SYNTHESIS OF VARIOUS PYRIDO- AND INDOLO[*g*]FUSED *1H*-QUINOLIN-4-ONE DERIVATIVES

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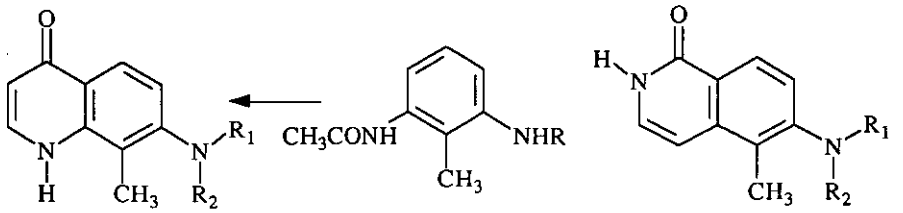
Abstract - Four series of linear tricyclic and quadricyclic heterocyclic derivatives related to oxolinic acid have been prepared : *1H*-pyrido[3,4-*g*]quinolin-4-ones (**1**), *1H*-pyrido[3,2-*g*]quinolin-4-ones (**2**), *1H,11H*-pyrido[3,2-*b*]acridine-4,6-diones (**8**) and *1H,10H*-indolo[3,2-*g*]quinolin-4-ones (**10**).

The quinolone antibacterial agents related to oxolinic and nalidixic acids are inhibitors of the bacterial topoisomerase II (DNAgyrase)[1,2] through a DNA-drug-enzyme complex leading to lethal DNA-breaks. Antitumor agents such as *N*-[4-(9-acridinylamino)-3-methoxyphenyl] methanesulfonamide (*m*-AMSA), ellipticines and their pyridopyrroloisoquinoline analogues behave in a similar way with mammalian topoisomerase II.[3-5] These drugs bind strongly to DNA. Though antibacterial quinolones have been shown to bind poorly to DNA, there is a correlation between their DNA binding affinity and their biological activity.[6]

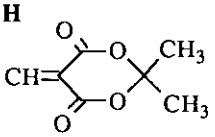
In view of the similarities in the mode of action between a variety of eukariotic topoisomerase II inhibitors and the antibacterial quinolones, we were interested to prepare and to study biological properties of new hybrid molecules related to *m*-AMSA and ellipticines class of cytotoxic compounds. Thus we have undertaken the synthesis of compounds having an isoquinoline, quinoline, acridine and carbazole ring system fused with the 1-substituted 4-pyridone-3-carboxylic acid part characteristic of antibacterial quinolones.In this paper we describe the synthesis of examples of these classes of heterocyclic compounds.

Scheme 1

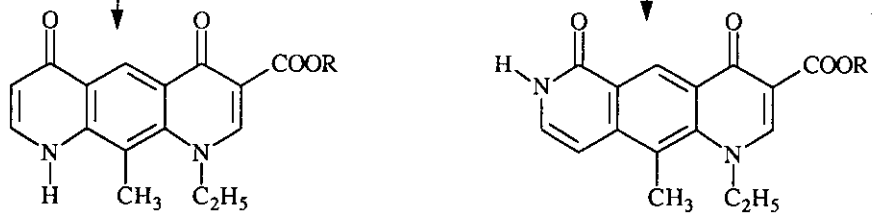


4 7 3

4a : R_1, R_2 = H, $COCH_3$
4b : R_1, R_2 = H
4c : R_1, R_2 = H, C_2H_5
4d : R_1 = C_2H_5; R_2 = $CH{=}C(COOC_2H_5)_2$

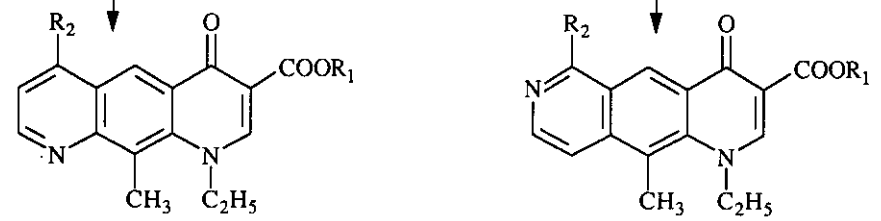
7a : R = H
7b : R = 

3a : R_1, R_2 = H
3b : R_1, R_2 = H, C_2H_5
3c : R_1 = C_2H_5
R_2 = $CH{=}C(COOC_2H_5)_2$



6 5

5a, 6a: R = C_2H_5
5b, 6b : R = H



2 1

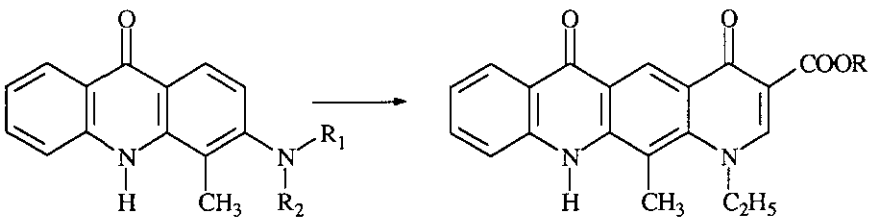
2a : R_1 = C_2H_5 ; R_2 = Cl
2b : R_1 = C_2H_5 ; R_2 = $N(CH_2)_4$
2c : R_1 = H ; R_2 = $N(CH_2)_4$
2d : R_1 = C_2H_5 ; R_2 = H

1a : R_1 = C_2H_5 ; R_2 = Cl
1b : R_1 = C_2H_5 ; R_2 = H
1c : R_1 = R_2 = H
1d : R_1 = C_2H_5 ; R_2 = $N(CH_2)_4$
1e : R_1 = H ; R_2 = $N(CH_2)_4$

1-Ethyl-10-methyl-*1H*-pyrido[3,4-*g*]quinolin-4-one-3-carboxylic acid derivatives (**1**) and 1-ethyl-10-methyl-*1H*-pyrido[3,2-*g*]quinolin-4-one-3-carboxylic acid derivatives (**2**) were synthetized from aminoisoquinolone (**3a**)[7] and aminoquinolone (**4b**) respectively via their 6-oxo intermediates (**5a**) and (**6a**) (Scheme 1). This route allowed us to introduce a substituent at the 6 position.

The 7-amino-8-methyl-*1H*-quinolin-4-one (**4b**) required for the synthesis of **2** was prepared from 3-acetylamino-2-methylaniline (**7a**) by condensation with 5-(ethoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione,[8] subsequent thermal cyclization/decarboxylation of the resulting aminomethylene derivative (**7b**) into acetylaminoquinolone (**4a**). Acid hydrolysis of **4a** then gave the desired amine (**4b**). *N*-Ethyl derivatives (**3b**) and (**4c**) were prepared from the corresponding amines (**3a**) and (**4b**) by reductive ethylation according to the method of Gribble.[9] Condensation of **3b** and **4 c** with diethyl ethoxymethylenemalonate followed by cyclization of the resulting aminomethylene derivatives (**3c**) and (**4d**) by heating in polyphosphoric ethyl ester afforded tricyclic compounds (**5a**) and (**6a**) from which acids (**5b**) and (**6 b**) were obtained by base hydrolysis. Chlorination of **5a** and **6a** in refluxing phosphorous oxychloride provided the corresponding chloro derivatives (**1a**) and (**2a**). Compound (**1c**) was obtained from **1a** by catalytic hydrogenation over 10 % palladium on charcoal and hydrolysis of the ester (**1b**). Its isomer 1-ethyl-10-methyl-*1H*-pyrido[3,2-*g*]quinolin-4-one-3-carboxylic acid has already been described.[10] Substitution of the chloro derivatives (**1a**) and (**2a**) with pyrrolidine in acetonitrile afforded the esters (**1d**) and (**2b**). These esters were converted to the corresponding acids (**1e**) and (**2c**) by alkaline hydrolysis.

Scheme 2



9 **8**

9a : R_1, R_2 = H **8a : R = C_2H_5**

9b : R_1, R_2 = H, C_2H_5 **8b : R = H**

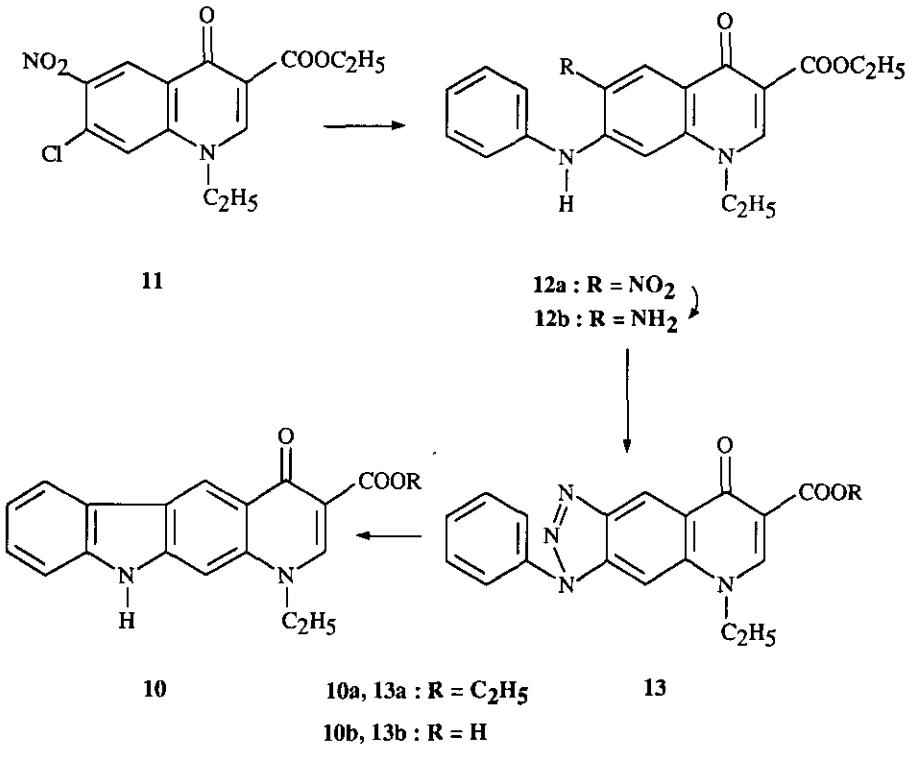
9c : R_1, R_2 = C_2H_5, CH=C($COOC_2H_5$)$_2$

1-Ethyl-12-methyl-*1H,11H*-pyrido[3,2-*b*]acridine-4,6-dione-3-carboxylic acid (**8b**) was prepared from 3-amino-4-methyl-*10H*-acridin-9-one (**9a**),[11] following the same general procedure employed for the

synthesis of **5a** and **6a** (Scheme 2). Several attempts to convert compound (**8a**) into the corresponding 6-chloro derivative led to materials which could not be purified.

1-Ethyl-*1H,10H*-pyrido[2,3-*b*]carbazol-4-one-3-carboxylic acid (**10b**) was synthetized using the preformed ethyl 7-chloro-1-ethyl-6-nitro-*1H*-quinolin-4-one-3-carboxylate (**11**)[12] as starting material (Scheme 3). Condensation of **11** with aniline afforded the nitro compound (**12a**), whose catalytic hydrogenation gave the 6-amino derivative (**12b**) which was diazotized with sodium nitrite in acetic acid. The resulting triazoloquinolone (**13a**) was then submitted to thermal cyclization to afford **10a**. The corresponding acids (**13b**) and (**10b**) were easily prepared from **13a** and **10a**, by alkaline hydrolysis.

Scheme 3



11 **10** **13**

The new compounds were tested against cultured L1210 cells *in vitro*. They were all found devoid of cytotoxicity at 10^{-5} M concentration. They were also assayed against gram positive and gram negative bacteria by standard serial dilutions methods. None of these compounds have significant antibacterial activity.

EXPERIMENTAL

All melting points were determined with a Reichert hot-stage microscope and are uncorrected. ^{1}H Nmr spectra were recorded on a Varian XL-100 apparatus. Mass spectra were obtained with a Ribermag spectrometer ICMO, Université de Paris XI, 91405 Orsay, or with a (AEI) MS-9 spectrometer ICSN, CNRS, 91190 Gif sur Yvette. Elemental analysis were performed at the Service Central de microanalyses du CNRS, ICSN, 91190 Gif-sur-Yvette, France.

7-Acetylamino-8-methyl-*1H*-quinolin-4-one (4a). To a stirred solution of 3-acetylamino-2-methylaniline (**7a**) (1.03 g, 6.28 mmol) in MeOH (90 ml) was added portionwise 5-(ethoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione[8] (1.5 g, 12 mmol). After 0.5 h the resulting precipitate was collected, washed with MeOH, dried to give the crude **7b** (1.898 g, 95 %) which was used in the next step without purification. The preceding crude enamine (**7b**) (1.66 g, 5.22 mmol) was added portionwise to vigorously stirred phenyl ether (20 ml) heated at 240°C. Stirring at 240°C was continued 5 min further. Hexane was added to the cooled reaction mixture and the resulting precipitate was filtered off, washed with hexane and dried to give **4a** (1.0 g, 88.6 %). Recrystallization from EtOH gave an analytical sample, mp > 300°C. ^{1}H Nmr ($(CD_3)_2SO$) δ 2.13 (s, 3H, $COC\underline{H}_3$), 2.31 (s, 3H, 8-CH_3), 6.07 (d, 1H, J = 7.3 Hz, 3-H), 7.35 (d, 1H, J = 8.7 Hz, 6-H), 7.85 (d, 1H, J = 7.3 Hz, 2-H), 7.95 (d, 1H, J = 8.7 Hz, 5-H), 9.75 (s, 1H, $N\underline{H}COCH_3$), 11.08 (s, 1H, 1-N<u>H</u>). <u>Anal.</u> Calcd for $C_{12}H_{12}N_2O_2$. 0.4 H_2O : C, 74.04 ; H, 6.52 ; N, 10.79. Found : C, 73.81 ; H, 6.17 ; N, 11.17.

7-Amino-8-methyl-*1H*-quinolin-4-one (4b). A suspension of **4a** (0.938 g, 4.35 mmol) in EtOH (25 ml) and concentrated HCl (5 ml) was refluxed for 5 h. After cooling the precipitate was filtered off and taken-up in water, the solution was basified with 28 % NH_4OH. The resulting precipitate was filtered off, washed with water, dried and recrystallized from EtOH-EtOAc to afford **4b** (513 mg, 68 %), mp 280-282°C. ^{1}H Nmr ($(CD_3)_2SO$) δ 2.13 (s, 3H, 8-CH_3), 5.57 (br s, 2H, 7-NH_2), 5.83 (d, 1H, J = 7.2 Hz, 3-H), 6.67 (d, 1H J = 8.7 Hz, 6-H), 7.59 (d, 1H, J = 7.2 Hz, 2-H), 7.70 (d, 1H, J = 8.7 Hz, 5-H), 9.90 (br s, 1H, 1-NH). Anal. Calcd for $C_{10}H_{10}N_2$. 0.6 H_2O : C, 64.92 ; H, 6.10 ; N, 15.14. Found : C, 64.95 H, 5.92 ; N, 15.12 .

***N*-Ethylation of amines (3a[7], 4b and 9a[11]) General procedure.**[9] *To a stirred solution of the* appropriate amine (0.02 mol) in AcOH (120 ml) was added portionwise $NaBH_4$ pellets (5,7 g 0.15 mol) over a 10 h period. The reaction mixture was then poured into ice-water. The resulting precipitate (**3b** and **9b**) was filtered off and recrystallized from EtOH. The solution (**4c**) was neutralized with 28 % NH_4OH and extracted with CH_2Cl_2. Evaporation of the solvent gave a residue which was recrystallized from EtOH.

6-Ethylamino-5-methyl-*2H*-isoquinolin-1-one (3b). Yield 62 %, mp 280°C. ^{1}H Nmr ($(CD_3)_2SO$) δ 1.24 (t, 3H, J = 7.0 Hz, $CH_2C\underline{H}_3$), 2.24 (s, 3H, 5-CH_3), 2.98 (m, 2H, $C\underline{H}_2CH_3$), 5.54 (m, 1H, $N\underline{H}CH_2$), 6.56 (d, 1H, J = 7.5 Hz, 4-H), 6.89 (d, 1H, J = 9.0 Hz, 7-H), 6.94 (dd, 1H, J = 7.5 Hz, J = 5.5 Hz, 3-H),

8.0 (d, 1H, J = 9.0 Hz, 8-H), 11.58 (br s, 1H, 2-NH). Anal. Calcd for $C_{12}H_{14}N_2O$. 0.5 H_2O : C, 68.22 ; H, 7.16 ; N, 13.26. Found : C, 68.23 ; H, 7.09 ; N, 13.24.

7-Ethylamino-8-methyl-*1H*-quinolin-4-one (4c). Yield 65 %, mp 305°C. ^1H Nmr ($(CD_3)_2SO$) δ 1.14 (t, 3H, J = 7.0 Hz, CH_2CH_3), 2.09 (s, 3H, 8-CH_3), 3.13 (m, 2H, CH_2CH_3), 5.35 (m, 1H, $NHCH_2CH_3$), 5.77 (d, 1H J = 7.2 Hz, 3-H), 6.65 (d, 1H, J = 8.9 Hz, 6-H) 7.55 (d, 1H, J = 7.2 Hz, 2-H), 7.78 (d, 1H, J = 8.9 Hz, 5-H), 10.3 (br s, 1H, 1-NH). Anal. Calcd for $C_{12}H_{14}N_2O$, 0.1 H_2O : C, 70.62 ; H, 7.01 ; N, 13.72. Found : C, 70.62 ; H, 6.83 ; N, 13.85.

3-Ethylamino-4-methyl-*10H*-acridin-9-one (9b). Yield 75 %, mp 247-248°C. ^1H Nmr ($(CD_3)_2SO$) δ 1.22 (t, 3H, J = 7.0 Hz, CH_2CH_3), 2.27 (s, 3H, 4-CH_3), 3.40 (m, 2H, CH_2CH_3), 5.7 (m, 1H, $NHCH_2CH_3$), 6.74 (d, 1H, J = 9.0 Hz, 2-H), 7.14 (m, 1H, 7-H), 7.60 (m, 1H, 5-H), 7.94 (m, 1H, 6-H), 8.02 (d, 1H, J = 9.0 Hz, 1-H), 8.13 (m, 1H, 8-H), 10.04 (br s, 1H, 10-NH). Anal. Calcd for $C_{16}H_{16}N_2O$. 0.4 H_2O : C, 74.04 ; H, 6.52 ; N, 10.79. Found : C, 73.81 ; H, 6.17 ; N, 11.17.

Preparation of aminomethylene derivatives (3c, 4d and 9c) from 3b, 4c and 9b. General procedure. A mixture of the required ethylamino derivative (1 mmol) and diethyl ethoxymethylenemalonate (0,65 g, 4 mmol) was heated at 155°-160°C with stirring (3 h for **3b** and **4c**, and ≈1.5 h for **9b**). After cooling, ethanol was removed in vacuo to afford crude products. Compounds (**3c**) and (**4d**) were isolated by recrystallization and the crude **9c** was used in the next step without further purification.

Diethyl [*N*-ethyl-*N*(5-methyl-*2H*-isoquinolin-1-one-6-yl)]aminomethylenemalonate (3c). Yield of 80 % after recrystallization from Et_2O. Recrystallization from EtOH gave an analytical sample, mp 180-182°C. ^1H Nmr ($CDCl_3$) δ 0.98 (t, 3H, J = 7.2 Hz, N-CH_2CH_3), 1.21 and 1.22 (2t, 6H, J = 7.2 Hz, 2 x $COCH_2CH_3$), 2.40 (s, 3H, 5-CH_3), 3.34 and 3.67 (2 br m, 4H, 2 x $COCH_2CH_3$), 4.17 (q, 2H, J = 7.2 Hz, NCH_2CH_3),6.71 (d, 1H, J = 7.5 Hz, 4-H), 7.23 (d, 1H, J = 7.5 Hz, 3-H), 7.29 (d, 1H, J = 8.6 Hz, 7-H), 7.70 (s, 1H, CH = C), 8.33 (d, 1H, J = 8.6 Hz, 8-H), 10.9 (br s, 1H, 2-NH). Anal. Calcd for $C_{20}H_{24}N_2O_5$. 0.33H_2O : C, 63.47 ; H, 6.57 ; N, 7.40. Found : C, 63.45 ; H, 6.55 ; N, 7.81.

Diethyl [*N*-ethyl-*N*(8-methyl-*1H*-quinolin-4-one-7-yl)]aminomethylenemalonate (4d). Yield of 84% after recrystallization from EtOAc. Recrystallization from EtOAc gave an analytical sample, mp 196°C. ^1H Nmr ($CDCl_3$) δ 0.98 (t, 3H, J = 7.0 Hz, NCH_2CH_3), 1.22 and 1.24 (2 x t, 6H, J = 7.0 Hz, 2 x $COCH_2CH_3$), 2.34 (s, 3H, 8-CH_3), 3.40 and 3.71 (2 br m, 4H, 2 x $COCH_2CH_3$), 4.18 (q, 2H, J = 7.0 Hz, NCH_2CH_3), 6.33(d, 1H,, J = 7.2 Hz 3-H), 7.15 (d, 1H, J = 8.6 Hz, 6-H), 7.72 (s, 1H, CH = C), 7.72 (br m, 1H, 2-H), 8.29 (d, 1H, J = 8.6 Hz, 5-H), 9.58 (br d, 1H, 1-NH). Anal. Calcd for $C_{20}H_{24}N_2O_5$. 0.25 H_2O : C, 63.72 ; H, 6.55 ; N, 7.53. Found : C, 63.89 ; H, 6.44 ; N, 7.72.

Diethyl [*N*-ethyl,*N*(4-methyl-*10H* acridin-9-one-3-yl)]aminomethylenemalonate (9c). A sample was purified by column chromatography (alumina, CH_2Cl_2-EtOH : 98-2) and recrystallized from Et_2O, mp 180°C. ^1H Nmr ($CDCl_3$) δ 0.95 (t, 3H, J = 7.0 Hz, NCH_2CH_3), 1.21 (t, 6H, J = 7.0 Hz, 2 x $COCH_2CH_3$), 2.40 (s, 3H, 4-CH_3), 3.30 and 3.70 (2 br m, 4H, 2 x $COCH_2CH_3$), 4.20 (q, 2H, J = 7.0 Hz, CH_2CH_3), 7.07 (d, 1H,, J = 9.0 Hz 2-H), 7.25 (m, 1H, 7-H), 7.40 (m, 1H, 5-H), 7.67 (m, 1H, 6-H), 7.73 (s, 1H,

CH= C), 8.22 (br s, 10-NH), 8.33 (d, 1H, J = 9.0 Hz, 1-H), 8.49 (m, 1H, 8-H). Anal. Calcd for $C_{24}H_{26}N_2O_5$. 0.25 H_2O : C, 67.50 ; H, 6.25 ; N, 6.56. Found : C, 67.74 ; H, 6.27 ; N, 6.49.

Cyclizations of aminomethylene derivatives (3c, 4d and 9c) into compounds (5a, 6a and 8a). General procedure. A stirred mixture of the appropriate aminomethylene derivative (1 mmol) and polyphosphoric ethyl ester (PPE) (0.8-3.8 g) was heated at 120-125°C for 1.5 - 2 h. The reaction mixture was cooled, diluted with water and neutralized with 28 % NH_4OH. The resulting precipitate (**5a** and **8a**) was filtered off, washed with water, dried and taken up in hot EtOH. After cooling the solid was collected and dried. The solution (**6a**) was extracted with CH_2Cl_2. The solvent was evaporated and the residue recrystallized from EtOH.

Ethyl 1-ethyl-10-methyl-*1H*, *7H*-pyrido[3,4-*g*]quinoline-4,6-dione-3-carboxylate (5a). 3c (3.72 g, 10 mmol) was treated with PPE (16 g) for 2 h to yield **5a** (1.64 g, 50.8 %). Recrystallization from DMF gave an analytical sample, mp > 300°C. ^1H Nmr ($(CD_3)_2SO$) δ 1.28 and1.33 (2t, 6H, J = 7.0 Hz, 2 x CH_2CH_3), 2.70 (s, 3H, 10-CH_3), 4.35 (m, 4H, 2 x CH_2CH_3), 6.73 (d, 1H, J = 7.5 Hz, 9-H), 7.34 (d, 1H, J = 7.5 Hz, 8-H), 8.67 (s, 1H, 2-H), 8.98 (s, 1H, 5-H), 13.62 (br s, 1H, NH). Anal. Calcd for $C_{18}H_8N_2O_4$. 0.25H_2O : C, 65.34 ; H, 5.64 ; N, 8.48. Found : C, 65.49 ; H, 5.34 N, 8.83.

Ethyl 1-ethyl-10-methyl-*1H*, *9H*-pyrido[3,2-*g*]quinoline-4,6-dione-3-carboxylate (6a). 4d (0.977 g, 2.62 mmol) was treated with PPE (10 g) for 2 h to yield **6a** (295 mg, 34.86 %). Recrystallization from EtOH gave an analytical sample, mp > 300°C. ^1H Nmr ($(CD_3)_2SO$) δ 1.31 and 1.33 (2t, 6H, J = 7.2 Hz, 2 x CH_2CH_3), 2.68 (s, 3H, 10-CH_3), 4.18 and 4.39 (2 q, 4H, J = 7.2 Hz, 2 x CH_2CH_3), 6.12 (d, 1H, J = 7.5 Hz, 7-H), 7.94 (d, 1H, J = 7.5 Hz, 8-H), 8.65 (s, 1H, 2-H), 8.91 (s, 1H, 5-H), 11.20 (br s, 1H, NH). Anal. Calcd for $C_{18}H_{18}N_2O_4$. 0.10 H_2O : C, 65.88 ; H, 5.59 ; N, 8.54. Found : C, 65,78 ; H, 5.49 ; N, 8.90.

Ethyl 1-ethyl-12-methyl-*1H*, *11H*-pyrido[3,2-*b*]acridine-4,6-dione-3-carboxylate (8a). The crude **9c** (from 1.8 g, 7.17 mmol of **9b**) was treated with PPE (6 g) for 1.5 h to yield **8a** (1.96 g, 72 %). Recrystallization from DMF gave an analytical sample, mp > 300°C. ^1H Nmr (CF_3COOD) δ 1.65 and 1.84 (2 t, 6H, J = 7.0 Hz, 2 x CH_2CH_3), 3.24 (s, 3H, 12-CH_3), 4.82 and 5.10 (2 q, 4H, J = 7.0 Hz, 2 x CH_2CH_3), 7.72 (m, 1H, 8-H), 7.94 (m, 1H, 10-H), 8.00 (m, 1H, 9-H), 8.66 (m, 1H, 7-H), 9.46 (s, 1H, 2-H), 10.03 (s, 1H, 5-H). Anal. Calcd for $C_{22}H_{20}N_2O_4$. 0.5H_2O : C, 68.56 ; H, 5.49 ; N, 7.27. Found : C, 68.46 ; H, 5.3 ; N, 7.42.

Hydrolysis of the esters (5a, 6a and 8a). General procedure. Method A : A suspension of the ester (1 mmol) in 1N NaOH (6 ml) was heated at reflux for 1.5 h. After cooling the solution was neutralized with AcOH. The resulting precipitate was filtered off, dried and recrystallized.

Method B : A suspension of the ester (1 mmol) in 1N NaOH (18 ml) and EtOH (18 ml) was heated at reflux. After 2 h the reaction mixture was worked up as described in method A.

1-Ethyl-10-methyl-*1H*,*7H*-pyrido[3,4-*g*]quinoline-4,6-dione-3-carboxylic acid (5b). Method A : Yield of 58 % after recrystallization from DMF, mp > 300°C. ^1H Nmr (CF_3COOD) δ 1.80 (t, 3H, J = 7.1 Hz, CH_2CH_3), 3.19 (s, 3H, 10-CH_3), 5.12 (q, 2H, J = 7.1 Hz, CH_2CH_3), 7.41 (d, 1H, J = 7.4 Hz, 9-H), 7.80

(d, 1H, J = 7.4 Hz, 8-H), 9.52 (s, 1H, 2-H), 9.89 (s, 1H, 5-H). Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 64.42 ; H, 4.73 ; N, 9.39. Found : C, 64.36 ; H, 4.64 ; N, 9.38.

1-Ethyl-10-methyl-*1H,9H*-pyrido[3,2-*g*]quinoline-4,6-dione-3-carboxylic acid (6b). Method A : Yield of 52.7 % after recrystalliation from DMF mp > 300°C. ^{1}H Nmr (CF_3COOD) δ 1.68 (t, 3H, J = 7.1 Hz, $CH_2C\underline{H}_3$), 3.20 (s, 3H, 10-CH_3), 4.96 (q, 2H, J = 7.1 Hz, $C\underline{H}_2CH_3$), 7.49 (d, 1H, J = 7.0 Hz, 7-H), 8.97 (d, 1H, J = 7.0 Hz, 8-H), 9.46 (s, 1H, 2-H), 9.82 (s, 1H, 5-H). Cims (isobutane) m/z : 299 $(M+H)^+$. Anal. Calcd for $C_{16}H_{14}N_2O_4$. 0.33 H_2O : C, 63.28 ; H, 4.64 ; N, 9.22. Found : C, 63.34 ; H, 4.73 ; N, 9.75.

1-Ethyl-12-methyl-*1H, 11H*-pyrido[3,2-b]acridine-4,6-dione-3-carboxylic acid (8b). Method B : Yield of 67.5 % after recrystallization from DMF ; mp > 300°C. ^{1}H Nmr (CF_3COOD) δ 1.84 (t, 3H, J = 7.0 Hz, $CH_2C\underline{H}_3$), 3.34 (s, 3H, 12-CH_3), 5.44 (q, 2H, J = 7.0 Hz, $C\underline{H}_2CH_3$), 8.04 (m, 1H, 8-H), 8.26 (m, 1H, 10-H), 8.46 (m, 1H, 9-H), 8.98 (m, 1H, 7-H), 9.84 (s, 1H, 2-H), 10.3 (s, 1H, 5-H). Cims (isobutane) m/z : 349 $(M+H)^+$. Anal. Calcd for $C_{20}H_{16}N_2O_4$. 0.10 H_2O : C, 68.50 ; H, 4.66 ; N, 8.02. Found : C, 68.36 ; H, 4.54 ; N, 7.86.

Chlorination of compounds (5a and 6a). A suspension of compound (**5a** or **6a**) (1 mmol) in $POCl_3$ (6.7 g, 43.7 mmol) was heated at 90-100°C. After 2.5 h for **5a**, 20 min for **6a** the excess of $POCl_3$ was evaporated under reduced pressure. The residue was triturated with ice water and basified with 28 % NH_4OH. The solution was stirred 2 h at room temperature and extracted with CH_2Cl_2. The solvent was evaporated to give crude products which were purified as indicated for each example.

Ethyl 6-chloro-1-ethyl-10-methyl-*1H*-pyrido[3,4-*g*]quinolin-4-one-3-caboxylate (1a). Yield of 67 % after column chromatography (silica gel, CH_2Cl_2-EtOH : 99-1) and recrystallization from EtOH mp 195°C. ^{1}H Nmr ($CDCl_3$) δ 1.39 and 1.41 (2t, 6H, J = 7.0 Hz, 2 x $CH_2C\underline{H}_3$), 2.89 (s, 3H, 10-CH_3), 4.37 (q, 6H, J = 7.0 Hz, 2 x $C\underline{H}_2CH_3$), 7.77 (dd, 1H, J = 7.0 Hz, J = 0.8 Hz, 9-H), 8.83 (d, 1H, J = 7.0 Hz, 8-H), 8.57 (s, 1H, 2-H), 9.37 (br s, 1H, 5-H). Anal. Calcd for $C_{18}H_{17}ClN_2O_3$. 0.25 H_2O : C, 61.89 ; H, 5.05 ; Cl, 10.15 ; N, 8.02. Found : C, 61.85 ; H, 4.80 ; Cl, 10.06 ; N, 8.04.

Ethyl 6-chloro-1-ethyl-10-methyl-*1H*-pyrido[3,2-*g*]quinolin-4-one-3-carboxylate (2a). Yield of 68 % after recrystallization from EtOH, mp 260°C. ^{1}H Nmr ($CDCl_3$) δ 1.41 and 1.45 (2 t, 6H, J = 7.0 Hz, 2 x $CH_2C\underline{H}_3$), 3.14 (s, 3H, 10-CH_3), 4.43 and 4.50 (2 q, 4H, J = 7.0 Hz, 2 x $C\underline{H}_2CH_3$), 7.54 (d, 1H, J = 4.7 Hz, 7-H), 8.62 (s, 1H, 2-H), 8.90 (d, 1H, J = 4.7 Hz, 8-H), 9.34 (s, 1H, 5-H). Anal. Calcd for $C_{18}H_{17}ClN_2O_3$: C, 62.69 ; H, 4.97 ; Cl, 10.29 ; N, 8.12. Found : C, 62.37 ; H, 4.76 ; Cl, 10.20 ; N, 8.04.

Ethyl 1-ethyl-10-methyl-*1H*-pyrido[3,4-*g*]quinolin-4-one-3-carboxylate (1b). The chloro derivative (**1a**) (348 mg, 1.01 mmol) in EtOH (40 ml) was hydrogenated at room temperature and atmospheric pressure in the presence of triethylamine (0.3 ml) using 10 % palladium on charcoal (50 mg) as catalyst . After 7 h the catalyst was filtered off, washed with EtOH and the filtrate was concentrated. The residue was taken up in CH_2Cl_2, the solution was washed with water, dried and concentrated. The product was purified by column chromatography (silica gel, CH_2Cl_2-EtOH : 99-1) to yield **1b** (190 mg, 61 %) which was recrystallized from CH_3CN, mp 229°C. ^{1}H Nmr ($CDCl_3$) δ 1.39 and 1.42 (2t, 6H, J = 7.1 Hz, 2 x $CH_2C\underline{H}_3$), 2.88 (s, 3H, 10-CH_3), 4.38 and 4.42 (2 q, 4H, J = 7.1 Hz, 2 x $C\underline{H}_2CH_3$), 7.82 (d, 1H, J =

6.4 Hz, 9-H) 8.58 (s, 1H, 2-H), 8.60 (d, 1H, J = 6.4 Hz, 8-H), 9.03 (s, 1H, 5-H), 9.41 (s, 1H, 6-H). Cims (NH_3) m/z : 311 $(M+H)^+$. Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66 ; H, 5.85 ; N, 9.03. Found : C, 61.61 ; H, 5.81 ; N, 9.20.

1-Ethyl-10-methyl-*1H*-pyrido[3,4-*g*]quinolin-4-one-3-carboxylic acid (1c). The ester (**1b**) (106 mg, 0.34 mmol) was hydrolized as described in method A. Acid (**1c**), mp > 300°C was obtained after recrystallization from DMF (68 mg, 70 %). ^1H Nmr (CF_3COOD) δ 1.82 (t, 3H, J = 7.2 Hz, CH_2CH_3), 3.41 (s, 3H, 10-CH_3), 5.03 (q, 2H, J = 7.2 Hz, CH_2CH_3), 8.86 and 8.99 (2d, 2 x 1H, J = 7.2 Hz, 8-H, 9-H), 9.59 (s, 1H, 2-H), 9.96 (s, 1H, 5-H), 10.20 (s, 1H, 6-H). Anal. Calcd for $C_{16}H_{14}N_2O_3$. 0.33 H_2O : C, 66.55 ; H, 5.13 ; N, 9.70. Found : C, 66.51 ; H, 4.92 ; N, 9.61.

Ethyl 1-ethyl-10-methyl-6-(*N*-pyrrolidino)-*1H*-pyrido[3,4-*g*]quinolin-4-one-3-carboxylate (1d). A suspension of the chloro compound (**1a**) (116 mg, 0.337 mmol) in CH_3CN (1.5 ml) and pyrrolidine (0.2 ml) was refluxed for 2 h. The solvent and excess of amine were evaporated under reduced pressure and the residue dissolved in CH_2Cl_2. The organic layer was washed with water, dried and concentrated to dryness. The residue was recrystallized from Et_2O to give **1d** (102 mg, 80 %) as yellow needles, mp 145°C. ^1H Nmr ($CDCl_3$) δ 1.39 and 1.44 (2 t, 6H, J = 7.2 Hz, 2 x CH_2CH_3), 2.02 (m, 4H, 2 x NCH_2CH_2), 2.29 (s, 3H, 10-CH_3), 3.96 (m, 4H, 2 x NCH_2CH_2), 4.32 and 4.42 (2 q, 4H, J = 7.2 Hz, 2 x CH_2CH_3), 7.04 (d, 1H, J = 6.0 Hz, 9-H), 8.10 (d, 1H, J = 6.0 Hz, 8-H), 8.55 (s, 1H, 2-H), 9.34 (s, 1H, 5-H). Anal. Calcd for $C_{22}H_{25}N_3O_3$. 0.25 H_2O : C, 68.81 ; H, 6.70 ; H, 10.95. Found : C, 68.72 ; H, 6.61 ; N, 11.07.

1-Ethyl-10-methyl-6-(*N*-pyrrolidino)-*1H*-pyrido[3,4-*g*]quinolin-4-one-3-carboxylic acid (1e). Base hydrolysis of **1d** (102 mg, 0.269 mmol) as described in Method A produced after recrystallization from MeOH the acid (**1e**) (58 mg, 61 %), mp 240°C. ^1H Nmr ($CDCl_3$) δ 1.46 (t, 3H, J = 7.0 Hz, CH_2CH_3), 2.04 (m, 4H, 2 x NCH_2CH_2), 2.80 (s, 3H, 10-CH_3), 3.96 (m, 4H, 2 x NCH_2CH_2), 4.44 (q, 2H, J = 7.0 Hz, CH_2CH_3), 7.07 (d, 1H, J = 7.0 Hz, 9-H), 8.16 (d, 1H, J = 7.0 Hz, 8-H), 8.78 (s, 1H, 2-H), 9.32 (s, 1H, 5-H), 10.44 (br s, 1H, COOH). Anal. Calcd for $C_{20}H_{21}N_3O_3$: C, 68.36 ; H, 6.02 ; N, 11.96. Found : C, 68.23 ; H, 6.01 ; N, 11.80.

Ethyl 1-ethyl-10-methyl-6-(*N*-pyrrolidino)-*1H*-pyrido[3,2-*g*]quinolin-4-one-3-carboxylate (2b). A suspension of compound (**2a**) (127 mg, 0.369 mmol) in CH_3CN (2 ml) and pyrrolidine (0.4 ml) was refluxed for 2 h. A precipitate formed upon cooling, the reaction mixture was diluted with water and the solids were collected by filtration giving **2b** (102 mg, 72 %). Recrystallization from CH_3CN gave an analytical sample, mp 210-212°C. ^1H Nmr ($CDCl_3$) δ 1.40 and 1.44 (2t, 6H, J = 7.0 Hz, 2 x CH_2CH_3), 2.07 (m, 4H, 2 x NCH_2CH_2), 3.04 (s, 3H, 10-CH_3), 3.83 (m, 4H, 2 x NCH_2CH_2), 4.44 and 4.43 (2 q, 4H, J = 7.0 Hz, 2 x CH_2CH_3), 6.43 (d, 1H, J = 5.5 Hz, 7-H), 8.59 (d, 1H, J = 5.5 Hz, 8-H), 8.59 (s, 1H, 2-H), 9.40 (s, 1H, 5-H). Anal. Calcd for $C_{22}H_{25}N_3O_3$: C, 69.63 ; H, 6.64 ; N, 11.08. Found : C, 69.27 ; H, 6.46 ; N, 10.99.

1-Ethyl-10-methyl-6-(*N*-pyrrolidino)-*1H*-pyrido[3,2-*g*]quinolin-4-one-3-carboxylic acid (2c). Base hydrolysis of **2b** (130 mg, 0.343 mmol) as described in method A produced after recrystallization from

MeOH the acid (**2c**) (70 mg, 58 %), mp 210-212°C. ^{1}H Nmr ($CDCl_3$) δ 1.46 (t, 3H, J = 7.0 Hz, $CH_2\underline{CH_3}$), 2.12 (m, 4H, 2 x $NCH_2\underline{CH_2}$), 3.10 (s, 3H, 10-CH_3), 3.86 (m, 4H, 2 x $NCH_2\underline{CH_2}$), 4.56 (q, 2H, J = 7.0 Hz, $\underline{CH_2}CH_3$), 6.64 (d, 1H, J = 5.5 Hz 7-H), 8.64 (d, 1H, J = 5.5 Hz, 8-H), 8.80 (s, 1H, 2-H), 10.02 (br s, 1H, COOH). Anal. Calcd for $C_{20}H_{21}N_3O_3$: C, 68.36 ; H, 6.02 ; N, 11.96. Found : C, 68.54 ; H, 6.08 ; N, 12.14.

Ethyl 1-ethyl-7-anilino-6-nitro-*1H*-quinolin-4-one-3-carboxylate (12a). A mixture of freshly distilled aniline (36 g, 0.38 mol) and **11**[12] (12 g, 0.037 mol) was treated at 110°C under argon for 6 h. Excess of amine was evaporated under reduced pressure and the reaction mixture was extracted with CH_2Cl_2. The extract was washed with water, dried, and evaporated. The residue was recrystallized from EtOH and then from CH_3CN to give **12a** (9.82 g, 70 %), mp 249-250°C ; ^{1}H Nmr ($CDCl_3$) δ 1.37 and 1.39 (2t, 6H, J = 7.1 Hz, 2 x $CH_2\underline{CH_3}$), 3.92 and 4.37 (2q, 4H, J = 7.1 Hz, 2 x $\underline{CH_2}CH_3$), 6.87 (s, 1H, 8-H), 7.40 (m, 5H, Ar), 8,32 (s, 1H, 5-H), 9.26 (s, 1H, 2-H), 9.52 (s, 1H, NH). Anal. Calcd for $C_{20}H_{19}N_3O_5$: C, 62.98 ; H, 5.02 ; N, 11.02. Found : C, 62.91 ; H, 5.24 ; N, 11.01.

Ethyl 1-ethyl-6-amino-7-anilino-*1H*-quinolin-4-one-3-carboxylate (12b). A suspension of **12a** (6.5 g, 17.06 mmol) in EtOH (500 ml) was hydrogenated at 30°C and atmospheric pressure using 10 % palladium on charcoal (500 mg) as catalyst. After 3 h the catalyst was filtered off washed with EtOH, the filtrate was evaporated to dryness and the residue recrystallized from EtOH, then from CH_3CN to afford **12b** (3.71 g, 62 %) as needles, mp 255-257°C. ^{1}H Nmr ($CDCl_3$) δ 1.40 and 1.43 (2 t, 6H, J = 7.0 Hz, 2 x $CH_2\underline{CH_3}$), 3.82 (br s, 2H, NH_2), 4.05 and 4.39 (2 q, 4H, J = 7.0 Hz, 2 x $\underline{CH_2}CH_3$), 5.94 (s, 1H, NH), 7.07-7.37 (m, 5H, Ar), 7.13 (s, 1H, 8-H), 7.91 (s, 1H, 5-H), 8.35 (s, 1H, 2-H). Anal. Calcd for $C_{20}H_{20}N_3O_3$: C, 68.36 ; H, 6.02 ; N, 11.96. Found : C, 68.33 ; H, 5.94 ; N, 11.84.

Ethyl 8-ethyl-1-phenyl-*1H,8H*-pyrido[3,2-*f*]benzotriazol-5-one-6-carboxylate (13a). To a stirred solution of **12b** (5.94 g, 6.95 mmol) in AcOH (30 ml) at 10° was added dropwise a solution of $NaNO_2$ (1.35 g, 19.5 mmol) in water (3.5 ml) while the temperature was maintained at 10-15°C. The mixture was stirred for 1 h at room temperature and was then diluted with water. The resulting precipitate was filtered off and recrystallized from EtOH to afford **13a** (5.28 g, 85 %), mp 285-287°C. ^{1}H Nmr ($CDCl_3$) δ 1.41 and 1.59 (2 t, 6H, J = 7.0 Hz, 2 x $CH_2\underline{CH_3}$), 4.35 and 4.42 (2 q, 4H, J = 7.0 Hz, 2 x $\underline{CH_2}CH_3$), 7.58 (s, 1H, 8-H), 7.58-7.75 (m, 5H, Ar), 8.52 (s, 1H, 2-H), 9.29 (s, 1H, 5-H). Anal. Calcd for $C_{20}H_{18}N_4O_3$: C, 66.48 ; H, 5.01 ; N, 15.46. Found : C, 66.11 ; H, 5.20 ; N, 15.32.

8-Ethyl-1-phenyl-*1H,8H* -pyrido[3,2-*f*]benzotriazol-5-one-6 carboxylic acid (13b). Base hydrolysis of the ester (**13a**) as described in method B gave the acid (**13b**) in 77.5 % yield after recrystallization from CH_3CN. mp > 300°C. ^{1}H Nmr (CF_3COOD) δ 1.62 (t, 3H, J = 7.2 Hz, $CH_2\underline{CH_3}$), 4.83 (q, 2H, J = 7.2 Hz, $\underline{CH_2}CH_3$), 7.55-7.63 (m, 5H, Ar), 8.47 (s, 1H, 8-H), 9.45 (s, 1H, 2-H), 9.64 (s, 1H, 5-H). Anal. Calcd for $C_{18}H_{14}N_4O_3$: C, 64.66 ; H, 4.22 ; N, 16.76. Found : C, 64.77 ; H, 4.36 ; N, 16.86.

Ethyl 1-ethyl-*1H, 10H*-pyrido[2,3-*b*]carbazol-4-one-3-carboxylate (10a). A stirred mixture of the triazole (**13a**) (1.5 g, 4.14 mmol) and phenantrene (2.8 g) was heated in a metal bath at 340°C for 15 min. Hexane was added to the cooled mixture, the solids were filtered off washed with hot hexane and

recrystallized from DMF to afford **10a** (291 mg, 21 %), mp > 300°C. ^{1}H Nmr ($(CD_3)_2SO$) δ 1.35 and 1.51 (2 t, 6H, J = 7.0 Hz, 2 x CH_2, CH_3), 4.27 and 4.53 (2 q, 4H, J = 7.0 Hz, 2 x CH_2CH_3), 7.17-7.58 (m, 3-H, 7-H, 8-H, 9-H), 7.69 (s, 1H, 11-H), 8.32 (d, 1H, J = 7.3 Hz, 6-H), 8.73 (s, 1H, 2-H), 9.05 (s, 1H, 5-H), 12.90 (br s, 1H, NH). Anal. Calcd for $C_{20}H_{18}N_2O_3$. 0.25 H_2O : C, 70.87 ; H, 5.51 ; N, 8.27. Found : C, 70.85 ; H, 5.45 ; N, 8.11.

1-Ethyl-*1H*, *10H*-pyrido[2,3-*b*]carbazol-4-one-3-carboxylic acid (10b). Base hydrolysis of **10a** as described in method B provided **10b** (80 %). Recrystallization from DMF gave an analytical sample, mp > 300°C. ^{1}H Nmr (CF_3COOD) δ 1.92 (t, 3H, J = 7.2 Hz, CH_2CH_3), 5.00 (q, 2H, J = 7.2 Hz, CH_2CH_3), 7.59-7.93 (m, 3H, 7-H, 8-H, 9-H), 8.15 (s, 1H, 11-H), 8.43 (d, 1H, J = 7Hz, 6-H), 9.39 (s, 1H, 2-H), 9.80 (s, 1H, 5-H). Anal. Calcd for $C_{18}H_{14}N_2O_3$: C, 70.58 ; H, 4.61 ; N, 9.15. Found : C, 70.46 ; H, 4.82 ; N, 8.99.

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