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THE STRUCTURE OF LOCHNERICINE AND LOCHNERININE

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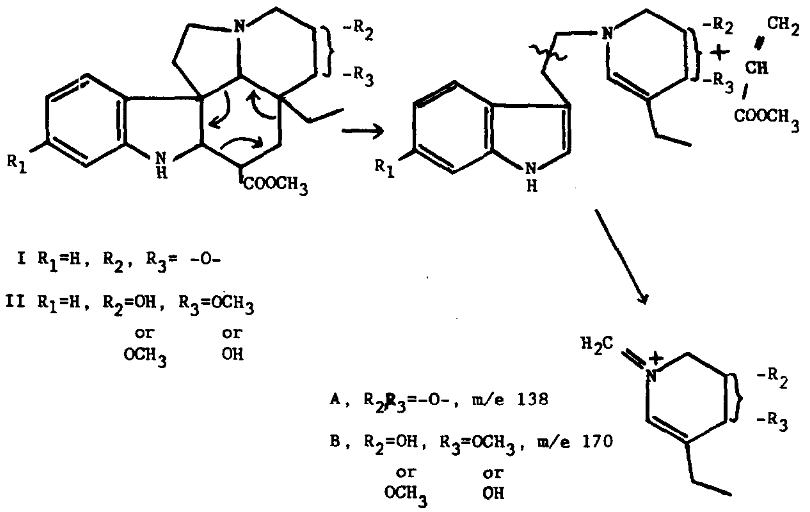
Lochnericine (1,2,3,4), $C_{21}H_{24}N_2O_3$, is a weak base to which a carbomethoxy-α-methyleneindoline structure was assigned (2,3,4) on the basis of its high specific rotation and its U.V. and I.R. spectra. Modified chromic acid oxidation indicated a C-ethyl group (4). One active hydrogen was found by reaction with lithium aluminum hydride while two active hydrogens were indicated by a Zerewitinoff determination using anisole as solvent at an elevated temperature. The absence of any isolated double bond was indicated by the failure to reduce lochnericine under catalytic conditions (4).

Scarcity of the alkaloid precluded the use of classical chemical methods for the elucidation of the structure of lochnericine. Physical methods were therefore employed extensively. The NMR spectrum of lochnericine showed peaks at 1.07 τ (N$\underline{H}$), 2.65-3.20 τ(4 vicinal aromatic protons), 6.24 τ(COOC$\underline{H}_3$) and a distorted triplet centered at 9.21 τ(-CH_2-C$\underline{H}_3$). Since the third oxygen could not be accounted for as a carbonyl or hydroxyl group it was concluded that this oxygen was part of an ether linkage. The molecular formula therefore corresponds to a hexacyclic structure.

The spectrum of lochnericine recorded on a model MCH 1303 (USSR) mass spectrometer by the direct introduction of the sample in the ion source showed the base peak at m/e 138. A similar spectrum was obtained on an Atlas CH4 mass spectrometer. The peak at m/e 138 is suggestive of an aspidospermine skeleton with an oxygen attached to the piperidine moiety.

Additional information was obtained from the mass spectra of such derivatives of lochnericine as could be prepared from samples of very small size. The reduction of lochnericine with zinc and sulfuric acid in methanol gave several products from which it was possible to isolate an indoline (λ_{max}^{MeOH} 250 mμ and 301 mμ) fraction. This fraction contained two compounds for which the partial structures I and II were deduced from mass spectral data. Each compound lost the elements of methyl acrylate. Compound I showed a peak at m/e 138 (A) while the base peak for compound II was at m/e 170 (B). It was apparent that II was obtained by the reduction of the double bond and the concomitant addition of a molecule of methanol to the piperidine moiety of lochnericine.



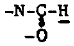
I R_1=H, R_2, R_3= -O-

II R_1=H, R_2=OH, R_3=OCH_3
or or
OCH_3 OH

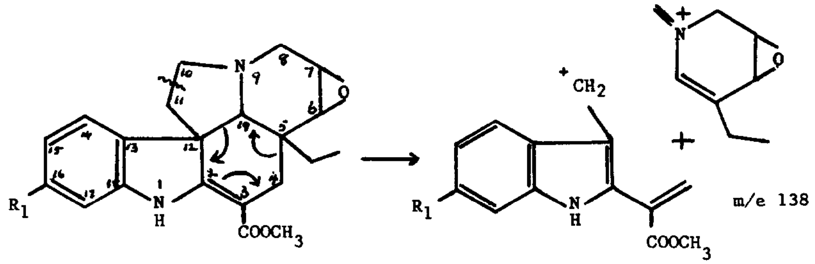
A, R_2R_3=-O-, m/e 138

B, R_2=OH, R_3=OCH_3, m/e 170
or or
OCH_3 OH

The size and the exact position of the ether-oxygen containing ring could now be deduced on the basis of the NMR spectrum of lochnericine.

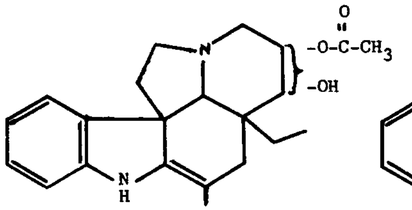
The lack of signals in the range 4.20-6.20 τ indicated the absence of any strongly deshielded protons such as  $-\text{N}-\underset{\underset{-\text{O}}{|}}{\text{C}}-\text{H}$ — . This precluded the attachment of an oxygen at C_8 or C_{10}. The ether oxygen must therefore bridge two of the three available positions, namely, C_6, C_7 and C_{19}.

On the basis of the data available at present, we propose the epoxide structure III for lochnericine. The Bohlmann band (5) at 2815 cm^{-1} in the I.R. spectrum of lochnericine is consistent with the presence of a hydrogen at C_{19} (6) that is <u>trans</u> to the lone electron pair on nitrogen.

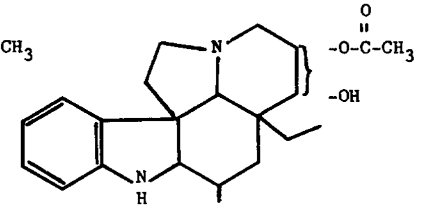


III R_1=H
IV R_1=OCH_3

The epoxide structure III is in agreement with the properties of a compound (V) obtained on heating lochnericine with glacial acetic acid at 100° for 2 hrs. The I.R. spectrum of V showed (besides the bands of the



V



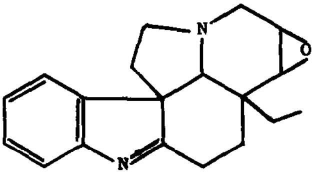
VI

original chromophore at 1613 cm^{-1} and 1645 cm^{-1}) a new band at 1748 cm^{-1} (ester carbonyl). Reduction of lochnericine with zinc and acetic acid at 120° afforded a compound VI U.V. λ_{max}^{MeOH} 247 mμ, 297 mμ; I. R. bands in chloroform at 1610 cm^{-1} (indoline), 1730 cm^{-1} (ester), 3450 cm^{-1} (NH), 3620 cm^{-1} (OH) which had a molecular weight of 414 and which could be accounted for by the structure VI.

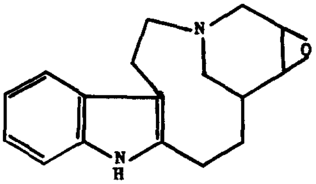
Upon heating with 5 N HCl in a sealed tube at 125° for 3 hrs. and basification with strong ammonia, lochnericine gave an indolenine (U.V. λ_{max}^{MeOH} 222 mμ, shoulder at 260 mμ; I.R. bands at 1580 cm^{-1} and 1615 cm^{-1}), no bands for NH/OH and CO groups . The reduction of this indolenine with potassium borohydride in alkaline medium afforded several products from which a fraction "A" (U.V.λ_{max}^{MeOH} 228 mμ, 285 mμ and 291 mμ; I.R. band at 3470 cm^{-1}) was isolated. The mass spectrum of "A" seemed to indicate the presence of two compounds with molecular ion peak at m/e 294 and 296. If lochnericine does have the structure III, heating with hydrochloric acid would be expected to lead to a halohydrin which under the influence of strong ammonia, could revert to an epoxide structure. For the end products of molecular weight 294 and 296, one can write the structures VII and VIII, respectively. It may be noted that VIII corresponds to an oxygenated form of quebrachamine.

The fragmentation pattern of deoxy-VII and deoxy-VIII has already been studied (7). The fragments of m/e 265 and 210 found in the spectrum of "A" would be expected of structure VII. The fragments of m/e 143,144,157 in this spectrum are consistent with the quebrachamine structure VIII.

VII



VIII



Lochnerinine (IV), $C_{22}H_{26}N_2O_4$, was shown previously to be methoxylochnericine (4). This was further confirmed by the similarity of its mass spectrum with that of lochnericine. Lochnerinine also shows a Bohlmann band (2790 cm^{-1}, shoulder at 2720 cm^{-1}). The U.V. spectrum of the indoline compound prepared from lochnerinine by zinc-acetic acid reduction was found to be very similar to that of 7-methoxyhexahydrocarbazole (8), establishing thereby the 16-methoxylochnericine structure IV for this alkaloid.

The structures III and IV are consistent with the current biogenetic view (9,10). The epoxidation of a similar compound with a $\Delta^{6:7}$ double bond, as for example in tabersonine (11), is quite possible in nature. Such a reaction is already known in the literature in connection with the conversion (12) of dehydrohyoscyamine to scopolamine by feeding experiments *in vivo* and also in the case of some steroid compounds (13).

In view of the restricted nature of the chemical investigation to date, it is essential to correlate lochnericine with a compound of known structure and stereochemistry. Should structures III and IV be confirmed, lochnericine and lochnerinine would be the first representatives of naturally occurring indole bases having an epoxide ring.

A detailed description of our work will appear in a future issue of *Lloydia*.

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