Heterotricyclic Systems. Part I. Synthesis of New Dipyridopyrazines [1]

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Pursuing our previous research on azaquinoxalinones (1,2-dihydropyrido[2,3-*b*]/[3,4-*b*]pyrazinones) we prepared, through a reductive cyclization of *N*-(3'-nitropyridin-2'-yl)piperidine-2-carboxylic acids **3a-c**, a set of derivatives of a new tricyclic structure, 7,8,9,10-tetrahydro-5*H*-dipyrido[1,2-*a*:3',2'-*e*]pyrazin-6(6a*H*)-ones **4a-c**. Starting from these compounds we obtained substituted amides **5a-c** and, from **4a**, the amidines **6a-c**. In the synthesis of **6**, a dehydrogenation reaction occurred giving rise to **7**. The compounds **9** and **10**, characterized by a different ring-fusion between the pyridine and pyrazine rings, were synthesized in a similar manner.

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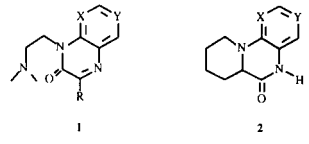
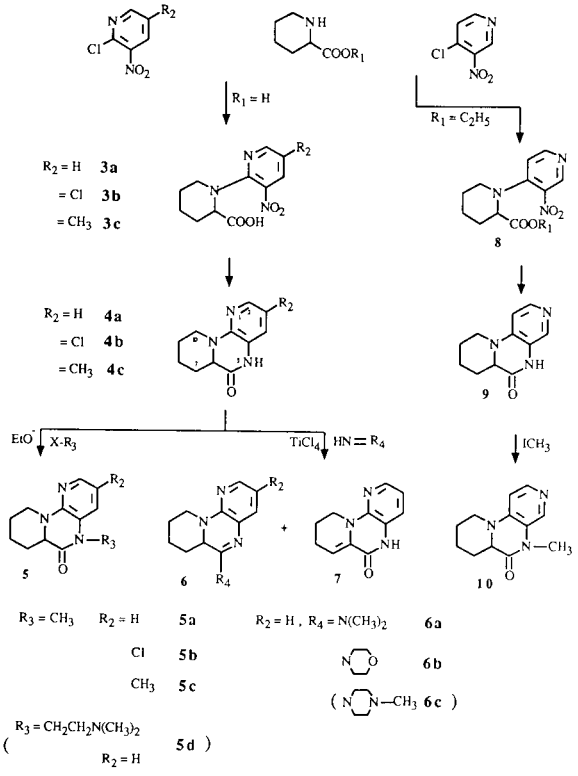
In carrying on our exploration of the pharmacological potential of heteropolycyclic structures we previously synthesized a set of azaquinoxalinones derivatives (pyrido-[2,3-*b*]pyrazin-3(4*H*)-ones and pyrido[3,4-*b*]pyrazin-2(1*H*)-ones, **1**, X = N/Y = CH and X = CH/Y = N respectively) [2]. The **1** derivatives, characterized by the presence of a dialkylaminoalkyl chain on the amide nitrogen, were endowed with an interesting neuroleptic activity, conditioned by the different reciprocal fusion of pyridine and pyrazine rings (X/Y = N). As an extension of the study on pyridopyrazinones, we prepared now some dipyridopyrazinones derivatives with the new structure **2** (see also Scheme 1). The previous observation [3] that the introduction of a chlorine atom was able to increase the biological activity of **1**, suggested the preparation of compounds **2** bearing a chlorine or a methyl group (Y = C-Cl, C-CH_3). Actually the methyl group, although endowed with different electronic effects, has steric and lipophilic properties corresponding to those of chlorine. The *N*-(3'-nitro-5-R_2-pyridin-2'-yl)piperidine-2-carboxylic acid and 5-chloro/-methyl derivatives **3a-c** (Scheme 1) were obtained by



1 2

X = N, Y = CH, C-Cl, C-CH_3
X = CH, Y = N

Scheme 1



reacting 2-chloro-3-nitropyridine-5-substituted and piperidine-2-carboxylic acid, in ethanol-water under experimental condition set up by other authors for analogous compounds [4,5]. The nitro acids **3a-c**, when hydrogenated in ethanol/tetrahydrofuran at room temperature and atmospheric pressure in the presence of palladium on charcoal, provided directly the 7,8,9,10-tetrahydro-3-R_2-5*H*-dipyrido[1,2-*a*:3',2'-*e*]pyrazin-6(6a*H*)-ones **4a-c** which were accomplished by means of an intramolecular condensation of the amino compounds, related to **3a-c**, which were not isolated.

The formation of **9** was accomplished from ethyl *N*-(3'-nitropyridin-4'-yl)piperidine-2-carboxylate (**8**) which was obtained from ethyl piperidine-2-carboxylate and 4-chloro-3-nitropyridine in toluene, because it was verified that protic solvents were not suitable for the last reactant.

The structures of the dipyridopyrazinone derivatives **4a-c** and of the intermediates **3a-c** were assigned by elemental analysis and spectral properties, listed in Tables I and II. In particular **3a-c** were characterized by uv/ir absorptions at about 400 nm, 1710 cm^{-1} and by a deuterium oxide exchangeable proton at δ 10.0 ppm in the ^1H nmr spectrum. The **4a-c** compounds exhibited absorptions at

Table I

Compounds **3-6**, Analytical Data

Compounds No.	Mp°C	Yield %	Molecular Formula	Elemental Analysis % Calcd./Found C		H		N	
3a	151-152 [a]	61	$C_{11}H_{13}N_3O_4$	52.58	52.38	5.22	5.13	16.73	16.41
3b	115-116 [a]	35	$C_{11}H_{12}ClN_3O_4$	46.24	46.21	4.23	4.18	14.70	14.26
3c	134-135 [a]	34	$C_{12}H_{15}N_3O_4$	54.33	54.31	5.70	5.74	15.84	15.62
4a	203-204 [a]	88	$C_{11}H_{13}N_3O$	65.00	65.38	6.45	6.54	20.68	20.37
4b	161-162 [a]	90	$C_{11}H_{12}ClN_3O \cdot H_2O$	51.66	51.84	5.52	5.66	16.43	16.30
4c	180-182 [a]	95	$C_{12}H_{15}N_3O$	66.34	66.36	6.96	6.97	19.34	19.47
5a	70-71 [b]	70	$C_{12}H_{15}N_3O$	66.34	65.90	6.96	6.81	19.34	18.95
5b	78-79 [b]	49	$C_{12}H_{14}ClN_3O$	57.25	56.95	5.60	5.29	16.69	16.91
5c	94-96 [b]	54	$C_{13}H_{17}N_3O$	67.50	67.24	7.41	7.34	18.17	18.10
6a	oil	47	$C_{13}H_{18}N_4$	67.79	68.03	7.88	7.92	24.33	23.97
6b	134-136 [c]	66	$C_{15}H_{20}N_4O$	66.15	65.87	7.40	7.36	20.57	20.08

[a] Ethanol. [b] Hexane. [c] Filtration on basic alumina.

Table II

Spectral Data of Compounds **3-6**

Compound No.	uv λ max nm (log ε)	ir ν cm^{-1}	^1H nmr, δ (ppm)
3a	239 (4.38), 287 (4.21), 401 (3.84)	1710 [a]	1.78 (m, 5H), 2.31 (m, 1H), 3.08 (m, 1H), 3.32 (m, 1H), 4.96 (m, 1H), 6.91 (dd, J = 12 Hz, H-β-pyr), 8.18 (dd, J = 14 Hz, H-γ-pyr), 8.34 (dd, J = 6.0 Hz, H-α-pyr), 10.0 (OH, exchangeable)
3b	247 (4.27), 294 (3.38), 414 (3.50)	1710 [a]	1.71 (m, 5H), 2.32 (m, 1H), 3.15 (m, 1H), 3.42 (m, 1H), 5.02 (m, 1H), 8.14 (dd, J = 2.2 Hz, H-γ-pyr), 8.24 (d, J = 2.2Hz, H-α-pyr), 11.20 (OH, exchangeable)
3c	239 (4.22) 291 (3.64), 412 (3.44)	1710 [a]	1.58-1.82 (m, 5H), 2.22-2.44 (m+*s*, 1H+3H), 3.05 (m, 1H), 3.24 (m, 1H), 4.82 (m, 1H), 8.04 (d, J = 1.8 Hz, H-γ-pyr), 8.19 (d, J = 1.8 Hz, H-α-pyr), 10.5 (OH, exchangeable)
4a	214 (4.57), 283 *sh* (3.75), 316 (3.97)	3140, 3090, 1680 [a]	1.48-1.82 (m 4H), 1.98 (m, 1H), 2.22 (m, 1H), 2.68 (m, 1H), 3.92 (m, 1H), 4.71 (m, 1H), 6.62 (dd, J = 12 Hz, H-β-pyr), 6.88 (dd, J = 14 Hz, H-γ-pyr), 7.78 (dd, J = 9.0 Hz, H-α-pyr), 8.93 (NH, exchangeable)
4b	223 (4.61), 281 (3.94) 331 (3.97)	3140, 3090, 1675 [a]	1.58 (m, 4H), 1.98 (m, 1H), 2.18 (m, 1H), 2.65 (m, 1H), 4.05 (m, 1H), 4.63 (m, 1H), 7.42 (d, J = 2.0 Hz, H-γ-pyr), 7.81 (d, J = 2.0 Hz, H-α-pyr), 9.57 (NH, exchangeable)
4c	216 (4.58), 280 *sh* (3.61) 323 (3.96)	3160, 3090, 1675 [a]	1.48-1.80 (m, 4H), 1.98 (m, 1H), 2.18 (m+*s*, 1H+3H), 2.76 (m, 1H), 3.88 (m, 1H), 4.62 (m, 1H), 6.72 (d, J = 1.9 Hz, H-γ-pyr), 7.71 (d, J = 1.9 Hz, H-α-pyr), 8.88 (NH, exchangeable)
5a	216 (4.46), 287 *sh* (3.63) 315 (3.83)	1665 [b]	1.45-1.82 (m, 4H), 1.98 (m, 1H), 2.22 (m, 1H), 2.68 (m, 1H), 3.32 (*s*, 3H), 3.89 (m, 1H), 4.66 (m, 1H), 6.69 (dd, J = 12 Hz, H-β-pyr), 7.01 (dd, J = 14 Hz, H-γ-pyr), 7.88 (dd, J = 6.0 Hz, H-α-pyr)
5b	222 (4.52), 281 (3.56) 329 (3.81)	1690 [b]	1.48-1.78 (m, 4H), 2.01 (m, 1H), 2.24 (m, 1H), 2.66 (m, 1H), 3.91 (m+*s*, 1H+3H), 4.68 (m, 1H), 7.24 (d, J = 2.2 Hz, H-γ-pyr), 7.82 (d, J = 2.2 Hz, H-α-pyr)
5c	216 (4.46), 275 (3.62) 322 (3.90)	1690 [b]	1.42-1.78 (m, 4H), 1.91 (m, 1H), 2.18 (m+*s*, 1H+3H), 2.63 (m, 1H), 3.28 (*s*, 3H), 3.77 (m, 1H), 4.51 (m, 1H), 6.81 (d, J = 1.8 Hz, H-γ-pyr), 7.68 (d, J = 1.8 Hz, H-α-pyr)
6a	229 (4.47), 331 (4.00)	1600 [b]	1.42-1.92 (m, 6H), 2.80 (m, 1H), 3.11 (m, 6H), 4.32 (m, 1H), 4.76 (m, 1H), 6.58 (dd, J = 12 Hz, H-β-pyr), 7.12 (dd, J = 14 Hz, H-γ-pyr), 7.78 (dd, J = 6.0 Hz, H-α-pyr)
6b	232 (4.35), 341 (4.14)	1605 [b]	1.41-1.97 (m, 6H), 2.77 (m, 1H), 3.59 (m, 4H), 3.74 (m, 4H), 4.28 (m, 1H), 4.77 (m, 1H), 6.59 (dd, J = 12 Hz, H-β-pyr), 7.11 (dd, J = 14 Hz, H-γ-pyr), 7.82 (dd, J = 6.0 Hz, H-α-pyr)

[a] Potassium bromide. [b] Chloroform.

315 nm, 1680 cm^{-1} and an exchangeable signal at δ 8.9 ppm. Each pyridine proton of **3a** and **4a** exhibited double doublet signals, with an upfield shift for those related to **4a**, while the piperidine ring protons showed multiplet resonance signals between δ 1.5 and 5.1 ppm corresponding to nine hydrogens (Table II). The pyridine protons of **3b-c** and **4b-c** exhibited doublet signals. Compound **9** was differentiated for two doublet signals and a singlet respec-

tively assigned to β-, α- and α'-pyridine hydrogens.

In order to achieve a closer correlation between the dipyridopyrazine derivatives **4** and **9** and the dialkylaminoalkylazaquinoxalinones **1**, previously studied, we attempted the introduction of a basic side chain on the lactam nitrogen of **4a**, but the results were rather disappointing and only a small quantity of **5d** was obtained. However the methylation of **4a-c** and **9** with methyl iodide gave satisfactory yields of **5a-c** and **10**. Further attempts to connect basic groups on the tricyclic system were made by reacting **4a** with secondary aliphatic amines in the presence of titanium tetrachloride as described by Press *et al.* [6] for analogous lactam derivatives. This reaction was successful with dimethylamine and morpholine, providing the amidines **6a,b**, but it failed completely with diethylamine and piperidine; with *N*-methylpiperazine only a very limited amount of amidine **6c** was obtained. The formation of amidines **6** was always associated with that of compounds **7** which was often the prevailing one. Compound **7** was the sole isolable product when amidine formation did not take place. The structures of **5a-c** were supported by analytical and spectroscopic data, listed in Tables I and II. To compound **7** was assigned the structure of 9,10-dihydro-5*H*-dipyrido[1,2-*a*:3',2'-*e*]pyrazin-6(8*H*)-one from the spectral data. In fact, the ^{1}H nmr of **7** shows, analogously to **4a**, an exchangeable proton at δ 9.4 ppm and three analogous double doublet signals for the pyridine hydrogens and, differently from **4a**, three multiplet signal centered at δ 1.9, 2.3, 4.05 ppm for, respectively, C-9, C-8, C-10 methylenes in addition to a triplet signal at δ 6.0 ppm attributable to olefinic hydrogen at C-7. Each methylene appears as a pair of chemically equivalent protons as a result of quick conformational equilibration. Moreover, the ^{13}C nmr spectrum shows methylene signals at δ 19.97, 22.23, 40.86 ppm, each one appears as a triplet in the off resonance spectrum. The aromatic carbons C-2,3,4 and ethylenic C-7 produced signals at δ 106.58, 114.32, 120.84, 141.79 ppm as doublets and the quaternary carbons C-4a, 6,6a,11a, at δ 120.45, 130.66, 142.26, 159.49 ppm as singlets. These data, as well as the ir spectrum absorption at 1675 cm^{-1} (CO-NH), led us to assign unambiguously structure **7** to the reaction product.

The prepared compounds will be subjected to broad screening to point out the eventual CNS activity as well as any other pharmacological activity.

EXPERIMENTAL

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 recorded on a Perkin-Elmer Model 297 spectrophotometer and the ^{1}H, ^{13}C nmr spectra were recorded on a Varian-Gemini 200 spectrometer with TMS as internal standard. The elemental analyses were performed on the Carlo Erba Elemental Analyser Model 1106 at the Microanalytical Laboratory of Istituto di Scienze Farmaceutiche, Università di Genova.

N-(3'-Nitropyridin-2'-yl)piperidine-2-carboxylic Acid (**3a**).

To a suspension of 2-chloro-3-nitropyridine (6.3 g, 40 mmoles) in ethanol (40 ml) was added a solution of piperidine-2-carboxylic acid (7.8 g, 60 mmoles) in water (40 ml) and triethylamine (6 ml) and the mixture was heated under reflux for 8 hours. After cooling the mixture was filtered to separate 1.15 g of unreacted 2-chloro-3-nitropyridine. The aqueous-ethanolic solution was extracted with methylene chloride and the organic layer, washed with water, dried (sodium sulfate) and evaporated under vacuum to give a deep red oily residue. This was dissolved by stirring with 8% sodium hydrogen carbonate solution at room temperature for 15 minutes, recovering an additional 1.1 g of unreacted 2-chloro-3-nitropyridine (overall yield 35%). From the basic filtrate, by acidification with a 20% tartaric acid solution, a solid was precipitated which was collected by filtration and washed several times with water to give 6.1 g (yield 61%) of **3a**, as yellow needles, mp 151-152° (ethanol) (Tables I, II).

Alternatively, the pipecolinic acid in 8% sodium hydrogen carbonate solution was added to the solution of 2-chloro-3-nitropyridine in ethanol and the mixture refluxed for 6 hours. After cooling, from the reaction mixture, the unreacted pyridine derivative was extracted with methylene chloride. From the aqueous-ethanolic solution, **3a** was collected by precipitation with tartaric acid solution as previously reported and in identical yield.

N-(5'-Chloro-3'-nitropyridin-2'-yl)piperidine-2-carboxylic Acid (**3b**).

The mixture of 2,5-dichloro-3-nitropyridine [7] (30 mmoles) in ethanol (40 ml), piperidine-2-carboxylic acid (33 mmoles) in water (20 ml) and triethylamine (3 ml) was stirred at room temperature for 24 hours. The reaction mixture was concentrated under vacuum to about one-third of the initial volume and the resulting solution was made alkaline with 2*N* sodium hydroxide solution and extracted with methylene chloride. The organic layer was washed with water, dried and evaporated to dryness to give 1.3 g (yield 21%) of unreacted 2,5-dichloro-3-nitropyridine. The alkaline solution was acidified with 20% tartaric acid solution and extracted with methylene chloride. The extract was washed, dried and evaporated to give 3.3 g of a brown solid which was purified by chromatography on silica gel. By elution with methylene chloride 2.9 g (yield 34%) of **3b** was obtained, as yellow needles, mp 115-116° (ethanol) (Tables I, II).

N-(5'-Methyl-3'-nitropyridin-2'-yl)piperidine-2-carboxylic Acid (**3c**).

The reaction mixture of piperidine-2-carboxylic acid and 2-chloro-5-methyl-3-nitropyridine [8] and triethylamine was refluxed for 24 hours and worked up as described for **3a**. Unreacted 2-chloro-5-methyl-3-nitropyridine (33%) was recovered and the compound **3c** was obtained with 35% yield, as yellow needles, mp 134-135° (ethanol) (Tables I, II).

7,8,9,10-Tetrahydro-3-R$_2$-5*H*-dipyrido[1,2-*a*:3',2'-*e*]pyrazin-6(6a*H*)-ones **4a-c**.

Compounds **3a-c** (10 mmoles) dissolved in a mixture of ethanol

and peroxide free tetrahydrofuran (1:1, 50 ml) were hydrogenated at room temperature and atmospheric pressure in the presence of 10% palladium on charcoal (50 mg for each g) until hydrogen absorption stopped spontaneously. The absorbed volumes of hydrogen differed from those required by less than 3%. (Compound **4b** was hydrogenated just until the required volume of hydrogen was taken up in order to prevent the hydrogenolysis of cholorine). After filtration of the catalyst, the solvent was removed under reduced pressure leaving an oily residue which, by trituration with ethanol, afforded **4a-c** as white crystals (Tables I, II).

The uv spectra of this material and the solution immediately after filtration of catalyst, were identical, indicating that the cyclization had already occurred.

7,8,9,10-Tetrahydro-3-R_2-5-methyldipyrido[1,2-*b*:3′,2′-*e*]pyrazin-6(6a*H*)-ones **5a, 5c**.

Compound **4a/4c** (10 mmoles) suspended in absolute ethanol (20 ml) was treated with an equivalent amount of 1*M* sodium ethoxide solution and methyl iodide (1 ml). The mixture was stirred overnight at room temperature. The reaction mixture was diluted with water and extracted with methylene chloride. The organic layer, washed with water, dried (sodium sulfate) and evaporated under vacuum gave an oily residue that was chromatographed on basic alumina. Elution with methylene chloride gave **5a/5c** (yields 70% and 54%) (Tables I, II), followed by unreacted **4a/4c** (5-15%).

7,8,9,10-Tetrahydro-3-chloro-5-methyldipyrido[1,2-*b*:3′,2′-*e*]pyrazin-6(6*H*)-one (**5b**).

The methylation of **4b** was carried out at 50°. The methyl iodide was added after solubilization of the precipitated sodium salt by gentle heating; **5b** was obtained as white needles (49%) (Tables I, II).

7,8,9,10-Tetrahydro-5-(dimethylaminoethyl)dipyrido[1,2-*b*:3′,2′-*e*]-pirazin-6(6*H*)-one (**5d**).

The reaction of **4a** with dimethylaminoethyl chloride or bromide, under the same conditions indicated for **5a,c**, afforded, besides the unreacted **4a** (70%), a very small amount of **5d** isolated by chromatography on basic alumina, colorless transparent oil purified by filtration through alumina ($bp_{0.01}$, 128°); ^{1}H nmr (deuteriochloroform): δ 1.48-1.83 (m, 4H), 1.98 (m, 1H), 2.22 (m, 1H), 2.32 (s, 6H), 2.68 (t + m, J = 6.6 Hz, 2H + 1H), 3.92 (m, 1H), 4.18 (t, J = 6.6 Hz, 2H), 4.64 (m, 1H), 6.71 (dd, J = 12 Hz, H-β-pyr), 7.41 (dd, J = 14 Hz, H-γ-pyr), 7.89 (dd, J = 6.0 Hz, H-α-pyr).

The same reaction of **4a** with dimethylaminoethyl chloride, effected in DMFA (dried over basic alumina) in the presence of sodium amide, at 60° for 24 hours, produced an unworkable oily mixture.

7,8,9,10-Tetrahydro-6-dimethylamino-(6a*H*)-dipyrido[1,2-*a*:3′,2′-*e*]pyrazine (**6a**) and 9,10-Dihydro-5*H*-dipyrido[1,2-*a*:3′,2′-*e*]pyrazin-6(8*H*)-one (**7**).

To a mixture of 20 ml of dry toluene, 1 ml of anisole, 0.68 ml (6.2 mmoles) of titanium tetrachloride and 3.1 ml (23 mmoles) of a solution 33% (w/v) of dimethylamine in dry toluene was added. To this complex 1.02 g (5 mmoles) of **4a** and 2.6 ml of solution 33% dimethylamine in dry toluene were added and the mixture refluxed for 6 hours. The reaction mixture was cooled to 60° and 2 ml of isopropyl alcohol was added, followed by 1 g of kieselgur and 1.5 ml of concentrated ammonium hydroxide solution. The mixture was filtered and the solid cake was washed extensively with toluene and methylene chloride. This washing solution, dried and evaporated under vacuum left an oily residue which was triturated with methylene chloride leaving 0.15 g (15%) of **7**, mp 234-236° (ethanol); uv: λ max (log ε) nm 271 (3.93), 350 (3.91); ir (chloroform): 3190, 3140, 3090, 1675, 1635, 1605 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.92 (m, 2H), 2.31 (m, 2H), 4.08 (t, J = 4.6 Hz, 2H), 6.01 (t, J = 4.6 Hz, 1H), 6.64 (dd, J = 9.0 Hz, H-β-pyr), 7.02 (dd, J = 7.5 Hz, H-γ-pyr), 7.88 (dd, J = 5.0 Hz, H-α-pyr), 9.57 (br, NH, exchangeable); ^{13}C nmr (deuteriochloroform): δ (multiplicity) 19.97 (t), 22.24 (t), 40.86 (t), 106.58 (d), 114.32 (d), 120.45 (s), 120.84 (d), 130.65 (s), 141.79 (d), 142.26 (s), 159.49 (s).

Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.67; H, 5.51; N, 20.88. Found: C, 65.58; H, 5.52; N, 20.79.

The organic solution, separated from the cake, was evaporated to leave an oil which was chromatographed on basic alumina. Elution with methylene chloride gave in succession 0.55 g of **6a** (Tables I, II) and unreacted **4a**.

7,8,9,10-Tetrahydro-6-morpholinyl-(6a*H*)-dipyrido[1,2-*a*:3′,2′-*e*]-pyrazine (**6b**) (Tables I, II) and 7,8,9,10-Tetrahydro-6-(4′-methyl-piperazinyl)-(6a*H*)-dipyrido[1,2-*a*:3′,2′-*e*]pyrazine (**6c**).

These were similarly obtained by reacting the appropriate amine (morpholine or *N*-methylpiperazine) with **4a**. Compound **7** was the prevailing product of the reaction for obtaining **6c**, which was isolated in very small amount and chromatographed on basic alumina; ^{1}H nmr (deuteriochloroform): δ 1.38-1.92 (m, 6H), 2.30 (s, 3H), 2.43 (t, J = 5.0 Hz, 4H), 2.77 (m, 1H), 3.58 (t, J = 5.0 Hz, 4H), 4.28 (m, 1H), 4.72 (m, 1H), 6.64 (dd, J = 12 Hz, H-β-pyr), 7.07 (dd, J = 14 Hz, H-γ-pyr), 7.78 (dd, J = 9.0 Hz, H-α-pyr).

From reaction with diethylamine and piperidine the compound **7** (31%) was the only product of reaction that could be isolated.

Ethyl *N*-(3′-Nitropyridin-4′-yl)piperidin-2-carboxylate (**8**).

To a solution of 7.11 g (38 mmoles) of ethyl piperidine-2-carboxylate in 70 ml of toluene, 3.0 g (19 mmoles) of 4-chloro-3-nitropyridine was added and the mixture was refluxed for 4 hours. The reaction mixture was filtered to separate 2.8 g of ethyl pipecolinate hydrochloride. The toluene solution, after filtration, was extracted with 2*N* hydrochloric acid and the acid solution, washed with ethyl ether, was made alkaline with potassium carbonate and extracted with methylene chloride. The organic layer washed, dried and evaporated to dryness gave an oily residue from which, by distillation (bulb to bulb apparatus under vacuum, 10^{-2}-10^{-3} torr, at 80°, air bath) 0.8 g of unreacted ethyl pipecolinate was collected. The residue of distillation was chromatographed on silica gel, eluting with methylene chloride, to give 1.8 g (34%) of **8** as a yellow oil. A small amount of it was distilled for analytical purposes ($bp_{0.01}$, 115°, air bath); uv: λ max (log ε) nm 251 (4.22), 266 sh (3.99), 376 (3.45); ir (chloroform): 1725 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.24 (t, J = 7.2 Hz, 3H), 1.68-2.35 (m, 6H), 3.18-3.52 (m, 2H), 4.20 (q + m, J = 7.2 Hz, 2H + 1H), 6.92 (dd, J = 7.2 Hz, H-β-pyr), 8.42 (dd, J = 7.2 Hz, H-α-pyr), 8.86 (s, H-α′-pyr).

Anal. Calcd. for $C_{13}H_{17}N_3O_4$: C, 55.90; H, 6.14; N, 15.05. Found: C, 55.93; H, 6.15; N, 15.32.

7,8,9,10-Tetrahydro-5*H*-dipyrido[1,2-*a*:3′,4′-*e*]pyrazin-6(6a*H*)-one (**9**).

Compound **8** (1.4 g, 5 mmoles) in ethanol was hydrogenated at room temperature and atmospheric pressure as described above for **4a**. Compound **9** was obtained in good yield (about 95%), as an oil which solidifies spontaneously or by trituration with ethanol, mp 191-193°; uv: λ max (log ε) nm 240 (4.37), 309 (3.99); ir (potassium bromide): 3080, 1680 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.04-2.22 (m, 5H), 2.27 (m, 1H), 2.3 (m, 1H), 3.85 and 4.00 (2m, 1H + 1H), 6.53 (d, J = 6.0 Hz, H-β-pyr), 8.02 (d, J = 6.0 Hz, H-α-pyr), 8.36 (s, H-α'-pyr), NH, obscured).

Anal. Calcd. for $C_{11}H_{13}N_3O$: C, 65.00; H, 6.45; N, 20.68. Found: C, 64.69; H, 6.51; N, 20.73.

7,8,9,10-Tetrahydro-5-methyldipyrido[1,2-*a*:3',4'-*e*]pyrazin-6(6a*H*)-one (**10**).

Compound **9** was methylated as indicated for lactam **4a** and compound **10** was obtained in 70% yield, mp 94-96° (hexane); uv: λ max (log ε) 220 (4.38), 238 (4.33), 318 (4.03); ir (chloroform): 1690 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.43-1.88 (m, 4H), 2.01 (m, 1H), 2.23 (m, 1H), 2.72 (m, 1H), 3.82 (m, 2H), 3.5 (s, 3H), 6.56 (d, J = 5.8 Hz, H-α-pyr), 8.15 (d, J = 5.8 Hz, H-β-pyr), 8.28 (s, H-α'-pyr).

Anal. Calcd. for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.15; H, 6.93; N, 19.37.

REFERENCES AND NOTES

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