# INVESTIGATION OF THE BEHAVIOR OF SUBSTITUTED BENZIMIDAZOLES UNDER THE INFLUENCE OF ELECTRON IMPACT

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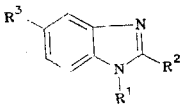
The mass spectra of eight benzimidazole derivatives were studied. The effect of the nature and position of the substituent on the principal pathways of the fragmentation of the molecular ion, which involve competitive detachment of an HCN particle and the substituent, was examined. The formation of rearranged ions in all cases was confirmed by metastable transitions.

The wide range of application of various benzimidazole derivatives explains the increased interest of chemists specializing in synthesis in this class of compounds. The utilization of benzimidazoles for the identification of aliphatic acids [1, 2], for the synthesis of dyes and medicinal preparations, as biologically active substances [3], and in a number of other fields is well known. Principal attention is being directed to polymers that contain benzimidazole fragments in the chain [4].

The goal of the present research was to study the behavior under electron impact of benzimidazole derivatives I-VIII, which are used as monomers [4]. Relatively little study has been devoted to the mass-spectrometric fragmentation of the indicated compounds, although the search for methods for the preparation of the most diverse derivatives of benzimidazole is continuing at an extremely intensive level.



I-VIII

I $R^1=C_6H_5$; II $R^2=C_6H_5$; III $R^1=D$, $R^2=C_6H_5$; IV $R^1=CH_3$, $R^2=C_6H_5$; V $R^1=CH_3$, $R^2=C_6H_4NO_2$; VI $R^1=CH_3$, $R^2=Cl$; VII $R^1=CH_3$, $R^2=Br$; VIII $R^3=NO_2$*

With the exception of II, the mass spectrum of which has been published [5], all of the indicated benzimidazoles have been investigated for the first time. The mass spectra are presented in Table 1, and the relative intensities of the principal fragment ions are presented in Table 2.

It follows from Table 2 that, owing to their aromatic character, the benzimidazoles that we investigated have rather high (although lower as compared with the methyl derivatives [6, 7]) stabilities with respect to electron impact ($W_M$) and that the maximum peaks in the mass spectra of I-VIII (for the indicated variations of the ionization energies) are the molecular-ion peaks ($M^+$). A decrease in $W_M$ is observed for V and VIII (Table 2); this is characteristic for nitro-substituted aromatic compounds [8].

In contrast to alkylbenzimidazoles [5-7, 9, 10], relatively intense $[M + H]^+$ ion peaks are present in the mass spectra of all of the investigated compounds (Table 2). The formation of protonated $M^+$ ions is evidently associated with an ion-molecular interaction, which is also manifested when the ionizing-electron energy is decreased. The probability of the occurrence of this process is lower for halo-substituted compounds. The ratio of the intensities of the

*The positions of the substituting groups are indicated; the remaining positions of the rings are occupied by hydrogen atoms.

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TABLE 1. Mass Spectra of the Investigated Compounds*

| Compound | m/z values (relative intensities of the ion peaks in percent of the maximum peak) |
|---|---|
| 1-Phenylbenzimidazole (I) | 50 (19), 51 (34), 52 (15), 63 (28), 64 (27), 65 (17), 66 (33), 75 (11), 76 (12), 77 (39), 78 (7), 89 (9), 90 (24), 91 (36), 92 (5), 115 (6), 117 (6), 118 (56), 119 (20), 129 (8), 131 (5), 132 (10), 139 (24), 140 (22), 164 (6), 165 (7), 166 (82), 167 (30), 168 (24), 191 (3), 192 (24), 193 (61), 194 (100), 195 (41) |
| 1-Methyl-2-phenylbenzimidazole (IV) | 50 (20), 51 (32), 52 (17), 55 (17), 56 (7), 57 (15), 63 (29), 64 (22), 65 (15), 66 (11), 67 (10), 75 (18), 76 (26), 77 (45), 78 (28), 79 (11), 89 (11), 90 (27), 91 (19), 97 (8), 102 (23), 103 (30), 104 (41), 105 (15), 129 (32), 130 (8), 131 (32), 132 (27), 151 (7), 152 (14), 153 (5), 165 (18), 166 (37), 167 (12), 168 (16), 179 (8), 180 (14), 192 (9), 193 (5), 194 (10), 205 (23), 206 (23), 207 (94), 208 (100), 209 (34) |
| 1-Methyl-2-(p-nitrophenyl) benzimidazole (V) | 51 (23), 55 (27), 56 (18), 57 (35), 65 (33), 69 (36), 70 (23), 71 (33), 73 (40), 76 (17), 77 (65), 78 (42), 79 (21), 81 (33), 82 (25), 83 (37), 84 (25), 85 (30), 90 (33), 91 (45), 92 (33), 93 (19), 96 (24), 97 (38), 98 (26), 102 (33), 103 (32), 104 (49), 105 (27), 116 (27), 117 (28), 118 (39), 119 (22), 123 (43), 129 (45), 130 (12), 131 (86), 132 (38), 143 (24), 144 (23), 145 (85), 146 (95), 147 (44), 149 (32), 150 (18), 152 (18), 153 (12), 156 (22), 157 (15), 164 (9), 165 (12), 166 (11), 167 (13), 168 (23), 169 (12), 178 (25), 179 (38), 180 (33), 185 (28), 191 (15), 192 (44), 193 (25), 194 (22), 195 (38), 205 (80), 206 (93), 207 (79), 208 (38), 221 (13), 222 (60), 223 (59), 224 (20), 236 (32), 237 (12), 251 (10), 252 (75), 253 (100), 254 (37) |
| 1-Methyl-2-chlorobenzimidazole (VI) | 50 (9), 51 (24), 52 (8), 63 (26), 64 (21), 65 (10), 66 (6), 76 (18), 77 (42), 78 (17), 90 (42), 91 (6), 102 (24), 103 (18), 104 (32), 105 (7), 129 (48), 130 (18), 131 (45), 132 (53), 133 (7), 138 (5), 152 (13), 164 (7), 165 (70), 166 (100), 167 (60), 168 (77), 169 (13) |
| 1-Methyl-5-bromobenzimidazole (VII) | 50 (21), 51 (23), 52 (25), 62 (26), 63 (34), 64 (19), 65 (20), 66 (16), 74 (22), 75 (31), 76 (29), 77 (31), 78 (15), 88 (23), 89 (18), 90 (23), 102 (16), 103 (25), 104 (38), 105 (31), 106 (24), 116 (31), 117 (8), 129 (8), 130 (33), 131 (48), 132 (36), 133 (5), 155 (16), 156 (8), 157 (15), 158 (6), 168 (20), 182 (37), 183 (9), 184 (6), 185 (7), 208 (9), 209 (78), 210 (100), 211 (87), 212 (95), 213 (28) |
| 5-Nitrobenzimidazole (VIII) | 51 (14), 52 (15), 57 (12), 60 (11), 62 (13), 63 (49), 64 (21), 65 (8), 77 (13), 78 (23), 79 (13), 80 (11), 81 (6), 89 (15), 90 (70), 95 (5), 97 (9), 105 (47), 106 (22), 116 (18), 117 (67), 118 (23), 125 (21), 133 (68), 134 (23), 162 (6), 163 (100), 164 (28) |

*The peaks of ions with intensities ≥5% of the maximum peak in the spectra are presented.

TABLE 2. Stabilities of the Molecular Ions ($W_M$) and Relative Intensities (in percent of the total current) of the Principal Characteristic Ions in the Mass Spectra of I-VIII at an Ionizing-Electron Energy of 50 eV

| Ion | Compound | | | | | | |
|---|---|---|---|---|---|---|---|
| | I | II | IV | V | VI | VII | VIII |
| $M^+$ ($W_M$) | 13,3 | 18,6 | 13,9 | 2,1 | 18,0 | 18,0 | 9,6 |
| $[M+H]^+$ | 4,0 | 6,0 | 2,3 | 1,0 | 1,3 | 2,0 | 2,7 |
| $[M-H]^+$ | 5,8 | 16,4 | 6,5 | 2,0 | 7,0 | 5,1 | 0,6 |
| $[M-H_2]^+$ | 2,3 | 5,8 | 3,9 | 0,3 | 0,7 | 0,6 | — |
| $[M-H_3]^+$ | 0,2 | 1,6 | 1,5 | — | — | — | — |
| $[M-CN]^+$ | 2,3 | 0,6 | — | — | — | 0,4 | — |
| $[M-HCN]^+$ | 2,8 | 2,3 | — | — | — | 0,6 | — |
| $[M-H_2CN]^+$ | 7,8 | 3,4 | 0,9 | — | — | 2,4 | — |
| $[M-H_3CN]^+$ | 0,7 | 1,3 | 0,5 | — | — | — | — |
| $[M-R_1]^+$ | 0,6 | — | — | — | — | — | — |
| $[M-R_1, -CN]^+$ | 0,9 | — | — | — | — | — | — |
| $[M-R_1, -HCN]^+$ | 4,0 | — | — | — | — | — | — |
| $[M-R_2]^+$ | — | 0,2 | 2,1 | 2,3 | 4,6 | — | — |
| $[M-R_2, -CN]^+$ | — | 3,8 | 1,0 | 0,7 | 0,8 | — | — |
| $[M-R_2, -HCN]^+$ | — | 1,0 | 2,7 | 1,3 | 3,2 | — | — |
| $[M-R_3]^+$ | — | — | — | — | — | 3,2 | 6,4 |
| $[M-R_3, -HCN]^+$ | — | — | — | — | — | 2,5 | 6,8 |

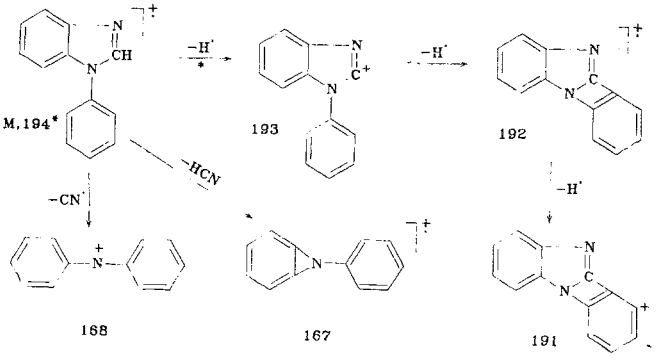
$[M + H]^+$ and $M^+$ ion peaks for benzimidazoles VI and VII is, on the average, 0.2, whereas it ranges from 0.4 to 0.3 for I-V and VIII.

The dissociative ionization of the investigated benzimidazoles is characterized by the successive detachment of two (V-VIII) and three (I-IV) hydrogen atoms from $M^+$; these processes

are not observed in the case of alkylbenzimidazoles [5-7, 9, 10]. In the case of I and II the indicated processes may evidently be due to the elimination of hydrogen atoms of the phenyl substituent. In addition to $[M - D]^+$ ions, peaks of $[M - DH]^+$ and $[M - DH_2]^+$ ions are present in the mass spectrum of deuterium-labeled III. This makes it possible to assume that stabilization of the $[M - H]^+$ and $[M - H_2]^+$ ions due to cyclization of the carbon atoms of the substituent and the nitrogen atom of the imidazole ring is possible for phenylbenzimidazoles I and II (see the scheme).

In the case of IV-VIII (with a methyl group in the 1 position) the formation of $[M - H]^+$ and $[M - H_2]^+$ ions is associated with a rearrangement process due to expansion of one of the condensed rings [7, 9]. The presence in the molecule of an electron-acceptor $NO_2$ group (V and VIII) or a halogen atom (VI and VII) decreases the relative intensities of the indicated ion peaks, but the rearrangement process noted above is always confirmed by metastable transitions.

Scheme




The principal pathway in the fragmentation of the $M^+$ ions of the compounds that we investigated involves the occurrence of two competitive processes that are absent in the fragmentation of alkylbenzimidazoles [5-7, 9, 10]. These processes are the detachment of a molecule of HCN and substituent $R^1$ (for I), $R^2$ (for II-VI), or $R^3$ (for VII and VIII). The probability of one or another process depends on the nature and position of the substituents. Thus in the case of derivatives I and II opening of the imidazole ring, which is responsible for the formation of $[M - HCN]^+$ ions, is realized with a much higher (by a factor of almost four) probability than splitting out of a phenyl group. The introduction of a methyl group into the 1 position of the molecule (IV-VII) suppresses the elimination of an HCN particle and promotes the loss of substituent $R^2$ by the molecular ion. This leads in all cases to a rearrangement process involving expansion of the imidazole ring to a six-membered ring [7, 9]; this process is confirmed by metastable ions and also (indirectly) by the fact that $[M - CH_3]^+$ fragment ions are absent in the mass spectra of IV-VII.

An examination of the data in Table 2 leads to the conclusion that opening of the imidazole ring for I-III plays an extremely important role in the subsequent stages of the decomposition of the rearranged ions, which involve splitting out of the corresponding substituent; competitive detachment of CN and HCN particles is characteristic for I-VI. In the case of derivatives VII and VIII elimination of only HCN is observed, just as in the case of alkylbenzimidazoles [5-7, 9, 10]. When the ionizing-electron energy is decreased to 12 eV, the probability of splitting out of the indicated particles from both $M^+$ and from the principal rearranged ions decreases, and this constitutes evidence for the high-energy character of this process.

It must be emphasized that the low $W_M$ values noted above for V and VIII are a consequence of the favorable (for these benzimidazoles) nitro-nitrite rearrangement [8]. As a result of this, a nitroso group is split out from $M^+$. This process is accompanied by a metastable ion with an apparent mass of 108.5. The subsequent fragmentation of the $[M - NO_2]^+$ ions involves the preferred splitting out of HCN.

Thus the dissociative ionization of the compounds that we investigated is determined by the nature and position of the substituent in the benzimidazole ring and is accompanied by the development of additional fragmentation pathways that are not observed for alkylbenzimidazoles.

*The numbers under the formulas are the m/z values.

These pathways are the successive detachment from $M^+$ of two or three hydrogen atoms in the case of compounds with functional or hydrocarbon substituents. In addition, competitive splitting out of HCN and a substituent from $M^+$, as well as CN and HCN particles from the principal rearranged ions, is observed.

## EXPERIMENTAL

The mass spectra of I-VIII were obtained with an MKh-1303 spectrometer with a system for direct introduction of the samples into the ion source at ionizing-electron energies of 50 and 12 eV, a cathode emission current of 1.5 mA, an accelerating voltage of 2 kV, and a vaporization temperature of 140-160°C. The benzimidazoles were obtained by the methods in [4, 11]. 2-Phenylbenzimidazole with a deuterium label at the nitrogen atom was obtained by the method in [12]. The degree of exchange determined by mass spectrometry was 50%.

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# REACTION OF CYCLIC THIOUREAS WITH CHLOROACYLPIPERAZINES


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S-Alkylation products are formed in the reaction of tetrahydropyrimidine-2-thione and hexahydro-1,3-diazepine-2-thione with chloroacylpiperazines in dimethylformamide at room temperature; dihydrothiazolo[3,2-a]pyrimidine and tetrahydrothiazolo[3,2-a]-[1,3]diazepine systems are obtained in refluxing ethanol. It is shown that the S-alkyl derivatives are very readily converted to condensed systems.


In a continuation of our research on the synthesis of new substances with hypotensive properties we have synthesized a number of different piperazine derivatives that contain pharmacophoric residues, viz., aminoalkyl, methoxybenzoyl, hydroxyaminoalkyl, and diphenylcarbamoyl. The next step in our research was to obtain piperazine compounds with an isothioureide residue, which is bioisosteric with respect to the guanidine grouping [1, 2].

We have previously accomplished the synthesis of imidazolinylthio- and benzimidazolylthioacylpiperazines by the reaction of imidazolidine-2-thione and benzimidazole-2-thione with chloroacylpiperazines in refluxing absolute ethanol [11].

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