Mass Spectral Fragmentation Patterns of 2-Methyl-, 3-Methyl-, 2,3-Dimethyl-, 2-Aryl- and 3-Phenylindole Derivatives

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The electron impact mass spectrometric fragmentation pathways for several 2-methyl-, 3-methyl-, 2,3-dimethyl-, 2-aryl- and 3-phenylindole derivatives were investigated. An interesting relationship between the substitution pattern in the framework of the indole derivatives and the fragmentation patterns was observed.

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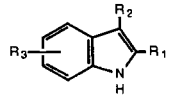
As it is known [1] by means of a photo-oxidation reaction it is possible to convert a methyl group into an ald ^{1}yde group when the methyl group is attached to the indole ring. In spite of the interest shown in the chemistry of these indole derivatives [1-3] their mass spectral fragmentation patterns have not been systematically studied. In connection with this we have focused our attention on the analysis of the electron impact mass spectra of these indole derivatives with special emphasis on the influence of the substituents. In the present paper we wish to report the mass spectral fragmentations of several indoles formulated in Scheme 1. The relative abundances of the ions are shown in the Tables I-V and the fragmentation pathways are discussed below.

Scheme 1



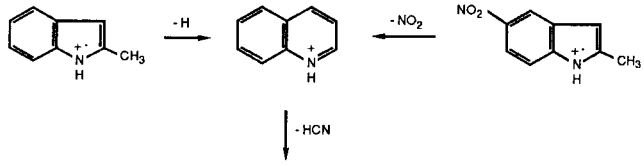
	R_1	R_2	R_3
1	Me	H	H
2	H	Me	H
3	Me	Me	H
4	Me	H	5-NO_2
5	Me	Me	4-NO_2
6	Me	Me	5-NO_2
7	Me	Me	6-NO_2
8	Me	Me	7-NO_2
9	Me	Me	5-Cl
10	H	Ph	H
11	Me	Ph	H
12	Me	Ph	4-NO_2
13	Me	Ph	5-NO_2
14	Me	Ph	6-NO_2
15	Me	Ph	7-NO_2
16	H	Ph	5-NO_2
17	Me	Ph	5-Cl
18	Ph	H	H
19	Ph	Me	H
20	Ph	Me	5-NO_2
21	Ph	Me	6-NO_2
22	Ph	Me	7-NO_2
23	p-Me-Ph	H	4-NO_2
24	m-NO_2-Ph	Me	H
25	Ph	Me	5-Cl
26	p-Cl-Ph	Me	H

Previously, Beynon [4,5] and Powers [6] described the spectra of compounds **1-3**, **10**, **11** and **18**. The spectra of these indoles have again been determined and the data are presented in the Tables I (**1-3**), III (**10**, **11**) and V (**18**).

I. Fragmentation Patterns of 2-Methyl-, 3-Methyl- and 2,3-Dimethylindole Derivatives (Scheme 1, Compounds **1-9**, Tables I and II).

The molecular ion is a very important peak, sometimes the base peak in the spectra of all the compounds listed in Tables I and II. Not including the (M-NO) and (M-NO_2) fragments the fragmentation pathways of **1** and **4** results are similar. The absence of significant (M-R_1) and (M-R_3-R_1) peaks in the mass spectrum of **4** as well as (M-R_1) peak in that of **1**, and the high abundance relative of the (M-R_3-HNC) ion (60%) in the mass specturm of **4** is a good evidence for the formation of an intermediate that could be represented as a quinolinium ion [7].

Scheme 2



The effect of introduction of a nitro group into the 5-, 6-or 7-position are surprisingly similar resulting in the diminishing of the relative abundance of the (M-1) ion and a fragmentation pattern from (M-NO_2) ion similar to that of the corresponding indole (Table II R_3 =NO_2: M-R_3-1, M-R_3-2, M-R_3-R_1, M-R_3-R_2, M-R_3-HNC peak).

Comparing the mass spectrum of **3** with the corresponding spectra of **6**, **7** and **8** we observed again that their fragmentation pathways are similar. As it was mentioned, loss of a methyl group from the parent ion of monomethylindole is very unlikely but is quite probably for dimethylindole [5]. So, the (M-R_1) ion is observed in the spectra of **3**, **6-8** and the (M-R_3-R_1) ion in those of **6**, **7** and **8**.

The absence of the (M-R) and the (M-R_3-R_1 or M-R_3-R_2) peak in the spectrum of **5** together with the formation of the (M-HO) (56%) and (M-R_3-1) fragments, being the latter the base peak, would agree with: a) the postulated rearrangement [5] involving the participation of a neighboring

Table I

Relative Abundance of Principal Fragments for 2-Methyl-, 3-Methyl- and 2,3-diMethylindole **1-3**

Compound No.	M	M-1	M-2	M-R_1	M-R_2	M-R_1-R_2	M-HNC	M-HNCR_1
1	90	100	15	—	100	—	18	—
2	87	100	18	100	—	—	16	—
3	100	99	30	78	78	16	7	12

Table II

Relative Abundance of Principal Fragments for Methyl-nitro- and Methyl-chloroindole Derivatives **4-9**

Compound No.	M	M-1	M-R (R_1,R_2)	M-HO	M-NO	M-R_3	M-R_3-1	M-R_3-2	M-R_3-R_1	M-R_3-R_2	M-R_3-R_1-R_2	M-R_3-HNC	M-R_3-NMCR_1
4	97	4	—	—	15	100	18	15	—	18	—	60	2
5	52	2	—	56	3	31	100	12	—	—	—	14	5
6	100	27	17	—	4	90	63	12	13	13	19	12	9
7	100	16	10	—	9	55	43	8	10	10	11	6	6
8	100	39	24	—	—	53	40	7	11	11	14	9	5
9	100 [a]	98	60 [b]	—	—	45	30	10	32	32	7	49	32

[a] (M + 1) (30%) and (M + 2) (32%). [b] (M-Me) m/e 164 (60%) and 166 (20%).

methyl group [9] for 2,3-dimethylindole and b) the spatial interaction of NO_2 and 3-methyl group, probably forming a six-membered transition state that accounts for the loss of the hydroxyl radical (M-HO) and the lack of the (M-Me) fragment.

Introduction of a Cl substituent into the 5 position results in a fragmentation pathway similar to that discussed for compounds **6**, **7** and **8** (see Table II, compound **9**).

All the spectra studied showed the characteristic fragments formed from aromatic molecules under electron impact: m/e 77, 65, 63 and 51 (relative abundances 5-30%).

II. Fragmentation Patterns of 3-Phenylindole Derivatives (Scheme 1, Compounds **10-17**, Tables III and IV).

Table III

Relative Abundance of Principle Fragments for 3-Phenyl- and 2-Methyl-3-phenylindole **10-11**

Compound No.	M	M-1	M-R_1	M-Ph	M-HNC	M-HNCR_1
10	100	12	12	—	23	5
11	100	58	—	27	18	16

Table IV

Relative Abundance of Principal Fragments for 3-Phenylindole Derivatives **12-17**

Compound No.	M	M-1	M-HO	M-NO	M-R_3	M-R_3-1	M-R_3-2	M-R_3-R_1	M-R_3-HNC	M-R_3-HNCR_1
12	100	2	64	10	22	62	76	8	39	15
13	100	4	—	2	32	9	16	10	14	7
14	100	22	—	8	22	7	12	22	10	4
15	100	16	—	5	25	6	8	15	18	6
16	100	3	—	1	39	17	9	17	52	16
17	100 [a]	41	—	—	10	22	34	—	16	17

[a] m/e 241 (100%), 242 (35%) and 243 (46%).

Table V

Relative Abundance of Principal Fragments for 2-Arylindole Derivatives **18-26**

Compound No.	M	M-1	M-R_1	M-HNC	M-HNCR_1	M-NO	M-NO_2	M-NO_2-1	M-NO_2-2	M-NO_2-R	M-NO_2-HNC	M-NO_2-HNCR
18	100	9	2	23	11	—	—	—	—	—	—	—
19	100	91	30	7	13	—	—	—	—	—	—	—
20	99	2	8	—	4	3	28	29	29	4 (R_1) 8 (R_2)	13	14 (R_1) 2 (R_2)
21	100	47	17	—	—	21	88	79	83	12 (R_1) 19 (R_2)	9	13 (R_1) 3 (R_2)
22	100	30	12	—	14	—	20	18	19	5 (R_1) 17 (R_2)	100	15 (R_1) 6 (R_2)
23	100	—	—	—	—	25	74	13	12	4 (R_1)	15	—
24	83	26	20	—	—	—	26	28	43	38 (R_1) 22 (R_2)	9	10 (R_1) 3 (R_2)
							M-Cl	M-Cl-1	M-Cl-2	M-Cl-R	M-Cl-HNC	M-Cl-HNCR
25	74 [1]	99	62 [2]	—	2	—	39	57	100	10 (R_1) 4 (R_2)	12	82 (R_1) 7 (R_2)
26	100 [3]	91	46	—	30	—	14	42	53	40 (R_1) 2 (R_2)	5	25 (R_1) 2 (R_2)

[1] m/e 244 (60%), 243 (69%), 242 (74%), 241 (74%) and 240 (99%). [2] m/e 166 (70%), 165 (11%) and 164 (62%). [3] m/e 243 (49%), 242 (59%), 241 (100%) and 240 (91%).

The molecular ion is the base peak in the spectra of all the 3-phenylindoles listed in Tables III and IV.

Consistent with the behavior of **10** (Table III), its 5-nitro derivative **16** (Table IV) does not undergo C-PH cleavage to yield the (M-Ph) and (M-R_3-Ph) ions. In both spectra the (M-HNC) (**10**) and the corresponding (M-R_3-HNC) ion (**16**) are the major cleavages upon electron impact.

We did not expect that the mass spectrum of **11** and its 4-, 5-, 6- and 7-nitro derivatives did not show similar fragmentation patterns (not including M-O, M-HO, M-NO and M-R_3 fragments). In spite of the fact that the (M-R_1) ion was not detected in the mass spectra of **11** and **12-15**, the (M-R_3-R_1) ion was formed from **12-15** under electron impact. Probably, in these compounds the presence of a nitro group would partially inhibit the formation of an intermediate quinolinium ion.

On the other hand, the (M-Ph) ion is detected in the mass spectrum of **11** but it is not observed (as M-Ph or M-R_3-Ph) in those of **12-16**.

A different pathway results in the loss of the 4-NO_2 substituent from **12** to give the (M-HO) ion and the (M-R_3-1) ion. As it has been previously proposed for **5** (Table II), a spatial interaction of the 4-NO_2 and the 3-Ph substituent would account for these fragments.

Finally, the introduction of a Cl into the 5 position of **17** (Table IV) results in the disappearance of the (M-R_3-R_1) ion together with the appearance of the (M-Ph) ion (17%). Not taking into account the fragments containing Cl, this spectrum resulted in one similar to that of the 2-methyl-3-phenylindole **11** (Table III).

In all the examples listed in Tables III and IV the m/e 77, 65, 63 and 51 ions were detected.

III. - Fragmentation Patterns of 2-Arylindole Derivatives (Scheme 1, Compounds **18-26**, Table V).

The molecular ion is the base peak or one of the most important fragments in the spectra of the 2-Arylindoles listed in Table V.

Loss of the (HNC) fragment from the molecular ion is the predominant fragment only in the spectrum of **18**. In all the others, the loss of the (R_1) and (HNCR_1) fragments (R_1 = Ph) occurs easily. The absence of the (M-R_2) peak in the mass spectrum of **19** would suggest the formation of a 2-arylquinolinium ion from the 2-phenyl-3-methylindole molecule upon electron impact. Introduction of a Cl or NO_2 group as a substituent results in the appearance of the (M-NO_2-R) (R_1 or R_2) and (M-NO_2-HNCR) (R_1 or R_2) ion simultaneously with the (M-NO_2-HNC) ion (correspondingly M-Cl-R, M-Cl-HNC and M-Cl-HNCR ion). This result suggests that both substituents would partially inhibit the formation of a quinolinium ion as the intermediate from compounds **20-22** and **24-26**.

In all the examples listed in Table V ions of m/e 77, 65, 63 and 51 were detected (5-22%).

In conclusion, 2-methyl- and 2,3-dimethylindoles show a

similar fragmentation pattern when NO_2 or Cl substituents are introduced into the 5-, 6- and 7-position. Introduction of the mentioned substituents in similar positions modify partially the fragmentation patterns of the 3-methylindoles. A special fragmentation is observed when 4-NO_2 and 3-methyl- or 3-phenyl-substituents are simultaneously present in the indole molecule. In all cases, the behavior of these indole derivatives upon electron impact in the mass spectrometer resulted much more complicated than that observed on uv irradiation [1,2].

Simultaneous introduction of a NO_2 and a Ph group as substituents in 2-methylindole results in an important modification of the fragmentation patterns (Tables III and IV).

EXPERIMENTAL

The mass spectra were recorded on a MS-Varian Mat CH-7A/Data System 166 at 15 and 70 eV. Data listed in Tables I-V were obtained at 70 eV. The samples were introduced by a direct inlet probe and were heated at 230°. Compound purity was checked by tlc and mp.

The indole derivatives employed in this work were prepared according to methods described in the literature [1, 10, 11]. Their mp, elemental analysis, uv and ^{1}H-nmr spectra have been previously reported, except in the cases indicated below.

2-Methyl-3-(*m*-nitrophenyl)indole (**24**).

This compound was obtained as yellow needles from ethanol, mp 153-154°; ^{1}H-nmr (DMSO): δ ppm 10.35 (1 H, s, NH), 8.52 (1 H, d, J = 2 Hz, H-11), 8.15 (2 H, m, H-13 and H-14), 7.87 (1 H, d, J = 8 Hz, H-15), 7.59 (1 H, dd, J = 8.5 and 2 Hz, H-7), 7.42 (1 H, dd, J = 8.5 and 2 Hz, H-4), 7.14 (2 H, m, H-5 and H-6) and 3.34 (3 H, s, CH_3).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.80; O, 12.69; N, 11.11. Found: C, 71.38; H, 4.75; O, 12.70; N, 11.17.

2-Methyl-3-(*p*-chlorophenyl)indole (**26**).

This compound was obtained as colourless prisms from ethanol, mp 168-170°; ^{1}H-nmr (DMSO): δ ppm 10.11 (1 H, s, NH), 7.22-7.80 (6 H, m, H-4, H-7, H-11, H-12, H-14 and H-15), 7.02 (2 H, m, H-5 and H-6) and 3.35 (3 H, s, CH_3).

Anal. Calcd. for $C_{15}H_{12}ClN$: C, 74.69; H, 4.79; N, 5.80; Cl, 14.72. Found: C, 74.65; H, 4.80; N, 5.73; Cl, 14.82.

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