Organic Mass Spectrometry, 1970, Vol. 3, pp. 1489 to 1498. Heyden & Son Limited. Printed in Northern Ireland

THE MASS SPECTRA OF INDOLIZINES

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(*Received* 11 *March* 1970; *accepted* 5 May 1970)

Abstract—The mass spectra of indolizine, the seven monomethylindolizines, the six 2,*x*-di-methyl-indolizines and a number of related simple indolizines are reported; the breakdown patterns are compared with those of the corresponding indoles.

NO COMPREHENSIVE examination of the mass spectra of indolizines appears to have been made. We are investigating possible routes to expand either the six or the five membered ring of indolizines to give azonia-azulenium ions (I) or quinolizinium ions (II) and we have determined the mass spectra of a number of simple indolizines, seeking evidence of such expansions in the mass spectral breakdown patterns.

By contrast, a number of groups have reported mass spectral data on indoles,[1to4] which might be expected to behave in an analogous manner to indolizines, and most have drawn the conclusion that the breakdown of methylindoles occurs after ring expansion to a stable 'quinolinium' or 'azonia-azulenium' ion; the first fragment lost in all indoles bearing C-methyl groups being HCN, followed by a second clean loss of an acetylene molecule.

The mass spectra of indolizine is shown in Fig. 1. The molecular ion is also the base peak (*m/e* 117) and as with indole[3] the first obvious loss is of HCN, giving a peak at *m/e* 90 with a second peak at *m/e* 89 indicating loss of H_2CN; the relative intensities are 38% (*m/e* 90) and 28% (*m/e* 89) which may be compared with corresponding figures of 40% and 24% in indole. The next ion of high relative intensity was at *m/e* 64 (loss of C_2H_2) in contrast to that reported for indole at *m/e* 63, $[C_5H_3]^+$.

Of much more interest are the mass spectra of the methylindolizines, as here the opportunity for ring expansion is more obvious (*cf.* indole[1to4]). The principal values of *m/e* and relative intensities for all the monomethylindolizines are shown in Table 1. The major peaks throughout are the $[M]^{+\cdot}$ and $[M-1]^+$ ions (*m/e* 131 and 130 respectively). The second fragmentation, in all cases, involves loss of HCN to give a peak *m/e* 103 (confirmed by a metastable peak at 81·6). The third clear fragmentation in all cases is loss of C_2H_2 to give *m/e* 77 ($[C_6H_5]^{+\cdot}$; again confirmed by a metastable peak at 57·5). Most spectra show strong peaks at *m/e* 65, due to doubly charged ions where [M] = 130. Finally, the next fragmentation is a second loss of C_2H_2 from *m/e* 77 giving *m/e* 51. In any discussion of these results certain points must be emphasized. Firstly, that the spectra of the various mono-methylindolizines are very similar—that the breakdown from *m/e* 130 $[M-1]^+$ gives ions in a very similar relative intensities, irrespective of the point of attachment of the methyl group. Secondly, that the ions and relative intensities reported by Powers[3] for the various methylindoles are again very similar to each other (for example, those reported for 2-methylindole are virtually the same as those reported for 4-methylindole) and very similar to our figures for methylindolizines. Power states[3] that 'the possibility that the $[M-1]^+$ ions from all methylindoles possess the same structure is considered remote

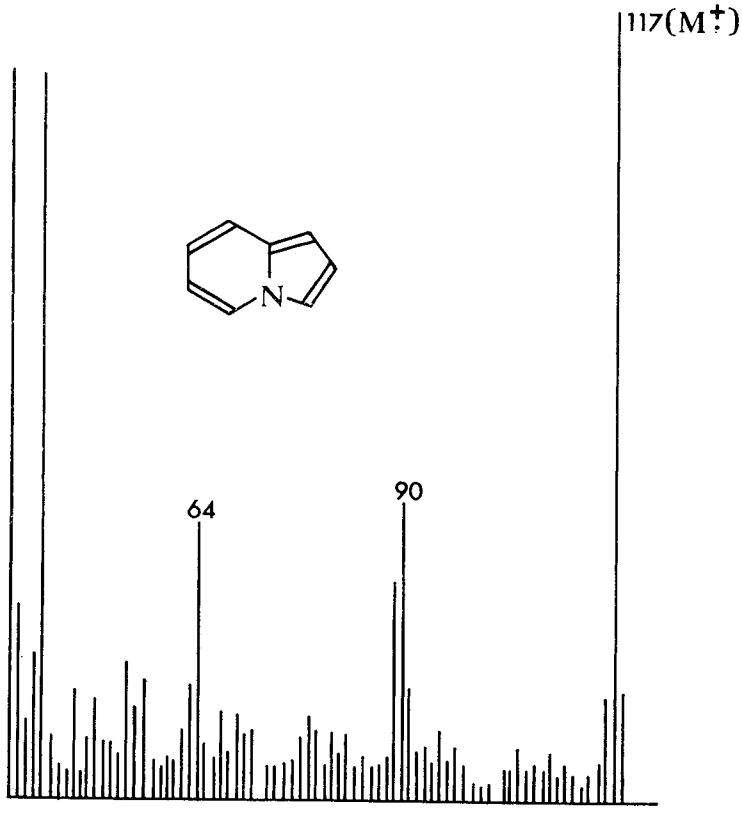


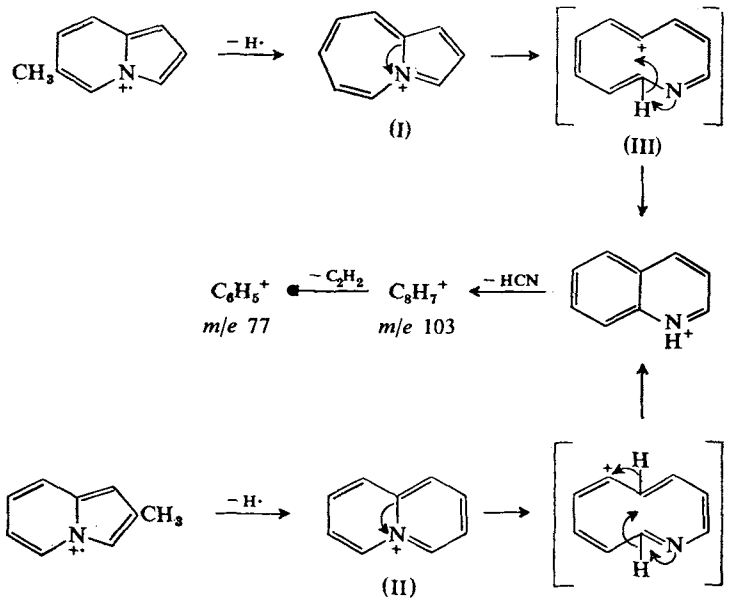
FIG. 1. Mass spectrum of indolizine

TABLE 1. MASS SPECTRA OF METHYL INDOLIZINES (RELATIVE ABUNDANCES %)

m/e	1-Me	2-Me	3-Me	5-Me	6-Me	7-Me	8-Me
131	89	99	60	100	100	96	96
130	100	100	100	92	91	100	100
104	3·9	3·9	3·1	4·9	6·6	5	5
103	7·1	8·6	7·9	9	14	12	10
102	4·7	6·2	3·9	4·9	5·8	5	5·8
78	7·9	8·6	7·9	4·1	5·8	5	18
77	15·7	16	11·8	13·9	18	17	25
65	7·1	20	7·9	9·8	8·2	7·5	19
63	6·3	6·2	4·7	8·2	9	6·6	8·2
51	13·4	14	15	8·2	10·7	9·9	26

Metastable peaks: 81·6 130 → 103
57·5 103 → 77

by the author because of the extensive molecular re-arrangements which would have to be invoked'. In our case, however, an extensive molecular rearrangement will have to be invoked to produce a feasible pathway for the initial loss of HCN, and it seems a smaller step therefore to suggest a common intermediate for all the methylindolizines, an intermediate perhaps common also to all the methyl indoles. It would appear to us also that such an intermediate would be best formulated as monocyclic, the ring enlargement being accompanied by a breaking of the 4,9 (N—C) central bond to give an azoniacyclodecapentaene (III) which could then reform the quinolinium ion or break down to a $[C_8H_7]^+$ ion directly (Scheme 1).



SCHEME 1

Two compounds which would be expected to give rise to the same ion at *m/e* 130 as is observed in the methylindolizines are the hydroxymethylindolizines (IV) and (V). In these compounds the basic breakdown pattern via the ion *m/e* 130 is still visible but the abundance for example of the peaks *m/e* 117 and *m/e* 116 relative to that at *m/e* 130 is changed because of a competing fragmentation. It is known[2] that benzyl alcohol can lose H_2 to give an aldehyde which then loses H· and CO; such a pathway is shown for 2-hydroxymethylindolizine (Fig. 2) by peaks at *m/e* 145 and 144, and an increased peak at *m/e* 116 over that found in 2-methylindolizine; a metastable ion at *m/e* 93·4 confirms the loss of CO from *m/e* 144 → *m/e* 116. This alternative fragmentation is very much suppressed in 3-hydroxymethylindolizine which may be a reflection of the very different electron densities at positions 2- and 3- in indolizine. The hydroxydideuteriomethyl indolizine (VI) shows evidence of retention of deuterium at least in the first two stages of the major breakdown path with substantial peaks at 132 (loss of OH) and 119 (loss of HCN) but from the information available it is difficult to be sure that randomization has not occurred.

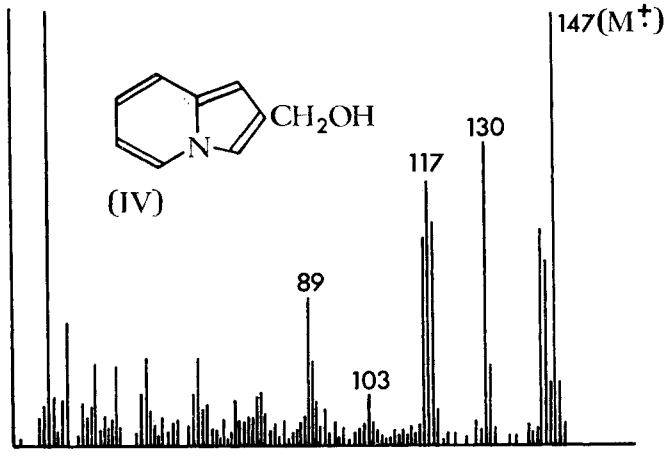
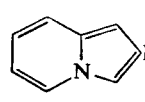
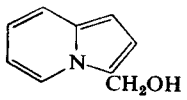


FIG. 2. Mass spectrum of 2-hydroxymethylindolizine.

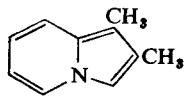
We have also examined the mass spectra of all the 2,*x*-dimethylindolizines, shown as (VII), (VIII) and (IX). Again tabulated spectra are given in Table 2. All dimethylindolizines show a large [M − 1] peak but there is more variety in the subsequent breakdown patterns. The peak at *m/e* 130 (loss of CH_3· from the molecular ion) is followed by peaks at *m/e* 103 and *m/e* 77, paralleling the pattern shown by monomethylindolizines; but there is evidence of sequential loss of two methyl groups in a peak at *m/e* 115. The 1,2-dimethyl- and 2,3-dimethylindolizines (VII) and (VIII) show greatly enhanced peaks at *m/e* 130; it seems unlikely that this reflects a preferential loss of the methyl group from the positions of high electron density (1- and 3- in indolizine) as the peak at *m/e* 130 in 3,5-dimethylindolizine (X) is not enhanced. The high peak at *m/e* 130 in these two compounds may reflect a 'vicinal effect'.[4] There is no evidence of any marked loss of CH_3CN in 2,3-dimethyl indolizine (VIII), 2,5-dimethylindolizine or 3,5-dimethylindolizine (X) all of which show only small peaks at *m/e* 103 (in line with the expected loss of HCN from the ion at *m/e* 130); this again appears to support a fragmentation mechanism which includes ring expansion or rearrangement.



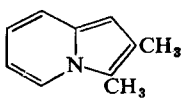
(IV) R = CH_2OH
(VI) R = CD_2OH



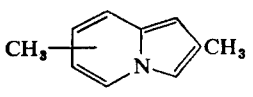
(V)



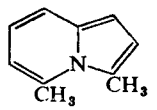
(VII)



(VIII)



(IX)



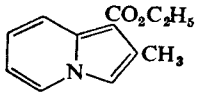
(X)

TABLE 2. MASS SPECTRA OF DIMETHYLINDOLIZINES (RELATIVE INTENSITIES %)

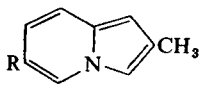
m/e	1,2-Me_2	2,3-Me_2	2,5-Me_2	2,6-Me_2	2,7-Me_2	2,8-Me_2	3,5-Me_2
145	100	100	100	100	97	100	100
144	100	100	100	95	100	96	100
143	25	21	16	11	18	15	14
142	14	16	13	7	10	9	14
131	69	7	—	—	2·6	2·6	—
130	83	51	38	8	22	18	11
117	10	15	6	6	5	5	3·5
115	8	7	13	11	11	10	5
104	5	4·5	3·5	2·6	1·8	1·8	—
103	7	5	5·5	3·5	6	4·5	6
102	4·5	3·5	3·5	1·8	2·6	2·6	4·5
78	14	12	4·5	1·8	1·8	2·6	3·5
77	14	12	12·5	6	12·5	6	14
65	17	15	14	6	7	5	13

Metastable peaks 81·6 $130 \rightarrow 103$

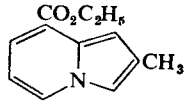
We have examined the mass spectra of a number of indolizine esters—the ethyl esters (XI), (XII) and (XIII) and the methyl esters (XIV) and (XV). The spectra of esters (XI) and (XII) are shown with that of (XIV) in Fig. 3. The fragmentations are as expected for esters of aromatic acids; in the ethyl esters the major peaks are at *m/e* 203 $[M]^{+\cdot}$, at *m/e* 175 (loss of C_2H_4, presumably by McLafferty rearrangement), *m/e* 158 (loss of $C_2H_5O\cdot$, notable only in ester (XI)) and *m/e* 130 (equivalent to the [M − 1] peak in methylindolizines and followed by loss of HCN and C_2H_2). The only notable difference in the region of *m/e* 130 is the increase in the peak at *m/e* 131 in esters (XI) and (XIII), not shown by ester (XII). This corresponds to a loss of $C_2H_4CO_2$ from the molecular ion (a metastable at 84·5 confirms this) and is probably due to an initial transfer of H· to the *peri* position, impossible in ester (XII). The methyl esters (XIV) and (XV) give, as expected, molecular ions at *m/e* 175 (base peak)



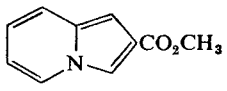
(XI)



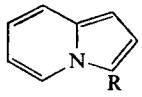
(XII) R = CO_2Et
(XIX) R = CN
(XXII) R = $CONH_2$



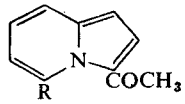
(XIII)



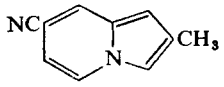
(XIV)



(XV) R = CO_2CH_3
(XXI) R = $CONH_2$



(XVI) R = H
(XVII) R = CH_3



(XX)

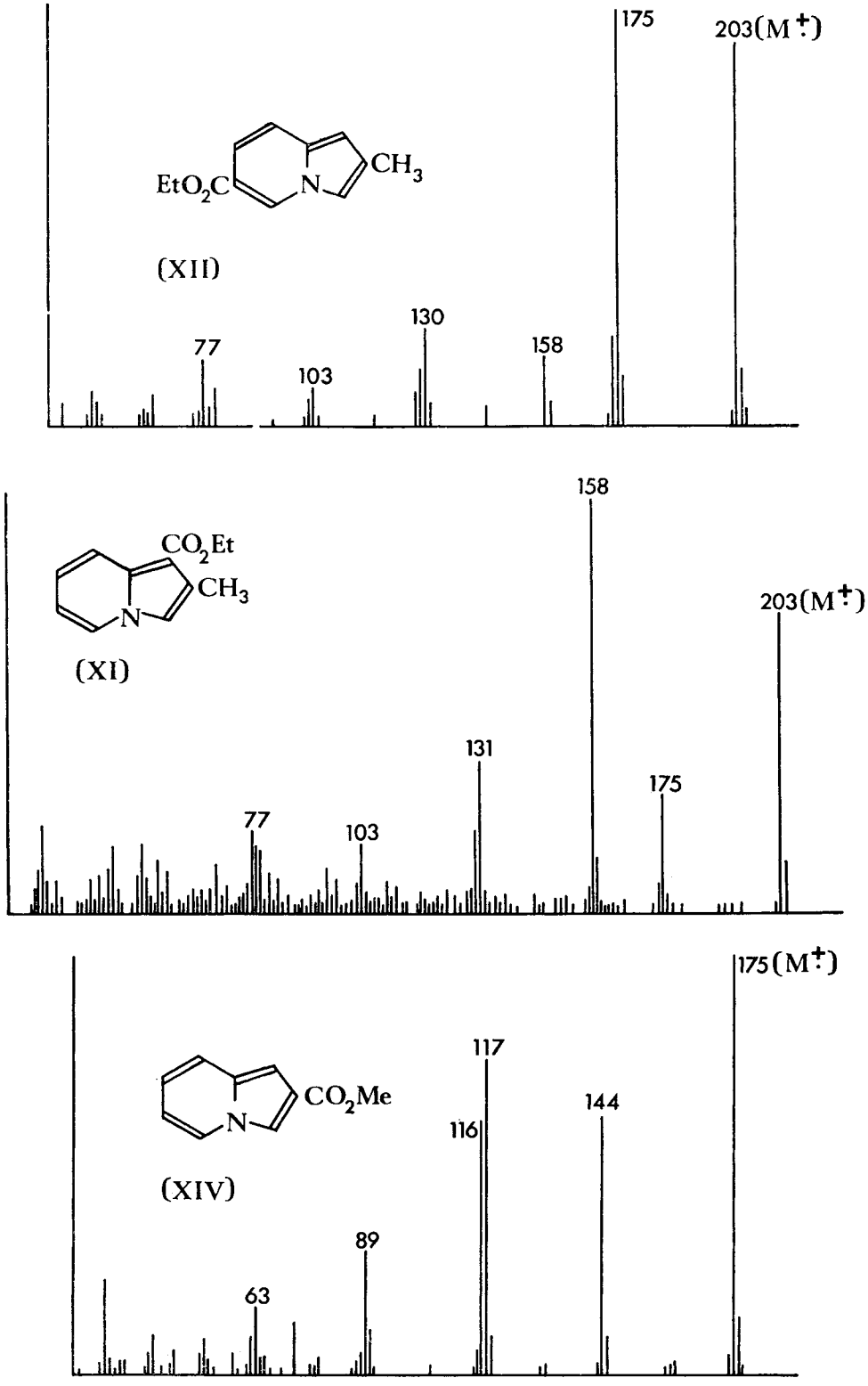


FIG. 3. Mass spectra of ethyl 2-methylindolizine-1-carboxylate (XI), ethyl 2-methylindolizine-6-carboxylate (XII), and methyl indolizine-2-carboxylate (XIV).

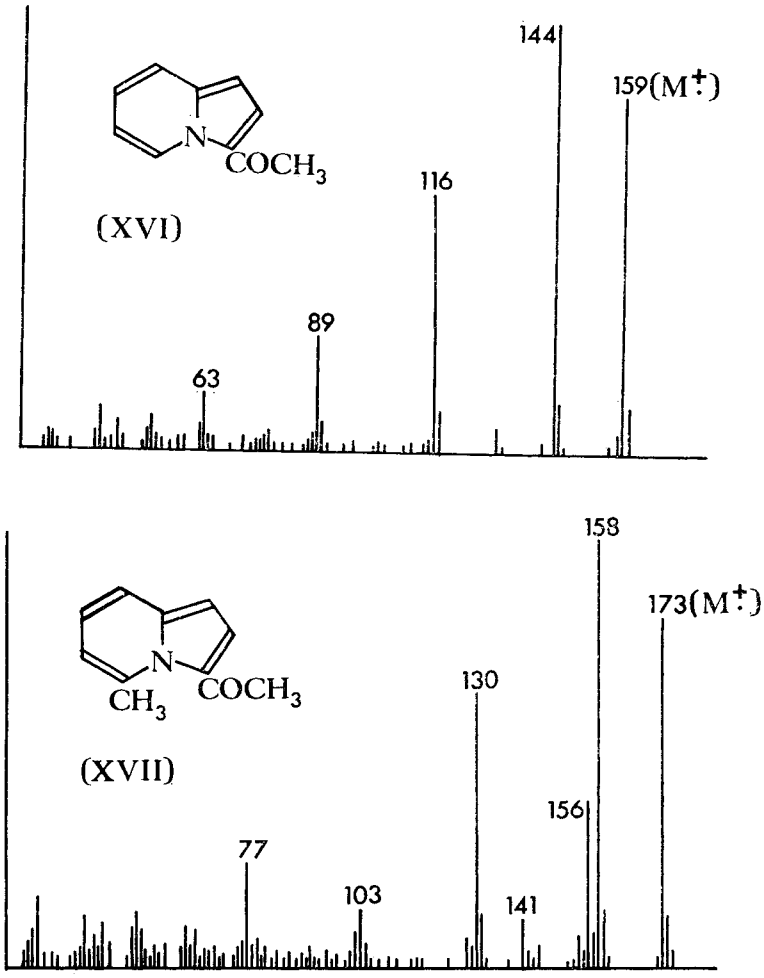
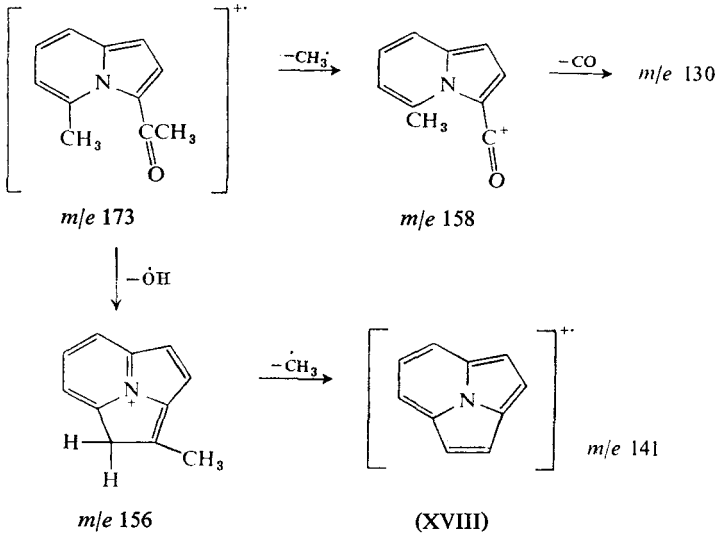


FIG. 4. Mass spectra of 3-acetylindolizine (XVI) and 3-acetyl-5-methylindolizine (XVII).

with peaks of high relative intensity at *m/e* 144 (loss of $CH_3O\cdot$) and 116 (loss of CH_3O + CO, m.s. at 93·4), with a subsequent fragmentation pattern similar to that of indolizine. The peak at *m/e* 117 corresponds to loss of CH_2CO_2 from the molecular ion (m.s. at 78·2).

The two acetylindolizines (XVI) and (XVII), Fig. 4, show interesting differences in their fragmentation. The 3-acetylindolizine spectrum is that expected for an aromatic methyl ketone; the molecular ion at *m/e* 159 loses $CH_3\cdot$ to give an ion *m/e* 144 (m.s. at 130·4) which in turn loses CO to give *m/e* 116 (m.s. at 93·4); the 5-methyl-3-acetylindolizine (XVII) shows in addition ions at *m/e* 156 (loss of OH) and then at *m/e* 141 (loss of CH_3 + OH). This could be interpreted as shown in Scheme 2 as a route to the [3,2,2] cyclazine (XVIII).[5] The last group of spectra examined (Fig. 5) are of amides and nitriles (compounds (XIX) → (XXII)). The methyl substituted nitriles (XIX) and (XX) show the expected large [M − 1] peak at *m/e* 155 (see discussion of



SCHEME 2

methyl indolizines) followed by successive loss of two molecules of HCN, giving peaks at *m/e* 128 and 101. The amides differ in their fragmentation pattern; compound (XXI) shows a base peak at *m/e* 160 (molecular ion) which loses $\cdot NH_2$ to give *m/e* 144 and then CO to give *m/e* 116, with subsequent breakdown after the indolizine pattern. The amide (XXII) shows additionally a route from the molecular ion 174 involving loss of H_2O to give *m/e* 156, and then some indication of a breakdown similar to that of the nitrile (XIX).

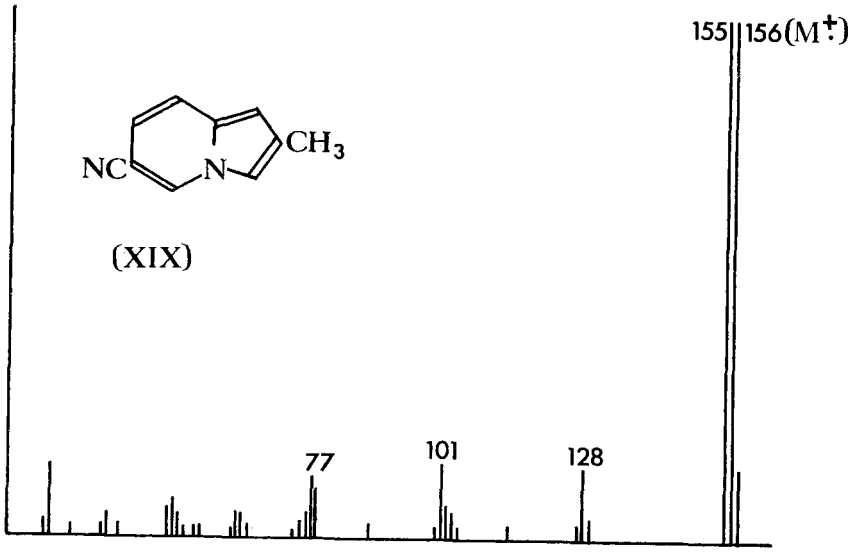


FIG. 5.

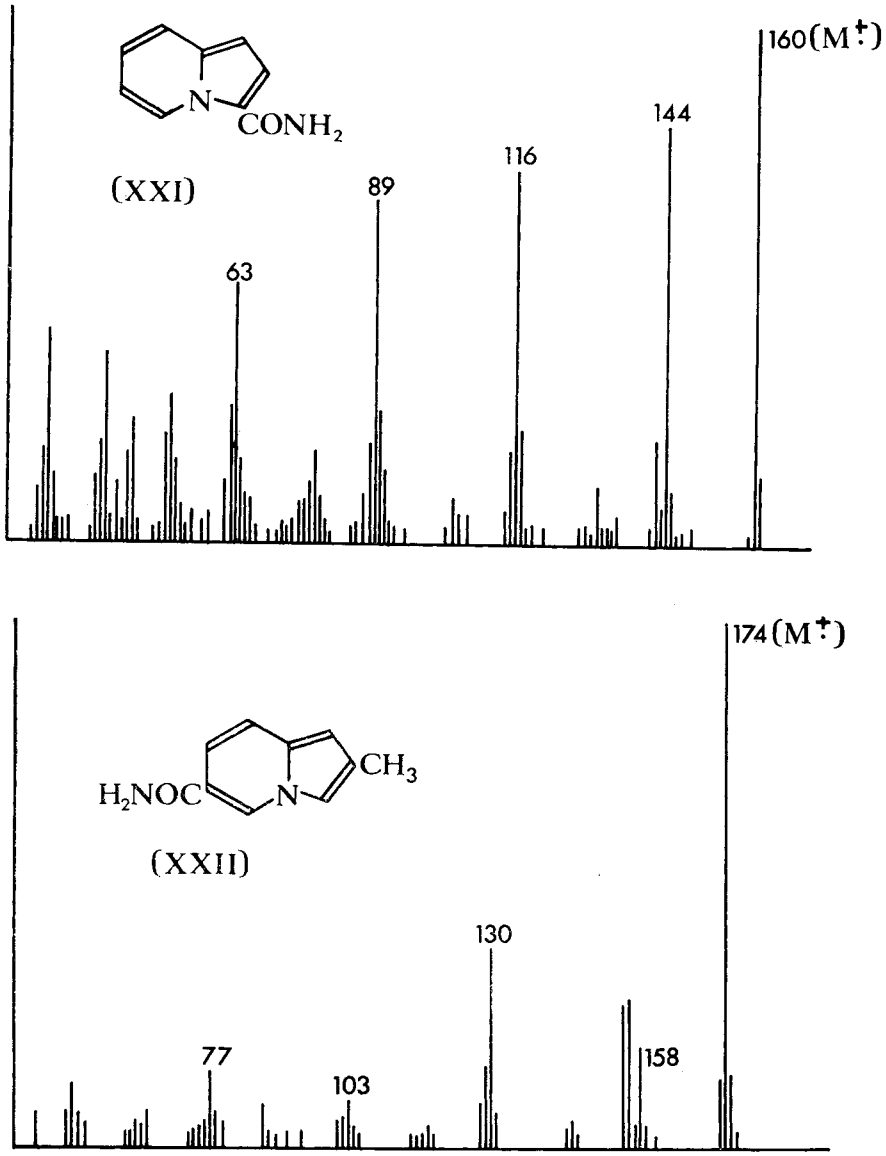


FIG. 5. Mass spectra of 6-cyano-2-methylindolizine (XIX), indolizine-3-carboxamide (XXI), and 2-methylindolizine-6-carboxamide (XXII).

EXPERIMENTAL

Most mass spectra were determined on AEI MS-9 instruments mainly at NIH, Bethesda, Maryland; a few were determined at ICI (Pharmaceuticals Division), Alderley Park. Some of the alkylindolizines showed extreme instability and for these an LKB instrument was used. Most indolizines were introduced through direct inlet at temperatures of ~180°, with an ionizing energy of 70 eV. Some were introduced via a g.c. inlet (on the LKB instrument) after final purification by gas chromatography. The latter spectra showed no evidence of any breakdown during chromatography. N.m.r. spectra were recorded on a 60 Mc Perkin–Elmer R10 instrument.

Monomethylindolizines. 1-Methylindolizine and 8-methylindolizine were prepared via the corresponding 2-carboxylic acids as described by Borrows and Holland;[6] decarboxylation was performed as described by Diels and Alder.[7] 2-Methylindolizine was prepared by a Chichibabin procedure;[8] 3-, 6- and 7-methylindolizines were prepared by the method of Scholz[9] as modified by Armarego.[10] 5-Methylindolizine was prepared from 2,6-lutidine as described by Boekelheide.[11]

Dimethylindolizines. The 1,2- and 2,3-dimethylindolizines were prepared by the method of Holland and Nayler.[8] 1,2-Dimethylindolizine had n.m.r. peaks (CCl_4)* at 7·7 (doublet, 5-proton) 7·25 (doublet, 8-proton), 7·03 (broad singlet, 3-proton) 7·1 to 7·4 (two proton multiplet) 2·25, (six proton singlet).

3,5-Dimethylindolizine was prepared by the method of Scholz,[9] modified by Armarego.[10]

The other dimethylindolizines were prepared by Chichibabin procedures, as exemplified by the preparation of 2,5-dimethylindolizine.

(a) A solution of 2,6-lutidine (10·7 g) and bromoacetone (14·0 g) in absolute ethanol (100 ml) was boiled (6 hrs.), evaporated, and the crude quaternary salt crystallized from acetone containing 5% of ethanol, to give 1-*acetonyl*-2,6-*dimethylpyridinium bromide*, m.p. 194° (6·7 g. 27·5%). (Found: C, 49·4; H, 5·8; N, 5·8. $C_{10}H_{14}BrNO$ requires C, 49·2; H, 5·7; N, 5·7%). ν_{max}^{Nujol} 1720 cm^{-1}.

(b) The quaternary salt (2·0 g) was heated with 10% aqueous sodium bicarbonate solution (50 ml, 0·5 hrs.) on the steam bath. The cooled solution was extracted with ether, the ethereal solution dried and distilled to give a small yield of 2,5-dimethylindolizine, b.p. 116°/15 mm agreeing in physical properties with those reported.[12] 2,8-Dimethylindolizine had n.m.r. peaks (CCl_4) at 7·55 (broadened doublet, 5-proton) 6·95 (broadened singlet, 3-proton), 6·2 to 6·4 (multiplet, 6- and 7-protons), 6·2 (broadened singlet, 1-proton) 2·3 (6 protons).*

The preparation of the other compounds mentioned has been previously described.[13]

Acknowledgements—We thank the SRC for a maintenance grant (to J. S.); Dr H. M. Fales and Dr J. D. Baty of the National Institutes of Health, and Dr B. Webster of ICI (Pharmaceuticals Division) for the determination of spectra.

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* All shifts are in ppm from TMS as internal standard.