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PROPOSED BIOGENESIS OF DITERPENOID ALKALOIDS

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UDC 547.944/945

Literature information is generalized and an analysis is made of investigations relating to the biogenesis of diterpene alkaloids.

The last forty years have been a period of intensive development in the chemistry of the diterpenoid alkaloids (DAs), the structures of which remained unknown until the middle of the 50s. The prime attention of researchers to this class of natural compounds was due to the wide popularity in folk medicine of the plants from which they had been isolated, the complexity of their structure, and the interesting chemistry and high toxicity of individual representatives. It was established that these alkaloids were based on new diterpenoid heterocyclic systems, chemical and physical methods of proving their structures were proposed, total syntheses of key alkaloids were performed, and classification was carried out. Recent advances in the field of the chemistry and pharmacology of the DAs have been reflected in a number of detailed reviews [1-5].

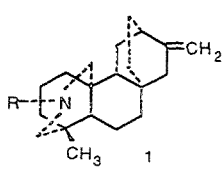
The biosynthesis of the DAs has been studied to a considerably smaller degree. There are only three experimental papers [6-8], on the whole devoted to the "isoprenoid pathway" of biosynthesis but giving nothing about the intermediate stages because of the absence of information on the preparative degradation of the molecules. Results of such investigations have now been given in a review by Edwards [9].

At the present time, there is a multiplicity of biogenetic hypotheses, proposals, and speculations based on biochemical analogies and an analysis of phytochemical facts and of *in vitro* chemical transformations. The present review acquaints the reader with the evolution of views and modern ideas on the biogenesis of the DAs, throwing light on possible pathways for the formation of the existing structural diversity.

DAs were first isolated from plants of the genera *Aconitum*, *Delphinium* (fam. Ranunculaceae), and *Garrya* (fam. Garryaceae), and it is these from which the majority of known alkaloids have been isolated. Later, they were detected in plants of the genera *Spiraea* (fam. Rosaceae), *Anopterus* (fam. Escaolloniaceae), and *Consolida* (fam. Ranunculaceae). This list has recently been supplemented by plants of the genera *Inula* (fam. Compositae), *Thalictrum* and *Atragene* (fam. Ranunculaceae), and *Lavandula* (fam. Labiatae).

With respect to their chemical structures, DAs are divided into four groups [10]:

1. Alkaloids having a skeleton of twenty carbon atoms that may be considered as atisane derivatives (**1**);
2. Alkaloids the skeleton of which consists of twenty carbon atoms derived from kaurane (**2**);
3. Alkaloids with a lycoctonine skeleton derived from aconane (**3**); and
4. Bisditerpenoid alkaloids (staphinine (**4**), etc.).



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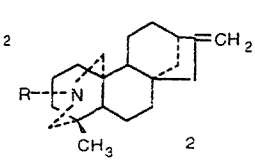

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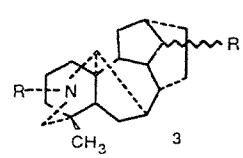

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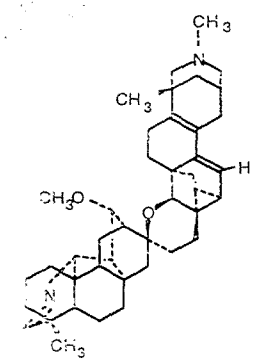

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The atisane alkaloids are distinguished by great structural diversity and can be divided into the following types: 1 — atisine (**5**); 2 — dihydroatisine (**6**); 3 — ajaconine (**7**); 4 — denudatine (**8**); 5 — hetidine (**9**); 6 — corifine (**10**); 7 — hetisine (**11**); 8 — isoatisine (**12**); 9 — spiradine D (**13**); 10 — spiramine A (**14**); 11 — brunonine (**15**); 12 — talasamine (**16**); 13 — vakognavine (**17**); 14 — albovionitine (**18**).

The alkaloid delnudine (**19**) has a new heterocyclic skeleton and is, obviously, a product of the rearrangement of hetisine; it has therefore been assigned to the atisane alkaloids.

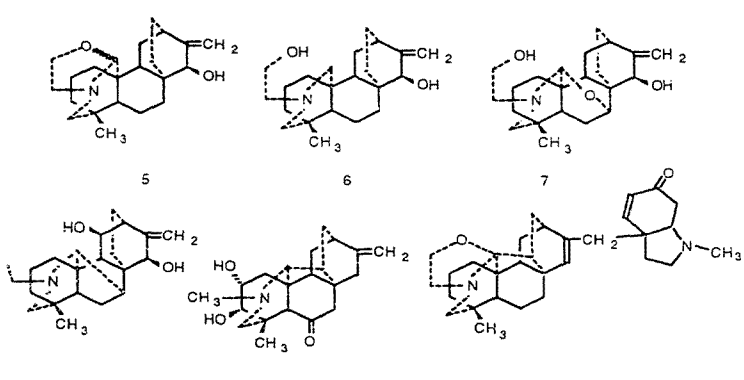
The kaurane alkaloids are divided into six types: 1 — veatchine (**20**); 2 — garryine (**21**); 3 — napelline (**22**); 4 — anopterine (**23**); 5 — anopterimine (**24**); 6 — lindheimerine (**25**).

Alkaloids with a lycoctine skeleton or aconanes include three groups of bases differing by the numbers of carbon atoms in the heterocyclic skeleton:

1. C_{20} lycoctonine alkaloids the carbon skeleton of which consists of twenty carbon atoms (**26**);
2. Norditerpenoid alkaloids (**27**) the carbon skeleton of which consists of 19 atoms as a result of the elimination of the C-17 carbon atom of an atisane–kaurane or the C-15 carbon atom of a C_{20} aconane precursor; and
3. Bisnorditerpene alkaloids (**28**) the carbon skeleton of which consists of 18 atoms and which differ from the norditerpene alkaloids by the absence of the C-18 carbon atom.

With respect to the positions of oxygen substituents and double bonds, which are responsible for their characteristic chemical properties, each of them may include alkaloids of the following types:

1. Aconitine (**29**), in which there is a hydroxyl or ester group at C-8 and there are no oxygen substituents at C-7 and C-9;
2. Lycoctonine (**30**) containing a 7,8-diol system;
3. Lappaconine (**31**) with a 8,9-diol grouping;
4. Pyrodelphinine(**32**) with a 8,15-double bond;
5. 7,17-Secoalkaloids of the type of vilmoritine (**33**) containing a 7,8-double bond;
6. Franchetine (**34**), containing a 7,17 ether bridge;
7. Barbeline (**35**) with an azomethine grouping; and
8. Heteratisine (**36**), containing a lactone grouping in place of the C-14 carbon atom.



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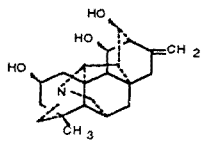

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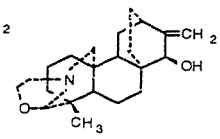

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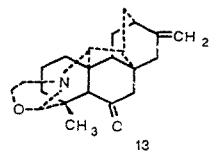

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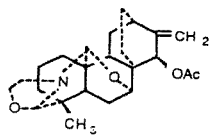

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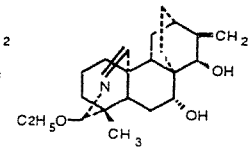

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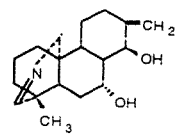

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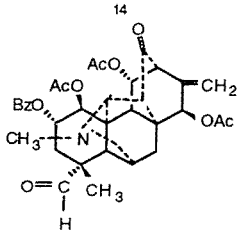

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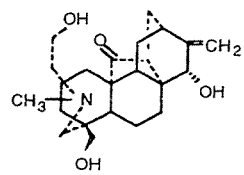

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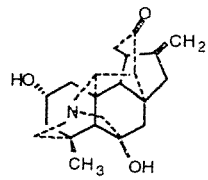

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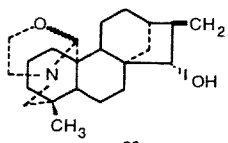

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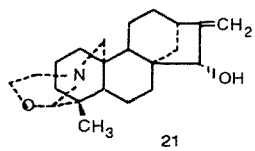

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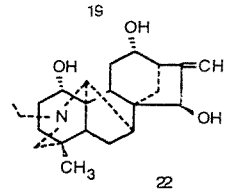

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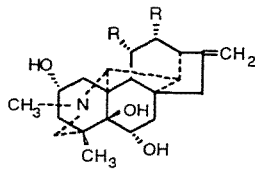

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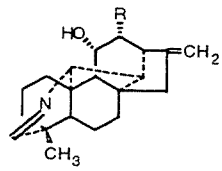

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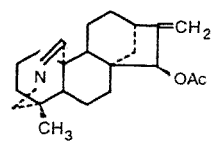

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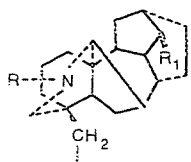
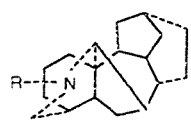


26 R_1=CH_2

27 R_1=H,H



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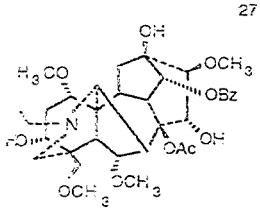

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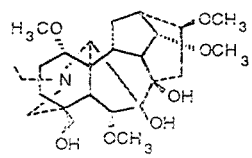

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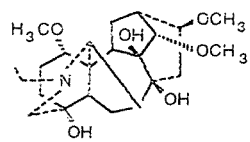

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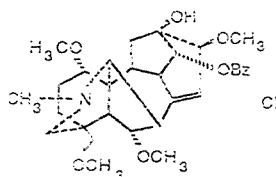

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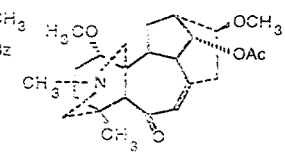

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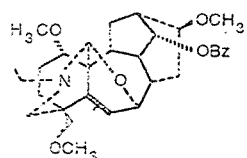

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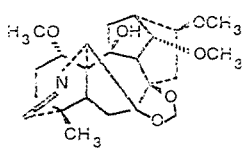

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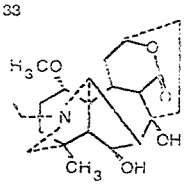

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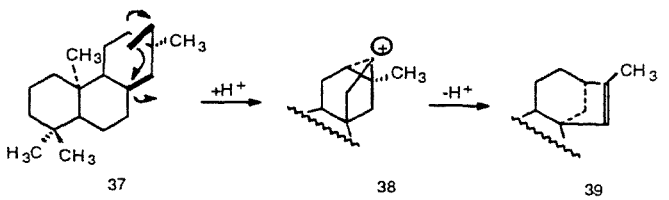
Biogenesis of the Atisane–Kaurane Alkaloids. As soon as structures were suggested for the DAs atisine (**5**) and veatchine (**20**) [11, 12], Wenkert put forward the hypothesis that pimaradienes of the type of formula (**37**) may be their biogenetic precursors (the stereochemical formulas and numbering of the carbon atoms adopted at the present time, differing from those appearing in the original papers, are given) [13].

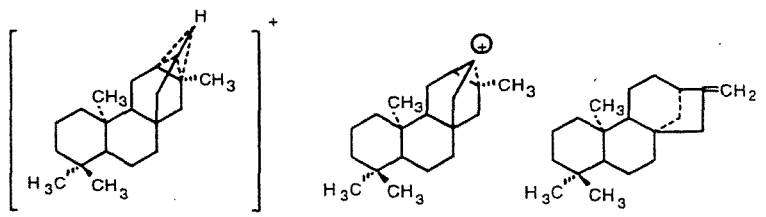
According to Wenkert's hypothesis (Scheme 1), the biosynthesis of the veatchine alkaloids begins from the protonation of the 8,14-double bond through the formation of a bridge cation (**38**). According to Wenkert, the occurrence of a Wagner–Meerwein rearrangement is promoted by the quasi-axial orientation of the vinyl group and the quasi-equatorial orientation of the methyl group, since in pimaradienes with the opposite configuration of these substituents this is prevented by steric factors.

Scheme 1



37 38 39

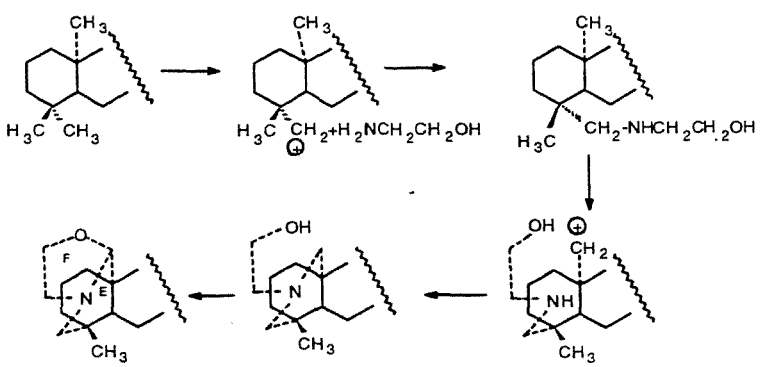
Another type of Wagner–Meerwein rearrangement may lead to the nonclassical cyclic cation (**40**), from which alkaloids of the atisine type are formed through a number of stages, including a 1:3-hydride shift reaction. Simplifying Wenkert's discussion, Whalley observed that the rearrangement of cation (**38**) as a result of a 1:3 hydride shift can lead to compound (**41**), a precursor of the atisine alkaloids [14].



40 41 42

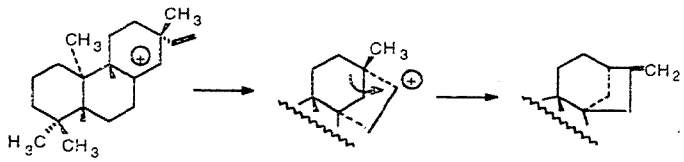
He also expressed the point of view that the biosynthesis of the nitrogen-containing rings *E* and *F* in the atisine and veatchine alkaloids may proceed by Scheme 2. It is not difficult to imagine that if ethylamine or methylamine participated in these transformations in place of ethanolamine we should obtain alkaloids with N-ethyl or N-methyl groups, which are frequently found among the DAs [10].

Scheme 2



In their chemical structure, alkaloids of the veatchine type are close to the diterpene kaurene (**42**), which has permitted the suggestion that they are formed from kaurene through the completion of the rings with nitrogen by a scheme analogous to that given above [10]. The biosynthesis of kaurene starts from geranylgeraniol pyrophosphate through the intermediate compounds shown in Scheme 3 [15].

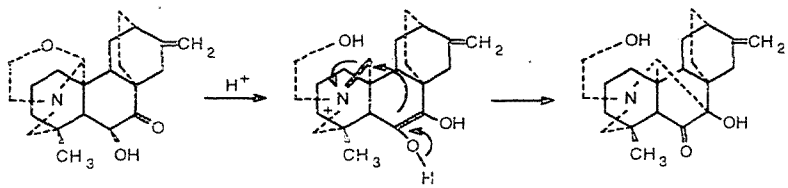
Scheme 3



If we start from atisine (**5**) and veatchine (**20**), the other structural types of the atisane–kaurane alkaloids are produced by the formation of the 7–20 and 14–20 carbon–carbon bonds and also the N–C-6 bond.

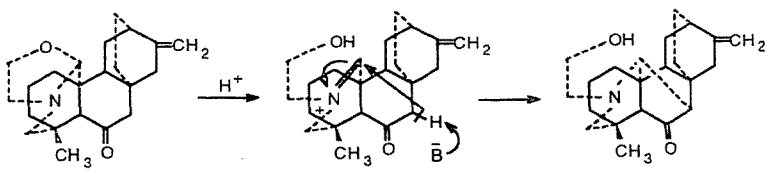
Cookson and Trevett assume that the 7–20 bond is formed by a cyclization reaction of the Mannich type (Scheme 4) [16].

Scheme 4



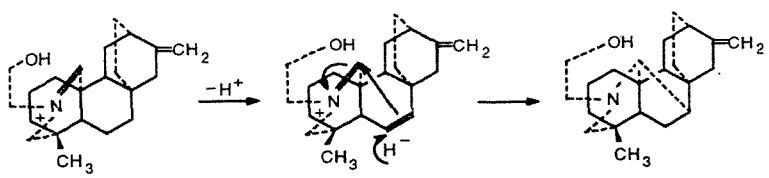
Valenta and Wiesner suggest the possibility of cyclization with the participation of Schiff's bases (Scheme 5) [17].

Scheme 5



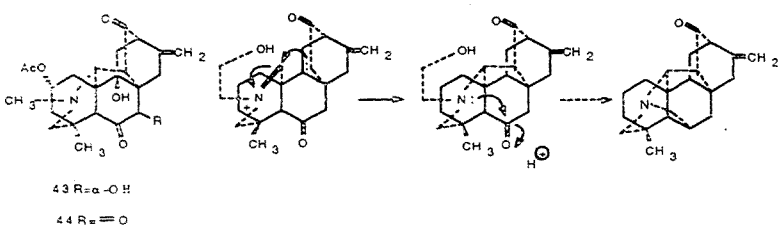
Basing ourselves on the fact that, up to the present time, no alkaloids of the denudatine and napelline type with an oxygen function at C-6 have been found, it may be suggested that biosynthesis takes place with the preliminary introduction and subsequent elimination of an oxygen substituent activating C-6. Or, as Edwards assumes [9], a different cyclization mechanism is realized in the plant. We do not exclude the possibility that in this case Prins cyclization with the participation of a hydride ion may take place (Scheme 6).

Scheme 6



Japanese scientists have isolated the new alkaloids miyaconitine (**43**) and miyaconitinone (**44**) from the plant *Aconitum miyabei* [18]. In view of the presence of active carbonyl groups at C-6 and C-13, they assume that these alkaloids are intermediate compounds in the biosynthesis of hetisine alkaloids from atisine alkaloids, proposing the mechanisms of the formation of the C-14−C-20 and N−C-6 bonds that are shown in Scheme 7.

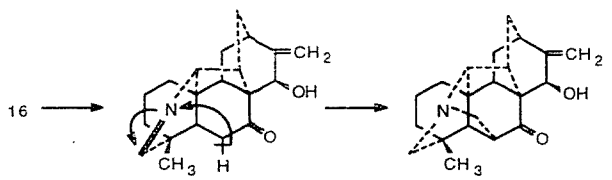
Scheme 7



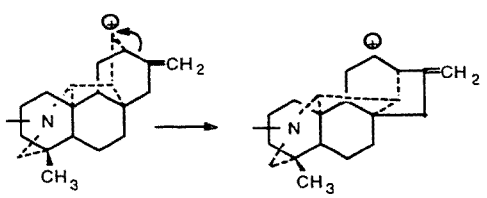
An N−C-6 bond is found in the hetisine (**11**) and delnudine (**19**) alkaloids. Edwards considers a possible formation of this bond on the cleavage of a 6-β-pyrophosphate group [9].

The alkaloid talasamine (**16**), which we have isolated from the plant *Aconitum talassicum* [19], may also be an intermediate in the biosynthesis of hetisine alkaloids. The formation of the N−C-6 bond may proceed by the mechanism shown in Scheme 8, after the preliminary oxidation of the C-7 hydroxy group to a carbonyl group.

Scheme 8

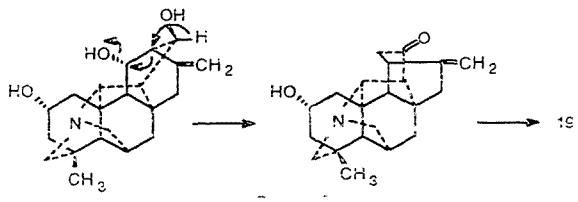


Anopterine (**23**) represents a new structural type of kaurane alkaloids differing from the veatchine alkaloids by the presence of a 14−20 carbon−carbon bond. Australian scientists suggest that the alkaloid is formed not from a kaurane precursor but from hetisine alkaloids by rearrangement of the intermediate compound (**45**) with the formation of the anopterine skeleton (**46**). The previous cleavage of the N−C-6 bond is, of course, assumed [20].



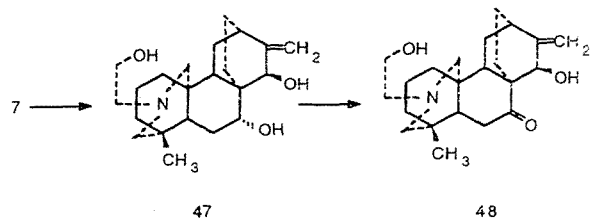
The alkaloid delnudine (**19**) has a new unusual heterocyclic skeleton. Gotz and Wiesner [21] suggest that delnudine is formed from hetisine by rearrangement followed by the introduction of a carbinolamine group (Scheme 9).

Scheme 9



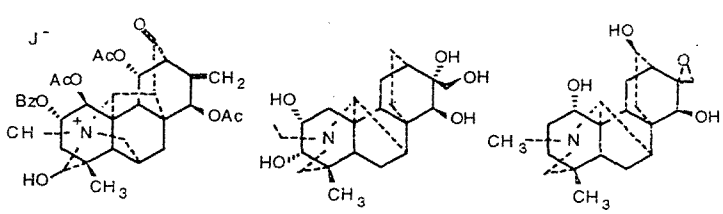
A possible biogenetic interconnection beween the alkaloids ajaconine (**7**), dihydroajaconine (**47**), and atidine (**48**) (Scheme 10) has been put forward by Pelletier et al. [22].

Scheme 10



47 48

Vakognavine (**17**) is the first N−C-19 secoterpenoid alkaloid. Pelletier et al. consider that it may be an intermediate in the biosynthesis of the hetisine skeleton. Here, attention is turned to the fact that the C-19 hydroxy group of vakognavine hydriodide (**49**) resembles the oxazolidine oxygen function of isoatisine [23].

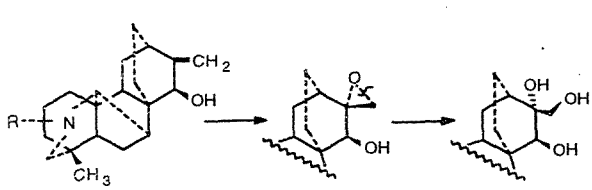


49 50 51

The majority of atisane−kaurane alkaloids contain an exocyclic methylene group at C-16, but there are alkaloids having other substituents.

Thus macrocentrine (**50**) contains a 16,17-diol system. Benn et al. [25] suggest that the diol system is formed through the epoxidation of a terminal methylene group, followed by hydroxylation of the epoxide ring (Scheme 11), and this idea is supported by the presence in nature of the alkaloid gomandonine (**51**), containing a 16,17-epoxy function [24]. The authors note that such alkaloids may be intermediates in the biosynthesis of alkaloids with the lycoctonine skeleton, since hydroxylation opens up a route for the splitting out of C-17 [25].

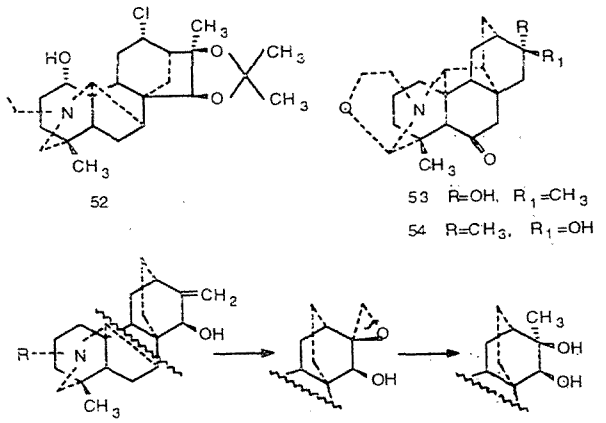
Scheme 11



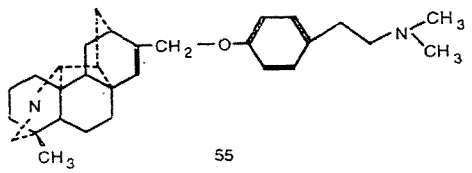
Acofine (**52**), and also a number of alkaloids similar to spirasine V (**53**) and spirasine VI (**54**), have methyl and oxygen functions with different stereochemistries at C-16.

We assume that these alkaloids are formed from stereoisomeric 16,17-epoxides. In this case, spirasine V (**53**) is obviously obtained on the hydrogenolysis of an epoxy function with the stereochemistry of gomandonine (**39**), while acofine (**52**) and spirasine VI (**54**) must be formed from a precursor with the opposite configuration of the spiro center (Scheme 12).

Scheme 12

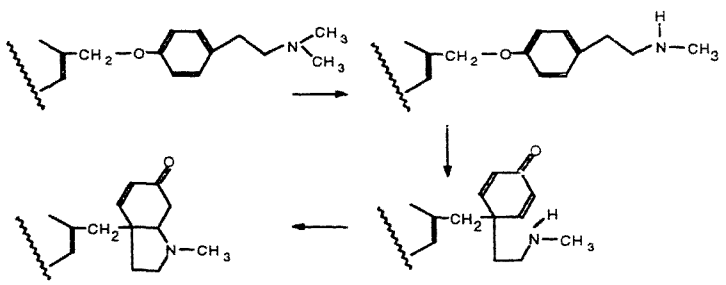


The alkaloids zeraconine (**55**) and corifine (**10**) were isolated from the plants *Aconitum zeravschanicum* [28] and *Aconitum coreanum* [29]. Zeraconine may be considered as the product of the biochemical condensation of hordenine with a diterpene alkaloid.



A biogenetic hypothesis linking the side-chains of these alkaloids has been put forward [29]. In the first stage, apparently, demethylation takes place at the nitrogen atom. Then, as the result of a biogenetic process analogous to a Claisen rearrangement, followed by the formation of a ring with the nitrogen atom by analogy with the mesembrine alkaloids [30], the hexahydro-N-methylindol-6-one fragment of the alkaloid corifine is formed (Scheme 13).

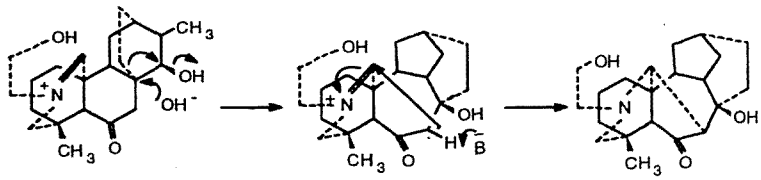
Scheme 13



Biogenesis of the Aconane Alkaloids. After the structure of de(oxymethylene)lycoctonine [31] and then that of lycoctonine itself had been established by x-ray structural analysis, Valenta and Wiesner [17] and, independently of them, Cookson and Trevett [16], put forward a hypothesis according to which bases of the atisine type may be the biogenetic precursors of alkaloids with the lycoctonine skeleton.

Valenta and Wiesner suggest that the biosynthesis of the lycoctonine alkaloids may begin from the atisine precursor (**56**), with the subsequent enzymatic demethylation of the C-17 methyl group. After this, a Wagner–Meerwein rearrangement leads to the intermediate compound (**57**). Under the action of quaternary Schiff's bases, the enolate ion (**57**) cyclizes with the formation of the lycoctonine skeleton (Scheme 14) [17].

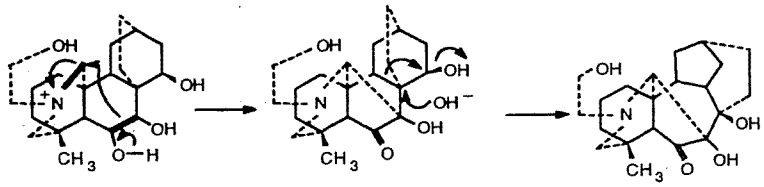
Scheme 14



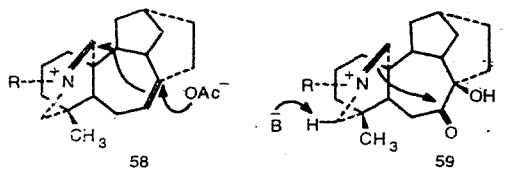
56 57

Cookson and Trevett's hypothesis differs from the preceding one by the fact that the C-7−C-20 bond is formed at the stage of the atisine precursor by condensation in a Mannich-type reaction, i.e., before the Wagner-Meerwein rearrangement (Scheme 15) [16].

Scheme 15



In Edwards' opinion, the formation of the C-7−C-17 bond may also take place as a result of a Prins cyclization of (**58**) or ring-closure with the participation of Schiff's bases (**59**) [32].

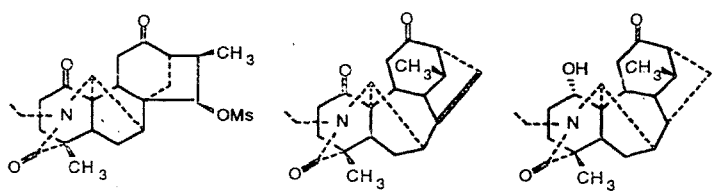


58 59

In the first case, alkaloids of the aconitine type and, in the second case, alkaloids of the lycoctonine type are formed. Both types of reactions have been conducted under laboratory conditions [32-34], which has given grounds for the hypotheses described above.

This stage of biogenesis — the conversion of atisane alkaloids into aconane alkaloids — has been achieved successfully under laboratory conditions by a number of workers [35-37].

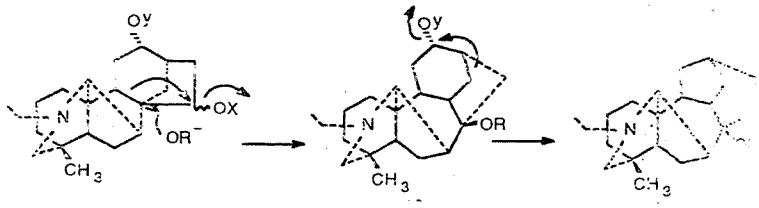
Ito et al. [38] have observed an interesting rearrangement of a compound with the napelline skeleton, and this has served as an impulse for biogenetic hypotheses. On being heated in DMSO, the mesylate (**60**) gives, together with the normal product of 1,2-elimination, the rearrangement product (**61**). The latter is converted by a series of transformations into compound (**62**).



60 61 62

Basing themselves on these transformations, the authors suggest that the formation of the C7−C20 bond and the skeletal rearrangement may take place independently of one another and propose an unusual Scheme of biosynthesis (Scheme 16) that may take place after the formation of the C7−C20 bond.

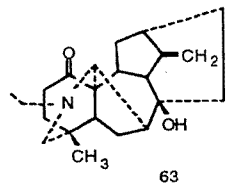
Scheme 16



The proposed scheme assumes the possibility of a direct passage from kaurane alkaloids to aconane alkaloids.

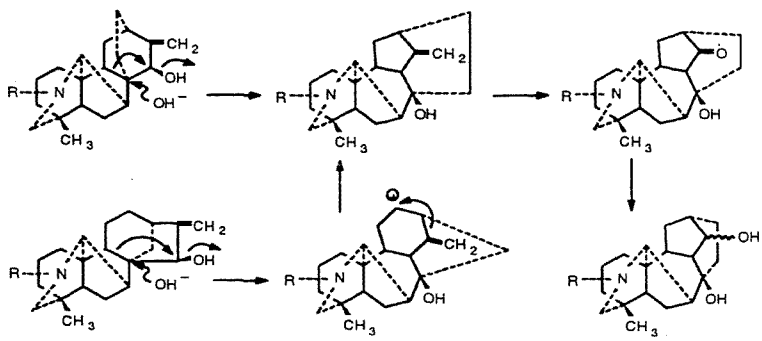
It must be mentioned that the majority of hypotheses relating to this stage of biosynthesis assume the preliminary enzymatic elimination of the C-17 carbon substituent.

Recently, we have isolated from the plant *Aconitum talassicum* the alkaloid actaline (**63**), which is the first C_{20} base with the lycoctine skeleton containing a methylene group at C-14. The isolation of actaline shows that a rearrangement may take place with retention of the terminal methylene group and its subsequent oxidation (Scheme 17). The initial compounds may be alkaloids of the denudatine (**8**) and napelline (**22**) types or their atisine–veatchine precursors.



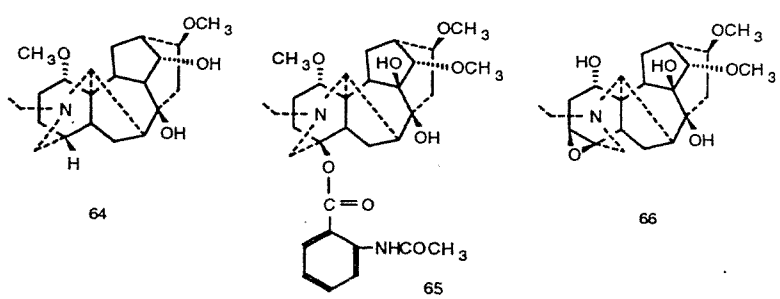
63

Scheme 17



Passage from the C_{20} lycoctonine alkaloids to the norditerpenid alkaloids the skeleton of which consists of 19 carbon atoms — i.e., the replacement of the terminal methylene group by an oxygen function — can be effected as the result of a biochemical oxidation reaction of the Baeyer-Villiger type or by one of the methods described above [39].

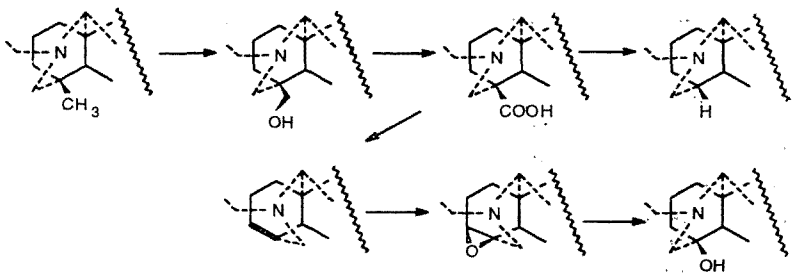
Lappaconine (**31**) is the first bisnorditerpenoid alkaloid in which the C-18 carbon atom is absent and the substituent at C-4 is a hydroxy group. At the present time bisnorditerpenoid alkaloids have been isolated that contain at C-4 a hydrogen atom (aconosine (**64**)), an ester group (lappaconitine (**65**) and others), and a 3,4-epoxide group (excelsine (**66**) and others). Edwards assumes that the elimination of the C-18 carbon atom takes place as the result of a biochemical reaction of the type of a Baeyer-Villiger oxidation [9].



64 65 66

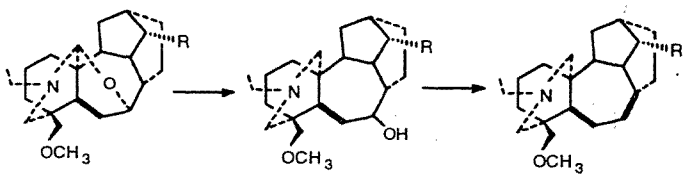
The plant *Aconitum monticola* has yielded the C_{19} alkaloids delsoline and deoxydelsoline and also the C_{18} bases monticoline, monticamine, and dihydromonticamine [41, 42]. The combined presence in the plant of nor- and bisnorditerpenoid alkaloids has permitted the proposal of a possible mechanism of biosynthesis (Scheme 18) including the hydroxylation of the C-18 methyl group, the oxidation of the hydroxymethyl group to a carboxy group with subsequent decarboxylation, and also the epoxidation of the 3,4-double bond [43].

Scheme 18



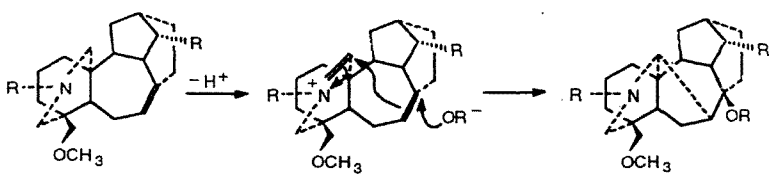
Scheme 19 demonstrates a possible biogenetic interrelationship between alkaloids of the type of franchetine (**34**), containing a 7,17-carbinolamine ether bridge, and 7,17-secoalkaloids of the type of vilmoritine (**33**).

Scheme 19



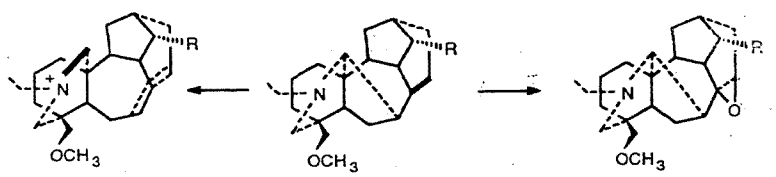
In its turn, vilmoritine (**33**) may linked with alkaloids of the aconitine type through the biochemical reactions shown in Scheme 20.

Scheme 20



The biogenetic significance of alkaloids of the type of pyrodelphinine (**32**) is apparently determined by the two possible transformations shown in Scheme 21 [44].

Scheme 21



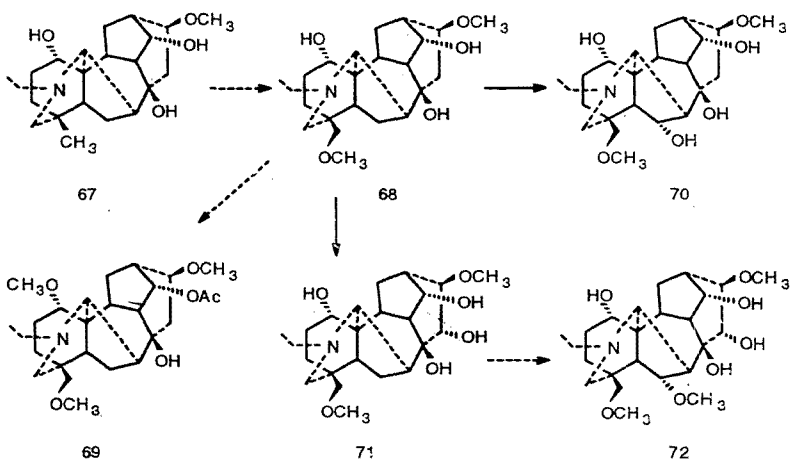
Alkaloids of the type of heteratisine (**36**) [45] have a lycoctonine skeleton in which the C-14 carbon atom has been replaced by a lactone grouping. Possible biogenetic precursors of the heteratisines are lycoctonine alkaloids containing C-14 keto groups that give lactone groupings on oxidation by a reaction of the Baeyer-Villiger type [9].

What has been said above related mainly to the formation of the skeleton. A number of conclusions on the sequence of introduction of the oxygen substituents have been based on the combined presence of alkaloids close in structure in one plant and also on an analysis of the statistics of phytochemical facts.

Karakoline — the first alkaloid of the aconitine type with a methyl group at C-4 [46] — is frequently considered as a biogenetic precursor, since it is one of the simplest representatives.

Hikino et al. have isolated from the plant *Aconitum carmichaeli* karakoline (**67**), isotalatisidine (**68**), 14-acetyltalatisamine (**69**), senbusine A (**70**), senbusine B (**71**), senbusine C (**72**), and aconitine (**29**). The authors consider that these alkaloids are intermediates in the biosynthesis of aconitine. Biosynthesis takes place through a series of successive hydroxylation, methylation, and etherification and esterification reactions (Scheme 22).

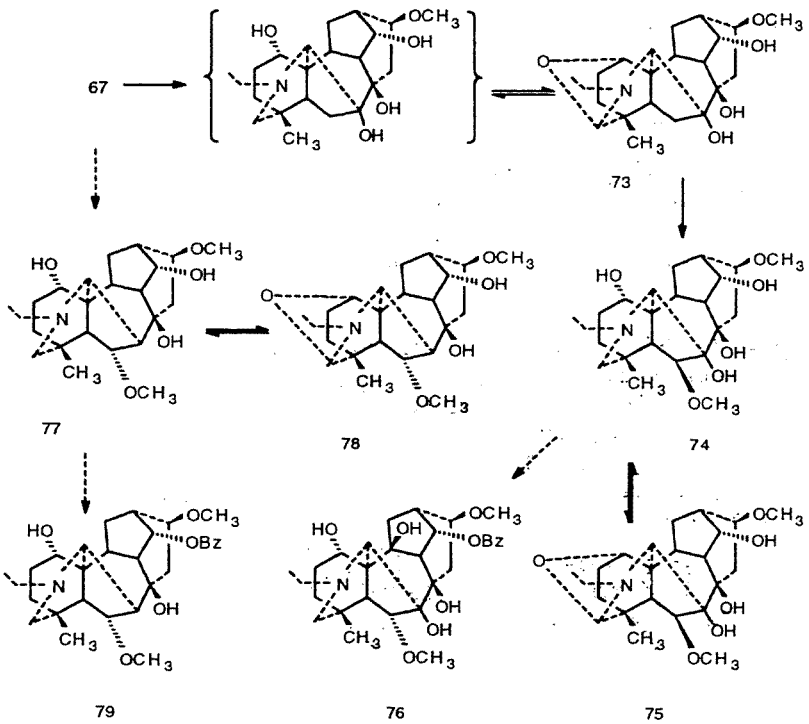
Scheme 22



Gonzalez et al., studying the alkaloids of *Delphinium pentagynum*, isolated karakoline and other, more complex, norditerpenoid alkaloids — pentagydine (**73**), dihydrogadesine (**74**), gadesine (**75**), gadenine (**76**), dihydropentagynine (**77**), pentagynine (**78**), and pentagyline (**79**) [48]. The authors assume that karakoline is a biogenetic precursor of the other alkaloids of this plant (Scheme 23). They conclude that the hydroxylation of C-1α, C-8, C-14α,and C-16β takes place in an early stage of biogenesis. The hydroxylation of karakoline first at C-7 and then at C-6 leads to alkaloids of the lycoctonine type, while the biosynthesis of the more complex aconitine-like alkaloids begins with C-6α hydroxylation.

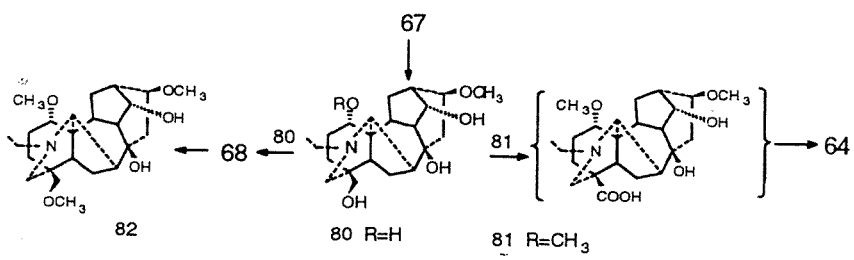
On analyzing the accumulated phytochemical knowledge on alkaloids of the aconitine type, Edwards et al. proposed the following sequence of introduction of oxygen functions during their biosynthesis [49]. In view of the presence of an oxygen function at C-8 in the majority of alkaloids it was assumed that this oxygen substituent is introduced in the formation of the 7−17 bond from a precursor with a 7,8-double bond at an early stage of biosynthesis. An oxygen function at C-14 is also formed in an early stage as a result of the substitution of a carbon atom of a C_{20} precursor. Then, in the authors' opinion, oxygenfunctions are introduced at C-1 and C-16, and, afterwards, at C-18. An oxygen function at C-6 is found far more rarely, and it probably arises at a later stage of biosynthesis. On the basis of analogous arguments, it may be concluded that the methylation of hydroxy groups must proceed in the following sequence: C-16, C-6 and C-8, C-16, and then C-14. The formation of alkaloids with 8-methoxy and 8-acetoxy groups, and also of alkaloids without an oxygen substituent at C-8 possibly takes place through a stage of the formation of the 7−17 bond with the participation of methanol, acetic acid, and the hydride ion in place of water.

Scheme 23



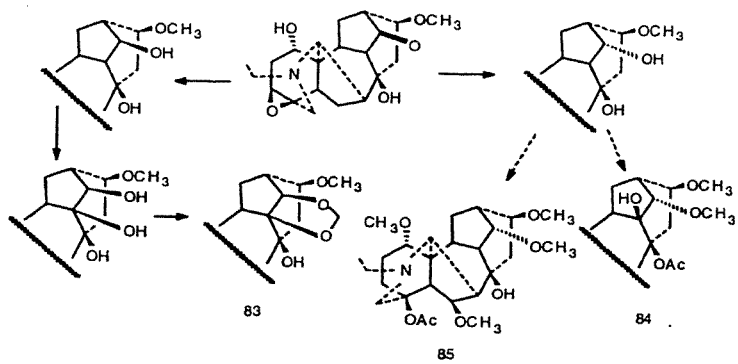
We have isolated from the plant *Aconitum nasutum* not only karakoline (**67**), but also columbianine (aconorine) (**80**), cammaconine (**81**), aconosine (**64**), isotalatisidine (**68**), and talatisamine (**82**) [50]. The possible Scheme 24 given below permits the detailed tracing of the biogenetic interrelationship between the alkaloids isolated. The biosynthesis includes hydroxylation and methylation reactions and elimination of the C-18 methyl group [4].

Scheme 24



We have isolated akirine (**83**) — the first alkaloid of the lycoctonine series with a β-oriented substituent at C-14 — from the plant *Aconitum kirinense,* together with other bisnorditerpenoid alkaloids: 8-acetylexcelsine (**84**) and akiran (**85**) [51-53]. It may be assumed that the epimeric alkaloids are synthesized from a precursor with a keto group at C-14 by Scheme 25.

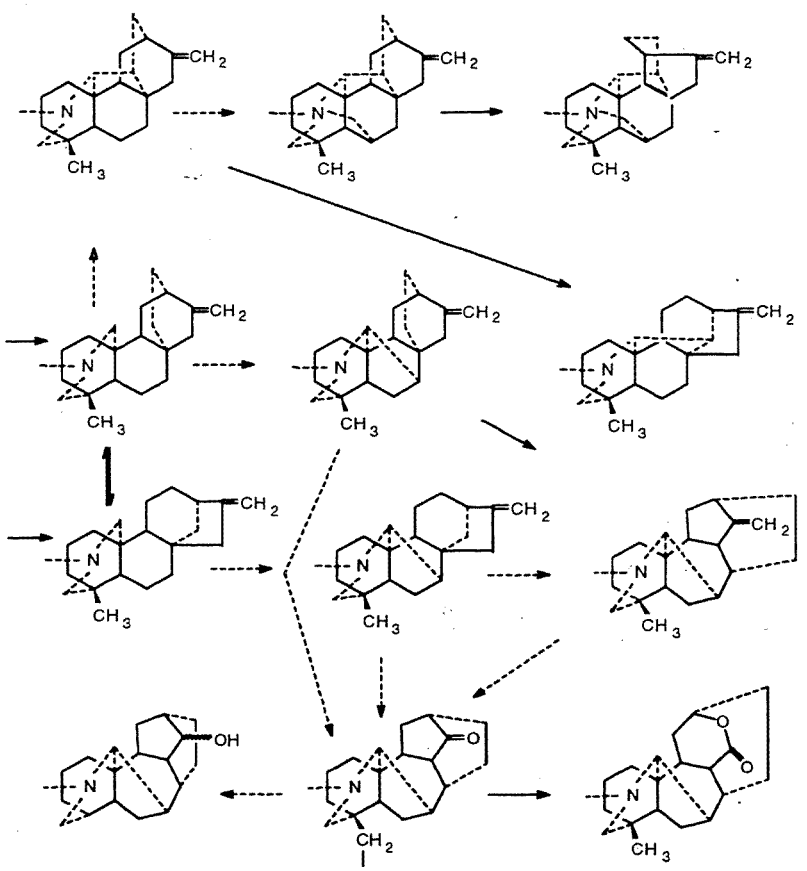
Scheme 25



Interesting results were obtained by S. Yu. Yunusov et al. in a study of the dynamics of the accumulation of alkaloids in the epigeal part of *Aconitum leucostomum* as a function of the phase of development [54]. In the early period, the plant contained 90% of DAs. As the plant developed, the relative level of DAs decreased and the level of isoquinoline alkaloids increased, amounting to more than 50% by weight of the total alkaloids in the fruit-bearing period. This case, where isoquinoline alkaloids predominate in a plant of the genus *Aconitum*, deserves attention and, as the authors consider, confirms the ideas of botanists on the closeness of the Ranunculaceae and Papaveraceae families

Thus, our knowledge on the main stages of the biosynthesis of DAs is based on hypotheses and analogies observed *in vitro*. Generalizing what has been said above, it is possible to propose a theoretical model (Scheme 26) reflecting the main tendency in the biosynthesis of DAs. Detailed experimental work could confirm or disprove current ideas on the biosynthesis of this interesting and numerous class of natural compounds.

Scheme 26



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