Synthesis of 3-Benzoyl-4,7-dihydro-7-oxopyrrolo[3,2-*b*]pyridine-6-carboxylic Acid Derivatives As Potential Antimicrobial Agents

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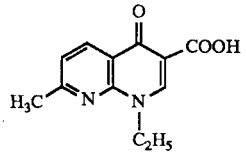
Received November 15, 1989

A series of twelve newly synthesized derivations of 3-benzoyl-4,7-dihydro-7-oxopyrrolo[3,2-*b*]pyridine-6-carboxylic acid from 2-methyl-3-benzoyl-4-aminopyrrole is reported.

J. Heterocyclic Chem., **27**, 1201 (1990).

Discovery of the first therapeutically useful antibacterial quinolone, nalidixic acid (**1**) [1] prompted the synthesis of a large number of structural variants that might have a broader spectrum of antimicrobial activity as well as increased potency. Peripheral and nuclear modifications of the pyridin-4-one portion of the nalidixic acid structure, together with those which involve the fused pyridine ring, have resulted in the preparation of various analogs, including cinoxacin [2], pyrido[2,3-*a*]indolizines [3], thieno[2,3-*b*]pyridines [4], furo[2,3-*b*]pyridines [5] and pyrazolo[3,4-*b*]pyridines [6].



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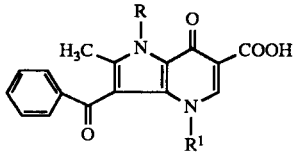

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In this report, we describe the synthesis of a series of 3-benzoyl-4,7-dihydro-7-oxopyrrolo[3,2-*b*]pyridine-6-carboxylic acids (**2**) (Schemes I and II). In this synthesis, 1-phenyl-1,3-butanedione (**3**) was condensed with aminoacetonitrile hydrochloride in the presence of sodium bicarbonate to yield 3-(cyanomethylamino)-1-phenyl-2-buten-1-one (**4**), which was cyclized in the presence of sodium ethoxide in absolute ethanol, according to the procedure described by Tarzia and Panzone [7], resulting in 2-methyl-3-benzoyl-4-aminopyrrole. After neutralization with acetic acid, the pyrrole was reacted *in situ* with diethyl ethoxymethylenemalonate to yield diethyl *N*-[2-methyl-3-benzoylpyrrol-4-yl]-aminomethylenemalonate (**5**). Selective alkylation of **5** at the 1-position was achieved through pyrrolyl anion generation using potassium *t*-butoxide in dimethylformamide or sodium hydride in tetrahydrofuran, followed by alkylation with methyl iodide or chloroacetonitrile to yield compounds **6** and **11**, respectively. The site of alkylation was assigned on the basis of the disappearance of the N_1H proton at 8.9 ppm in the nmr spectrum. The introduction of the alkyl substituent had little effect upon the chemical shift and coupling of the remaining protons in the compounds. Compounds **6** was *N*-alkylated using sodium hydride in tetrahydrofuran followed by dimethyl sulfate to yield compound **8**. The *N*-methylation of the nitrogen off the 4-position abolished the (-NH-CH=) coupling which was previously observed in the non-alkylated precursor **6**. Utilizing a cyclization procedure described by Okumura *et al.* [8], compound **8** was cyclized by heating in polyphosphoric ester (PPE) to yield the pyrrolo[3,2-*b*]pyridine (**9b**).

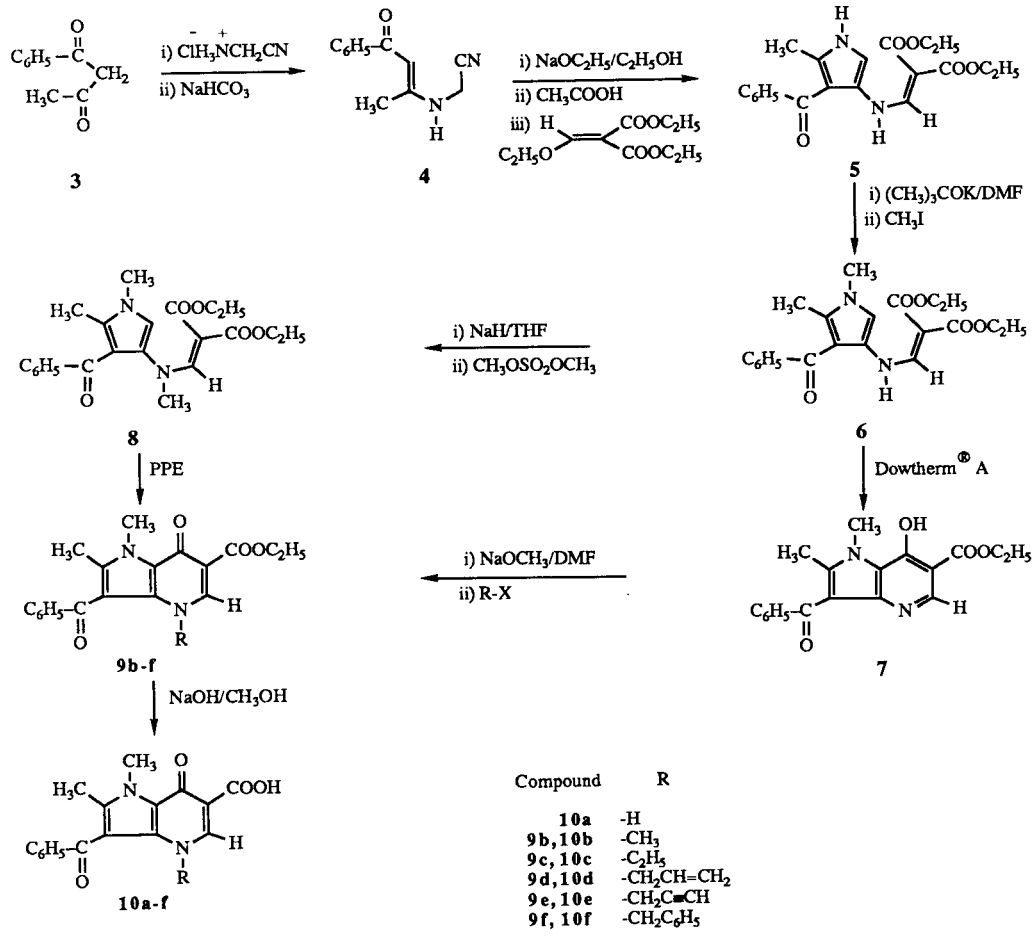
In an alternate route, compound (**6**) was thermally cyclized in refluxing Dowtherm® A resulting in 1,2-dimethyl-3-benzoyl-6-carbethoxy-7-hydroxypyrrolo[3,2-*b*]pyridine (**7**). Alkylation of the nitrogen at the 4-position in compound **7** with methyl iodide, ethyl iodide, allyl bromide, propargyl bromide and benzyl bromide resulted in the preparation of compounds **9b-f**. Cleavage of the ethyl ester in compounds **9b-f** was achieved through alkaline hydrolysis using an excess of sodium hydroxide in methanol to give compounds **10b-f** in good yields upon the acidification of the alkaline reaction solution.

Treatment of compound (**5**) with sodium hydride in dry tetrahydrofuran, followed by chloroacetonitrile produced diethyl *N*-[1-cyanomethyl-2-methyl-3-benzoylpyrrol-4-yl]-aminomethylenemalonate (**11**) in an 84% yield (Scheme II).

Compound **11** was thermally cyclized in refluxing Dowtherm® A to yield 1-cyanomethyl-2-methyl-3-benzoyl-6-carbethoxy-7-hydroxypyrrolo[3,2-*b*]pyridine (**12**) in 74% yield. Alkylation of the nitrogen at the 4-position in compound **12** with methyl iodide, ethyl iodide, allyl bromide, propargyl bromide and benzyl bromide was accomplished using sodium methoxide in dry dimethylformamide to yield compounds **13a-f**.

The final carboxylic acids **14a-f** were obtained upon refluxing compounds **12** and **13b-f** in concentrated hydrochloric acid over a period of 12-18 hours. The infrared and ^1H nmr spectra of the monoacids **10a-f** and the diacids **14a-f** were consistent with the assigned structures. These compounds showed typical carbonyl absorptions in the

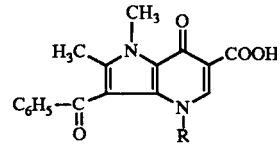
Scheme I



Compound	R
10a	-H
9b,10b	$-CH_3$
9c,10c	$-C_2H_5$
9d,10d	$-CH_2CH{=}CH_2$
9e,10e	$-CH_2C{\equiv}CH$
9f,10f	$-CH_2C_6H_5$

Table I

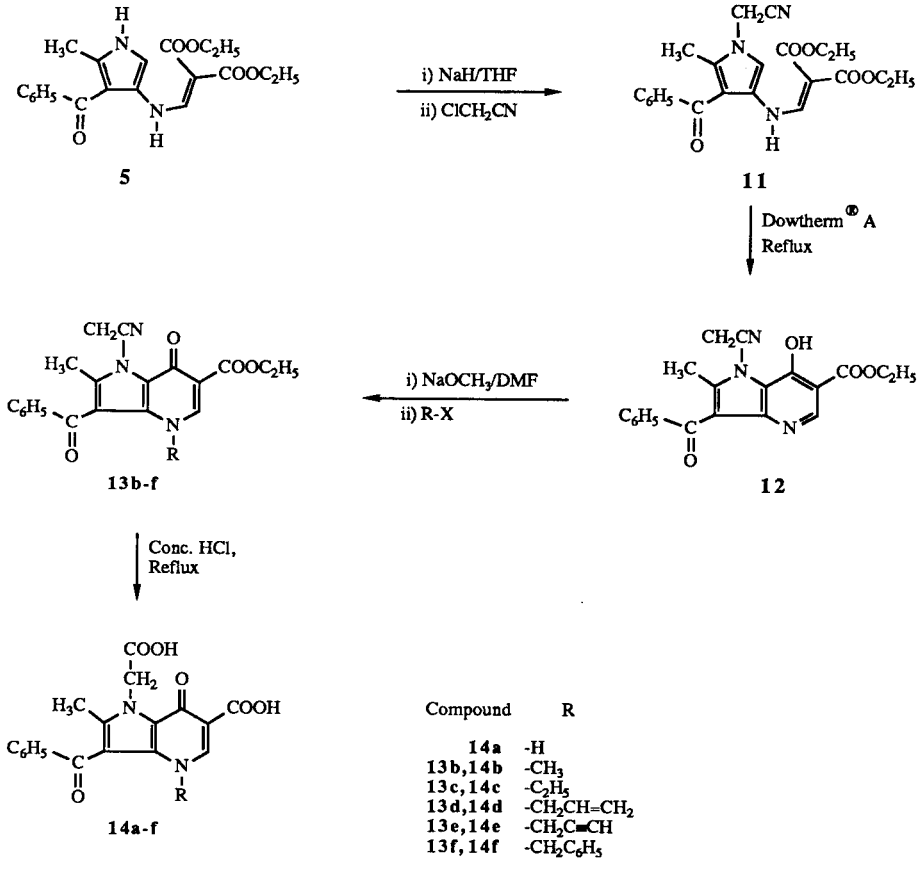
Substituted 3-Benzoyl-4,7-dihydro-7-oxopyrrolo[3,2-*b*]pyridine-6-carboxlic Acids



Compound Number	R	Yield (%)	MP °C	Recrystallization Solvent	NMR Data (ppm)
10a	-H	78	293-294	Methanol/water	2.1 (s, 3H), 4.05 (s, 3H), 7.25-7.8 (m, 5H), 8.27 (s, 1H)
10b	$-CH_3$	80	219-221	Methanol	2.07 (s, 3H), 3.55 (s, 3H), 4.10 (s, 3H), 7.20-7.85 (m, 5H), 8.20 (s, 1H)
10c	$-C_2H_5$	69	243-245	Methanol/water	1.05 (t, 3H), 2.05 (s, 3H), 4.02 (q, 2H), 4.10 (s, 3H), 7.25-7.80 (m, 5H), 8.25 (s, 1H)
10d [a]	$-CH_2CH{=}CH_2$	65	257-259	Methanol/water	2.05 (s, 3H), 4.10 (s, 3H), 4.45-5.05 (m, 5H), 7.25-7.8 (m, 5H), 8.3 (s, 1H)
10e	$-CH_2C{\equiv}CH$	62	242-244	Methanol/water	2.15 (s, 3H), 4.10 (s, 3H), 5.3-5.4 (d, 3H), 7.25-7.80 (m, 5H), 8.35 (s, 1H)
10f [b]	$-CH_2C_6H_5$	57	254-256	Methanol	2.1 (s, 3H), 4.05 (s, 3H), 5.6 (s, 2H), 6.7-7.05 (m, 5H) 7.25-7.8 (m, 5H) 8.6 (s, 1H)

[a] *Anal.* Calcd. for $C_{20}H_{18}N_2O_4$: C, 68.57; H, 5.14; N, 8.00. Found C, 68.38; H, 5.25: N, 7.95. [b]*Anal.* Calcd. for $C_{24}H_{20}N_2O_4$: C, 72.00; H, 5.00; N, 7.00. Found: C, 69.91; H, 5.13; N, 7.02

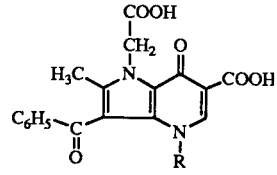
Scheme II



Compound	R
14a	-H
13b,14b	$-CH_3$
13c,14c	$-C_2H_5$
13d,14d	$-CH_2CH{=}CH_2$
13e,14e	$-CH_2C{\equiv}CH$
13f,14f	$-CH_2C_6H_5$

Table II

Substituted 3-Benzoyl-6-carboxy-4,7-dihydro-7-oxopyrrolo[3,2-*b*]pyridine-1-acetic Acids



Compound Number	R	Yield (%)	MP °C	Recrystallization Solvent	NMR Data (ppm)
14a	-H	66	301-302	Methanol	2.10 (s, 3H), 5.45 (s, 2H), 7.3-7.75 (m, 5H), 8.4 (d, 1H), 12.6 (d, 1H)
14b	$-CH_3$	68	185-187	Methanol	2.05 (s, 3H), 3.55 (s, 3H), 5.45 (s, 2H), 7.30-7.8 (m, 5H), 8.52 (s, 1H)
14c [a]	$-C_2H_5$	76	285-286	Methanol	0.95 (t, 3H), 2.05 (s, 3H), 4.05 (q, 2H), 5.40 (s, 2H) 7.4-7.9 (m, 5H), 8.60 (s, 1H)
14d [b]	$-CH_2CH{\equiv}CH_2$	63	172-174	Methanol	1.97 (s, 3H), 4.6-5.0 (m, 5H), 5.38 (s, 2H), 7.25-7.80 (m, 5H) 8.55 (s, 1H)
14e [c]	$-CH_2C{=}CH$	69	168-169	Methanol	2.0 (s, 3H), 4.88-5.1 (d, 3H), 5.40 (s, 2H), 7.30-7.80 (m, 5H), 8.62 (s, 1H)
14f [d]	$-CH_2C_6H_5$	68	226-227	Methanol	1.85 (s, 3H), 5.37 (s, 2H), 5.48 (s, 2H), 6.5-6.9 (m, 5H), 7.25-7.75 (m, 5H), 8.8 (s, 1H)

[a] *Anal.* Calcd. for $C_{20}H_{18}N_2O_6$: C, 62.83; H, 4.71; N, 7.33. Found C, 62.67; H, 4.84; N, 7.29 [b]*Anal.* Calcd. for $C_{21}H_{18}N_2O_6$: C, 63.96; H, 4.57; N, 7.11. Found: C, 63.90; H, 4.62; N, 7.05. [c] *Anal.* Calcd. for $C_{21}H_{16}N_2O_6$: C, 64.29; H, 4.08; N, 7.14. Found: C, 64.15; H, 4.20; N, 7.09. [d] *Anal.* Calcd. for $C_{25}H_{20}N_2O_6$: C, 67.57; H, 4.50; N, 6.30. Found: C, 67.39; H, 4.65; N, 6.32.

region from 1700-1725 cm^{-1}. In the ^1H nmr spectra, the aromatic proton at the 5-position appeared as a sharp singlet from 8.1-8.60 ppm for **10a-f** and from 8.25-8.80 ppm for **14a-f**. The methyl group at the 2-position appeared as a singlet from 1.95-2.10 ppm. The methylene group attached to the nitrogen at 1-position in compounds **14a-f** appeared as a sharp singlet in the region from 5.3-5.4 ppm. The remaining protons in the compounds were observed in the expected region of the spectra.

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 or DMSO-d_6 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.

3-(Cyanomethylamino)-1-phenyl-2-buten-1-one (**4**).

A suspension of aminoacetonitrile hydrochloride (20.26 g, 0.22 mole) in absolute ethanol (400 ml) was treated with sodium bicarbonate (18.48 g, 0.22 mole). After stirring at room temperature for 10 minutes, 1-phenyl-1,3-butanedione (32.4 g, 0.2 mole) was added. The mixture was diluted with toluene (200 ml) and then was refluxed under a Dean-Stark trap with continuous removal of ethanol-water. Once a one phase distillate was achieved, the toluene mixture was refluxed under the Dean-Stark trap for 2 hours. The yellow solution was allowed to cool to room temperature. A yellow solid was formed which was dissolved in chloroform (200 ml) and poured into water (300 ml). The organic layer was separated and the aqueous layer was extracted three times with chloroform (50 ml). The organic layers were combined and dried over anhydrous sodium sulfate. After filtration, the solvent was removed *in vacuo* resulting in a light yellow solid. The crude product was purified by recrystallization from methanol (200 ml) to yield light yellow needles (35.6 g, 89%), mp 102-104°; ir (potassium bromide): 3600-3370, 2980, 1590, 1440, 1280, 1245, 1170, 1110, 1080, 1060, 1020, 960, 865, 750, 710, 660 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.15 (s, 3H, methyl at 4-position), 4.05 (d, 2H, methylene), 5.8 (s, 1H, vinyl porton), 7.25-7.9 (m, 5H, aromatic protons), 10.9-11.4 (broad s, 1H, NH) ppm.

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 71.97; H, 6.04; N, 13.99. Found: C, 72.06; H, 6.09; N, 13.96.

Diethyl *N*-[2-Methyl-3-benzoylpyrrol-4-yl]aminomethylenemalonate (**5**).

The general procedure reported by Tarzia and Panzone [7] was utilized for the pyrrole synthesis. 3-(Cyanomethylamino)-1-phenyl-2-buten-1-one (**4**) (32 g, 0.16 mole) was added to a solution of sodium ethoxide (13.06 g, 0.192 mole) in absolute ethanol (300 ml). An exothermic reaction occurred and the mixture was stirred at room temperature for 15 minutes. The resulting light orange solution was refluxed for 2 hours under argon atmosphere. After cooling, glacial acetic acid (11.52 g, 0.192 mole) was added, followed by the addition of diethyl ethoxymethylenemalonate (34.6 g, 0.16 mole). Immediately, an exothermic reaction occurred and the contents of the flask solidified. Additional ethanol (150 ml) was added and the mixture was heated until a clear solution was achieved. The solution was kept in the freezer overnight and the resulting solid was collected, washed with cold ethanol (150 ml) and air dried. The product was recrystallized from absolute ethanol (800 ml) to yield a dark yellow powder (47.8 g, 81%), mp 194-195°; ir (potassium bromide): 3425, 3120, 2985, 1675, 1635, 1580, 1465, 1397, 1370, 1325, 1280, 1250, 1220, 1150, 1075, 1005, 925, 785, 730, 685 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.15 (two t, 6H methyl of ethyl ester), 1.85 (s, 3H, methyl at 2-position), 3.95 (two q, 4H, methylenes of ethyl ester), 7.05 (s, 1H, aromatic proton at 5-position), 7.35-7.65 (m, 5H, aromatic protons), 8.1 (d, 1H, vinyl proton), 11.2 (d, 1H, NH at 4-position) ppm.

Anal. Calcd. for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.99; N, 7.56. Found: C, 64.83; H, 5.99; N, 7.56.

Diethyl *N*-[1,2-Dimethyl-3-benzoylpyrrol-4-yl]aminomethylenemalonate (**6**).

Compound **5** (8.5 g, 0.023 mole) in dry dimethylformamide (25 ml) was treated with potassium *t*-butoxide (3.36 g, 0.03 mole) and stirred at room temperature for 15 minutes. A dark yellow solution was obtained. Methyl iodide (4.26 g, 0.03 mole) was added and an exothermic reaction ensued. After stirring for 90 minutes at room temperature, the reaction solution was poured into ice-water (250 ml). A grey colored solid was formed which was collected by filtration and air dried. The crude product was recrystallized from 155 ml of methanol-water (7:3) to yield light brown crystals (7.8 g, 88%), mp 111-113°; ir (potassium bromide): 3430, 2985, 1665, 1635, 1574, 1500, 1375, 1320, 1255, 1200 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.15 (two t, 6H, methyl of ethyl ester), 1.85 (s, 3H, methyl at 2-position), 3.45 (s, 3H, methyl at 1-position), 4.05 (two q, 4H, methylenes of ethyl ester), 6.45 (s, 1H, aromatic proton at 5 position), 7.2-7.8 (m, 5H, aromatic protons), 8.05 (d, 1H, vinyl proton), 11.30 (d, 1H, NH at 4-position) ppm.

Anal. Calcd. for $C_{21}H_{24}N_2O_5$: C, 65.63; H, 6.25; N, 7.29. Found: C, 65.53; H, 6.30; N, 7.24.

1,2-Dimethyl-3-benzoyl-6-carbethoxy-7-hydroxypyrrolo[3,2-*b*]-pyridine (**7**).

A solution of compound **6** (9.6 g, 0.025 mole) in warm Dowtherm® A (40 ml) was added over a period of 5 minutes to boiling Dowtherm® A (80 ml) under an argon atmosphere. After the addition was complete, the solution was refluxed for 25 minutes and the Dowtherm® A was removed under reduced pressure. The residue was triturated with hexane (100 ml) and the light brown solid was collected and air dried. The crude product was purified by recrystallization from acetone (400 ml) to yield a light green-white powder (5.32 g, 63%), mp 254-256°; ir (potassium bromide): 3225, 3120, 3045, 2985, 1705, 1605, 1410, 1255, 1230, 1170, 1085, 1010, 930, 820 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.25 (t, 3H, methyl of ethyl ester), 2.1 (s, 3H, methyl at 2-position), 4.15 (s, 3H, methyl at 1-position), 4.10 (q, 2H, methylene of ethyl ester), 7.40-7.55 (m, 5H, aromatic protons), 8.30 (s, 1H, aromatic proton at 5-position) ppm.

Anal. Calcd. for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found; C, 67.23; H, 5.41; N, 8.23.

1,2,4-Trimethyl-3-benzoyl-6-carbethoxy-4,7-dihydro-7-oxopyrrolo[3,2-*b*]pyridine (**9b**).

Method A.

Compound **6** (5.76 g, 0.015 mole) was added to a suspension of

60% sodium hydride (0.72 g, 0.018 mole) in dry tetrahydrofuran (25 ml) and stirred at room temperature for 15 minutes. Dimethyl sulfate (3.78 g, 0.03 mole) was added and the mixture was refluxed overnight. A light yellow solution was obtained which was allowed to cool to room temperature. After filtration, tetrahydrofuran was removed *in vacuo* to yield a dark yellow oil **8**, which was determined to be *N*-methylated by nmr spectrum and used without further purification. The *N*-alkylated product **8** was treated with polyphosphoric ester (15.0 g) and was heated at 90° with vigorous stirring for 75 minutes. After cooling, ice (45 g) was added and stirred at room temperature for 20 minutes. The mixture was filtered and the *p*H of the filtrate was adjusted to 8 by dropwise addition of 50% sodium hydroxide. The yellow precipitate was collected, washed twice with cold water (25 ml) and air dried. The product was further purified by recrystallization from 50 ml of methanol-water (7:3) to yield a silver white-yellow solid (3.64 g, 69%), mp 138-140°; ir (potassium bromide): 3430, 3050, 2930, 1730, 1670, 1605, 1570, 1527, 1465, 1435, 1315, 1250, 1215, 1150, 1100, 1060, 1005, 950, 785 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.25 (t, 3H, methyl of ethyl ester), 2.10 (s, 3H, methyl at 2-position), 3.52 (s, 3H, methyl at 4-position), 4.2 (s, 3H, methyl at 1-position), 4.2 (q, 2H methylene of ethyl ester), 7.35-7.85 (m, 5H, aromatic protons), 8.05 (s, 1H, aromatic proton at 5-position) ppm.

Anal. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68.16; H, 5.72; N, 7.95. Found: C, 67.92; H, 5.77; N, 7.89.

Method B.

A solution of compound **7** (2.0 g, 0.006 mole) in dry dimethylformamide (10 ml) was treated with sodium methoxide (0.49 g, 0.009 mole) and stirred at room temperature for 15 minutes. Methyl iodide (0.73 g, 0.0135 mole) was added. An exothermic reaction occurred, and the mixture was stirred at room temperature for 12 hours. The light yellow solution was poured into ice-water (100 ml). The precipitate was collected, washed with water and air dried. The product was recrystallized from 20 ml of methanol-water (7:3) to give a light yellow-white solid (1.82 g, 86%). The ir, nmr spectra and melting point were identical to the product obtained under Method A.

1,2-Dimethyl-3-benzoyl-7-hydroxypyrrolo[3,2-*b*]pyridine-6-carboxylic Acid (**10a**).

Compound **7** (1.69 g, 0.005 mole) was treated with concentrated hydrochloric acid (10 ml) and the mixture was heated at 50° for 10 hours. A dark yellow solution was obtained. After cooling, cold water (25 ml) was added and the yellow precipitate was collected, washed and air dried. The crude product was purified by recrystallization from 20 ml of methanol-water (7:3), (1.21 g, 78%), mp 293-294°; ir (potassium bromide): 3470, 3070, 1705, 1610, 1440, 1170, 950, 780, 690 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.1 (s, 3H, methyl at 2-position), 4.05 (s, 3H, methyl at 1-position), 7.25-7.8 (m, 5H, aromatic protons), 8.27 (s, 1H, aromatic proton at 5-position) ppm.

1,2,4-Trimethyl-3-benzoyl-4,7-dihydro-7-oxopyrrolo[3,2-*b*]pyridine-6-carboxylic Acid (**10b**).

A solution of **9b** (1.0 g, 0.0028 mole) in hot methanol (30 ml) was treated with 1% sodium hydroxide solution (40 ml). After stirring for 1 hour in a boiling water bath, the reaction mixture was cooled, filtered, then acidified by dropwise addition of 6*N* hydrochloric acid. The brown precipitate was collected and air dried. The crude product was recrystallized from methanol (15 ml) resulting in a light brown solid (0.73 g, 80%), mp 219-221°; ir (potassium bromide): 3640, 3060, 2940, 1710, 1605, 1445, 1365, 1320, 1290, 1250, 1155, 1095, 945, 840, 785, 690 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.07 (s, 3H, methyl at 2-position), 3.55 (s, 3H, methyl at 4-position), 4.10 (s, 3H, methyl at 1-position), 7.20-7.85 (m, 5H, aromatic protons), 8.20 (s, 1H, aromatic proton at 5-position) ppm.

Anal. Calcd. for $C_{18}H_{16}N_2O_4$: C, 66.67; H, 4.94; N, 8.64. Found: C, 66.50; H, 5.04; N, 8.60.

1,2-Dimethyl-3-benzoyl-4-ethyl-4,7-dihydro-7-oxopyrrolo[3,2-*b*]-pyridine-6-carboxylic Acid (**10c**).

The procedure given for the synthesis of **10c** was utilized in the preparation of **10d**. A solution of compound **7** (2.0 g, 0.006 mole) in dry dimethylformamide (20 ml) was treated with an anhydrous sodium carbonate (1.88 g, 0.0176 mole) and stirred at room temperature for 10 minutes. Ethyl iodide (5.54 g, 0.0356 mole) was added and the solution was heated at 70° for 20 hours. A dark yellow solution was obtained and was concentrated to dryness and then partitioned between water and chloroform. The organic layer was separated, dried over anhydrous sodium sulfate and concentrated to give a dark yellow oil. The crude oily product **9c** was determined to be *N*-ethylated by the ^1H nmr spectrum and used without further purification. The *N*-alkylated product was hydrolyzed directly by dissolving it in hot methanol (50 ml) and was treated while hot with 1% sodium hydroxide (40 ml). The mixture was heated on a boiling water bath while stirring it for 75 minutes, cooled and filtered. The filtrate was acidified by dropwise addition of 1*N* hydrochloric acid. A light yellow precipitate was formed, which was collected and air dried. The product was recrystallized from 20 ml of methanol-water (7:3) to yield a light yellow solid (1.4 g, 69%), mp 243-245°; ir (potassium bromide): 3445, 3055, 2980, 1715, 1605, 1440, 1370, 1280, 1235, 1150, 945, 845, 780 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.05 (t, 3H, methyl of ethyl group at 4-position), 2.05 (s, 3H, methyl at 2-position), 4.02 (q, 2H, methylene of ethyl group at 4-position), 4.10 (s, 3H, methyl at 1-position), 7.25-7.80 (m, 5H, aromatic protons), 8.25 (s, 1H, aromatic proton at 5-position) ppm.

Anal. Calcd. for $C_{19}H_{18}N_2O_2 \cdot 0.3H_2O$: C, 66.39; H, 5.24; N, 8.15. Found: C, 66.45; H, 5.49; N, 8.15. (See Table I for Analogs).

1,2-Dimethyl-3-benzoyl-4-propargyl-4,7-dihydro-7-oxopyrrolo-[3,2-*b*]pyridine-6-carboxylic Acid (**10e**).

The procedure given for the synthesis of **10e** was utilized in the preparation of **10f**. A solution of compound **7** (2.0 g, 0.006 mole) in dry dimethylformamide (20 ml) was treated with sodium methoxide (0.39 g, 0.0072 mole) and stirred at room temperature for 15 minutes. Eighty percent propargyl bromide (2.15 g, 0.0144 mole) was added. An exothermic reaction occurred and the reaction mixture was stirred at room temperature overnight. Dimethylformamide was removed under vacuum to yield a dark brown oil which was determined to be the *N*-alkylated product **9e** by nmr spectrum. The crude oil was hydrolyzed directly by dissolving it in hot methanol (50 ml) and was treated while hot with 1% sodium hydroxide (50 ml). The mixture was heated on a boiling water bath for 1 hour with continuous stirring and then was cooled and filtered. The filtrate was acidified by dropwise addition of 6*N* hydrochloric acid. A light yellow precipitate was formed which was collected and air dried. The product was purified by recrystallization from 25 ml methanol-water (7:3) to yield a light yellow solid (1.3 g, 62%), mp 242-244°; ir (potassium bromide):

3450, 3065, 2955, 1720, 1600, 1445, 1290, 1240, 1152, 950, 785 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.15 (s, 3H, methyl at 2-position), 4.10 (s, 3H, methyl at 1-position), 5.3-5.4 (d, 3H, protons of the propargyl group at 4-position), 7.25-7.80 (m, 5H, aromatic protons), 8.35 (s, 1H, aromatic proton at 5-position) ppm.

Anal. Calcd. for $C_{20}H_{16}N_2O_4$: C, 68.97; H, 4.60; N, 8.05. Found: C, 69.12; H, 4.66; N, 8.00. (See Table I for Analogs).

Diethyl *N*-[1-Cyanomethyl-2-methyl-3-benzoylpyrrol-4-yl]aminomethylenemalonate (**11**).

Compound (**5**) (9.25 g, 0.025 mole) was added to a suspension of 60% sodium hydride (1.1 g, 0.028 mole) in dry tetrahydrofuran (200 ml) and stirred at room temperature for 10 minutes. Chloroacetonitrile (4.15 g, 0.055 mole) was added dropwise and the mixture was refluxed for 30 hours. After cooling, the dark yellow solution was filtered and tetrahydrofuran was removed *in vacuo* to yield a dark yellow brown oil which solidified within 2 minutes. The crude product was further purified by recrystallization from absolute methanol (75 ml) to yield a light brown solid (8.65 g, 84%), mp 174-176°; ir (potassium bromide): 3460, 3295, 3050, 2970, 1718, 1600, 1510, 1455, 1415, 1370, 1320, 1230, 1195, 1140, 1055, 970, 930, 895, 790, 725, 685 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.2 (two t, 6H, methyl of ethyl ester), 2.02 (s, 3H, methyl at 2-position), 4.01 (two q, 4H, methylenes of ethyl ester), 5.75 (s, 2H, methylene at 1-position), 6.65 (s, 1H, aromatic proton at 5-position), 7.25-7.7 (m, 5H, aromatic protons), 8.00 (d, 1H, vinyl proton), 11.15 (d, 1H, NH at 4-position) ppm.

Anal. Calcd. for $C_{22}H_{23}N_3O_5$: C, 64.55; H, 5.62; N, 10.27. Found: C, 64.61; H, 5.69; N, 10.24.

1-Cyanomethyl-2-methyl-3-benzoyl-6-carbethoxy-7-hydroxy pyrrolo[3,2-*b*]pyridine (**12**).

A solution of compound **11** (5.0 g, 0.012 mole) in warm Dowtherm® A (25 ml) was added over a period of 10 minutes to boiling Dowtherm® A (75 ml) under an argon atmosphere. After the addition was complete, the solution was refluxed for 30 minutes and the Dowtherm® A was removed under reduced pressure. The residue was triturated with hexane (75 ml) and a light grey precipitate was collected and air dried. The product was further purified by recrystallization from 80 ml of methanol-water (7:3) to yield a yellow solid (3.25 g, 74%), mp 249-250°; ir (potassium bromide): 3215, 3135, 3060, 2985, 1720, 1615, 1565, 1485, 1440, 1410, 1275, 1170, 1115, 1025, 970, 915, 830, 775, 735, 685 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.15 (t, 3H, methyl of ethyl ester), 2.15 (s, 3H, methyl at 2-position), 3.95 (q, 2H, methylene of ethyl ester), 5.85 (s, 2H, methylene at 1-position), 7.28-7.85 (m, 5H, aromatic protons), 8.15 (s, 1H, aromatic proton at 5-position) ppm.

Anal. Calcd. for $C_{20}H_{17}N_3O_4$: C, 66.12; H, 4.68; N, 11.57. Found: C, 66.18; H, 4.75; N, 11.53.

1-Cyanomethyl-2,4-dimethyl-3-benzoyl-6-carbethoxy-4,7-dihydro-7-oxopyrrolo[3,2-*b*]pyridine (**13b**).

A solution of compound **12** (3.20 g, 0.0088 mole) in dry dimethylformamide (10 ml) was treated with sodium methoxide (0.62 g, 0.0115 mole) and stirred at room temperature for 15 minutes. Methyl iodide (3.74 g, 0.026 mole) was added. An exothermic reaction occurred and the mixture was stirred at room temperature for 1 hour. The dark brown solution was poured into ice-water (200 ml). The precipitate was collected, washed twice with cold water and air dried. The crude product was recrystallized from 40 ml of methanol-water (7:3) to yield a light yellow solid (2.76 g, 83%), mp 213-215°; ir (potassium bromide): 3455, 3060, 2960, 1718, 1675, 1607, 1570, 1535, 1440, 1407, 1315, 1260, 1213, 1118, 935, 709, 705, 680 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.15 (t, 3H, methyl of ethyl ester), 2.15 (s, 3H, methyl at 2-position), 3.52 (s, 3H, methyl at 4-position), 4.15 (q, 2H, methylene of ethyl ester), 5.98 (s, 2H, methylene at 1-position), 7.24-7.82 (m, 5H, aromatic protons), 8.05 (s, 1H, aromatic proton at 5-position) ppm.

Anal. Calcd. for $C_{21}H_{19}N_3O_4 \cdot 0.5H_2O$: C, 65.18; H, 5.20; N, 10.86. Found: C, 65.19; H, 5.20; N, 10.86.

2-Methyl-3-benzoyl-6-carboxy-7-hydroxypyrrolo[3,2-*b*]pyridine-1-acetic Acid (**14a**).

Compound **12** (2.4 g, 0.0066 mole) in concentrated hydrochloric acid (20 ml) was refluxed for 20 hours. After cooling, a light brown solid was formed which was poured into cold water (20 ml). The solid was collected, washed with distilled water and air dried. The crude product was purified by recrystallization from methanol to yield a light brown powder (1.54 g, 66%), mp 301-302°; ir (potassium bromide): 3460, 3235, 1724, 1600, 1490, 1450, 1420, 1300, 1230, 1170, 1050, 980, 935, 810, 755, 690 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.10 (s, 3H, methyl at 2-position), 5.45 (s, 2H, methylene at 1-position), 7.3-7.75 (m, 5H, aromatic protons), 8.4 (d, 1H, aromatic proton at 5-position), 12.6 (d, 1H, NH) ppm.

Anal. Calcd. for $C_{18}H_{14}N_2O_6 \cdot 0.5H_2O$: C, 59.51; H, 3.86; N, 7.71. Found: C, 59.56; H, 4.15; N, 7.68.

2,4-Dimethyl-3-benzoyl-6-carboxy-4,7-dihydro-7-oxopyrrolo[3,2-*b*]pyridine-1-acetic Acid (**14b**).

The procedure given for the synthesis of **14b** was utilized in the preparation of **14c-f**. A solution of compound **12** (1.6 g, 0.0044 mole) in dry dimethylformamide (7 ml) was treated with sodium methoxide (0.31 g, 0.0057 mole) and stirred at room temperature for 15 minutes. Methyl iodide (1.87 g, 0.0132 mole) was then added. An exothermic reaction occurred and the mixture was stirred at room temperature overnight. A dark brown solution was obtained which was concentrated to dryness and was used without further purification. The product was determined to be *N*-methylated by the ^1H nmr spectrum. Concentrated hydrochloric acid (10 ml) was added and the mixture was refluxed for 15 hours. A light orange solution was obtained which was allowed to cool to room temperature. Upon the addition of cold water (25 ml), a light brown precipitate was formed which was kept in the freezer for 30 minutes. The solid was collected, washed and air dried. The crude product was further purified by recrystallization from methanol (30 ml) to yield a light brown powder (1.1 g, 68%), mp 185-187°; ir (potassium bromide): 3440, 3080, 2950, 1725, 1615, 1455, 1420, 1340, 1310, 1265, 1195, 1130, 950, 825, 797, 690 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.05 (s, 3H, methyl at 2-position), 3.55 (s, 3H, methyl at 4-position), 5.45 (s, 2H, methylene at 1-position), 7.30-7.8 (m, 5H, aromatic protons), 8.52 (s, 1H, aromatic proton at 5-position) ppm.

Anal. Calcd. for $C_{19}H_{16}N_2O_6$: C, 61.96; H, 4.35; N, 7.61. Found: C, 62.07; H, 4.45; N, 7.70. (See Table II for Analogs).

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