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Mass Spectrometric Fragmentation of Some Lignans (1)

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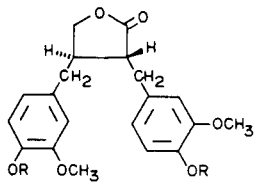
Mass spectra of some lignans containing either γ-butyrolactone, 1,2,3,4-tetrahydronaphthalene or the 3,7-dioxabicyclo[3.3.0]octane ring systems are reported. Probable structures are presented for the more abundant ions in the mass spectra of these lignans.

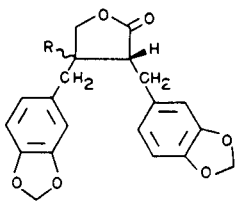
Mass spectrometry was first extensively utilized in natural product chemistry in the structure elucidation of alkaloids (2) and since that time it has been applied in helping to assign structures to a host of different naturally occurring compounds (3). Lignans (4) constitute a group of natural products widely distributed in nature (5) which until recently had not been submitted to mass spectral scrutiny (6). This recent investigation (6) was limited to those lignans containing a tetrahydrofuran ring and indicated the future utility of mass spectrometry in supplementing structural studies of this type. We now wish to report on the mass spectrometry of some other types of lignans frequently isolated from plant sources.

Lignans Containing the 2,3-Bis[substituted benzyl]-γ-butyrolactone Unit.



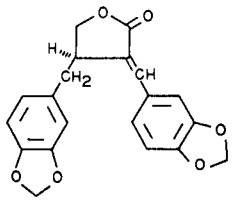
Ia, R = H

b, R = CH_3



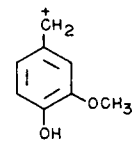
IIa, R = ····H

b, R = ▬ H

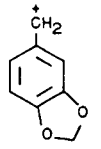


III

Five members of this group of lignans have been included in the present investigation ((-)-matairesinol (Ia), (-)-matairesinol dimethyl ether (Ib), (-)-hinokinin (IIa), (-)-*iso*hinokinin (IIb) and (-)-savinin (III)). All exhibit easily identifiable molecular ions as is exemplified by the mass spectra (Figures 1 and 2) of matairesinol (Ia) and hinokinin (IIa) while the dominating fragment peak in both cases (*m/e* 137 and 135) arises from benzylic cleavage of the molecular ion such that these fragments are assigned structures *a*, (*m/e* 137) and *b*, (*m/e* 135) respectively (7). In agreement with these assignments the base



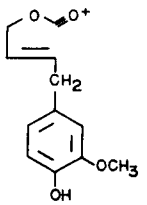
a, m/e 137



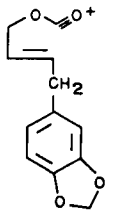
b, m/e 135

peak in the spectra of matairesinol dimethyl ether (Ib) and *iso*hinokinin (IIb) occur at *m/e* 151 and 135 respectively.

Peaks of low ion yield at *m/e* 221 and 219 in the spectra (Figures 1 and 2) of matairesinol (Ia) and hinokinin (IIa) correspond to ions formed by the loss of fragments *a* and *b* as radicals such that the charged fragments could correspond to *c*, (*m/e* 221) and *d*, (*m/e* 219). These assignments received support from the location of an ion at mass 235 in the spectrum of matairesinol dimethyl ether (Ia).



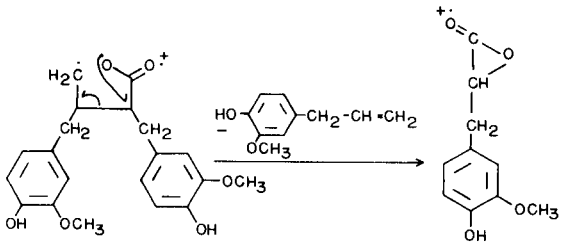
c, m/e 221



d, m/e 219

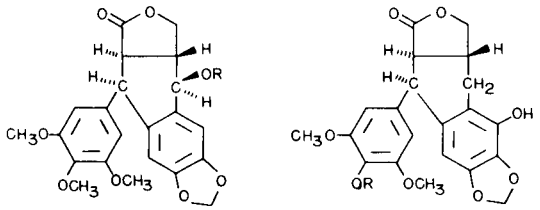
A peak of low abundance at *m/e* 194 in the spectrum (Figure 1) of matairesinol was displaced to *m/e* 208 in the tetramethoxy derivative (Ib). The origin of this ion corresponds to the loss of a

substituted 3-phenyl propene molecule from the molecular ion of matairesinol such that the charged entity can be depicted by *e*, (*m/e* 194). An analogous ion was present at mass 192 in the spectrum (Figure 2) of hinokinin (IIa).



Ia e, m/e 194

Lignans Containing the 1,2,3,4-Tetrahydronaphthalene Ring System.



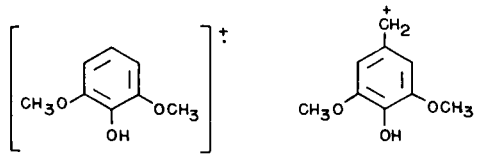
IVa, R = H
b, R = CH_3
c, OR = H

Va, R = H
b, R = CH_3

Of this class of lignans (-)-podophyllotoxin (IVa), (-)-methyl podophyllotoxin (IVb), α-(-)-peltatin (Va) and β-(-)-peltatin (Vb) may be taken as typical examples.

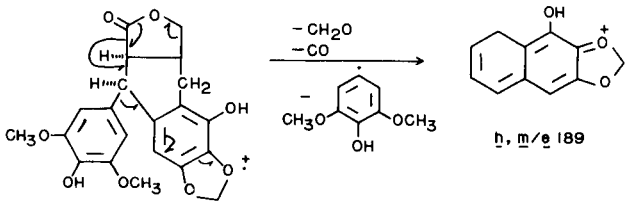
Simple benzylic cleavage of one bond in the molecular ion of members of this group of lignans no longer suffices to fragment the molecule and this explains the virtual dominence of the molecular ion peak in the spectra of these compounds especially in view of the absence of other labile bonds. This is particularly apparent in the spectra of podophyllotoxin (IVa, Figure 3) and methyl podophyllotoxin (IVb, spectrum not reproduced) in which only two fragment ions attain 10% relative abundance. The mass spectrum (Figure 4) of α-(-)-peltatin (Va) does display relatively more fragmentation and a rationalization for the formation of the more prominent ions will be discussed below.

Ions of mass 154 and 167 in the spectrum (Figure 4) of α-(-)-peltatin (Va) (displaced to 168 and 181 in Vb) can be assigned structures *f*, (*m/e* 154) and *g*, (*m/e* 167).



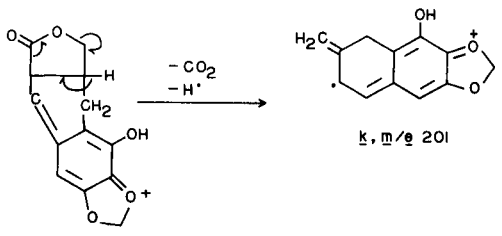
f, m/e 154 g, m/e 167

The location of a peak at *m/e* 189 in the spectrum (Figure 4) of α-(-)-peltatin was unaffected in the spectrum of its methylated analog Vb and this fragment can be envisaged as arising via Va → *h*, (*m/e* 189).



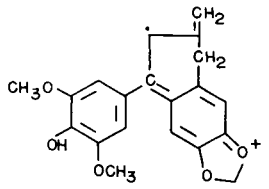
Va h, m/e 189

Loss of 154 mass units (ion *f* as a neutral molecule) from the molecular ion of α-(-)-peltatin affords a fragment of mass 246 which can be assigned structure *j*, (*m/e* 246). Furthermore, loss of an additional 45 mass units yields a peak at *m/e* 201 and structure *k* can be given to this ion. Recognition of a metastable ion at mass 164.2 (201^2/246 = 164.2) testifies to the parent-daughter ion relationship between ions *j* and *k*. The presence of peaks at *m/e* 246 and 201 in the spectrum of β-(-)-peltatin (Vb) is completely compatible with the assigned structures *j* and *k* for these ions. No metastable ion could be discerned which would correspond to the transition *j*, (*m/e* 246) → *h*, (*m/e* 189).

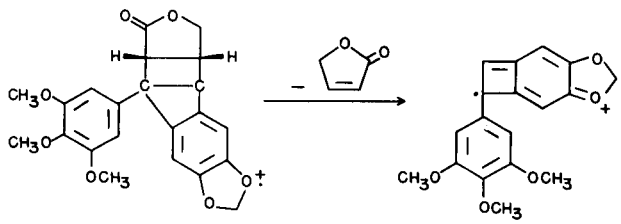


j, m/e 246 k, m/e 201

A peak of low abundance at *m/e* 355 (M-45) in the spectrum (Figure 4) of α-(-)-peltatin (Va) could correspond to the elimination of carbon dioxide and a hydrogen atom. The genesis of this fragment is thus analogous to *j* → *k*, (*m/e* 201) and it may be represented by *n*, (*m/e* 355). Similar weak peaks at M-45 were observed in the spectra of β-(-)-peltatin (Vb) and podophyllotoxin (IVa).



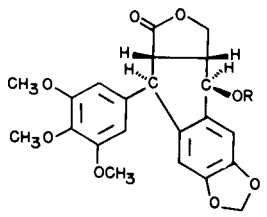
n, m/e 355



o, m/e 396 p, m/e 312

The mass spectrum of desoxypodophyllotoxin (IVc) lends support to the above structural representation for the principal ions in the spectrum of α-(-)-peltatin. Thus, the mass spectrum of IVc contains peaks (corresponding α-(-)-peltatin ions shown in parenthesis) at *m/e* 168 (*f*, *m/e* 154), 181 (*g*, *m/e* 167), 173 (*h*, *m/e* 189) and at 230 (*j*, *m/e* 246).

The mass spectrum of *epi*podophyllotoxin (OH α in IVa) contains a much more pronounced peak (11% relative abundance) due to the loss of water than did its epimer IVa. This phenomenon was more striking in the spectrum (Figure 5) of picropodophyllin (VIa) in which the lactone ring is fused in the *cis* configuration. In this instance the molecular ion is of 4% relative abundance while the peak due to loss of water is over sixteen times as intense.



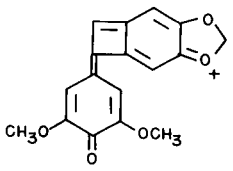
VIa, R = H

b, R = CH_2CH_3

The elimination of ethanol from picropodophyllin ethyl ether (VIb) on electron impact yields a peak of 57% relative abundance (8). The mass spectrum of epipicropodophyllin (OH α in VIa), however, has a peak of 21% relative abundance due to the loss of water while the base peak is the molecular ion and this is in marked contrast to its epimer (VIa).

The base peak in the mass spectrum (Figure 5) of picropodophyllin (VIa) occurs at *m/e* 312 (M-102) and the corresponding ethyl ether (VIb) also displays a prominent peak at this value. Electron impact dehydration of VIa could yield a species which might be represented by *o* (*m/e* 396) (9) which by further loss of an α,β unsaturated γ-butyrolactone molecule would yield the ion *p*, *m/e* 312.

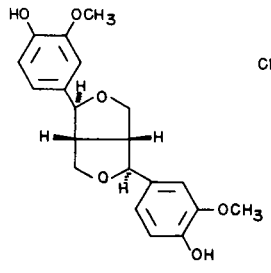
The ion *p*, (*m/e* 312) further decomposes by expelling a methyl radical (metastable ion at 282.9, $297^2/312 = 282.7$) to give an even electron species which can be represented as *q*, *m/e* 297.



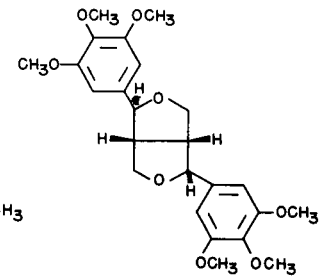
q, m/e 297

An ion of mass 168 in the spectrum of picropodophyllin (VIa) would correspond to the fully methylated species *f*.

Lignans Containing the 3,7-Dioxabicyclo[3.3.0]octane Ring System.



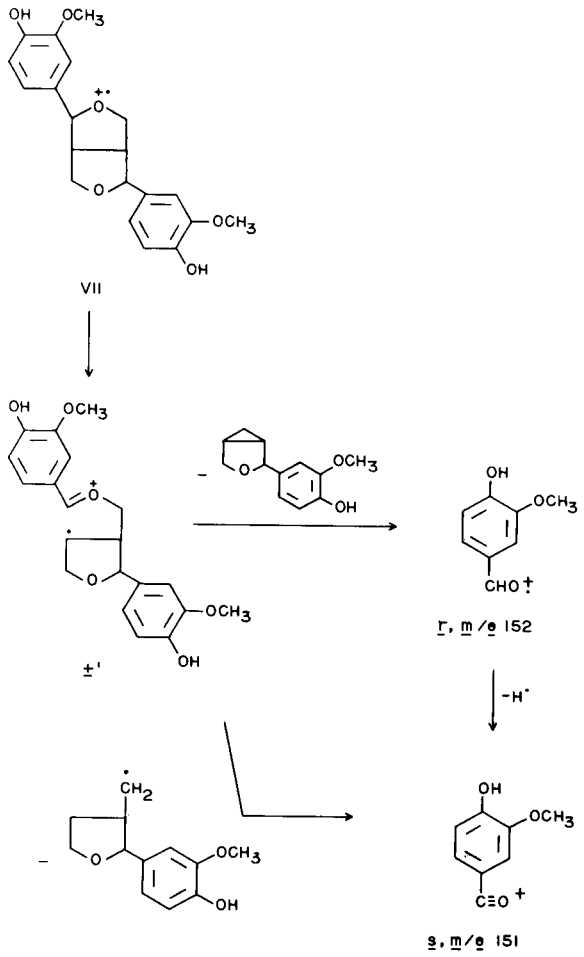
VII



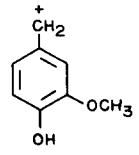
VIII

Pinoresinol (VII) and lirioresinol β-dimethyl ether (VIII) are two representatives of this class of lignans and the spectra of both (Figures 6 and 7) display strong molecular ion peaks. A prominent ion of mass 152 in the spectrum (Figure 6) of pinoresinol (VII) could be formed via the sequence VII → *r'* → *r*, (*m/e* 152). Ejection of a hydrogen atom from this species would be a possible origin for the formation of the base peak (*m/e* 151) (10). Alternatively, the species *s*, (*m/e* 151) may arise directly from the molecular ion with transfer of a hydrogen

atom in r' to the radical site. Support for the structures (r and s) assigned to the ions at mass 152 and 151 in the mass spectrum of pinoresinol was obtained from the spectrum (Figure 9) of compound VIII in which these ions were located at mass 195 and 196 respectively.

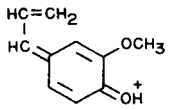


A second important fragment in the spectrum (Figure 6) of pinoresinol (VII) occurs at mass 137 (see analogous ion at mass 181 in the spectrum (Figure 7) of lirioresinol β-dimethyl ether (VIII), which may be assigned to the benzylic cation (7) t, (m/e 137).



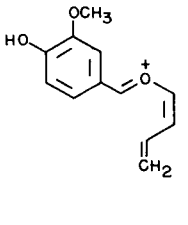
t, m/e 137

An ion present at mass 163 in the spectrum (Figure 6) of pinoresinol VII could correspond to the entity u, (m/e 163) and this hypothesis is enhanced by the occurrence of an ion of appreciable intensity at mass 207 in the spectrum (Figure 7) of lirioresinol β-dimethyl ether (VIII).

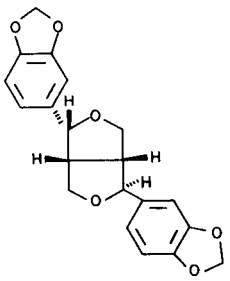


u, m/e 163

Pinoresinol (VII) displays a peak at m/e 205 in its mass spectrum (analogous peak in VIII (Figure 7) at m/e 249) and to this fragment we assign structure v, (m/e 205).



v, m/e 205



IX

The naturally occurring lignan (-)-asarinin (IX), which differs from VII and VIII by the stereochemistry of one center, displays peaks in its mass spectrum (Figure 8) which are analogous to those present in the spectrum (Figure 6) of pinoresinol. Thus (-)-asarinin contains peaks (11) at m/e 135 (137), 149 (151), 150 (152), 161 (163) and 203 (205). It would appear as though differing stereochemical orientations of the oxygenated benzene rings have little effect on the resulting mass spectra.

Summary: The spectra of all the lignans investigated afforded easily recognizable molecular ions and generally fragmentation was minimal being confined to cleavage of benzylic bonds. Stereochemical differences within the same group of lignans did not cause any major differences to their mass spectra with the exception of podophyllotoxin (IVa) and picropodophyllin (VIa). The molecular ion of picropodophyllin was relatively unstable (4% relative abundance) preferring to lose water and the five-membered lactone ring.

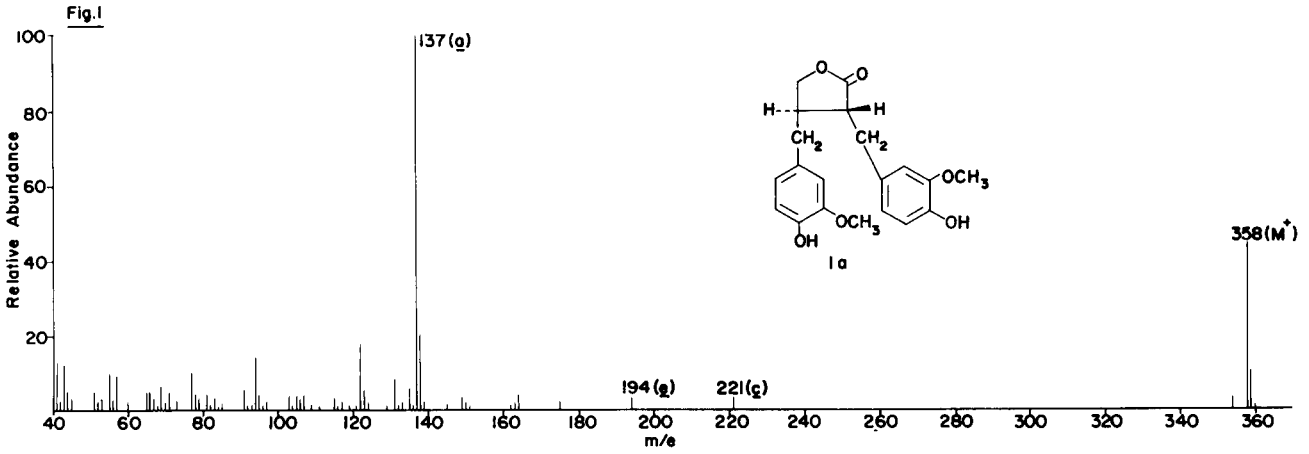


Fig. 1. Mass spectrum of (-) matairesinol.

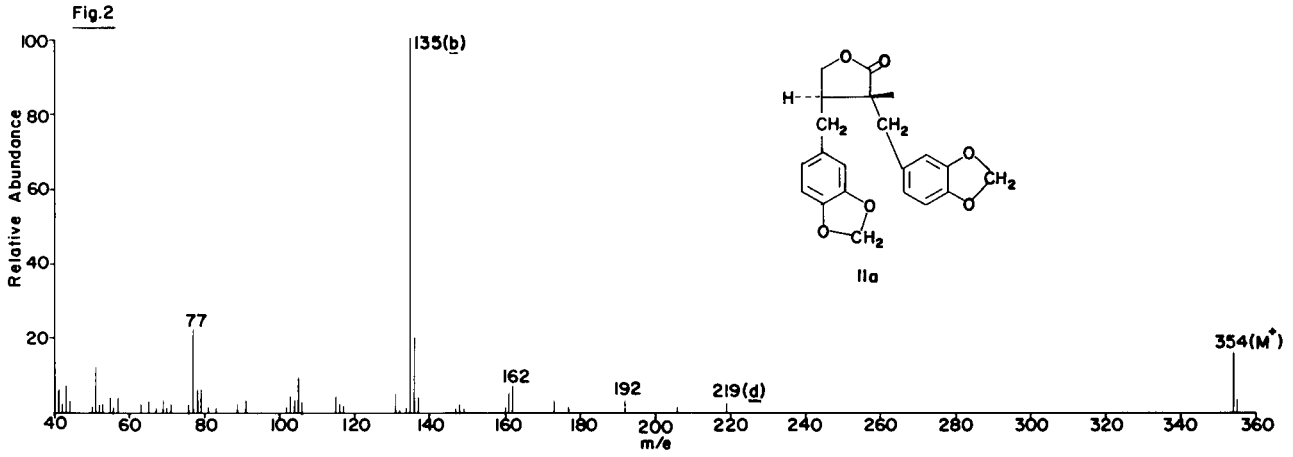


Fig. 2. Mass spectrum of (-) hinokinin.

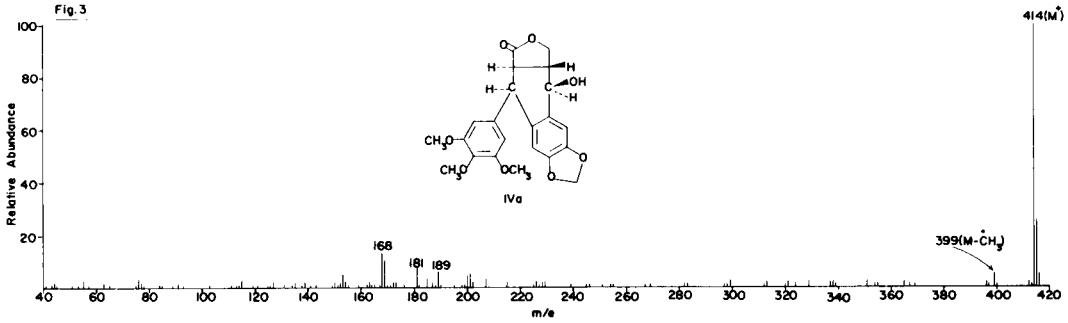


Fig. 3. Mass spectrum of (-) podophyllotoxin.

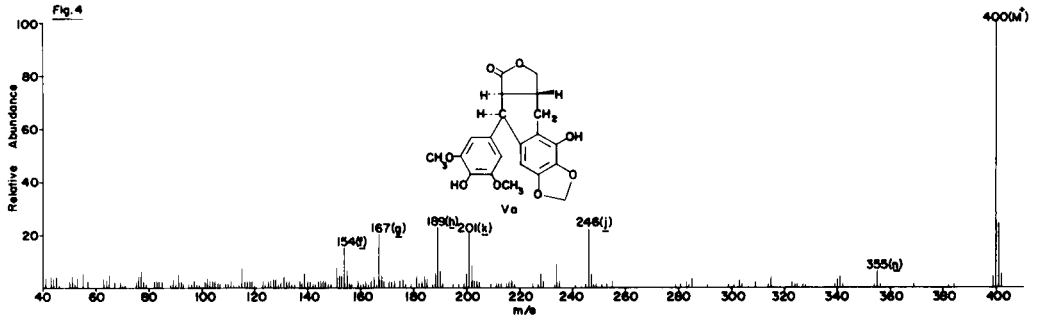


Fig. 4. Mass spectrum of α-(-)-peltatin.

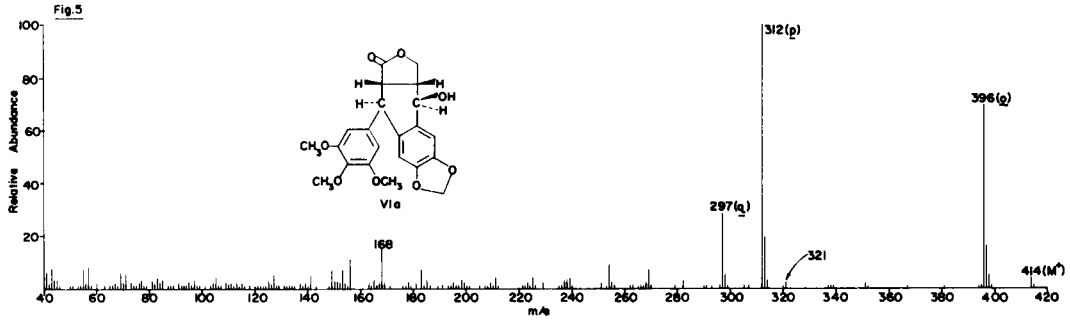


Fig. 5. Mass spectrum of picropodophyllin.

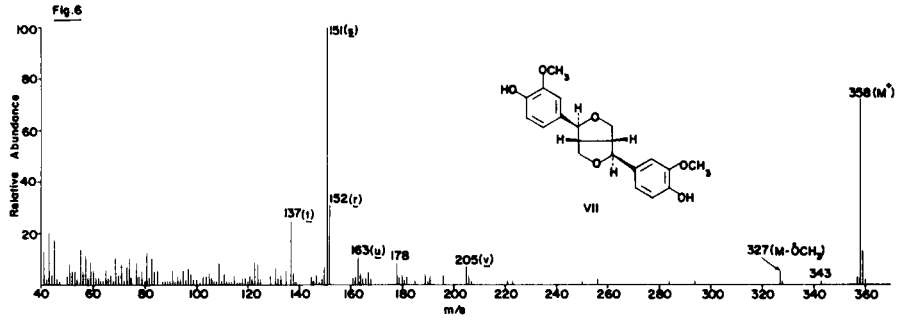


Fig. 6. Mass spectrum of pinoresinol.

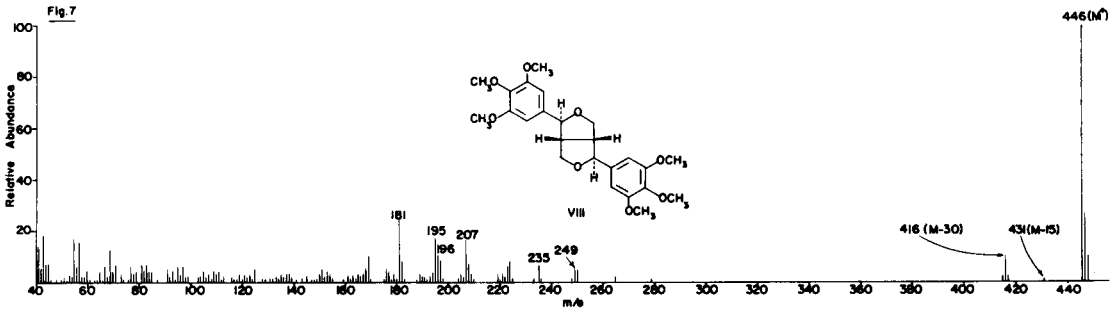


Fig. 7. Mass spectrum of lirioresinol β-dimethyl ether.

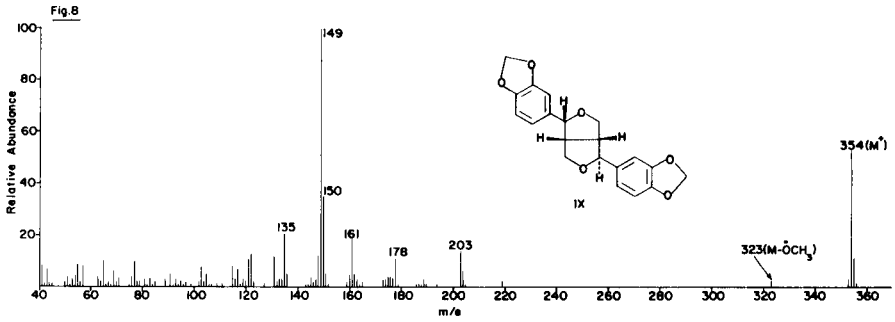


Fig. 8. Mass spectrum of (-) asarinin.

EXPERIMENTAL

The mass spectra of (-)-podophyllotoxin and α-(-)-peltatin were determined on an AEI MS-9 mass spectrometer using the direct inlet procedure. The remaining spectra were obtained with an Atlas CH-4 spectrometer using the TO-4 ion source. 70 e.v. Electrons were used with both instruments.

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REFERENCES

(1) I am indebted to the National Institutes of Health of the U. S. Public Health Service (Grants No. GM-11309 and AM-04257) for financial support. The purchase of the Atlas CH-4 mass spectrometer was made possible by the National Aeronautics and Space Administration (Grant No. NsG 81-60).

(2) For a review of the mass spectrometry of Alkaloids see H. Budzikiewicz, C. Djerassi and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. I, Holden-Day Inc., San Francisco, Calif., 1964.

(3) For a review of the applications of mass spectrometry to natural product chemistry see H. Budzikiewicz, C. Djerassi and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. 2, Holden-Day, Inc., San Francisco, Calif., 1964.

(4) M. S. Adjangba, *Bull. Soc. chim. France*, 2344 (1963).

(5) K. Freudenberg and K. Weinges, *Tetrahedron*, **15**, 115 (1961).

(6) A. Pelter, A. P. Stainton and M. Barber, *J. Heterocyclic Chem.*, 3, 191 (1966).

(7) Species such as *a* and *b* may rearrange to tropylium ions but throughout this paper only the benzylic cation will be represented for the sake of simplicity.

(8) The loss of water and ethanol in these compounds is not considered to be thermal in nature since all spectra were obtained using direct inlet procedures in which the sample is vaporized very close to the electron beam.

(9) Electron impact dehydration of cyclohexanol has been shown to occur preferentially (83%) via 1,4 and 1,3-elimination processes. See H. Budzikiewicz, Z. Pelah and C. Djerassi, *Monatsh. Chem.*, 95, 158 (1964).

(10) Although no metastable ion corresponding to this transition was observed it has been shown that benzaldehyde loses the α-hydrogen atom in the formation of an abundant M-1 species. See, J. D. McCollum and S. Meyerson, *J. Am. Chem. Soc.*, 85, 1739 (1963).

(11) Corresponding peaks present in the mass spectrum of pinoresinol are given in parenthesis.

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