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OBSERVATIONS ON THE NMR AND MASS SPECTROMETRY OF THALMINE AND RELATED ALKALOIDS

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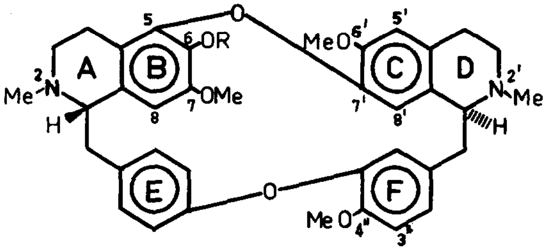
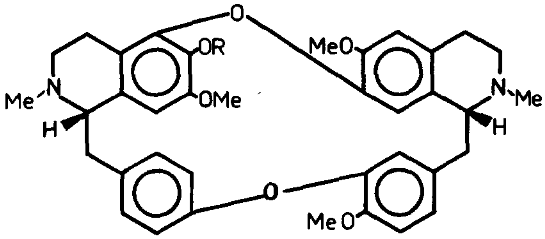
The alkaloid thalmine, first isolated from the Soviet Asian plant Thalictrum minus L (1), has recently been shown to have the novel type of biscoclaurine structure (I) with a 5,7' ether link between the two isoquinoline residues (2).



Thalmine I, R = H

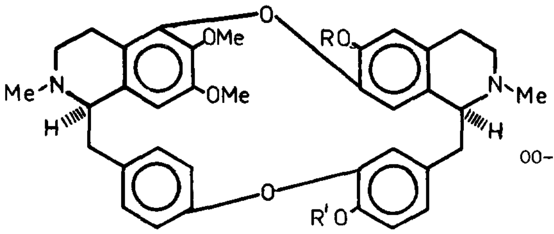
O-Methylthalmine II, R = Me



Lauberine III, R = H

O-Methyllauberine IV, R = Me

O-Ethyllauberine V, R = Et



Dryadine VI, R = H, R' = Me
Dryadodaphnine VII, R = R' = H
O-Methyldryadine VIII, R = R' = Me
OO-Diethyldryadodaphnine IX, R = R' = Et

More recently, the diastereomeric structure (III) has been demonstrated for the alkaloid lauberine isolated from the Brazilian plant Berberis laurina (3), and two further alkaloids of the same type, dryadine (VI) and dryadodaphnine (VII) have been discovered in the New Guinea plant Dryadodaphne novoguineensis (4).

In the case of the well-known types of biscoclaurine bases with an 8,7' ether link between the isoquinoline units, some useful structural and stereochemical correlations have been observed with certain features of the NMR spectra (5). These alkaloids have a central 18-membered heterocyclic ring to which other rings with bulky substituents are fused; as a result, the methoxyl and methylimino protons in these substituents are forced to lie over the top of adjacent aromatic rings in certain cases and hence resonate at higher field than usual (5). For similar reasons, protons at the 8 positions of isoquinoline residues are shielded and likewise absorb at higher fields (6).

In the case of the 5,7' linked biscoclaurines, the heterocyclic ring is now a 21-membered one, so that the O- and N-methyl groups are in general less crowded, and the corresponding proton resonances (Table 1) are found close to the normal positions in the NMR spectrum with the exception of those at the 2 and 6 positions: molecular models indicate that these groups pass over adjacent aromatic rings in certain conformations. Moreover, this type of biscoclaurine has free 8 positions in both isoquinoline residues, which are evidently shielded by other aromatic rings, and the fact that two high-field resonances appear in the spectra may prove diagnostically useful for this type of alkaloid.

Apart from oxy groups in the 6 position, on which information is directly obtainable from the spectrum, the replacement of a methoxyl by a hydroxyl group at the remaining positions can be inferred by deuterium labelling experiments: thus in the case of dryadine(VI), acid-catalysed equilibration with deuterium oxide led to the disappearance of a singlet in the NMR

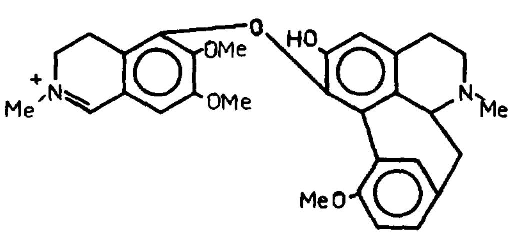
TABLE 1

Portion of NMR Spectra of Thalmine-type Alkaloids (τ values)

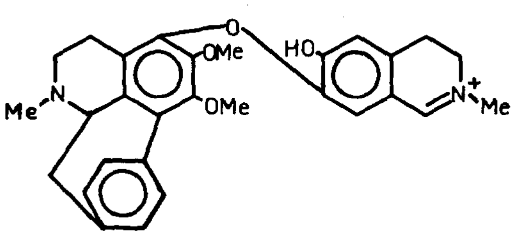
	$N-CH_3$		$O-CH_3$				High-field aromatic H (8 and 8')	
	2	2'	4"	6	6'	7		
Thalmine(I)	7.78	7.36	6.07	-	6.07	6.07	3.94	3.94
O-Methylthalmine(II)	7.84	7.35	6.09	6.31	6.10	6.13	3.91	4.12
Lauberine(III)	7.70	7.35	6.05	-	6.08	6.08	3.88	3.94
O-Methyllauberine(IV)	7.75	7.33	6.07	6.36	6.07	6.07	3.80	3.97
O-Ethyllauberine(V)	7.77	7.35	6.07	-	6.07	6.10	3.89	4.04
Dryadine(VI)	7.70	7.35	6.07	6.52	-	6.07	3.72	4.00
Dryadodaphnine(VII)	7.75	7.34	-	6.56	-	6.10	3.75	3.98
O-Methyldryadine(VIII)	7.77	7.35	6.08	6.38	6.08	6.08	3.83	4.00

spectrum at τ 3.32, which can be ascribed to the proton at the 5' position since the only other singlets are the high-field 8 and 8' ones. The remainder of the spectrum remained virtually unchanged in the case of dryadine, but with dryadodaphnine(VII) there was an additional change around τ 3.17, evidently produced by the replacement of the 3" proton with deuterium. A hydroxyl at position 7 would also be readily detectable by a deuteration experiment, which should result in the loss of one of the high-field aromatic protons. On the other hand, an attempted deuteration of lauberine(III), in which the phenolic group has no free ortho or para position, showed as expected no incorporation of deuterium.

The mass spectra of thalmine and its analogues show a general similarity to those of the more usual 8 7'-linked types (7,8), but are distinguished from them by the absence of a peak



X

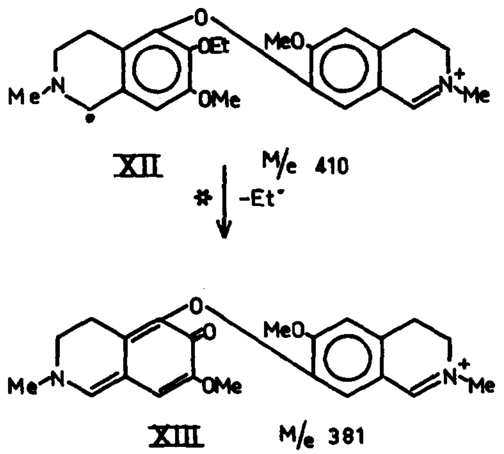


XI

corresponding to loss of rings C and D, and also by the fact that they have two free 8 positions in the isoquinoline rings: weak but reproducible ions corresponding to the loss of either benzyl group with hydrogen transfer from 8 or 8' are observed (8), and thus for dryadine (VI), peaks of approximately equal intensity appear corresponding to ions M-107 (X) and M-137 (XI). They are accompanied by a M-121 peak of strength comparable to the latter two, which is probably formed by loss of ring E with methyl transfer from the 7-methoxyl. Other types of biscoclaurine do not show three peaks of comparable intensity in this region.

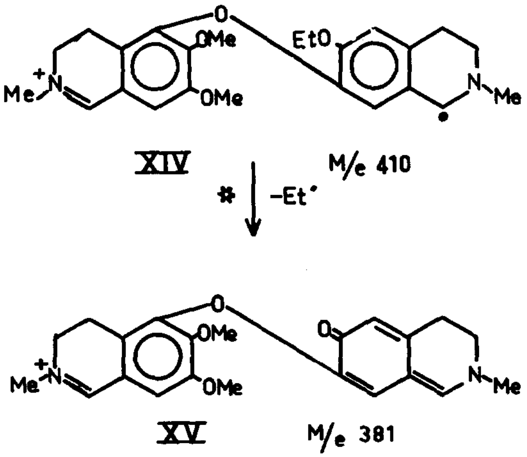
The members of the thalmine group so far isolated all have a phenolic group at position 6 or 6'. With thalmine and lauberine in particular, this suggests a biogenetic pathway through a phenol oxidation process from a coclaurine and an isococlaurine unit, instead of two coclaurines as for the other types of bisbenzylisoquinolines, in which hydroxyls at 6 or 6' are rare. The presence of these hydroxyls in thalmine-type bases can be deduced from the spectra of the corresponding O-ethyl derivatives: thus O-ethyllauberine (V) gives a singly-charged ion (XII) at $^{m}/e$ 410 which fragments further to give an ion at $^{m}/e$ 395 by loss of Me$^{\bullet}$, and one of three times the intensity at $^{m}/e$ 381 (XIII) by loss of Et$^{\bullet}$. The ion (XIV) from O,O-diethyldryadodaphnine (IX) fragments similarly to give an ion of moderate intensity by loss of Me$^{\bullet}$, and a weaker one (XV) by loss of Et$^{\bullet}$. Further evidence is furnished by the corresponding strong doubly-charged ions (XVI, R = Et) and (XVIII, R = Et) at $^{m}/e$ 205, which both lose methyl ethyl ether to give the same ion at $^{m}/e$ 175; loss of dimethyl ether from either is insignificant.

By examining the decomposition of the corresponding doubly-charged ions (XVI, R = H) and



XII

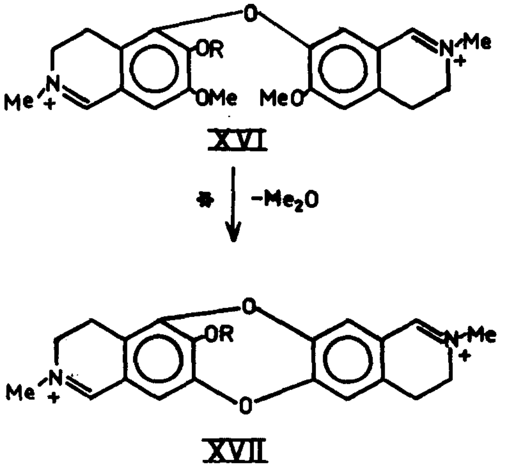
XIII

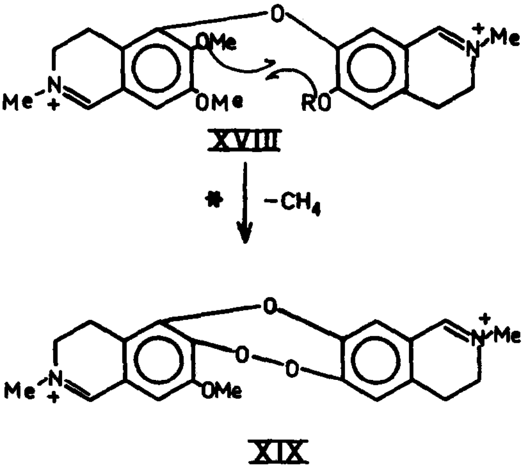


XIV

XV

(XVIII, R = H) formed from the free bases, it is possible to differentiate between hydroxyl groups at the 6 or 6' positions: thus the ion (XVI, R = H) derived from lauberine (III) loses dimethyl ether to give (XVII, R = H), while the ion (XVIII, R = H) from dryadine (VI) shows only a weak loss of dimethyl ether, and fragments preferably by the loss of methane to give a prominent ion (XIX, R = H) at $^{m}/e$ 183; on the other hand, loss of methane is only of minor importance from (XVI, R = H).





The formation of the ions (XII), (XIV), (XVI) and (XVIII) by loss of the benzyl residues from the molecular ion also shows the nature of the oxy groups present in those residues. While direct evidence concerning the 7-oxy group is not available from mass spectrometry, their nature may be deduced indirectly after allocation of the remaining oxy functions.

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