CONVERSION OF PYRROLO[1,2-*a*]PYRAZINIUM SALTS TO 8-AMINOINDOLIZINES*

V. I. Terenin, E. V. Kabanova, and Yu. G. Bundel'

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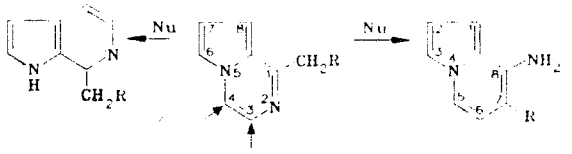
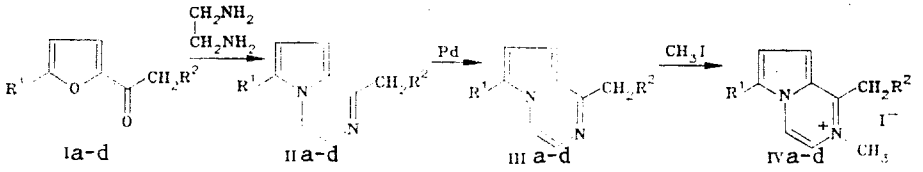
The recyclization of pyrrolo[1,2-a]pyrazinium salts under the influence of a base leads to 8-aminoindolizine derivatives and is a new method for the synthesis of indolizines, as well as the first example of the Kost—Sagitullin rearrangement in the pyrazine series.

The Kost—Sagitullin rearrangement has heretofore been investigated in the case of two types of heteroaromatic rings — pyridine and pyrimidine [2] — for both their monocyclic and condensed structures. We have investigated the possibility of the Kost—Sagitullin rearrangement of the pyrazine ring in the pyrrolo[1,2-*a*]pyrazine system. The pyrrolo[1,2-*a*]pyrazine molecule with an alkyl substituent in the 1 position can undergo nucleophilic attack at two positions. Attack at the $C_{(4)}$ atom and subsequent cleavage of the $C_{(4)}$—$N_{(5)}$ bond are less likely, since instances of rearrangement of the indolizine ring to an indole ring are known only for an indolizine ring activated by the introduction of nitro groups into the 6 and 8 positions, i.e., in the *ortho* and *para* positions relative to the site of initial nucleophilic attack. However, recyclization with attack of the nucleophile at the $C_{(3)}$ atom should lead to 8-aminoindolizines; in this case quaternization at the $N_{(2)}$ atom should activate the reaction.



Starting pyrrolo[1,2-*a*]pyrazinium salts IVa-d were synthesized by the reaction of 2-acylfurans Ia-d with ethylenediamine [3] with subsequent aromatization of the products by heating with palladium black and quaternization.



I—IV a $R^1=CH_3$, $R^2=H$; b $R^1=R^2=CH_3$; c $R^1=H$, $R^2=C_6H_5$; d $R^1=R^2=H$

Depending on the structure of the starting substrate, various nucleophilic agents with basic character are used in the Kost—Sagitullin reaction [2]. Taking into account the properties of the hypothetical reaction products we initially selected an alcohol solution of methylamine as the recyclizing agent. The conversion of 1,2,6-trimethylpyrrolo[1,2-*a*]pyrazinium salt IVa under these conditions at 150°C gives 3-methyl-8-methylaminoindolizine (Va) (in 80% yield), the structure of which was proved by spectral methods (see [1]).

On the basis of data on the rearrangement of pyridinium salts [2] one may propose a scheme for the synthesis of aminoindolizine Va in which the formation of an acyclic intermediate from the quaternary salt may proceed both through direct attack by the nucleophile at the 3 position of the pyrazine ring and through the formation of an anhydro base with the subsequent addition of the nucleophile. The subsequent cyclization of the intermediate takes place at the electron-enriched β-carbon atom of the enamine fragment.

3-Methyl-8-methylaminoindolizine is an unstable compound that darkens rapidly in air and in solutions. It can be acylated at the amino group with acetic anhydride in benzene and isolated from the reaction mixture in the form of the acylamino derivative. 3-Methyl-8-acetylaminoindolizine (VIa) is more stable than the corresponding amino

*See [1] for our preliminary communication.

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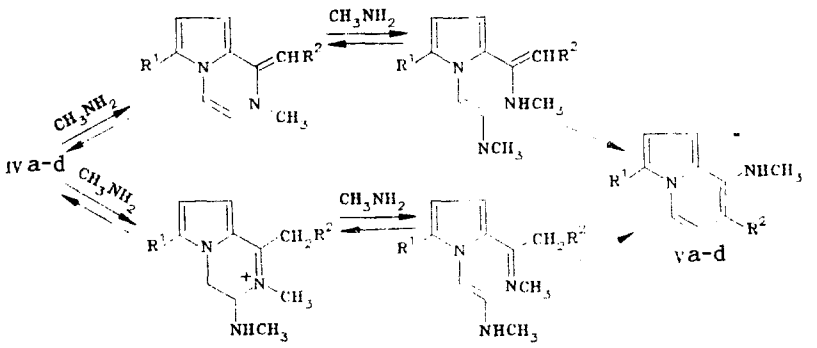

derivative Va but also undergoes decomposition during prolonged storage or in solution. It should be noted that, according to TLC data, in the recyclization of salt IVa under the influence of an alcohol solution of methylamine a dealkylation product — 1,6-dimethylpyrrolo[1,2-*a*]pyrazine (IIIa) — is present in trace amounts in the reaction mixture in addition to aminoindolizine Va.

When the alcohol solution of methylamine was replaced by aqueous alcoholic and aqueous solutions of alkali one might have expected the formation of 8-hydroxyindolizine derivatives. However, as has been previously shown [4], such phenolic structures are relatively stable only when there is an electron-acceptor substituent in the 3 position in the pyrrole ring. The instability of phenolic structures is evidently due to the high reactivities of their zwitter-ion tautomers. The results that we obtained for salt IVa are in agreement with the results of studies of the instability of 8-hydroxyindolizines with a free 3 position or an electron-donor substituent in this position — the compounds that are formed according to the TLC data cannot be isolated because of resinification of the reaction mixtures during workup.

Replacement of the methyl substituent in the 1 position of salt IV by an ethyl substituent, in which the acidity of the protons of the methylene group in the ethyl radical is somewhat lower than that of the methyl protons, does not lead to an appreciable decrease in the yield of product Vb, the structure of which was confirmed by spectral methods. At the same time, as a consequence of the high acidity of the protons of the methylene group of the benzyl radical, the recyclization of salt IVc gives 7-phenyl-8-methylaminoindolizine (Vc) in high yields (75-83%) even in the case of brief heating to 100°C. The higher reactivity of the benzyl radical in the Kost—Sagitullin reaction is also manifested in the fact that there is a possibility of the realization of the recyclization of unquaternized 1-benzylpyrrolo[1,2-*a*]pyrazine (IIIc); however, according to TLC data, a recyclization product is formed in only trace amounts.

In the recyclization of 1,2-dimethylpyrrolo[1,2-*a*]pyrazinium iodide (IVd), which does not contain substituents in the pyrrole ring, the yield of the principal product — 8-methylaminoindolizine (Vd) — is 35% at both high temperatures (with pronounced resinification) and when the reaction temperature is lowered to 120°C. Thus the presence of an alkyl substituent in the 6 position of starting salt IV makes it possible to increase the yield of the rearrangement product.

EXPERIMENTAL

The PMR spectra of solutions of IIa-d and IIIa-d in $CDCl_3$ were recorded with a Tesla BS-467 spectrometer (60 MHz), while the PMR spectra of solutions of Va-d in $CDCl_3$ were recorded with a Bruker WP-200SY spectrometer (200 MHz) with tetramethylsilane (TMS) as the internal standard. The course of the reactions and the purity of the compounds obtained were monitored by TLC on Silufol UV-254 plates in benzene or in a benzene—ethyl acetate (1:1) system.

The characteristics of the compounds obtained are presented in Table 1. The results of elementary analysis of the newly synthesized compounds for C, H, and N were in agreement with the calculated values.

3,4-Dihydropyrrolo[1,2-*a*]pyrazines IIa-d. A 100-mmole sample of the corresponding 2-acylfuran I was refluxed in 26 g (300 mmole) of 70% aqueous ethylenediamine for 3 h, after which 50 ml of water was added, and the mixture was extracted with benzene. The benzene extracts were dried over $MgSO_4$, the benzene was removed by distillation, and the residue was fractionated in vacuo.

Pyrrolo[1,2-*a*]pyrazines IIIa-d. A 50-mmole sample of the corresponding II was heated with palladium black at 225-260°C for 5-8 h until hydrogen evolution ceased, after which the reaction mixture was dissolved in chloroform, and the catalyst was removed by filtration. The solvent was removed by distillation, and the residue was fractionated in vacuo.

TABLE 1. Constants and Yields of the Synthesized Compounds

Compound	Empirical formula	bp, °C (mm)	mp, °C*	PMR spectrum, δ, ppm (J, Hz)	Yield, %
IIa	$C_9H_{12}N_2$	138...139 (15)	191...193	2,2 (6H, s, 1-CH_3, 6-CH_3); 3,7 (4H, s, 3-H, 4-H); 5,8 (1H, d, J_{78}=4,0, 7-H); 6,3 (1H, d, J_{87}=4,0, 8-H)	65
IIb	$C_{10}H_{14}N_2$	117...118 (7)	175...176	1,2 (3H, t, J=7,0, CH_3CH_2); 2,2 (3H, s, 6-CH_3); 2,55 (2H, q, J=7,0, CH_2CH_3); 3,7 (4H, s, 3-H, 4-H); 5,8 (1H, d, J_{78}=4,0, 7-H); 6,3 (1H, d, J_{87}=4,0, 8-H)	50
IIc	$C_{15}H_{16}N_2$	197...198 (9) [3]	146...148	3,75 (4H, s, CH_2CH_2); 3,9 (2H, s, CH_2); 6,05 (1H, dd, J_{78}=4,0, J_{76}=2,5, 7-H); 6,3 (1H, dd, J_{87}=4,0, J_{86}=2,0, 8-H); 6,6 (1H, dd, J_{67}=2,5, J_{68}=2,0, 6-H); 7,1...7,3 (5H, m, C_5H_5)	58
IId	$C_9H_{10}N_2$	110 (14) [3]	196...198	2,2 (3H, s, 1-CH_3); 3,7 (4H, s, 3-H, 4-H); 5,9 (1H, d, J_{87}=4,0, 8-H); 6,25 (1H, m, 7-H); 6,75 (1H, d, J_{67}=4,0, 6-H)	62
IIIa	$C_9H_{13}N_2$	93...98 (3)	192...194	2,4 (3H, s, 6-CH_3); 2,65 (3H, s, 1-CH_3); 6,68 (1H, d, J_{78}=4,0, 7-H); 6,7 (1H, d, J_{87}=4,0, 8-H); 7,45 (2H, 3-H, 4-H)	76
IIIb	$C_{10}H_{12}N_2$	100...103 (1)	175...177	1,4 (3H, t, J=7,0, CH_3CH_2); 2,4 (3H, s, 6-CH_3); 3,0 (2H, q, J=7,0, CH_2CH_3); 6,6 (1H, d, J_{78}=4,0, 7-H); 6,7 (1H, d, J_{87}=4,0, 8-H); 7,4 (1H, d, J_{34}=5,0, 3-H); 7,5 (1H, d, J_{43}=5,0, 4-H)	70
IIIc	$C_{15}H_{14}N_2$	185...190 (1)	149...150	4,2 (2H, s, CH_2); 6,7 (2H, m, 7-H, 8-H); 7,2...7,4 (6H, m, 6-H, C_6H_5); 7,5 (1H, d, J_{34}=5,0, 3-H); 7,7 (1H, d, J_{43}=5,0, 4-H)	58
IIId	$C_9H_9N_2$	81...83 (1)	197...199	2,55 (3H, s, 1-CH_3); 6,75 (2H, m, 7-H, 8-H); 7,3 (2H, m, 3-H, 6-H); 7,6 (1H, d, J_{43}=5,0, 4-H)	63
IVa	$C_{10}H_{13}IN_2$		272...274		93
IVb	$C_{11}H_{15}IN_2$		175...176		90
IVc	$C_{16}H_{17}IN_2$		203...204		89
IVd	$C_9H_{11}IN_2$		137...139		91
Va [1]	$C_{10}H_{12}N_2$				80
Vb	$C_{11}H_{14}N_2$		121...123	2,17 (3H, s, 7-CH_3); 2,38 (3H, s, 3-CH_3); 3,03 (3H, s, CH_3N); 3,60 (1H, br.s, NH); 6,28 (1H, d, J_{65}=7,0, 6-H); 6,34 (1H, d, J_{12}=4,0, 1-H); 6,43 (1H, d, J_{21}=4,0, 2-H); 7,25 (1H, d, J_{56}=7,0, 5-H)	78
Vc	$C_{16}H_{16}N_2$		191...193	2,92 (3H, s, CH_3N); 6,38 (1H, d, J_{65}=7,0, 6-H); 6,57 (1H, d, J_{12}=4,0, 1-H); 6,75 (1H, dd, J_{21}=4,0, J_{23}=3,0, 2-H); 7,26 (1H, m, 3-H); 7,32...7,40 (5H, m, C_6H_5); 7,97 (1H, d, J_{56}=7,0, 5-H)	83
Vd	$C_9H_{10}N_2$		102...103	2,97 (3H, s, CH_3N); 3,93 (1H, br.s, NH); 5,75 (1H, d, J_{78}=7,0, 7-H); 6,30 (1H, d, J_{12}=4,0, 1-H); 6,45 (1H, dd, J_{65}=7,0, J_{67}=7,0, 6-H); 6,71 (1H, dd, J_{21}=4,0, J_{23}=3,0, 2-H); 7,25 (1H, m, 3-H); 7,49 (1H, d, J_{56}=7,0, 5-H)	35

*The melting points of the picrates are presented for IIa-d and IIIa-d; the melting points of the acetyl derivatives are presented for Vb-d.

Pyrrolo[1,2-*a*]pyrazinium Iodides IVa-d. A solution of 25 mmole of the corresponding III in 5 ml of acetone and excess methyl iodide (3-5 ml) was allowed to stand for 24 h. The precipitated crystals were removed by filtration, washed with acetone, and air dried.

8-Methylaminoindolizines Va-d. A mixture of 1 mmole of iodide IV and 5 ml of a 42% alcohol solution of methylamine was heated in a sealed ampul for 10-20 h at 150°C (for 2-3 h at 100-120°C for salt IVc), after which the alcohol was removed by distillation.

A. To isolate indolizines V the residue was separated with a column packed with silica gel 100/160 μ in benzene or in a benzene—ethyl acetate (1:1) system.

B. To obtain VI the residue was dissolved in 3 ml of benzene, and excess (1-3 ml) acetic anhydride was added. The solvent and acetic anhydride were removed by distillation, and the residue was chromatographed with a column packed with silica gel 100/160 μ in a benzene—ethyl acetate (1:1) system and recrystallized from hexane.

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