Synthesis of 4,7-Dihydro-4-oxopyrrolo[2,3-*b*]pyridine-5-carboxylic Acid Derivatives as Potential Antimicrobial Agents

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Synthetic approaches to 1-benzyl-7-alkyl-2,3-dimethyl-4,7-dihydro-4-oxopyrrolo[2,3-*b*]pyridine-5-carboxylic acids from 1-benzyl-2-amino-3-*t*-butoxycarbonyl-4,5-dimethylpyrrole are reported.

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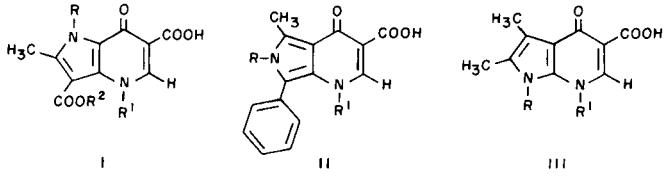
In previous communications [1,2], we described the synthesis and antibacterial properties of two series of fused pyrrolopyridines, 4,7-dihydro-7-oxopyrrolo[3,2-*b*]pyridine-6-carboxylic acids I and 1,4-dihydro-4-oxopyrrolo[3,4-*b*]-pyridine-3-carboxylic acids II, respectively. As a result of our continued interest in fused pyrrolopyridines as potential antimicrobial agents, we now wish to report the synthesis of a series of 4,7-dihydro-4-oxopyrrolo[2,3-*b*]pyridine-5-carboxylic acids III.

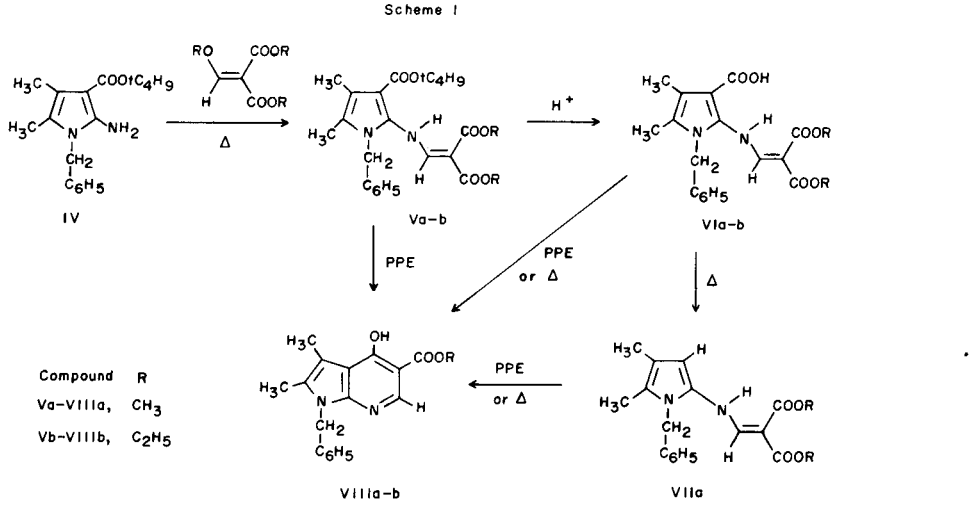


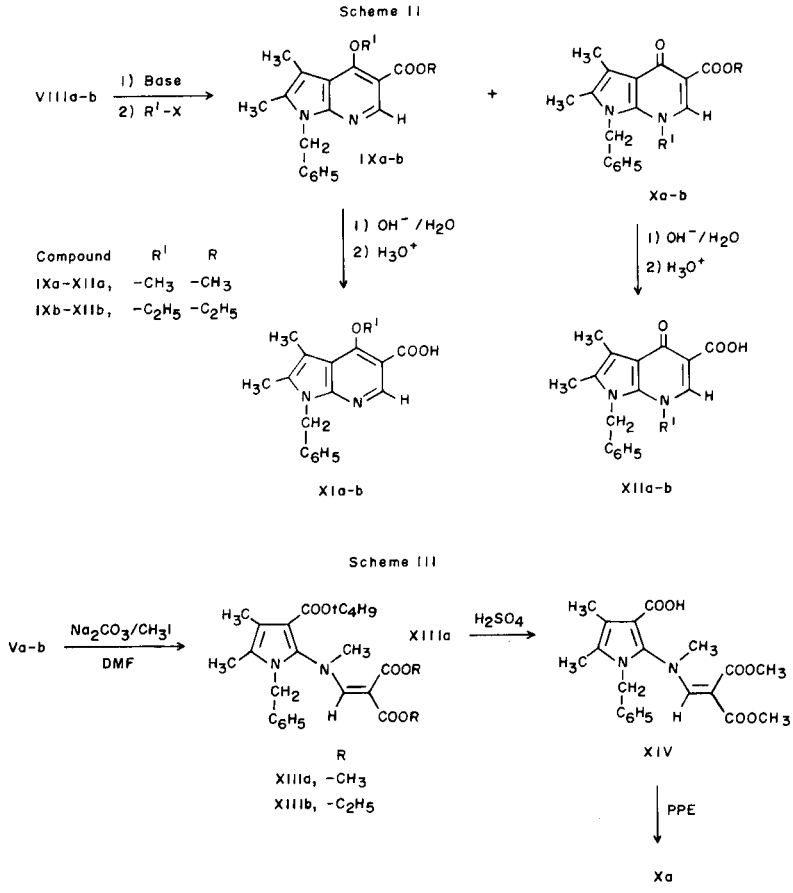
I II III

In the first synthetic approach to compounds of series III (Scheme I and II), 1-benzyl-2-amino-3-*t*-butoxycarbonyl-4,5-dimethylpyrrole (IV) [3] was condensed with dimethyl methoxymethylenemalonate and diethyl ethoxymethylenemalonate to yield the tri-esters Va and Vb, respectively. The *t*-butyl ester of compounds Va and Vb was selectively hydrolyzed with methane sulfonic acid or concentrated sulfuric acid at 0° to yield the corresponding carboxylic acids, VIa and VIb. The carboxylic acid VIa undergoes facile decarboxylation upon heating to give VIIa. 1-Benzyl-2,3-dimethyl-4-hydroxypyrrolo[2,3-*b*]pyridine-5-methylcarboxylate (VIIIa) was obtained by refluxing compound VIIa in Dowtherm® A [4] or by heating it in polyphosphoric ester [5]. The precursors Va and VIa were also cyclized in polyphosphoric ester to give VIIIa, although the yields were lower. The carboxylic acids VIa and VIb in refluxing Dowtherm® A underwent intramolecular decarboxylative cyclization to yield VIIIa and VIIIb, respectively. The synthesis of VIIIb from other precursors was not investigated.

In a wide variety of systems that are structurally related to VIIIa-b, alkylation of the pyridone nitrogen atom has been easily accomplished. In direct contrast, attempts to *N*-alkylate compounds VIIIa or VIIIb (Scheme II), utilizing conventional *N*-alkylation procedures [7-13], gave exclusively the *O*-alkylated compounds 1Xa,b. The *N*-alkylated compounds Xa,b were obtained as products from thallous ethoxide induced alkylation [14] of VIIIa and VIIIb with methyl iodide and ethyl iodide, respectively. Even under these conditions, the *O*-alkylated compounds IXa and IXB were also obtained. The R_f values for the

Scheme I





O-alkylated and *N*-alkylated products were significantly different; therefore, the isomers were easily separated using column chromatography. The four pure esters, IXa-b, Xa-b, were hydrolyzed in aqueous sodium hydroxide to yield the corresponding carboxylic acids, XIa-b, XIIa-b.

The second synthetic approach is illustrated in Scheme III. Because of the difficulties encountered in the selective *N*-alkylation of VIIIa-b, we explored this alternate approach wherein *N*-alkylation was accomplished prior to cyclization. Thus, Va was selectively *N*-alkylated with methyl iodide to yield XIIIa by utilizing anhydrous sodium carbonate as the base and dry dimethylformamide as the solvent. The *t*-butyl ester of XIIIa was hydrolyzed in concentrated sulfuric acid to yield the carboxylic acid XIV. The acid was cyclized in polyphosphoric ester to yield Xa. Attempts to *N*-alkylate Vb with ethyl iodide were unsuccessful, however compound Vb was successfully alkylated with methyl iodide to yield XIIIb utilizing the procedure described for the alkylation of Va. The failure of Vb to alkylate with ethyl iodide was possibly due to steric hindrance. As an alternate means of obtaining the *N*-ethyl analog of XIIIa, 1-benzyl-2-ethylamino-3-*t*-butoxycarbonyl-4,5-dimethylpyrrole [15] was condensed with dimethyl methoxymethylenemalonate under the conditions previously described. Only unidentifiable products were obtained from that reaction.

The carboxylic acids XIIa-b were found to exhibit a relatively broad spectrum of antimicrobial activity when tested *in vitro*. The minimum inhibitory concentrations ranged from 16-32 micrograms per milliliter in most of the bacteria that were selected for testing.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. The nmr spectra were determined on a Varian EM360A or EM390 spectrometer using tetramethylsilane as an internal standard and deuteriochloroform as the solvent. Infrared spectra were determined on a Beckman Acculab 4 spectrophotometer using the potassium bromide technique. Elemental analyses were performed by Atlantic Microlab, Inc. Atlanta, Georgia. The tlc were performed on Eastman Chromatogram Sheets, type 6060 (silica gel).

Dimethyl *N*-[1-Benzyl-3-*t*-butoxycarbonyl-4,5-dimethylpyrrol-2-yl]aminomethylenemalonate (Va).

A mixture of 1-benzyl-2-amino-3-*t*-butoxycarbonyl-4,5-dimethylpyrrole (IV) [3] (120.0 g, 0.4 mole) and dimethyl methoxymethylenemalonate (73.0 g, 0.42 moles) was heated for 3 hours at 150-160° while stirring under an argon atmosphere. The residue was dissolved in methanol and stored in a freezer overnight. The yellow crystals (114.7 g, 65%) were collected and air dried. A small sample was recrystallized from hexanes to yield yellow crystals (homogeneous on tlc; in ethyl acetate, Rf 0.62), mp 125-126°; ir (potassium bromide): 3280, 2980, 1720, 1670, 1600, 1440, 1390, 1220, 1110, 720, 690 cm^{-1}; nmr (deuteriochloroform): δ 1.5 (s, 9H, methyls of *t*-butoxycarbonyl), 2.05 (s, 3H, methyl at C_4), 2.20 (s, 3H, methyl at C_5), 3.5 (s, 3H, methoxy of malonate), 3.75 (s, 3H, methoxy of malonate), 5.0 (s, 2H, benzylic methylene), 6.8-7.4 (m, 5H, ArH), 7.83 (d, 1H, J

= 13.5 Hz, olefinic proton), 10.5 (d, 1H, J = 13.5 Hz, NH) ppm.

Anal. Calcd. for $C_{24}H_{30}N_2H_6$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.31; H, 6.91; N, 6.29.

Diethyl *N*-[1-Benzyl-3-*t*-butoxycarbonyl-4,5-dimethylpyrrol-2-yl]aminomethylenemalonate (Vb).

A mixture of IV (9.0 g, 0.03 mole) and diethyl ethoxymethylenemalonate (8.65 g, 0.04 mole) was heated for 2 hours at 150-160° while stirring under vacuum (15 mm Hg). The crude residue was recrystallized from methanol to yield a yellow solid (5.4 g, 38%). A one gram sample was recrystallized from hexanes (40 ml) to yield 0.9 gram of yellow crystals (homogeneous on tlc - in ethyl acetate, Rf 0.63), mp 98-99°; ir (potassium bromide): 3240, 2970, 1720, 1660, 1600, 1200, 1160, 1100, 1070, 730, 690 cm^{-1}; nmr (deuteriochloroform): δ 1.13 (t, 3H, J = 7.0 Hz, methyl group of ethyl ester), 1.27 (t, 3H, J = 7.0 Hz, methyl group of ethyl ester), 1.5 (s, 9H, methyls of *t*-butoxycarbonyl), 2.03 (s, 3H, methyl at C_4), 2.20 (s, 3H, methyl at C_3), 4.05 (q, 2H, J = 7.0 Hz, methylene of ethyl ester), 4.23 (q, 2H, J = 7.0 Hz, methylene of ethyl ester), 4.97 (s, 2H, benzylic methylene), 6.8-7.3 (m, 5H, ArH), 7.83 (d, 1H, J = 13.5 Hz, olefinic proton), 10.45 (d, 1H, J = 13.5 Hz, NH) ppm.

Anal. Calcd. for $C_{26}H_{34}N_2O_6$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.42; H, 7.30; N, 5.92.

Dimethyl *N*-[1-Benzyl-3-carboxy-4,5-dimethylpyrrol-2-yl]aminomethylenemalonate (VIa). Method A.

Compound Va (5.0 g, 0.0113 mole) was added to concentrated sulfuric acid (20 g) that had been previously cooled to 0°. The resulting solution was stirred for one minute at 0°, then for an additional minute after removing from the ice bath. Crushed ice (150 g) was added and the resulting suspension was diluted with water. The precipitated solid was collected, washed free of mineral acid with water, and air dried. The solid (4.3 g, 98%) was recrystallized from ethyl acetate to yield pale yellow flakes, mp 183-185° with decarboxylation; ir (potassium bromide): 2400-3600 broad, 2940, 1720, 1660, 1600, 1330, 1290, 1215, 1075, 790, 745, 690 cm^{-1}; nmr (deuteriochloroform): δ 2.05 (s, 3H, methyl at C_4), 2.23 (s, 3H, methyl at C_3), 3.50 (s, 3H, methoxy of malonate), 3.76 (s, 3H, methoxy of malonate), 5.03 (s, 2H, benzylic methylene), 6.8-7.4 (m, 5H, ArH), 7.9 (d, 1H, J = 14.1 Hz, olefinic proton), 9.2 (s, 1H, -COOH), 10.85 (d, 1H, J = 14.1 Hz, NH) ppm.

Anal. Calcd. for $C_{20}H_{22}N_2O_6$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.09; H, 5.77; N, 7.22.

Method B.

Compound Va (36.0 g, 0.0813 mole) was added to methane sulfonic acid (108 g) that had been previously cooled to 0°. The resulting solution was stirred for 5 minutes at room temperature, then diluted with ice and water (700 ml). The resulting solid was collected, washed with water, then dissolved in 500 ml of 0.2 *M* potassium hydroxide. The solution was filtered and the carboxylic acid was precipitated with 1*N* hydrochloric acid. The carboxylic acid (26.0 g, 83%) was recrystallized from methanol and characterized as VIa by spectral data and melting point.

Diethyl *N*-[1-Benzyl-3-carboxy-4,5-dimethylpyrrol-2-yl)aminomethylenemalonate (VIb).

Compound Vb (22.0 g, 0.047 mole) was hydrolyzed in concentrated sulfonic acid described in Method A. The dark yellow product (5.0 g, 26%) was recrystallized from methanol, mp 151-152°; ir (potassium bromide): 3600-3300 (broad), 2290, 1715, 1625, 1589, 1540, 1475, 1440, 1405, 1380, 1340, 1290, 1240, 1220, 1125, 1080, 1020, 790, 688 cm^{-1}; nmr (deuteriochloroform): δ 1.58 (t, 3H, J = 7.0 Hz, methyl of ethyl ester), 1.78 (t, 3H, J = 7.0 Hz, methyl of ethyl ester), 2.45 (s, 3H, C_4-methyl), 2.63 (s, 3H, C_5-methyl), 4.50 (q, 2H, J = 7.0 Hz, methylene of ester), 4.60 (q, 2H, J = 7.0 Hz, methylene of ester), 5.4 (s, 2H, benzylic methylene), 7.68-7.12 (m, 5H, ArH), 8.15 (d, 1H, J = 12 Hz, olefinic proton), 10.85 (d, 1H, J = 12 Hz, NH), carboxylic acid proton merged into base line) ppm.

Anal. Calcd. for $C_{22}H_{26}N_2O_6$: C, 63.77; H, 6.28; N, 6.76. Found: C, 63.54; H, 6.32; N, 6.74.

Dimethyl *N*-[1-Benzyl-4,5-dimethylpyrrol-2-yl]aminomethylenemalonate (VIIa).

Compound VIa (11.6 g, 0.03 mole) was heated under argon in an oil-bath at 190-200° until bubbling ceased (≈5-7 minutes). The residue was crystallized from methanol (50 ml) after storing in a freezer overnight. The solid (7.5 g, 73%) was recrystallized twice from methanol to yield yellow needles (homogeneous on tlc, in ethyl acetate, Rf 0.56), mp 103-104°; ir (potassium bromide): 3240, 3140, 2950, 1720, 1660, 1610, 1440, 1310, 1250, 1080, 790, 750, 720, 690 cm^{-1}; nmr (deuteriochloroform): δ 2.03 (s, 3H, methyl at C_4), 2.07 (s, 3H, methyl at C_5), 3.67 (s, 3H, methoxy of malonate), 3.75 (s, 3H, methoxy of malonate), 4.94 (s, 2H, benzylic methylene), 5.80 (s, 1H, proton at C_3), 6.8-7.4 (m, 5H, ArH), 8.0 (d, 1H, J = 13.8 Hz, olefinic proton), 10.48 (d, 1H, J = 13.8 Hz, NH) p p m .

Anal. Calcd. for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.61; H, 6.50; N, 8.14.

Methyl 1-Benzyl-2,3-dimethyl-4-hydroxypyrrolo[2,3-*b*]pyridine-5-carboxylate (VIIIa). Method A.

A solution of VIIa (6.85 g, 0.02 mole) in 20 ml of warm Dowtherm® A was added over a period of 8 minutes to 40 ml of refluxing Dowtherm® A. After the addition was complete, the solution was refluxed for an additional 8 minutes, the Dowtherm® A was removed *in vacuo*, and the residue was treated with hexane (100 ml). The hexanes suspension was stirred in a dry ice bath for 15 minutes and the insoluble product collected by filtration. The crude solid was boiled with 50 ml methanol, cooled, and again the solid collected. The cyclized product (5.2 g, 84%) was recrystallized from methanol (1 g per 50 ml) to yield golden colored crystals (homogeneous on tlc; in ethyl acetate, Rf 0.58), mp 142-143°; ir (potassium bromide): 2800-2500 broad, 2920, 1660, 1620, 1435, 1350, 1280, 1200, 800, 790, 770, 725, 690 cm^{-1}; nmr (deuteriochloroform): δ 2.17 (s, 3H, methyl at C_3), 2.4 (s, 3H, methyl at C_2), 3.95 (s, 3H, methyl of ester), 5.4 (s, 2H benzylic methylene), 6.9-7.3 (m, 5H, ArH), 8.6 (s, 1H, proton at 6-position), 11.63 (s, 1H, OH) ppm.

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.84; N, 9.03. Found: C, 69.51; H, 5.88; N, 8.99.

Method B.

A mixture of Va (12.0 g, 0.027 mole) in polyphosphoric esters [6] (50 g) was heated with stirring at 90-100° for 3.5 hours. The reaction mixture was cooled, poured over ice-water (350 ml) and neutralized with aqueous sodium hydroxide (10%). The precipitate was collected and recrystallized several times from methanol to yield a yellow solid (4.1 g, 49%). The compound was characterized as VIIIa by infrared and nmr spectra and melting point.

Method C.

A mixture of compound VIa (5.6 g, 0.014 mole) in polyphosphoric ester (30 g) was heated at 100° for 2.5 hours. The cooled reaction mixture was poured over ice-water (250 ml) and neutralized with aqueous sodium hydroxide (5%). The precipitate was collected, washed with water, and air dried. The crude product (3.1 g, 69%) was recrystallized several times from methanol and characterized as VIIIa by the infrared and nmr spectra and melting point.

Method D.

A suspension of VIa (4.5 g, 0.0116 mole) in 60 ml of Dowtherm® A was added to 50 ml of refluxing Dowtherm® A. The mixture was vigorously refluxed for 15 minutes, the solvent removed *in vacuo*, and the residue triturated with *n*-hexanes. The crude solid (2.8 g, 54%) was purified by Florisil column chromatography by eluting with *n*-hexane. The light yellow solid was characterized as VIIIa by the infrared and nmr spectra and melting point, 141-142°.

Ethyl 1-Benzyl-2,3-dimethyl-4-hydroxypyrrolo[2,3-*b*]pyridine-5-carboxylate (VIIIb).

A mixture of VIb (4.0 g, 0.0097 mole) and polyphosphoric ester (20 g) was heated with stirring at 125-135° for 1 hour under argon. Workup as

described under Method B gave a crude brownish-yellow solid (2.3 g, 73%), mp 110-112°. The product was further purified by silica gel column chromatography eluting with hexane, yield = 1.1 g (35% isolated), mp 115-116°; ir (potassium bromide): 3600-3300 (broad, phenolic OH), 1665 (COOEt), 1620, 1535, 1485, 1450, 1400, 1370, 1342, 1320, 1270, 1245, 1185, 1125, 1090, 1020, 970, 945, 910, 890, 800, 770, 728 and 690 cm^{-1}; nmr (deuteriochloroform): δ 1.37 (t, 3H, J = 7.0 Hz, methyl of ethyl ester), 2.15 (s, 3H, C_3-CH_3), 2.40 (s, 3H, C_2-CH_3), 4.35 (q, 2H, J = 7.0 Hz, methylene of ester), 5.40 (s, 2H, benzylic methylene), 6.80-7.28 (m, 5H, ArH), 8.55 (s, 1H, C_6-H), 11.65 (s, 1H, OH, exchangeable with deuterium oxide) ppm.

Anal. Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.37; H, 6.17; N, 8.64. Found: C, 70.22; H. 6.24; N, 8.61.

Methyl 1-Benzyl-2,3-dimethyl-4-methoxypyrrolo[2,3-*b*]pyridine-5-carboxylate (IXa).

Compound VIIIa (3.1 g, 0.01 mole) in anhydrous dimethylformamide (30 ml) was stirred in an ice-bath as sodium hydride (0.29 g, 0.012 mole) was added. After the bubbling had ceased, methyl iodide (2.8 g, 0.02 mole) was added and the ice-bath removed. The mixture was heated with stirring at 40° for 2 days. The mixture was poured over ice-water (300 g), the solid was collected by filtration, and air dried. The off-white solid (2.4 g, 75%) was recrystallized from cyclohexane (150 ml) (homogeneous on tlc - in ethyl acetate, Rf 0.69), mp 124-125°; ir (potassium bromide): 2960, 1730, 1600, 1580, 1440, 1220, 1200, 700 cm^{-1}; nmr (deuteriochloroform): δ 2.20 (s, 3H, CH_3 at C_3), 2.37 (s, 3H, CH_3 at C_2), 3.93 (s, 3H, methyl of ester), 4.03 (s, 3H, methyl of methoxy at 4-position), 5.43 (s, 2H, benzylic methylene), 6.8-7.3 (m, 5H, ArH), 8.7 (s, 1H, proton at 6-position) ppm.

Anal. Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.27; H. 6.26; N, 8.61.

Methyl 1-Benzyl-2,3,7-trimethyl-4,7-dihydro-4-oxopyrrolo[2,3-*b*]pyridine-5-carboxylate (Xa). Method A.

A hot solution of compound VIIIa (1.55 g, 0.005 mole) in dry methanol (100 ml) was treated with thallous ethoxide (1.6 g, 0.0064 mole) and stirred under nitrogen at room temperature for 2 hours. The solvent was removed *in vacuo*, and the residual thallous complex was covered with methyl iodide (25 ml), and stirred at room temperature overnight. The excess methyl iodide was removed *in vacuo*, and the crude residue was recrystallized from a small volume of methanol. The first crop of crystals (60 mg) were characterized as the *O*-alkylated product IXa by its infrared and nmr spectra and melting point, 124-125°. The major *N*-alkylated product (Xa) slowly crystallized from the mother liquor as the solvent evaporated. The light yellow residue was triturated with hexane and further purified by silica gel column chromatography eluting with ethyl acetate to yield the pure product (0.2 g), mp 190-191°; ir (potassium bromide): 3600-3200 (broad hump, hydrated form), 3040, 2990, 2960, 2922, 2860, 1720, 1700, 1690, 1615, 1570, 1530, 1435, 1388, 1348, 1300, 1250, 1200, 1140, 1110, 1060, 1020, 970, 950, 865, 795, 755, 720 and 690 cm^{-1}; nmr (deuteriochloroform): δ 7.59 (s, 1H, olefinic), 7.35-6.50 (m, 5H, ArH), 5.32 (s, 2H, benzylic methylene), 3.80 (s, 3H, $COOCH_3$), 3.70 (s, 3H, N-CH_3), 2.40 (s, 3H, C_2-Me), and 2.05 (s, 3H, C_3-Me).

Anal. Calcd. for $C_{19}H_{20}N_2O_3 \cdot 0.5\ H_2O$: C, 68.45; H, 6.35; N, 8.40. Found: C, 68.49; H, 6.33; N, 8.34.

Method B.

The carboxylic acid XIV (5.0 g, 0.015 mole) in polyphosphoric ester (30 g) was cyclized according to the procedure described for VIIIa under Method C. The crude black solid (5.0 g) was purified by silica gel column chromatography eluting with methylene chloride. The white product (0.94 g, 15%) was characterized as Xa by the infrared and nmr spectra and melting point, 192-193°.

Ethyl 1-Benzyl-2,3-dimethyl-4-ethoxypyrrolo[2,3-*b*]pyridine-5-carboxylate (IXb) and Ethyl 1-Benzyl-2,3-dimethyl-7-ethyl-4,7-dihydro-4-oxopyrrolo-[2,3-*b*]pyridine-5-carboxylate (Xb).

To a solution of VIIIb (1.28 g, 0.0039 mole) in dry ethanol (100 ml), thallous ethoxide (1.08 g, 0.0043 mole) was added. The mixture was stirred at room temperature under argon for 30 minutes, then refluxed for 2 hours. The solvent was remove *in vacuo*, the light yellow thallous salt was transferred to a smaller reaction vessel, and covered immediately with iodoethane (30 ml). The reaction mixture was refluxed for 20 hours under an argon atmosphere. The deep yellow thallous iodide salt was filtered off through a fluted filter paper. The residue was washed with 100 ml of methylene chloride and the filtrate was evaporated to dryness which gave 1.38 g (99%) of light brown viscous material; tlc (acetone:methanol, 8:2): Rf = 0.53 (*N*-Ethyl product) and Rf = 0.65 (*O*-Ethyl product). Separation was achieved by silica gel column chromatography applying gradient elution technique with hexane and ethyl acetate (2:10 mixture of hexane in ethyl acetate). The *O*-ethylated product IXb was obtained in a yield of 0.06 g (4.3%) which had mp 91-92°; ir (potassium bromide): 3080, 3040, 2990, 2950, 2910, 2870, 1705, 1595, 1572, 1540, 1490, 1475, 1440, 1390, 1355, 1322, 1290, 1244, 1222, 1200, 1180, 1120, 1105, 1040, 1025, 950, 915, 895, 870, 800, 780, 755, 740, 700 and 650 cm^{-1}; nmr (deuteriochloroform): δ 1.25-1.60 (two t, 6H, J = 7.0 Hz, methyl groups), 2.18 (s, 3H, C_3-CH_3), 2.32 (s, 3H, C_2-CH_3), 3.85-4.58 (two q, 4H, J = 7.0 Hz, methylenes), 5.38 (s, 2H, benzylic CH_2), 6.85-7.30 (m, 5H, ArH), 8.65 (s, 1H, C_6-H) ppm; ms: M^+ (m/e) 352; Rf = 0.61 (ethyl acetate:hexanes, 3:7).

Anal. Calcd. for $C_{21}H_{24}N_2O_3$: C, 71.59; H, 6.82; N, 7.95. Found: C, 71.64; H, 6.87; N, 7.93.

The *N*-ethylated product Xb was obtained in a yield of 0.01 g (0.7%), mp 193-194°; ir (potassium bromide): 3600-3200 (broad, hydrated form), 3040, 2990, 2920, 1722, 1710, 1690, 1680, 1620, 1590, 1530, 1448, 1390, 1370, 1345, 1300, 1260, 1242, 1200, 1130, 1115, 1060, 1020, 910, 800, 725 and 690 cm^{-1}; nmr (deuteriochloroform): δ 7.82 (s, 1H, olefinic), 7.50-6.50 (m, 5H, ArH), 5.28 (s, 2H, benzylic methylene), 4.28 (s, 2H, $COOC_2H_5$, J = 8 Hz), 3.85 (distorted quartet, 2H, N-C_2H_5, J = 7 Hz and 4 Hz), 2.5 (s, 3H, C_2-Me), 2.15 (s, 3H, C_3-Me), 1.38 (t, 6H, two methyl protons of the two ethyl groups, J = 7 Hz).

Anal. Calcd. for $C_{21}H_{24}N_2O_3 \cdot 0.5\ H_2O$: C, 69.81; H, 6.92; N, 7.75. Found: C, 70.05; H, 6.89; N, 7.73.

1-Benzyl-2,3-dimethyl-4-methoxypyrrolo[2,3-*b*]pyridine-5-carboxylic Acid (XIa).

A mixture of IXa (0.8 g, 0.0025 mole), sodium hydroxide (0.2 g, 0.005 mole) and distilled water (100 ml) was refluxed with stirring until a homogeneous solution was achieved. After cooling, the solution was filtered and acidified by dropwise addition of 6*N* hydrochloric acid. The white precipitate was collected, washed with water, and air-dried. The dried product was triturated with n-hexane, collected, and dried. The white powder (0.42 g, 54%) was analytical pure, mp 214-215°; ir (potassium-bromide): 3600-2200 (broad), 3080, 3040, 2930, 2860, 2830, 2600-2380 (broad hump), 1705 (CO), 1600, 1580, 1545, 1490, 1450, 1385, 1342, 1300, 1265, 1210, 1120, 1090, 1070, 1045, 1005, 920, 805, 752, 720, and 690 cm^{-1}; nmr (deuteriochloroform): δ 2.20 (s, 3H, C_3-CH_3), 2.38 (s, 3H, C_2-CH_3), 4.02 (s, 3H, -OCH_3), 5.45 (s, 2H, benzylic methylene), 6.75-7.30 (m, 5H, ArH), 7.7-8.7 (broad s, 1H, COOH), 8.8 (s, 1H, C_6-H) ppm.

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.68; H, 5.81; N, 9.03. Found: C, 69.48; H, 5.90; N, 8.98.

1-Benzyl-2,3-dimethyl-4-ethoxypyrrolo[2,3-*b*]pyridine-5-carboxylic Acid (XIb).

A mixture of IXb (1.84 g, 0.0052 mole), sodium hydroxide (0.8 g, 0.02 mole) in water (50 ml) and 2-methoxyethylether (60 ml) was refluxed for 1 hour. After cooling, the solution was filtered and the solvents removed *in vacuo*. The residue was dissolved in water (100 ml) and the solution acidified by dropwise addition of 6N hydrochloride acid. The precipitate was collected, washed with water, and air dried. The white powder (1.68 g, 100%), mp 203-204° was homogeneous on tlc, acetone/methanol (1:1) Rf = 0.54; ir (potassium bromide): 3050, 2990, 2920, 2700-2500 (broad), doublet at 1710 and 1695, 1600, 1582, 1545, 1495, 1480, 1452, 1385, 1360, 1300, 1265, 1250, 1215 (very strong), 1130, 1110, 1050, 1035, 950, 930, 910, 875, 815, 765, 730, 690, 670 and 615 cm^{-1}; nmr (deuteriochloro-

form): δ 1.50 (t, 3H, J = 7.0 Hz, CH_3 of ethyl), 2.22 (s, 3H, C_3-CH_3), 2.35 (s, 3H, C_2-CH_3), 4.30 (q, 2H, J = 7.0 Hz, methylene of ethyl), 5.45 (s, 2H, benzylic methylene), 6.60-7.35 (m, 5H, ArH), 8.82 (s, 1H, C_6-H) ppm.

Anal. Calcd. for $C_{19}H_{20}N_2O_3 \cdot 0.25\ H_2O$: C, 69.40; H, 6.25; N, 8.52. Found: C, 69.39; H, 6.24; N, 8.53.

1-Benzyl-2,3,7-trimethyl-4,7-dihydro-4-oxopyrrolo[2,3-*b*]pyridine-5-carboxylic Acid (XIIa).

A mixture of Xa (0.94 g, 0.0029 mole), sodium hydroxide (0.2 g, 0.005 mole) in water (100 ml) was refluxed until a homogeneous solution was achieved. Workup as described for compound XIa yielded a white powder (0.85 g, 94%), mp 262-263°, (homogeneous on tlc, acetone/methanol (8:2), Rf = 0.44); ir (potassium bromide): 3680-3200 (broad), 3060, 2980, 2920, 2860, 2500-2100 (broad hump), 1698 (very strong), 1632-1580 (very strong), 1632-1580 (very strong), 1540-1380 (strong multiplets), 1335, 1265, 1210, 1140, 1010, 990, 940, 900, 885, 800, 735, 690, 660 and 640 cm^{-1}; nmr (deuteriochloroform): δ 2.14 (s, 3H, C_3-CH_3), 2.39 (s, 3H, C_2-CH_3), 3.88 (s, 3H, N-CH_3), 5.42 (s, 2H, benzylic methylene), 6.52-7.40 (m, 5H, ArH), 7.80 (s, 1H, C_6-H), 16.55 (broad s, 1H, COOH) ppm; ms: M^+ (m/e) 310.

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.68; H, 5.81; N, 9.03. Found: C, 69.49; H, 5.83; N, 8.98.

1-Benzyl-2,3-dimethyl-7-ethyl-4,7-dihydro-4-oxopyrrolo[2,3-*b*]pyridine-5-carboxylic Acid (XIIb).

Compound Xb (0.2 g) was hydrolyzed according to the procedure described for XIa. The light yellow crystals were homogeneous on tlc, acetone, Rf = 0.60, mp 214-215°; ir (potassium bromide): 3600-3200 (broad), 2990, 2920, 2860, 1720, 1700, 1685, 1620, 1595, 1575, 1540, 1490, 1435, 1390, 1335, 1235, 1210, 1145, 1035, 970, 910, 885, 795, 725 and 690 cm^{-1}; nmr (deuteriochloroform): δ 1.45 (t, 3H, J = 7.0 Hz, CH_3 of ethyl), 2.20 (s, 3H, C_3-CH_3), 2.45 (s, 3H, C_2-CH_3), 4.1 (q, 2H, J = 7.0 Hz, methylene of ethyl) 5.35 (s, 2H, benzylic methylene), 6.60-7.32 (m, 5H, ArH), 8.10 (s, 1H, C_6-H) ppm. The carboxylic acid proton merged into the base line.

Anal. Calcd. for $C_{19}H_{20}N_2O_3 \cdot 0.25\ H_2O$: C, 69.39; H, 6.29; H, 8.52. Found: C, 69.21; H, 6.20; N, 8.45.

Dimethyl *N*-[1-Benzyl-3-*t*-butoxycarbonyl-4,5-dimethylpyrrol-2-yl]methylaminomethylenemalonate (XIIIa).

Compound Va (4.42 g, 0.01 mole) was dissolved in 80 ml of dry dimethylformamide and stirred magnetically at room temperature in presence of anhydrous sodium carbonate (1.16 g, 0.011 mole) under a nitrogen atmosphere. Iodomethane (1.56 g, 0.011 mole), dissolved in 5 ml of dry dimethylformamide, was added all at once to the reaction mixture and stirred for 48 hours at room temperature. The reaction mixture was poured into 200 ml of ice-water and stirred with a glass rod. The resulting white precipitate was filtered on a Buchner funnel after the ice had melted. It was washed with cold water and air-dried which had mp 52-58°. Its nmr showed a mixture of starting material and product in approximately 70:30 ratio. Its tlc in hexane-ethyl acetate (7:3) showed two spots having Rf_1 0.39 (N-CH_3 product) and Rf_2 0.29 (starting material). The dry crude material was further treated with additional amounts of anhydrous sodium carbonate and iodomethane at room temperature for 16 hours. Its tlc showed the presence of starting material. Some more iodomethane was added and heated briefly at 40-50° for 30 minutes. Its tlc showed complete consumption of the starting material. The reaction was worked up by pouring into water and extracting with ether. The ether layer was dried over anhydrous sodium sulfate, filtered and ether was removed. It gave 2.4 g of the product which had mp 114-115° after triturating and washing with hexane. About 500 mg of this material was recrystallized from minimum amount of hexane. The recrystallized material was recovered almost quantitatively, mp 129-130°; ir (potassium bromide): 3040, 2980, 2960, 1720, 1690, 1610, 1590, 1525, 1490, 1475, 1425, 1385, 1365, 1285, 1265, 1200, 1140, 1105, 1090, 1055, 985, 885, 832, 775, 758, 735, 720 and 690 cm^{-1}; nmr (deuteriochloroform): δ 7.32 (s, 1H, olefinic), 7.30-6.70 (m, 5H, ArH), 4.88 (s, 2H, benzylic methylene), 3.62 (s, 3H, $COOCH_3$), 3.32 (s, 3H, $COOCH_3$), 2.90 (s, 3H, N-CH_3), 2.2 (s, 3H, C_5-Me), 2.0 (s, 3H, C_4-Me), 1.50 (s, 9H, *t*-butyl) ppm.

Anal. Calcd. for $C_{25}H_{32}N_2O_6$: C, 65.79; H, 7.02; N, 6.14. Found: C, 65.92; H, 7.08; N, 6.08.

Diethyl *N*-[1-Benzyl-3-*t*-butoxycarbonyl-4,5-dimethylpyrrol-2-yl]methylaminomethylenemalonate (XIIIb).

Compound Vb (1.57 g, 0.0033 mole), anhydrous sodium carbonate (0.71 g, 0.0067 mole) and iodomethane (0.95 g, 0.0067 mole) in 10 ml of dry dimethylformamide was stirred at room temperature for 4 days. At that time, additional anhydrous sodium carbonate (0.35 g, 0.0033 mole) and iodomethane (0.47 g, 0.0033 mole) were added and the reaction mixture was stirred for an additional day. Workup as described for compound XIIIa gave a light yellow gum (1.3 g, 81%), homogeneous on tlc, hexanes/ethyl acetate (8:2), Rf = 0.67; ir (neat): 2980, 2940, 1720, 1695, 1610, 1430, 1280, 1260, 1200, 1005, 1050, 720 cm^{-1}; nmr (deuteriochloroform): δ 7.38 (s, 1H, olefinic), 6.8-7.3 (m, 5H, ArH), 4.97 (s, 2H, benzylic methylene), 4.15 (q, 2H, J = 7.2 Hz, methylene of ethyl ester) 3.95 (q, 2H, J = 7.2 Hz, methylene of ethyl ester), 2.95 (s, 3H, N-CH_3), 2.20 (s, 3H, C_5-Me), 2.03 (s, 3H, C_4-CH_3), 1.50 (s, 9H, *t*-butyl), 1.20 (t, 3H, J = 7.2 Hz, methyl of ethyl ester), 1.10 (t, 3H, J = 7.2 Hz, methyl of ethyl ester) ppm.

Anal. Calcd. for $C_{27}H_{36}N_2O_6$: C, 66.92; H, 7.49; N, 5.78. Found: C, 66.94; H, 7.51; N, 5.78.

Dimethyl *N*-[1-Benzyl-3-carboxy-4,5-dimethylpyrrol-2-yl]methylaminomethylenemalonate (XIV).

Compound XIIIa (4.6 g, 0.01 mole) in concentrated sulfuric acid (23 g) was hydrolyzed according to the procedure for obtaining VIa from Va. The crude carboxylic acid (3.5 g, 88%) was recrystallized from methanol to white crystals, mp 221-222° with decarboxylation; ir (potassium bromide): 3400 (broad), 2950 (broad), 2600 (broad), 1735 (shoulder), 1700, 1665, 1600, 1575, 1525, 1470, 1425, 1380, 1348, 1280, 1260, 1220, 1190, 1140, 1105, 1050, 925, 895, 870, 830, 810, 800, 750, 730, 710, and 685 cm^{-1}; nmr (deuteriochloroform): δ 9.10 (broad hump, 1H, COOH), 7.38 (s, 1H, olefinic), 7.25-6.70 (m, 5H, ArH), 4.85 (s, 2H, benzylic methylene) 3.68 (s, 3H, $COOCH_3$), 3.35 (s, 3H, $COOCH_3$), 2.98 (s, 3H, N-CH_3), 2.25 (s, 3H, C_5-Me), and 2.05 (s, 3H, C_4-Me).

Anal. Calcd. for $C_{21}H_{24}N_2O_6$: C, 63.00; H, 6.00; N, 7.00. Found: C, 62.82; H, 6.07; N, 6.98.

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