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Recent developments in diterpene alkaloid chemistry in China

LIANG Xiao-Tien
Institute of Materia Medica, Chinese Academy of Medical Sciences, Beijing 100050, China

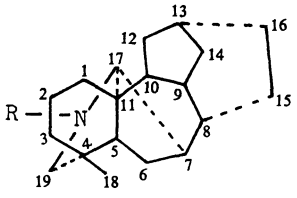
Abstract - This review covers 61 new diterpene alkaliids studied in China in recent years. They were isolated mainly from Aconitum species, and also from one Delphinium and one Spiraea species. The structurally new features in the C_{19}-alkaloids include 5-OH and 15 -OH. In the C_{18}- category, C-6 oxygenation was observed for the first time. ^{13}C-NMR of some alkaloids were discussed. In alkaline media, the spontaneous rupture of the C(14)-C(20) bond of hetidine (63) is captured by the 2 -OH to form a new oxygen heterocycle. Acidification leads to facile regeneration of this bond. The hydrochloride of spiredine exists mainly in the form (68) where the C-6 keto group is involved. The immonium form (67) can be detected as the minor isomer in aqueous solution. CD spectra can be used to differentiate the positions of the keto functions at C-6, C-11 and C-13 of the hetidine type alkaloids.

The advent of ^{13}C-NMR spectrometry as a routine tool has vastly facilitated the unraveling of complex structures of the diterpene alkaloids. This review deals with 61 new structures uncovered in China from 1979 onward. At the time of this writing, more than twenty of these have not yet been published. To avoid excessive duplication of structural sketches, these compounds are grouped into skeletal types I-VI. All of the 61 new compounds are assembled in Table 1. Here the arbitrary distinction between V and VI is mainly dictated by convenience of presentation. Following the suggestion of some authors (ref. 1), type II has been set apart from I and designated as C_{18}-alkaloids.

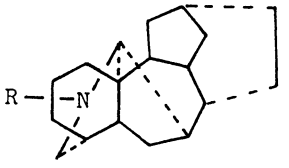
In the period covered, about 30 Aconitum species were examined, along with a few Delphinium and one Spiraea species. However, species yielding only known akaloids are not listed in Table 1.

Configurational designations of and for C-13 substituents in a few compounds of type III tend to be confusing, although they are in accord with literature practice. They become unequivocal if one flattens out any of the six-membered rings containing C-13 with the N-atom away from the viewer.

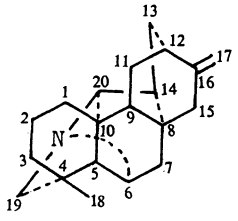
As can be seen from Table 1, C_{19}-alkaloids comprise about half of the total. Novel features worthy of note in the C_{19}-category include the following. For the first tome in nature, we have in 8 a 15β-hydroxy aconitine-type alkaloid. So is also the case for the novel NH group of compound 15. In compounds 21



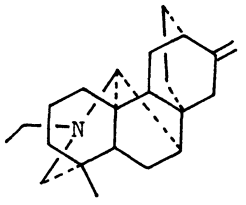
I (C_{19}-)
30 entries



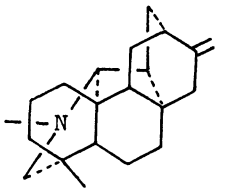
II (C_{18}-)
11 entries



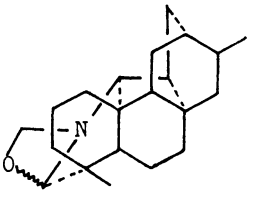
III (C_{20}-)
11 entries



IV (C_{20}-)
4 entries



V (C_{20}-)
1 entry

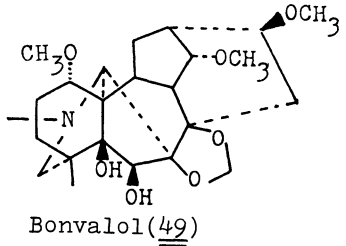


VI (C_{20}-)
4 entries

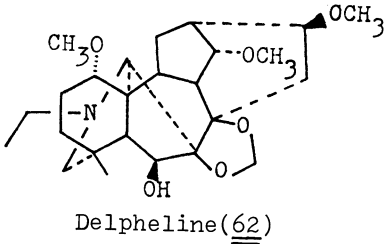
and 22 there is a tertiary hydroxyl at C-14 while C-15 is not oxygenated. Compound 32 is the first diaroyl ester on record. And compounds 48, 49 and 50 distinguish themselves as lycoctonine-type alkaloids oxygenated at C-5.

Compounds 46 and 47 are the first examples of C-6 oxygenated C_{18}-alkaloids.

The structures of bonvalol(49) and delpheline(62) (ref.32) are very similar, the main difference being the presence of an extra β-OH group at C-5 in 49. The ^{13}C-NMR data of 62 for C-9 and C-10 are 47.9 and 40.3 ppm, respectively, to be compared with the corresponding values of 40.4 and 40.4 for 49. This is in contradiction with the expected γ-effect which should be operative in 49 to give a sizable upfield shift for the C-10 signal, leaving C-9 relatively unaffected. Thus the C-9 and C-10 assignments for 62 and quite a number of related structures probably need revision.



Bonvalol(49)



Delpheline(62)

TABLE 1. New diterpene alkaloids

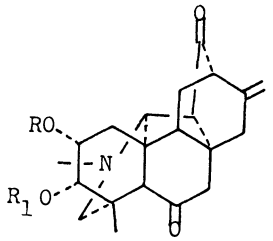
Source	Compound & structure[a]	ref.
Aconitum jinyangense W.T. Wang		
	(1) jynosine IV,11β-OH,15β-OAc	2
A. franchetii Fin. et Gagn.		
	(2) ludaconitine I,3α,8,13-triOH,1α,6α,16β,18-tetraOMe,14α-OBz,NEt	3
	(3) franchetine I,1α,16β,18-triOMe,14α-OBz,NEt,$\Delta^{5,6}$,7,17-ether	4
A. stapfianum H.M.		
	(4) 8-deoxy-14-dehydroaconosine II,1α,16β-diOMe,14-keto,NEt	5
A. crassicaule		
	(5) crassicauline A I,13-OH,1α,6α,16β,18-tetraOMe,8-OAc,14α-OAn,NEt	6
	(6) crassicauline B III,1β,7α-diOH,13β-OBz	7
	(7) crassicaulidine I,1α,3α,8,14α,15β-pentaOH,6α,16β,18-triOMe,NEt	6,7
	(8) crassicaulisine I,1α,8,14α,15β-tetraOH,6α,16β,18-triOMe,NEt	8
A. episcopale Le'vl.		
	(9) episcopalisine II,8,9β-diOH,1α,16β-diOMe,14α-OBz,NEt	1
	(10) episcopalisinine II,8,9β,14α-triOH,1α,16β-diOMe,NEt	1
	(11) episcopalitine II,8,13-diOH,1α,16β-diOMe,14α-OBz,NEt	1
	(12) episcopalidine V,2α-OAc,3α-OBz,6,13-diketo	1,9
	(13) scopaline II,1α,8,14α-triOH,16β-OMe,NEt	10
A.flavum Hand.-Mazz.		
	(14) 3-acetylaconitine I,13,15α-diOH,1α,6α,16β,18-tetraOMe, 3α,8-diOAc,14α-OBz,NEt	11
	(15) flavaconitine I,1α,10β,13,15α-tetraOH,6α,16β,18-triOMe, 8-OAc,14α-OBz,NH	12
A. gymnandrum Maxim.		
	(16) gymnaconitine I,1α,8-diOH,16β,18-diOMe,14α-ODc,NEt	13
	(17) methylgymnaconitine I,8-OH,1α,16β,18-triOMe,14α-ODc,NEt	13
A. finetianum Hand.-Mazz.		
	(18) finaconitine II,7,8,9β,10β-tetraOH,1α,14α,16β-triOMe,4-OAb,NEt	14
	(19) N-deacetylranaconitine II,7,8,9β-triOH,1α,14α,16β-triOMe,4-OAt,NEt	15
	(20) N-deacetylfinaconitine II,7,8,9β,10β-tetraOH,1α,14α,16β-triOMe, 4-OAt,NEt	15
A. coreanum (Le'vl.) Rapaics		
	(21) guan-fu base A III,13α,14-diOH,2α,11α-diOAc	16
	(22) guan-fu base G III,14-OH,2α,11α,13α-triOAc	16
A. busnezoffii Reichb.		
	(23) beiwutine I,3α,10β,13,15α-tetraOH,1α,6α,16β,18-tetraOMe, 8-OAc,14α-OBz,NMe	17
A. hemsleyanum Pritz.		
	(24) guayewuanine A I,8,10β,13,15α-tetraOH,1α,18-diOMe,14α-OAn,NEt	18
A. nagarum Stapf var. lasiandrum W.T. Wang		
	(25) 14-acetylneoline I,1α,8-diOH,6α,16β,18-triOMe,14α-OAc,NEt	19
	(26) 10-hydroxyaconitine I,3α,10β,13,15α-tetraOH,1α,6α,16β,18-tetraOMe, 8-OAc,14α-OBz,NEt	20
A. pendulum Busch		
	(27) penduline I,15α-OH,1α,6α,16β,18-tetraOMe,8-OAc,14α-OBz,NEt	21

TABLE 1. (continued)

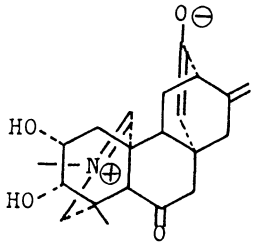
A. pseudohuiliense	
(28) lepenine IV,1α,11β,15β-triOH	22
(29) lepedine IV,11β,15β-diOH,1α-OMe	22
(30) lepetine IV,1α,15β-diOH,11β-OAc	22
A. tanguticum	
(31) tanwusine A III,2α,7β,13α,15β-tetraOH	22
A. forrestii	
(32) liwaconitine I,13-OH,1α,6α,16β,18-tetraOMe,8,14α-diOAn,NEt	23
(33) 8-deacetylyunaconitine I,3α,8,13-triOH,1α,6α,16β,18-tetraOMe, 14α-OAn,NEt	24
(34) 6-hydroxytalatisamine I,6α,8,14α-triOH,1α,16β,18-triOMe,NEt	24
A. scaposum var. vaginatum	
(35) vaginatine I,6β,7,8,14α-tetraOH,1α,16β,18-triOMe,NEt	22
(36) vaginaline I,6β,7,8-triOH,1α,16β,18-triOMe,14-keto,NEt	22
(37) vaginadine I,7,8-diOH,1α,16β,18-triOMe,6,14-diketo,NEt	22
A. duclouxii	
(38) duclouxine I,12β,13-diOH,1α,6α,16β,18-tetraOMe,8-OAc,14α-OBz,NEt	25
A. vilmorrianum Kom.	
(39) vilmorrianine A I,3α-OH,1α,6α,16β,18-tetraOMe,8-OAc,14α-OAn,NEt	26
(40) vilmorrianine C I,1α,6α,16β,18-tetraOMe,8-OAc,14α-OAn,NEt	26
(41) vilmorrianine D I,8,14α-diOH,1α,16β-diOMe,NEt	26
A. hemsleyanum var. circinatum	
(42) yunaconitine I,3α,13-diOH,1α,6α,16β,18-tetraOMe,8-OAc,14α-OAn,NEt	27
A. delavyi	
(43) delavaconitine II,8,13-diOH,1α,16β-diOMe,14α-OBz,NEt	28
Delphinium bonvalotii Franch.	
(44) delbotine I,1α,7-diOH,6β,8,14α,16β,18-pentaOMe,NEt	29
(45) delbonine I,1α,7-diOH,6β,8,16β,18-tetraOMe,14α-OAc,NEt	29
(46) delbine II,1α,4,7,8,14α-pentaOH,6β,16β-diOMe,NEt	29
(47) delboxine II,1α,7-diOH,6β,8,14α,16β-tetraOMe,3β,4β-epoxy,NEt	29
(48) bonvalotine I,5β-OH,1α,14α,16β-triOMe,7,8-OCH_2O-,6β-OAc,NMe	30
(49) bonvalol I,5β,6β-diOH,1α,14α,16β-triOMe,7,8-OCH_2O-,NMe	30
(50) bonvalone I,5β-OH,1α,14α,16β-triOMe,7,8-OCH_2O-,6-keto,NMe	30
Spiraea japonica L.f. var. fortunei(Planch.)Rehd.	
(51) III,13-keto	31
(52) III,13α-OH	31
(53) III,11-keto	31
(54) III,6,13α-diOH	31
(55) III,6,13β-diOH	31
(56) III,6,13α-diOH,11-keto	31
(57) III,6,13β-diOH,11-keto	31
(58) VI,16α-OH,6-keto	31
(59) VI,16β-OH,6-keto	31
(60) VI,9β-OH,6,11-diketo,$\Delta^{16,17}$	31
(61) VI,9β-OH,6-keto,$\Delta^{15,16}$	31

[a] Bz=COC_6H_5, An=COC_6H_4OMe(p), Dc=COCH:$CHC_6H_3(OMe)_2$(3,4), Ab=COC_6H_4NHAc(o), At=$COC_6H_4NH_2$(o).

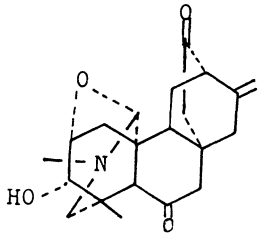
Episcopalidine(12) is an esterified form of hetidine(63) recently available to us in gram quantities. We were at first led astray in the elucidation of the structure(12) by the absence of the C-6 carbonyl signal in the ^{13}C-NMR spectrum and the presence of a spurious peak in the middle-field region. The missing C-6 signal in episcopalidine turned out to be due to its long relaxation time T_1 as the result of the presence of the benzoyl group which serves as part of a major axis of rotational motion for the whole molecule. A delay of 10 seconds is needed for the detection of the C-6 signal. In contrast, the cyclohexanecarboxylic ester as well as hetidine itself apparently are devoid of a major axis and behave normally toward ^{13}C-NMR data acquisition.



(12) R=Ac, R_1=COC_6H_5
(63) R=R_1=H



(64)



(65)

Spatial proximity of the amino nitrogen to the C-6 carbonyl in hetidine(63) and its analogs results in a trans-annular effect and the carbonyl oxygen is the site of protonation upon salt formation. The ^{13}C-NMR signal for C-6 in the salt form is thus in the neighborhood of 100 ppm as contrasted with the shift of ca. 200 ppm for the original carbonyl. Thus the adventitious presence of trace amounts of acidic impurities, almost unavoidable with $CDCl_3$ as the solvent, will give rise to large deviations for the C-6 signal. As an example, we obtained a signal at 202.2 for the C-6 of a hetidine sample which moved to 207.6 upon shaking with aqueous base. Apparently the last-mentioned value is the true chemical shift. A rough estimate shows that in the unwashed solution the hetidine molecules were transformed into the salt form to the extent of about 5%. The chemical shifts of the other carbons are of course barely affected.

We have devised a number of approaches (ref. 9) for the rupture and regeneration of the C(14)-C(20) bond in hetidine(63) or episcopalidine(12). One successful approach thus far was by simple refluxing of hetidine in methanolic alkali. Here spontaneous cleavage of the C(14)-C(20) bond gives the intermediate 64, the immonium moiety of which is trapped intramolecularly by the 2α-OH group to form an oxa-heterocycle. The product (65) reverts easily to 63 upon treatment with acid, regenerating the C(14)-C(20) bond.

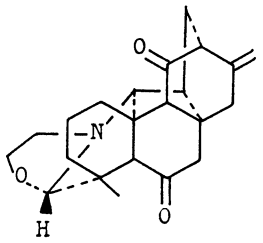
The formation of 65 was actually foreshadowed by the fact that saponification of 12 even at room temperature would give alongside of the expected 63 an additional faint spot on TLC with higher Rf value, which was later shown to be 65.

The only species of Spiraea japonica recently examined by us turned out to be

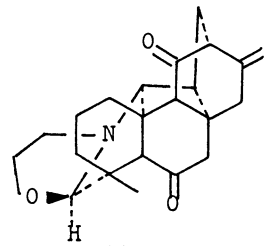
a rich source of unreported structures. We have listed a major part of them in Table 1 (51 to 61).

CD has proved very useful for the allocation of certain keto groups in structural types III-VI (ref. 31). Thus C-11 and C-13 keto groups give rise to strongly positive and negative Cotton effects, respectively, at ca. 305 nm. 6-Keto groups have a negative extremum at 290 nm with much lower amplitude, which can be completely quenched by acidification (salt formation). The contribution and hence the presence of the C-6 carbonyl can be readily assessed by the attendant change upon acidification even if it is hidden in the much stronger C-13 carbonyl extremum.

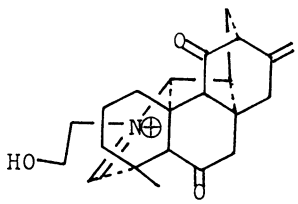
Compounds of type VI contain an oxazolidine ring which gives rise to two epimers at C-19, a phenomenon with ample precedence. Spiredine(66), for example, exists in two forms (66a & 66b) in about equal proportions(ref. 31). Upon



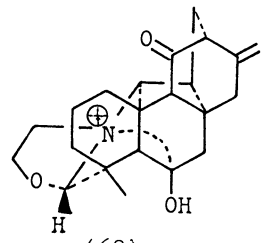
(66a)



(66b)



(67)



(68)

acidification, there are two possibilities for salt formation. One is the open chain immonium (67), and the other is 68. Both forms are by nature configurationally homogeneous. This is obviously true for the sp^2-trigonal C-19 of 67, and in 68 (with C-19 S) the C-19R epimeric alternative has prohibitively high strain. ^{13}C-NMR of the salt in methanol showed the salt to be predominantly in the form of 68, to the virtual exclusion of 67. The latter, however, must have had at least transient existence in order to mediate the conversion of 66b to 66a, leading to the ultimate formation of 68. In aqueous medium, the existence of 67 as a minor isomer was detected.

Facile interconversions with the intermediacy of 67 have thus far thwarted our attempts of obtaining epimer 66a as a pure entity by basification of 68 with rapid work-up.

The interaction of the lone pair of electrons on nitrogen with the C-6 carbonyl would lead to trans- and cis-fusions of the oxazolidine rings in 66a and 66b, respectively, the N-atom behaving here as if configurationally inflexible. Here the involvement of the electron pair further accentuates the situation during salt formation, which utilizes only the oxygen atoms as sites of protonation, forming 67 and 68. It remains to be seen if N-protonation occurs to any extent in oxazolidine-containing molecules with no C-6 carbonyl.

Out of the rich sources of Aconitum and Delphinium genera in China, about 65 species have been used in traditional herbal medicine as well as in folk-lore prescriptions (ref. 33) for anti-inflammatory, anti-bacterial, analgesic and anti-rheumatic purposes, and for the treatment of cardio-vascular diseases. As promising clinical applications of pure isolates with rather recent vintage, we may cite the use of the analgesic lappaconitine, addiction-free (ref. 34), and also of 3-acetylaconitine (ref. 35). However, much pharmacologic work still remains to be done in order to fully exploit the multifaceted activities of various diterpene alkaloids.

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