INVESTIGATION OF THE MASS-SPECTROMETRIC FRAGMENTATION OF SOME ISOINDOLE DERIVATIVES

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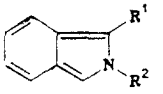
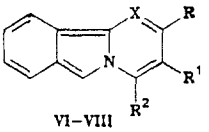
UDC 547.759.3:543.51

The results of a mass-spectrometric investigation of isoindole derivatives have made it possible to ascertain specific pathways in their fragmentation that differ from those for analogous indole derivatives and to also confirm the previously advanced concept regarding the structures of isoindoles, which have a complete 10π-electron system with substantial interannular conjugation.

A number of isoindole derivatives have high biological activity [1, 2]. Mass spectrometry and chromatographic mass spectrometry have recently begun to be used extensively to identify physiologically active compounds in natural substances; this, in turn, requires a knowledge of the character of the fragmentation of these substances under electron impact [3, 4]. At the same time, as already noted in [1], the mass-spectral behavior of isoindole derivatives has been studied extremely inadequately. This compelled us to examine the principal fragmentation pathways of isoindoles I-VIII, the synthesis of which was described in [5-10].



I-V



VI-VIII

I R^1=H, R^2=Me; II R^1=H, R^2=Ph; III R^1=H, R^2=C_6H_4—OCH_3-p; IV R^1=$N(CH_3)_2$, R^2=Ph; V R^1=$N(CH_3)_2$, R^2=C_6H_4—OCH_3-p; VI X=CH, R=R^1=R^2=H; VII X=N, R=R^2=CH_3, R^1=H; VIII X=N, R=OMe, R^1+R^2=(—CH_2—)$_3$

TABLE 1. Mass Spectra of I-VIII*

Compound	m/z(I_{rel}, %)
I	131 (100), 130 (50), 116 (32), 103 (15), 90 (27), 89 (36), 77 (11), 66 (13), 63 (18), 62 (8), 51 (9)
II	193 (93), 192 (16), 166 (42), 165 (100), 91 (10), 90 (50), 89 (46), 77 (36), 63 (14), 51 (36), 50 (11)
III	223 (100), 208 (85), 180 (32), 152 (27), 90 (21), 89 (35), 77 (35), 76 (22), 63 (20), 51 (30), 50 (20)
IV	236 (94), 235 (10), 222 (18), 221 (100), 193 (27), 159 (10), 118 (30), 91 (12), 89 (12), 77 (41), 51 (20)
V	266 (91), 265 (10), 251 (100), 236 (12), 223 (12), 208 (14), 143 (10), 133 (22), 121 (12), 118 (36), 77 (11)
VI	167 (100), 166 (20), 165 (5), 140 (10), 139 (15), 89 (3), 83 (15), 82 (3), 71 (4), 70 (3), 63 (5)
VII	196 (100), 195 (32), 181 (6), 154 (9), 129 (5), 127 (4), 115 (9), 114 (4), 98 (8), 67 (4), 65 (5)
VIII	238 (100), 224 (9), 223 (54), 195 (7), 140 (5), 130 (5), 129 (6), 119 (11), 116 (6), 67 (6), 65 (10)

*The M^+ peak and the 10 most intense peaks are presented.

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 0009-3122/91/2707-0732$12.50

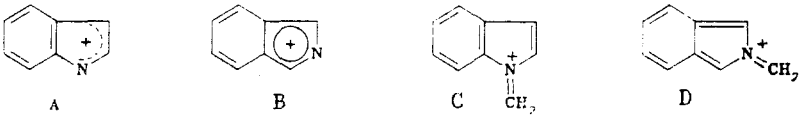
TABLE 2. Ratios of the Intensities of Some Peaks of the Characteristic Ions in the Mass Spectra of Comparable Compounds

Compound	W_{M^+}*1	$[M-H]^+/M^+$	$[M-CH_3]^+/M^+$	$[M-H_2CN]/M^+$	$[M-CH_3CN]^+/M^3$
N-Methylisoindole	27,6	0,50	0,32	0,29	0,36
N-Methylindole	—	0,83	0,11	0,20	0,22
N-Phenylisoindole	18,0	0,14	—	0,84	0,42*2 0,39*3
N-Phenylindole	—	0,12	—	0,17	0,12*2
N-(p-anisyl)isoindole	23,7	0,04	—	—	0,11*3 0,15*2 0,25*3
Pyrido[2,1-a]isoindole	42,5	0,19	—	0,19	—
Carbazole	37,8	0,14	—	0,10	—
2,4-Dimethylpyrimido[2,1-a]isoindole	33,7	0,32	0,06	0,09	0,02*4
2,4-Dimethylpyrimido[1,2-a]indole	27,8	0,15	—	0,03	—

*Percentage (%) of M^+ in the total ion current.
**The $[M - C_6H_5CN]^+$ or $[M - MeOC_6H_4CN]^+$ ion, respectively.
***The $[M - ArCHN]^+$ ion.
****The $[M - CH_3CNH]^+$ ion.

It follows from the mass-spectral data (Table 1) that the molecular ion (M^+) of N-methylisoindole (I) has the highest intensity; the peaks of the other ions formed in the fragmentation do not exceed 50% of the intensity of the M^+ peak. The general form of the spectrum, which is customary for aromatic compounds, confirms our previously advanced (on the basis of calculated data) concept regarding the electron structure of isoindole [11], with allowance for which, the latter should be conceived of as a complete 10π-electron system with substantial interannular conjugation. Significant π bonding through the nitrogen atom in isoindole I is proved by the fact that the introduction of a phenyl substituent into the 2 position (II) leads to a decrease in the intensity of M^+ to 93% in view of the competitive conjugation of the free electron pair of the nitrogen atom with the phenyl ring. This sort of competition is manifested to a lesser extent in N-(p-anisyl)isoindole (III); this is predetermined by the positive mesomeric effect of the methoxy group. This conclusion is also in agreement with the data in Table 2, from which it follows that the contribution of M^+ to the overall ion current decreases on passing from isoindole I to III to a lesser extent than on passing from I to II.

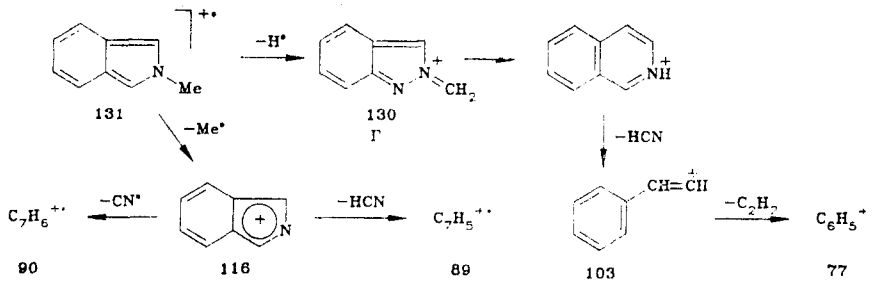
A comparison of the mass-spectrometric fragmentation of N-methylindole [12, 13] with the isomeric isoindole I may also served as a confirmation of our concept regarding the electron structure [11]. According to the data in Table 2, the stability of ion **A** is lower than the stability of ion **B** (see the $[M - CH_3]^+/M^+$ values), which indicates greater interannular conjugation in the isoindole system.



A B C D

However, the intensity of the $[M - H]^+$ ion peak is considerably higher in the case of N-methylindole as compared with I (see Table 2), since we are dealing here with completely different sorts of systems (**C** and **D**), within the limits of which π bonding through the nitrogen atom is excluded. In this case ion **D** loses the advantages

Scheme 1

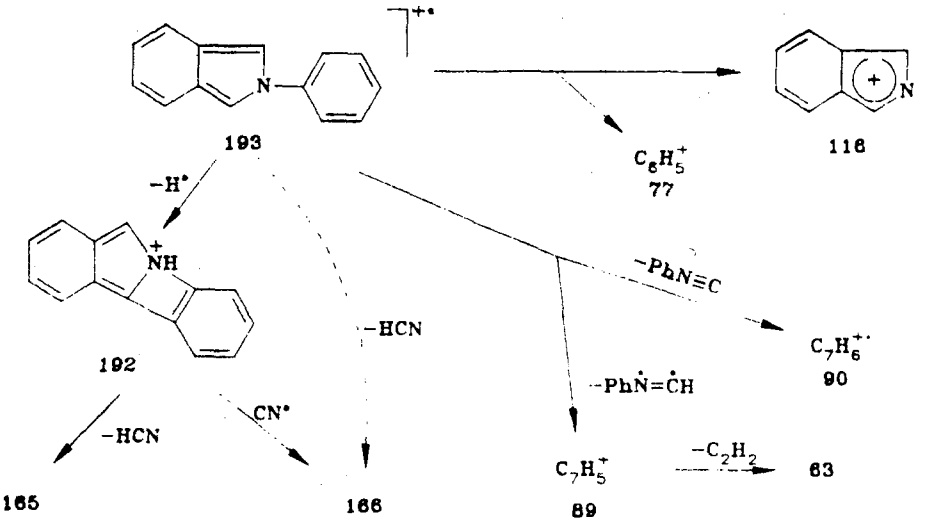


of isoindole as a complete 10π-electron system and is actually an open polyene, while ion C remains aromatic (in view of the aromatic character of the benzene ring), which also determines to a greater extent the stability of the indole system as a whole [11].

The hypothetical structures of the ions formed in the fragmentation of N-methylisoindole are presented in Scheme 1. Just as one assumes rearrangement to quinolines for N-substituted indoles, in the case of isoindole I one may assume the conversion of the ion with mass 130 to an isoquinolinium cation.

The mass spectra of the 2-arylisoindoles, like the spectrum of N-methylisoindole (I), indicate low relative intensity of the $[M - H]^+$ ion, although in this case localization of the positive charge on the nitrogen atom proves to be just as unfavorable as for N-phenylindole [14] (see Table 2), possibly because of the formation of an energically strained four-membered ring (see Scheme 2).

Scheme 2

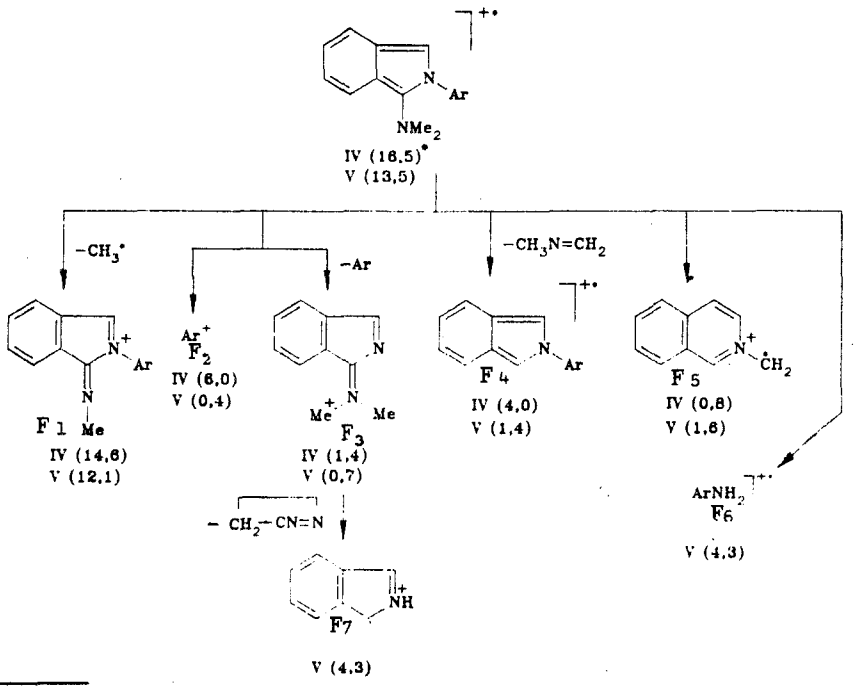


The intensity of ion **B** in the spectrum of II is comparable to that observed for I. The introduction of a methoxy group into the para position of the benzene ring leads to intensive fragmentation, which makes it possible to assume that rearrangement t give a seven-membered ring occurs after splitting out of a molecule of CO from the ion with mass 208. The structures of the principal fragments recorded in the spectra of the 2-arylisoindoles are proposed in Schemes 2 and 3.

The introduction of a dimethylamino group (to give IV and V) into 2-phenylisoindole (W_M = 18) and 2-(p-methoxyphenyl)isoindole (W_M = 23.7) decreases the stabilities of the molecules with respect to electron impact (W_M = 16.5 and 13.5, respectively). Despite the difference in the structure of the aryl fragment in the 1-dimethylaminoisoindoles, the general character of fragmentation, which involves first and foremost with the intensive loss of a methyl group (ion F_1), splitting out of an aryl substituent (ions F_2 and F_3), and the elimination of a molecule of N-methylmethylenimine (F_4), which is characteristic for dimethylamino azines [15, 16], is retained. It is also interesting that ion F_3 then eliminates a C_2H_3N fragment to give a fragment of the protonated isoindole type (see Scheme 3: F_7, m/z 118). Also unusual is the loss by the molecular ions of IV and V of an arylamine molecule (see ions F_5 and F_6), which evidently occurs with the participation of a hydrogen atom of the dimethylamino group. Processes of this sort have not been noted in the mass spectra of nitrogen heterocycles that contain an amidine fragment [3]. Let us note that the overall intensities of the M^+ and ion F_1-F_6 peaks in the spectra of 2-aryl-1-dimethylaminoisoindoles range from 36% to 49%, which indicates the rather high selectivity of the fragmentation of these compounds (see scheme below).

The investigation of the fragmentation of the M^+ ions of condensed isoindoles VI-VIII indicates the aromatic character of these compounds (see Table 1). A comparison of the mass spectra of pyrido[2,1-*a*]isoindole VI and carbazole [17] and 2,4-dimethylpyrimido[2,1-*a*]isoindole VII and 5,7-dimethylpyrimido[3,4-*a*]indole [18] (see Table

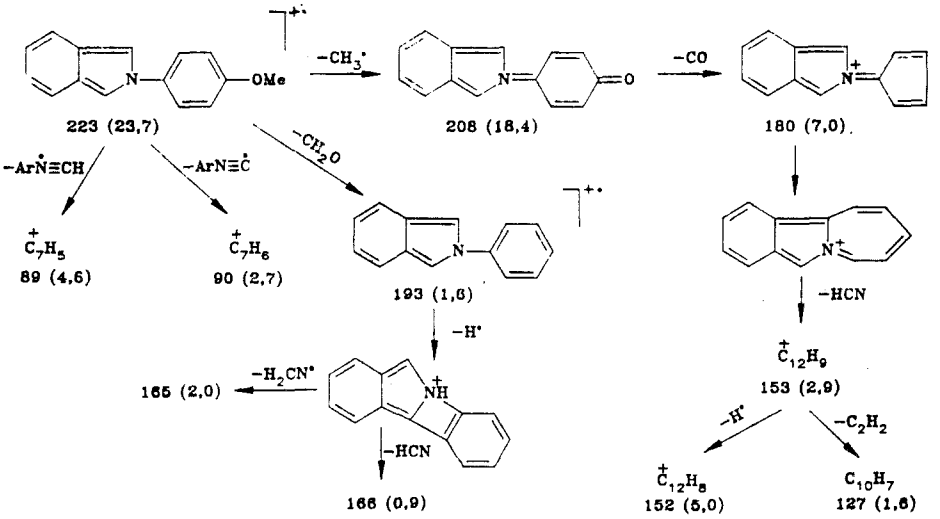
Scheme 3



*Here and in Scheme 4, the intensities of the ion peaks in percent relative to the total ion current are presented in parentheses.

2) illustrates the resistance of isoindole systems to electron impact. This is in good agreement with our previous conclusions (drawn on the basis of calculated data) regarding the possibility of conceiving of VI and VII in the form of 14π-electron aromatic systems with significant interannular conjugation [9]. The stability of the M^+ ion of VI is higher than for all of the other examined isoindoles and their positional isomers (see Table 2). It is interesting that pyrido[2,1-*a*]isoindole, which we isolated in pure form [9], is actually stable and can be stored for a long time at room temperature (which is uncharacteristic for the simplest isoindoles). The introduction of a polymethine chain and an alkoxy group (to give VIII) into the pyrimidine part of the pyrimidoisoindole molecule leads to a certain degree of destabilization of the M^+ ion and a sharp increase in the intensity of the $[M - CH_3]^+$ ion peak. The M^+ ion then eliminates a molecule of CO, which proves the retention of a trimethylene ring in the resulting ion. It should also be noted that the ejection of a hydrogen atom is uncharacteristic for this compound.

Scheme 4



Thus our analysis of the mass spectra of isoindole derivatives has made it possible to ascertain the specific pathways of their mass-spectrometric fragmentation, which differs from that observed for the analogous indole derivatives, and also to confirm the previously advanced concept of the structure of isoindoles.

EXPERIMENTAL

The mass spectra of I-VIII were recorded with an LCB-2091 spectrometer by direct introduction of the samples into the ion source at 70 eV and vaporization temperatures 10-20°C below their melting points.

N-Methylisoindole (I). This compound, with mp 90-91°C (mp 90°C [6]), was obtained by the method in [5].

N-Arylisoindoles II and III. These compounds, with mp 143-144°C and 177-178°C (mp 143-144°C [7] for II and 178°C [7] for III), respectively, were obtained b y the method in [7].

2-Aryl-1-dimethylaminoisoindoles IV and V. These compounds, with mp 89°C and 117-118°C (mp 88-90°C for IV [8] and 135-138°C for V [8]), respectively, were obtained by the method in [8].

Pyrido[2,1-*a*]isoindole. This compound, with mp 121°C (mp 121°C [9]), was obtained by the method in [9].

2,4-Dimethylpyrimido[2,1-*a*]isoindole. This compound, with mp 95-97°C (mp 95-97°C [10]), was obtained by the method in [10].

2-Methoxy-3,4-trimethylene-5H-pyrimido[2,1-*a*]isoindolium Tosylate ($C_{22}H_{22}N_2SO_4$). This compound was obtained by the method in [19]. A 1-g (4 mmole) sample of 3,4-trimethylenepyrimido[2,1-*a*]isoindol-2-one, with mp 292-295°C (mp 292-295°C [19]), was fused with 2 g (10 mmole) of methyl p-toluenesulfonate, and the reaction mixture was heated for 2 h at 100°C. It was then diluted with acetone, and the resulting precipitate was removed by filtration and purified by crystallization from water to give 1.2 g (66%) of a product with mp 174-176°C.

2-Methoxy-3,4-trimethylenepyrimido[2,1-*a*]isoindole ($C_{15}H_{14}N_2O$). A 1-g (2 mmole) sample of the corresponding tosylate was mixed with 0.32 g (8 mmole) of ground sodium hydroxide, and the reaction mixture was placed in a vacuum sublimator. Sublimation was carried out at 175°C and 1.33 hPa to give 0.4 g (69%) of a yellow crystalline substance. Resublimation gave a substance with mp 109°C.

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