Mass Spectrometry of Bisbenzylisoquinoline Alkaloids. Part I. Alkaloids derived from Coclaurine Units joined Tail-to-tail

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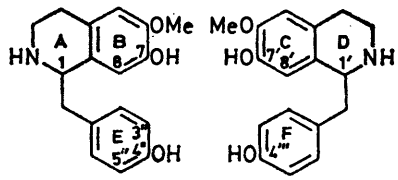
Mass spectrometric data are presented for some simple types of biscoclaurine alkaloids in which the two halves of the molecule are joined tail-to-tail by one, two, or three ether links. The cleavage patterns, supported in part by deuteriation experiments, are discussed.

Mass spectrometry has proved valuable in the structural elucidation of bisbenzylisoquinoline alkaloids,[1-10] and in these papers the principal fragmentation patterns for some simple types, supported in certain instances by deuteriation experiments, are discussed.

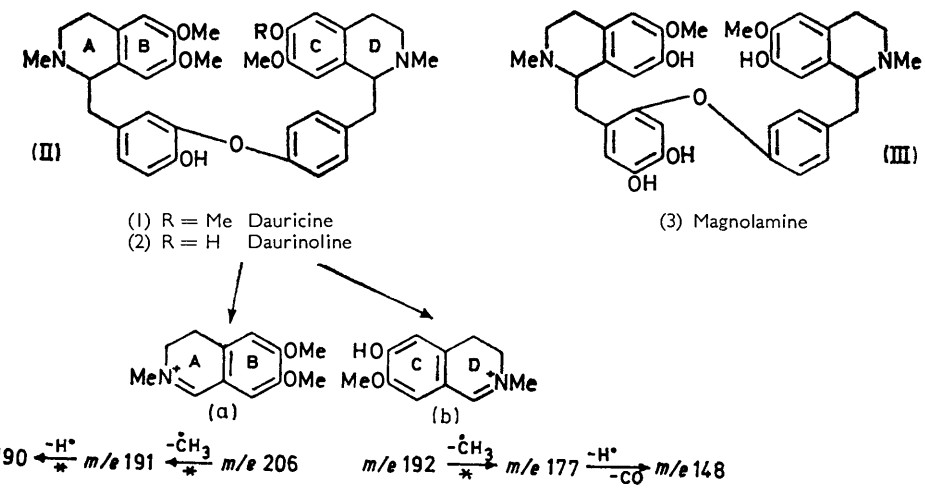


(I)

The structural types dealt with in this paper can be considered to arise biogenetically by oxidative coupling of two units of coclaurine (I) to produce an ether link between positions 3″ and 4‴ (type A), followed by further linkage between 7′ and 8, or 7 and 8′ (type B). In a further group (type C) there are three diaryl ether links, or one biaryl and two diaryl ether links.

For the most part, each type gives a characteristic spectrum, in which the overall fragmentation pattern is little affected by number or nature of substituents, so that well defined mass shifts are observed which can be used to locate and determine substituents. However, stereoisomers give practically identical spectra.

The highly favoured benzylic cleavages result in very weak molecular ions (*ca.* 0·1%) and intense ions due to rings A and B, and C and D, which for daurinoline (2) are at *m/e* 206 (a) and 192 (b) respectively. Further degradation of (a) and (b) is relatively minor. Loss of rings A and B or C and D as neutral fragments occurs largely with hydrogen transfer to the charged ring C, D, E, and F or A, B, E, and F fragments, but is unimportant (0·1—0·2%). Dauricine has the same A and B and C and D rings, and hence gives only (a) (100%);



(I) R = Me Dauricine
(2) R = H Daurinoline

(3) Magnolamine

Alkaloids of type A

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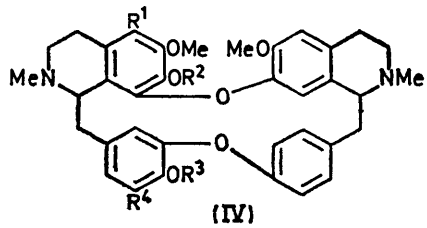
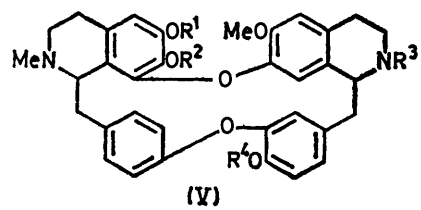
likewise magnolamine gives only one ion isomeric with (b) (100%).



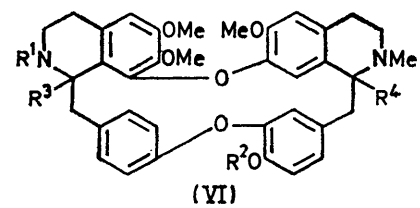
(IV)

(4) $R^1 = R^4 = H$, $R^2 = R^3 = Me$ Tetrandrine (*S,S*); phaeanthine (*R,R*); isotetrandrine (*R,S*)
(5) $R^1 = R^3 = R^4 = H$, $R^2 = Me$ Pycnamine (*R,R*); berbamine (*R,S*)
(6) $R^1 = R^2 = R^4 = H$, $R^3 = Me$ Fangchinoline
(7) $R^1 = R^2 = R^3 = R^4 = H$ Atherospermoline (*S,S*); obamegine (*R,S*)
(8) $R^1 = R^4 = H$, $R^2 = R^3 = CD_3$ [7,4″-*dimethoxy*-$^2H_6$]isotetrandrine
(9) $R^4 = H$, $R^2 = R^3 = Me$, $R^1 = OMe$ Hernandezine
(10) $R^1 = R^2 = H$, $R^3R^4 = CH_2O$ Nortenuipine
(11) $R^1 = H$, $R^2 = Me$, $R^3R^4 = CH_2O$ Tenuipine



(V)

(12) $R^4 = H$, $R^1 = R^2 = R^3 = Me$ Oxyacanthine (*S,R*); repandine (*S,S*)
(13) $R^1 = R^2 = R^3 = Me$, $R^4 = CD_3$ [4‴-*methoxy*-$^2H_3$]Obaberine
(14) $R^1 = R^2 = R^3 = R^4 = Me$ Obaberine (*S,R*); *O*(4‴)-methylrepandine (*S,S*)
(15) $R^2 = R^3 = R^4 = H$, $R^1 = Me$ Daphnoline
(16) $R^2 = R^3 = H$, $R^1 = R^4 = Me$ Daphnandrine
(17) $R^3 = R^4 = H$, $R^1 = R^2 = Me$ Sepeerine
(18) $R^3 = R^4 = Me$, $R^1R^2 = CH_2$ Cepharanthine



(VI)

(19) $R^1 = R^4 = H$, $R^3 = D$, $R^2 = Me$ [1-^{2}H]-1,2-Dihydroepistepanine
(20) $R^1 = R^4 = H$, $R^3 = D$, $R^2 = CD_3$ [1,4‴-*methoxy*-$^2H_4$]-1,2-Dihydroepistephanine
(21) $R^4 = H$, $R^3 = D$, $R^1 = Me$, $R^2 = CD_3$ [1,4‴-*methoxy*-$^2H_4$]-2-Methyl-1,2-dihydroepistephanine
(22) $R^4 = H$, $R^3 = D$, $R^1 = R^2 = Me$ [1-^{2}H]-2-Methyl-1,2-dihydroepistephanine
(23) $R^3 = R^4 = D$, $R^1 = R^2 = Me$ [1,1′-$^2H_2$]-2-Methyl-1,2-dihydroepistephanine

Alkaloids of type B

Molecular Ions and Ions due to Loss of Rings E *and* F.—A characteristic feature of this group is a series of doubly and singly charged ions arising from double benzylic cleavage and loss of rings E and F. The doubly charged molecular ion is generally weak (1—3%), but double heterolytic benzylic cleavage gives in the case of alkaloids (4), (5), (8), (9), (11)—(14), and (17) an intense doubly charged ion (c) (generally the base peak) (Scheme 1). Ion (c) characteristically loses dimethyl ether, probably to give the dibenzo-1,4-dioxin structure (d), since ion (c) from alkaloid (8) loses MeO·CD_3 exclusively. Loss of dimethyl ether is also characteristic of ion (e) derived from alkaloids (6), (7), (10), (15), and (16), which have a 7-hydroxy-group (Scheme 2). Ion (f) may be formed initially and rearrange to a less strained dibenzo-1,4-dioxin structure [*cf.* (d)]. As expected, loss of dimethyl ether does not occur from the analogue of ions (c) and (e) (*m/e* 190) formed from alkaloid (18).

The singly charged molecular ion is generally intense (45—100%), and is cleaved to give a peak composed of ions (g) and (h), with negligible charge retention on the ring E and F fragment (Scheme 3). These ions readily fragment by loss of H· or Me·. Thus, ion (h) gives ions of the type (i) and (j) respectively. Ions (g) and (h) derived from alkaloid (8), which has a 7-trideuteriomethoxy-group, lose Me· from the 6- or 6′-methoxy-groups preferentially to give a conjugated quinonoid ion such as (j), but some loss of $\dot{C}D_3$ also occurs. For most of the alkaloids (4)—(17) a metastable transition is observed for $M^{+\cdot} \longrightarrow$ (i) indicating that the sequence $M^{+\cdot} \longrightarrow$ (h) $\longrightarrow$ (i) is rapid or concerted. The further fragmentation of ions (i) and (j) is minor (Scheme 4).

All alkaloids show a prominent $M - 1$ ion, but the spectra of alkaloids (22) and (23) show rather surprisingly that loss of the 1- or 1′-hydrogen atoms is a relatively minor process.

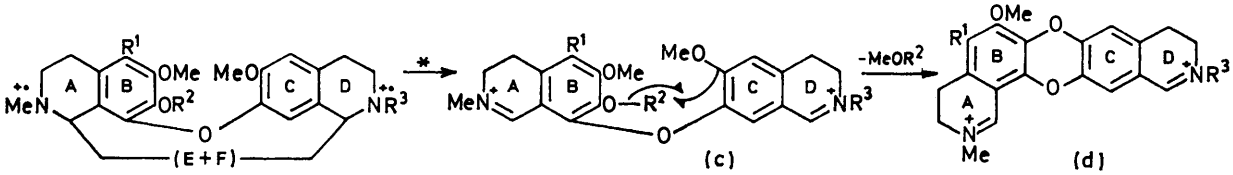
Ions due to Loss of Rings C *and* D.—Weak ions at $M - 191$ and $M - 192$ ($R^2 = Me$), or $M - 177$ and $M - 178$ ($R^2 = H$) (Scheme 5) generally occur and correspond to the sequence (n) $\longrightarrow$ (o) $\longrightarrow$ (p). Surprisingly the analogous ions for loss of rings A and B are not observed. This feature is diagnostically useful as the total substitution of rings C and D can be determined, and hence that of rings A and B by difference.

Ions due to Loss of Ring E.—Weak but reproducible ions (2—8%) due to loss of ring E together with a transferred hydrogen atom are a constant feature. The origin of this hydrogen is not clear, but from ^{2}H-labelling experiments [*cf.* (8), (14), (22), and (23)] it evidently does not originate from the 1- or 1′-positions, nor from the 7- or the 4″-methoxy-groups. The suitably-placed 8′-H may be involved, with loss of radical (r) in the case of alkaloids (4)—(8), (s) for (10) and (11) (type IV), and (t) for (12)—(18) (type V) (Scheme 6). The resulting ions may rearrange to the less strained aporphine structure (q).

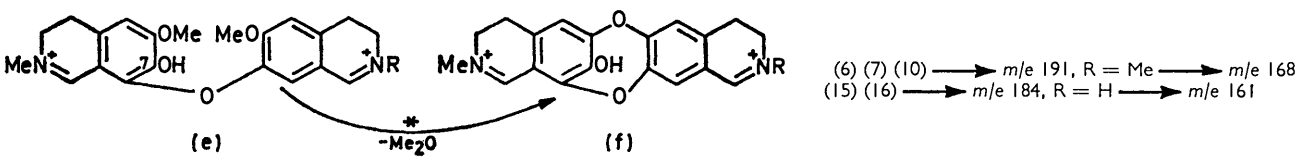
The analogous loss of ring F is not observed; hence alkaloids of type IV can be clearly distinguished from type V, and the nature of the ring E (or by difference, ring F) substituent can be determined.

Ions due to Rings A *and* B *or* C *and* D.—A prominent

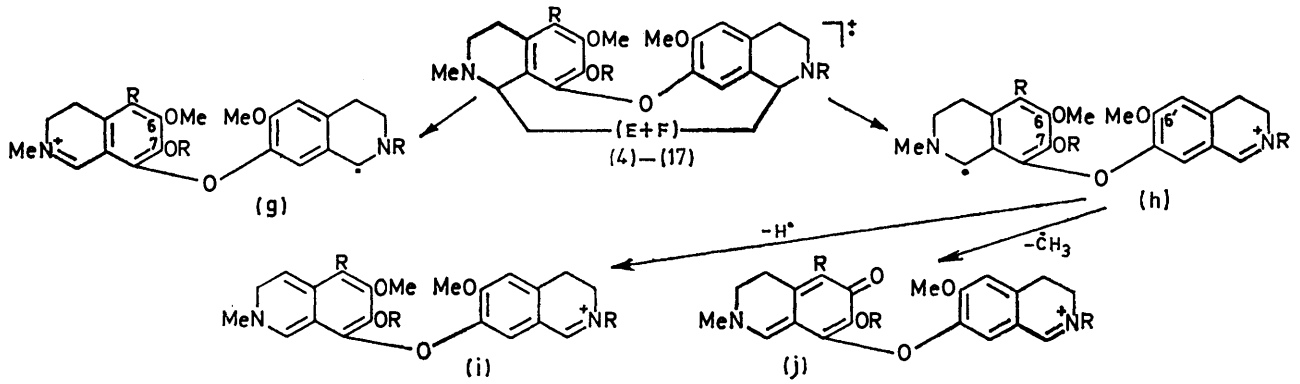
ion at *m/e* 174 (u) in the spectra of alkaloids (4)—(14) and (18) may be attributed to cleavages ii and iv (VII) accompanied by loss of a hydrogen atom from rings C and D (Scheme 7). This is substantiated by the ion at *m/e* 174 in the spectra of alkaloids (19)—(22) with a ^2H atom at C-1, and the shift to *m/e* 175 for alkaloid (23), which has an additional ^2H atom at C-1′. The process is



SCHEME 1 Molecular ions and ions due to loss of rings E and F



SCHEME 2



SCHEME 3

$$\text{(i)} \xrightarrow[*]{-OMe} \text{(k) (ca. 3\%)} \xrightarrow[*]{-Me} \text{(l) (ca. 2\%)}$$

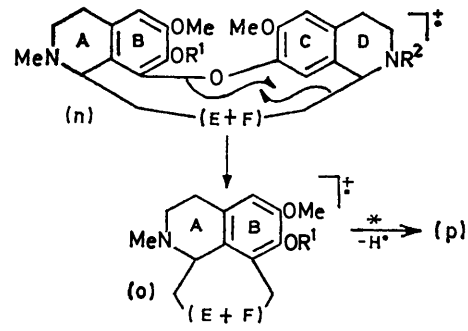
$$\text{(j)} \xrightarrow[*]{-MeOMe} \text{(m) (ca. 1—3\%)}$$

SCHEME 4

confirmed by the ion at *m/e* 160 in the spectra of alkaloids (15)—(17) which have a hydrogen atom attached to N-2′.

Alkaloids with a 7-hydroxy-group [(6), (7), (10), (15), and (16)] give an intense peak (v) at *m/e* 192 (30—90%). For alkaloids (15) and (16) this ion can only originate by cleavages i and iii (VII), with hydrogen transfer to the rings A and B charged fragment, but for alkaloids (6), (7), and (10), which have a methyl group at N-2′, it may arise in part from rings C and D. The analogous ion at *m/e* 206 from alkaloids with a 7-methoxy-group is unimportant (2—7%).

Alkaloids (4), (5), (8), (9), (11)—(13), and (18) show an ion (w) of variable intensity at *m/e* 192 (4—28%), which

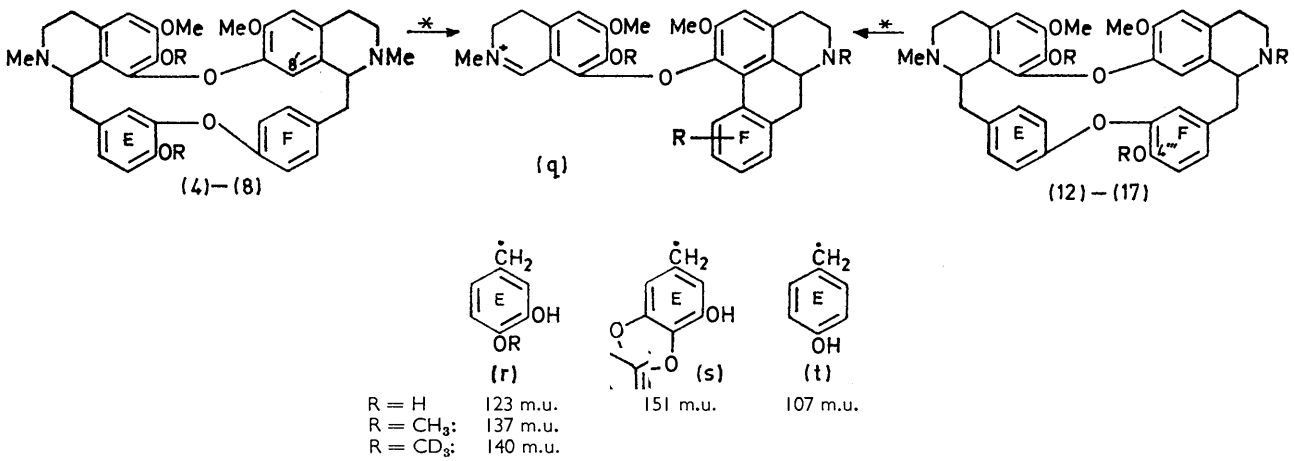


SCHEME 5

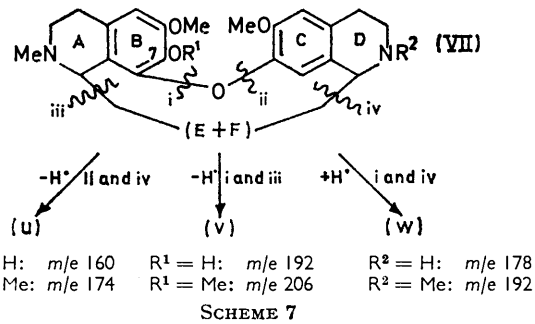
presumably is due to cleavages i and iv (VII) accompanied by hydrogen transfer to the charged rings C and D

fragment. For alkaloids (15)—(17), which have a secondary amino-group, this ion appears at *m/e* 178.

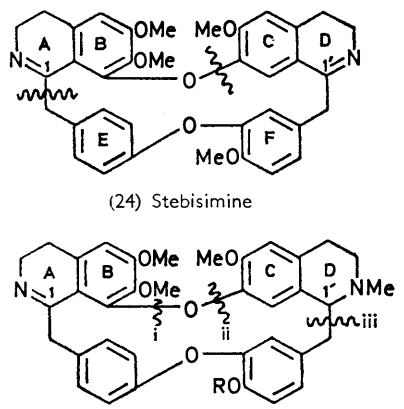
Dehydrobiscoclaurine Types.—For stebisimine (24) suppression of cleavages at C-1 and C-1′ results in an intense (100%) singly charged and a considerable (13%) doubly charged molecular ion. The only other significant ion is at *m/e* 206 (17%), which may be rationalised by the cleavages shown, with hydrogen transfer to the rings A and B charged fragment (Scheme 8). The single imino-groups of alkaloids (25) and (26) also largely suppress fragmentation, except for an $M-R\cdot$ peak, and ions at *m/e* 174 and 190 derived from cleavages ii and iii, and i and iii respectively, with loss of a hydrogen atom from the charged rings C and D fragment. Loss of $R\cdot$ from the molecular ion presumably occurs after cleavage iii. A weak $M-123$ ion (2%) whose origin is not clear is also observed for alkaloids (25) and (26).



SCHEME 6



SCHEME 7



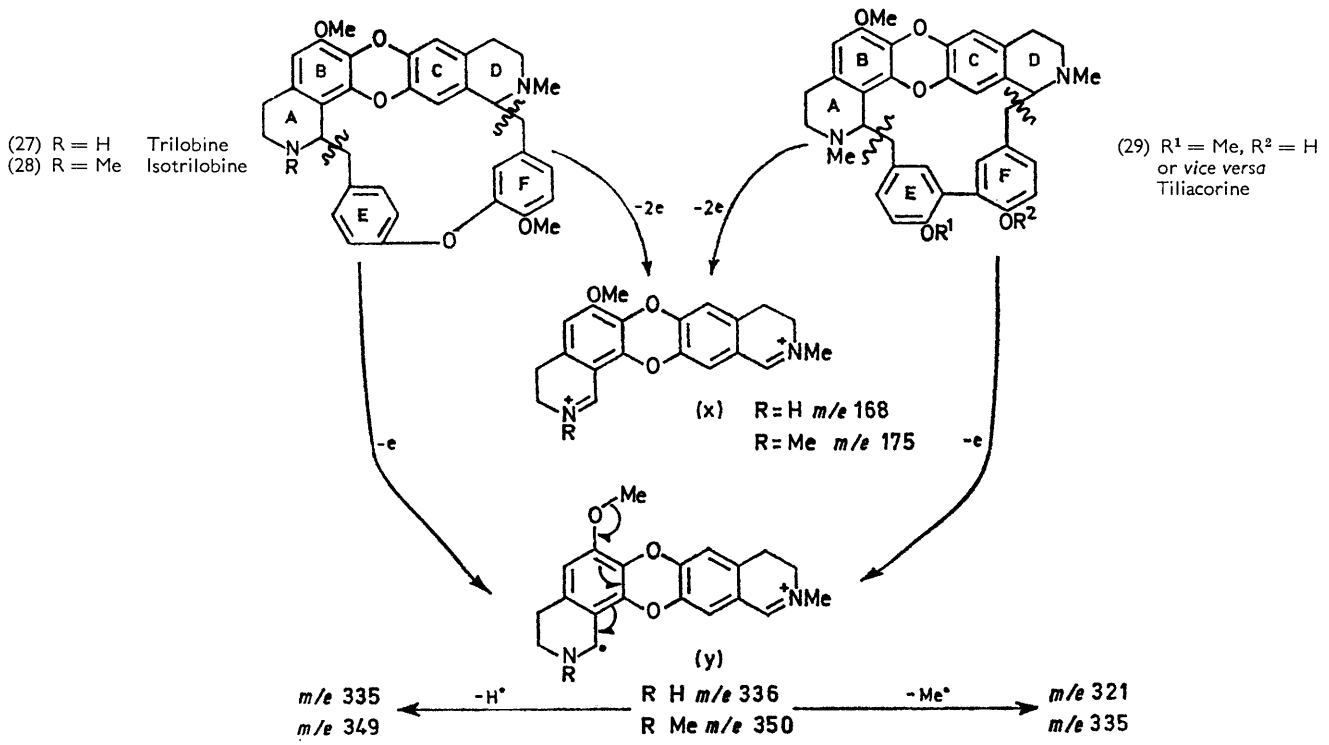
SCHEME 8

The mass spectra of alkaloids (27) and (28) are as expected: double benzylic cleavage yields ion (x) from the doubly charged molecular ion, and ion (y) from the singly charged one. Ion (x) does not fragment further, but ion (y) loses H• and Me• as usual [*cf.* (i) and (j)]. No ions corresponding to charged fragments from rings A and B or C and D, or to the loss of rings C and D are observed.

The spectrum of alkaloid (29) is essentially the same as that of alkaloid (28). Loss of ring E is not observed for alkaloids of type C, and thus a distinction between the two possible structures for tiliacorine (29) cannot be drawn.

EXPERIMENTAL

Mass spectra were recorded on an A.E.I. MS9 spectrometer operating at 70 eV and a source temperature of 220—240°. The following peaks were mass-measured using heptacosafluorotributylamine as standard: (1) *m/e* 162 (20% $C_9H_8NO_2$, 80% $C_{10}H_{12}NO$), 178 ($C_{10}H_{12}NO_2$), 190 ($C_{11}H_{12}NO_2$), 192 ($C_{11}H_{14}NO_2$), 206 ($C_{12}H_{16}NO_2$), 297 ($C_{18}H_{19}NO_3$), 314 ($C_{18}H_{20}NO_4$), and 329 ($C_{19}H_{23}NO_4$); (4) *m/e* 145 ($C_{10}H_{11}N$), 146 ($C_{10}H_{12}N$), 174 ($C_{11}H_{12}NO$), 192 ($C_{11}H_{14}NO_2$), 335 ($C_{20}H_{19}N_2O_3$), 364 ($C_{22}H_{24}N_2O_3$), 430 ($C_{27}H_{28}NO_4$), and 485 ($C_{30}H_{33}N_2O_4$); (11) *m/e* 174 ($C_{11}H_{12}NO$), 175 [84% $\frac{1}{2}(C_{21}H_{22}NO_3)$, 16% $C_{11}H_{13}NO$], 198 [$\frac{1}{2}(C_{23}H_{28}N_2O_4)$], 335 ($C_{20}H_{19}N_2O_3$), 349 ($C_{21}H_{21}N_2O_3$), 364 ($C_{22}H_{24}N_2O_3$), 379 ($C_{22}H_{23}NO_4$), 381 ($C_{22}H_{25}N_2O_4$), 395 ($C_{23}H_{27}N_2O_4$), and 445 ($C_{27}H_{27}NO_5$); (12) *m/e* 174 ($C_{11}H_{12}NO$), 175 [80% $\frac{1}{2}(C_{21}H_{22}N_2O_3$), 20% $C_{11}H_{13}NO$], 198 [$\frac{1}{2}(C_{23}H_{28}N_2O_4)$], and 395 ($C_{23}H_{27}N_2O_4$); (15) *m/e* 192 ($C_{11}H_{14}NO_2$); and (18) *m/e* 153·5 [$\frac{1}{2}(C_{19}H_{19}N_2O_2)$] and 167·5 [$\frac{1}{2}(C_{20}H_{19}N_2O_3)$].



Alkaloids of type C

Detailed mass spectral data are given in Supplementary Publication No. SUP 20262 (11 pp., 1 microfiche).*

Preparation of Trideuteriomethylated Compounds.—General procedure. To diazomethane in dioxan (6 ml)–deuterium oxide (1 ml) [11] a solution of phenolic alkaloid (50 mg) in dioxan (2 ml)–deuterium oxide (1 ml) was added slowly with stirring, and the mixture was set aside overnight at room temperature. The solvent was evaporated off *in vacuo* and the residue was dissolved in hydrochloric acid (5%). The solution was washed with ether, made alkaline with aqueous sodium hydroxide (5%), and extracted with ether. The extract was washed with water, dried ($MgSO_4$), and evaporated to dryness. Recrystallization from ether or ether–hexane afforded mass-spectrometrically pure crystalline trideuteriomethylated products (*ca.* 40 mg).

[1-^{2}H]-1,2-*Dihydroepistephanine.*—Epistephanine (5 mg) was dissolved in [$^2H_4$]methanol (2 ml) containing 5 drops of deuterium oxide, and was treated with a slight excess of sodium borodeuteride. The mixture was warmed for 30 min and set aside for 24 h at room temperature. The solvent was removed and the residue was taken up in water and chloroform. The chloroform layer was separated and washed twice with water, dried, and evaporated to yield the product (4 mg).

[1,4‴-methoxy-$^2H_4$]-1,2-*Dihydroepistephanine.*—This was prepared by the above method from [4‴-*methoxy*-$^2H_3$]-epistephanine.

[1-^{2}H]-1,2-*Dihydro*-2-*methylepistephanine.*—[1-^{2}H]-1,2-Dihydroepistephanine (2 mg) was dissolved in methanol (2 ml) containing formalin (37%; 5 drops), and the solution was set aside for 24 h at room temperature. A slight excess of sodium borohydride was added; the solution was warmed for 15 min, and then set aside for 2 h. The solvent was removed and the residue was taken up in water and chloroform. The chloroform layer was separated and washed twice with water, dried, and evaporated to yield the product (2 mg).

[1,4‴-methoxy-$^2H_4$]-1,2-*Dihydro*-2-*methylepistephanine.*—This was prepared by the above method from [1,4‴-*methoxy*-$^2H_4$]-1,2-dihydroepistephanine.

[1,1′-$^2H_2$]-1,2-*Dihydro*-2-*methylepistephanine.*—Stebisimine (24) was deuteriated and *N*-methylated by the same method as for epistephanine.

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* For details of Supplementary Publications see Notice to Authors No. 7 in *J. Chem. Soc.* (*A*), 1970, Issue No. 20. (Items less than 10 pages will be supplied as full size copies.)

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