Synthesis of Pyrido[3,2-*e*]pyrrolo[2,1-*c*][1,2,4]triazines from Pyrido[3,2-*e*][1,2,4]triazine Derivatives [1]

Francesco Savelli* and Alessandro Boido

Dipartimento di Scienze Farmaceutiche, Università di Genova, Viale Benedetto XV 3, 16132 Genova, Italy

Giovanni Ciarallo

Dipartimento di Chimica e Tecnologie Farmaceutiche ed Alimentari, Via Brigata Salerno, 16147 Genova, Italy

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In carrying on our interest in heteropolycyclic structures with biological activities, we projected the preparation of compounds containing the pyrido[3,2-*e*][1,2,4]triazine or pyrido[2,3-*b*][1,4]triazepine systems. The established synthetic approach for the preparation of latter system led to the triazine derivatives **5a-f** while a new bicyclic triazepine structure **6** is accomplished with difficulty.

In expanding the pyridotriazine structure, we obtained derivatives of a new tricyclic structure, 5-substituted-6a-ethyloxycarbonyl-5,6,6a,7-tetrahydropyrido[2,3-*e*]pyrrolo[2,1-*c*][1,2,4]triazin-9(8*H*)-ones **8** in which the triazine ring is fused with a pyrrole nucleus.

Compounds **5a-f** and **8a,b** will be tested as potential CNS depressant, antiinflammatory, analgesic and antibacterial agents.

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While exploring the pharmacological potentiality of heteropolycyclic structures with a pyridine nucleus, we described the synthesis of structures including pyrido[2,3-*b*]-pyrazine [2-4] and pyrido[2,3-*b*][1,4]diazepine systems [3,5] which exhibited interesting CNS depressant and analgesic activities. We have now tried the synthesis of compounds with pyrido[3,2-*e*][1,2,4]triazine or pyrido-[3,2-*f*][1,2,5]triazepine system but, up to now, the chosen synthetic route mainly provided derivatives from the first structure **5** (Scheme) and only compound **6** of a novel bicyclic pyridotriazepinone structure [6].

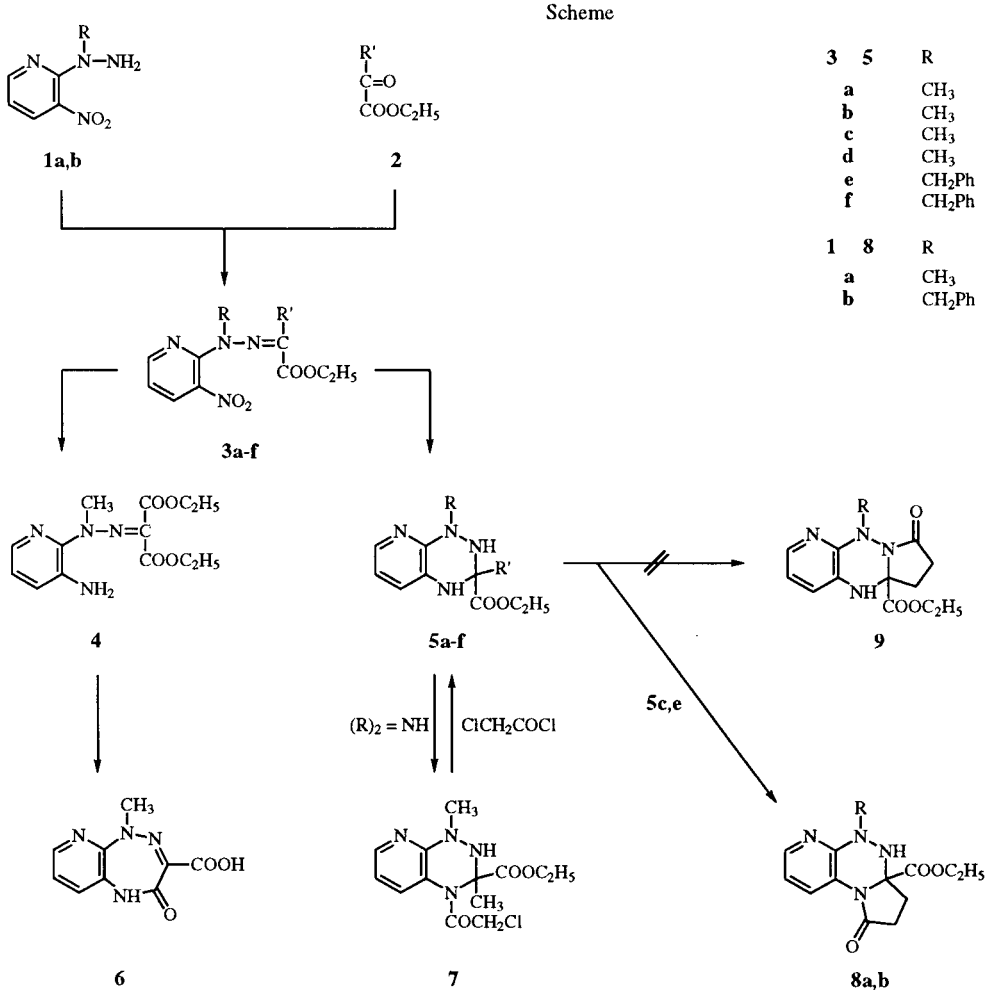
The synthetic approach which involves the condensation of 2-methyl/benzyl-2-[2'-(3'-nitro)pyridyl]hydrazine **1a,b** with α-ketoesters **2** (Scheme) led to nitro-intermediates **3a-f**. These were reduced (hydrogen-C/Pd) so as to obtain the corresponding amino-derivatives but, in fact, the reaction evolved and the amino group obtained supplied nearly all the pyridotriazine derivatives **5a-f**, by an internal addition to the azometine double bond with ring-closure. The alternative reduction (Ni-Raney) [4] furnished similar results and the selective reduction of azomethine (sodium borohydride) have not given an effective isolation of the reduction product for the concomitant hydrolysis of the ethyloxycarbonyl group. Only in the reduction reaction of compound **3b**, besides triazine **5b**, did we isolate the amino-intermediate **4**, from which we obtained the pyridotriazepine derivative **6**, by an alkaline hydrolysis and subsequent cyclization

The structures described were supported by analytical and spectroscopic data. In particular, derivative **5a** (Table 1) was characterized by ^{1}H nmr, with triplet and multiplet (methylene group in a chiral structure) signals related to ethyloxycarbonyl, exchangeable signals at δ 4.05 and 4.52 related to two NH groups and three double doublets at δ 6.58 (J = 8.0 Hz), 6.76 (J = 8.0) and 7.66 (J = 4.6) ppm related to pyridine β-H, γ-H and α-H respectively. On the other hand, the structure of **4** was determined by the mass spectrum (M^+, 394), ^{1}H nmr spectrum (exchangeable NH_2 signal at δ 4.45 and two quarters and two triplets nearly overlaid at δ 4.22 and 1.45 for 2 CH_2 and 2 CH_3 respectively) and its reactivity. On the basis of these data, the transformation from **4** to **6** is significant.

By developing the triazine derivatives, we tried to synthesize some compounds of a new structure in which the pyridotriazine skeleton is fused with a pyrrole or a pyridine nucleus. For this purpose we started from **5c** and **5e**, and, by cyclocondensation of the ethyloxycarbonyl group with the N_4-H group, the new structure 5-substituted-6a-ethyloxycarbonyl-5,6,6a,7-tetrahydropyrido[3,2-*e*]pyrrolo-[2,1-*c*][1,2,4]triazin-9(8*H*)-one derivatives **8a,b** were obtained. The analogous reaction to obtain the designed dipyridotriazine structure **9**, starting from **5d** and **5f** and carried out in the same manner failed, recovering the unreacted compounds.

In order to prepare isomer **9** by cyclocondensation of ethyloxycarbonyl with the alternative N_2-H group of **5c,e**, the structural identification of compounds **8a,b** was not easy. These, unlike **5c,e**, besides their disappearance, on the ^{1}H nmr, of one ethyl group and an exchangeable NH signals, exhibited a downfield shift of double doublet signals related respectively to the pyridine β-H, α-H and γ-H at δ 6.75 (J = 8.0 Hz), 7.95 (J = 5.0) and 8.61 (J = 8.0). The latter shift of the pyridine γ-H signal (from 6.76 to 8.61 ppm) is particularly strong and attributable to a car-

Scheme



3 5	R	R'
a	CH_3	CH_3
b	CH_3	$COOC_2H_5$
c	CH_3	$(CH_2)_2COOC_2H_5$
d	CH_3	$(CH_2)_3COOC_2H_5$
e	CH_2Ph	$(CH_2)_2COOC_2H_5$
f	CH_2Ph	$(CH_2)_3COOC_2H_5$

1 8	R
a	CH_3
b	CH_2Ph

bonyl group field effect. These findings led to the proposed structure.

From **5a**, we attempt to synthesize derivatives related to the pyrazinopyridopyrazine structure [4] through intermediate **7**, but the chloro substitution with secondary amines was not accomplished because, even at room temperature, the hydrolysis of chloroacetyl group occurs.

Compounds **5a-f** and **8a,b** will be investigated for CNS depressant, antiinflammatory, analgesic and antibacterial activities already underlined from analogues [7-11].

Table 1

Spectral and Analytical Data of Compounds **3a-f**

Compound	R	R'	Yield %	Formula mp °C (solvent) bp °C (Kb)	Analyses Calcd./Found C	H	N	UV, λ_{max} nm (log ε)	IR, cm^{-1}	^1H NMR, δ ppm (deuteriochloroform)
3a	CH_3	CH_3	30	$C_{11}H_{14}N_4O_4$ 76-78 [c]	49.62 49.50	5.30 5.28	21.04 21.35	233 (4.16) 314 (3.99)	[a] 1711	1.35 (t, J = 7.4 Hz, CH_3), 2.36 (s, CH_3),3.58 (s, N-CH_3), 4.30 (q, J = 7.4 Hz, CH_2), 7.01 (dd, J = 8.0 Hz, pyr β-H), 7.98 (dd, J = 8.0 Hz, pyr γ-H), 8.43 (dd, J =4.6 Hz, pyr α-H)
3b	CH_3	$COOC_2H_5$	76	$C_{13}H_{16}N_4O_6$ 82-83 [c]	48.15 48.31	4.97 4.99	17.28 17.49	220 (4.11) 303 (4.42)	[b] 1718 1698	1.37 and 1.42 (d+d, J = 7.1 Hz, 2 CH_3), 3.72 (s, CH_3), 4.28 (q, J = 7.1 Hz, CH_2), 4.41 (q, J = 8.4 Hz, CH_2), 7.13 (dd, J = 8.0 Hz, pyr β-H), 7.97 (dd, J = 8.0 Hz, pyr γ-H), 8.42 (dd, J = 4.6 Hz, pyr α-H)
3c	CH_3	$(CH_2)_2COOC_2H_5$	48 [f]	$C_{15}H_{20}N_4O_6$ 122-130 (0.2 mm Hg)	51.13 51.16	5.72 5.88	15.90 15.60	—	[a] 1727 1701	1.21 (t, J = 7.1 Hz, CH_3), 1.37 (t, J = 7.1 Hz, CH_3), 2.54 (m, CH_2), 2.81 (m, CH_2), 3.53 (s, N-CH_3), 4.13 (q, J = 7.1 Hz, CH_2), 4.28 (q, J = 7.1 Hz, CH_2), 6.94 (dd, J = 7.9 Hz, pyr β-H), 7.92 (dd, J = 7.9 Hz, pyr γ-H), 8.37 (dd, J = 4.7 Hz, pyr α-H)
3d	CH_3	$(CH_2)_3COOC_2H_5$	52 [f]	$C_{16}H_{22}N_4O_6$ 145-155 (0.2 mm Hg)	52.45 52.60	6.05 6.50	15.29 14.88	—	[e] 1730	1.28 (t, J = 7.1 Hz, CH_3), 1.35 (t, J = 7.1 Hz, CH_3), 1.95 (m, CH_2), 2.46 (t, J = 7.1 Hz, CH_2), 2.84 (m,CH_2), 3.70 (s, N-CH_3), 4.12 (q, J = 7.1 Hz, CH_2), 4.28 (q, J = 7.1 Hz, CH_2), 7.01 (dd, J = 8.0 Hz, pyr β-H), 7.98 (dd, J = 8.0 Hz, pyr γ-H), 8.42 (dd, J = 4.6 Hz, pyr α-H)
3e	CH_2Ph	$(CH_2)_2COOC_2H_5$	60 [f]	$C_{21}H_{24}N_4O_6$ 77-78 [d]	58.87 59.16	5.65 5.72	13.08 13.02	225 (4.10) 305 (4.10)	[e] 1727 1701	1.21 (t, J = 7.1 Hz, CH_3), 1.35 (t, J = 7.1 Hz, CH_3), 2.48 (m, CH_2), 2.85 (m, CH_2), 4.08 (q, J = 7.1 Hz, CH_2), 4.24 (q, J = 7.1 Hz, CH_2), 5.59 (s, CH_2), 7.08 (dd, J = 8.0 Hz, pyr β-H), 7.30 (m, 5 Ar-H), 8.05 (dd, J = 8.0 Hz, pyr γ-H), 8.38 (dd, J = 4.6 Hz, pyr α-H)
3f	CH_2Ph	$(CH_2)_3COOC_2H_5$	58	$C_{22}H_{26}N_4O_6$ 106-107 [c]	59.72 59.35	5.92 5.92	12.66 12.78	—	[a] 1735 1708	1.24 (t, J = 7.1 Hz, CH_3), 1.36 (t, J = 7.1 Hz, CH_3), 1.82 (m, CH_2), 2.26 (t, J = 8.5 Hz, CH_2), 2.55 (m, CH_2), 4.10 (q, J = 7.1 Hz, CH_2), 4.24 (q, J = 7.1 Hz, CH_2), 5.58 (s, CH_2), 7.05 (dd, J = 8.0 Hz, pyr β-H), 7.30 (m, 5 Ar-H), 8.05 (dd, J = 8.0 Hz, pyr γ-H), 8.36 (dd, J = 4.6 Hz, pyr α-H)

[a] potassium bromide; [b] chloroform; [c] ethanol; [d] ethyl ether; [e] film; [f] as crude product.

Table 2

2,3-Substituted-3-(ethyloxycarbonyl)-1,2,3,4-tetrahydropyrido[3,2-*e*][1,2,4]triazines
Spectral and Analytical Data

Compound	R	R'	Formula mp °C (solvent)	Analyses Calcd./Found C	H	N	UV, λ_{max} nm (log ε)	IR, cm^{-1} [a]/[b]	* ^1H NMR, δ ppm (deuteriochloroform) # ^{13}C NMR, δ ppm (deuteriochloroform)
5a	CH_3	CH_3	$C_{11}H_{16}N_4O_2$ 112-113 [c]	55.91 55.93	6.83 6.82	23.72 23.76	262 (3.67) 322 (3.87)	[a] 3361 3162 1721	* 1.29 (t, J = 8.0 Hz, CH_3), 1.52 (s, CH_3), 3.21 (s, N-CH_3), 4.05 (s, NH exchangeable), 4.22 (m, CH_2), 4.52 (s, NH exchangeable), 6.58 (dd, J = 8.0 Hz, pyr β-H), 6.76 (dd, J = 8.0 Hz, pyr γ-H), 7.66 (dd, J = 4.6 Hz, pyr α-H) # 14.6 (CH_3), 24.4 (CH_3), 38.1 (CH_3), 62.4 (CH_2), 72.0 (C), 115.7 (CH), 119.6 (CH), 128.3 (C), 137.9 (CH), 148.5 (C), 172.3 (CO)
5b	CH_3	$COOC_2H_5$	$C_{13}H_{18}N_4O_4$ 101-103 [c]	53.05 53.02	6.16 6.23	19.04 18.98	255 (3.36) 319 (3.71)	[a] 3355 3150 1727	* 1.32 (t, J = 8.0 Hz, 2 CH_3), 3.19 (s, N-CH_3), 4.30 (m, 2 CH_2), 4.60 (s, NH exchangeable), 4.88 (s, NH exchangeable), 6.63 (dd, J = 8.0 Hz, pyr β-H), 6.85 (dd, J = 8.0 Hz, pyr γ-H), 7.70 (dd, J = 4.6 Hz, pyr α–H) # 14.5 (2 CH_3), 38.1 (CH_3), 63.3 (2 CH_2), 75.9 (C), 116.5 (CH), 120.9 (CH), 128.1 (C), 138.7 (CH), 149.3 (C), 166.6 (2 CO)
5c	CH_3	$(CH_2)_2COOC_2H_5$	$C_{15}H_{22}N_4O_4$ 51-52 [c]	55.88 55.41	6.88 6.89	17.38 16.99	—	[b] 3370 1725	* 1.25 (m, 2 CH_3), 2.20 (m, CH_2), 2.45 (m, CH_2), 3.19 (s, N-CH_3), 4.04 (s, NH exchangeable), 4.20 (m, 2 CH_2), 4.60 (s, NH exchangeable), 6.58 (dd, J = 8.0 Hz, pyr β-H), 6.72 (dd, J = 7.9 Hz, pyr γ-H), 7.62 (dd, J = 4.6 Hz, pyr α-H)
5d	CH_3	$(CH_2)_3COOC_2H_5$	$C_{16}H_{24}N_4O_4$ 112-118 (0.2 mm Hg)	57.13 57.23	7.19 7.24	16.66 16.22	—	[e] 3356 3260 1732	* 1.25 (m, 2 CH_3), 1.80 (m, 2 CH_2), 2.30 (m, CH_2), 3.15 (s, N-CH_3), 4.20 (bs+m, NH exchangeable + 2 CH_2), 4.60 (s, NH exchangeable), 6.55 (dd, J = 8.0 Hz, pyr β-H), 6.71 (dd, J = 8.0 Hz, pyr γ-H), 7.60 (dd, J = 4.6 Hz, pyr α-H)
5e	CH_2Ph	$(CH_2)_2COOC_2H_5$	$C_{21}H_{26}N_4O_4$ 132-140 (0.2 mm Hg)	63.28 62.96	6.58 6.25	14.06 14.01	265 (3.88) 326 (3.97)	[e] 3350 3265 1733	* 1.25 (m, 2 CH_3), 2.15 (m, CH_2), 2.0 (m, CH_2), 4.10 (m+bs, 2 CH_2 + NH exchangeable), 4.52 (s, NH exchangeable), 4.58 and 5.24 (AB, J = 16 Hz, CH_2), 6.59 (dd, J = 8.0 Hz, pyr β-H), 6.78 (dd, J = 8.0 Hz, pyr γ-H), 7.25 and 7.40 (2m, 5 Ar-H), 7.68 (dd, J = 4.6 Hz, pyr α-H) # 14.6 (CH_3), 14.6 (CH_3), 28.91 (CH_2), 32.4 (CH_2), 53.3 (CH_2), 61.1 (CH_2), 62.5 (CH_2), 73.5 (C), 115.6 (CH), 120.3 (CH), 127.4 (CH), 127.7 (C), 128.7 (2 CH), 129.1 (2 CH), 138.1 (CH), 138.7 (C), 147.8 (C), 171.1 (CO), 173.1 (CO)
5f	CH_2Ph	$(CH_2)_3COOC_2H_5$	$C_{22}H_{28}N_4O_4$ 70-71 [d]	64.05 63.63	6.84 6.66	13.58 13.57	—	[a] 3380 3200 1733	* 1.25 (m, 2 CH_3), 1.70 (m, 2 CH_2), 2.23 (t, J = 12.0 Hz, CH_2), 4.06 (bs, NH exchangeable), 4.16 (m, 2 CH_2), 4.46 (bs, NH exchangeable), 4.56 and 5.14 (AB, J = 16.0 Hz, CH_2), 6.59 (dd, J = 8.0 Hz, pyr β-H), 6.78 (dd, J = 8.0 Hz, pyr γ-H), 7.25 and 7.40 (2m, 5 ArH), 7.68 (dd, J = 4.6 Hz, pry α-H)

[a] potassium bromide; [b] chloroform; [c] ethyl ether; [d] ethyl ether/hexan; [e] film.

EXPERIMENTAL

All melting points were determined by the capillary method on a Büchi 510 apparatus and are uncorrected. Distillations were performed under vacuum in a bulb to bulb apparatus and the indicated boiling points actually correspond to the air bath temperature. 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; chemical shifts are reported in ppm with TMS as internal standard and are given in δ units. The mass spectra were recorded on a Hewlett-Pakard 5989-A spectrometer at 70 eV coupled with a Hewlett-Pakard 5890 gaschromatograph. 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.

Preparation of 2-(1-Substituted-hydrazino)-3-nitropyridines **1a**, **1b**.

2-(1-Methylhydrazino)-3-nitropyridine (**1a**) [12] was obtained, by condensation of 2-chloro-3-nitropyridine and two equivalent of methylhydrazine (yield 80%), as a red oil (bp 1.0 mm Hg, 120-125°) which gives rise to orange plates, mp 58-60°; ^1H nmr (deuteriochloroform): δ 3.31 (s, CH_3), 3.98 (bs, NH_2 exchangeable), 6.67 (dd, J = 8.0 Hz, pyr β-H), 7.85 (dd, J = 8.0 Hz, pyr γ-H), 8.25 (dd, J = 4.6 Hz, pyr α-H).

2-(1-Benzylhydrazino)-3-nitropyridine (**1b**) was obtained by refluxing for 6 hours 2-chloro-3-nitropyridine (4.77 g, 30 mmoles), benzylhydrazine (3.66 g, 30 mmoles, obtained from correspondent dihydrochloride salt in absolute ethanol and sodium ethoxide) and triethylamine in ethanol (50 ml). After cooling, the reaction mixture was evaporated, diluted with ethyl ether and the precipitate was filtered. The organic layer was evaporated and the oily residue, triturated with dilute hydrochloric acid, gave unreacted 2-chloro-3-nitropyridine undissolved (10%). The acid solution obtained from filtration, was made alkaline with sodium hydroxide and extracted with methylene chloride. The organic layer was dried (sodium sulphate) and evaporated to dryness to give a red oil (yield 77%) of **1b**; ^1H nmr (deuteriochloroform): δ 3.74 (bs, NH_2 exchangeable), 5.08 (s, CH_2), 6.65 (dd, J = 7.9 Hz, pyr β-H), 7.42 (m, 5 ArH), 7.88 (dd, J = 7.9 Hz, pyr γ-H), 8.28 (dd, J = 4.6 Hz, pyr α-H). For the elemental analysis the *p*-nitrobenzaldeyde derivative was prepared, mp 176-177° (ethanol).

Anal. Calcd. for $C_{19}H_{15}N_5O_4$: C, 60.47; H, 4.01; N, 18.56. Found: C, 60.06; H, 3.95; N, 18.89.

General Procedure for the Preparation of Diethyl 2-[*N*-(3-Nitro-2-pyridyl)-*N*-alkyl)hydrazono]alkyldicarboxylates **3c-f** or Malonate **3b** or Ethyl Propionate **3a**.

Compound **1a** or **1b** (10 mmoles) was dissolved in ethanol (35 ml), and the appropriate α-ketoester (10 mmoles) was added and refluxed for 16 hours. The reaction solution, evaporated to dryness, supplies compounds **3a** [6], **3b** and **3f** (Table 1) as yellow solids and **3c**, **3d**, **3e** (Table 1) as oily residues. The solid compounds were triturated with ethanol and purified by crystallization. Oily compounds **3c**, **3d**, **3e** were suspended in hexane (10 ml) and stirred for 2 hours at room temperature. The organic layer was decanted and the oily mixture partitioned between ethyl ether and dilute hydrochloric acid to remove unreacted **1a** or **1b**. The organic layer was washed with water, dried (sodium sulphate) and the solvent distilled to afford an oily residue which was chromatographed on silica gel. By elution with methylene chloride the nitropyridylhydrazone derivatives and a small amount of unextracted **1a** or **1b** was collected in succession. For analytical data a portion of the oily compounds was purified by distillation *in vacuo*. Compound **3e**, which was kept in the freezer, gradually crystallized.

3-(Ethyloxycarbonyl)-1,2,3,4-tetrahydro-1-R-3-R'-pyrido[3,2-*e*]-[1,2,4]triazine Derivatives (**5a-f**) and Diethyl 2-[*N*-(3-Amino-2-pyridyl)-*N*-methylhydrazono]malonate (**4**).

A peroxide free tetrahydrofurane solution of **3a-f** (10 mmoles) was hydrogenated at room temperature and atmospheric pressure in the presence of 10% palladium on charcoal (50 mg for each g) until the required volume of hydrogen was adsorbed and the reaction stopped spontaneously. After filtration of the catalyst, the solvent was removed under reduced pressure leaving an oily residue which, after cooling, supplied solid compounds **5a**,**b**,**c**,**f** (Table 2) which were triturated with diethyl ether and recrystallized, or oily compounds **5d**,**e** (Table 2) which were purified by chromatography on alumina with diethyl ether as the eluent, in quantitative yield.

Compound **3b**, hydrogenated by the above procedure, supplied a yellow solid from which, compound **4** was occasionally isolated, mp 82-83° (ethanol); uv: λ_{max} nm (log ε) 243 (4.30), 267 sh (3.98), 351 (4.09); ir (potassium bromide): ν 3462, 3353, 1724, 1659 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.45 (2t, 2 CH_3), 3.70 (s, N-CH_3), 4.22 (2q, 2 CH_2), 4.45 (bs, NH_2 exchangeable), 6.88 (dd, J = 7.6 Hz, pyr β-H), 6.98 (dd, J = 7.6 Hz, pyr γ-H), 7.71 (dd, J = 4.6 Hz, pyr α-H). ms: m/z 294 $[M]^+$ (30), 221 (100), 193 (8), 173 (36), 147 (79), 134 (6).

Anal. Calcd. for $C_{13}H_{18}N_4O_4$: C, 53.05; H, 6.16; N, 19.04. Found: C, 53.27; H, 6.02; N, 18.97.

3-Carboxy-1-methyl-1*H*-pyrido[3,2-*f*][1,2,5]triazepin-4(5*H*)-one (**6**).

Compound **4** (0.295 g, 1 mmole) was suspended in sodium hydroxide 2*N* (6 ml) and stirred at room temperature for 6 hours. The alkaline solution was washed with methylene chloride, neutralized with a solution of tartaric acid 8% and extracted with methylene chloride. The pasty residue, obtained from evaporation under reduced pressure of a dried organic layer, was triturated with diethyl ether and filtered to give a solid compound which was kept at melting temperature under reduced pressure (10^{-1} mm Hg) for one hour. After cooling the residue, which was triturated with ethanol/diethyl ether and recrystallized from ethanol, provided 0.10 g of **6** (yield 45%, mp 166-168°) which decomposes slowly with decarboxylation, therefore in the ms spectrum the peak related to molecular weight is absent, ms: m/z 176 $[M^+-CO_2]$ (23), 148 (14), 132 (4), 120 (100), 106 (5); ^1H nmr (dimethyl-d_6 sulfoxide): δ 3.73 (bs, N-CH_3), 7.22 (dd, J = 7.8 Hz, pyr β-H), 7.45 (dd, J = 7.8 Hz, pyr γ-H), 7.85 (bs, NH exchangeable), 8.08 (dd, J = 4.6 Hz, pyr α-H), 10.30 (bs, OH exchangeable).

Anal. Calcd. for $C_9H_8N_4O_3.0.25\ H_2O$: C, 48.10; H, 3.81; N, 24.93. Found: C, 48.13 H, 3.73; N, 24.77.

4-Chloroacetyl-3-(ethyloxycarbonyl)-1,2,3,4-tetrahydro-1,3-dimethylpyrido[3,2-*e*][1,2,4]triazine (**7**).

A dry toluene solution of **5a** (1.15 g, 5 mmoles) with an excess of dimethylaniline was added dropwise with stirring at room temperature with an equivalent of chloroacetyl chloride

and continued for 12 hours. The reaction mixture was filtered and the organic solution evaporated under reduced pressure to dryness, affording an oily residue that was chromatographed on neutral alumina. By elution with methylene chloride 55% of the unreacted compound was recovered in succession with a small amount (0.200 g, 13%) of **7**, as beige plates, mp 90-91°; uv: λ_{max} nm 230, 249, 318; ^{1}H nmr (deuteriochloroform): δ 1.36 (t, J = 7.1 Hz, CH_3), 2.37 (s, CH_3), 3.78 (s, N-CH_3), 4.23 (s, CH_2), 4.34 (q, J = 7.1 Hz, CH_2), 7.06 (dd, J = 8.0 Hz, pyr β-H), 8.11 (dd, J = 4.7 Hz, pyr α-H), 8.54 (dd, J = 8.0 Hz, pyr γ-H), 10.85 (bs, NH partially exchangeable).

Anal. Calcd. for $C_{13}H_{17}ClN_4O_3$: C, 49.92; H, 5.48; N, 17.91. Found, C, 50.03; H, 5.50; N, 17.65.

Compound **7**, suspended in dry toluene, was added to 2 equivalents of morpholine and the mixture was heated for 6 hours at 50°. The warm reaction mixture was filtered and from the toluene solution which had been evaporated *in vacuo*, compound **5a** was obtained.

6a-Ethyloxycarbonyl-5,6,6a,7-tetrahydro-5-methylpyrido[3,2-*e*]-pyrrolo[2,1-*c*][1,2,4]triazin-9(8*H*)-one (**8a**).

Compound **5c** (0.65 g, 20 mmoles) was kept at 160° under reduced pressure (10^{-1} mm Hg) for 4 hours. After cooling the residue was triturated with ethyl ether and stirred at room temperature for 30 minutes. From the suspension, 0.24 g of crude **8a** was filtered and, from the organic solution standing at room temperature, an additional portion (0.2 g, overall yield 80%) was collected. By evaporation to dryness of diethyl ether solution, 0.18 g of unreacted **5c** were recovered. Compound **8a** had mp 146-147° (ethanol); uv: λ_{max} nm (log ε) 222 (3.70), 270 (3.74), 321 (3.58); ir (potassium bromide): ν 3208, 1751, 1677, 1588 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.24 (t, J = 7.1 Hz, CH_3), 1.94 (m, H), 2.55 (m, 3H), 3.28 (s, N-CH_3), 4.16 (bs, NH exchangeable), 4.21 (q, J = 7.2 Hz, CH_2), 6.75 (dd, J = 8.0 Hz, pyr β-H), 7.95 (dd, J = 5.0 Hz, pyr α-H), 8.61 (dd, J = 8.0 Hz, pyr γ-H); ^{13}C nmr (deuteriochloroform): δ 14.5 (CH_3), 28.8 (CH_2), 30.3 (CH_2), 38.5 (CH_3), 63.0 (CH_2), 79.3 (C), 114.9 (CH), 119.5 (C), 125.6 (CH), 143.4 (CH), 147.5 (C), 169.2 (CO), 172.1 (CO).

Anal. Calcd. for $C_{13}H_{16}N_4O_3$: C, 56.51; H, 5.84; N, 20.28. Found: C, 56.50; H, 5.73; N, 20.35.

5-Benzyl-6a-ethyloxycarbonyl-5,6,6a,7-tetrahydropyrido[3,2-*e*]-pyrrole[2,1-*c*][1,2,4]triazin-9(8*H*)-one (**8b**).

According to the above procedure, **8b** was obtained in a 48% yield, mp 132-133° (diethyl ether); uv: λ_{max} nm (log ε) 270 (3.89), 324 (3.66); ir (potassium bromide): ν 3208, 1746, 1686 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.20 (t, J = 7.1 Hz, CH_3), 1.90 (m, H), 2.55 (m, 3H), 4.06 (s, NH exchangeable), 4.14 (q, J = 7.2 Hz, CH_2), 4.46 and 6.40 (AB, J = 16 Hz, CH_2), 6.76 (dd, J = 8.0 Hz, pyr β-H), 7.98 (dd, J = 5.0 Hz, pyr α-H), 8.62 (dd, J = 8.0 Hz, pyr γ-H).

Anal. Calcd. for $C_{19}H_{20}N_4O_3$: C, 64.76; H, 5.72; N, 15.90. Found, C, 64.43; H, 5.78 N, 15.67.

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