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TRANSFORMATIONS OF SOME ALKALOIDS OF THE CARBOLINE SERIES UNDER THE INFLUENCE OF ALKALI

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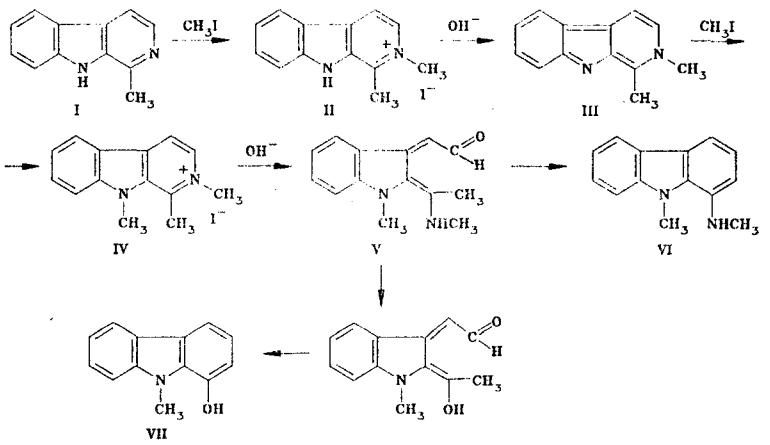
The reaction of quaternized forms of two alkaloids of the β-carboline series — harman and brevicarine — with alkali was investigated. It was established that, under the reaction conditions, the harman derivative undergoes recyclization of the pyridine part of the molecule, whereas in the analogous brevicarine derivative the pyridine ring does not undergo transformations.

The β-carboline ring is included in the composition of many natural and synthetic alkaloids with hypotensive, anti-inflammatory, and antipyretic activity [1-3]. These properties of derivatives of the group of isomeric carbolines for decades have led to the unflagging interest of chemists and pharmacologists, who have set out to search for new methods for the synthesis of these systems and to study their biological activity. The problems relating to the reactivities of carboline derivatives and their transformations under the influence of various agents have not been studied, although the presence in their structures of a π-deficient pyridine ring condensed with a typical π-surplus system (the indole fragment) makes it possible to expect the manifestation of interesting chemical properties, one of which may be the transformation of the ring under the influence of nucleophiles. The study of the transformation of these systems under the influence of nucleophiles, particularly the hydroxide



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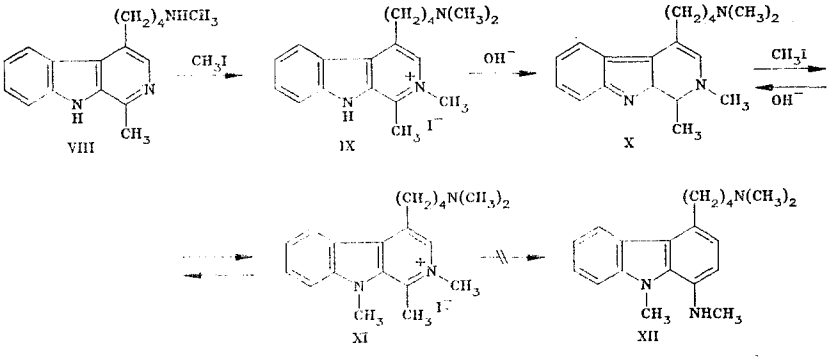
ion, helps one to arrive at an understanding of the mechanism of the influence of biologically active substances since, when they are introduced into the human organism and into animals, they enter into active aqueous media.

We have investigated the behavior of two alkaloids of the β-carboline type — harman (I) and brevicarine (VIII) — under the influence of a solution of alkali on their quaternized forms. We have previously shown that quaternary salts of 1,3-dimethyl-9H-pyrido[3,4-b]indole, under the influence of alcohol solutions of alkalis, undergo a number of transformations, both those involving ring transformation and those with no effect on the ring [4]. We found that harman methiodide II reacts also quite readily with alkali under mild conditions to give anhydro base II, as previously observed in [2]. This anhydro base is stable and does not undergo transformations even in the case of very prolonged heating with alkali. Methylharman methiodide IV, however, obtained by alkylation of anhydro base III, upon reaction with an alcohol solution of KOH, undergoes opening of the pyridine ring with the subsequent formation of open form V to give carbazole derivative VI. Compound VI is the principal reaction product but, in addition to it, we were also able to isolate a small amount of the hydroxy derivative (VII) of the carbazole.

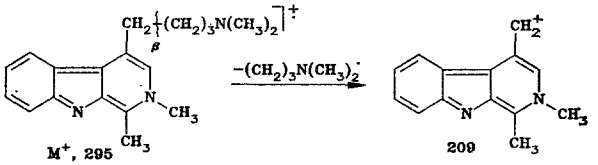
N-Methyl-1-hydroxycarbazole (VII) is formed as a result of side hydrolysis of open form V. We were unable to detect products of dealkylation or products of the transformation of the indole part of the molecule, as has been observed previously for the 1,3-9H-pyrido[3,4-b]indole system [4]. The structures of VI and VII were confirmed by the results of mass-spectrometric analysis. In the mass spectrum of carbazole VI one sees a molecular-ion peak (M^+) with m/z 210* (the isotopic correction of 16.6% found corresponds to the empirical formula $C_{14}H_{14}N_2$). The primary fragment ions are due to β elimination relative to the carbazole ring with the formation of $[M - H]^+$ and $[M - CH_3]^+$ ions; the $[M - CH_3]^+$ ion peak (195) is the maximum peak in the mass spectrum. Both processes lead to ring expansion to give cations that include an azatropylium fragment [5, 6]. The ensuing process, which is typical for nitrogen-containing heterocycles, is the successive ejection of neutral HCN (with respect to the number of heteroatoms) and C_2H_2 molecules from the $[M - CH_3]^+$ and $[M - H, -CH_3]^+$ ions to give fragment ions at 169, 168, 167, 142, 141, and 140, which retain a cyclic structure, as indicated by the appearance of rather intense peaks of doubly charged ions at 97.5, 84.5, and 83.5. The definite similarity in the mass-spectrometric fragmentation of VII suggests the existence of an identical heterocyclic system. An M^+ peak (at 197; the isotropic correction of 15.0% corresponds to the empirical formula $C_{13}H_{11}NO$) is recorded. In addition to the elimination of a hydrogen atom and a methyl radical from M^+ (ion peaks at 196 and 182, respectively), in the mass spectrum one observes ion peaks at 168, 167, 166, 154, and 153, which are due to splitting out of CO and CHO particles from both the M^+ ions and the $[M - H]^+$ and $[M - CH_3]^+$ ions. The indicated fragmentation processes are typical for hydroxy-substituted heterocyclic compounds. In addition, in the spectrum we recorded ion peaks at 141, 140, 139, 127, and 126, the appearance of which is explained by splitting out of an HCN molecule from the ions indicated above.

Brevicarine alkaloid VIII, which differs from harman only with respect to the presence of an aminoalkyl grouping in the 4 position of the system, behaves differently under the conditions described above. Upon reaction with methyl iodide, one observes quaternization of the pyridine nitrogen atom, but one also observes simultaneously alkylation of the side secondary amino group in the molecule, as a result of which quaternary salt IX is formed.



*Here and subsequently, the numbers that characterize the ions determine the m/z values.

As one should have expected, methiodide IX, upon reaction with an alcohol solution of alkali, undergoes deprotonation to give anhydro base X which, upon subsequent reaction with methyl iodide, gives a product of exhaustive alkylation, viz., salt XI. We assume that this quaternary salt, as in the preceding case, would, by the action of alkali, undergo opening of the pyridine ring and ultimately give carbazole derivative XII. However, we were unable to detect even traces of this product in the reaction mixture. Instead of the expected recyclization, we observed dealkylation of the system; of the two possible dealkylation pathways, viz., the pyridine and indole nitrogen atoms, we realized exclusively the second variant, which again leads to anhydro base X. We recorded an M^+ peak (295) in the mass spectrum of anhydro base X. An accurate measurement of the mass showed that it corresponds to the empirical composition $C_{19}H_{25}N_3$ (value found 295.2037; value calculated 295.2048). The initial processes in the fragmentation of M^+ involve the elimination of CH_3 (280), $(CH_3)_2N$ (251), $(CH_3)_2N(CH_2)_2$ (223), and $(CH_3)_2N(CH_2)_3$ (209) radicals. One might assume the characteristic β elimination of the substituent relative to the hetaryl ring, and then the structure of the substituent would be $(CH_3)_2N(CH_2)_4$. This fact was confirmed by intense fragment ions at 44 ($[N(CH_3)_2]^+$) and 58 ($[CH_2N(CH_3)_2]^+$). The data obtained suggest the following structure of the compound:



Additional evidence in favor of this structural assignment is provided by the PMR data. Signals of the following protons are recorded in the PMR spectrum: 1.84 (8H, s m, CH_2), 2.5 (3H, s, C—CH_3), 3.07 (6H, s, $N(CH_3)_2$), 3.42 (3H, s, CH_3—N), and 7.01-8.12 ppm, due to a group of aromatic protons (5H, s m, aromatic).

EXPERIMENTAL

The IR spectra of solutions of the compounds in chloroform were recorded with a UR-20 spectrometer. The PMR spectra of solutions in trifluoroacetic acid were recorded with a Tesla-80 spectrometer with hexamethyldisiloxane as the internal standard. The mass spectra* were obtained with a Variant MAT-311A spectrometer at an accelerating voltage of 3 kV, a cathode emission current of 1 mA, an ionizing voltage of 70 eV, and a sample vaporization temperature of 200-300°C (with direct introduction of the samples into the ion source).

Reaction of N-Methylharman Methiodide IV with an Alcohol Solution of Alkali. A suspension of 1 g (2 mmole) of N-methylharman methiodide IV in 10 ml of a saturated solution of alkali was maintained at 100°C for 30 h, after which it was cooled and poured into water, and the resulting precipitate was removed by filtration and purified with a column packed with activity II Al_2O_3 by elution with chloroform to give 0.2 g (43%) of N-methyl-1-methylaminocarbazole (VI) with mp 110-111°C (from methanol) and R_f 0.9 (chloroform, Al_2O_3). IR spectrum: 3320 cm^{-1} (NH). Mass spectrum, m/z (%): 51 (12), 63 (14), 76 (30), 77 (35), 83.5 (10), 84 (10), 84.5 (10), 89 (15), 90 (21), 97 (10), 97.5 (10), 115 (16), 123 (16), 140 (21), 141 (23), 142 (36), 167 (13), 168 (27), 169 (16), 194 (42), 195 (100), 196 (15), 209 (40), 210 (61), M^+ 211 (10). Found, %: C 80.1, H 6.5, N 13.4. $C_{14}H_{14}N_2$. Calculated, %: C 80.0, H 6.7, N 13.3. Workup of the succeeding fraction yielded 0.1 g (24%) of N-methyl-1-hydroxycarbazole (VII) with mp 93-94°C (from acetonitrile) and R_f 0.3 (chloroform, Al_2O_3). IR spectrum: 3590 cm^{-1} (OH). Mass spectrum, m/z (%): 51 (11), 63 (10), 76 (16), 77 (24), 83.5 (16), 89 (14), 89.5 (28), 98.5 (45), 126 (20), 127 (36), 139 (15), 140 (10), 141 (10), 153 (24), 154 (81), 165 (14), 167 (42), 168 (34), 182 (44), 196 (92), 197 (100), 198 (15). Found, %: C 79.1, H 5.7, N 7.2. $C_{13}H_{11}NO$. Calculated, %: C 79.2, H 5.6, N 7.1.

1-Methyl-4-(N,N-dimethylaminobutyl)-9H-pyrido[3,4-b]indole Methiodide (IX). A 2.8-g (20 mmole) sample of methyl iodide was added to 2.5 g (10 mmole) of brevicarine VIII in 40 ml of methanol, and the mixture was refluxed for 0.5 h. The precipitate was removed by filtration, washed with ether, and recrystallized from n-butanol to give 2.7 g (63%) of a product with mp 300-302°C. Found, %: C 53.8, H 6.2, N 10.0. $C_{19}H_{26}N_3$. Calculated, %: C 53.9, H 6.1, N 9.9.

*The intensities in the mass spectra are given in percent of I_{max}. The peaks with intensities ≥10% are presented.

1,2-Dimethyl-4-(N,N-dimethylaminobutyl)-9H-pyrido[3,4-b]indole (X). A suspension of 1.6 g (3 mmole) of IX in a saturated alcohol solution of alkali (KOH) was refluxed for 5 min, after which it was poured into water, and the resulting precipitate was removed by filtration to give 0.8 g (96%) of X with mp 174-175°C (from acetonitrile). IR spectrum: 1670 cm^{-1} (C=N). Mass spectrum, m/z (%): 42 (16), 44 (16), 58 (100), 84 (16), 142 (10), 167 (10), 209 (11), 210 (12), 223 (40), 224 (19), 235 (25), 238 (10), 251 (10), 280 (17), 295 (13). Found, %: C 77.5, H 8.4, N 14.3. $C_{19}H_{25}N_3$. Calculated, %: C 77.3, H 8.5, N 14.2.

1,9-Dimethyl-4-(N,N-dimethylaminobutyl)-9H-pyrido[3,4-b]indole Methiodide (XI). A mixture of 0.8 g (3 mmole) of X with excess methyl iodide was refluxed in 10 ml of methanol for 1 h, after which it was cooled and treated with ether. The resulting precipitate was removed by filtration and recrystallized from methanol to give 1 g (79%) of a product with mp 292-294°C. Found, %: C 54.8, H 6.7, N 9.5. $C_{20}H_{28}IN_3$. Calculated, %: C 54.9, H 6.4, N 9.6.

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MASS-SPECTROMETRIC STUDY OF NITRO-SUBSTITUTED DIHYDROSILAAZAANTHRONES

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The effect of the position of the nitro group on the character of the dissociative ionization of nitro-substituted dihydrosilaazaanthrones was studied. It was established that a change in the position of the nitro group in the molecule affects not only the probability of the occurrence of monotypic fragmentations but is also responsible for the development of new pathways of the fragmentation of the molecular ions. This makes it possible to identify the isomeric nitrodihydrosilaazaanthrones from their mass spectra.

The dissociative ionization of a new type of heterocyclic compounds, viz., dihydrosilaazaanthracenes that contain various substituents in the 9 position, was studied in [1-3]. The mass-spectrometric properties of such systems with substituents in the benzene and pyridine rings had not been previously studied, since these substances were unknown until recently.

In the present research we examined the mass-spectrometric behavior of 4(5,6,7,8)-nitro-10,10-dimethyl-9,10-dihydro-10-sila-2-azaanthrones (I-V) in order to establish the principles involved in the fragmentation as a function of the position of the nitro group. The mass spectra of the investigated compounds are presented in Table 1.

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