The Mass Spectrometry of Simple Indoles

JAMES C. POWERS[1]

Contribution No. 2089 from the Department of Chemistry, University of California at Los Angeles, Los Angeles, California 90024

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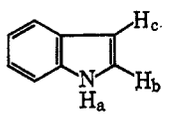
The mass spectra of a variety of substituted indoles have been examined and the major fragmentation routes ascertained. Indole loses HCN and H_2CN upon electron impact; the position of the hydrogen lost was established by examination of the spectra of deuterated indoles. Indoles substituted with methyl groups in the benzene ring give intense M − 1 ions due to the formation of azaazulenium ions. N-Methylindole could be distinguished from other isomers since it was the only methylindole to give an M − CH_3 ion. Considerable scrambling was shown to take place upon electron impact of arylindoles since loss of CH_2N was an important fragment in the spectra of a variety of arylindoles. Indoles substituted with a methoxyl group in the 6 position could be distinguished from either the 5 or 7 isomer because of a more intense M − CH_3 ion and a less intense molecular ion. The mass spectra of several indole aldehydes, ketones, and carboxylic acid are discussed. Indole-2- and 7-carboxylic acid derivatives show an "*ortho* effect" and can be differentiated from other isomers. From an examination of the spectra of several disubstituted indoles, it was concluded that one substituent preferentially directed the fragmentation. A scheme was derived which allows the prediction of which substituent this would be. Oxindoles can be characterized by the presence of a benzazetinium ion in their mass spectra.

Mass spectroscopy has become exceedingly important in the chemistry of natural products, and in particular, the chemist working with indole alkaloids is fortunate in being able to draw upon the wealth of information which is available due to the elegant work of Biemann and his coworkers at M.I.T. and Djerassi and his coworkers at Stanford on the mass spectra of these complex molecules.[2] In contrast, the chemist or biochemist who is working with less complex indolic molecules is unable to draw upon such a backlog of experience to aid in unraveling their mysteries. Simple indoles, although widely distributed in both the plant and animal kingdoms,[3] have been neglected by the mass spectroscopist except for a few cases.[4,5] This study was begun in order to reverse this neglect.

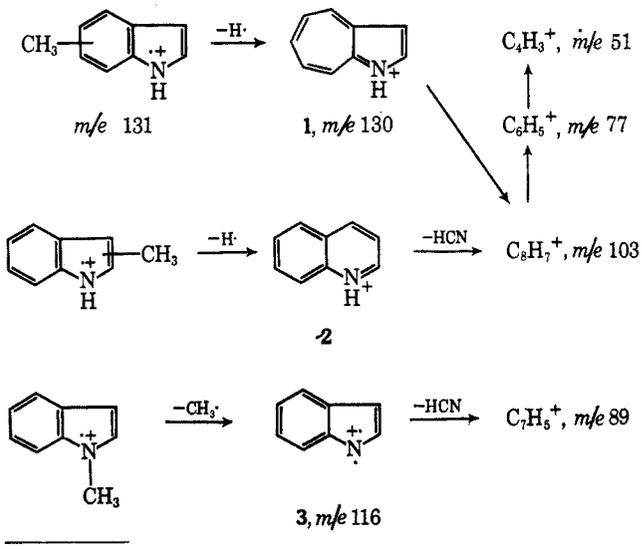
Indole.—The mass spectrum of indole has been reported.[6] The molecular ion (*m/e* 117, base peak) loses HCN and H_2CN to give strong peaks at *m/e* 90 (relative abundance 40%) and 89 (24%). These peaks are shifted one mass unit in the spectrum of 3-deuterioindole showing that H_c is not involved in either fragmentation. The loss of HCN involves both H_a and H_b. The spectrum of 1-deuterioindole is consistent with loss of 79% H_bCN and 21% H_aCN with transfer of the other hydrogen to the fragment ion.[7]



The *m/e* 89 peak is not shifted in the spectrum of 1-deuterioindole indicating that most of the deuterium is lost with the H_2CN fragment. No smaller fragment ions contained deuterium. Further fragmentation of indole gives rise to $C_5H_3^+$ (*m/e* 63). This is partially shifted to *m/e* 64 in the spectrum of 3-deuterioindole and 1,3-dideuterioindole. This demonstrates that H_c and probably C-3 of indole are partially retained in this fragment.

Methylindoles.—The mass spectra of a series of 11 alkylindoles including 2-methyl- and 3-methylindole have been investigated by Beynon and and Williams.[5] The spectra of the remaining methylindoles have been determined and the data are presented in Table I. The spectra of 4-, 5-, 6-, and 7-methylindole are surprisingly similar; the M − 1 peak is the base peak in all cases. The similarity of the spectra is good evidence for the formation of a common intermediate in the fragmentation of these methylindoles. This is best represented as the azaazulenium ion **1**[8] in analogy with the formation of tropylium ion from alkylbenzenes. This ion then sequentially loses HCN and two C_2H_2.

CHART I



(1) Department of Biochemistry, University of Washington, Seattle, Wash. 98105.

(2) (a) K. Biemann, "Mass Spectrometry: Organic Chemical Applications," McGraw-Hill Book Co., Inc., New York, N. Y., 1962; (b) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. 1, Holden-Day, Inc., San Francisco, Calif., 1964.

(3) B. B. Stowe in L. Zechmeister, Ed., "Fortschritte der chemie organischer Naturstoffe," Vol. 17, Springer-Verlag, Vienna, 1959.

(4) Mass spectroscopy has been invaluable in the structure determination of several naturally occurring indoleacetic acid and tryptophan derivatives. A. B. Lerner, J. D. Case, K. Biemann, R. V. Heinzelman, J. Szmuszkovicz, W. C. Anthony, and A. Krivis, *J. Amer. Chem. Soc.*, **81**, 5264 (1959); J. C. Sheehan, P. E. Drummond, J. N. Gardner, K. Maeda, D. Mania, S. Nakamura, A. K. Sen, and J. A. Stock, *ibid.*, **85**, 2867 (1963); M. S. v. Wittenau and H. Els, *ibid.*, **85**, 3425 (1963).

(5) J. H. Beynon and A. E. Williams, *Appl. Spectrosc.*, **13**, 101 (1959); **14**, 27 (1960); J. H. Beynon, "Mass Spectroscopy and Its Application to Organic Chemistry," Elsevier Publishing Co., Amsterdam, 1960, pp 397–403.

(6) Catalog of Mass Spectra Data, American Petroleum Institute Research Project 44, Carnegie Institute of Technology, Pittsburgh, Pa., spectra no. 623.

(7) The calculation of the isotopic distribution in fragments from a labeled compound is beset with several pitfalls (ref 1a, Chapter 5), and these numbers should be considered approximate.

(8) The mass spectrum of 7-methylbenzofuran has an intense M − 1 (49%) peak. This has been postulated to have an oxonium ion structure analogous to **1**. R. I. Reed and W. K. Reid, *J. Chem. Soc.*, 5933 (1963).

TABLE I

MASS SPECTRA OF METHYLINDOLES

m/e	1-Me[a]	2-Me[b,h]	3-Me[c,h]	4-Me[d]	5-Me[e]	6-Me[f]	7-Me[g]
131	100	85	69	76	79	77	78
130	83	100	100	100	100	100	100
116	11						
103	17	15	16	15	10	11	9
102	7	5	8	7	5	5	7
90	11	3	1				
89	22	4	1	2	1	1	2
77	12	19	28	21	15	16	20
65		10	16		8	5	3
63	11	5	4	4	3	2	3
51	8	7	11	8	5	4	6
Metastable peaks	81.60 130 → 103 68.20 116 → 89 57.50 103 → 77				81.60 130 → 103 57.50 130 → 77		

Registry numbers are as follows: [a] 603-76-9; [b] 95-20-5; [c] 83-34-1; [d] 16096-32-5; [e] 614-96-0; [f] 3420-02-8; [g] 933-67-5. [h] See ref 5.

TABLE II

MASS SPECTRA OF ARYLINDOLES

m/e	1-C_6H_5[a]	2-C_6H_5[b,f]	3-C_6H_5[c]	3-(2-Py)[d]	2,3-di-C_6H_5[e]
M^+	100	100	100	100	100
M − 1	12	7	12	50	28
M − HCN	4	4	5	7	
M − CH_2N	17	20	22	16	6
M − CH_2N − C_2H_2	2	3	2	4	
M − CH_2N − HCN				6	
M − C_6H_5	2	1			
M − C_7H_5N	12	15	2		
M − C_7H_6N	11	15			21
$C_6H_5^+$	5	4			
$C_5H_4N^+$				5	
Metastable peaks	142.20 M → (M − CH_2N)		142.20 M → (M − CH_2N)	142.70 (M − 1) → (M − H_2CN) 116.40 (M − H_2CN) → (M − HCN − H_2CN)	

Registry numbers are as follows: [a] 16096-33-6; [b] 948-65-2; [c] 1504-16-1; [d] 3139-24-0; [e] 3469-20-3. [f] See ref 3, spectra no. 1561.

The fragmentation of 2-methyl- and 3-methylindole follows a similar course. The M − 1 peak is the most intense in the spectrum and has been given the quinolinium ion structure **2** by Beynon.[5,9] The formation of such an ion explains the loss of HCN (rather than CH_3CN) from the M − 1 ion in 2-methylindole; the *m/e* 90 (M − CH_3CN) and *m/e* 89 (M − H − CH_3CN) peaks are more intense than in 3-methylindole, but this is still not a major fragmentation pathway. Another characteristic of 2- and 3-methylindole is the intense doubly charged ions at *m/e* 65.

In contrast to the other methylindoles, the base peak in the spectrum of 1-methylindole is the molecular ion. This is also the only methylindole to give a M − CH_3 ion (**3**). This fragments further to yield $C_7H_5^+$ (*m/e* 89) by loss of HCN.

The mass spectra of various indoleacetic acid and tryptophan derivatives are discussed by Budzikiewicz, *et al.*[1b] The base peak in the spectra of these compounds usually occurs at *m/e* 130 (*e.g.*, **2**).

(9) The possibility that the M − 1 ions from all methylindoles possess the same structure is considered remote by the author because of the extensive molecular rearrangements which would have to be invoked. At present there is no evidence which bears on this point.

Arylindoles.—The mass spectra of 3-(2-pyridyl)-indole and several phenylindoles are listed in Table II. The molecular ion is the base peak in the spectra of all of the arylindoles we have investigated. Loss of CH_2N from the molecular ion is the predominant fragment in the spectra of 1-, 2-, and 3-phenylindole.[10] This peak was mass measured in the spectrum of 1-phenylindole and found to have a composition corresponding to the florenyl cation $C_{13}H_9^+$. Surprisingly, the intensity of this peak did not vary greatly with location of the phenyl substituent. The molecular ion must then undergo considerable scrambling before the loss of CH_2N. On the other hand, loss of C_6H_5–CHN and C_6H_5–CN (or C_6H_5NC) occurs more readily from 1-phenylindole and 2-phenylindole, indicating the lack of scrambling in this fragmentation pathway. The M − C_6H_5NC ion was mass measured in the spectrum of 1-phenylindole and had the expected composition.

The predominant peak in the spectra of 2,3-diphenylindole and 3-(2-pyridyl)indole is the M − 1 peak. Introduction of a nitro group into the 6 position, or into

(10) A. L. Jennings, Jr., and J. E. Boggs [*J. Org. Chem.*, **29**, 2065 (1964)] discuss the significance of the M − CH_2N peak in the mass spectra of various heterocyclic molecules.

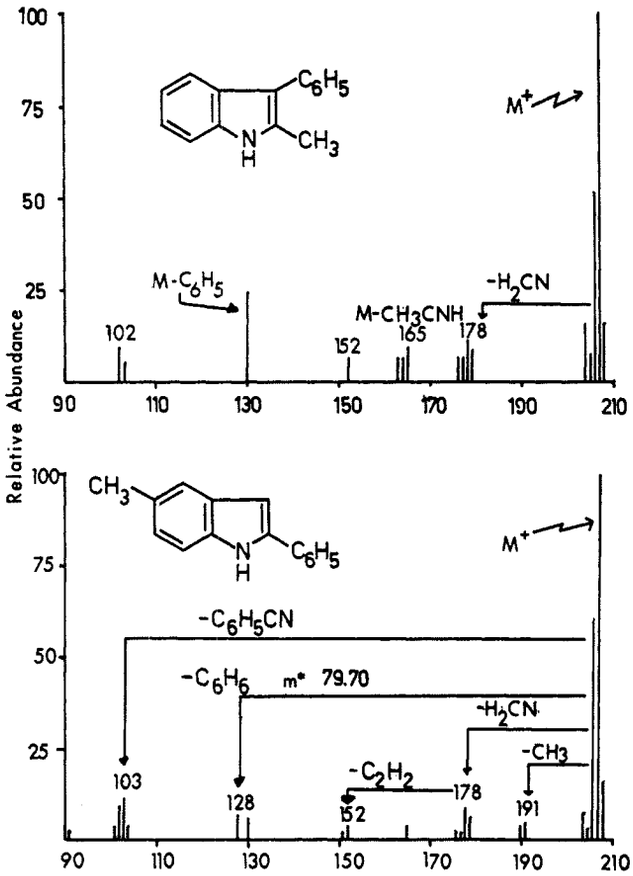


Figure 1.—Mass spectra of 3-phenyl-2-methylindole and 5-methyl-2-phenylindole.

the *para* position of the 3-phenyl substituent, or into both positions of 2,3-diphenylindole results in the disappearance of the M − 1 and M − C_6H_5CHN ions from the spectra of these compounds. Concurrently, a small peak at M − C_6H_6 appears which was not present in the unsubstituted parent. These effects could be due to either destabilization of the M − 1 ion by the nitro groups or by localization of the charge at the nitro group rather than in the indolic portion of the molecule.

The spectra of two methylphenylindoles are reproduced in Figure 1. The most intense peak in the spectrum of 3-phenyl-2-methylindole is the M − 1 peak. Further fragment ions result from loss of H_2, HCN, H_2CN, CH_3CN, CH_3CNH, C_6H_5CN, and C_6H_5CNH from the *m/e* 206 ion. The spectrum of 5-methyl-2-phenylindole is quite similar. The M − 1 peak is the most intense peak after the molecular ion. This undergoes further fragmentation through loss of C_6H_6 (metastable ion), HCN (metastable ion), H_2CN, C_6H_5CN, C_6H_5CNH, and to a small extent CH_3.

The question then arises whether it is necessary to represent the M − 1 ions of methylindoles as quinolinium ion (*e.g.*, **2**) or as azaazulenium ions (*e.g.*, **1**) rather than as simple unrearranged indolinium ions. The case seems clear-cut with regards to the simple methylindoles. The spectral similarity between isomers and the lack of a significant (M − 1) − CH_3 ion in the spectra of all the monomethylindoles except the 1 isomer (the *m/e* 115 ion has a relative abundance of 1.6%) require the M − 1 ion to have a rearranged structure. The case is not so clear with the methylphenylindoles. The presence of (M − 1) − CH_3 ions in the spectra of 5-methyl-2-phenylindole (relative abundance = 6%) and 2-methyl-3-phenylindole (relative abundance = 3%) points to an unrearranged structure for the M − 1 ion. On the other hand, certain features such as the (M − 1) − HCN and (M − 1) − H_2CN ions in the spectrum of 2-methyl-3-phenylindole can best be derived from a M − 1 ion having a rearranged structure. It is therefore highly likely that the M − 1 of the methylphenylindoles is not a discreet species, but rather represents a blend of several structures.

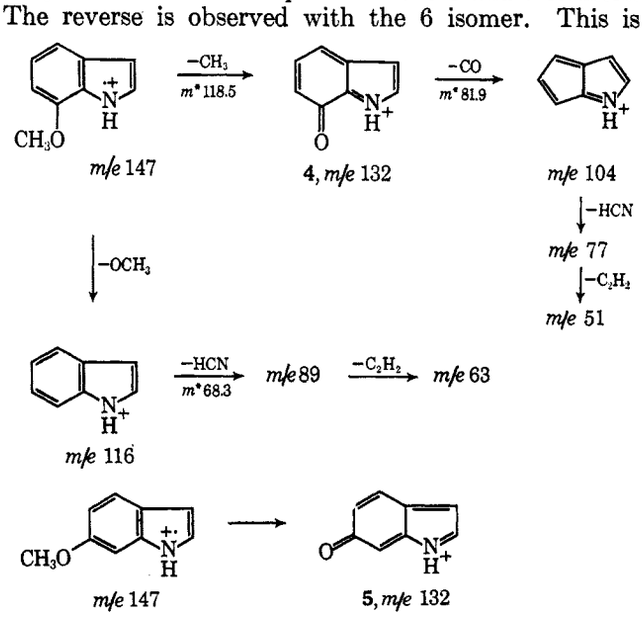
Methoxy- and Hydroxyindoles.—Indoles containing hydroxyl or methoxyl groups on the benzenoid ring are very widely distributed and important biological substances. Thus when we began an investigation of these compounds, we were quite interested in determining if mass spectrometry would be useful for locating the position of the methoxy or hydroxy substituent. The mass spectra of several methoxyindoles are listed in Table III. From an examination of the

TABLE III
MASS SPECTRA OF METHOXYINDOLES

m/e		5-OCH_3[a]	6-OCH_3[b]	7-OCH_3[c]
147, M^+		100	88	100
146, M − 1		6	7	...
132, M − CH_3		65	100	71
116, M − OCH_3		5	5	12
104		38	66	83
89		5	9	13
77		6	21	19
63		3	7	5
51		6	14	11
	Metastable	118.60	118.50	118.50
	peaks	147 → 132	147 → 132	147 → 132
		81.90	82.00	81.90
		132 → 104	132 → 104	132 → 104
		57.00	57.00	68.30
		104 → 77	104 → 77	111 → 89

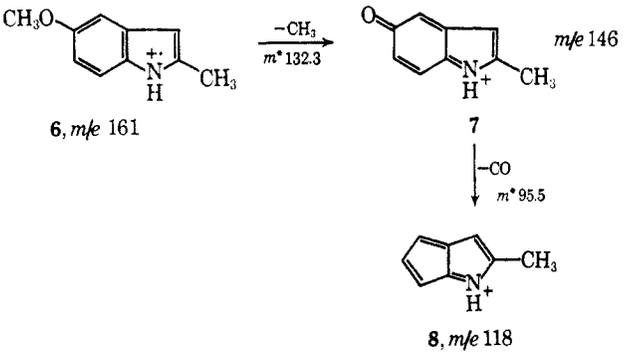
Registry numbers are as follows: [a] 1006-94-6; [b] 3189-13-7; [c] 3189-22-8.

data, it can be seen that 6-methoxyindole can readily be distinguished from either 5-methoxy- or 7-methoxyindole (the major fragmentation pathways are outlined below). The molecular ion is the most intense ion and the M − CH_3 ion is next in the spectra of the 5 and 7 isomers. The reverse is observed with the 6 isomer. This is

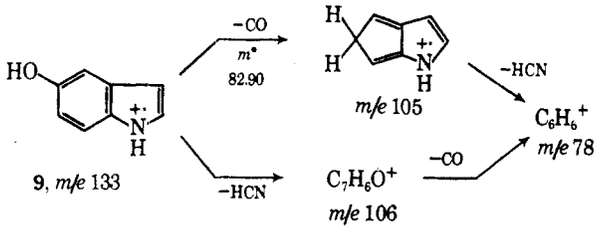


probably an electronic effect and is due either to a difference in stabilities of the M − CH_3 ions (**4** *vs.* **5**) or of the corresponding molecular ions.

The mass spectrum of 2-methyl-5-methoxyindole is reproduced in Figure 2. As would be predicted, the intensity of the molecular ion (**6**) is greater than that of the M − CH_3 ion (**7**). In this case, however, the base peak in the spectrum (*m/e* 118) is assigned a azapentalene structure **8**. The presence of ions due to loss of CH_3 and CH_3CN from **8** supported the azapentalene structure rather than a rearranged pyridinium structure.



The mass spectrum of 5-hydroxyindole (**9**) is reproduced in Figure 2. The fragmentation pathway is reproduced below.[11]



Indole Aldehydes and Ketones.—The mass spectra of five indole aldehydes are listed in Table IV.

TABLE IV

MASS SPECTRA OF INDOLE CARBOXALDEHYDES

m/e	3-CHO[a]	4-CHO[b]	5-CHO[c]	6-CHO[d]	7-CHO[e]
145, M^+	78	59	100	100	100
144, M − 1	100	100	87	82	61
117, M − CO	4	16	7	12	16
116, (M − 1) − CO	26	52	52	64	56
90, $C_7H_6^+$	5	13	6	5	13
89, $C_7H_5^+$	23	20	18	13	25
63, $C_5H_3^+$	4	10	8	6	8
Metastable peaks	93.50	93.50	93.40	93.40	93.40
	144 → 116	144 → 116	68.30	68.30	68.30
	68.20	68.30	44.60		
	116 → 89	116 → 89	89 → 63		

Registry numbers are as follows: [a] 487-89-8; [b] 1074-86-8; [c] 1196-69-6; [d] 1196-70-9; [e] 1074-88-0.

The fragmentation pathway is outlined as shown.

$$145\ (M^+) \xrightarrow{-H} 144 \xrightarrow{-CO} 116 \xrightarrow{-HCN} 89 \xrightarrow{-C_2H_2} 63$$

The spectra of the various isomers were very similar; the only major difference being the fact that the base peak in the spectra of 5-, 6-, and 7-aldehyde was the molecular ion while in the others it was the M − 1 peak.

The only ketone investigated, 3-benzoylindole, showed behavior characteristics of other diaryl ketones. The only intense peaks were due to the molecular ion (*m/e* 221), 3-indole CO^+ ion (*m/e* 144), and to the 3-indolyl radical ion (*m/e* 116).

After examining the spectra of several disubstituted indoles, we concluded that in most cases one of the substituents was preferentially directing the fragmentation of the molecule. For example, the spectrum of 5-methylindole-3-carboxyaldehyde is readily explained on the basis of the above fragmentation pathway showing that the formyl group is dominating the picture. On the other hand, the fragmentation of 5-methoxyindole-3-carboxyaldehyde is directed by the methoxyl group; the only influence of the formyl group being to produce a large M − 1 ion. In the case of nitrophenylindoles, most of the fragmentation took place at the nitro group. And clearly the methoxyl group rather than methyl was directing the fragmentation of 5-methoxy-2-methylindole. Thus the following scheme was set up which should be useful for predicting which substituent in a disubstituted indole will direct the fragmentation.

$$-CO_2H > CH_3O- > -CHO > CH_3$$

$$-NO_2 > C_6H_5- \text{ or } CH_3$$

$$-CO_2H > Cl$$

Indole Carboxylic Acids, Amides, Esters, and Nitriles.—The mass spectra of six indole carboxylic acids are listed in Table V. Several correlations can be made. The 2- and 3-carboxylic acid give very intense M − CO_2

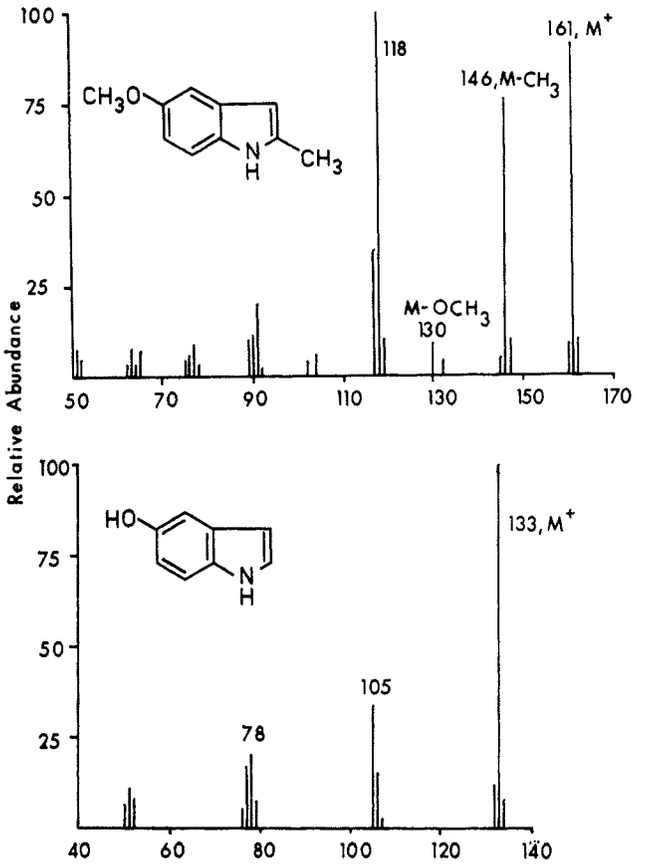


Figure 2.—Mass spectra of 5-methyl-2-methylindole and 5-hydroxyindole.

(11) G. Spiteller [*Advan. Heterocycl. Chem.* (1966)] discusses the mass spectra of heterocyclic compounds. This fragmentation pathway possesses many of the features which other hydroxy heterocyclic molecules exhibit.

TABLE V

MASS SPECTRA OF INDOLECARBOXYLIC ACIDS

m/e	2-CO_2H[a]	3-CO_2H[b]	4-CO_2H[c]	5-CO_2H[d]	6-CO_2H[e]	7-CO_2H[f]
161, M^+	49	86	100	100	68	100
144, M − OH	12	100	59	69	55	10
143, M − H_2O	92	...	...	...	...	76
117, M − CO_2	64	27	8	7	12	6
116, M − CO_2H	18	35	49	50	100	13
115, M − CO_2H_2	100	8	5	7	5	62
114	15	...	...	...	2	9
90	38	17	5	4	7	3
89	55	38	16	21	18	11
63	31	11	6	10	7	6
Metastable peaks		128.70	128.90	128.70		127.00
		161 → 144				161 → 143
						92.50
		93.60	93.60	93.40	93.50	143 → 115
		144 → 116	68.20	68.20	68.30	
			116 → 89			

Registry numbers are as follows: [a] 1477-50-5; [b] 771-50-6; [c] 2124-55-2; [d] 1670-81-1; [e] 1670-82-2; [f] 1670-83-3.

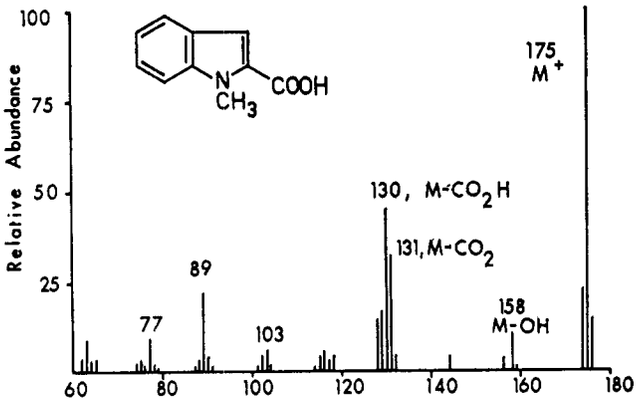
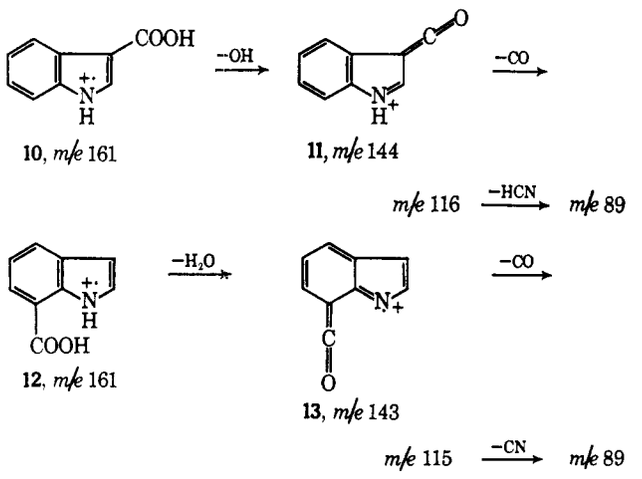


Figure 3.—Mass spectrum of 1-methylindole-2-carboxylic acid.

peaks. This is probably due to decarboxylation in the inlet system since both the 2- and the 3-carboxylic acid will undergo ready thermal decomposition.[12] The other acids are stable and show weaker M − CO_2 peaks. The 2- and 7-carboxylic acids (**12**) give intense ions (*e.g.*, **13**) due to loss of H_2O, while the others (*e.g.*, **10**) lose OH to give M − 17 ions (*e.g.*, **11**). This is an example of the "*ortho* effect."[13] The spectrum of 1-methylindole-2-carboxylic acid (Figure 3) shows no



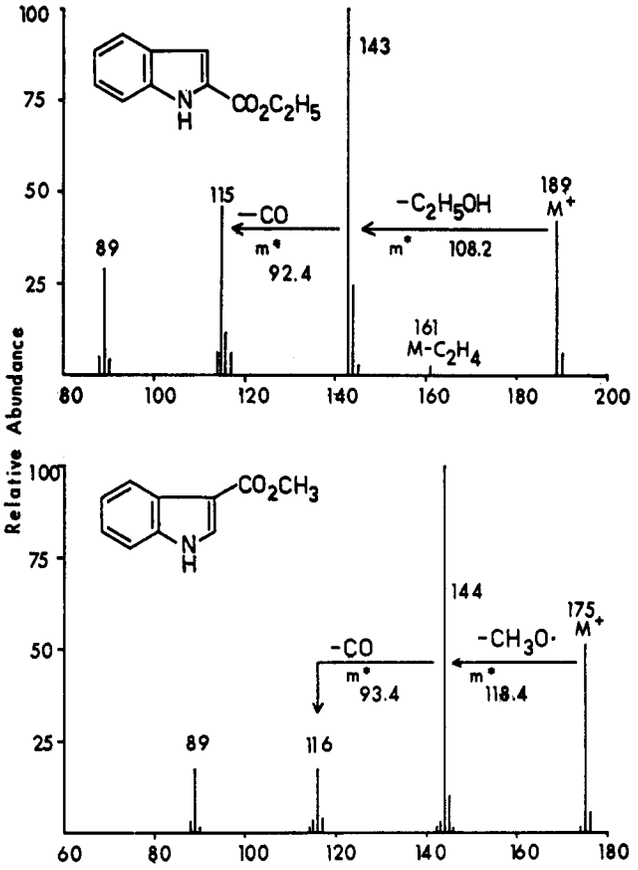


Figure 4.—Mass spectra of ethyl indole-2-carboxylate and methyl indole-3-carboxylate.

ortho effect and the fragmentation is analogous to that of **10**.

The mass spectra of indole amides (Table VI), esters (Figure 4), and nitriles (Table VII) offered very few surprises. The nitriles underwent fragmentation by successive loss of HCN. This is shown below.

$$M^+,\ m/e\ 142 \xrightarrow{-HCN} m/e\ 115 \xrightarrow{-HCN} m/e\ 88$$

The carboxamides either lost water to give an ion corresponding to the nitrile (*m/e* 142) or they lost NH_2 to give *m/e* 144 (*e.g.*, **11**). From this point fragmentation was similar to that of the corresponding acid or nitrile.

(12) T. S. Stevens in E. H. Rodd, "Chemistry of Carbon Compounds," Vol. IVa, Elsevier Publishing Co., New York, N. Y., 1957, p 96.

(13) F. W. McLafferty and R. S. Gohlke, *Anal. Chem.*, **31**, 2076 (1959).

TABLE VI

MASS SPECTRA OF INDOLECARBOXAMIDES

m/e	2-CONH$_2$[a]	3-CONH$_2$[b]	4-CONH$_2$[c]	5-CONH$_2$[d]	6-CONH$_2$[e]
160, M$^+$	80	20	41	5	100
144, M − NH$_2$	15	37	43	5	84
143, M − NH$_3$	100	13	12	12	5
142, M − H$_2$O	26	100	100	100	29
116	13	12	45	7	62
115	82	41	51	37	20
114	12	16	21	15	7
90	8	7	6	...	5
89	30	12	21	4	24
88	9	9	15	9	7
63	12	6	16	4	8
Metastable peaks	128.0	129.50	129.50	129.60	129.60
	160 → 144	160 → 144	113.60	113.60	160 → 144
	113.60	113.60	93.10	93.10	93.40
	142 → 115	142 → 115	142 → 115	142 → 115	
	93.50		67.30	67.30	144 → 116
	143 → 115	93.30	115 → 88	115 → 88	68.30
		142 → 115	68.28		116 → 89
		or 144 → 116	116 → 89		

Registry numbers are as follows: [a] 1670-84-4; [b] 1670-85-5; [c] 1670-86-6; [d] 1670-87-7; [e] 1670-88-8.

TABLE VII

MASS SPECTRA OF INDOLE NITRILES

m/e	4-CN[a]	5-CN[b]	6-CN[c]
142, M$^+$	100	100	100
115, M − HCN	48	48	26
114, M − H$_2$CN	20	21	11
88	14	14	5
87	6	6	2
63	6	7	3
62	7	7	2
Metastable peaks	93.10		
	142 → 115	93.20	93.10
	67.40		
	115 → 88		

Registry numbers are as follows: [a] 16136-52-0; [b] 15861-24-2; [c] 15861-36-6.

The 2-amide showed the "*ortho* effect" and lost NH_3 instead of NH_2. Indole 2- and 3-carboxylic esters can likewise be differentiated because of the *ortho* effect. The 3 ester loses alkoxide to give **17** while the 2-ester lost alcohol instead.[14]

The one anomalous feature of the spectra of indole carboxylic acid derivatives was the unusual behavior of the 6-substituted derivatives. The base peak in the spectrum of indole-6-carboxylic acid was the ion due to loss of CO_2H, while the molecular ion was the major peak in the spectrum of the other benzene ring substituted carboxylic acids. Since McLafferty has shown that the process

$$YC_6H_5COR^+ \longrightarrow YC_6H_5^+$$
$$R = H, \text{alkyl, aryl, OH, } OCH_3$$

is aided by electron-withdrawing substituents and hindered by electron-donating substituents,[15] the 6 position of the indole ring must possess less electron density in the molecular ion than the others. This relative deficiency of electron density at the 6 position of indole ring must also be responsible for the stabilization of the molecular ion of indole-6-carboxamide relative to M − H_2O ion. The exact opposite behavior is observed in the spectra of the other benzene ring substituted indolecarboxamides. The 6-cyanoindole shows considerable stability toward any fragmentation relative to the behavior of other indole nitriles. The behavior of the carboxylic acid derivatives substituted in the 6 position should be contrasted with that of indole-6-carboxylic acid and 6-methoxyindole where increased fragmentation is observed.

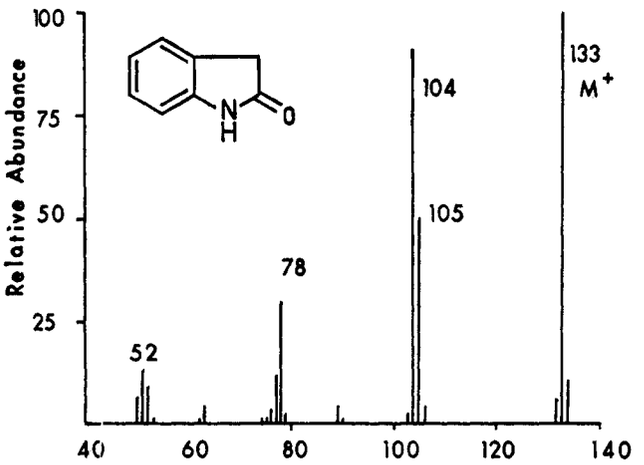
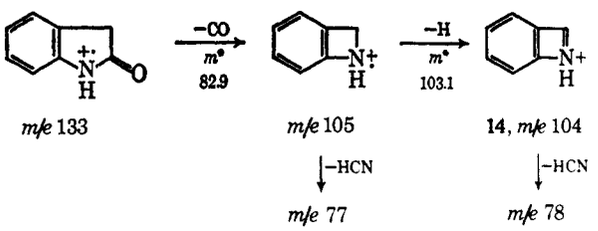


Figure 5.—Mass spectrum of oxindole.

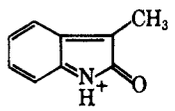
Oxindoles.—The mass spectrum of oxindole is shown in Figure 5. The fragmentation pathway is shown below.



The base peak in the spectrum of 3-chloro-3-methyloxindole corresponds to loss of chlorine (**15**). This loses CO to give a series of ions at *m/e* 118–116 corresponding to protonated, unprotonated, and dehydro-

(14) This behavior is also exhibited by benzindole and dihydrobenzindole carboxylic acids and esters: V. K. Pandit, H. J. Hofman, and H. O. Huisman, *Tetrahedron*, **20**, 1679 (1964).

(15) F. W. McLafferty, *Anal. Chem.*, **31**, 477 (1959).



15

indole ions. Surprisingly, the ion **15** also loses water to give $C_9H_6N^+$ (m^* 112.20).

The benzazetinium ion (**14**) is characteristic of oxindoles. It appears in the spectra of oxindole, 3-chloro-3-methyloxindole, and 3-oxindolyl cyanoacetic acid. This peak is shifted down to m/e 102 in the spectrum of 3,4-dichloro-3-methyloxindole owing to the ready loss of the ring chlorine in previous fragmentations. The spectrum of 2-(3-methyl-2-indolyl)-3-methyloxindole, on the other hand, lacks a peak due to this ion probably because heterolysis of the molecule results predominantly in charge retention with the indolic portion of the molecule.

In conclusion, it can be seen that the fragmentation of simple indoles is largely determined by the nature of the substituent. This fact should make mass spectrometry a valuable tool in the determination of both the nature and the location of substituents in the structure elucidation of naturally occurring indoles.

Experimental Section

The mass spectra were measured with an AEI MS-9 instrument using an ionization energy of 70 eV. The heated inlet system was used for the introduction of the deuterated indoles (source temperature 200°), methylindoles (210°), 1-phenylindole (200°), methoxyindoles (200°), 5-hydroxyindole (200°), and oxindole (200°). The direct inlet probe was used in the case of the arylindoles (180–200°) except for 1-phenylindole, indolecarboxaldehydes (190–210°), indolecarboxylic acids (200°), esters (200°), amides (190–220°), nitriles (200–220°), and oxindoles (190–220°) except for oxindole itself. Only the intense peaks in the spectra are listed in Tables I–VII. All metastable peaks discussed or listed are within ±0.2 of the calculated values. All intensities are reported relative to the base peak in the spectrum.

Chemical samples were either donated or were commercial samples of high purity. No indication of impurities was detected in the mass spectrum of any compound except 4-methylindole (Research Organic Chemicals, Sun Valley, Calif.). This was found to be a 60:40 mixture of two compounds. Pure 4-methylindole was obtained by chromatography and distillation of the mixture.

1-Deuterioindole.—A mixture of 100 mg of indole and 4.0 g of D_2O was heated in a stoppered test tube for 2 min. The indole liquefied and the mixture was vigorously shaken. Hexane (7 ml) was added and the mixture shaken. The hexane was removed with a pipet and filtered through 500 mg of anhydrous magnesium sulfate in a coarse sintered-glass filter into a stoppered flask. Upon cooling 20 mg of indole crystallized. This was about 40% d_1-indole. The mass spectrum was run after the instrument had been treated with D_2O for 10–12 times.

1,3-Dideuterioindole.—Indole-3-carboxylic acid (1.5 g) and 6 ml of D_2O were refluxed overnight. The D_2O was distilled off, fresh D_2O was added, and the process was repeated twice. The solid acid thus obtained was heated at 230° for 15–20 min. A dark oil was obtained which yielded pure indole upon distillation (88° at 0.5 mm). The infrared (CCl_4) indicated that the compound consisted of at least 60% N–D species.

The spectrum of 3-deuterioindole was obtained simply by running the sample in the instrument which had not been previously treated with D_2O. The deuterium on nitrogen is extremely labile and is easily lost before ionization.

Registry No.—3-Phenyl-2-methylindole, 4757-69-1; 5-methyl-2-phenylindole, 13228-36-9; 5-methyl-2-methylindole, 1196-79-8; 5-hydroxyindole, 1953-54-4; 1-methylindole-2-carboxylic acid, 16136-58-6; ethyl indole-2-carboxylate, 3770-50-1; methyl indole-3-carboxylate, 942-24-5; oxindole, 59-48-3.

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