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THE DITERPENE ALKALOIDS. THREE NEW DITERPENE LACTONE ALKALOIDS FROM ACONITUM HETEROPHYLLUM WALL

S. W. Pelletier and R. Aneja*

The Department of Chemistry, The University of Georgia, Athens, Georgia, U. S. A.

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The rhizomes of the Indian plant, Aconitum heterophyllum Wall (Ranunculaceae), to date have yielded five well-characterized diterpene alkaloids,[1] atisine[1b,2,3], atidine[4,5], hetisine[6-9], heteratisine[6,10,11,12] and benzoylheteratisine[13]. We have isolated from this plant three new alkaloids for which we propose the names heterophyllisine, heterophylline, and heterophyllidine, and the structures (I), (II), and (III) respectively. They are, thus, further representatives of the lactone-type diterpene skeleton, hitherto unique to heteratisine (IV)[6,10,11,12].

These alkaloids occur in extremely small amounts in the plant and were isolated from the heteratisine mother liquors accumulated during the processing of about 225 kg. of A. heterophyllum roots. The mother liquors were chromatographed in benzene over Woelm neutral alumina (activity-3), and the eluate was monitored by thin layer chromatography on silica gel. Final purification was affected by crystallization.

The physical data on the new alkaloids are summarized in Table I. In addition, heterophylline was characterized as a monoacetate, m.p. 174-76°.

TABLE I

New Alkaloids from A. heterophyllum

	Heterophyllisine (I)	Heterophylline (II)	Heterophyllidine (III)
m.p.	178-179°	221.5-223°	269-272°
$[\alpha]_D$ (CH_3OH)	+15.5° (c 0.9)	+10.5° (c 2.0)	+42.3° (c 1.26)
Mol. formula[14]	$C_{22}H_{33}NO_4$	$C_{21}H_{31}NO_4$	$C_{21}H_{31}NO_5$
I.R. $_{max}$ (Nujol)	3584 cm.$^{-1}$ (OH); 1727 cm.$^{-1}$ (δ-lactone)	3534 cm.$^{-1}$ (OH); 1745 cm.$^{-1}$ (δ-lactone)	3546, 3205, 2778-2381 cm.$^{-1}$ (OH); 1748 cm.$^{-1}$ (δ-lactone)

* Present address; Unilever Research Laboratory, Welwyn, Hertfordshire, England.

All three alkaloids contain a δ-lactone ring since (i) they show strong absorption in the I.R. at 1727-1748 $cm.^{-1}$ (Table I), and (ii) they dissolve slowly in hot aqueous sodium hydroxide and can be recovered from such solution after acidification. A close structural similarity to heteratisine was therefore suspected. The structures were derived mainly by comparison of the mass spectra[15] of the new alkaloids and heteratisine. The most abundant ions in the high mass region are listed in Chart I and comprise the three types of ions discussed under (a), (b) and (c) below.

Heteratisine:

(a) the molecular ion peak (V) at m/e 391;

(b) ions obtained by elimination of the peripheral substituents from the molecular ion:

(1) m/e 376, loss of CH_3 (from N-ethyl by α-cleavage)[16].

(2) m/e 374, by loss of OH (from C-8) †

(3) m/e 373, by loss of H_2O (from the sec. OH at C-6) †

(4) m/e 360; this is the most abundant ion in the spectrum. It arises by loss of OCH_3 from the molecular ion peak since (i) high resolution studies showed it to be homogeneous and to have the composition $(C_{21}H_{30}NO_4)^+$ and (ii) a metastable peak appears at m/e 331.5 ($360^2/391$ = 331.4). Presumably the diradical (VI) formed initially, rapidly rearranges to the immonium ion (VII).

(c) Ions obtained by further eliminations from m/e 360 (VII);

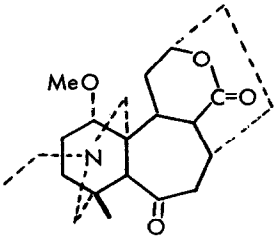
(1) m/e 342, loss of H_2O (from C-6-hydroxyl) †.

(2) m/e 332, loss of ethylene from N-C_2H_5 by hydrogen rearrangement[16].

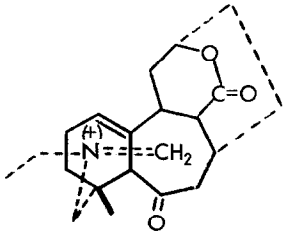
(3) m/e 344; high resolution studies showed this peak to be composed of two ions, m/e 344.1960 and m/e 344.1860 ($C_{20}H_{26}NO_4$). There is also a metastable peak at m/e 328.5 ($344^2/360$ = 328.7). Taking this data* together with the steric-electronic limitations inherent in (VII), we surmise that the $(C_{20}H_{26}NO_4)^+$ component (VIII) of this peak is obtained from m/e 360 by loss of $CH_3^\bullet$ from N-Et and $H^\bullet$ from C(7) in a single step.

† These assignments could be made only after studies on heterophyllidine discussed in the sequel.

* Also, we have studied the mass spectrum of the closely related molecule, dihydropyroheteratisine[11] which lacks the C-17 to C-7 bond involved in the CH_4 elimination. The molecular ion (i) loses OMe to yield the most abundant ion (ii), but the (ii-16) peak is virtually absent from the spectrum.

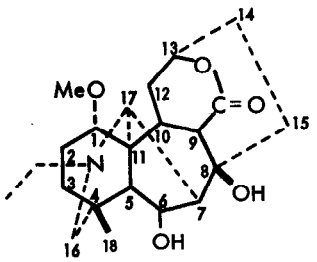


(i)



(ii)

CHART I



Heteratisine (IV)

M^+ 391 [6] $\xrightarrow{-15}$ 376 [9]

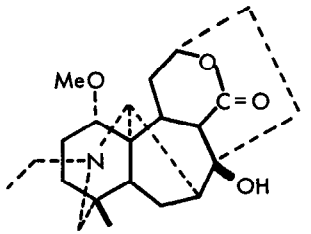
$\xrightarrow{-17}$ 374 [10]

$\xrightarrow{-18}$ 373 [9]

$\xrightarrow{-31}$ 360 [100] (VII)

-16 ↓ ↓-18

344 [10] 342 [22]



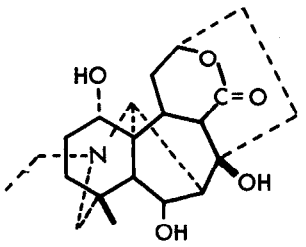
Heterophyllisine (I)

M^+ 375 [5] $\xrightarrow{-15}$ 360 [5]

$\xrightarrow{-17}$ 358 [2.5]

$\xrightarrow{-18}$ 357 [1]

$\xrightarrow{-31}$ 344 [100] $\xrightarrow{-16}$ 328 [5]



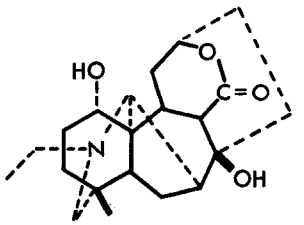
Heterophyllidine (III)

M^+ 377 (35) $\xrightarrow{-15}$ 362 [35]

$\xrightarrow{-17}$ 360 [100] $\xrightarrow{-16}$ 344 [12]

$\xrightarrow{-18}$ 342 [13]

$\xrightarrow{-13}$ 359 [20]



Heterophylline (II)

M^+ 361 [25] $\xrightarrow{-15}$ 346 [30]

$\xrightarrow{-17}$ 344 [100] $\xrightarrow{-16}$ 328 [37]

$\xrightarrow{-18}$ 343 [19]

Note: Numbers in [ ] represent relative peak height.

In addition to the peaks discussed under (a), (b) and (c), there are several peaks of low abundance from m/e 98 to 300. Most of these appear to arise by breakdown of the skeleton after initial elimination of the peripheral substituents.

Heterophyllidine: The mass spectrum in the m/e 98-300 region is identical with the spectrum of heteratisine. The molecular ion (M^+) at m/e 377, the absence of a peak at (M^+-31) and the presence of the most abundant peak at (M^+ -17) suggest the 1-O-nor-heteratisine structure (III) for it. All other peaks expected from III by analogy with the mass spectrum of heteratisine (IV), are present. Presumably, m/e 360 arises largely by the elimination of C(1)-hydroxyl group from (M^+) with some contribution from the C(8)- and C(6)-hydroxyl.

The n.m.r. spectrum (Table II) of heterophyllidine is very similar to that of heteratisine and is in complete agreement with structure III. Notably, absorption due to $-OCH_3$ is absent.

TABLE II

60 Mc. N.M.R. Chemical Shift Data (τ)[†]

For Diterpene Lactone Alkaloids*

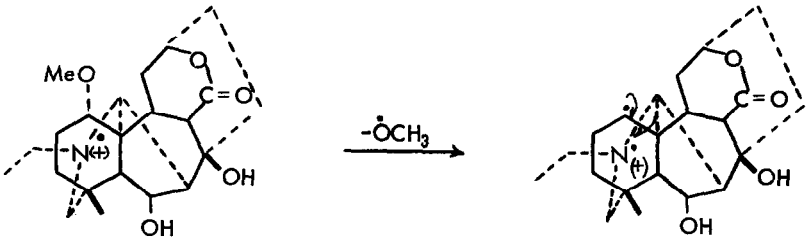
	Hetero-phyllisine	Hetero-phylline	Hetero-phyllidine	Heter-atisine
CH_3-C<	9.19	9.08	8.92	9.03
CH_3-CH_2N	8.94	8.87	8.92	8.98
CH_3-O	6.72	-	-	6.75
HC(17)N	6.62	6.70	6.57	6.51
HC(13)-OCO	5.26	5.14	5.08	5.26
HC(9)-CO-O		6.18	6.19	5.97
HC(6)OH		-	5.33	5.5

[†] In deuterochloroform solution with tetramethylsilane as the internal standard, measured on a Varian A-60 spectrometer.

* Appropriate splitting and coupling constants were observed in all cases; for heteratisine, see reference 10.

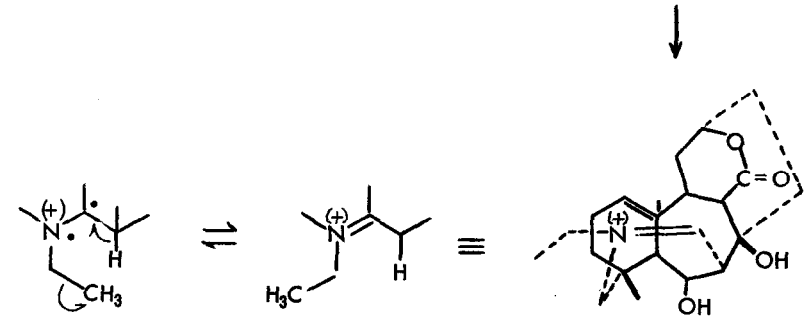
Heterophylline and heterophyllisine: Analysis of the mass spectra readily leads to the structures of these alkaloids as desoxy-heterophyllidine and desoxy-heteratisine, respectively. Absence of peaks at m/e (344-18), corresponding to loss of H_2O from the most abundant ion, suggests that the oxygen is missing from either the C(8)- or the C(6)-hydroxyl group. The latter alternative is confirmed by n.m.r. and chemical data below.

Heterophylline contains a tertiary hydroxyl group (resists acetylation, c.f., mono-acetate, vide supra). If this is at C(8), then the second hydroxyl (acetylated, secondary) cannot be at C(6) since pyrolysis of heterophylline acetate does not yield an enone corresponding to pyroheteratisine[11].

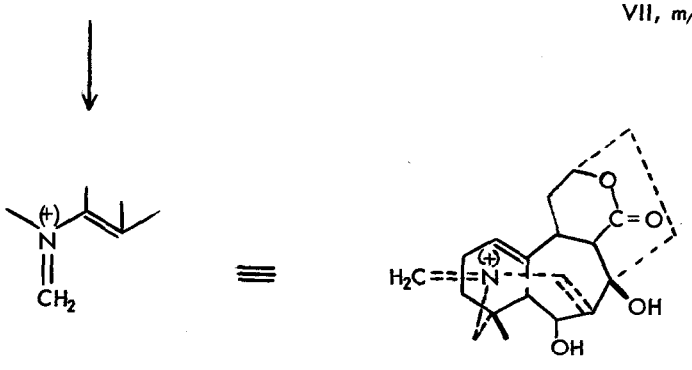


V, m/e 391

VI



VII, m/e 360



VIII, m/e 344

The n.m.r. spectra (Table II) of the pairs heterophylline-heterophyllidine and heterophyllisine-heteratisine are remarkably similar, but with two significant differences. In the desoxy-compounds, (i) signals assignable to H-C(6)OH are absent, and (ii) the 3H singlet for CH_3-C< occurs at τ 0.16 higher field, presumably because the deshielding effect of the neighboring hydroxyl at C(6) is absent.

Hence, heterophylline and heterophyllisine have structures (II) and (I) respectively.

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REFERENCES

1. Recent review articles on the diterpene alkaloids are: (a) S. W. Pelletier, Experientia, 20, 1-10 (1964); (b) S. W. Pelletier, Tetrahedron, 14, 77-112 (1961); (c) Hans-G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960," Academie-Verlag, Berlin, 1961, pp. 851-905, 1009-1011; (d) E. S. Stern, in The Alkaloids, by R. H. F. Manske, Vol. VII, Academic Press, New York, 1960, pp. 473-503; (e) K. Wiesner and Z. Valenta, "Progress in the Chemistry of Organic Natural Products," Vol. XVI, Springer-Verlag, Vienna, 1958, pp. 26-63.
2. J. Broughton, Blue Book, East India Cinchona Cultivation, 133, (1877).
3. W. A. Jacobs and L. C. Craig, J. Biol. Chem., 143, 589 (1942).
4. S. W. Pelletier, Chemistry and Industry, 1016 (1956).
5. S. W. Pelletier, Chemistry and Industry, 1670 (1957).
6. W. A. Jacobs and L. C. Craig, J. Biol. Chem., 143, 605 (1942).
7. W. A. Jacobs and C. F. Huebner, J. Biol. Chem., 170, 189 (1947).
8. A. J. Solo and S. W. Pelletier, J. Org. Chem., 27, 2702 (1962).
9. M. Przybylska, Can. J. Chem., 40, 566 (1962).
10. R. Aneja and S. W. Pelletier, Tetrahedron Letters, No. 12, 669 (1964).
11. R. Aneja and S. W. Pelletier, Tetrahedron Letters, No. 3, 215 (1965).
12. M. Przybylska, Can. J. Chem., 41, 291 (1963).
13. W. A. Jacobs and L. C. Craig, J. Biol. Chem., 147, 571 (1943).
14. Correct analytical data were obtained for all compounds cited. The molecular weight of each compound was confirmed by mass spectral analysis.
15. The mass spectra were recorded on a CEC-103-C and an AEI-MS9 mass spectrometer. The latter was used for the high resolution studies, at a resolution of 12,000.
16. See e.g., C. Djerassi and C. Fenselau, J. Am. Chem. Soc., 87, 5754 (1966); F. W. McLafferty, Chem. Commun., 80 (1966).