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Reaction mechanism and chemotaxonomy in the formation of the type I indole alkaloids derived from secologanin†

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ABSTRACT: The history of biomolecules is written into the structure of their educts and products. The group of indole alkaloids derived from secologanin and tryptamine has more than 2000 individual compounds isolated mainly from the Rubiaceae, Loganiaceae, and Apocynaceae plant families and having strictosidine as a common precursor. To detect their history in its main lines, the compounds isolated from the same or closely related species were ordered as intermediates into reaction sequences according to the principles of basic organic reaction mechanisms. The analysis is restricted to the main lines of the monomeric alkaloids having one un-rearranged secologanin subunit (type I) closed to N-4 atom and one tryptamine subunit in intact or cleaved form. Deglucosylation of strictosidine opens the way for different types of cyclizations. Subsequent key bond-braking and bond-making reactions involve bond C-5—C-6 in the tryptamine subunit, bond C-15—C-16 in the secologanin subunit, and bond C-3—C-7 at the attachment of the two subunits, and indicate the crucial importance of a strong long-range through-bond interaction between the two nitrogen atoms. With a few principles it was possible to interpret such important biogenetic-type steps, as the formation of the akuammidan and akuammilan bridges, the transition from the vincosan into the strychnan and further to the aspidospermatan skeleton, the breaking and transformation of the side-chain of the triptamine subunit and the cleavage of the strategic bond C-15—C-16 toward the formation of the formation of type II and type III alkaloids. The transformations are finely tuned by the stable chirality of C-15, and activation of C-7 and N-4. Fragmentations and rearrangement are important reactions in these transformations, and abundantly supported by chemotaxonomic data based on the *Dictionary of Natural Products* Database (Version 14.1, 2006, Chapman and Hall/CRC, New York, London, 2005). Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: indole alkaloids; chemotaxonomy; secologanin; strictosidine; biogenetic; rearrangement; fragmentation; chirality

INTRODUCTION

The history of the biomolecules is written into the structure of the products and educts. It is possible to detect this history, at least in its main lines, by comparing their structures and chemotaxonomic properties and by considering the well-established organic reaction mechanisms.

It is well known that the uniform group of 'indole alkaloids' (as it will be called in this paper) comprising more than 2000 individual compounds is constructed in a Mannich-type coupling reaction of secologanin **1** and tryptamine **2** mainly in the three plant families Rubiaceae (RUB) (involving also Naucleaceae), Loganiaceae (LOG) (involving also Strychnaceae) and Apocynaceae (APO). The first step of their biosynthesis is catalyzed by strictosidine synthase and gives strictosidine **3**a with complete stereoselectivity (Scheme 1). Strictosidine having *S* configuration at C-3[1,2] is an alkaloid glucoside and the common precursor of most indole alkaloids.[3,4] (Throughout this paper, the biogenetic numbering system shown in the formula **3** is used in the alkaloid structures and in the partial structures of the secologanin aglucone.[5] However, the structure of secologanin itself **1** was numbered according to the iridan skeleton.[6]) After removal of the β-D-glucopyranosyl subunit, the formal aglucone **4** ('all-oxo aglucone') may and really do exist in a large number of structural and stereoisomers, several of which are stabilized in certain substructures of the alkaloids.[7] The rich chemistry of secologanin **1** and strictosidine/vincoside **3** is the main source of the large variety of the indole alkaloids.[8–10]

Previously the chemical–biological relations of these alkaloids were mainly based on formal characteristics, for example, the type and number of cycles and functional

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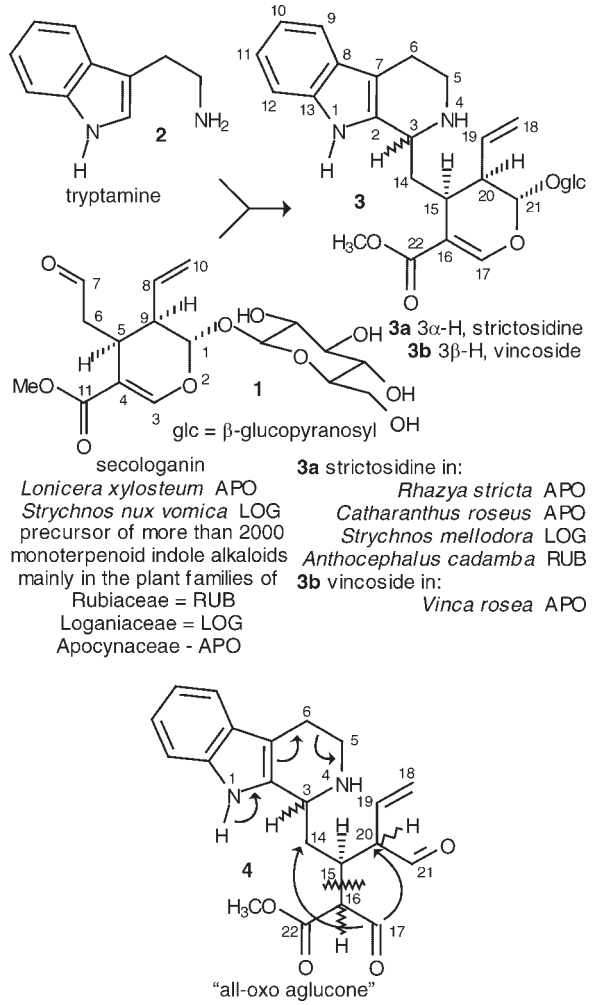


Scheme 1. The coupling reaction

groups,[3,10–12] and the main methods of research were the isotopic labeling technique and the biomimetic reactions in presence or absence of enzymes. However, the results of the isotopic labeling should be interpreted with great care, which was shown in the problems of biosynthesis of the isoprenoids through the mevalolacton *versus* deoxyxylulose pathway.[13] Concerning the biomimetic model reactions, it is not easy to prove that such reactions do run in the cells, that is, the model reactions really 'mimic' those running under biological conditions. Therefore it was decided to apply a different approach.

The plant cells may be considered as chemical reactors in which the final products are formed from the educts through a large number of steps. The compounds isolated from the same or closely related species may be ordered as really existing intermediates into biogenetic reaction sequences according to the principles of basic organic reaction mechanisms. The coexistence of two compounds in the same species, genera or families, or the isolation of compounds having two identical or different subunits in the same molecule (homo- or heterodimers, respectively) would suggest the common (consecutive or parallel) pathway of their formation. Of course, the coexistence or the coabsence of certain compounds neither proves nor refute rigorously biogenetic connections, and the results should be completed by other methods. In addition, some compounds obtained from plant extracts may be artificial products formed during the isolation and purification procedure. However, the majority of compounds isolated from biological sources are suggested to be really existing 'natural products' and more reliable milestones along the biosynthetic routes than some arbitrarily postulated structures which are alien in the cells. Of course, as generally the intermediates are highly reactive species, which might be present in small actual concentration in the cells, their isolation or even the demonstration of their presence in the biological medium could prepare difficulties. Therefore at certain points it would be necessary to take up some structures as 'missing links'. However, isolated compounds afforded by natural sources would more reliably suggest even such structures.

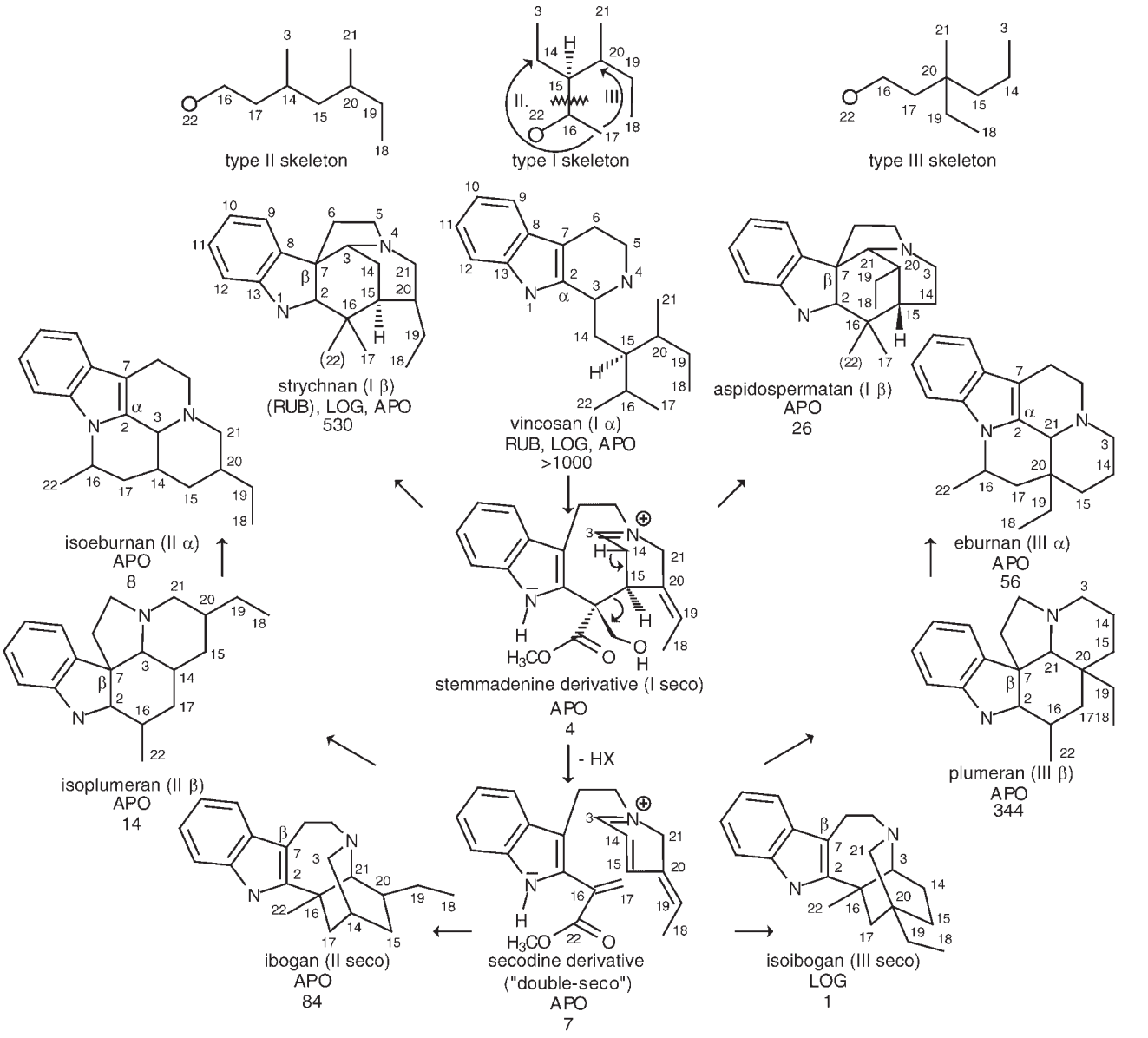
The large databases not only collect the huge and rapidly increasing amount of information about natural products, but also facilitate its electronic searching along multiple aspects. The aim of the present work is to investigate some chemical aspects of the formation of the indole alkaloids in relation to their chemotaxonomic properties. For this purpose the Dictionary of Natural Products[14] database (hereafter DNP, occasionally completed by the Beilstein Crossfire and the Chemical Abstracts online databases) proved to be especially useful in this respect because of its well organized and logically targeted structure. As the chemotaxonomical data reflect real biological properties, which help to interpret the chemical data, it was hoped, that the large number of structures can detect the internal chemical relations and organising principles of this uniform group of natural products.

To keep the extent of the paper under rational limits, the following restrictions were applied: (a) only the type I alkaloids (more than 2/3 of all indole alkaloids), and even in that group only the main lines were involved into the detailed study; (b) only the monomeric indole alkaloids (i.e., alkaloids formed from one tryptamine and one secologanin subunit) were considered; (c) the alkaloids cyclized to N-1 (about 50 alkaloids) were likewise disregarded.

THE SYSTEM

For directing our search, it was necessary to construct a new, really biogenetic system of indole alkaloids because those published up till now[3,10,11] used rather mechanical than biochemical principles for the classification.

In one of our previous papers, in which the chirality transfer was investigated in the biogenesis of indole alkaloids,[15] a simplified bioorganic-type system of these compounds (version 01) was proposed which is shown in



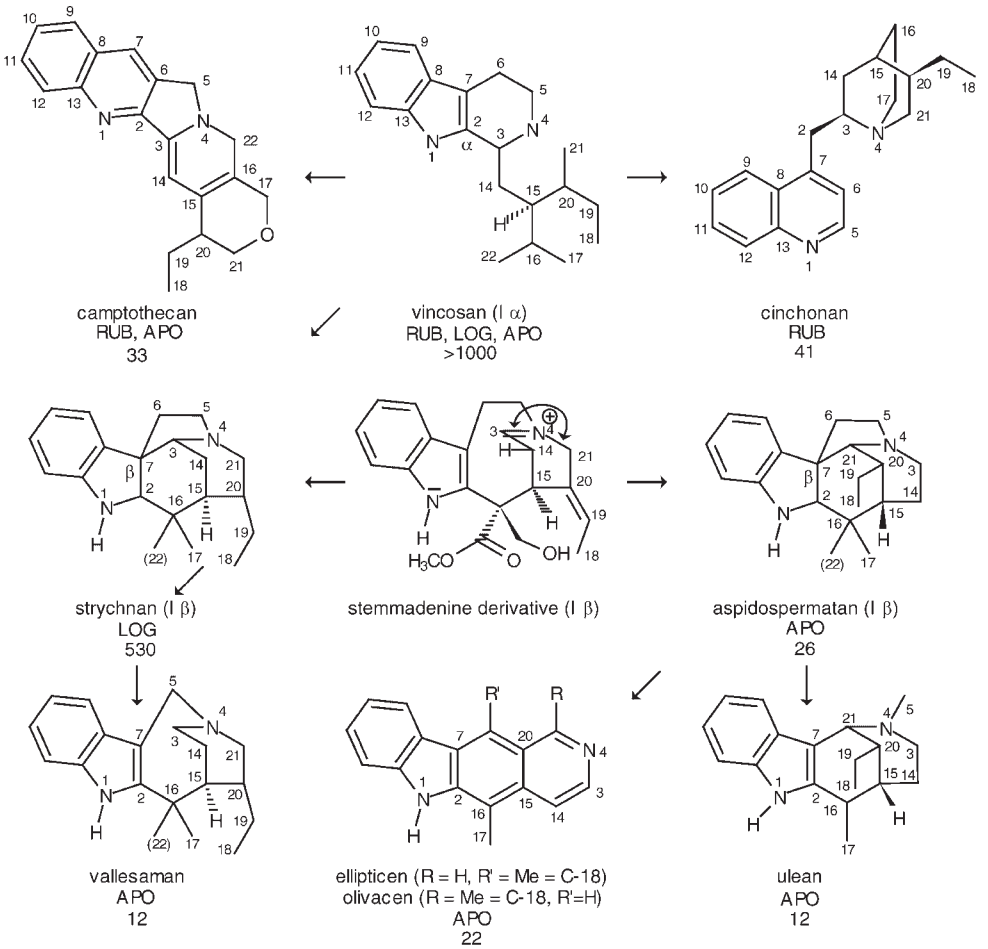
Scheme 2. Indole alkaloids derived from secologanin and having an intact tryptamine subunit

a partially modified form (version 02) in Scheme 2. The following principles were applied in this work:

1. The system is based on the fact, that most indole alkaloids can be classified into one of the three main skeletons derived from secologanin. This principle is common in our system and in the previously published classifications.[3,10,11] Skeleton type I has the carbon frame in the unchanged, skeleton type II and skeleton type III in a rearranged form (numbering according to structure **3**). The rearrangement formally involves the cleavage of the strategic bond C-15—C-16 of strictosidine and reattachment of the C_3-unit through its C-17 atom either to C-14 or C-20, respectively. This strategic bond could be cleaved also under acidic or basic conditions in secologanin[16] and strictosidine as well as their simple derivatives. However, the details of this point are outside of the subject of the present study.
2. Inside of the main skeletons, C-3 or the formally analogous C-21 may be attached either to α or β position of the indole ring and afford type α or type β alkaloids, respectively, in addition to the type 'seco' alkaloids when C-7 is not connected to the either of them. C-3 and C-21 have a distance of equal numbers of covalent bonds from C-15, which is the center of the secologanin subunit. This aspect was not clearly appreciated in the previous classifications, although the individual compounds have characteristic differences and the proposed pathways strongly suggest this

aspect of classification. (The figures below the structural formulae of Schemes 2,3, and elsewhere, as well as in the text in parentheses give the approximate number of isolated alkaloids in the DNP database. They should be considered approximate because they are continuously changing by new isolations, as well as by modification of the principles of selection and registration.)

3. On the third level of the system (which is already not shown in Scheme 2) the further ring formations were considered, according to their supposed biogenetic relations. Azacyclizations involving N-4 and/or N-1 were preferred over oxacyclizations (in exceptional cases carbacyclizations) (Schemes 4 and 5). The problem will be partially detailed later in the case of the type Iα (vincosan) alkaloid group. In our system, the type Iα alkaloids are represented by the single vincosan skeleton, from which all other subskeletons can be derived. In the classification of *M. Hesse*,[12] the Iα group is represented by the vincosan skeleton and two more or less arbitrarily selected tetracyclic skeletons (corynanthean and vallesiachotaman), although it could be demonstrated, that at this level 8 tetracyclic and 16 pentacyclic skeletons may exist, many of which are present in individual alkaloids (see it in the next chapter).
4. Some small subgroups having either the indole ring (in the camptothecan and cinchonan alkaloids) or its side chain (in the vallesaman, ulean, ellipticen, and olivacen alkaloids) in cleaved or truncated form, were not included into the version 01 of our system. However, in the present version 02, they were integrated, although shown in the separate Scheme 3 because of space restriction. Schemes 2 and 3 together form the whole system. The common structures in the two schemes indicate their connections.
5. Our analysis is firmly based on the tight interplay of the standard organic reaction mechanisms and the chemotaxonomical data. This interaction may contribute to the detection of the chemical background in the biogenesis of these natural products. It was not our intention to propose exact biogenetic (or even chemical) mechanisms, but to recognize some basic real chemical connections among the individual compounds or groups of the species, genera and/or families of plants.



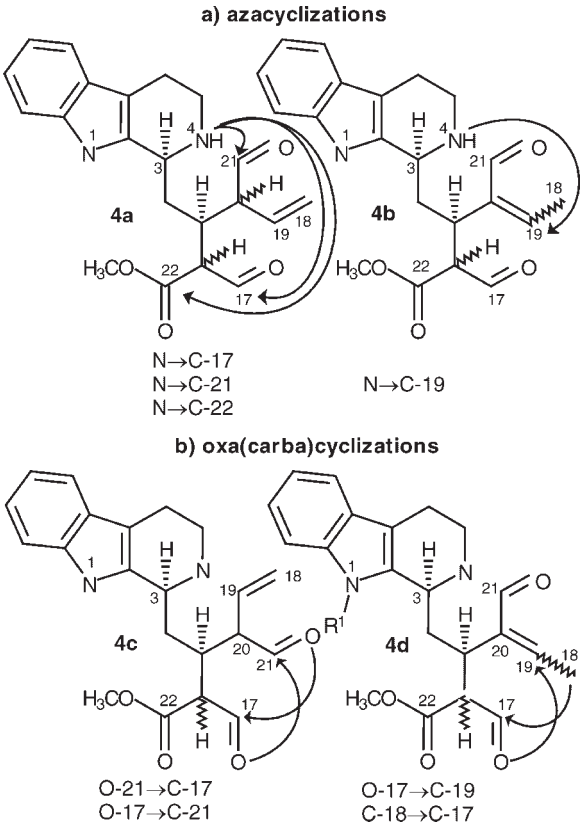
Scheme 3. Indole alkaloids derived from secologanin and having a modified tryptamine subunit

THE PRIMARY CYCLIZATIONS

After deglucosylation of strictosidine **3** and related compounds, a cascade of reactions starts, which could be partially modeled also under pure chemical circumstances. In the primary aglucone, two types of reactions may run which are shown in Scheme 4: (a) azacyclizations, that is, cyclizations between one of the nucleophilic N atoms (N-1 or N-4) of the tryptamine subunit and one of the electrophilic atoms (C-17, C-19, C-21, and C-22) of the secologanin subunit (**4a** and **4b**); (b) oxacyclizations (in one case carbacyclization) between the nucleophilic (O-17, C-18, O-21) and electrophilic (C-17, C-19, C-21) centers inside of the secologanin subunit (**4c** and **4d**). The two types of interactions may result in the formation of 8 tetracyclic (**N402**–**N409**) and 16 pentacyclic (**N410**–**N425**) aglucone types; the latter may be formed on two different ways depending on the order of the two types of cyclizations. The relations are shown in Scheme 5 which is a partially modified form of the previously published one.[7] In this scheme, the starting 'alkaloid aglucone' corresponds to the 'all-oxo aglucone' form of strictosidine (**4** in Scheme 1), and the aglucone types are represented in circles by the atoms between which the cyclization takes place; for example, in **N414** the indication 'N → C-21, O-17 → C-19' means that according to the code number **N4** the first cyclization takes place between N-4 and C-21, and the second one between O-17 and C-19 in the primary aglucone. Many but not all aglucone types were found in the natural products. The three most frequent types (type **N404**, type **N414**, and type **N417**, covering more than 75% of the simple indole alkaloids) are shown in Scheme 5 in bold circle. In Scheme 6, each of the three skeletons is represented by an individual alkaloid (corynan in corynantheine **5**, 17*O*,19-cyclocorynan = oxayohimban in ajmalicine **6**, 17,18-cyclocorynan = yohimban in yohimbine **7**, respectively).

It should be mentioned, that some primary cyclizations (especially those inside of the secologanin subunit) may run also at higher levels of the biosynthesis.

As mentioned above, the indole alkaloids formed by azacyclization to N-1 (about 50 natural compounds) were not considered in this paper, however, the same basic types of aglucones and similar organising principles could be derived for them.

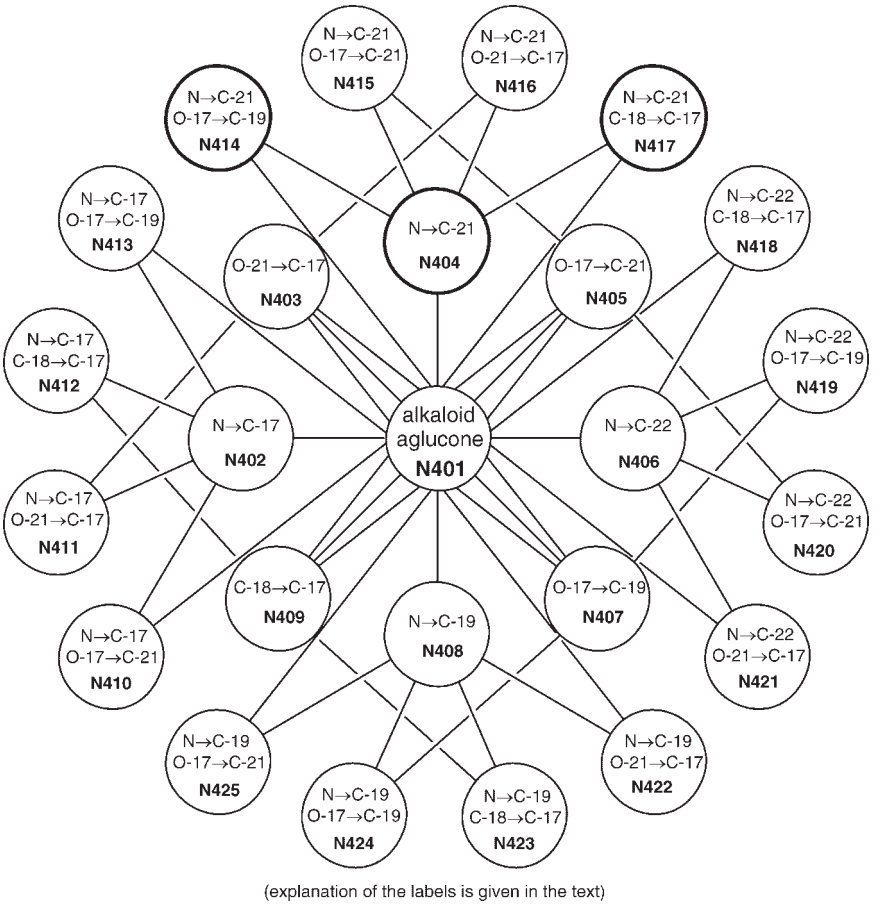


Scheme 4. Primary cyclizations in the strictosidine aglucone involving N-4

CYCLIZATIONS IN THE TYPE Iα ALKALOIDS BY BRIDGE FORMATION

The further elaboration of the more complicated structures proceeds in different directions (Scheme 7). The most important secondary cyclizations take place between C-16 and either C-5 or C-7 (carbacyclizations), and result in the formation of bridged ring systems of akuammidan and akuammilan, typical representatives of which are akuammidine (**15**) and akuammiline (**18**), respectively.

As in the formation of the akuammidine skeleton (in **15**) no signals indicate a preliminary functionalization to facilitate the cyclization of C-16 to C-5, the only possibility seems to be the long-range interaction in the corynan skeleton (**11**) between N-1 and N-4 for that purpose. The curved arrows in the formula **11** suggest a preformed electron stream from N-1 toward N-4 in the presence of an electrophilic element, however, the system should be activated in order to be effective in the formation of the akuammidine skeleton. The formation of the N-oxides (**12**) seems to be specially suitable for activation because by protonation or acetylation (or even by enzyme) the electrophilicity of N-4 and the nucleofugicity of the leaving ligand can be increased. In DNP more than 100 N-oxides are registered. Then, the tertiary ammonium structure (**13**) formed by cleavage of bond C-5—C-6 is ready to take up the nucleophilic C-16 at C-5. Deprotonation of C-16 is activated by one or two strongly electron-withdrawing groups, that is, the methoxycarbonyl (as ligand C-22) and/or the masked formyl group (as ligand C-17). Both groups can be transformed, or completely removed at different levels of the further biosynthesis. However, at least one of these activating ligands may be retained till to the late steps of the biosynthesis (see e.g., vallesamine in **46** in Scheme 12). In a subsequent, probably proton- or base-catalyzed,



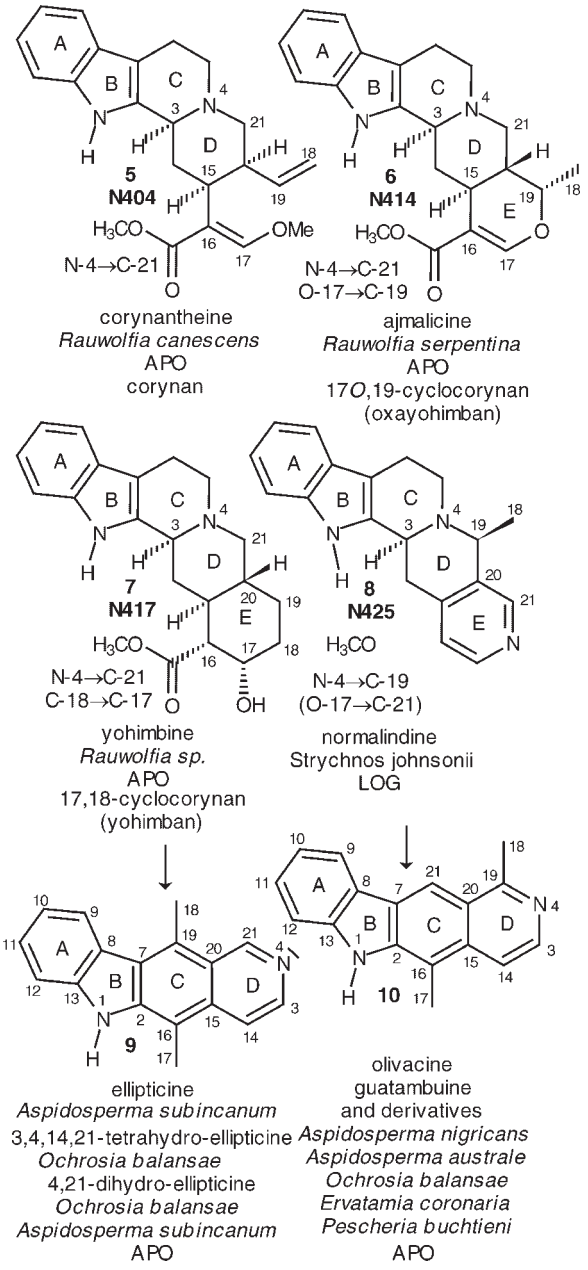
Scheme 5. Basic types of aglucones derived from strictosidine involving cyclization to N-4

special, intramolecular Michael type reaction, bond C-5—C-6 can be reformed affording the akuammidine skeleton (in **15**) (more than 200 alkaloids). The efficiency of the proposed fragmentation (actually a retro-Michael reaction) and recyclization is certainly facilitated by special embeddedness of N-1 and N-4 into a tightly arranged polycyclic system. Analogous reaction sequences might be supposed in the formation of the vallesaman, ulean, and related alkaloids (see Schemes 12 and 13).

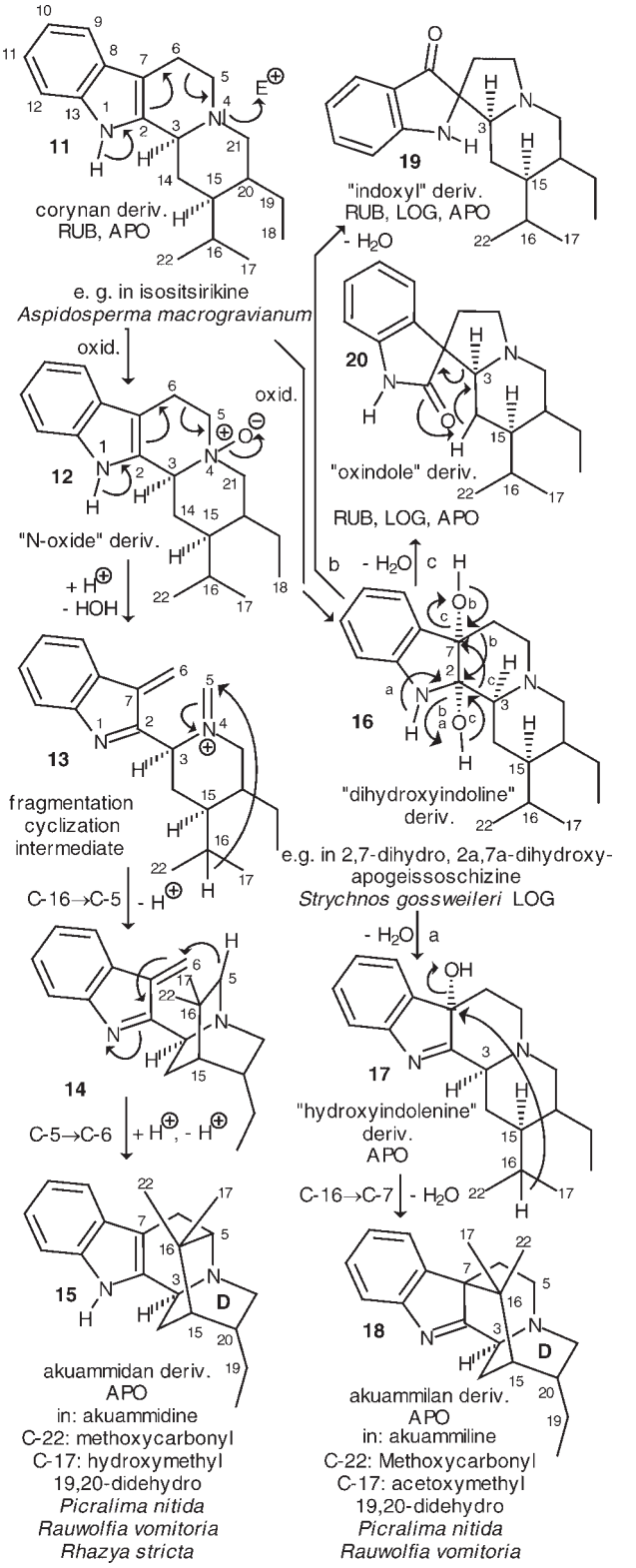
The formation of the akuammidine skeleton is highly stereoselective. In all alkaloids derived from secologanin, the configuration of C-15 (coming from C-5 of this secoiridoid) is always *S* (supposed that it is chiral at all, and the original configuration was reserved during the biosynthesis). In type I indole alkaloids which have strictosidine as precursor, the configuration of C-3 is likewise *S*. In the usual representation both H-3 and H-15 of the corynan skeleton have α *cis* and consequently both bonds C-3—N-4 and C-15—C-16 in β *cis* orientation (**11**). Only this common orientation allows the bridge formation and exclusively on the upper face of the β-carboline unit. It should be noted that simple type Iα alkaloids with 3*R* configuration (3β-H) were also isolated, among others vincoside (**3b** in Scheme 1) and reserpine. However, alkaloids with 3*R* configuration and having a bridged arrangement in their ring system could not be formed because of the opposite (i.e., α) trans orientation of bond C-3—N-4 to bond C-15—C-16. Formation of alkaloids in the 3*R* series is not catalyzed by strictosidine synthase and the origin of the *R* chirality at C-3 is not yet clear.

In the formation of the akuammilan skeleton (in **18**), the key point of the ring closure is C-7, and it should be likewise activated. It could be arrived by appropriately introduced OH groups at C-2 and/or C-7 of the formal double bond of the pyrrole ring. As shown in Scheme 7, this bond can be oxidized selectively under different conditions and at different positions.[17–19] One of the products may be a *cis*-2α,7α-dihydroxy-2,7-dihydroindoline compound **16** (three such specially arranged cyclocorynan alkaloids are available in the DNP database, e.g., dihydroxyapogeissoschizine). Dehydrations and further reactions may operate on this system, probably by proton-catalysis.

Dehydration involving N-1 and the OH group of C-2 affords 7-hydroxyindolenine derivatives **17** (pass a, shown by curved arrows in formula **16** of Scheme 7). A few natural compounds of this type are known (e.g., ajmalicine hydroxyindolenine **26** in Scheme 9) in which



Scheme 6. Some characteristic indole alkaloids referred in the text



Scheme 7. Fragmentation and rearrangements in type Iα indole alkaloids

the possibility is given for the formation of the akuammilan compounds (in **18**) (~150 compounds) by nucleophilic association of the preactivated C-16 to C-7, followed by formal dissociation of the OH group from this latter carbon. As the stereochemical situation is analogous to that of the akuammidine skeleton, and the requirements and restrictions are the same, alkaloids having 3*R* configuration may not be formed and were not found.

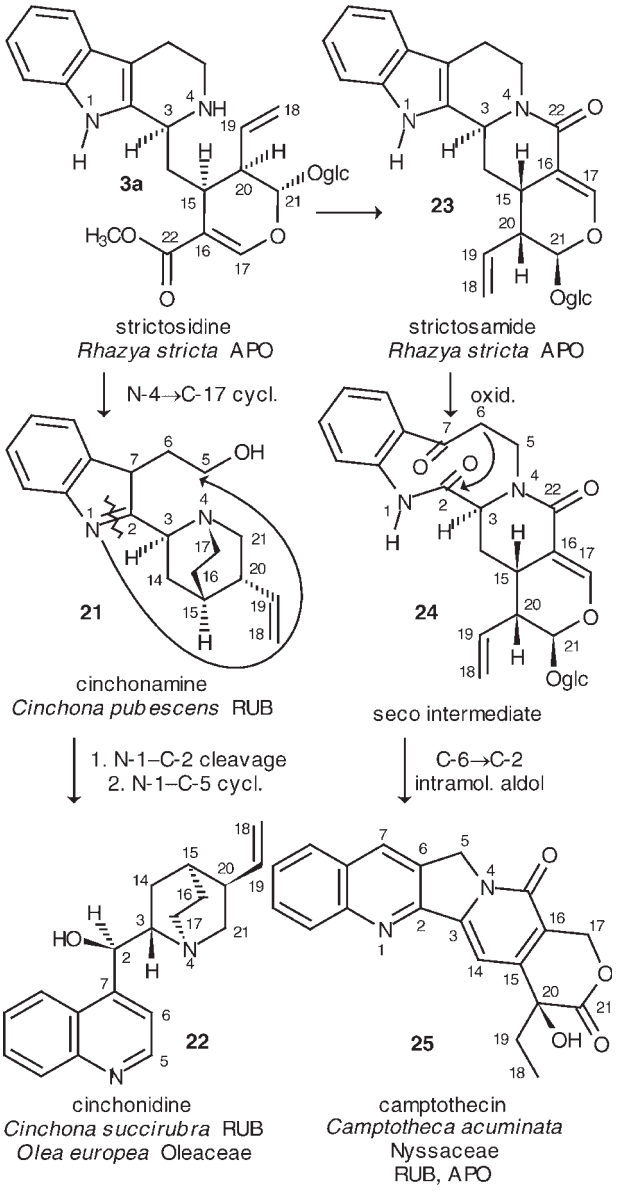
Another type of dehydration in **16** may start at the OH group of C-7, involves the 1,2-rearrangement of ligand C-6 from C-7 to C-2 with elimination again of the OH group of C-2 (pass b, curved arrows in **16**) and affords the 'indoxyl' alkaloids **19** (~10 alkaloids). As such rearrangements are generally stereospecific, the configuration of C-3 should be retained, and that of C-2 reversed. The configuration of the C-3 is really conserved, however, for the configuration of C-2 exactly established data in sufficient number fail.

Finally, an opposite, third type of dehydration (reaction pass c, curved arrows in **16**) affords already the type Iβ 'oxindole' alkaloids **20** (see later).

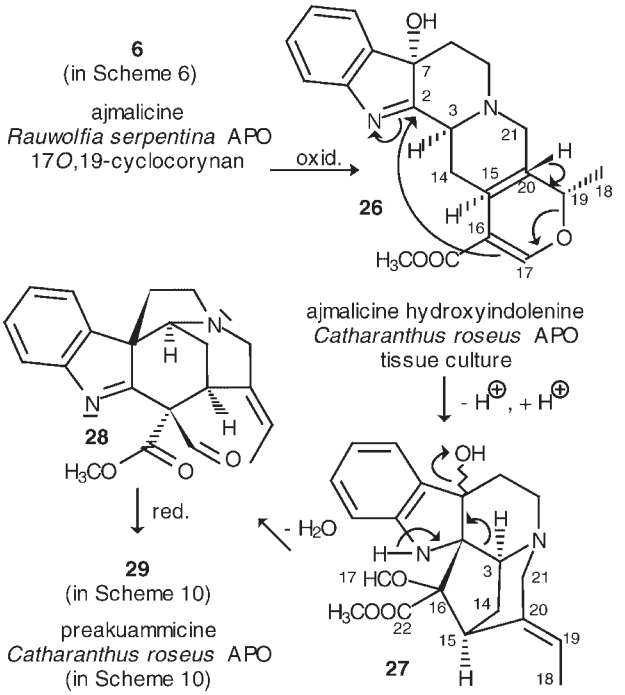
At this point it should be mentioned that some 'indoxyl' and 'oxindole' alkaloids are found also in the type II and type III groups.

DERIVATION OF CINCHONAN AND CAMPTOTHECAN ALKALOIDS

Now, the problem of the cinchonan and camptothecan alkaloids should be discussed very briefly (Scheme 8). The cinchonan alkaloids (about 40 compounds, a typical representative is cinchonidine = demethoxyquinine **22**),

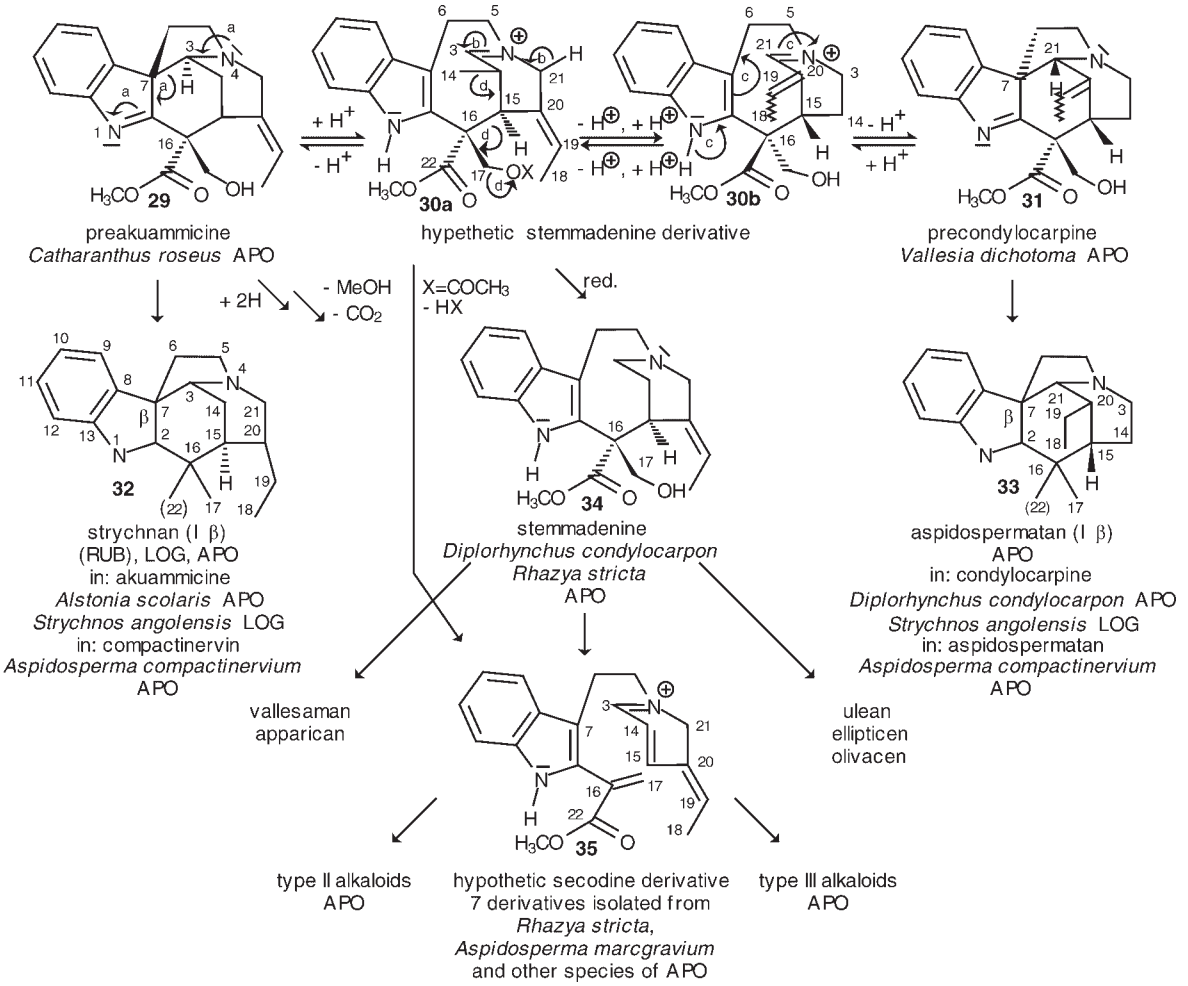


Scheme 8. Derivation of cinchonan and camptothecan alkaloids



Scheme 9. Transition of the Iα into the Iβ skeleton

were isolated mainly from the Rubiaceae family, the camptothecan alkaloids (35 compounds, the main alkaloid is camptothecin **25**) also from the Apocynaceae, and in addition from the Nyssaceae and Icacinaceae families. Their biogenesis is satisfactorily documented in the literature,[20,21] therefore only the key steps are sketched here, in order to show their relation to the 'real' indole alkaloids. Neither of them contains an indole ring. However, it was proved that their biosynthesis starts from secologanin (**1**) and tryptamine (**2**). In both groups, the skeleton of the secologanin subunit is unchanged, and the pyrrole ring of the tryptamine subunit enlarged into a pyridine ring, that is, their skeleton has a quinoline subunit instead of an indole one. The precursor of both groups is strictosidine **3a**, that is, a type Iα alkaloid. In the case of camptothecin, the C-2—C-7 double bond of the indole ring of strictosamide **23** (the lactam derivative of strictosidine) is cleaved by oxidation, and from the seco intermediate **24** the quinoline ring is formed in a subsequent C-6 → C-2 intramolecular aldol reaction. The formation of cinchonidine **22** is more complicated. At first, from a strictosidine aglucone in several steps cinchonamine **21** (shown in its tautomeric form) is formed by N-4 → C-17 cyclization (the DNP database contains 15 cinchonamine derivatives), in which formal double bond N-1—C-2 (formally an intramolecular Schiff base) is hydrolytically cleaved, and finally an N-1 → C-5 recyclization gives the quinoline ring system (in **22**). In both skeletons the changes can be followed according to the biogenetic numbering system.

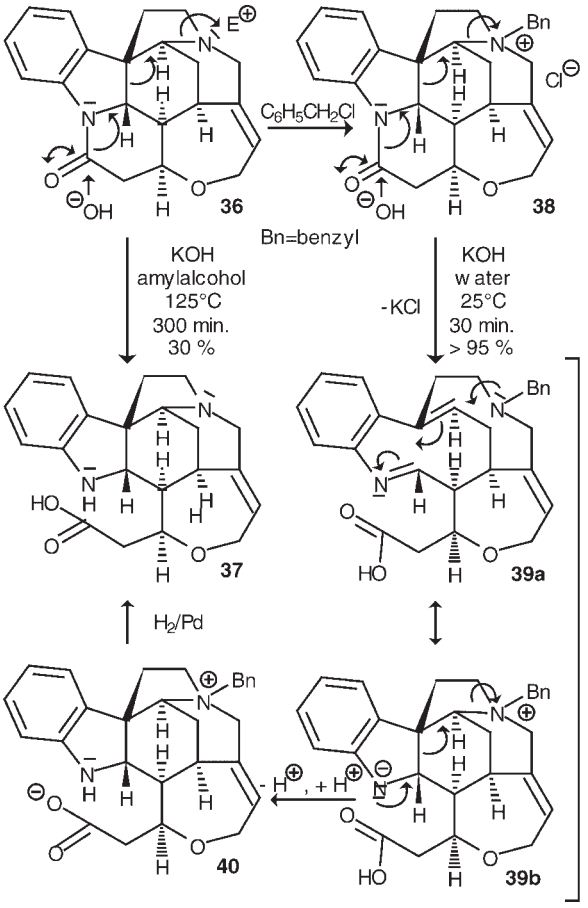


Scheme 10. Isomerization of the strychnan into the aspidospermatan skeleton

TRANSITIONS FROM THE TYPE Iα INTO THE TYPE Iβ SKELETON

The third type of dehydration of the 2α,7α-dihydroxyindoline system (**16** in Scheme 7) starts with deprotonation at OH group of C-2, followed by an opposite 1, 2-rearrangement of C-3 from C-2 to C-7, and formal dissociation of OH from the latter carbon atom gives the large group of oxindole alkaloids **20** (pass c, curved arrows in **16**). As in this case the C-3 ligand is shifted from the α into the β position of the indole ring, the oxindole type I alkaloids may be already considered as a special subclass of type Iβ alkaloids (2,16-secostrychnan alkaloids). In principle, in this stereospecific (suprafacial) rearrangement the configuration of C-3 should be retained, and of C-7 reversed. However, it was proved that by a reversible ring-chain tautomerism (curved arrows in **20**), both configurations could be partially epimerized. Moreover, as this reaction sequence does not involve the formation of a bridged system, the 1, 2-rearrangement may and does run also in the 3*R* series. Actually all the four possible configurations (at C-3 and C-7) were found in the oxindole alkaloids of type I (about 210 alkaloids including also their further derivatives).

An alternative route (shown in Scheme 9) for the formation of another type Iβ alkaloid skeleton would start likewise from a 7-hydroxyindolenine derivative **26** (produced in tissue culture from ajmalicine **6** in Scheme 6). In this case, however, the activated C-16 approaches C-2, which may happen again *only* from the upper (β) face of the β-carboline system either with or without formation of an addition intermediate **27**. In a subsequent stereospecific suprafacial 1,2-rearrangment, the α-oriented C-3 should be moved, with retention of its configuration, on the lower face of the indole ring from C-2 to C-7. It is expected that a smooth rearrangement would require β orientation of the leaving OH group of C-7. Therefore, if the primary precursor is really an α-*cis* 2,7-dihydroxyindoline structure **16**, and ajmalicine hydroxyindolenine **26** has its functional group at C-7 likewise in α-orientation, the rearrangement should be preceded by an epimerization at C-7, which would probably easily proceed under proton-catalysis, being C-7 an allylic–benzylic center. In any case, with elimination



Scheme 11. A special example for the interaction between N-1 and N-4 in indole alkaloids

of the OH group, the strychnan skeleton (in **28**) is formed in which the C_2-unit (C-5 and C-6) has β orientation in all natural products. The first product is probably dehydroakuammicine **28**, but, the first isolated compound is its reduced derivative preakuammicine **29**. The transition is important because more than 300 alkaloids, including such special ones as strychnine and its congeners, were isolated in this large group. Its importance is further increased by the fact that the main line of the subsequent molecular evolution passes the strychnan skeleton toward the aspidospermatan (in **30**) and the rearranged type II and type III skeletons (in Scheme 10).

As it was already mentioned in the preceding discussion, neither of the cyclizations involving C-16 toward the akuammidine, akuammilan, and strychnan groups may run in alkaloids having 3*R* configuration, and these compounds cannot take part in the further biogenesis.[9,15] Actually, the formation of 3*R* series is a side-track.

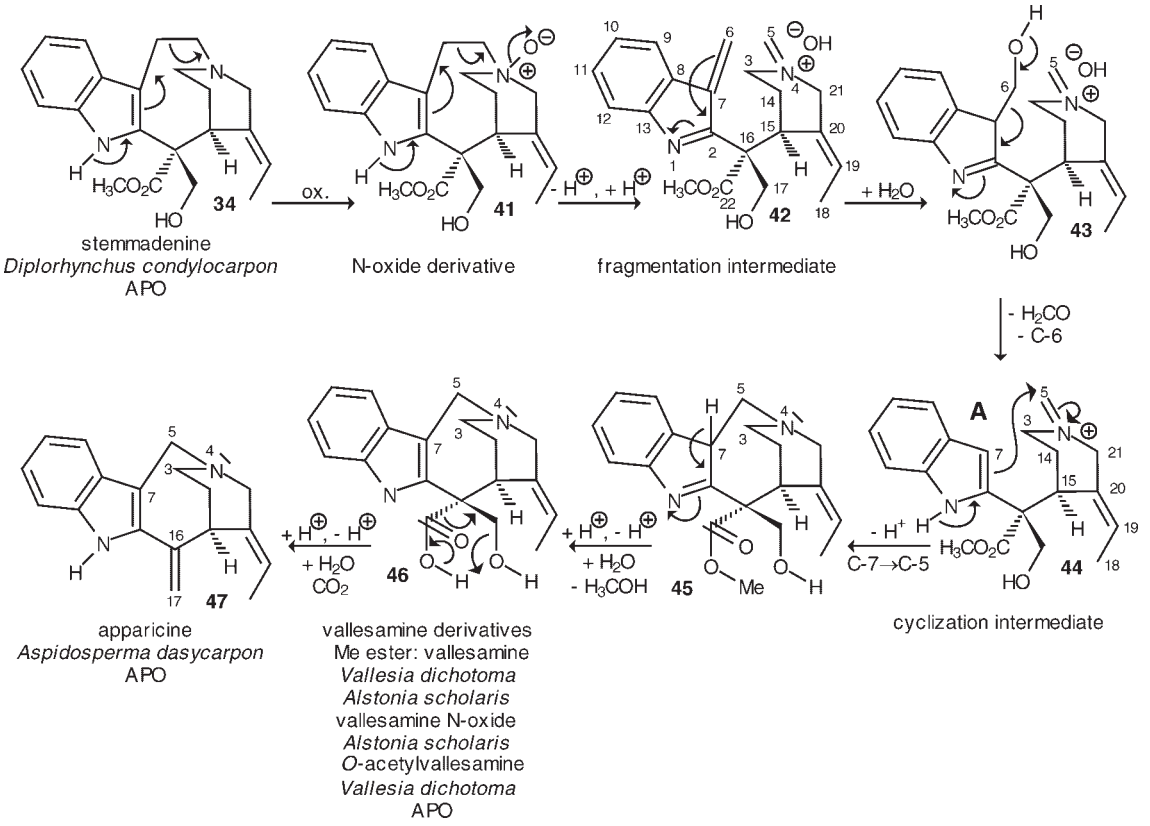
It is interesting that the akuammilan and strychnan derivatives are supposed to be formed from the same precursor type (7-hydroxyindolenine derivative **17** in Scheme 7) through different steps, and the two types of products were isolated from different species. Moreover, the akuammilan (and the akuammidine) derivatives were obtained exclusively from the Apocynaceae, the strychnan derivatives also from the Loganiaceae, but neither of them from the Rubiaceae species. Similar difference was observed in the two types of Iβ alkaloids: the strychnans were isolated from the Loganiaceae and the Apocynaceae, and the oxindoles in addition also from the Rubiaceae species, but never from common species.

ISOMERIZATION AND FRAGMENTATIONS IN THE STRYCHNAN SKELETON

The formation and transformation of the strychnan skeleton was discussed in great length in the golden age of the indole alkaloids (in 1960s and 70s[22]). In preakuammicine **29** three connections may be detected between the indole and the piperidine ring: a two-carbon bridge (C-5—C-6 ethylene group), a one-carbon bridge (C-16, connected to C-2 and C-15) and the sigma bond C-3—C-7. Each of them may be cleaved under special conditions, and has an important role in the formation of further groups of indole alkaloids.

Bond C-3—C-7 in preakuammicine **29** is part of an interesting five-centered, partially sigma-delocalized system having at its two ends an electron-donating (N-4) and an electron-attracting (N-1) nitrogen, that is, polarized in the reversed direction as indicated in corynan derivatives **11** and **12**. The polarization of the system should be increased by proton-catalysis, which might result in the cleavage of that bond (arrows a in **29**) affording a hypothetic stemmadenine derivative **30a** which is a key structure of the strychnan alkaloid group. It can be tautomerized by deprotonation–reprotonation (arrows b in **30a**) and simultaneous rotation along the bonds C-5—C-6 and C-15—C-16 into another hypothetic stemmadenine derivative **30b**, in which C-7 could be cyclized to C-21 (arrows c in **30b**), and gives precondylocarpin **31**. Probably this compound is the first member of the aspidospermatan group (about 35 compounds). Formally the difference between the two skeletons is the position of the C_2-unit, and suggests, as it was mentioned, a close analogy of position C-3 and C-21. In reality, the strychnan and the aspidospermatan skeletons have opposite stereochemistry and further differences. The analogous structural elements appear also in the type II and type III alkaloids. Although not the tautomers **30a** and **30b**, but the reduced derivative stemmadenine **32** and its C-15 epimer, as well as the two pivot compounds preakuammicine **29** and precondylocarpine **31** and in addition their analogous derivatives akuammicine (according to **33**) and condylocarpine (according to **34**) were isolated from common or closely related species, and this fact supports their common origin.

At this point it should be referred to our previous observation shown in Scheme 11 (not published yet) concerning the cleavage of lactam in strychnine **36** into



Scheme 12. Fragmentation in type Iβ strychnan alkaloids

strychnic acid **37** compared to that in benzylstrychninium chloride **38** into benzylstrychnine **40**. As it is seen, the lactam ring in the quaternary strychnine derivative can be cleaved much easier, under milder reaction conditions, in shorter reaction time and with better yield, than in strychnine itself. This fact reflects again the special connection between N-1 and N-4, and the electron flow shown by curved arrows and characterized by two valence tautomers **39a** and **39b** should be more effective in the quaternary derivative.

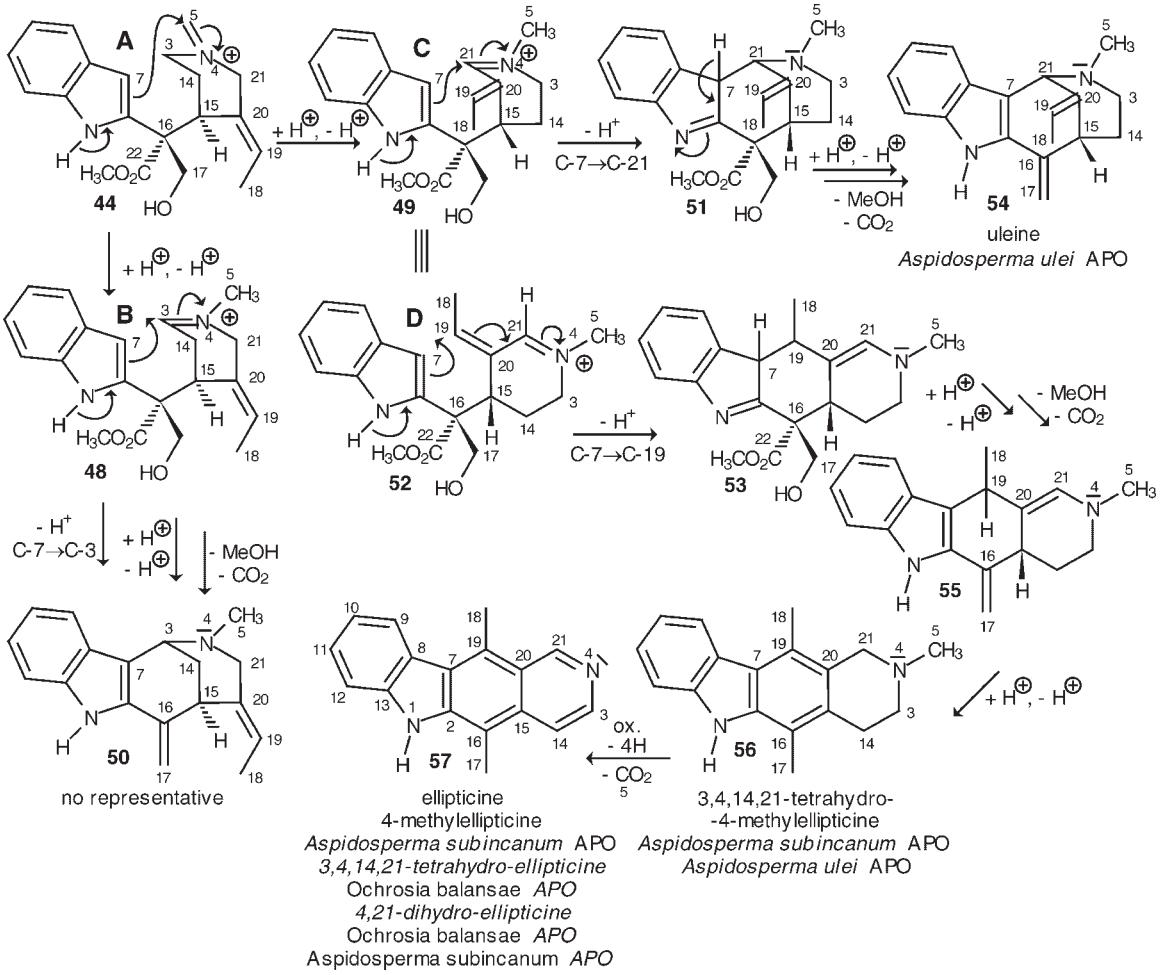
If in the hypothetic stemmadenine derivative **30a** (X=H) (Scheme 10) the leaving tendency of the original OH group at C-17 is increased, for example, by acetylation (X = acetyl) (*cf.* the *O*-acetyl derivative of vallesamine, a secoderivative of stemmadenine **34**; see **46** in Scheme 12), in a further fragmentation (arrows d on **30a**) the bond C-16—C-15 is cleaved, and formally a hypothetic cationic secodine derivative **35** having conjugated double bond systems may be formed. As it was already mentioned, this strategic bond could be cleaved under acidic or basic conditions even in secologanin, as well as in strictosidine derivatives.[16] Seven close derivatives of **35** were isolated from Apocynaceae species. These structures might be considered as precursors or intermediates on the way toward the formation of the type II and type III, that is, 'rearranged' indole alkaloids. However, it is already another story.

Finally, the third connection between the two subunits of preakuammicine **29**, precondylocarpine **31** and related compounds can be likewise cleaved, and affords alkaloids, in which the side-chain of the tryptamine subunit is truncated or lost.

CLEVAGE OF THE SIDE-CHAIN OF THE TRYPTAMINE SUBUNIT IN TYPE Iβ INDOLE ALKALOIDS

Products of these fragmentations are found in three smaller, but characteristic groups (vallesaman, ulean, and ellipticen-olivacen, 48 compounds). Their formations and transformations can be most easily interpreted from stemmadenine **34** itself.[23]

In stemmandenine (**34** of Scheme 12) the same characteristic connection exists between N-1 and N-4 (curved arrows in **34**) as in the corynan skeleton (in **11** and **12** of Scheme 7). Therefore, it might be expected that in its N-oxide **41** the polarization of the system is strongly increased, and by cleavage of the bond C-5—C-6 the fragmentation intermediate **42** is formed analogously to **13** (in Scheme 7). (In the appropriate alkaloid groups four N-oxides were found as natural compounds.) The final structures of these groups of alkaloids suggest that one of the carbon atoms of the ethylene bridge (C-5 or C-6)



Scheme 13. Fragmentation in type Iβ aspidospermatan alkaloids

should be lost during the further biosynthesis. As in the formation of ulein (**54** in Scheme 13) and ellipticine (**57** in Schemes 6 and 13) should be necessarily lost, the same was taken up analogously also in the formation of vallesamine **46** and apparicine **47** as well as in their derivatives (Scheme 12). In **42** the aza analog of an α,β-conjugated oxo system can be recognized, and C-6 is a part of it. Therefore it would be expected, that C-6 might be lost through **43** in a retro-Mannich reaction. The cyclization intermediate **44** formed by that way may be the center of further transformations.

The subsequent C-7 → C-5 cyclization and stabilizing tautomerization from **44** through **45** to **46** again might be considered to be analogous to the cyclization C-16 → C-5 and tautomerization from the secocorynan derivative **13** through **14** to **15**. In the vallesamine derivatives **46** formed by that way both ligands of C-16 (i.e., C-17 and C-22) are still retained. Further hydrolysis of the methoxycarbonyl group coupled with an intramolecularly facilitated decarboxylation yields apparicine **47** (and its derivatives).

The cyclization intermediate **A** (**44**) offers additional possibilities for stabilization (Scheme 13). The primarily developed N-4—C-5 double bond of the hypothetic ammonium salt can take up two alternative positions by tautomerization: N-4—C-3 in intermediate **B** (**48**) and N-4—C-21 in intermediate **C** (**49**). Of course, this latter position is more favored because of its conjugated position to double bond C-19—C-20. No cyclized compound (**50**) along C-7 → C-3 was isolated according to the intermediate **B**. However, the conjugated system of intermediate **C** (**49**) can be cyclized after rotation according to C-7 → C-21 giving **51** or after a second rotation from intermediate **D** (**52**) according to C-7 → C-19 giving **53**. From **51** by tautomerization, hydrolysis and decarboxylation (details in the case of apparicine) ulein **54** and its derivatives can be formed.

Analogous stabilization is open from **53** toward ellipticine **57**. Multiple tautomerizations coupled again with hydrolysis of the ester group and with decarboxylation assisted by intramolecular dehydration gives through **55** the tetrahydro-4-methylellipticine **56**. However, in this case the long reaction sequence from stemmadenine is further prolonged by stepwise dehydrogenation (aromatization). The intermediates, even the penultimate quaternary ammonium derivative of ellipticine (not shown in the scheme), were isolated from natural sources.

Removal of the N^4-methyl (C-5) (probably by oxidative decarboxylation) affords ellipticine **57** as the most stable skeleton with the maximum number of non-cumulated double bounds. It should be pointed out that while **47** is derived from the strychnan skeleton, **53** and **57** (=**9** of Scheme 6) and even olivacine **10** (of Scheme 6, *cf*. the next paragraph) from the aspidospermatan skeleton.

Finally, a last variation illustrates the importance of analogy in the biogenesis. Interestingly, also olivacine **10** (in Scheme 6), a structural isomer of ellipticine ('isoellipticine') (together with guatambuine and other derivatives) was isolated from the same or closely related species of *Ochrosia* and *Aspidosperma* spp (Apocynaceae). In contrast to ellipticine, olivacine **10** contains a methyl group at the pyridine (D) rather than at the benzene ring (C). However, transposition of a methyl group during the biosynthesis in such position is very improbable. Careful comparison of the two structures **9** and **10**, as indicated by the biogenetic numbering of the compounds, suggests that the methyl group in the benzene ring (C) of ellipticine corresponds to C-18, and in the pyridine ring (D) of olivacine to C-21 of strictosidine. On this base, it should be concluded that not strictosidine (through ajmalicine **6**) with the usual N-4 → C-21cyclization (aglucone type **N417**), but another strictosidine derivative with the unusual alternative cyclization N-4 → C-19 (aglucone type **N425**) should be the precursor of olivacine. The DNP database contains only four closely related compounds of aglucone type **N425** (one of them is normalindine **8** in Scheme 6) which were isolated from Strychnos species (Loganiaceae). Fortunately, the species of the Loganiaceae (like of the Apocynaceae, but unlike of the Rubiaceae) are able to synthesize Iβ type (not oxindole) alkaloids, which may be intermediates in the formation of ellipticen and olivacen alkaloids. However, the mechanism of formation and transformation its special transformation of the **N425** type aglucones is outside of the subject of this analysis.

At the end of this study, some final remarks and conclusions might be made. (1) Although only the main lines were analyzed in this work, and the fine details are still to come, it is encouraging that by using a relatively small number of principles and structural elements it was possible to give a general and unifying overview about a chemical background of the formation of a large number of individual compounds. The work, at least for the author revealed the order, that is, the unity in the multiplicity. (2) In the analysis of the olivacen and ellipticen derivatives, a long sequence of intermediates could be documented by isolated natural products (except, of course, the probably highly reactive carbocation species), and this fact means that the chemotaxonomical approach with tight interplay of the standard organic reaction mechanisms may be fruitful also in the future in that type of work. (3) The electronic databases are indispensable not only to collect, but also to search and work up the larger and larger amount of data about natural compounds. It was found that the interaction between the chemical and biological aspects and data mutually increases their proving force.

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