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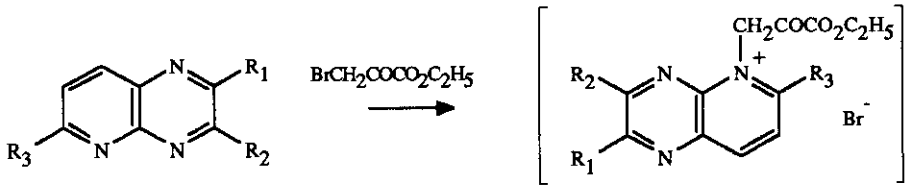
Abstract- The synthesis of somes imidazo[1',2':1,2]pyrido[5,6-*b*]pyrazines by treatment of quaternary salts of pyrido[2,3-*b*]pyrazines with ammonium acetate in acetic acid media is described.

The interest of the pyrido[2,3-*b*]pyrazinic 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[1] or anxiolytic[2] properties.

Synthesis of starting materials (**1-4**) was achieved according to published methods.[3-5] 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 quaternarisation 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.[6] The same results are observed in the quinoline series.[1]

Scheme 1

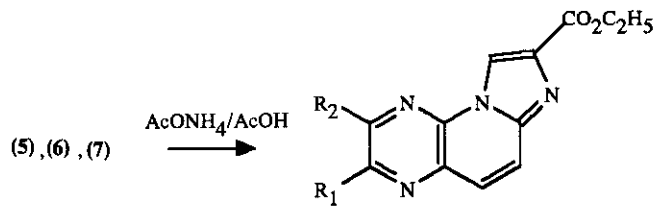


(1) $R_1=R_2=R_3=H$
(2) $R_1=R_2=CH_3$, $R_3=H$
(3) $R_1=CH_3$, $R_2=R_3=H$
(4) $R_1=R_2=H$, $R_3=CH_3$

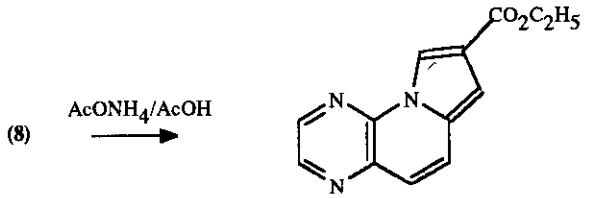
(5) $R_1=R_2=R_3=H$
(6) $R_1=R_2=CH_3$, $R_3=H$
(7) $R_1=CH_3$, $R_2=R_3=H$
(8) $R_1=R_2=H$, $R_3=CH_3$

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 δ 9.06 for H-1, an AB system at δ 7.86 for H-4 and H-5, and two doublets at δ 8.69 and 8.89 for H-7 and H-8.

Scheme 2



(9) $R_1=R_2=H$
(10) $R_1=R_2=CH_3$
(11) $R_1=CH_3$, $R_2=H$



(12)

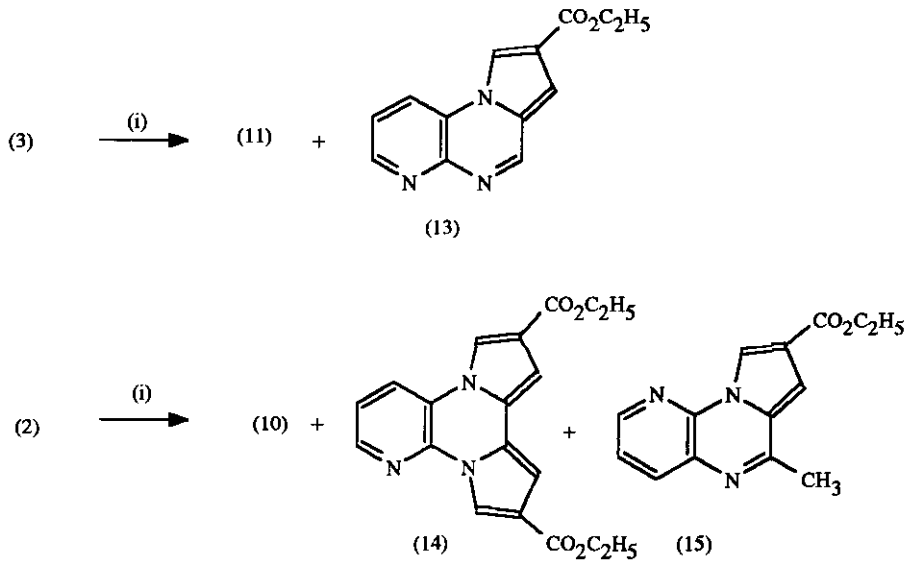
In a similar manner, treatment of the methyl derivatives (**6**) and (**7**) provided ethyl 7,8-dimethyl-

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 ^{1}H-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 theses 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**) . 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: $BrCH_2COCO_2C_2H_5/C_2H_5OH$, b: evaporation of solvent and addition of $AcONH_4/AcOH$

^{1}H-Nmr spectrum of **13** showed two doublets at δ 7.40 and 8.90 (J= 2 Hz). Their assignement 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 sytem 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 ^{1}H-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 ^{13}C-nmr spectrum showed a signal at δ 136.79 caracteristic of the pyrido[3,2-*e*]pyrrolo[1,2-*a*]pyrazine series.[8]

In conclusion, the pyrido[2,3-*b*]pyrazinic system shows the preferential nucleophilicity at the N-5 nitrogen atom.[9] 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 perfomed by Microanalytical Center, ENSCM, Montpellier. Spectral measurements were taken using the following instruments: ^{1}H-Nmr spectra were taken on a Varian EM 360 (60 MHz) or a Brüker MSL 300, or AM 400 WB; ^{13}C-Nmr spectra were obained at 26°C with proton noise decoupling at 75 MHz with a Brüker MSL 300 instument. Chemical shifts are expressed relative to internal tetramethylsilane in $CDCl_3$ at a concentration of *ca* 5%. Mass spectra were recorded on a LKB 2091 spectrometer at 70eV [$\theta_{(source)}$=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 pourred into ice, neutralised with sodium carbonate, and extracted with ether. After purification by chomatography on

neutral alumina eluted with ethyl acetate, coumpound (**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, J = 7 Hz, CH_3), 4.50 (q, 2H, J = 7 Hz, CH_2), 7.86 (AB system, 2H, H-4,5), 8.69 (d, 1H, J = 2.1 Hz, H-7 or H-8), 8.89 (d, 1H, J = 2.1 Hz, H-8 or H-7), 9.06 (s, 1H, H-4). *Anal.* Calcd. for $C_{12}H_{10}N_4O_2$: 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, J = 6.9 Hz, CH_3), 2.74 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 4.49 (q, 2H, J = 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 $C_{14}H_{14}N_4O_2$: 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, J =7.1 Hz, CH_3), 2.81 (s, 3H, CH_3), 4.50 (q, 2H, J =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 $C_{13}H_{12}N_4O_2$: 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 solvant, 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%, recristallisation from acetonitrile); mp: 144-146°C. ^{1}H-Nmr ($CDCl_3$, 60 MHz) δ: 1.45 (t, 3H, J = 6.7 Hz, CH_3), 4.43 (q, 2H, J = 6.7 Hz, CH_2), 7.40 (d, 1H, J = 2 Hz, H-3), 7.51 (dd, J = 8 and 6 Hz, H-8), 8.30 (dd, 1H, J = 8 and 1.5 Hz, H-9), 8.61 (dd, 1H, J = 6 and 1.5 Hz, H-7), 8.88 (s, 1H, H-4), 8.90 (d, 1H, J = 2 Hz, H-1); ms (*m/z*, %) 241 (48), 213 (12), 196 (67), 169 (33). *Anal.* Calcd for $C_{13}H_{11}N_3O_2$: 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-e]dipyrrolo[1,2-a;1',2'-c]pyrazine-2,5-dicarboxylate (14), ethyl 4-methyl pyrido[3,2-e] pyrrolo[1,2-a]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}H-Nmr ($CDCl_3$, 300 MHz) δ: 1.40 (m, 6H, $2CH_3$), 4.36 (m, 4H, $2CH_2$), 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 $C_{19}H_{17}N_3O_4$: 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 (recristallisation from acetonitrile); mp = 148-150°C. ^{1}H-Nmr ($CDCl_3$, 300 MHz) δ: 1.41 (t, 3H, J = 7 Hz CH_3), 2.72 (s, 3H, CH_3), 4.39 (q, 2H, J = 7 Hz, CH_2), 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}C-Nmr ($CDCl_3$, 100 MHz) δ: 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=0); *Anal.* Calcd for $C_{14}H_{13}N_3O_2$: 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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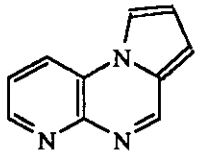
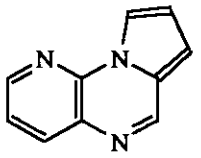
REFERENCES AND NOTES

1. I.R. Ager, A.C. Barnes, G.W. Danswan, P.W. Hairsine, D.P. Kay, P.D. Kemewell, S.S. Matharu, P. Miller, P. Robson, D.A. Rowlands, W.R. Tully, and R. Westwood, J. Med. Chem., 1988, **31**, 1098.
2. S. Clement-Jewery, G. Danswan, C.R. Gardner, S.S. Matharu, R. Murdoch, W.R. Tully, and R. Westwood, J. Med. Chem., 1988, **31**, 1220.
3. C.L. Leese and H.N. Rydon, J. Chem. Soc., 1955, 303.
4. V. Petrow and J. Saper, J. Chem. Soc., 1948, 1389.
5. Y. Blache, A. Gueiffier, H. Viols, O. Chavignon, J.C. Teulade, G. Dauphin, and J.P. Chapat, J. Heterocycl. Chem., submitted.

6. R.F. Cookson, D.P. Nowotnik, R.T. Parfitt, J.E. Airey, and A.S. Kende, J. Chem. Soc., Perkin Trans I, 1976, 201; R.F. Cookson, D.P. Nowotnik, and R.T. Parfitt, J. Chem. Soc., Chem. Comm., 1974, 911.
7. O. Chavignon, J.C. Teulade, A.E. Hakmaoui, A. Gueiffier, Y. Blache, and J.P. Chapat, J. Heterocycl. Chem., submitted.
8. Discrimination between the two series A and B cannot be realised by their ^{1}H-nmr spectra which shows only minor differences.


A


B

In addition, comparison of their ^{13}C-nmr spectra showed that the carbon localised at the γ position of nitrogen in the pyridinic nucleus, exhibits mayor differences with δ 122.24 for A and δ 137.15 for B; for more details see ref. 5.
9. This experimental data is in accord with theorical values of proton affinities ($PA_{N\text{-}1}$ = 205.56 Kcal./mol., $PA_{N\text{-}4}$ = 212.02 Kcal./mol., $PA_{N\text{-}5}$ = 216.32 Kcal./mol.) which indicates a preferential basicity of the N-5 nitrogen atom. Theses values were obtained from the AM_1 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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