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REACTION OF METHIODIDES OF 1,2,3,4-TETRAHYDRO- $\gamma$ -CARBOLINES  
WITH NUCLEOPHILIC AGENTS

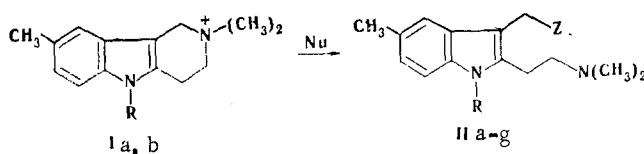
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It is shown that C, N, and O nucleophiles smoothly cleave the hydrogenated ring of quaternized tetrahydro- $\gamma$ -carbolines to give isotryptamine derivatives with a  $\text{CH}_2\text{Z}$  substituent in the 3 position ( $\text{Z} = \text{Me, Ph, CN, OEt, piperidino, and morpholino}$ ). The principles of the mass-spectral fragmentation of the synthesized compounds as a function of the character of the substituent attached to the methylene group in the 3 position were established.

The reaction of gramine (3-dimethylaminomethylindole) and its quaternary salts with nucleophilic agents, which leads to the most diverse indole derivatives, is widely known (for example, see [1]). Tetrahydro- $\gamma$ -carbolines are cyclic analogs of gramines. Their reaction with nucleophilic agents should lead to opening of the hydrogenated ring to give isotryptamine derivatives that are difficult to obtain by other methods. However, the literature contains only individual patent data on the cleavage of the quaternized tetrahydro- $\gamma$ -carboline system under the influence of thiolate ions [2, 3] and some C anions [4].

In the present research we investigated the reaction of 3,6-dimethyl- (Ia) and 3,6,9-trimethyl-1,2,3,4-tetrahydro- $\gamma$ -carboline methiodide (Ib) with C, N, and O nucleophiles. We selected the readily accessible 3,6-dimethyl-1,2,3,4-tetrahydro- $\gamma$ -carboline (IIIa) as the principal starting model.



I a R=H, b R=CH<sub>3</sub>; II a-f R=H, g R=CH<sub>3</sub>; II a Nu=CH<sub>3</sub>MgI, Z=CH<sub>3</sub>;  
b Nu=C<sub>6</sub>H<sub>5</sub>MgBr, Z=C<sub>6</sub>H<sub>5</sub>; c Nu=CN<sup>-</sup>, Z=CN; d Nu=OC<sub>2</sub>H<sub>5</sub><sup>-</sup>, Z=OC<sub>2</sub>H<sub>5</sub>; e Nu=  
piperidine, Z=piperidino; f, g, Nu=morpholine, Z=morpholino

The methylation of carboline IIIa at the indole nitrogen atom was accomplished by the action of equimolar amounts of sodium hydride and methyl iodide in dimethyl sulfoxide (DMSO). The low yields (25-30%) of N-methylated IIb in this case are evidently due to competitive quaternization of both carbolines to give their methiodides.

In contrast to the methods described in the literature for the preparation of quaternary salts of gramine, which are accompanied by side processes or give the products in low yields [5], we carried out the quaternization of carbolines IIIa, b with a 2.5-fold excess of methyl iodide in benzene and obtained methiodides Ia, b in quantitative yields. Side

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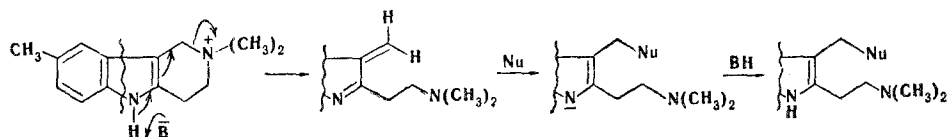
processes were excluded under these conditions because of the virtually complete insolubility of the methiodides in benzene.

The reaction of methiodide Ia with C nucleophiles such as methylmagnesium iodide, phenylmagnesium bromide, and cyanide ion proceeds smoothly with cleavage of the tetrahydrocarboline ring to give IIa (Z = CH<sub>3</sub>), IIb (Z = C<sub>6</sub>H<sub>5</sub>), and IIc (Z = CN) in good yields. We carried out the reaction of methiodide Ia with Grignard reagents under considerably milder conditions than those described for quaternary salts of gramine [1]. Instead of heating for many hours in dibutyl ether at 100-120°C, which in the case of gramine leads to alkylation products in only 15-35% yields, we used a tenfold excess of the Grignard reagent in diethyl ether, which made it possible to raise the yields to 74-78%.

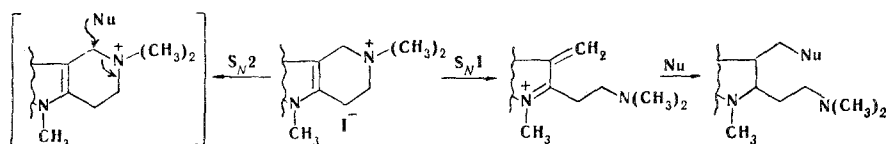
We carried out the reaction of Ia with sodium ethoxide in various solvents, viz., alcohol, DMSO, dioxane, and ether. We found that a compound with ring opening, viz., 2-(2-dimethylaminoethyl)-3-ethoxymethylindole (IIId), is formed in highest yield (46%) in the reaction of suspensions of sodium ethoxide and methiodide Ia in ether. The reaction proceeds ambiguously in all of the solvents listed above, and seven to 10 other substances of basic character are detected, in addition to IIId, in the reaction mixture by chromatography. A strong base such as the ethoxide ion is evidently capable of giving rise to a large number of side processes: splitting out of a proton from the methylene groups adjacent to the quaternary nitrogen atom with subsequent Stevens rearrangement, Hofmann elimination, etc.

The reaction with less basic N nucleophiles (piperidine and morpholine) gives the products in considerably higher yields (70-75%) in the case of refluxing in piperidine and heating in morpholine, as a result of which IIe (Z = piperidino) and IIIf (Z = morpholino), respectively, are formed.

It is known that quaternary salts of gramine and its indole ring N-methylated analog display different activities with respect to nucleophilic agents due to the differences in the reaction mechanisms (for example, see [6, 7]). To verify whether these differences are retained in cyclic systems we used model methiodide Ib. As in the case of gramine, methiodide Ib proved to be substantially less active with respect to nucleophilic agents. Thus methiodide Ib is virtually unreactive in the reaction with morpholine under the conditions used for methiodide Ia (heating in morpholine at 90-100°C for 2.5 h). This compound undergoes cleavage after 20 min only when it is refluxed in morpholine (and the temperature is raised 30°C) to give 1,5-dimethyl-2-(2-dimethylaminoethyl)-3-morpholinomethylindole (IIIf). As in the case of quaternized gramines, this difference in the reactivities of quaternary salts Ia and Ib with respect to nucleophilic agents indicates a difference in the mechanisms that are operative in the case of indole ring N-unsubstituted and N-substituted compounds. Since the behavior of methiodide Ia in reactions with nucleophilic agents was found to be completely similar to the behavior of the corresponding gramine derivatives both with respect to the character of the reaction and with respect to the level of reactivity, it may be assumed that the reaction in this case proceeds via a cleavage-addition mechanism [6] with the formation of an intermediate of the 3-methylene-[3H]-indole type:



In analogy with [7], a mechanism involving direct substitution with a different ratio of S<sub>N</sub>1 and S<sub>N</sub>2 processes can be proposed for methiodide Ib, which is similar with respect to its properties to quaternized 1-methylgramine:

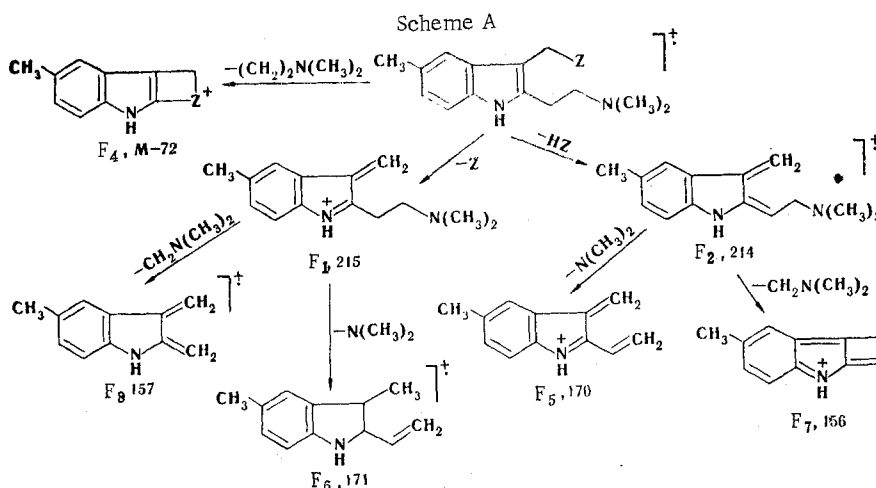


The basic principles of the mass-spectral fragmentation of the synthesized IIa-g are shown in Schemes A and B.\* The intensities of the peaks of the molecular ions for all II

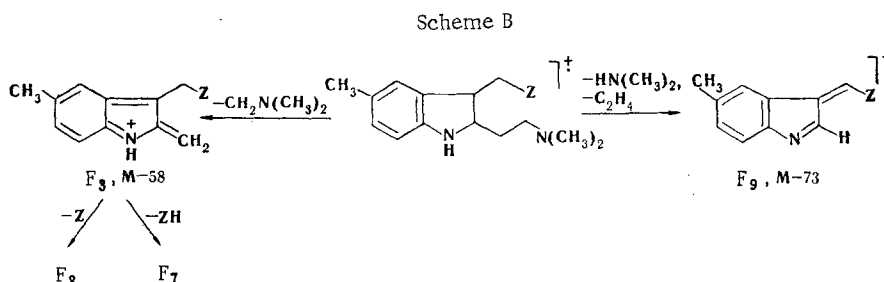
\*We thank P. B. Terent'ev for his consultation regarding the mechanism of the mass-spectral fragmentation of the compounds that we synthesized.

do not exceed 10% of the maximum peak (in connection with the exceptionally high intensity of the peaks of the maximum ion with  $m/e$  58,\* the peaks with relative intensities of no less than 0.2% were taken into account in the discussion of the fragmentation; see Table 1), which is characteristic for the mass spectra of tertiary amines. These intensities increase as follows: IIe ( $Z = \text{piperidino}$ , 0.5%) $\rightarrow$ IIId ( $Z = \text{OC}_2\text{H}_5$ , 0.6%) $\rightarrow$ IIIf ( $Z = \text{morpholino}$ , 1.4%) $\rightarrow$ IIc ( $Z = \text{CN}$ , 2.0%) $\rightarrow$ IIa ( $Z = \text{CH}_3$ , 3.0%) $\rightarrow$ IIb ( $Z = \text{C}_6\text{H}_5$ , 9.1%).

Compounds II can be divided into two groups with respect to the character of the primary fragmentation of II (see Schemes A and B). For compounds of the first group (Scheme A), in which the C-Z bond is a bond with a heteroatom (IIId-f), the primary fragmentation process is elimination of a fragment that contains the heteroatom and leads to  $F_1$  (215) or  $F_2$  (rearranged, 214) ions. Whereas the formation of a rearranged  $F_2$  ion is characteristic for the fragmentation of IIe, g (at the C-N bond), and peaks of "normal"  $F_1$  ions are virtually absent in their spectra, the intensities of the peaks of the  $F_1$  and  $F_2$  ions are of comparable magnitude for IIId (fragmentation at the C-O bond); this is in agreement with the electronegativities of the oxygen and nitrogen atom. Elimination of a  $(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$  fragment to give an  $F_4$  ion with a quaternary nitrogen atom included in a four-membered ring is an alternative process for primary fragmentation of the molecular ions of IIe, g, whereas this process is not observed in the case of oxygen-containing IIId; this is associated with the instability of a hypothetical structure of the  $F_4$  type ( $Z = \text{O}$ ) with a positively charged oxygen atom.



The formation of  $F_1$  and  $F_2$  fragments under dissociative ionization conditions is not characteristic for compounds of the second group (Scheme B), viz., IIa-c, in which the C-Z bond is a bond with carbon. The principal pathway of primary fragmentation for them is splitting out of  $\text{CH}_2\text{N}(\text{CH}_3)_2$  (the  $F_3$  ion,  $M - 58$ ) and  $(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$  (the  $F_9$  ion,  $M - 73$ ) fragments.



Such intergroup differences in the behavior of the investigated molecules under the influence of electron impact are a natural consequence of the character of the C-C and C-heteroatom bonds.

The secondary fragmentation pathways in the A and B groups also differ but lead to common characteristic ions for all II. Both the elimination of  $\text{CH}_2\text{N}(\text{CH}_3)_2$  fragments from the  $F_1$  and  $F_2$  fragments (group A) and detachment of a Z or ZH fragment by the  $F_3$  ion (group B) lead to  $F_8$  (157) and  $F_7$  (156) ions, respectively. It should also be noted that frag-

\*Here and subsequently, the  $m/e$  values are given for all of the ion peaks.

TABLE 1. Mass Spectra of Ib and Iia-g

Compound	m/e (relative intensity in percent relative to the maximum ion peak)
Ib	51 (41), 56 (9.4), 57 (100), 69 (55.1), 70 (6.3), 71 (43.6), 81 (13.0), 83 (14.0), 85 (18.0), 95 (4.3), 97 (9.0), 111 (2.7), 156 (2.9), 170 (6.3), 171 (97.4), 172 (7.2), 213 (8.3), 214 (12.0)
Iia	55 (4.4), 56 (1.4), 57 (10.7), 58 (100), 59 (6.5), 60 (0.8), 67 (0.8), 69 (7.3), 70 (1.1), 71 (6.0), 73 (0.8), 81 (2.2), 82 (0.8), 83 (2.7), 84 (0.8), 85 (3.0), 95 (1.0), 97 (2.0), 111 (0.8), 156 (1.0), 158 (0.7), 170 (0.7), 171 (0.5), 172 (0.7), 185 (0.2), 230 (3.0), 231 (0.3)
Iib	55 (10.3), 56 (2.8), 57 (22.6), 58 (100), 59 (1.3), 67 (2.0), 68 (1.3), 69 (12.4), 70 (2.2), 71 (11.5), 81 (3.9), 82 (1.7), 83 (6.5), 84 (2.0), 85 (6.2), 95 (2.8), 96 (1.3), 97 (5.3), 98 (1.3), 99 (1.2), 109 (1.2), 111 (2.2), 123 (0.8), 125 (0.9), 137 (0.8), 156 (0.6), 157 (0.7), 171 (0.6), 217 (1.6), 218 (1.5), 219 (0.5), 230 (0.7), 231 (0.8), 232 (1.4), 233 (0.5), 234 (1.3), 292 (9.1)
Iic	55 (5.9), 57 (14.6), 58 (100), 59 (3.5), 60 (1.3), 67 (1.5), 68 (1.2), 69 (11.0), 70 (2.2), 71 (9.6), 81 (3.8), 82 (1.5), 83 (4.8), 84 (1.7), 85 (5.4), 95 (1.6), 97 (3.4), 98 (1.0), 99 (1.0), 111 (1.1), 115 (2.8), 127 (1.3), 128 (0.9), 129 (1.0), 140 (1.2), 141 (0.9), 154 (1.3), 156 (2.0), 157 (1.6), 168 (1.8), 169 (0.7), 170 (0.7), 181 (2.0), 182 (1.3), 183 (2.2), 195 (0.7), 196 (0.7), 241 (2.0)
Iid	55 (0.9), 57 (2.7), 58 (100), 59 (3.7), 69 (1.7), 70 (0.6), 73 (0.2), 77 (0.2), 81 (0.3), 83 (0.2), 85 (0.2), 115 (0.7), 116 (0.2), 127 (0.1), 128 (0.3), 129 (0.2), 130 (0.1), 141 (0.1), 142 (0.2), 143 (0.3), 144 (0.4), 154 (0.3), 156 (1.4), 157 (2.0), 158 (1.0), 170 (0.6), 171 (1.1), 172 (0.2), 213 (0.1), 214 (0.2), 215 (0.2), 260 (0.6), 261 (0.1)
Iie	55 (32.7), 56 (20.3), 57 (55.8), 58 (100), 59 (3.7), 60 (6.1), 67 (6.8), 68 (5.3), 69 (37.2), 70 (10.4), 71 (3.0), 73 (5.6), 81 (11.8), 82 (5.1), 83 (13.5), 84 (29.5), 85 (24.2), 95 (4.9), 96 (3.2), 97 (9.3), 98 (5.2), 99 (2.1), 109 (2.1), 111 (3.3), 115 (2.0), 123 (1.4), 129 (1.7), 137 (1.4), 156 (2.4), 157 (6.8), 158 (5.6), 169 (1.3), 170 (2.3), 171 (2.0), 214 (5.2), 227 (0.9), 299 (0.5)
Iif	55 (7.9), 56 (5.3), 57 (22.3), 58 (100), 59 (3.7), 69 (9.5), 71 (5.5), 81 (2.5), 83 (3.5), 85 (2.4), 86 (1.0), 87 (2.4), 97 (2.3), 115 (2.7), 128 (1.1), 143 (1.0), 156 (6.1), 157 (14.1), 158 (9.6), 169 (1.4), 170 (3.8), 171 (1.7), 183 (0.5), 197 (0.6), 214 (5.4), 215 (0.9), 229 (0.5), 256 (0.3), 301 (1.4)
Iig	55 (34.9), 56 (11.4), 57 (79.7), 58 (100), 59 (3.7), 67 (6.8), 68 (4.2), 69 (32.9), 70 (7.5), 71 (35.9), 81 (9.9), 82 (6.8), 83 (23.6), 85 (18.6), 87 (2.8), 95 (8.8), 96 (5.4), 97 (18.6), 98 (4.8), 99 (3.5), 109 (3.7), 111 (6.8), 112 (3.0), 123 (2.5), 170 (2.4), 171 (9.7), 172 (7.5), 173 (1.4), 183 (1.3), 184 (5.2), 185 (1.5), 228 (6.9), 229 (1.5), 243 (1.2), 270 (1.1), 278 (1.1), 315 (5.2)

mentation to  $F_3$  (171) fragments is characteristic for the  $F_1$  and  $F_2$  ions (group A), while such fragmentation is not observed in the spectra of the group B compounds. The subsequent transformation of the  $F_7$  and  $F_8$  fragments is typical for the mass-spectral behavior of the indole structures [8].

The mass spectrum of the indole nitrogen-methylated Iig is completely similar to the mass spectrum of N-unsubstituted Iif; however, the m/e values of all of the ion peaks are increased by 14 units, which once again confirms the proposed structure.

Since the structures of all II are very similar to one another and differ only with respect to substituent Z attached to the methylene group in the 3 position, their PMR spectra are very similar, contain a number of identical signals, and differ only with respect to the position of the signal of the protons of the 3- $CH_2Z$  group, which depends on the character of the substituent (see Table 2).

#### EXPERIMENTAL

The PMR spectra of solutions of the compounds in  $CCl_4$  were recorded with PS-60 (Varian) and BS-497 (Tesla, with an operating frequency of 100 MHz) spectrometers with hexamethyldisiloxane as the internal standard. The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The mass spectra of the compounds were recorded with an MKh-1303 spectrometer with a modified system for introduction of the samples into the ion source at temperatures close to the melting points of the samples (the ionizing voltage was 50 eV, and the emission current was 1.5 mA). The course of the reactions and the purity of the compounds obtained were monitored by thin-layer chromatography (TLC) on Silufol UV-254 in chloroform saturated with ammonia; the chromatograms were developed with iodine vapors.

TABLE 2. PMR Spectra of IIa-g<sup>a</sup>.

Compound	$\delta$ , ppm				
	N(CH <sub>2</sub> ) <sub>2</sub>	2-CH <sub>2</sub> CH <sub>2</sub> N	2-CH <sub>2</sub> CH <sub>2</sub> N	3-CH <sub>2</sub>	aromatic protons
IIa <sup>b</sup>	2,30 (6H, s)		2,53-2,97 (6H, m)		6,68-7,28 (4H, m)
IIb	2,34 (6H, s)	2,56 (2H, br t, J=6 Hz)	2,77 (2H, br t, J=6 Hz)	3,98 (2H, s)	6,74-7,28 (9H, m)
IIc	2,30 (6H, s)	2,60 (2H, br t, J=6 Hz)	2,82 (2H, br t, J=6 Hz)	3,51 (2H, s)	6,73-7,21 (4H, m)
II <sup>c</sup> <sub>d</sub>	2,30 (6H, s)	2,45-2,95 (4H, m)		4,49 (2H, s)	6,80-7,29 (4H, m)
II <sup>d</sup> <sub>e</sub>	2,29-2,35 <sup>e</sup> (10H, m)	2,45-3,00 (4H, m)		3,47 (2H, s)	6,70-7,32 (4H, m)
II <sup>f</sup> <sub>f</sub>	2,26-2,34 <sup>g</sup> (10H, m)	2,58 (2H, br t, J=6 Hz)	2,88 (2H, br t, J=6 Hz)	3,45 (2H, s)	6,68-7,30 (4H, m)
II <sup>g</sup> <sub>h</sub>	2,15-2,35 <sup>g</sup> (10H, m)	2,41-3,10 (4H, m)		3,46 (2H, s)	6,63-7,30 (3H, m)

<sup>a</sup>All of the compounds have a signal of a 5-CH<sub>3</sub> group at 2.36 ppm; in the case of IIg one observes a singlet signal of 5-CH<sub>3</sub> and 1-CH<sub>3</sub> groups. <sup>b</sup>1.10 ppm (3H, t, 3-CH<sub>2</sub>CH<sub>3</sub>, J = 8 Hz). <sup>c</sup>1.06 ppm (3H, t, OCH<sub>2</sub>CH<sub>3</sub>, J = 8 Hz) and 3.22 ppm (2H, q, OCH<sub>2</sub>, J = 8 Hz). <sup>d</sup>1.30-1.70 ppm (6H, m, 3-, 4-, and 5-CH<sub>2</sub> groups from the piperidine group). <sup>e</sup>The protons of the N(CH<sub>2</sub>)<sub>2</sub> group of the piperidine ring are included. <sup>f</sup>3.46-3.61 ppm [4H, m, O(CH<sub>2</sub>)<sub>2</sub>]. <sup>g</sup>The protons of the N(CH<sub>2</sub>)<sub>2</sub> group of the morpholine ring are included. <sup>h</sup>3.51-3.72 ppm 4H, m, O(CH<sub>2</sub>)<sub>2</sub>].

3,6,9-Trimethyl-1,2,3,4-tetrahydro- $\gamma$ -carboline (IIIb). A suspension of 1 g (0.04 mole) of sodium hydride in 5 ml of hexane was added with vigorous stirring to a solution of 6 g (0.03 mole) of carboline IIIa in 50 ml of dry dimethyl sulfoxide (DMSO), after which stirring was continued for 20 min. A solution of 1.9 ml of methyl iodide in 5 ml of dry DMSO was then added dropwise, and the mixture was stirred for another 10 min. The unchanged sodium hydride was then decomposed with water, and the mixture was poured into 0.5 liter of water. The aqueous mixture was extracted with ether (two 150-ml portions), and the extract was dried with MgSO<sub>4</sub>. The ether was removed by distillation, and the residue was refluxed with 10 ml of petroleum ether (40-70°C). The mixture was cooled, and the precipitate was removed by filtration and washed with petroleum ether to give 1.8 g (28%) of a slightly yellowish substance with mp 111-113°C (from benzene-petroleum ether). PMR spectrum: 2.36 (6H, s, 6-CH<sub>3</sub>, 9-CH<sub>3</sub>), 2.50-2.80 (4H, m, CH<sub>2</sub>CH<sub>2</sub>N), 3.33 (3H, s, 3-CH<sub>3</sub>), 3.42 (2H, s, 4-H), and 6.63-7.12 ppm (3H, m, aromatic protons). Found: C 78.5; H 8.3%. C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>. Calculated: C 78.4; H 8.5%.

3,6-Dimethyl-1,2,3,4-tetrahydro- $\gamma$ -carboline Methiodide (Ia). A 10-g (0.05 mole) sample of carboline IIIa was dissolved in 200 ml of benzene by heating to 50-60°C, after which 4 ml of CH<sub>3</sub>I was added with stirring. The mixture was then cooled to ~20°C, another 3 ml of CH<sub>3</sub>I was added, and the mixture was refluxed for 10 min. The precipitated methiodide was removed by filtration and washed successively with 100 ml of hot benzene and 50 ml of absolute ether to give 16.9 g (100%) of a cream-colored powder with mp 226°C (from absolute alcohol). Found: C 49.6; H 5.7%. C<sub>14</sub>H<sub>19</sub>IN<sub>2</sub>. Calculated: C 49.2; H 5.6%.

3,6,9-Trimethyl-1,2,3,4-tetrahydro- $\gamma$ -carboline Methiodide (Ib). A 1.6-ml sample of CH<sub>3</sub>I was added to a solution of 1.07 g (0.005 mole) of carboline IIIb in 30 ml of benzene, and the mixture was stirred for 15 min. The precipitate was removed by filtration and washed with absolute ether to give 1.65 g (92%) of methiodide Ib with mp 247-248°C (from alcohol). Found: C 51.1; H 6.4%. C<sub>15</sub>H<sub>21</sub>IN<sub>2</sub>. Calculated: C 50.6; H 5.9%.

2-(2-Dimethylaminoethyl)-3-cyanomethyl-5-methylindole (IIc). A 3.4-g (0.01 mole) sample of methiodide Ia was added to a solution of 2 g (0.03 mole) of potassium cyanide in 50 ml of water, and the mixture was heated at 80-90°C for 2 h. It was then cooled, and the solidified oil was extracted with ether (three 100-ml portions). The extract was dried with MgSO<sub>4</sub>, and the ether was removed by distillation to give 2.2 g (91%) of IIc with mp 107-108°C [from petroleum ether (40-70°C)]. Found: C 74.0; H 7.8%. C<sub>15</sub>H<sub>19</sub>N<sub>3</sub>. Calculated: C 74.6; H 7.9%.

2-(2-Dimethylaminoethyl)-3-ethyl-5-methylindole (IIa). A 3.4-g (0.01 mole) sample of methiodide Ia was added in portions to a solution of methylmagnesium iodide obtained from 0.1 mole of CH<sub>3</sub>I in 150 ml of absolute ether, and the resulting clear solution was stirred at room temperature for 5 h, after which it was allowed to stand overnight. The excess Grignard reagent was decomposed with a saturated solution of NH<sub>4</sub>Cl, the ether layer was separated, and the aqueous layer was extracted with ether (three 100-ml portions). The combined ether extracts were dried with MgSO<sub>4</sub>, and the ether was removed by vacuum distillation to give 1.7 g (74%) of IIa with mp 103-104°C [from petroleum ether (40-70°C)]. Found: C 78.0; H 9.4%. C<sub>15</sub>H<sub>22</sub>N<sub>2</sub>. Calculated: C 78.2; H 9.6%.

2-(2-Dimethylaminoethyl)-3-benzyl-5-methylindole (IIb). A 1.7-g (0.005 mole) sample of quaternary salt Ia was added in portions to an ether solution of 100 ml of phenylmagnesium bromide obtained from 0.05 mole of bromobenzene, and the mixture was refluxed for 4 h. It was then cooled, and the excess organomagnesium compound was decomposed with a saturated solution of NH<sub>4</sub>Cl. The ether layer was separated, and the aqueous layer was extracted with ether (three 100-ml portions). The combined ether extracts were dried with MgSO<sub>4</sub>, and the ether was removed by vacuum distillation to give 1.1 g (78%) of IIb with mp 109°C [from petroleum ether (40-70°C)]. Found: C 82.9; H 8.5%. C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>. Calculated: C 82.1; H 8.3%.

2-(2-Dimethylaminoethyl)-3-ethoxymethyl-5-methylindole (IIId). A suspension of sodium ethoxide (from 1 g of sodium metal) and 2 g (0.059 mole) of methiodide Ia in 50 ml of absolute ether was stirred at room temperature for 5 days, after which it was poured into 200 ml of water, and the ether layer was separated. The aqueous layer was extracted with ether (two 150-ml portions), the extract was dried with MgSO<sub>4</sub>, and the ether was removed by vacuum distillation. The residue was dissolved in the minimum amount of benzene, and a tenfold amount of pentane was added to the solution. The resulting precipitate was removed by filtration and washed with a small amount of pentane to give 0.7 g (46%) of IIId with mp 80°C (from pentane). Found: C 74.2; H 9.1%. C<sub>16</sub>H<sub>24</sub>N<sub>2</sub>O. Calculated: C 73.8; H 9.3%.

2-(2-Dimethylaminoethyl)-3-piperidinomethyl-5-methylindole (IIe). A 1.7-g (0.005 mole) sample of methiodide Ia was refluxed with 10 ml of piperidine for 2.5 h, after which the piperidine was removed by vacuum distillation, and 100 ml of water was added to the residue. The aqueous mixture was extracted with ether (two 100-ml portions), and the extract was dried with MgSO<sub>4</sub>. The ether was removed by distillation to give 1.05 g (79%) of IIe with mp 138-139°C [from petroleum ether (40-70°C)]. Found: C 75.7; H 9.3%. C<sub>19</sub>H<sub>29</sub>N<sub>2</sub>. Calculated: C 76.2; H 9.8%.

2-(2-Dimethylaminoethyl)-3-morpholinomethyl-5-methylindole (IIf). A 1.7-g (0.005 mole) sample of methiodide Ia was heated with 10 ml of morpholine on a boiling-water bath, after which the morpholine was removed by vacuum distillation, and 200 ml of water was added to the residue. The aqueous mixture was extracted with ether (two 150-ml portions), and the extract was dried with MgSO<sub>4</sub>. The ether was removed by distillation to give 1.3 g (86%) of IIf with mp 118°C [from petroleum ether (40-70°C)]. Found: C 71.4; H 8.6%. C<sub>18</sub>H<sub>27</sub>N<sub>3</sub>O. Calculated: C 71.7; H 9.0%.

1,5-Dimethyl-2-(2-dimethylaminoethyl)-3-morpholinomethylindole (IIg). A 0.89-g (0.0025 mole) sample of methiodide Ib was refluxed with 5 ml of morpholine. After 20 min, the solid material dissolved completely. The solution was refluxed for another 10 min, and the morpholine was removed by vacuum distillation. Water (50 ml) was added to the residue, and the aqueous mixture was extracted with ether (three 30-ml portions). The extract was dried with MgSO<sub>4</sub>, and the ether was removed by distillation to give 0.65 g (82%) of IIg with mp 77-78°C (from petroleum ether). Found: C 72.3; H 9.3%. C<sub>19</sub>H<sub>29</sub>N<sub>3</sub>O. Calculated: C 72.3; H 9.3%.

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EFFECT OF THE ELECTRONIC STRUCTURE OF THE HETEROATOM  
ON THE BASICITIES OF HETEROCYCLIC COMPOUNDS

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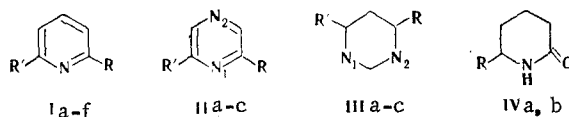
The proton-acceptor capacities of heterocyclic nitrogen compounds (pyridine, pyrazine, pyrimidine, and some of their derivatives) were subjected to a theoretical study by means of the molecular electrostatic-potential method. The wave functions of the examined compounds were obtained by the INDO method. It was found that the difference in the proton-acceptor capacities of the examined compounds is due to the difference in the electronic structures of the unshared pairs of the most basic atoms in these compounds.

The accurate description of the protonation of polybasic molecules requires a determination of the effectiveness of protonation of each center. This is often a complex task from an experimental point of view [1]. For a theoretical evaluation it is convenient to use the molecular electrostatic potentials (MESP), which are the energies of the electrostatic interactions of an individual positive charge with the unperturbed charge distribution of the molecule. The set of MESP values at all points of the space that surrounds the molecule determines the hypersurface of the electrostatic energy of the interaction of the molecule with the individual positive charge. Despite the fact that this surface is an initial approximation of the total potential surface of the interaction, an analysis of it makes it possible to obtain diverse information regarding the reactivity of the molecules [2, 3].

The aim of the present research was to make a theoretical study of the reactivities of a number of heterocyclic nitrogen compounds and to establish the relationship between the electronic structures of the heteroatoms and the basicities of the examined compounds by means of the indicated approach.

The MESP values were calculated in this research by means of the wave functions obtained by various methods based on the zero-differential-overlap (ZDO) approximation by means of the program described in [4].

In the present research we investigated pyridine, pyrimidine, pyrazine, and their derivatives (Ib-f, IIb, c, IIIb, c, and IVa, b) in the ground electronic state.



I-IV a R=R'=H; b R=NH<sub>2</sub>, R'=H; c R=R'=NH<sub>2</sub>; d R=OH, R'=H; e R=OH, R'=NH<sub>2</sub>; f R=O<sup>-</sup>, R'=H

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