Synthesis of 1,4-Dihydro-4-oxopyridazino[1,6-*a*]indole-3-carboxylic Acids and 1,4-Dihydro-4-oxopyrido[3',2':4,5]pyrrolo[1,2-*b*]-pyridazine-3-carboxylic Acids as Potential Antibacterial Agents

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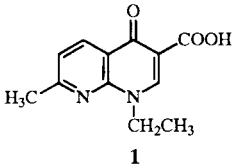
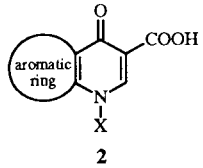
A few aza analogues of the quinolones have been prepared in the two families of the 1,4-dihydro-4-oxopyridazino[1,6-*a*]indole-3-carboxylic acids and the 1,4-dihydro-4-oxopyrido[3',2':4,5]pyrrolo[1,2-*b*]-pyridazine-3-carboxylic acids to check their antibacterial potential. One compound **6c** shows antibacterial activities of the level of nalidixic acid and represents a new lead structure differing from the classical quinolones.

J. Heterocyclic Chem., **31**, 1561 (1994).

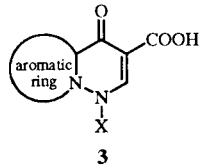
The discovery of nalidixic acid **1** (Figure 1) [1], was the starting of the very fruitful quinolone family used with great success in the treatment of infective diseases. The common structure **2** of the most active products of this family gave us the idea to prepare aza-bridged analogues of structure **3**.



1
Nalidixic Acid

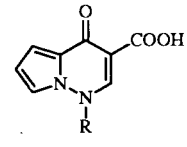


2
Quinolone Common Structure

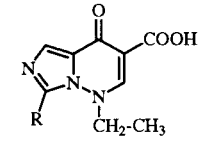


3
Aza-bridged Analogues

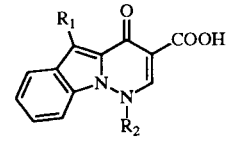
Figure 1



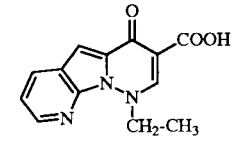
4
1,4-Dihydro-4-oxopyrrolo-[1,2-*b*]pyridazine-3-carboxylic Acids



5
1,4-Dihydro-4-oxoimidazo-[1,5-*b*]pyridazine-3-carboxylic Acids



6a-e
1,4-Dihydro-4-oxopyridazino-[1,6-*a*]indole-3-carboxylic Acids



6f
1,4-Dihydro-4-oxopyrido-[3',2':4,5]pyrrolo[1,2-*b*]pyridazine-3-carboxylic Acid

	R_1	R_2
a	H	H
b	H	CH_3
c	H	CH_2CH_3
d	H	CH_2CF_3
e	CH_3	CH_2CH_3

Figure 2

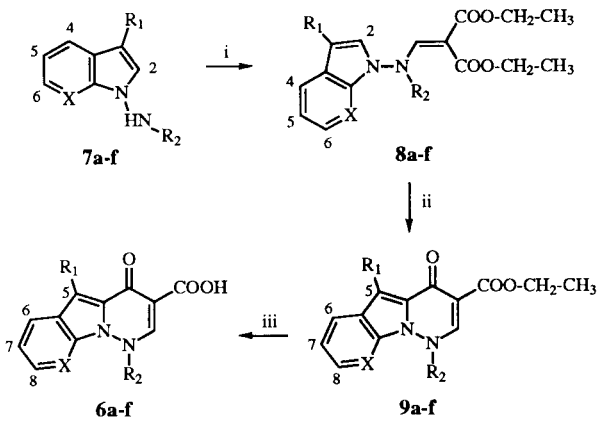
In a previous paper [2], we described two families (Figure 2): the 1,4-dihydro-4-oxopyrrolo[1,2-*b*]pyridazine-3-carboxylic acids **4** and the 1,4-dihydro-4-oxoimidazo[1,5-*b*]pyridazine-3-carboxylic acids **5**, which showed no antibacterial activity. Following this classical variation, we now prepared a few compounds in the families of the 1,4-dihydro-4-oxopyridazino[1,6-*a*]indole-3-carboxylic acids **6a-e** and the 1,4-dihydro-4-oxopyrido-[3',2':4,5]pyrrolo[1,2-*b*]pyridazine-3-carboxylic acid **6f** (Figure 2) to check their antibacterial activity.

Chemistry.

The compounds **6a-f** were synthetized by the method generally used for quinolones and outlined in Scheme 1. The starting products were the described 1-alkylaminoindoles **7a-c** [3a-b] and **7e** [3b]. Unknown compounds **7d** and **7f** were prepared according to Scheme 2, respectively for **7d** in one step from **7a** (75%) and for **7f** in two steps from the commercially available 7-azaindole **10** (59% overall yield for the two steps).

Condensation of the aminoindoles with diethyl ethoxymethylenemalonate gave the diethyl propanedioic acids **8a-f** in variable yields (28% to 95%). These compounds show (except for **8a**) in the ^1H nmr a typical ABX_3 feature for one of the two ethyl carboxylates. This was not seen with the similar pyrroles prepared earlier [2] and can be explained by the greater dissymmetry brought

Scheme 1



Reagents:

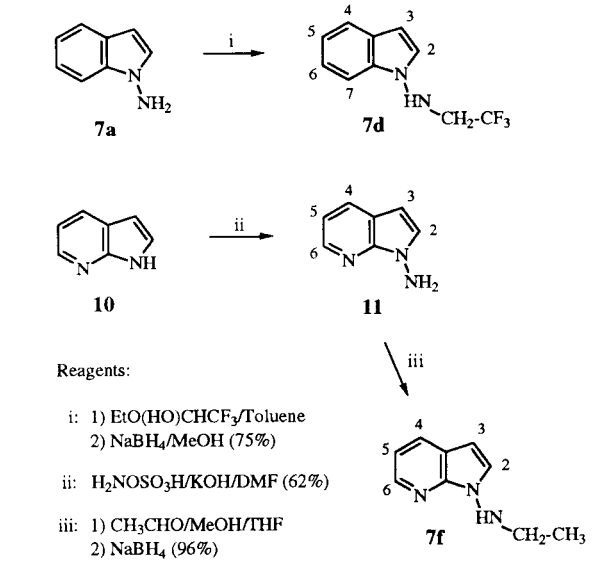
i: EMME/Δ (78% for **8a**; 38% for **8b**; 95% for **8c**; 28% for **8d**; 35% for **8e**; 77% for **8f**)

ii: DOWTHERM A/Δ (52% for **9a**) or PPA/Δ (13% for **9b**; 48% for **9c**; 23% for **9d**; 66% for **9e**; 15% for **9f**)

iii: 1) MeOH/MeONa
2) LiOH/MeOH
3) H_3O^+ (88% for **6a**)
or AcOH/H_2O (45% for **6b**; 37% for **6c**; 14% for **6d**; 33% for **6e**)
or 1) NaOH/EtOH/CH_2Cl_2
2) CH_3COOH (66% for **6f**)

	X	R_1	R_2
a	CH	H	H
b	CH	H	CH_3
c	CH	H	CH_2CH_3
d	CH	H	CH_2CF_3
e	CH	CH_3	CH_2CH_3
f	N	H	CH_2CH_3

Scheme 2



Reagents:

i: 1) EtO(HO)CHCF$_3$/Toluene
2) $NaBH_4$/MeOH (75%)

ii: H_2NOSO_3H/KOH/DMF (62%)

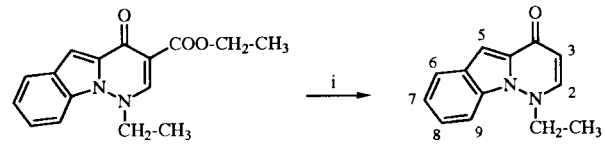
iii: 1) CH_3CHO/MeOH/THF
2) $NaBH_4$ (96%)

about by the indole (or azaindole) ring in this case giving a non equivalence for the two CH2 protons of one of the ester functions.

Compound **8a** was cyclised to **9a** at 200° in Dowtherm A in 52% yield. The ^1H nmr spectrum of this compound favors the 4-OH tautomeric form. The other cyclizations to **9b-f** were performed (yields from 13 to 66%) in polyphosphoric acid at temperatures between 60° and 130° depending on the thermal stability and reactivity of the starting compounds **8b-f**.

Conversion of the esters **9a-f** to the acids **6a-f** could be achieved under different conditions but was generally performed in aqueous acetic acid with variable yields (45% for **6b**, 37% for **6c**, 14% for **6d** and 33% for **6e**) depending on the stability of the compounds. Conditions too drastic (temperature or stronger acids) for this step only furnished the decarboxylated derivatives as exemplified for **9c** (Scheme 3) giving **12** in 54% yield by refluxing in aqueous trifluoroacetic acid. Hydrolysis of **9a** was accomplished in a two step procedure, preparing first the methyl ester which was easily hydrolyzed by lithium hydroxide to **6a** in 88% overall yield. Compound **9f** could be hydrolyzed with the classical ethanol-sodium hydroxide method in 66% yield.

Scheme 3

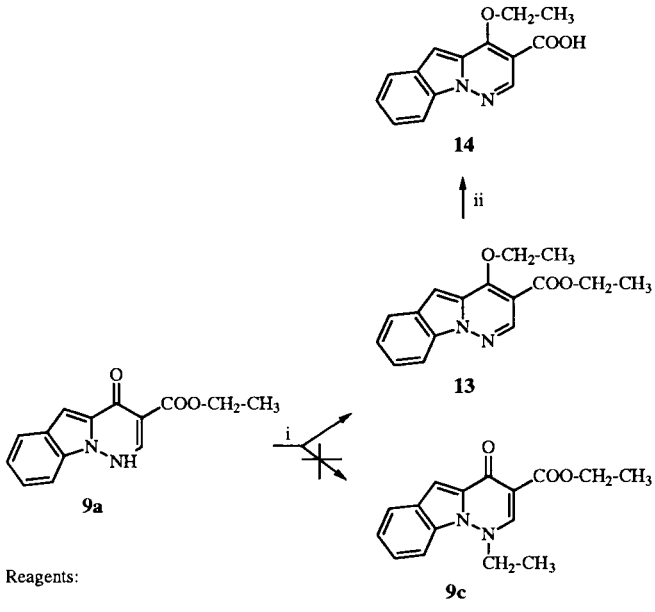


i: CF_3COOH/H_2O (54%)

With analogy to our previous work [2], we also tried alkylation of the cyclized compound **9a** (Scheme 4). Alkylation of **9a** only yielded the *O*-alkylated product **13** in 73% yield and the desired *N*-alkylated compound **9c** could not be detected contrary to the results observed with the 1,4-dihydro-4-oxopyrrolo[1,2-*b*]pyridazine-3-carboxylic acids **4** [2]. An explanation can be a greater steric hindrance around the nitrogen to be alkylated and brought about by the annelated benzo ring in this case. Compound **13** was converted to the corresponding acid **14** in 40% yield with sodium hydroxide in ethanol.

Similarly to our previous work [2] on the 1,4-dihydro-4-oxopyrrolo[1,2-*b*]pyridazine-3-carboxylic acids **4**, the alkylation of the diethyl propanedioic acid **8a** (Scheme 5) gave a mixture of the *C*-alkylated compound **15** (37% isolated) with the desired *N*-alkylated compound **8c** (50% isolated). The best synthetic pathway for these aza-bridged analogues of the quinolones remains the one described in Scheme 1 avoiding the problem of isomer separation.

Scheme 4

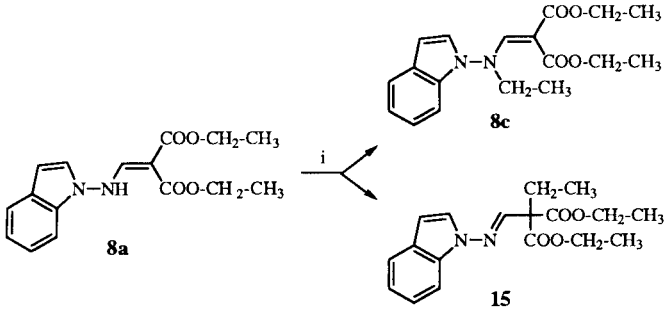


Reagents:

i: K_2CO_3/CH_3CH_2I/DMF (73%)

ii: 1) NaOH/EtOH
2) H_3O^+ (40%)

Scheme 5



Reagents:

i: K_2CO_3/CH_3CH_2I/DMF (37% for **15** and 50% for **8c**)

Microbiological Results.

Compounds **6a-f** and **14** were evaluated *in vitro* for antibacterial activity on the classical aerobes, *Staphylococcus aureus, Streptococcus pyogenes, Pseudomonas aeruginosa, E. Coli, Klebsellia aerogenes, Enterobacter cloacae* and the anaerobes *Bacteriodes fragilis, Bacteriodes thetaiotaom, Fusobacterium varium, Propionibacterium acnes.*

Coumpound **14** was inactive but all the derivatives **6a-f** showed some activity and especially compound **6c** which shows the same antibacterial spectrum and activity level as nalidixic acid. The 1,4-dihydro-4-oxopyridazino-[1,6–a]indole-3-carboxylic acids represent an interesting alternative to the classical quinolone structure. This original lead structure will be further studied by introduction of the classical fluorine and aminated moieties already attached to quinolones to increase their activity. A more detailed structure activity relationship study of this family will be presented later.

EXPERIMENTAL

Commercially available reagents were used without further purification and were purchased from the usual suppliers like Aldrich, Janssen and Prolabo. Yields are not optimized. Melting points were determined on a Kofler block and are uncorrected. The nmr spectra were recorded on a Bruker AC 200 MHz spectrometer. Chemical shifts are given in ppm relative to tetramethylsilane as the internal standard. Infrared spectra (ir) were obtained on a Fourier Nicolet 5DXB FT-IR spectrophotometer and only the prominent peaks are indicated. Chromatographic separations were accomplished with a Büchi System 680 medium pressure apparatus using silica gel 60 (15-40 μm particule size) from Merck as solid phase. Thin layer chromatography (tlc) were performed on silica gel 60 F_{254} precoated glass plates from Merck and the spots were located by the uv light or by iodine vapors. Elemental analysis were accomplished with a Carlo-Erba model 1106 apparatus. The *in vitro* antibacterial activities were determined by conventional agar dilution procedures. 1-Amino-1*H*-indole **7a**, 1-methylamino-1*H*-indole **7b**, 1-ethylamino-1*H*-indole **7c** and 1-ethylamino-3-methyl-1*H*-indole **7e** were prepared according to the procedures described in the literature [3a-b] and showed the analytical characteristics already described. 1*H*-Pyrrolo[2,3-*b*]pyridine **10** is commercially available from Aldrich.

1-[(2,2,2-Trifluoroethyl)amino]-1*H*-indole (**7d**).

A mixture of 1-amino-1*H*-indole **7a** (1.32 g, 10 mmoles) and 2,2,2-trifluoroacetaldehyde ethyl hemiacetal (1.5 g, 10.4 mmoles) with a small pellet of sodium hydroxide in 25 ml of toluene is refluxed until the starting material has disappeared (approximately 1 hour) on tlc (pure dichloromethane). The reaction mixture is evaporated to dryness and the imine formed is immediately reduced in 50 ml of methanol with sodium borohydride (1.5 g, 40 mmoles). The reaction mixture is then refluxed until the imine has disappeared (approximately 1 hour) on tlc (pure dichloromethane). The reaction mixture is evaporated under reduced pressure and the remaining oil taken up with methylchloroform, then filtrated. The filtrate is evaporated to dryness and the residue taken up with dichloromethane for charcoal decolorization. The final residue obtained after evaporation under reduced pressure is the desired compound **7d** (1.6 g, 75%), light yellow unstable oil used without further purification for the next step; an analytical sample was obtained by chromatography on silica gel eluting with a mixture of dichloromethane-heptane (50-50 v/v) giving an oil; tlc Rf 0.8 (pure dichloromethane); ir (potassium bromide): 3328, 3108, 3058, 2934, 1618, 1518, 1457, 1403, 1299, 1272, 1221, 1154, 1098, 1067, 1030, 953, 845, 745, 720, 637 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.67 (m, 2H, $J_{H,F}$ = 8.9 Hz, $J_{H,NH}$ = 5.0 Hz, CH_2CF_3), 4.97 (br t, 1H, $J_{NH,H}$ = 5.0 Hz, NH), 6.40 (dd, 1H, $J_{3,2}$ = 3.3 Hz, $J_{3,7}$ = 0.7 Hz, H_3), 7.09-7.29 (m, 2H, H_5 and H_6), 7.14 (br d, 1H, $J_{2,3}$ = 3.3 Hz, H_2),

7.35 (br dd, 1H, $J_{7,6}$ = 8.1 Hz, $J_{7,3}$ = 0.7 Hz, H_7), 7.60 (br dd, 1H, $J_{4,5}$ = 7.8 Hz, $J_{4,6}$ = 0.9 Hz, H_4).

Anal. Calcd. for $C_{10}H_9F_3N_2$: C, 56.08; H, 4.24; N, 13.08. Found: C, 56.2; H, 4.3; N, 13.5.

1*H*-Pyrrolo[2,3-*b*]pyridin-1-amine (**11**).

To a well stirred suspension of finely powdered potassium hydroxide (213 g, 3.8 moles, 15.2 equivalents) in 300 ml of dry dimethylformamide and cooled at -10°, is added 1*H*-pyrrolo-[2,3-*b*]pyridine **10** (30 g, 0.25 mole) in small portions maintaining the temperature under +5°. After the reaction mixture has again been cooled to -10°, hydroxylamine-*o*-sulfonic acid (114.9 g, 1.02 moles, 4 equivalents) is added maintaining again the exotherm under 0°. The mixture is stirred at 0° during 3 hours and then 400 ml of dichloromethane is added. The suspension is filtered on Celite and the filtrate evaporated to dryness under reduced pressure. The residue is recrystallized from hot cyclohexane with charcoal decolorization giving light colored crystals of compound **11** (20.8 g, 62%), mp 105°; tlc Rf 0.4 (methanol-dichloromethane 5-95 v/v); ir (potassium bromide): 3332, 3264, 3172, 3086, 1627, 1595, 1574, 1507, 1438, 1357, 1324, 1285, 1239, 1210, 1124, 1110, 1047, 970, 927, 892, 801, 787, 773, 759, 716, 597, 504 cm^{-1}; ^1H nmr (deuteriochloroform): δ 5.03 (br s, 2H, NH_2), 6.34 (d, 1H, $J_{3,2}$ = 3.6 Hz, H_3), 7.09 (dd, 1H, $J_{5,4}$ = 7.8 Hz, $J_{5,6}$ = 4.7 Hz, H_5), 7.33 (d, 1H, $J_{2,3}$ = 3.6 Hz, H_2), 7.90 (dd, 1H, $J_{4,5}$ = 7.8 Hz, $J_{4,6}$ = 1.4 Hz, H_4), 8.33 (dd, 1H, $J_{6,5}$ = 4.7 Hz, $J_{6,4}$ = 1.4 Hz, H_6).

Anal. Calcd. for $C_7H_7N_3$: C, 63.14; H, 5.30; N, 31.56. Found: C, 63.2; H, 5.2; N, 32.0.

1-Ethylamino-1*H*-pyrrolo[2,3-*b*]pyridine (**7f**).

To a stirred solution of 1*H*-pyrrolo[2,3-*b*]pyridin-1-amine **11** (20 g, 0.15 mole) in 300 ml of methanol and 300 ml of tetrahydrofuran and cooled at +10° under argon, is added acetaldehyde (17 ml, 13.2 g, 0.30 mole, 2 equivalents). A small exotherm is noted and the disappearance of the starting material is followed by tlc (dichloromethane). After approximately one half hour, the reaction is completed and sodium borohydride (56.7 g, 1.5 moles, 40 equivalents) is added in small portions maintaining the temperature of the mixture under +20° (10 to 20 minutes). The reaction mixture is then stirred during the night at room temperature, evaporated to dryness and the residue decolorized with charcoal in dichloromethane, then it is evaporated to dryness leaving compound **7f** (23.3 g, 96%). An analytical sample was obtained by recrystallization from petroleum ether, mp 30°; tlc Rf 0.5 (methanol-dichloromethane 5-95 v/v/v); ir (potassium bromide): 3220, 3072, 3051, 3023, 2973, 2924, 2868, 1592, 1577, 1523, 1503, 1479, 1425, 1381, 1347, 1312, 1283, 1229, 1205, 1116, 1107, 1033, 940, 896, 871, 798, 769, 734, 720 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.14 (t, 3H, J = 7.2 Hz, CH_3), 3.34 (dq, 2H, J = 7.2 Hz, $J_{H,NH}$ = 4.8 Hz, CH_2), 5.49 (br t, 1H, $J_{NH,H}$ = 4.8 Hz, NH), 6.32 (d, 1H, $J_{3,2}$ = 3.6 Hz, H_3), 7.07 (dd, 1H, $J_{5,4}$ = 7.8 Hz, $J_{5,6}$ = 4.7 Hz, H_5), 7.30 (d, 1H, $J_{2,3}$ = 3.6 Hz, H_2), 7.90 (dd, 1H, $J_{4,5}$ = 7.8 Hz, $J_{4,6}$ = 1.5 Hz, H_4), 8.31 (dd, 1H, $J_{6,5}$ = 4.7 Hz, $J_{6,4}$ = 1.5 Hz, H_6).

Anal. Calcd. for $C_9H_{11}N_3$: C, 67.06; H, 6.88; N, 26.07. Found: C, 67.1; H, 7.2; N, 25.8.

Diethyl [1-(1*H*-Indolyl)amino]methylenepropanedioate (**8a**).

A mixture of 1-amino-1*H*-indole **7a** (1.0 g, 7.6 mmoles) and diethyl ethoxymethylenemalonate (1.8 g, 8.3 mmoles, 1.1 equivalents) is heated at 90° while the ethanol which is formed is distilled off under reduced pressure and until the starting indole has disappeared on tlc (dichloromethane), usually after 1 hour. The mixture is cooled and the crystals recrystallized twice from *n*-hexane with decolorization on charcoal giving **8a** as a white solid (1.8 g, 78%), mp 123°; tlc Rf 0.3 (pure dichloromethane); ir (potassium bromide): 3277, 3131, 2981, 1719, 1661, 1623, 1455, 1428, 1375, 1370, 1350, 1285, 1216, 1098, 1069, 1015, 983, 799, 765, 741, 716 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.25 (t, 3H, J = 7.0 Hz, CH_3), 1.38 (t, 3H, J = 7.0 Hz, CH_3), 4.18 (q, 2H, J = 7.0 Hz, CH_2), 4.30 (q, 2H, J = 7.0 Hz, CH_2), 6.55 (d, 1H, $J_{3,2}$ = 3.3 Hz, H_3), 7.15-7.37 (m, 3H, H_5-H_6-H_7), 7.16 (d, 1H, $J_{2,3}$ = 3.3 Hz, H_2), 7.63 (dd, 1H, $J_{4,5}$ = 7.6 Hz, $J_{4,6}$ = 1.0 Hz, H_4), 8.16 (d, 1H, J = 11 Hz, vinylic H), 10.8 (br d, 1H, J = 11 Hz, NH).

Anal. Calcd. for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.8; H, 6.2; N, 9.3.

Ethyl 4-Hydroxypyridazino[1,6-*a*]indole-3-carboxylate (**9a**).

A mixture of **8a** (4.5 g, 15 mmoles) and Dowtherm-A (5 ml) is heated at 200° under reduced pressure until the starting material has disappeared (4 hours) on tlc (dichloromethane). The cooled reaction mixture is added to hexane, filtered and the solid recrystallized from absolute ethanol giving light tan crystals of **9a** (2.0 g, 52%), mp 145°; tlc Rf 0.7 (pure dichloromethane); ir (potassium bromide): 3450, 2985, 1663, 1595, 1526, 1478, 1451, 1428, 1372, 1335, 1304, 1268, 1204, 1170, 1029, 940, 797 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.46 (t, 3H, J = 7.2 Hz, CH_3), 4.46 (q, 2H, J = 7.2 Hz, CH_2), 7.18 (d, 1H, $J_{5,9}$ = 0.6 Hz, H_5), 7.33-7.49 (m, 2H, H_7-H_8), 7.85 (br dd, 1H, $J_{9,8}$ = 7.0 Hz, $J_{9,7}$ = 1.6 Hz, $J_{9,5}$ = 0.6 Hz, H_9), 8.14 (dd, 1H, $J_{6,7}$ = 9.2 Hz, $J_{6,8}$ = 1.0 Hz, H_6), 8.32 (s, 1H, H_2), 12.5 (s, 1H, OH).

Anal. Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.7; H, 4.7; N, 10.9.

1,4-Dihydro-4-oxopyridazino[1,6-*a*]indole-3-carboxylic Acid (**6a**).

To a suspension of **9a** (1.66 g, 6.5 mmoles) in 10 ml of methanol is added a solution of sodium methylate in methanol [prepared by dissolving sodium (0.26 g, 11.3 mmoles) in 10 ml of methanol]. The mixture is heated at 100° in a sealed tube during 15 hours. The cooled solution is evaporated to half volume under reduced pressure and glacial acetic acid (0.9 ml, 15.7 mmoles) with 50 ml of water is added. The yellow solid is filtered and dried under vacuum. This solid suspended in 10 ml of methanol is added to an aqueous 2*N* solution of lithium hydroxide (32.5 ml, 65 mmoles, 10 equivalents) and again heated at 100° in a sealed tube during one half hour and then kept at room temperature during the night. The reaction mixture is neutralized with 2*N* hydrochloric acid (32.5 ml, 65 mmoles) and the yellow precipitate filtered, washed thoroughly with water and dried at 75° under vacuum. The yellow-green solid of **6a** (1.3 g, 88%) obtained was not further purified (decarboxylation), mp 160° dec; tlc Rf 0.1 (methanol-ethyl acetate-dichloromethane 10-10-80 v/v/v); ir (potassium bromide): 3450, 3054, 2930, 2910, 1630, 1514, 1466, 1439, 1360, 1301, 1258, 1204, 1135, 969, 940, 782 cm^{-1}; ^1H nmr (DMSO-d_6): δ 6.27 (br s, 2H, OH and COOH), 7.12 (s, 1H, H_5), 7.31-7.46 (m, 2H, H_7-H_8), 7.86 (dd, 1H, $J_{6,7}$ = 7.3 Hz, $J_{6,8}$ = 1.4 Hz, H_6), 8.05 (d, 1H, $J_{9,8}$ = 7.9 Hz, H_9), 8.34 (s, 1H, H_2).

Anal. Calcd. for $C_{12}H_8N_2O_3$: C, 63.16; H, 3.53; N, 12.28. Found: C, 63.2; H, 3.5; N, 12.4.

Diethyl [*N*-[1-(1*H*-Indolyl)]methylamino]methylenepropanedioate (**8b**).

A mixture of **7b** (1.46 g, 10 mmoles) and diethyl ethoxymethylenemalonate (2.38 g, 11 mmoles) is heated at 130° under reduced pressure during 1 hour until the starting materials have disappeared on tlc (dichloromethane). The cooled reaction mixture is taken up with hot 1,1,1-trichloroethane and *n*-hexane is added until crystallization and the solution is cooled at +4°. The solid is collected, dried, giving, **8b** as light yellow crystals (1.2 g, 38%), mp 85°; tlc Rf 0.3 (ethyl acetate-dichloromethane-*n*-hexane 10-40-50 v/v/v); ir (potassium bromide): 3450, 3135, 3107, 2986, 2917, 2901, 1715, 1686, 1638, 1478, 1458, 1399, 1374, 1347, 1308, 1283, 1221, 1121, 1078, 1061, 986, 955, 864, 769, 752 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.79 (t, part X of ABX_3, 3H, J = 7.1 Hz, CH_3), 1.22 (t, 3H, J = 7.1 Hz, CH_3), 3.03-3.28 (br m, 1H, part A of ABX_3, CH_2), 3.37 (s, 3H, NCH_3), 3.50-3.75 (br m, 1H, part B of ABX_3, CH_2), 4.16 (q, 2H, J = 7.1 Hz, CH_2), 6.51 (d, 1H, $J_{3,2}$ = 3.5 Hz, H_3), 7.09 (d, 1H, $J_{2,3}$ = 3.5 Hz, H_2), 7.12-7.31 (m, 3H, H_5-H_6-H_7), 7.59 (dd, 1H, $J_{4,5}$ = 7.6 Hz, $J_{4,6}$ = 1.1 Hz, H_4), 7.62 (s, 1H, vinylic H).

Anal. Calcd. for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.85. Found: C, 64.9; H, 6.3; N, 8.8.

Ethyl 1,4-Dihydro-1-methyl-4-oxopyridazino[1,6-*a*]indole-3-carboxylate (**9b**).

A mixture of **8b** (35 g, 0.11 mole) and polyphosphoric acid (250 g) is heated at 60° under nitrogen until the starting material has disappeared (2 hours) on tlc (dichloromethane-hexane-ethyl acetate 40-50-10 v/v/v). 2-Propanol (100 ml) is added and the mixture poured on 1.5 liters of saturated sodium bicarbonate and 200 g of sodium carbonate is added. The aqueous phase is extracted four times with 200 ml of dichloromethane, the collected organic phases are evaporated to dryness and the residue chromatographed on silica gel eluting with a mixture of dichloromethane-ethyl acetate-ethanol (50-30-3 v/v/v). The required fractions after evaporation give crystals of **9b** (4 g, 13%), mp 220° dec; tlc Rf 0.6 (dichloromethane-ethyl acetate-ethanol 50-40-10 v/v/v); ir (potassium bromide): 3436, 3048, 2977, 2927, 1717, 1695, 1645, 1635, 1620, 1480, 1441, 1405, 1316, 1295, 1241, 1195, 1154, 1126, 1086, 782, 733 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.35 (t, 3H, J = 7.1 Hz, CH_2CH_3), 4.27 (q, 2H, J = 7.1 Hz, CH_2), 4.44 (s, 3H, CH_3), 7.20-7.36 (m, 2H, H_7-H_8), 7.32 (br s, 1H, H_5), 7.73 (dd, 1H, $J_{9,8}$ = 8.1 Hz, $J_{9,7}$ = 1.4 Hz, H_9), 7.87 (dd, 1H, $J_{6,7}$ = 7.7 Hz, $J_{6,8}$ = 1.0 Hz, H_6), 8.23 (s, 1H, H_2).

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.8; H, 5.1; N, 10.4.

1,4-Dihydro-1-methyl-4-oxopyridazino[1,6-*a*]indole-3-carboxylic Acid (**6b**).

A mixture of **9b** (4 g, 15 mmoles) in 20 ml of distilled water and 20 ml of glacial acetic acid is heated at 105° until the starting material has disappeared (30 hours) on tlc (acetonitrile-dichloromethane-ethyl acetate-methanol 50-30-10-10 v/v/v/v). The reaction mixture is cooled and extracted with dichloromethane. The organic fractions are collected extracted with 2*N* sodium hydroxide and the basic aqueous phase extracted twice with chloroform to eliminate the neutral byproducts. The remaining basic phase is acidified to *p*H = 1 with 1*N* hydrochloric acid. The precipitated solid is filtered and recrystallized from hot acetonitrile giving yellow crystals of **6b** (1.64 g, 45%), mp 260° dec; tlc Rf 0.2 (chloroform-ethyl acetate-ethanol 50-40-10 v/v/v); ir (potassium bromide): 3424, 3123, 3067, 3035, 2919, 1719, 1632, 1605, 1555, 1503, 1490, 1414, 1318, 1293, 1160, 897, 847, 818, 791 cm^{-1}; ^1H nmr (DMSO–d_6): δ 4.67 (s, 3H, CH_3), 7.34-7.50 (m, 2H, H_7-H_8), 7.42 (s, 1H, H_5), 7.92 (br d, 1H, $J_{6,7}$ = 8.6 Hz, H_6), 8.33 (br d, 1H, $J_{9,8}$ = 8.4 Hz, H_9), 8.96 (s, 1H, H_2), 11.0 (br s, 1H, COOH).

Anal. Calcd. for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.56. Found: C, 64.5; H,4.2; N, 11.5.

Diethyl [*N*-[1-(1*H*-Indolyl)]ethylamino]methylenepropanedioate (**8c**).

A mixture of **7c** (80 g, 0.5 mole) and diethyl ethoxymethylenemalonate (108 g, 0.5 mole) is heated at 110° until the starting material has disappeared (1.5 hours) on tlc (pure dichloromethane) collecting the formed ethanol. After cooling, the reaction mixture is added to 200 ml of dichloromethane, decolorized with charcoal and evaporated to dryness. The oily residue is the desired compound **8c** (157 g, 95%) sufficiently pure for the next step. An analytical sample was obtained by chromatography on silica gel eluting with a mixture of methanol-dichloromethane (1-99 v/v) giving an oil; tlc Rf 0.5 (methanol-dichloromethane 2.5-97.5 v/v); ir (potassium bromide): 2983, 2938, 2905, 1725, 1703, 1626, 1615, 1455, 1385, 1285, 1254, 1190, 1180, 1137, 1110, 1085, 1059, 1031, 868, 799, 760, 745 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.69 (t, 3H, J = 7.2 Hz, OCH_2CH_3A), 1.12 (t, 3H, J = 7.2 Hz, NCH_2CH_3), 1.24 (t, 3H, J = 7.1 Hz, OCH_2CH_3B), 2.84-2.97 (m, part A of ABX_3, 1H, OCH_2A), 3.44-3.57 (m, part B of ABX_3, 1H, OCH_2A), 3.68 (q, 2H, J = 7.2 Hz, NCH_2), 4.15 (q, 2H, J = 7.1 Hz, OCH_2B), 6.49 (d, 1H, $J_{3,2}$ = 3.4 Hz, H_3), 7.07 (d, 1H, $J_{2,3}$ = 3.4 Hz, H_2), 7.12-7.28 (m, 3H, H_5-H_6-H_7), 7.57 (dd, 1H, $J_{4,5}$ = 7.6 Hz, $J_{4,6}$ = 1.0 Hz, H_4), 7.66 (s, 1H, vinylic H).

Anal. Calcd. for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.4; H, 6.9; N, 8.4.

Ethyl 1-Ethyl-1,4-dihydro-4-oxopyridazino[1,6-*a*]indole-3-carboxylate (**9c**).

A mixture of **8c** (6.3 g, 19 mmoles) and polyphosphoric acid (7 g) is heated at 120° until the starting material has disappeared (1/2 hour) on tlc (methanol-dichloromethane 5-95 v/v). The cooled reaction mixture is neutralized with 2*N* sodium hydroxide and the aqueous phase is extracted with dichloromethane. The organic phases are dried over sodium sulfate, decolorized with charcoal and evaporated to dryness. The residue is recrystallized from absolute ethanol giving yellow crystals of **9c** (2.6 g, 48%), mp 182°; tlc Rf 0.8 (dichloromethane-methanol-formic acid 95-5-1 drop v/v); ir (potassium bromide): 3450, 3206, 3061, 2986, 1710, 1638, 1595, 1484, 1435, 1420, 1385, 1310, 1295, 1237, 1193, 1150, 1092, 976, 926, 815, 743 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.41 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 1.59 (t, 3H, J = 7.1 Hz, NCH_2CH_3), 4.38 (q, 2H, J = 7.1 Hz, OCH_2), 4.73 (q, 2H, J = 7.1 Hz, NCH_2), 7.30-7.45 (m, 2H, H_7-H_8), 7.39 (br s, 1H, H_5), 7.72 (br d, 1H, $J_{9,8}$ = 8.7 Hz, H_9), 7.83 (br d, 1H, $J_{6,7}$ = 7.4 Hz, H_6), 8.39 (s, 1H, H_2).

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.2; H, 5.7; N, 9.6.

1-Ethyl-1,4-dihydro-4-oxopyridazino[1,6-*a*]indole-3-carboxylic Acid (**6c**).

A mixture of **9c** (3 g, 10.5 mmoles) in 15 ml of glacial acetic acid and 15 ml of water is refluxed during 5 days. After cooling,

the solid is filtered and recrystallized from a mixture of dioxane-acetonitrile (50-50 v/v) with decolorization with charcoal giving yellow crystals of **6c** (1.0 g, 37%), mp 233° dec; tlc Rf 0.2 (methanol-dichloromethane 5-95 v/v); ir (potassium bromide): 3450, 3054, 2925, 2853, 1709, 1630, 1565, 1501, 1478, 1416, 1302, 1256, 1193, 1158, 1088, 1042, 901, 822, 789, 737 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.51 (t, 3H, J = 7.0 Hz, CH_3), 5.00 (q, 2H, J = 7.0 Hz, CH_2), 7.37-7.57 (m, 2H, H_7-H_8), 7.48 (s, 1H, H_5), 7.96 (br d, 1H, $J_{6,7}$ = 7.8 Hz, H_6), 8.16 (br d, 1H, $J_{9,8}$ = 8.8 Hz, H_9), 9.00 (s, 1H, H_2), 14.1 (br s, 1H, COOH).

Anal. Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.6; H, 4.8; N, 10.9.

Diethyl [*N*-[1-(1*H*-Indolyl)](2,2,2-trifluoroethyl)amino]methylenepropanedioate (**8d**).

A mixture of compound **7d** (1 g, 4.6 mmoles) with diethyl ethoxymethylenemalonate (0.98 g, 4.5 mmoles) is heated under reduced pressure at 130° until the starting material has disappeared (3 hours) on tlc (pure dichloromethane). The reaction mixture is cooled, 150 ml of hot diisopropyl ether are added and the solution decolorized with charcoal. The solution is evaporated and the residue purified by chromatography on silica gel eluting with a mixture of methanol-dichloromethane (1-99 v/v). The fractions containing the first eluting compound are collected, concentrated to dryness and the solid recrystallized from petroleum ether giving **8d** (0.5 g, 28%), mp 84°; tlc Rf 0.4 (pure dichloromethane); ir (potassium bromide): 3450, 2985, 2915, 1725, 1701, 1630, 1615, 1451, 1297, 1223, 1205, 1167, 1140, 1130, 1085, 768 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.70 (t, 3H, J = 7.1 Hz, CH_3A), 1.22 (t, 3H, J = 7.1 Hz, CH_3B), 2.83-3.07 (m, part A of ABX_3, 1H, CH_2A), 3.41-3.66 (m, part B of ABX_3, 1H, CH_2A), 3.80-4.05 (m, part A of ABF_3, 1H, J_{HF} = 8.8 Hz, NCH_2), 4.10-4.34 (m, part B of ABF_3, 1H, J_{HF} = 8.8 Hz, NCH_2), 4.17 (q, 2H, J = 7.1 Hz, OCH_2B), 6.49 (d, 1H, $J_{3,2}$ = 3.3 Hz, H_3), 7.10 (d, 1H, $J_{2,3}$ = 3.3 Hz, H_2), 7.11-7.35 (m, 3H, H_5-H_6-H_7), 7.54 (s, 1H, vinylic H), 7.59 (d, 1H, $J_{4,5}$ = 7.6 Hz, H_4).

Anal. Calcd. for $C_{18}H_{19}F_3N_2O_4$: C, 56.25; H, 4.98; N, 7.29. Found: C, 56.3; H, 5.0; N, 7.2.

Ethyl 1-(2,2,2-Trifluoroethyl)-1,4-dihydro-4-oxopyridazino-[1,6-*a*]indole-3-carboxylate (**9d**).

A mixture of **8d** (46 g, 0.12 mole) and polyphosphoric acid (120 g) is heated at 100° under reduced pressure until the starting material has disappeared (1 hour) on tlc (dichloromethane-ethyl acetate 50-50 v/v). After cooling, 100 ml of 2-propanol is added and the solution poured into 500 ml of a saturated sodium bicarbonate solution. The aqueous phase is extracted with dichloromethane and the organic phases collected and evaporated to dryness. The residue is chromatographed on silica gel eluting with a mixture of ethyl acetate and *n*-heptane (50-50 v/v). The interesting fractions are collected, evaporated and recrystallized from a mixture of acetonitrile and ethyl acetate giving yellow crystals of **9d** (9.3 g, 23%), mp 185°; tlc Rf 0.7 (dichloromethane-ethyl acetate-methanol 47-47-6 v/v/v); ir (potassium bromide): 3133, 3058, 3002, 2981, 2928, 2911, 1721, 1619, 1603, 1410, 1340, 1313, 1294, 1267, 1254, 1235, 1194, 1175, 1160, 1088, 1052, 924, 899, 841, 827, 787, 730, 702, 662, 600 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.37 (t, 3H, J = 7.1 Hz, CH_3), 4.31 (q, 2H, J = 7.1 Hz, OCH_2), 5.17 (q, 2H, $J_{H,F}$ = 7.5 Hz, NCH_2), 7.28-7.49 (m, 2H, H_7-H_8), 7.31 (br s, 1H, H_5), 7.60 (br d, 1H, $J_{9,8}$ = 8.7 Hz, H_9), 7.82 (br d, 1H, $J_{6,7}$ = 8.0 Hz, H_6), 8.37 (s, 1H, H_2).

Anal. Calcd. for $C_{16}H_{13}F_3N_2O_3$: C, 56.81; H, 3.87; F, 16.85; N, 8.28. Found: C, 56.6; H, 3.8; F, 16.8; N, 8.2.

1-(2,2,2-Trifluoroethyl)-1,4-dihydro-4-oxopyridazino[1,6-*a*]-indole-3-carboxylic Acid (**6d**).

A sealed tube containing **9d** (3.38 g, 10 mmoles), 30 ml of distilled water and 30 ml of glacial acetic acid is heated at 120° until the starting ester has disappeared (100 hours) on tlc (dichloromethane-acetonitrile-ethyl acetate-methanol 50-30-10-10 v/v/v/v). The reaction mixture is evaporated to dryness and the residue recrystallized from acetonitrile with charcoal decolorization giving the acid **6d** (0.44 g, 14%), mp 254° dec; tlc Rf 0.7 (chloroform-ethyl acetate-methanol-acetonitrile 30-10-10-50 v/v/v/v); ir (potassium bromide): 3066, 2981, 2918, 1727, 1624, 1605, 1452, 1420, 1308, 1295, 1270, 1175, 1102, 826, 795, 737 cm^{-1}; ^1H nmr (DMSO-d_6): δ 6.11 (q, 2H, $J_{H,F}$ = 8.2 Hz, CH_2), 7.35-7.53 (m, 2H, H_7-H_8), 7.51 (s, 1H, H_5), 7.94 (br d, 1H, $J_{6,7}$ = 7.9 Hz, H_6), 8.25 (br d, 1H, $J_{9,8}$ = 8.6 Hz, H_9), 9.12 (s, 1H, H_2), 13.5 (br s, 1H, COOH).

Anal. Calcd. for $C_{14}H_9F_3N_2O_3$: C, 54.20; H, 2.92; F, 18.37; N, 9.03. Found: C, 54.2; H, 2.9; F, 18.3; N, 9.0.

Diethyl [*N*-[(3-Methyl-1-(1*H*-indolyl))]ethylamino]methylenepropanedioate (**8e**).

A mixture of **7e** (0.5 g, 2.87 mmoles) and diethyl ethoxymethylenemalonate (0.62 g, 2.87 mmoles) is heated at 130° under reduced pressure until the starting amine has disappeared (1 hour) on tlc (pure dichloromethane). The cooled reaction mixture is treated with a hot mixture of petroleum ether-diisopropyl ether (50-50 v/v), filtered hot with charcoal decolorization and the filtrate cooled. The white crystals are filtered and dried under reduced pressure giving **8e** (0.35 g, 35%), mp 63°; tlc Rf 0.3 (pure dichloromethane); ir (potassium bromide): 3450, 3058, 2985, 2934, 1727, 1700, 1632, 1452, 1360, 1291, 1258, 1218, 1189, 1140, 1102, 1065, 803, 795 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.73 (t, 3H, J = 7.1 Hz, OCH_2CH_3A), 1.12 (t, 3H, J = 7.2 Hz, NCH_2CH_3), 1.23 (t, 3H, J = 7.1 Hz, OCH_2CH_3B), 2.29 (d, 3H, $J_{CH3,H2}$ = 1Hz, CH_3), 2.95-3.05 (m, part A of ABX_3, 1H, OCH_2A), 3.45-3.55 (m, part B of ABX_3, 1H, OCH_2A), 3.65 (q, 2H, J = 7.2 Hz, NCH_2), 4.16 (q, 2H, J = 7.1 Hz, OCH_2B), 6.84 (d, 1H, $J_{H2,CH3}$ = 1Hz, H_2), 7.14-7.20 (m, 2H, H_5-H_6), 7.26 (dd, 1H, $J_{7,6}$ = 7.0 Hz, $J_{7,5}$ = 1.0 Hz, H_7), 7.53 (dd, 1H, $J_{4,5}$ = 6.5 Hz, $J_{4,6}$ = 1.0 Hz, H_4), 7.66 (s, 1H, vinylic H).

Anal. Calcd. for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 66.5; H, 7.2; N, 8.2.

Ethyl 1-Ethyl-1,4-dihydro-5-methyl-4-oxopyridazino[1,6-*a*]-indole-3-carboxylate (**9e**).

A mixture of compound **8e** (45.5 g, 0.132 mole) and polyphosphoric acid (90 g) is heated under reduced pressure at 60° during 3 hours (disappearance of starting material by tlc methanol-dichloromethane 5-95 v/v). The cooled mixture is neutralized with saturated sodium bicarbonate and extracted with dichloromethane. The organic extracts are collected and evaporated to dryness. The solid residue is recrystallized from acetonitrile giving **9e** (26.2 g, 66%), mp 170°; tlc Rf 0.5 (methanol-dichloromethane 10-90 v/v); ir (potassium bromide): 3450, 3137, 3062, 2983, 2915, 2853, 1709, 1638, 1605, 1439, 1420, 1360, 1312, 1285, 1236, 1206, 1179, 1115, 942, 795 cm^{-1};

^{1}H nmr (deuteriochloroform): δ 1.42 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 1.50 (t, 3H, J = 7.1 Hz, NCH_2CH_3), 2.83 (s, 3H, CH_3), 4.39 (q, 2H, J = 7.1 Hz, OCH_2), 4.65 (q, 2H, J = 7.1 Hz, NCH_2), 7.27-7.45 (m, 2H, H_7-H_8), 7.65 (dd, 1H, $J_{9,8}$ = 7.5 Hz, $J_{9,7}$ = 0.9 Hz, H_9), 7.82 (dd, 1H, $J_{6,7}$ = 7.3 Hz, $J_{6,8}$ = 1.0 Hz, H_6), 8.36 (s, 1H, H_2).

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.4; H, 6.1; N, 9.5.

1-Ethyl-1,4-dihydro-5-methyl-4-oxopyridazino[1,6-*a*]indole-3-carboxylic Acid (**6e**).

A mixture of **9e** (6.0 g, 20 mmoles) in 60 ml of glacial acetic acid and 60 ml of water is refluxed during 30 hours. To the reaction mixture is added 60 ml of water and the whole is cooled at +4°. The crystals formed are collected and dried. The solid is dissolved in 50 ml of 2*N* sodium hydroxide, diluted with 200 ml of water and washed with dichloromethane. The aqueous phase is acidified to *p*H 4 with acetic acid, cooled and the crystals collected giving after drying **6e** (1.8 g, 33%), mp 227° dec; tlc Rf 0.4 (methanol-dichloromethane 5-95 v/v); ir (potassium bromide): 3450, 3038, 2995, 2917, 1721, 1632, 1601, 1570, 1555, 1497, 1484, 1441, 1420, 1302, 1237, 1198, 1150, 1133, 930, 799, 756, 735 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.43 (t, 3H, J = 7.0 Hz, CH_3), 2.78 (s, 3H, CH_3), 5.00 (q, 2H, J = 7.0 Hz, CH_2), 7.37-7.56 (m, 2H, H_7-H_8), 7.93 (d, 1H, $J_{6,7}$ = 7.5 Hz, H_6), 8.10 (d, 1H, $J_{9,8}$ = 8.7 Hz, H_9), 8.89 (s, 1H, H_2), 13.0 (br s, 1H, COOH).

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.2; H, 5.2; N, 10.4.

Diethyl [*N*-[1-(1*H*-pyrrolo[2,3-*b*]pyridinyl)]ethylamino]methyleneпropanedioate (**8f**).

A mixture of **7f** (1.56 g, 9.6 mmoles) and diethyl ethoxymethylenemalonate (2.51 g, 11.6 mmoles, 1.2 equivalents) is heated at 130° under nitrogen until the starting amine disappeared (3 hours) on tlc (dichloromethane). The reaction mixture is chromatographed on silica gel eluting with a mixture of dichloromethane-ethyl acetate (80-20 v/v). The required fractions are collected, evaporated to dryness and the solid recrystallized from cyclohexane giving **8f** (2.46 g, 77%), mp 77°; tlc Rf 0.6 (methanol-dichloromethane 5-95 v/v); ir (potassium bromide): 3131, 3114, 2986, 2955, 2901, 1715, 1700, 1625, 1592, 1513, 1480, 1468, 1449, 1414, 1387, 1368, 1287, 1258, 1214, 1196, 1138, 1111, 1094, 1059, 1034, 893, 870, 803, 779, 768, 739 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 0.72 (t, 3H, J = 7.2 Hz, OCH_2CH_3A), 1.10 (t, 3H, J = 7.1 Hz, NCH_2CH_3), 1.18 (t, 3H, J = 7.1 Hz, OCH_2CH_3B), 2.93 (br s, part A of ABX_3, 1H, OCH_2A), 3.47 (br s, part B of ABX_3, 1H, OCH_2A), 3.78 (br s, 2H, NCH_2), 4.11 (q, 2H, J = 7.1 Hz, OCH_2B), 6.45 (d, 1H, $J_{3,2}$ = 3.8 Hz, H_3), 7.13 (dd, 1H, $J_{5,4}$ = 7.9 Hz, $J_{5,6}$ = 4.8 Hz, H_5), 7.18 (d, 1H, $J_{2,3}$ = 3.8 Hz, H_2), 7.70 (s, 1H, vinylic H), 7.89 (dd, 1H, $J_{4,6}$ = 1.5 Hz, $J_{4,5}$ = 7.9 Hz, H_4), 8.38 (dd, 1H, $J_{6,4}$ = 1.5 Hz, $J_{6,5}$ = 4.8 Hz, H_6).

Anal. Calcd. for $C_{17}H_{21}N_3O_4$: C, 61.62; H, 6.39; N, 12.68. Found: C, 61.7; H, 6.4; N, 12.7.

Ethyl 1-Ethyl-1,4-dihydro-4-oxopyrido[3',2':4,5]pyrrolo[1,2-*b*]-pyridazine-3-carboxylate (**9f**).

A mixture of compound **8f** (22.4 g, 67.6 mmoles) and polyphosphoric acid (108 g) is heated under reduced pressure at 100° until the starting material has disappeared (6 hours) on tlc (methanol-acetonitrile-dichloromethane 5-5-90 v/v/v). The reaction mixture is treated with a saturated sodium bicarbonate solution and the aqueous phase extracted with dichloromethane. The solvant is distilled under reduced pressure and the residue treated with the minimum of hot diethylether and cooled. The crystals are collected and recrystallized from absolute ethanol giving light colored crystals of **9f** (3.0 g, 15%), mp 148°; tlc Rf 0.5 (dichloromethane-methanol-acetonitrile 90-5-5 v/v/v); ir (potassium bromide): 3066, 2971, 2922, 1667, 1645, 1609, 1585, 1560, 1482, 1453, 1405, 1372, 1314, 1210, 1029, 793, 758 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.42 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 1.57 (t, 3H, J = 7.0 Hz, NCH_2CH_3), 4.39 (q, 2H, J = 7.1 Hz, OCH_2), 5.27 (q, 2H, J = 7.0 Hz, NCH_2), 7.29 (dd, 1H, $J_{7,6}$ = 8.0 Hz, $J_{7,8}$ = 4.5 Hz, H_7), 7.30 (s, 1H, H_5), 8.13 (dd, 1H, $J_{6,8}$ = 1.5 Hz, $J_{6,7}$ = 8.0 Hz, H_6), 8.42 (s, 1H, H_2), 8.47 (dd, 1H, $J_{8,6}$ = 1.5 Hz, $J_{8,7}$ = 4.5 Hz, H_8).

Anal. Calcd. for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.9; H, 5.2; N, 14.7.

1-Ethyl-1,4-dihydro-4-oxopyrido[3',2':4,5]pyrrolo[1,2-*b*]pyridazine-3-carboxylic Acid (**6f**).

A mixture of ester **9f** (2.0 g, 7 mmoles) and sodium hydroxide (2.8 g, 70 mmoles) in 20 ml of water, 20 ml of ethanol and 20 ml of dichloromethane is heated at 40° until the ester has disappeared (2.5 hours) on tlc (dichloromethane-methanol-acetonitrile 90-5-5 v/v/v). The solution is cooled and acidified with acetic acid. The solid is collected and dried giving **6f** (1.2 g, 66%), mp 251° dec; tlc Rf 0.3 (dichloromethane-methanol-acetonitrile 90-5-5 v/v/v); ir (potassium bromide): 3450, 3042, 2925, 2853, 1711, 1626, 1561, 1495, 1482, 1441, 1416, 1395, 1312, 1266, 1191, 1164, 1040, 915, 797, 758 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.50 (t, 3H, J = 6,9 Hz, CH_3), 5.41 (q, 2H, J = 6.9 Hz, CH_2), 7.43 (s, 1H, H_5), 7.52 (dd, 1H, $J_{7,6}$ = 8.1 Hz, $J_{7,8}$ = 4.5 Hz, H_7), 8.43 (br d, 1H, $J_{6,8}$ = 1.4 Hz, $J_{6,7}$ = 8.1 Hz, H_6), 8.66 (dd, 1H, $J_{8,6}$ = 1.4 Hz, $J_{8,7}$ = 4.5 Hz, H_8), 9.06 (s, 1H, H_2), 13.3 (br s, 1H, COOH).

Anal. Calcd. for $C_{13}H_{11}N_3O_3$: C, 60.70; H, 4.31; N, 16.33. Found: C, 60.5; H, 4.3; N, 16.5.

1-Ethyl-1,4-dihydro-4-oxopyridazino[1,6-*a*]indole (**12**).

A mixture of compound **9c** (0.5 g, 1.75 mmoles) in 5 ml of trifluoroacetic acid and 5 ml of distilled water is heated under reflux during 10 hours until the starting material has disappeared on tlc (methanol-dichloromethane 10-90 v/v). The reaction mixture is evaporated to dryness under reduced pressure and chromatographed on silica gel (methanol-dichloromethane 1-99 v/v). The interesting fractions are collected giving crystals of the wanted compound (0.2 g, 54%). An analytical sample was obtained by recrystallization from a mixture of diisopropylether and petroleum ether, mp 118°; tlc Rf 0.5 (methanol-dichloromethane 10-90 v/v); ir (potassium bromide): 3430, 3110, 3002, 2995, 1609, 1595, 1435, 1330, 1310, 1274, 1250, 1191, 1146, 840, 739 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.21 (t, 3H, J = 7.1 Hz, CH_3), 4.47 (q, 2H, J = 7.1 Hz, CH_2), 6.00 (d, 1H, $J_{3,2}$ = 7.9 Hz, H_3), 7.26 (s, 1H, H_5), 7.29-7.39 (m, 2H, H_7-H_8), 7.45 (d, 1H, $J_{2,3}$ = 7.9 Hz, H_2), 7.68 (br d, 1H, $J_{6,7}$ = 8.2 Hz, H_6), 7.85 (br d, 1H, $J_{9,8}$ = 7.3 Hz, H_9).

Anal. Calcd. for $C_{13}H_{12}N_2O$: C, 73.57; H, 5.70; N, 13.20. Found: C, 73.4; H, 5.7; N, 13.3.

Ethyl 4-Ethoxypyridazino[1,6-*a*]indole-3-carboxylic Acid (**13**).

A mixture of compound **9a** (2.5 g, 9.8 mmoles) and potas-

sium carbonate (2.0 g, 14.5 mmoles) in 50 ml dimethylformamide is heated at 80° during half an hour and then 2.3 ml of iodoethane (4.5 g, 29 mmoles) are added and the temperature maintained at 80° during 24 hours. During this time, potassium carbonate (2.0 g, 14.5 mmoles) and 2.3 ml of iodoethane (4.5 g, 29 mmoles) are added twice. The starting material has then disappeared on tlc (methanol-dichloromethane 5-95 v/v). The reaction mixture is evaporated under reduced pressure and the residue chromatographed on silica gel (dichloromethane). The interesting fractions after evaporation to dryness give the *O*-alkylated compound **13** (2.05 g, 73%). An analytical sample was obtained by recrystallization from absolute ethanol, mp 95°; tlc Rf 0.6 (dichloromethane); ir (potassium bromide): 3390, 3134, 2977, 2910, 1673, 1601, 1515, 1475, 1428, 1385, 1337, 1264, 1225, 1163, 1150, 1106, 1019, 978, 957, 897, 820, 779, 751, 731 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.42 (t, 3H, J = 7.1 Hz, CH_3), 1.55 (t, 3H, J = 7.0 Hz, OCH_2CH_3), 4.40 (q, 2H, J = 7.1 Hz, CH_2), 4.64 (q, 2H, J = 7.0 Hz, OCH_2), 7.10 (d, 1H, $J_{5,9}$ = 0.6 Hz, H_5), 7.37-7.45 (m, 2H, H_7-H_8), 7.81 (br dd, 1H, $J_{9,8}$ = 6.9 Hz, $J_{9,7}$ = 2.2 Hz, H_9), 8.16 (br dd, 1H, $J_{6,7}$ = 8.5 Hz, $J_{6,8}$ = 1.4 Hz, H_6), 8.45 (1H, s, H_2).

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.8; H, 5.8; N, 9.9.

4-Ethoxypyridazino[1,6-*a*]indole-3-carboxylic Acid (**14**).

A mixture of ester **13** (10.3 g, 36 mmoles) and 91 ml of aqueous 2*N* sodium hydroxide in 145 ml of ethanol is heated under reflux until the solid has dissolved. After cooling, 91 ml of 2*N* hydrochloric acid are slowly added maintaining the temperature under +5°. The solid is filtered and recrystallized twice from dioxane-water with charcoal decolorization. The solid dried under reduced pressure gives yellow crystals of the desired acid **14** (3.7 g, 40%), mp 222°; tlc Rf 0.4 (methanol-dichloromethane 5-95 v/v); ir (potassium bromide): 3450, 3054, 2967, 2932, 1690, 1675, 1596, 1495, 1461, 1420, 1387, 1326, 1256, 1135, 1104, 1021, 951, 778 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.44 (t, 3H, J = 7.0 Hz, CH_3), 4.64 (q, 2H, J = 7.0 Hz, CH_2), 7.26 (br s, 1H, H_5), 7.39-7.46 (m, 2H, H_7-H_8), 7.89 (dd, 1H, $J_{6,7}$ = 8.8 Hz, $J_{6,8}$ = 2.1 Hz, H_6), 8.10 (dd, 1H, $J_{9,7}$ = 2.2 Hz, $J_{9,8}$ = 8.8 Hz, H_9), 8.43 (s, 1H, H_2), 13.2 (s, 1H, COOH).

Anal. Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.5; H, 4.8; N, 10.8.

Diethyl [*N*-[1-(1*H*-Indolyl)]ethylamino]methylenepropanedioate (**8c**) and Diethyl 2-Ethyl-2-[1-(1*H*-indolyl)aminomethylene]propanedioate (**15**).

A mixture of compound **8a** (1.0 g, 3.3 mmoles), potassium carbonate (0.5 g, 3.6 mmoles, 1.1 equivalents) in 20 ml of dimethylformamide is heated at 75° during half an hour. Iodoethane (2.05 g, 13.2 mmoles, 4 equivalents) is then added and the reaction mixture is maintained at 75° until the starting material has disappeared (2 hours) on tlc (dichloromethane). The reaction mixture is evaporated to dryness under reduced pressure, added 100 ml of water and extracted with dichloromethane. The organic phases are dried over sodium sulfate and evaporated to dryness giving a oil chromatographed on silica gel (dichloromethane).

The first fractions after evaporation yield compound **15** (0.41 g, 37%), oil; tlc Rf 0.6 (dichloromethane); ir (potassium bromide): 3139, 3058, 2985, 2942, 2907, 1737, 1457, 1370, 1299, 1247, 1214, 1131, 1098, 1027, 967, 909, 863, 747, 708 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.99 (t, 3H, J = 7.4 Hz, CCH_2CH_3), 1.26 (t, 6H, J = 7.1 Hz, $2CH_3$), 2.41 (q, 2H, J = 7.4 Hz, C-CH_2), 4.26 (q, 4H, J = 7.1 Hz, $2CH_2$), 6.60 (d, 1H, $J_{3,2}$ = 3.6 Hz, H_3), 7.08-7.29 (m, 2H, H_5-H_6), 7.53-7.67 (m, 3H, H_2-H_4-H_7), 8.17 (s, 1H, vinylic H).

Anal. Calcd. for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.4; H, 6.7; N, 8.7.

The second eluting compound is **8c** (0.54 g, 50%) having the characteristics described before.

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