Derivatives of Pyrido[2,3-*b*][1,4]diazepine and of the Dipyrido[1,2-*a*:2',3'-*d*]imidazole Heterocyclic System [1]

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With a continuing interest in heteropolycyclic systems which may show biological activities, we studied the reaction of 3-amino-2-(methylamino)pyridine with diethyl 1,3-acetonedicarboxylate in order to develop pyridodiazepinone derivatives. From the reaction mixture, we separated dipyrido[1,2-*a*:2',3'-*d*]imidazole derivatives (**3** and **4**) besides two isomeric pyrido[2,3-*b*][1,4]diazepine derivatives (**5** and **6**) in which the complex structural differentiation was achieved through nmr experiments and chemical evidence. Several attempts to elaborate isomers **5** and **6** have not yet given significant results.

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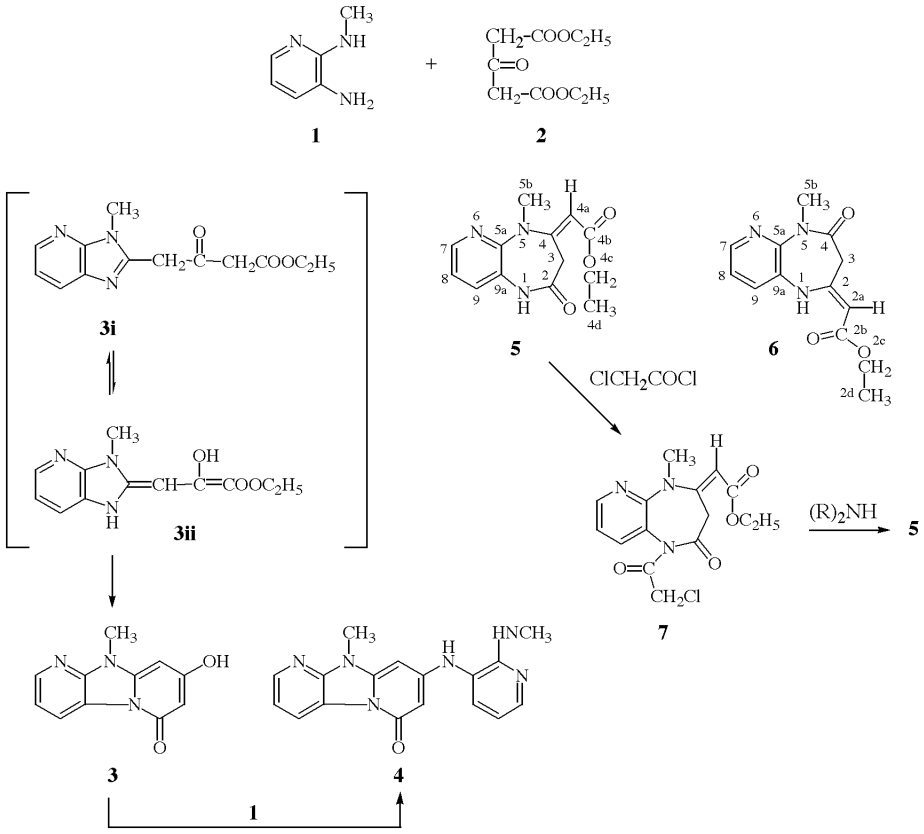
In previous papers [2-4], we described pyrido[2,3-*b*]-[1,4]diazepine structures, some of which revealed interesting neuroleptic properties which were recently confirmed for analogous compounds [5]. As a further development of this program, we have explored an approach towards the synthesis of novel pyrido[2,3-*b*]-[1,4]diazepine derivatives.

For this purpose, we have reacted, in boiling toluene, the 3-amino-2-(methylamino)pyridine (**1**) with diethyl 1,3-diacetondicarboxylate (**2**) (Scheme I) in order to obtain novel pyridodiazepine derivatives. The reaction actually afforded the expected isomers **5** and **6**, along with small amounts of compounds **3** and **4**, derivatives representing a dipyrido[1,2-*a*:2',3'-*d*]imidazole system. The same

Scheme 1



reaction, carried out under various conditions, either afforded only compound **6** (protic solvent) or did not improve (xylene) the yield of compounds **3** and **4**.

Compound **3**, identified as 6,10-dihydro-8-hydroxy-10-methyl-dipyrido[1,2-*a*:2',3'-*d*]imidazol-6-one, likely arose through the initial cyclocondensation of the ethoxycarbonyl group of **2** with the diamino moiety of **1** to give the imidazopyridine intermediate (**3i**) whose tautomeric form (**3ii**) then cyclized affording compound **3**. The structure of **3** was confirmed on the basis of the Mass (M^+, 215), ^{13}C NMR (11 C) and ^1H NMR spectra: in this connection the ^1H NMR signals at δ 5.52 and 5.58 attributable to C_9-H and C_7-H, respectively, and at δ 10.32 (exchangeable hydroxy group) appear particularly diagnostic. The 8-[3'-ammino-(2'-methylaminopyridine)]-6,10-dihydro-10-methyl-dipyrido[1,2-*a*:2',3'-*d*]imidazol-6-one (**4**), most likely arose by further one pot condensation of **3** with 3-amino-2-(methylamino)pyridine reagent. This was subsequently confirmed by direct reaction of these aforementioned compounds. Moreover, the double series of doublet of doublet signals at δ 6.63, 7.38 and 7.98 and, like **3**, at δ 7.21, 8.26 and 8.56, related to the two pyridine rings of **4**, the doublet at δ 2.85 coupled with the exchangeable proton at δ 6.07 which is assigned to the secondary methylamino group, the singlet at δ 3.60 of N_{10}-methyl, the two doublets at δ 5.08 and 5.69 related to C_9-H and C_7-H were diagnostic of the proposed structure for **4**.

The assignment of structures **5** and **6** to the diazepine isomers was difficult, owing to their similar spectral properties, and has been performed on the basis of both spectral and reactivity data. The ^{13}C NMR spectrum showed, for either isomer, 13 signals and the DEPT experiment indicated that four of them correspond to CH, two to CH_2, two to CH_3 and five to Cq. The ^1H NMR spectrum of compound **5** exhibited, along with the signals ascribable to the aromatic protons at δ 7.12 (1H, dd, J = 4.0 and 7.9 Hz), 7.45 (1H, dd, J = 1.2 and 7.9 Hz) and 8.28 (1H, dd, J = 1.2 and 4.0 Hz), a singlet at δ 5.11 due to the olefinic proton, signals at δ 4.17 (2H, q, J = 7.0 Hz) and 1.26 (3H, t, J = 7.0 Hz) typical of the ethoxy group, and signals due to the methyl group on nitrogen and to the methylene group overlapping at δ 3.44. An exchangeable broad singlet due to NH appeared at δ 9.41 (Table 1). The ^1H NMR spectrum of compound **6** was similar to that of compound **5** (Table 1). Main differences between the two spectra are the signal due to the olefinic proton (δ 4.87 in **6** vs δ 5.11 in **5**) and the signal ascribable to the methylene group (δ 3.16 in **6** vs δ 3.44 in **5**). Furthermore in the ^1H NMR spectrum of **6** the signal due to the NH was deshielded at δ 10.40 because of its hydrogen bond to a carbonyl group. The definitive identification of the structures related to compounds **5** and **6** was performed by HSQC and HMBC experiments. HSQC experiment correlated the proton resonances with those of each corresponding carbon, allowing us to assign all the carbon signals except the quaternary carbons. The HMBC experiment of compound **5** showed diagnostic long range correlation between the methyl group at δ 3.44 and the quaternary carbons at δ 148.6 and 154.1 and between the proton signal at δ 9.41 and the carbon signal at δ 34.1 (Table 2) allowing us to deduce the occurrence of a cyclic methylene group and to define the location of the side chain at C-4.

The HMBC experiment of **6** clearly showed correlations between the methyl signal at δ 3.44 and the carbonyl group at δ 166.9 and between this carbon and the signal at δ 3.16. On the basis of these findings it was possible to establish

Table 1

^1H and ^{13}C NMR data of compound **5** and **6** in $CDCl_3$ [a]

	Compound **5**		Compound **6**	
Position	$\delta H_{(JHH\ in\ Hz)}$	δC	$\delta H_{(JHH\ in\ Hz)}$	δC
1	9.41		10.40	
2		170.7		154.0
3	3.44, s	34.1	3.16, s	41.6
4		154.1		166.9
5a		148.6		146.8
5b	3.44, s	37.2	3.44, s	33.8
7	8.28, dd(1.2, 4.0)	145.0	8.28, dd(1.2, 4.0)	144.1
8	7.12, dd(4.0, 7.9)	120.2	7.13, dd(4.0, 7.9)	121.0
9	7.45, dd(1.2, 7.9)	130.8	7.41, dd(1.2, 7.9)	130.6
9a		127.1		128.5
2a			4.87, s	86.9
2b				170.4
2c			4.14, q (7.0)	59.5
2d			1.26, t (7.0)	14.0
4a	5.11, s	91.2		
4b		168.3		
4c	4.17, q (7.0)	59.4		
4d	1.26, t (7.0)	14.4		

[a] Assignment confirmed by HSQC and HMBC experiment.

Table 2

HMBC Correlations of Compound **5** and **6**

Compound **5**		Compound **6**	
δ_H	δ_C	δ_H	δ_C
3.44	148.6 (C-5a)	3.44	146.8 (C-5a)
	154.1 (C-4)		166.9 (C-4)
3.44	91.2 (C-4a)	3.16	86.9 (C-2a)
			154.0 (C-2)
			166.9 (C-4)
4.17	14.4 (C-4d)	4.14	14.0 (C-2d)
	168.3 (C-4b)		170.4 (C-2b)
5.11	34.1 (C-3)	4.87	41.6 (C-3)
	154.1 (C-4)		154.0 (C-2)
7.12	127.1 (C-9a)	7.13	128.5 (C-9a)
	145.0 (C-7)		144.1 (C-7)
7.45	127.1 (C-9a)	7.41	128.5 (C-9a)
	145.0 (C-7)		144.1 (C-7)
	148.6 (C-5a)		146.8 (C-5a)
8.28	120.2 (C-8)	8.28	121.0 (C-8)
	130.8 (C-9)		130.6 (C-9)
			146.8 (C-5a)
9.41	34.1 (C-3)	10.40	41.6 (C-3)
	127.1 (C-9a)		128.5 (C-9a)
	148.6 (C-5a)		146.8 (C-5a)

that the anular methylene group was also present in this case, but the side chain was linked at C-2.

On the other hand chloroacetyl chloride did not react with compound **6** while the reaction occurred with compound **5** (treatment with sodium hydride), to give compound **7** in which the chloro substitution with secondary amines was not possible due to aminolysis of the chloroacetamide moiety [6].

Molecular modeling studies of the above described structures are in progress.

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 determined on a Varian-Gemini 200 spectrometer with TMS as internal standard. The HSQC and HMBC spectra of compounds **5** and **6** were acquired on a Bruker DRX-600 spectrometer operating at 599.19 MHz for ^1H and 150.86 MHz for ^{13}C using the UX-NMR software package. Chemical shifts are expressed in δ referring to the solvent peaks δ_H 7.26 and δ_C 77.0 for $CDCl_3$. ^1H-^{13}C HSQC [7] and HMBC [8] experiments were carried out using the convenient pulse sequence as described in literature. The Mass spectra were recorded on a Hewlett-Pakard 5989-A spectrometer at 70 eV coupled with a Hewlett-Pakard 5890 gas chromatograph. Elemental analyses for C, H, N were performed on the Carlo Erba Elemental Analyser Model 1106 at the Microanalytical Laboratory, Dipartimento di Scienze Farmaceutiche, Università di Genova.

Reaction of 3-Amino-2-(methylamino)pyridine (**1**) with Diethyl 1,3-Acetonedicarboxylate (**2**).

Compound **1** (4.9 g, 40 mmoles), obtained by hydrogenation at atmospheric pressure of 2-methylamino-3-nitropyridine, was added to a solution of **2** (8.90 g, 44 mmoles) in dry toluene (100 ml) and the mixture was refluxed with stirring for 18 hours. The reaction suspension was filtered at a warm temperature to obtain a solid which was washed in boiling ethanol and filtered hot to afford **3** or **4** (0.1-0.4 g, yield 2-5%) or, occasionally, a mixture of **3** and **4** which was resolved by crystallization from pyridine.

6,10-Dihydro-8-hydroxy-10-methyl-dipyrido[1,2-*a*:2',3'-*d*]-imidazol-6-one (**3**).

Compound **3** has mp 290° (pyridine); uv : λ_{max} nm (log ε) 225 (3.86), 259 (3.67), 269 (3.64), 352 (3.76); ir (potassium bromide): ν 3358, 1672, 1655-1646 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.65 (s, CH_3), 5.52 and 5.58 (2d, J = 3.2 Hz, C_7-H and C_9-H), 7,25 (dd, J = 8.0 Hz, C_3-H), 8.32 (dd, J = 8.0 Hz, C_4-H), 8,64 (dd, J = 4.6 Hz, C_2-H), 10.32 (bs, OH exchangeable); ^{13}C nmr (deuteriochloroform): δ 27.8 (CH_3), 75.8 (CH), 88.6 (CH), 117.5 (CH), 121.3 (C), 122.2 (CH), 144.2 (CH), 145.3 (C), 146.0, (C) 160.0, (C=O) 168.2 (C=O).

Anal. Calcd. for $C_{11}H_9N_3O_2$•0.25 H_2O: C, 60.12; H, 4.36 N, 19.12. Found: C, 60.30; H, 4.11; N, 19.00.

8-Amino[3'(2'-methylaminopyridine)]-6,10-dihydro-10-methyl-dipyrido[1,2-*a*:2',3'-*d*]imidazol-6-one (**4**).

Compound **4** has mp >300° (pyridine); uv : λ_{max} nm (log ε) 236 (4.44), 264 (4.21), 295 (3.99), 354 (4.30); ir (potassium bromide) : ν 3370, 3237, 1693 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6) : δ 2.85 (d, J = 4.6 Hz, NH-CH_3), 3.60 (s, N-CH_3), 5.08 and 5.69 (2d, J = 1.8 Hz, C_7-H and C_9-H), 6.07 (bm, NH-C), 6.63 (dd, J = 8.0 Hz, $C_{3'}$-H), 7.21 (dd, J = 7.9 Hz, C_3-H), 7.38 (dd, J = 8.3 Hz, $C_{4'}$-H), 7,98 (dd, J = 5.0 Hz, $C_{2'}$-H), 8.16 (bs, NH), 8.26 (dd, J = 5.1 Hz, C_4-H), 8,56 (dd, J = 7.8 Hz, C_2-H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 27.45 (CH_3), 28.29 (CH_3), 73.53 (CH), 85.09 (CH), 111.50 (CH), 116.83 (C), 120.48 (C), 121.47 (CH), 121.79 (CH), 133.40 (CH), 143.91 (CH), 144.88 (C), 145.30 (CH), 146.02 (C), 155.60 (C), 156.21 (C), 159.33 (C=O); ms: m/z 320.3 (M^+, 100), 304 (19), 278 (24), 263 (8), 200 (10), 174 (19).

Anal. Calcd. for $C_{17}H_{16}N_6O$•0.5 H_2O: C, 61.99; H, 5.20; N, 25.52. Found: C, 61.70; H, 5.03; N, 25.52.

The toluene solution resulting from the filtration of the reaction mixture was mixed with the ethanolic solution obtained from the washing of **3** or **4** and evaporated under reduced pressure to give a solid residue which was washed several time with ethyl ether and filtered. Ethyl 3,5-dihydro-5-methyl-2(1*H*)-oxo-pyrido[2,3-*b*][1,4]diazepin-4-ylidene carboxylate (**5**) (0.8-1.0 g, 8-10%), mp 232-233° (ethanol) was obtained. uv: λ_{max} nm (log ε) 224 (3.11), 257 (3.72), 282 (3.15), 323 (4.19); ir (potassium bromide): ν 3440, 3197, 1685, cm^{-1}.

Anal. Calcd. for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08. Found: C, 60.04 ; H, 5.78; N, 16.14

The ethyl ether solution from **5** was concentrated to small volume to give 3.5-4.4 g (28-42 %) of ethyl 3,5-dihydro-5-methyl-4(1*H*)-oxo-pyrido[2,3-*b*][1,4]diazepin-2-ylidene carboxylate (**6**), mp 131-132° (ethyl ether). uv : λ_{max} nm (log ε): 225 (4.10), 293 (4.24), 319 (4.33); ir (potassium bromide): ν 3449, 3230-3205, 1691-1675 cm^{-1}.

Anal. Calcd. for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08. Found: C, 59.61 ; H, 5.70; N, 15.96.

Preparation of **4** from **3.**

A suspension of **3** (g 0.215, 1 mmole) and **1** (1 mmole) in toluene (20 ml) was refluxed for 6 hours. The reaction mixture was filtered at warm temperature to obtain a solid which crystallized from pyridine and supplied 0.18 g (yield 56%) of **4**.

Ethyl 1-Chloroacethyl-3,5-dihydro-5-methyl-2(1*H*)-oxo-pyrido[2,3-*b*][1,4] diazepin-2-yliden] Carboxylate (**7**).

Sodium hydride 60% in mineral oil (180 mg, 4 mmoles) was added to a solution of **5** (1.04 g, 4 mmoles) in anhydrous tetrahydrofurane (70 ml). After stirring at 50° for 2 hours, 0.4 ml (5 mmoles) of chloroacetylchloride in 5 ml of anhydrous toluene was added and the mixture was further stirred at 80° for 12 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 evaporated to afford a solid mixture which, after washing several time with ethyl ether, was filtered. The organic solution leaves 0.4 g (30%) of undissolved **7**, mp 78-79° (ethyl ether); uv: λ_{max} nm (log ε) 242 (3.92), 312 (3.70); ir (chloroform): ν 1721, 1654 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.30 (t, J = 7.1 Hz, CH_3), 3.03 and

5.65 (AX, J = 13.3 Hz, CH_2), 3.47 (s, N-CH_3), 4.19 (q, J = 7.1 Hz, CH_2), 4.85 (AB, J = 29.2 Hz, CH_2), 5.20 (s, CH), 7,22 (dd, J = 8.0 Hz, C_8-H), 7.65 (dd, J = 6.9 Hz, C_9-H), 8,45 (dd, J = 4.6 Hz, C_7-H); 13C nmr (deuteriochloroform): δ 17.5, 36.9, 37.1, 47.8, 60.1, 93.8, 120.5, 126.0, 138.4, 149.1, 151.0, 152.0, 168.0, 169.0, 170.0.

Anal. Calcd. for $C_{15}H_{16}ClN_3O_4$: C, 53.33; H, 4.77; N, 12.44. Found: C, 53.58 ; H, 4.82; N, 12.16.

Reaction of **7** with Bases

A solution of **7** (0.34 g, 1 mmole) and morpholine (2 mmoles) in toluene was refluxed for 2 hours. From reaction mixture washed with water, dried with sodium sulphate and evaporated to dryness, **5** was recovered.

The attempt to effect this transformation under different conditions failed.

REFERENCES AND NOTEs

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[2] F. Savelli, A. Boido, I. Vazzana and F. Sparatore, *J. Heterocyclic Chem.*, **24**, 1709 (1987).

[3] F. Savelli, A. Boido, M. Satta, A. Peana and C. Marzano, *Il Farmaco*, **49**, 259 (1994).

[4] F. Savelli, A. Boido and G. Damonte, *J. Heterocyclic Chem.*, **33**, 1737 (1996).

[5] M.Satta, Cattedra di Farmacognosia Università di Sassari, Preliminary communication .

[6] F. Savelli, A. Boido and G. Ciarallo, *J. Heterocyclic Chem.*, **36**, 857 (1999).

[7] A. Bax, S. Subramanian, *J.Magn. Reson.*, **69**, 565 (1986)

[8] A. Bax, D.G. Davis, *J.Magn. Reson.*, **68**, 568 (1985).