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CYCLOTRANSFORMATION OF 6-CYANO-PYRROLO[1,2-*a*]PYRAZINIUM SALTS

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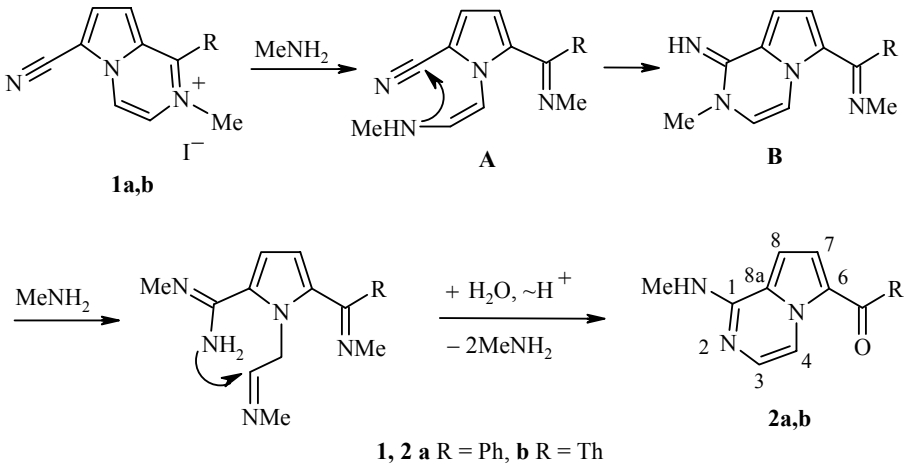
The involvement of various exocyclic groups in the cyclotransformation of azoloazines is well known in numerous examples of heterocyclic systems containing a pyridine and a pyrimidine ring [1]. In the case of the pyrrolo[1,2-*a*]pyrazine system, which has been studied little in nucleophilic rearrangements, a previously unknown double rearrangement involving a nitrile group at position 6 was unexpectedly discovered and investigated.

When the salts **1a**,**b** were heated with an alcohol solution of methylamine the 1-methylamino derivatives of pyrrolo[1,2-*a*]pyrazines **2a**,**b**, which can only be formed as a result of two successive rearrangements, were obtained.



1, 2 a R = Ph, **b** R = Th

The mechanism of the discovered cyclotransformation includes opening of the pyrazine ring by the nucleophile with the formation of the intermediate **A**, the enamine component of which attacks the distant electrophilic center of the nitrile group. The cyclic amidine **B** produced in this way contains all the necessary structural fragments for the subsequent amidine rearrangement, leading to the 6-acyl-1-methylaminopyrrolo-[1,2-*a*]pyrazines **2a**,**b**.

The reaction of the 6-cyano-1-isopropylpyrrolo[1,2-*a*]pyrazinium methiodide **1c** with an alcohol solution of methylamine leads to the formation of two compounds **3** and **4**, which are the products from concurrent rearrangements.

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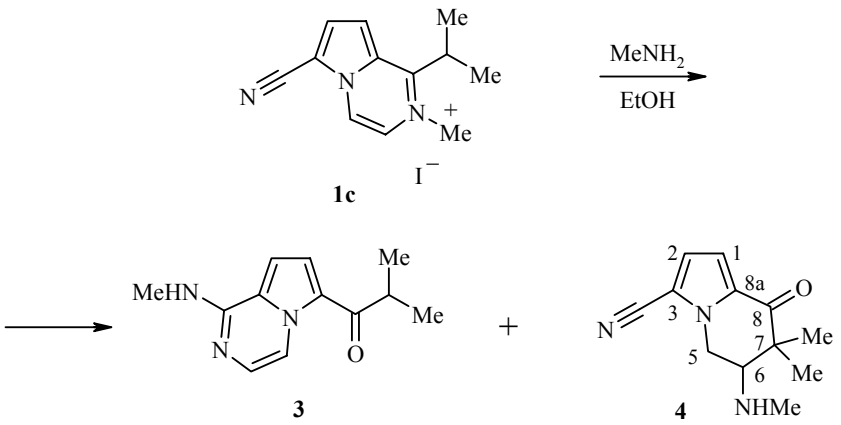
Compound **3** is the product from rearrangement involving the nitrile group, while compound **4** is the product from rearrangement involving the isopropyl group [2].



Variation of the reaction temperature has practically no effect on the overall yield but changes the ratio of the reaction products. At a lower temperature (70°C) the product from cyclization at the nitrile group predominates (3.5:1, **3**:**4**), while at a lower temperature (140°C) the ratio of the products becomes equimolar. The overall yield amounted to 30% (at 70°C) and 28% (at 140°C).

The discovered cyclotransformation belongs to a previously unknown structural type, since it contains two successive rearrangements as a result of which two carbon atoms of the pyrazine ring are first exchanged for the two exocyclic carbon atoms, and the cyclic nitrogen atom is then exchanged for the exocyclic nitrogen atom in a Dimroth reaction.

The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-400 spectrometer (400 MHz) in deuterochloroform at 28°C with TMS as internal standard. The EI mass spectra were recorded on a Kratos MS-30 instrument at 70 eV at 210°C. The reactions and the purity of the compounds were monitored on Silufol plates in the benzene and 1:1 benzene–ethyl acetate systems with development in iodine vapor.

Rearrangement of Salts (1) (General Procedure). A mixture of the quaternary salt **1a-c** (1 mmol) and a 40% alcohol solution of methylamine (5-6 ml) was heated for 2 h in a sealed glass tube at 70-80°C. A few drops of water were added to the reaction mixture, the mixture was evaporated to dryness, and the residue was separated on a chromatographic column in the 2:1 benzene–ethyl acetate system. In the case of the salt **1c** the reaction was conducted at 70°C (2 h) and at 140°C (1 h 30 min). Compounds **2a**,**b**, **3**, and **4** were obtained using this procedure.

6-Benzoyl-1-methylaminopyrrolo[1,2-*a*]pyrazine (2a). Yield 40%; mp 108-110°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.09 [3H, d, *J* = 4.3, NH(C<u>H</u>$_3$); 5.28 (1H, br. s, NH); 8.62 (1H, d, $J_{8,7}$ = 4.5, H-8); 7.19 (1H, d, $J_{7,8}$ = 4.5, H-7); 7.50 (3H, m, *m*-C_6H_5, H-3); 7.60 (1H, *m*,*p*-C_6H_5); 7.84 (2H, m, *p*-C_6H_5); 9.00 (1H, dd, *J* = 4.1, $J_{4,3}$ = 4.9, H-4). ^{13}C NMR spectrum, δ ppm: 28.11 (NH<u>C</u>H$_3$); 100.12 ($C_{(8)}$); 110.21 ($C_{(7)}$); 123.78 ($C_{(3)}$); 124.19 ($C_{(6)}$); 125.12 ($C_{(8a)}$); 128.28 (2C, *m*-C_6H_5); 129.04 (2C, *o*-C_6H_5); 129.17 (*p*-C_6H_5); 131.58 ($C_{(4)}$); 139.87 (*ipso*-C_6H_5); 151.02 ($C_{(1)}$); 186.03 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 257 $[M]^+$ (100), 228 (49), 169 (35), 111 (37). Found, %: C 71.60; H 4.99; N 16.73. $C_{15}H_{13}N_3O$. Calculated, %: C 71.71; H 5.17; N 16.73.

1-Methylamino-6-thenoylpyrrolo[1,2-*a*]pyrazine (2b). Yield 35%; mp 140-142°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.18 (3H, d, *J* = 4.1, NH(C<u>H</u>$_3$)); 5.34 (1H, br. s, NH); 6.69 (1H, d, $J_{8,7}$ = 4.4, H-8); 7.19 (1H, dd, $J_{\beta',\beta}$ = 5.0, $J_{\beta',\alpha'}$ = 3.7, β'-C_4H_3S); 7.45 (1H, d, $J_{\alpha',\beta'}$ = 5.0, α'-C_4H_3S); 7.52 (1H, d, $J_{7,8}$ = 4.4, H-7); 7.68 (1H, d, $J_{3,4}$ = 4.9, H-3); 7.82 (1H, d, $J_{\beta,\beta'}$ = 3.7, β-C_4H_3S); 8.85 (1H, d, $J_{4,3}$ = 4.9, H-4). ^{13}C NMR spectrum, δ, ppm: 28.26 (NH<u>C</u>H$_3$); 101.56 ($C_{(8)}$); 112.05 ($C_{(7)}$); 121.95 ($C_{(3)}$); 124.11 ($C_{(6)}$); 124.93 ($C_{(8a)}$); 127.75 (β'-C_4H_3S);

128.58 (α'-C_4H_3S); 132.27 (β-C_4H_3S); 132.38 ($C_{(4)}$); 144.33 (α-C_4H_3S); 150.91 ($C_{(1)}$); 176.82 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 251 $[M]^+$ (94), 223 (83), 146 (24), 117 (45). Found, %: C 60.50; H 4.20; N 16.29. $C_{13}H_{11}N_3OS$. Calculated, %: C 60.70; H 4.28; N 16.29.

6-Isobutyryl-1-methylaminopyrrolo[1,2-*a*]pyrazine (3). Mp 100-102°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.33 [6H, d, *J* = 6.8, CH($\underline{CH_3}$)$_2$]; 3.22 (3H, d, *J* = 4.9, NH$\underline{CH_3}$); 3.50 [1H, m, C$\underline{H}$(CH$_3$)$_2$]; 5.45 (1H, br. s, NH); 6.67 (1H, d, $J_{8,7}$ = 4.5, H-8); 7.43 (1H, d, $J_{7,8}$ = 4.5, H-7); 7.51 (1H, d, $J_{3,4}$ = 5.0, H-3); 9.06 (1H, d, $J_{4,3}$ = 5.0, H-4). ^{13}C NMR spectrum, δ, ppm: 19.72 [CH($\underline{C}H_3$)$_2$]; 28.03 (NH$\underline{C}H_3$); 36.96 [$\underline{C}$H(CH$_3$)$_2$]; 100.65 ($C_{(8)}$); 112.22 ($C_{(7)}$); 119.99 ($C_{(3)}$); 123.91 ($C_{(6)}$); 124.32 ($C_{(8a)}$); 129.38 ($C_{(4)}$), 151.13 ($C_{(1)}$); 195.64 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 217 $[M]^+$ (67), 174 (100), 145 (23), 119 (18). Found, %: C 66.27; H 6.89; N 19.28. $C_{12}H_{15}N_3O$. Calculated, %: C 66.35; H 6.91; N 19.34.

3-Cyano-7,7-dimethyl-6-methylamino-5,6,7,8-tetrahydroindolizin-1-one (4). Mp 78-80°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.32, 1.43 [3H each, both s, 7-(CH_3)$_a$, 7-(CH_3)$_b$]; 2.61 (3H, s, 6-NH$\underline{CH_3}$); 3.13 (1, dd, $J_{6,5a}$ = 5.6, $J_{6,5b}$ = 5.6, $J_{6,5b}$ = 3.7, H-6); 4.29 (1H, dd, $J_{5a,5b}$ = 13.5, $J_{5a,6}$ = Ha-5); 4.49 (1H, dd, $J_{5b,5a}$ = 13.5, $J_{5b,6}$ = 3.7, Hb-5); 6.92 (1H, d, $J_{2,1}$ = 4.3, H-2); 7.02 (1H, d, $J_{1,2}$ = 4.3, H-1). ^{13}C NMR spectrum, δ, ppm: 19.16, 22.59 [7-(CH_3)$_a$, 7-(CH_3)$_b$]; 35.27 (6-NH$\underline{C}H_3$); 43.78 ($C_{(5)}$); 45.92 ($C_{(7)}$); 64.05 ($C_{(6)}$); 106.85 ($C_{(3)}$); 112.31 (CN); 113.48 ($C_{(1)}$); 119.70 ($C_{(2)}$); 132.20 ($C_{(8a)}$); 191.38 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 217 $[M]^+$ (17), 98 (100). Found, %: C 66.20; H 6.70; N 19.20. $C_{12}H_{15}N_3O$. Calculated, %: C 66.35; H 6.91; N 19.34.

REFERENCES

1. H. C. van der Plas, *Tetrahedron*, **41**, 281 (1985).
2. V. I. Terenin and A. S. Ivanov, *Khim. Geterotsikl. Soedin.*, 1551 (2005). [*Chem. Heterocycl. Comp.*, **41**, 1300 (2005)].