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DEVIATIONS FROM THE GENERALITY OF THE 'MASS SPECTROMETRIC METHOD' FOR DETERMINING THE MODE OF ESTER ATTACHMENT IN PYRROLIZIDINE ALKALOIDS

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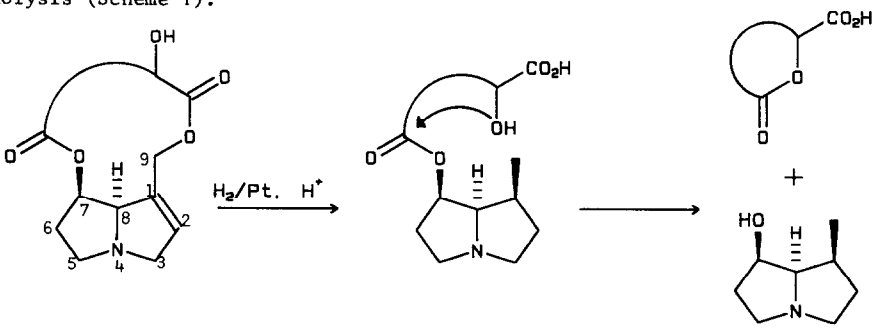
Abstract: The general use of mass spectrometry for determining the mode of ester attachment in pyrrolizidine alkaloids is based on what appears to be an over simplification of complex fragmentation pathways, and seems to produce unreliable results when applied to macrocyclic pyrrolizidine alkaloids.

The widespread occurrence of hepatotoxic pyrrolizidine alkaloids in flowering plants[3] have stimulated research in diverse disciplines for several decades.[4] Although the pyrrolizidine alkaloids are generally toxic, posing a threat to both man and animal, some of the N-oxides show antitumour activity. Indicine N-oxide has been clinically tested.[5] Furthermore, a number of nonnatural N-oxides have been synthesised in a search for enhanced antitumour activity.[6,7]

The structure elucidation of pyrrolizidine alkaloids was essential for an understanding of the biochemistry of these compounds. Determination of the position of ester attachment of the necic acids to the necine in the diester pyrrolizidine alkaloids was, and still is the most problematic aspect of their structure elucidation.

The major part of these alkaloids have 1,2-unsaturated necine moieties, rendering the acid esterified to position 9 an allylic ester. In the past, catalytic hydrogenolysis (Pt/H^+) was generally used to selectively cleave the allylic ester, thus providing a mechanism for determining the mode of ester attachment.[8] Some of the macrocyclic pyrrolizidine alkaloids, however, would spontaneously transesterify on hydrogenolysis, liberating the necic acid moiety at position 7 also, thus preventing the determination of the mode of ester attachment by way of hydrogenolysis (Scheme 1).[9-11]



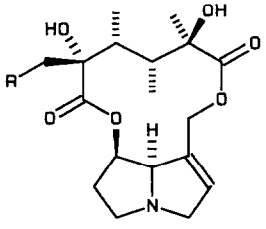
Scheme 1

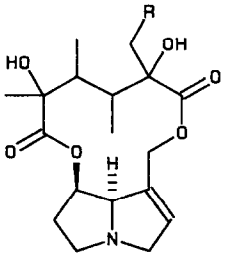
Currently mass spectrometry is used for determining the mode of ester attachment in the 1,2-unsaturated pyrrolizidine alkaloids. The major fragmentation sequences are initiated by electron impact at the allylic ester group.[12] The ensuing fragmentation pathway indicates which necic acid group remains esterified to the 7-hydrozyl group of the necine.

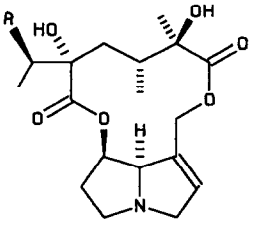
On reinvestigating the alkaloids of *Senecio latifolius* DC[13] we isolated merenskine [1][14] and sceleratine [2],[15] which have physical properties that correlate with those reported for [3][9] and [4],[11] respectively, previously isolated from *Senecio latifolius* DC. Mass spectra of merenskine [1] and sceleratine [2] seemed to confirm the modes of ester attachment proposed for [3] and [4], respectively.

It is therefore evident that viable fragmentation pathways, accommodating the major peaks in the mass spectra of merenskine [1] and sceleratine [2], may be formulated for both their possible modes of ester attachment. Parallel fragmentation pathways for merenskine [1] and its isomer by reversed ester attachment [3] are presented in Scheme 2. The significant peaks having m/z above 200 dalton justify mass spectrometric fragmentation of either compound. Below each pair of fragments their m/z value is given, followed by the relative intensity of that fragment as a percentage of the intensity of the base peak, in brackets. Where a frag= ment contains a chlorine atom, both the isotopic m/z values are indicated. The m/z values which have been determined accurately are underlined, details of which are listed below the scheme. The fragmentation pathway that leads to the ion of 210 dalton is uncertain. Its formulation, however, is inplicated by the analogous ion of jaconine [6] having m/z 224 dal= ton.[16]

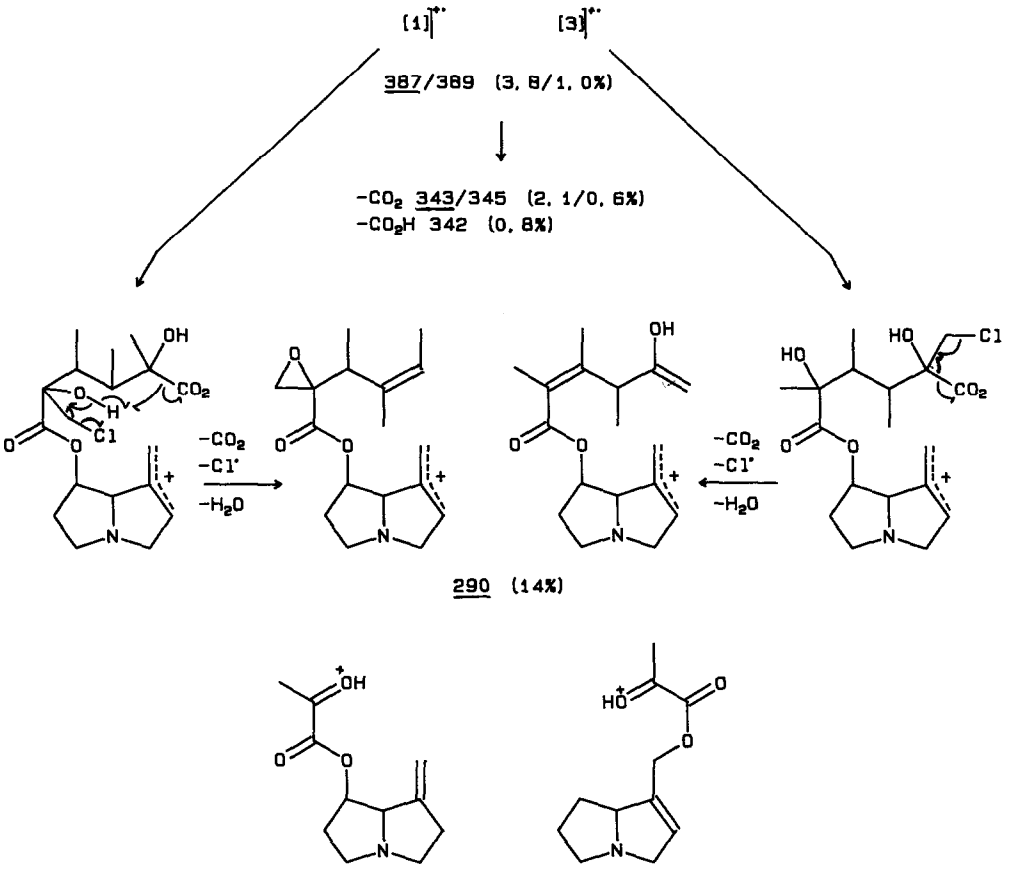
The relatively major ion with m/z 290 dalton would normally be considered significant in indicating the mode of ester attachment in merenskine [1]. Superficially it seems to imply the reversed mode of ester attachment [3]. However, after loss of CO_2, the free radical centre is transfered to the north-western side of the molecule by abstraction of the tertiary hydroxy proton *via* a six-membered transition. The tertiary hydroxy group which is α with respect to the north-western ester group seems to favour this mechanism which features in the mass spectra of sceleratine [2],[15] sceleratine monomesylate [7],[17] jaconine [6][16] and jacoline [8].[18]







[1] Merenskine, R=Cl
[2] Sceleratine, R=OH
[3], R=Cl
[4], R=OH
[6] Jaconine, R=Cl
[8] Jacoline, R=OH
[5] Merenskine N-oxide, (N-oxide of [1])
[7] Sceleratine monomesylate, R=OSO_2Me



Found 387, 1448. $C_{18}H_{26}ClNO_6$ requires m/z 387, 1448
Found 343, 1549. $C_{17}H_{26}ClNO_4$ requires m/z 343, 1550
Found 290, 1756. $C_{17}H_{24}NO_3$ requires m/z 290, 1756
Found 210, 1129. $C_{11}H_{16}NO_3$ requires m/z 210, 1130

Scheme 2

Ironically, most of the macrocyclic pyrrolizidine alkaloids have a tertiary hydroxy group α with respect to the north-eastern ester group. If the mode of ester attachment of these alkaloids were reversed, the tertiary hydroxy group would be favourably situated for this anomalous transfer of the free radical centre. This fact exposes an element of uncertainty as to the correctness of the structures of macrocyclic pyrrolizidine alkaloids which have had their modes of ester attachment determined solely by the mass spectrometric method.

In conclusion, there seems to be a need for a more reliable method of determining the mode of ester attachment in macrocyclic pyrrolizidine alkaloids.

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NOTES AND REFERENCES:

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