Synthesis of 1*H*-Pyrazino[1,2-*a*]pyrido[2,3-*e*]pyrazine and 2*H*-Pyrano[2,3-*b*]pyrido[2,3-*e*]pyrazine Derivatives [1]

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With a continuing interest on heteropolycyclic structures which may show biological activities, we synthesized new tricyclic derivatives in which the pyridopyrazine skeleton is fused with pyrazine **7** and **8**, **B**, n = 1. However, the initial design of obtaining also the cyclohomologous structure **B** (n = 2) produced instead a pyranopyridopyrazine derivative **11**. Thus during the attempt to prepare a pyridodiazepine intermediate, beside a very small amount of the desired product **10**, the pyridopyrazine **9** was obtained. The latter compound reacted with chloroacetyl chloride/chloroketene to give 4-carbethoxy-10-(chloroacetyl)-5,10-dihydro-5-methyl-2*H*-pyrano[2,3-*b*]pyrido[2,3-*e*]pyrazin-2-one (**11**). In studying the behavior of this derivative, compounds **12-14** were obtained. Compounds **4b,c**, **5a,b**, **7**, **8**, **9** and **14** have been submitted to preliminary pharmacological screening as CNS depressant agents.

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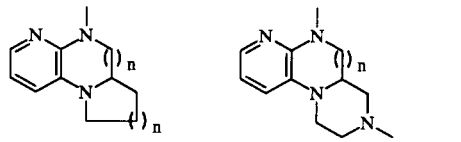
In previous papers [2,3,4] we described the synthesis of some heteropolycyclic systems with neuroleptic activity. Now, in developing the study on structure **A** derivatives [4], some of which possessed appreciable CNS depressant and analgesic activities, we attempted to prepare derivatives of the new structure **B**, stemming from **A** by replacement of pyrrolidine or piperidine with tetrahydropyrazine ring. The designed pyrazinopyridopyrazine **B** (n = 1) and pyrazinepyridodiazepine **B** (n = 2) systems would allow us to ascertain the effect resulting from this structural modification on pharmaceutical response. Moreover, the novel compounds **7**, **8**, appear analogous to compounds which exhibited antihypertensive activity [5].

The synthetic approach to obtain 3-benzyl-2,6-dihydro-6-methyl-1*H*-pyrazino[1,2-*a*]pyrido[2,3-*e*]pyrazin-1,4,5(3*H*,4a*H*)-trione (**7**, structure **B**, n = 1) and the corresponding reduced compound (lithium aluminum hydride) 3-benzyl-2,3,4,4a,5,6-esahydro-6-methyl-1*H*-pyrazino[1,2-*a*]pyrido[2,3-*e*]pyrazine (**8**) (Scheme I) starts with the condensation, in boiling ethanol, of 3-amino-2-(methylamino)pyridine (**1**) with diethyl 2-oxomalonate to afford 2-carbethoxy-4-methylpyrido-[2,3-*b*]pyrazin-3(4*H*)-one (**2**). To the reduction of **2** to **3** (hydrogen/Ni-Raney) followed first the treatment of **3** with chloroacetyl chloride to give 2-carbethoxy-1-chloroacetyl-1,2-dihydro-4-methylpyrido[2,3-*b*]-pyrazin-3(4*H*)-one (**4a**) and subsequently the cyclocondensation (boiling toluene) of latter compound with benzylamine to give **7**. Compounds **4b** and **4c** were prepared from **3**, with the aim of obtaining, by an intramolecular Claisen condensation, compound **6**, related to structure **A** (n = 1) and possibly bioactive [4], but the attempt failed.



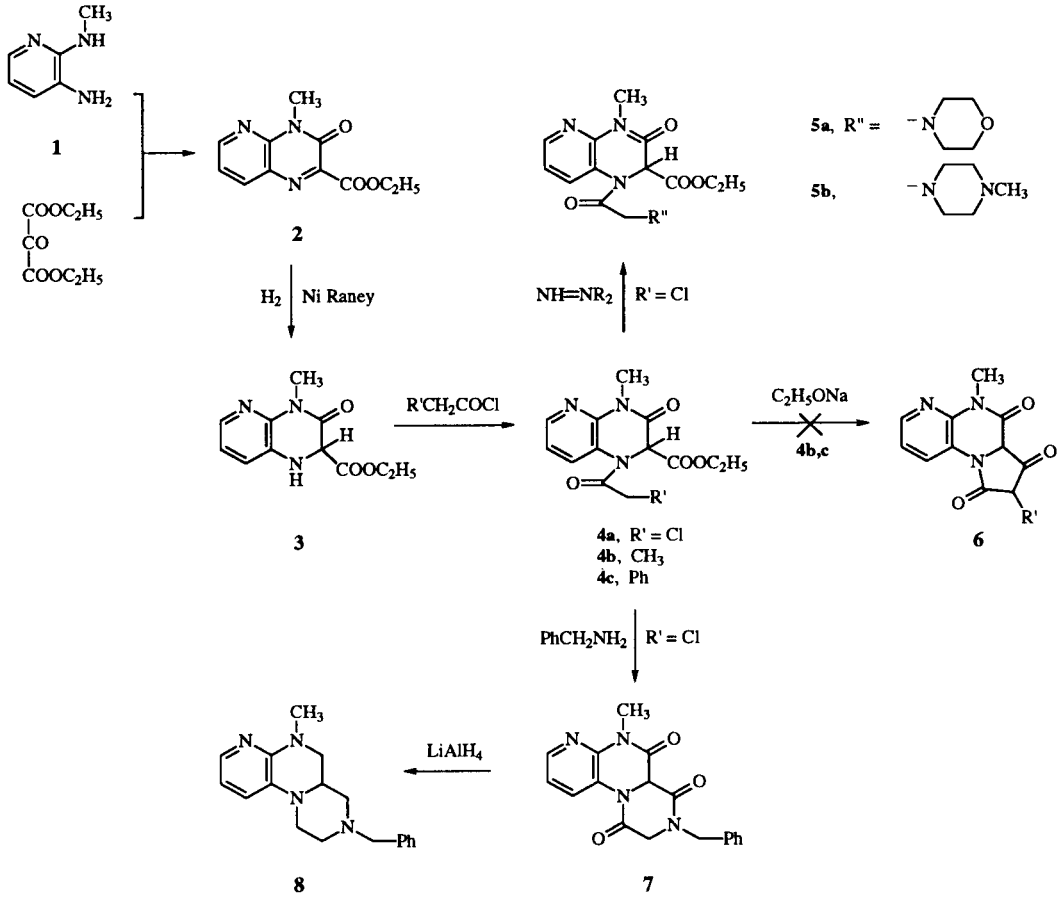
A **B** n = 1, 2

The structures of the compounds described were supported by analytical and spectroscopic data. Particularly, the ^{1}H nmr spectrum of pyridopyrazine derivative **3** exhibited two singlets at δ 4.62 and 4.67 ppm related to methine and NH hydrogens which confirms that the reduction occurred; the pyrazinopyridopyrazine derivative **7** exhibited an AB system (4.74 δ, J = 19.0 Hz) for the 2-CH_2 group which is shifted downfield with respect to that of corresponding group of the intermediate **4a** (4.20 δ), while the structure of compound **8** was ascertained on the basis of ^{1}H nmr and ^{13}C-DEPT spectrum which revealed five methylene signals.

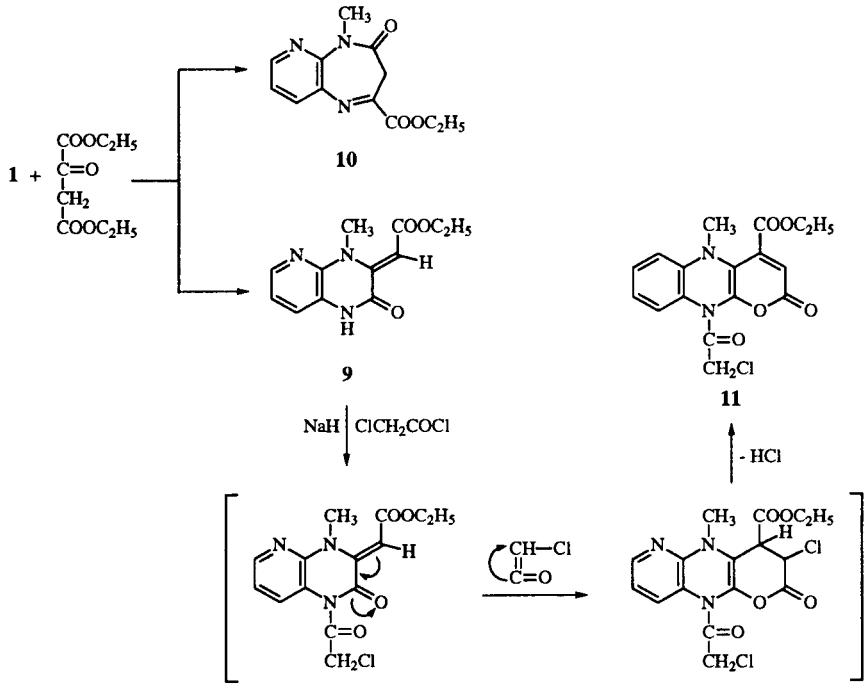
From **4a**, by alkylation in toluene of the appropriate secondary amine, **5a** and **5b** were prepared in order to establish pharmaceutical relations with previously studied analogs which revealed deconditioning activity [6].

The synthetic route established to synthesize the pyrazinepyridodiazepine system (**B**, n = 2) starting from pyridodiazepinone **10**, cyclohomologous with **2**, was impracticable because the condensation of **1** with diethyl oxalacetate, carried out under various conditions, supplied occasionally a very small amount of the desired compound **10**, while always an appreciable amount (about yield 60%) of **9** was obtained (Scheme II). The structural identification of **9** was not easy owing to the isomers compatible with the analytical and ^{1}H nmr data. However, the two ^{1}H nmr singlets at δ 5.9 and 11.15 seem to be most likely attributable

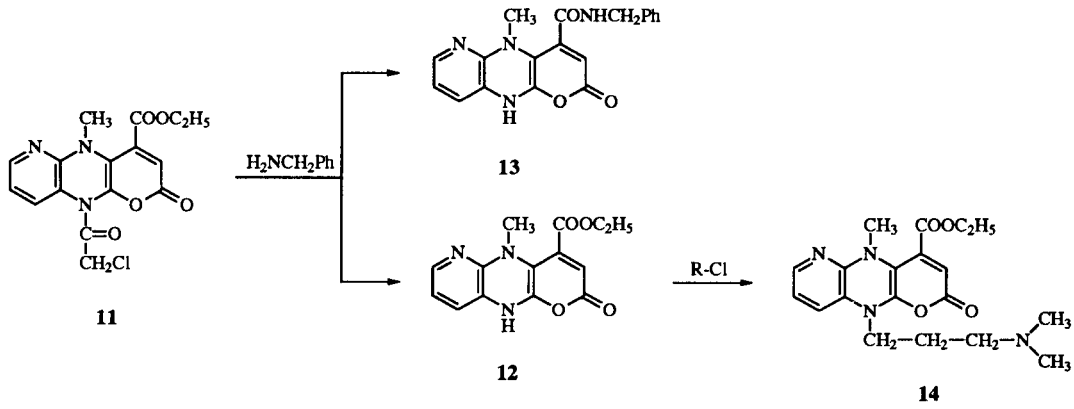
Scheme I



Scheme II



Scheme III



to the methine and NH hydrogens of the proposed structure (Scheme II). Furthermore, the proposed structure for **9** was preferred to those of the isomeric pyrazine and diazepine derivatives on the basis of the very strong ultraviolet absorption at higher wavelength (λ max, 373 nm) than those corresponding to pyrido[2,3-*b*]pyrazinone **2** and analogous derivatives, λ max, 347 nm [4,6] and pyrido[2,3-*b*][1,4]diazepinone structures **10** and analogous, λ max, 318 nm [2,7]. Moreover the ir spectrum of **9** exhibited bands at 3290, 3200 cm^{-1} related to -NH-CO- and 1681, 1650 cm^{-1}, attributed to ester and amide-CO groups.

Compound **9** did not react with chloroacetyl chloride under the same conditions employed for the transformation of **3** to **4a**. On the other hand, when **9**, after treatment with sodium hydride, was refluxed in dry THF/toluene with chloroacethyl chloride, 10-chloroacetyl-4-carbethoxy-5,10-dihydro-5-methyl-2*H*-pyrano[2,3-*b*]pyrido-[2,3-*e*]pyrazin-2-one (**11**) was unexpectedly obtained most likely through the reaction pattern suggested in Scheme II. It supposes the condensation of chloroacethyl chloride with the amidic sodium salt of **9** and, from chloroacethyl chloride, the base catalysed formation of chloroketene. This intermediate produces an addition to the pyrazinic conjugated system of **9** with ring closing and, by hydrochloride acid elimination, formation of **11**. The latter was identified on the basis of mass (M^+, 364), ^{13}C nmr (16 C) and ^1H nmr spectra. In this connection CH_2Cl (δ 4.36) and the H-3 (δ 7.85) ^1H nmr singlets are particularly significant.

The chloro substitution of **11** with secondary amines was not accomplished because, at room temperature in toluene, 4-carbethoxy-5,10-dihydro-5-methyl-2*H*-pyrano[2,3-*b*]-pyrido[2,3-*e*]pyrazin-2-one (**12**) was obtained. From **11** with benzylamine, in refluxing toluene, beside **12**, a small amount of 4-benzylcarbamoyl-5,10-dihydro-5-methyl-2*H*-pyrano[2,3-*b*]pyrido[2,3-*e*]pyrazin-2-one (**13**) was isolated (Scheme III). The alkylation of **12** with dialkylaminoalkyl chloride (sodium hydride/boiling toluene) to **14** occurs with difficulty.

Attempts to pursue the initial purpose to synthesize derivatives related to structure **B** (C = 2) are in progress and results will be reported in due course.

Compounds **4b,c, 5a,b, 7, 8, 9 and 14**, submitted to preliminary pharmacological screening, will be tested differentially as deconditioning, antihypertensive, CNS depressant agents [8] and, some of these, for their capacity to inhibit DNA synthesis in Ehrlich ascites tumor cells [9].

EXPERIMENTAL

All melting points were determined by the capillary method on a Büchi 510 apparatus and are uncorrected. The uv spectra were measured in 95% ethanol with a Perkin-Elmer Model 550S spectrophotometer. The ir spectra were taken on a Perkin-Elmer Paragon 1000 PC spectrometer. The ^1H and ^{13}C nmr spectra were recorded on a Varian-Gemini 200 spectrometer with TMS as the internal standard. The mass spectra were obtained on a Hewlett-Packard 5989-A spectrometer at 70 eV coupled with a Hewlett-Packard 5890 gas chromatograph. Elemental analyses for C, H, N were performed on the Carlo Erba Elemental Analyser Model 1106 at the Microanalytical Laboratory, Istituto di Scienze Farmaceutiche, Università di Genova.

2-Carbethoxy-4-methylpyrido[2,3-*b*]pyrazin-3(4*H*)-one **2**.

To a suspension in ethanol (15 ml) of 3-amino-2-methylaminopyridine (5.0 g, 40 mmoles) obtained by hydrogenation at atmospheric pressure of 2-methylamino-3-nitropyridine, was added an ethanol solution (25 ml) of diethyl ketomalonate (7.6 g, 44 mmoles) and the mixture was refluxed with stirring for 90 minutes. The reaction solution, concentrated under reduced pressure to half volume, supplies, after cooling, g 8.0 of **2** as bright plates (yield 84%), mp 115-117° (ethanol); uv: λ max nm (log ε) 226 (4.42), 347 (4.05); ir (potassium bromide): ν 1736, 1675 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.44 (t, J = 12.0 Hz, 3H, CH_3), 3.86 (s, 3H, N-CH_3), 4.52 (q, J = 12.0 Hz, 2H, CH_2), 7.38 (dd, J = 7.9 Hz, pyr β-H), 8.26 (dd, J = 7.9 Hz, pyr γ-H), 8.69 (dd, J = 4.6 Hz, pyr α-H).

Anal. Calcd. for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.59; H, 4.67; N, 17.97.

Compound **2** (2.3 g, 10 mmoles) was suspended in 2*N* sodium hydroxide (10 ml). After stirring at room temperature for 6 hours, the alkaline solution, extracted with dichloromethane, was neutralized with tartaric acid 10% solution and extracted with dichloromethane. The dichloromethane layer was washed with water, dried over anhydrous sodium sulphate and then evaporated to dryness to give 2-carboxy-4-methylpyrido[2,3-*b*]pyrazin-3(4*H*)-one which was recrystallized from ethanol, mp 179-181° (1.25 g, 63%); ir (potassium bromide): ν 1747 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.98 (s, 3H, N-CH_3), 7.58 (dd, J = 14 Hz, pyr β-H), 7.38 (dd, J = 14 Hz, pyr γ-H), 7.79 (dd, J = 10 Hz, pyr α-H), 11.00 (bs, OH exchangeable).

Anal. Calcd. for $C_9H_7N_3O_3$: C, 52.68; H, 3.44; N, 20.48. Found: C, 52.80; H, 3.39; N, 20.65.

2-Carbethoxy-1,2-dihydro-4-methylpyrido[2,3-*b*]pyrazin-3(4*H*)-one **3**.

A THF suspension of **2** (3.0 g, 13 mmoles) and Raney nickel (3.0 g) was shaken at room temperature in a Parr apparatus under 60 psi of hydrogen. After 8 hours the uptake of hydrogen ceased, the catalyst was filtered off and washed with THF/ethanol. The filtrate was concentrated to dryness under reduced pressure affording a crude solid mixture which recrystallized from toluene (ratio 1:5) give g 2.25 (74%) of **3**, mp 107-109° and, from the filtered solution, g 0.5 of unreacted **2** was recovered, uv: λ max nm (log ε) 213 (4.36), 314 (3.83); ir (potassium bromide): ν 3334, 1726, 1669 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.21 (t, J = 9.5 Hz, 3H, CH_3), 3.52 (s, 3H, N-CH_3), 4.19 (q, J = 9.5 Hz, 2H, CH_2), 4.62 (s, NH exchangeable), 4.67 (s, 1H, CH), 6.88 (dd, J = 10.0 Hz, pyr β-H), 7.07 (dd, J = 10.0 Hz, pyr γ-H), 7.90 (dd, J = 7.5 Hz, pyr α-H).

Anal. Calcd. for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.16; H, 5.55; N, 17.94.

1-Acyl-2-carbethoxy-1,2-dihydro-4-methylpyrido[2,3-*b*]pyrazin-3(4*H*)-ones **4a-c**.

General Procedure.

To a suspension of **3** (3.0 g, 13 mmoles) in dry toluene (30 ml) was added 1 ml of TEA and refluxed with stirring while a solution of 13 mmoles of the appropriate acyl chloride in 10 ml of dry toluene was added dropwise over a period of 30 minutes. Reflux was continued for an additional 3,5 hours. The reaction mixture was filtered hot to obtain an organic solution:

2-Carbethoxy-1-(chloroacetyl)-1,2-dihydro-4-methylpyrido[2,3-*b*] pyrazin-3(4*H*)-one (**4a**).

The organic solution was evaporated under reduced pressure to dryness to give an oily residue which was triturated with ethyl ether to afford g 2.90 (71%) of a crude solid which then was purified or by chromatography on neutral alumina, eluting with dichloromethane, or by crystallization from ethyl ether, mp 101-102°; ir (potassium bromide): ν 1743, 1693 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.19 (t, J = 8.5 Hz, 3H, CH_3), 3.52 (s, 3H, N-CH_3), 4.20 (m, 4H, $2CH_2$), 6.12 (bs, 1H, CH), 7.12 (dd, J = 8.0 Hz, pyr β-H), 7.80 (bs, pyr γ-H), 8.30 (dd, J = 8.0 Hz, pyr α-H).

Anal. Calcd. for $C_{13}H_{14}ClN_3O_4$: C, 50.08; H, 4.52; N, 13.48. Found: C, 50.17; H, 4.52; N, 13.55.

2-Carbethoxy-1-propionyl-1,2-dihydro-4-methylpyrido[2,3-*b*]pyrazin-3(4*H*)-one (**4b**).

According to the above procedure, was obtained in yield 69% beside unreacted **3** (~ 8%), mp 104-105° (ethanol); ir (potassium bromide): ν 1745, 1689 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.20 (m, 6H, $2CH_3$), 2.56 (m, 2H, CH_2), 3.53 (s, 3H, N-CH_3), 4.13 (q, J = 9.5 Hz, 2H, CH_2), 6.20 (bs, 1H, CH), 7.18 (dd, J = 8.0 Hz, pyr β-H), 7.65 (bs, pyr γ-H), 8.22 (dd, J = 7.0 Hz, pyr α-H).

Anal. Calcd for $C_{14}H_{17}N_3O_4$: C, 57.72; H, 5.88; N, 14.43. Found: C, 57.63; H, 5.90; N, 14.34.

2-Carbethoxy-1-(phenylacetyl)-1,2-dihydro-4-methylpyrido-[2,3-*b*]pyrazin-3(4*H*)-one (**4c**).

This compound was obtained, in yield 41%, by concentration to half volume of a filtered toluene solution, mp 98-100° (ethanol); ir (potassium bromide): ν 1742, 1688 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.11 (t, J = 8.0 Hz, 3H, CH_3), 3.42 (s, 3H, N-CH_3), 3.90 (s, 2H, CH_2), 4.10 (q, J = 8.0 Hz, 2H, CH_2), 6.22 (bs, 1H, CH), 7.04 (dd, J = 7.0 Hz, pyr β-H), 7.12 and 7.26 (m+m, 5H Ph), 7.63 (bs, pyr γ-H), 8.22 (dd, J = 7.0 Hz, pyr α-H).

Anal. Calcd. for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89. Found: C, 64.46; H, 5.40; N, 11.84.

1-(Dialkylaminoacetyl)-2-carbethoxy-1,2-dihydro-4-methylpyrido-[2,3-*b*]pyrazin-3(4*H*)-one **5a,b**.

General Procedure.

To a solution of **4a** (1.5 g, 5 mmoles) in toluene (15 ml) was added a solution of 10 mmoles of the appropriate dialkylamine in toluene and refluxed for 4 hours. The reaction mixture, filtered and evaporated *in vacuo* to dryness, affords an oily residue which, by trituration with diethyl ether, supplied white solids:

1-(Morpholinylacetyl)-2-carbethoxy-1,2-dihydro-4-methylpyrido[2,3-*b*]pyrazin-3(4H)-one (**5a**).

This compound had mp 102-103° (ethyl ether); ir (potassium bromide): ν 1743, 1698 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.21 (t, J = 8.0 Hz, 3H, CH_3), 2.52 (t, J = 4.2 Hz, 4H, $2CH_2$), 3.38 (m, 2H, CH_2), 3.51 (s, 3H, N-CH_3), 3.68 (t, J = 4.2 Hz, 4H, $2CH_2$), 4.20 (q, 2H, J = 8.0 Hz, CH_2), 6.18 (s, 1H, CH), 7.19 (dd, J = 8.0 Hz, pyr β-H), 8.22 (m, pyr γ-H and pyr α-H).

Anal. Calcd. for $C_{17}H_{22}N_4O_5$: C, 56.34; H, 6.12; N, 15.46. Found: C, 56.59; H, 6.03; N, 15.38.

1-(*N*-Methylpiperazinylacetyl)-2-carbethoxy-1,2-dihydro-4-methylpyrido[2,3-*b*]pyrazin-3(4*H*)-one (**5b**).

This compound had mp 84-85° (ethyl ether); ir (potassium bromide): ν 1743, 1698 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.20 (t, J = 8.0 Hz, 3H, CH_3), 2.25 (s, 3H, N-CH_3), 2.38 (m, 4H, $2CH_2$), 2.58 (m, 4H, $2CH_2$), 3.36 (m, 2H, CH_2), 3.50 (s, 3H, N-CH_3), 4.16 (m, 2H), 6.12 (s, 1H, CH), 7.09 (dd, J = 8.0 Hz, pyr β-H), 8.20 (m, pyr γ-H and pyr α-H).

Anal. Calcd. for $C_{18}H_{25}N_5O_4$: C, 57.58; H, 6.71; N, 18.66. Found: C, 57.56; H, 6.82; N, 18.26.

3-Benzyl-2,3-dihydro-6-methyl-1*H*-pyrazino[1,2-*a*]pyrido-[2,3-*e*]pyrazin-1,4,5(3*H*,4a*H*)-trione **7**.

To a solution of **4a** (3.5 g, 11.2 mmoles) in dry toluene (ml 100), benzylamine (2.40 g, 22.4 mmoles) in dry toluene (ml 10) was added and refluxed for 4 hours. The reaction mixture, after cooling, was filtered off and the solution, concentrated *in vacuo* to half volume, furnishes 2.5 g (67%) of **7**, as white crystals, mp 209-211° (ethanol); λ max nm (log ε) 286 (3.94); ir (potassium bromide): ν 1701, 1664 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.55 (s, 3H, CH_3), 4.08 (s, 2H, CH_2), 4.74 (AB, J = 19.0 Hz, 2H, CH_2), 4.78 (s, 1H exchangeable, CH), 7.12 (dd, J = 10.0 Hz, pyr

β-H), 7.55 (m, 5H Ph), 7.87 (dd, J = 8.0 Hz, pyr γ-H) 8.37 (dd, J = 5.0 Hz pyr α-H).

Anal. Calcd. for $C_{18}H_{16}N_4O_3$: C, 64.27; H, 4.80; N, 16.66. Found: C, 63.98; H, 4.73; N, 16.41.

3-Benzyl-2,3,4,4a,5,6-esahydro-6-methyl-1*H*-pyrazino[1,2-*a*]-pyrido[2,3-*e*]pyrazine **8**.

To a solution of (2.0 g, 6 mmoles) of **7** in dry THF-toluene (1:1, 120 ml), a suspension of lithium aluminium hydride (2.3 g, 30 mmoles) in dry THF (20 ml) was added dropwise (1 hour) at room temperature with vigorously magnetic stirring. The mixture was then refluxed for 8 hours and the stirring continued overnight at room temperature. The reduction mixture, after addition with successive dropwise of 2.3 ml of water, 2.3 ml of sodium hydroxide 15% solution and 6.9 ml of water, was filtered and the residue often washed with warm THF. The organic solution was evaporated under reduced pressure and the oily residue (1.8 g) was chromatographed on basic alumina and eluted with dichloromethane; 0.85 g of a very viscous oily compound was obtained; uv: λ max nm (log ε) 272 (3.99), 325 (4.09); ^{1}H nmr (deuteriochloroform): δ 1.86 (t, J = 10 Hz, 1H), 2.18 (dt, J = 12 Hz, 1H), 2.71-3.65 [m, 12H (superimposed, s at 3.08, 3H)], 6.58 (dd, J = 8.0 Hz, pyr β-H), 6.71 (dd, J = 8.0 Hz, pyr γ-H), 7.33 (m, 5H), 7.62 (dd, J = 4.5 Hz pyr α-H); ^{13}C nmr (deuteriochloroform): δ 30.2 (CH_2), 36.8 (CH_3), 46.3 (CH_2), 51.6 (CH), 52.7 (CH_2), 56.8 (CH_2), 63.4 (CH_2), 112.8 (CH Ph), 116.1 (C_2), 127.7 (C_1), 128.8 (2 CH Ph), 129.6 (2 CH Ph), 131.3 (C Ph) 137.8 (C_3), 138.1 (C_{11a}), 148.7 (C_{4a}).

Anal. Calcd. for $C_{18}H_{22}N_4$: C, 73.43; H, 7.53; N, 19.03. Found: C, 73.68; H, 7.08; N, 18.65.

Reaction of 2-Methylamine-3-aminopyridine with Diethyl-Oxalylacetate Affording **9**.

To a solution of 3-amino-2-methylaminopyridine (**1**, 2.5 g, 20 mmoles) in ethanol (30 ml), 4.5 g (22 mmoles) of diethyloxalylacetate in ethanol (10 ml) was added and the mixture was refluxed for 12 hours. The reaction solution was concentrated to half volume and, after cooling, 2.7 g of **9** were filtered. The ethanolic solution was evaporated *in vacuo* to give an oily residue that was chromatographed on basic alumina. By elution with dichloromethane were collected in succession 0.5 g of unreacted ester, 0.4 g of a mixture (0.4 g) and 0.6 g (25%) of unreacted **1**. The mixture was fractionated by several recrystallization from ethanol to supply 0.2 g of **9** (overall yield 58%) beside 50 mg of a thick oil, nearly unitary, likely **10**.

Ethyl [2(1*H*)-oxo-5-azaquinoxalin-3(4*H*)-ylidene]carboxylate (**9**).

This compound had mp 134-136°C; uv: λ max nm (log ε) 291 (4.03), 356 (4.45), 374 (4.48), 390sh (4.25); ir (chloroform): 3290, 3200, 1681(w), 1650, 1635 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.32 (t, J = 8.5 Hz, 3H, CH_3), 3.71 (s, 3H, N-CH_3), 4.24 (q, J = 8.5 Hz, 2H, CH_2), 5.90 (s, 1H, CH), 7.05 (dd, J = 8.0 Hz, pyr β-H), 7.25 (dd, J = 7.5 Hz, pyr γ-H), 8.09 (dd, J = 4.0 Hz pyr α-H), 11.15 (bs, NH exchangeable); ^{13}C nmr (deuteriochloroform): δ 14.8 (CH_3), 28.8 (N-CH_3), 60.5 (CH_2), 88.2 (C_8), 119.8 (C_7), 121.5 (CH), 122.8 (C_3), 139.9 (C_{8a}), 141.4 (C_6), 142.8 (C_{4a}), 157.6 (C=O), 171.2 (C=O).

Anal. Calcd. for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.47; H, 5.27; N, 16.99.

2-Carbethoxy-3,4-dihydro-5-methyl-5*H*-pyrido[2,3-*b*][1,4]-diazepin-4-one (**10**).

This compound had uv λ max 318 nm; ^{1}H nmr (deuteriochloroform): δ 1.28 (t, J = 8.0 Hz, 3H, CH_3), 2.68 (dd, J = 20.0 Hz, 1H), 3.18 (dd, J = 20.0 Hz, 1H), 3.48 (s, 3H, N-CH_3), 4.20 (q, J = 8.0 Hz, 2H, CH_2), 6.85 (dd, J = 8.0 Hz, pyr β-H), 6.95 (dd, J = 8.0 Hz, pyr γ-H), 7.85 (dd, J = 4.0 Hz pyr α-H).

4-Carbethoxy-10-(chloroacetyl)-5,10-dihydro-5-methyl-2*H*-pyrano-[2,3-*b*]pyrido[2,3-*e*]pyrazin-2-one **11**.

To a solution of **9** (2.47 g, 10 mmoles) in anhydrous tetrahydrofuran (70 ml), 0.6 g of sodium hydride 60% in mineral oil (10 mmoles) was added. After stirring at 50° for 2 hours, 0.88 ml (11 mmoles) of chloroacetyl chloride in 4 ml of anhydrous toluene was added and the mixture was further stirred at 80° for 24 hours. The solvent was then removed *in vacuo* and the residue was partitioned between dichloromethane and water. The organic layer was dried (anhydrous sodium sulphate) and the solvent removed to afford a solid mixture that was washed several times with ethyl ether leaving undissolved 1.05 g (29%) of **11**, mp 171-172°(ethyl acetate); uv: λ max nm (log ε) 238 (4.36), 326 (4.34); ir (chloroform): ν 1786, 1735, 1663 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.43 (t, J = 7.1 Hz, 3H, CH_3), 3.78 (s, 3H, N-CH_3), 4.36 (s, 2H, CH_2), 4.46 (q, J = 7.1 Hz, 2H, CH_2,) 7.23 (dd, J = 8.2 Hz, pyr β-H), 7.85 (s, 1H, CH), 7.95 (dd, J = 8.0 Hz, pyr γ-H), 8.45 (dd, J = 4.8 Hz, pyr α-H). ^{13}C-nmr (deuteriochloroform): δ 14.2 (CH_3), 28.0 (N-CH_3), 41.2 (CH_2-Cl) 62.1 (CH_2), 107.5, 112.0, 118.5, 119.2, 119.6, 122.5, 138.5, 142.5, 146.0, 154.2, 162.5, 164.5; ms: m/z 363.7 $[M]^+$, 318 $[M- OC_2H_5]^+$, 287 $[M- ClCH_2CO]^+$, 241 ($[M- OC_2H_5$-$ClCH_2CO]^+$, RA 100), 214 $[M- OC_2H_5$- $ClCH_2CO$ - CO$]^+$, 186 $[M- OC_2H_5$ - $ClCH_2CO$ - CO - CO$]^+$.

Anal. Calcd. for $C_{16}H_{14}N_3O_5Cl$: C, 52.82; H, 3.87; N, 11.55. Found: C, 52.82; H, 3.82; N, 11.42.

From the combined diethyl ether phases, dried with anhydrous sodium sulphate and evaporated, 1.1 g of unreacted **9** (47%) was recovered.

The reagents employed in different ratios afforded a result no better than that described.

Behavior of **11** with Bases.

a) To a suspension of **11** (0.5 g, 1.4 mmoles) in dry toluene, benzylamine (0.31 g, 3 mmoles) was added and mixture was refluxed for 7 hours. The worm reaction mixture was filtered off and from toluene solution, concentrated to small volume, 0.25 g of a yellow solid, 4-carbethoxy-5,10-dihydro-5-methyl-2*H*-pyrano[2,3-*b*]pyrido[2,3-*e*]pyrazin-2-one (**12**), mp 194-195° (ethanol) was obtained; uv: λ max (log ε) 245 (4.36), 336 (4.46) nm; ir (chloroform): ν 3457, 1682 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.51 (t, J = 7.4 Hz, 3H, CH_3), 3.80 (s, 3H, N-CH_3), 4.52 (t, J = 7.4 Hz, 2H, CH_2), 7.22 (dd, J = 8.2 Hz, pyr β-H), 7.27 (s, 1H), 7.88 (dd, J = 8.0 Hz, pyr γ-H), 8.44 (dd, J = 4.8 Hz, pyr α-H), 9.22 (s, NH exchangeable); ^{13}C nmr (deuteriochloroform): δ 14.2 (C-CH_3), 28.2 (N-CH_3), 62.1 (CH_2), 100.5, 104.8, 118.5, 119.2, 119.6, 123.0, 142.5, 146.0, 152.5, 154.0, 167.5.

Anal. Calcd for $C_{14}H_{13}N_3O_4$: C, 58.53; H, 4.56; N, 14.63. Found: C, 58.69; H, 4.49; N, 14.49.

The toluene solution was evaporated *in vacuo* and the oily residue was triturated with ethyl ether to afford, beside 0.1 g of **12** (overall yield 87%), 0.05 g of 4-benzylcarbamide-5,10-dihydro-5-methyl-2*H*-pyrano[2,3-*b*]pyrido[2,3-*e*]pyrazin-2-one, as white solid (**13**), mp 231-232° (ethanol); ir (chloroform): ν

3449, 3209, 1636 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.91 (s, 3H, CH_3), 4.34 (d, J = 7.4 Hz, 2H, CH_2), 7.18 (m, 5H Ph+CH+pyr β-H), 7.95 (dd, J = 8.0 Hz, pyr γ-H), 8.42 (dd, J = 4.8 Hz, pyr α-H), 11.30 (bs, NH exchangeable), 11.58 (s, NH exchangeable).

Anal. Calcd. for $C_{19}H_{16}N_4O_3$: C, 65.51; H, 4.63; N, 16.08. Found: C, 65.68; H, 4.51; N, 16.50.

b) A toluene suspension of **11** (0.36 g, 1 mmole) and morpholine or diethylamine (2 mmoles) was kept at room temperature for 12 hours. From reaction mixture, concentrated to half volume under reduced pressure, **12** was obtained in about quantitative yield.

4-Carbethoxy-10-(dimethylaminopropyl)-5,10-dihydro-5-methyl-2*H*-pyrano[2,3-*b*]pyrido[2,3-*e*]pyrazin-2-one **14**.

To a solution in toluene of **12** (1 g, 3.5 mmoles), the equivalent of sodium hydride 60% in mineral oil was added and, after stirring at 50° for 2 hours, a toluene solution of dimethylaminopropyl chloride (3.5 mmoles) was added and refluxed for 12 hours. After cooling, the reaction mixture was filtered off and the organic solution evaporated under reduced pressure. The oily residue was suspended several time in ethyl ether (5 ml), stirred and filtered to recover 0.4 g of unreacted **12**. The residue proceeded from evaporation to dryness of diethyl ether layer was chromatographed on basic alumina, eluting with dichloromethane to give **14** (0.3 g, 23%), mp 70°; ^1H nmr (deuteriochloroform): δ 1.43 (t, J = 8.0 Hz, 3H, CH_3), 2.0 (m, 2H, CH_2), 2.28 (s, 6H, $2CH_3$), 2.46 (t, J = 8.0 Hz, 2H, CH_2), 3.76 (s,3H, N-CH_3), 4.07 (t, J = 7.2 Hz, 2H, CH_2), 4.46 (q, J = 8.0 Hz, 2H, CH_2), 7.18 (dd+s, CH+pyr β-H), 7.80 (dd, J = 8.0 Hz, pyr γ-H), 8.38 (dd, J = 4.8 Hz, pyr α-H).

Anal. Calcd. for $C_{19}H_{24}N_4O_4$: C, 61.28; H, 6.50; N, 15.04. Found: C, 61.66; H, 6.83; N, 14.73.

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