Tetrahedron Letters No.49, pp. 6169-6173, 1966. Pergamon Press Ltd.
Printed in Great Britain.

ON THE STRUCTURE OF METAPHANINE AND ITS HOFMANN DEGRADATION PRODUCT

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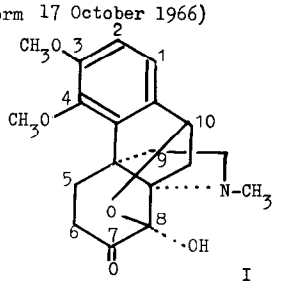
(Received 4 August 1966; in revised form 17 October 1966)

In a recent communication by Tomita et al.,[1] structure I was proposed for the alkaloid metaphanine. This has prompted us to publish independent findings leading to the same structure for this alkaloid.



I

From Stephania abyssinica (Dill. and Rich. Walp) Menispermaceae, a Stephania species indigenous to Southern Africa, an alkaloid was isolated,[2] m.p. 233°, $[\alpha]_D^{25}$ -21° (c, 1.0 in $CHCl_3$) $\lambda_{max.}$ (ethanol) 205, 285 mμ (ε 44,900 and 2,200, respectively), $\nu_{max.}$ (chloroform) 3450 cm^{-1} (OH) and 1740 cm^{-1} (CO) and its empirical formula was shown by analysis and mass spectrometry to be $C_{19}H_{23}O_3N$. This alkaloid was found to be identical with metaphanine* (m.p., mixed m.p. and chromatographic behaviour), a morphine-type alakloid.[3] The nuclear magnetic resonance spectrum‡ of the alkaloid apart from

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* Generously provided by K. Takeda, ITSUU Laboratory, Tokyo, Japan.

‡ Unless otherwise stated, all n.m.r. spectra were done on the Varian A-60 instrument in $CDCl_3$ with $SiMe_4$ as internal standard.

showing $>N-CH_3$, τ 7.43 (3 H), and two ortho aromatic protons τ 3.12 and τ 3.14, demonstrated the presence of two methoxyl substituents on the aromatic ring and therefore the absence of a 4:5 oxide bridge can be deduced.

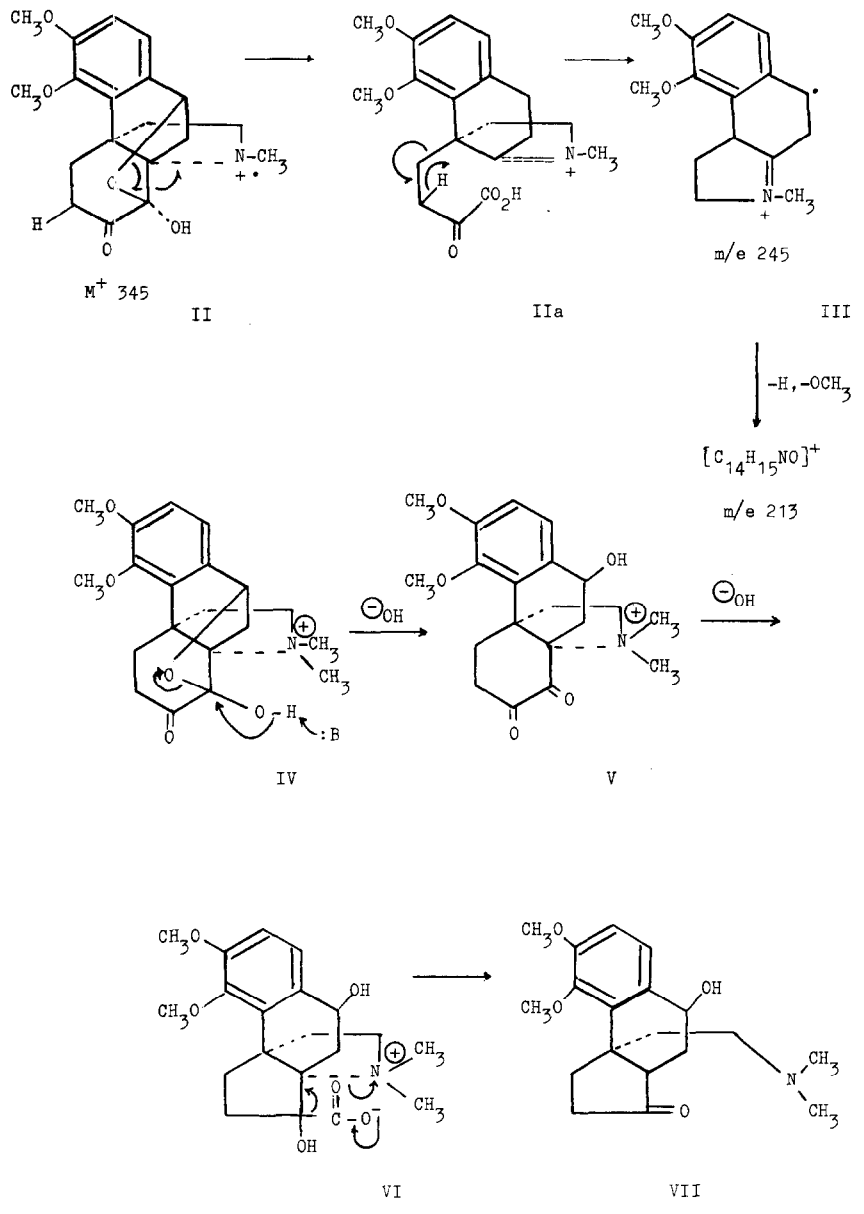
Biogenetic reasoning[4] as well as the above information suggests that the 7-position is substituted. The remaining oxygen is assigned to an ether group, consistent with active hydrogen determination on the alkaloid and the absence of carbonyl absorption in the infrared spectrum of the mono-oxime (m.p. 210 - 212°). That the hydroxyl and ketone groups were situated on adjacent carbon atoms was demonstrated by the consumption of one mole equivalent of periodate by the alkaloid. The hydroxyl group could not be acetylated under non-forcing conditions (acetic anhydride - pyridine) and was stable to oxidation. The tertiary nature of the hydroxyl was confirmed by the sharp singlet hydroxyl band at τ 4.74 in the nuclear magnetic resonance spectrum of its dimethylsulphoxide solution.[5]

Further support for the proposed structure I for metaphanine was obtained from the investigation of the product obtained from the Hofmann degradation of the methiodide of the alkaloid.

On refluxing metaphanine with methanol - methyliodide, the corresponding methiodide $C_{19}H_{23}O_5N.CH_3I$, m.p. 195° (from acetone - hexane) was obtained. The mass spectrum of this quaternary salt was identical to that of the alkaloid superimposed on the mass spectrum of methyliodide,[6] peaks at m/e 142 (CH_3I) and 127 (I). The proposed fragmentation mechanism[7] (II - III) received further support from the accurate mass determination on the base peak m/e 245 ($C_{15}H_{19}NO_2$) and peak m/e 213 ($C_{14}H_{15}NO$). The formation of III can only be rationalized

with the carbonyl group being in the 7-position. Additional proof for the position of the ketone group and the origin of the hydrogen migrating during formation of the m/e 245 fragment was obtained from the C-6 deuterium-labelled alkaloid. The active methylene hydrogens were exchanged with deuterium in a mixture of DCl in deuteriophosphoric acid and deuterium oxide[8] prepared by dissolving phosphorous pentachloride in deuterium oxide. Although the process of exchange was slow, a product consisting of 35% d_2, 50% d_1, and 15% d_0-species was obtained after prolonged heating at 130°. In the mass spectrum of the deuterio-compound, the base peak was at m/e 246, i.e. a shift of one mass unit, in accordance with the mechanism proposed (II ⟶ III).

When the iodide was refluxed in 10% methanolic potassium hydroxide, a non-quaternary product $C_{19}H_{27}O_4N$ was isolated, m.p. 158 - 159° from cyclohexane - methylene chloride, $\nu_{max.}$ (chloroform) 3480 cm^{-1} (OH), 1730 cm^{-1} (five-membered ring ketone). The ultraviolet spectrum was identical to that of metaphanine and therefore no change in the chromophore had occurred. The nuclear magnetic resonance spectrum of this product showed the presence of a $-N(CH_3)_2$ group at τ 7.91, (6H), and two methoxyl groups at τ 6.13 (3H) and τ 6.09 (3H). The two ortho aromatic protons appeared as an AB quartet (τ 2.72 and τ 2.31, J = 7 c./s.). A quartet representing the X part of an ABX pattern was observed at τ 5.37 (J = 9 c./s. and J = 5 c./s.). This is assigned to a $CH_2-C(OH)H$ hydrogen. That this alcohol was benzilic was proved by the oxidation with activated manganese dioxide in chloroform to a diketone ($C_{19}H_{25}O_4N$) M^+ 331, $\nu_{max.}$ (chloroform) 1730 cm^{-1} and 1670 cm^{-1} (a five-membered ring ketone and a conjugated ketone, respectively), no hydroxyl absorption, $\lambda_{max.}$ (ethanol) 230 and 277 mμ (ε 17,300 and 7,800, respectively).


M+ 345
II
IIa
m/e 245
III
-H,-OCH3
[C14H15NO]+
m/e 213
IV
V
VI
VII

The mass spectrum of the Hofmann degradation product gave a strong molecular ion m/e 333 and is consistent with the presence of a $-CH_2-CH_2-N(CH_3)_2$ side chain by the appearance of the base peak at m/e 57 $[CH_2=^+N(CH_3)_2]$ and strong peaks at m/e 73 $[CH_2-CH_2-^+N(CH_3)_2]$ and m/e 260 (M-73).

Structure VII for this Hofmann degradation product is in accordance with the above evidence and its formation from the methiodide IV can be visualized through the intermediates V and VI. The first step is the cleavage of the hemiketal in the presence of a base to afford the α-diketone V, followed by a benzilic acid rearrangement to yield the α-hydroxycarboxylic acid VI which then finally through a novel Hofmann degradation loses carbon dioxide to give compound VII.

One of the authors (R.R.A.) wishes to thank Smith, Kline and French for financial support.

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