkaloids, the following dependence of their properties on the positions of substituting groups was established [43]:

- the specific rotations of aporphine alkaloids with substituents in positions 1,2,9,10 and 1,2,10 are several times smaller than those of bases with substituents in positions 1,2,10,11 and 1,2,11;
- a methylenedioxy group is almost always present in the 1,2 position;
- a hydroxy group in position 1 possesses attenuated phenolid properties; and

– the nature of the products of the oxidation of aporphine bases by concentrated nitric acid depends on the substituents in the benzene rings. Depending on the substituents, mellophanic or benzenedi- or tricarboxylic acids are formed. A high reactivity of the methoxy groups at C-8 in pancorine has been revealed [38].

In order to obtain physiologically active compounds, β-phenylethylamines have been synthesized, and, following these, analogues of benzylisoquinoline, aporphine, and diisoquinoline alkaloids. Among the latter, d,ℓ-tetrahydropalmatine and d,ℓ-tetrahydroberberine are superior to seduxen in sedative activity [44].

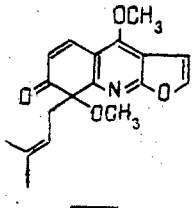
A biological and pharmacological study of the activity of the isoquinoline alkaloids has shown a definite directivity of their action as cholegogic, antihistamine, sedative, hypotensive, antiarrhythmic, and antimicrobial agents. New compounds have been found that are antigonists of GAMA receptors [45]. Approaches to the purposeful search for drugs of practical value have been found on the basis of a study of the dependence of pharmacological properties on the structure of the isoquinoline alkaloids and their analogues.

QUINOLINE ALKALOIDS

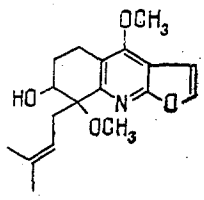
This group of alkaloids is found in plants of the genera Haplophyllum and Dictamnus (family Rutaceae).

At the present time, 20 plants of the genus Haplophyllum and two species of Dictamnus have been investigated. This has led to the isolation of 70 alkaloids, including 51 new ones, the structures of which have been established. They are all quinoline derivatives with the exception of two, which have proved to be amides [46].

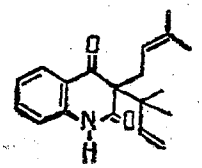
Plants of the genus Haplophyllum have been discovered to the greatest extent, these being remarkable by the fact that they contain representatives of all known types of quinoline groups found in plants of the Rutaceae family. These are derivatives of 4-hydroxyquinolin-2-one, pyranoquinolin-2-one, dihydropyranoquinolin-4-one, 2-phenylquinoline, 2-phenyl- or alkylquinoline-4-ones, furanoquinoline, dihydrofuranoquinoline, and dihydrofuranoquinolin-4-one. In addition to these, new structural systems have been found – furanoquinolines with gem-substituted cyclohexadiene rings (perfamine (XXIX) [47], 5, 6, 7,8-tetrahydrofuranoquinolines (haplophyllidine (XXX) [46]), gem-substituted hemiterpenoid quinoldiones (buchapine (XXXI) [48]), dimers with cyclobutane rings (haplodimerine (XXXII) [49]), glycoalkaloids including biosides and acylbiosides (haplosidine (XXXIII) [50]), and quinoline alkaloids with terpenoid substituents (bucharaine (XXXIII) and others [46]).



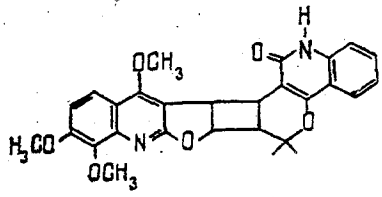
XXIX



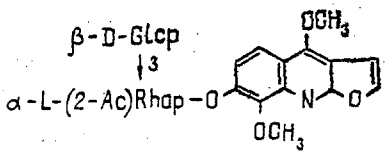
XXX



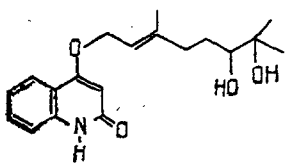
XXXI



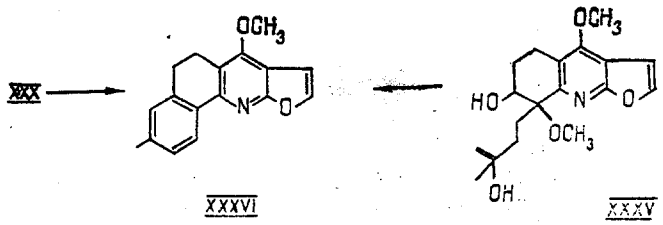
XXXII



XXXIII



XXXIV

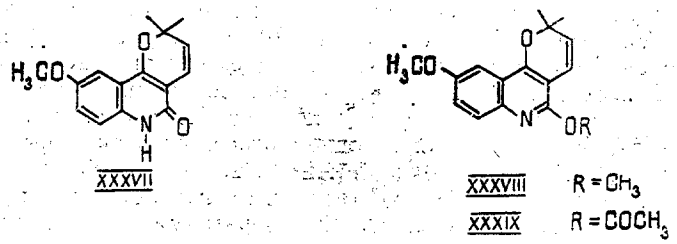


XXXVI XXXV

A new methodological approach to the separation of alkaloids has been proposed which permits the qualitative and quantitative composition in a plant to be taken more fully into account [46].

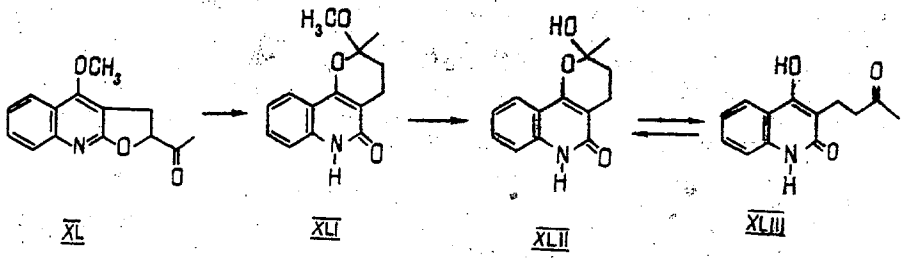
The chemistry of alkaloids with new structural systems has been studied. Methods have been developed for establishing their structures. Differences have been revealed in the behavior of individual functional groups in dependence structure. Thus, a methoxy group at C-4 in a furanoquinoline is more reactive than one in a 5,6,7,8-tetrahydrofuranoquinoline. In the latter, it is not demethylated on heating with solutions of acids and alkalis and is not isomerized under the action of methyl iodide [46].

An unusual cyclocondensation reaction has been found in the 5,6,7,8-tetrahydrofuranoquinolines (XXX) and (XXXV), leading to the formation of compound (XXXVI), containing an aromatic ring [51]. On methylation and acetylation, the pyranoquinolin-2-one haplamine (XXXVII) reacts in the lactim form, giving O-methyl- and O-acetyl derivatives (XXXVIII and XXXIX, respectively); this is probably due to a redistribution of the electron density under the influence of the electron-donating substituent, which increases the delocation of the double bonds in the system [46].



XXXVII XXXVIII R = CH_3 XXXIX R = $COCH_3$

The hydrogenolysis of the dihydrofuran ring on the Clemmensen reduction of dubinidinone (XL) with migration of the methyl group at C-4 to the δ-carbonyl position, to form a six-membered ketal (XLI), which is a new reaction for dihydrofuranoquinolines, has been detected. The ketal (XLI) is readily demethylated to the hemiketal (XLII). It has been established that in solutions the hemiketal is present in tautomeric equilibrium with the ketol (XLIII), while in deuteropyridine and deuterodimethyl sulfoxide solutions the tautomeric equilibrium is displaced in the direction of a predominance of the cyclic hemiketal, and in trifluoroacetic acid the linear ketol predominates.



XL XLI XLII XLIII

The existence of ring-chain tautomerism (XLII) ⇄ (XLIII) has been shown by ^{13}C NMR spectroscopy [52].

A study of the properties of furanoquinoline alkaloids with O-isopentenyl and O-carbohydrate substituents in the homocyclic benzene ring has shown that these substituents are saponified more readily than a methoxy group in the C-4 position. This permitted us to consider as erroneous the conclusion known in the literature that only the alkaloids with phenolic hydroxyls at C-4 can be nonnative.

Plants of the genus Dictamnus contain mainly furanoquinoline, isofuranoquinoline, and 3-alkyl-4methoxyquinolin-2-one alkaloids [53, 54]. Isofuranoquinoline alkaloids have not been found in plants of the genus Haplophyllum. Since they are present in all the species

of the genus Dictamnus investigated, they may be considered as a taxonomic characteristic of plants of this genus.

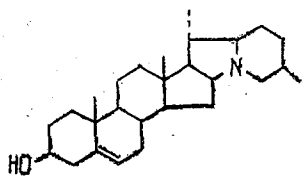
From the number of alkaloids isolated and their structural diversity, the genus Haplophylum is unique among the genera of the family Rutaceae that have been studied.

The majority of alkaloids isolated possess a depressive action on the central nervous system. Individual alkaloids exhibit, together with this property, a pronounced tranquilizing, anticonvulsive, antiarrhythmic, and estrogenic activity. A number of the alkaloids cause pronounced stimulation of respiration and an increase in reflex excitability [55, 56].

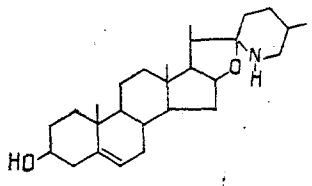
STEROID ALKALOIDS

This group of alkaloids has been found in plants of the genera Korolkowia, Petilium, Veratrum, Rhinopetalum, Fritillaria, and Zygadenus (family Liliaceae), Buxus (family Buxaceae), and Solanum (family Solanaceae).

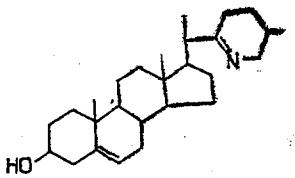
More than 120 steroid alkaloids have been isolated from the 12 species of these genera that have been investigated, and the structures of 80 new compounds have been established [2, 29, 30, 57, 58]. They are all, in the main, typical steroid alkaloids [the solanidine (XLIV), solasodine (XLV), verazine (XLVI), and veralkamine (XLVII) groups] or C-nor, D-homosteroid alkaloids [the imperialine (XLVIII), jervine (XLIX), and veratramine (L) groups]. Alkaloids from plants of the Buxus genus contain the heterocyclic skeleton of pregnane with two nitrogen atoms at C-3 and C-20 [2, 57].



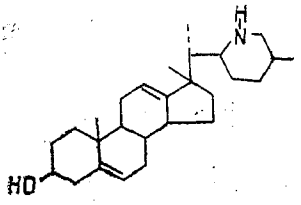
XLIV



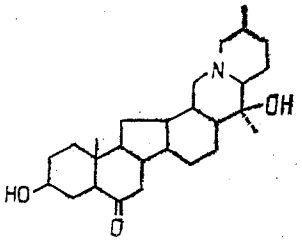
XLV



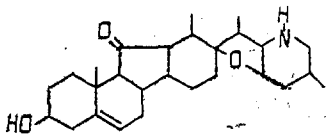
XLVI



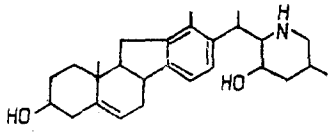
XLVII



XLVIII



XLIX



L

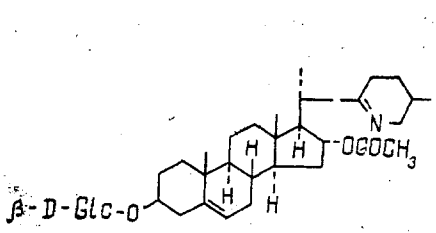
Changes in the qualitative and quantitative total amounts of alkaloids according to the growth site and plant organ have been determined.

In the course of structural studies it has been established that the chemical shift of the signal of the 18-methyl group in typical steroid alkaloids depends on the orientation of an acetoxy group at C-16. Differences have been found in the chemical shifts of the signals of gem-acetoxy progons at C-3 (4.46-4.62 ppm) and C-16 (4.69-5.13 ppm) [57].

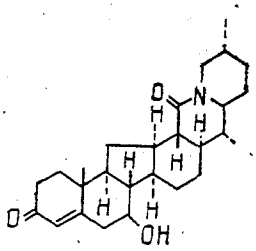
The mass spectra of alkaloids of the imperialine group have been studied, schemes of their fragmentation have been proposed, and it has been shown that characteristic ions in the spectra of these compounds are those with m/z 98, 111, 112, 124, 125, 146, 154, 155, 156, 164, 180, and 190, formed from the heterocyclic part of the molecule [59]. It has been established that the presence of peaks of ions with m/z 154, 155, and 156 in their spectra is a characteristic feature for the C-nor, D-homosteroid alkaloids of the imperialine group with a tertiary hydroxy substituent at C-20.

A difference has been found in the hydrolysis of the N-acetyl group at C-3 as a function of its orientation. Alkaloids with the 3β-equatorial orientation of a N-acyl group regularly undergo acid hydrolysis (buxaline-C, acetylcycloprotobuxine-C), and those with a 3α-axially oriented N-acyl group do not undergo acid or alkaline hydrolysis (ℓ-cycloprotobuxine-C) [60].

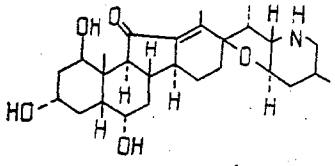
Ester-glycoalkaloids (veralosine (LI) [61]), N-oxides, alkaloids having as substituents an amide group (veralodine (LII) [62]), 16-acetoxy and 20β-dimethylamino groups, and a carbonyl group at C-3 and a double bond at $\Delta^{8(9)}$ have been detected for the first time among steroid compounds. Verdine (LIII) [63] is the first representative among steroid alkaloids of the jervine group that has a hydroxy group at C-1. Petisidine (LIV) is the only representative among this group of substances with a pyridine ring [64], and radpetine (LV) is the only one with a epoxyethylidene group [65]. An interesting fact is the discovery of seco-C-nor, D-homosteroid alkaloids [severidine (LVI)] and also such alkaloids as edpetilidinine (LVII) and sevcoridinine (LVIII) [66, 67].



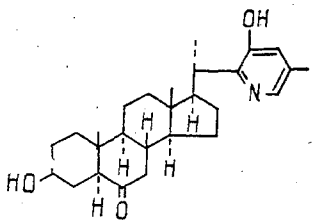
LI



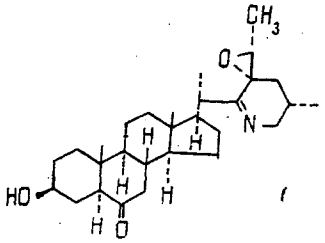
LII



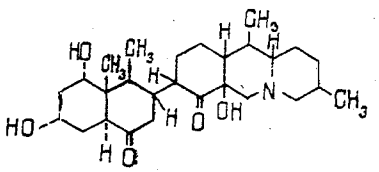
LIII



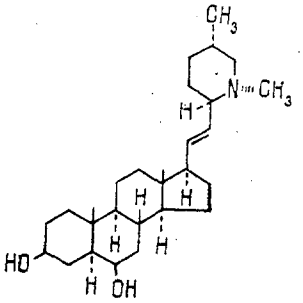
LIV



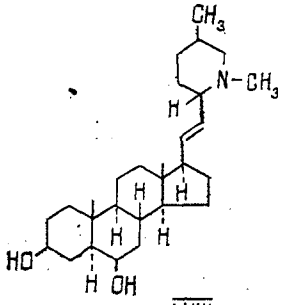
LV



LVI



LVII



LVIII

Biosides and trisides, which are characteristic for plants of the genus Solanum have been found for the first time among steroid alkaloids from the genus Rhinopetalum [68].

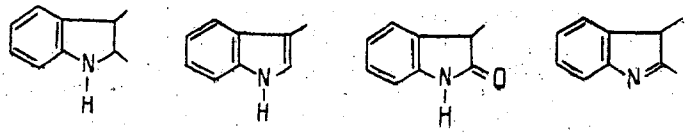
Work has been done to reveal the dependence of pharmacological properties of the steroid alkaloids on their structure [69]. A total of 89 alkaloids and their derivatives have been studied. Among them have been found substances possessing pronounced hypotensitive, anti-inflammatory, antimicrobial, curaremimetic, cardiotropic, bronchodilatory, and spasmolytic properties.

Original drugs with an aphrodisiac action have been obtained. Work on the creation of drugs with an aphrodisiac action forms a new direction in the investigation of steroid alkaloids.

A number of bioreagents for medicobiological investigations have been proposed.

INDOLE AND SPIROPIPERIDINE ALKALOIDS

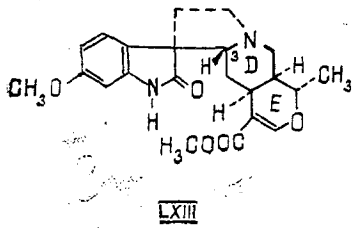
Sources of indole alkaloids are plants of the genera Vinca (family Apocynaceae) and Nitraria (family Zygophyllaceae), from which about 120 alkaloids have been isolated [70-83]. The richest has proved to be the plant Vinca erecta, from which more than 70 alkaloids have been isolated [70-75], these being derivatives of indoline (LIX), indole (LX), oxindole (LXI), and indolenine (LXII).



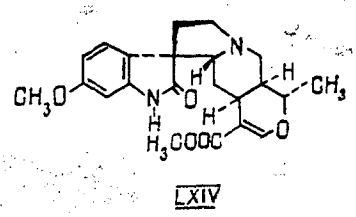
LIX LX LXI LXII

The indoline skeleton is possessed by the structural analogues kopsinine, pseudokopdinine, kopsanone, picrinine, akuammine, akummicine, quebrachidine, and vincadifformine [2].

The indole group of alkaloids is the most diverse in structure. It includes derivatives of quebrachamine, tombozine, and vincamine [2]. All the oxindole alkaloids are derivatives of carapanaubine and are found in the form of pairs of stereoisomers – for example, vinerine (LXIII) and vineridine (LXIV) [71].



LXIII



LXIV

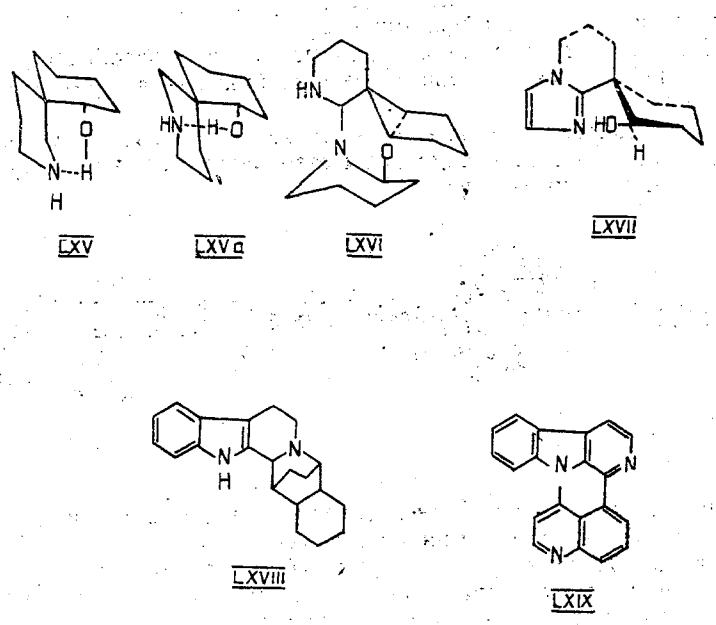
The indolenine alkaloids contain the heterocyclic nucleus of ajmaline and picrinine [2].

Each of these groups of alkaloids has its characteristic reactions and spectral features. In addition to this, some functional groups are diagnostic for the determination of the type of alkaloids. Thus, while for bases of the akuammicine, tombosine, akuammine, quebrachidine, and picridine type the presence of an ethylidene ($C=CH-CH_3$) group is characteristic, alkaloids of the vincadifformine, vincamine, and quebrachamine type contain a $C-C_2H_5$ group in their structure.

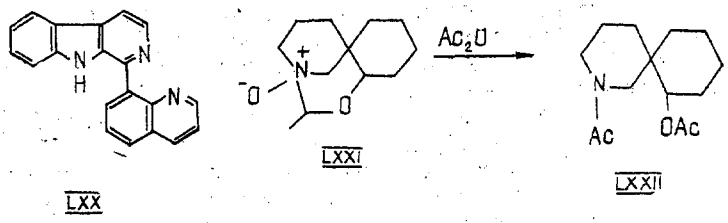
Striking is the detection of a dependence of the sign of the specific rotation in oxindole alkaloids with a cis-linkage of rings D/E on the spatial position of the protein at C-3. In the case of its α-orientation, the oxindole alkaloids rotate the plane of polarization to the left, while for β-orientation they rotated to the right.

Characteristic (distinctive) features of the PMR spectra of oxindole bases of the allo and epiallo series have been found [76]. In spite of the great structural differences between these compounds, a definite interrelationship exists, which is shown by the isolation of the corresponding intermediate analogues from the plant. The Vinca alkaloids of a definite type differ in structure from one another for the most part by the nature and positions of the substituting groups. By studying color reactions, the possibility has been shown of a preliminary determination of the chromophoric groups of these substances.

Great interest was presented by the discovery in plants of the genus Nitraria of a group of indole and spiropiperidine alkaloids with a new heterocyclic skeleton. As a result of the investigations performed, about 30 alkaloids forming a new class of nitrogen bases have been isolated and their structures have been determined [77-85]. These alkaloids are based on the new heterocyclic systems 2-azaspiro[5,5]undecane (nitramine (LXV) [77, 78], isonitramine (LXVb) [77], nitraramine (LXVI) [79], and nitrabirine (LXVII) [80]); 14,21-ethano-16-azayohimbane (nitrarine (LXVIII) [81, 82]); and indolo[3,2,1-ij]quinolino[4,5-bc]-1,5-naphthyridine (komarovidinine (LXIX) [83]). Alkaloids with new types of structures — 1-quinolinyl-β-carboline (komarovine (LXX) [84]), yohimbine, and quinazoline structures — have also been detected.



The chemistry of these alkaloids has been studied and their absolute configurations and preferred conformations have been established. Thus, under the action of acetic anhydride, sibirinine (LXXI) [85], undergoing a Polonovski transformation, is converted into diacetylisonitramine (LXXII).



The dehydrogenation reactions of the indole alkaloid nitrarine in the prsence of selenium and sulfur on palladium by mercury acetate and other transformations serving as a methodological basis for proving the structures of alkaloids of this subgroup have been studied in detail [82]. From a study of the structure-activity relationship approaches have been found to a purposeful search for drugs of practical value. According to the results of biological trials, among the alkaloids isolated and their synthetic analogues substances have been found which possess pronounced spasmolytic, hydrotensive, antimicrobial, curaremimetic, antiarrhythmic, and anti-inflammatory actions [56, 86].

SULFUR-CONTAINING ALKALOIDS

Plants of the genera Dipthychocarpus (family Crucifereae) and Reseda (family Resedaceae) are sources of sulfur-containing alkaloids, and 25 alkaloids have been isolated from them, 18 being new and, of these, 12 containing sulfur.

The alkaloids of Diphychocarpus strictus represent a new class of sulfur-containing alkaloids including the structural types of the N-alkylureas in various combinations with methyl sulfoxide, sulfide, nitrile, and imine groups. The structures of 11 new sulfur-containing compounds have been shown [87-100].

By a study of the dynamics of the accumulation of the alkaloids of D. strictus it has been established that the epigeal part of the plant contains sulfur alkaloids in the sulfoxide form, while at the end of vegetation their deoxy products predominate in the ripe seeds. The majority of the substances isolated are optically active compounds.

In the molecules of these alkaloids the sulfur is present as a component of a sulfide or a sulfoxide group. Nine of the 11 sulfur-containing alkaloids proved to be N-alkyl derivatives of urea. A characteristic feature of the alkaloids with sulfoxide groups was the detection of an intense band at 1030-1045 cm^{-1} the absence or presence of which indicated the nature of the bond of the sulfur atom (C−S−C or C−S−O, respectively).

$$\begin{array}{c} \\ | \\ CH_3 \end{array}$$

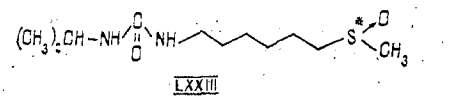
To prove the structures of the alkaloids isolated we used hydrogenolytic desulfation on Raney nickel, the formation of deoxy derivatives (when a sulfoxide group was present), oxidation reactions, etc. The basic principle for proving the structures amounted to obtaining dethio products, their complete characterization, and the partial or complete synthesis of the initial bases.

All the new sulfur-containing alkaloids have been separated into four groups: the diptocarpaine group [89], the diptocarpamine group [90], the diptocarpidine group [91], and the diptocarpilidine group [92].

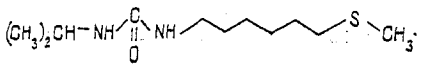
The diptocarpamine group combines three alkaloids that are derivatives of N,N'-dialkylurea: diptocarpamine, deoxydiptocarpamine, and diptamine. Their distinguishing feature consists in the fact that the substitution at one of the nitrogen atoms in the form of an isopropyl group is the same for all three compounds. The second alkyl substituent at this nitrogen atom is a methylthiohexyl, a methylsulfoxyhexyl, or a methylsulfoxyheptyl radical.

The reduction of diptocarpamine with lithium tetrahydroaluminate or zinc in a mineral acid leads to the optically inactive deoxydiptocarpamine. The desulfuration of both alkaloids gives one and the same dethio product — N-hexyl-N'-isopropylurea. Diptamine is a homologue of diptocarpamine.

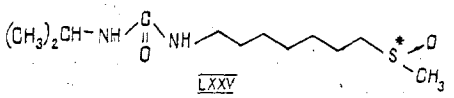
The diptocarpaine group consists of three alkaloids that are derivatives of monoalkyl ureas: diptocarpaine, deoxydiptocarpaine, and diptaline.



LXXIII

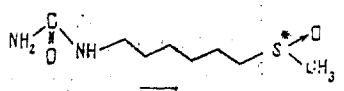


LXXIV

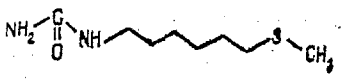


LXXV

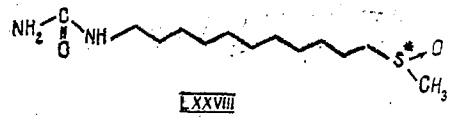
On reduction with Raney nickel, two alkaloids (LXXVI) and (LXXVII) gave a dethio product which was identified as N-hexylurea. Diptaline (LXXVIII) is a homologue of diptocarpaine.



LXXVI

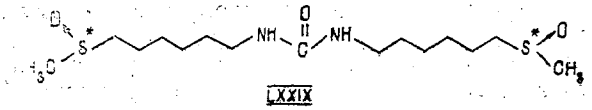


LXXVII

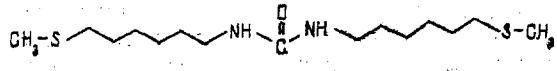


LXXVIII

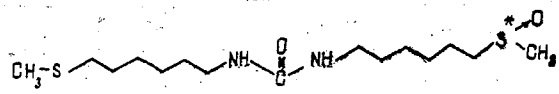
The diptocarpadine group also includes three alkaloids: diptocarpidine (LXXIX), deoxydiptocarpidine (LXXX), and diptocarpiline (LXXXI), which are derivatives of N,N'-dialkylureas.



LXXIX



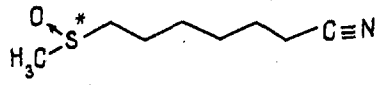
LXXX



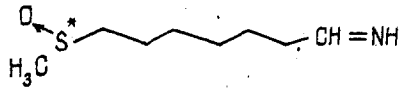
LXXXI

On desulfuration with Raney nickel in a current of hydrogen, all three alkaloids gave a dethio product which was identified as N,N'-di(6-hexyl)urea, which has been synthesized from hexyl bromide and urea.

Diptocarpilidine (LXXXII) and diptocarpinine (LXXXIII) are assigned to a fourth group. Their distinguishing feature is that they are not urea derivatives. The molecules of (LXXXII) and (LXXXIII) each contains a methyl sulfoxide group as a component of a methylsulfohexyl [in the case of (LXXXII)] and a methylsulfoheptyl [in the case of (LXXXIII)] radical. The terminal group in the case of diptocarpidine is a nitrile group and in the case of diptocarpinine it is an imine (-CH=NH-) group. The reduction of (LXXXII) by active hydrogen led to an optically inactive deoxy derivative, and alkaline hydrolysis to a substance of acidic nature. The desulfuration of the latter with Raney nickel gave enanthic acid, which unambiguousy established the structure of diptocarpilidine:

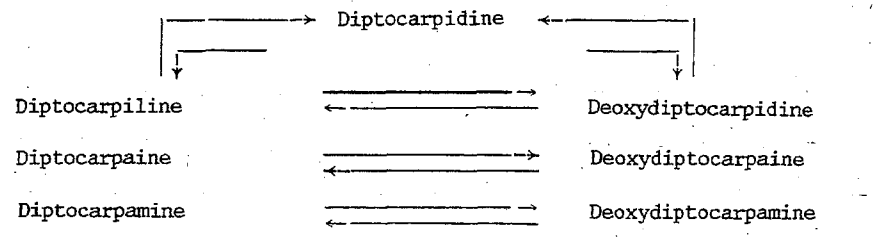


LXXXII



LXXXIII

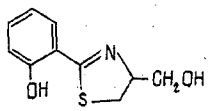
Interconversions of some of the sulfur-containing analogues have been achieved:



Together with workers from the Institute of Chemistry of the Bashkir Scientific Center, Ural Division of the Russian Academy of Sciences under the leadership of Academician G. A. Tolstikov schemes have been developed for the synthesis of six alkaloids (diptocarpamine, deoxydiptocarpamine, diptocarpiline, diptocarpidine, deoxydiptocarpidine, and diptocarpilidine) and their analogues [96-99].

Other sources of sulfur-containing alkaloids have proved to be the plants Reseda luteola, and R. lutea, from which eight alkaloids, including seven new ones, have been isolated [100]. The latter proved to be various derivatives of oxazolidone, thiooxazolidone, β-naphthylamine, and benzoxazine. The oxazolidone, β-naphthylamine, and benzoxazine derivatives are new types of plant substances found in Nature for the first time. The single sulfur-containing alkaloid, which was called resedinine, proved to be the known compound barbarin.

It is interesting to note the detection in the culture liquid of the microorganism Pseudomonas aeruginosa of the sulfur-containing alkaloid aerugine – a thiazoline derivative having the structure of 4-hydroxymethyl-2-o-hydroxyphenyl-2-thiazoline [101].



LXXXIV

On the basis of the results of biological trials of the alkaloids of Dipthychocarpus strictus a structure—activity relationship has been revealed and it has been established that they possess pronounced antihypoxic activity, exceeding that of the corresponding analogues used in medical practice [102]. The antihypoxic effect is enhanced with an increase in the number of sulfoxide groups and when the alkaloid molecules are symmetrical.

TROPANE AND PYRROLIDINE ALKALOIDS

Tropane alkaloids have been found in plants of the genera Convolvulus [103, 108], Physchlaina [109], Datura [110], and Hyoscyamus [111], belonging to the families Solanaceae and Convolvulaceae. From the 10 species of plants studied 35 alkaloids have been isolated of which 16 were new, and the structures of these have been established. Mutual transitions between them have been carried out.

Great interest is presented by the discovery of bimolecular alkaloids in the plants studied [112].

The monomeric tropane alkaloids are mainly esters of nortropine or tropane-3,6-diols substituted at the nitrogen atom and the aromatic acids veratric, vanillic, tropic, and atropic acid.

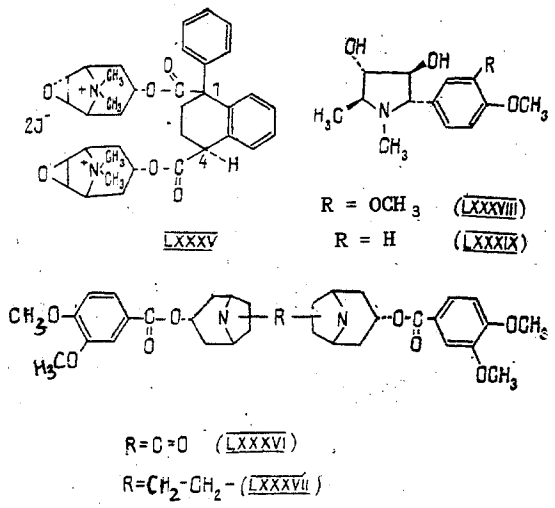
A distinguishing feature of the monomeric bases of the Convolvulus genus is that the majority of them are N-substituted derivatives of the basic tropane system. An interesting alkaloid in this respect is convoline which, has a formyl radical, found only rarely in the structure of natural compounds, at the nitrogen atom.

In the dimeric alkaloids, veratric and α- and β-isotropic acids are represented as the esterifying acids. The new dimeric alkaloids of the Solanaceae and Convolvulaceae families have different structures and can be assigned to two different types. Thus, the dimeric alkaloids isolated from Physochlaina alaica [109], Datura inoxia [110], and Datura stramonium [111] are united by the fact that they are esterified with isatropic acid (α- and β-forms). The aminoalcohol is most frequently tropine or scopine (as in the case of the monomers). The dimeric alkaloids of plants of the Solanaceae family (α- and β-belladonnines, α- amd β-forms). scopodonnines) which were known in the literature as synthetic compounds, have been isolated from the above-mentioned plants for the first time. The stereochemical structure of β-scopodonnine has been studied by x-ray structural analysis and it has been established that one of the tropane systems has the axial and the other the equatorial orientation and they have the cis arrangement with respect to one another. From this follows the trans-position of the proton at C-4 and of the carboxy substituent at C-1, which permitted the alkaloid isolated to be the assigned to the β-series [110].

A correlation has been made of the CSs of the carbon atoms in the ^{13}C NMR spectra with the structures of the tropane alkaloids, and the values of the α-, β-, and γ-contributions

of the $-OH$, $-CH_3$, and $-OCH_3$ groups and of the spatial influence of NCH_3 groups on the magnitudes of the CSs of the ^{13}C carbon atoms of the propane ring have been established.

The dimeric alkaloids of plants of the Convolvulaceae family are of a somewhat different type. Two representatives of this group are known: subhirsine (LXXXVI) and convolvidine (LXXXVII), each of which has an asymmetric structure and consists of two structural residues of convolvine linked through the nitrogen atoms by means of a carbonyl (subhirsine) or an ethylene (convolvidine) group.



LXXXV

R = OCH_3 (LXXXVIII)

R = H (LXXXIX)

R=C=O (LXXXVI)

$R=CH_2-CH_2-$ (LXXXVII)

Codonopsine (LXXXVIII) and codonopsinine (LXXXIX) – representatives of a new type of pyrrolidine bases – have been isolated from the plant Codonopsis clematidea [113].

Among the compounds studied and their synthetic analogues substances have been found that, according to the results of biological tests, possess pronounced curaremimetic and biostimulating effects [114].

QUINAZOLINE ALKALOIDS

Quinazoline alkaloids have been isolated from the genera Peganum and Nitraria (Zygophyllaceae), Linaria (Scrophylariaceae), and Biebersteinia (Ceraniaceae) [2, 115-117]).

The plant Peganum harmala, which is popular in folk medicine, has yielded 13 alkaloids of this group, and the structures of seven new ones have been established. Bases with substituents at C-4, such as peganidine (XC) [118] and the bimolecular compound dipegine (XCI) [119] have been detected for the first time among quinazoline alkaloids (see scheme top of next page).

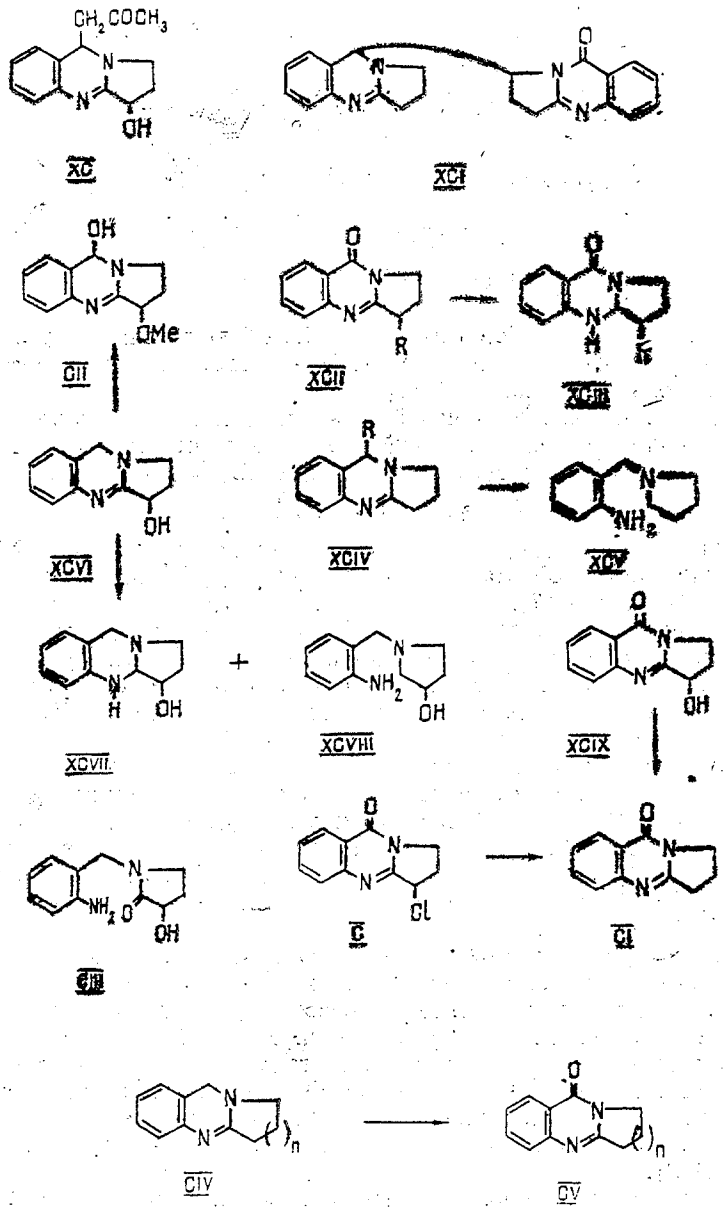
It has been shown that the reduction of the quinazole alkaloids (XCII, R = H, OH) with sodium tetrahydroborate leads to the dihydro derivatives (XCIII, R = H, OH); while the reduction of the quinazoline compounds (XCIV, R = H, OH) takes place with the cleavage of ring B and the formation of an aniline derivative (XCV). Under these conditions, peganine (XCVI) gives the dihydro derivative (XCVII) and a very small amount of the tetrahydro derivative (XCVIII) [120].

Conditions have been found for the direct halogenation of the benzene rings of the quinazoline alkaloids and their analogues [121, 122].

The unusual ease of reduction of vasicinone (XCIX) and of 9-chlorodeoxyvasicinone (C) to deoxyvasicinone (CI) on bromination with phosphorus tribromide and on alkylation under conditions of phase-transfer catalysis, respectively, has been revealed, and also the unusual introduction of a hydroxy group at C-4 on the methylation of (XCVI) with methyl iodide in the presence of sodium hydride, with the formation of 4-hydroxy-O-methylpeganine (CII) [123].

The structure of the known alkaloid vasicol (CIII) has been corrected [124].

In view of the high biological activity of the quinazoline alkaloids, analogues of them have been synthesized [125]. In the course of the synthetic studies it was found that in the series of trimethylene-, tetramethylene-, and pentamethylenequinazolines (CIV, n = 1-3), the most resistant to photooxidation was deoxypeganine (XIV, n = 1) while the least resistant was



tetramethylenequinazoline (CIV, n = 2). In this reaction, the corresponding oxo derivatives (CV, n = 1-3) are formed [126].

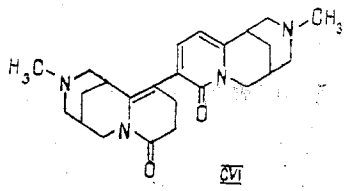
As the result of pharmacological investigations of more than 70 quinazoline alkaloids and their synthetic analogues, information on their active-structure relationships have been obtained.

The relatively nontoxic anticholinesterase drug deoxypeganine hydrochloride has been introduced into medical practice; it is used in myasthenia, myopathies, and motor and sensory disturbances connected with diseases and traumatic damage to the nervous system [127]. The drug is being produced by the Tashkent Pharmaceutical Chemistry Factory.

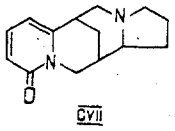
QUINOLIZIDINE ALKALOIDS

This group of alkaloids is found in plants of the genera Ammopiptanthus, Goebelia, Sophora, and Thermopsis (family Fabaceae), and Leontice (family Berberidaceae). The number of alkaloids that have been isolated is 42, and the structures of 19 new ones have been established. The existence of bimolecular alkaloids of the quinolizidine series has been established for the first time, and these include dimethamine (CVI), consisting of molecules of N-methylcytisine and of dihydro-N-methylcytisine linked through the carbon atoms of ring A [128].

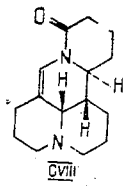
Leontidine (XVII) is the first representative of a new type of quinolizidine alkaloids. Its structure has been confirmed by its synthesis from cytisine [129].



CVI



CVII



CVIII

New methods have been proposed for establishing the stereochemistry of the quinolizidine alkaloids by the ORD method [130].

In [131], an attempt was made to link the contributions of various processes of the breakdown of matrine and three of its stereoisomers with the stereochemistry of rings A-D.

The mass-spectrometric fragmentations of a large number of quinolizidine alkaloids have been given in the literature [128, 132-135].

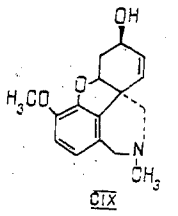
In toxic doses, leontalbine (CCVIII) causes a suppression of respiration. In its ganglion-blocking action it resembles pachycarpine. It stimulates the smooth musculature of the uterus [56].

It has been established that the epigeal part of Thermopsis alterniflora is a rich source for the industrial production of cytisine. A method has been developed for obtaining pachycarpine, which is used in medicine, from cytisine production wastes.

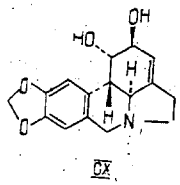
AMARYLLIS ALKALOIDS

Sources of amaryllis alkaloids are plants of the genera Ungernia, Narcissus, and Sternbergia (family Amarylidaceae). Plants of the genus Ungernia have been studied in the greatest detail. From the 15 species investigated 26 alkaloids have been isolated, and the structures of 14 new ones among them have been established [136-145].

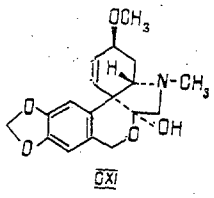
The new alkaloids belong to the types of galanthamine (CIX), lycorine (CX), tazettine (CXI), lycorenine (CXII), and crinine (CXIII).



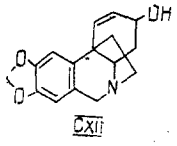
CIX



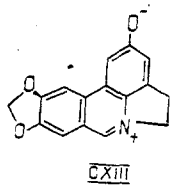
CX



CXI



CXII



CXIII

Interconversions have been carried out between alkaloids of different types; alkaloids of the phenol-betaine type have been detected [141]. Features of the mass spectrometric fragmentation of the Ungernia alkaloids have been found.

A substantial influence of an isolated double bond in ring B on the direction of breakdown of the molecular ion has been shown [146].

Recommendations have been developed on the exploitation of the growth and on the times of collection of wild-growing and cultivated species: Ungernia ferganica, U. victoris, U. sewertzovii, and U. tadschicorum for obtaining lycorine (CX) – an effective expectorant and emetic drug – and galanthamine (CIX) – a valuable medicinal preparation that is used in the treatment of the aftereffects of poliomyelitis [56].

More than 140 derivatives have been obtained from the alkaloids isolated. Among them have been found galanthamine analogues – in particular, its hydroxymethylate which is more than 20 times effective as (CIX).

Some derivatives of this group possess sedative and hypotensitive properties (apochlorine).

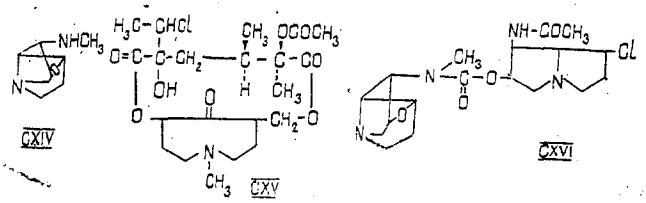
PYRROLIZIDINE ALKALOIDS

Pyrrolizidine alkaloids have been found in plants of the genera Caccina, Cynoglossum, Heliotropium, Lindelofia, Paracaryum, Rindera, Solenanthus, Symphytum, Trachelanthus, Tournefortia, Ulugbekia, Trichodesma, and Ehium (family Boraginaceae), Doronicum and Senecio (family Compositeae) and Lolium (family Gramineae).

From 41 plant species have been isolated 52 bases, and the structures of 20 new ones have been established [2, 29, 30]. Among plants of the genus Trachelanthus have been found the unique plant T. korolkovii, the alkaloid content in the epigeal part of which reaches 18%.

A large part of the bases consists of esters of heliotridane, heliotridine, retronecine, and otonecine.

The Lolium alkaloids belong to the new heterocyclic system of the type of loline (CXIV) [147]. The molecules of doronine (CXV) [148] and lolidine (CXVI) [149] each contain a chlorine atom. Lolidine is the first representative of bimolecular species of the pyrrolizidine series.



CXIV CXV CXVI

The great structural diversity of the alkaloids of the pyrrolizidine series that have been isolated has enabled us to find a number of correlations in their mass-spectrometric breakdown [150-151].

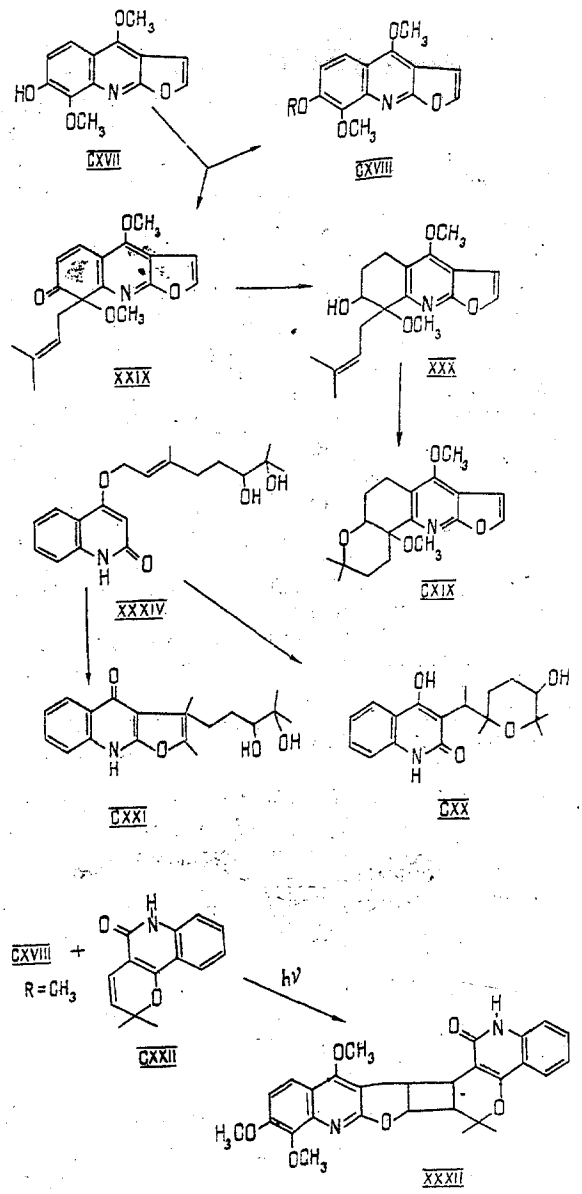
POSSIBLE ROUTES FOR THE BIOSYNTHESIS OF SOME GROUPS OF ALKALOIDS

Systematic investigations over many years of alkaloid-bearing plants from different growth sites according to vegetation periods and the study as far as possible of each organ of the plant separately have permitted a great diversity of alkaloids to be obtained, the dynamics of their accumulation to be followed, and their interconversion to be performed under laboratory conditions. In the light of the available information, hypotheses have been put forward concerning possible routes for the biosynthesis of some groups of alkaloids.

Thus, the simultaneous presence of furanoquinoline alkaloids (CXVII, CXVIII) and their modified derivatives (XXIX, XXX, XXXV, CXIX) in one plant [2], and also the important role of cyclohexadienones in the processes of phenol metabolism give grounds for the assumption that a definite link exists between perfamine (XXIX), haplophyllidine (XXX), and 7-isopentyloxy-γ-fagarine [CXVIII, R = $CH_2CH=C(CH_3)_2$]. The precursor of these compounds may be the phenolic alkaloid haplopine (CXVII), which, on methylation, allylation, and glycosylation, can give a diverse series of furanoquinoline alkaloids, such as skimmianine (CXVIII, R = CH_3), 7-isopentyloxy-γ-fagarine, glycoperine (CXVIII, R = Rhap), etc. On the other hand, haplopine (CXVII), on isolation under certain conditions, may react in the cyclodienone form, giving alkaloids of the type of perfamine (XXIX). The hydrogenation of the latter forms the 5,6,7,8-tetrahydrofuranoquinoline alkaloid haplophyllidine (XXX). The alkaloids perforine (XXXV) and anhydroperforine (CXIX) can be formed from (XXX) by hydroxylation and cyclization, respectively (see scheme top of next page).

Transitions from perforine (XXXV) to haplophyllidine (XXX) and to anhydroperforine (CXIX) have been achieved under laboratory conditions [152].

Thus, haplopine (CXVII) may be the key intermediate compound in the biosynthesis of the 7,8-disubstituted furanoquinoline alkaloids with different structures of the homocyclic ring.



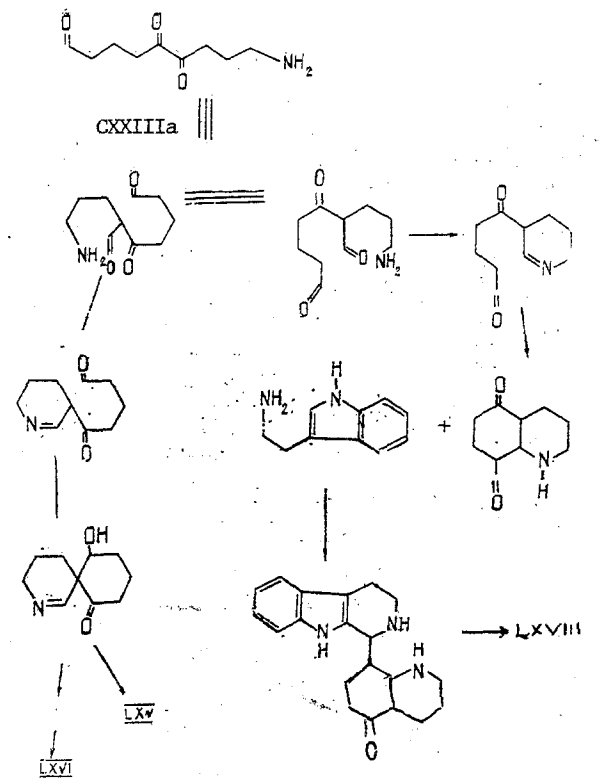
Consequently, alkaloids of the type of perfamine (XXIX) and haplophyllidine (XXX), the molecules of which lack the element of anthranilic aid, may nevertheless be formed in the plant by the general anthanilic acid mechanism of biosynthesis.

Among plants studied throughout the world, the only one producing quinoline alkaloids with terpene substituents [bucharaine (XXXIV), bucharidine (CXX), and bucharaminol (CXXI)] is Haplophyllum bucharicum [2]. The biogenetic link of these alkaloids is obvious, since it has been established with labeled compounds [153] that the Claisen rearrangement takes place the plant. A study of the Claisen rearrangement of bucharaine led to the isolation of a series of individual compounds, including bucharidine and bucharaminol [154].

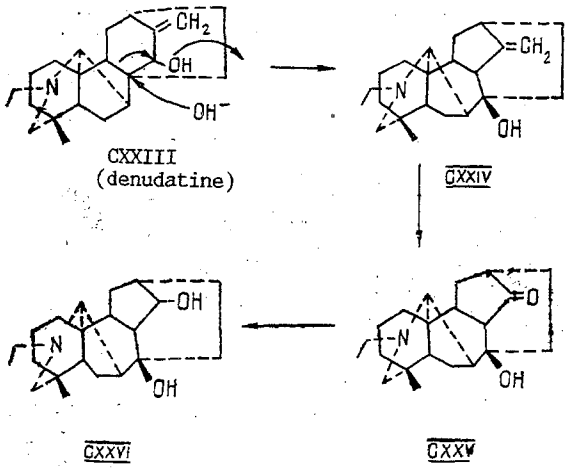
The biogenetic route for the synthesis of the dimeric alkaloid haplodimerine (XXXII) isolated from the plant Haplophyllum foliosum [49] can be represented as the photocycloaddition of aromatic compounds – skimmianine (CXVIII, R = CH_3) and flindersine (CXXII) – with the formation of the cyclobutane dimer (XXXII) [155].

A hypothesis has been put forward on the biosynthesis of the specific alkaloids of the Nitraria genus [2] which explains the formation of a plant of both spiropiperidine (LXV, LXVI) and indole (LXVIII) bases from a common polyketide precursor (CXXIII) [5] (see scheme top of next page).

Individual fragments of this scheme – in particular, the formation of nitrarine (CXXIII) – have been shown by synthesis under laboratory conditions.

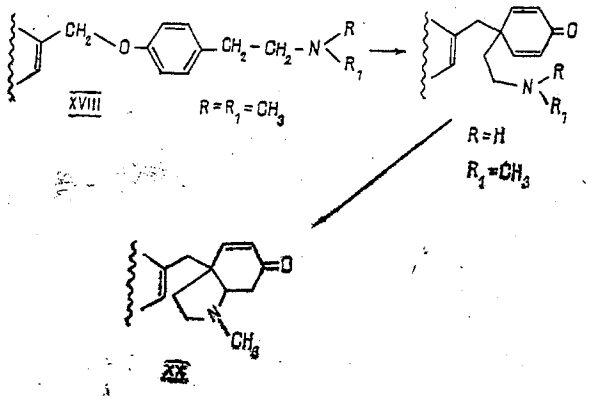


Actaline (XV) – the first C_{20}-diterpenoid alkaloid with a lycoctonine skeleton and an exomethylene group at C-14 – is interesting from the point of view of the biosynthesis of the diterpene bases. It is suggested [23] that actaline may be formed in the first stage of the transformation of the atisine alkaloids [of the type of denudatine (CXXIII)] into lycoctonine alkaloids (CXXV, CXXVI), i.e., the formation of the lycoctonine skeleton may take place with retention of the exomethylene group (CXXIV).



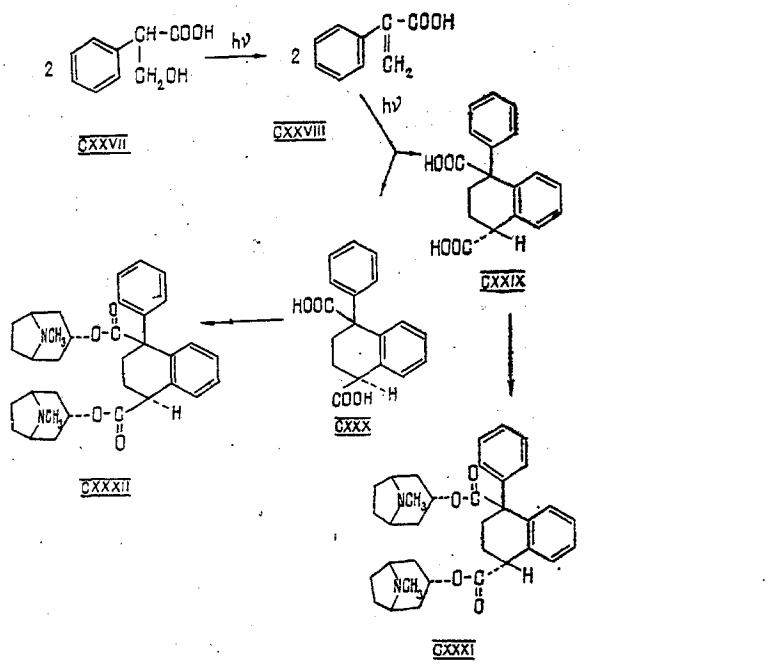
The simultaneous presence in the plant Aconitum monticola of the C_{19}-diterpenoid alkaloids delsoline and deoxydelsoline and of the C_{18}-diterpenoid alkaloids monticamine, monticoline, and dihydromonticamine [156, 157], has permitted a scheme of biosynthesis to be proposed according to which the C_{18}-diterpenealkaloids may be formed by a series of successive reactions: oxidation of the 18-methyl groups of C_{19}-diterpene alkaloids to carboxy groups, followed by decarboxylation [158].

The C_{20}-diterpene alkaloids coryphine (XX) and coryphidine (XIX), each containing a hexahydro N-methylindole fragment at C-17, have been isolated from the plant Aconitum coreanum. The formation of this fragment may take place from compounds having, like zeraconine (XVIII), a p-hydroxy-β-aminophenethyl residue through a Claisen rearrangement in the para-position with the subsequent cyclization of the dienone obtained.



A biogenetic link between these types of alkaloids is also shown by the simultaneous presence in the plant Aconitum zeravschanicum of zeraconine (XVIII) and an alkaloid with hexahydro-N-methylindo-6-one substituent [28].

The route for the formation of dimeric tropane alkaloids can be represented not as the dimerization of monomeric tropane alkaloids but as the photochemical dimerization of atropic acid (CXXVIII) obtained from tropic acid (CXXVII) with the formation of α- and β-isatropic acids (CXXIX) and (CXXX). The latter are esterified with aminoalcohols to form the corresponding dimers (CXXXI and CXXXII).



The schemes for the formation of some new types of alkaloids given above, based, in the main, on structural analogies, in vitro transformations, and the combined presence of related compounds in a single plant, make it possible to trace the main routes for the biogenesis of various alkaloids and to introduce clarity into the role of intermediate compounds in their synthesis.

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