REAMINATION IN THE RECYCLIZATION OF PYRROLO-[1,2-a]PYRAZINE SALTS INTO 6- AND 8-AMINOINDOLIZINES. GENERAL PROCESS SCHEME

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Rearrangement of the methyl iodides of 1- and 3-alkyl-substituted pyrrolo[1,2-a]pyrazines in the presence of various alkylamines afforded a mixture of 8- and 6-aminoindolizines, respectively, with and without exchange of the methylamine fragment. The ratio of the products of direct and exchange recyclization was dictated by the size of the N-alkyl substituents in the reagent and starting salt. Rearrangement of the 1-alkylpyrrolo[1,2-a]pyrazinium salts proceeded via the breaking of the $C_{(3)}-N_{(2)}$ bond, and rearrangement of the 3-alkylpyrrolo-[1,2-a]pyrazinium salts via the breaking of the $C_{(1)}-N_{(2)}$ bond.

As we showed in a previous report [1], on treatment with alcoholic methylamine solution 1,2,6-trimethylpyrrolo[1,2-a]pyrazinium iodide (Ia) recyclizes into 3-methyl-8-methylaminoindolizine (IIa). Rearrangement of other 1-alkyl- and 1-aralkyl-substituted pyrrolo[1,2-a]pyrazine salts proceeds in a similar manner [2].

It can be inferred from the Kost–Sagitullin rearrangement mechanism [3] that the pyrrolo[1,2-a]pyrazinium cation undergoes nucleophilic attack by methylamine at the $C_{(3)}$ atom, the $C_{(3)}-N_{(2)}$ bond being broken and intermediate III being formed as a consequence (route A, Scheme 1). The methyl group providing the β-carbon atom of the intermediate III enamine fragment takes part in the subsequent closure of the pyridine ring, the alkylamine reagent being excluded from the composition of the resultant 8-methylaminoindolizine IIa. However, when an alkylamine with an alkyl substituent different from the N-substituent in the starting salt Ia is used as the reagent, reamination can occur at the acyclic intermediate stage. This yields intermediate IV, which contains the alkylamine fragment of the reagent. Acyclic enaminoketones are known to enter into similar reamination reactions [4]. Cyclization of intermediate IV leads to the formation of recyclization products IIb-g with exchange of the alkylamino group. The ratio of the products of direct and exchange recyclization probably depends on the rates of reamination and cyclization of the acyclic intermediate III. Thus, if the recyclization of salt Ia in the presence of alkylamines proceeds via route A (Scheme 1), both direct and exchange recyclization products may be formed (provided the N-alkyl substituents in the starting salt and reagent are different).

At the same time, it has been shown from quantum chemical calculations that the π-electron density at atom $C_{(1)}$ of the pyrrolo[1,2-a]pyrazine molecule is less than that at the $C_{(3)}$ atom [5], and the nucleophile generally attacks pyrrolo[1,2-a]pyrazine at position 1 [6]. Thus, a second pathway is possible for the formation of aminoindolizine II (route B, Scheme 1). This involves nucleophilic attack at the $C_{(1)}$ atom of salt Ia, breaking of the $C_{(1)}-N_{(2)}$ bond and subsequent cyclization of intermediate V, the reagent entering into the composition of the resultant 8-alkylaminoindolizines IIb-g. The direct rearrangement product IIa cannot be formed in this case, however.

To throw some light on the recyclization mechanism a study was made of the reaction between 1,2,6-trimethylpyrrolo-[1,2,-a]pyrazinium iodide (Ia) and alcoholic solutions of alkylamines other than methylamine. The reagents used were 35-40% alcoholic solutions of ethylamine, n- and iso-propylamines, n-, sec-, and tert-butylamine, and dimethylamine; molar excesses of the reagent in the order of 20-25 times the amount of the starting salt were employed in the reactions. The direct rearrangement product, 8-methylaminoindolizine IIa, was seen to form in all the experiments. In most of the tests the

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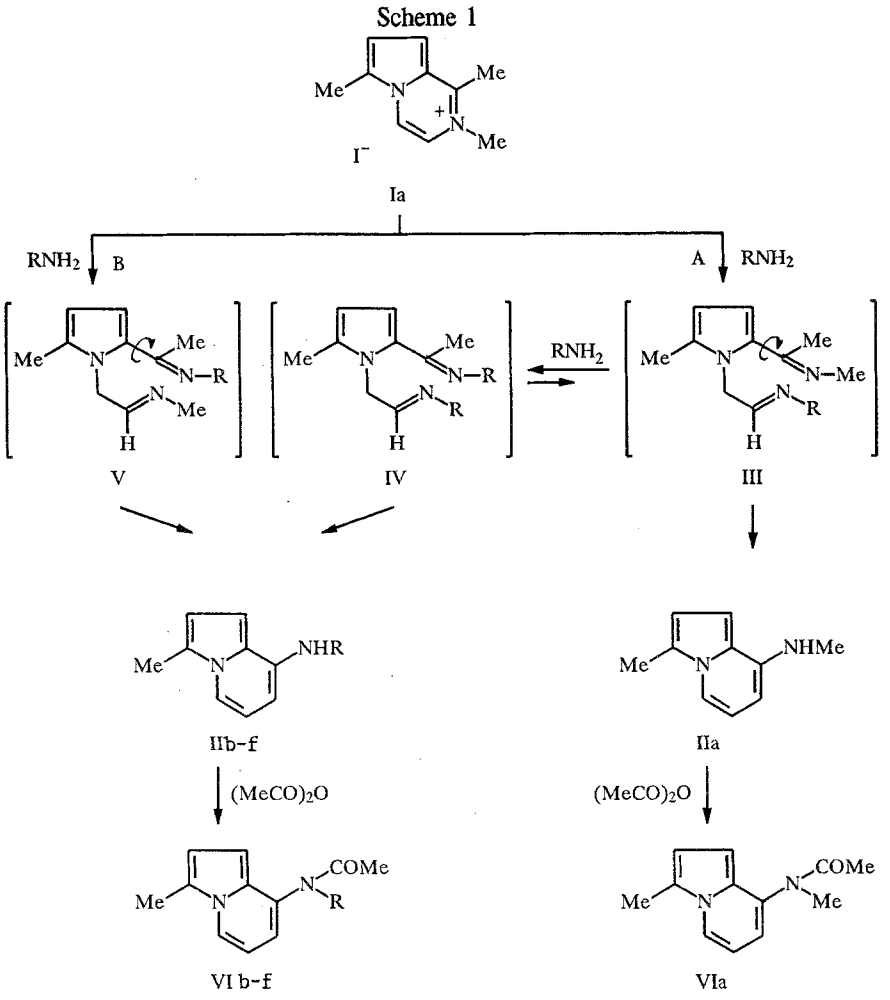
Scheme 1

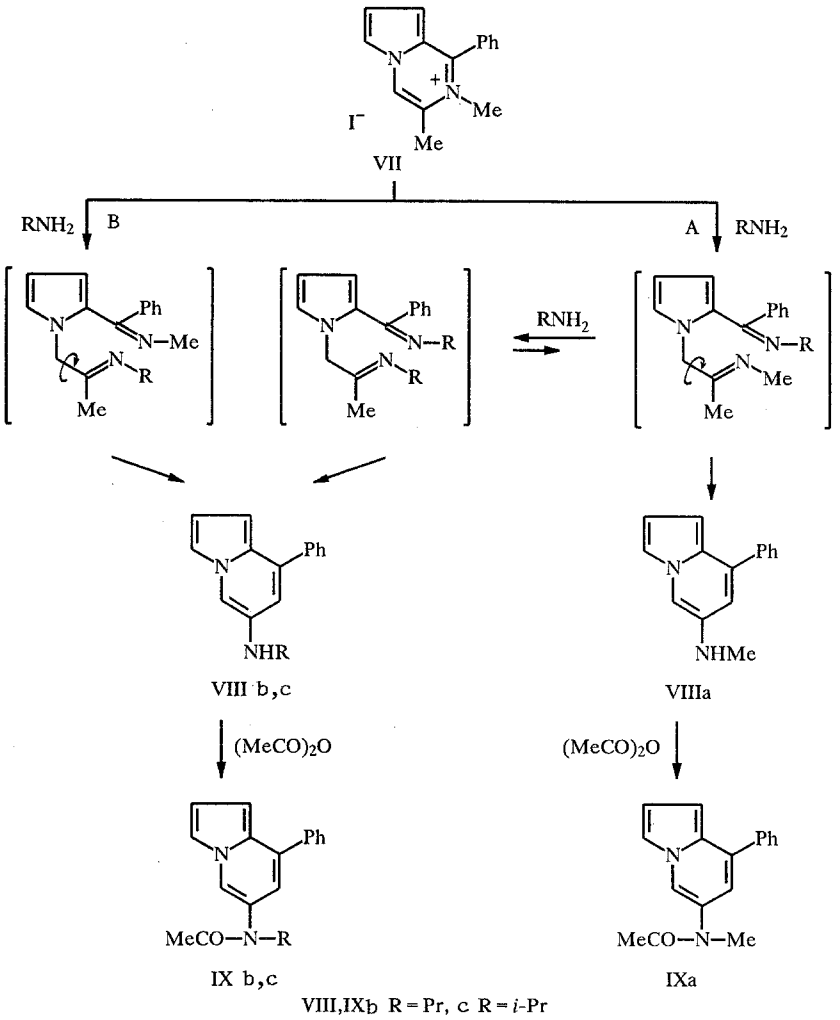


II—VIb R = Et, c R = Pr, d R = *n*-Bu, e R = *i*-Pr, f - R = *i*-Bu

products of alkyl fragment exchange recyclization, namely the 8-alkylaminoindolizines IIb-g,* were observed in addition to amine IIa. The fact that methylaminoindolizine IIa was formed in all the reactions lent support to the view that the recyclization proceeded via route A, i.e., with nucleophilic attack at the $C_{(3)}$ atom of salt Ia and breaking of the $C_{(3)}-N_{(2)}$ bond. When ethylamine was used as the reagent, there was almost total exchange of the methylene fragment of salt Ia for ethylamine, giving 8-ethylaminoindolizine IIb in 81% yield, while the yield of methylaminoindolizine IIa was no more than 2%. The preferential formation of ethylaminoindolizine IIb is probably due to the fact that the rate of reamination of the acyclic intermediate III by ethylamine, a reagent not having a bulky alkyl substituent, was considerably greater than its rate of cyclization into methylaminoindolizine IIa. Although the enamine reamination is a reversible reaction, it may be assumed that with a twentyfold excess of the reagent the equilibrium between the initially formed enamine III and its reamination product IV is almost completely shifted toward the latter. When the length of the alkylamine alkyl radical chain was increased to three or four carbon atoms (in the reactions with n-propyl- and n-butylamine), the yields of exchange recyclization products IIc and IId decreased to 68 and 65%, respectively, while that of the rearrangement product IIa rose to 9%. As expected, when the size of the alkyl radical in the reagent was increased (in the reactions with iso-propyl- and sec-butylamine), the yields of exchange recyclization products IIe and IIf dropped further to 47-55%, the yield of methylaminoindolizine IIa rising to 18-20%.

*As alkylaminoindolizines II and VIII were unstable compounds, they were analyzed in the form of their acetyl derivatives (III and IX, respectively) from this point onward.

Scheme 2



VIII,IXb R = Pr, c R = *i*-Pr

When salt Ia was reacted with tert-butylamine, the rearrangement product, methylaminoindolizine IIa, was formed in its highest yield (40%), i.e., the rate of reamination of intermediate III by tert-butyl-amine was at its lowest with respect to its rate of cyclization. No reamination product was found in this case. It would seem that steric hindrances created by the alkyl radical impeded both the reamination of intermediate III and the cyclization of intermediate IV. In the case of tert-butylamine the cyclization of intermediate IV was hindered to such an extent that no tert-butylaminoindolizine was formed, resinification probably occurring on this occasion.

It should be noted that the total yield of recyclization products declined as the length and size of the alkyl substituent in the reagent increased. In every case a dealkylation product, namely 1,6-dimethylpyrrolo[1,2-a]pyrazine (4-7%), was formed in the recyclization of salt Ia.

Secondary amines are known to enter into the reaction to a much lesser extent than primary amines, affording, in the main, recyclization products that do not include the dialkylamine moiety [7]. The reaction between salt Ia and an alcoholic solution of dimethylamine yielded both methylaminoindolizine IIa (18%) and an exchange recyclization product, namely 3-methyl-8-N,N-dimethylaminoindolizine (IIg) (13%), the total yield of recyclization products being considerably lower than in the reactions involving the primary alkylamines. An appreciable increase was also seen in the yield of the salt Ia dealkylation product (16%).

When the N-methyl substituent in the starting salt Ia was replaced by an iso-propyl group, the recyclization of 1,6-dimethyl-2-isopropylpyrrolo[1,2-a]pyrazinium iodide (Ib) in the presence of alcoholic methylamine solution proceeded with the iso-propyl radical being almost completely exchanged for a methyl radical; the yield of methylaminoindolizine IIa was 67%, while the direct rearrangement product, isopropylaminoindolizine IIe, was found in trace amounts (from TLC data).

TABLE 1. Yields of Recyclization Products

Compound (solvent)	Reagent	Recyclization product yield, %			Dealkylation product yield, %
		w/o exchange of alkylation	with exchange of alkylation	total	
Ia	$EtNH_2$	IIa, 2	IIb 81	83	7
Ia	$PrNH_2$	IIa, 9	IIc, 68	77	Traces
Ia	$BuNH_2$	IIa, 9	IId, 65	74	Traces
Ia	*i*-$PrNH_2$	IIa, 20	IIe, 55	75	Traces
Ia	*s*-$BuNH_2$	IIa, 18	IIf, 47	65	5
Ia	*t*-$BuNH_2$	IIa, 38	—	38	4
Ia	Me_2NH	IIa, 18	IIg, 13	31	16
Ib	$MeNH_2$	IIe, traces	IIa, 67	67	Traces
VII	$PrNH_2$	VIIIa*, 17	VIIIb*, 41	58	24
VII	*i*-$PrNH_2$	VIIIa*, 39	VIIIb*, 29	68	17

*Acetyl derivative yields shown.

Rearrangement of 3-methyl-substituted pyrrolo[1,2-a]pyrazine salts on treatment with nucleophiles affords the corresponding 6-aminoindolizines [8]. Two reaction mechanisms are also possible in this case: nucleophilic attack at the $C_{(1)}$ atom and breaking of the $C_{(1)}-N_{(2)}$ bond (route A, Scheme 2) or attack at the $C_{(3)}$ atom and rupture of the $C_{(3)}-N_{(2)}$ bond (route B). The reaction path can also be established in this case from the competing reamination process (using an alkylamine with a different N-alkyl substituent from the initial salt) that yields exchange recyclization products.

Thus, for example, the reaction between 1-phenyl-2,3-dimethylpyrrolo[1,2-a]pyrazinium iodide and alcoholic solutions of n-propyl- and iso-propylamine gave rise to both a rearrangement product, 6-methylaminoindolizine VIIIa, and products of recyclization involving exchange of the alkylamino group, namely n-propylaminoindolizine VIIIb or isopropylaminoindolizine VIIIc, respectively. This suggested that the reaction proceeded by route A: In this case the nucleophile attacks the $C_{(1)}$ atom and the $C_{(1)}-N_{(2)}$ bond is broken. The yields of direct and exchange recyclization products were 17 and 41%, respectively, in the reaction with n-propylamine. In both cases, a dealkylation product, 1-phenyl-3-methylpyrrolo[1,2-a]pyrazine, was formed in quite high yields (17-24%) during the recyclization process. As in the case of the 8-aminoindolizines, using an alkylamine with a bulkier substituent (iso-propylamine) as the reagent reduced the exchange recyclization product yield and increased the product yield from rearrangement not involving exchange of the alkylamino group.

EXPERIMENTAL

PMR spectra were recorded with a Tesla B-467 instrument (60 MHz, internal standard TMS), using CCl_4 for compounds VIb-f and $CDCl_3$ for compounds IXb and IXc. Mass spectra of compounds VIb-f, IIg, IXb, and IXc were taken on an MX-1321A with 70 eV ionization energy.

General methodology.

A mixture of 1 mmole of pyrrolo[1,2-a]pyrazinium iodide and 5 ml of a 35-40% alcoholic solution of alkylamine was heated for 10-20 h in a sealed ampul at 150°C. The alcohol was then evaporated off.

A. In experiments 1-8 the residue was fractionated using a column with 5/40 μm silica gel, eluting with a 6:1 heptane–ethyl acetate mixture. The resultant alkylaminoindolizines IIb-f were acylated with acetic anhydride in benzene.

B. In experiments 9 and 10 the residue was dissolved in 5 ml of a 1:1 heptane–ethyl acetate mixture and filtered. An excess (1-3 ml) of acetic anhydride was then poured into the extract. Thirty minutes later the solvent and excess acetic anhydride were evaporated off. The residue was then fractionated as in method A.

Because of their instability aminoindolizines IIb-f and VIIIb were analyzed in the form of their acetyl derivatives VIb-e, IXb, and IXc. Acetylaminoindolizines VIb-f, IXb, and IXc consisted of oils that darkened on contact with air. Aminoindolizine yields are shown in Table 1 and spectral data for compounds VIb-f, IIg, and IXb in Table 2. Compounds VIa and IXa are described in [2, 8].

TABLE 2. Spectral Data for the Synthesized Compounds

Compound	Empirical formula	MW_{calc}	Mass spectrum, m/z ($I_{rel.}$, %)	PMR spectrum, δ, ppm (J, Hz)
VIb[1]	$C_{13}H_{16}N_2O$	216	216 (M^+, 89), 174 (22), 173 (32), 159 (17), 149 (7), 147 (35), 146 (14), 131 (21), 130 (11), 70 (100)	1,1 (3H, t, J = 7, CH_2CH_3), 1,75 (3H, s, $COCH_3$), 2,5 (3H, s, 3-CH_3), 3,2...4,2 (2H, m, CH_3CH_2), 6,35 (1H, d, J_{12} = 4, 1-H), 6,5 (3H, m, 2,6,7-H), 7,65 (1H, m, 5-H)
VIc	$C_{14}H_{18}N_2O$	230	230 (M^+, 100), 188 (21), 187 (25), 173 (11), 159 (28), 147 (34), 146 (26), 131 (16), 84 (70), 78 (13)	0,9 (3H, t, J = 7, CH_2CH_3), 1,2...1,7 (2H, m, CH_3CH_2), 1,8 (3H, s, $COCH_3$), 2,55 (3H, s, 3-CH_3), 3,25...4,15 (2H, m, N-CH_2), 6,35 (1H, d, J_{12} = 4, 1-H), 6,6 (3H, m, 2,6,7-H), 7,8 (1H, m, 5-H)
VId	$C_{15}H_{20}N_2O$	244	244 (M^+, 100), 201 (24), 188 (14), 173 (16), 159 (42), 147 (34), 146 (29), 131 (19), 98 (61), 57 (26)	0,8...1,05 (3H, m, CH_2CH_3), 1,2...1,7 (4H, m, $CH_3CH_2CH_2$), 1,8 (3H, s, $COCH_3$), 2,5 (3H, s, 3-CH_3), 3,2...4,2 (2H, m, N-CH_2), 6,3 (1H, d, J_{12} = 4, 1-H), 6,5 (3H, m, 2,6,7-H), 7,65 (1H, m, 5-H)
VIe	$C_{14}H_{18}N_2O$	230	230 (M^+, 100), 188 (17), 187 (27), 173 (22), 171 (12), 147 (72), 146 (58), 145 (26), 131 (16), 84 (81)	1,05 (3H, d, J = 7, $CHCH_3$), 1,2 (3H, d, J = 7, $CHCH_3$), 1,75 (3H, s, $COCH_3$), 2,55 (3H, s, 3-CH_3), 4,7...5,2 (1H, m, NCH), 6,3...6,8 (4H, m, 1,2,6,7-H), 7,8 (1H, m, 5-H)
VIf	$C_{15}H_{20}N_2O$	244	244 (M^+, 100), 201 (19), 189 (15), 188 (26), 173 (36), 147 (91), 146 (91), 145 (34), 131 (18), 98 (87)	0,8...1,5 (8H, m, $CHCH_2CH_3$, $CHCH_3$), 1,75 (3H, s, $COCH_3$), 2,5 (3H, s, 3-CH_3), 3,4...3,9 (1H, m, N-CH), 6,35...6,7 (4H, m, 1,2,6,7-H), 7,8 (1H, m, 5-H)
IIg	$C_{11}H_{14}N_2$	174	174 (M^+, 100), 173 (20), 159 (40), 157 (11), 145 (16), 144 (15), 132 (10), 131 (48), 130 (26), 87 (11)	
IXb	$C_{19}H_{20}N_2O$	292	292 (M^+, 100), 250 (16), 249 (8), 221 (25), 220 (16), 209 (15), 208 (11), 193 (13), 192 (11), 84 (24)	0,9 (3H, m, CH_2CH_3), 1,35...1,9 (2H, m, CH_3CH_2), 2,0 (3H, s, $COCH_3$), 3,5...3,95 (2H, m, N-CH_2), 6,5 (1H, m, 7-H), 6,6 (1H, m, 1-H), 6,9 (1H, m, 2-H), 7,3...7,8 (6H, m, C_6H_5, 3-H), 7,8 (1H, m, 5-H)
IXc	$C_{19}H_{20}N_2O$	292	292 (M^+, 100), 250 (23), 249 (14), 235 (16), 210 (32), 208 (35), 193 (15), 180 (12), 84 (46), 58 (11)	1,1 (6H, d, J = 9, $CHCH_3$), 1,95 (3H, s, $COCH_3$), 4,8...5,2 (1H, m, N-CH), 6,45 (1H, m, 7-H), 6,65 (1H, m, 1-H), 6,9 (1H, m, 2-H), 7,4...7,8 (6H, m, C_6H_5, 3-H), 7,8 (1H, m, 5-H)

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