Pyrrolopyridine Analogs of Nalidixic Acid. 1. Pyrrolo[2,3-*b*]pyridines

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A series of 4,7-dihydro-4-oxo-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylic acids was synthesized from ethyl 5-methyl(or 5*H*)-2-aminopyrrole-3-carboxylate. The starting pyrroles were obtained by reaction of carbethoxyacetamidine with bromoacetone or chloroacetaldehyde. One compound (**10**) showed antibacterial activity *in vitro*.

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Since the introduction of nalidixic acid in the treatment of urinary tract infections, an extensive effort has been made to find analogs with increased potency and broader spectrum of activity [2].

A 1-substituted-1,4-dihydro-4-oxo-3-pyridinecarboxylic acid with an additional aromatic or heteroaromatic ring fused at the 5,6-position is the basic structure of this class of antibacterial agents, and the alterations in the 1 substituent and in the 5,6-annulated ring have led to a large number of structural variants [3].

The recent reports on the synthesis and antibacterial activity of pyrrolo[3,2-*b*]pyridines and pyrrolo[3,4-*b*]pyridines [4], prompt us to report our independent findings on the synthesis of a series of 7-ethyl-4,7-dihydro-4-oxo-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylic acids (Schemes 1 and 2).

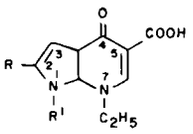
These compounds, due to their similarity with the quinolones antimicrobial agents would in principle be expected to show antibacterial activity.

Chemistry.

In 1975 a novel synthetic route was reported for the preparation of pyrrolo[2,3-*b*]pyridines starting from 1-substituted-2-amino-4-cyanopyrroles [5]. The cyano group was necessary to confer stability on the pyrrole ring and was retained in the final structure. In the same paper the authors stated that the use of methyl 2-aminopyrrole-3-carboxylate and of the corresponding 3-carbonitrile proved unsuccessful to obtain pyrrolo[2,3-*b*]pyridines. We have now found that ethyl 2-aminopyrrole-3-carboxylates **1a,b** with or without a methyl group in position 5 is a convenient starting material for this purpose and the synthetic

Table 1

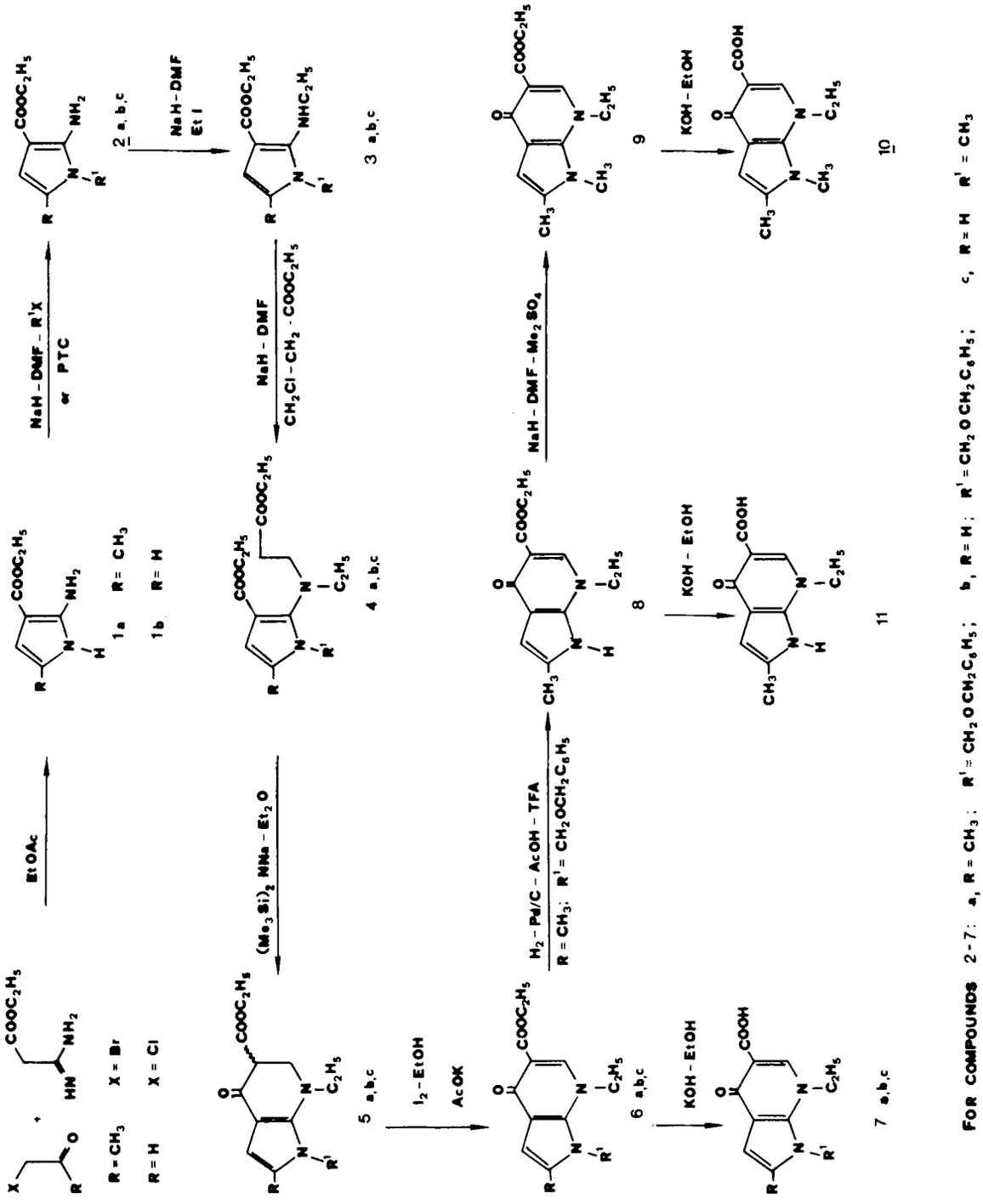
4,7-Dihydro-4-oxo-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylic Acids



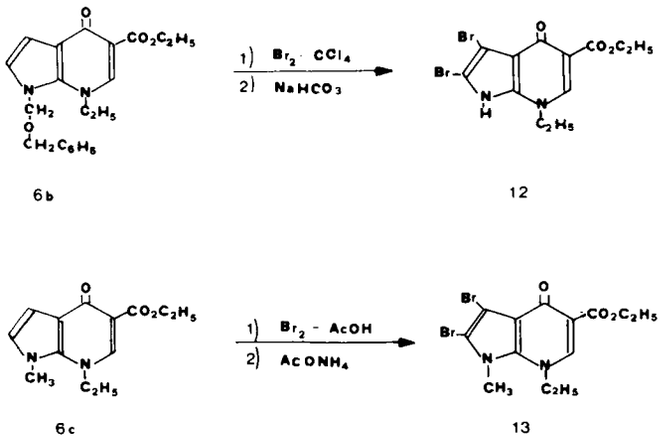
Compound No.	R	R'	mp	Yield (%)	IR (nujol) ν (C=O) cm^{-1}	^{1}H-NMR (DMSO-d_6) δ H-C2	H-C3	H-C6	COOH	Molecular formula	Analysis (%) Calcd.	Found
7a	CH_3	$CH_2OCH_2C_6H_5$	124-126°	62	1700, 1630	--	6.57	8.68	16.68	$C_{19}H_{20}N_2O_4$	C 67.04	66.78
											H 5.92	5.95
											N 8.23	7.95
7b	H	$CH_2OCH_2C_6H_5$	202-204°	98	1720, 1620	7.00 a)	6.94 [a]	8.57	15.40	$C_{18}H_{16}N_2O_4$	C 66.24	65.89
											H 5.56	5.49
											N 8.58	8.47
7c	H	CH_3	244-245°	56	1720, 1620	6.82 b)	6.77 [b]	8.33	16.22	$C_{11}H_{12}N_2O_3$	C 59.99	60.05
											H 5.49	5.56
											N 12.72	12.50
10	CH_3	CH_3	286-287°	90	1700, 1630	--	6.49	8.51	12.90	$C_{12}H_{14}N_2O_3$	C 61.53	61.23
											H 6.02	6.15
											N 11.96	11.69
11	CH_3	H	>300°	52	1660, 1630	--	6.35	8.58	17.1 [c]	$C_{11}H_{12}N_2O_3$	C 59.99	59.65
											H 5.49	5.67
											N 12.72	12.45

[a] d, J = 4 Hz. [b] d, J = 3 Hz. [c] NH appears as a broad singlet at 12.2 ppm.

SCHEME 1


EtOAc
R = CH3 X = Br
R = H X = Cl
1a R = CH3
1b R = H
NaH - DMF - R'X
or PTC
2 a,b,c
NaH - DMF
Et I
3 a,b,c
NaH - DMF
CH2Cl - CH2 - COOC2H5
4 a,b,c
(Me3Si)2 NNa - Et2O
5 a,b,c
I2 - EtOH
AcOK
6 a,b,c
H2 - Pd/C - AcOH - TFA
R = CH3; R' = CH2OCH2C6H5
8
NaH - DMF - Me2SO4
9
KOH - EtOH
7 a,b,c
11
KOH - EtOH
10
FOR COMPOUNDS 2-7: a, R = CH3; R' = CH2OCH2C6H5; b, R = H; R' = CH2OCH2C6H5; c, R = H R' = CH3

SCHEME 2



6b 12

6c 13

route is shown in Scheme 1.

The reaction between bromoacetone [6] or chloroacetaldehyde [7] and carbethoxyacetamidine [8] gave good yield of **1a,b** (~ 70%). The formation of 2-aminopyrroles by reaction of α-haloketones and carbethoxyacetamidine is reported for the first time here [9].

An alternative procedure for the preparation of esters of 2-aminopyrrole-3-carboxylic acid was described by Wamhoff and Wehling who synthesized *t*-butyl 2-amino-4-methylpyrrole-3-carboxylate by reaction of acetylaminoacetone with *t*-butylcyanacetate [10].

The ^{1}H-nmr spectra of **1a,b** showed three deuterium exchangeable protons of which the amino group appeared at δ 4.84 (**1a**) and δ 5.00 (**1b**) and the pyrrole NH at δ 7.96 (**1a**) and δ 8.24 (**1b**). In compound **1b** the H-C4 and H-C5 protons appeared as two narrow multiplets and after addition of deuterium oxide as two doublets with J = 3 Hz centered at δ 6.14 and 6.29 respectively, while in **1a** the singlet H-C4 appeared at δ 5.93. The 5-methyl group was confirmed by the presence in the mass spectrum of the fragment with m/z = 42 with a relative intensity of 49% and attributed to CH_3-C=NH^+.

Alkylation of the 2-amino group proved difficult, the pyrrolic ring nitrogen reacting preferentially. It was therefore necessary to alkylate the 1-position by reaction with either benzyloxymethyl chloride (**2a,b**) [11] or with methyl iodide (**2c**) before proceeding to stepwise alkylation of the corresponding sodium 2-pyrrolylamides with ethyl iodide (**3a-c**) and subsequently with ethyl 3-chloropropionate (**4a-c**). Dieckmann cyclization to **5a-c** proceeded eventually with sodium bis(trimethylsilyl)amide [12].

This base, in comparative experiments, gave better yields of **5a-c** than potassium *t*-butoxide in toluene, potassium ethoxide in ethanol and sodium hydride in dimethylformamide.

Reaction of **5a,b,c** with equimolar amounts of iodine in ethanol in the presence of excess potassium acetate, gave cleanly **6a,b,c**. Hydrogenolysis of the benzyloxymethyl group of **6a** proceeded under more stringent conditions than those expected from the literature [11]. The use of Palladium on carbon in acetic acid as a solvent allowed the removal of the protective group in one step at room temperature and atmospheric pressure, however, satisfactory results as for yield and time of reaction were obtained by adding two molar amounts of trifluoroacetic acid to the solution of **6a** in acetic acid and operating at 5 atmospheres. The *N*-unsubstituted pyrrole **8a** was then methylated with dimethyl sulfate and sodium hydride in dimethylformamide to give **9**. The final carboxylic acids **7a,b,c**, **10** and **11** were readily obtained by hydrolysis of the corresponding esters with potassium hydroxide in ethanol.

Bromination of **6b,c** (Scheme 2) gave the dibromo derivatives **12**, **13**. It is of interest to note, in the case of **6b**, the removal of the benzyloxymethyl group probably due to the formation of benzyl bromide and formaldehyde by the action of the generated hydrobromic acid.

The new pyrrolopyridines **7a,b,c**, **10** and **11** (Table 1) were tested *in vitro* against a variety of Gram-negative and Gram-positive bacterial strains. Compound **10** only showed some marginal antimicrobial activity on some of these strains with a MIC of 8 μg/ml, 16 μg/ml and 64 μg/ml against *Proteus vulgaris* X19H (ATCC 881), *Escherichia coli* (SKF 12140) and *Klebsiella Pneumoniae* ISM, respectively.

In view of these results this class of compounds was not pursued further.

EXPERIMENTAL

Melting points were determined on a Büchi SMP-510 capillary apparatus and are uncorrected. The ir spectra were obtained with Perkin-Elmer 297 or 580 spectrophotometers, ν are given in cm^{-1}. The ^{1}H-nmr spectra were recorded on a Brüker WP-270 MHz spectrometer, chemical shifts are given in ppm (δ) relative to tetramethylsilane and J in Hz. Mass spectral data were registered on a Varian MAT-112 spectrometer, direct inlet system, E.I. = 70 eV. The elemental analyses were performed by the Analytical Department of the Gruppo Lepetit. The tlc were performed on Merck silica gel plates, type 60 F-254. The purification on silica gel columns were all obtained by the flash chromatography procedure [13], by using freshly distilled solvents.

Ethyl 2-Amino-5-methylpyrrole-3-carboxylate (**1a**).

To a solution of carbethoxyacetamidine [8] (24.2 g, 0.186 mole) in ethyl acetate (240 ml) under argon was rapidly added bromoacetone [6] (12.73 g, 0.093 mole) under vigorous stirring. An exothermic reaction took place and the hydrobromide of carbethoxyacetamidine began to precipitate. After heating at reflux for 20 minutes the reaction mixture was cooled to room temperature and filtered on a layer of silica gel (500 g) which was washed with ethyl acetate (1500 ml). Evaporation of the solvent under reduced pressure gave 11 g (70%) of **1a** containing only trace amounts of by-products (tlc, dichloromethane-ethyl acetate, 70:30). The analytical sample was obtained by recrystallization from ethyl ether, mp 108-109°; ir (nujol); ν 3500, 3350, 3300 (NH_2, NH), 1650, 1600, 1580 (CO-C=C-N), 1525 (pyrrole); ^{1}H-nmr (deuteriochloroform): δ 1.31 (t, J = 6, 3H,

$CO_2CH_2CH_3$), 2.12 (s, CH_3), 4.29 (q, 2H, $CO_2CH_2CH_3$), 4.84 (br s, NH_2), 5.93 (s, H-C4), 7.96 (br s, NH); ms: (m/z) 168 (80%) M^+, 122 (100%) M-C_2H_5OH, 94 (90%) M-C_2H_5OH-CO, 53 (42%) M-C_2H_5OH-CO-CH_3CN, 42 (49%) M-$C_6H_8NO_2$.

Anal. Calcd. for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.65. Found: C, 56.97; H, 7.33; N, 16.55.

Ethyl 2-Aminopyrrole-3-carboxylate (**1b**).

To a solution of carbethoxyacetamidine (27.83 g, 0.213 mole) in ethyl acetate (270 ml) under argon was rapidly added anhydrous chloroacetaldehyde [7] (7.5 ml, 0.118 mole) under vigorous stirring. An exothermic reaction took place and the hydrochloride of carbethoxyacetamidine began to precipitate. After heating at reflux for 20 minutes the reaction mixture was cooled to room temperature and filtered on a layer of silica gel (400 g) which was washed with ethyl acetate. The oily residue in the reaction flask was repeatedly extracted with the same solvent and filtered. A total volume of 2 ℓ of ethyl acetate was collected which was evaporated under reduced pressure to give 10.9 g (66%) of **1b** containing only trace amounts of by products (tlc, chloroform-acetone, 70:30). This compound is fairly stable for about one week when stored under argon in the dark at −30°. The analytical sample was obtained by recrystallization from methyl *t*-butyl ether, mp 96-98°; ir (nujol): ν 3450, 3400, 3340 (NH_2, NH), 1650, 1600 (CO-C=C-N), 1530 (pyrrole); ^{1}H-nmr (deuteriochloroform): δ 1.31 (t, J = 6, 3H, $CO_2CH_2CH_3$), 4.24 (q, 2H, $CO_2CH_2CH_3$), 5.00 (br s, NH_2), 6.14 (H-C4), 6.29 (H-5), 8.24 (br s, NH).

Anal. Calcd. for $C_7H_{10}N_2O_2$: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.28; H, 6.50; N, 17.78.

Ethyl 2-Amino-1-benzyloxymethyl-5-methylpyrrole-3-carboxylate (**2a**).

To a solution of **1a** (15.9 g, 0.094 mole) in dry DMF (160 ml) cooled at 0° was added in portions under argon 55% sodium hydride in mineral oil (4.5 g, 0.103 mole). The reaction mixture was stirred at room temperature until the evolution of hydrogen ceased (1 hour), then was again cooled at 0° and a solution of benzyl chloromethyl ether (14.38 ml, 0.103 mole) in dry DMF (40 ml) was added. After stirring for 10 minutes, the reaction mixture was poured into 10% aqueous ammonium acetate (1800 ml) and the *p*H was brought to 7 by addition of acetic acid. The aqueous phase was extracted with ethyl ether which was dried and evaporated. The residue was first distilled at 80°, 0.5 mm Hg to remove benzyl alcohol then chromatographed on a silica gel column by eluting with 30% ethyl acetate in cyclohexane to give 15.5 g (57%) of **2a**. The analytical sample was obtained by recrystallization from pentane, mp 58-59°; ir (nujol): ν 3550, 3400 (NH_2), 1650, 1630 (CO-C=C-N), 1540 (pyrrole); ^{1}H-nmr (deuteriochloroform): δ 1.29 (t, J = 6.4, 3H, $CO_2CH_2CH_3$), 2.11 (s, CH_3), 4.26 (q, 2H, $CO_2CH_2CH_3$), 4.47 (s, CH_2-Ph), 5.08 (s, NH_2), 5.11 (s, NCH_2), 6.02 (s, H-C4), 7.36 (m, 5H-aromat).

Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.71. Found: C, 66.53; H, 7.01; N, 9.69.

By employing this procedure compound **2b** was obtained as an oil in 54% yield from **1b** and purified by flash chromatography.

Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.63; H, 6.73; N, 10.15.

Ethyl 2-Amino-1-methylpyrrole-3-carboxylate (**2c**).

To a vigorously stirred solution of **1b** (9.36 g, 0.06 mole), benzyltributylammonium bromide (21.3 g, 0.06 mole) and dimethyl sulfate (6.26 ml, 0.066 mole) in methylene chloride (100 ml) cooled at 0° was added 50% aqueous sodium hydroxide. The reaction mixture was stirred for 2 hours at 0° and for 1 hour at room temperature, then was diluted with methylene chloride and the organic phase was separated, washed with 10% aqueous ammonium acetate, dried and evaporated. The residue was chromatographed on a silica gel column by eluting with 20% acetone in toluene to give 6.7 g (66%) of **2c**. The analytical sample was obtained by recrystallization from ethyl ether-hexane, mp 55-57°; ir (nujol): ν 3450, 3400, 3340, 3300 (NH_2), 1650, 1640, 1620 (CO-C=C-N), 1540, 1530, 1510 (pyrrole); ^{1}H-nmr (deuteriochloroform): δ 1.31 (t, J = 5.8, 3H $CO_2CH_2CH_3$), 3.36 (s, N-CH_3), 4.24 (q, 2H, $CO_2CH_2CH_3$), 4.87 (br s, NH_2), 6.07 (d, J = 3, H-C4), 6.24 (d, H-C5).

Anal. Calcd. for $C_6H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.65. Found: C, 56.99; H, 7.26; N, 16.64.

Ethyl 1-Benzyloxymethyl-2-ethylamino-5-methylpyrrole-3-carboxylate (**3a**).

To a solution of **2a** (27.7 g, 0.096 mole) in dry DMF (270 ml) cooled at 0° was added in portions under argon 55% sodium hydride in mineral oil (4.6 g, 0.105 mole). The reaction mixture was stirred at room temperature until the evolution of hydrogen ceased (3 hours) then was cooled at 0° and a solution of ethyl iodide (8.6 ml, 0.105 mole) in dry DMF (40 ml) was added. After stirring for 2 hours at 0°, the reaction mixture was poured into 10% aqueous ammonium acetate (2800 ml) and extracted with ethyl ether. The organic phase was dried, evaporated and the residue chromatographed on a silica gel column by eluting with 20% ethyl acetate in cyclohexane to give 20.4 g (67%) of **3a** as an oil, which rapidly turned brown; ir (film): ν max 3400, 1670, 1580, 1560, cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.14 (t, J = 6, 3H, N-CH_2CH_3), 1.31 (t, J = 6, 3H, $CO_2CH_2CH_3$), 2.21 (s, CH_3), 3.08 (q, 2H, N-CH_2CH_3), 4.23 (q, 2H, $CO_2CH_2CH_3$), 4.49 (s, CH_2Ph), 5.13 (br s, NH), 5.20 (s, CH_2N), 6.13 (s, H-C4), 7.38 (m, 5H-aromat).

The hydrochloride was recrystallized from ethanol-ether, mp 109-110°; ms: m/z = 316 M^+ (5.4%).

Anal. Calcd. for $C_{18}H_{24}N_2O_3$.HCl: N, 7.94. Found: N, 7.81.

By employing this procedure, compounds **3b** (oil, 79%) and **3c** (oil, 51%) were obtained from **2b** and **2c** and purified by flash chromatography; ms: m/z = 196 $M^{\cdot+}$ (60.8%), 167 $[M^{\cdot+}-C_2H_5]^+$ (12.6%), 150 $[M-C_2H_5OH]^{\cdot+}$ (21.0%), 149 [m/z 150-H] (32.2%), 135 $[m/z\ 150-CH_3]^+$ (100.0%), 139 $[m/z\ 167-C_2H_4]^+$ (17.2%), 108 $[m/z\ 135-HCN]^+$ (40.6%), 122 $[m/z\ 150-C_2H_4]^{\cdot+}$ (22.8%), 121 $[m/z\ 149-C_2H_4]^+$ (24.2%).

3b. *Anal.* Calcd. for $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33; N, 9.26. Found: C, 67.59; H, 7.42; N, 9.21.

3c. *Anal.* Calcd. for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.27. Found: C, 60.86; H, 8.19; N, 14.23.

Ethyl *N*[1-Benzyloxymethyl-3-carbethoxy-5-methyl-2-pyrryl]-*N'*-ethyl-3-aminopropionate (**4a**).

To a solution of **3a** (21.8 g, 0.069 mole) in dry DMF (95 ml) was added in portions under argon 55% sodium hydride in mineral oil (3.58 g, 0.082 mole). The reaction mixture was stirred at 35-40° until the evolution of hydrogen ceased (3 hours), then was cooled at −20° and an excess of ethyl 3-chloropropionate (44 ml) was added. Stirring was continued until the room temperature was reached, then the reaction mixture was poured into 10% aqueous ammonium acetate (1300 ml) and extracted with ethyl ether. The organic phase was dried, evaporated and the residue chromatographed on a silica gel column by eluting with 25% ethyl ether in hexane to give first 8.3 g of starting compound **3a** and 14.35 g (50%) of **4a** as an oil. Recovered **3a** was made to react again with ethyl-3-chloropropionate and the final yield was 19.4 g (67%) of **4a**; ir (film): ν max 1730, 1700 (C=O), 1190 (C-O-C); ^{1}H-nmr (deuteriochloroform): δ 0.98 (t, J = 6, 3H, N-CH_2CH_3), 1.22 (t, J = 6.3, 3H, N-$(CH_2)_2$-$CO_2CH_2CH_3$), 1.33 (t, J = 6, 3H, $CO_2CH_2CH_3$), 2.22 (s, CH_3), 2.37 (t, J = 6.5, 2H, N-CH_2-CH_2-$CO_2C_2H_5$), 3.16 (q, 2H, N-CH_2CH_3), 3.46 (br m, 2H, N-CH_2-CH_2-$CO_2C_2H_5$), 4.08 (q, 2H, N-$(CH_2)_2$-$CO_2CH_2CH_3$), 4.27 (q, 2H, $CO_2CH_2CH_3$), 4.53 (s, CH_2Ph), 5.27 (br s, NCH_2O), 6.29 (s, H-C4), 7.38 (m, 5H-aromat).

Anal. Calcd. for $C_{23}H_{32}N_2O_5$: C, 66.32; H, 7.74; N, 6.73. Found: C, 66.66; H, 7.71; N, 6.60.

By employing this procedure, compounds **4b** (oil, 56%) and **4c** (oil, 31%) were obtained from **3b** and **3c** and purified by flash chromatography.

4b. *Anal.* Calcd. for $C_{22}H_{30}N_2O_5$: C, 65.64; H, 7.52; N, 6.96. Found: C, 65.62; H, 7.57; N, 6.90.

4c. *Anal.* Calcd. for $C_{15}H_{24}N_2O_4$;C, 60.80; H, 8.16; N, 9.45. Found: C, 60.56; H, 8.18; N, 9.24.

Ethyl 1-Benzyloxymethyl-7-ethyl-2-methyl-4,5,6,7-tetrahydro-4-oxo-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (**5a**).

A solution of **4a** (19.4 g, 0.046 mole) in anhydrous ethyl ether (2200 ml) was added during 4 hours to a solution of sodium bis(trimethylsilyl)amide (46.5 g, 0.253 mole) in the same solvent (2300 ml). The reaction mixture was stirred for an additional 20 minutes and washed with 5% aqueous sodium phosphate monobasic (2000 ml). The organic phase was dried and evaporated. The hexamethyldisilazane formed was distilled at 50°, 0.3 mm Hg and the residue was chromatographed on a silica gel column by eluting with 40% cyclohexane in ethyl acetate to give first 2.9 g of compound **3a** and then 12.5 g (73%) of **5a** as an oil; ir (film): ν max 1720 (ester), 1650 (ketone); ^{1}H-nmr (deuteriochloroform): δ 1.17 (t, J = 6, 3H, N-CH_2CH_3), 1.29 (t, J = 6.5, 3H, COO-CH_2CH_3), 2.20 (s, 3H, CH_3), 3.24 and 3.33 (AB part of an ABX_3 system - Irradiation at 1.17 ppm gives $^2[J]_{AB}$ = 13.5, 2H, N-CH_2CH_3), 3.57 and 3.67 (dd, 2H, $^2[J]$ = 12, $^3[J]$ = 12 and 3 CH_2 quinoline), 3.49 (dd, 1H, $^3[J]$ = 12 and 3, CH quinoline), 4.24 (q, 2H, COO-CH_2-CH_3. Two further resonance lines in the expanded spectra due to the two epimers); 4.49 and 4.56 (d, 2H, $^2[J]$ = 13.5, CH_2Ph), 5.02 and 5.11 (d, 2H, $^2[J]$ = 12, N-CH_2-O), 6.17 (s, 1H, H pyrrole), 7.40 (m, 5H, aromatic).

Anal. Calcd. for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.56. Found: C, 68.01; H, 7.06; N, 7.50.

By employing this procedure, compounds **5b** (oil, 58%) and **5c** (oil, 75%) were obtained from **4b** and **4c** and purified by flash chromatography; ms: m/z = 250 [M·] (0.8%), 248 [M-H_2]· (40.6%).

5b. *Anal.* Calcd. for $C_{20}H_{24}N_2O_4$: C, 67.39; H, 6.78; N, 7.86. Found: C, 67.64; H, 7.09; N, 7.92.

5c. *Anal.* for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.00; H, 7.22; N, 10.88.

Ethyl 1-Benzyloxymethyl-7-ethyl-4,7-dihydro-2-methyl-4-oxo-1*H*-pyrrolo-[2,3-*b*]pyridine-5-carboxylate (**6a**).

A 0.1 *M* solution of iodine in absolute ethanol (310 ml) was dropped during 2 hours to a solution of **5a** (12.5 g, 0.034 mole) and dry potassium acetate (33.1 g, 0.337 mole) in the same solvent (330 ml). The end of the oxidation was checked on tlc, cyclohexane-ethyl acetate, 30:70. The solvent was evaporated, the residue was dissolved in 10% aqueous ammonium acetate (100 ml) and extracted with methylene chloride. The organic layer was dried, evaporated and chromatographed on a silica gel column by eluting with 2% methanol in methylene chloride to give 10.5 g (85%) of **6a**. The analytical sample was obtained by recrystallization from ethyl acetate, mp 115-116°; ir (nujol): ν 1720 (ester), 1610 (ketone); ^{1}H-nmr (deuteriochloroform): δ 1.33 (t, J = 6, 3H, N-CH_2CH_3), 1.42 (t, J = 6, 3H, $CO_2CH_2CH_3$); 2.29 (s, CH_3); 4.31 (q, 2H, N-CH_2CH_3); 4.43 (q, 2H, $CO_2CH_2CH_3$), 4.55 (s, CH_2Ph), 5.48 (s, N-CH_2O), 6.44 (s, H-C3), 7.27-7.47 (m, 5H-aromat), 8.18 (s, H-C6).

Anal. Calcd. for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.37; H, 6.58; N, 7.48.

By employing this procedure, compounds **6b** (82%) and **6c** (72%) were obtained from **5b** and **5c** and were recrystallized from ethyl acetate; ms: m/z = 250 [M·] (91.5%), 205 [M-·OC_2H_5]$^+$ (14.3%), 203 [205-H_2]$^+$ (17.6%), 177 [M-$CO_2C_2H_5$]$^+$ (100.0%), 149 [177-C_2H_4]$^+$ (41.8%), 135 [M-$CO_2C_2H_5$-·CH_3]$^+$ (55.1%).

6b. mp 135-136° *Anal.* Calcd. for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.25; N, 7.90. Found: C, 67.55; H, 6.46; N, 8.05.

6c. mp 107-109° *Anal.* Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.49; N, 11.28. Found: C, 62.61; H, 6.38; N, 11.00.

Ethyl 7-Ethyl-2-methyl-4,7-dihydro-4-oxo-1*H*-pyrrolo[2,3-*b*]pyridin-5-carboxylate (**8**).

A solution of **6a** (3.7 g, 10 mmoles) and trifluoroacetic acid (1.54 ml, 20 mmoles) in glacial acetic acid (185 ml) was hydrogenated at room temperature and 5 atmospheres of pressure in the presence of 10% palladium on carbon (3.7 g) for 4 hours. The exhausted catalyst was filtered off, replaced with 3.7 g of fresh catalyst and the hydrogenation was continued at the same pressure overnight.

The reaction mixture was filtered and potassium acetate (3.7 g) was added to the filtrate which was then evaporated under reduced pressure. The residue was repeatedly extracted with chloroform which was evaporated. Recrystallization of the residue from ethyl acetate and chromatography of the mother liquor on a silica gel column eluted with 2% methanol in chloroform gave a total amount of 2.4 g (96%) of **8**, mp 263-265°; ir (nujol): ν 1730 (ester), 1630 (ketone), 1600, 1550 (C=C); ^{1}H-nmr (DMSO-d_6): δ 1.22 (t, J = 6, 3H, NCH_2CH_3), 1.34 (t, J = 6, 3H, $CO_2CH_2CH_3$), 2.29 (s, CH_3), *ca.* 3.40 (NH), 4.17 and 4.21 (each q, 4H, CH_2-CH_3), 6.14 (s, H-C3), 8.20 (s, H-C6); ms: m/z = 248 [M·] (40.6%), 202 [M-C_2H_5OH]· (58.6%), 174 [M-$HCO_2C_2H_5$]· (100.0%), 146 [174-C_2H_4]· (18.6%), 145 [174-·C_2H_5]$^+$ (16.1%).

Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.49; N, 11.28. Found: C, 62.56; H, 6.45; N, 11.09.

Ethyl 1,2-Dimethyl-7-ethyl-4,7-dihydro-4-oxo-1*H*-pyrrolo[2,3-*b*]pyridin-5-carboxylate (**9**).

To a solution of **8** (620 mg, 2.49 mmoles) in dry DMF (8 ml) at 0° under argon was added 55% sodium hydride in mineral oil (120 mg, 2.74 mmoles). After stirring at 0° for 2 hours a solution of dimethyl sulphate (0.26 ml, 2.74 mmoles) in dry DMF (2 ml) was added and stirring was continued for an additional hour. Excess hydride was decomposed with acetic acid and the solvent was evaporated under reduced pressure. The residue was taken up with saturated solution of sodium chloride and chloroform. The organic layer was dried, evaporated and the residue was chromatographed on a silica gel column by eluting with 10% methanol in chloroform to give 350 mg (57%) of **9**, and 200 mg of starting material **8**. The analytical sample of **9** was obtained by recrystallization from acetone, mp 175-177°; ir (nujol): ν 1700 (ester), 1630 (ketone), 1580, 1560 (C=C); ^{1}H-nmr (deuteriochloroform): δ 1.24 (t, J = 6, 3H, NCH_2CH_3), 1.38 (t, J = 6.3, 3H, $CO_2CH_2CH_3$), 2.29 (s, CH_3), 3.77 (s, N-CH_3), 4.20 (q, 2H, NCH_2CH_3), 4.44 (q, 2H, $CO_2CH_2CH_3$), 6.29 (s, H-C3), 8.20 (s, H-C6).

Anal. Calcd. for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N,10.68. Found: C, 64.00; H, 7.01; N, 10.42.

2-Substituted-7-ethyl-4,7-dihydro-4-oxo-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylic Acids **7a**, **b**, **c**, **10**, **11**.

General Procedure for the Hydrolysis of Esters **6a**, **b**, **c**, **8**, **9** (Table 1).

A solution of 1 mmole of the appropriate ester in ethanol (6 ml) containing 2 mmoles of potassium hydroxide was heated at reflux for 1 hour. The solvent was evaporated, the residue dissolved in the minimum amount of water filtered and acidified at *p*H 5 with glacial acetic acid. The precipitate was collected by filtration and dried under vacuum. The yield ranged from 52% to 98% and the results are summarized in Table 1.

Ethyl 2,3-Dibromo-7-ethyl-4,7-dihydro-4-oxo-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (**12**).

To a dispersion of **6b** (708 mg, 2 mmoles) in refluxing carbon tetrachloride (180 ml) was dropped a 0.4 *M* solution of bromine in the same solvent (10 ml) and the mixture was heated at reflux for 1 hour.

After cooling to room temperature, the precipitate was collected by filtration, dissolved in absolute ethanol (80 ml) and the solution was heated at 60° for 1 hour to complete the removal of the protective benzyloxymethyl group. The solvent was evaporated and the residue was triturated with ethyl ether to give 830 mg (87%) of the hydrobromide of **12**. The free base (550 mg) was obtained by partitioning this salt between chloroform and 5% sodium bicarbonate and evaporating the organic phase, mp 184° dec; ir (nujol): ν 1680 (ester), 1630 (ketone), 1610, 1550 (C=C); ^{1}H-nmr (deuteriochloroform): δ 1.46 (t, J = 6, 3H, N-CH_2CH_3), 1.60 (t, J = 6.3, 3H, $CO_2CH_2CH_3$), 4.49 (q, 2H, N-CH_2CH_3), 4.58 (q, 2H, $CO_2CH_2CH_3$), 8.28 (s, H-C6), 12.25 (br s, NH).

Anal. Calcd. for $C_{12}H_{12}Br_2N_2O_3$: C, 36.76; H, 3.08; N, 7.14. Found: C, 36.75; H, 3.04; N, 7.12.

When the bromination was run in acetic acid as described for **13**, compound **12** was obtained in low yield together with four unidentified by products.

Ethyl 2,3-Dibromo-7-ethyl-1-methyl-4,7-dihydro-4-oxo-1*H*-pyrrolo[2,3-*b*]-pyridine-5-carboxylate (**13**).

To a solution of **6c** (110 mg, 0.44 mmole) in glacial acetic acid (4 ml) cooled at 16° was dropped a 0.39 *M* solution of bromine in glacial acetic acid (2.25 ml, 0.88 mmole) in which dried potassium acetate (86 mg, 0.88 mmole) had been dissolved. After stirring for 15 minutes, the yellow precipitate was collected by filtration, dissolved in methylene chloride and washed with 10% aqueous ammonium acetate. The organic phase was dried, evaporated and the residue was triturated with ethyl ether to give 70 mg (39%) **13**, mp 222-224° dec.

Anal. Calcd. for $C_{13}H_{14}Br_2N_2O_3$: C, 38.45; H, 3.47; N, 6.89. Found: C, 38.49; H, 3.77; N, 6.78.

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