Formation of Hydroxy-lactone (IV)

The mixed esters (1.4 g) in acetic acid (25 ml) were refluxed with *p*-toluene sulphonic acid (800 mg) for 18 hours. The acetic acid was removed *in vacuo* below 40° and after addition of water to the residue it was extracted with ether. Evaporation of the ether gave an oil (800 mg) from which acidic material was removed by extraction of an ethereal solution with sodium carbonate to give a neutral residue (400 mg). This was separated on a Carbowax column at 200°. The largest peak was collected (25%) and the material crystallized from ether – light petroleum to give the hydroxy-lactone, m.p. 113° (IV), described below. Infrared spectroscopy indicated that the remaining fractions were unsaturated or hydroxy-lactones.

Continuous ether extraction of the original aqueous phase for 24 hours gave material (390 mg) which, after extraction in ethereal solution with small amounts of aqueous sodium carbonate, gave a crystalline neutral product (IV) (180 mg), m.p. 112–113°, ν_{max} 3550, 1780 cm^{-1}. Calc. for $C_9H_{14}O_3$: C, 63.57; H, 8.29. Found: C, 63.70; H, 8.34%.

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SOME CHEMISTRY OF HETERATISINE[1]

O. E. EDWARDS AND C. FERRARI[2]

The minor alkaloid heteratisine from *Aconitum heterophyllum* is of special interest as the only base from aconite and delphinium species known to contain a lactone ring. A recent note outlines the determination of its structure by X-ray crystallography[3] (1). Simultaneous with this determination a number of simple transformation products of the alkaloid were prepared. A study of the physical properties of these enabled recognition of the environment of most of the functional groups of the alkaloid, but fell short of permitting unambiguous assignment of total structure. This evidence is now shown to be completely consistent with the assigned structure.

The early work of Jacobs and Craig on heteratisine (2) demonstrated the presence of a lactone ring, a methoxyl group, an N-alkyl group (presumed to be methyl), and two hydroxyl groups (Zerewitinoff). No easily reduced double bond was found, hence if none is present the empirical formula $C_{22}H_{33}NO_5$ corresponds to a 6-ring structure.

The present work showed that only one hydroxyl of heteratisine was readily acetylated, and that chromium trioxide in acetic acid oxidized the same hydroxyl giving a keto base. The alkaloid hence contains one secondary and probably one tertiary hydroxyl group. Chromium trioxide pyridine complex oxidized heteratisine to a keto-lactam $C_{22}H_{29}NO_6$, thus showing the presence of a methylene group attached to nitrogen. In the infrared spectra of chloroform solutions of the keto-base and keto-lactam, the lactone carbonyl

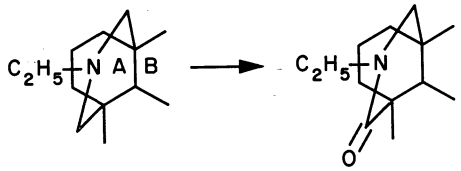
[1]*Issued as N.R.C. No. 7630.*
[2]*National Research Council Postdoctoral Fellow 1961–63.*
[3]*We are grateful to Dr. M. Przybylska for informing us of her conclusions prior to publication.*

absorbed at 1735 cm^{-1} (δ-lactone) and the ketone carbonyl absorbed above 1725 cm^{-1}. In mull spectra of various derivatives the carbonyl absorbed near 1750 cm^{-1}. The secondary hydroxyl of the alkaloid thus appeared to be on a 5-membered ring.

The pK_a of the keto-base (6.6) was two units below that of heteratisine (8.6). This dramatic difference is characteristic of the hydroxyl to carbonyl transformations when the oxygen is on rings A or B of diterpenoid alkaloids (3, 4, 5), and is identical with that for delpheline which has a 6-hydroxyl.

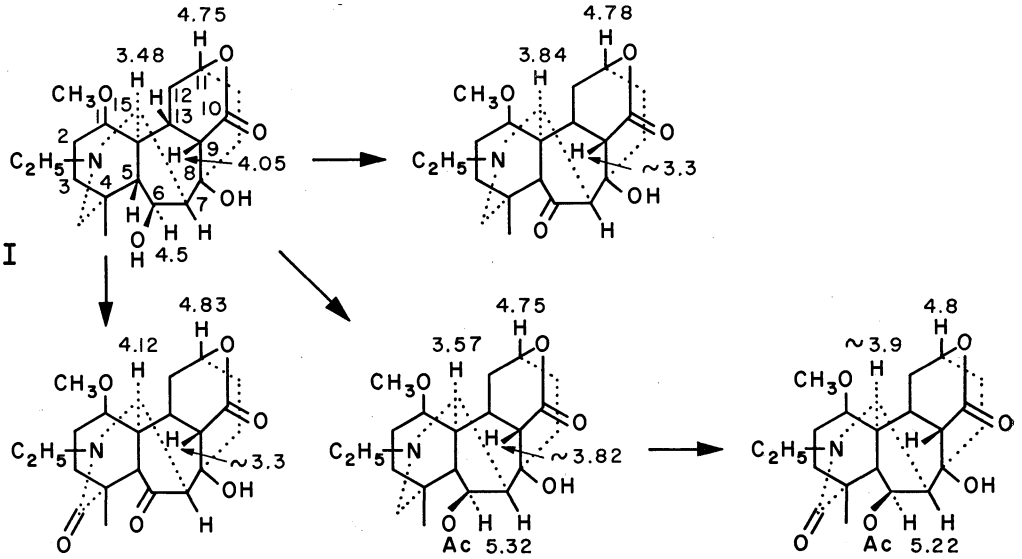
Potassium permanganate in acetone converted heteratisine monoacetate to a complex mixture from which a lactam and a N-desethyl lactam could be isolated. The analysis of the latter and the absence from its spectrum of the characteristic 3-hydrogen triplet which appears near $\delta = 1$ in the n.m.r. spectra of the bases and $\delta = 1.2$ in that of the lactam proved the N-alkyl group to the ethyl.

An unsplit methyl group resonated at $\delta = 1$ in the n.m.r. spectrum of heteratisine and at slightly higher field in that of the keto base and O-acetate. However, the methyl was deshielded markedly in the keto-lactam, resonating at $\delta = 1.25$. The evidence about the hetero ring was thus consistent with the presence of the usual ring A arrangement of the diterpenoid alkaloids:



That the lactone ring and the hydroxyl groups were isolated from one another was demonstrated by the inertness to lead tetraacetate of the tetrahydroxy base produced by lithium aluminum hydride reduction of heteratisine.

The above evidence is consistent with structure I deduced in the X-ray crystallographic study. The remaining structural information obtained in this work was derived by analysis of the n.m.r. spectra of heteratisine and its transformation products. For economy of presentation this will be described using structure I. The chemical shift assignments that could be made with confidence are noted on the formulae:



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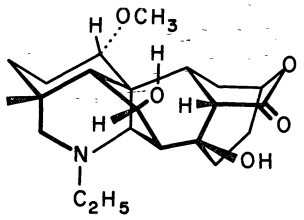
The 11-hydrogen gave a very broad (~20 c.p.s.) signal, relatively invariant in chemical shift as the nitrogen and secondary hydroxyl functions were modified. The chemical shift corresponded to tertiary hydrogen on carbon carrying an acyloxy group. The width of the signal suggested coupling with three or more α-hydrogens. The 15-hydrogen signal was always a doublet (J = 2 c.p.s.). The downfield shift on lactam formation identified this as due to a tertiary hydrogen on carbon carrying the nitrogen, and the multiplicity indicated at least one α-hydrogen. The 6-hydrogen gave a rather complex signal in the base and lactam, shifting downfield and becoming a doublet with J = 6.5 c.p.s. on acetylation and disappearing when the secondary hydroxyl group became a ketone. Thus at least one α-hydrogen was again present. A fourth low field hydrogen could be assigned to the carbon carrying the lactone carbonyl (C-9) or the methoxyl group (C-1). It was a doublet (J = 7 c.p.s.) and was strongly shielded by the ketone carbonyl. The possibility that this hydrogen was adjacent to and coupled with the 6-hydrogen, since the splitting of the doublet in each case was nearly the same, was discounted by spin-decoupling experiments. It was found that the 6-hydrogen was coupled with a hydrogen 161 c.p.s. upfield (hence probably tertiary) and the other was coupled with a hydrogen 91 c.p.s. upfield (again probably tertiary).* On the basis of I this signal corresponds unambiguously to the 9-hydrogen.

Two points, the negligible coupling of the 5- and 6-hydrogens ($\theta \simeq 90°$) and the marked shielding of the 9-hydrogen by the carbonyl on C-6, are beautifully accounted for by formula I.

The perfect correspondence of all the above properties with those expected for the X-ray structure I leaves no doubt about its correctness.

An attempt to test the structure by elimination of the 8-hydroxyl to give an analogue of the very characteristic pyroderivatives of pseudaconitine (6) and delphinine (7) was made. The major component of the resulting mixture proved so unstable, however, that no useful information was obtained from it.



II

Evidence is available that the absolute stereochemistry of heteratisine is correctly represented by I and II. The 6-hydroxyl of heteratisine has the same relative configuration as that of delpheline, whose absolute stereochemistry is known (8, 9, 10). The ΔM_D on oxidation of this hydroxyl in delpheline derivatives is large and negative (−200° to −670°) (11). Since the ΔM_D on oxidation of the 6-hydroxyl of heteratisine is −370°, the absolute stereochemistry is undoubtedly the same as delpheline and all other known diterpenoid alkaloids.

A chair form of ring A has been illustrated in II although the X-ray study showed this ring to be a boat in the crystals of the hydrobromide. Two factors stabilize the boat conformation in the salt: (*a*) hydrogen bonding between the proton on the nitrogen and

*We are grateful to Dr. L. Hall, University of Ottawa, who obtained the spin-decoupled spectra.

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the 1-oxygen; (*b*) repulsive interaction of the 1-methoxyl and the 12-β hydrogen in the chair conformation of ring A which destabilizes this relative to the boat. Whether or not factor (*b*) is enough to make the boat or a half-boat conformation stable in the case of the free base is not certain.

The biogenesis of heteratisine must involve a Baeyer–Villiger type oxidation of a precursor having the commonly occurring lycoctonine skeleton and a 10-carbonyl group.

EXPERIMENTAL

Heteratisine

A solution of the total alkaloids of *Aconitum heterophyllum* in dilute sulphuric acid was adjusted to pH 8 using sodium carbonate, then extracted with benzene. The "weak" bases which were recovered from the benzene extracts crystallized in part from methanol solution. The colorless prisms melted at 267–268° (lit. m.p. 267°) and had $[\alpha]_D$ +29° (*c*, 1.55 in $CHCl_3$), ν_{max}^{Nujol} 3380, 1741 cm^{-1}. Found: C, 67.63; H, 8.41. Calc. for $C_{22}H_{33}O_5N$: C, 67.47; H, 8.50. The perchlorate of heteratisine crystallized as needles, m.p. 252–256° (dec.). Found: C, 53.90; H, 6.46. Calc. for $C_{22}H_{34}ClNO_9$: C, 53.70; H, 6.96. The pK_a' of the base (pH at half titration of the hydrochloride in 50% aqueous ethanol) was 8.6.

Heteratisine Monoacetate

Heteratisine (100 mg) was dissolved in 1 ml of pyridine, and 1 ml of acetic anhydride was added. The solution was left at room temperature overnight and then taken to dryness under reduced pressure. The crystalline residue was dissolved in boiling cyclohexane and when it was cooled 90 mg of white crystals separated, m.p. 155–165°. A second recrystallization from the same solvent raised the melting point to 161–166°. The compound retained solvent and before analysis had to be dried 9 hours at 120°, *in vacuo*. Heteratisine monoacetate sublimed at 145° at 10^{-4} mm, m.p. 161.5–167°. It had ν_{max}^{Nujol} 3430, (tertiary OH), 1738 (δ-lactone), and 1707 cm^{-1} (O-acetyl); pK_a' 7.8 (in 50% ethanol); $[\alpha]_D$ +16° (*c*, 1.66 in $CHCl_3$). Found: C, 66.10, 65.89; H, 8.01, 7.99; N, 3.35. Calc. for $C_{21}H_{35}O_6N$: C, 66.49; H, 8.14; N, 3.23.

N-Desethyl Lactam Acetate and Lactam Acetate

Heteratisine monoacetate (250 mg) was dissolved in 25 ml of acetone, at room temperature. A few drops of acetic acid was added followed by small amounts of finely ground potassium permanganate until the color was permanent for 30 minutes. The small excess was reduced with a few drops of alcohol, and the solution filtered through a bed of diatomaceous earth. The manganese dioxide was thoroughly washed with acetone, and the solution taken to dryness. The oily residue was dissolved in hot methanol and, when it was cooled, 50 mg of colorless platelets of N-desethyl lactam acetate were obtained, m.p. 268–272°. Recrystallization raised the melting point to 271–274°. This gave only one spot on thin-layer chromatography (TLC). It had ν_{max}^{Nujol} 3190 (OH and NH), 1737 (lactone), 1727 (O-acetyl), and 1647 cm^{-1} (lactam). Found: C, 62.80; H, 6.97; N, 3.47. Calc. for $C_{22}H_{29}O_7N$: C, 62.99; H, 6.97; N, 3.34.

The mother liquors of the first crystallization were taken to dryness, and chromatographed on a column of grade IV neutral alumina. Elution with benzene–chloroform 1:1 gave two fractions, the second of which was mainly the above N-desethyl lactam. The first fraction was dissolved in hot methanol; when it had been cooled 40 mg of colorless crystals of the lactam acetate appeared, m.p. 282–286°. A second recrystallization gave m.p. 286–288°. TLC showed only one spot. ν_{max}^{Nujol} 3380 (tertiary OH), 1732 (lactone and O-acetyl), and 1623 cm^{-1} (lactam). Found: C, 64.57; H, 7.42; N, 3.15. Calc. for $C_{24}H_{33}O_7N$: C, 64.41; H, 7.47; N, 3.13. Further elution of the column with 1% methanol in chloroform gave another crystalline fraction that was shown by TLC to be a mixture. This was not investigated further.

N-Desethyl Lactam

N-Desethyl lactam acetate (80 mg) was dissolved in 10 ml of methanol. One milliliter of 10% aqueous solution of sodium hydroxide was added, and the whole boiled 1 hour under reflux. Water was added and the methanol evaporated under reduced pressure. The remaining solution was acidified with sulphuric acid and extracted with chloroform. Evaporation of the extract left an oily residue that crystallized from methanol. TLC showed impurities that could not be removed by crystallization. The product was therefore chromatographed on a large silica gel plate. The main band was scraped off and extracted, giving approximately 50 mg of N-desethyl lactam. Crystallization from methanol gave colorless crystals melting at 266–269°. It had ν_{max}^{Nujol} 1733 (lactone) and 1630 cm^{-1} (lactam) and several peaks above 3000 cm^{-1}. Found: C, 63.66; H, 7.51. Calc. for $C_{20}H_{27}O_6N$: C, 63.64; H, 7.21. (Sample dried 48 hours at 120°.)

Dehydroheteratisine

Heteratisine (200 mg) was dissolved in 4.5 ml of acetic acid, and a suspension of 155 mg of chromium trioxide in 6 ml of acetic acid was added. The mixture was left 50 minutes at room temperature, with occasional shaking. It was then diluted with 3 *N* sulphuric acid and the excess chromic acid reduced with sulphur dioxide. The resulting green solution was extracted with methylene chloride and the extracts discarded. The remaining solution was made alkaline with solid sodium carbonate and then extracted with

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methylene chloride. The extracts were taken to dryness, giving approximately 200 mg of slightly brown froth. This was shown by TLC to be mainly one product, with a small amount of starting material. The mixture failed to crystallize, so it was chromatographed on large silica gel plates, using chloroform–*n*-hexane–diethylamine (10:10:3) as developing solvent. The main band was scraped off and extracted. This afforded 140 mg of keto-base, that again failed to crystallize. It was then dissolved in methanol and a dilute solution of perchloric acid in methanol added until the pH was near 5. The perchlorate which separated immediately as a gel was dissolved by boiling and addition of more solvent. When the solution had been cooled, bulky white needles formed. These were collected and again crystallized from methanol–water, m.p. 266–269.5°. Weight: 85 mg. This had ν_{max}^{Nujol} 3390 (tertiary OH), 1750 (cyclopentanone), and 1715 cm^{-1} (lactone). Found: C, 53.88; H, 6.68; N, 2.98. Calc. for $C_{22}H_{31}O_5N.HClO_4$ ($C_{22}H_{32}ClNO_9$): C, 53.92; H, 6.58; N, 2.85. The free base finally crystallized from cyclohexane, m.p. 135–139°. A second recrystallization gave m.p. 130–135°; pK_a' 6.6 (in 50% ethanol); $[\alpha]_D$ −66° (*c*, 1.42 in $CHCl_3$). Found: C, 67.76; H, 7.93; N, 3.81. Calc. for $C_{22}H_{31}O_5N$: C, 67.84; H, 8.02; N, 3.60. The ultraviolet spectrum of dehydroheteratisine perchlorate only showed a very small peak at 302 mμ, $\epsilon \simeq 30$ unchanged on addition of sodium hydroxide.

Keto Lactam

Heteratisine (100 mg) was dissolved in 1.5 ml of pyridine, and the suspension of the complex from 80 mg of chromium trioxide in 2 ml of pyridine was added. The suspension was left overnight at room temperature, diluted with 3 *N* sulphuric acid, and the excess chromic acid reduced with sulphur dioxide. A base-neutral separation gave a basic fraction that was shown using TLC to be dehydroheteratisine. The neutral fraction (55 mg) contained two main components. Crystallization of this mixture from methanol gave colorless crystals, m.p. 268–275°. A second recrystallization gave m.p. 270–274°. The compound had ν_{max}^{Nujol} 3480 (tertiary OH); 1748 (cyclopentanone); 1735 (lactone); and 1635 cm^{-1} (lactam). Found: C, 65.46; H, 7.41; N, 3.38. Calc. for $C_{22}H_{29}O_6N$: C, 65.49; H, 7.25; N, 3.47.

Dehydration of Heteratisine with $POCl_3$–Pyridine

A solution of 100 mg of alkaloid in 3 ml of pyridine was cooled to 0°. One milliliter of phosphorus oxychloride was added dropwise during 15 minutes, and the resulting solution left 1 hour at room temperature. It was then slowly poured over ice, made alkaline with solid sodium carbonate, and extracted with methylene chloride. On evaporation to dryness under reduced pressure the solution turned purple, possibly due to oxidation. A thin layer chromatogram showed one main component that was separated on a preparative plate. The n.m.r. spectrum of this fraction showed possibly one olefinic proton, but a new TLC revealed that the compound had decomposed giving a complex mixture.

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N-SULPHONYLIMINO ESTERS

Bernard Loev and Minerva F. Kormendy

Orthoaminobenzenesulphonamide (I*a*) and orthoaminobenzylsulphonamide (I*b*) cyclize readily on heating with an orthoester to give, respectively, the six-membered benzothiadiazinedioxide (II*a*) (1) and the seven-membered benzothiadiazepinedioxide (II*b*) (2).

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