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OCHOTENSIMINE: A NOVEL BENZYLISOQUINOLINE ALKALOID

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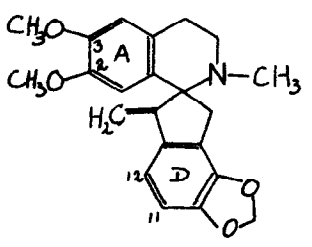
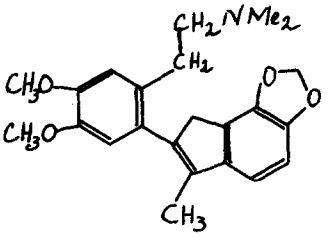
Manske[1] reported the isolation of the alkaloids ochotensine and ochotensimine from Corydalis ochotensis and showed that the latter is simply the O-methyl ether of the phenolic base, ochotensine. Our own investigation of ochotensimine has now shown that these alkaloids have the skeleton represented in structure I, but some ambiguity remains concerning the position of the oxygen functions.



I



II

Ochotensimine, $C_{22}H_{23}O_4N$ (by analysis of its crystalline methiodide[1]) is isolated as an optically active, yellow-brown, amorphous solid which, despite its physical appearance, gives a beautifully clean and well-resolved n.m.r. spectrum which

serves as a basis for almost all the structural assignments we have made.

The 60 Mc/s spectrum shows a two-proton AB quartet centred at 3.04 τ with J = 8.0 c/s (internal chemical shift 19 c/s) and one-proton singlets at 3.47 τ and 3.70 τ, features compatible with the aromatic substitution pattern in I. A two-proton singlet at 4.03 τ arises from the methylenedioxy function, and one-proton singlets at 4.37 τ and 5.10 τ are attributed to the two vinyl protons which must therefore have J = 0 (supporting evidence for this is reported in the sequel). Three-proton singlets appear at 6.17 τ and 6.38 τ for the O-methyl groups and at 7.87 τ for the N-methyl group. A moderately complex pattern of peaks of total area corresponding to six protons appears between 6.65 τ and 7.3 τ and, in this pattern, two peaks each of area approximating that for one proton stand isolated at 6.67 τ and 6.95 τ while the other signals form an unresolved multiplet near 7.1 τ. The 100 Mc/s spectrum[3] shows the same general features as that at 60 Mc/s, but at the highest resolution the methylenedioxy signal becomes broadened and is compatible with that of an AB system with virtually zero chemical shift between its components and $J < 1$ c/s. More importantly, the pattern just below 7 τ is considerably clarified and the two isolated peaks can be recognized to be components of an AB pattern, as was originally suspected; analysis shows this pattern to be centred at 6.80 τ with J = 18.0 c/s (internal chemical shift 50 c/s), and this assignment was confirmed by the spin-spin decoupling technique.

The important deductions regarding the skeletal structure

of the alkaloid that can be drawn from the n.m.r. data are: (i) the molecule contains an $H_2C = C<$ group, the protons of which are in distinctly different chemical environments, and they are not in a position that allows coupling with other protons; (ii) a $>CH_2$ group is present and it also has no neighboring protons with which it can couple; its chemical shift is compatible with a methylene α to phenyl and the J value, which requires a geminal relationship between the two protons, is compatible with that of an indane[3].

Chemical evidence supporting the assigned structure comes mainly from experiments leading to C-N cleavage. Manske[1] has already noted that the Hofmann degradation of ochotensimine methiodide does not lead to a characterizable product, but the Emde degradation yields a crystalline product, $C_{23}H_{27}O_4N$. We have isolated the same product, which was optically inactive, very cleanly and in excellent yield by hydrogenation of the methiodide in the presence of a platinum catalyst. Hydrogenation of ochotensimine in the presence of 30% Pd/C yielded a non-crystalline dihydro-ochotensimine $[\alpha]_{Hg}^{22°}$ + 112° with a pKa 7.4 (50% EtOH), a change from that of ochotensimine (pKa 6.7) in keeping with the relationship of the nitrogen and the double bond in I. The n.m.r. of the product was also in accord with that of the compound resulting from hydrogenation of the $H_2C = C<$ in I, the most significant features being the absence of the 4.37 τ and 5.10 τ signals and the appearance of a three-proton doublet with J = 7.2 c/s at 9.05 τ. Hofmann degradation of dihydro-ochotensimine methiodide led to a product identical with the Emde product from ochotensimine. The n.m.r. spectrum is best accounted for by assigning II to this

product: there is a closely-spaced triplet (3 protons) at 8.07 τ, the NMe_2 singlet appears at 7.84 τ, complex multiplets appear at 6.42 τ (2 protons) and 7.48 τ (4 protons) and there is no signal that can be attributed to vinyl hydrogen.

Hofmann degradation of the methiodide of II removed the nitrogen and led to a product, $C_{21}H_{30}O_4$, m.p. 142-144°, which appeared to be that predicted from II. The most significant change in the n.m.r. spectrum was the disappearance of the NMe_2 singlet and the multiplet at 7.48 τ and their replacement by the highly-characteristic three-proton pattern of a styrene in the vinyl region (it was, in fact, almost superimposable on the spectrum of styrene in this region, but very slightly shifted to higher field). Hydrogenation of this degradation product in the presence of a Pt catalyst produced a dihydro derivative, the n.m.r. spectrum of which was entirely compatible with that of the compound in which the acyclic double bond had been reduced; the most critical feature was the disappearance of vinyl protons and the appearance of an $ArCH_2CH_3$ group which produced the highly characteristic ethyl quartet (7.48 τ) and triplet (8.87 τ) with $J = 7.8$ c/s.

This degradative evidence conclusively shows the presence in ochotensimine of the part structure $ArCH_2CH_2\overset{|}{N}CH_3$. Taken in conjunction with the n.m.r. evidence already cited for the presence of isolated $H_2C = C<$ and $>CH_2$ groupings in the molecule and with the knowledge that the alkaloid is optically active, this evidence leads us to propose that structure I possesses the only skeleton entirely in accord with all the data. The positions of the oxygen functions have not been established

with certainty yet; our evidence shows that they are distributed between two aromatic rings, one of which has two hydrogens in an ortho relationship, and the other has two hydrogens in a para relationship. The ring having the latter feature also carries the two methoxyl groups since Dr. R.H. Manske[4] has recently informed us that he has isolated metahemipinic acid after oxidative degradation of an ochotensimine Emde product. This provides us with persuasive evidence (but not proof) that ring A of ochotensimine is correctly represented in I since, with the exception of the cularine alkaloids[5] which constitute a small group that is distinctive in several respects, every benzylisoquinoline alkaloid of which we are aware carries oxygen functions at positions 2 and 3. The methylenedioxy function must then be placed on ring D in one of two ways; structure I shows one possibility, but placing it at positions 11 and 12 would not be at variance with any of our present results.

The u.v. spectra of ochotensimine and its transformation products (tabulated below) are explicable in terms of the proposed structures.

Ultraviolet Spectra

	λ	ε
Ochotensimine	226 mμ (max.)	25,700
	287 mμ (max.)	13,100
Dihydro-ochotensimine	233 mμ (shoulder)	12,400
	282 mμ (max.)	5,900
First Hofmann product (II)	278 mμ (max.)	12,700
	310 mμ (inflex.)	4,800
Second Hofmann product	266 mμ (max.)	14,400
	274 mμ (inflex.)	14,000
	~300 mμ (broad shoulder)	~ 10,000
Dihydro derivative of second Hofmann product	277 mμ (max.)	16,100
	310 mμ (inflex.)	5,800

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2. For which we thank Professor R.U. Lemieux, University of Alberta, Edmonton.
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4. Personal communication.
5. R.H.F. Manske, "The Alkaloids", Vol. IV, Academic Press, New York, N.Y., 1954, pp. 249-252.