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DIMERIZATION OF 1-METHYL-SUBSTITUTED PYRROLO[1,2-*a*]PYRAZINES DURING ACETYLATION

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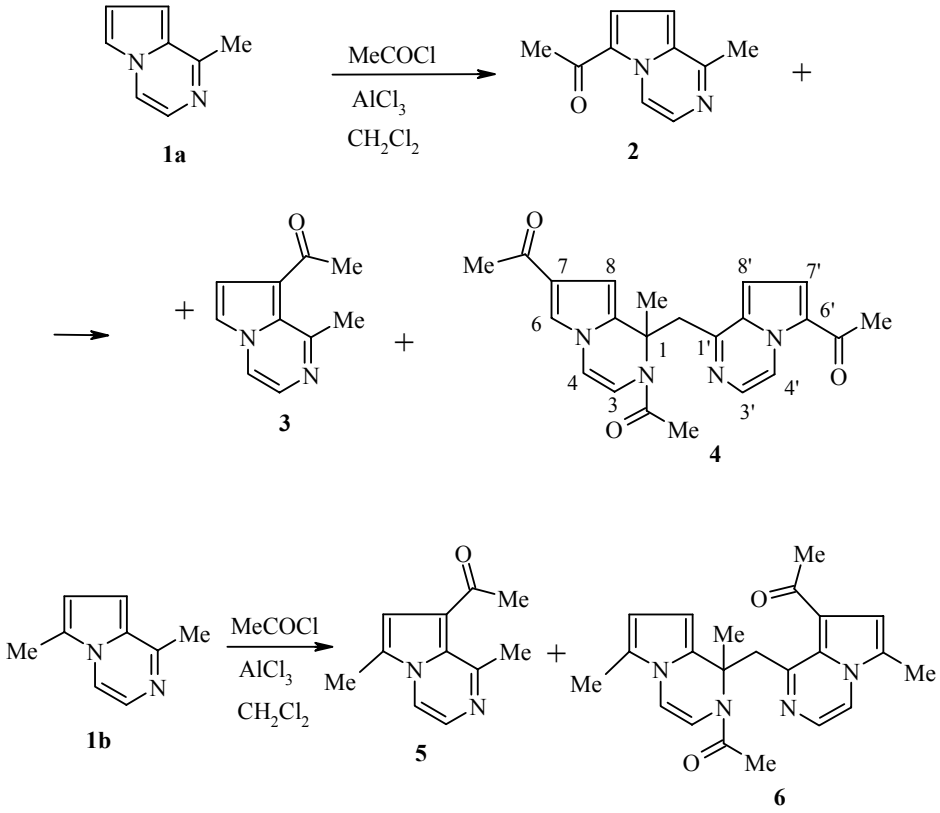
The pyrrolo[1,2-*a*]pyrazine system is relatively stable against the action of weak electrophiles, as shown by the fact that 6-acetylpyrrolo[1,2-*a*]pyrazine is formed with a yield of only 16% when unsubstituted pyrrolo[1,2-*a*]pyrazine is boiled with an excess of acetic anhydride for 24 h [1].

While studying the acetylation of 1-methylpyrrolo[1,2-*a*]pyrazine (**1a**) and 1,6-dimethylpyrrolo[1,2-*a*]-pyrazine (**1b**), in addition to the products from substitution of the pyrrole ring, we quite unexpectedly obtained the products from the cross-linking of two molecules of the heterocycle.



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The ^{13}C NMR spectra of compounds **4** and **6** are characterized by a signal for a carbon atom at 152.77 (J_{CH} = 4.13, J = 10.98 Hz) and 151.57 ppm (J_{CH} = 5.86, J = 9.51 Hz) respectively in the form of a doublet of triplets. On the basis of this it can be concluded that the molecules are linked through the methyl substituent at the $C_{(1')}$ atom.

Peaks for molecular ions $[M]^+$ at 390 and 376 respectively are observed in the mass spectra of pyrrolo[1,2-*a*]pyrazines **4** and **6**.

The structure of the dimer **4** was also confirmed by the data from X-ray crystallographic analysis, which together with the proposed reaction mechanism will be presented in future publications.

The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance-400 instrument (400 and 100 MHz respectively) with TMS as internal standard. The mass spectra were obtained on a Kratos MS-30 instrument at 70 eV and 210°C. The initial pyrrolo[1,2-*a*]pyrazines **1a** and **1b** were obtained according to the previously described procedure [2]. The reaction was monitored by TLC on Silufol UV-254 plates in the 1:1 benzene–ethyl acetate system.

Acetylation of Compounds 1a,b. To a solution of pyrrolo[1,2-*a*]pyrazine **1a** or **1b** (7.6 mmol) in methylene chloride (40 ml) at 20°C with stirring we added dropwise 76 mmole of acetyl chloride, and then over 30 min we added aluminum chloride (76 mmol). The mixture was stirred at 20°C for 24 h and was then poured onto crushed ice. The aqueous solution was neutralized with sodium carbonate, and the precipitate was filtered off and washed with methylene chloride. The mother solution was extracted with methylene chloride and dried with 3Å sieves. In the case of 1-methylpyrrolo[1,2-*a*]pyrazine the oil remaining after evaporation of the solvent was recrystallized from hexane, and 6-acetyl-1-methylpyrrolo[1,2-*a*]pyrazine was isolated. When acetone was added to the residue after recrystallization the dimer **4** was precipitated. In the case of 1,6-dimethylpyrrolo-[1,2-*a*]pyrazine the residue after evaporation of the solvent was chromatographed on a column of Silpearl silica gel in the 1:1 benzene–ethyl acetate system.

6-Acetyl-1-methylpyrrolo[1,2-*a*]pyrazine (2). Yield 49%; mp 96.2-97.5°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 2.61 (3H, s, $COCH_3$); 2.76 (3H, s, 1-CH_3); 6.79 (1H, d, $J_{8,7}$ = 4.51, H-8); 7.50 (1H, d, J = 4.51, H-7); 7.80 (1H, d, $J_{3,4}$ = 4.79, H-3); 9.43 (1H, d, $J_{4,3}$ = 4.79, H-4). Found %: C 68.82; H 5.75; N 15.88. $C_{10}H_{10}N_2O$. Calculated %: C 68.97; H 5.75; N 16.09.

8-Acetyl-1-methylpyrrolo[1,2-*a*]pyrazine (3). Yield 7.0%. ^1H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 2.63 (3H, s, $COCH_3$); 3.04 (3H, s, 1-CH_3); 7.25 (1H, d, $J_{6,7}$ = 2.83, H-6); 7.63 (1H, d, $J_{7,6}$ = 2.83, H-7); 7.69 (1H, d, J = 4.52, H-3); 7.77 (1H, d, $J_{4,3}$ = 4.52, H-4).

2,7-Diacetyl-1-[(6-acetylpyrrolo[1,2-*a*]pyrazin-1-yl)methyl]-1-methyl-1,2-dihydropyrrolo[1,2-*a*]-pyrazine (4). Yield 3%; mp 214.9-215.8°C (decomp., from methanol). ^1H NMR spectrum (acetone-d_6), δ, ppm (J, Hz): 2.29 (3H, s, 1-CH_3); 2.36 (3H, s, $NCOCH_3$); 2.63 (3H, s, 6'-$COCH_3$); 2.93 (3H, s, 7-$COCH_3$); 3.60 [1H, d, $J_{9,10}$ = 13.20, H-9(10)]; 4.32 [1H, d, $J_{9,10}$ = 13.20, H-9(10)]; 6.13 (1H, dd, $J_{4,3}$ = 6.58, $J_{4,8}$ = 0.82, H-4); 6.33 (1H, d, $J_{3,4}$ = 6.58, H-3); 6.64 (1H, dd, $J_{8',7'}$ = 4.69, $J_{8',4'}$ = 0.78, H-8'); 6.70 (1H, dd, $J_{8,6}$ = 1.76, $J_{8,4}$ = 0.82, H-8); 7.26 (1H, d, $J_{6,8}$ = 1.76, H-6); 7.68 (1H, d, $J_{7',8'}$ = 4.69, H-7'); 7.83 (1H, d, $J_{3',4'}$ = 4.89, H-3'); 9.47 (1H, dd, $J_{4',3'}$ = 4.89, $J_{4',8'}$ = 0.78, H-4'). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm (J, Hz): 25.15 (CH_3); 27.29 (CH_3); 27.54 (CH_3); 27.88 (CH_3); 44.22 (CH_2); 60.99 ($C_{(1)}$); 104.05, 105.71, 106.80, 116.96, 118.09, 122.16, 123.39, 123.74, 125.95, 130.74, 132.06, 132.11, 152.77 (1C, dt, J_{CH} = 4.13, J = 10.98, $C_{(1')}$); 170.73 ($NCOCH_3$); 188.83 (7-$COCH_3$); 192.29 (6'-$COCH_3$). Found %: C 66.77; H 5.75; N 14.48. $C_{22}H_{22}N_4O_3$. Calculated %: C 67.69; H 5.64; N 14.36.

8-Acetyl-1,6-dimethylpyrrolo[1,2-*a*]pyrazine (5). Yield 26%; mp 146.0-149.6 (decomp.). ^1H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 2.49 (3H, s, 6-CH_3); 2.61 (3H, s, $COCH_3$); 2.98 (3H, s, 1-CH_3); 7.04 (1H, s, H-7); 7.56 (1H, d, $J_{3,4}$ = 4.60, H-3); 7.75 (1H, d, $J_{4,3}$ = 4.60, H-4). Found %: C 70.06; H 6.26; N 14.84. $C_{11}H_{12}N_2O$. Calculated, %: C 70.21; H 6.38; N 14.89.

2-Acetyl-1-(8-acetyl-6-methylpyrrolo[1,2-*a*]pyrazin-1-ylmethyl)-1,6-dimethyl-1,2-dihydropyrrolo-[1,2-*a*]pyrazine (6). Yield 3.0%. ^1H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 2.11 (3H, s, 1-CH_3); 2.29 (3H, s, $NCOCH_3$); 2.35 (3H, s, 6'-CH_3); 2.36 (3H, s, 6-CH_3); 2.41 (3H, s, 8'-$COCH_3$); 3.25 [1H, d, $J_{9,10}$ = 12.91,

H-9(10)]; 3.90 [1H, d, $J_{10,9}$ = 12.91, H-10(9)]; 5.76 (1H, d, $J_{4,3}$ = 5.76, H-4); 5.80 (1H, d, $J_{3,4}$ = 5.76, H-3); 6.35 (1H, s, H-7'); 6.40 (1H, d, $J_{8,7}$ = 3.91, H-8); 6.50 (1H, d, $J_{7,8}$ = 3.91, H-7); 7.30 (1H, d, $J_{3',4'}$ = 4.89, H-3'); 7.43 (1H, d, $J_{4',3'}$ = 4.89, H-4'). ^{13}C NMR spectrum (methanol-d_4), δ, ppm (*J*, Hz): 9.04 (CH_3); 9.65 (CH_3); 23.44 (CH_3); 25.68 (CH_3); 27.17 (CH_3); 44.65 (CH_2); 61.34 ($C_{(1)}$); 102.96, 103.07, 108.35, 113.95, 114.02, 115.98, 120.91, 123.55, 124.89, 128.24, 129.17, 131.06, 151.57 (1C, dt, J_{CH} = 5.86, *J* = 9.51, $C_{(1')}$); 171.57 (N<u>C</u>OCH_3); 196.12 (8'-<u>C</u>OCH_3). Found %: C 71.69; H 6.43; N 15.03. $C_{22}H_{24}N_4O_2$. Calculated %: C 71.21; H 6.38; N 14.89.

REFERENCES

1. R. Buchan, M. Fraser, and P. V. S. Kong Thoo Lin, *J. Org. Chem.*, **54**, 1075 (1989).
2. V. I. Terenin, E. V. Kabanova, and Yu. G. Bundel', *Khim. Geterotsikl. Soedin.*, 763 (1991). [*Chem. Heterocycl. Comp.*, **27**, 597 (1992)].