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Diterpenoid Alkaloids

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Reviewing the literature published between July 1983 and June 1985

(Continuing the coverage of literature in *Natural Product Reports*, 1984, Vol. 1, p. 375)

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1 Introduction

Current research interest in the diterpenoid alkaloids has been focused primarily on their presence in traditional medicinal preparations. Therefore, some of the toxicological and pharmacological studies are discussed in this review, particularly those related to phytochemical analyses. Thirty-one new diterpenoid alkaloids have been identified in studies of plant materials from *Aconitum* and *Delphinium* species. Synthetic efforts toward these complex bases have remained at a low level over the past five years. While no biosynthetic studies have been reported, several papers have included speculation on the biotransformations of these alkaloids, based on phytochemical analyses. No chemical studies of the *Daphniphyllum* alkaloids have been reported.

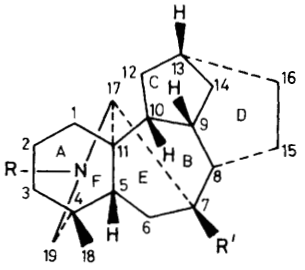
A noteworthy historical perspective that has appeared is Professor Karel Wiesner's summary of his research on the diterpenoid alkaloids.[1] A practical review of the techniques for the isolation of these and other alkaloids has been published.[2] Since the proper botanical identification of materials under investigation is a key requirement for legitimate phytochemical analyses, two recent descriptions of species of *Aconitum* and *Delphinium* should be examined by researchers in this area. Wang[3] has reviewed the botanical identification of Chinese species of the Ranunculaceae. These species include *Aconitum alboflavidum* W. T. Wang, *A. laevicaule* W. T. Wang, *Delphinium altissimum* Wall., *D. yanwaense* W. T. Wang, *D. pergameneum* W. T. Wang, *D. lasiantherum* W. T. Wang, *D. pseudohamatum* W. T. Wang, and *D. autumnale* Hand.-Mazz. Brink[4] has reviewed the *Aconitum* species of the continental United States of America.

The numbering systems for the aconitine, lycoctonine, atisine, and veatchine skeletons are indicated in structures (A), (B), (C), and (D), respectively. The following abbreviations are used: Ac = acetyl, Bz = benzoyl, As = anisoyl, Ms = mesyl.

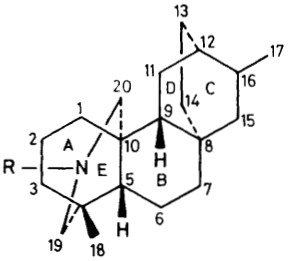
2 General Studies

2.1 Toxicology and Pharmacology

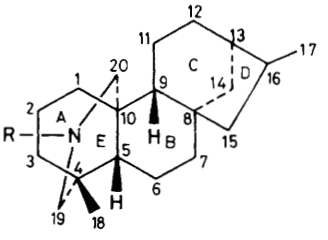
In the western United States of America, species of *Delphinium* have a long history of causing significant problems to range management, associated with the poisoning of cattle and sheep. In a recent study of the tall duncecaps larkspur (*D. occidentale* S. Wats.), the total alkaloid content of the plant material has been correlated with its toxicity in mice.[5] The percentage of total alkaloids in the samples decreased over the growing season. The toxicity (LD_{50}) in mice changed in an exponential relationship with the total alkaloid content. Because of the differences in toxicity and alkaloid profile of different species of larkspur, the mouse bioassay was predicted to correlate better than the total alkaloid content with the toxicity of each



(A) Aconitine skeleton, R′= H
(B) Lycoctonine skeleton, R′ = OH



(C) Atisine skeleton
(R = Me or Et)



(D) Veatchine skeleton

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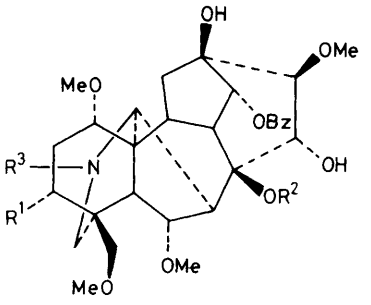
species to cattle. However, chromatographic analytical correlation of specific alkaloid compositions was not addressed in this research. Given the significant differences in toxicity of these bases, chromatographic profiles with appropriate toxicity weighting factors might be a viable alternative to the bioassay.

Kitagawa and co-workers[6] have published studies on the anti-inflammatory and analgesic effects of several diterpenoid alkaloids. These studies include measurements of LD_{50} [mg per kg, subcutaneous, in mice] for the fatty acid esters of the diterpenoid alkaloids lipoaconitine (1) [100—200], lipohypaconitine (2) [>400], lipomesaconitine (3) [10—40], and lipo-3-deoxyaconitine (4) [100—200] as compared with aconitine (5) [0.5—2.0] and mesaconitine (6) [0.25—1.0]. Of the lipo-bases, only (3) showed significant anti-inflammatory effects on carrageenin-induced oedema in rats and significant analgesic activity in the mouse/acetic acid writhing assay. These authors concluded that the substitution of a fatty acid moiety for the acetyl group at C-8 may decrease the toxicity and improve the therapeutic ratios. More importantly, because of their different solubilities and chromatographic properties, the presence of alkaloid derivatives that are analogous to these lipo-bases may have been overlooked in other plant materials.

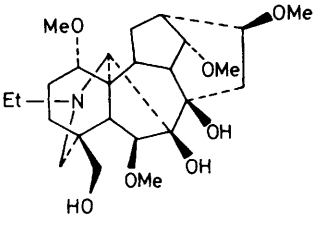
Two studies of the toxicity of Chinese *Aconitum* species and their alkaloids have appeared.[7,8] In their investigations on twenty-seven species of *Aconitum*, Xiao, Wang, and Tong[7] included correlations of the root morphology, plant phylogeny, major identified diterpenoid alkaloid constituents, and toxicity. These species were divided into eight types. Roots of the niu bian (*A. apetalum*, *A. scaposum*, *A. sinomontanum*, and *A. barbatum* var. *puberulum* Ledeb.), xiao wutou (*A. naviculare*), and kuan baifu (*A. coreanum*) types contain primarily monoesterified C_{19}-bases [*e.g.* lycoctonine (7) and lappaconitine (8)] or the C_{20}-alkaloids [*e.g.* atisine (9) and heteratisine (10)]. These preparations had relatively low toxicities, with values of LD_{50} (intravenous) in mice ranging from 1600 to 3400 mg per kg of body weight. Of intermediate toxicity were plants of the baoshan wutou type (*A. subrosulatum*, *A. dulouxii* var. *ecalcaratum*, and *A. hicksii*). These contained neoline (11) as the major identified alkaloid and the values of LD_{50} ranged from 215 to 261 mg per kg. The most toxic plant materials belonged to the da wutou type (*A. franchetii*, *A. forrestii*, *A. taipaicum*, *A. transsecium*, and *A. kongboense*), the teng wutou type (*A. hemsleyanum*, *A. crassicaule*, *A. vilmorrianum*, *A. austroyunanense*, and *A. sungpanense*), the caowu type (*A. carmichaeli*, *A. kusnezoffii*, *A. paniculigerum* var. *wulingense*, *A. karakolicum*, and *A. jaluense* var. *glabrescens*), and the xueshang yizhihao type (*A. brachypodum*, *A. polyschistum*, and *A. pendulum*). These plants contained alkaloids with an acetoxy-group at C-8 and benzoyloxy or anisoyloxy functions at C-14 [*e.g.* aconitine (5) and yunaconitine (12)]. The values of LD_{50} of these root preparations varied from 24 to 283 mg per kg. The LD_{50} data in mice for eleven pure alkaloids were also presented, with yunaconitine (12) being the most toxic compound that was tested. The cardiotoxicity of aconitine (5) and nine of its analogues has been studied.[8] Data for LD_{50} (intravenous) in mice, for the absolute lethal dose in rats, and for the induction of arrhythmia were reported. Aconitine was the most toxic compound in their test system. From these data, several generalizations regarding structure–activity relations were made. The toxicity of these alkaloids is primarily associated with the presence of the 8-acetoxy and 14-benzoyloxy functions. In addition, the 14-benzoyloxy-group is essential for the induction of arrhythmia. All of the alkaloids that were tested, except aconitine, reduced blood pressure and inhibited myocardial contraction. With aconitine, no such activities were observed before arrhythmia appeared. Heart rate was not affected by any of these bases at the doses that were administered. These researchers concluded that aconitine and related alkaloids showed no beneficial effects on cardiac contractive functions.

In other studies of the effects of aconitine on cardiovascular functions, doses of 1—10 μg, when injected into the locus

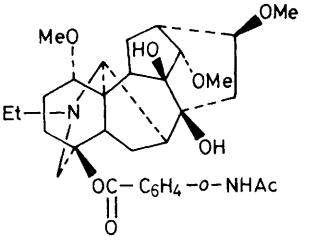


		R^1	R^2	R^3
Lipoaconitine	(1)	OH	FA	Et
Lipohypaconitine	(2)	H	FA	Me
Lipomesaconitine	(3)	OH	FA	Me
Lipo-3-deoxyaconitine	(4)	H	FA	Et
Aconitine	(5)	OH	Ac	Et
Mesaconitine	(6)	OH	Ac	Me
Benzoylaconine	(18)	OH	H	Et
Hypaconitine	(19)	H	Ac	Me
Benzoylhypaconine	(20)	H	H	Me
Benzoylmesaconine	(21)	OH	H	Me
3-Deoxyaconitine	(23)	H	Ac	Et

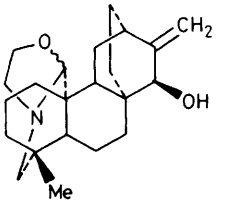
(FA = linoleoyl, palmitoyl, oleoyl, stearoyl, or linolenoyl)



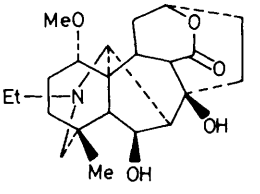
Lycoctonine (7)



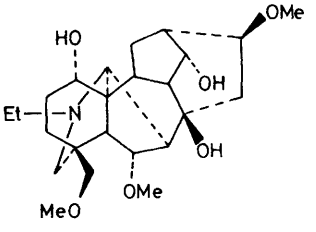
Lappaconitine (8)



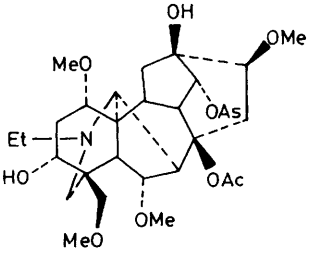
Atisine (9)



Heteratisine (10)



Neoline (11)



Yunaconitine (12)

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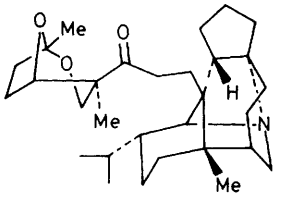
ceruleus of unanaesthetized, unrestrained rats, increased heart rates and blood pressure and caused arrhythmia.[9] The authors concluded that these effects may involve α-adrenergic and serotoninergic mechanisms. In a study of the effects of aconitine and veratrine on isolated perfused heart cells of the eel *Anguilla anguilla* L., Pennec and Aubin[10] observed that, at concentrations of less than 10^{-6} mol dm^{-3}, aconitine decreased heart rate, whereas at concentrations greater than 10^{-6} mol dm^{-3} it produced tachycardia and led to a depolarization of the cells. In a study of the inhibition of pig heart aconitase by aconitine *in vitro*, this inhibition was shown to be highly specific and totally non-competitive.[11] From these observations it was suggested that the toxic and pharmacological activities of aconitine in causing auricular fibrillation and tachycardia could be attributed to the inhibition of aconitase in the heart. In addition, the results of this work suggest that the aconitine-type alkaloids may play a metabolic role of inhibition of aconitase during the flowering of aconite species by increasing the production of fatty acids from an increased pool of acetyl-coenzyme A.

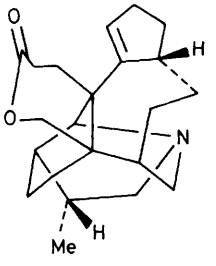
Chen[12] has reviewed the biological activities of the diterpenoid alkaloids and presented a summary of the reported values of LD_{50} for fifty four of these compounds. In research on the synaptosomal sodium channels of the brain of the mouse, aconitine was shown to be an activator of the voltage-dependent sodium channel.[13] A review on modifications of sodium channel, including the work with aconitine, has appeared.[14] Traditional Oriental medicines that contain aconitine alkaloids have been used for the stimulation of metabolic functions in feeble patients. Murayama and Hikino[15] have studied the effects of mesaconitine on the incorporation of orotic acid into liver nuclear RNA. These data support the conclusion that the aconitine alkaloids can accelerate the synthesis of RNA in the liver primarily by their effects on the increase in RNA polymerase.

Many plants of the Daphniphyllaceae are hepatotoxic. The daphniphyllum diterpenoid alkaloids have been isolated from some of these species, and their toxicities correlate with the toxic effects of the plant materials. In studies of the potential for other chronic toxic effects, the mutagenicities of five of the alkaloids were studied.[16] None of these compounds [codaphniphylline (13), daphnilactone-B (14), yuzurimine (15), yuzurimine-C (16), or deoxy-yuzurimine (17)] exhibited mutagenic activity in Ames-type assays against *Salmonella typhimurium*.

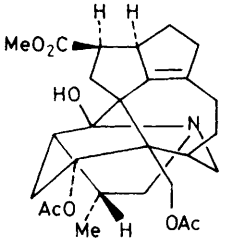
In work to develop haemosorbent therapies for detoxification of several toxins, researchers in the USSR have reported studies of the use of macroporous, spherical carbon granules and porous carbon fibres for the haemosorption of lidocaine, which is used as an antidote to poisoning by aconitine.[17]



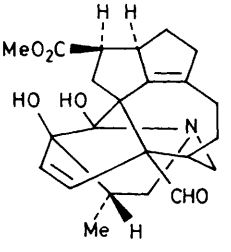
Codaphniphylline (13)



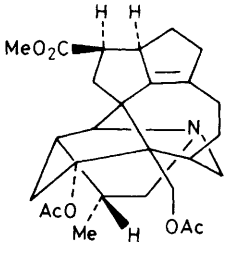
Daphnilactone-B (14)



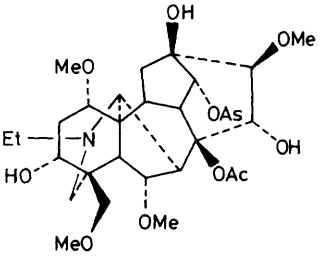
Yuzurimine (15)



Yuzurimine-C (16)



Deoxy-yuzurimine (17)



Jesaconitine (22)

[Structures (18)–(21) and (23) are with structure (1)]

2.2 Analytical Methodology

To study the use of plant materials that contain the diterpenoid alkaloids as traditional medicines and to ensure some control of the quality of these preparations, adequate methods of analyses for these compounds are required. Given the differences in toxicity of these alkaloids and the wide variabilities in their natural concentrations, such information can be literally vital. Two high-performance liquid-chromatographic procedures have been developed to characterize these alkaloids in traditional medicinal preparations. Kitagawa and co-workers[18] have developed a quantitative procedure for the determination of the ten aconitine alkaloids aconitine (5), benzoylaconine (18), hypaconitine (19), benzoylhypaconine (20), mesaconitine (6), benzoylmesaconine (21), lipoaconitine (1), lipohypaconitine (2), lipomesaconitine (3), and lipo-3-deoxyaconitine (4). This procedure includes extraction of the dried root material with methanol, partitioning into chloroform from ammonium hydroxide, column chromatography with chloroform on aluminium oxide, followed by chromatography on a C_{18} reverse-phase mini-column with methanol and methanol–water as eluants. The h.p.l.c. measurements were accomplished on a CN-bonded phase column with CH_3CN–0·01M-dibutylamine phosphate as the mobile phase, using ultraviolet detection (at 254 nm). Recoveries for the ten alkaloids in fortified samples ranged from 95 to 100%.

Nakano and Yamagishi[19] developed a procedure in which extracts into dilute HCl (pH 3) were passed through a C_{18} reverse-phase mini-column. After washing the column with aqueous methanol and aqueous acetonitrile, the alkaloids were eluted from the column with methanol. The methanol eluate was analysed by h.p.l.c., using a C_{18}-bonded phase column (of particle size 5 μm) with H_2O–THF–MeCN–citric acid (80 : 15 : 5 : 1) as the mobile phase and ultraviolet detection (at 250 nm). The concentrations of mesaconitine (6) hypaconitine (19), aconitine (5), and jesaconitine (22) in the traditional medicines 'bushi' and 'uzu' were measured by this procedure.

Wang, Li, and Gao[20] have reported a more rapid procedure, using h.p.l.c. as the determination step, for screening the alkaloid content of root materials. After treatment with ammonium hydroxide, the powdered sample was extracted with diethyl ether. This extract was evaporated to dryness and β-methylnaphthalene was added to the residue as an internal standard. This mixture was dissolved in methanol. An aliquot of the resulting solution was analysed by h.p.l.c. on a C_{18}-bonded phase column with a mobile phase of MeOH–H_2O–$CHCl_3$–Et_3N (70 : 30 : 2 : 0.1). The recoveries of aconitine (5), mesaconitine (6), and hypaconitine (19) from fortified samples were 99.3, 97.4, and 97.2%, respectively. Using this method, specimens of *A. carmichaeli* from different sources were found to contain from 0.002 to 0.024% aconitine (5), from < 0.001 to 0.094% mesaconitine (6), and from 0.001 to 0.208% hypaconitine (19). In root materials from *A. kusnezoffii*, the concentra-

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tion of (5) varied from 0.028 to 0.055%, of (6) from 0.105 to 0.578%, and of (19) from 0.019 to 0.171%.

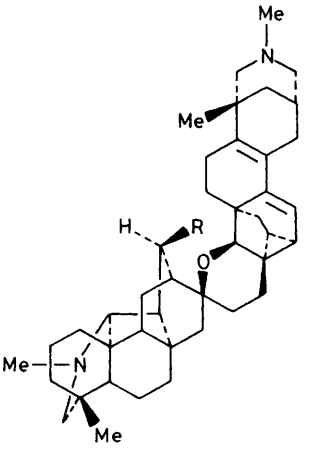
Japanese workers[21] have employed thin-layer procedures to screen for diterpenoid alkaloids, including the fatty acid derivatives, in processed *Aconitum* root material. The powdered sample was treated with chloroform that was saturated with ammonium hydroxide, at room temperature. The chloroform extract was chromatographed on silica gel 60 F_{254} plates with cyclohexane–AcOEt–Et_2NH (10 : 5 : 1) and the alkaloids were visualized with Dragendorff reagent for a qualitative identification. Quantitative determinations were made by using a dual-wavelength (excitation at λ = 250 nm, emission at λ = 400 nm) densitometer.

Assays for the total alkaloids and for aconitine in root materials that are used in traditional Chinese medicine have been reported.[22] For the determination of the total alkaloids, an acid–base titration procedure was used. The alkaloids were extracted from the root material with NH_4OH–diethyl ether. A solution (in ethanol–water) of the residue from the ether extract and methyl red/methylene blue was titrated with 0.1M-HCl. For the colorimetric determination of aconitine, the powdered root material was extracted with NH_4OH and $CHCl_3$. Tragacanth was added to the mixture and the organic phase was separated, washed with water, and evaporated to dryness. The residue was dissolved in $CHCl_3$ and subjected to paper chromatography, with benzene–petroleum ether as the eluant. The spots that were visible in ultraviolet light were eluted from the paper with 95% EtOH, and this eluate was analysed at 231 nm. Recoveries of fortified samples averaged 104%. Nineteen crude and processed samples of *A. carmichaeli* and *A. kusnezoffii* were analysed by these methods. The range of the total alkaloids was 0.082 to 0.79%. The concentration of aconitine ranged from 0.00058 to 0.19%.

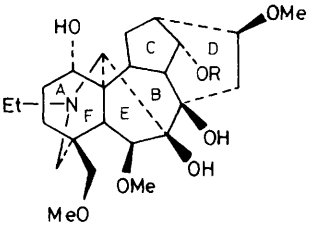
A simple assay for the total alkaloids in *Delphinium* species, using either thin-layer (on silica gel G) or column (on alumina) separations followed by fluorometric detection, has been reported.[23]

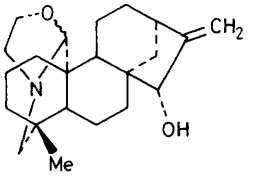
Japanese workers[24] have reported the use of g.c.–m.s. techniques in their studies of callus tissue cultures of *Aconitum ibukiense* var. *eizanense*. These tissues were cultured on Murashige–Skoog agar media that were supplemented with 2,4-dichlorophenoxyacetic acid and kinetin. The alkaloids were analysed by t.l.c. on silica gel G plates, by elution with $CHCl_3$–EtOH–Et_3N (40 : 10 : 1) and scanning at wavelengths of 235 and 350nm with a densitometer. The trimethylsilyl derivatives of the alkaloids were prepared by reaction with pyridine–hexamethyldisilazane–chlorotrimethylsilane and chromatographed on a 2mm × 1mm 3% OV-1 m Gas Chrom E column for the g.c.–m.s. analyses. The total extracted bases in the mother plant material amounted to 1.42%, of which mesaconitine (6) and hypaconitine (19) were the major alkaloids; aconitine was also present. The total concentration of base that could be extracted from the callus tissue was 0.05%, with aconitine (5) and mesaconitine (6) as the major components. Two unidentified, less polar alkaloid components that were in the mother plant material were not detected in the callus tissue at significant levels.

A new thin-layer-chromatographic instrument, employing a centrifugally accelerated radial system, has been used for the preparative-scale separation of diterpenoid alkaloids.[25] Several classical separations which had previously been accomplished by laborious and time-consuming column chromatography and conventional thin-layer chromatography were completed rapidly and easily. These separations included aconitine (5) from 3-deoxyaconitine (23) and from mesaconitine (6), staphisine (24) from staphidine (25), delsoline (26) from 14-acetyldelcosine (27), and veatchine (28) from garryine (29). Rotors of silica gel or alumina were used. The use of an atmosphere of nitrogen in the system and a non-transparent cover assisted in the quantitative recovery of even air- or light-sensitive compounds. Gradient elution and eluent-recycling techniques were used to improve the resolution of components.



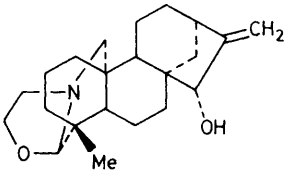
Staphisine (24) R = OMe
Staphidine (25) R = H





Veatchine (28)

Delsoline (26) R = Me
14 - Acetyldelcosine (27) R = Ac
Delcosine (37) R = H



Garryine (29)

This work demonstrates the significant advantages in the use of such systems in preparative separations of the diterpenoid alkaloids.

2.3 More on the Mechanism of the Oxidation of Aconitine by Potassium Permanganate

The mechanism of the oxidation of aconitine (5) by potassium permanganate to form oxonitine (30) continues to attract interest. Oxidation of aconine penta-acetate (31), labelled in the *N*-ethyl group (as $^{13}CH_2CH_3$), with potassium permanganate for 4 days at room temperature in acetone–water (95 : 5) gave (32) [m.pt 239—241 °C] in 79% yield.[26] The ^{13}C n.m.r. spectrum of (32) showed that 75% of the ^{13}C label from (31) had been retained. Oxidation of aconitine (5) under the same conditions in [$^2H_6$]acetone–water gave (30) in 80% yield. The n.m.r. spectra of this product showed that there had been no incorporation of deuterium. Under these specific conditions, the *N*-formyl group of (30) appears to be derived from the methylene group of the *N*-ethyl group of (5). The previous study of the mechanism of this reaction had shown that, during the oxidation of (5) by potassium permanganate in various acetone–protic solvent systems, the *N*-formyl group in (30) was derived from both the acetone solvent and the methylene group of the *N*-ethyl group.[27] Based on these studies, Amiya and co-workers[26] proposed that, under the conditions that were used,

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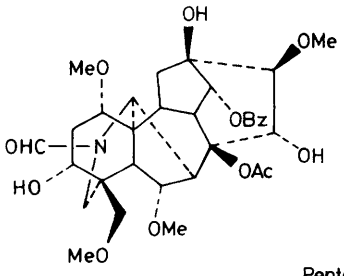
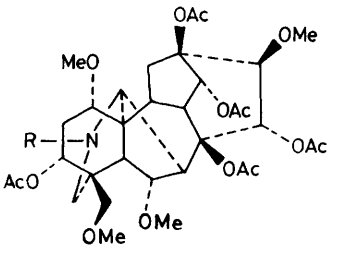
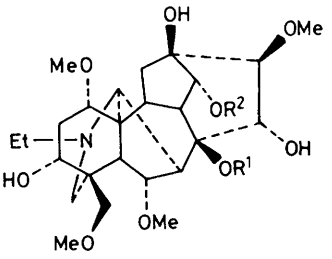
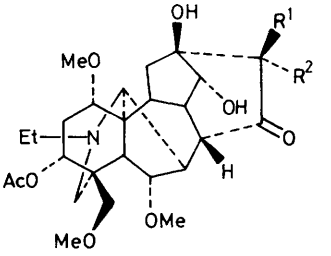
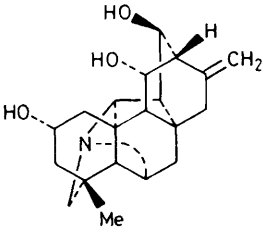
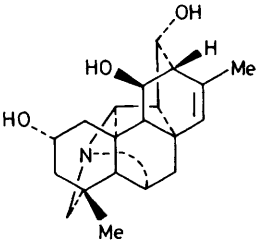

Oxonitine (30)

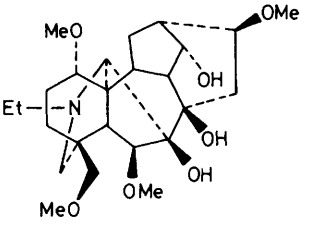

Penta-acetylaconine (31) R = $^{13}CH_2CH_3$
(32) R = ^{13}CHO

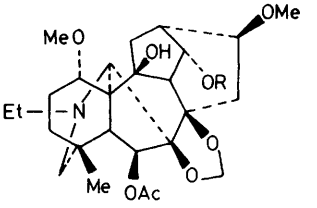

Aconitine (5) R^1 = Ac, R^2 = Bz
Aconine (33) R^1 = R^2 = H
(34) R^1 = OMe, R^2 = H


(35) R^1 = OMe, R^2 = H
(36) R^1 = H, R^2 = OMe
[structure (37) is with (26)]


Hetisine (38)


(39)


Browniine (40)


Dictyocarpine (41) R = H
Deltaline (64) R = Me

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the oxidation first produces an enamine, which can undergo oxidative cleavage to give the *N*-formyl derivative; in the presence of excess water, an immonium salt may be formed. This tautomer then can be hydrolysed to form the *N*-desethyl compound, which can react with the acetone to form the *N*-formyl compound.

2.4 Mild Hydrolysis of Aconitine

Katz and Rudin[28] have thoroughly studied the mild, basic hydrolysis of aconitine (5). Hydrolysis of (5) with 0.04M-K_2CO_3 in 90% MeOH at room temperature yielded aconine (33) as the major product, considerable amounts of 8-*O*-methylaconine (34), and the C-16 epimers (35) and (36) as minor products. The yields of (35) and (36) were increased if a solution of (5) and 0.04M-K_2CO_3 in 90% ethanol was heated at reflux.

Carbon-13 and proton n.m.r. spectral data and assignments for (34) and for (35) and the proton data for (36) were presented.

2.5 *X*-Ray-Crystallographic Analyses

2.5.1 Delcosine

The structure (37) for delcosine has been confirmed by an *X*-ray-crystallographic analysis, using direct methods, with refinement in the full-matrix anisotropic approximation to $R = 0.104$.[29] The hydroxyl group at C-1 was confirmed to be in the α configuration. Rings A, B, and D were shown to be in boat conformations. Rings C and F were in envelope conformations. The heterocyclic ring E had a chair conformation. These stereochemistries are identical with those for lycoctonine (7). The co-ordinates for all atoms and the interatomic bond distances and angles for all atoms other than hydrogen were presented.

2.5.2 Hetisine Perchlorate

The structure and stereochemistry (38) for hetisine have been confirmed by an *X*-ray-crystallographic study of its perchlorate salt.[30] A previous *X*-ray study of a rearrangement product (39) of hetisine had raised some question as to the configurations of the hydroxyl groups at C-11 and C-13.[31] The structure was solved by multi-solution methods and refined to $R = 0.069$ for 4004 observed reflections. Bond angles and lengths and the co-ordinates and thermal parameters for all atoms except hydrogen were presented.

2.5.3 Browniine Perchlorate

An error in an early determination of the crystallographic structure for a transformation product of lycoctonine had resulted in considerable confusion over the configuration of the oxygen function at C-1 in lycoctonine (7) and in the numerous C_{19}-diterpenoid alkaloids whose structures were correlated with lycoctonine.[32,33] In continuing studies to determine unequivocally the structures and stereochemistries of the alkaloids which have been correlated with lycoctonine, an *X*-ray analysis of the perchlorate salt of browniine (40) has been carried out.[34] The structure was solved by using multi-resolution methods. The twenty four hydrogen atoms were located stereochemically and included in the refinement to a final value of $R = 0.078$. The co-ordinates and thermal parameters for all atoms except hydrogen were tabulated. As indicated in structure (40), the configuration of the methoxy group at C-1 is α; ring A was shown to be in a boat conformation.

2.5.4 The Dictyocarpine–Acetone Complex

The structural assignment (41) for dictyocarpine was based on a multi-step correlation with lycoctonine (7).[35,36] Therefore, to confirm this structure, an *X*-ray-crystallographic study was completed.[34] Dictyocarpine crystallized from acetone as a 1 : 1 solvent complex. The structure was solved by multi-solution methods. Using the parameters for the twenty two hydrogen atoms that could be located from stereochemical considerations in the refinement, a value of $R = 0.085$ for 2483 reflections was obtained. The co-ordinates and thermal parameters for the atoms other than hydrogen were given in the paper. Ring A was in a chair conformation, with the methoxyl group at C-1 in the α configuration. The oxygen atom of the acetone appears to be hydrogen-bonded to the hydroxyl group at C-14.

3 Phytochemical Studies

3.1 Alkaloids of *Aconitum carmichaeli* Debx.

In their continuing chemical characterization of the plant materials from *Aconitum* species that are used in traditional

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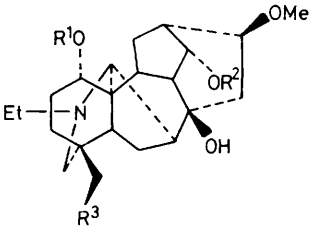
Chinese and Japanese medicines, Kitagawa and co-workers[6,18,21] have published several studies of the diterpenoid alkaloids of *A. carmichaeli* Debx. The dried tubers 'chuan-wu', imported from Sichuan Province, China, were shown to contain twelve diterpenoid alkaloids: these were aconitine (5), hypaconitine (19), mesaconitine (6), talatizamine (42), 14-*O*-acetyltalatizamine (43), isotalatizidine (44), karakoline (45), neoline (11), lipoaconitine (1), lipohypaconitine (2), lipomesaconitine (3), and lipo-3-deoxyaconitine (4).[21] These alkaloids were isolated and their structures confirmed by spectral (i.r., n.m.r., m.s., and optical rotation) studies. The acetyl function at C-8 in aconitine, hypaconitine, and mesaconitine could readily be transesterified to form the fatty acid esters at this position.

This research group has also screened fifteen processed and unprocessed herbal preparations for *Aconitum* alkaloids, using t.l.c. and h.p.l.c. procedures.[6,18] These preparations included chuan-wu, banshu-fuzi, fupian, two samples of wutou, heifupian, cao-wu, four samples of fuzi, three samples of pao-fuzi, and shirakawa-fuzi. Thirteen of these fifteen samples contained the lipo-alkaloids (1), (2), and (3) as the major alkaloids. The other alkaloids that were identified in these materials were aconitine (5), hypaconitine (19), mesaconitine (6), talatizamine (42), 14-*O*-acetyltalatizamine (43), isotalatizidine (44), karakoline (45), neoline (11), benzoylaconine (18), benzoylhypaconine (20), benzoylmesaconine (21), and another fatty acid ester, *i.e.* lipo-3-deoxyaconitine (4). The concentrations of the lipo-alkaloids were greater in processed roots while the concentrations of the more toxic bases were decreased in comparison with the unprocessed plant material.

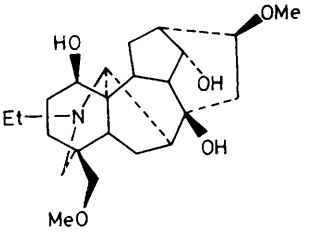
3.2. Alkaloids of *Aconitum columbianum*

Two studies of the aerial parts of *Aconitum columbianum* Nutt. have been reported.[37,38] Canadian workers[37] isolated 0.45% of the total weight as alkaloids from plant material growing in central British Columbia. Cammaconine (46) and talatizamine (42) were the major bases that were found. The minor alkaloids that were identified were sachaconitine (47), talatizidine (48), isotalatizidine (44), and 14-*O*-acetyltalatizamine (43). Two new bases were also isolated; these were 8-*O*-methyltalatizamine (49) [$C_{25}H_{41}NO_5$] and columbianine (50) {$C_{22}H_{35}NO_5$; m.pt 202–205 °C; $[\alpha]_D$ −6 ° (EtOH)}. These structural assignments were made primarily from the mass-spectral and n.m.r. data. Methylation of (50) [by MeI and NaH in dioxane under reflux for 4 hours, followed by 48 hours at room temperature] gave (51); refluxing under the same conditions for 17 hours gave (52), which was identical with permethylated cammaconine or permethylated talatizamine. The following derivatives were prepared and characterized: 14-oxo-14-deoxytalatizamine (53), *N*-formyl-14-oxo-*N*-desethyl-14-deoxytalatizamine (54), 1,14-di-*O*-methylisotalatizidine (55), cammaconine triacetate (56), demethoxyisopyrocammaconine (57), oxotalatizamine (58), 14-oxo-14-deoxyoxotalatizamine (59), 8-*O*-methyloxotalatizamine (60), 8-*O*-methyl-14-oxo-14-deoxyoxotalatizamine (61), 14-oxo-14-deoxyoxosachaconitine (62), and *N*-formyl-8-*O*-methyl-*N*-desethyltalatizamine (63). The ^{13}C n.m.r. data for most of these compounds were tabulated and a brief discussion of their biogenesis was also presented. Since an oxygen function occurs at C-8 in all aconitine-type bases, this function may be introduced early in the biosynthesis, during the formation of a 7—17 bond from a 7—8 double-bond. The oxygen at C-14 is presumably introduced as one carbon of the original C_{20} skeleton is removed. The sequence of the remaining oxidations was proposed to be C-16, C-1, C-18, and C-6. Methylation of the oxygen atoms probably occurs in the order 16, 6, 18, 1, and 14. The formation of the rare 8-methoxy-function was attributed to the addition of an equivalent of methanol instead of water or acetic acid in the formation of the 7—17 bond.

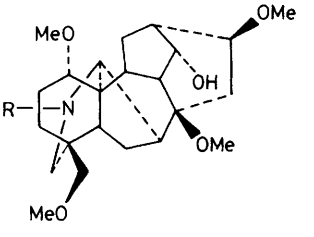
In studies of *Aconitum columbianum* Nutt. subsp. *columbianum*, five known and one new alkaloid were isolated.[38] The aerial parts of these plants, primarily in the pre-bud stage, were collected in Idaho, USA. The known bases cammaconine (46), deltaline (64), dictyocarpine (41), talatizamine (42), and 8-*O*-



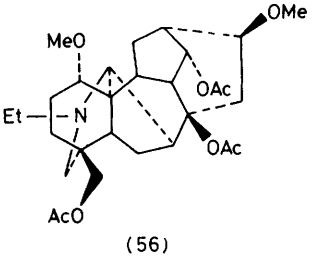
Talatizamine (42) R^1 = Me, R^2 = H, R^3 = OMe
14-*O*-Acetyltalatizamine (43) R^1 = Me, R^2 = Ac, R^3 = OMe
Isotalatizidine (44) R^1 = R^2 = H, R^3 = OMe
Karakoline (45) R^1 = R^2 = R^3 = H
Cammaconine (46) R^1 = Me, R^2 = H, R^3 = OH
Sachaconitine (47) R^1 = Me, R^2 = R^3 = H
Columbianine (50) R^1 = R^2 = H, R^3 = OH
(55) R^1 = R^2 = Me, R^3 = OMe



Talatizidine (48)



8-*O*-Methyltalatizamine (49) R = Et
(63) R = CHO



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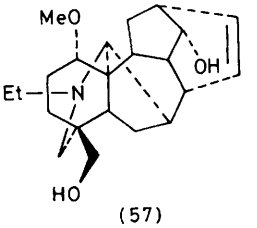

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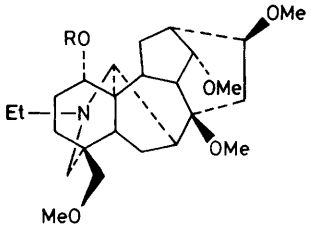
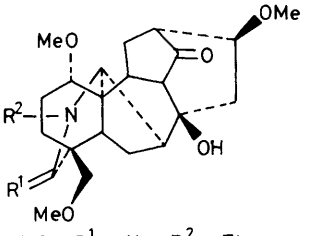
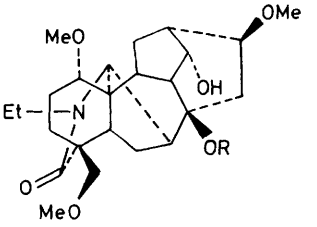


(51) R = H
(52) R = Me



(53) R^1 = H_2, R^2 = Et
(54) R^1 = H_2, R^2 = CHO
(59) R^1 = O, R^2 = Et



(58) R = H
(60) R = Me

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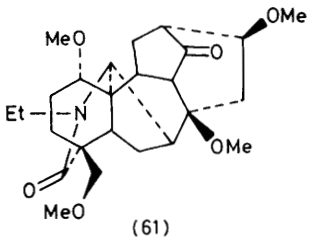

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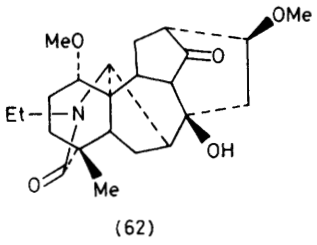
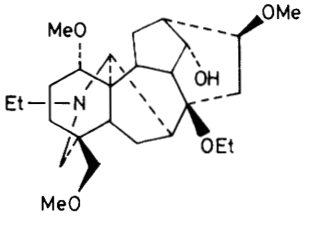


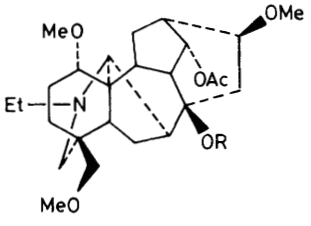
(62)

[Structure (63) is with (49)]

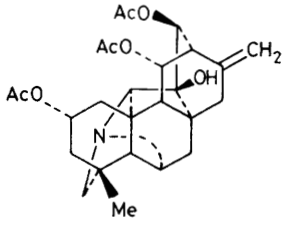
[Structure (64) is with (41)]



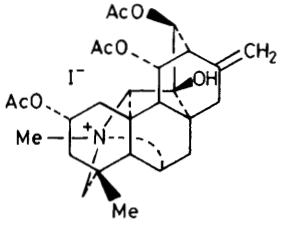
Columbidine (65)



(66) R = Ac
(67) R = Et



Guan-fu base G (68)



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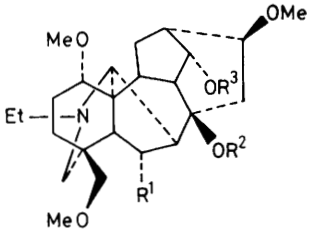
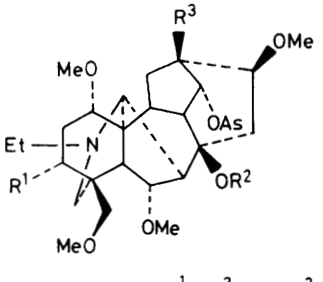


Chasmanine (70) R^1 = OMe, R^2 = R^3 = H
Talatizamine (42) R^1 = R^2 = R^3 = H
Foresticine (72) R^1 = OH, R^2 = R^3 = H
(73) R^1 = OAc, R^2 = H, R^3 = Ac
(74) R^1 = OMe, R^2 = H, R^3 = Me



Yunaconitine (12) R^1 = R^3 = OH, R^2 = Ac
Forestine (71) R^1 = R^2 = H, R^3 = OH
(75) R^1 = R^3 = OH, R^2 = H

methyltalatizamine (49) were identified from their spectral and physical properties and, in most cases, from comparisons with authentic samples. The major alkaloid was talatizamine (42). The new base columbidine {$C_{26}H_{43}NO_5$; mol. wt. 449; amorphous; $[\alpha]^{25}$ −6.4° (*c* 1.4 in $CHCl_3$)} was assigned structure (65) from the ^1H and ^{13}C n.m.r. data and by the hydrolysis of (65) with aqueous sulphuric acid to afford talatizamine (42). The ^{13}C n.m.r. data for (42), (49), (65), (46), (53), (66), and (67), including several revisions in the assignments of previous reports, were presented. Since the ^{13}C n.m.r. spectrum for 14-oxo-14-deoxytalatizamine was not reported in the description of its isolation from *A. saposhnikovii*,[39] compound (53) [m.pt 129—130 °C] was prepared by the oxidation of talatizamine (42) with CrO_3 in acetic acid.

3.3 Alkaloids of *Aconitum coreanum* (Levl.) Rapcs.

The structure of guan-fu base G {$C_{26}H_{33}NO_7$; m.pt 178 °C; $[\alpha]^{30}$ +97.3° (*c* 1.0 in $CHCl_3$)} can be assigned as (68), based on the reported *X*-ray-crystallographic determination of the structure of its methiodide derivative (69) [m.pt 292 °C].[40] The final value of the *R* factor, with all hydrogen atoms included in the refinement, was 0.0528. The indicated absolute configuration was assigned on the basis of calculation of the *R* factors for the two possible configurations. The co-ordinates and bond angles and the lengths of bonds between atoms other than hydrogen were presented.

3.4 Alkaloids of *Aconitum forrestii*

In a thorough study of the alkaloids of the roots of *Aconitum forrestii* Stapf, five diterpenoid alkaloids have been identified.[41] These were the known bases chasmanine (70), talatizamine (42), and yunaconitine (12) and two new alkaloids that were designated as forestine and foresticine. Forestine [$C_{33}H_{47}NO_9$; mol. wt 601; amorphous] was assigned structure (71), primarily from ^{13}C and ^1H n.m.r. data. Foresticine {$C_{24}H_{39}NO_6$, m.pt 79—80 °C, $[\alpha]^{21}$ −1.9° (*c* 1 in $CHCl_3$)} was assigned structure (72) from the n.m.r. spectral data for the alkaloid and its diacetate (73) and confirmed by methylation of (72) to form 6,14-di-*O*-methylforesticine (74), which was identical with the methylation product of chasmanine (70).

Chinese researchers[42] have reported the isolation of a new alkaloid from the roots of *A. forrestii*. Structure (75), corresponding to 8-deacetylyunaconitine, was assigned to this base [$C_{33}H_{47}NO_{10}$; amorphous powder] from the i.r., mass, and ^1H and ^{13}C n.m.r. spectral data, and also by comparisons with the data for yunaconitine (12) and 8-deacetyl-3-deoxy-yunaconitine (71). The latter structure corresponds to that of forestine.

3.5 Alkaloids of *Aconitum franchetii* Fin. et Gagn.

A novel C_{19}-base, franchetine {$C_{31}H_{41}NO_6$; $[\alpha]^{24}$ −106.4° ($CHCl_3$)}, has been isolated as a minor component of the weakly basic fraction of *A. franchetii*.[43] Structure (76) was assigned to franchetine primarily on the basis of comparisons of its proton and carbon n.m.r. spectral data with those for pyrodelphinine (77) and chasmanine (70). The 5,6-dihydro-2*H*-pyran ring system in franchetine is unique among the reported C_{19}-diterpenoid alkaloids, but occurs in several C_{20}-bases, *e.g.* ajaconine (78).

3.6 Alkaloids of *Aconitum gymnandrum* Maxim.

In a very brief communication, Wu and Zhu[44] have reported the isolation of atisine, as the hydrochloride salt (79), from plants of this species.

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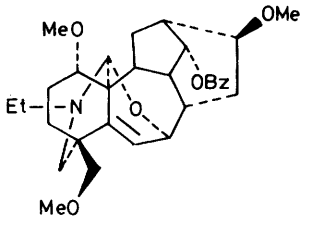
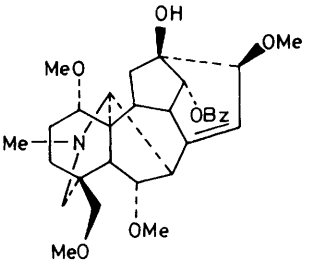
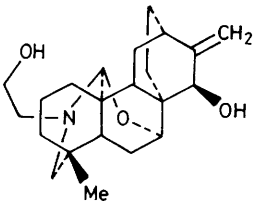


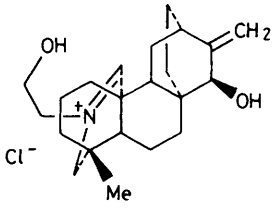
Franchetine (76)



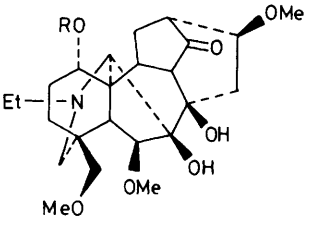
Pyrodelphinine (77)



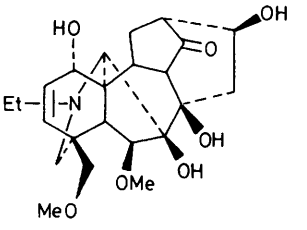
Ajaconine (78)



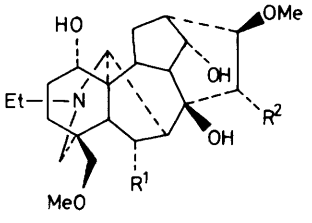
Atisinium chloride (79)



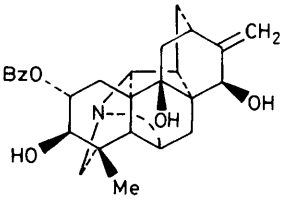
14-Oxo-14-deoxybrowniine (80) R = Me
14-Oxo-14-deoxydelcosine (81) R = H



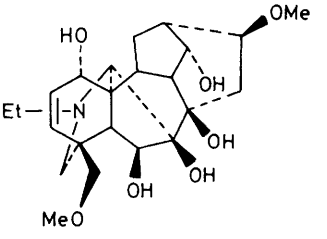
Takaonine (82)



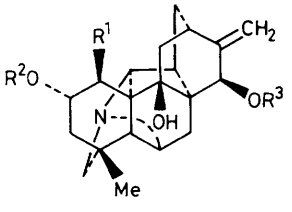
Neoline (11) R^1 = OMe, R^2 = H
Senbusine C (83) R^1 = OMe, R^2 = OH
Senbusine A (84) R^1 = OH, R^2 = H



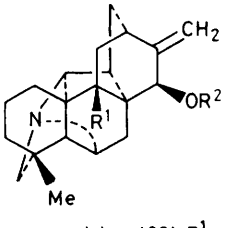
Ignavine (85)



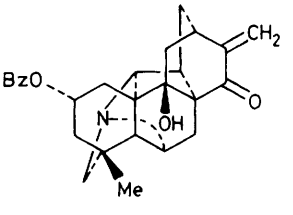
Ibukinamine (86)



Ryosenamine (87) R^1 = R^3 = H, R^2 = Bz
Ryosenaminol (88) R^1 = R^2 = R^3 = H
(91) R^1 = H, R^2 = Bz R^3 = Ac



9-Hydroxynominine (89) R^1 = OH, R^2 = H
(92) R^1 = OH, R^2 = Ac
Nominine (93) R^1 = R^2 = H



(90)

3.7 Alkaloids of *Aconitum ibukiense* Nakai

Sixteen diterpenoid alkaloids have been isolated from the roots of this species, collected at Mt. Ryosen, Japan.[45,46] These bases were purified by preparative t.l.c. Twelve of the alkaloids were known compounds: mesaconitine (6), hypaconitine (19), aconitine (5), 3-deoxyaconitine (23), 14-oxo-14-deoxybrowniine (80), 14-oxo-14-deoxydelcosine (81), delcosine (37), takaonine (82), neoline (11), 15α-hydroxyneoline (senbusine C) (83), senbusine A (84), and ignavine (85). The four new diterpenoid alkaloids were ibukinamine (86), ryosenamine (87), ryosenaminol (88), and 9-hydroxynominine (89). The structure (86) for ibukinamine {$C_{23}H_{35}NO_7$; mol. wt 437; m.pt 243—246 °C; $[\alpha]^{19}$ +71.7 ° (*c* 12 in MeOH)} was assigned from a single-crystal *X*-ray analysis, using direct methods. These data were refined to a final R = 0.075. Ryosenaminol {$C_{20}H_{27}NO_3$; m.pt 287—290 °C; $[\alpha]^{29}$ +66.8 ° (*c* 0.38 in MeOH)} was assigned structure (88) from a single-crystal *X*-ray analysis. The final least-squares refinement gave a value of R = 0.071. Hydrolysis of ryosenamine {$C_{27}H_{31}NO_4$; mol. wt 433; m.pt 213—215 °C; $[\alpha]^{12}$ +96.8 ° (*c* 0.20 in MeOH)} gave ryosenaminol. From this conversion and the spectral data, structure (87) could be assigned for ryosenamine. Oxidation of (87) with pyridinium dichromate gave 15-oxo-15-deoxyryosenamine (90), confirming that the benzoyl group is at C-2 in (87). Acetylation of (87) gave the monoacetate (91). 9-Hydroxynominine {$C_{20}H_{27}NO_2$; mol. wt 313; m.pt 287—291 °C; $[\alpha]^{23}$ +68.5 ° (MeOH)} formed a monoacetate derivative (92) when acetylated with Ac_2O in pyridine. These structures were assigned from the spectral data, primarily by comparisons of ^{13}C n.m.r. spectral data with those for nominine (93).

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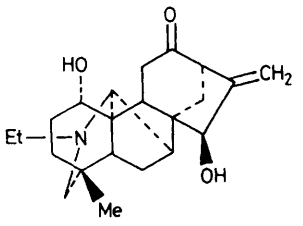
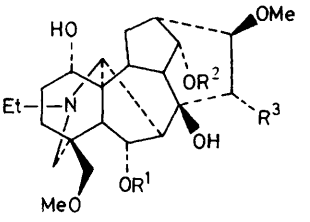
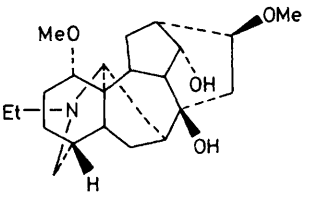


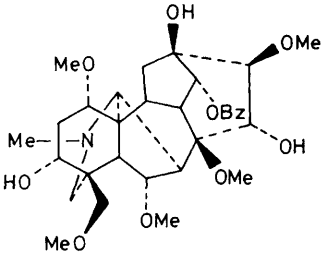
Songorine (94)



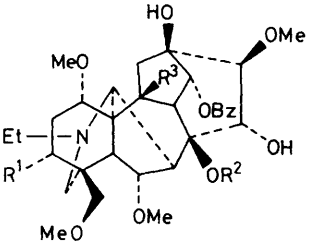
Neoline (11) R^1 = Me, R^2 = R^3 = H
14-Acetylneoline (95) R^1 = Me, R^2 = Ac, R^3 = H
Senbusine C (83) R^1 = Me, R^2 = H, R^3 = OH
Senbusine A (84) R^1 = R^2 = R^3 = H



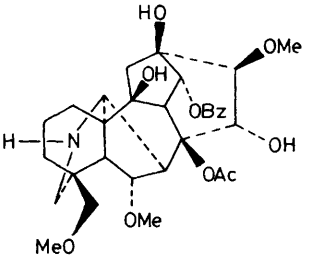
Aconosine (96)



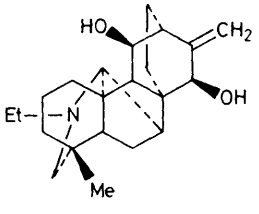
Hokbusine A (97)



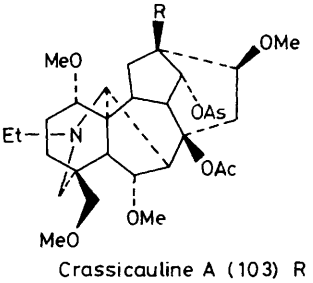
Polyschistine A (98) R^1 = OAc, R^2 = Et, R^3 = H
Polyschistine B (99) R^1 = H, R^2 = Ac, R^3 = OH
3-Acetylaconitine (101) R^1 = OAc, R^2 = Ac, R^3 = H



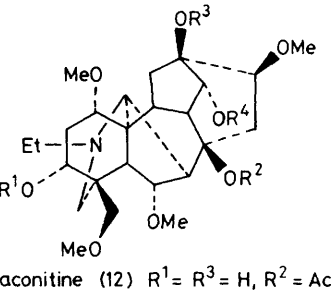
Polyschistine C (100)



Denudatine (102)



Crassicauline A (103) R = OH
Foresaconitine (Vilmorrianine C) (104) R = H



Yunaconitine (12) R^1 = R^3 = H, R^2 = Ac R^4 = As
Pseudaconine (105) R^1 = R^2 = R^3 = R^4 = H
(106) R^1 = R^2 = R^3 = R^4 = Ac

3.8 Alkaloids of *Aconitum karakolicum* Rapcs.

Chinese researchers at the Institute of Materia Medica, Beijing,[47] have studied the alkaloids of this species, which provides the traditional Chinese drug 'duo gen wutou'. Aconitine (5) was identified as the major alkaloid, being present at a concentration of 0.49% in the dried tuber. The other alkaloids that have been identified were neoline (11) (0.008%), 3-deoxyaconitine (23) (0.003%), and songorine (94) (0.0014%). The identities of these bases were determined by comparisons of physical and i.r., n.m.r., and mass-spectral data with those of the literature. The LD_{50} (intravenous, in mice) for the crude extract was 25 mg per kg of body weight and was attributed to the relatively high level of aconitine.

3.9 Alkaloids of *Aconitum napellus* L.

Japanese researchers[48] have reported their phytochemical studies of the dried roots of this species, obtained in Switzerland. The following diterpenoid alkaloids were identified by comparisons of the physicochemical and spectral data with those of authentic samples [% yield; dry weight]: aconitine (5) [0.0001], mesaconitine (6) [0.00015], 14-acetylneoline (95) [0.0003], aconosine (96) [0.0003], hokbusine A (97) [0.00045], neoline (11) [0.00506], senbusine A (84) [0.00140], and senbusine C (83) [0.00032]. This is the first report of the isolation of (95), (96), (97), (84) and (83) from *A. napellus*.

3.10 Alkaloids of *Aconitum polyschistum* Hand.-Mazz.

Fujimoto and co-workers[49] have reported the isolation and structure elucidation of three new alkaloids from this species, which is used as a traditional medicine in China. The structures for polyschistines A (98), B (99), and C (100) were assigned from the mass-spectral and ^1H and ^{13}C n.m.r. data. N.m.r. chemical shifts are presented for all of the compounds. The authors noted that polyschistine A (98) might be an artifact, resulting from 3-acetylaconitine (101) during the isolation procedures. Polyschistine C (100) is unique among the known C_{19}-diterpenoid alkaloids in that it contains neither an oxygen function at C-1 nor an *N*-alkyl group.

3.11 Alkaloids of *Aconitum pseudogeniculatum* W. T. Wang

Chen and Sung[50] have described their studies of this species, collected in western Sichuan province. The following known alkaloids were isolated by acid/base partitioning and column chromatography on Al_2O_3: denudatine (102), chasmanine (70), talatizamine (42), yunaconitine (12), crassicauline A (103), and foresaconitine (vilmorrianine C) (104). These alkaloids were identified by comparisons of their t.l.c. properties and their physical and spectral data with those for the known bases. Yunaconitine was the major alkaloid. This alkaloid, its hydrolysis product pseudaconine (105), and the tetra-acetyl derivative (106) had anti-inflammatory activity. The configur-

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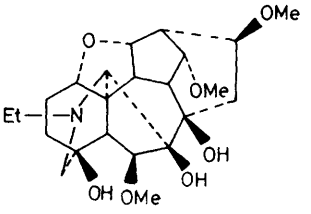
ation for the methoxyl group at C-1 and other errors that were given for (12), (42), (70), (103), and (104) in the original text are corrected in this review.

3.12 Alkaloids of *Aconitum sibiricum*

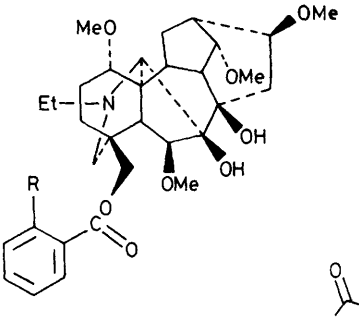
A new diterpenoid alkaloid, tuguaconitine [$C_{23}H_{35}NO_7$; m.pt 196—198 °C], has been isolated from the roots of *A. sibiricum*; this species is native to Korea.[51] Structure (107) was assigned for this compound from the spectroscopic data. This structure is almost certainly incorrect, being based on a faulty interpretation of ^{13}C n.m.r. data. Instead of a C(1)—C(12) ether linkage and 4β-OH, the structure probably possesses a hydroxyl group at C-1 and is a 3,4β-epoxide, as in monticoline.

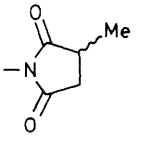


Tuguaconitine (107)

3.13 Alkaloids of *Aconitum zeravschanicum* Steinb.

A preliminary report has been published on the study of the alkaloids of the aerial parts of this species, of which specimens were collected at two locations in the Kirghiz S.S.R.[52] Plant material from the Alai range yielded 0.95% total alkaloids, while material that was collected in the Trans-Alai range gave 0.67% total alkaloids. Nine alkaloids were isolated. These included the known compound heteratisine (10), the benzyltetrahydroisoquinoline reticuline (base VII), and seven unidentified bases: base II [$C_{20}H_{27}NO$; mol. wt 297; m.pt 258—259 °C], base III [m.pt 148—150 °C], base IV [m.pt 87.5—88.5 °C], base V [m.pt 130—131 °C], base VI [amorphous; m.pt of HCl salt 296 °C], base VIII [m.pt 235—237 °C], and base IX [m.pt 206.5—207.5 °C].





Methyl-lycaconitine (108) R =

Anthranoyl-lycoctonine (109) R = NH_2

3.14 Alkaloids of *Delphinium* species of Tajikistan

Narzullaev and co-workers[53–55] have surveyed the alkaloids of five species growing in Tajikistan, USSR. The alkaloids were isolated by extraction with chloroform. Plants of *D. batalinii* Huth. contained 0.50% total alkaloids. None of these bases was identified, but the absence of methyl-lycaconitine (108) was indicated. The roots of *D. biternatum* Huth. contained 0.56% total alkaloids, while the aerial parts contained 1.04%. Methyl-lycaconitine (108) (0.20% of the dry weight of the plant material) was isolated from the aerial parts. Anthranoyl-lycoctonine (109), (108), and an unidentified base [$C_{26}H_{41}NO_7$; m.pt 195—198 °C] were isolated from the roots of *D. confusum* M. Pop., which contained 2.5% total alkaloids. The aerial parts of these plants contained 0.43% total alkaloids, of which 0.13% was identified as (108). The aerial parts of *D. oreophilum* Huth. contained the largest quantity of alkaloids of any of the plants that were studied (1.52%). Of this alkaloid fraction, 73% was methyl-lycaconitine (108). The roots of these same plants contained 1.1% total alkaloids (0.66% was methyl-lycaconitine). The aerial parts of plants of this species that had been collected at another location contained 0.92% total bases. The alkaloids from plants of *D. ternatum* Huth. that were harvested from the Varzob River Basin at several different times were studied. From the roots that had been collected in 1974, 0.16% total alkaloids were isolated; of this, 0.03% was (108). An unidentified alkaloid [$C_{30}H_{41}N_2O_8$; m.pt 157—159 °C] was also found in this material. The aerial parts of these plants contained 0.14% total bases. The aerial parts and the roots of the plants that had been collected in 1979 contained 0.18% and 0.43% total alkaloids, respectively. Delpheline (111) and lycoctonine (7) were identified in both parts.[53] From the aerial parts of *D. ternatum* that had been collected during the flowering phase in June 1979, 0.15% total bases were isolated.[54] Delcorine (110) and delpheline (111) were isolated and identified from the ether-soluble non-phenolic fraction of the total alkaloids. In a continuation of this study,[55] dictyocarpine (41), the aporphine alkaloid glaucine, and the diterpenoid alkaloid 6-oxo-6-deoxydeltamine (6-oxo-6-deoxyeldelidine) (112) [$C_{25}H_{37}NO_7$; mol. wt 463; m.pt 120—122 °C] were identified. Structure (112) was assigned from the i.r., mass, and ^1H n.m.r. spectral data and from the oxidation of deltamine [eldelidine (113)] with CrO_3 in acetone to yield (112).[56] Another unidentified alkaloid, designated base B [mol. wt 415; m.pt 236—238 °C], was also isolated. This is the first report of the natural occurrence of (112) and of the occurrence of glaucine in a *Delphinium* species.

3.15 Alkaloids of *Delphinium bonvalotii* Franch.

Jiang and Sung[57,58] have reported the isolation and structure determination of seven new C_{19}-diterpenoid alkaloids from the roots of this plant. *D. bonvalotii* has been used as a traditional medicine for its claimed analgesic, anti-inflammatory, and anti-rheumatic activities. Three of these new alkaloids contain the novel feature of a hydroxyl function at C-5: bonvalotine (114) {$C_{26}H_{39}NO_8$; mol. wt 493; m.pt 218—220 °C; $[\alpha]^{32}$ −35.7° (*c* 0.6 in $CHCl_3$)}, bonvalol (115) {$C_{24}H_{37}NO_7$; mol. wt 451, m.pt 165—166 °C; $[\alpha]^{32}$ −26.3° (*c* 0.4 in $CHCl_3$)}, and bonvalone (116) {$C_{24}H_{35}NO_7$; mol. wt 449; m.pt 235—236 °C; $[\alpha]^{32}$ −89.3° (*c* 0.3 in $CHCl_3$)}.[57] Structure (114) was assigned from the i.r., ^1H and ^{13}C n.m.r., and mass-spectral data, and by comparisons of those data for delpheline (111). Bonvalotine (114) could not be acetylated under any of the conditions that were used. Structure (114) for bonvalotine was confirmed by an *X*-ray-crystallographic analysis, which is as yet unreported. Hydrolysis of (114) yielded a compound that was identical in all respects to bonvalol (115). Oxidation of (114) with CrO_3 in pyridine gave bonvalone (116). The assignments of ^{13}C n.m.r. chemical shifts for (111), (114), (115), and (116) were presented. The 6-epimer (117) of bonvalotine was prepared in four steps. In further studies, deltamine (113), deltaline (64), and four new alkaloids were identified: these were delbotine (118) {$C_{26}H_{43}NO_7$; mol. wt 481; m.pt 155—157 °C; $[\alpha]^{18}$ +13.6°

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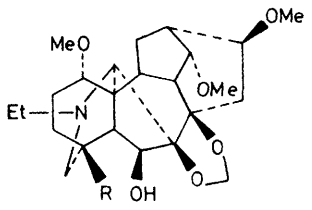
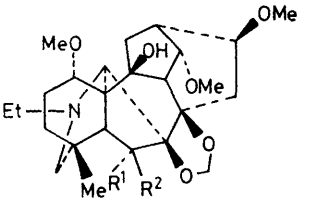
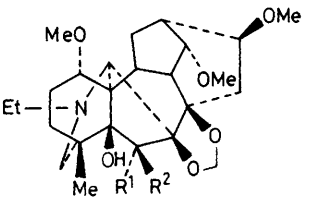


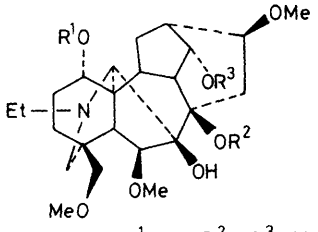
Delcorine (110) R = CH_2OMe
Delpheline (111) R = Me



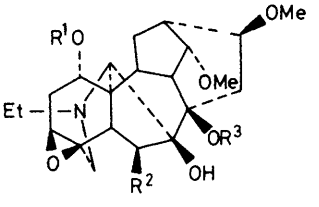
6-Oxo-6-deoxydeltamine (112) R^1 R^2 = O
Deltamine (113) R^1 = H, R^2 = OH



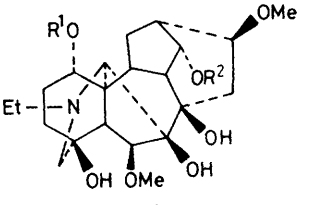
Bonvalotine (114) R^1 = H, R^2 = OAc
Bonvalol (115) R^1 = H, R^2 = OH
Bonvalone (116) R^1 R^2 = O
(117) R^1 = OAc, R^2 = H



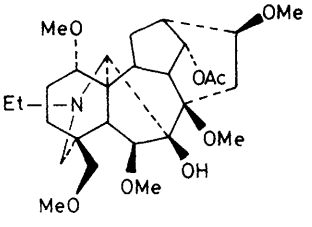
Delbotine (118) R^1 = H, R^2 = R^3 = Me
Delbonine (120) R^1 = H, R^2 = Me, R^3 = Ac
(122) R^1 = Ac, R^2 = R^3 = Me



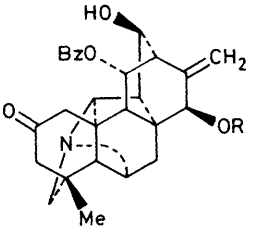
Delboxine (119) R^1 = R^3 = H, R^2 = OMe
(124) R^1 = Ac, R^2 = OMe, R^3 = H
Monticoline (125) R^1 = R^2 = R^3 = H



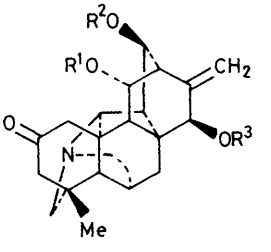
Delbine (121) R^1 = R^2 = H
(126) R^1 = R^2 = Ac



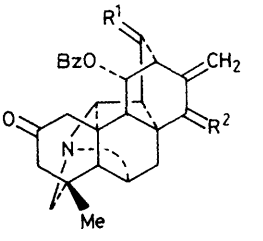
Ambiguine (123)



Cardiopetamine (127) R = H
15-Acetylcardiopetamine (128) R = Ac



(129) R^1 = Bz, R^2 = R^3 = Ac
(130) R^1 = R^2 = R^3 = H



(131) R^1 = H, β-OH; R^2 = O
(132) R^1 = O; R^2 = H, β-OH
(133) R^1 = O; R^2 = H, β-OAc

(*c* 0.1 in $CHCl_3$)}, delboxine (119) {$C_{24}H_{37}NO_7$; mol. wt 451; m.pt 200—202 °C; $[\alpha]^{13}$ +43.5 ° (*c* 0.1 in $CHCl_3$)}, delbonine (120) {$C_{27}H_{43}NO_8$; mol. wt 509; non-crystalline; $[\alpha]^{16}$ +41.1 ° (*c* 0.1 in $CHCl_3$)}, and delbine (121) {$C_{22}H_{35}NO_7$; mol. wt 425; m.pt 116—118 °C; $[\alpha]^{27}$ +53.3 ° (*c* 0.1 in MeOH)}.[58] Acetylation of (118) with Ac_2O in pyridine gave a monoacetate (122). These structures (118) and (122) were assigned primarily from the ^1H and ^{13}C n.m.r. spectral data, and by comparisons with the data for delsoline (26) and ambiguine (123). Acetylation of (119) yielded monoacetyldelboxine (124). Comparisons of the spectral data of these compounds with those for monticoline (125) suggested these structures. In reference 58 there is a reference to a personal communication that these structures for delboline and delboxine had been confirmed by *X*-ray analyses. Delbonine was tentatively assigned structure (120) from the i.r., mass, and ^1H n.m.r. spectral data, by analogy with those for (118) and (119). When delbine (121) was acetylated it formed a diacetate (126). Given the spectral similarities of (126) and 14-acetyldelcosine (27), structure (121) was assigned for delbine. Delboxine and delbine are the first reported examples of 18-nor-bases in which there is a methoxyl function at C-6.

3.16 Alkaloids of *Delphinium cardiopetalum* DC.

Two new C_{20}-bases have been isolated from these plants.[59] Cardiopetamine (127) {$C_{27}H_{29}NO_5$; mol. wt 447; m.pt 302—305 °C; $[\alpha]_D$ +16° (*c* 1.4 in EtOH)} and 15-acetylcardiopetamine (128) {$C_{29}H_{31}NO_6$; mol. wt 489; m.pt 236—237 °C; $[\alpha]_D$ +12 ° (*c* 0.51 in EtOH)} gave the same derivatives [(129) and (130)] when acetylated with Ac_2O in pyridine and hydrolysed with 5% KOH in MeOH, respectively. Oxidation of (127) with Cornforth's reagent at 25 °C yielded (131) and (132), in 48% and 36% yield, respectively. Acetylation of (132) and Cornforth oxidation of (128) gave the same product (133). The indicated structures were assigned from these chemical and the spectroscopic (i.r., u.v., mass, and ^1H n.m.r.) data. The structure for cardiopetamine (127) was confirmed by an *X*-ray analysis, using direct methods and being refined to a final R = 0.057 for 2318 reflections.

3.17 Alkaloids of *Delphinium gracile* DC.

Gonzalez and co-workers[60] have reported the isolation of five alkaloids, including a new lycoctonine-type alkaloid, from plants of this species growing in Cadiz, Spain. In addition to the C_{20}-alkaloids hetisinone (134), 13-acetylhetisinone (135), cardiopetamine (127), and atisinium chloride (79), a new C_{19}-alkaloid, which was named graciline (136) [$C_{21}H_{31}NO_4$; mol. wt 361; m.pt 98—100 °C], was identified. The structure was assigned primarily by comparisons of the ^{13}C n.m.r. data of (136) with those for karakoline (137), cardiopetaline (138), and cardiopetalidine (139). Oxidation of (139) with $KMnO_4$ gave graciline (136) in 83% yield. Treatment of (136) with Ac_2O in pyridine produced a monoacetate (140).

3.18 Alkaloids of *Delphinium pentagynum* Lam.

Two new C_{19}-diterpenoid alkaloids have been reported from this species.[61] Pentagyline (141) [$C_{30}H_{41}NO_7$; mol. wt 527; m.pt 198—200 °C] and gadenine (142) [$C_{30}H_{41}NO_8$; mol. wt 543; m.pt 147—150 °C] gave the monoacetates (143) and (144),

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respectively, when acetylated. These structures were assigned from the mass-spectral and from ^1H and ^{13}C n.m.r. spectral data. The ^{13}C n.m.r. spectral assignments for (141) and (142) in comparison with those for neoline (11) and 14-acetyldelcaroline (145) were presented. Since karakoline (137), dihydropentagynine (146), pentagynine (147), dihydrogadesine (148), gadesine (149), and pentagydine (150) had previously been isolated from this species,[62] these authors suggested that karakoline (137) was the biogenetic precursor for the other alkaloids. Hydroxylation at C-7 and then at C-6 (β) affords the lycoctonine-type alkaloids, while in the aconitine-type bases the hydroxylation first occurs at C-6 (α).

3.19 Alkaloids of *Delphinium speciosum* M. Bieb.

Extraction (with chloroform) of the aerial parts of these plants of Soviet Georgia yielded 1.01% total alkaloids.[63] The following known alkaloids were identified: methyl-lycaconitine (108), lycoctonine (7), anthranoyl-lycoctonine (109), gigactonine (151), and alkaloid B (152).

3.20 Alkaloids of *Delphinium tatsienense* Franch.

In continuing studies of the alkaloids of this Chinese species, two new diterpenoid alkaloids have been isolated and identified: deltatsine (153)[64] {$C_{25}H_{41}NO_7$; mol. wt 467; amorphous; $[\alpha]^{20}$ +28.6° (*c* 2.4 in EtOH)} and tatsinine (154)[65] {$C_{22}H_{35}NO_6$; mol. wt 409; m.pt 163—164 °C; $[\alpha]_D$ +9°}. Methylation of deltatsine (153) with MeI and NaH gave a mixture of (155) and (156). Acetylation of (155) afforded (157). Hydrolysis of (153) with 3M-H_2SO_4, gave a compound which was identical in all respects with the known alkaloid delcosine (37). Based on these data and the correlation of its ^{13}C n.m.r. spectral data with those for (155), (156), delsoline (26), delcosine (37), delcosine 7-methyl ether (158), (159), (160), and (161), deltatsine was assigned structure (153). Tatsinine (154) afforded a diacetyl derivative (162) when it was acetylated. From biogenetic considerations and the i.r. and ^1H and ^{13}C n.m.r. spectral data, these structural assignments were made. Comparisons of the ^{13}C n.m.r. spectral data for (154) and (162) with those for karakoline (137), alkaloid B (152), and ranaconine (163) were presented.

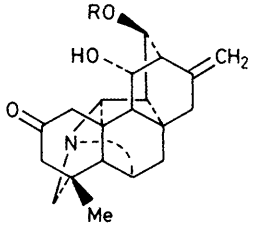
3.21 Alkaloids of *Delphinium yunnanense* Fr.

Studies of the alkaloids of this species resulted in the isolation of two major and two minor bases.[66] One of the major alkaloids was identified as delsoline (26), from its melting point and from i.r., ^1H n.m.r., and mass-spectral data. The other major component was a new alkaloid, yunnadelphinine [$C_{24}H_{35}NO_6$; mol. wt 433; m.pt 217—219 °C]. Structure (164) was determined for this compound by a single-crystal *X*-ray-crystallographic analysis (R = 0.0504). The i.r., ^1H n.m.r., and mass-spectral data were also reported.

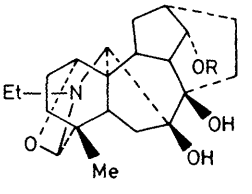
4 Synthetic Studies

4.1 Partial Synthesis of Isodelphinine and Penduline

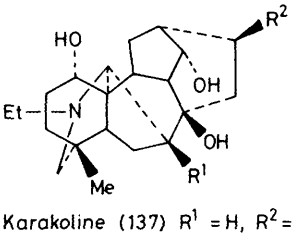
Sakai and co-workers[67] have reported on their synthetic conversions of chasmanine (70) into isodelphinine (165) and



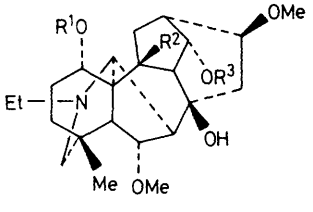
Hetisinone (134) R = H
13-Acetylhetisinone (135) R = Ac



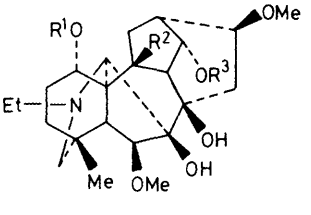
Graciline (136) R = H
(140) R = Ac



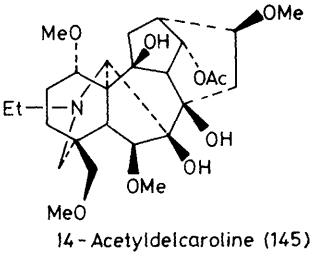
Karakoline (137) R^1 = H, R^2 = OMe
Cardiopetaline (138) R^1 = R^2 = H
Cardiopetalidine (139) R^1 = OH, R^2 = H



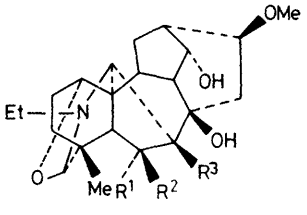
Pentagyline (141) R^1 = H, R^2 = OH, R^3 = Bz
(143) R^1 = Ac, R^2 = OH, R^3 = Bz
Dihydropentagynine (146) R^1 = R^2 = R^3 = H



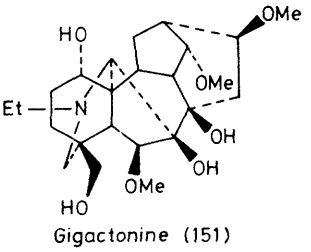
Gadenine (142) R^1 = H, R^2 = OH, R^3 = Bz
(144) R^1 = Ac, R^2 = OH, R^3 = Bz
Dihydrogadesine (148) R^1 = R^2 = R^3 = H



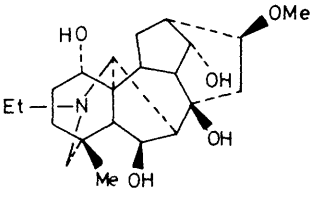
14-Acetyldelcaroline (145)



Pentagynine (147) R^1 = OMe, R^2 = R^3 = H
Gadesine (149) R^1 = H, R^2 = OMe, R^3 = OH
Pentagydine (150) R^1 = R^2 = H, R^3 = OH



Gigactonine (151)



Alkaloid B (152)

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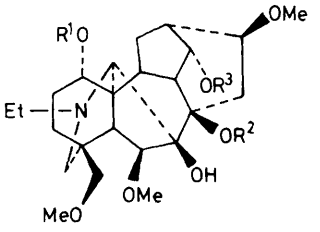
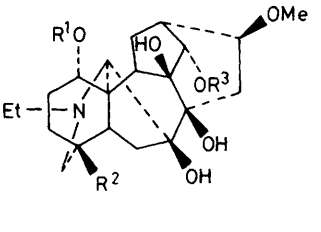
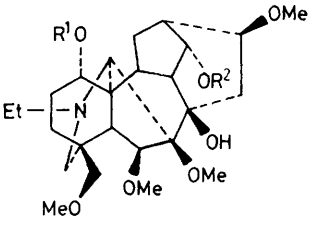


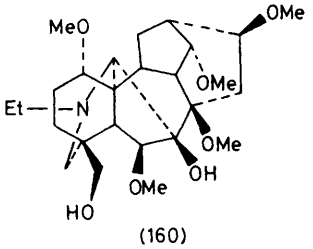
Deltatsine (153) $R^1 = R^3 = H$, $R^2 = Me$
(155) $R^1 = H$, $R^2 = R^3 = Me$
(156) $R^1 = R^2 = R^3 = Me$
(157) $R^1 = Ac$, $R^2 = R^3 = Me$
Delcosine (37) $R^1 = R^2 = R^3 = H$
(161) $R^1 = R^3 = Ac$, $R^2 = H$



Tatsinine (154) $R^1 = R^3 = H$, $R^2 = Me$
(162) $R^1 = R^3 = Ac$, $R^2 = Me$
Ranaconine (163) $R^1 = R^3 = Me$, $R^2 = OH$



(158) $R^1 = R^2 = H$
(159) $R^1 = R^2 = Me$



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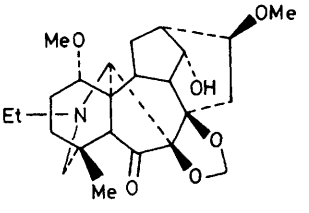
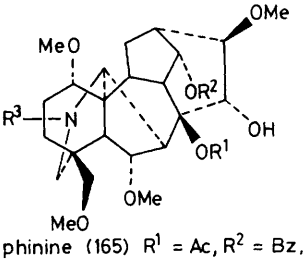
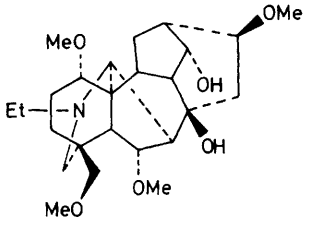


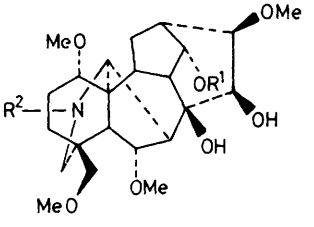
Yunnadelphinine (164)



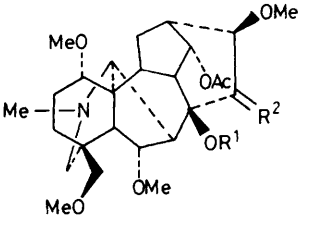
Isodelphinine (165) $R^1 = Ac$, $R^2 = Bz$, $R^3 = Me$
Penduline (166) $R^1 = Ac$, $R^2 = Bz$, $R^3 = Et$
Isodelphonine (167) $R^1 = R^2 = H$, $R^3 = Me$
(173) $R^1 = H$, $R^2 = Bz$, $R^3 = Me$



Chasmanine (70)



(168) $R^1 = Ac$, $R^2 = CHO$
(169) $R^1 = H$, $R^2 = Me$
(171) $R^1 = Ac$, $R^2 = Me$



(170) $R^1 = Ac$, $R^2 = H_2$
(172) $R^1 = H$, $R^2 = O$

penduline (166). Since chasmanine had previously been synthesized by Wiesner *et al.*,[68] the present work constitutes formal syntheses of (165) and (166). Two routes were studied for the preparation of isodelphonine (167), which is the target alkamine of isodelphinine. Chasmanine (70) was converted into (168) in a six-step sequence: acetylation with Ac_2O and TsOH, oxidation with $KMnO_4$ in aqueous acetone, formylation with HCO_2H and Ac_2O, pyrolysis, oxidation with *m*-chloroperoxybenzoic acid in CH_2Cl_2, and hydrolysis of an epoxide with HCO_2H. Reduction of (168) with $LiAlH_4$ gave 15-*epi*-isodelphonine (169). This structure was confirmed by an *X*-ray-crystallographic analysis (by direct methods) and refined to a final $R = 0.077$, based on 1852 reflections. The bond lengths and angles and the atomic parameters for all atoms other than hydrogen were presented. The β configuration of the 15-hydroxyl group in (168) was converted into the α configuration of isodelphonine (167) by oxidation of (168) (by Swern's method) followed by reduction with $LiAlH_4$, which gave a mixture of (167) and (169). These isomers were separated by flash chromatography, in yields of 35% and 41%, respectively. An improved route to (167) was later developed. Chasmanine (70) was converted into (170) by acetylation, oxidation by potassium permanganate, and methylation with CH_2O and $NaB(CN)H_3$. Pyrolysis of (170) followed by oxidation with OsO_4 gave (171). Oxidation of (171) produced (172), which was stereospecifically reduced to (167) with $LiAl(OMe)_3H$ at −70 °C. Treatment of (167) with one equivalent of PhCOCl in pyridine gave the 14-benzoate derivative (173). Protection of the 15-hydroxyl group as the trichloroethoxycarbonyl derivative, followed by acetylation of the hydroxyl at C-8 with AcCl or Ac_2O and TsOH and then deprotection with Zn in AcOH, afforded isodelphinine (165). Penduline (166) was prepared from chasmanine by a synthetic sequence that is analogous to the latter procedure.

4.2 Construction of the C/D Ring System of Isodelphonine

Botta[69,70] has published an account of the synthesis of a model compound (174) for the C/D ring system of isodelphonine (167). Similar procedures were used by Sakai and co-workers[67] (see Section 4.1) in their synthesis of isodelphinine. Starting from (175), which had previously been prepared by Wiesner and co-workers,[71] treatment with OsO_4 in pyridine–dioxane gave the diol (176) in quantitative yield. Oxidation of (176) with pyridine, DMSO, CF_3CO_2H, and dicyclohexylcarbodi-imide afforded (177) in 70% yield. Reduction of (177) with $NaBH_4$ in MeOH gave the *trans*-diol (178) in 80% yield. Acetylation of (178) with Ac_2O and TsOH, followed by treatment with 80% acetic acid, gave (179). Reduction of (179) with $LiAlH_4$ produced the *trans*-triol (174) in 70% yield.

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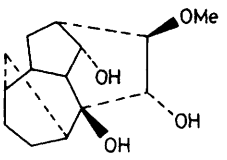

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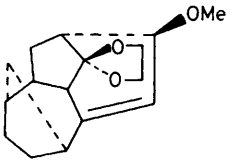

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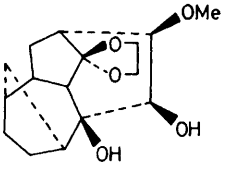

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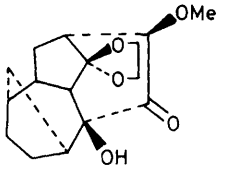
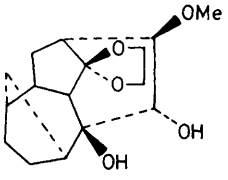
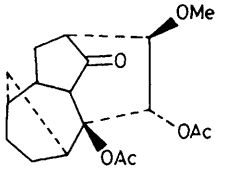


(177)



(178)



(179)

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5 References

1 K. Wiesner, *Tetrahedron*, 1985, **41**, 485.
2 S. W. Pelletier, B. S. Joshi, and H. K. Desai, 'Techniques for Isolation of Alkaloids', in 'Advances in Medicinal Plant Research', Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, 1985, pp. 153—195.
3 W. Wang, *Acta Bot. Yunnanica*, 1983, **5**, 153.
4 D. Brink, *Bull. Torrey Bot. Club*, 1982, **109**, 13.
5 J. D. Olsen, *J. Range Manage.*, 1983, **36**, 550.
6 I. Kitagawa, Z. Chen, M. Yoshihara, K. Kobayashi, M. Yoshikawa, N. Ono, and Y. Yoshimura, *Yakugaku Zasshi*, 1984, **104**, 858.
7 P. Xiao, L. Wang, and Y. Tong, *Yaowu Fenxi Zazhi*, 1983, **3**, 276.
8 Y. Zhou, W. Liu, G. Zeng, D. Chen, H. Li, and W. Song, *Yaoxue Xuebao*, 1984, **19**, 641.
9 R. Perlman and G. Guideri, *Arch. Int. Pharmacodyn. Ther.*, 1984, **268**, 202.
10 J. P. Pennec and M. Aubin, *Comp. Biochem. Physiol., C*, 1984, **77**, 367.
11 A. Hernanz and F. Silio, *Comp. Biochem. Physiol., C*, 1983, **76**, 335.
12 D. Chen, *Zhongcaoyao*, 1984, **15**, 180.
13 S. M. Ghiasuddin and D. M. Soderlund, *Comp. Biochem. Physiol., C.*, 1984, **77**, 267.
14 A. P. Naumov, *Toxins Tools Neurochem., Proc. Symp.*, 1983, 13.
15 M. Murayama and H. Hikino, *J. Ethnopharmacol.*, 1984, **12**, 25.
16 K. Hashimoto and J. Ushijima, *J. Coll. Dairy., Nat. Sci. (Ebetsu, Jpn.)*, 1983, **10**, 29.
17 T. N. Burushkina, V. M. Evdokimenko, V. G. Aleinikov, V. B. Stavinskii, and M. G. Kokarovtseva, *Vrach. Delo*, 1984, No. 2, p. 72.
18 I. Kitagawa, Z. Chen, M. Yoshihara, and M. Yoshikawa, *Yakugaku Zasshi*, 1984, **204**, 867.
19 M. Nakano and T. Yamagishi, *Hokkaidoritsu Eisei Kenkyushoho*, 1982, No. 32, p. 21.
20 M. Wang, B. Li, and F. Gao, *Yaoxue Xuebao*, 1983, **18**, 689.
21 I. Kitagawa, Z. Chen, M. Yoshihara, and M. Yoshikawa, *Yakugaku Zasshi*, 1984, **104**, 848.
22 W. Sun, X. Mu, and Z. Yang, *Zhongyao Tongbao*, 1984, **9**, 125.
23 S. Luo, S. Wu, and J. Tang, *Zhongcaoyao*, 1983, **14**, 399.
24 T. Hasegawa, M. Hasegawa, and S. Ohnishi, *Koenshu — Iyo Masu Kenkyukai*, 1983, **8**, 205.
25 H. K. Desai, B. S. Joshi, A. M. Panu, and S. W. Pelletier, *J. Chromatogr.*, 1985, **322**, 223.
26 T. Amiya, Y. Kanaiwa, H. Bando, and H. Suginome, *Chem. Lett.*, 1984, 859.
27 S. W. Pelletier, J. A. Glinski, and N. V. Mody, *J. Am. Chem. Soc.*, 1982, **104**, 4676.
28 A. Katz and H. Rudin, *Helv. Chim. Acta*, 1984, **67**, 2017.
29 B. Tashkhodzhaev and B. T. Salimov, *Khim. Prir. Soedin.*, 1983, 754.
30 K. I. Varughese and S. W. Pelletier, *J. Nat. Prod.*, 1984, **47**, 470.
31 S. W. Pelletier, J. A. Glinski, K. I. Varughese, J. A. Maddry, and N. V. Mody, *Heterocycles*, 1983, **20**, 413.
32 S. W. Pelletier, N. V. Mody, K. I. Varughese, J. A. Maddry, and H. K. Desai, *J. Am. Chem. Soc.*, 1981, **103**, 6536.
33 O. E. Edwards and M. Przybylska, *Can. J. Chem.*, 1982, **60**, 2661.
34 S. W. Pelletier and K. I. Varughese, *J. Nat. Prod.*, 1984, **47**, 643.
35 A. S. Narzullaev, M. S. Yunusov, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 1972, **8**, 498.
36 A. S. Narzullaev, M. S. Yunusov, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 1973, **9**, 443.
37 V. Boido, O. E. Edwards, K. L. Handa, R. J. Kolt, and K. K. Purushothaman, *Can. J. Chem.*, 1984, **62**, 778.
38 S. W. Pelletier, S. K. Srivastava, B. S. Joshi, and J. D. Olsen, *Heterocycles*, 1985, **23**, 331.
39 M. N. Sultankhodzhaev, M. S. Yunusov, and S.Yu. Yunusov, *Khim. Prir. Soedin.*, 1982, 265.
40 S. Chen, X. Ma, and Y. Wang, *Huaxue Xuebao*, 1984, **42**, 109.
41 S. W. Pelletier, S.-Y. Chen, B. S. Joshi, and H. K. Desai, *J. Nat. Prod.*, 1984, **47**, 474.
42 S. Chen and Y. Liu, *Yunnan Zhiwu Yanjiu*, 1984, **6**, 338.
43 D. Chen and W. Song, *Huaxue Xuebao*, 1983, **41**, 843.
44 F. Wu and Z. Zhu, *Lanzhou Daxue Xuebao, Ziran Kexueban*, 1983, **19**, 183.
45 S. Sakai, K. Yamaguchi, I. Yamamoto, K. Hotoda, T. Okazaki, N. Aimi, J. Haginiwa, and T. Okamoto, *Chem. Pharm. Bull.*, 1983, **31**, 3338.
46 S. Sakai, I. Yamamoto, K. Hotoda, K. Yamaguchi, N. Aimi, E. Yamanaka, J. Haginiwa, and T. Okamoto, *Yakugaku Zasshi*, 1984, **104**, 222.
47 W. Song, D. Chen, L. Wang, and P. Xiao, *Zhongcaoyao*, 1984, **15**, 5.
48 H. Hikino, Y. Kuroiwa, and C. Konno, *J. Nat. Prod.*, 1984, **47**, 190.
49 H. Wang, A. Lao, Y. Fujimoto, and T. Tatsuno, *Heterocycles*, 1985, **23**, 803.
50 D. Chen and W. Sung, *Zhiwu Xuebao*, 1984, **26**, 82.
51 B. S. Chung, S. K. Kim, H. K. Lee, and S. H. Kim, *Saengyak Hakhoe Chi (Hanguk Saengyak Hakhoe)*, 1984, **15**, 108.
52 Z. M. Vaisov, B. T. Salimov, and M. S. Yunusov, *Khim. Prir. Soedin.*, 1984, 800.
53 A. S. Narzullaev, V. M. Matveev, and S. S. Sabirov, *Rastit. Resur.*, 1984, **20**, 123.
54 V. M. Matveev, A. S. Narzullaev, and S. S. Sabirov, *Khim. Prir. Soedin.*, 1983, 657.
55 V. M. Matveev, A. S. Narzullaev, S. S. Sabirov, and M. S. Yunusov, *Khim. Prir. Soedin.*, 1985, 131.
56 A. S. Narzullaev, M. S. Yunusov, and S.Yu. Yunusov, *Khim. Prir. Soedin.*, 1973, **9**, 497.
57 Q. Jiang and W. Sung, *Heterocycles*, 1984, **22**, 2429.
58 Q. Jiang and W. Sung, *Heterocycles*, 1985, **23**, 11.
59 A. G. Gonzalez, G. de la Fuente, M. Reina, P. G. Jones, and P. R. Raithby, *Tetrahedron Lett.*, 1983, **24**, 3765.
60 A. G. Gonzalez, G. de la Fuente, M. Reina, and I. Timon, *Heterocycles*, 1984, **22**, 667.
61 A. G. Gonzalez, G. de la Fuente, and R. Diaz Acosta, *Heterocycles*, 1984, **22**, 17.
62 A. G. Gonzalez, G. de la Fuente, R. Diaz, P. G. Jones, and G. M. Sheldrick, *Tetrahedron Lett.*, 1983, **22**, 959.
63 L. V. Beshitaishvili, M. N. Sultankhodzhaev, and M. S. Yunusov, *Khim. Prir. Soedin.*, 1984, 671.
64 B. S. Joshi, J. A. Glinski, H. P. Chokshi, S. Chen, S. K. Srivastava, and S. W. Pelletier, *Heterocycles*, 1984, **22**, 2037.
65 J. A. Glinski, B. S. Joshi, S. Chen, and S. W. Pelletier, *Tetrahedron Lett.*, 1984, **25**, 1211.
66 S. Luo, M. Liou, and W. Chen, *Yunnan Zhiwu Yanjiu*, 1984, **6**, 108.
67 S. Sakai, H. Takayama, K. Yamaguchi, N. Ide, and T. Okamoto, *Yakugaku Zasshi*, 1984, **104**, 731.
68 K. Wiesner, T. Y. R. Tsai, and K. P. Nambiar, *Can. J. Chem.*, 1978, **56**, 1451.
69 M. Botta, *Gazz. Chim. Ital.*, 1983, **113**, 439.
70 M. Botta, *Diss. Abstr. Int. B*, 1980, **60**, 1766 (*Chem. Abstr.*, 1981, **94**, 175341).
71 K. Wiesner, P. T. Ho, W. C. Liu, and M. N. Shanbhag, *Can. J. Chem.*, 1975, **53**, 2140.

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