Mass Spectrometry of Bisbenzylisoquinoline Alkaloids. Part II.[1] Alkaloids derived from One Coclaurine and One Isococlaurine Unit

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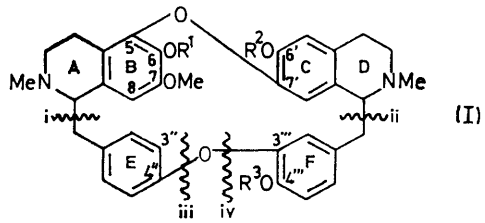
The mass spectra of thalmine, thalicberine, and related alkaloids have been analysed and the fragmentation patterns have in part been substantiated by deuteriation experiments.

THE mass spectra of thalmine and related C(5)–C(7′) ether linked alkaloids run parallel to those of the C(8)–C(7′) linked types described in Part I.[1] Intense molecular ions are observed in all cases, and double

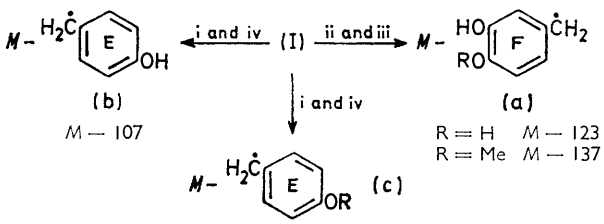


(I)

(1)	$R^1 = H$, $R^2 = R^3 = Me$	Thalmine (*S,S*); lauberine (*S,R*)
(2)	$R^1 = R^2 = R^3 = Me$	*O*-Methyl-lauberine (*S,R*); *O*-methyldryadine (*R,S*)
(3)	$R^1 = R^3 = Me$, $R^2 = H$	Dryadine
(4)	$R^1 = Me$, $R^2 = R^3 = H$	Dryadodaphnine
(5)	$R^1 = CD_3$, $R^2 = R^3 = Me$	[6-*methoxy*-$^2H_3$]Methyl-lauberine
(6)	$R^1 = R^3 = Me$, $R^2 = CD_3$	[6′-*methoxy*-$^2H_3$]Methyldryadine
(7)	$R^1 = Et$, $R^2 = R^3 = Me$	*O*-Ethyl-lauberine
(8)	$R^1 = Me$, $R^2 = R^3 = Et$	*OO*-Diethyldryadodaphnine

Alkaloids of type A

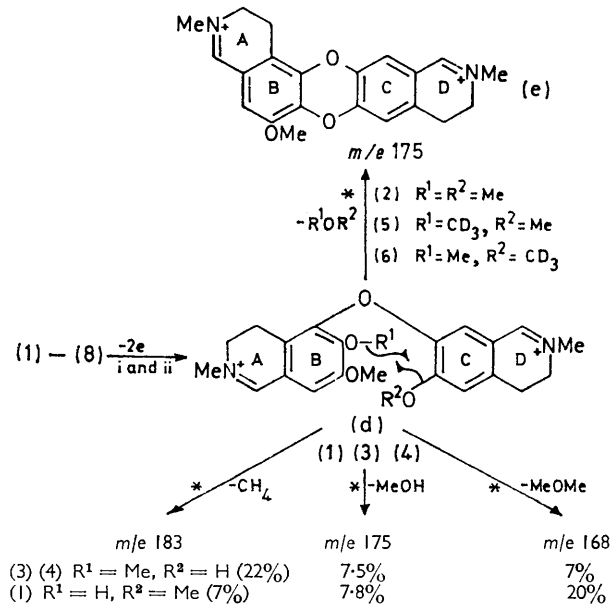
benzylic cleavage of the singly and doubly charged molecular ions are the major fragmentation processes. There are, however, some features (Scheme 1) by which



SCHEME 1

this group are distinguished.[2] A weak ion (a) is observed due to loss of ring F as well as the ion (b) (M — 107) due to the loss of ring E, with hydrogen transfer in each case; thus the distinction between rings E and F, possible in the C(8)–C(7′) linked types,[1] is lost. Alkaloids (2)—(4) and (6) which have a 6-methoxy-group show in addition an M — 121 ion (c) of comparable intensity due to loss of ring E with methyl transfer. That the transferred methyl originates from the 6-methoxy-group is shown by the shift to M — 124 in the spectrum of alkaloid (5). In the examples studied, no methyl transfer to ring F was observed, but a distinction between rings E and F on this basis is not feasible in the absence of examples with the alternative C(3″)–C(4″) ether link.

Ions due to loss of rings C and D are either extremely weak or not observed.[2]



SCHEME 2 Intensities corrected for isotope peaks

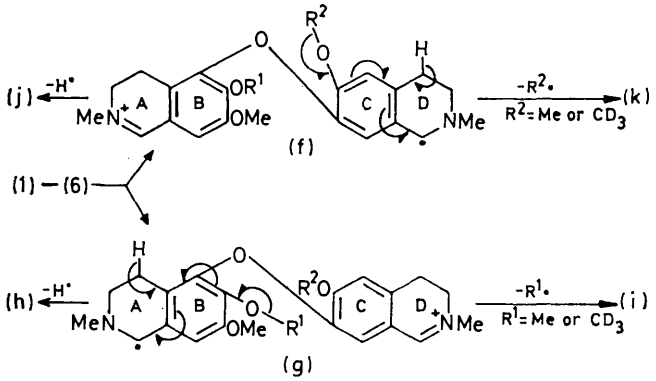
The fragmentation of ion (d), generally the base peak, formed by double benzylic cleavage (i and ii) of the weak doubly charged molecular ion, depends on the nature of R^1 and R^2 (Scheme 2). For alkaloid (2), loss of dimethyl ether from ion (d) to give an ion at *m/e* 175 is the only important process. Alkaloids (5) and (6) lose Me·O·CD_3 exclusively, showing that the 6- and 6′-methoxy-groups only are involved in forming the ion with *m/e* 175, which may thus be formulated as (e). Alkaloids with a 6-hydroxy-group (1) likewise fragment preferentially by loss of dimethyl ether, but those with a 6′-hydroxy-group [(3) and (4)] fragment largely by loss of methane from ion (d) and partly by loss of methanol and dimethyl ether. These observations assist in locating a hydroxy-group in these bases: the *m/e* value of ion (d) shows

[1] Part I, I. R. C. Bick, T. Ibuka, R. S. Kapil, and Q. N. Porter, preceding paper.

[2] J. Baldas, Q. N. Porter, I. R. C. Bick, G. K. Douglas, M. R. Falco, J. X. de Vries, and S. Yu. Yunusov, *Tetrahedron Letters*, 1968, 6315.

whether the group is in rings B and C or in E and F, and in the former case the fragmentation of the trideuteriomethylated ion (d) enables the 7-position to be differentiated from the 6- and 6′-positions; the latter two are distinguished by the fragmentation of the unalkylated ion (d). In the case of alkaloids (7) and (8), loss of ethyl methyl ether from ion (d) occurs,[2] but the fragmentation is complicated by the loss of ethylene to give ions (d) ($R^1 = H$, $R^2 = Me$ and $R^1 = Me$, $R^2 = H$ respectively), which then fragment as previously described.

Double benzylic cleavage (Scheme 3) of the singly charged molecular ion gives an ion composed of the species (f) and (g), which fragment in the usual manner by loss of H· and Me· in the case of alkaloids (1)—(4) to



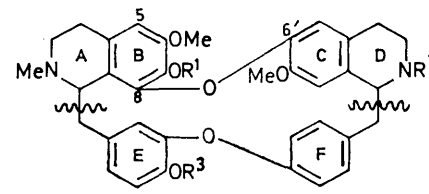
SCHEME 3

give the intense ions (h), (j), (i), and (k). Loss of CD_3· and Me· in the ratio 2 : 1 to give ions (i) and (k) is observed from ions (f) and (g) derived from alkaloid (5), indicating that (g) is the major component; this is confirmed by the preferential loss of Me· from ions (f) and (g) derived from alkaloid (6). Similarly, the intensities of the (f) + (g) — Et· and (f) + (g) — Me· ions in the case of alkaloids (7) and (8) are 51 and 18%, and 17 and 29%, respectively, but the (f) + (g) — Et· ion may arise in part by loss of H· followed by C_2H_4.

Acid-catalysed deuteriation of lauberine (1) under mild conditions gives a $^2H_2$-derivative for which the doubly-charged ion (d) is shifted from *m/e* 191 to 192, indicating that both deuteriums are located in rings B and C. Under more drastic conditions, five deuterium atoms are introduced, and ion (a) is shifted from $M - 137$ to $M - 140$, showing that the extra deuteriums have entered ring F.

The mass spectra of thalicberine[3] and related C(8)–C(6′) linked alkaloids very closely resemble those of the correspondingly substituted C(8)–C(7′) linked types discussed in Part I.[1] However, ions due to loss of rings C and D [$M - 191$ and $M - 192$ for (9)—(13), and $M - 177$ and $M - 178$ for (14) and (15)] are weaker, and a noteworthy difference is that very weak ions due to loss of ring F as well as ring E are observed as with the alkaloids of type A just discussed; on the other hand these can be distinguished from alkaloids of type B since the latter do not give ions involving methy transfer [*cf.* (c)].

As with bases of type A, the doubly charged ion (1; $R = CD_3$) derived from alkaloid (12) fragments

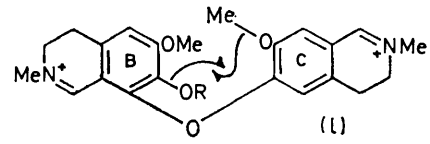


(II)

(9)	$R^1 = R^2 = Me$, $R^3 = H$	Thalicberine
(10)	$R^1 = R^2 = R^3 = Me$	*O*-Methylthalicberine (*S,S*); *O*-Methylisothalicberine (*R,S*)
(11)	$R^1 = H$, $R^2 = R^3 = Me$	Belarine
(12)	$R^1 = CD_3$, $R^2 = R^3 = Me$	[7-*methoxy*-$^2H_3$]Methylbelarine
(13)	$R^1 = Et$, $R^2 = R^3 = Me$	*O*-Ethylbelarine
(14)	$R^1 = Me$, $R^2 = R^3 = H$	Dihydrothalmetine
(15)	$R^1 = R^3 = Me$, $R^2 = H$	*O*(4″)-Methyldihydrothalmetine

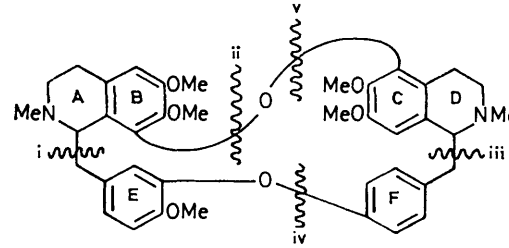
Alkaloids of type B

exclusively by loss of $MeO{\cdot}CD_3$; similarly (1; $R = Et$) derived from alkaloid (13) loses ethyl methyl ether



R = Et *m/e* 205
R = CD_3 *m/e* 199·5
R = H *m/e* 191

exclusively. Acid-catalysed deuteriation of alkaloid (11) gives a monodeuterio-derivative in which the deuterium has entered ring B or C as shown by the shift of ion (l) to *m/e* 191·5; the ions at *m/e* 417 ($M - 192$) and 418 ($M - 191$) show that it is in ring B and thus in the 5-position.



(16) Thalidasine

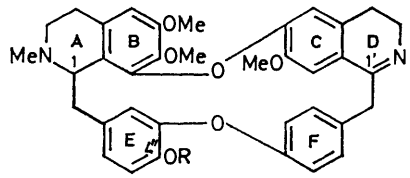
Alkaloid of type C

Thalidasine (16) fragments in the same manner as the C(8)–C(7′) linked types discussed in Part I.[1] In rather surprising contrast to types A and B just discussed, loss of ring E (cleavages i and iv and hydrogen transfer to the ring E fragment) is specific: no loss of ring F is observed, nor any methyl transfer to ring E. Cleavages ii and iii with loss of rings C and D also occur to give $M - 221$ and $M - 222$ ions, but these ions could also originate in part from cleavages i and v with loss of rings A and B.

As with epistephanine (Part I [1]), cleavage at C-1′ is suppressed and both alkaloids (17) and (18) give intense singly and doubly charged molecular ions with

[3] D. C. DeJongh, S. R. Shrader, and M. P. Cava, *J. Amer. Chem. Soc.*, 1966, **88**, 1052.

no ring A, B, C, and D ions arising from either.[4] The $M - 1$ ion is of comparable intensity for both alkaloids (17) (93%) and (18) (83%), but the $M - Me^{\cdot}$ ion is



(17) R = H Thalmetine
(18) R = Me O-Methylthalmetine

Alkaloids of type D

much stronger in the latter case [56% for (18), 6% for (17)], indicating that it is largely the 4''-methoxymethyl group which is lost after cleavage at C-1 (*cf.* epistephanine [1]). Metastable ions confirm the loss of dimethyl ether from the $M - 1$ ion of alkaloid (17) and the $M - 15$ ion of alkaloid (18) to give ions at $M - 47$ and $M - 61$ respectively; in addition, weak ions due to the loss of dimethyl ether directly from the doubly charged molecular ions are observed in both cases. Very weak ions appear at $M - 123$ and $M - 137$ for alkaloids (17) and (18), respectively, showing that specific loss of ring E occurs; the doubly charged molecular ions also lose this ring specifically.

EXPERIMENTAL

Mass spectra for all compounds were recorded on an A.E.I. MS9 spectrometer operating at 70 eV and at a source temperature of 210—220°. The compositions of the peaks at *m/e* 168 [½($C_{20}H_{20}N_2O_3$)], 174 [60% $C_{11}H_{12}NO$, 40% ½($C_{21}H_{20}N_2O_3$)], 183 [½($C_{21}H_{22}N_2O_4$)], 204 ($C_{12}H_{14}NO_2$), and 471 ($C_{29}H_{31}N_2O_4$), were determined by mass measurements with heptacosafluorotributylamine as standard. In addition, complete high resolution spectra for alkaloids (1), (2), and (7) were recorded on a CEC 21—100 spectrometer.

Detailed mass spectral data are given in Supplementary Publication No. 20263 (7 pp. 1 microfiche).*

Deuteriation of Belarine.[5]—Belarine (40 mg) in 2M-deuterium chloride (1 ml) was heated in a sealed tube at 100° for 12 h. The alkaloid was recovered from the acid solution in the usual manner to give the monodeuteriated derivative.

Deuteriation of Lauberine.—Lauberine deuteriated as above gave a monodeuteriated derivative; when the period of heating was extended to 48 h, the corresponding [$^2H_5$]-derivative was obtained.

The trideuteriomethyl compounds (5), (6), and (12) were prepared from the corresponding phenolic bases in dimethyl sulphoxide by use of diazomethane equilibrated with heavy water.[6]

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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.)

[4] N. M. Mollov, V. St. Georgiev, and H. B. Dutschewska, *Doklady Bolg. Akad. Nauk*, 1970, **23**, 383.
[5] M. R. Falco, J. X. de Vries, Z. Macció, and I. R. C. Bick, *Chem. Comm.*, 1971, 1056.
[6] J. Baldas, I. R. C. Bick, Q. N. Porter, and M. J. Vernengo, *Chem. Comm.*, 1971, 132.