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THE DITERPENE ALKALOIDS. THE STRUCTURE OF HETERATISINE.

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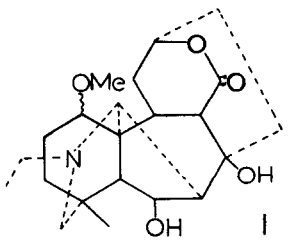
The alkaloid heteratisine[2] (Aconitum heterophyllum) is the only lactone-type diterpene alkaloid which has been reported. This paper summarizes chemical and spectral evidence which leads us to propose structure I for heteratisine[3].



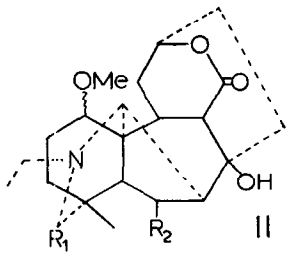
I

The molecular formula[2] $C_{22}H_{33}NO_5$ has been confirmed by our crystallographic studies.[4] The functional groups[2,5] (two OH, OCH_3, N-C_2H_5 and δ-lactone) account for all the hetero-atoms and leave a 19 carbon skeleton of six rings. The high level of oxygenation and failure to yield phenanthrenes on dehydrogenation[6] suggest[7] that heteratisine is modeled on a modified lycoctonine-type skeleton.[8]

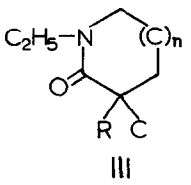
The infrared spectrum[9] of heteratisine shows absorption at 3472 cm^{-1} (OH) and 1739 cm^{-1} (δ-lactone[2] or larger). Methoxyl[2,5] and N-ethyl[5] groups are confirmed by their respective proton NMR[10] signals at τ 6.75 (3H singlet) and τ 8.98 (3H triplet, J7.5 cps, CH_3 of N-ethyl). Other structural features readily recognizable in the NMR spectrum are, a quaternary C-CH_3 (τ9.03, 3H singlet), H-C-hydroxyl (ca.τ5.5, 1 H multiplet), H-C-O-CO (lactone) (ca.τ5.26, 1 H unresolved broad multiplet), OH (τ4.97, 1 H singlet). One of the two hydroxyls is tertiary (resistant to acetylation and oxidation) and the other secondary. It forms a basic mono-acetate (II, $R_1=H_2$, R_2=OAc) $C_{24}H_{35}NO_6$[11], m.p. 175-177°; ν max 3395 cm^{-1} (OH), 1746 cm^{-1} (δ-lactone),

1714 cm^{-1} (O-acetyl), 1727 cm^{-1} ($CHCl_3$) (δ-lactone and O-acetyl); τ 9.15, 3H singlet ($C-CH_3$); τ 8.97, 3H triplet, J7 cps (CH_3-CH_2N); τ 6.74, 3H singlet (CH_3O); τ 6.42, 1H doublet, J2 cps (N-CH); ca. τ 5.28, 1H multiplet (H-C-OCO, lactone; τ 4.71, 1H quartet (H-C-OAc).

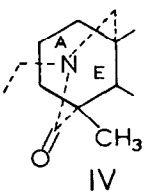
Oxidation of heteratisine acetate (II, $R_1=H_2$, $R_2=OAc$) with chromium trioxide-pyridine complex gives, as the major neutral product, oxoheteratisine acetate (II, $R_1=O$, $R_2=OAc$), $C_{24}H_{33}NO_7$, m.p. 280-82°; ν max 3436 cm^{-1} (OH), 1739 cm^{-1} (δ-lactone and O-acetyl), 1625 cm^{-1} (δ-lactam); τ 8.78, 3H singlet ($C-CH_3$); τ 8.88, 3H triplet, J7 cps (CH_3-CH_2N); τ 7.94, 3H singlet ($CH_3CO\cdot O$); τ 6.77, 3H singlet (CH_3O); τ 6.17, 1H doublet, J2.5 cps (N-CH); ca. τ 5.22, 1H multiplet (H-C-OCO, lactone); τ 4.77, 1H quartet (H-C-OAc). On alkaline hydrolysis oxoheteratisine acetate gives oxoheteratisine[12] (II, $R_1=O$, $R_2=OH$), $C_{22}H_{31}O_6N$, m.p. 345-347°; $[\alpha]_D^{22}$ + 50°;[13] ν max 3460 cm^{-1} and 3205 cm^{-1} (OH); 1730 cm^{-1} (δ-lactone), 1609 cm^{-1} (δ-lactam), which on further oxidation with chromium trioxide in acetic acid or chromium trioxide-pyridine yields oxoheteratisone,[12] (II, $R_1=R_2=O$) $C_{22}H_{29}NO_6$, m.p. 313-317°; $[\alpha]_D^{22}$ - 31°; λ max 310mμ (ε30)[14]; ν max 3534 cm^{-1} (OH), 1733 cm^{-1} (cyclopentanone), 1748 cm^{-1} (δ-lactone), 1626 cm^{-1} (δ-lactam); τ 8.78, 3H singlet ($C-CH_3$); τ 8.83, 3H triplet, J7 cps (CH_3-CH_2N); τ 6.68, 3H singlet (CH_3O); τ 6.58, 1H singlet (OH); τ 5.91, 1H doublet J2.5 cps (N-CH); τ 5.25, 1H multiplet (H-C-OCO, lactone). IR and NMR spectra show that these derivatives contain the N-ethyl lactam structure III ($n \geq 1$).



II



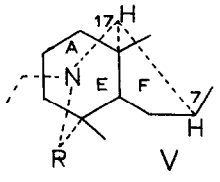
III



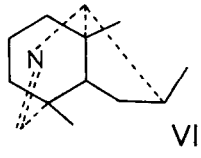
IV

The CH_3-C absorption in the NMR of the above lactams occurs ca. τ 0.25 lower field than its average chemical shift (τ 9.1) in heteratisine and several derivatives. This deshielding indicates that (i) the lactam carbonyl has been introduced in a

position β- to the methyl group and (ii), the methyl group lies in the plane of the carbonyl group. III may thus be extended to III (R = Me). However, the geometrical requirement (ii) above is admirably satisfied by the A-E ring system common to all the aconite alkaloids and hence the partial structure (IV). Introduction of the lactam carbonyl also causes deshielding of another proton (N-C (17) H). The NMR signal of this proton is at τ 6.51 (1 H doublet, J1.5 cps) in heteratisine, τ 6.42 (1H doublet, J2 cps) in heteratisine acetate and at 6.15 in heteratisone. Its assignment to N-C(17)H is correct since in oxoheteratisine acetate this is shifted downfield to τ 6.12 (1H doublet, J2.5 cps) and to τ 5.91 in oxoheteratisone (1 H doublet, J2.5 cps). The dihedral angle H-C(17)-C(7)-H in the lycoctonine skeleton (Dreiding models)[15] is ca. 70° which gives a calculated[16] value of 1.5 cps for the 17H-7H coupling constant. This value is in agreement with the observed splitting of C(17)H in heteratisine and its derivatives (1.5 to 2.5 cps) and partial structure IV therefore may be extended to V(R = O) for the oxo derivatives. Heteratisine thus contains the A-E-F ring system (V, R = H_2) which distinguishes lycoctonine from atisine and hypognavine types.[17]



V



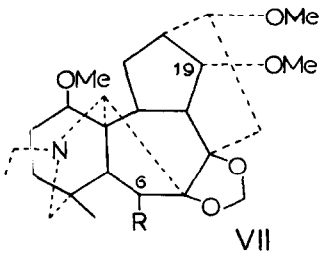
VI

Partial structure V is also supported by a study of the basic by-product of chromium trioxide-pyridine oxidation of heteratisine acetate, N-desethyl-dehydro-heteratisine acetate, (VI), $C_{22}H_{29}NO_6$, m.p. 294-298°, $[\alpha]_D^{27}$ + 125°; ν max 3195 cm^{-1} (OH), 1739 cm^{-1} (δ-lactone and O-acetyl), 1642 cm^{-1} (C=N); hydrochloride $C_{22}H_{29}O_6N \cdot HCl$, m.p. 325-30°; ν max 3571 cm^{-1}, 3311 cm^{-1} (OH), 2558, 2123 and 1923 cm^{-1} (= N^+H—), 1742 cm^{-1} (δ -lactone and O-acetyl), 1644 cm^{-1} (>C=N^+H—). The base shows absorption at τ 8.80, 3H singlet (C-CH_3); τ 7.92, 3H singlet (CH_3COO); τ 6.77, 3H singlet (CH_3O); τ 5.6, 1H multiplet (N-CH); τ 5.1, 1H multiplet (H—C—OCO, lactone); τ 2.68, 1 H multiplet (HC=N). There is no signal for N—C_2H_5 and the deshielding of the C—CH_3 is caused by the C=N β- to it.

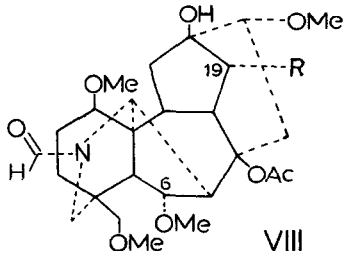
Oxidation of heteratisine with chromium trioxide in acetic acid gives a basic ketone, heteratisone (II, $R_1 = H_2$, $R_2 = O$) $C_{22}H_{31}NO_5$, m.p. 124-125°, $[\alpha]_D^{26}$ - 56°

(c, 1.87, $CHCl_3$); λmax. 270mμ (ϵ 69); ν max. 3472 cm^{-1} (OH), 1732 cm^{-1} (CS_2) (cyclopentanone), 1750 cm^{-1} (CS_2) (δ-lactone); τ 9.06, 3H singlet ($C-CH_3$); τ 8.90, 3H triplet J7.5 cps (CH_3-CH_2N); τ 6.67, 3H singlet (CH_3O); τ 6.15, 1 H doublet, J 1.5 cps (N—CH); τ 5.22, 1H multiplet (H—C—OCO, lactone). Oxoheteratisone (vide supra) is the lactam analog of heteratisone.

On biogenetic analogy, positions 19 and 6 of the unmodified lycoctonine skeleton (VII) need consideration as the site of the cyclopentanone carbonyl in heteratisone and oxoheteratisone. The former position corresponds to α-oxodelphonone (VIII, R=O) and the latter to dehydro-delpheline (VII, R=O). The decision in favor of the latter was made as follows. The molar rotation change, $\Delta[M]_D$ is -375° for the oxidation of heteratisine to heteratisone (II, $R_1=H_2$, $R_2=O$) and -325° for the oxo derivatives. These compare well with value −202° [18] for oxidation of delpheline (VII, R=OH) to dehydro-delpheline (VII, R=O) and -470° for oxodelpheline to dehydro-oxodelpheline.[19] $\Delta[M]_D$ for α-oxodelphonine (VIII, R=OH) to α-oxodelphonone (VIII, R=O) is + 186°, and for dihydropyro-α-oxodelphonone[20,21] is + 148°. Furthermore, the R.D. curve of α-oxodelphonone shows a positive maximum (λmax 320mμ, a = + 1600°)[22] whereas heteratisone shows a negative maximum (λ max 320mμ, a= - 1290°) in agreement with sign predicted by application of the octent rule[23] to the 6-keto structure (II, $R_1=H_2$, $R_2=O$).



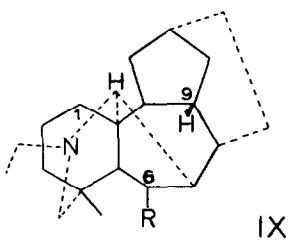
VII



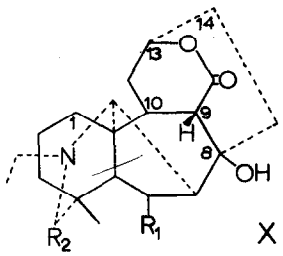
VIII

The similarity noted for $\Delta[M]_D$ extends also to the UV absorption in the two series. For example λ max 270mμ (ϵ 69) for heteratisone shifts to λ max 310 (ϵ 30) in oxoheteratisone. The values for dehydro-delpheline and dehydro-oxodelpheline are λ max 269mμ (ϵ 160) and λ max 313 (ϵ 44) respectively. The 6 β-OH structure (IX, R = OH) analogous to delpheline (VII, R = OH) may therefore be adopted for

heteratisine with the proviso that a methoxyl, a tertiary hydroxyl and a δ-lactone (or larger) ring are to be suitably accommodated in it.



IX



X

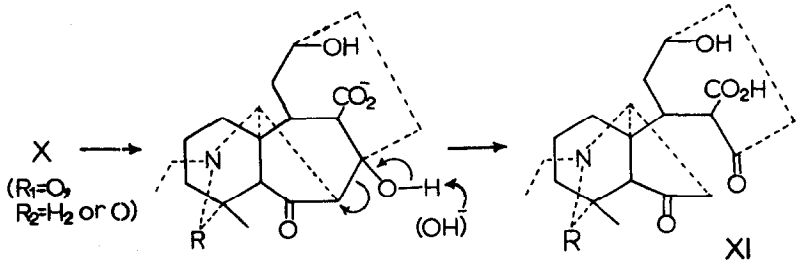
Analysis of the NMR spectra of heteratisine and its derivatives, at lower field than the methoxyl resonance, provides additional support for structure IX. In conjunction with biogentic analogies, it also permits location of the lactone, the tertiary hydroxyl and, with some reservation, the methoxyl group to give the complete structure I for heteratisine. Thus, the observed splitting of the H-C- acetoxyl signal in heteratisine acetate and oxoheteratisine acetate, into a doublet of doublets is in harmony with its location at C(6) and spin coupling to HC(7) and HC(5).[24] Conversion of heteratisine to heteratisone occasions a 0.35τ paramagnetic shift of the NC(17)H resonance. In molecular model[15] of IX (R = O), C(17)H lies approximately in the plane of the trigonal C(6), which is the region of negative shielding of the anisotropic carbonyl group.[25] The magnitude of this shift is comparable to the values observed earlier for similar long range negative shielding effects.[26]

A one proton signal at τ 5.97 in heteratisine spectrum is missing from the corresponding region in heteratisone.[27] Presumably it has been shifted to higher field by the shielding effect of the carbonyl group.[25] The large magnitude[28] of this diamagnetic shift indicates that the proton in question is located close to the axis through the carbonyl group, perpendicular to the trigonal plane. In Dreiding models[15] of IX (R = O) only the C(9)β-proton occupies such a position relative to the 6-keto carbonyl. The chemical shift, τ 5.97 in heteratisine requires location of an electron withdrawing group adjacent to C(9). This must be the lactone carbonyl.[29] The lactone ether oxygen may then be linked to C(13) or C(14) to obtain 6-membered or larger lactone ring (IR).

The broad unresolved multiplet NMR signal of H-C-OCO is in agreement with linkage at either position.

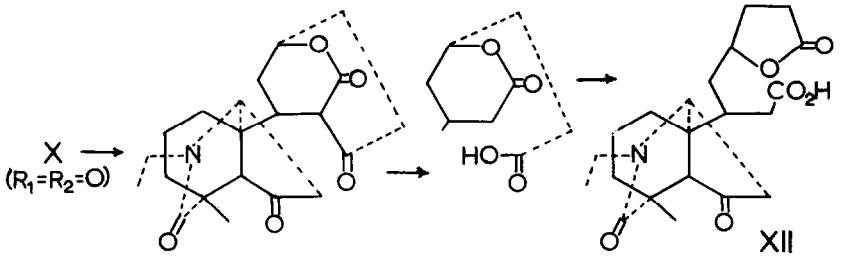
Chemical proof for location of the lactone bridge between C(9) and C(13), as in X, is presented in the sequel. Meanwhile, further discussion of the HC(9) NMR signal is instructive. This appears as a nearly symmetrical doublet, J7 cps. HC(9) is therefore spin coupled to only one proton on an adjacent carbon, C(8) or C(10). Vis a vis, one of these two carbons is quarternary;[30] and carries the methoxyl or the tertiary hydroxyl. On biogenetic analogy, C(8) - OH structure (X, R_1=OH, R_2=H_2) is preferred.

Action of hot aqueous alkali on heteratisine or oxoheteratisine causes mere hydrolytic opening of the lactone ring. With the corresponding ketones, however, further profound degradation occurs readily. The products lack lactone or carboxyl group (no IR absorption for δ-lactone; insoluble in alkali.). Structure (X, R_1=O, R_2=H_2 or O) provides a plausible path for decarboxylation through the β-keto acid (XI, R=H_2 or O) formed by retroaldol cleavage of the β-hydroxy ketone system. It also explains the positive Zimmermann test given by the heteratisones.



Treatment of oxoheteratisone with potassium t-butoxide in t-butanol leads to a γ-lactone carboxylic acid (XII) (methyl ester $C_{23}H_{33}NO_7$, m.p. 90-92°; λmax 255 mμ (ϵ 200), shoulder 300 mμ (ϵ 60); ν max (CCl_4) 1787 cm^{-1} (γ-lactone), 1748 cm^{-1} (cyclopentanone), 1728 cm^{-1} (COOMe), 1648 cm^{-1} (δ-lactam), — no OH or NH absorption; τ 8.83, 3H singlet (C-CH_3); τ 8.78, 3H triplet J7.5 cps (CH_3—CH_2N); τ 6.67, 3H singlet (OMe); τ 6.27, 3H singlet (COOMe). Its formation (by cleavage of the initial retroaldol product to a δ-lactone carboxylic acid and isomerization to the γ-lactone) provides decisive proof for location of

the tertiary hydroxyl β- to both the cyclopentanone and the δ -lactone carbonyls, and four carbons removed from the δ -lactone ether oxygen, as in X (R_1=R_2=O).



XII

The NMR spectrum of heteratisine or heteratisine acetate does not contain a signal at lower field than the OMe singlet, ascribable to H-C-OMe. If the methoxyl in heteratisine is secondary,[31] this signal must be located at a value higher than normal.[32] The one proton multiplet between τ 6.02 to 6.63 in oxoheteratisone, however, is assigned to H-C-OMe. The combined negative shielding effect of the lactam and the cyclopentanone carbonyl groups on H-C-OMe thus brings this resonance back to a more normal field value. Only the C(1) proton in X (R_1=R_2=O) is suitably placed for the observed deshielding[25] since it is nearly coplaner with both the trigonal C(6) and C(16) and is ca. 5A^0 distant from either carbonyl (Dreiding models).[15] Moreover, alkaloids for which the lycoctonine C-N skeleton has been established, all contain methoxyl (or hydroxyl) groups at C(14) and C(1).[17] A methoxyl at C(14) in structure X (R_1 = R_2 = O), however, would suffer ready β-elimination during treatment of oxoheteratisone with potassium t-butoxide. Therefore, the C(1) methoxy[33] structure I, may be assigned to heteratisine.[34]

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9. Infrared spectra were taken as nujol mulls unless noted otherwise.

10. NMR spectra were run at 60 mc in $CDCl_3$ solution with tetramethylsilane as an internal reference. Hydroxyl assignments are confirmed by loss of signal on deuterium exchange.

11. Satisfactory analytical values were obtained for all compounds.

12. Also obtained directly by oxidation of heteratisine with chromium trioxide-pyridine complex.

13. Optical rotations were measured for methanol solution (c, 1.0) unless noted otherwise.

14. U.V. Spectra were obtained for 95% ethanol solutions.

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16. M. Karplus, J. Chem. Phys., 30, 11 (1959).

17. See, L. Marion, Pure and Applied Chemistry, 6, 621 (1963).

18. The value (-120^0) quoted in reference 19(a) is in error.

19. (a) R. C. Cookson and M. E. Trevett, J. Chem. Soc., 2689 (1956); (b) ibid., 3121 (1956).

20. W. A. Jacobs and S. W. Pelletier, J. Org. Chem., 22, 1428 (1957).

21. The possibility that the large negative $\Delta [M]_D$ was the result of 19 OH to 19 keto oxidation followed by an acyloin rearrangement to a 13 keto derivative (see e.g., K. Wiesner, M. Götz, D. L. Simmons, L. R. Fowler, F. W. Bachelor, R.F.C. Brown, and G. Buchi, Tetrahedron Letters, No. 2, 15(1959)) was discarded since heteratisine does not contain vicinal oxygen functions (no reaction with periodic acid or lead tetraacetate).

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24. Distinction between α-H or β-H is not possible since calculated[16] coupling constants for the two configurations are equal and in agreement with the observed values (7 cps and 1 cps for heteratisine acetate and 7 cps and 2 cps for oxoheteratisine acetate).

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27. Absence of OH and H-C-hydroxyl signals (τ 4.97 and ca. 5.5 respectively in heteratisine) in heteratisone is expected and observed.

28. The signal is conceivably lost under the OCH_3 or the general methine-methylene signals. The $\Delta\delta$ is therefore at least 0.7τ.

29. Location of a secondary methoxyl at C(9) is also compatible with the chemical shift, but will destroy the lycoctonine ring system.

30. Dihedral angles H-C(8)-C(9)-H and H-C(9)-C(10)-H are each approximately equal to 30° (Dreiding models[15]). Hence J H(8) - H(9) and J H(9) - H(10) would equal 6 cps[16]. This rules out the possibility that there is a proton on both carbons adjacent to C(9) and the coupling constant for one of them is zero.

31. Structure X (R_1 = OH, R_2 = H_2) has no primary carbon and protons have already been located at all tertiary positions.

32. The cause of this shielding is not certain. It is not due to the lactone carbonyl. It could arise from the anistropy of nitrogen or the lactone ether oxygen. We favor the latter cause.

33. Since both α- and β- C(1) - oxygen functions have been encountered earlier (reference 17) the configuration of the OMe in heteratisine is not definite.

34. The absolute stereochemistry indicated in I follows from the O.R.D. and molar rotation change correlation with delpheline (cf. page 4) and C(9)-β-H indicated by NMR (cf. page 5). Moreover, this configuration is the same as that established for other diterpene alkaloids.