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REACTION OF 5-BROMO-6-AMINO-3-(4-METHYLAMINOBUTYL)PYRIDINE WITH POTASSAMIDE

V. G. Klimenko, A. M. Zhidkova,
F. M. Stoyanovich, and V. G. Granik

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It has been found that potassamide reacts with 5-bromo-6-amino-3-(4-methylaminobutyl)pyridine to give a mixture of the starting material, 6-aminonicotine, and 1-methyl-8-amino-2,3,4,5-tetrahydro[4,3-b]azepine. The latter has been obtained independently from 1-methyl-9-cyano-2,3,4,5,7,8-hexahydropyrido[4,3-b]azepin-8-one.

It has previously been shown [1] that the reaction between potassamide and 5-bromo-2-amino-3-(4-methylaminobutyl)pyridine (I) affords a mixture of 2-aminonicotine (II) and 1-methyl-6-amino-2,3,4,5-tetrahydropyrido[4,3-b]azepine (III). However, when the isomeric 5-bromo-6-amino-3-(4-methylaminobutyl)pyridine (IV) was used in this reaction, no reliable data could be obtained for the occurrence of similar heterocyclization reactions [1].

The aim of this investigation was to examine the reaction of the substituted pyridine IV with potassamide, which, as in the case of compound I, could involve an intermediate 3,4-dehydro-compound. The reaction of the pyridine IV with potassamide was carried out under the conditions described in [1]. A mixture of compounds was obtained which proved extremely difficult to separate, and it was not possible to obtain the components of the mixture in the pure state. Consequently, in the initial stages of the investigation attempts were made to synthesize independently 1-methyl-8-amino-2,3,4,5-tetrahydropyrido[4,3-b]azepine (V), which is presumed (by analogy with the findings in [1]) to be a product of the reaction of the pyridine IV with KNH_2. The bicycle V was synthesized as follows: condensation of N-methylcaprolactam diethyl acetal VI with cyanoacetamide afforded the enaminoamide VII, which was cyclized with dimethylformamide diethyl acetal to 1-methyl-9-cyano-2,3,4,5,7,8-hexahydropyrido[4,3-b]azepin-3-one (VIII) [2]. The latter was treated with phosphoryl chloride in the presence of triethylamine hydrochloride (the use of NN-diethylaniline gave much lower yields) to give high yields of the 8-chloro-compound IX, which was reacted with ammonia to give 1-methyl-8-amino-9-cyano-2,3,4,5-tetrahydropyrido[4,3-b]azepine (X). On heating X with polyphosphoric acid, the cyano-group was hydrolyzed followed by decarboxylation to yield the bicycle V.

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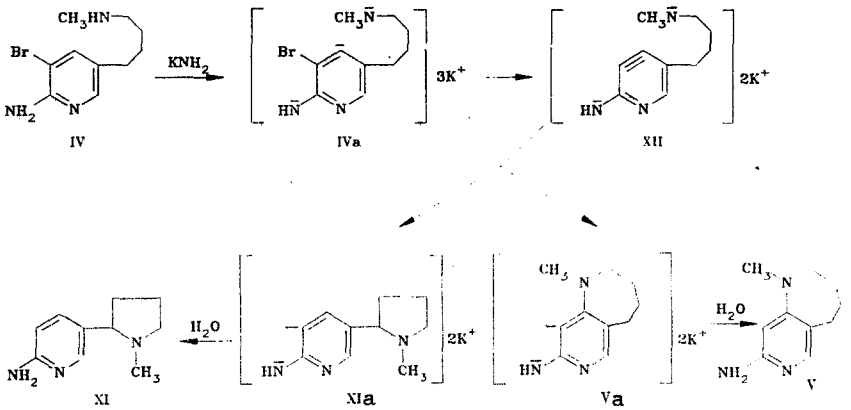
TABLE 1. PMR Spectral Parameters of IV, V, XI, and the Mixture of Products from the Reaction of IV with Potassamide

Compound	Chemical shifts of protons, ppm					
	2-H	4-H	5-H	$N-CH_3$	NH_2	alicyclic protons
IV	7,74, d	7,39, d	—	2,32, s	5,03, br	
XI	7,86, m	7,36, m	6,33, m	2,06, s	5,02, br	1,48—2,32, m, 2,83—3,13,m
V	7,55, s	—	5,79, s	2,80, s	4,31, br	1,68,m ; 2,57,t , 3,05,t
Mixture of products from the reaction of (IV) with potassamide	7,86 7,75 7,51	7,37	6,34 5,76			

TABLE 2. UV Spectra of IV, V, and XI, and the Mixture of Products from the Reaction of IV with Potassamide

Compound	Maximum 1			Maximum 2			Minimum, λ, nm
	λ, nm	D	lg ε	λ, nm	D	lg ε	
IV	236,1	0,23	4,05	312,1	0,11	3,73	272,7
XI	239,1	0,30	4,18	302,8	0,08	3,59	268,3
V	230,4	0,54	4,43	287,0	0,17	3,94	261,0
Mixture of products from the reaction of (IV) with potassamide	235,2	0,69		310,6	0,29		272,7



The IR spectrum (CCl_4) of V contained bands at 980, 1030, 1100, 1240, 1450, 1490, 1550, 1600 (pyridine ring), 2825, 2835, 2910, 2960, 2980 (CH_2 and CH_3 groups), 3370 and 3470 cm^{-1} (NH_2). The PMR spectrum ($CDCl_3$) showed signals at 1.68 (4H, m, 3,4-CH_2CH_2), 2.57 (2H, m, 5-H), 3.05 (2H, m, 2-H), 2.80 (3H, s, N-CH_3), 4.31 (2H, br. s, disappeared on adding D_2O, NH_2), 5.79 (1H, s, 9-H), and 7.55 ppm (1H, s, 6-H).

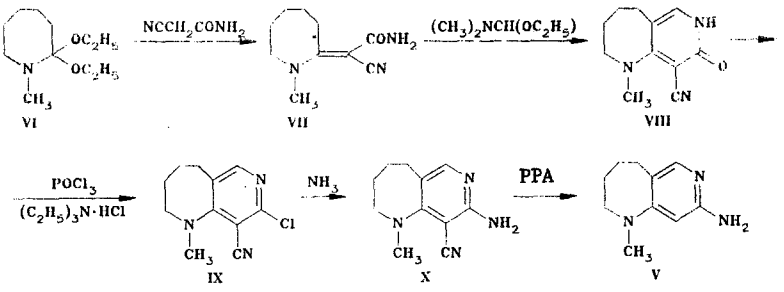
The mixture of compounds obtained from the reaction of IV with KNH_2 was analyzed by thin-layer and gas chromatography, and UV and PMR spectroscopy. Thin layer chromatography showed that apart from the starting material IV, the mixture contained two compounds with the same mobilities as 6-aminonicotine (XI) and the pyridinoazepine V respectively. GLC analysis gave similar results.

The PMR spectra of the pure compounds IV, V, XI, and the mixture of these obtained by reacting V with KNH_2 were obtained (Table 1). Examination of these spectra showed that in addition to the starting material IV, the mixture contained the aminonicotine XI (doublet at around 6.34 ppm) and the bicycle V (singlets at around 7.51 and 7.75 ppm). The successive

addition to the ampul containing the reaction mixture of authentic samples of V and XI resulted in increases in the intensity of the appropriate peaks. No other reaction products were observed. From the integral intensities in the PMR spectrum, the quantitative composition of the reaction mixture was calculated for IV, XI, and V (93, 3, and 4% respectively). The yield of new reaction products based on starting material was 3.5% for XI and 5% for V.

The UV spectra in 96% ethanol were also recorded for the same samples of IV, V, and XI and the reaction mixture (Table 2). Examination of these spectra showed that using this method it is also possible to calculate the amount of the bicycle V in the reaction mixture, although the accuracy of this method is low. The analysis was carried out at 274 nm, the amount of the bicycle V found by this method being substantially higher than that found by PMR (<10%).

It has therefore been shown that the reaction of (IV) with potassamide in a boiling mixture of benzene and ether affords the two cyclization products V and XI.



It is assumed that both compounds are formed from a common intermediate, namely the highly reactive 6-amino-3-(4-methylaminobutyl)-4,5-dehydropyridine (XII). Compound XI appears to be formed as a result of the transfer of a hydride ion from the α-carbon atom of the side chain to the 4,5-dehydro bond and nucleophilic attack of the terminal methylamide anion on the α-carbon atom. Formation of V requires nucleophilic attack of the terminal methylamide anion on the 4,5-dehydro bond (at the 4-position of the pyridine ring).

EXPERIMENTAL

PMR spectra were obtained on a BS-497 instrument (100 MHz) (Czech SSR) in $CDCl_3$, internal standard HMDS, IR spectra on a UR-20 spectrometer (East Germany) for the 3% solutions in CCl_4, and UV spectra on a Specord M40 spectrophotometer (East Germany) in 96% ethanol. TLC was carried out on alumina in the system benzene–ethanol, 3:1 (the R_f values of IV, V, and XI were 0.27, 0.64, and 0.82 respectively). GLC was carried out using an LKhM-7A chromatograph (catharometer, column with PEGA/KhrR, temperature 185–215°C).

Reaction of 5-Bromo-6-amino-3-(4-methylaminobutyl)pyridine (IV) with Potassamide. To 0.2 mole of KNH_2 (from 7.8 g of potassium and 300 ml of liquid ammonia) was added a solution of 5.2 g (0.02 mole) of 5-bromo-6-amino-3-(4-methylaminobutyl)pyridine (IV) [1] in 250 ml of dry benzene. The mixture was boiled for 2 h with stirring, then cooled, 100 ml of ethanol added, and the solution filtered and evaporated to dryness. The residue was dissolved in dilute HCl, and the acid was then neutralized and the solution saturated with potassium carbonate. The semicrystalline mass was extracted with acetone, and the extract filtered and evaporated. The residue was boiled several times with benzene, and the solution treated with activated charcoal and evaporated to dryness. The residue was a dark brown oil (4.3 g). Analysis of the oil by PMR spectroscopy gave a IV:V:XI ratio of 93:4:3%.

1-Methyl-8-chloro-9-cyano-2,3,4,5-tetrahydropyrido[4,3-b]azepine (IX). A mixture of 15.7 g (0.77 mole) of VIII in 80 ml of $POCl_3$ and 8 g of triethylamine hydrochloride was boiled for 1.5 h, the $POCl_3$ distilled off under reduced pressure, and the residue treated with chloroform followed by 1 N NaOH until the pH of the aqueous layer was 9-10. The layers were then separated, the aqueous layer extracted with chloroform (3 × 20 ml), and the combined extracts dried over Na_2SO_4, filtered, and evaporated to give 16.3 g of IX, yield 95%, mp 88-89°C (from propan-2-ol). Found: C 59.5; H 5.3; Cl 16.0; N 19.1%. $C_{11}H_{12}ClN_3$. Calculated: C 59.6; H 5.4; Cl 16.0; N 19.0%.

1-Methyl-8-amino-9-cyano-2,3,4,5-tetrahydropyrido[4,3-b]azepine (X). 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%.

1-Methyl-8-amino-2,3,4,5-tetrahydropyrido[4,3-b]azepine (V). 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 × 50 ml), the combined extracts dried over Na_2SO_4, 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%. $C_{10}H_{15}N_3$. Calculated: C 67.8; H 8.5; N 23.7%.

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REARRANGEMENT OF 2-HETARYLALKYLPYRIDINIUM SALTS

A. N. Rumyantsev, V. I. Terenin, and L. G. Yudin

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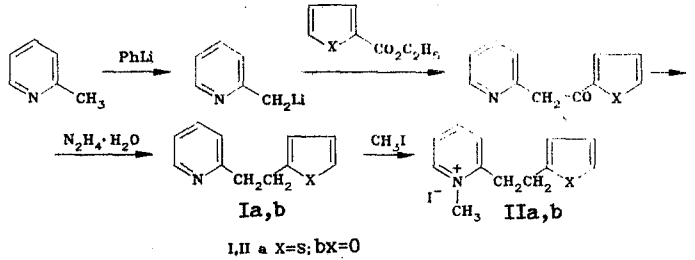
The rearrangement of 2-thienyl- and 2-furylalkylpyridinium salts to the corresponding anilines by the action of methylammonium sulfites has been studied. It has been shown that the rearrangement of these salts is accompanied in many cases by the formation of phenols and dealkylation products. The influence 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 (Ia,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-(2-furylmethyl)-N-methylaniline was achieved with a yield of 40% when the reaction temperature was reduced to 150°.



M. V. Lomonosov Moscow State University, Moscow.

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