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THE SEED ALKALOIDS OF *HUNTERIA UMBELLATA*

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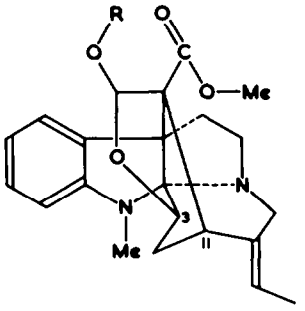
Abstract—The major seed alkaloids of *Hunteria umbellata* and their isolation are described. Their mass spectra are recorded and interpreted, leading to a revised structure for isocorymine based on the probe spectrum which is significantly different from that obtained from the heated glass inlet system.

Hunteria umbellata (K. Schum.) *Stapf* is a glabrous tree, up to about 50 feet in height, found growing abundantly in Western Nigeria. Its leaves, bark and roots, but not the seeds are used in local medicine. All parts of the plant have been shown to contain alkaloids[1] and the main ones in the seeds have been briefly reported.[2] These are acetylcorymine (1a), corymine (I) and isocorymine.



I (R = H) corymine Ia (R = Ac) acetylcorymine II.

All three alkaloids have the same type of UV spectrum showing the shift in acid characteristic of the Ar—N—C—N chromophore.[3]

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[1] M. B. Patel and J. M. Rowson, *Planta Medica* **12**, 33 (1964).
[2] C. W. L. Bevan, D. R. Harris, M. L. Marshak, H. H. Mills, M. B. Patel and A. H. Rees, *Chem. & Ind.* 603 (1965).
[3] H. F. Hodson and G. F. Smith, *Proc. Chem. Soc.* 1877 (1957).

TABLE 1. UV DATA FOR ALKALOIDS

λ_{max}	log e	Acid maxima
215 mμ	4·25	213 mμ
258	4·04	248
324	3·65	303

The NMR spectra (in $CDCl_3$) of acetylcorymine and isocorymine are tabulated below (relative to TMS as internal standard).

TABLE 2. NMR SPECTRA OF ACETYLCORYMINE AND ISOCORYMINE

	Acetylcorymine	Isocorymine
ArH_4	2·7–3·9 (m)	2·7–3·7 (m)
—CH(OR)O—	3·9 (s, R = Ac)	4·8 (s, R = D)
—OCHCH$_2$—	5·5, 5·6	5·1 (t)
=CHMe	4·6 (q)	4·65 (q)
	8·35 (d)	8·55 (d)
—OCH$_2$R	6·2 (s, R = H)	*5·6, 6·15 (J = 12 c/s)
NMe	7·3 (s)	7·05 (s) and 7·5 (s)
OR	8·0 (s, R = Ac)	4·7 (broad, R = H)

* In isocorymine there is no R group.

Relative to benzene the ring A protons are displaced up field and their relative chemical shifts increased. This is due to the lone pair of electrons on the adjacent N-Me grouping (compare 1,3,3-trimethyl-2-methyleneindole).[4]

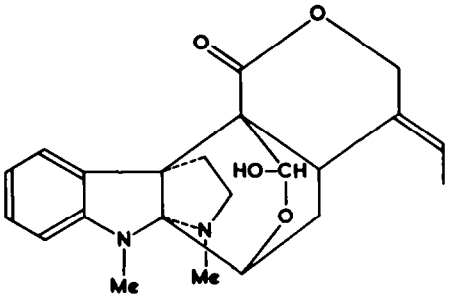
At high resolution the ethylidene Me doublet (J = 6·5 c/s) in acetylcorymine shows further fine splitting, thought to be due to the nearness of the proton at position II.[5] This coupling is not seen in isocorymine which suggests a greater distance, and hence less steric interaction, between the relevant atoms.

The asymmetric doublet assigned to the proton at C-3 in acetylcorymine is consistent with it subtending a dihedral angle of about 90° with one of the adjacent CH_2 protons, this angle's value being confirmed from Dreiding models. This is not so in isocorymine where it appears as an irregular triplet. In isocorymine and corymine the signal due to the acetal proton is a doublet due to coupling with the OH proton. This is confirmed by its collapse to a singlet on deuteration. In isocorymine alone there is a significant AB quartet (J = 12 c/s) consistent with a ring methylene next to oxygen, but also showing further weak coupling as expected from the allylic position of the methylene group.

[4] *Varian Associates Catalogue of NMR Spectra* Vol. 1; Spectrum No. 596. National Press, New York (1963).

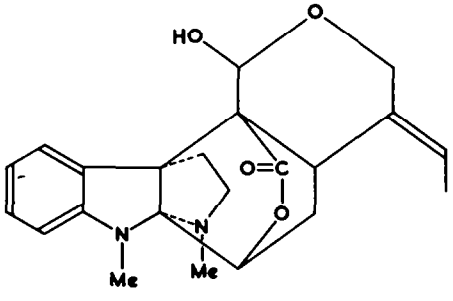
[5] H. H. Mills, personal communication.

The similarities of the two NMR spectra suggested that many structural features were common to both molecules. Assuming the biosynthesis of both alkaloids from tryptamine, C_1 and C_{10} units,[7] we tentatively proposed structure II for isocorymine.



The old structure II for isocorymine.

This was in accord with the original mass spectrum and more closely related to corymine than the alternative structure III. In addition, corymine could be related to the structure II via corymine betaine.



The probe spectrum, however, decided in favour of structure III. The use of the direct insertion technique gave a better defined spectrum than the use of the older heated glass inlet method.

In deciding on structure III for isocorymine, comparisons were drawn between the mass spectra of these compounds and those of erinin (V) and the 19, 20 dihydro compound erinicin (VI) and their derivatives, as described by Schmid *et al.*[8] Although these alkaloids come from the same plant, this comparison confirms that isocorymine does not have a dihydroerinin type structure. With the exception of dehydroisocorymine (IV) the major fragmentation peaks have had their ionic formulae determined unambiguously by high resolution mass measurements. As an example, the

[6] G. F. Smith, personal communication; see also *Proc. Chem. Soc.* 298 (1962).
[7] R. Thomas, *Tetrahedron Letters* No. 16, 554 (1961).
[8] B. W. Bycroft, M. Hesse and H. Schmid, *Helv. Chim. Acta* **48**, 1958 (1965).

results for isocorymine are given in full in the experimental section. Also the metastable peaks and their assignments are given there.*

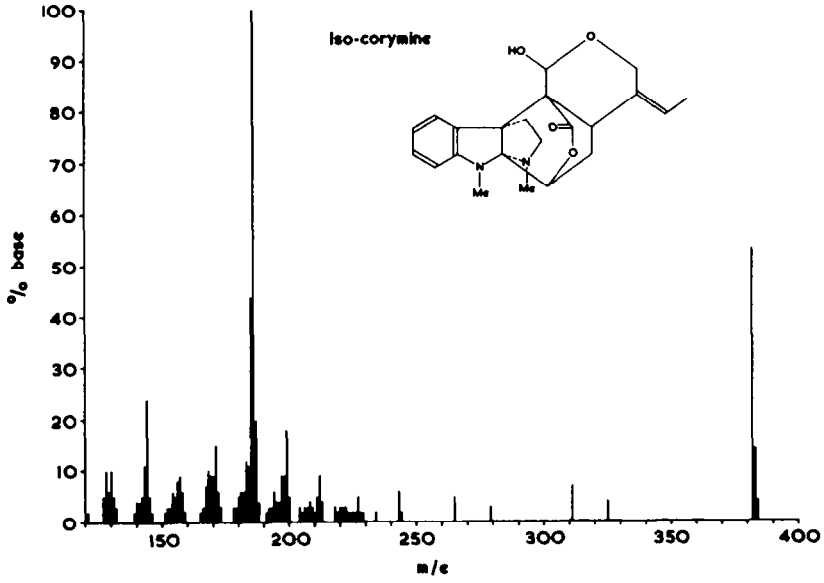
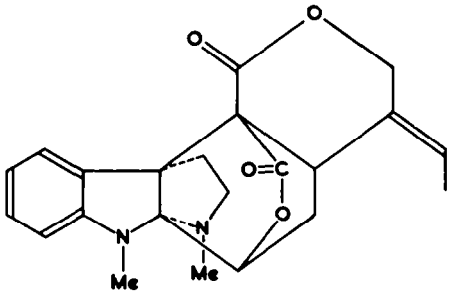
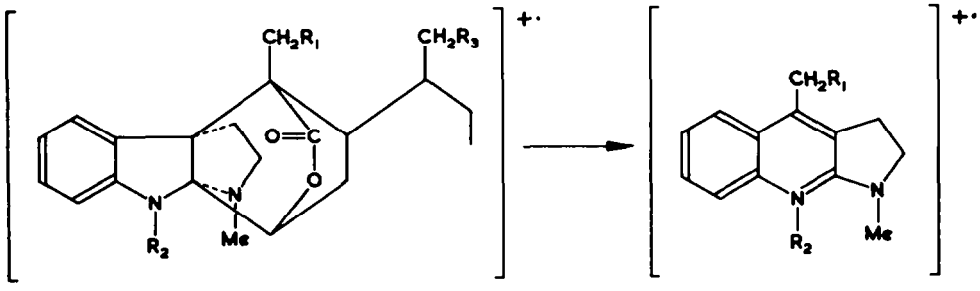


FIG. 1 The partial mass spectrum of isocorymine III.



IV dehydroisocorymine.

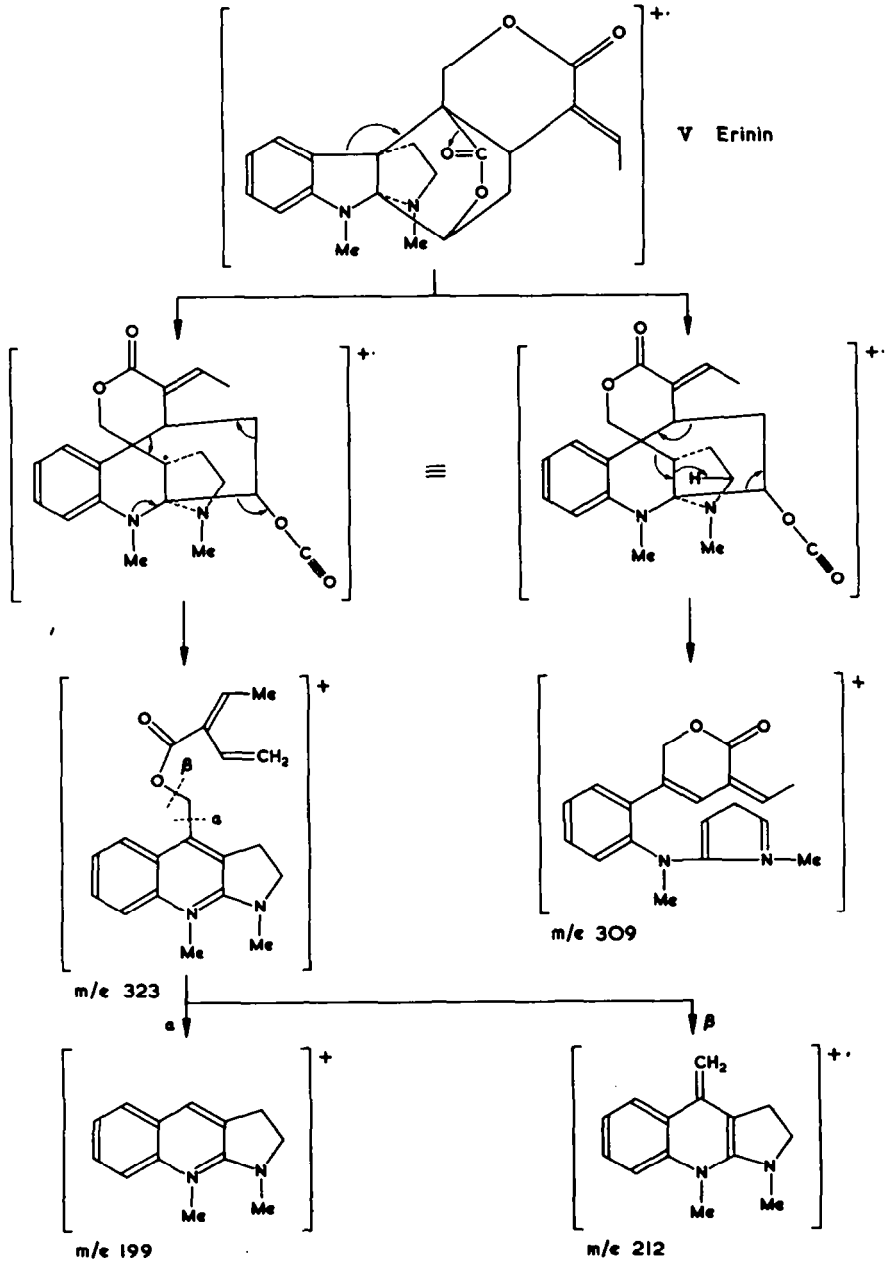


VII a

Scheme I. Production of the type a ions from compounds of Type VII.

* Metastables in the medium and low mass range of a high mol. wt compound cannot be assigned unambiguously, the most likely transition is quoted in each case.

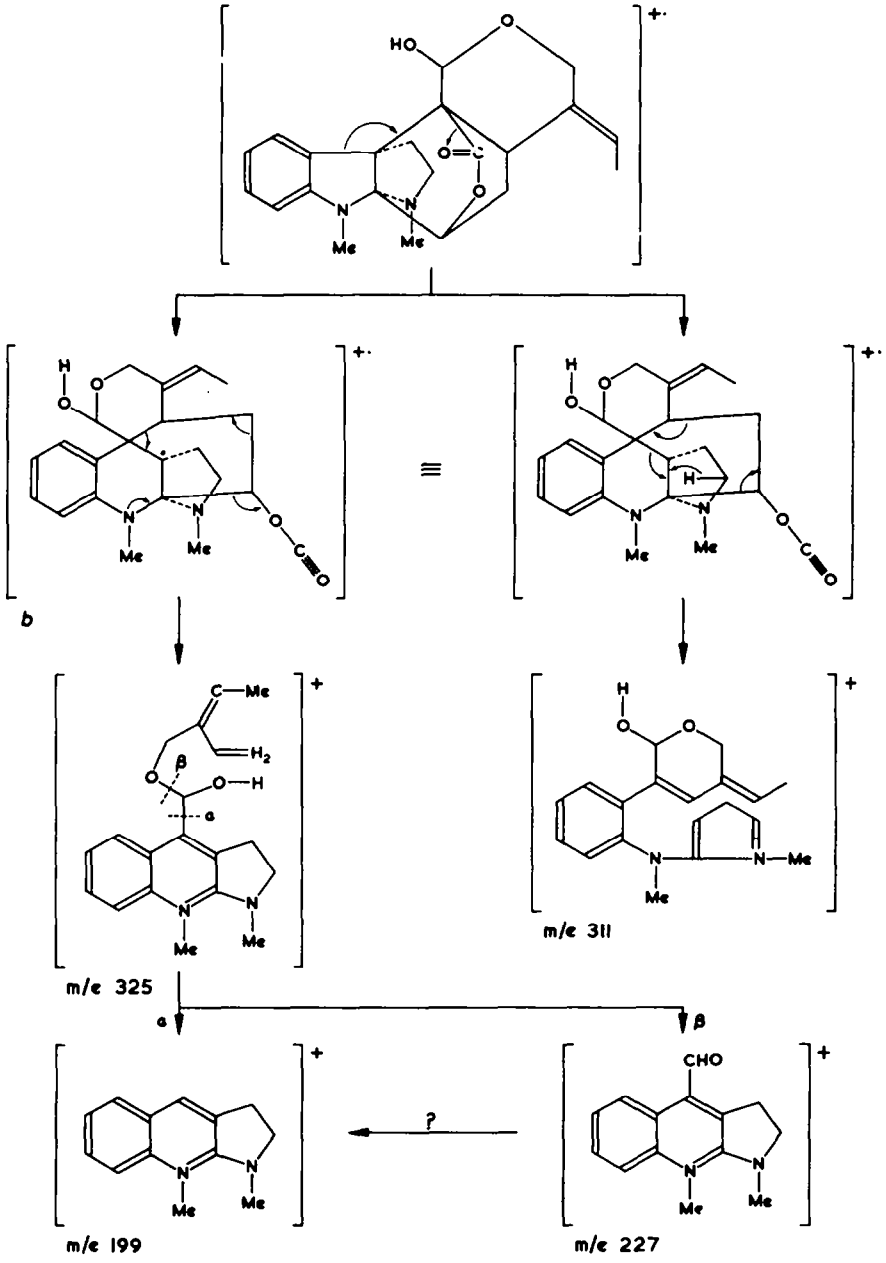
In Schmid's paper it is shown that amongst other modes of fragmentation compounds of the type VII give rise, by ring expansion, to type *a* ions. Similar peaks appear in the spectrum of erinin (V) and erinicin (VI) at *m/e* 212 and 199 in both cases.[8] The process as proposed by us in Scheme II to account for these peaks is necessarily more complicated than that for compounds of type VII proposed by Schmid,[8] but



Scheme II. Fragmentation pathways for erinin V.

follows the same pattern. It also explains the origin of the peaks at *m/e* 309, 323 in erinin (V) and those two units higher in erinicin (VI). Part of the driving force for these fragmentations may be the release of steric strain, also cleavage α to a carbonyl group is a well-established mass spectrometric reaction.

In the mass spectrum of isocorymine, the corresponding ions are at *m/e* 311 and 325. This, as shown in Scheme II, is as would be expected for structure III. If structure



Scheme III. Fragmentation pathways for isocorymine III.

II was correct these ions would, by analogy with erinin (V), be expected to be at *m/e* 309 and 323. The acetate of isocorymine also shows these peaks at *m/e* 311 and 325, although the latter is small. This must involve an additional loss of ketene. A peak in the spectrum of this compound at *m/e* 353 may be the acetyl analogue of the peak at *m/e* 311 in isocorymine (III), although the former has not been mass measured. The ion at *m/e* 325 can then give rise to the ions at *m/e* 227 and 199, 198 as outlined in Scheme III.

The peaks at *m/e* 212 and 211 in the spectrum of isocorymine and its acetate probably arise from a second ring expansion of the ion *b* (Scheme III), as outlined in Scheme IV).

These peaks also occur in the spectrum of dehydroisocorymine (IV) and can be explained in a similar fashion. It seems that the presence of a methylene group next

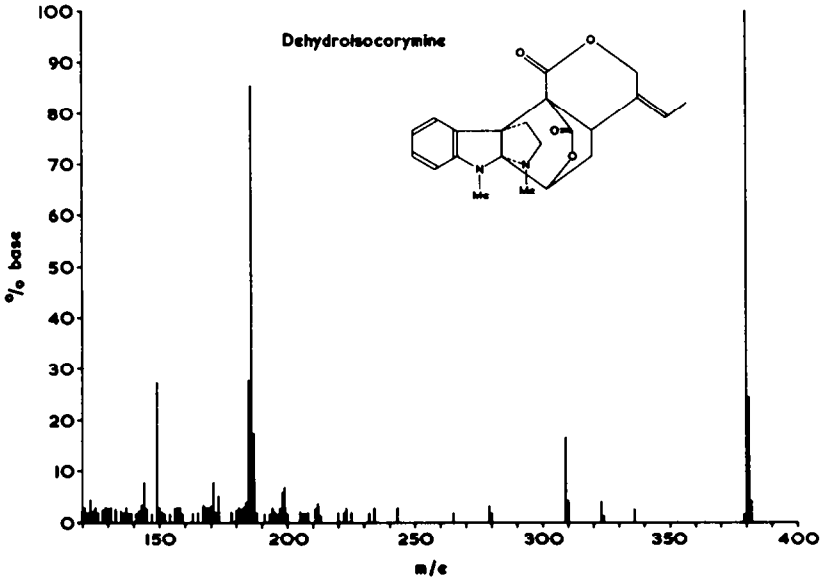
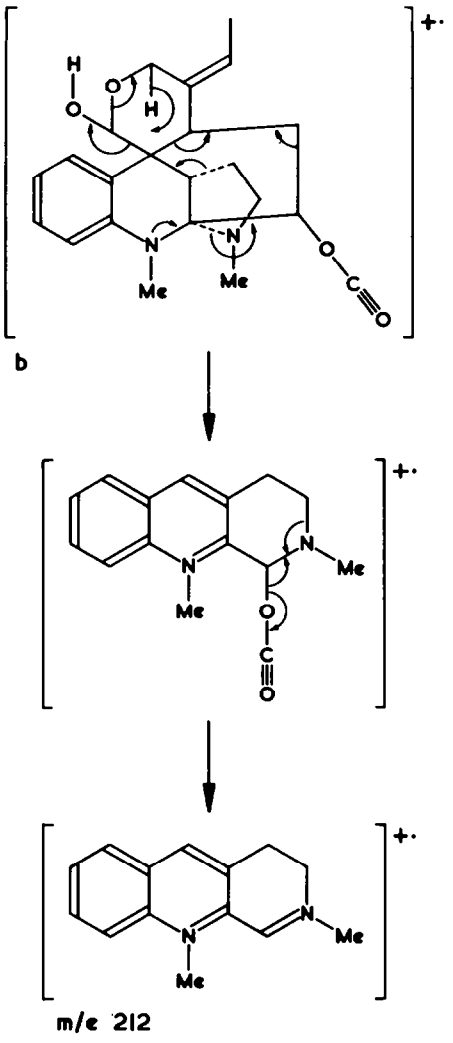


FIG. 2 The partial mass spectrum of dehydroisocorymine IV.

to the double bond in the lactone ring is necessary to produce this third type of fragmentation (Scheme IV). This shows the difference between the lactone rings in the isocorymine and erinin series.

The physical as well as mass spectral properties of dehydroisocorymine (IV) also show the difference between the two series. If isocorymine (III) had a dihydro erinin structure, then dehydroisocorymine (IV) should be identical to erinin (V) or, at any rate, its optical enantiomer. In fact both its physical and mass spectral properties are quite different even when allowance is made in the latter case for different machines. In particular the ion at *m/e* 186 is much smaller relative to the parent ion in this compound than in the case of erinin. Also a peak at P-44 is seen in dehydroisocorymine (IV) which is not reported in the case of erinin (V).[8] This is presumably due to the loss of carbon dioxide and arises from the more favourable allylic cleavage in this



Scheme IV. Fragmentation pathways for isocorymine III.

case. It would require vinylic cleavage in the case of erinin (V). The exact structure of this ion is not clear, as the simple structure violates Bred's rule. More extensive rearrangements probably occurs which accounts for the smallness of the ion. In isocorymine there is a small unmeasured peak at P-45, *m/e* 337, but in the acetate at P-78, *m/e* 336. In the former case it seems that the OH proton is transferred to the ion.

The mass spectrum of corymine (I) as determined by us seems to differ from that published by Kump *et al.*[9] and has several points of interest. The largest fragment ion appears at *m/e* 171 and probably comes via two fragmentation routes. The most obvious is a retro-Diels–Alder reaction on the 6-membered carbocyclic ring followed

[9] Ch. Kump, M. B. Patel, J. M. Rowson, M. Hesse and H. Schmid, *Pharmaceutica Acta Helviticae* **40**, 589 (1966).

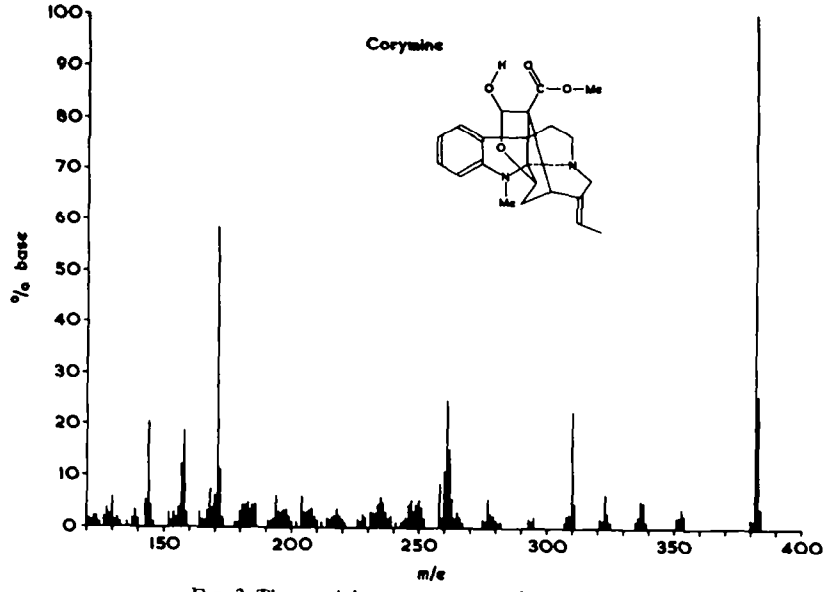
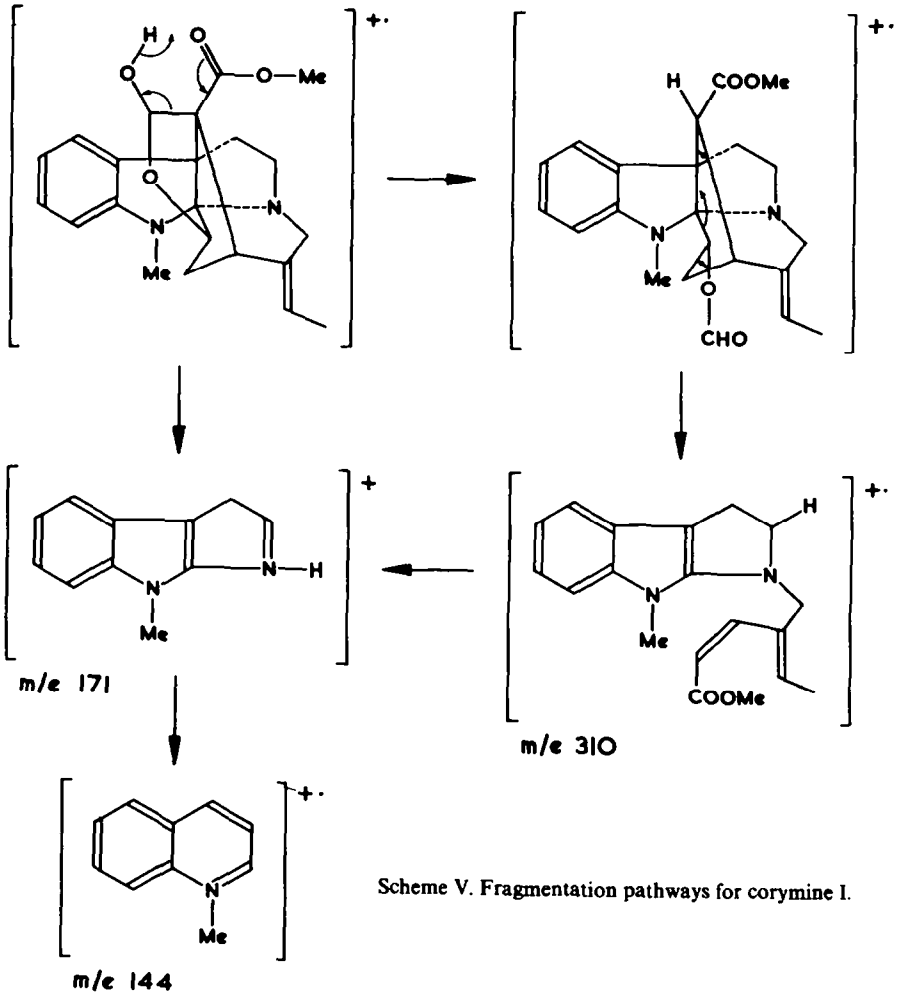


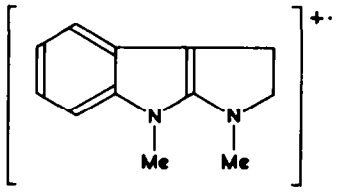
FIG. 3 The partial mass spectrum of corymine I.



Scheme V. Fragmentation pathways for corymine I.

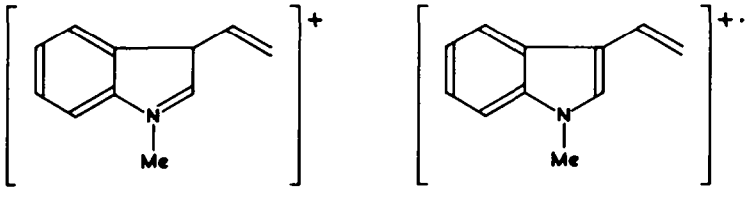
by allylic cleavage. This would account for the presence of this ion in the spectra of corymine and its acetate and propionate. However, in corymine (I) alone there is a peak at *m/e* 310 and a metastable at *m/e* 94·4 (*) suggests that this in turn could give rise to the ion at *m/e* 171. This ion at *m/e* 171 can then give rise to that at *m/e* 144 as shown by the metastable at *m/e* 121·4(*) in the spectrum of corymine. These processes are outlined in Scheme V.

The base fragment peak in isocorymine (III), the ion *c* arises in the same way as the same ion in erinin and confirms that portion of the structure of this compound. Notice that in this case, unlike corymine, there is no need for an extra cleavage.

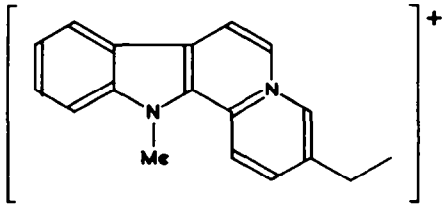


The ion *c*.

Several other peaks deserve a mention. The peaks at *m/e* 158, 157 are more noticeable in the case of corymine (I) than isocorymine (III). Mass measurements in the case of the former compound suggest the structures *d*, *d'*. The peaks at *m/e* 261, 262 in the spectrum of corymine have no counterpart in the spectrum of isocorymine (III) and probably have a structure like the ion *e*.



The ion *d'* and the ion *d*.



The ion *e*.

Thus by the examination of the small peaks in the mass spectrum of isocorymine (III) and other data, the structure of isocorymine has been determined.

EXPERIMENTAL

Extraction. Ripe fruits were collected in June 1963 from wild plants around Olokemeji in Western Nigeria. The seeds were removed and dried.

2·5 Kg. seed powder, in 3 batches, was extracted continuously in glass soxhlets with light pet. ether (b.p. 40–60°). The combined extracts were evaporated to 1 l. and extracted with 1N HCl (6 × 500 ml). The acid extracts were combined, washed with light petroleum (2 × 800 ml) and made alkaline with strong ammonia soln. The liberated bases were then taken up in isopropyl ether (4 × 1 l.), the soln dried over Na_2SO_4, and evaporated to give a residue of 14 g bases, fraction I.

The defatted powder was dried, then further continuously extracted in 3 batches with industrial methylated spirit (63–95% alcohol) for 24 hr in glass soxhlets. The extracts were combined and concentrated to a thick syrup under reduced press, dissolved in 1N HCl (4 l.) and filtered. The clear extract was then made alkaline with strong ammonia soln and the bases extracted with Chf (5 × 1 l. and 4 × 500 ml). The Chf extracts were washed with 20% Na_2CO_3 aq and evaporated to 1 l., then extracted with 1N HCl (6 × 500 ml and 4 × 200 ml). The acid extracts were kept. The Chf soln still gave positive tests for alkaloids. It was dried over Na_2SO_4 and evaporated giving a residue of 35 g alkaloid bases, fraction II.

The reserved acid extracts above were made alkaline and extracted with Chf (4 × 1 l.), the soln dried and evaporated to give a residue of alkaloid bases, 95 g, fraction III.

Purification

Fraction I (14 g) in Chf was treated with charcoal and filtered through a small alumina column (25 g). The filtrate was evaporated to dryness and crystallized from MeOH. Two further recrystallizations gave alkaloid No. 1 (7·5 g). The mixture of alkaloids (5·8 g) obtained from the mother liquor was added to Fraction III.

Fraction II (35 g) is still under examination.

Fraction III (104 g) in MeOH (150 ml) was diluted with isopropyl ether and allowed to stand overnight when crystals separated and were collected. These were combined with a second crop obtained in a similar manner from the mother liquor. After 3 recrystallizations alkaloid No. 2 (18 g) was obtained.

The crude bases, from evaporation of the mother liquors, were dissolved in 200 ml Chf and chromatographed on 2·5 Kg alumina (75 × 6 cm), prepared in Chf. After development, the column was eluted with Chf (60 × 150 ml), then Chf: MeOH (95:5, 30 × 150 ml), (90:10, 30 × 150 ml), (80:20, 50 × 150 ml). Each of these fractions was examined by TLC, combined according to the pattern of alkaloids revealed and evaporated to dryness.

Fraction A (1–15) contained 1·3 g oily material with only very faintly positive indications of alkaloid content.

Fraction B (16–20) contained 1·19 g solid which was chromatographed on Keiselguhr G (32 g) and eluted with Chf: acetone (95:5, 20 × 25 ml) giving 120 mg alkaloids No. 1 from fractions 1–8, 20 mg alkaloid No. 2 from fractions 9–12 and 200 mg alkaloid No. 2 from fractions 13-18.

Fraction C (21–30) contained 11·9 g mixed alkaloids.

Fraction D (31–60) contained 18·5 g material which after several recrystallizations gave 15 g alkaloid No. 2.

Fraction E (61–72) contained 17 g material which was re-chromatographed on Keiselguhr (400 g) and eluted with Chf:acetone (98:2, 35 × 150 ml) giving 700 mg alkaloid-free oil from fractions 1-5, 3·2 g mixed alkaloids from fractions 6–10, and 4·5 g material from fractions 10–20 which on repeated recrystallization from MeOH—CH_2Cl_2 gave 2·8 g alkaloid No. 3. Fractions 21–27 gave a mixture of alkaloids, 1·72 g and fractions 27–35 gave 3·6 g alkaloid No. 2.

The column was stripped with Chf:acetone (90:10, 400 ml) which gave 3 g mixed alkaloids.

Fraction F (73–170) gave only mixtures of alkaloids.

Acetylcorymine. Alkaloid No. 1, had m.p. 194-195° from n-propanol. (Found: C, 68·05, H, 6·66; N, 6·51; O, 18·8; M.W. 424 (mass spec). Calc. for $C_{24}H_{28}N_2O_5$: C, 67·9; H, 6·65; N, 6·6; O, 18·8%; M.W. 424). Metastables observed at *m/e* 342·5, 314·7 were assigned to the fragmentations 424–381 calc. *m/e* 342·5 and 424–365 calc. *m/e* 314·4.

The dipicrolonate had m.p. 200° dec from propanol. (Found: C, 55·98; H, 4·76; N, 14·6; $C_{44}H_{44}N_{10}O_{15}$ requires: C, 55·46; H, 4·65; N, 14·7%). The IR spectrum of the alkaloid suggested it was acetylcorymine. Alkaline hydrolysis did not, however, give corymine, but a substance chromatographically identical with alkaloid 2′ and considered to be deformylcorymine.

Corymine. Alkaloid No. 2 had m.p. 182° from aqueous propanol. (Found: C, 69·1; H, 6·60; N, 7·0;

O, 17·6; OMe, 8·8; NMe, 3·9; H^+, 0·36; C=C, 1·6; CMe, 2·7; M.W. 382 (mass spec). Calc. for $C_{22}H_{26}N_2O_4$: C, 69·1; H, 6·85; N, 7·3; O, 16·7; OMe, 8·4; NMe, 4·1; H^+, 0·27; C=C, 1·0; CMe, 3·9%; M.W. 382.)

The alkaloid gave a blood-red colour with strong HNO_3 and a yellow one with $FeCl_3$. The tetranitromethane test was very positive, turning green. $[\alpha]_D = +48°$. The *picrolonate* had m.p. 200° from propanol, depressed by acetylcorymine picrolonate. (Found: C, 59·4; H, 5·3; N, 12·9. $C_{32}H_{34}N_6O_9$ requires: C, 59·4; H, 5·3; N, 13·0%.) The hydrobromide, prepared for X-ray work, had m.p. 210° from water. (Found: C, 54·7; H, 5·9; Br, 16·9; N, 5·6. $C_{22}H_{26}N_2O_4 \cdot HBr \cdot H_2O$ requires: C, 54·9; H, 6·1; Br, 16·6; N, 5·8%.)

TABLE 3. METASTABLES IN THE SPECTRA OF CORYMINE (I)

Metastable obs.	Transition	Calc. value
273·1	283–323	273·1
347	382–364	346·8
180	382–262	179·7
251·7	382–310	257·6
326·1	382–353	326·2
297·4	382–337	297·3
94·3	310–171	94·3(*)
121·5	171–144	121·3

Acetylation of corymine. Treatment of corymine with Ac_2O in pyridine gave the acetyl derivative, identical in m.p. and spectra with the natural acetate, undepressed in mixed m.p.

Propionylcorymine. Using propionic anhydride as above, the propionate was obtained with m.p. 170–172° from EtOH). (Found: M.W. 438·2170 ± 20, $C_{25}H_{30}N_2O_5$ requires: 438·2155).

TABLE 4.
METASTABLES IN THE SPECTRA OF PROPIONYLCORYMINE

Metastable obs.	Transition	Calc. value
331·5	438–381	331·4
358·0	438–396	358·0
304·0	438–365	304·2
66·8	438–171	66·8

Isocorymine. m.p. 183–185° from propanol. (Found: C, 69·0; H, 6·7; N, 7·3; O, 16·7; CMe, 3·9; NMe, 7·2; OMe, nil. $C_{22}H_{26}N_2O_4$ requires: C, 69·1; H, 6·8; N, 7·3; O, 16·7; CMe, 4·1; 2NMe, 8·2%.)

TABLE 5.
METASTABLES IN THE SPECTRA OF ISOCORYMINE (III)

Metastable obs.	Transition	Calc. value
327	381–353	327·1
347	382–364	346·8
301	382–339	300·85
142·1	144–143	142

TABLE 6. MASS MEASUREMENTS FOR ISOCORYMINE

m/e	Ion formulae	Error in ppm
382	$C_{22}H_{26}N_2O_4$	−3
364	$C_{22}H_{24}N_2O_3$	−6
325	$C_{20}H_{25}N_2O_2$	+4
311	$C_{19}H_{23}N_2O_2$	−4
227	$C_{14}N_{15}N_2O$	+3
212	$C_{14}H_{16}N_2$	+3
199	$C_{13}H_{15}N_2$	−1
186	$C_{12}H_{14}N_2$	+4
185	$C_{12}H_{13}N_2$	−2
144	$C_{10}H_{10}N$	−5

Acetylation as for corymine gave *acetylisocorymine* m.p. 160° from propanol. (Found: M.W. 424·2005 ± 20, $C_{24}H_{28}N_2O_5$ requires: 424·1998).

TABLE 7.
METASTABLES IN THE SPECTRA OF ACETYLISOCORYMINE

Metastable obs.	Transition	Calc. value
368·1	424–395	367·9
342·2	424–381	342·4
314·1	424–365	314·2
320	364–338	319·9
184·1	186–185	184·0
210	212–211	210·0

Dehydroisocorymine. Oxidation of isocorymine[10] gave after purification by TLC (benzene–AcOEt, 4:1, developed several times), dehydroisocorymine m.p. 203° $[\alpha]_D^{20°}$ − 370°, UV spectrum typical of the corymine alkaloids. (M.W. Found: 380·1733 ± 20, $C_{22}H_{24}N_2O_4$ requires: 380·1736). Only one metastable at 184·1 was observed and assigned to the transition 186–185 (calc. 184·0).

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[10] J. D. Albright and L. Goldman, J. Org. Chem. **30**, 1107 (1965).