<u>1-Methyl-8-amino-9-cyano-2,3,4,5-tetrahydropyrido[4,3-b]azepine (X).</u> A mixture of 16.3 g (0.73 mole) of IX and 180 ml of an alcoholic solution of ammonia was heated in a bomb for 16 h at 200°C, cooled, and 12 g of the amino-compound X filtered off, yield 81%, mp 200-201°C (from DMF). Found: C 65.0; H 7.2; N 28.0%. $C_{11}H_{14}N_{4}$. Calculated: C 65.4; H 6.9; N 27.7%.

<u>1-Methyl-8-amino-2,3,4,5-tetrahydropyrido[4,3-b]azepine (V).</u> A solution of 4 g (0.02 mole) of the aminocyano-compound X was heated in 62 g of PPA at 160-170°C for 4 h, cooled, poured into 250 ml of water, extracted with chloroform (4 \times 50 ml), the combined extracts dried over Na₂SO₄, filtered evaporated, and the residue triturated with heptane to give 2.7 g of V, yield 76%, mp 84-85°C (sublimation). Found: C 67.5; H 8.9; N 24.0%. C₁₀H₁₅N₃. Calculated: C 67.8; H 8.5; N 23.7%.

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REARRANGEMENT OF 2-HETARYLALKYLPYRIDINIUM SALTS

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The rearrangement of 2-thienyl- and 2-furylalkylpyridinium salts to the corresponding anilines by the action of methylammonium sulfites has been studied. It has been shown that the rearrangement of these salts is accompanied in many cases by the formation of phenols and dealkylation products. The influence of the length of the alkyl chain between the heterocyclic rings on the ratio of the rearrangement products has been investigated.

It has been demonstrated earlier that the quaternary salts of 2-(2-phenylethyl)pyridinium are rearranged into 2-benzyl-N-alkylanilines under the action of aqueous solutions of alkylammonium sulfites [1]. It has also been found that under these conditions the 2-benzylpyridinium salts are rearranged into o-alkylaminobiphenyls [2]. In the present work we have investigated the rearrangement of pyridinium salts in which the pyridine ring is connected to furan or thiophene in the α -position through one or two methylene groups. With this in mind we have synthesized 2-(2-thienylethyl)- and 2-(2-furylethyl)pyridines (la,b) and obtained their quaternary salts IIa,b.

It has been found that, under the action of an aqueous solution of methylammonium sulfite (heating in a sealed ampul at 185°C), the salt IIa is rearranged with a yield of 80% into 2-(2-thienylmethyl)-N-methylaniline (IIIa). The rearrangement of salt IIb into 2-(2furylmethyl)-N-methylaniline was achieved with a yield of 40% when the reaction temperature was reduced to 150°.



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In both cases the rearrangement was accompanied by the simultaneous dealkylation of the pyridine ring due to the attack of the nucleophilic reagent on the carbon atom of the N-methyl group as this is usually the case in such systems.



The IR spectra of the obtained anilines IIIa, b contain a valence oscillation band of the NH group in the region of 3370 cm^{-1} which is characteristic for aromatic amines. The PMR spectra of compounds IIIa, b show a singlet of the three protons of the methyl group in the region 2.7-2.9, a singlet of the two protons of the methylene group in the region 4.0, and a broadened singlet of the proton of the NH group in the region 3.8 ppm. The mass spectra* of compounds IIIa, b show maximum intensity peaks of the molecular ions 203 and 187 respectively that are equal to the molecular mass of these compounds. The main directions for the decomposition of the molecular ions are by splitting off of a methyl radical or of the entire aminomethyl group; this is evidently accompanied by cyclization of the radical centers formed via the charged atom of the heterocycle. The M-CH₃ ions further eliminate NHX with the formation of a 141 fragment which is common to both compounds.



In order to establish the effect of the length of the alkyl chain between the heterocyclic rings on the direction of the reaction, we have studied the rearrangement of models with one methylene unit. For this purpose we have prepared, starting from 2-cyanopyridine and metalloorganic derivatives of thiophene and furan, 2-thienyl- and 2-furyl-2-pyridyl ketones [3]; the latter were then reduced to the compounds Ic, d and converted by quaternization with methyl iodide to the quaternary salts IIc, d.



The PMR spectra of the bases Ic, d are characterized by a singlet of the two protons of the methylene group in the region 4.2-4.4 ppm. The quaternization of compounds Ic,d was performed in an argon atmosphere in a sealed ampul by heating on a water bath. The rearrangement was carried out right after formation of the salts due to their instability. The reaction of 1-methyl-2-(2-thienylmethyl)pyridinium iodide with the methylammonium sulfite lead to a rearrangement which gave 2-(2-thienyl)-N-methylaniline (IIIc); 2-(2-thienyl)phenol (IVc) (25-30%) and 2-(2-thienylmethyl)pyridine (Ic) were also isolated from the reaction mixture and identified. The formation of phenol in the rearrangement of salt IIc is evidently due to the reduced rearrangement ability of the enamine fragment of the opened intermediate, conjugated with the 5-membered heterocycle, in comparison with the enol form of the molecule. Hydrolysis of the enamine fragment of the intermediate and subsequent ring formation lead to the formation of phenol IVc. The bases Ic, dare formed by nucleophilic attack on the non-ring carbon atom linked to the heteroatom.

*Here and in the further text the values of m/z are given for the ion peaks; the intensities in % of the maximum peak are given in brackets. Ion peaks with intensities higher than 10% are shown. The PMR spectrum of compound IIIc contains a singlet of the three protons of the methyl group in the region 2.8 and a singlet of the proton of the NH group in the region 4.2 ppm. In distinction from compound IIIc the IR spectrum of compound IVc contains a valence oscillation band of the hydroxyl group in the region 3560 cm^{-1} . A singlet of the proton of the hydroxyl group in the region 5.6 ppm is present in the PMR spectrum of this compound.



The reaction of 1-methyl-2-(2-furylmethyl)pyridinium iodide with methylammonium sulfite proceeds in the same way. GLC-mass spectrometry showed the presence of three substances in the reaction mixture: 2-(2-furyl)-N-methylaniline (IIId), 2-(2-furyl)phenol (IVd), and 2-(2-furylmethyl)pyridine (Id). In the mass spectra of the anilines IIIc,d the peaks of the molecular ions 189 and 173 respectively show the maximum intensities; however, these compounds are less resistent towards electron impact than compounds IIIa-c that contain amethylene bridge between the hetero- and the carbocycle and decompose with rupture of the heterocycle. The thienyl derivative splits off a HS radical and the furyl derivative a HCO radical.

Thus, in the present work we have studied for the first time the enamine rearrangement of hetarylalkylpyridinium salts, containing one or two methylene groups in the α -position to the heterocycle. It has been shown that 2-hetarylmethyl-N-methylanilines are the main product of rearrangement of the hetarylethylpyridinium salts. The rearrangement of the 2-hetarylmethylpyridinium salts to the corresponding anilines is accompanied by a side reaction which leads to the formation of phenols.

EXPERIMENTAL

The IR spectra were taken on an UR-20 (in Vaseline oil) and an IKS-22 spectrometer (as a film); the PMR spectra were obtained on Varian T-60 and Tesla BS-497 spectrometers (working frequency 100 MHz, internal standard TMS). The mass spectra were obtained on a MKh-1303 spectrometer with direct introduction of the sample into the ionization chamber with an ionization energy of 50 eV. The GLC-mass spectra were taken on a Varian MAT-112 chromatograph with a OV-17 column (l = 1.8 m) and a Varian MAT-44S chromatograph with an SE-54 capillary column (l = 25 m). The progress of the reaction was controlled by means of LKhM-3 chromatograph (model 3) with a SE-30 column (l = 3 m), packed with N-AW.

2-(2-thienylethyl)pyridine (Ia)(yield 39%, mp 79-81° from ethanol) and 2-(2-furylethyl)pyridine (Ib) (yield 43%, bp 99-101°, 1 mm, n_D^{20} 1.5132) were prepared according to [4] from α -picoline and 2-carbethoxythiophene, and 2-carbethoxyfuran.

2-(2-Thienylmethyl)pyridine (Ic) was prepared in the same way as compound Ia from 2thienyl-2-pyridyl ketone, yield 80%, bp 258-260° (1 mm). PMR spectrum (CCl₄): 4.3 (2H, s, CH₂); 6.8-7.6 (6H, m, 3,4,5-H of thiophene, 3,4,5-H of pyridine); 8.4-8.6 ppm (1H, m, 6-H of pyridine). Mass spectrum: 175 (100), 129 (25), 97 (46), 78 (10), 77 (11). Found: C 68.2; H 5.0; N 8.2%. C₁₀H₉NS. Calculated: C 68.6; H 5.1; N 8.0%.

2-(2-Furylmethyl)pyridine (Id) is obtained in the same way as compound Ia from 2-furyl-2-pyridyl ketone, yield 75%, bp 170-172° (1 mm). PMR spectrum (CC14): 4.1 (2H, s, CH₂), 6.0 (1H, m, 4-H of furane); 6.2 (1H, m, 3-H of furane); 6.8-7.8 (4H, m, 5-H of furane, 3,4,5-H of pyridine). Mass spectrum: 159(100), 130 (132), 81 (37), 78 (10), 77 (12). Found: C 74.5; H 5.8; N 9.0%. C10H9NO. Calculated: C 74.8; H 5.6; N 8.8%.

<u>1-Methyl-2-(2-thienylethyl)pyridinium Iodide (IIa).</u> A mixture of 0.55 g (3 mmoles) of compound Ia and 1.4 g (10 mmoles) methyl iodide is kept for 24 h at room temperature. The precipitated salt is filtered off and washed with acetone. Yield 0.9 g (92%), mp 208-210° (from acetone). Found I 38.6%. $C_{12}H_{14}INS$. Calculated I 38.4%.

l-Methyl-2-(2-furylethyl)pyridinium Iodide (IIb) is obtained in the same way as salt IIa, starting from compound Ib; yield 80%. mp 203-204° (from acetone). Found: I 40.6%. $C_{12}H_{14}INO$. Calculated: I 40.3%.

<u>1-Methyl-2-(2-thienylmethyl)pyridinium Iodide (IIc)</u>. A mixture of 0.18 g (1 mmole) of compound Ic and 0.5 g (3 mmoles) of methyl iodide is heated in a sealed ampul for 2 h in an argon atmosphere at 100°. The precipitate is recrystallized from acetone, yield 0.27 g (85%), mp 140-142°. Found: I 40.3%. $C_{11}H_{12}INS$. Calculated: I 40.1%.

l-Methyl-2-(2-furylmethyl)pyridinium Iodide (IId) is obtained in the same way as salt IIc starting from compound Id, yield 73%, mp 127-129° (from acetone). Found: I 42.3%. $C_{11}H_{12}INO$. Calculated: I 42.2%.

Rearrangement of 1-Methyl-2-(2-thienylethyl)pyridinium Iodide (IIa). A mixture of 0.33 g (1 mmole) of salt IIa, 2 ml of 50% aqueous solution of methylammonium sulfite and 2 ml of 25% aqueous methylamine is heated in a sealed ampul for 12 h at 185°. After cooling the reaction mixture is extracted with ether (3 × 10 ml), and dried with magnesium sulfate. The ether is evaporated and the residue separated on a silica gel column (100 × 160 µm) with benzene as the eluent. Yield 2-(2-thienylmethyl)-N-methylaniline (IIIa) 0.15 g (75%), mp 47-48° (from benzene). IR spectrum: 3420 cm⁻¹ (NH). PMR spectrum (CC1₄): 2.7 (3H, s, CH₃): 3.5 (1H, s, NH): 4.0 (2H, s, CH₂): 6.5-7.8 ppm (7H, m, arom.). Mass spectrum: 203 (100), 188 (46), 173 (57), 155 (21), 141 (28), 118 (45), 107 (49), 88 (12). Found: C 70.5; H 6.6: N 7.0%. C₁₂H₁₃NS. Calculated: C 70.8; H 6.4; N 6.9%. 2-(2-thienyl)pyridine (Ia) was separated with a yield of 5% besides substance IIIa, mp 79-81° [4].

Rearrangement of 1-Methyl-2-(2-furylethyl)pyridinium Iodide (IIb). As in the preceding synthesis 0.32 g (1 mmole) of salt IIb gave at 150° after separation of the reaction mixture on a column: 0.08 g (44%) 2-(2-furylmethyl)-N-methylaniline (IIIb), mp 41-42° (from hexane). IR spectrum: 3380 cm⁻¹ (NH). PMR spectrum (CC1₄): 2.8 (3H, s, CH₃); 3.6 (1H, s, NH); 3.85 (2H, s, CH₂;)5.9-6.2 (2H, m, 3,4-H of furane); 6.5-7.7 ppm (5H, m, 5-H of furane, arom.). Mass spectrum: 187 (100), 186 (17), 172 (22), 157 (36), 144 (36), 141 (14), 131 (12), 118 (13), 91 (11). Found: C 77.2; H 6.8; N 7.3%. $C_{12}H_{13}NO$. Calculated: C 77.0; H 7.0; N 7.5%. 2-(2-Furylethyl)pyridine (Ib) was separated with a yield of 4% besides compound IIIb, $n_D^{2°}$ 1.5132 [4].

Rearrangement of 1-Methyl-2-(2-thienylmethyl)pyridinium Iodide (IIc). As in the preceding synthesis 0.32 g (1 mmole) of salt IIc gave after separation of the reaction mixture on a column 0.12 g (60%) 2-(2-thienyl)-N-methylaniline (IIIc). IR spectrum: 3420 cm⁻¹(NH). PMR spectrum (CCl₄): 2.8 (3H, s, CH₃); 4.3 (1H, s, NH); 6.5-7.6 ppm (7H, m, arom.). Mass spectrum: 189 (100), 156 (21), 154 (11), 144 (12), 130 (23), 117 (45). The benzoyl derivative was prepared, mp 169-170° (from ethanol). Found: C 73.3; H 4.9%. $C_{17}H_{13}NOS$. Calculated: C 73.2; H 4.7%; 0.05 g (24%). 2-(2-thienyl)phenol (IVc) was also obtained, mp 51-52° (from ethanol). IR spectrum: 3500 cm⁻¹(OH). PMR spectrum (CCl₄): 5.6 (1H, s, OH); 6.8-7.5 ppm (7H, m, arom.). Mass spectrum: 176 (100), 147 (21), 131 (25), 115 (16), 77 (12). Found: C 68.4; H 4.6%. $C_{10}H_8OS$. Calculated: C 68.2; H 4.5%; 2-(2-thienylmethyl)pyridine (Ic) was also isolated, yield 3%, identical to the reference sample, besides compounds IIIc and IVc.

Rearrangement of 1-Methyl-2-(2-furylmethyl)pyridinium Iodide (IId). As in the preceding synthesis, three substances were identified by GC-MS in the reaction mixture after rearrangement of 0.3 g (1 mmole) of salt IId: 2-(2-furyl)-N-methylaniline (IIId) (mass spectrum: 173 (100), 172 (18), 144 (45), 143 (17), 130 (51), 117 (67), 115 (23), 103 (10)); 2-(2-furyl)-phenol (IVd) (mass spectrum: 160 (100), 131 (36), 117 (24), 115 (21), 77 (10)); and 2-(2-furyl)-furylmethyl)pyridine (Id) (mass spectrum: 159 (100), 130 (32), 81 (37), 78 (10), 77 (12)).

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