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

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A route for the synthesis of various derivatives of 7-oxopyrrolo[3,2-*b*]pyridine-6-carboxylic acid from 2-methyl-3-carbomethoxy-4-aminopyrrole is reported.

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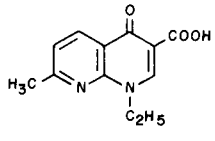
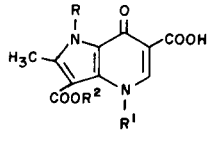
In 1962, Lesher, *et al.* [3] reported the synthesis of the 1,8-naphthyridine derivative, nalidixic acid (I). The antimicrobial properties exhibited by this drug have served as an impetus for the synthesis of analogous compounds that might possess a broader spectrum of antimicrobial activity, as well as increased potency.

The research efforts may be broadly categorized as those which involve peripheral and nuclear modifications of the pyridin-4-one portion of the nalidixic acid structure or those which involve the fused pyridine ring. These efforts are far too voluminous to adequately summarize in the present communication. A few examples of the compounds which have resulted from these research efforts include the cinnoline derivative, cinoxacin [4], the pyrido[2,3-*d*]pyrimidines, piromidic acid [5] and pipemidic acid [6], thieno[2,3-*b*]pyridines [7], furo[2,3-*b*]pyridines [8], pyrazolo[3,4-*b*]pyridines [9], and pyrido[2,3-*b*]pyrazines [10].



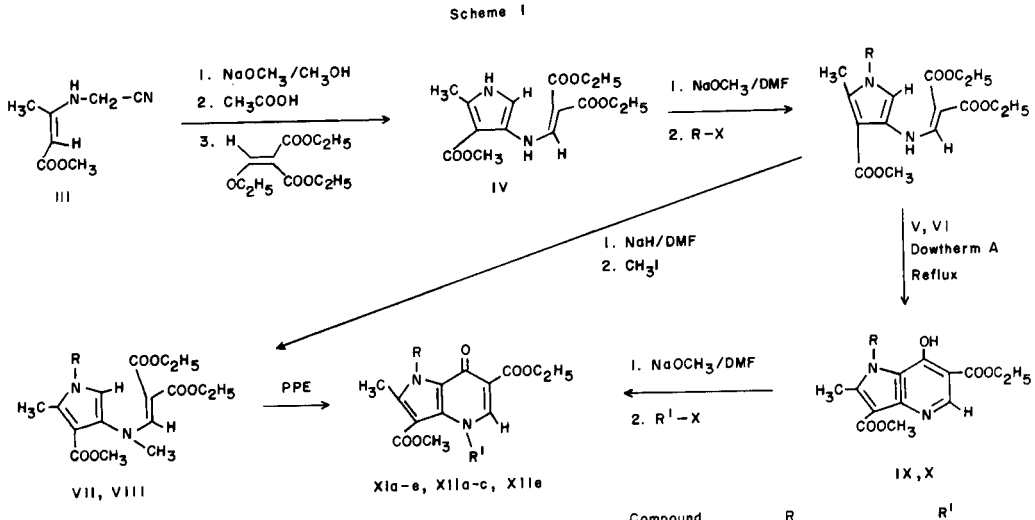
I



II

We now wish to report the synthesis of a series of 7-oxopyrrolo[3,2-*b*]pyridine-6-carboxylic acids II (Scheme I). In this synthesis, methyl 3-(cyanomethylamino)-2-butenoate (III) was cyclized in the presence of sodium methoxide in methanol, according to the procedure described by Tarzia and Panzone [11], to yield 2-methyl-3-carbomethoxy-4-am-

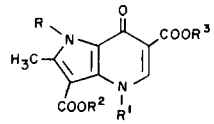
Scheme I



Compound	R	R¹
V, VII, IX	$-CH_2C_6H_5$	—
XIa, XIIIa, XVa	$-CH_2C_6H_5$	$-CH_3$
XIb, XIIIb, XVb	$-CH_2C_6H_5$	$-CH_2C_6H_5$
XIc, XIIIc	$-CH_2C_6H_5$	$-C_2H_5$
XId, XIIId	$-CH_2C_6H_5$	$-CH_2CH{=}CH_2$
XIe	$-CH_2C_6H_5$	$-CH_2C{\equiv}CH$
VI, VIII, X	$-CH_3$	—
XIIa, XIVa	$-CH_3$	$-CH_3$
XIIb, XIVb	$-CH_3$	$-CH_2C_6H_5$
XIIc, XIVc, XVIc	$-CH_3$	$-C_2H_5$
XIVd	$-CH_3$	$-CH_2CH{=}CH_2$
XIIe, XIVe	$-CH_3$	$-CH_2C{\equiv}CH$

Table I

Substituted 7-Oxopyrrolo[3,2-*b*]pyridines



Compound No.	R	R^1	R^2	R^3	Yield (%)	Mp, °C	Recrystallization Solvent	formula		Analysis (%) Calcd.	Found
XIa	$-CH_2C_6H_5$	$-CH_3$	$-CH_3$	$-C_2H_5$	100	163-164	Methanol/water	$C_{21}H_{22}N_2O_5 \cdot 0.5H_2O$	C	64.43	64.43
									H	5.92	5.93
									N	7.16	7.14
XIb	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CH_3$	$-C_2H_5$	94	164-165	Methanol/water	$C_{27}H_{26}N_2O_5$	C	70.72	70.59
									H	5.71	5.72
									N	6.11	6.10
XIc	$-CH_2C_6H_5$	$-C_2H_5$	$-CH_3$	$-C_2H_5$	84	132-134	Acetone/water	$C_{22}H_{24}N_2O_5$	C	66.31	66.52
									H	6.07	6.10
									N	7.03	7.02
XId	$-CH_2C_6H_5$	$-CH_2CH=CH_2$	$-CH_3$	$-C_2H_5$	95.5	113-115	Ethanol/water	$C_{23}H_{24}N_2O_5$	C	67.63	67.69
									H	5.92	5.96
XIe	$-CH_2C_6H_5$	$-CH_2-C\equiv CH$	$-CH_2$	C_2H_5	100	162-164	Methanol/water	$C_{23}H_{22}N_2O_5$	C	67.91	67.87
									H	5.45	5.48
									N	6.86	6.85
XIIa	$-CH_3$	$-CH_3$	$-CH_3$	$-C_2H_5$	78	118-120	Methanol	$C_{15}H_{18}N_2O_5 \cdot 0.5H_2O$	C	57.13	57.17
									H	6.07	6.05
									N	8.88	8.88
XIIb	$-CH_3$	$CH_2C_6H_5$	$-CH_3$	$-C_2H_5$	72	170-171	Ethanol/water	$C_{21}H_{22}N_2O_5$	C	65.95	65.68
									H	5.80	5.81
									N	7.32	7.26
XIIc [a]	$-CH_3$	C_2H_5	$-CH_3$	$-C_2H_5$	87	viscous oil		$C_{16}H_{20}N_2O_5$			
XIId [b]	$-CH_3$	$-CH_2CH=CH_2$	$-CH_3$	$-C_2H_5$	—	—	—	$C_{17}H_{20}N_2O_5$			
XIIe [c]	$-CH_3$	$-CH_2-C\equiv CH$	$-CH_3$	$-C_2H_5$	70	169-170	Ethanol	$C_{17}H_{18}N_2O_5$	C	61.80	61.89
									H	5.49	5.50
									N	8.48	8.46
XIIIa	$-CH_2C_6H_5$	$-CH_3$	$-CH_3$	H	50	218-220	Methanol	$C_{19}H_{18}N_2O_5$	C	64.39	64.42
									H	5.11	5.15
									N	7.90	7.90
XIIIb	$-CH_2C_6H_5$	$-CH_2C_6H_5$	$-CH_3$	-H	33	220-222	Methanol	$C_{25}H_{22}N_2O_5$	C	69.75	69.85
									H	5.15	5.20
									N	6.50	6.50

inopyrrole. After neutralization with acetic acid, the pyrrole was reacted *in situ* with diethyl ethoxymethylenemalonate to yield *N*-[2-methyl-3-carbomethoxypyrrol-4-yl]aminomethylenemalonic acid, diethyl ester (IV).

Selective alkylation of IV at the 1-position was achieved through pyrrolyl anion generation, utilizing sodium methoxide in DMF, followed by alkylation with benzyl bromide or methyl iodide to yield compounds V or VI, respectively. The site of alkylation was assigned on the basis of the disappearance of the N_1H proton at 8.7-9.1 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 V and VI were *N*-alkylated, utilizing sodium hydride in DMF followed by methyl iodide, to yield the corresponding (pyrrol-4-yl)methylaminomethylene malonic acid, diethyl esters VII and VIII, respectively. The *N*-methylation of the nitrogen off the 4-position abolished the (-NH-CH=) coupling which was previously observed in non-alkylated precursors IV-VI. Utilizing a cyclization procedure described by Okumura, *et al.* [12], compounds VII and VIII were cyclized by heating in polyphosphoric ester (PPE) [13] to yield the pyrrolo[3,2-*b*]pyridines XIa and XIIa, respectively.

In an alternate route, compounds V and VI were thermally cyclized in refluxing Dowtherm A to give 1-benzyl-2-methyl-3-carbomethoxy-6-carbethoxy-7-hydroxypyrrolo-[3,2-*b*]pyridine (IX) in 87% yield and the 1-methyl analog X in 75% yield. Alkylation of the nitrogen at the 4-position in compounds IX and X with methyl iodide, benzyl bromide, ethyl iodide, allyl bromide, and propargyl bromide resulted in XIa-XIe, XIIa-XIIc, and XIIe in excellent yields. During the alkylation of X with allyl bromide, cleavage of the ethyl ester occurred leading to the

Table I Continued

Compound No.	R	R¹	R²	R³	Yield (%)	Mp, °C	Recrystallization Solvent	Formula		Analysis (%) Calcd.	Found
XIIIc	$-CH_2C_6H_5$	$-C_2H_5$	$-CH_3$	-H	82.3	158-160	Methanol/water	$C_{20}H_{20}N_2O_5$	C	65.20	65.13
									H	5.47	5.51
									N	7.60	7.55
XIIId	$-CH_2C_6H_5$	$-CH_2CH=CH_2$	$-CH_3$	-H	80.0	135-137	Methanol/water	$C_{21}H_{20}N_2O_5$	C	66.30	66.07
									H	5.29	5.37
									N	7.36	7.34
XIVa	$-CH_3$	$-CH_3$	$-CH_3$	-H	86.2	266-268	Chloroform/-methanol	$C_{13}H_{14}N_2O_5$	C	56.10	56.03
									H	5.07	5.09
									N	10.06	10.04
XIVb	$-CH_3$	$-CH_2C_6H_5$	$-CH_3$	-H	92.0	256-258	Methanol	$C_{19}H_{18}N_2O_5 \cdot 0.25H_2O$	C	63.59	63.60
									H	5.19	5.23
									N	7.81	7.78
XIVc	$-CH_3$	$-C_2H_5$	$-CH_3$	-H	68.0	215-217	Ethanol	$C_{14}H_{16}N_2O_5$	C	57.53	57.69
									H	5.52	5.54
									N	9.59	9.59
XIVd	$-CH_3$	$-CH_2CH=CH_2$	$-CH_3$	-H	68.0	200-201	Methanol	$C_{15}H_{16}N_2O_5$	C	59.20	59.18
									H	5.30	5.33
									N	9.20	9.19
XIVe	$-CH_3$	$-CH_2C\equiv CH$	$-CH_3$	-H	65.0	191-193	Methanol	$C_{15}H_{14}N_2O_5$	C	59.59	59.51
									H	4.66	4.68
									N	9.26	9.26
XVa	$-CH_2C_6H_5$	$-CH_3$	-H	-H	83.0	250-251	Methanol	$C_{18}H_{16}N_2O_5$	C	63.52	63.44
									H	4.73	4.74
									N	8.23	8.19
XVb	$-CH_2C_6H_5$	$-CH_2C_6H_5$	-H	-H	45.0	228-230	Methanol	$C_{24}H_{20}N_2O_5 \cdot 0.5H_2O$	C	67.75	67.99
									H	4.98	5.09
									N	6.59	6.46
XVIc	$-CH_3$	$-C_2H_5$	-H	-H	72.0	250-251	Ethanol	$C_{13}H_{14}N_2O_5$	C	56.10	56.02
									H	5.07	5.07
									N	10.06	10.05

[a] The ir and nmr spectra were consistent with assigned structure; therefore, the viscous oil was directly hydrolyzed to XIVc. [b] During the alkylation, the ethyl ester was cleaved to yield XIVd directly. [c] A small quantity (0.49 g) of XIVe was obtained upon workup of the alkylation reaction.

carboxylic acid XIVd in 68% yield.

Selective hydrolysis of the ethyl ester in compounds XIa-XId, XIIa-XIIc, and XIIe was achieved through alkaline hydrolysis with one equivalent or a very slight excess of one equivalent of sodium hydroxide in aqueous or hydroalcoholic media. The 7-oxopyrrolo[3,2-*b*]pyridine-6-carboxylic acids XIIIa-XIIId, XIVa-XIVc, and XIVe were readily isolated upon acidification of the alkaline reaction solution.

Under more drastic conditions and with the utilization of two or more equivalents of alkali, the more sterically hindered methyl ester at the 3-position was also hydrolyzed to yield the 7-oxopyrrolo[3,2-*b*]pyridine-3,6-dicarboxylic acids XVa, XVb, and XVIc.

The results of microbiological evaluation of the final products are presented in Table II. The compounds posessing a benzyl group at the 1-position XIIIa, XIIIc, XIIId as well as those in which the methyl ester at the 3-position were hydrolyzed XVa, XVb, and XVIc were considerably less active than the 1-methyl-3-carbomethoxy-7-oxopyrrolo[3,2-*b*]pyridine-6-carboxylic acids XIVa-XIVe. The latter compounds exhibit a relatively broad spectrum of activity but are only moderately active against most of the microorganisms. Noteworthy is the activity of compounds XIVa and XIVc against *S. sonnei* (A-9516) with minimum inhibitory concentrations of 1 and 2 micrograms per milliliter, respectively.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. The nmr spectra were determined on a Varian EM360A NMR 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).

N-[2-Methyl-3-carbomethoxypyrrol-4-yl]aminomethylenemalonic Acid, Diethyl Ester (IV).

The general procedure reported by Tarzia and Panzone [11] was utilized for the pyrrole synthesis. Methyl 3-(cyanomethylamino)-2-butenoate (III) (46.2 g, 0.3 mole) was added to a solution of sodium methoxide (19.5 g, 0.36 mole) in 300 ml of methanol. The resulting solution was refluxed

Table II

Antibacterial Activity of Substituted 7-Oxopyrrolo[3,2-*b*]pyridine-6-carboxylic Acids

Organism		MIC (μg/ml) [a] XIIIa	XIIIc	XIIId	XIVa	XIVb	XIVc	XIVd	XIVe	XVa	XVb	XVIc
S. aureus	A-9537	16	16	16	32	32	32	32	32	125	>125	>125
S. aureus	A-9606	16	16	16	32	32	32	32	32	>125	>125	>125
S. faecalis	A-9612	—	—	—	32	32	32	32	32	—	—	—
S. faecalis	A-9808	32	16	16	32	32	32	32	32	>125	>125	>125
E. coli	A-9675	125	125	125	32	32	32	32	32	125	125	125
E. coli	A15119	>125	>125	>125	32	63	32	63	63	>125	>125	>125
K. oxytoca	A20345	>125	>125	>125	63	63	63	63	63	>125	>125	>125
K. pneumoniae	A-9664	>125	>125	>125	63	63	63	63	63	>125	>125	>125
E. aerogenes	A20985	>125	>125	>125	63	63	63	63	63	>125	>125	>125
E. cloacae	A-9656	>125	>125	>125	63	63	63	63	63	>125	>125	>125
E. cloacae	A20464	>125	>125	>125	63	63	63	63	63	>125	>125	>125
P. mirabilis	A-9900	125	125	125	32	32	32	32	32	125	125	>125
P. vulgaris	A21559	125	>125	>125	32	32	32	32	32	>125	>125	>125
M. morganii	A15153	125	>125	>125	32	32	32	32	32	>125	>125	>125
P. rettgeri	A22424	>125	>125	>125	32	32	32	32	32	>125	>125	>125
P. stuartii	A20615	>125	>125	>125	32	32	32	32	32	>125	>125	>125
S. marcescens	A20019	>125	>125	>125	63	63	63	63	63	>125	>125	>125
S. enteritidis	A-9531	>125	>125	>125	32	32	32	32	32	>125	>125	>125
S. sonnei	A-9516	32	32	32	1	32	2	32	32	>125	>125	63
P. aeruginosa	A-9843 [a]	125	>125	>125	32	32	32	32	32	>125	>125	>125
P. aeruginosa	A21213	125	125	125	32	32	32	32	32	125	125	>125
H. influenzae	A-9833	>125	>125	>125	63	>125	32	>125	>125	>125	>125	>125
H. influenzae	A21518	>125	>125	>125	63	>125	>125	>125	>125	>125	>125	>125
N. gonorrhoeae	A22412	>125	>125	>125	63	>125	16	>125	>125	>125	>125	>125

[a] Dynatech's MIC-20000.

for one hour under an argon atmosphere. After cooling, glacial acetic acid (21.6 g, 0.36 mole) was added followed by the addition of diethyl ethoxymethylenemalonate (64.8 g, 0.3 mole). Immediately, an exothermic reaction occurred and the contents of the flask solidified. Additional methanol (300 ml) was added and the mixture heated until solution was achieved. After standing in a freezer overnight, the solid was collected, washed with 200 ml of cold methanol, then recrystallized from methanol (600-700 ml). A small sample of the light yellow fluffy crystals (69.2 g, 71%) was further recrystallized from methanol, mp 187-188°; ir (potassium bromide): 3260, 2980, 1720, 1670, 1610, 1330, 1220, 1085, 1060, 800 cm^{-1}; nmr (deuteriochloroform): δ 1.25 (t, 3H, methyl of ethyl ester), 1.30 (t, 3H, methyl of ethyl ester), 2.40 (s, 3H, methyl at 2-position), 3.8 (s, 3H, methyl of methyl ester), 4.0-4.5 (two q, 4H, methylenes of ethyl ester), 6.5 (s, 1H, aromatic proton at 5-position), 8.2 (d, 1H, vinyl proton), 8.7-9.1 (broad s, 1H, NH at 1-position), 11.5 (d, 1H, NH at 4-position) ppm.

Anal. Calcd. for $C_{15}H_{20}N_2O_6$: C, 55.55; H, 6.22; N, 8.64. Found: C, 55.47; H, 6.26; N, 8.60.

N-[1-Benzyl-2-methyl-3-carbomethoxypyrrol-4-yl]aminomethylenemalonic Acid, Diethyl Ester (V).

N-[2-Methyl-3-carbomethoxypyrrol-4-yl]aminomethylenemalonic acid, diethyl ester (IV) (12.97 g, 0.04 mole) in dry DMF (25 ml) was treated with sodium methoxide (2.27 g, 0.042 mole) and stirred at room temperature for 10 minutes. Benzyl bromide (7.53 g, 0.044 mole) was added and an exothermic reaction ensued. After stirring for one hour at room temperature, the reaction mixture was poured into ice/water (100 ml). The water was decanted and the residue was triturated with 75% methanol/water and filtered. The crude product was washed with 100 ml of cooled methanol/water (3:1) and air dried. The crude product (15.0 g, 91%) was recrystallized from methanol/water (4:1) to give a fine powder, mp 101-103°; ir (potassium bromide): 3250, 2980, 1700, 1675, 1660, 1225, 1180, 1050 cm^{-1}; nmr (deuteriochloroform): δ 1.25 (t, 3H, methyl of ethyl ester), 1.34 (t, 3H, methyl of ethyl ester), 2.38 (s, 3H, methyl at 2-position), 3.85 (s, 3H, methyl of methyl ester), 3.90-4.47 (two q, 4H, methylenes of ethyl esters), 4.90 (s, 2H, benzylic methylene), 6.49 (s, 1H, aromatic proton at 5-position), 6.70-7.40 (m, 5H, aromatic protons), 8.14 (d, 1H, vinyl proton), 11.5 (d, 1H, NH at 4-position) ppm.

Anal. Calcd. for $C_{22}H_{26}N_2O_6 \cdot 0.4H_2O$: C, 62.66; H, 6.41; N, 6.65. Found: C, 62.71; H, 6.39; N, 6.66.

N-[1,2-Dimethyl-3-carbomethoxypyrrol-4-yl]aminomethylenemalonic Acid, Diethyl Ester (VI).

N-[2-Methyl-3-carbomethoxypyrrol-4-yl]aminomethylenemalonic acid, diethyl ester (IV) (23.5 g, 0.0725 mole) in 100 ml of dry DMF was treated with sodium methoxide (4.3 g, 0.0797 mole) and stirred at room temperature for 10 minutes. Methyl iodide (15.44 g, 0.109 mole) was added and an exothermic reaction ensued. After stirring for one hour at room temperature, the DMF solution was poured into 600 ml of ice-water and the insoluble product was collected by filtration. The crude product was recrystallized from 125 ml methanol-water (4:1) to yield an off-white powder (22.2 g, 91%). Two g of the product was further recrystallized from 60 ml of cyclohexane to yield a beige powder (1.8 g), mp 98.5-99.5°; ir (potassium bromide): 3260, 2980, 1700, 1675, 1600, 1250, 1075, 790 cm^{-1}; nmr (deuteriochloroform): δ 1.30 (t, 3H, methyl of ethyl ester), 1.35 (t, 3H, methyl of ethyl ester), 2.43 (s, 3H, methyl at 2-position), 3.50 (s, 3H, methyl at 1-position), 3.85 (s, 3H, methyl of methyl ester), 4.0-4.5 (two q, 4H, methylenes of ethyl ester), 6.44 (s, 1H, aromatic proton at 5-position), 8.2 (d, 1H, vinyl proton), 11.5 (d, 1H, NH at 4-position) ppm.

Anal. Calcd. for $C_{16}H_{22}N_2O_6$: C, 56.79; H, 6.55; N, 8.28. Found: C, 56.70; H, 6.57; N, 8.28.

1-Benzyl-2-methyl-3-carbomethoxy-6-carbethoxy-7-hydroxypyrrolo[3,2-*b*]-pyridine (IX).

A solution of V (15.0 g, 0.036 mole) in 50 ml of warm Dowtherm® A was

added over 7 minutes to 100 ml of boiling Dowtherm^R A under an argon atmosphere. After the addition was complete, the solution was refluxed for 30 minutes and the Dowtherm^R A was removed under reduced pressure. The residue was triturated with cyclohexane and then cyclohexane decanted. The crude solid was boiled with 75 ml of ethyl acetate and poured over hexanes (300 ml), cooled, and the light tan solid (11.6 g, 87%) was suitable for alkylation reactions. A small sample (0.5 g) was recrystallized from ethyl acetate (15 ml) to yield light beige plates (0.4 g), mp 205-207° ir (potassium bromide): 3500-3020 (broad), 3210, 1715, 1690, 1610, 1270, 1240, 1100 cm^{-1}; nmr (deuteriochloroform): δ 1.28 (t, 3H, methyl of ethyl ester), 2.48 (s, 3H, methyl at 2-position), 3.78 (s, 3H, methyl of methyl ester), 4.30 (q, 2H, methylene of ethyl group), 5.92 (s, 2H, benzylic protons), 6.8-7.3 (m, 5H, aromatic protons), 8.35 (s, 1H, aromatic proton at 5-position), 10.25-10.80 (broad s, 1H, phenolic OH) ppm.

Anal. Calcd. for $C_{20}H_{20}N_2O_5$: C, 65.20; H, 5.47; N, 7.60. Found: C, 65.30; H, 5.48; N, 7.57.

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

A solution of VI (30.0 g, 0.0887 mole) in 50 ml of warm Dowtherm^R A was added over 10 minutes to 150 ml of refluxing Dowtherm^R A under an argon atmosphere. After the addition was complete, the solution was refluxed for 30 minutes and the Dowtherm^R A was removed under reduced pressure. The residue was triturated hexanes and the hexanes decanted. The crude solid was boiled with acetone (150 ml), cooled, and the insoluble product collected. The product (20.4 g) was again boiled with acetone (150 ml), cooled, and the light tan solid (19.4 g, 75%) was suitable for alkylation reactions. A small sample (0.5 g) was recrystallized from acetone (50 ml) to yield a light beige powder (0.4 g), mp 191-192°; ir (potassium bromide): 3600-3000 (broad), 3230, 1710, 1680, 1610, 1270, 1240, 1100 cm^{-1}; nmr (deuteriochloroform): δ 1.33 (t, 3H, methyl of ethyl ester), 2.53 (s, 3H, methyl at 2-position), 3.85 (s, 3H, methyl at 1-position), 4.06 (s, 3H, methyl of methyl ester), 4.30 (q, 2H, methylene of ethyl group), 8.30 (s, 1H, aromatic proton at 5-position), 10.0-10.3 (broad s, 1H, phenolic OH) ppm.

Anal. Calcd. for $C_{14}H_{16}N_2O_5 \cdot 0.5H_2O$: C, 55.80; H, 5.69; N, 9.30. Found: C, 55.71; H, 5.71; N, 9.31.

1-Benzyl-2,4-dimethyl-3-carbomethoxy-6-carbethoxy-7-oxopyrrolo[3,2-*b*]-pyridine (XIa). Method A.

The procedure given for the synthesis of XIa is a general route for the synthesis of XIb-XIe. A solution of pyrrolo[3,2-*b*]pyridine IX (3.69 g, 0.01 mole) in 25 ml dry DMF was treated with sodium methoxide (0.7 g, 0.0126 mole) and stirred at room temperature for 10 minutes. Methyl iodide (4.5 g, 0.0317 mole) was added and the solution stirred overnight. The DMF was removed *in vacuo* and the residue treated with 150 ml of ice-water. The precipitate was collected, washed with water, and air dried. The product (3.8 g, 100%) was recrystallized from methanol/water, mp 163-164°; ir (potassium bromide): 1695, 1610, 1270, 1090 cm^{-1}; nmr (DMSO-d_6): δ 1.25 (t, 3H, methyl of ethyl ester), 2.28 (s, 3H, methyl at 2-position), 3.8 (s, 3H, methyl of methyl ester), 3.85 (s, 3H, methyl at 4-position), 4.15 (q, 2H, methylene of ethyl ester), 5.97 (s, 2H, benzylic protons), 6.80-7.40 (m, 5H, aromatic protons), 8.28 (s, 1H, proton at 5-position) ppm. (See Table I for Elemental Analyses and Analogs.)

Method B.

N-[1-Benzyl-2-methyl-3-carbomethoxypyrrol-4-yl]aminomethylenemalonic acid, diethyl ester (V) (6.22 g, 0.015 mole) in dry DMF (25 ml) was treated with sodium hydride (0.4 g, 0.0167 mole) and stirred at room temperature for 10 minutes. Methyl iodide (4.29 g, 0.03 mole) was added and continuously stirred overnight. The reaction mixture was poured over water-ice (150 ml) and the aqueous layer extracted with methylene chloride (3 × 40 ml). The combined organic layer was extracted with brine, dried over anhydrous sodium sulfate, and the methylene chloride removed *in vacuo*. The crude oily product VII (6.3 g, 100%) was determined to be *N*-methylated by the infrared and nmr spectra and used without further purification. The *N*-alkylated product VII (4.7 g) was treated with polyphosphoric ester (22 g) and was heated at 95-100° with stirring for 2.5 hours. After cooling, ice (50 g) was added on the *p*H of the mixture was adjusted to 7 by dropwise addition of 50% sodium hydroxide. The precipitate was collected, washed with water, and air dried. The product (2.95 g, 72%) was recrystallized from methanol/water to yield fine needles, mp 163-164°. The ir and nmr spectra were identical to the product obtained under Method A.

1,2,4-Trimethyl-3-carbomethoxy-6-carbethoxy-7-oxopyrrolo[3,2-*b*]pyridine (XIIa). Method A.

The procedure given for the synthesis of XIIa is a general route for the synthesis of XIIb, XIIc, and XIIe. A solution of pyrrolo[3,2-*b*]pyridine (X) (4.35 g, 0.0149 mole) in 25 ml of dry DMF was treated with sodium methoxide (1.0 g, 0.0185 mole) and stirred at room temperature for 10 minutes. Methyl iodide (4.5 g, 0.0317 mole) was added and the solution stirred overnight. The DMF was removed *in vacuo*, the residue was suspended in water (50 ml), and the aqueous layer was extracted with chloroform (3 × 30 ml). The combined organic layer was extracted with water, brine, then dried over anhydrous sodium sulfate. The chloroform was removed *in vacuo* to yield the crude product (4.1 g). Recrystallization from methanol (40 ml) gave crystals (2.9 g) with an additional 0.6 g isolated upon concentration of the mother liquor. Further recrystallization from ethyl acetate/methanol (9:1) gave fine needles, mp 118-120°; ir (potassium bromide): 1700, 1670, 1620, 1260, 1090 cm^{-1}; nmr (deuteriochloroform): δ 1.3 (t, 3H, methyl of ethyl ester), 2.40 (s, 3H, methyl at 2-position), 3.80 (s, 3H, methyl at 1- or 4-position), 3.83 (s, 3H, methyl at 1- or 4-position), 4.10 (s, 3H, methyl of methyl ester), 4.30 (q, 2H, methylene of ethyl ester), 7.98 (s, 1H, proton at 5-position) ppm. (See Table I for Elemental Analyses and Analogs.)

Method B.

N-[1,2-Dimethyl-3-carbomethoxypyrrol-4-yl]aminomethylenemalonic acid, diethyl ester (VI) (5.0 g, 0.0148 mole) in 25 ml of dry DMF was treated with sodium hydride (0.40 g, 0.0167 mole) and stirred at room temperature for 10 minutes. Methyl iodide (4.2 g, 0.03 mole) was added and continuously stirred overnight. The reaction mixture was poured over ice-water (150 ml) and the aqueous layer extracted with chloroform (3 × 40 ml). The combined organic layer was removed *in vacuo*. The crude product (5.26 g, 100%) was determined to be *N*-methylated by the ir and nmr spectra and used without further purification. The *N*-alkylated product VIII (2.2 g) was treated with polyphosphoric ester (7.0 g) and was heated at 95-100° with stirring for 1.5 hours. After cooling, ice (25 g) was added and the *p*H of the mixture was adjusted to 7 by dropwise addition of 50% sodium hydroxide. The aqueous mixture was extracted with chloroform (4 × 15 ml), the combined organic layer was further extracted with water, brine, and dried over anhydrous sodium sulfate. Removal of the solvent yielded a tan solid (0.95 g, 50%). The crude solid was recrystallized from ethyl acetate/methanol (9:1) to yield fine needles, mp 118-120°. The ir and nmr spectra were identical to the product described under Method A.

1-Benzyl-2,4-dimethyl-3-carbomethoxy-7-oxopyrrolo[3,2-*b*]pyridine-6-carboxylic acid (XIIIa).

The procedure given for the synthesis of XIIIa was utilized in the preparation of XIIIb-XIIId, XIVa-XIVc and XIVe. To a hot stirred solution of diester XIa (1.3 g, 0.0036 mole) in methanol (20 ml) a solution of 1% sodium hydroxide (15 ml) was added dropwise. The solution was heated on a boiling water bath with stirring for 1 hour. The reaction mixture was cooled, filtered, then acidified by dropwise addition of 6*N* hydrochloric acid. The white precipitate was collected, washed with distilled water and air dried. The product (0.6 g, 50%) was recrystallized from methanol to give reddish crystals, mp 218-220°; ir (potassium bromide): 3065, 1720, 1705, 1610, 1420, 1090 cm^{-1}; nmr (DMSO-d_6): δ 2.40 (s, 3H, methyl at 2-position), 3.84 (s, 3H, methyl of methyl ester), 4.04 (s, 3H, methyl at 4-position), 5.94 (s, 2H, benzylic methylene protons), 6.80-7.42 (m, 5H, aromatic protons), 8.90 (s, 1H, aromatic proton at 5-position), 15.58 (broad s, 1H, COOH) ppm. (See Table I for Analogs.)

1-Benzyl-2,4-dimethyl-7-oxopyrrolo[3,2-*b*]pyridine-3,6-dicarboxylic Acid (XVa).

The diester XIa (1.5 g, 0.0039 mole) was suspended in water (20 ml) and treated with aqueous sodium hydroxide (32 ml of a 1% solution). The suspension was heated with stirring until a homogeneous solution was achieved (40 minutes). The resulting solution was cooled, filtered, then acidified by dropwise addition of 6*N* hydrochloric acid. The white precipitate was collected, washed with distilled water and air dried. The product (1.1 g, 83%) was recrystallized from methanol to give fine crystals, mp 250-251°; ir (potassium bromide): 3600-2000 (broad), 1690, 1600, 1215, 1045 cm^{-1}; nmr (DMSO-d_6): δ 2.40 (s, 3H, methyl at 2-position), 4.05 (s, 3H, methyl at 4-position), 5.90 (s, 2H, benzylic protons), 6.85-7.38 (m, 5H, aromatic protons), 8.57 (s, 1H, proton at 5-position), 15.68 (s, 1H, COOH) ppm. (See Table I for Analog.)

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