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REVIEW ARTICLE
RECENT CHEMISTRY OF SOME DITERPENOID ALKALOIDS

B S JOSHI, F.N.A.

Institute of Natural Products Research, Chemistry Building, The University of Georgia, Athens, Georgia 30602-2556, *USA*

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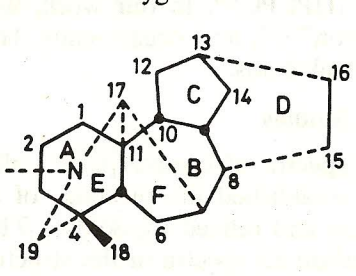
This review summarises some of our work on the chemistry of norditerpenoid and diterpenoid alkaloids

Key Words: Alkaloids Diterpenoid & Norditerpenoid; Isolation Technique; Studies—NMR Spectral & Phytochemical

Introduction

The diterpenoid alkaloids occur in the plant species of Compositae, Daphnyphillaceae, Garryaceae, Ranunculaceae, and Rosaceae. By far the largest number of deterpenoid alkaloids have been reported from *Aconitum*, *Delphinium* and *Consolida* genera of the Ranunculaceae family[1-3]. *Delphiniums* have been used as arrow poisons since antiquity, plants containing these alkaloids have been traditionally used in India and China as medicines for centuries[4,5]. These plants are primarily used as cardiotonics, febrifuges, sedatives and anti rheumatics. Recent studies have shown that the diterpenoid alkaloids contained in these plants are the active constituents responsible for the medicinal properties[6].

Diterpenoid alkaloids have been divided on the basis of their skeletal ring system into two major groups, usually called C_{19} diterpenoid (norditerpenoid) (**1**) and C_{20}-diterpenoid (diterpenoid) (**2**) alkaloids. Each group may be further subdivided into various types. Norditerpenoid alkaloids are highly oxygenated bases with one seven-, three six-, and two-five membered rings. They are subdivided mainly in four types; *a*) aconitine-type, having the skeleton (**1**) but no substituent at C(7) other than hydrogen. Some members of this class only, bear hydroxyl groups at C(3), C(13) and C(15); *b*) lycoctonine-type having the skeleton (**1**) with an oxygen substituent at C(7); *c*) pyro-type having a double bond



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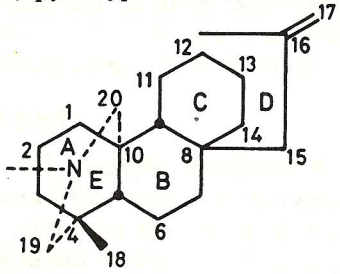


2

Structures 1 & 2

between C(8) and C(15)—most probably, these compounds are not naturally occurring and are artifacts obtained during isolation of the alkaloids; and *d*) heterotype is a very small group of alkaloids in which a δ-lactone moiety is present in ring C.

The diterpenoid alkaloids include the basic skeleton shown in (**2**), differing in the attachment of the C(15) bridge at either C(11), C(12) or C(13)[3], e.g. *a*) atisane-type alkaloids contain a [2.2.2]-bicyclo ring system with the C(15)-C(16) bridge attached at C(12)—such a ring system incorporates an *ent*-atisine skeleton, but does not obey the isoprene rule; *b*) veatchine-type possessing a [3.2.1] bicyclo ring system in a C(15)-C(16) bridge connected to C(13), forming the five membered ring D. These are modeled on a *ent*-kaurane nucleus and obey the isoprene rule; and *c*) delundine-type in which the presence of the five membered ring C in the skeleton differs from the veatchine type in that the C(15)-C(16) bridge is linked to C(11). It is difficult to explain how it could be derived from the atisane or a pimaric acid skeleton. Several hypotheses of biogenetic pathways for the formation of norditerpenoid and diterpenoid alkaloids have been postulated although detailed biosynthetic experimental studies have not been reported so far[7].

Although the isolation of the first diterpenoid alkaloid was reported in 1819[8] the structures of these complex natural products were not determined for well over hundred years. The structure of lycoctonine was established in 1956 by X-ray crystallographic studies of a degradation product[9], the results of which marked a milestone in the history of diterpenoid alkaloids. Chemical and degradative studies to establish the structures of these alkaloids almost ended in the 1970's when ^{1}H and ^{13}C nmr spectroscopy became available.

Isolation Techniques

Since the isolation of the first pure alkaloid morphine by Serturner in 1805, a variety of methods have been used for the isolation of pure alkaloids from crude plant-extracts. Many of the newer techniques include *p*H gradient extraction, preparative thin layer chromatography, gel permeation chromatography, high performance thin layer chromatography (HPTLC), high performance liquid chromatography (HPLC), vacuum liquid chromatography (VLC), centrifugally accelerated radial thin layer chromatography (Chromatotron), counter current distribution, droplet counter current chromatography (DCCC), high performance centrifugal partition chromatography (HPCPC)[10]. In our work, we have made extensive use of VLC[11], "Chromatotron"[12,13], and occasionally, HPLC[14], DCCC[15] and HPCPC[16] for the purification of alkaloids.

NMR Spectral Studies

The only systematic study of the ^{1}H nmr spectra of norditerpenoid alkaloids was published by Tsuda and Marion who established the presence of acetate and benzoate groups in aconitine, delphinine and related alkaloids[17]. The proton nmr spectra are not as useful as the carbon-13 spectra in the structure determination of these alkaloids. Jones and Benn made the initial contribution to ^{13}C nmr spectroscopy of diterpenoid alkaloids[18,19]. This technique was further developed by Pelletier and co-workers[1,2] which greatly accelerated progress in

structure elucidation of these complex natural products. Today the availability of new nmr techniques, such as 2D nmr, *n*Oe, HMBC, HMQC, COLOC and selective INEPT experiments allow structure determination of small amounts of isolated alkaloids. So far, the structures of more than 400 norditerpenoid and diterpenoid alkaloids have been established.

The structure determination of norditerpenoid alkaloids has become now straight forward, as all these alkaloids fall in the four major structure types discussed earlier and have well defined substituent and configurational patterns. In addition to these, a ^{13}C nmr "data bank" is readily available for comparison of data of alkaloids which have similar structures[1,2]. However, the structure determination of diterprenoid alkaloids (C_{20}) is more challenging because of their diverse substructures and also the fewer number of alkaloids for which the ^{13}C nmr data are available.

The general procedure for ^{13}C data acquisition and assignments of the resonances for each of the alkaloids, involved determination of the single frequency off resonance decoupled (SFORD) spectrum. The signals were assigned by means of the single frequency proton off resonance decoupling technique, direct analysis of non-protonated carbon centers, application of known chemical shift rules for substituent shifts, steric effects and comparison of spectra of closely related compounds. The first detailed studies involving COSY, and C/H correlations were carried out on 3α-hydroxy-bikhaconitine, obtained by the hydrolysis of foresaconitine (yunaconitine)[20]. We have carried out detailed nmr spectral investigations of aconitine[21], tatsidine[22], delphinine[23], dictyzine[23], ajabicine[24], andersobine[15], tatsirine[25], and many other alkaloids, which study has enabled not only the structure derivation but also the accurate chemical shift assignments in these alkaloids. Our work indicated that the study of ^{13}C nmr spectra of diterpenoid alkaloids is valuable in the determination of structures of newly isolated compounds. Also, in the case of amorphous alkaloids, where an X-ray structure determination is not possible, ^{13}C nmr spectroscopy is a very useful tool for derivation of structures.

This review concerns our work on the isolation, determination of structures, partial synthesis, transformations and spectroscopic studies of diterpenoid alkaloids isolated from plants of the *Acontium*, *Delphinium* and *Consolida* species. The chemical structures given in the review are predominantly those of new alkaloids; however, structures of known alkaloids are also given where necessary.

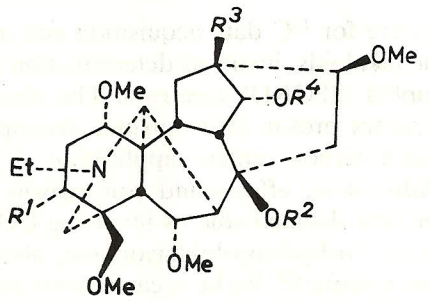
Phytochemical Studies

Aconitum balfourii

The roots of *A. balfourii* Stapf. are found in the sub-alpine and alpine Himalayas from Garhwal to Nepal between 7,500 and 14,000 ft[4] and are reported to be highly poisonous. Henry and Sharp[26] reported the isolation of pseudaconitine from *A. balfourii* and this alkaloid was first isolated in 1877 from the roots of *A. ferox* Wall[27] a species which is used in Ayurvedic medicines[4]. After a series of investigations, the structure of pseudaconitine as (**3**) was established in 1963 by Tsuda and Marion[28].

Three new norditerpenoid alkaloids, 8-O-methylveratroylpseudaconine (**4**), veratroylbikhaconine (**5**) and balfourine (**6**) were isolated from the roots, together with eight known alkaloids, pseudaconitine (**3**), veratroylpseudaconine, indaconitine, ludaconitine, 8-deacetylyunaconitine, bikhaconitine, neoline and chasmanine. Structures of the new alkaloids were determined by spectral data and chemical correlation with alkaloids of established structures[29].

From the aerial parts of *A. balfourii*, nine known norditerpenoid alkaloids: condelphine, bullatine C, neoline, isotalatizidine, 1-O-methyldelphisine, pseudaconitine (**3**), yunaconitine, bikhaconitine and indaconitine were isolated. Detailed nmr studies (^1H, ^{13}C, ^1H-^1H COSY, hetero COSY, and selective INEPT) were carried out on condelphine, neoline, isotalatizidine and indaconitine to provide chemical shift assignments for these alkaloids[30].



3 R^1 R^3= OH, R^2= Ac, R^4= Vr (Vr=Veratroyl)
4 R^1, R^3= OH, R^2= Me, R^4= Vr
5 R^1, R^2= H, R^3= OH, R^4= Vr
10 R^1= OH, R^2, R^3= H, R^4= Vr
11 R^1= OH, R^2= Ac, R^3= H, R^4= Vr
12 R^1, R^3= H, R^2= Ac, R^4= Vr
13 R^1, R^2, R^3= H, R^4= Vr
14 R^1, R^2= H, R^3= OH, R^4= As (As=Anisoyl)
18 R^1= H, R^2= Et, R^3= OH, R^4= As
19 R^1, R^3= OH, R^2= Et, R^4= As

Structures 3-5, 10-14, 18 & 19

Aconitum columbianum

A. columbianum Nutt. ssp. *columbianum* is a perennial shrub growing in the western parts of the United States. The presence of aconine and aconitine has been recorded although no reference has been cited for their original isolation[31]. Some preliminary studies on the isolation of amorphous alkaloids from the roots and assays of the toxicity to sheep and cattle have been recorded[32]. A chemical investigation of the Canadian variety reported as major alkaloids, talatizamine and cammaconine and as minor alkaloids, sachaconitine, talatizidine, isotalatizidine, 14-O-acetyltalatizamine and columbianine[34].

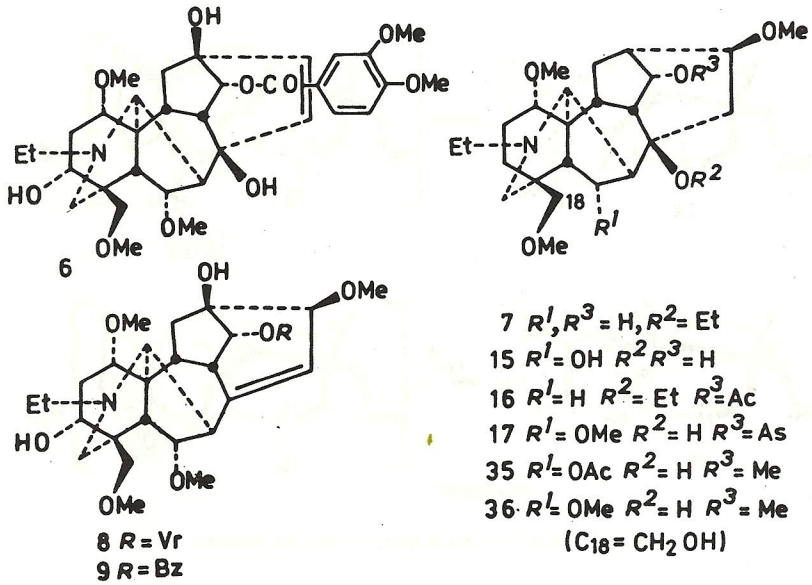
In addition to the known alkaloids cammaconine, deltaline, dictyocarpine, talatizamine and 8-O-methyltalatizamine, a new base columbidine (**7**) was isolated by us. The structure of (**7**) was derived on the basis of spectral and chemical correlation studies. Some chemical shifts of the known compounds were reassigned[35]. The 8-acetoxyl group in norditerpenoid alkaloids can be replaced by an alkoxyl group by treatment with the corresponding alcohol under reflux

or in a sealed tube at 110-130°C. 8-Acetyltalatizamine has not been isolated from a natural source and we were unable to isolate it from *A. columbianum*. Talatizamine which has an OH group at C(8), does not furnish (7) when heated with ethanol at 50°C for a prolonged period.

Aconitum falconeri

The roots of *A. falconeri* Stapf. (Hindi: *Bish, Bikh* or *Meetha Tellia*) are found in the sub-alpine and alpine regions of the Himalayas of Garhwal and are reported to be poisonous[4]. Singh *et al.* reported the isolation of alkaloids bishatisine and bishaconitine without giving any structures[36]. Pelletier *et al.* isolated two pyro-type of norditerpenoid alkaloids, falaconitine (**8**) mithaconitine (**9**)[37] apart from the known compounds, pseudaconitine (**3**), indaconitine and veratroylpseudaconine[38]. The alkaloids (**8**) and (**9**) are most probably artifacts formed by the pyrolysis of pseudaconitine (**3**) and indaconitine, during the isolation procedure.

A reexamination of the alkaloids from the roots by isolation mild conditions did not show the presence of these pyro-type alkaloids. The new alkaloids, falconerine (**10**), falconerine 8-acetate (**11**)[39], falconericine (**12**) and falconeridine (**13**) were isolated[40], in these investigations. Another alkaloid falconeridinine isolated from this plant, is probably an artifact resulting from the replacement of the 8-acetate in (**11**) with an ethoxy group. This was confirmed by refluxing (**11**) with ethanol[40].



Structures 6-9, 15-17, 35-36

Aconitum forrestii

The roots of *A. forrestii* Stapf. are used in the Chinese traditional medicine for the treatment of rheumatism. Chen and Breitmaier have reported the isolation of a foresaconitine (vilmorrianine C) from *A. forrestii* Stapf. var. *albo-*

villosum (Chen *et* Liu) W.T. Wang[41]. Our investigation of the roots resulted in the isolation of two novel norditerpenoid alkaloids forestine (**14**) and foresticine (**15**), together with the known alkaloids, chasmanine, talatizamine, and yunaconitine[42].

In another study, we isolated four alkaloids, acoforine (16), acoforesticine (17), acoforestine (**18**) acoforestinine (**19**), besides crassicauline A. The structures of these alkaloids were determined on the basis of nmr spectral data and correlation with alkaloids of established structures. The structure and stereochemistry of acoforestine (**18**) was confirmed by an X-ray crystal structure determination[43].

A few norditerpenoid alkaloids containing a methoxyl group at C(8) have been reported in the literature, e.g. alkaloid A (bicoloridine), ambiguine, puberaconitidine, sepentriosine and hokbusine A[1,2]. Columbidine is one of the alkaloids containing an ethoxyl group at C(8)[35]. The question as to whether the alkaloids containing a methoxy or an ethoxyl group at C(8) are artifacts or are present in the plant cannot be answered unequivocally without careful investigation. The precursor of acoforine (**16**) should be 8,14-diacetyltalatizamine, but this has not been isolated so far from this plant. The facile conversion of the 8-acetoxy group in some norditerpenoid alkaloids to the 8-alkoxy compounds can be considered as synchronous fragmentation process such as described by Grob[44]. The free electron pair of the nitrogen atom is oriented anti and parallel (anti-periplanar) with respect to the C−C bond which undergoes cleavage as shown in Fig. 1.

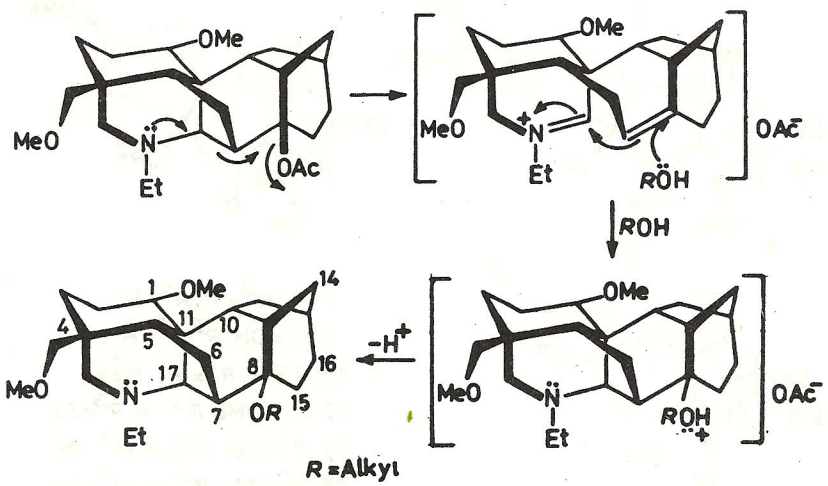
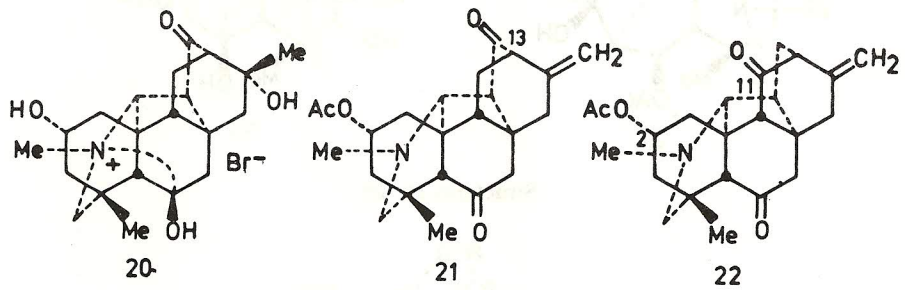


Fig 1 Synchronous fragmentation mechanism

Aconitum heterophylloides, Aconitum paniculatum

An amorphous alkaloid heterophylloidine was isolated by Pelletier *et al.*[45], from the Indian plant *A. heterophylloides* Stapf. On the basis of an X-ray analysis of a bromo derivative (**20**), the structure and absolute configuration were assigned to heteropyhylloidine (**21**). Later, Katz and Staehelin isolated panicutine

from *A. paniclatum* and proposed the structure (**22**) for this alkaloid on the basis of uv, ^{1}H and ^{13}C nmr[46]. By comparison of the samples we have shown that the alkaloids heterophylloidine and panicutine are identical. Location of the keto-groups at C(6) and C(13) was confirmed by CD measurements[47].



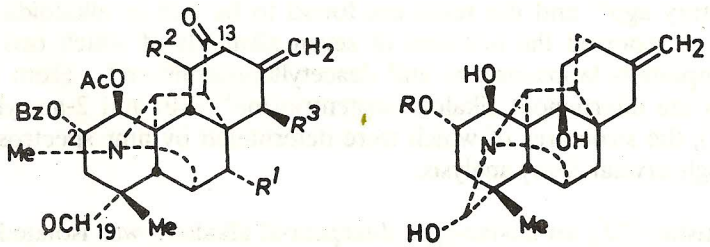
20 21 22

Structures 20-22

Aconitum palmatum

The species *A. palmatum* D. Don. (Hindi: Vakhma) occurs in the alpine Himalayas of Nepal, Sikkim at elevations of 10,000-16,000 ft and the roots are reported to be non-poisonous. They are used in the Ayurvedic medicine as a tonic, and in the treatment of diarrhoea and rheumatism[4]. The isolation of five diterpenoid alkaloids: vakognavine, palmatisine, vakatisine, vakatisinine and vakatidine was reported without assigning any structures[48]. The structure of vakognavine (**23**) was based on an X-ray crystal structure determination[49]. Later publications were concerned with chemical and spectral confirmation of (**23**)[50,51] and that of vakatisine[52].

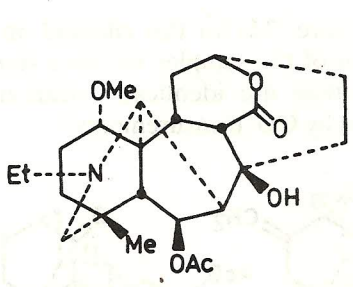
Six new diterpenoid alkaloids 15-deacetylvacognavine (**24**), palmadine (**25**), palmasine (**26**), 6-acetylheteratisine, (**27**), vakhmatine (**28**), and vakhmatine (**29**) together with the known alkaloids vakognavine, heteratisine, isoatisine, hetisine and hetidine, were isolated from the roots[53,54]. Palmadine (**25**) and palmasine (**26**) are the first examples of diterpenoid alkaloids (C_{20}) bearing a cinnamoyl group.



23 R^1 = H, R^2 = α-OAc, R^3 = OAc
24 R^1 = H, R^2 = α-OAc, R^3 = OH
48 R^1 = OAc, R^2 = β-OH, R^3 = H

30 R = H
31 R = Ac

Structures 23-24, 31 & 48



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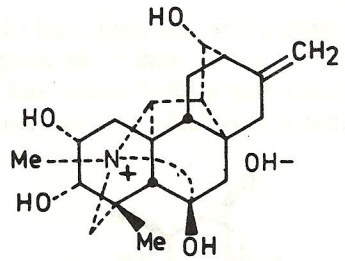

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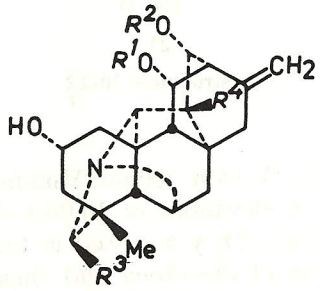
Structures 27, 29



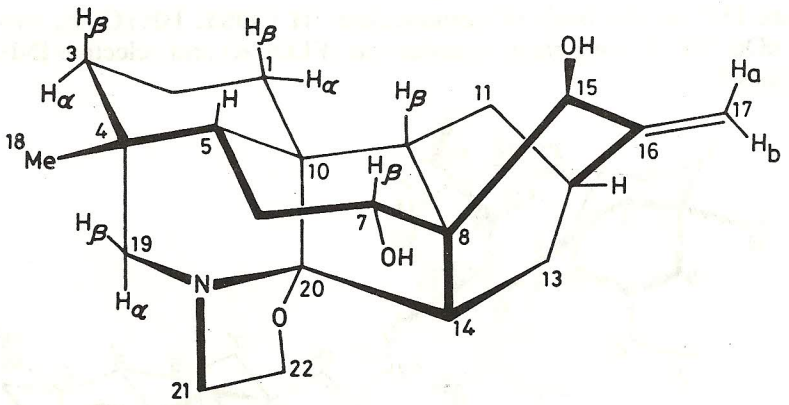
25 R^1= Ac, R^2= CO-CH=CH-Ph, R^3, R^4= H
26 R^1= H, R^2= CO-CH=CH-Ph, R^3, R^4= H
28 R^1, R^2, R^4= H, R^3= OH
37 R^1, R^2, R^3= H, R^4= OH
39 R^1, R^4= H, R^2= Ac, R^3= OH

Structures 25, 26, 28, 37 & 39

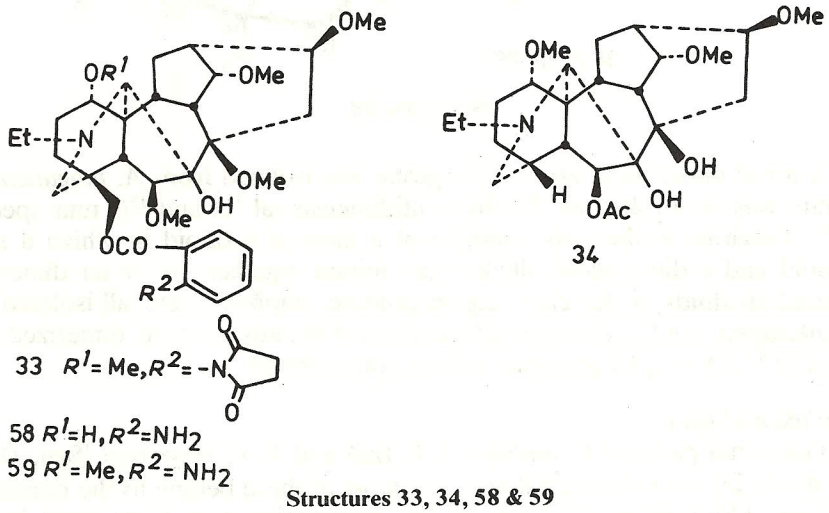
Aconitum septentrionale

The presence of alkaloids in *A. septentrionale* Koelle was recorded more than a century ago[55] and the roots are found to be rich in alkaloids. In 1967, Marion *et al.* reported the isolation of seven alkaloids of which two were the known compounds lappaconitine and deacetyllappaconitine[56]. From the roots, we isolated the diterpenoid alkaloid septentriosine[57] (**30**) and 2-acetylseptentriosine[58] (**31**), the structures of which were determined by nmr spectroscopic data and a single crystal X-ray analysis.

Septatisine (**32**), an atisine-type diterpenoid alkaloid, was isolated from the roots of *A. septentrionale.* Its structure was established on the basis of ^{1}H COSY, LRCOSY, NOESY, DNOE, fixed-evolution HETCOR and selective INEPT nmr techniques[59]. It is noteworthy that septatisine (**32**) is the only example of an atisane-type diterpenoid alkaloid in which the C(20) carbon of the oxazolidine ring is bridged with C(14). In the case of atisine, the oxazolidine ring gives rise to a mixture of inseparable epimers differing in configuration at C(20)[60].



Structures 32



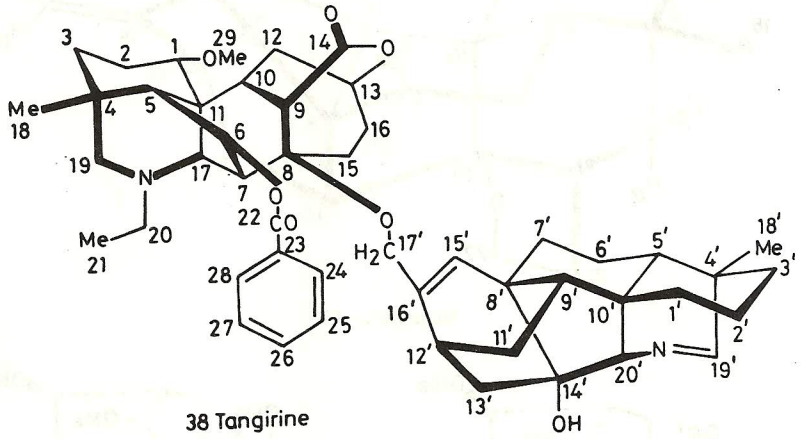
Structures 33, 34, 58 & 59

Four norditerpenoid alkaloids, 8-O-methyllycaconitine (**33**), 6-O-acetylacosepticine (**34**), acoseptrigine (**35**), acoseptriginine (**36**) and seven known alkaloids: *N*-acetylsepaconitine, *N*-deacetyllappaconitine, lapaconidine, lappaconine, lappaconitine, lycoctonine and puberaconitine, were isolated from the roots[61]. By the ion exchange method, eight norditerpenoid alkaloids: acosepticine, acoseptridine, acoseptridinine, acoseptrine, acoseptrinine, 4-anhydroanthranoyllappaconidine, 6-demethyldelphatine, and 14-O-methylforesticine, along with seven known alkaloids were isolated. Their structures were derived on the basis of nmr spectral data[62].

Aconitum tanguticum

A. tanguticum (Maxim.) Stapf. W.T. Wang had been reported to contain the known alkaloids atisine, heteratisine, benzoylheteratisine and tanwusine; the structure of the last alkaloid was not determined[63]. From the same species, a new diterpenoid alkaloid tangutisine was isolated and it has been assigned the

structure (**37**) on the basis of homonuclear ^{1}H COSY, HETCOR, two dimensional *n*Oe, ^{1}H-^{13}C long range correlations (FLOCK) and selective INEPT nmr techniques[64].



Structures 38

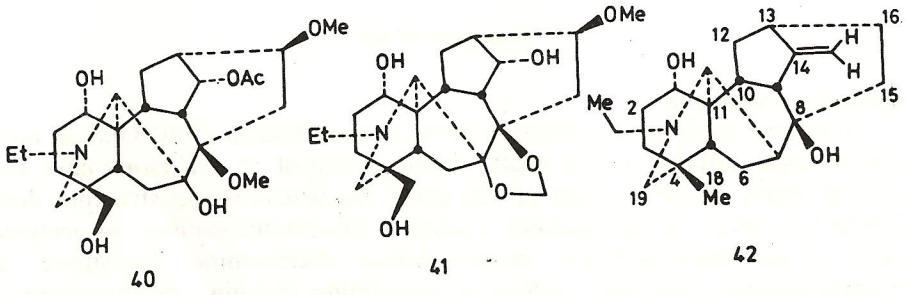
A novel diterpenoid alkaloid tangirine was isolated from *A. tanguticum*. Its structure was established as (**38**) by multidimensional ^{1}H and ^{13}C nmr spectroscopy[65]. Tangirine is the only example of a dimeric alkaloid in which a norditerpenoid and a diterpenoid alkaloid are joined together. Six other dimeric diterpenoid alkaloids of this class: e.g. staphidine, staphisine, etc. all isolated from *D. staphisagria*, are C_{20} diterpenoid alkaloids of the atisane-type, dimerized at the C(17), C(17′), O(15′), 16 positions to form spiro ethers[3].

Consolida ambigua

The aerial parts of *C. ambigua* L.P. Ball and V. H Heywood (Syn. *Delphinium ajacis* Li) are rich in alkaloids, and most of these belong to the norditerpenoid-type. Thirty-three alkaloids of the lycoctonine-type have been isolated from the seeds and various parts of this plant. These are: 14-acetylbrowniine, 14-acetyldelcosine, 14-acetyldelectine, ajacine, ajacusine, ajadelphine, ajadine, ajadinine, ajanine, ambiguine, anthranoyllycoctonine, browniine, 14-deacetylajadine, 14-deacetylambiguine, delajacine, delajacirine, delajadine, delcosine, deltaline, deltatsine, gigactonine, lycoctonine, 18-methoxygadesine, methyllycaconitine, 19-oxoanthranoyllycoctonine, 19-oxodelphatine, and takaosamine[1,2]. Two diterpenoid alkaloids (C_{20}) isolated from the seeds are ajaconine and dihydroajaconine. From the seeds of *C. ambigua* vakhmatine (**28**) and the new alkaloid 13-O-acetylvakhmatine (**39**), were isolated. The structure (**39**) was established on the basis of spectroscopic data and chemical correlation with (**28**)[16]. Two new norditerpenoid alkaloids ajadelphine (**40**) and ajadelphinine (**41**) were isolated from the roots of C. *ambigua* and their structures established with the aid of nmr spectral data[66].

The structure of ajabicine, a novel diterpenoid alkaloid ($C_{22}H_{33}NO_2$) isolated from the seeds of *C. ambigua* has been established as (**42**), on the basis of

^{1}H, ^{13}C, COSY, HETCOR, selective INEPT and FLOCK nmr experiments. To date more than 250 norditerpenoid alkaloids (C_{19}) have been shown to possess the hexacyclic ring skeleton comprised of one seven membered, three six membered and two five membered rings as in (**1**). On the other hand, the entire group of over 150 naturally occurring diterpenoid alkaloid (C_{20}) are found to be pentacyclic (atisane-type) or hexacyclic, containing a bicyclo[2.2.2]octane or bicyclo[3.2.1]octane (veatchine-type) ring system.



Structures 40-42

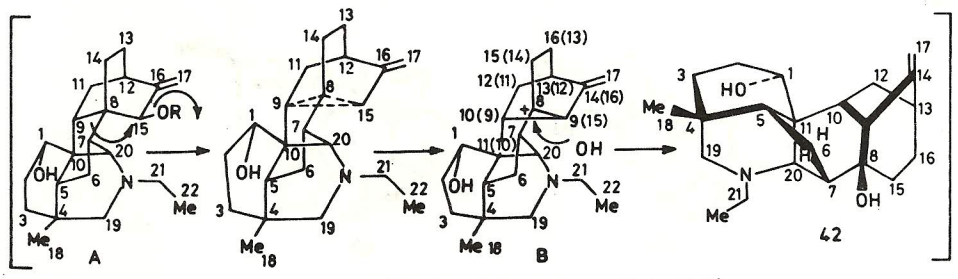
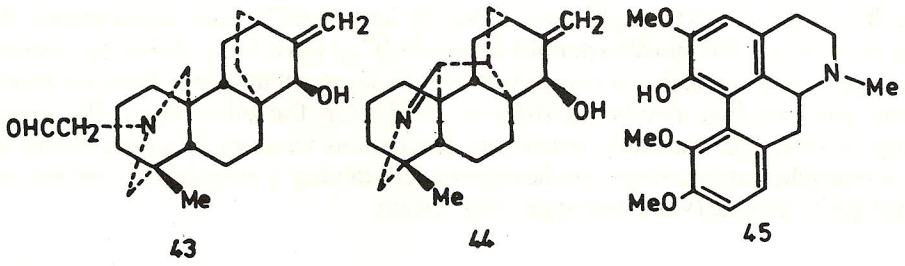


Fig 2

The biogenesis of ajabicine (**42**) may be assumed to proceed through a rearrangement of the fused bicyclo[2.2.2]octane **A** to give the bicyclo[3.2.1]octane rearrangement product (**42**) via the homo allylic carbocation **B** which on hydration gives (**42**) as shown in Fig. 2[24]. There are many precedents in the literature for the rearrangement of a bicyclo[2.2.2]octane system to the bicyclo[3.2.1]octane[67].

Consolida hellespontica

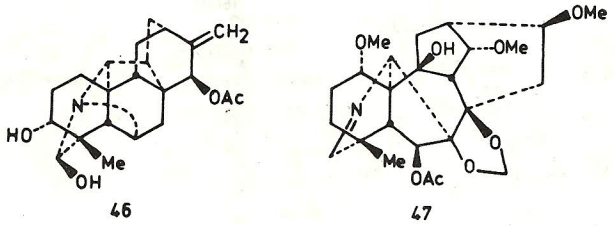
From the aerial parts of *C. hellespontica* (Boiss) Chater we isolated the new diterpenoid alkaloids chellespontine (**43**) and azetidine (**44**). The norditerpenoid alkaloid 1-O-methyldelphisine has not been reported earlier to be occurring in nature and the aporphine alkaloid (+)-corydine (**45**) was isolated for the first time in the Ranunculaceae family. Besides these, the known alkaloids delphinine, delphisine, and bullatine C (14-acetylneoline) have been isolated from this plant. The structures of these alkaloids were determined by chemical correlation and spectroscopic studies[68].



Structures 43-45

Delphinium andersonii

D. andersonii Gray is a shrub growing in the 'Wildcat Hills' Utah at an altitude of about 4800 ft. Cattle deaths from grazing of *D. andersonii* have been observed. From the aerial parts of this plant, the isolation and structure determination of sixteen norditerpenoid alkaloids: 14-acetylbrowniine, 14-acetyldelcosine, 14-acetylnudicaulidine, andersonidine, andersonine, browniine, 14-deacetylnudiculine, delavaine, delcosine, delectinine, deltaline, dictyocarpine, lycoctonine, methyllycaconitine, nudicauline and takaosamine have been reported[69].



Structures 46 & 47

An investigation of the minor alkaloidal constituents of *D. andersonii* by droplet counter current chromatographic separation led to the isolation of a new, polar diterpenoid alkaloid andersobine (**46**). Its structure was established on the basis of ^{1}H, ^{13}C, ^{1}H homonuclear COSY, HETCOR, one dimensional *n*Oe, 2D *n*Oe and selective INEPT nmr spectral studies. Two separate attempts to solve the structure of andersobine and its 4-dimethylaminobenzoate ester were unsuccessful, in spite of the availability of suitable crystals[15].

Delphinium barbeyi

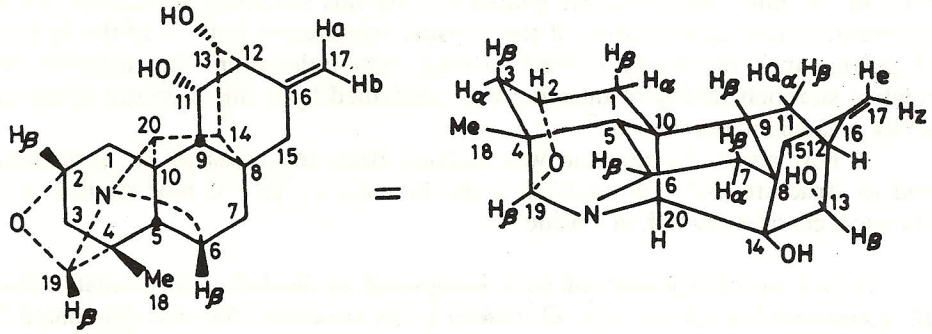
The occurrence of anthranoyllycoctonine, delphinine, deltaline, dictyocarpine and lycoctonine from *D. barbeyi* Huth (*D. glaucum* S. Watts) was reported in earlier literature[70,71]. From the ethanolic extract of *D. barbeyi* Huth, a novel norditerpenoid alkaloid barbeline (**47**) was isolated and its structure determined by spectroscopic data and an X-ray crystal diffraction study. Barbeline was the first example of an alkaloid containing a C(19)=N-azomethine group among the 230 naturally occurring norditerpenoid alkaloids. Two new alkaloids,

6-acetyldelpheline and 6-deoxydelpheline and the known alkaloids browniine, delphatine and glaucenine were also isolated from this plant[72].

The structure and stereochemistry of barbesine (**48**) a new diterpenoid alkaloid from *D. barbeyi*, were deduced by a combination of nmr spectroscopy and a single crystal X-ray diffraction analysis[73].

Delphinium elatum

D. elatum L. has proven to be a rich source of norditerpenoid and diterpenoid alkaloids. Delpheline, deltaline, deltamine, elatine, and methyllycaconitine were isolated from the whole plant. However, the following norditerpenoid (*i-xiv*) and diterpenoid (*xv*) alkaloids were found to be present in the seeds: *i*) 14-acetylnudicauline, *ii*) delectinine, *iii*) delelatine, *iv*) delpheline, *v*) deltaline, *vi*) eladine, *vii*) elanine, *viii*) elsasine, *ix*) elatine, *x*) isodelpheline, *xi*) lycoctonine, *xii*) methyllycaconitine, *xiii*) nudicauline, *xiv*) pacinine and *xv*) ajaconine[1,2].



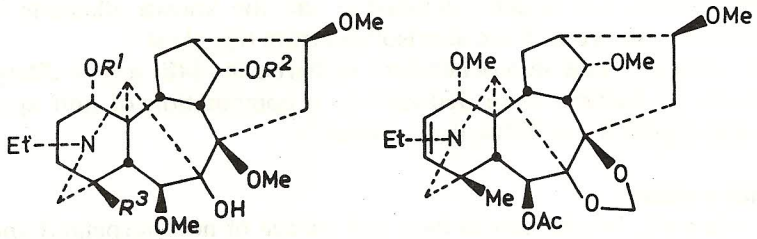
49

Structures 49

Chemical investigation of the seeds of *D. elatum* L. resulted in the isolation of a new diterpenoid alkaloid delatisine whose structure (**49**) was established by ^{1}H COSY, long range COSY, HETCOR, 2D *n*Oe, fixed evolution HETCOR and selective INEPT experiments. The structure of the alkaloid was confirmed by an X-ray crystal structure determination[74]. A number of diterpenoid alkaloids possessing an oxide ring between C-1 and C-19 have been isolated; e.g. dehydroluciduscuIine, 12-acetyldehydroluciduscuIine, dehydronapelline, songoramine, and subdesculine. The structure of delatisine is unusual in that there is no other diterpenoid alkaloid which contains an oxygen bridge between C-2 and C-19 to form a furan ring.

Delphinium tatsienense

No work was reported earlier on the chemical constituents of the Chinese plant *D. tatsienense* Franch. Two novel norditerpenoid alkaloids, deacetylambiguine (**50**) and tatsiensine (**51**) were isolated. The structure of tatsiensine was established on the basis of spectroscopic data and correlation with delpheline. The known norditerpenoid alkaloids browniine, delcosine, lycoctonine and the diterpenoid alkaloids ajaconine, hetisine and hetisinone were also isolated[75].



50 R^1=Me, R^2=H, R^3=CH_2OMe 51

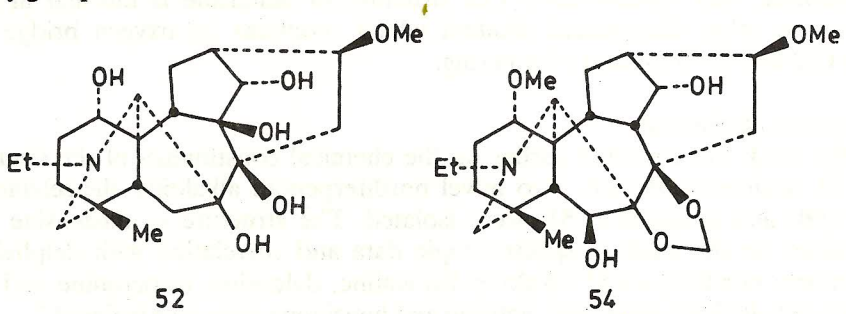
53 R^1, R^2=H, R^3=CH_2OMe

Structures 50-51 & 53

A novel highly polar norditerpenoid alkaloid designated as tatsinine was isolated from the roots of *D. tatsienense* and its structure (**52**) was derived from ^1H and ^{13}C nmr spectroscopic evidence[76]. As this structure dependend purely on spectral data, and because of the unusual substitution pattern of the hydroxyl groups, an X-ray crystal diffraction study was undertaken. The structure and relative stereochemistry of tatsinine was confirmed by a single crystal X-ray analysis of tatsinine perchlorate[77].

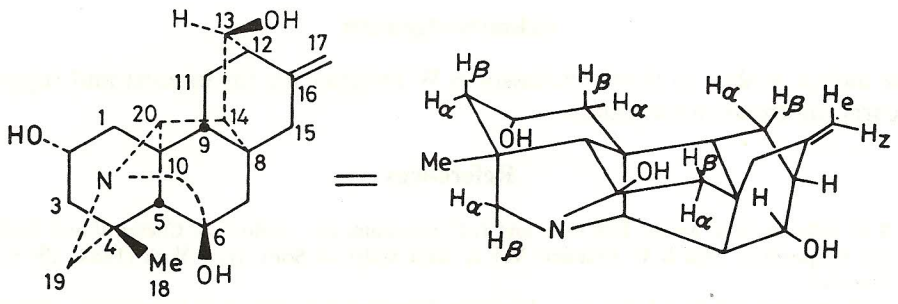
A new alkaloid deltatsine was isolated from the roots of *D. tatsienense* and its structure (**53**) was established on the basis of ^1H, ^{13}C nmr studies and a chemical correlation with delcosine[78].

A new norditerpenoid alkaloid designated as delelatine was isolated from *D. tatsienense* Franch and also *D. elatum* L. Its structure (**54**) was elucidated by spectroanalytical methods. Delelatine was correlated with 14-acetyl-10-deoxydictyocarpine and synthesized from dictyocarpine, thus confirming its structure and stereochemistry[79]. By chromatographic separation on silica gel rotors, another norditerpenoid alkaloid tatsidine was isolated from the *p*H 8 alkaloidal fractions of *D. tatsienense* Franch[80]. Homonuclear ^1H COSY, long-range COSY, and relay coherence transfer correlation spectroscopy nmr experiments were used together with fixed evolution HETCOR and selective INEPT spectra for complete ^{13}C and ^1H spectral peak assignments for tatsidine (**55**). Stereochemical and conformational assignments were made from the two dimensional *n*Oe spectrum. The results of these studies confirmed the location of the methylenedioxy group at C7/C-8[81].



52 54

Structures 52-54



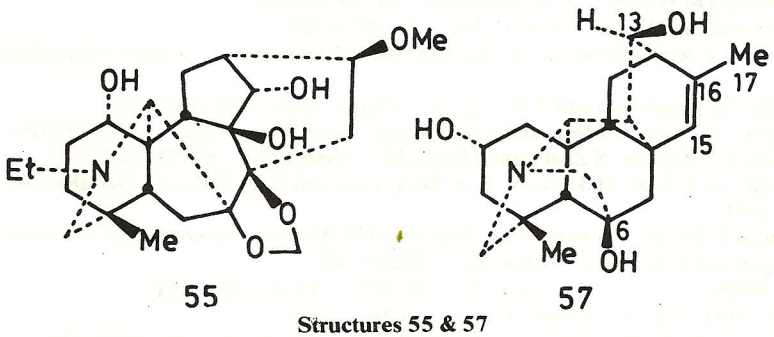
56

Structures 56

Tatsirine, isolated from the roots *D. tatsienense* Franch was assigned the structure (**56**). The structure was established on the basis of ^{1}H COSY, fixed evolution HETCOR, two-dimensional *n*Oe and selective INEPT studies on (**57**)[82]. There are very few hetisane-type diterpenoid alkaloids in which a hydroxyl group at C-13 is located in a β-position (equatorial hydroxyl in the boat conformation of ring formed by carbons 8, 9, 11, 12, 13, 14). Two examples are spirasine XIII and spirasine XV, isolated from *Spirea japonica* L. var. *fortunei* (Pl.) Rehd. (Rosaceae)[83]. The facile isomerization of the exocyclic double bond of tatsirine (**56**) to afford (**57**) can be explained by the formation of a carbonium ion (with traces of HCl from $CDCl_3$), which is stabliszed with the suitably placed β-hydroxyl group to form an oxitane. On alumina, the more stable isomer is readily formed by loss of a proton from C-15.

Delphinium vestitum

D. vestitum Wall. groups in the Western Himalayas and inner Tibetan valleys at elevations of 10,000-12,000 ft and is reported to be poisonous to goats[4].



55 57

Structures 55 & 57

An earlier investigation reported the isolation of two weak bases one of which on saponification gave lycoctonine[84]. Our investigation of the aerial parts of the *D. vestitum* gave two new norditerpenoid alkaloids delvestine (**58**) and delvestidine (**59**)[85]. The structures were based on nmr spectral evidence and chemical conversion to known alkaloids. An X-ray crystallographic study of delvestine confirmed the structure and stereochemistry of the alkaloid as (**58**)[86].

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