REACTION OF 1-ETHOXALYLMETHYLPYRIDO[2,3-b]PYRAZINIUM BROMIDE WITH AMMONIUM ACETATE: SYNTHESIS OF IMIDAZO[1',2':1,2]PYRIDO[5,6-b] PYRAZINES

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Abstract: The synthesis of some imidazo[1',2':1,2]pyrido[5,6-b]pyrazines by treatment of quaternary salts of pyrido[2,3-b]pyrazines with ammonium acetate in acetic acid media is described.

The interest of the pyrido[2,3-b]pyrazinim system resides in the potentiality to undergo heterocyclisation on three positions (N-1, N-4, N-5). Biological potentiality of the resulting tricyclic systems resides principally in their structural analogy with the imidazo[1,2-a]quinoxaline or quinoline series, well known for their antiallergic or anxiolytic properties.

Synthesis of starting materials (1-4) was achieved according to published methods. Treatment of pyrido[2,3-b]pyrazine (1) and its methyl derivatives (2-4) with ethyl bromopyruvate in DME gave their corresponding quaternary salts (5-8) (Scheme 1). In order to determine the position of the quaternisation on the N-5 position, we investigated their cyclisation with ammonium acetate. This reaction is well known in the isoquinoline series to give the corresponding imidazo[1,2-a]isoquinolines and their 4,5-dihydro derivatives hydrogenated derivatives. The same results are observed in the quinoline series.
In our case, treatment of 5 with ammonium acetate in refluxing acetic acid gave only one product identified as ethyl imidazo[1',2':1,2] pyrido[5,6-b]pyrazine-2-carboxylate (9) (Scheme 2). No cyclisation on the pyrazinic moiety was found. Structural determination of 9 was made by examination of its $^1$H-nmr spectrum with a singlet at $\delta$ 9.06 for H-1, an AB system at $\delta$ 7.86 for H-4 and H-5, and two doublets at $\delta$ 8.69 and 8.89 for H-7 and H-8.

In a similar manner, treatment of the methyl derivatives (6) and (7) provided ethyl 7,8-dimethyl-
imidazo[1',2':1,2]pyrido[5,6-b]pyrazine-2-carboxylate (10), and ethyl 7-methylimidazo[1',2':1,2]-pyrido[5,6-b]pyrazine-2-carboxylate (11) respectively. No cyclisation on the pyrazinic moiety was observed in these cases too. Structural determinations of 10, 11 were made by ¹H-nmr, ms spectra, and by comparison with the unsubstituted compound (9).

In contrast, the reaction of compound (8) derived from 6-methyl derivative (4) followed another course which involved the participation of the active 6-methyl group and led to the formation of ethyl pyrazino[2,3-g]indolizine-2-carboxylate (12) previously described.⁵

In order to realise cyclisation on the pyrazinic moiety, we investigated another process which involved the generation in situ of the quaternary salts (method B). This process has previously been developed for the cyclisation of some phenacylnaphthyridinium bromides into imidazo[1,2-a]naphthyridines and their hydrogenated derivatives.⁷ Under these conditions, treatment of pyrido[2,3-b]pyrazine (1) with ethyl bromopyruvate in absolute ethanol followed by addition of ammonium acetate in acetic acid did not rise to the expected heterocyclisation on the pyrazinic nucleus, but led to compound (9)⁵. However, a similar treatment of the 2-methyl derivative (3) gave ethyl pyrido[2,3-e]pyrrolo[1,2-a]pyrazine-2-carboxylate (13, 42%) together with 11 (Scheme 3).

**Scheme 3**

(i) a: BrCH₂CO₂C₂H₅/C₂H₅OH, b: evaporation of solvent and addition of AcONH₄/AcOH

¹H-Nmr spectrum of 13 showed two doublets at δ 7.40 and 8.90 (J = 2 Hz). Their assignment to H-3 and H-1 respectively was easy to make by comparison with the nmr spectrum of the 8-bromo derivative.⁵
The singlet at δ 8.88 was assigned to H-4, and the AMX system to the pyridinic moiety. The 2,3-dimethyl derivative (2) produced also two pyrrolo derivatives (14: 55%, 15: 25%) besides the imidazo derivative 10. Structure of 14 was easily determined by mass spectrometry (M+ peak at 351) and by 1H-nmr spectrum (two pyrrolic systems and one pyridinic system). Structural determination of 15 was more difficult because of the two possibilities of cyclisation on the N-1 or N-4 positions. Examination of its 13C-nmr spectrum showed a signal at δ 136.79 characteristic of the pyrido[3,2-e]pyrrolo[1,2-a]pyrazine series.

In conclusion, the pyrido[2,3-b]pyrazinic system shows the preferential nucleophilicity at the N-5 nitrogen atom. Quaternary salts formed on this position constitute common intermediates in the synthesis of the original imidazo[1',2':1,2]pyrido[5,6-b]pyrazinic series except for 6-methyl derivative (4) which gives a pyrrolo-pyridine (12). Compounds (3) and (2), bearing active methyl groups on the pyrazine moiety, can also undergo pyrrolo-condensation on the pyrazinic nucleus by method B (using this method, the excess of ethyl bromopyruvate can react thermodynamically on the N-1 or N-4 positions to give the corresponding pyrido[2,3-b]pyrazinium salts).

EXPERIMENTAL

general. Mp were determined on a Büchi capillary melting point apparatus and are not corrected. Elemental analysis was performed by Microanalytical Center, ENSCM, Montpellier. Spectral measurements were taken using the following instruments: 1H-Nmr spectra were taken on a Varian EM 360 (60 MHz) or a Bruker MSL 300, or AM 400 WB; 13C-Nmr spectra were obtained at 26°C with proton noise decoupling at 75 MHz with a Bruker MSL 300 instrument. Chemical shifts are expressed relative to internal tetramethylsilane in CDCl3 at a concentration of ca 5%. Mass spectra were recorded on a LKB 2091 spectrometer at 70eV [θ(source) = 180°C]. Compounds were purified by highperformance liquid chromatography (hplc), Waters M 590, on a preparative alumina or silica gel column. When necessary, solvents and reagents were dried prior to use. Dichloromethane was dried over activated alumina and distilled from calcium hydride. Thin layer chromatography (Tlc) were performed on 0.25 mm E. Merck precoated neutral alumina plates.

Ethyl imidazo[1',2':1,2]pyrido[5,6-b]pyrazine-2-carboxylate (9). A solution of 1 (1 g, 8 mmol) and ethyl bromopyruvate (2.5 g, 12.8 mmol) in DME (25 ml) was stirred at room temperature overnight. After filtration, the precipitate was washed with ether to give 5. The salt was dissolved in acetic acid (5 ml), and ammonium acetate (2 g, 26 mmol) was added. After refluxing for 2 h, the mixture was poured into ice, neutralised with sodium carbonate, and extracted with ether. After purification by chromatography on
neutral alumina eluted with ethyl acetate, compound (9) was obtained in 42% yield (0.8 g) as a brown oil. $^1$H-Nmr (CDCl$_3$, 300 MHz) δ: 1.47 (t, 3H, $\beta = 7$ Hz, CH$_3$), 4.50 (q, 2H, $\beta = 7$ Hz, CH$_2$), 7.86 (AB system, 2H, H-4,5), 8.69 (d, 1H, $\beta = 2.1$ Hz, H-7 or H-8), 8.89 (d, 1H, $\beta = 2.1$ Hz, H-8 or H-7), 9.06 (s, 1H, H-4). Anal. Calcd. for C$_{12}$H$_{10}$N$_4$O$_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.25; H, 4.21; N, 23.11.

Ethyl 7,8-dimethylimidazo[1',2':1,2]pyrido[5,6-b]pyrazine-2-carboxylate (10). Compound (10) was obtained following the method given for the synthesis of 9 in a 59% yield (1 g) as a dark oil. $^1$H-nmr (CDCl$_3$, 300 MHz) δ: 1.47 (t, 3H, $\beta = 6.9$ Hz, CH$_3$), 2.74 (s, 3H, CH$_3$), 2.76 (s, 3H, CH$_3$), 4.49 (q, 2H, $\beta = 6.9$ Hz, CH$_2$), 7.76 (AB system, 2H, H-4,5), 9.03 (s, 1H, H-1); ms (m/z, %): 270 (33), 225 (32), 198 (100), 158 (60). Anal. Calcd for C$_{14}$H$_{14}$N$_4$O$_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 62.13; H, 5.24; N, 20.59.

Ethyl 7-methylimidazo[1',2':1,2]pyrido[5,6-b]pyrazine-2-carboxylate (11). This compound was obtained following the method given for the synthesis of 9 in a 41% yield (0.72 g) (brown oil); $^1$H-nmr (CDCl$_3$, 400 MHz) δ: 1.47 (t, 3H, $\beta = 7.1$ Hz, CH$_3$), 2.81 (s, 3H, CH$_3$), 4.50 (q, 2H, $\beta = 7.1$ Hz, CH$_2$), 7.82 (AB system, 2H, H-4,5), 8.75 (s, 1H, H-8), 9.06 (s, 1H, H-1); ms (m/z, %): 256 (43), 228 (2), 211 (51), 184 (100). Anal. Calcd for C$_{13}$H$_{12}$N$_4$O$_2$: C, 60.93; H, 4.72; N, 21.86. Found: C, 60.89; H, 4.78; N, 21.81.

Ethyl pyrido[2,3-e]pyrrolo[1,2-a]pyrazine-2-carboxylate (13). A solution of 3 (1 g, 8 mmol) and ethyl bromopyruvate (2.5 g, 18.8 mmol) in ethanol (30 ml.) was stirred overnight. After evaporation of the solvent, 5 ml of acetic acid and 2.5 g (25.9 mmol) of ammonium acetate were added. The mixture was heated at 150°C for 2 min on a oil bath. After cooling, the solution was neutralised with sodium carbonate, extracted with ether and submitted to a chromatography on neutral alumina eluted with ethyl acetate to give 13 (0.8 g, 42%, recrystallisation from acetonitrile); mp: 144-146°C. $^1$H-Nmr (CDCl$_3$, 60 MHz) δ: 1.45 (t, 3H, $\beta = 6.7$ Hz, CH$_3$), 4.43 (q, 2H, $\beta = 6.7$ Hz, CH$_2$), 7.40 (d, 1H, $\beta = 2$ Hz, H-3), 7.51 (dd, $\beta = 8$ and 6 Hz, H-8), 8.30 (dd, 1H, $\beta = 8$ and 1.5 Hz, H-9), 8.61 (dd, 1H, $\beta = 6$ and 1.5 Hz, H-7), 8.88 (s, 1H, H-4), 8.90 (d, 1H, $\beta = 2$ Hz, H-1); ms (m/z, %) 241 (48), 213 (12), 196 (67), 169 (33). Anal. Calcd for C$_{13}$H$_{11}$N$_3$O$_2$: C, 64.72; H, 4.60; N, 17.42. Found: C, 64.89; H, 4.78; N, 17.61. Further elution gave 11 in 15% yield (0.26 g).
Ethyl pyrido[2,3-\textit{a}:1',2'-\textit{c}]pyrazine-2,5-dicarboxylate (14). ethyl 4-methyl pyrido[1,2-\textit{a}]
pyrido[1,2-\textit{a}]:1',2'-\textit{c}]pyrazine-2-carboxylate (15). Compounds 14, 15 were obtained using the same method
employed for the preparation of 13. Chromatography on silica gel eluted with ethyl acetate gave 14 as an
oil in 55\% yield. $^1\text{H-Nmr}$ (CDCl$_3$, 300 MHz) $\delta$: 1.40 (m, 6H, $Z\text{CH}_2$), 4.36 (m, 4H, $2\text{CH}_2$), 6.91 (d, 1H,
$J = 1.2$ Hz, H-3 or H-4), 6.94 (d, 1H, $J = 1.5$ Hz, H-4 or H-3), 7.33 (dd, 1H, $J = 8.3$ and 4.7 Hz, H-10),
7.98 (d, 1H, $J = 8.3$ and 1.5 Hz, H-1 or H-6), 7.99 (dd, 1H, $J = 4.7$ and 1.2 Hz, H-11), 8.37 (dd,
1H, $J = 8.3$ and 1.2 Hz, H-9), 8.47 (d, 1H, $J = 1.5$ Hz, H-6 or H-1); ms (m/z, %): 351 (55), 323 (15),
306 (13), 295 (20), 279 (18), 251 (12), 205 (13). *Anal.* Calcd for C$_{19}$H$_{17}$N$_3$O$_4$: C, 64.95; H, 4.88;
N, 11.96. Found: C, 64.99; H, 4.79; N, 12.06. Further elution gave 15 in 25\% yield (recrystallisation from
acetonitrile); $mp = 148-150^\circ$C. $^1\text{H-Nmr}$ (CDCl$_3$, 300 MHz) $\delta$: 1.41 (t, 3H, $J = 7$ Hz CH$_3$), 2.72 (s, 3H,
CH$_3$), 4.39 (q, 2H, $J = 7$ Hz CH$_3$), 7.32 (d, 1H, $J = 0.95$ Hz, H-3), 7.45 (dd, 1H, $J = 7.8$ and 4.6 Hz,
H-7), 8.16 (dd, 1H, $J = 7.8$ and 1.4 Hz, H-6), 8.50 (dd, 1H, $J = 4.6$ and 1.4 Hz, H-8), 8.81 (d, 1H, $J$
= 0.95 Hz, H-1). $^{13}\text{C-Nmr}$ (CDCl$_3$, 100 MHz) $\delta$: 14.36 (CH$_3$), 21.79 (CH$_3$), 60.59 (CH$_2$), 108.66 (C-3),
118.43 (C-1), 120.65 (C-2), 122.41 (C-7), 127.65 (C-3a), 131.05 (C-5a), 136.79 (C-6), 138.89 (C-9a),
146.58 (C-8), 155.57 (C-4), 164.09 (C=O); *Anal.* Calcd for C$_{14}$H$_{13}$N$_3$O$_2$: C, 65.87; H, 5.13; N, 16.46.
Found: C, 65.79; H, 4.89; N, 16.31. Further elution gave 10 (7\%).

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REFERENCES AND NOTES

5. Y. Blache, A. Gueffier, H. Viols, O. Chavignon, J.C. Teulade, G. Dauphin, and J.P. Chapat, J.


8. Discrimination between the two series A and B cannot be realised by their \(^1\)H-nmr spectra which shows only minor differences.

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\begin{align*}
\text{A} & \\
\text{B}
\end{align*}
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In addition, comparison of their \(^{13}\)C-nmr spectra showed that the carbon localised at the \(\gamma\) position of nitrogen in the pyridinic nucleus, exhibits major differences with \(\delta 122.24\) for A and \(\delta 137.15\) for B; for more details see ref. 5.

9. This experimental data is in accord with theoretical values of proton affinities (\(\text{PA}_{N-1} = 205.56\) Kcal./mol., \(\text{PA}_{N-4} = 212.02\) Kcal./mol., \(\text{PA}_{N-5} = 216.32\) Kcal./mol.) which indicates a preferential basicity of the N-5 nitrogen atom. Theses values were obtained from the AM1 method. Calculation were performed using the MOPAC (version 5.0) program. For more details, see M. Szafran and J. Kopat, *J. Comput. Chem.*, 1991, 8, 675.

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