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THE DITERPENE ALKALOIDS: THE PYROLYSIS AND ABSOLUTE CONFIGURATION OF HETERATISINE

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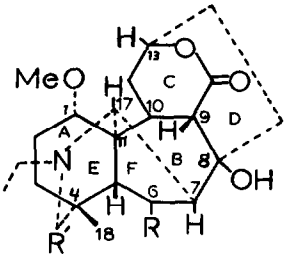
The structure and the relative stereochemistry of the lactone-type diterpene alkaloid heteratisine (Aconitum heterophyllum Wall) have been established recently by crystallographic[2] and by chemical[3] methods. The absolute configuration I has been suggested[2-4] on the basis of the expected biogenetic relationship to the aconitines[5] possessing the regular lycoctonine-type skeleton. The large negative ΔM_D observed on the oxidation of heteratisine to dehydroheteratisine,[5a] and delpheline to dehydrodelpheline has been cited in support of this assignment.[3,4,6] We present evidence and arguments which establish the absolute configuration of heteratisine as I (1S, 4R, 5R, 6S, 7R, 8S, 9S, 10R, 11S, 13S, 17R, 22S)[7].



I; R = OH, $R' = H_2$
II; R = $OCOCH_3$, $R' = H_2$
III; R = $OCOC_6H_5$, $R' = H_2$
IV; R = O, $R' = H_2$
V; R = $OCOCH_3$, $R' = O$

Our conclusion follows from a study of the optical rotatory dispersion curve (O.R.D.) of pyroheteratisine, (and its derivatives) a product obtained from esters of heteratisine, e.g., II[3] and III[8], by way of a facile thermally-induced ring cleavage reaction. The pyrolysis reaction has unusual features and intrinsic interest also. Initially, therefore, we present a study of this reaction and the structures of the products[9].

Pyrolysis of heteratisine acetate (II)[3] proceeds smoothly at 210°/0.2 mm; the benzoate (III)[8] requires a somewhat higher temperature (240°). One mole of the respective carboxylic acid is eliminated to give two $C_{22}H_{31}NO_4$ bases[10], pyroheteratisine,

m.p. 191-92°, (yield > 90%) and isopyroheteratisine, m.p. 154-55°, (yield ca. 1%). The spectral data for pyroheteratisine, [λ max. 238 mμ (ϵ 10,600); ν max. (Nujol) 1751 cm.$^{-1}$ (δ-lactone), 1658 cm.$^{-1}$ (s) and 1628 cm.$^{-1}$ (w), no OH or NH absorption in the IR; p.m.r. (see Table I) τ 3.94 (HC=C<)], suggest the presence of the chromophore O=C-C(H)=C< with the C=O in a six-membered or larger ring, which is confirmed by the following transformations. Hydrogenation (Pd-C catalyst) gives dihydropyroheteratisine, $C_{22}H_{33}NO_4$, m.p. 179-80°; λ max. 310-14 mμ (ϵ 24), ν max. (chf.) 1742, 1701 cm.$^{-1}$ Hydroxylation effected by OsO_4 in acetic acid (followed by H_2S) gives a cis diol, O=C-CH(OH)-C(OH)<, $C_{22}H_{33}NO_6$; m.p. 215-17°; λ max. 326-28 mμ (ϵ 31); ν max. (Nujol) 3356, 1727, 1715 cm.$^{-1}$ The diol forms a basic monoacetate, O=C-CH(OAc)-C(OH)<, $C_{24}H_{35}NO_7$, m.p. 251-51°; λ max. 322-26 mμ (ϵ 38); ν max. 3521, 1754, 1739, 1724 cm.$^{-1}$ The H-C-hydroxyl p.m.r. signal at τ 6.18 in the diol and the H-C-acetoxyl signal at τ 5.30 in the mono-acetate both appear as sharp singlets and thus confirm the assigned partial structures.

The quaternary C-CH_3, OCH_3, NC_2H_5 and H-C-O-C=O (lactone) groups are unscathed by the pyrolysis reaction (p.m.r., Table I)[11] and presumably therefore, the A-E and C-D rings of the heteratisine skeleton are intact. Valency considerations ($C_{22}H_{31}NO_4$; one C=C, two C=O) require a 5-ring skeleton for pyroheteratisine. Since the heteratisine skeleton has six rings[3], the pyrolysis reaction must involve fission of one ring. The enone chromophore is formed concomitantly with the loss of acetoxyl and hydroxyl groups and therefore is most likely in the B-F ring part of the molecule. The site of this ring fission and the situation of the enone group were determined by analysis of the p.m.r. data.

The p.m.r. spectrum of heteratisine acetate[3] has signals for H-C(17)-N at τ 6.42 and for H-C(9)-C(=O)-O at τ 5.97. The 6 τ region in pyroheteratisine has only one signal (τ 6.05), whose line width or chemical shift is practically unaffected by protonation of the nitrogen (in pyroheteratisine hydrochloride). This signal, therefore, is assigned not to H-C(17)-N but rather to H-C(9). It appears as a broad unresolved single peak which changes to a doublet, on saturation of the double bond by hydroxylation, in the diol and the hydroxy-acetate derivatives. Allylic spin-spin coupling of H-C(9) with the vinylic proton is thus demonstrated and this enables its location in a position α-to the C=C, as in HC(9)-C=C(H)-.

The large chemical shift of H-C(9) in dihydropyroheteratisine (τ 6.89)[12] is reminiscent of the remarkable shielding of this proton in dehydroheteratisine (IV)[3], and

suggests location of the carbonyl group at position 6 in the pyro-derivatives. The relative spatial orientation of the 6-carbonyl and the 18-CH_3, however, must be different in dehydroheteratisine (τ 9.06), and derivatives in the dihydro-pyro-series since the 18-CH_3 resonance occurs at noticeably higher field values in the latter[13]. As the E-F ring system in dehydroheteratisine (IV) is devoid of conformational mobility, the diamagnetic shielding effect of the 6-carbonyl could be brought to bear on the 18-CH_3 only by ring fission, conceivably between C(7)-C(17), an eventuality suggested also by the absence of the H-C(17)-N p.m.r. signal. Structure VI thus appeared to be the most plausible one for pyroheteratisine.

TABLE I*

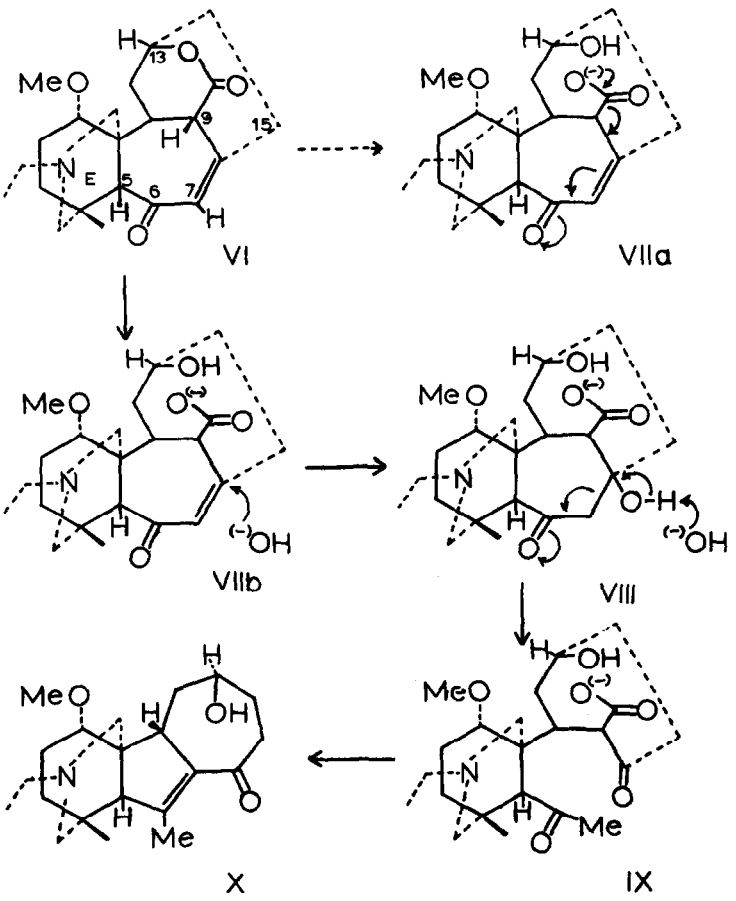
Position of H	No. of H	Pyro-heter-atisine	Dihydro-pyro-heter-atisine	Diol	Hydroxy acetate
CH_3O	3	6.68 s	6.69 s	6.68 s	6.68 s
CH_3CH_2N	3	9.02 tr (7)	8.99 tr (7)	9.00 tr (7)	8.97 tr (7)
CH_3-C	3	9.08 s	9.22 s	9.26 s	9.35 s
H-C(13)	1	5.16 m	5.22 m	5.22 m	5.22 m
H-C(9)	1	6.05 bs	6.89 bs	6.42 d (4)	6.50 d (4)
H-C(7)	1	3.94d (2,5)[14]	-	6.18 s	5.30 s

* Chemical shifts in τ units, (J in c.p.s.)
s=singlet; d=doublet; tr=1:2:1 triplet; m=very broad multiplet; bs=broad single peak.

Brief treatment of pyroheteratisine with $NaOCD_3$ in CD_3OD effects exchange of H-C (9) by deuterium; the H-C (9) p.m.r. signal vanishes and the vinylic proton doublet degenerates to a singlet[15]. This facile deuterium exchange and the accompanying loss of allylic coupling further support structure VI.

Decisive proof for structure VI by decarboxylation of the derived vinylogous β-keto carboxylate (VII a) looks facile but is not since generation of the Δ^8-double bond is sterically impossible. On extended boiling with aqueous alkali at pH 9, VIIb does suffer decarboxylative degradation, but the reaction appears to follow the path VI—>VIIb—>VIII—>IX —> X since the spectral properties of the product permit its

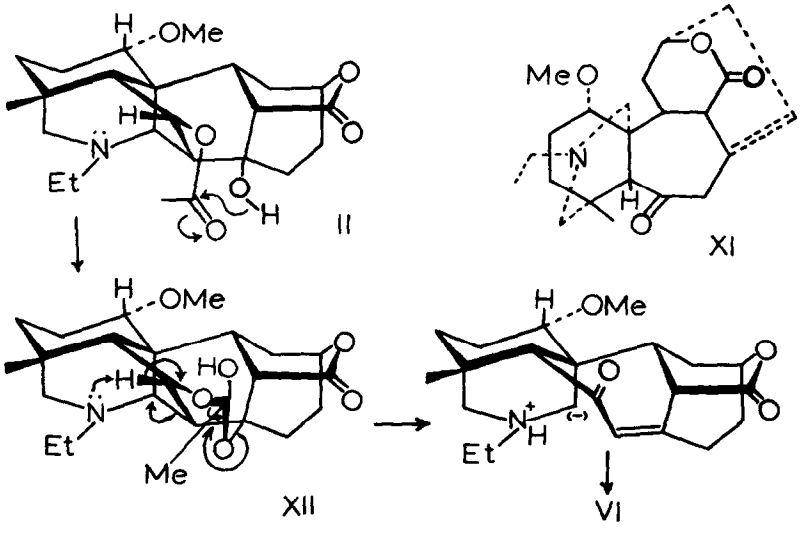
formulation as X [amorphous base, characterized as its crystalline hydrochloride, $C_{21}H_{33}NO_3 \cdot HCl$; m.p. 200-201°; λmax 254 mμ (ε 8,100); νmax (Nujol) 3390 $cm.^{-1}$ (OH), 2747 $cm.^{-1}$ (OH and NH^+), 1667 $cm.^{-1}$ and 1592 $cm.^{-1}$, both strong (cisoid enone); p.m.r. of the free base X, τ 8.93, 3H singlet (C-CH_3); τ 9.03, 3H triplet J 7.5 c.p.s. (CH_3-CH_2N); τ 7.90, 3H singlet (CH_3-C=C); τ 6.60, 3H singlet (OCH_3); ca. τ 5.75, 1H very broad multiplet (H-C-hydroxyl, shifts to ca. τ 4.8 on acetylation); no vinylic proton signal].



Reduction of pyroheteratisine with $NaBH_4$ results in saturation of the C=C rather than the carbonyl double bond. This uncommon circumstance lends credence to the postulated nucleophilic attack by $HO^{(-)}$ β-to the carbonyl and protonation at the α-position (VII b —> VIII).

The minor product of the pyrolysis reaction, isopyroheteratisine, shows: λ max 327 mμ (ε 115); ν max (chf.) 1748 $cm.^{-1}$, 1695 $cm.^{-1}$; τ 9.17, 3H singlet (C-CH_3); τ 9.00, 3H triplet J 6.8 c.p.s. (CH_3-CH_2-N); τ 6.67, 3H singlet (OCH_3); τ 6.23, 1H unresolved single peak, (H-C-C=C-O-); τ 5.05, 1H broad multiplet (H-C-O-C=O); τ 4.10, 1H unresolved single peak, width at half height 4 c.p.s. (H-C=C). It isomerizes to pyroheteratisine on treatment with acid or on heating and gives a dihydro derivative identical with dihydropyroheteratisine. Therefore, it must have structure XI.

Additional facts pertaining to the pyrolysis reaction are the following: 8-(OD)-des(8-OH)-benzoyl heteratisine[16] [ν max (Nujol) 2597 $cm.^{-1}$, O-D] yields benzoic acid-d_1 [ν max (Nujol) 2232, 2066 and 1916 $cm.^{-1}$, O-D]. Dehydroheteratisine (IV) and oxo-heteratisine acetate (V)[3] fail to undergo a parallel reaction, the latter even on admixture with heteratisine acetate. The extreme facility and high yield of the reaction, in conjunction with the aforementioned facts, suggest that the reaction proceeds by a concerted process involving intramolecular participation of the basic nitrogen. A plausible reaction path leading to pyroheteratisine is presented below; isopyroheteratisine is then formed by thermal C=C migration.



Among the conformational changes accompanying the pyrolysis reaction, the change in ring E is significant to the mechanism of the reaction. For approach of nitrogen's lone pair of electrons within effective distance of the 6-hydrogen, ring E must pass from a chair form in heteratisine acetate to a boat in the transition state, and is probably in that form in pyroheteratisine. Ring B appears to suffer no profound conformational change. On cleavage of the C(7)-C(17) bond, the two separating atoms do move farther apart, but still stay in juxtaposition. This conclusion follows from the observation, vide supra, that in dihydropyroheteratisine both H-C(9) and 18-CH_3 lie in the diamagnetic shielding regions of the 6-carbonyl (Table I). In other words, the gross chirality of the system described by C(5)-C(6)-C(7)-C(8) in pyroheteratisine (VI) and in heteratisine is identical. Molecular models show that this chirality uniquely defines the absolute configuration of these molecules; in pyroheteratisine it also determines the helicity of the enone group located at C(6)-C(7)-C(8).

The helicity of the enone chromophore in pyroheteratisine can be ascertained from experimental O.R.D. data. In Dreiding models of pyroheteratisine (structure VI or mirror image), the transoid enone group is held rigidly and has a large angle of skew. For such systems the amplitude of the Cotton effect associated with the $\pi \longrightarrow \pi^*$ transition is very large and the sign of this Cotton effect depends predominantly on the helicity of this inherently dissymetric chromophore.[17] According to the diene helicity rule[18], as extended to enone chromophores[17], a negative Cotton effect is associated with a negative helicity and a positive effect with a positive helicity of the skewed chromophore. The O. R. D. curve of pyroheteratisine shows a negative Cotton effect, (Fig. 1) $[\alpha]_{250}$+650, $[\alpha]_{208}$+21,000. Pyroheteratisine hydrochloride also exhibits a negative Cotton effect, ($[\alpha]_{250}$ -415) in the enone absorption region, but the trough at 250 mμ is comparatively more pronounced. The corresponding dihydro derivatives(XIII)lack these large amplitude Cotton effects. Therefore, a negative helicity for the enone group in pyroheteratisine is indicated. This is consistent with structure VI but not with its mirror image (Dreiding models). Hence, pyroheteratisine has the absolute configuration indicated in VI. The absolute configuration I for heteratisine then follows from the conformational correlations discussed in the previous paragraph.

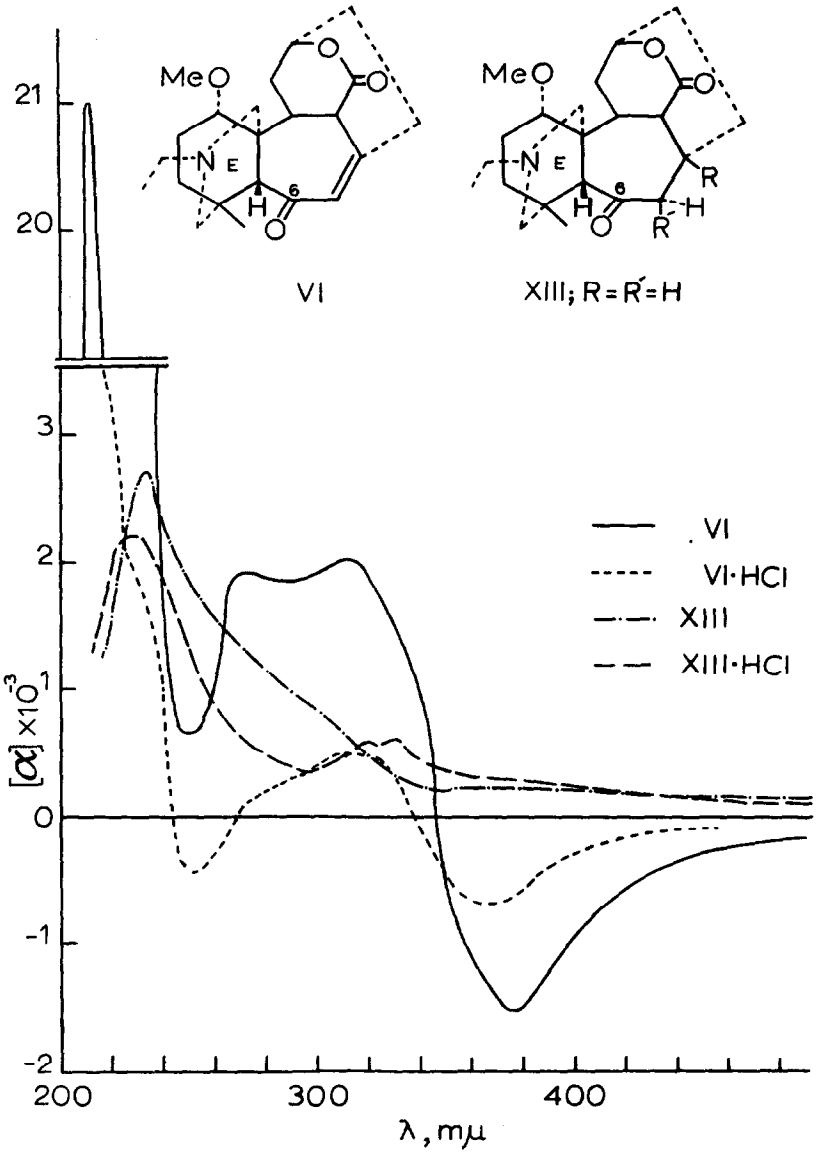

MeO
N E
H
6
O
VI
XIII; R = R' = H
R
H
21
20
3
2
1
0
-1
-2
[α] x10⁻³
VI
VI·HCl
XIII
XIII·HCl
200
300
400
λ, mμ

Figure 1

Acknowledgment: We thank Dr. David Locke for preliminary experiments on the pyrolysis of heteratisine. We are grateful to Dr. James O. Grote, The Bendix Corporation Cincinnati Division, Professor J. Cymerman Craig, and Professor Carl Djerassi for the O. R. D. spectra. This work was supported by Grants RG 5807 and GM 10921 from the National Institutes of Health, United States Public Health Service.

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5a. In the paper cited in reference 3, dehydroheteratisine was termed heteratisone.

6. In the absence of valid analogies, the agreement between the sign of the Cotton effect observed, and that predicted by the Octant rule, for the cyclopentanone carbonyl in dehydroheteratisine[3], is, at best, merely suggestive.
7. On the Cahn-Ingold-Prelog notation: see, R. S. Cahn, J. Chem. Ed., 41, 116 (1964).
8. W. A. Jacobs and L. C. Craig, J. Biol. Chem., 147, 571 (1943).
9. Pyrolysis of heteratisine gives the same products, albeit in poor yield.
10. Correct analytical values were obtained for all compounds. U. V. Spectra were obtained for methanol solutions. The proton nuclear magnetic resonance spectra (p.m.r.) were run on a Varian A-60 spectrometer; deuterochloroform was employed as solvent and tetramethylsilane as an internal standard.
11. For the p.m.r. spectra of heteratisine and its other derivatives, see ref. 3.
12. The chemical shift is slightly lower for the diol and the hydroxy acetate derivatives since the tertiary OH, at C(8), occasions some deshielding of the cis H-(9).
13. In pyroheteratisine itself the 18-CH_3 has a 'normal' chemical shift (τ 9.08).
14. J 2.5 c.p.s. arises from 1:3 coupling of the vinylic proton to H-C(9) (structure VI) and not due to the two other allylic protons at C(15). Of the latter, the one which is co-planar with H-C(7) is not expected to show significant coupling to it, and in its presence, the second H-C(15) can cause merely a slight increase of the width of the H-C(7) signal but no observable splitting. C.f., T. A. Wittstruct, S. K. Malhotra and H. J. Ringold, J. Am. Chem. Soc., 85, 1699 (1963).

15. Actually two singlets appear at τ 3.94 and 4.12. The spectrum of the product resulting from treatment of pyroheteratisine with $NaOCH_3$ in CH_3OH shows a pair of doublets centered at τ 3.94 and 4.12, for the vinylic proton and two signals, τ 6.05 and 6.23, for H-C(9). The second set of peaks appears to belong to the A/B cis isomer formed by equilibration at C(5) induced by alkoxide.

16. Prepared by desiccating benzoyl heteratisine[8] with deuterium oxide.

17. C. Djerassi, R. Records, E. Bunnenberg, K. Mislow and A. Moscowitz, J. Am. Chem. Soc., 84, 870 (1962).

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