spectrum: 1590 (C=C), 2250 cm^{-1} (C≡N). PMR spectrum: 1.37 (6H, s, CH_3), 2.80 (2H, s, CH_2—C=C), 2.90 ppm (4H, CH_2CH_2).

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TRANSFORMATIONS OF THE SULFUR ANALOGS OF β-CARBOLINS UNDER THE INFLUENCE OF NUCLEOPHILES*

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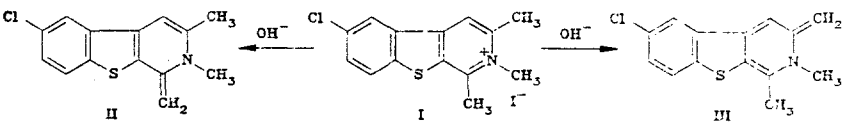
The reaction of the quaternary salts of some thienopyridines (the sulfur analogs of β-carbolins) with nucleophilic reagents was investigated. It was shown that either the methylene anhydro bases are formed or one or both heterocyclic rings are transformed, depending on the structure of the thienopyridine and on the reaction conditions.

Earlier [2] we showed that under the action of alcohol solutions of alkalis the quaternary salts of β-carbolins undergo a series of transformations both associated with the transformation of the ring and without such transformation. For instance, the reaction of the quaternary salts of β-carbolins not substituted at the NH group with alkali results in deprotonation with the formation of a stable anhydro base, which does not undergo further transformations. If, however, the NH group is substituted by an N-alkyl radical, the action of alkali leads to the products from the transformation of both rings (both the pyridine and the indole rings).

In the present work we undertook an investigation into the behavior of the quaternary salts of some thienopyridines (the sulfur analogs of β-carbolins) in reaction with nucleophiles. In the case of these compounds it is possible to trace the effect of the condensed thiophene ring on the reactivity of the adjacent pyridine ring and, in particular, in relation to nucleophilic reagents.

One of the subjects we selected for investigation was the methyl derivative of benzothioenopyridine (I), i.e., the closest structural analog of β-carbolins. It was found that the methiodide (I) eliminates a proton from one of the methylene groups in reaction with a methanol solution of methylamine and gives the stable methylene anhydro base (II). The formation of stable anhydro bases with an unsubstituted methylene group is an extremely rare effect, which is restricted to only a few examples [3, 4]:



*For the previous communication, see [1].

Donetsk State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 398-403, March, 1987. Original article submitted July 22, 1985.

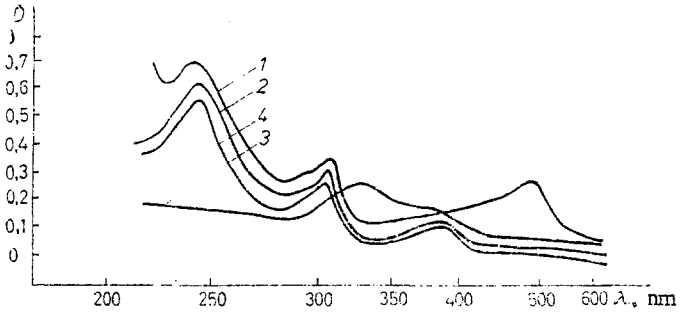


Fig. 1. The UV spectra of compound (II) (1-3) and of the methiodide (4): 1,4) in methanol; 2) in a methanol solution of HCl; 3) in a methanol solution of KOH.

The elimination of the proton in the salt (I) can take place also from the methyl group at position 3 of the pyridine ring, giving the anhydro base (III). In previous investigations of such systems [2, 5] it was shown that anhydro-bases with structure (II) are formed preferentially on account of the more acidic character of the proton in the methyl group at position 1.

The electronic spectrum of the anhydro base (II), recorded in a methanol solution of alkali, is characterized by the main band for the $\pi-\pi^*$ transition at 486 nm. When the electronic spectrum of the anhydro base (II) is recorded in methanol or water, there is a hypsochromic shift of the long-wave band of the $\pi-\pi^*$ transition to 390 nm, and the spectrum becomes close to the electronic spectrum of the initial cation (I) (Fig. 1). This is evidently due to the orientation of the solvent molecules at the main methylene group and, possibly, to the partial protonation of the anhydro base. With the addition of alkali to a methanol solution of the anhydro bases the long-wave band in the electronic spectrum is again shifted to 486 nm. However, the spectrum of the anhydro base, recorded in an aqueous solution of hydrochloric acid, fully reproduces the spectrum of the initial methiodide. This fact favors protonation of the anhydro base in proton-donating media at the methylene group. The anhydro base (II) is a weaker base than a series of previously investigated compounds [6], and its pK_a value is 7.35. The decrease in the basicity compared with the methylene anhydro bases of pyridine, quinoline, and isoquinoline is due to the effect of the annellated thiophene ring and, in particular, the electro-negative sulfur atom. The PMR spectrum (Fig. 2) contained signals for the three protons of the methyl groups in the form of singlets at the carbon (2.27 ppm) and nitrogen (3.15 ppm) atoms and also a doublet for the two protons of the methylene group (3.77 ppm). The proton at position 4 of the pyridine ring gives a clear singlet at 5.95 ppm. In addition, the spectrum contains a quartet, due to the presence of the proton at position 7 of the aromatic ring, at 7.30 ppm ($J_{7,8}$ = 10 Hz; $J_{7,5}$ = 2Hz). The proton at position 8 of the ring gives a doublet at 7.70 ppm ($J_{8,7}$ = 10 Hz), while the proton at the fifth carbon atom gives a doublet at 7.73 ppm ($J_{5,7}$ = 2 Hz). In the mass spectrum of the anhydro base (II) there are molecular ion peaks (M^+) with m/z 261:263 (3:1). The high intensity of the $(M + 2)^+$ ion is due to the presence of ^{37}Cl and ^{34}S isotopes in the molecule. The fairly high stability of the molecule (W_M = 11.8% of ΣI) to electron impact confirms the cyclic (aromatic) structure (about thienopyridines, which have structure similar in topology [7]). Thus, the initial data obtained from the mass spectrum confirm the structure of (II) [8]. In addition, from the mass spectrum it follows that the strongest recorded fragment ions demonstrate well the structure of the pyridine fragment of the molecule, including the substituents. The following fragment ions are seen (m/z): 247:249 (3:1) and 246:248 (3:1), the elimination of the CH_2 and CH_3 particles from the nitrogen heteroatom (in the presence of a methyl substituent in the heteroaryls at the nitrogen atom the process involving the removal of hydrogen with subsequent ring enlargement is preferred even under the conditions of ortho-substitution [8]); 233:235 (3:1), the removal of H_2CN from M^+, and 219:221 (3:1), the removal of CH_3CN from $[M - H]^+$ (these processes are characteristic of the pyridine ring); 205:207 (3:1), the ejection of the $CH_3N{=}CCH_3$ proton from M^+ by a mechanism of the retrodiene decomposition type indicates the positions of the substituents in the pyridine ring. The detection of the ion with m/z 184 is due to the elimination of Cl from the ion with m/z 219.

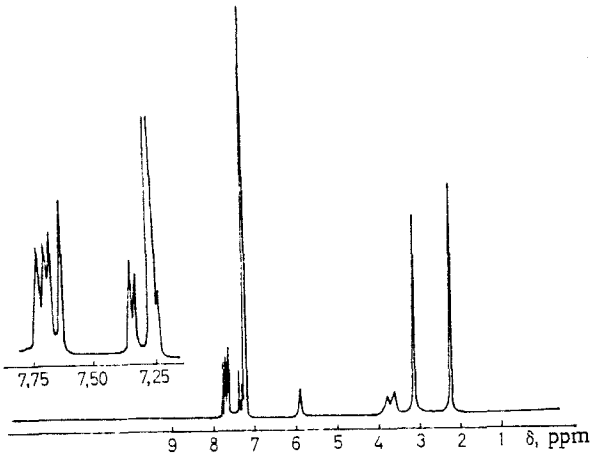
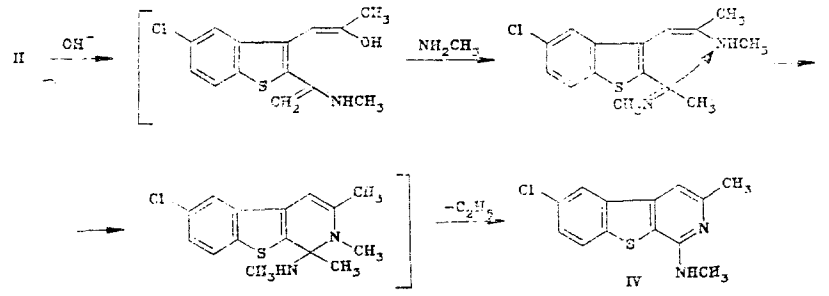


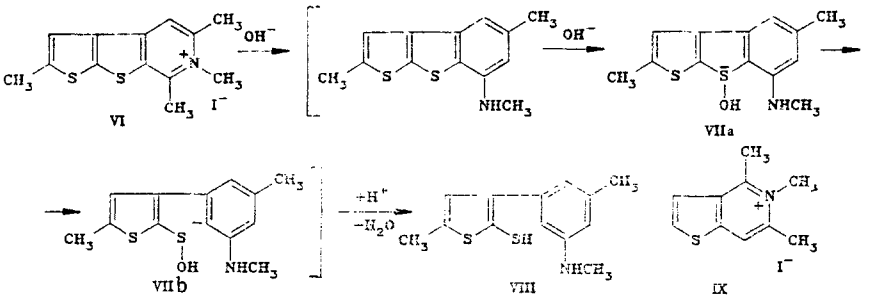
Fig. 2. The PMR spectrum of compound (II).

After a prolonged heating in an aqueous solution of methylamine in a sealed tube at 100°C, the anhydro base (II) undergoes transformations leading to the thienopyridine (IV).



The result of the reaction was for us quite unexpected. In no case had we observed such an effect during investigations in the series of β-carbolins; indeed, there are no analogies at all in reactions involving the recyclization of the pyridine ring, which have already been investigated fairly well. We suppose that reaction takes place with opening of the pyridine ring, subsequent exchange processes at the stage of the open form, and closure of a new ring, which is then aromatized to the thienopyridine (IV) with cleavage of a C—C bond. The ready cleavage of the carbon—carbon bond has been observed many times both by ourselves [9] and by a series of other authors [10]. It is quite likely that alternative reaction schemes are not excluded. The structure of (IV) was demonstrated by mass spectrometry. The mass spectrum contains a peak for M^+ with m/z 262:264 (3:1). According to the data from high-resolution mass spectrometry, the composition of the molecule is described by the formula $C_{13}H_{11}N_2{}^{35}ClS$ (found 262.0318, calculated 262.0331). The M^+ peak has maximum intensity in the mass spectrum, which favors the structure of a substance in the form of a condensed heteroaromatic system, and the latter is further confirmed by the detection of a doubly charged M^{2+} ion with m/z 131:132. The structure of the thienopyridine (IV) is also confirmed by the fragmentation. Thus, an ion with m/z 247:249 (3:1), $[M - CH_3]^+$ is recorded, and a Cl atom is eliminated directly from M^+ (an ion with m/z 227). Secondary dissociation processes associated with the removal of the CH_2NH and CH_3NH particles from the $[M - Cl]^+$ ions (m/z 198 and 197, respectively), characterize and confirm the presence of the $NHCH_3$ substituent in the molecule. For the ions given above the corresponding peaks of the doubly charged ions are recorded in the mass spectrum, and this once again confirms the assignment in favor of the cyclic condensed structure. The proposed structure of compound (IV) is also confirmed by the data from the PMR spectrum. The PMR spectrum contains a singlet at 2.26 ppm, due to the presence of the CH_3 group attached to the ring, and also a singlet for the three protons of the methyl group in the secondary amino group at 2.38 ppm. In addition, at 7.63 ppm there is a quartet due to the proton at position 7 of the aromatic ring ($J_{7,8}$ = 9 Hz and $J_{7,5}$ = 1.2 Hz), and at 7.78 ppm there is a singlet for the proton at the $C_{(4)}$ atom of the heteroaromatic ring. The protons at the $C_{(8)}$ and $C_{(5)}$ atoms correspond to doublets at 7.99 ppm ($J_{7,9}$ = 9 Hz) and 8.31 ppm ($J_{5,7}$ = 1.2 Hz). The proton of the amino group corresponds to a singlet at 9.40 ppm.

The heterocyclic thieno[2',3':2,3]thieno[2,3-c]pyridine system (V), which has hardly been studied at all, was synthesized recently [11]. In the case of this compound it is possible to trace the effect of the adjacent condensed ring on the behavior of the system during nucleophilic attack. It was found that the methiodide of this thienopyridine (VI) behaves quite differently in reaction with nucleophiles. When the salt (VI) is heated with a methanol solution of alkali at 120°C in a sealed tube, the pyridine ring opens with subsequent closure of a new benzene ring at one of the side methyl groups. It is interesting that the C—S bond in the adjacent thiophene ring is cleaved simultaneously with this process, as a result of which N-methyl-5-(2-methyl-5-mercapto-4-thienyl)-meta-toluidine (VIII) is formed:



The transformations of the pyridine ring in the molecule take place by the usual mechanism, as has been observed many times before, and we do not therefore give details of this process in the reaction scheme. The opening of the thiophene ring is also nucleophilic in nature and takes place as a result of attack by the nucleophile on the sulfur atom, which has free d orbitals with the formation of the intermediate anion (VIIa) and then the anion (VIIb), as described in [12].

The mass spectrum of (VIII) contains a peak for M^+ with m/z 249 (found, 249.0633, calculated for $C_{13}H_{15}S_2N$ 249.0646). In addition to the strong peaks of the fragment ions $[M - H]^+$ and $[M - CH_3]^+$, which characterize the β-cleavage in relation to the aryl and heteroaryl rings, the ejection of a sulfur atom and the elimination of the SH particle are observed (m/z 217 and 216, respectively). The last two processes are specific for the thiol group. The presence of ortho-substitution promotes cleavage of the bond between the rings [an ion with m/z 129 (the thienyl fragment) and 120 (the aniline fragment)], and this characterizes the structure of (VIII).

During an attempt to realize the recyclization of the methiodide of thienopyridine (IX) itself with the non-annellated thiophene ring we obtained an unidentifiable mixture of high-molecular-weight products, which are clearly formed as a result of the opening of the two heterocyclic rings and subsequent polymerization of the unsaturated aliphatic intermediates. To judge from the results of the experiments described above the presence of the aromatic or heteroaromatic ring condensed with the thiophene ring in the thienopyridine molecule is an essential condition for successful realization of the recyclization reaction, having a stabilizing effect on the system as a whole.

EXPERIMENTAL

The IR spectra were recorded in chloroform and Vaseline oil on a UR-20 instrument. The UV spectra were obtained in methanol and water on a Specord UV-vis instrument. The PMR spectra were recorded on a Brucker WH-90 instrument in DMSO-D_6 with TMS as internal standard. The mass spectra were recorded on a Varian MAT-311A instrument with direct injection and with a cathode emission current of 1000 μA, an ionizing potential of 70 eV, and an accelerating potential of 3 kV. The high-resolution mass spectra were recorded under the same conditions on a Jeol JMS-01-SG2 instrument. The pK_a values were determined by a potentiometric method on a pH-340 pH-meter by titration of a solution of the compound (10^{-3} M) in a 10% methanol solution of hydrogen chloride (10^{-2} M). The pK_a value was taken as equal at the half-neutralization point. Chromatography in an unfixed thin layer of aluminum oxide of II Brockman activity was realized with chloroform as eluant and iodine vapor as developer.

1-Methylene-2,3-dimethyl-6-chloro-1,2-dihydrobenzo[b]thieno[2,3-c]pyridine (II). A suspension of 1 g (26 mmole) of 1,2-dimethyl-6-chlorobenzo[b]thieno[2,3-c]pyridine methiodide (I) in 10 ml of a saturated methanol solution of methylamine was kept at 70°C for 40 min.

The precipitate was filtered off, washed with water, and recrystallized from methanol. The yield was 0.52 g (78%); mp 214-215°C. UV spectrum, λ_{max} (log ε): 390 (4.03), 486 nm (4.08); pK_a 7.35. Mass spectrum, m/z (%): 56 (9); 92 (4); 126 (6); 130.5 (13); M^{2+}; 139 (9); 171 (18); 183 (7); 184 (46); 185 (20); 196 (7); 197 (7); 205 (20); 207 (7); 219 (23); 220 (6); 221 (8); 233 (17); 235 (6); 246 (47); 247 (46); 248 (24); 249 (16); 260 (25); 261 (100); 262 (23); 263 (44). Found, %: C 64.3, H 4.8, N 5.2, S 12.4. $C_{14}H_{12}ClNS$. Calculated, %: C 64.4, H 4.6, N 5.4, S 12.3.

1-Methylamino-3-methyl-6-chlorobenzo[b]thieno[2,3-c]pyridine (IV). A suspension of 0.26 g (1 mmole) of the anhydro base (II) in 10 ml of an aqueous solution of methylamine was kept at 100°C for 20 h. On cooling, the precipitate was filtered off and recrystallized from a 1:2 mixture of chloroform and hexane. The yield was 0.45 g (45%); mp 218-219°C, R_f 0.45. IR spectrum: 3320 cm^{-1}. Mass spectrum, m/z (%): 79 (5); 91 (10); 91.5 (7); 92 (9); 104 (12); 113 (20); 113.5 (9); 131 (14); 132 (5); 139 (11); 184 (32); 185 (6); 197 (22); 198 (28); 199 (10); 227 (12); 247 (70); 248 (13); 249 (26); 261 (33); 262 (100); 263 (17); 264 (34). Found, %: C 59.6, H 4.2, N 10.8, S 12.1. $C_{13}H_{11}ClN_2S$. Calculated, %: C 59.5, H 4.2, N 10.7, S 12.2.

N-Methyl-5-(2-methyl-5-mercapto-4-thienyl)-m-toluidine (VIII). A suspension of 0.74 g (2 mmole) of thieno[2',3':2,3]thieno[2,3-c]pyridine (VI) in 10 ml of a saturated methanol solution of potassium hydroxide was kept at 100°C for 8 . On cooling the mixture was poured into water, and the precipitate was filtered off and purified on a column of aluminum oxide with chloroform as eluant. The yield was 0.2 g (41%); mp 223-225°C (from a 1:2 mixture of chloroform and hexane), R_f 0.6. IR spectrum: 3320 (NH); 2550 cm^{-1} (SH). Mass spectrum, m/z (%): 77 (13); 89 (10); 92 (16); 93 (17); 96 (15); 105 (20); 120 (13); 128 (10); 129 (35); 216 (46); 217 (39); 233 (70); 234 (100); 248 (32); 249 (55); 250 (7). Found, %: C 62.5, H 6.1, N 5.7, S 25.3. $C_{13}H_{15}NS_2$. Calculated, %: C 62.6, H 6.0, N 5.6, S 25.7.

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