Synthesis of 1,4-Dihydro-4-oxopyrrolo[3,4-*b*]pyridine-3-carboxylic Acid Derivatives As Potential Antimicrobial Agents

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A route for the synthesis of various derivatives of 1,4-dihydro-4-oxopyrrolo[3,4-*b*]pyridine-3-carboxylic acid from 2-phenyl-3-amino-4-*t*-butoxycarbonyl-5-methylpyrrole hydrochloride is reported.

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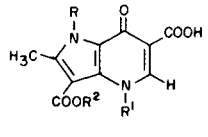
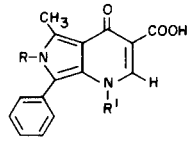
In a previous communication [3], we described the synthesis and antimicrobial properties of a series of 4,7-dihydro-7-oxopyrrolo[3,2-*b*]pyridine-6-carboxylic acids I. As an extension of our interest in fused pyrrolopyridines as potential antimicrobial agents, we now wish to report the synthesis of a series of 1,4-dihydro-4-oxopyrrolo[3,4-*b*]pyridine-3-carboxylic acids II (Scheme I and II).



I

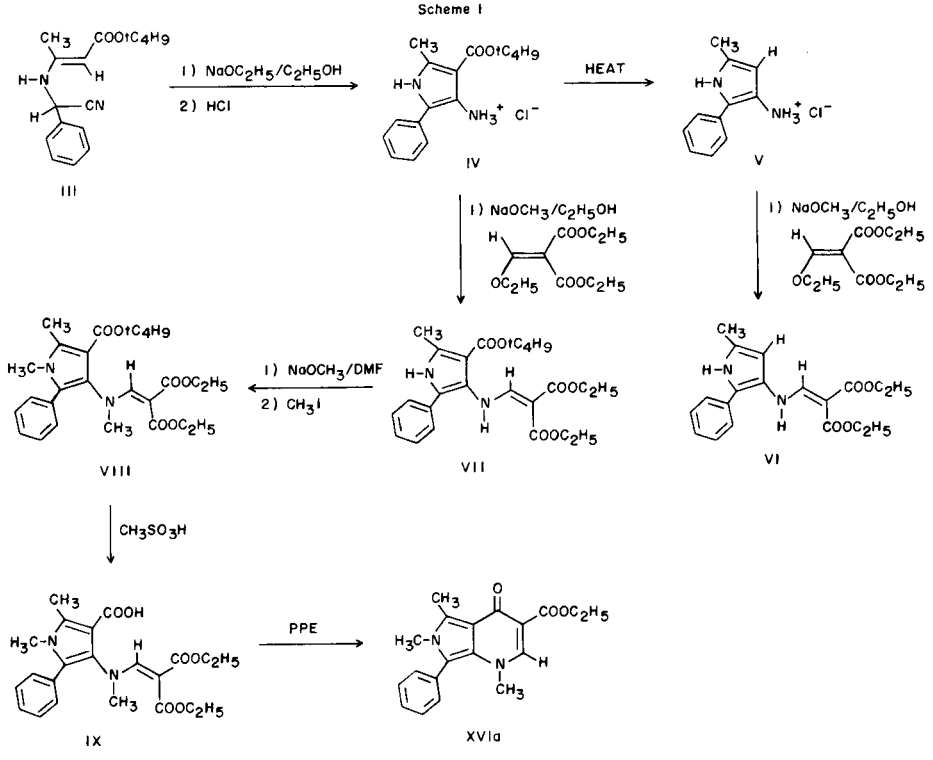


II

t-Butyl acetoacetate was condensed with (±)-2-phenylglycinonitrile in cyclohexane under a Dean-Stark trap to yield the enamine, *t*-butyl 3-(α-cyanobenzylamino)-2-butenoate (III). The viscous enamine was cyclized in the presence of sodium ethoxide in ethanol, according to the pyrrole synthesis described by Tarzia and Panzone [4]. Acidification of the alkaline reaction mixture with approximately three equivalents of concentrated hydrochloric acid in ethanol resulted in separation of the insoluble 2-phenyl-3-amino-4-*t*-butoxycarbonyl-5-methylpyrrole hydrochloride (IV). The amine hydrochloride IV was practically insoluble in cold water; therefore, the co-precipitated sodium chloride was easily removed by suspending the salt IV in cold water.

The observation that compound IV melted with the evolution of gas served as the basis for the reaction conditions for the pyrolysis of the *t*-butyl ester of IV and subsequent decarboxylation to yield the hydrochloride salt V. This process was smoothly accomplished by refluxing a suspension of IV in *m*-diisopropylbenzene under an argon atmo-

Scheme I



III IV V VI VII VIII IX XVIa

sphere.

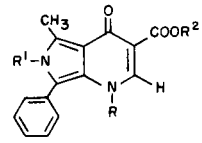
Compound VI was obtained by condensation of the free base of V with diethyl ethoxymethylenemalonate in ethanol. After the initial exothermic reaction, the condensation was carried out at ambient temperature to yield the product in 85% yield.

Selective alkylation of the nitrogen off the 3-position of VI was achieved through anion generation with sodium hydride in tetrhydrofuran, followed by alkylation with dimethyl sulfate, benzyl bromide, or ethyl iodide to yield compounds X, XI, and XII, respectively. The site of alkylation was assigned on the basis of the disappearance of the typical doublet-doublet absorption pattern in the ^{1}H-nmr for the (-NH=CH-) coupling. The precursor VI exhibited this typical coupling pattern with the -NH appearing as a doublet at 10.95 ppm and the vinyl proton appearing as a doublet at 8.13 ppm. The vinyl proton of the alkylated products, X, XI, and XII appeared as a sharp singlet in the region from 7.7-8.0 ppm.

Utilizing a cyclization procedure described by Okumura, *et al.* [5], compounds X, XI, and XII were cyclized by heating at 100-110° in polyphosphoric ester (PPE)

Table I

Substituted 1,4-Dihydro-4-oxopyrrolo[3,4-*b*]pyridines



Compound Number	R	R^1	R^2	Yield (%)	Mp (°C)	Recrystallization Solvent	Molecular Formula		Analysis (%) Calcd.	Found
XIII	$-CH_3$	-H	$-C_2H_5$	70.0	309-312	Methanol	$C_{18}H_{18}N_2O_3$	C	69.66	69.53
								H	5.85	5.87
								N	9.03	8.96
XIV	$-CH_2C_6H_5$	-H	$-C_2H_5$	72.0	285-287	Acetone	$C_{24}H_{22}N_2O_3$	C	74.59	74.69
								H	5.74	5.77
								N	7.25	7.21
XV	$-C_2H_5$	-H	$-C_2H_5$	90.0	285-287	Acetone/Water (3:2)	$C_{19}H_{20}N_2O_3$	C	70.35	70.27
								H	6.22	6.24
								N	8.64	8.61
XVIa	$-CH_3$	$-CH_3$	$-C_2H_5$	92.0	233-235	Ethanol/Water (6:4)	$C_{19}H_{20}N_2O_3$	C	70.35	70.25
								H	6.22	6.23
								N	8.64	8.61
XVIb	$-CH_3$	$-CH_2CH=CH_2$	$-C_2H_5$	86.0	162-164	Ethanol/Water (1:1)	$C_{21}H_{22}N_2O_3$	C	71.98	71.75
								H	6.33	6.35
								N	8.00	7.92
XVIc	$-CH_3$	$-CH_2C_6H_5$	$-C_2H_5$	100.0	158-160	Ethanol/Water (8:2)	$C_{25}H_{24}N_2O_3$	C	74.98	74.86
								H	6.04	6.10
								N	7.00	6.98
XVIIa	$-CH_2C_6H_5$	$-CH_3$	$-C_2H_5$	97.0	196-198	Methanol/Water (1:1)	$C_{25}H_{24}N_2O_3$	C	74.98	75.02
								H	6.04	6.09
								N	7.00	6.95
XVIIb	$-CH_2C_6H_5CH_2CH=CH_2$		$-C_2H_5$	98.5	157-159	Acetone/Water (7:3)	$C_{27}H_{26}N_2O_3 \cdot 0.5H_2O$	C	74.45	74.42
								H	6.25	6.28
								N	6.43	6.36
XVIIc	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-C_2H_5$	93.5	141-143	Acetone/Cyclo-hexane (4:6)	$C_{31}H_{28}N_2O_3$	C	78.13	78.00
								H	5.92	5.93
								N	5.88	5.82
XVIIe	$-CH_2C_6H_5$	$-C_2H_5$	$-C_2H_5$	100.0	194-196	Acetone	$C_{26}H_{26}N_2O_3$	C	75.34	75.06
								H	6.32	6.35
								N	6.76	6.72
XVIIIa	$-C_2H_5$	$-CH_3$	$-C_2H_5$	93.0	229-231	Acetone/Water (8:2)	$C_{20}H_{22}N_2O_3$	C	70.98	71.09
								H	6.55	6.56
								N	8.28	8.26
XIXa	$-CH_3$	$-CH_3$	-H	75.0	273-275	Methanol	$C_{17}H_{16}N_2O_3$	C	68.90	68.97
								H	5.44	5.49
								N	9.46	9.45
XIXb	$-CH_3$	$-CH_2CH=CH_2$	-H	78.0	199-201	Methanol/Water (7:3)	$C_{19}H_{18}N_2O_3$	C	70.78	70.61
								H	5.63	5.68
								N	8.69	8.61

Table I continued

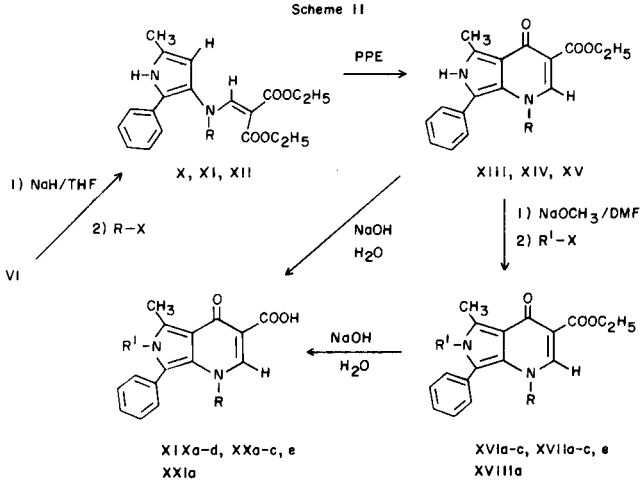
Compound Number	R	R¹	R²	Yield (%)	Mp (°C)	Recrystallization Solvent	Molecular Formula		Analysis (%) Calcd.	Found
XIXc	$-CH_3$	$-CH_2C_6H_5$	-H	88.0	217-219	Ethanol/Water (9:1)	$C_{23}H_{20}N_2O_3$	C	74.17	74.02
								H	5.41	5.45
								N	7.52	7.51
XIXd	$-CH_3$	-H	-H	70.0	332-334	Methanol	$C_{16}H_{14}N_2O_3$	C	68.07	67.89
								H	5.00	5.06
								N	9.93	9.89
XXa	$-CH_2C_6H_5$	$-CH_3$	-H	86.0	299-301	Methanol	$C_{23}H_{20}N_2O_3$	C	74.17	74.14
								H	5.41	5.43
								N	7.52	7.50
XXb	$-CH_2C_6H_5$	$-CH_2CH=CH_2$	-H	95.0	171-173	Methanol/Acetone (3:1)	$C_{25}H_{22}N_2O_3$	C	75.35	75.44
								H	5.57	5.59
								N	7.03	7.01
XXc	$-CH_2C_6H_5$	$-CH_2C_6H_5$	-H	92.0	210-212	Methanol	$C_{29}H_{24}N_2O_3$	C	77.66	77.70
								H	5.39	5.42
								N	6.25	6.24
XXe	$-CH_2C_6H_5$	$-C_2H_5$	-H	90.0	255-257	Methanol/Water (8:2)	$C_{24}H_{22}N_2O_3$	C	74.59	74.56
								H	5.74	5.77
								N	7.25	7.21
XXIa	$-C_2H_5$	$-CH_3$	-H	80.0	312-314	Methanol/Acetone (3:1)	$C_{18}H_{18}N_2O_3$	C	69.66	69.75
								H	5.85	5.88
								N	9.03	9.02

[6] to yield the 1,4-dihydro-4-oxopyrrolo[3,4-*b*]pyridines XIII, XIV, XV, respectively. Alkylation of the nitrogen atom at the 6-position of compound XIII, XIV, and XV with methyl iodide, allyl bromide, benzyl bromide or ethyl iodide yielded the series of compounds XVIa-c, XVIIa-c,e and XVIIIa (Scheme II). In an alternate method for the synthesis of compound XVIa, (Scheme I), the free base of IV was condensed with diethyl ethoxymethylenemalonate to give compound VII in 90% yield. Dialkylation of both nitrogen atoms, utilizing 2.4 equivalents of sodium methoxide as a base and 3.0 equivalents of methyl iodide as the alkylating agent, gave compound VIII in 88% yield. Acid catalyzed hydrolysis of the *t*-butyl ester of compound VIII in methane sulfonic acid gave the carboxylic acid (IX) which was cyclized in polyphosphoric ester to yield XVIa (Scheme I).

The infrared and ^{1}H-nmr spectra of the esters XVIa-c, XVIIa-c,e and XVIIIa were consistent with the assigned structures. These compounds showed typical carbonyl absorptions in the region from 1700-1720 and 1660-1670 cm^{-1}. In the ^{1}H-nmr spectra, the vinyl proton at the 2-position appeared as a sharp singlet from 7.95-8.12 ppm. The methyl group at the 5-position appeared as a singlet from 2.65-2.80 ppm. A typical quartet-triplet pattern was observed for the ethyl ester, with the quartet appearing from 4.28-4.30 ppm while the triplet was observed from 1.32-1.36 ppm. The remaining protons in the compounds were observed in the expected region of the spectra.

The final carboxylic acids (XIXa-d, XXa-c,e, XXIa) were obtained by hydrolysis of the corresponding ethyl esters with sodium hydroxide in aqueous or hydroalcoholic media. The free carboxylic acids were obtained in yields ranging from 70-95%.

Scheme II



Compound	R	R¹
X, XIII	$-CH_3$	-----
XVIa, XIXa	$-CH_3$	$-CH_3$
XVIb, XIXb	$-CH_3$	$-CH_2CH=CH_2$
XVIc, XIXc	$-CH_3$	$-CH_2C_6H_5$
XIXd	$-CH_3$	-H
XI, XIV	$-CH_2C_6H_5$	-----
XVIIa, XXa	$-CH_2C_6H_5$	$-CH_3$
XVIIb, XXb	$-CH_2C_6H_5$	$-CH_2CH=CH_2$
XVIIc, XXc	$-CH_2C_6H_5$	$-CH_2C_6H_5$
XVIIe, XXe	$-CH_2C_6H_5$	$-C_2H_5$
XII, XV	$-C_2H_5$	-----
XVIIIa, XXIa	$-C_2H_5$	$-CH_3$

The final products were evaluated *in vitro* for their antimicrobial properties. Compounds XIXa-d were found to exhibit a relatively broad spectrum of activity with minimum inhibitory concentrations in the range of 8-63 micrograms per milliliter. Compound XIXa was the most potent of the compounds evaluated, having a minimum inhibitory concentration of 8 micrograms per milliliter against *Proteus mirabilis* (A-9900) and *Morganella morganii* (A-15153). Compounds XXa-c,e and XXIa were devoid of antimicrobial activity at concentrations less than 125 micrograms per milliliter.

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. The tlc were performed on Eastman Chromatogram Sheets, type 6060 (silica gel).

2-Phenyl-3-amino-4-*t*-butoxycarbonyl-5-methylpyrrole Hydrochloride Monohydrate (IV).

The general procedure reported by Tarzia and Panzone [4] was utilized for the pyrrole synthesis. A suspension of (±)-2-phenylglycinonitrile hydrochloride (50.0 g, 0.2965 mole) in methanol (125 ml) was treated with sodium methylate (16.0 g, 0.2965 mole). After stirring at room temperature for 5 minutes, *t*-butyl acetoacetate (50.0 g, 0.3160 mole) was added. The mixture was diluted with cyclohexane (300 ml) then refluxed under a Dean-Stark trap with continuous removal of methanol-water. Once a one-phase distillate was achieved, the cyclohexane mixture was refluxed under the Dean-Stark trap for 3 hours. The organic solvent was removed *in vacuo*. The oily enamine was treated with sodium ethoxide (0.39 mole) in 150 ml of absolute ethanol. The resulting orange colored solution was refluxed under argon for 75 minutes. After cooling in an ice-bath, the reaction mixture was treated with 92 ml of a solution consisting of concentrated hydrochloric acid (83.3 ml, 1.0 mole) and absolute ethanol (150 ml). The neutral reaction mixture was then diluted with ethyl acetate (600 ml), followed by the remainder of the concentrated hydrochloric acid-ethanol solution. The thick suspension was chilled for several hours, the precipitate collected, washed with ethyl acetate and dried. The crude hydrochloride salt (mixed with sodium chloride) was suspended in distilled water (300 ml), stirred for 10 minutes, the insoluble hydrochloride salt collected by filtration, washed with water (100 ml) and air dried. The crude white product (65.0 g, 67%) was recrystallized from ethanol/ethyl acetate (600 ml/1200 ml) to yield white crystals (61.0 g, 63%), mp 183.5-185.0° dec; ir (potassium bromide): 3600-2400 broad (3400, 3200, 2980, 2580), 1660, 1470, 1360, 1300, 1120 cm^{-1}; nmr (DMSO-d_6): δ 1.53 (s, 9H, *t*-butoxy), 2.43 (s, 3H, methyl at C5 position), 3.2-5.0 (broad s, 3H, salt protons), 7.3-7.8 (m, 5H, ArH), 11.0-11.3 (broad s, 1H, NH) ppm.

Anal. Calcd. for $C_{16}H_{21}ClN_2O_2 \cdot H_2O$: C, 58.79; H, 7.09; Cl, 10.85; N, 8.57. Found: C, 58.72; H, 7.11; Cl, 10.90; N, 8.57.

N-[5-Methyl-2-phenyl-4-*t*-butoxycarbonylpyrrol-3-yl]aminomethylenemalonic Acid, Diethyl Ester (VII).

A suspension of pyrrole hydrochloride (IV) (30.8 g, 0.1 mole) in absolute ethanol (200 ml) was treated with sodium methylate (6.0 g, 0.11 mole) and stirred at room temperature for 5 minutes. Diethyl ethoxymethylenemalonate (21.6 g, 0.1 mole) was added and the mixture was refluxed for 15 hours. After cooling, the mixture was poured into 600 ml of ice-water and the insoluble product was collected by filtration. The crude product was recrystallized from ethanol to yield a yellow powder, (39.5 g, 90%), mp 205-207°; ir (potassium bromide): 3250, 2980, 1665, 1590, 1315, 1210, 1155, 1080 cm^{-1}; nmr (deuteriochloroform): δ 0.94 (t, 3H, methyl of ethyl ester), 1.24 (t, 3H, methyl of ethyl ester), 1.55 (s, 9H, *t*-butyl), 2.40 (s, 3H, methyl at 5-position), 3.86 (q, 2H, methylene of ethyl ester), 4.18 (q, 2H, methylene of ethyl ester), 7.0-7.3 (m, 5H, aromatic protons), 7.94 (d, 1H, vinyl proton), 9.30 (broad s, 1H, NH at N^1-position), 10.94 (d, 1H, NH at N^3-position) ppm.

Anal. Calcd. for $C_{24}H_{30}N_2O_6$: C, 65.13; H, 6.83; N, 6.33. Found: C, 65.20; H, 6.84; N, 6.29.

N-[2-Phenyl-1,5-dimethyl-4-*t*-butoxycarbonylpyrrol-3-yl]methylaminomethylenemalonic Acid, Diethyl Ester (VIII).

N-[2-Phenyl-5-methyl-4-*t*-butoxycarbonylpyrrol-3-yl]aminomethylenemalonic acid, diethyl ester (VII) (4.42 g, 0.01 mole) in dry DMF (15 ml) was treated with sodium methoxide (1.4 g, 0.024 mole) and stirred at room temperature for 10 minutes. Methyl iodide (4.65 g, 0.03 mole) was added and an exothermic reaction ensued. After stirring overnight at room temperature, the DMF solution was poured into ice water (50 ml) and the insoluble product was collected by filtration. The crude product was recrystallized from ethanol/water (8:3) to give white crystals (4.18 g, 88%), mp 120-122°; ir (potassium bromide): 3440, 2980, 1715, 1690, 1595, 1150 cm^{-1}; nmr (deuteriochloroform): δ 0.94-1.38 (complex m, 6H, 2 methyl of ethyl ester), 1.52 (s, 9H, *t*-butyl), 2.54 (s, 3H, methyl at 5-position), 2.95 (s, 3H, methyl at N^3-position), 3.32 (s, 3H, methyl at N^1-position), 3.50-4.35 (two q, 4H, methylene of ethyl ester), 7.35 (s, 6H, aromatic protons and vinyl proton) ppm.

Anal. Calcd. for $C_{26}H_{34}N_2O_6$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.28; H, 7.32; N, 5.91.

N-[1,5-Dimethyl-2-phenyl-4-carboxypyrrol-3-yl]methylaminomethylenemalonic Acid, Diethyl Ester (IX).

The pyrrolo triester VIII (2 g, 0.004 mole) was stirred with methane sulfonic acid (8.0 g) at ambient temperatures for 10 minutes. Ice-water (100 ml) was added, and the precipitated carboxylic acid was collected by filtration. The crude product was crystallized from methanol to give white crystals (1.6 g, 91%), mp 178-180°; ir (potassium bromide): 3460 broad, 2980, 1710, 1675, 1590, 1250 cm^{-1}; nmr (deuteriochloroform): δ 0.94-1.32 (t, 6H, methyl of ethyl ester), 2.58 (s, 3H, methyl at 5-position), 3.10 (s, 3H, methyl at N^3-position), 3.32 (s, 3H, methyl at N^1-position), 3.55-4.30 (two q, 4H, methylene of ethyl esters), 5.60 (broad s, 1H, carboxylic acid proton), 7.2 (s, 1H, vinyl proton), 7.32 (s, 5H, aromatic protons) ppm.

Anal. Calcd. for $C_{22}H_{26}N_2O_6$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.75; H, 6.32; N, 6.75.

2-Phenyl-3-amino-5-methylpyrrole Hydrochloride (V).

A suspension of 2-phenyl-3-amino-4-*t*-butoxycarbonyl-5-methylpyrrole hydrochloride monohydrate (IV) (9.24 g, 0.0283 mole) in 25 ml of *m*-diisopropylbenzene was heated with stirring under argon at 210-235° (silicone bath temperature) for 15 minutes. The suspension was rapidly cooled and the contents of the reaction vessel were diluted with hexanes (50 ml). The insoluble product was collected, washed with hexanes (50 ml), and air dried to yield a light tan powder (5.58 g, 95%). One g was suspended in acetone (25 ml), collected and air dried to yield a light beige powder (0.56 g), mp 238-239° dec; ir (potassium bromide): broad 3600-2500, 1565, 1500, 1380 cm^{-1}; nmr (DMSO-d_6): δ 2.16 (s, 3H, methyl at 5-position), 5.93 (s, 1H, aromatic H at 4-position), 7.0-7.7 (m, 5H, aromatic protons of phenyl), 9.7-10.3 (broads, 3H, salt protons), 11.3 (s, 1H, NH proton) ppm.

Anal. Calcd. for $C_{11}H_{13}ClN_2 \cdot 0.15H_2O$: C, 62.50; H, 6.34; Cl, 16.77; N, 13.26. Found: C, 62.52; H, 6.22; Cl, 16.82; N, 13.26.

N-[2-Phenyl-5-methylpyrrol-3-yl]aminomethylenemalonic Acid, Diethyl Ester (VI).

A suspension of 2-phenyl-3-amino-5-methylpyrrole hydrochloride (V) (5.58 g, 0.0267 mole) in absolute ethanol (35 ml) was treated with sodium methylate (1.44 g, 0.0267 mole). After stirring at room temperature for 5 minutes, diethyl ethoxymethylenemalonate (6.10 g, 0.0282 mole) was added. An exothermic reaction ensued and a precipitate had formed within five minutes. The suspension was stirred at room temperature for 2

hours, then poured onto ice (50 g). The gummy precipitate was collected, suspended in diethyl ether (100 ml), collected and air dried. The crude product (7.8 g, 85%) was recrystallized from methanol (100 ml) to yield a light tan solid (6.45 g). Two g of the product was further recrystallized from methanol (100 ml) to yield golden colored flakes, mp 162-163°; ir (potassium bromide): 3290, 3200, 2980, 1680, 1640, 1610, 1200, 1060, 800, 760, 690 cm^{-1}; nmr (DMSO-d_6): δ 1.20 (two t, 6H, methyls of ethyl ester), 2.2 (s, 3H, methyl at 5-position), 4.03 (q, 2H, methylene of ethyl ester), 4.10 (q, 2H, methylene of ethyl ester), 5.93 (s, 1H, aromatic proton at 4-position), 7.2-7.5 (m, 5H, phenyl protons), 8.13 (d, 1H, vinyl proton), 10.95 (d, 1H, NH), 10.97 (broad s, 1H, NH at 1-position) ppm.

Anal. Calcd. for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.61; H, 6.52; N, 8.17.

3-Carbethoxy-1,5-dimethyl-7-phenyl-1,4-dihydro-4-oxopyrrolo[3,4-*b*]pyridine (XIII).

Pyrrole diester VI (10.27 g, 0.03 mole) was added to a suspension of sodium hydride (0.75 g, 0.0315 mole) in dry THF (75 ml) and stirred for 10 minutes. Then, dimethyl sulfate (4.15 g, 0.033 mole) in THF (20 ml) was added dropwise over 10 minutes and the mixture refluxed for 2 hours. The reaction mixture was then stirred at room temperature overnight. After evaporation of the solvent, the residue was suspended in water and extracted with methylene chloride (3 × 50 ml). The combined organic layer was washed with water and dried over anhydrous sodium sulfate. To the residue left after evaporation of methylene chloride *in vacuo*, polyphosphoric ester (35 g) was added and the mixture was heated at 100-110° with stirring for 2 hours. After cooling, ice-water (300 ml) was added and the mixture was filtered. The *p*H of the filtrate was adjusted to 7 by dropwise addition of 50% sodium hydroxide. The yellow precipitate was collected, washed with water and air dried. The crude solid (6.65 g, 70%) was recrystallized from the methanol to give yellow crystals, mp 309-312°; ir (potassium bromide): 3440, 3080, 1695, 1615, 1585, 1230, 1135, 1075 cm^{-1}; nmr (DMSO-d_6): δ 1.29 (t, 3H, methyl of ethyl ester), 2.50 (s, 3H, methyl at 5-position), 3.3 (s, 3H, methyl at N^1-position), 4.08 (q, 2H, methylene of ethyl ester), 7.34 (s, 5H,aromatic protons), 8.05 (s, 1H, proton at 2-position) and 11.82 (broad s, 1H, N^6-proton) ppm (see Table I for elemental analysis).

1-Benzyl-3-carbethoxy-5-methyl-7-phenyl-1,4-dihydro-4-oxopyrrolo[3,4-*b*]pyridine (XIV).

Pyrrole diester (VI) (8.0 g, 0.023 mole) was added to a suspension of 60% sodium hydride (1.0 g, 0.025 mole) in dry THF (15 ml) and stirred for 10 minutes. Then, benzyl bromide (4.27 g, 0.02 mole) in THF (10 ml) was added dropwise over 15 minutes and the mixture refluxed for 4 hours then stirred overnight at room temperature. The inorganic precipitate was filtered off and the filtrate was concentrated *in vacuo*. To the residue left after evaporation of the solvent, polyphosphoric ester (35 g) was added and the mixture was heated at 100-110° with stirring for 2 hours. After cooling, ice-water (300 ml) was added and the solution was neutralized with 50% sodium hydroxide. The precipitate was collected, washed with water and air dried. The crude product (6.5 g, 72%) was suspended in acetone (50 ml) and warmed then cooled in the refrigerator. The precipitate was filtered and recrystallized from acetone to give yellow crystals, mp 285-287°; ir (potassium bromide): 3300-2900, 1720, 1700, 1620, 1580, 1460, 1285, 1220, 1115, 1090 and 685 cm^{-1}; nmr (deuteriochloroform): δ 1.30 (t, 3H, methyl of ester), 2.64 (s, 3H, methyl at 5-position), 4.21 (q, 2H, methylene of ethyl ester), 6.25-7.38 (m, 10H, aromatic protons), 8.11 (s, 1H, proton at 2-position) and 11.14 (broad s, 1H, N^6 proton) ppm (see Table I for elemental analysis).

3-Carbethoxy-1-ethyl-5-methyl-7-phenyl-1,4-dihydro-4-oxopyrrolo[3,4-*b*]pyridine (XV).

Pyrrole diester VI (3.43 g, 0.01 mole) was added to a suspension of 60% sodium hydride (0.4 g, 0.01 mole) in dry THF (35 ml) and stirred for 10 minutes. Ethyl iodide (3.1 g, 0.02 mole) in dry THF (10 ml) was added dropwise over 5 minutes and the mixture was refluxed for 3 hours then stirred overnight at room temperature. The inorganic precipitate was removed by filtration and the THF was evaporated *in vacuo*. To the residue, polyphosphoric ester (16 g) was added and the mixture was heated at 100-110° for 2 hours. After cooling, water was added to dissolve the contents of the flask and the mixture was filtered. The solution is neutralized with 50% sodium hydroxide and the insoluble product was collected by filtration, washed with water and air dried. The crude product (3.0 g, 90%) was recrystallized from acetone/water (3:2) to give reddish crystals, mp 285-287°; ir (potassium bromide): 3060, 2990, 1695, 1615, 1580, 1455, 1305, 1225, 1095, 795, 690 cm^{-1}; nmr (deuteriochloroform): δ 0.98 (t, 3H, methyl of ethyl group), 1.30 (t, 3H, methyl of ethyl ester), 2.66 (s, 3H, methyl at 5-position), 3.82 (q, 2H, methylene of ethyl group), 4.23 (q, 2H, methylene of ethyl ester), 7.36 (s, 5H, aromatic protons), 8.08 (s, 1H, proton at 2-position) and 11.52 (broad s, 1H, N^6-proton) ppm (see Table I for elemental analysis).

3-Carbethoxy-7-phenyl-1,5,6-trimethyl-1,4-dihydro-4-oxopyrrolo[3,4-*b*]-pyridine (XVIa). Method A.

The procedure given in the synthesis of XVIa is a general route for the synthesis of XVIb-c, XVIIa-c,e and XVIIIa. A solution of 3-carbethoxy-1,5-dimethyl-7-phenyl-1,4-dihydro-4-oxopyrrolo[3,4-*b*]pyridine (XIII) (1.55 g, 0.005 mole) in dry DMF (10 ml) was treated with sodium methoxide (0.30 g, 0.0055 mole) and the mixture was stirred for 10 minutes at room temperature. Methyl iodide (1.42 g, 0.01 mole) was added and an exothermic reaction ensued. The reaction mixture was stirred overnight at room temperature, then poured into ice-water (50 ml). The insoluble product was collected, washed with water and air dried. The crude product (1.49 g, 92%) was recrystallized from ethanol-water (6:4) to yield yellow crystals. The ir and nmr spectra and melting point were identical to the product obtained under Method B (see Table I for analogs).

Method B.

A mixture of carboxylic acid IX (1.5 g, 0.0036 mole) and polyphosphoric ester (6 g) was heated at 100-110° for 1.5 hours with stirring. The reaction mixture was cooled to room temperature and poured into 50 ml of ice-water. The *p*H was adjusted to 8 by dropwise addition of 50% aqueous sodium hydroxide solution. The yellowish brown precipitate was collected by filtration, washed with cold water, and air dried. Recrystallization from ethanol/water gave yellow crystals (1.10 g, 94%) mp 233-235°; ir (potassium bromide): 3440, 3050, 2995, 1715, 1665, 1600, 1315, 1225, 1170, 1080 cm^{-1}; nmr (deuteriochloroform): δ 1.32 (t, 3H, methyl of ethyl ester), 2.74 (s, 3H, methyl at 5-position), 3.14 (s, 3H, methyl at N^1-position), 3.25 (s, 3H, methyl at 6-position), 4.30 (q, 2H, methylene of ethyl ester), 7.32 (s, 5H, aromatic protons), 7.96 (s, 1H, proton at 2-position) ppm.

7-Phenyl-1,5,6-trimethyl-1,4-dihydro-4-oxopyrrolo[3,4-*b*]pyridine-3-carboxylic Acid (XIXa).

The procedure given for the hydrolysis of XIXa is the general method for the synthesis of XIXb-d, XXa-c,e, and XXIa. The ester (XVIa) (2.66 g, 0.008 mole) was dissolved in methanol/water (1:2) (40 ml) and treated while hot with 1% sodium hydroxide (35 ml). The mixture was heated on a boiling water bath with stirring for 1 hour, cooled and filtered. The filtrate was acidified by the dropwise addition of 6*N* hydrochloric acid. The white precipitate was collected, washed with water and air dried. The product (1.84 g, 75%) was recrystallized from methanol to give crystals, mp 273-275°; ir (potassium bromide): 3460, 3060, 1695, 1615, 1465, 1470, 1330, 800, 720 cm^{-1}; nmr (deuteriochloroform): δ 2.69 (s, 3H, methyl at 5-position), 3.24 (s, 3H, methyl at N^1-position), 3.32 (s, 3H, methyl at 6-position), 7.38 (s, 5H, aromatic protons), 8.10 (s, 1H, proton at 2-position), 15.30 (broad s, 1H, carboxylic acid proton) ppm (see Table I for analogs).

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REFERENCES AND NOTES

[1] On leave from the Faculty of Pharmacy, University of Mansoura, Mansoura, Egypt.

[2] Bristol-Myers Company, Pharmaceutical Research and Development Division, Thompson Road, Syracuse, New York, 13057.

[3] Said M. Bayomi, Kenneth E. Price and J. Walter Sowell, Sr., *J. Heterocyclic Chem.*, **22**, 83 (1985).

[4] G. Tarzia and G. Panzone, *Ann. Chim., (Rome)*, **64**, 807 (1974).

[5] K. Okumura, T. Adachi, M. Tomie, K. Kondo and I. Inoue, *J. Chem. Soc., Perkin Trans. I*, 173 (1972).

[6] W. Pollmann and G. Schramm, *Biochem. Biophys. Acta*, **80**, 1 (1964).