X-RAY CRYSTAL STRUCTURES OF C_{19}-DITERPENOID ALKALOIDS

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Abstract - The X-ray diffraction analysis of 30 C_{19}-diterpenoid alkaloids is reviewed. During the course of structure determination, many naturally-occurring alkaloids have been correlated with alkaloids whose structures were established by X-ray crystal studies. The relative stereochemistry of these alkaloids at all the centres can be assumed to be correct. The absolute stereochemistry has been established for some of the alkaloids.

Contents

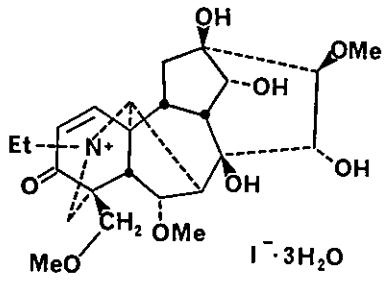
1. INTRODUCTION

Plants belonging to the *Delphinium* and *Aconitum* genera (Ranunculaceae) and *Inula royleana* (Compositae) have yielded almost all known C_{19}-type of diterpenoid alkaloids. Some of these alkaloids, which are esters of bases containing a number of acetoxyl, hydroxyl and methoxyl groups, have exhibited high toxicity in mammalian species. Because of their complex structures and interesting and diverse pharmacological properties, these alkaloids have attracted the attention of chemists and pharmacologists for many years. Progress in the complete structure elucidation of these alkaloids by classical degradation studies was very slow. In recent years, nmr spectral methods have greatly facilitated the structure elucidation of this complex group of alkaloids. The C_{19}-diterpenoid alkaloids have been broadly divided into three groups: (i) the aconitine-type, characterized by the lack of an oxygen function at C(7) in the aconitan skeleton; (ii) the lycoctonine-type which bears an oxygen function at C(7); and (iii) the heteratisine-type which possesses a lactone moiety in ring C of the aconitan skeleton. Some of the naturally-occurring aconitine and lycoctonine alkaloids and their derivatives have been subjected to X-ray crystal structure analysis and the absolute stereochemistry has been established in some cases. Among the variety of methods used, e.g. ORD, CD, chemical interconversions involving the chiral centers, asymmetric synthesis, etc., the Bijvoet method for determining the absolute configuration by X-ray analysis is the only reliable and widely applicable direct method. The complete structure of lycoctonine was initially derived from the X-ray analysis of des-(oxymethylene)-lycoctonine hydriodide monohydrate, but later investigations on other lycoctonine transformation products indicated that the β-configuration assigned to the C(1) methoxyl was in error. The wrong set of mirror-image peaks was chosen for the interpretation of the Fourier synthesis. This is another instance among many of X-ray assignments of chirality, where a re-examination has shown that an error of some kind was made in the original assignment. There are many places where a slip can occur and it is possible that still other errors may have remained undetected. However, with the sophisticated facilities and techniques available today, an error in X-ray derivation of structure is highly unlikely.

2. ACONITINE-TYPE C_{19}-DITERPENOID ALKALOIDS

2.1 Aconitine (2) — Aconitine known since 1833, is one of the most accessible and highly complicated alkaloids of the C_{19}-diterpenoid class. The structure elucidation of this alkaloid based on chemical degradation studies was independently supported by X-ray crystallographic analysis of demethanolaconinone hydriodide trihydrate (1).[1] This investigation not only confirmed the position of the methoxyl and hydroxyl groups in ring A but also provided the absolute configurations of 13 out of the 15 asymmetric centres of aconitine (2). Wiesner and coworkers showed that the C(1)-methoxyl group of delphinine has an α-equatorial configuration by an X-ray crystal structure determination of the acid oxalate salt of a degradation product (3) obtained from delphinine.[2] As delphinine was correlated earlier with aconitine[3], the configuration of C(1) in the latter alkaloid was established as shown in 2. It was also inferred that rings A and B are in the chair conformation and the methoxyl group at C(1) is equatorial. The five-membered ring C is in the envelope conformation and ring D is a distorted chair.[4] Since the conformation of ring A in aconitine was not determined, a recent X-ray crystallographic analysis of aconitine has established unequivocally the following[5]: rings A, B and E occur in chair form; ring C is an

envelope with C(14) at the flap; ring F is a half-chair and ring D is a boat with the end at C(15) flattened.



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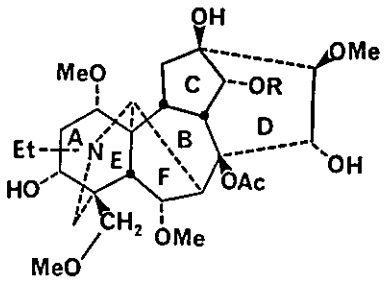
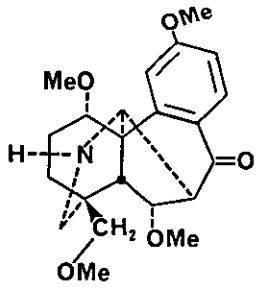


2: R = Bz (CO-C6H5)

17: R = As (CO-C6H4-OMe)

The naturally-occurring alkaloids which have been correlated with aconitine are: 3-acetylaconitine[6], acoforestinine[7], 14-benzoylmesaconine[8], bikhaconitine[9], chasmaconitine[10], chasmanthinine[10], crassicautine[11], 3-deoxyaconitine[12], 3,13-diacetylpseudaconitine[13], falaconitine[13], hokbusine A[14], hypaconitine[12], indaconitine[15], liwaconitine[16], mesaconitine[17,18], mithaconitine[13], pseudaconitine[19], veratroylpseudaconine[20] and yunaconitine[21].



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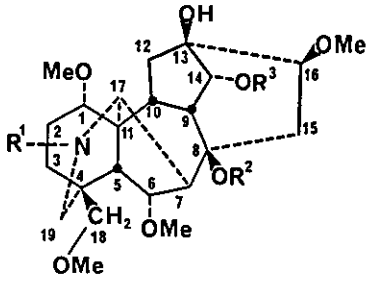


4: R^1, R^2 = Et; R^3 = As

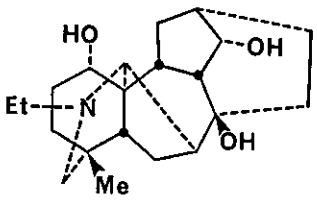
9: R^1 = Me; R^2 = Ac; R^3 = Bz

2.2 Acoforestine (4) — The structure and stereochemistry of acoforestine (4) isolated from *Aconitum forrestii* Stapf was confirmed by X-ray crystal structure determination using direct methods.[7] Three of the four six-membered rings of 4 are in a chair conformation while ring D has a boat conformation. Ring A [C(1), C(2), C(3), C(4), C(5), C(11)] is a flattened distorted chair with C(1) and C(4) below (0.4Å) and above (0.7Å) respectively, of the plane through the atoms C(2), C(3), C(5) and C(11). The E ring [(C(4), C(5), C(11), C(17), N, C(19)] has a chair conformation with C(4), 0.7Å below and C(17) 0.8Å above the plane through C(5), C(11), N and C(19). The six-membered ring [(C(7), C(8), C(9), C(10), C(11), C(17)] is also a distorted chair with C(7) 0.8Å below and C(10) 0.5Å above the plane through C(8), C(9), C(11), C(17). Ring D [C(8), C(9), C(14), C(13), C(16), C(15)] has a half-boat conformation with C(14) and C(15) forming the end atoms above the plane through C(8), C(9), C(13) and C(16) by 0.86Å and 0.26Å, respectively. The five-membered rings F [C(5), C(6), C(7), C(17), C(11)] and C (C(9), C(10), C(12), C(13), C(14)] have a distorted half-chair conformation.

The structure and stereochemistry of crassicauline A, the major alkaloid of *A. crassicaule*[2] was established by converting to acoforestine.[7] Crassicauline A has been converted to crassicausine.[11]

2.3 Cardiopetaline (5) — This minor alkaloid from *Delphinum cardiopetalum* DC (Syn. *D. verdunense* Balbis) was shown to have the structure 5 by an X-ray crystal structure determination. It is the first example of a C_{19}-diterpenoid alkaloid which lacks an oxygen function at C(16).[23]

Benzoylheteratisine, heteratisine[24], heterophyllidine, heterophylline and heterophyllisine[25], all containing a δ-lactone in the C ring (of structure 2), are devoid of an oxygen function at the C(16) position.



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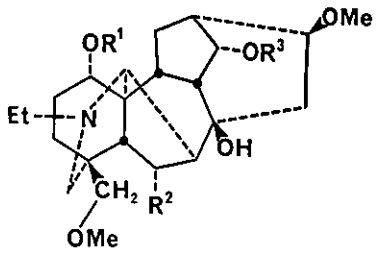


6: R^1 = Me; R^2 = OMe; R^3 = H

7: R^1,R^3 = H; R^2 = OMe

8: R^1,R^2 = H; R^3 = Ac

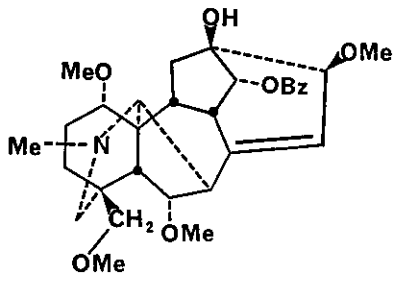
2.4 Chasmanine (6) — Because of the correlation of browniine and neoline[26], chasmanine (neoline-1-methyl ether) was reported to possess a C(1)-β-methoxyl group. However, a subsequent correlation of neoline with delphisine[27] (bears a C(1)-α-hydroxl) cast doubt on the correctness of this assignment. An X-ray crystal study of chasmanine 14-α-benzoate hydrochloride established structure 6 for chasmanine. The A ring (of the derivative) is stabilized in a boat form by intramolecular hydrogen bonding and the methoxyl at C(1) is α-oriented. The C(1)-hydroxyl group of neoline (7) should therefore have an α-configuration.

The other naturally-occurring alkaloids which have been correlated with chasmanine are: acoforesticine[7], anisoezochasmaconitine[28], crassicaudine[11], ezochasmaconitine[28], ezochasmanine[28], falconerine[29], falconerine-8-acetate[29], foresaconitine[30], foresticine[31], homochasmanine[32], isodelphinine[33] and pyrochasmanine[28,34].

2.5 Condelphine (8) — This alkaloid, first isolated from *D. confusum*[35] and subsequently from *D. denudatum*,[36] has been assigned structure 8 from an X-ray crystal structure determination of condelphine hydriodide.[37] The absolute configuration of the alkaloid was established as: 1S, 4S, 5R, 7S, 8S, 9R, 10R, 11S, 13R, 14S, 16S, 17R by examination of the Friedel pairs of reflexions. Intramolecular hydrogen bonding between the protonated nitrogen atom and the C(1)-hydroxyl group stabilizes ring A in a boat form.

The structure and absolute configuration of 14-acetyltalatizamine[38], acoforine[7], aconosine[39], cammaconine[40], columbianine[41], columbidine[42], *N*-deacetylscaconitine[43], 14-dehydrotalatizamine[44,45], 8-deoxy-14-dehydroaconosine[46], dolaconine[47], gymnaconitine[48], isotalatizidine[36], methylgymnaconitine[48], 8-O-methyltalatizamine[41], nevadenine[49], scaconine[43], scaconitine[43] and talatizamine[40] are established since all these alkaloids have been correlated with condelphine (8).

2.6 Delphinine (9) and Pyrodelphinine (10) — The structures of delphinine (9) and pyrodelphinine (10) were based on chemical evidence[3] and the X-ray structure of compound 3 derived from delphinine.[2] In order to decide whether pyrodelphinine is a resonance hybrid of



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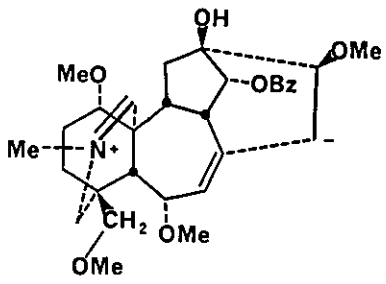

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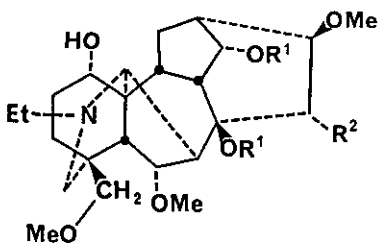
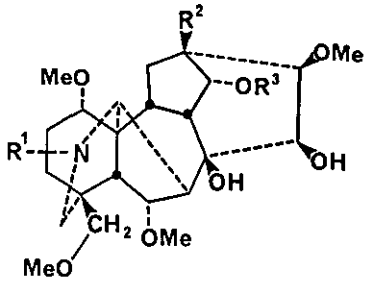
forms **10** and **11**, an X-ray analysis of delphinine and pyrodelphinine was carried out.[50] This study confirmed the structures of delphinine and pyrodelphinine as **9** and **10**, respectively. Rings A, C, E and F have the same conformations in both alkaloids. The D ring in **9** is in a bent-chair conformation with C(8), C(9), C(13), C(15) and C(16) nearly coplanar and C(14) forming a flap. In **10**, ring D has a half-chair conformation flattened at the C(8)-C(15) double bond.

2.7 Delphisine (12) and Fuziline (13) — The structure and absolute configuration of this alkaloid from *D. staphisagria* was established as **12** by an X-ray crystallographic analysis of its hydrochloride. The A ring is in a boat form, stabilized by an intramolecular N-H---O hydrogen bond, and the D ring is also in a boat conformation flattened at C(15).[27] The absolute configuration of delphisine was shown to be 1S, 4S, 5R, 6R, 7R, 8R, 9R, 10R, 11S, 13R, 14S, 16S, 17R.





12: R^1 = Ac; R^2 = H

13: R^1 = H; R^2 = OH

14: R^1 = CHO; R^2 = OH; R^3 = Bz

16: R^1 = Me; R^2,R^3 = H

The naturally-occurring alkaloids that have been correlated with delphisine are: benzoylneoline[51], bullatine C[52,53], delphidine[27], delphirine[54], delstaphisagrine[55], 15-α-hydroxyneoline[56] (fuziline[57b], senbusine C[57c]) (**13**) and neoline.[27] The X-ray crystal structure of fuziline has also been carried out recently[57a].

2.8 *N*-Desmethyl-N-Formyl-8-Deacetyl-15-β -Hydroxydelphinine (**14**) — Osmium tetroxide oxidation of pyrodelphinine (**10**) afforded the 8,15-*cis*-diol and as a minor product, *N*-desmethyl-*N*-formyl-8-deacetyl-15-β -hydroxydelphinine (**14**), the structure of which was established by X-ray analysis.[58]

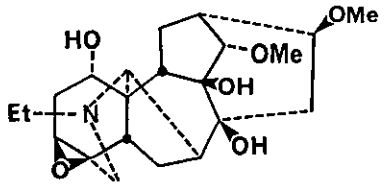
2.9 Excelsine (15) — The structure of excelsine (**15**), from *A. excelsum* Reichb (*A. leucostomum* Worosch), was established by an X-ray crystal structure of the monohydrate of its hydrochloride. It is the first C_{19}-diterpenoid alkaloid to have an epoxide ring at the

C(3) - C(4) position. The absolute stereochemistry of excelsine was found to be 1S, 3S, 4R, 5S, 7S, 8S, 7S, 10S, 11R, 13R, 14S, 16S, 17R, (N)S.[59]

2.10 15-*epi*-Isodelphonine (**16**) — Sakai and coworkers synthesized 15-*epi*-isodelphonine from chasmanine (**6**) through a series of transformations involving acetylation, oxidation with potassium permanganate, formylation, pyrolysis to the 8,15-dehydro derivative, epoxidation, diol formation and reduction of the *N*-formyl group with lithium aluminium hydride to the corresponding *N*-methyl derivative (**16**). The structure of this alkaloid was confirmed by an X-ray analysis which showed that the C(15)-hydroxyl group is in the β-configuration.[60]

2.11 Jesaconitine (**17**) — When jesaconitine was first investigated, the C(1)-methoxyl group was assigned a β-configuration.[61] However, the crystal structure of jesaconitine perchlorate has shown that the C(1)-methoxyl is in an α-configuration (**17**).[62] The A ring assumes a boat conformation and is stabilized by intramolecular hydrogen bonding between the nitrogen and the oxygen substituents at C(1) and C(3). Aljesaconitine A and aljesaconitine B[63] from *A. japanicum* Thunb. and 3-deoxyjesaconitine[64] from *A. subcuneatum* Nakai have been correlated with jesaconitine.

2.12 Lappaconine (**19**) — Lappaconitine (**18**), the major alkaloid of *A. septentrionale* Koelle was extensively investigated by Marion and coworkers.[65] Hydrolysis of **18** gave lappaconine (**19**), the structure of which was confirmed by X-ray analysis of lappaconine hydrobromide.[66] The A ring was shown to have a boat conformation as in condelphine (**8**). Lapaconidine, from *A. leucostomum* Worosch and *A. septentrionale* Koelle, has been correlated with lappaconine.[67]



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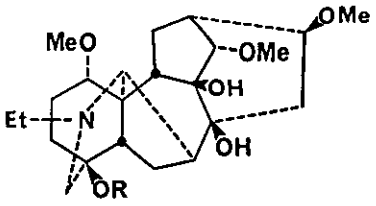
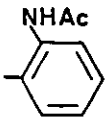


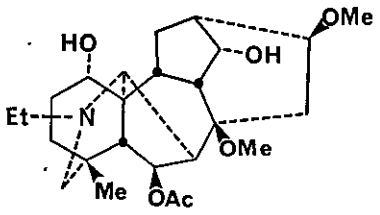


18: R = CO

19: R = H

3. ACONITINE-TYPE WITH 6-β-OXYGEN FUNCTION

3.1 Bicoloridine (Alkaloid A) (**20**) — This alkaloid, initially named 'Alkaloid A'[68], was isolated from *D. bicolor* Nutt. and subsequently redesignated as bicoloridine.[69] An X-ray crystallographic analysis of bicoloridine hydroiodide led to structure **20** for bicoloridine.[70] Most of the aconitine-type alkaloids that bear an oxygen function at C(6), have this group in an α-configuration.[71] Bicoloridine is unusual in that the C(6) acetoxyl group is present in a β-orientation. Bicoloridine has been converted to bicolorine (alkaloid B), and bicolorine-6-*O*-acetate has been hydrolysed to bicolorine.[69] Other aconitine-type alkaloids that possess a C(6)-β oxygen function are heteratisine,[24] and heterophyllidine,[25] alkaloids that contain a δ-lactone moiety instead of a cyclopentane ring C.



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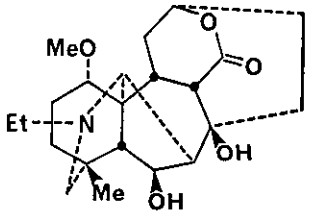

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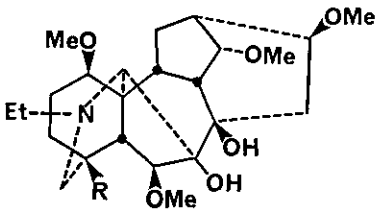
3.2 Heteratisine (**21**) — Some preliminary crystallographic data were collected for heteratisine and its derivatives, but the crystals of the hydrobromide were found to be unsuitable for structure analysis as they were effervescent and crumbled to a powder.[72] Heteratisine hydrobromide monohydrate was suitable for X-ray structure determination which showed that in heteratisine (**21**) the six-membered A ring containing the methoxyl group is in a distorted boat form. The absolute stereochemistry of the molecule was not determined; however, an ORD study of heteratisine derivatives indicated that heteratisine has the same absolute configuration as delphisine and other diterpenoid alkaloids having the aconitan skeleton.[73]

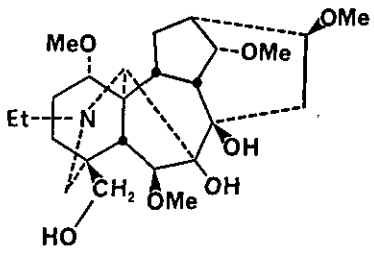
4. LYCOCTONINE-TYPE C_{19}-DITERPENOID ALKALOIDS

4.1 Lycoctonine (**24**), Des-(oxymethylene)-lycoctonine (**22**) — A large majority of C_{19}-diterpenoid alkaloids are in this class which is characterized by the presence of an oxygen function at C(7). Inspite of a large amount of work to elucidate the structure of lycoctonine, the complete structure defied chemical methods. The structure was finally solved in 1956 by X-ray crystallographic analysis of (+)-des-(oxymethylene)-lycoctonine hydroiddide monohydrate, which established the structure of this derivative.[74] The absolute stereochemistry (**22**) of this compound was determined by the Bijvoet anomalous dispersion method[75] and the structure of lycoctonine was derived as **23**.[76] Based on this result, all the alkaloids which were directly or indirectly correlated with lycoctonine were assigned structures and stereochemistry based on this alkaloid.[77] In all these structures, the C(1)-methoxyl or hydroxyl group was considered to



22: R = H

23: R = CH_2OH



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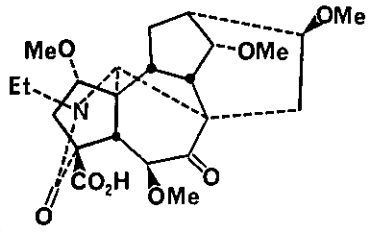
be in the β-configuration. Recent work, however, has shown that the assignment of a β-configuration to C(1) in lycoctonine is an error and lycotonine is correctly represented as **24**.[78,79] An X-ray crystal structure determination of the ketolactam (**25**) and other transformation products derived from lycoctonine has shown that the C(1)-methoxyl is in an α-configuration. A redetermination of the X-ray crystal structure of **22** has shown that in the original Fourier synthesis, a wrong choice was made between the real and false mirror-image peaks for atoms of the C(1)-methoxyl group. Lycoctonine samples from many sources were shown to be identical and that no rearrangement had occurred in the formation of **22**.[78] All alkaloids related to lycoctonine should therefore have a C(1)-α-methoxyl group.[78,79] Lycoctonine, browniine, and delsoline have been chemically transformed to delphatine.[79] Since the α-configuration of C(1)-hydroxyl in delsoine was firmly established[80], all these correlated alkaloids must have a C(1)-α-methoxyl group.

These results led to the revision of structures of the following naturally occurring alkaloids with the C(1)-methoxyl or hydroxyl group in an α-configuration[79]: 14-acetylbrowniine[81], 14-acetyldelectine[82], *N*-acetyldelectine[83], ajacine[84], anthranoyllycoctonine[84,85], avadharidine[84], 14-benzoylbrowniine[86], 14-dehydrobrowniine[86], delbiterine[86], delectine[87], delectinine[88], delpheline[89], delsemine[84], deltaline[84,89], deltamine[84], demethylene-deltamine[84], dictyocarpine[90], dictyocarpinine[90], 7,18-di-*O*-methyllycoctonine[79,87], elatine[84], gigactonine[91], lycaconitine[84] and methyllycaconitine.[84] Other alkaloids correlated with lycoctonine are: delbiterine[79,86], delvestine[92], delvestidine[92], elatine[79,84] and tatsiensine.[93]

4.2 Bonvalotine (**26**), Delbotine (**27**), Delboxine (**28**) — The structure of bonvalotine (**26**), an unusual alkaloid from *D. bonvalotii* Franch, hydroxylated at the C(5)-position was derived by spectral methods and confirmed by an X-ray crystal structure determination.[94,95] The co-occurring alkaloids bonvalol and bonvalone have been correlated with bonvalotine. The structures of delbotine (**27**) and delboxine (**28**) from the same plant[94,95,96] have been also established by X-ray analysis.



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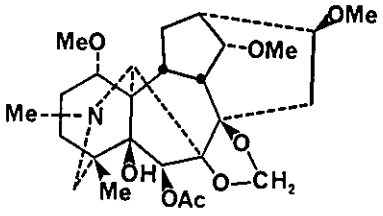

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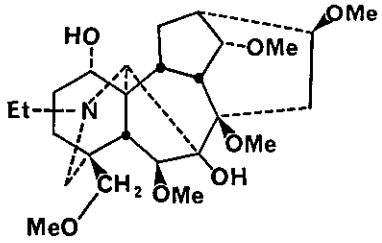

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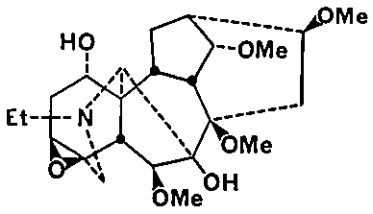

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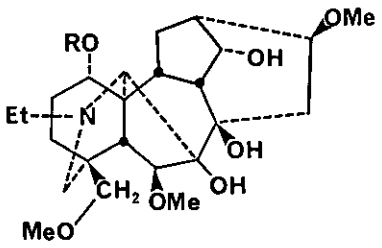
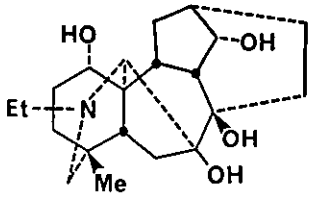
4.3 Browniine (**29**) — In order to confirm the revised assignment of the C(1)-α-methoxyl group based on chemical correlation studies[79], an X-ray structure determination of browniine perchlorate was carried out. The structure was solved by multisolution methods and refined to an R of 0.078 for 2766 observed reflexions; browniine has structure **29**.[97]

4.4 Cardiopetalidine (**30**) — The structure (**30**) assigned to the alkaloid isolated from *D. cardiopetalum* DC was derived from spectral considerations and confirmed by an X-ray analysis.[23] Cardiopetalidine is the first alkaloid with a lycoctonine skeleton that does not have an oxygen function at C(16). Cardiopatalidine has been oxidized with $KMnO_4$ to give graciline, an alkaloid isolated from *D. gracile* DC.[98]





29: R = Me

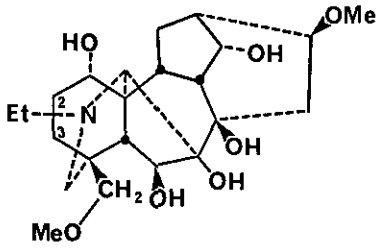
31: R = H

30

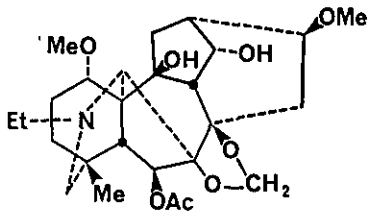
4.5 Delcosine (31) — This alkaloid was isolated from *D. ajacis*[99] in 1945 and all attempts by Marion and coworkers to correlate delcosine with lycoctonine were unsuccessful.[100] An unpublished X-ray crystallographic analysis of delcosine hydrobromide indicated that in delcosine (31) all the substituents with the exception of C(1)-hydroxyl group are oriented as in lycoctonine (as then formulated with a β-OCH_3).[101] The A ring of delcosine was shown to be in a boat conformation with the C(1)-hydroxyl forming a hydrogen bond with the loan pair of nitrogen, whereas in lycoctonine, ring A exists in a chair form. A recent Russian X-ray analysis has established that delcosine is correctly formulated as **31** having the hydroxyl group at C(1) in an α-configuration.[102] The rings A, B and D have a boat conformation, rings C and F are an envelope and ring E is a chair. The rings A/B are *trans* and all the other ring junctions (A/E, B/C, B/D and B/F) are *cis*.

4.6 Delphinifoline (32) — The structure of delphinifoline (32), a minor alkaloid from *A. delphinifolium* DC, was confirmed by X-ray crystallography.[103] It is a lycoctonine-type alkaloid closely related to browniine, decosine and delsoline.

4.7 Dictyocarpine (33) — This alkaloid was assigned the structure **33** on the basis of nmr studies and correlation with lycoctonine via a long sequence of reactions involving dictyocarpinine, 6,10-dimethyldeltamine, deltamine, deltaline, delpheline, 6-*O*-methyldelpheline and deoxylycoctonine.[84,90] The structure and stereochemistry of dictyocarpine have been confirmed by an X-ray analysis of its acetone complex.[97] The configuration of the methoxyl group at C(1) is shown to be α. In ring A, C(2) can be located either *cis* or *trans* to C(5) with reference to the planes passing through C(1), C(3), C(4) and C(11); hence this ring may assume either a boat or a chair conformation. In the case of browniine perchlorate, the A ring is a boat, whereas in dictyocarpine, it is in a chair conformation.



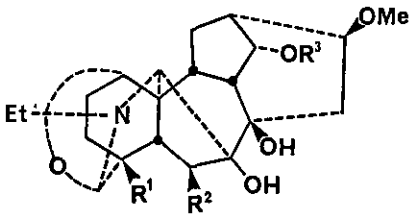
32



33

36: C(2)=C(3)

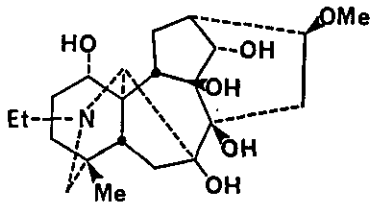
4.8 Gadesine (34), 18-Hydroxy-14-O-methylgadesine (35) — *D. pentagynum* Lam. afforded an interesting alkaloid gadesine (**34**), the structure of which was solved by spectral methods and confirmed by an X-ray analysis.[104] The A ring exists in the skew form and is stablized through an ether oxygen bridge between C(1) and C(19); it forms a rigid unit C(1)-C(2)-C(3)-C(4)-C(19)-N-C(17)-C(11) bridged twice through O(1) and C(5). Two intramolecular hydrogen bonds are formed between O(8)—H(8)---O(6) and O(14)-H(14)---O(16). 18-Hydroxy-14-*O*-methylgadesine (**35**) was isolated from *Consolida orientalis* Gay and its structure was determined by X-ray analysis which showed that ring A exists as a skew-boat form.[105] The naturally-occurring alkaloids which have been correlated with gadesine are: 14-acetylgadesine[106], 14-benzoyldihydrogadesine[106], 14-benzoylgadesine[106], dihydrogadesine[107] and gadeline.[106]



34: R^1 = Me; R^2 = OMe; R^3 = H

35: R^1 = CH_2OH; R^2 = OMe; R^3 = Me

37: R^1 = Me; R^2,R^3 = H



38

4.9 Ibukinamine (36) — *A. ibukiense* Nakai afforded a lycoctonine-type alkaloid designated ibukinamine. The structure of the alkaloid (**36**) was determined on the basis of spectral data and confirmed by X-ray analysis.[108] It is a 2,3-dehydro derivative of delphinifoline (**32**).

4.10 Pentagydine (37) — The structure of pentagydine, a constituent of *D. pentagynum* Lam., was solved by X-ray crystallography. The structure (37) was solved by direct methods and refined to R=0.042.[109]

4.11 Tatsinine (38) — This alkaloid isolated from *D. tatsienense* Franch was assigned structure **38** on the basis of ^{1}H and ^{13}C nmr spectral evidence,[110] and has recently been confirmed by an X-ray crystal structure determination of tatsinine perchlorate.[111]

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Received, 2nd March, 1987