STUDIES ON THE DITERPENE ALKALOIDS OF THE CHINESE DRUG, ACONITUM SPP.

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Abstract— Ten new diterpene alkaloids recently isolated from Chinese aconites are reviewed.

Chinese aconites, a kind of important and common drug in Chinese traditional medicine, were widely used for a long time to improve blood circulation, assuage pain and fracture. It was stated that there are 167 species of aconites grown in China, among them 44 kinds have been used in medicine. Aconitic roots contain many diterpene alkaloids which have very complex chemical structures and high biological activity. Our work about Chinese aconites have been started since the 50's of this century, and more than thirty diterpene alkaloids have been isolated from fifteen species of those roots during these years.[1] In this paper some diterpene alkaloids recently isolated from Chinese aconites in our laboratory are summarized.

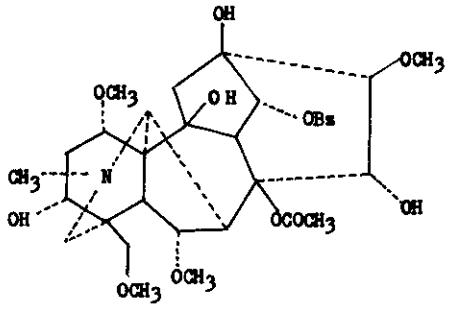
1. Aconitine-type alkaloids

1) Beiwutine and Nagarine

Aconitum kusnezoffii is commonly used as an analgesic agent in the northeast district of China. Besides aconitine, mesaconitine and hypaconitine, a new alkaloid named beiwutine (1), $C_{33}H_{45}NO_{12}$, mp 196-198°, has been isolated from this plant. This alkaloid was found to possess the same skeleton as mesaconitine (2) but with one more hydroxy group after comparing their molecular formulae, functional groups and spectra data such as ir, uv, ms and nmr. The C-14 proton signal of beiwutine (δ 5.28) showing a downfield shift of 0.4 ppm in comparison with that of mesaconitine (δ 4.84) should be due to the effect of a hydroxy group at C-10 position as in the case of known aconitine-type alkaloids, dictyocarpine, elidamine and elidenine. This together with the downfield change of C-10 (31.5 ppm) in ^{13}C nmr suggests the C-10 location of the additional hydroxy group.[2]

In recent years another new alkaloid, called nagarine (3), $C_{34}H_{47}NO_{12}$, mp 198-200°, has been obtained from Aconitum nagarum stapf var. lasiandrum, collected in yunnan province. The structural difference between nagarine and aconitine (4) is just the same as bewutine and mesaconitine according to spectral analyses. The presence of a C-10 hydroxy group was indicated in nmr of nagarine, showing a 0.54 ppm downfield shift of the signal at C-14 and

confirmed by NOE, a 20% enhancement was observed on irradiating δ 3.00 (OH) signal. The hydroxy group at position C-10 must be in the same direction as C-14 proton, say at β-configuration.[3]



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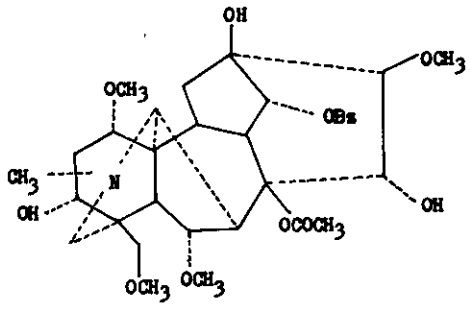

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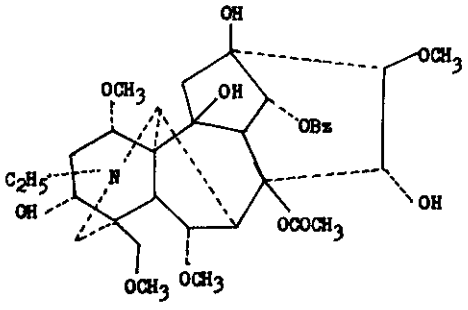

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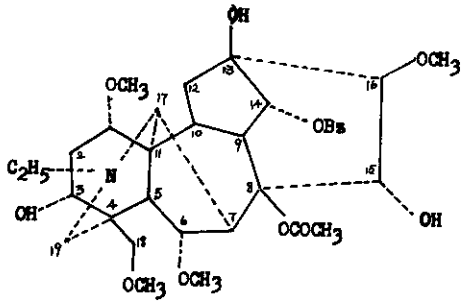

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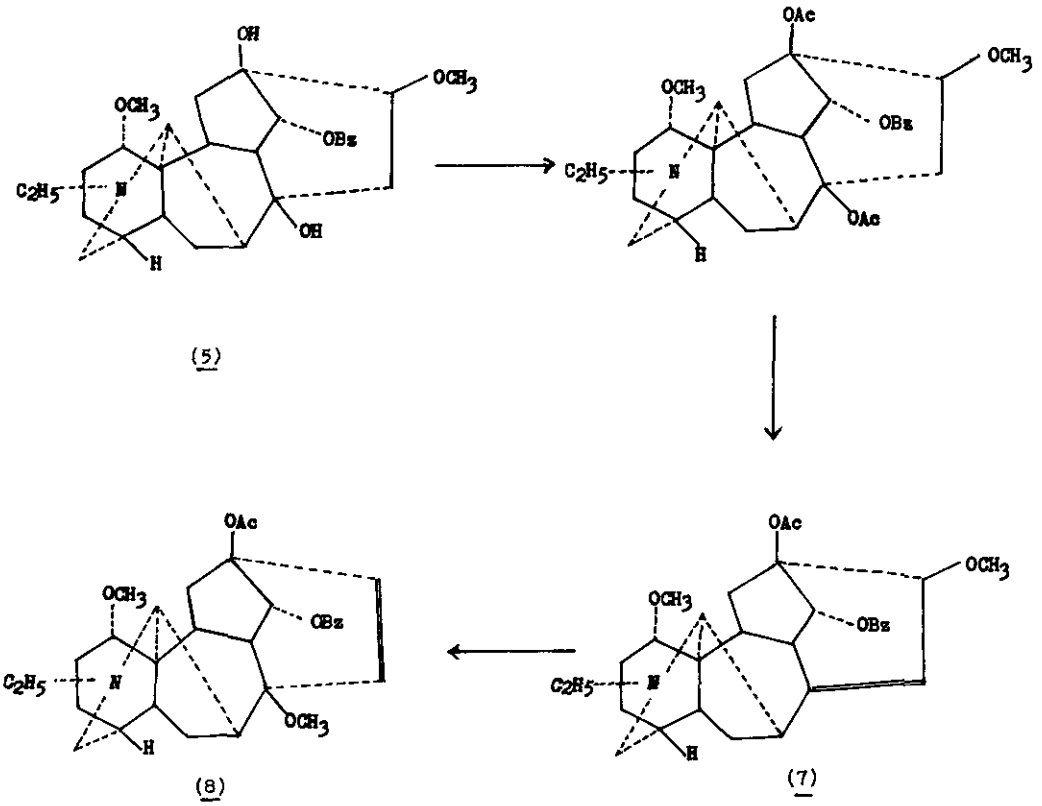
2) Delavaconitine and Isoaconitine

Delavaconitine (5) and isoaconitine (6) have been isolated from Aconitum delavayi in 1955[4,5], but their structures were unsolved.

We have revised the molecular formula of delavaconitine as $C_{29}H_{39}NO_6$, and established a rational formula $C_{18}H_{21}(OCH_3)_2(OH)_2(OCOC_6H_5)NC_2H_5$ for it, on the basis of spectral data and hydrolysis. It favored a deoxymethylene aconitine-type skeleton. Delavaconitine after acetylation was pyrolysed to afford pyrodelavaconitine (7) (($C_{31}H_{39}NO_6$ $HClO_4$, mp 268-269°) which possesses a characteristic change at λ_{max} 224 mμ in uv spectrum as pyroaconitine. Pyrodelavaconitine in acidic medium can be isomerized to isopyrodelavaconitine (8), mp 76-79°. Nmr spectra of the latter showed a shift of the two signals of olefinic protons δ 5.50 and δ 4.24, to δ 5.59 and δ 5.89 and the methoxyl protons (3H) at C_{16} from δ 3.68 to δ 2.98. This indicates that delavaconitine may possess C_{14}-OBz, C_8-OH, and C_{16}-OCH_3. Besides, a peak at

m/e 464 ($M-OCH_3$) in mass spectrum showed the presence of a methoxyl group at C-1 position. Therefore, the structure of delavaconitine is suggested as follows.[6]



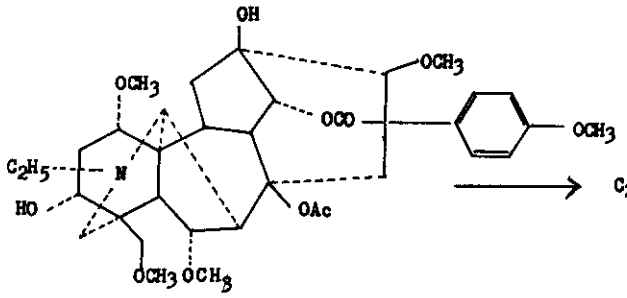
Isoaconitine (6), $C_{25}H_{49}NO_{11}$, mp 144-146°, on hydrolysis with 5 % methanolic potassium hydroxide afforded the corresponding amino alcohol (9), acetic acid and anisic acid. The physical and chemical properties of the amino alcohol and its acetate are similar to those of pseudoaconine and acetylpseudoaconine respectively. An upfield shift (about δ 1.00) of the signal of acetyl protons in nmr spectrum indicates the connection of an aromatic acid at C_{14} position. Hence the structure of isoaconitine may be represented as (6).[7]

3) Penduline and Deoxyaconitine

Deoxyaconitine (10) was first found as an impurity in market aconitine and may be obtained also from aconitine through dehydration and hydrogenation. However, it is a common constituent in Chinese aconites such as A. kusnezoffii and A. pendulum etc.

Deoxyaconitine differs from aconitine only in the absence of a hydroxy group at C-3 position. Another new alkaloid named penduline (11), $C_{34}H_{47}NO_9$, mp 166-167°, with still one less hydroxy group has been isolated from A. pendulum.

Based on the mass spectrum and nmr analysis the structure of penduline was provisionally assigned to be 3,13-dideoxyaconitine.[8]



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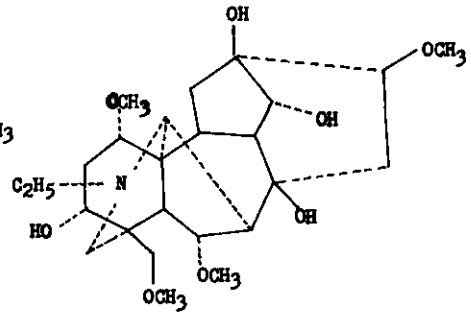

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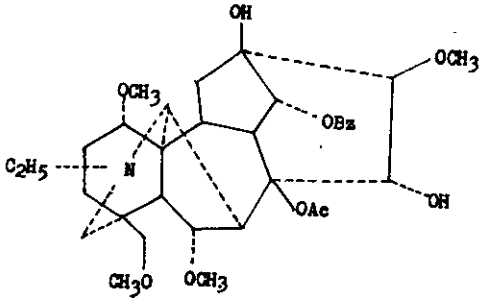

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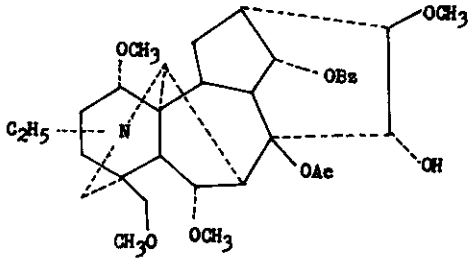

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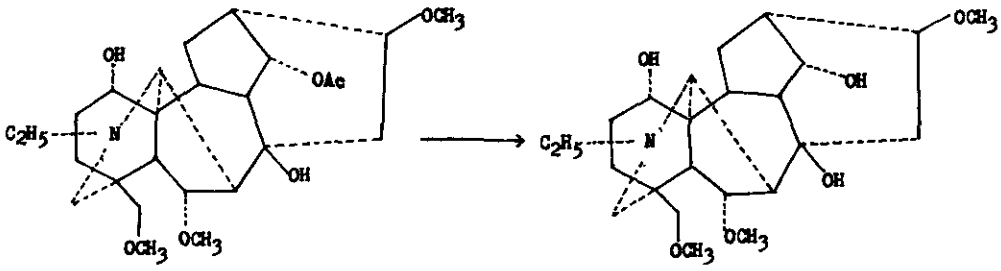
4) 3-Acetylaconitine and 14-Acetylneoline

3-Acetylaconitine (12), $C_{36}H_{49}NO_{12}$, mp 196-197°, as a naturally occurring alkaloid has been recently isolated from Chinese aconites, A. pendulum and A. feavum.[9]

It can be obtained by acetylation of aconitine with acetic anhydride and pyridine at room temperature. Nmr and ^{13}C nmr spectra support that acetylation occurs at the C-3 hydroxy group.

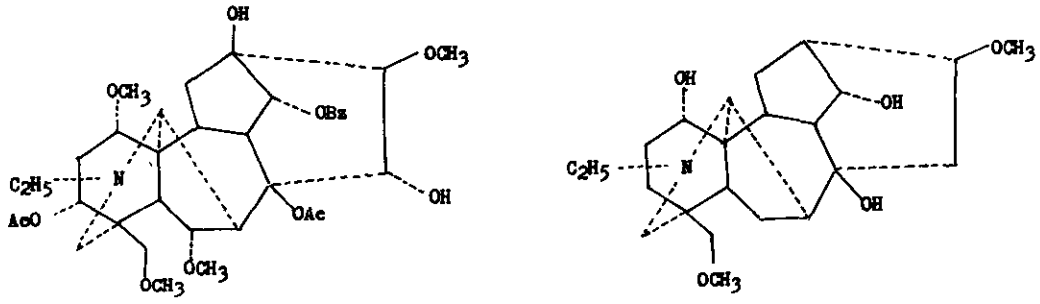
Besides songoring (13), bullatine-A, aconitine, deoxyaconitine, neoline and nagarine, an unknown alkaloid, bullatine C (14), $C_{26}H_{41}NO_7$, mp 198-202°, has been isolated from Aconitum nagarum var. lasiandrum. When bullatine C was hydrolyzed with alkali, an amino alcohol, identical with neoline (15), was obtained along with acetic acid. Thus bullatine C is an acetylneoline. A downficed shift of 1.13 ppm of C-14 proton in nmr of bullatine C in comparison with neoline indicated the C-14 location of the acetylated hydroxy group which was further

confirmed by oxidizing it to give a six-memberered ring ketone (ir 1690 cm^{-1}).[10]



(14) (15)

Chuan-wu and Fu-tzu, Aconitum carmichadi are famous Chinese traditional drug. Among the six alkaloids isolated from it, five ones were identified as aconitine, hypaconitine, mesaconitine, talatisamine and isotalatisamine, and one was reported to be a new compound, previsionally named chuan-wu base A, $C_{22}H_{35}NO_5$, mp 111°. But later it was proved to be identical in all respects with isotalatizidine (16) after comparing with an authentic sample.



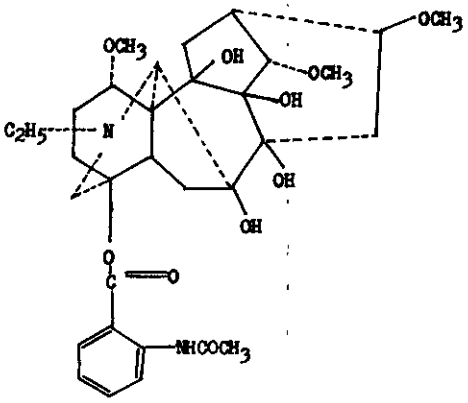
(12) (16)

2. Lycoctonine-type alkaloids

Recently, a few lycoctonine-type alkaloids such as rannaconitine (17), $C_{32}H_{44}N_2O_9$, mp 130-131°, avadcharidine, lycoctonine and a new alkaloid finaconitine (18), $C_{32}H_{44}N_2O_{10}$, mp 220-221°, have been isolated from Aconitum finetianum.[11, 12] The structure of rannaconitine was proved to be a lycoctonine-type alkaloid with N-acetylanthranilic acid jointed to C-4 position by Pelletier using ^{13}C nmr spectrum in 1978.[13]

Treatment of finaconitine with 1 % KOH in methanol yielded N-acetylanthranilic acid. A correlation of the ^{13}C nmr of finaconitine was made with rannaconitine. The pattern of ^{13}C chemical shifts of finaconitine is similar to that of rannaconitine except a few changes.

The appearance of a new signal at 78.5 ppm and disappearance of a peak at 36.5 ppm in the ^{13}C nmr spectrum of finaconitine in comparison with that of rannaconitine suggested the presence of a tertiary hydroxy group at C-10 position in finaconitine. Downfield changes in ^{13}C chemical shift of the adjacent C-11, C-9 and C-12 carbons also favor the above suggestion.[11]



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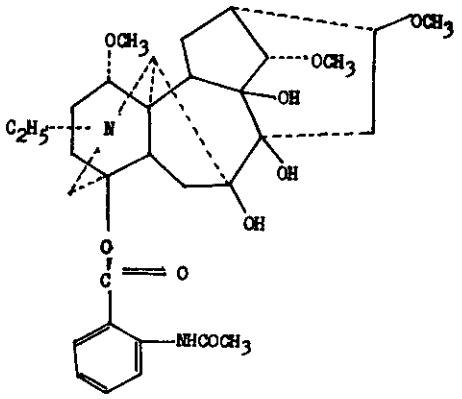

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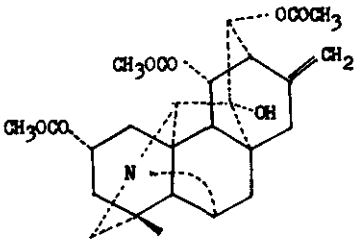
It was noted that all Chinese aconites containing lycoctonine-type alkaloid belong to rattan aconites. This fact may be interesting to taxonomist.

3. Veatchine and Atisine type alkaloids.

Some C-20 diterpene alkaloids such as bullatine A, $C_{22}H_{33}NO_2$, bullatine G, $C_{22}H_{31}NO_3$; guan-fu base A, $C_{24}H_{31}NO_6$; guan-fu base B, $C_{22}H_{29}NO_5$ and guan-fu base C, $C_{22}H_{33}NO_2$, have been isotated from Aconitum bullatifolium var. homotorichum and A. koreanum a few years ago.[14, 15] Other two new alkaloids guan-fu base G (19) $C_{26}H_{33}NO_7$, mp 178°, and guan-fu base F, $C_{26}H_{35}NO_6$, mp 184°, have also been isolated from the same plant. The formula of base G can be expressed as $C_{20}H_{23}N(OCOCH_3)_3OH$ which belongs to hetisine type.

The structure and configuration of guan-fu base G has been determined by x-ray analysis of the methyl iodide of guan-fu base G crystalized from a mixture of acetone and ethyl ether. Precession photographs showed the crystal to be of space group D_2^4-$P2_12_12_1$. The following cell dimensions were obtained from diffractometer measurements: a=16.781Å, b=16.730Å, C=10.093 Å, Z=4. Three dimensional data were collected on a Phillips diffractometer. Ring A is a chair trans-fused to ring B which is in chair form; ring C has a boat conformation and is also transfused to ring B. It is interesting to note that base G presents the first example

in hitisine-type alkaloid with a C-13 tertiary alcohol while the oxygen containing group at C-15 is missing.



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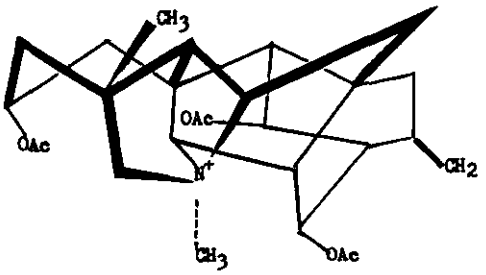
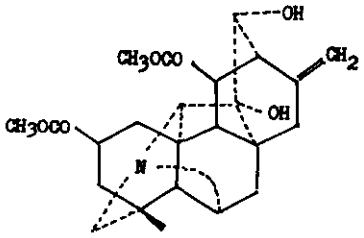


(19)

Both guan-fu base A and guan-fu base G gave the same amino alcohol besides acetic acid on hydrolyisi. Acetyl guan-fu base G was proved to be identical with diacetyl guan-fu base A. This indicates that guanOfu base G is a monoacetate of guan-fu base A. The result of double resonance decoupling technique showed that a hydroxy group and an acetyl group of guan-fu base A must be located vicinial to C-12, Consequently, the structure of guan-fu base A could be represented as (20).[16]



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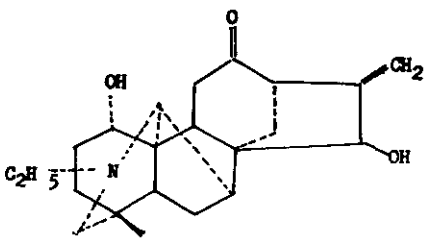

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Preliminary animal tests revealed that songorine, neoline, nagarine, beiwutine, penduline, lappaconitine and 3-acetylaconitine exhibited analgesic and local anethesia acetivity.[17] Further chemical and pharmacological studies in this field are in progress with the aim of exploring the possibilities of utilizing the abundent resources of Chinese aconite plants in medical practice.

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