Synthesis of 1,4-Dihydro-4-oxopyrrolo[1,2-*b*]pyridazine-3-carboxylic Acids and 1,4-Dihydro-4-oxoimidazo[1,5-*b*]pyridazine-3-carboxylic Acids as Potential Antibacterial Agents

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To check the antibacterial potential of two families of aza analogues of the quinolones, 1,4-dihydro-4-oxopyrrolo[1,2-*b*]pyridazine-3-carboxylic acids and 1,4-dihydro-4-oxoimidazo[1,5-*b*]pyridazine-3-carboxylic acids, we have prepared a few derivatives in theses families using *N*-aminopyrrole and *N*-aminoimidazole derivatives as starting building blocks and the classical pathways of the quinolone series. The compounds showed no interesting antibacterial activity.

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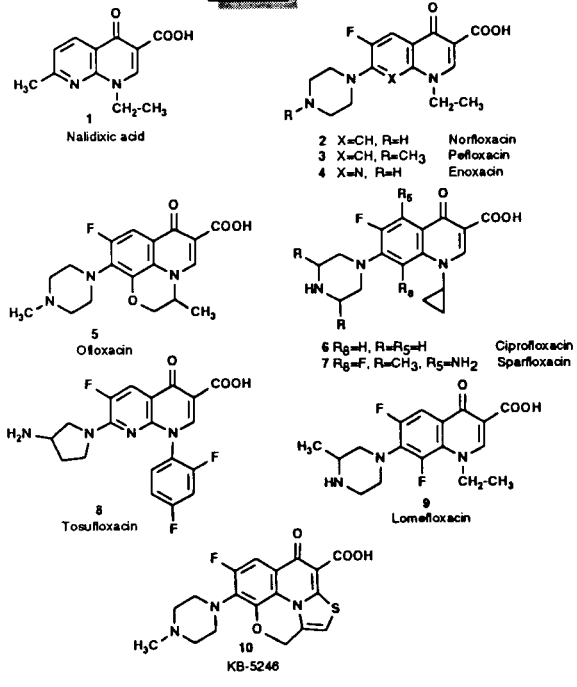
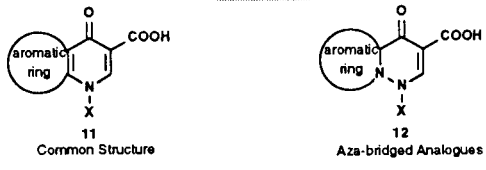
Since the discovery of nalidixic acid **1** (Figure 1) [1], the quinolones have gained a full place in the chemotherapeutic arsenal with compounds like norfloxacin **2** [2], pefloxacin **3** [3], enoxacin **4** [4], ofloxacin **5** [5], ciprofloxacin **6** [6], sparfloxacin **7** [7], tosufloxacin **8** [8], lomefloxacin **9** [9] and KB-5246 **10** [10], only mentioning some of the most interesting molecules of this family. The activity of the compounds is explained by inhibition of DNA-gyrase [11a-b] an essential enzyme for DNA replication in bacteria.

Figure 1



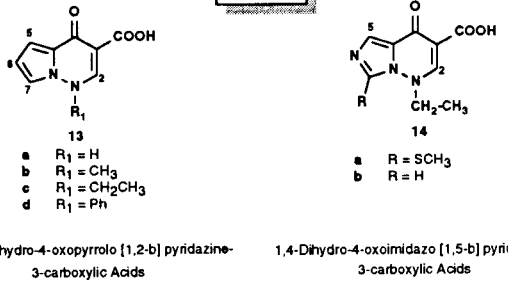
Many analogues have been prepared [12a-h] needing always the common structure **11** (Figure 2) to express any measurable activity: such as the 1,4-dihydro-4-pyridone-3-carboxylic acid moiety with an annelated aromatic ring like benzene, pyridine (compounds of Figure1), thiophene [13] or pyrrole [14a-g].

Figure 2



However, to our knowledge, the aza-bridged analogues of general formula **12** have never been prepared and tested. We decided to synthetize such compounds in the two families (Figure 3) of the 1,4-dihydro-4-oxopyrrolo[1,2-*b*]pyridazine-3-carboxylic acids **13a-d** and the 1,4-dihydro-4-oxoimidazo[1,5-*b*]pyridazine-3-carboxylic acids **14a-b** to check their potential antibacterial activity.

Figure 3



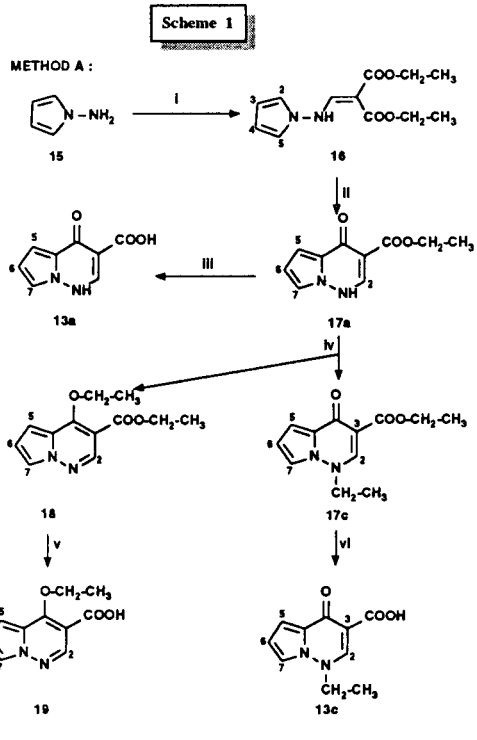
Chemistry.

a) 1,4-Dihydro-4-oxopyrrolo[1,2-*b*]pyridazine-3-carboxylic Acids **13a-d**.

The classical synthetic route used for the preparation of

quinolones (method A - Scheme 1) was first tried starting from the known 1*H*-pyrrol-1-amine **15** [15], which was condensed with diethyl ethoxymethylenemalonate (EMME) at 125° to yield product **16** (74%). Cyclisation at 220° using Dowtherm A (mixture of diphenyl and diphenyl oxide 26.5%-73.5% w/w) as solvent afforded ethyl 1,4-dihydro-4-oxopyrrolo[1,2-*b*]pyridazine-3-carboxylate **17a** in 58% yield. The corresponding acid **13a** was obtained by saponification of this ester **17a** with aqueous 2*N* sodium hydroxide in ethanol and neutralization of the formed sodium salt but in very poor yield (3% isolated and much tarry material). The alkylation of **17a** under the conditions preparing the sodium salt with sodium hydride in dry dimethylformamide and then heating with iodoethane gave a mixture of the *O*-alkylated product **18** with the wanted *N*-alkylated product **17c**. The products were separated by chromatography but the *N*-alkylated compound **17c** (13% isolated) was the minor product (average isolated ratio of 1:3 in favour of **18**). This can be probably explained by the unfavored pyridone like structure of **17a** compared with the 4-hydroxy

Scheme 1

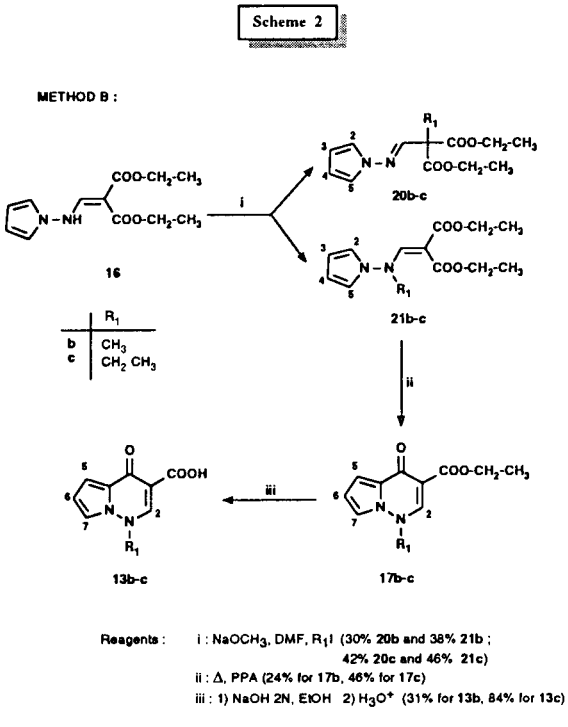


contribution leading to **18** in opposition to the preparation of the known active quinolones of Figure 1 where the *O*-alkylated compound only appears in traces.

Structural assignment of the *O*-alkylated compound **18** and the *N*-alkylated compound **17c** was easily accomplished by recording the proton undecoupled ^{13}C nmr spectra of the two compounds. Compound **17c** shows $^{3}J_{C-H}$ couplings between the NCH_2 carbon and the H2 proton of the ring and reciprocally between the C-2 carbon of the ring and the NCH_2 protons. These couplings are non-existant for compound **18**. This assignment was also confirmed by the classical chemical ethoxy group functional determination by the method of Elek [16]. The assignment of the ethyl groups was accomplished by classical two dimensional ^{1}H-^{13}C nmr correlation. Conversion of the ethyl carboxylic esters **18** and **17c** to their corresponding acids was achieved by saponification with 2*N* sodium hydroxide and neutralization giving respectively **19** in 70% yield and **13c** in 84% yield.

To avoid the chromatographic separation of **18** and **17c** but also to get access to **17c** with better yields, we tried the alkylation before the cyclisation on compound **16** (method B - Scheme 2). In this case, we also obtained a mixture of the *C*-alkylated products **20b-c** with the wanted *N*-alkylated products **21b-c** respectively. The compounds are easily separated by chromatography.

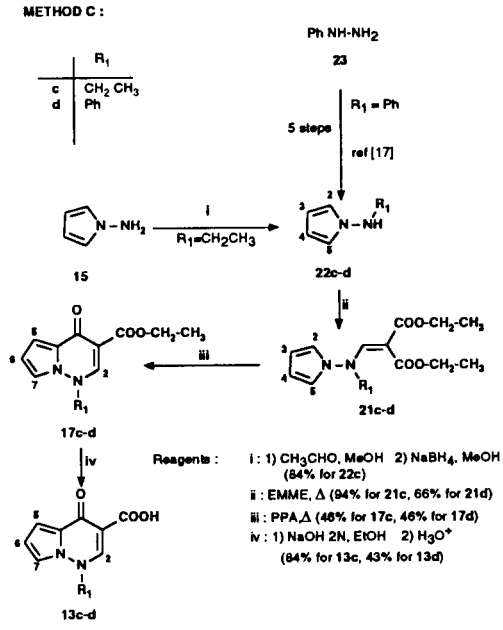
Scheme 2



Structural assignment for the *C*-alkylated compounds **20b-c** and the *N*-alkylated compounds **21b-c** could be easily deduced from the chemical shifts in ^{1}H nmr of the new introduced chain (lower shielding for the *N*-alkylated derivative). The mixture was obtained in a ratio of 1 to 1 representing only a slight improvement in comparison with method A. Cyclisation to the ethyl esters was

accomplished by heating in polyphosphoric acid and giving compounds **17b** and **17c** in 24% and 46% yield respectively. Saponification of **17b** and **17c** by the usual way gave the acids **13b** and **13c** in 31% and 84% yield respectively. To overcome the separation problem, we finally accomplished the alkylation before condensation with EMME (method C -Scheme 3).

Scheme 3

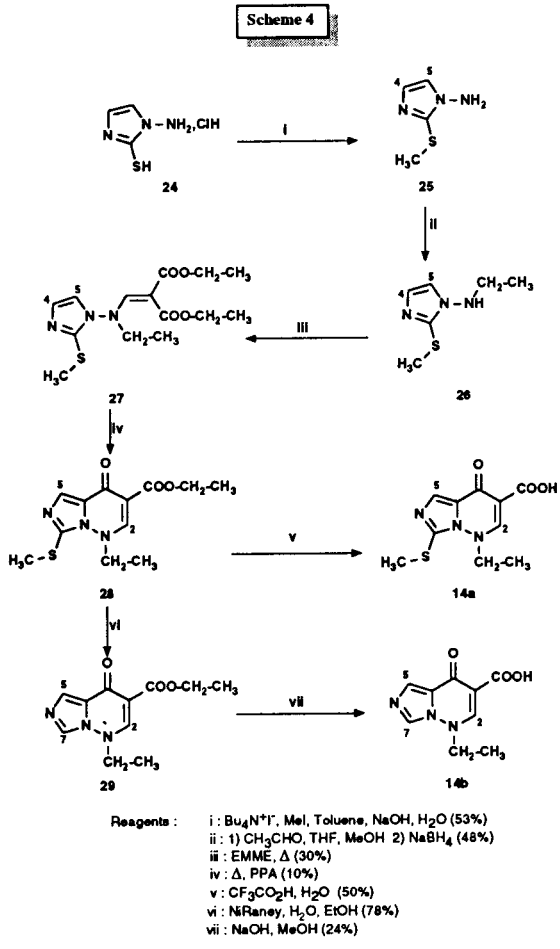


Finally, 1*H*-pyrrol-1-amine **15** was condensed with acetaldehyde to give the intermediate imine (not isolated) which was reduced with sodium borohydride to the *N*-ethyl-1*H*-pyrrol-1-amine **22c** in 84% overall yield. Compound **22d** is known and was prepared in 5 steps by the described method [17] starting from phenylhydrazine **23** (Scheme 3). The substituted amines **22c** and **22d** were condensed to the EMME-adducts **21c** and **21d** in 94% and 66% yield respectively. The cyclisations performed by heating in polyphosphoric acid gave compounds **17c** and **17d** in 46% yield both. The saponification and neutralisation occurred without problems and gave compounds **13c** (84%) and **13d** (43%). The 3 methods described give access to all the usual types of substituents on the nitrogen of the 1,4-dihydro-4-oxopyrrolo[1,2-*b*]-pyridazine-3-carboxylic acids.

b) 1,4-Dihydro-4-oxoimidazo[1,5-*b*]pyridazine-3-carboxylic Acids **14a-b**.

Taking benefit of our previous experience, we took method C for the preparation of these derivatives (Scheme 4). The starting material was 2-mercapto-1*H*-imidazol-1-amine, hydrochloride **24** described in a patent [18]. Methylation to **25** was achieved under phase-transfer conditions in 53% yield. The characteristics of **25** were in agreement with these described in the literature [19] for the product obtained by an other synthetic route. Treatment with acetaldehyde in methanol followed by *in-situ* reduction of the intermediate imine gave **26** in 48% yield. The EMME condensation step to **27** gave only a poor yield (30%) because of degradation. The ^1H nmr spectrum of **27** indicates for one CH_2 an AB feature which was established by ^1H-^1H correlation and ^1H-^{13}C correlation to one of the $COOCH_2CH_3$ groups and not to the NCH_2CH_3 group. This can be explained by the asymmetry of the imidazole moiety in comparison with the symetrical pyrrole ring of the family described before. The cyclisation to **28** in polyphosphoric acid with 10% yield confirmed a greater thermal instability of this family. Removal of the methylthio group was achieved by refluxing an aqueous ethanolic solution of compound **28** with Raney Nickel (78% yield). Cleavage of the esters was possible with aqueous trifluoroacetic acid, giving **14a** (50%) or by saponification with aqueous sodium hydroxide for **14b** (24% yield).

Scheme 4



Microbiological Results.

Compounds **13a-d** and **14a-b** 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 *Bacteroides fragilis*, *Bacteroides thetaiotaom*, *Fusobacterium varium*, and *Propionibacterium acnes*.

None of the compounds showed a minimum inhibitory concentration of the level of nalidixic acid and therefore the study of these families was discontinued due to the emergence of other more attractive families.

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 bank and are uncorrected. The nmr spectra were recorded on a Brucker 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*H*-Pyrrol-1-amine **15**, *N*-phenyl-1*H*-pyrrol-1-amine **22d** and 2-mercapto-1*H*-imidazol-1-amine, hydrochloride **24** were prepared according to the procedures described in the literature [15], [17] and [18] respectively and showed the analytical characteristics already described.

Diethyl (1-Pyrrolyl)aminomethylenepropanedioate (**16**).

A mixture of **15** (2.05 g, 25 mmoles) and diethyl ethoxymethylenemalonate (6.48 g, 30 mmoles, 1.2 equivalents) is heated at 125° during 45 minutes, while the ethanol formed is distilled off. The mixture is concentrated under vacuum. The residue treated with 15 ml of hot carbon tetrachloride is decolorized with charcoal, filtered and then 10 ml of *n*-hexane are added. The solution is cooled at +4° and the white crystals of **16** are collected (4.64 g, 74%), mp 111°; tlc Rf 0.3 (pure dichloromethane); ir (potassium bromide): 3272, 3141, 2983, 2909, 1727, 1657, 1619, 1428, 1385, 1347, 1231, 1092, 1065, 1030, 973, 867, 799, 746 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.27 (t, 3H, J = 7.1 Hz, CH_3A), 1.36 (t, 3H, J = 7.1 Hz, CH_3B), 4.19 (q, 2H, J = 7.1 Hz, CH_2A), 4.28 (q, 2H, J = 7.1 Hz, CH_2B), 6.17 (t, 2H, J = 2.2 Hz, H_3-H_4), 6.79 (t, 2H, J = 2.2 Hz, H_2-H_5), 8.12 (d, 1H, J = 11 Hz, vinylic H), 10.85 (d, 1H, J = 11 Hz, NH).

Anal. Calcd. for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.10. Found: C, 57.1; H, 6.5; N, 11.1.

Ethyl 1,4-Dihydro-4-oxopyrrolo[1,2-*b*]pyridazine-3-carboxylate (**17a**).

A mixture of **16** (15.1 g, 60 mmoles) in Dowtherm-A (15.1 g) is heated at 220° during 2 hours. The disappearance of the starting material is followed by tlc (dichloromethane) and the ethanol formed is distilled off. The mixture is then cooled, triturated with *n*-hexane and the crystals filtered and chromatographed on silica gel (dichloromethane). The interesting fractions are collected and recrystallized from cyclohexane giving **17** as a pale yellow solid (7.2 g, 58%), mp 99°; tlc Rf 0.8 (dichloromethane); ir (potassium bromide): 3436, 3116, 2996, 1652, 1509, 1439, 1412, 1330, 1289, 1261, 1196, 1115, 1066, 1032, 965, 870, 830, 810, 784, 766 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.41 (t, 3H, J = 7.1 Hz, CH_3), 4.41 (q, 2H, J = 7.1 Hz, CH_2), 6.73-6.77 (m, 1H, $J_{6,5}$ = 4,3 Hz, $J_{6,7}$ = 2,5 Hz, H_6), 6.93-6.96 (m, 1H, $J_{5,6}$ = 4.3 Hz, $J_{5,7}$ = 1.3 Hz, H_5), 7 71-7 73 (m 1H, $J_{7,5}$ = 1.3 Hz, $J_{7,6}$ = 2.5 Hz, H_7), 8.26 (s, 1H, H_2), 12.3 (br s, 1H, OH).

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.2; H, 4.8; N, 13.6.

1,4-Dihydro-4-oxopyrrolo[1,2-*b*]pyridazine-3-carboxylic Acid (**13a**).

A mixture of **17a** (4.12 g, 20 mmoles) in 200 ml of ethanol is added 100 ml of concentrated sodium hydroxide (50% w/w) and maintained at room temperature until the starting material has disappeared (16 hours) on tlc (dichloromethane-methanol 90-10 v/v). After careful acidification on cooling with hydrochloric acid, the solid which formed is filtered and the aqueous phase extracted with dichloromethane. The organic phase is concentrated and the former filtered solid added. This mixture is treated with 0.5 litres of hot diisopropyl ether, filtered and the filtrate concentrated below 40° under vacuum. The residual heat unstable yellow solid is **13a** (0.12 g, 3%), mp 151° dec; tlc Rf 0.1 (methanol-dichloromethane-acetic acid 10-90-0.1 v/v/v); ir (potassium bromide): 3444, 2927, 2857, 1638, 1530, 1509, 1445, 1328, 1260, 1112, 1067, 948, 739, 714 cm^{-1}; ^1H nmr (DMSO-d_6): δ 5.00 (br s, 2H, OH and COOH), 6.79-6.82 (m, 1H, $J_{6,5}$ = 4.4 Hz, $J_{6,7}$ = 2.6 Hz, H_6), 6.88-6.91 (m, 1H, $J_{5,6}$ = 4.4 Hz, $J_{5,7}$ = 1.6 Hz, H_5), 7.90-7.92 (m, 1H, $J_{7,6}$ = 2.6 Hz, $J_{7,5}$ = 1.6 Hz, H_7), 8.27 (s, 1H, H_2).

Anal. Calcd. for $C_8H_6N_2O_3$: C, 53.94; H, 3.39; N, 15.72. Found: C, 53.8; H, 3.4; N, 15.5.

Ethyl 1-Ethyl-1,4-dihydro-4-oxopyrrolo[1,2-*b*]pyridazine-3-carboxylate (**17c**) and Ethyl 4-Ethoxypyrrolo[1,2-*b*]pyridazine-3-carboxylate (**18**).

Method A.

A mixture of compound **17a** (51.5 g, 0.25 mole) in 620 ml of dry dimethylformamide under nitrogen is treated with small portions of sodium hydride 60% dispersed in oil (15 g, 0.38 mole) maintaining the temperature under 20°. The solution is heated to 50° and then 60 ml of iodoethane (117 g, 0.75 mole) are added within an hour. The reaction mixture is maintained at 50° following the starting material disappearance by tlc (dichloromethane). After 92 hours, the reaction mixture is added 22 ml of acetic acid under cooling and 100 ml of water. After evaporation to dryness under reduced pressure, the residue is chromatographed on silica gel (dichloromethane). The fractions containing the first eluting compound are evaporated yielding after recrystallization from *n*-hexane **18** (21.3 g, 36%), mp 76°; tlc Rf 0.4 (dichloromethane); ir (potassium bromide): 3154, 3118, 2992, 2917, 1673, 1609, 1519, 1441, 1385, 1287, 1262,

1187, 1083, 1032, 780, 731 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.38 (t, 3H, J = 7.1 Hz, $COOCH_2CH_3$), 1.51 (t, 3H, J = 7.0 Hz, OCH_2CH_3), 4.35 (q, 2H, J = 7.1 Hz, $COOCH_2$), 4.61 (q, 2H, J = 7.0 Hz, OCH_2), 6.78 (dd, 1H, $J_{6,5}$ = 4.5 Hz, $J_{6,7}$ = 2.6 Hz, H_6), 6.90 (dd, 1H, $J_{5,6}$ = 4.5 Hz, $J_{5,7}$ = 1.6 Hz, H_5), 7.75 (dd, 1H, $J_{7,5}$ = 1.6 Hz, $J_{7,6}$ = 2.6 Hz, H_7), 8.43 (s, 1H, H_2); ^{13}C nmr proton undecoupled (deuteriochloroform): δ 14.3 (q of t, $^1J_{CH}$ = 127 Hz, $^2J_{CH}$ = 2.4 Hz, $COOCH_2CH_3$), 15.7 (q of t, $^1J_{CH}$ = 127 Hz, $^2J_{CH}$ = 2.4 Hz, OCH_2CH_3), 60.7 (t of q, $^1J_{CH}$ = 147 Hz, $^2J_{CH}$ = 4.0 Hz, $COOCH_2$), 70.4 (t of q, $^1J_{CH}$ = 146 Hz, $^2J_{CH}$ = 4.0 Hz, OCH_2), 101.1 (d, $^2J_{CH}$ = 4.8 Hz, C_3), 104.2 (d of dd, $^1J_{CH}$ = 176 Hz, $^2J_{CH}$ = 7.7 Hz, $^3J_{CH}$ = 3.8 Hz, C_5), 112.9 (d of dd, $^1J_{CH}$ = 172 Hz, $^2J_{CH}$ = 7.5 Hz, $^3J_{CH}$ = 3.0 Hz, C_6), 120.2 (d of t, $^1J_{CH}$ = 190 Hz, $^2J_{CH}$ = 7.5 Hz, C_7), 121.0 (dd, 2^2J_{CH} = 6.5 Hz, C_{4a}), 144.0 (d, $^1J_{CH}$ = 185 Hz, C_2), 159.6 (d,$^3J_{CH}$ = 5.5 Hz, C_4), 164.2 (dd, 2^3J_{CH} = 3.0 Hz, COO).

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.4 ; H, 6.1; N, 11.9.

The fractions containing the second eluting compound are evaporated and give after recrystallization from a mixture of 2-propanol and *n*-hexane compound **17c** (7.5 g, 13%), mp 134°; tlc Rf 0.2 (methanol-dichloromethane 5-95 v/v); ir (potassium bromide): 3450, 3141, 2981, 2948, 2902, 1711, 1627, 1409, 1384, 1312, 1281, 1231, 1194, 1108, 1034, 878, 784, 726 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.33 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 1.56 (t, 3H, J = 7.2 Hz, NCH_2CH_3), 4.28 (q, 2H, J = 7.1 Hz, OCH_2), 4.29 (q, 2H, J = 7.2 Hz, NCH_2), 6.49 (dd, 1H, $J_{6,5}$ = 4,4 Hz, $J_{6,7}$ = 2.9 Hz, H_6), 6.98 (dd, 1H, $J_{5,6}$ = 4.4 Hz, $J_{5,7}$ = 1.7 Hz, H_5), 7.14 (dd, 1H, $J_{7,5}$ = 1.7 Hz, $J_{7,6}$ = 2.9 Hz, H_7), 8.25 (s, 1H, H_2); ^{13}C nmr proton undecoupled (deuteriochloroform): δ 12.3 (q of t, $^1J_{CH}$ = 128 Hz, $^2J_{CH}$ = 2.5 Hz, NCH_2CH_3), 14.3 (q of t,$^1J_{CH}$ = 126 Hz, $^2J_{CH}$ = 2.5 Hz, $COOCH_2CH_3$), 49.8 (t of dq, $^1J_{CH}$ = 141 Hz, $^2J_{CH}$ = 4.0 Hz, J_{AB} = 4.0 Hz, NCH_2), 60.5 (t of q, $^1J_{CH}$ = 147 Hz, $^2J_{CH}$ = 4.1 Hz, $COOCH_2$), 103.2 (s, C_3), 106.5 (d of dd, $^1J_{CH}$ = 177 Hz, $^2J_{CH}$ = 6.9 Hz, $^3J_{CH}$ = 3.8 Hz, C_5), 110.2 (d of dd, $^1J_{CH}$ = 174 Hz, $^2J_{CH}$ = 5.0 Hz, $^3J_{CH}$ = 4.4 Hz, C_6), 111.2 (d of t, $^1J_{CH}$ = 189 Hz, $^2J_{CH}$ = 8.5 Hz, C_7), 129.9 (d of dd, $^2J_{CH}$ = 7.5 Hz, 2^3J_{CH} = 4.2 Hz, C_{4a}), 142. 1 (d of t, $^1J_{CH}$ = 178 Hz, $^3J_{CH}$ = 3.3 Hz, C_2), 164.9 (q, $^3J_{CH}$ = 3.0 Hz, $^3J_{CH}$ = 3.5 Hz, COO), 167.6 (d, $^3J_{CH}$ = 6.5 Hz, CO).

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.3 ; H, 6.1; N, 12.1.

4-Ethoxypyrrolo[1,2-*b*]pyridazine-3-carboxylic Acid (**19**).

A mixture of **18** (1.4 g, 6 mmoles) in 15 ml of 2*N* sodium hydroxide (30 mmoles) and 1.5 ml of ethanol are refluxed during 15 minutes. The cooled solution is filtered and the filtrate acidified to *p*H 2-3 with 15 ml of 2*N* hydrochloric acid. The solid is filtered and recrystallized from aqueous ethanol giving **19** (0.86 g, 70%), mp 176° dec; tlc Rf 0.3 (methanol-dichloromethane 5-95 v/v); ir (potassium bromide): 3448, 3152, 2977, 2853, 1696, 1607, 1497, 1431, 1382, 1347, 1260, 1216, 1205, 1083, 1048, 1017, 797, 778, 722 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.62 (t, 3H, J = 7.0 Hz, CH_3), 4.86 (q, 2H, J = 7.0 Hz, CH_2), 6.85-6.89 (m, 1H, $J_{6,5}$ = 4.5 Hz, $J_{6,7}$ = 2.5 Hz, H_6), 6.98-7.02 (m, 1H, $J_{5,6}$ = 4.5 Hz, $J_{5,7}$ = 1.3 Hz, H_5), 7.84-7.86 (m, 1H, $J_{7,6}$ = 2.5 Hz, $J_{7,5}$ = 1.3 Hz, H_7), 8.57 (s, 1H, H_2), COOH not visible; ^1H nmr (DMSO-d_6): δ 1.39 (t, 3H, J = 7.0 Hz, CH_3), 4.59 (q, 2H, J = 7.0 Hz, CH_2), 6.89 (dd, 1H, $J_{6,5}$ = 4.5 Hz, $J_{6,7}$ = 2.6 Hz, H_6), 7.05 (dd, 1H, $J_{5,6}$ = 4.5 Hz, $J_{5,7}$ = 1.3 Hz, H_5), 7.97 (dd, 1H, $J_{7,6}$ = 2.6 Hz, $J_{7,5}$ = 1.3 Hz, H_7), 8.35 (s, 1H, H_2), 12.7 (br s, 1H, COOH).

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.4 ; H, 5.0; N, 13.4.

1-Ethyl-1,4-dihydro-4-oxopyrrolo[1,2-*b*]pyridazine-3-carboxylic Acid (**13c**).

A mixture of **17c** (5.38 g, 23 mmoles) in 10 ml of ethanol and 23 ml (46 mmoles) of 2*N* sodium hydroxide is heated at 60° during 1/2 hour. The cooled solution is decolorized with charcoal, filtered and the filtrate neutralized with 2*N* hydrochloric acid. The precipitated solid is filtered and recrystallized from a mixture of 1,4-dioxane and water (90-10 v/v) giving a light tan solid of **13c** (4.0 g, 84%), mp 246° dec; tlc Rf 0.4 (methyl ethyl ketone-acetic acid 100-10 v/v); ir (potassium bromide): 3455, 3118, 3111, 2990, 1711, 1620, 1561, 1492, 1463, 1401, 1295, 1263, 1196, 1152, 1123, 1086, 1048, 938, 862, 789, 728 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.68 (t, 3H, J = 7.2 Hz, CH_3), 4.40 (q, 2H, J = 7.2 Hz, CH_2), 6.74-6.78 (m, 1H, $J_{6,5}$ = 4.4 Hz, $J_{6,7}$ = 2.8 Hz, H_6), 7.19-7.26 (m, 1H, $J_{5,6}$ = 4.4 Hz, $J_{5,7}$ = 1.4 Hz, H_5), 7.34-7.36 (m, 1H, $J_{7,6}$ = 2.8 Hz, $J_{7,5}$ = 1.4 Hz, H_7), 8.56 (s, 1H, H_2), 14.3 (br s, 1H, COOH).

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.5 ; H, 4.9; N, 13.5.

Diethyl 2-Methyl-2-[(1-pyrrolyl)aminomethylene]propanedioate (**20b**) and Diethyl [*N*-(1-Pyrrolyl)methylamino]methyl-enepropanedioate (**21b**).

Method B.

To a solution of **16** (37.8 g, 0.15 mole) in 225 ml of dry dimethylformamide is added in small portions sodium methoxide (21 g, 0.39 mole). One notes a small exothermy. The reaction mixture is cooled to room temperature and 30 ml of iodomethane (68.4 g, 0.48 mole) are added within an hour. The reaction mixture is allowed to stand at room temperature during the night and then poored on crushed ice. The aqueous phase is extracted three times with dichloromethane and the organic phases collected and evaporated under reduced pressure after drying on sodium sulfate. The oily residue is chromatographed on silica gel (dichloromethane). The fractions containing the first eluted compound are collected and evaporated to dryness yielding **20b** (12.0 g, 30%); oil; tlc Rf 0.9 (methanol-dichloromethane 2-98 v/v); ir (potassium bromide): 3437, 2986, 2940, 1738, 1470, 1384, 1260, 1233, 1196, 1125, 1069, 1023, 965, 863, 726 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.28 (t, 6H, J = 7.1 Hz, $2CH_3$), 1.71 (s, 3H, CH_3), 4.26 (q, 4H, J = 7.1 Hz, $2CH_2$), 6.21 (t, 2H, J = 2.3 Hz, H_3-H_4), 7.06 (t, 2H, J = 2.3 Hz, H_2-H_5), 8.08 (s, 1H, vinylic).

Anal. Calcd. for $C_{13}H_{18}N_2O_4$: C, 58.64; H, 6.81; N, 10.52. Found: C, 58.9 ; H, 6.6; N, 10.7.

The fractions containing the second eluting compound are collected and evaporated to dryness yielding **21b** (15.0 g, 38%), oil; tlc Rf 0.4 (methanol-dichloromethane 2-98 v/v); ir (potassium bromide): 3480, 3160, 3000, 2980, 1724, 1716, 1706, 1624, 1480, 1448, 1384, 1304, 1247, 1210, 1112, 1080, 1060, 1016, 936, 712 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.21 (t, 3H, J = 7.1 Hz, CH_3), 1.24 (t, 3H, J = 7.1 Hz, CH_3), 3.37 (s, 3H, CH_3), 3.94 (q, 2H, J = 7.1 Hz, CH_2), 4.17 (q, 2H, J = 7.1 Hz, CH_2), 6.12 (t, 2H, J = 2.3 Hz, H_3-H_4), 6.71 (t, 2H, J = 2.3 Hz, H_2-H_5), 7.50 (s, 1 H, vinylic H).

Anal. Calcd. for $C_{13}H_{18}N_2O_4$: C, 58.64; H, 6.81; N, 10.52. Found: C, 58.7 ; H, 6.6; N, 10.5.

Ethyl 1,4-Dihydro-1-methyl-4-oxopyrrolo[1,2-*b*]pyridazine-3-carboxylate (**17b**).

Method B.

A mixture of compound **21b** (10 g, 37.5 mmoles) and 31 g of polyphosphoric acid is heated at 140° under nitrogen during a quarter of an hour. The reaction mixture darkened rapidly. After cooling to room temperature, it is treated with 50 ml of water and 50 ml of dichloromethane. The phases are separated and the aqueous phase extracted twice again with dichloromethane. The collected organic fractions are evaporated to dryness after drying on sodium sulfate and the residue chromatographed by hplc (partisil 10 with methanol dichloromethane 5-95 v/v). The interesting fractions after recrystallization from absolute ethanol yield compound **17b** (2.0 g, 24%), mp 236° dec; tlc Rf 0.4 (methanol-dichloromethane 5-95 v/v); ir (potassium bromide): 3096, 3058, 2978, 1667, 1609, 1447, 1408, 1378, 1320, 1285, 1245, 1223, 1148, 1125, 1098, 1044, 1019, 971, 882, 814, 785, 745, 724 cm^{-1}; ^1H nmr (DMSO-d_6) : δ 1.26 (t, 3H, J = 7.1 Hz, CH_3), 4.05 (s, 3H, CH_3), 4.18 (q, 2H, J = 7.1 Hz, CH_2), 6.57 (dd, 1H, $J_{6,5}$ = 4.3 Hz, $J_{6,7}$ = 2.8 Hz, H_6), 6.80 (dd, 1H, $J_{5,6}$ = 4.3 Hz, $J_{5,7}$ = 1.6 Hz, H_5), 7.63 (dd, 1H, $J_{7,6}$ = 2.8 Hz, $J_{7,5}$ = 1.6 Hz, H_7), 8.65 (s, 1H, H_2).

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.8 ; H, 5.5; N, 12.5.

1,4-Dihydro-1-methyl-4-oxopyrrolo[1,2-*b*]pyridazine-3-carboxylic Acid (**13b**).

A suspension of **17b** (4.9 g, 22 mmoles) in 100 ml of ethanol and 22.5 ml (45 mmoles) of 2*N* sodium hydroxide is heated. The solid dissolves slowly and then gives a gel which is evaporated to dryness under reduced pressure. The residue is treated with 750 ml of water and acidified to *p*H 4 with acetic acid. The precipitate is filtered and recrystallized from a mixture of 1,4-dioxane and acetonitrile, giving compound **13b** (1.29 g, 31%), mp 270° dec; tlc Rf 0.4 (methanol-dichloromethane 5-95 v/v); ir (potassium bromide): 3143, 3071, 3040, 2921, 1713, 1642, 1563, 1534, 1503, 1486, 1450, 1433, 1345, 1310, 1233, 1206, 1148, 1094, 965, 911, 809, 785, 708, 652 cm^{-1}; ^1H nmr (DMSO-d_6): 4.16 (s, 3H, CH_3), 6.79 (dd, 1H, $J_{6,5}$ = 4.5 Hz, $J_{6,7}$ = 2.9 Hz, H_6), 7.07 (dd, 1H, $J_{5,6}$ = 4.5 Hz, $J_{5,7}$ = 1.4 Hz, H_5), 7.91 (dd, 1H, $J_{7,6}$ = 2.9 Hz, $J_{7,5}$ = 1.4 Hz, H_7), 8.94 (s, 1H, H_2), 14.7 (br s, 1H, COOH).

Anal. Calcd. for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.4; H, 4.2; N, 14.7.

Diethyl 2-Ethyl-2-[(1-pyrrolyl)aminomethylene]propanedioate (**20c**) and Diethyl [*N*-(1-Pyrrolyl)ethylamino]methylenepropanedioate (**21c**).

Method B.

To a solution of **16** (25.2 g, 0.1 mole) in 150 ml of dry dimethylformamide is added in small portions sodium methoxide (13 g, 0.24 mole) maintaining the temperature under +15° with an ice bath. After the addition is complete, iodoethane (25.5 ml, 0.32 mole) is added and the reaction mixture is allowed to stand at room temperature during the night. The solution is poured on crushed ice and the aqueous phase extracted three times with dichloromethane. The collected organic layers are evaporated under reduced pressure after drying over sodium sulfate. The residue is chromatographed on silica gel (dichloromethane).

The first fractions after evaporation yielded compound **20c** (12 g, 42%). An analytical sample was obtained by recrystallization from *n*-hexane with decolorization, mp 43°; tlc Rf 0.7 (*n*-heptane-ethylacetate 75-25 v/v); ir (potassium bromide): 3420, 3137, 2981, 1760, 1719, 1655, 1632, 1476, 1374, 1310, 1246, 1214, 1167, 1129, 1094, 1079, 1019, 959, 920, 853, 745, 700 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.93 (t, 3H, J = 7.5 Hz, CH_3), 1.28 (t, 6H, J = 7.2 Hz, 2 ester CH_3), 2.32 (q, 2H, J = 7.5 Hz, CH_2), 4.26 (q, 4H, J = 7.2 Hz, 2 ester CH_2), 6.21 (t, 2H, J = 2.3 Hz, H_3-H_4), 7.07 (t, 2H, J = 2.3 Hz, H_2-H_5), 8.13 (s, 1H, vinylic H).

Anal. Calcd. for $C_{14}H_{20}N_2O_4$: C, 59.99; H, 7.19; N, 9.99. Found: C, 60.4; H, 7.4; N, 10.0.

The fractions containing the second eluting compound were evaporated to dryness giving **21c** (13 g, 46%) as an oil. An analytical sample can be obtained by distillation under reduced pressure, bp 170-180°/0.04 mm Hg; tlc Rf 0.4 (*n*-heptane-ethyl acetate 75-25 v/v); ir (potassium bromide): 3108, 2985, 2940, 2907, 1727, 1701, 1621, 1468, 1385, 1283, 1237, 1202, 1135, 1113, 1073, 1034, 967, 868, 801, 766, 724 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.13 (t, 3H, J = 7.2Hz, CH_3), 1.17 (t, 3H, J = 7.2 Hz, CH_3), 1.23 (t, 3H, J = 7.2 Hz, CH_3), 3.61 (q, 2H, J = 7.2 Hz, CH_2), 3.81 (q, 2H, J = 7.2 Hz, CH_2), 4.15 (q, 2H, J = 7.2 Hz, CH_2), 6.10 (t, 2H, J = 2.3 Hz, H_3-H_4), 6.66 (t, 2H, J = 2.3 Hz, H_2-H_5), 7.51 (s, 1H, vinylic H).

Anal. Calcd. for $C_{14}H_{20}N_2O_4$: C, 59.99; H, 7.19; N, 9.99. Found: C, 60.0; H, 7.4; N, 9.6.

Ethyl 1-Ethyl-1,4-dihydro-4-oxopyrrolo[1,2-*b*]pyridazine-3-carboxylate (**17c**).

Methods B and C.

To polyphosphoric acid (266 g) preheated at 60° with powerful stirring is added in portions under nitrogen **21c** (92.5 g, 0.33 mole). The reaction is exothermic and the ethanol formed is distilled off. The reaction mixture is maintained between 55° and 60° during 1 hour. The solution is poured on a solution of sodium bicarbonate and extracted three times with dichloromethane. The organic phases are collected, dried over sodium sulfate and evaporated to dryness. The residue is chromatographed on silica gel (dichloromethane) and the interesting fractions collected after evaporation are recrystallized from a mixture of methanol and 1,1,1-trichloroethane giving compound **17c** (36 g, 46%) having the characteristics described before.

N-Ethyl-1*H*-pyrrol-1-amine (**22c**).

To a solution of **15** (41.0 g, 0.5 mole) in 640 ml of methanol is added rapidly acetaldehyde (44.0 g, 1 mole) and after an exothermic reaction, the mixture is maintained at room temperature until the starting material has fully disappeared on tlc (dichloromethane). The formed imine is reduced by adding small portions of sodium borohydride (37.8 g, 1 mole) keeping the reaction mixture under +45°. After the end of the addition, the solution is refluxed during half an hour and allowed to stand at room temperature during the night. The solvant is removed under reduced pressure and the solid residue taken with 800 ml of water and 750 ml of dichloromethane. The phases are decanted and the aqueous phase extracted twice with dichloromethane. The organic layers are mixed, dried over sodium sulfate and evaporated to dryness. The residual oil is distilled under reduced pressure giving **22c** as an oil (46.2 g, 84%), bp 49-55°/18 mm Hg; tlc Rf 0.4 (dichloromethane); ir (potassium bromide): 3285,

3129, 3104, 2977, 2938, 2865, 1455, 1385, 1291, 1252, 1065, 1044, 971, 722, 606 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.00 (t, 3H, J = 7.1 Hz, CH_3), 3.05 (q, 2H , J = 7. 1 Hz, CH_2), 4.51 (br s, 1H, NH), 6.01 (t, 2H, J = 2.3 Hz, H_3-H_4), 6.69 (t, 2H, J = 2.3 Hz, H_2-H_5).

Anal. Calcd. for $C_6H_{10}N_2$: C, 65.42; H, 9.15; N, 25.43. Found: C, 65.0; H, 9.0; N, 25.1.

Diethyl [*N*-(1-Pyrrolyl)ethylamino]methylenepropanedioate (**21c**).

Method C.

A mixture of **22c** (55 g, 0.5 mole) and diethyl ethoxymethylenemalonate (108 g, 0.5 mole) is heated approximatively during 4 hours under argon at 120°, while the formed ethanol is distilled off and until the starting materials have disappeared on tlc (*n*-heptane-ethyl acetate 80-20 v/v). After cooling, the oil is added 0.5 litre ethyl acetate, decolorized with charcoal and the filtrate evaporated to dryness under reduced pressure. The residual oil is the wanted compound **21c** (131.5 g, 94%) used without further purification for the cyclisation described before.

Diethyl [*N*-(1-Pyrrolyl)phenylamino]methylenepropanedioate (**21d**).

Method C.

A mixture of **22d** (23.7 g, 0.15 mole) and diethyl ethoxymethylenemalonate (35.7 g, 0.165 mole) is heated at 150° while the ethanol which forms is distilled off and until the starting materials have disappeared on tlc (dichloromethane). After approximatively four hours, the solution is cooled and dichloromethane added with charcoal. The solution filtered and the filtrate evaporated to dryness. The residue is recrystallized from petroleum ether (bp 40-60°) yielding a light colored solid of **21d** (32.4 g, 66%), mp 95°; tlc Rf 0.6 (dichloromethane); ir (potassium bromide): 3450, 3125, 2984, 2903, 1733, 1707, 1625, 1590, 1493, 1478, 1462, 1449, 1383, 1360, 1316, 1219, 1177, 1082, 1027, 969, 940, 901, 764, 741, 710, 695, 654 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.17 (t, 3H, J = 7.1 Hz, CH_3), 1.27 (t, 3H, J = 7.1 Hz, CH_3), 3.80 (q, 2H, J = 7.1 Hz, CH_2), 4.23 (q, 2H, J = 7.1 Hz, CH_2), 6.21 (t, 2H, J = 2.3 Hz, H_3-H_4), 6.72 (t, 2H, J = 2.3 Hz, H_2-H_5), 6.67-6.73 (m, 2H, aromatics), 7.13-7.17 (m, 1H, *para* aromatic), 7.26-7.35 (m, 2H, aromatics), 8.05 (s, 1H, vinylic H).

Anal. Calcd. for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53. Found C, 65.7; H, 6.1; N, 8.5.

Ethyl 1,4-Dihydro-4-oxo-1-phenylpyrrolo[1,2-*b*]pyridazine-3-carboxylate (**17d**).

A mixture of **21d** (3.28 g, 10 mmoles) and polyphosphoric acid (32.8 g) is heated at +80° under vacuum during 2 hours. The reaction is followed by tlc (methanol-dichloromethane 5-95 v/v). The hot reaction mixture is poured on ice, the solution neutralized with sodium hydrogenocarbonate and extracted with dichloromethane. The organic layers are collected, dried over sodium sulfate and evaporated to dryness. The residue is recrystallized from diisopropyl ether and 2-propanol giving compound **17d** (1.3 g, 46%), mp 178°; tlc Rf 0.4 (ethylacetate); ir (potassium bromide): 3445, 3095, 3052, 2977, 2907, 1729, 1611, 1493, 1403, 1322, 1277, 1231, 1202, 1100, 1034, 973, 922, 780, 709 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.38 (t, 3H , J = 7.1 Hz, CH_3), 4.36 (q, 2H, J = 7.1 Hz, CH_2), 6.41-6.45 (m, 1H, $J_{6,5}$ = 4.4 Hz, $J_{6,7}$ = 2.9 Hz, H_6), 6.71-6.73 (m, 1H, $J_{7,6}$ = 2.9 Hz, $J_{7,5}$ = 1.8 Hz, H_7), 7.07-7.11 (m, 1H, $J_{5,6}$ = 4.4 Hz, $J_{5,7}$ = 1.8 Hz, H_5), 7.56-7.72 (m, 5H, aromatics), 8.36 (s, 1H, H_2).

Anal. Calcd. for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.93. Found: C, 68.2; H, 5.0; N, 9.9.

1,4-Dihydro-4-oxo-1-phenylpyrrolo[1,2-*b*]pyridazine-3-carboxylic Acid (**13d**).

A suspension of **17d** (1.3 g, 4.6 mmoles) in 10 ml of ethanol and 4.6 ml (9.2 mmoles) of 2*N* sodium hydroxide is refluxed during half an hour. The hot solution is decolorized with charcoal, filtered and the filtrate neutralized with 2*N* hydrochloric acid. The solid is filtered and recrystallized from diisopropyl ether and 2-propanol giving white crystals of **13d** (0.5 g, 43%), mp 171° dec; tlc Rf 0.4 (methanol-dichloromethane 10-90 v/v); ir (potassium bromide): 3436, 3139, 2919, 1649, 1603, 1509, 1439, 1395, 1316, 1289, 1252, 1158, 1133, 1081, 1005, 884, 816, 737, 693, 660 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.37-6.41 (m, 1H, $J_{6,7}$ = 2.8 Hz, $J_{6,5}$ = 4.6 Hz, H_6), 6.63-6.66 (m, 1H, $J_{7,6}$ = 2.8 Hz, $J_{7,5}$ = 1.6 Hz, H_7), 7.05-7.09 (m, 1H, $J_{5,6}$ = 4.6 Hz, $J_{5,7}$ = 1.6 Hz, H_5), 7.42-7.47 (m, 2H, *ortho* phenyl), 7.58-7.67 (m, 3H, *meta* and *para* phenyl), 9.95 (s, 1H, H_2), 11.7 (br s, 1H, COOH).

Anal. Calcd. for $C_{14}H_{10}N_2O_3$: C, 66.14; H, 3.96; N, 11.02. Found: C, 66.3; H, 4.1; N, 11.1.

2-Methylthio-1*H*-imidazol-1-amine (**25**).

A mixture of 2-mercapto-1*H*-imidazol-1-amine, hydrochloride **24** (0.45 g, 3 mmoles) and tetrabutylammonium iodide (0.15 g, 0.4 mmoles) in 10 ml of toluene and 3 ml of caustic sodium hydroxide are vigorously stirred at room temperature and 0.37 ml (6 mmoles) of iodomethane are added. A small exothermy is noted and the reaction mixture is stirred further for 72 hours at room temperature. The reaction mixture is treated with dichloromethane and the aqueous phase acidified with concentrated hydrochloric acid with cooling. The organic phase is discarded, the aqueous phase brought to *p*H 11 with concentrated sodium hydroxide and then reextracted with dichloromethane. These organic phases are dried over sodium sulfate and evaporated to dryness giving a solid residue of compound **25** (0.20 g, 53%). An analytical sample was obtained by recrystallization from carbon tetrachloride, mp 70-71° (Lit 71-73° [19]); tlc Rf 0.5 (methanol-dichloromethane 10-90 v/v); ir (potassium bromide): 3329, 3249, 3134, 3113, 2926, 1655, 1621, 1543, 1503, 1457, 1410, 1312, 1273, 1108, 1071, 984, 955, 914, 830, 710, 683 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 2.60 (s, 3H, CH_3) , 4.70 (br s, 2H, NH_2), 6.95 (d, 1H, J = 1.3 Hz, aromatic), 7.03 (d, 1H, J = 1.3 Hz, aromatic); ^{13}C nmr proton undecoupled (deuteriochloroform): δ 15.4 (q, $^1J_{CH}$ = 143 Hz, CH_3), 122.6 (dd, $^1J_{CH}$ = 191 Hz, $^2J_{CH}$ = 15 Hz, C_4), 127.3 (dd,$^1J_{CH}$ = 191 Hz, $^2J_{CH}$ 9 Hz, C_5), 143.6 (C_2).

Anal. Calcd. for $C_4H_7N_3S$: C, 37.19; H, 5.46; N, 32.53; S, 24.82. Found: C, 37.0; H, 5.5; N, 32.5; S, 24.8.

N-Ethyl-2-methylthio-1*H*-imidazol-1-amine (**26**).

To a solution of 2-methylthio-1*H*-imidazol-1-amine **25** (1.29 g, 10 mmoles) in 10 ml of tetrahydrofurane and 40 ml of methanol is added acetaldehyde (3.25 g, 74 mmoles) and then refluxed until the starting material has disappeared on tlc (ethyl acetate) usually after half an hour. The reaction mixture is cooled and sodium borohydride (1.89 g, 50 mmoles) is added in

small portions maintaining the temperature under 20°. The solution is stirred at room temperature during 2 hours, evaporated to dryness and the solid treated with 100 ml of water and 100 ml of dichloromethane. The phases are separated and the aqueous phase extracted twice with dichloromethane. The organic layers are collected, dried over sodium sulfate and evaporated to dryness. The residue is recrystallized from petroleum ether (40-60°) giving white crystals of compound **26** (0.76 g, 48%), mp 64-65°, tlc Rf 0.5 (ethyl acetate); ir (potassium bromide): 3185, 3135, 2967, 2921, 2859, 1673, 1563, 1501, 1439, 1391, 1318, 1277, 1175, 1121, 1102, 872, 724, 685 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.12 (t, 3H, J = 7.2 Hz, CH_3), 2.59 (s, 3H, CH_3), 3.13 (dq, 2H, J = 7.2 Hz, J_{NH} = 5.0 Hz, CH_2), 4.72 (br t, 1H, J = 5.0 Hz, NH), 6.99 (d, 1H, J = 1.4 Hz, aromatic), 7.04 (d, 1H, J = 1.4 Hz, aromatic).

Anal. Calcd. for $C_6H_{11}N_3S$: C, 45.83; H, 7.05; N, 26.72; S, 20.39. Found: C, 45.5; H, 6.9; N, 27.0; S, 20.5.

Diethyl [*N*-(2-Methylthio-1-imidazolyl)ethylamino]methylenepropanedioate (**27**).

A mixture of *N*-ethyl-2-methylthio-1*H*-imidazol-1-amine **26** (36 g, 0.23 mole) and diethyl ethoxymethylenemalonate (49.5 g, 0.23 mole) is heated at 130° in maintaining the reaction vessel under vacuum (distillation of the ethanol formed) until the starting material has disappeared on tlc (ethyl acetate) usually 3 hours. The reaction mixture is evaporated to dryness under reduced pressure and the residue chromatographed on silica gel (*n*-hexane-ethyl acetate 95-5 v/v). The interesting fraction is collected and recrystallized twice from *n*-pentane giving the wanted compound **27** (22 g, 30%), mp 50°; tlc Rf 0.3 (ethyl acetate); ir (potassium bromide): 3137, 3108, 2985, 2944, 1710, 1627, 1447, 1350, 1285, 1243, 1206, 1135, 1100, 1067, 1029, 863, 751, 724 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.15 (t, 3H, J = 7. 1 Hz, OCH_2CH_3A), 1.18 (t, 3H, J = 7.2 Hz, NCH_2CH_3), 1.21 (t, 3H, J = 7.1 Hz, OCH_2CH_3B), 2.64 (s, 3H, SCH_3), 3.62 (q, 2H, J = 7.2 Hz, NCH_2), 3.81 (dq, 2H, J = 7.1 Hz, J_{AB} = 1.8 Hz, OCH_2A), 4.14 (q, 2H, J = 7.2 Hz, OCH_2B), 6.94 (d, 1H, J = 1.6 Hz, H_4), 6.98 (d, 1H, J = 1.6 Hz, H_5), 7.41 (s, 1H, NCH); ^{13}C nmr proton undecoupled (deuteriochloroform): δ 13.1 (q, $^1J_{CH}$ = 127 Hz, NCH_2CH_3), 13.6 (q, $^1J_{CH}$ = 126 Hz, OCH_2CH_3A), 14.1 (q, $^1J_{CH}$ = 126 Hz, OCH_2CH_3B), 14.7 (q, $^1J_{CH}$ = 142 Hz, SCH_3), 53.1 (tm, $^1J_{CH}$ = 139 Hz, other J not measurable, NCH_2), 60.7 (tq, $^1J_{CH}$ = 147 Hz, $^2J_{CH}$ = 5.5 Hz, OCH_2A), 61.4 (tq, $^1J_{CH}$ = 147 Hz, $^2J_{CH}$ = 5.5 Hz, OCH_2B), 100.7 (s, $C(COOCH_2CH_3)_2$), 121.3 (dd, $^1J_{CH}$ = 194 Hz, $^2J_{CH}$ = 15 Hz, C_4), 127.3 (dd, $^1J_{CH}$ = 192 Hz, $^2J_{CH}$ = 9 Hz, C_5), 144.6 (dt, $^1J_{CH}$ = 170 Hz, $^2J_{CH}$ = 2.5 Hz, vinylic C), 144.9 (m, $CSCH_3$), 164.8 and 165.4 (2m, COO).

Anal. Calcd. for $C_{14}H_{21}N_3O_4S$: C, 51.36; H, 6.47; N, 12.83; S, 9.79. Found: C, 51.7; H, 6.6; N, 13.0; S, 9.8.

Ethyl 1-Ethyl-1,4-dihydro-7-methylthio-4-oxoimidazo[1,5-*b*]pyridazine-3-carboxylate (**28**).

A mixture of compound **27** (50 g, 0.15 mole) in polyphosphoric acid (83 g) is heated at 100° during 1.5 hour and then at 130° during 1/4 hour maintaining the whole reaction vessel under reduced pressure. After cooling to room temperature, the reaction mixture is brought to *p*H 7-8 with a saturated solution of sodium hydrogenocarbonate and extracted three times with dichloromethane. The organic layers are collected, dried over sodium sulfate and evaporated to dryness. The residue is chromatographed on silica gel (ethyl acetate) and the interesting fractions collected giving a solid crop of compound **28** (4.25 g, 10%). An analytical sample was obtained by recrystallization from diisopropyl ether, mp 110°; tlc Rf 0.5 (methanol-dichloromethane 10-90 v/v); ir (potassium bromide): 2986, 2936, 1735, 1611, 1405, 1341, 1305, 1247, 1208, 1090, 1034, 903, 787 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.39 (t, 3H, J = 7.1 Hz, CH_3), 1.43 (t, 3H, J = 7. 1 Hz, CH_3), 2.80 (s, 3H, SCH_3), 4.36 (q, 2H, J = 7.1 Hz, CH_2), 4.62 (q, 2H, J = 7.1 Hz, CH_2), 7.88 (s, 1H, H_5), 8.21 (s, 1H, H_2).

Anal. Calcd. for $C_{12}H_{15}N_3O_3S$: C, 51.23; H, 5.37; N, 14.94; S, 11.40. Found: C, 51.2; H, 5.3; N, 14.8; S, 11.3.

1-Ethyl-1,4-dihydro-7-methylthio-4-oxoimidazo[1,5-*b*]pyridazine-3-carboxylic Acid (**14a**).

A mixture of compound **28** (0.5 g, 1.8 mmoles) in 3 ml of trifluoroacetic acid and 3 ml of water is heated at 65° during 24 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 the residual solid recrystallized from acetonitrile giving compound **14a** (0.23 g, 50%) as light yellow crystals, mp 240° dec; tlc Rf 0.4 (methanol-dichloromethane 10-90 v/v); ir (potassium bromide): 3450, 3123, 3073, 2985, 2920, 1711, 1625, 1580, 1461, 1435, 1392, 1341, 1296, 1117, 1091, 1048, 899, 793 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.40 (t, 3H, J = 7.0 Hz, CH_3), 2.77 (s, 3H, CH_3), 4.86 (q, 2H, J = 7.0 Hz, CH_2), 7.98 (s, 1H, H5), 8.88 (s, 1H, H_2), 13.6 (br s, 1H, COOH); ^{13}C nmr (DMSO-d_6): δ 14.7 (CH_3), 17.0 (SCH_3), 52.0 (CH_2), 101.5 (C_3), 127.2 (C_5), 129.4 (C_{4a}), 137.4 (C_7), 148.1 (C_2), 164.7 (CO), 171.2 (COOH).

Anal. Calcd. for $C_{10}H_{11}N_3O_3S$: C, 47.42; H, 4.38; N, 16.59. Found: C, 47.3; H, 4.3; N, 16.7.

Ethyl 1-Ethyl-1,4-dihydro-4-oxoimidazo[1,5-*b*]pyridazine-3-carboxylate (**29**).

A mixture of compound **28** (2.0 g, 7.1 mmoles) in 15 ml of water and 15 ml of ethanol and 10 g of Raney Nickel is refluxed during 10 hours until the starting material has disappeared on tlc (methanol-dichloromethane 10-90 v/v). After cooling to room temperature, the reaction mixture is filtered on Celite and the filtrate evaporated to dryness under reduced pressure. The solid residue is the wanted compound **29** (1.3 g, 78%). An analytical sample was obtained by recrystallization from ethyl acetate, mp 220° dec; tlc Rf 0.3 (methanol-dichloromethane 5-95 v/v); ir (potassium bromide): 3438, 3114, 2979, 2938, 1715, 1615, 1536, 1410, 1311, 1195, 1123, 1085, 903, 791, 650, 531 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.27 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 1.41 (t, 3H, J = 7.0 Hz, NCH_2CH_3), 4.20 (q, 2H, J = 7. 1 Hz, OCH_2), 4.57 (q, 2H, J = 7.0 Hz, NCH_2), 7.68 (s, 1H, H_5), 8.65 (s, 1H, H_7), 8.70 (s, 1H, H_2); ^{13}C nmr (DMSO-d_6): δ 12.1 (NCH_2CH_3), 14.4 (OCH_2CH_3), 49.6 (NCH_2), 59.7 (OCH_2), 102.9 (C_3), 125.7 (C_5), 127.5 (C_7), 128.2 (C_{4a}), 145.1 (C_2), 163.7 (CO), 166.7 (COO).

Anal. Calcd. for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.2 ; H, 5.5; N, 17.8.

1-Ethyl-1,4-dihydro-4-oxoimidazo[1,5-*b*]pyridazine-3-carboxylic Acid (**14b**).

A mixture of **29** (0.95 g, 4.0 mmoles) in 20 ml (20 mmoles) of 1*N* sodium hydroxide and 5 ml of ethanol is heated at 40° during 3 hours following the disappearance of the starting mate-

rial on tlc (methanol-dichloromethane 10-90 v/v). The reaction mixture with cooling is brought to *p*H 4 with 1*N* hydrochloric acid and evaporated to dryness under reduced pressure. The residue is recrystallized from a mixture of water and 2-propanol and then from acetonitrile giving white crystals of **14b** (0.20 g, 24%), mp 237° dec; tlc Rf 0.3 (methanol-dichloromethane 10-90 v/v); ir (potassium bromide): 3465, 3149, 3039, 1719, 1621, 1536, 1509, 1461, 1415, 1304, 1266, 1154, 1131, 1054, 957, 872, 797, 762, 652 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.45 (t, 3H, J = 7.0 Hz, CH_3), 4.66 (q, 2H, J = 7.0 Hz, CH_2), 7.95 (s, 1H, H_5), 8.89 (s, 1H, H_7), 8.97 (s, 1H, H_2), 12.2 (br s, 1H, COOH).

Anal. Calcd. for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 51.9; H, 4.2 ; N, 20.4.

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