MASS SPECTRA OF PYRAZINO- AND PIPERAZINOINDOLE DERIVATIVES*

A. I. Ermakov, Yu. N. Sheinker, V. I. Shvedov, L. B. Altukhova, É. S. Krichevskii, and A. N. Grinev

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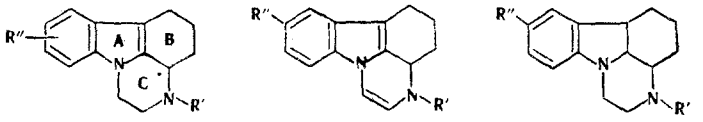
The behavior of compounds of the pyrazino- and piperazinoindole series under the influence of electron impact was studied. The fragmentation was examined as a function of the type of substituents attached to the nitrogen atom in the piperazine ring and the degree of saturation of the condensed rings. Deuterium labeling and model analogs were used to prove the fragmentation mechanisms. It is shown that the positive charge in the molecular and fragment ions may be localized both on the bridge nitrogen atom of the indole ring and on the N atoms of the pyrazine or piperazine ring. The characteristic fragments for each type of compound were found. The results can be used to study the structures of new derivatives of pyrazino- and piperazinoindoles or the products of their metabolism.

An active psychotropic preparation — pyrazidol [2] — was discovered during a study of the biological activity of compounds in the pyrazino- and piperazinoindole series of the 1-3 type:



1 2 3

In the present communication we examine the mass-spectral behavior of compounds 1-3 as a function of substituents R', the degree of saturation of the A, B, and C rings, and the distribution of charge between the nodal nitrogen atom of the indole ring and the N atoms of the pyrazine and piperazine rings. The results of this sort of study can be used in the establishment of the structures of the products of metabolism of pyrazidol and its analogs. The mass spectra of pyrazino- and piperazinoindoles have not been previously investigated.

The primary pathways of fragmentation of the molecular ions (M^+) of I-IV, which involve detachment of hydrogen atoms and H_2 and C_2H_4 molecules, were confirmed by the metastable transitions. It follows from the mass spectrum of the deutero analogs of IV that the deuterium atom attached to the nitrogen atom of the piperazine ring does not participate in these processes; this can be explained if it is assumed that the charge in the molecular ion is concentrated primarily on the nitrogen atom of the piperazine ring (Scheme 1). In this case retrodiene detachment of a C_2H_4 molecule leads to ion radical a, which gives the maximum peak in the spectrum and makes the principal contribution to the total ion current. Even-electron fragments of the b, c, and d type are characterized by less intense peaks.

The formation of fragments a and c should be considered to be the result of α cleavage of the bonds with respect to the ion-radical center at the nitrogen atom of the saturated ring; this is typical for aliphatic and alicyclic amines [3]. However, in the case of fragmentation of V and VI, in which R' is an alkyl group, the $[M - C_2H_4, -R']^+$ ion is formed

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S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow 119021. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 827-832, June, 1978. Original article submitted December 20, 1976; revision submitted November 14, 1977.

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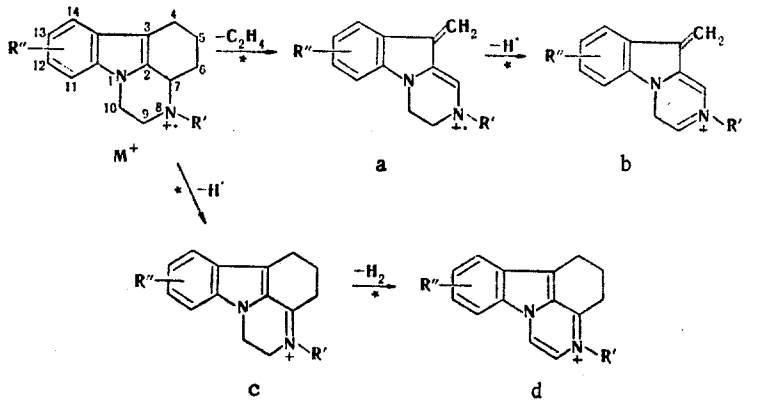
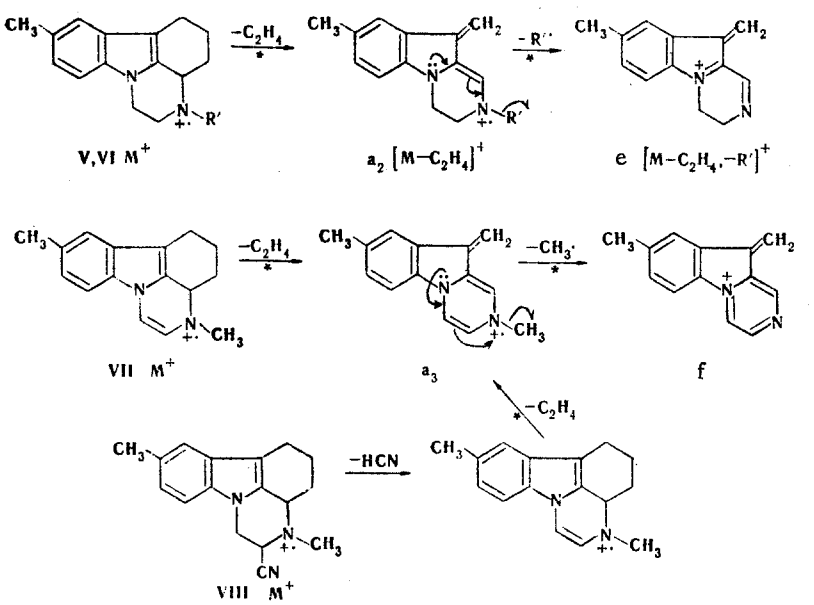
Scheme 1



I R″=H, R′=H; II R″=(11)CH_3, R′=H; III R″=(13)CH_3, R′=H; IV R″=(13)CH_3, R′=D

along with the $[M - C_2H_4]^+$ fragment. The latter process suggests charge transfer to the nodal nitrogen atom of the indole ring (Scheme 2).

Scheme 2



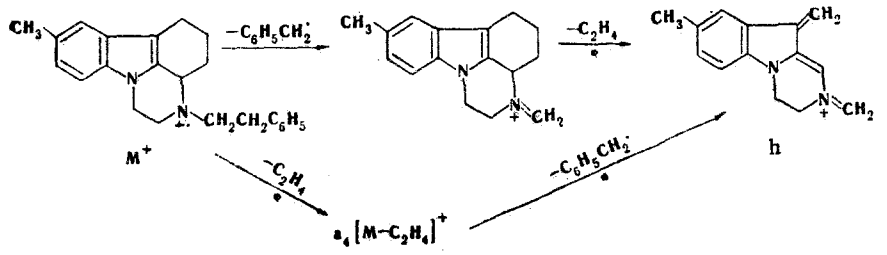
V R′=CH_3; VI R′=C_2H_5

The migration of charge can be conceived of as the result of a concerted shift of electrons to give stable ion e in which the C–C bonds in the C ring are partially or completely conjugated. It should be noted that the tendency toward aromatization of the C ring and stabilization of the charge on the nodal nitrogen atom is probably the principal driving force of this process.

In the fragmentation of VII and VIII charge migration to the N atom of the indole ring is facilitated due to the double bond in the C ring, and the maximum peak in the spectra probably therefore corresponds to the ion with conjugated bonds (f), whereas the most intense peak in the spectrum of analogs V and VI corresponds to the $[M - C_2H_4]^+$ fragment. It is interesting to note that the fragmentation processes cited above are absent in the case of bridged bicyclic saturated amines with a nodal nitrogen atom at the bridgehead (for example, quinuclidines [4]).

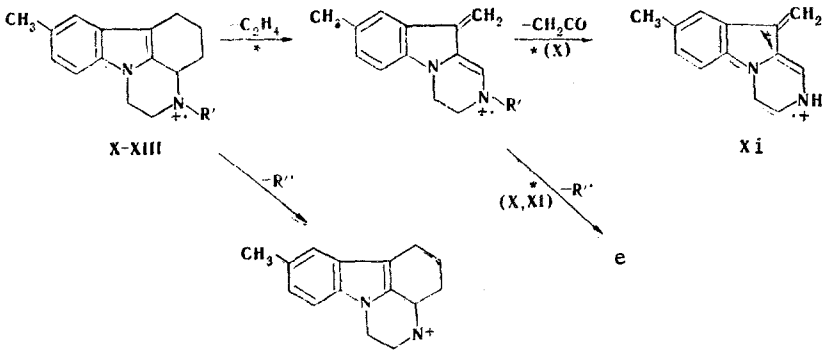
Charge localization on the bridged nitrogen atom is less likely in the fragmentation of IX in view of the fact that the fragmentation is realized via a mechanism of the amine type, and ion h is formed as a result of detachment of C_2H_4 and $CH_2C_6H_5$ particles in a different sequence, during which the charge on the nitrogen atom of the piperazine ring is retained (Scheme 3).

Scheme 3



Fragmentation of the retrodiene type with the formation of an $[M - C_2H_4]^+$ ion is also characteristic for acyl analogs X-XIII (Scheme 4). An acyl group may be detached from both the $[M - C_2H_4]^+$ ion and directly from the molecular ion. The $[M - C_2H_4]^+$ ion in the fragmentation of X subsequently splits out a molecule of ketone to give fragment i. This sort of process is impossible for XI-XIII. The behavior of X-XIII under electron impact also follows the general principles (Scheme 4):

Scheme 4

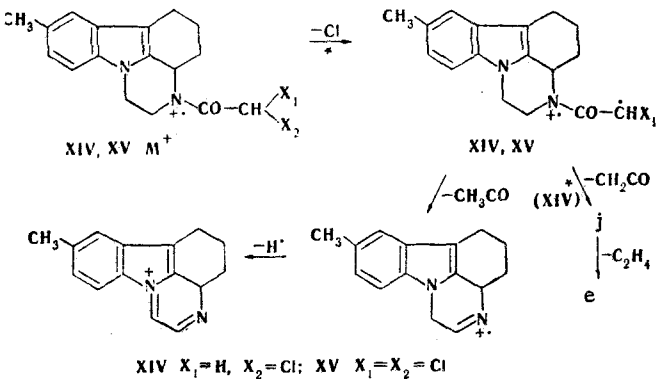


X R′=CH_3CO; XI R′=C_6H_5CO; XII R′=n-Cl—C_6H_4CO; XIII R′=$(CH_3O)_3C_6H_2CO$

The principal mechanisms of the fragmentation of chloracyl derivatives XIV and XV specify that the C—Cl bond in the substituents is easily cleaved. The peaks of maximum intensity in the spectra of XIV and XV correspond to $[M - Cl]^+$ fragments.

The fact that the $[M - Cl]^+$ ion peaks also retain their maximum intensities at an ionizing-electron energy of 12 eV, whereas $[M^+ - C_2H_4]$, $[M^+ - R]$, and $[M^+ - C_2H_4 - R]$ processes are not observed, is noteworthy. The formation of characteristic (for analogs I-XII) fragments e and j can be represented by the following scheme:

Scheme 5



XIV X_1=H, X_2=Cl; XV X_1=X_2=Cl

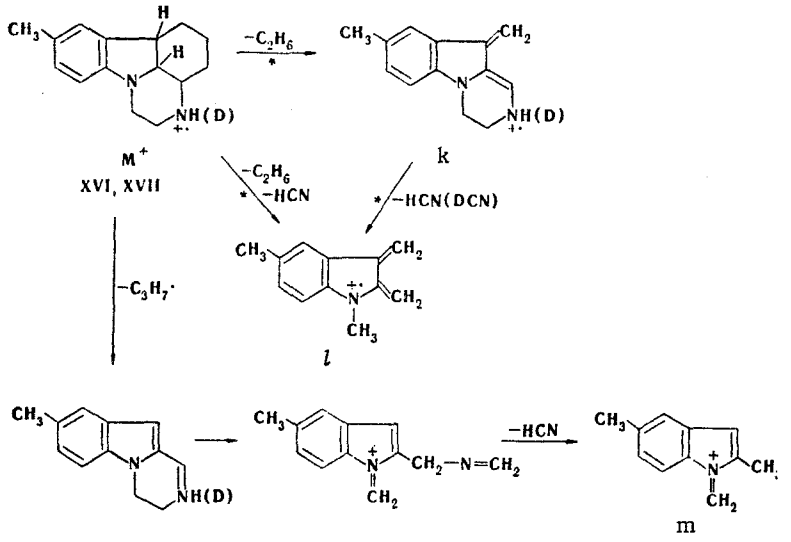
One's attention is drawn to the fact that even- and odd-electron fragments, to the hypothetical structures of which an aromatic skeleton and (or) a structure with conjugated double bonds can be formally assigned, are formed in the fragmentation of I-XIII. First, the maximum peak in the spectra of I-XIII corresponds to an odd-electron fragment of the $[M - C_2H_4]^+$ type, the formation of which in the fragmentation of saturated nitrogen-containing

TABLE 1. Mass Spectra of I-XV Obtained at Ionizing Energies of 70 (a) and 12 eV (b)

Compound	m/e values (relative intensities of the ion peaks in percent of the maximum peak)
1	2
I[a]	127 (4), 128 (6), 129 (6), 130 (4), 139 (4), 140 (4), 141 (4), 142 (5), 143 (5), 144 (3), 153 (6), 154 (8), 155 (7), 156 (7), 157 (8), 158 (6), 166 (6), 167 (8), 168 (7), 169 (7), 170 (5), 180 (8), 181 (9), 182 (9), 183 (15), 184 (100), 185 (10), 208 (4), 209 (8), 210 (8), 211 (26), 212 (42), 213 (10)
II[a]	167 (5), 168 (5), 169 (5), 170 (4), 180 (4), 181 (4), 182 (6), 183 (7), 184 (4), 195 (3), 196 (8), 197 (10), 198 (100), 199 (16), 223 (4), 224 (6), 225 (32), 226 (56), 227 (10)
III[a]	167 (4), 168 (7), 169 (5), 170 (6), 180 (6), 181 (7), 182 (5), 183 (6), 195 (4), 196 (8), 197 (12), 198 (100), 199 (12), 211 (5), 223 (9), 224 (12), 225 (25), 226 (46), 227 (7)
IV[a]	167 (7), 168 (7), 169 (5), 170 (7), 171 (4), 181 (6), 182 (9), 183 (7), 184 (5), 195 (4), 195 (4), 196 (12), 197 (8), 198 (100), 199 (98), 200 (14), 212 (4), 213 (4), 213 (4), 223 (6), 224 (8), 225 (34), 226 (72), 227 (54), 228 (8)
V[a]	167 (5), 168 (4), 169 (3), 170 (3), 180 (5), 181 (6), 182 (6), 183 (4), 196 (8), 197 (23), 198 (4), 211 (4), 212 (100), 213 (16), 225 (5), 239 (22), 240 (40), 241 (6)
V[b]	197 (6), 212 (94), 213 (16), 239 (14), 240 (100), 241 (18), 115 (4), 127 (9),
VI[a]	128 (4), 167 (7), 168 (6), 169 (5), 170 (4), 180 (6), 181 (9), 182 (12), 183 (4), 195 (4), 196 (12), 197 (34), 198 (14), 211 (5), 223 (4), 224 (3), 225 (6), 226 (100), 227 (20), 239 (4), 253 (14), 254 (30), 255 (6)
VII[a]	194 (8), 195 (100), 196 (17), 197 (3), 210 (98), 211 (15), 221 (20), 222 (3), 223 (8), 237 (23), 238 (80), 239 (14)
VIII[a]	165 (4), 166 (4), 167 (7), 168 (4), 180 (6), 181 (6), 182 (4), 192 (4), 193 (5), 194 (8), 195 (100), 196 (17), 197 (4), 209 (4), 210 (66), 211 (4), 221 (6), 222 (4), 223 (6), 237 (17), 238 (32), 239 (6), 265 (3), 266 (1)
IX[a]	91 (8), 181 (8), 182 (16), 183 (7), 196 (12), 197 (4); 198 (7), 211 (55), 212 (13), 235 (18), 239 (61), 240 (12), 302 (100), 303 (16), 329 (15), 330 (56), 331 (10)
X[a]	167 (6), 168 (8), 169 (6), 170 (6), 180 (6), 181 (9), 182 (12), 183 (5), 194 (5), 195 (6), 196 (12), 197 (76), 198 (38), 199 (6), 223 (3), 224 (3), 225 (20), 226 (4), 240 (100), 241 (18), 253 (5), 266 (4), 267 (4), 268 (76), 269 (16)
XI[a]	77 (32), 105 (48), 167 (5), 168 (5), 169 (4), 184 (15), 194 (6), 195 (8), 196 (12), 197 (88), 198 (16), 209 (5), 210 (4), 224 (6), 225 (22), 226 (6), 273 (5), 274 (4), 301 (3), 302 (100), 303 (24), 315 (4), 329 (6), 330 (100), 331 (26), 332 (4)
XII[a]	111 (16), 112 (5), 139 (34), 140 (4), 141 (14), 144 (16), 167 (6), 168 (6), 169 (4), 170 (4), 178 (10), 179 (2), 180 (6), 181 (12), 182 (18), 183 (6), 194 (12), 195 (8), 196 (12), 197 (100), 198 (20), 199 (3), 206 (14), 207 (3), 223 (7), 224 (7), 225 (12), 226 (6), 235 (12), 336 (74), 337 (16), 338 (24), 354 (66), 355 (16), 356 (24), 357 (6)
XIIb	197 (10), 198 (6), 224 (10), 225 (9), 336 (52), 337 (12), 338 (18), 339 (5), 364 (100), 365 (26), 366 (30)
XIII[a]	154 (8), 155 (10), 167 (6), 168 (25), 169 (6), 180 (5), 181 (10), 182 (9), 194 (6), 195 (100), 196 (56), 197 (40), 198 (10), 209 (5), 210 (6), 223 (9), 224 (10), 225 (60), 336 (16), 337 (3), 420 (46), 421 (6)
XIV[a]	180 (4), 181 (8), 182 (9), 183 (4), 184 (5), 194 (5), 195 (6), 196 (8), 197 (28), 198 (16), 207 (10), 208 (14), 209 (10), 210 (8), 211 (4), 223 (25), 224 (13), 225 (52), 226 (12), 240 (20), 253 (3), 266 (8), 267 (100), 268 (30), 302 (14), 303 (3), 304 (5)
XIV[b]	224 (8), 225 (5), 224 (3), 240 (12), 266 (16), 267 (100), 268 (42), 302 (40), 303 (12), 304 (12)
XV[a]	167 (14), 168 (18), 169 (10), 170 (4), 180 (14), 181 (30), 182 (22), 183 (8), 194 (15), 195 (18), 196 (23), 197 (52), 198 (22), 222 (14), 223 (52), 224 (64), 225 (40), 226 (10), 240 (12), 253 (4), 254 (4), 265 (6), 266 (10), 267 (46), 268 (14), 300 (14), 301 (100), 302 (34), 303 (20), 336 (24), 337 (3), 338 (8)
XV[b]	223 (12), 224 (46), 225 (12), 266 (6), 267 (34), 268 (12), 300 (30), 301 (100), 302 (40), 303 (50), 336 (32), 337 (8), 338 (20)
XVI[a]	142 (6), 143 (5), 144 (25), 145 (17), 156 (6), 157 (8), 158 (40), 159 (10), 170 (10), 171 (38), 172 (12), 184 (4), 185 (42), 197 (6), 198 (24), 199 (8), 200 (5), 225 (4), 226 (8), 227 (14), 228 (100), 229 (18)
XVII[a]	144 (10), 145 (6), 146 (12), 147 (4), 157 (4), 158 (7), 159 (24), 160 (7), 170 (4), 171 (8), 172 (25), 173 (6), 184 (8), 185 (30), 186 (26), 187 (3), 198 (6), 199 (14), 200 (4), 201 (4), 226 (4), 227 (26), 228 (26), 229 (100), 230 (18)

compounds is less favorable than, for example, the formation of b, c, e, f, g, h, and j ions (Schemes 1-4). However, the $[M - C_2H_4]^+$ ion peak in the mass spectra of analogs of I-XIII makes the principal contribution to the total ion current, whereas the overall intensities of the peaks of the even-electron fragments are lower by a factor of two in, for example, the spectra of I-IV. The high intensity of the peak of the odd-electron $[M - C_2H_4]^+$ fragment can apparently be explained by a concerted shift of electrons during splitting out of an olefin molecule and the formation of an ion radical, the unpaired electron in which is effectively stabilized by the system of conjugated bonds. It also follows from Scheme 2 that in the fragmentation of V-VIII the formation of conjugated structures promotes stabilization of the charge on the bridge nitrogen atom of the indole ring, as a result of which the peaks of ions of this type are characterized by high intensities. For example, it is interesting to compare the intensities of the peaks (with respect to the maximum peak) of fragment e in the spectrum of V and ion f in the spectrum of analog VII. The formation of fragments e and f as a result of detachment of a methyl radical is realized via $a_2 \rightarrow e$ and $a_3 \rightarrow f$ mechanisms (Scheme 2). The f/e intensity ratio of five is an argument in favor of fragment f with completely conjugated bonds.

Scheme 6



The fragmentation of XVI and its deuteroanalog XVII (Scheme 6) with a hydrogenated double bond in the A ring may serve as confirmation of all of the above. Retrodiene fragmentation of the B ring is impossible in this case. In fact, fragment k is formed as a result of double hydrogen rearrangement, and its intensity in the spectra of XVI and XVII is low.

The primary fragmentation of these compounds is realized with opening of the B and C rings, simultaneous or successive elimination of C_3H_6 and HCN molecules, and the formation of *l* ions or successive detachment of $C_3H_7^{\cdot}$ and HCN to give m ions. Processes of this sort are characteristic for the fragmentation of bicyclic amides with a nodal nitrogen atom [4]. It should evidently be assumed that localization of the charge is equally likely on both nitrogen atoms in the case of XVI. The proposed fragmentation scheme is confirmed by deuterium analog XVII and the metastable ions.

Thus in the case of the fragmentation of pyrazino- and piperazinoindoles 1-3 the charge is localized both on the nitrogen atom of the pyrazine or piperazine rings and on the bridged nitrogen atom of the indole ring. The formation of even- and odd-electron fragments with a quaternary nitrogen atom and a system of partially or completely conjugated bonds is characteristic for the investigated compounds. The fragmentation principles found in this research can be used to study the structures of new derivatives of pyrazino- and piperazinoindoles and the products of their metabolism.

EXPERIMENTAL

The mass spectra of I-XVII were obtained with an LKB-9000 chromatographic mass spectrometer at ionizing voltages of 70 and 12 eV, an emission current of 60 μA, an accelerating

voltage of 3.5 kV, and an ion-source temperature of 230-250°C. The substances were introduced into the mass spectrometer through a direct admission system at 40-100°C. The purity of the compounds was monitored by thin-layer chromatography. The synthesis of the compounds was published in [5-7].

LITERATURE CITED

1. A. I. Ermakov, Yu. N. Sheinker, Zh. K. Torosyan, and V. V. Zamureenko, Khim. Geterotsikl. Soedin., No. 12, 1647 (1975).
2. M. D. Mashkovskii, A. N. Grinev, V. I. Shvedov, L. B. Altukhova, N. I. Andreeva, G. Ya. Avrutskii, and V. V. Gromova, USSR Inventor's Certificate No. 427713; Byul. Izobr., No. 18, 14 (1974).
3. H. Budziekiewicz, C. Djerassi, and D. H. Williams, Interpretation of the Mass Spectra of Organic Compounds, San Francisco (1967), p. 297.
4. A. I. Ermakov, Yu. N. Sheinker, E. E. Mikhlina, L. I. Mastafanova, V. Ya. Vorob'eva, A. D. Yanina, L. N. Yakhontov, and R. G. Kostyanovskii, Org. Mass Spectrom., 5, 1029 (1971).
5. V. I. Shvedov, V. V. Alekseev, L. B. Altukhova, and A. N. Grinev, Khim.-Farm. Zh., No. 12, 3 (1968).
6. V. I. Shvedov, L. B. Altukhova, and A. N. Grinev, Khim.-Farm. Zh., No. 3, 25 (1967).
7. V. I. Shvedov, L. B. Altukhova, V. V. Alekseev, and A. N. Grinev, Khim. Geterotsikl. Soedin., No. 10, 1348 (1970).

HETEROCYCLIC ANALOGS OF PLEIADIENE. XXXIV.* RECYCLIZATION REACTIONS OF 1,3-DIALKYL-SUBSTITUTED PERIMIDONES, THIOPERIMIDONES, AND 2,3-DIHYDROPERIMIDINES. NEW TYPE OF PHENALENONES WITH CONDENSED HETEROCYCLIC RINGS

I. V. Borovlev and A. F. Pozharskii

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The corresponding phenalenones are formed immediately in the reaction of 1,3-dialkyl-substituted perimidones, thioperimidones, and 2,3-dihydroperimidines with propiolic acids and β-keto acid esters in polyphosphoric acid (PPA) at 40-75°C. Acylation of the perimidone and 2,3-dihydroperimidine derivatives with cinnamic and acrylic acids in PPA occurs in the 6 position and is accompanied by recyclization with the formation of a dihydrophenalenone ring. Acylation of 1,3-dialkylperimidones with aliphatic acids in PPA leads to 6,7-diacyl derivatives, by crotonization of which the corresponding phenalenones were also synthesized. The properties of the compounds are discussed.

We recently observed [2] that 1,3,8-trimethyl-2,6-dioxo-1,2,3,6-tetrahydro-1,3-diazapyrene (Va), which is evidently the first phenalenone with a condensed heterocyclic ring, is formed along with 6-acetyl-1,3-dimethylperimidone (IIa) in the acylation of 1,3-dimethylperimidone (Ia) with acetic acid in polyphosphoric acid (PPA). In view of the known theoretical significance of phenalenones and their occurrence in nature [3-5], we made a more detailed study of this reaction and also worked out other methods (including methods that were heretofore unknown in the chemistry of phenalenones) for recyclization that lead to the formation of compounds of the V type. It should emphasized that 1,3-dialkylperimidones are extremely convenient compounds for the study of recyclization reactions, since the peri positions in them are uniquely accessible to electrophilic attack. This is explained by the fact that the 4 and 9 positions are blocked by N-alkyl groups [2, 6, 7], whereas the 5 and 8

*See [1] for communication XXXIII.

Rostov State University, Rostov-on-Don 344006.

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