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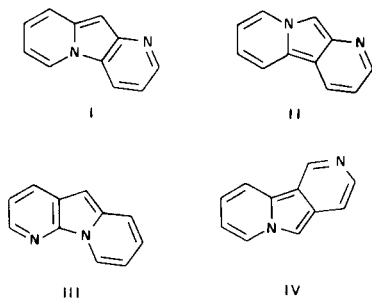
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The synthesis of a new pyridoindolizine, in particular, pyrido[2,3-*a*]indolizine, was carried out using 2-methyl-3-*t*-butoxycarbonyl-4-aminopyrrole as the starting material.

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Upon careful review of *Chemical Abstracts*, a variety of pyridoindolizine derivatives have been reported, mainly using derivatives of pyridine as the starting material. Since 1967, a variety of derivatives of pyrido[2,3-*b*]indolizines I [1], pyrido[3,2-*a*]indolizines II [2-4], pyrido[3,2-*b*]indolizine III [5], and pyrido[3,4-*a*]indolizines IV [6] have been reported.



A novel synthetic method was used in the approach to the synthesis of the pyrido[2,3-*a*]indolizine nucleus. In contrast to previously reported methods [3-6], a pyrrole, in particular, 2-methyl-3-*t*-butoxycarbonyl-4-aminopyrrole, was chosen as the starting material. The synthesis of 3-carbomethoxy-5-methyl-8,9-dihydropyrido[2,3-*a*]indolizine-4,10(1*H*,7*H*)-dione is reported in Scheme I.

In the initial step of the synthesis, *t*-butyl 3-(cyanomethylamino)-2-butenate (VII) was cyclized in the presence of sodium methoxide in methanol, according to a modification of the procedure described by Tarzia and Panzone [7]. The product of the reaction was 2-methyl-3-*t*-butoxycarbonyl-4-aminopyrrole. Upon neutralization with acetic acid, the pyrrole was reacted *in situ* with dimethyl methoxymethylenemalonate to yield *N*-[2-methyl-3-*t*-butoxycarbonylpyrrol-4-yl]aminomethylenemalononic acid, dimethyl ester (VIII).

Next, selective acylation was achieved either at the one or five position of the pyrrole. If compound VIII is refluxed with acetic anhydride, attack occurs at the one position with formation of the acetamide IX. In contrast, if compound VIII is dissolved in THF with addition of pyridine and an acid chloride and refluxed, carbon acylation occurs at the five position. Utilizing this information, 4-chlorobutyryl chloride was reacted with compound VIII to yield *N*-[2-(4-chlorobutyryl)-4-*t*-butoxycarbonyl-5-methylpyrrol-

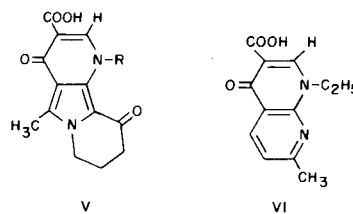
3-yl]aminomethylenemalononic acid, dimethyl ester (XB).

Selective intramolecular alkylation of compound XB at the one position was achieved through pyrrolyl anion generation, utilizing potassium *t*-butoxide in THF. The result being generation of the 6,7-dihydroindolizine derivative XI.

According to Clezy, *et al.* [8], trifluoroacetic acid in the presence of a *t*-butyl ester on a pyrrole at 40-50° will result in hydrolysis to the acid and subsequent decarboxylation of that acid. This process was utilized to hydrolyze and decarboxylate compound XI to *N*-[8-oxo-3-methyl-6,7-dihydro-5*H*-indolizin-1-yl]aminomethylene malonic acid, dimethyl ester (XII).

The final step of the reaction scheme involves compound XII being thermally cyclized in refluxing Dowtherm A to yield 3-carbomethoxy-5-methyl-8,9-dihydropyrido[2,3-*a*]indolizine-4,10(1*H*,7*H*)-dione (XIII).

The possible biological activity of this compound V, after ester hydrolysis, was envisioned as an antimicrobial agent, since it is a structural analog of nalidixic acid (VI).



EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. The nmr spectra were determined on a Varian EM 360A or EM 390 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).

t-Butyl 3-(Cyanomethylamino)-2-butenate (VII).

A 1000 ml round bottomed flask was charged with aminoacetonitrile hydrochloride (48.57 g, 0.525 mole), sodium bicarbonate (43.06 g, 0.5125 mole) and DMF (100 ml). The contents of the vessel were stirred in a boiling water bath until the evolution of carbon dioxide had ceased. *t*-Butyl acetoacetate (79.1 g, 0.50 mole) and cyclohexane (200 ml) were added and the mixture was refluxed with stirring under a Dean-Stark trap for 3 hours (water yield 24 ml). After cooling, the contents of the reaction

Scheme I

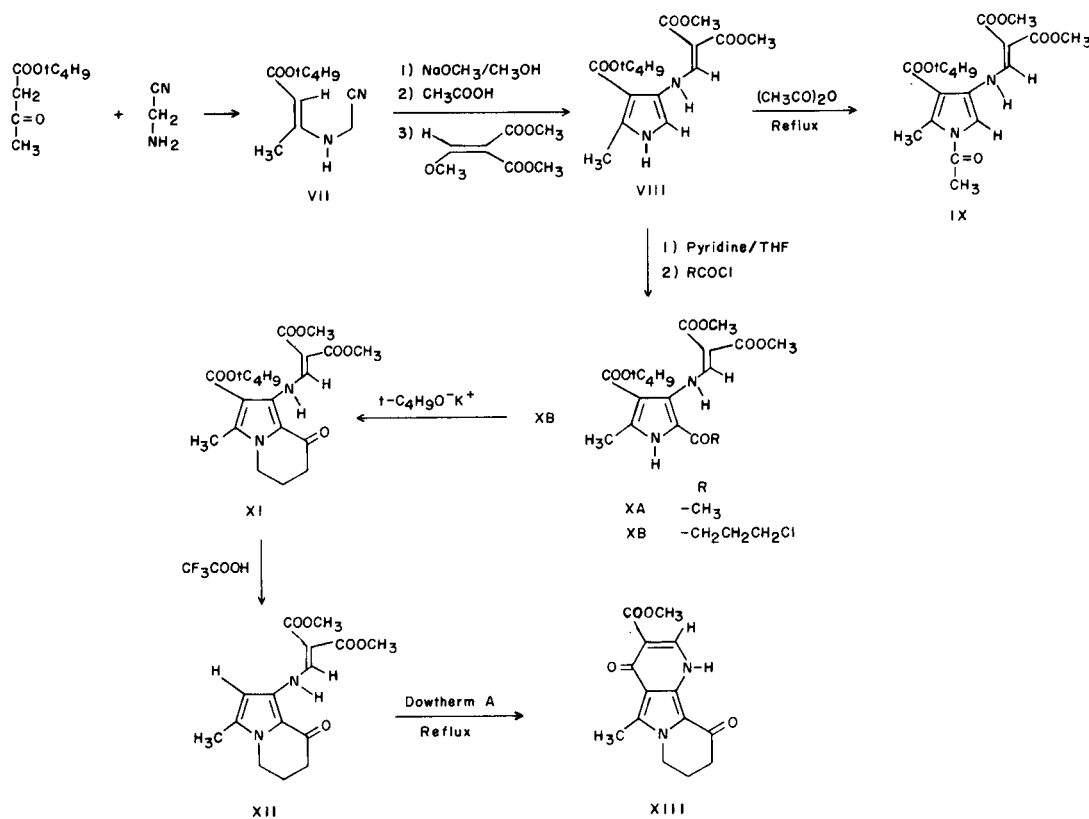


Table I

Compound No.	Mp (°C)	Yield (%)	Molecular Formula	Analysis (%)		
				Calcd.	Found	
VIII	200-202	76	C ₁₆ H ₂₂ N ₂ O ₆	C	56.79	56.50
				H	6.56	6.60
				N	8.28	8.24
IX	193-194	81	C ₁₈ H ₂₄ N ₂ O ₇	C	56.83	56.73
				H	6.36	6.37
				N	7.37	7.34
XA	213-214	51	C ₁₈ H ₂₄ N ₂ O ₇	C	56.83	56.94
				H	6.36	6.40
				N	7.37	7.34
XB	163-164	67	C ₂₀ H ₂₇ ClN ₂ O ₇	C	54.23	54.00
				H	6.15	6.17
				N	6.33	6.31
XI	134-135	94	C ₂₀ H ₂₆ N ₂ O ₇	Cl	8.01	7.94
				C	59.10	58.95
				H	6.45	6.48
XII	204-205	61	C ₁₅ H ₁₈ N ₂ O ₅ ·0.4H ₂ O	N	6.89	6.85
				C	57.46	57.45
				H	6.04	6.03
XIII	250-251	71	C ₁₄ H ₁₄ N ₂ O ₄	N	8.94	8.70
				C	61.30	61.05
				H	5.14	5.19
				N	10.22	10.17

vessel were transferred to a separatory funnel and further diluted with 500 ml water and 100 ml cyclohexane. After partitioning, the aqueous layer was discarded. The organic layer was further extracted with distilled water (100 ml), then twice with brine (2 × 100 ml). After drying over anhydrous sodium sulfate, the cyclohexane was removed *in vacuo* to yield an oil. The oil was crystallized from hexanes (400 ml) to yield a pale yellow granular solid (87.0 g, 89%), mp 62-63° which was used without further purification; ir (potassium bromide): 3300, 2960, 2240, 1640, 1590, 1280, 1130, 1100, 975, 780 cm⁻¹; nmr (deuteriochloroform): δ 1.43 (s, 9H, methyls of *t*-butyl ester), 1.97 (s, 3H, methyl), 4.05 (d, 2H, methylene adjacent to nitrile), 4.60 (s, 1H, vinyl proton), 8.6 (t, 1H, NH) ppm.

N-[2-Methyl-3-*t*-butoxycarbonylpyrrol-4-yl]aminomethylenemalonic Acid, Dimethyl Ester (VIII).

The general procedure reported by Tarzia and Panzone [7] was utilized for the pyrrole synthesis. *t*-Butyl 3-(cyanomethylamino)-2-butenate (VII) (49.06 g, 0.25 mole) was added to a solution of sodium methoxide (16.2 g, 0.3 mole) in 250 ml of methanol. The resulting solution was refluxed under an argon atmosphere for one hour. After cooling, glacial acetic acid (18.0 g, 0.3 mole) was added, followed by the addition of dimethyl methoxymethylenemalonate (43.55 g, 0.25 mole). Immediately an exothermic reaction occurred, and within five minutes, a heavy precipitate had formed. The mixture was refluxed for one hour under argon and diluted with 250 ml of methanol. After standing in a freezer overnight, the crude product was collected by filtration and, later, recrystallized from methanol (600 ml) to yield a yellow solid (64.0 g, 75.6%). A two g sample was further purified by recrystallization from methanol (40 ml) to yield pale yellow crystals (1.6 g), mp 200-202° dec; ir (potassium bromide): 3270, 2980, 1725, 1670, 1600, 1440, 1240, 1090 cm⁻¹; nmr (deuteriochloroform): δ 1.57 (s, 9H, methyls of *t*-butoxycarbonyl), 2.40 (s, 3H, methyl at 2-position), 3.70 (s, 3H, methyl ester), 3.80 (s, 3H, methyl ester), 6.50 (s, 1H, proton at 5-position), 8.24 (d, 1H, vinyl proton), 11.35 (d, 2H, NH at 4-position) ppm.

Anal. Calcd. for C₁₈H₂₂N₂O₆: C, 56.79; H, 6.56; N, 8.28. Found: C, 56.50; H, 6.60; N, 8.24.

N-[1-Acetyl-2-methyl-3-*t*-butoxycarbonylpyrrol-4-yl]aminomethylenemalonic Acid, Dimethyl Ester (IX).

N-[2-Methyl-3-*t*-butoxycarbonylpyrrol-4-yl]aminomethylenemalonic acid, dimethyl ester (1.0 g, 0.00284 mole) in acetic anhydride (5 ml) was refluxed with stirring for one hour. After cooling, water (20 ml) was added and the mixture rapidly stirred for one hour. The precipitate was collected and air dried. The crude product (0.9 g, 81%) was recrystallized from methanol to yield a peach colored powder (homogeneous on tlc, in ethyl acetate/hexanes (4:1), R_f 0.88), mp 193-194°; ir (potassium bromide): 3220, 2995, 2960, 1735, 1680, 1650, 1590, 1430, 1385, 1360, 1225, 1100 cm⁻¹; nmr (deuteriochloroform): δ 1.62 (s, 9H, methyls of *t*-butyl ester), 2.60 (s, 3H, methyl at 2-position), 2.77 (s, 3H, methyl of acetyl), 3.77 (s, 3H, methyl of ester), 3.85 (s, 3H, methyl of ester), 7.07 (s, 1H, proton at 5-position) 8.25 (d, 1H, vinyl proton), 11.3 (d, 1H, NH) ppm.

Anal. Calcd. for C₁₈H₂₄N₂O₇: C, 56.83; H, 6.36; N, 7.37. Found: C, 56.73; H, 6.37; N, 7.34.

N-[2-Acetyl-4-*t*-butoxycarbonyl-5-methylpyrrol-3-yl]aminomethylenemalonic Acid, Dimethyl Ester (XA).

A solution of *N*-[2-methyl-3-*t*-butoxycarbonylpyrrol-4-yl]aminomethylenemalonic acid, dimethyl ester (13.5 g, 0.04 mole) in pyridine (12.65 g, 0.16 mole) and THF (60 ml) was stirred as acetyl chloride (6.28 g, 0.08 mole) was added. The suspension was refluxed for one hour. At that time, acetyl chloride (3.14 g, 0.04 mole) was added and the suspension refluxed for an additional hour. Again, acetyl chloride (3.14 g, 0.04 mole) was added and the suspension was refluxed for another hour. The THF was removed *in vacuo* and the residue was triturated with water to give a dark oily insoluble residue. The oily residue was crystallized from methanol. The crude product was further purified by recrystallization from methanol to yield light yellow crystals (7.8 g, 51.3%) (homogeneous on tlc, in ethyl acetate/hexanes (3:1), R_f 0.49), mp 213-214°; ir (potassium bromide): 3240, 2980, 1710, 1680, 1660, 1430, 1210, 1100 cm⁻¹; nmr (deuterio-

chloroform): δ 1.5 (s, 9H, methyls of *t*-butyl ester), 2.33 (s, 3H, methyl of acetyl), 2.40 (s, 3H, methyl at 5-position), 3.63 (s, 3H, methyl of ester), 3.77 (s, 3H, methyl of ester), 8.7 (d, 1H, vinyl proton), 11.45 (broad s, 1H, NH at 1-position), 10.55 (d, 1H, NH at 4-position) ppm.

Anal. Calcd. for C₁₈H₂₄N₂O₇: C, 56.83; H, 6.36; N, 7.37. Found: C, 56.94; H, 6.40; N, 7.34.

N-[2-(4-Chlorobutyl)-4-*t*-butoxycarbonyl-5-methylpyrrol-3-yl]aminomethylenemalonic Acid, Dimethyl Ester (XB).

A solution of *N*-[2-methyl-3-*t*-butoxycarbonylpyrrol-4-yl]aminomethylenemalonic acid, dimethyl ester (33.8 g, 0.10 mole) in dry THF (300 ml) was treated with pyridine (15.8 g, 0.20 mole) and stirred for five minutes at room temperature. A warm water bath was needed to place the starting material into solution. Then, 4-chlorobutyl chloride (22.4 ml, 0.20 mole) was injected into the solution and immediately a precipitate formed. The reaction was exothermic. This solution was refluxed for one hour and cooled to room temperature. A second portion of pyridine (15.8 g, 0.20 mole) and 4-chlorobutyl chloride (22.4 ml, 0.20 mole) was added. The solution was refluxed for an additional hour. The insoluble salt was removed by vacuum filtration, the THF was removed *in vacuo* and the residue dissolved in methylene chloride. The product in methylene chloride was extracted with water (3 × 100 ml), once with 10% sodium carbonate and finally with 1% hydrochloric acid. The methylene chloride layer was dried with anhydrous sodium sulfate and removed *in vacuo*. The residue was mixed with diethyl ether, the suspension stored in a freezer for several hours and the precipitate collected (30.18 g, 67%). A 0.52 g sample was further recrystallized from methanol (10 ml) to yield 0.32 g of yellow crystals (homogeneous on tlc, in ethyl acetate, R_f = 0.82), mp 163-164°; ir (potassium bromide): 3240, 3130, 2990, 1710, 1670, 1610, 1560, 1500, 1430, 1370, 1210, 960, 795 cm⁻¹; nmr (deuteriochloroform): δ 1.6 (s, 9H, methyls of *t*-butyl ester), 2.2 (m, 2H, methylene β to carbonyl), 2.5 (s, 3H, methyl at the 5-position), 2.9 (t, 2H, methylene α to carbonyl), 3.6 (t, 2H, methylene α to halogen), 3.7 (s, 3H, methyl of ester), 3.85 (s, 3H, methyl of ester), 8.75 (d, 1H, vinyl proton), 11.6 (s, 1H, proton of pyrrole ring), 11.7 (d, 1H, NH) ppm.

Anal. Calcd. for C₂₀H₂₇ClN₂O₇: C, 54.23; H, 6.15; N, 6.33; Cl, 8.01. Found: C, 54.00; H, 6.17; N, 6.31; Cl, 7.94.

N-[8-Oxo-3-methyl-2-*t*-butoxycarbonyl-6,7-dihydro-5*H*-indolizin-1-yl]aminomethylenemalonic Acid, Dimethyl Ester (XI).

A suspension of *N*-[2-(4-chlorobutyl)-4-*t*-butoxycarbonyl-5-methylpyrrol-3-yl]aminomethylenemalonic acid, dimethyl ester (28.60 g, 0.065 mole) in 300 ml of dry THF was treated with potassium *t*-butoxide (11.00 g, 0.0975 mole). The resulting brown solution was stirred at room temperature for 2 hours. The majority of the THF was removed *in vacuo* and the compound poured over ice water while stirring rapidly. The product was collected by vacuum filtration (24.67 g, 94%). An analytical sample (1.0 g) was further recrystallized from cyclohexane (50 ml) to yield 0.90 g of yellow crystals (homogeneous on tlc, in ethyl acetate, R_f = 0.26), mp 134-135°; ir (potassium bromide): 3150, 2980, 2960, 1760, 1690, 1600, 1525, 1430, 1270, 1230, 1200, 1120, 1095, 830, 775 cm⁻¹; nmr (deuteriochloroform): δ 1.6 (s, 9H, methyls of *t*-butyl ester), 2.2 (m, 2H, methylene β to carbonyl), 2.5 (s, 3H, methyl at 3-position), 2.6 (t, 2H, methylene α to carbonyl), 3.7 (s, 3H, methyl of ester), 3.85 (s, 3H, methyl of ester), 3.90 (t, 2H, methylene α to N of pyrrole ring), 9.10 (d, 1H, vinyl proton), 11.8 (d, 1H, NH) ppm.

Anal. Calcd. for C₂₀H₂₆N₂O₇: C, 59.10; H, 6.45; N, 6.89. Found: C, 58.95; H, 6.48; N, 6.85.

N-[8-Oxo-3-methyl-6,7-dihydro-5*H*-indolizin-1-yl]aminomethylenemalonic Acid, Dimethyl Ester (XII).

N-[8-oxo-3-methyl-2-*t*-butoxycarbonyl-6,7-dihydro-5*H*-indolizin-1-yl]aminomethylenemalonic acid, dimethyl ester (15.7 g, 0.0386 mole) was treated with 30 g of trifluoroacetic acid. The flask was placed in a water bath kept at a constant temperature of 50° and stirred for 45 minutes. At the end of the reaction, the trifluoroacetic acid was removed *in vacuo*. The product was then dissolved in a minimum amount of ethyl acetate and placed in the freezer. The product was further recrystallized from

methanol to yield an orange crystal (7.37 g, 61%), mp 204-205°.

The crystals were homogeneous on tlc (in ethyl acetate, Rf = 0.316); ir (potassium bromide): 3270, 2950, 1740, 1620, 1550, 1430, 1310, 1250, 1120, 1070, 940, 800, 740 cm⁻¹; nmr (DMSO-d₆) δ 2.10 (m, 2H, methylene β to carbonyl), 2.20 (s, 3H, methyl at 3-position), 2.50 (t, 2H, methylene α to carbonyl), 3.65 (s, 3H, methyl of ester), 3.70 (s, 3H, methyl of ester), 3.90 (t, 2H, methylene α to N on pyrrole ring), 6.30 (s, 1H, hydrogen at 2-position), 8.30 (d, 1H, vinyl proton), 11.50 (d, 1H, NH) ppm.

Anal. Calcd. for C₁₅H₁₈N₂O₅·0.4H₂O: C, 57.46; H, 6.04; N, 8.94. Found: C, 57.45; H, 6.03; N, 8.70.

3-Carbomethoxy-5-methyl-8,9-dihydropyrido[2,3-*a*]indolizine-4,10(1*H*,7*H*)-dione (XIII).

N-[8-Oxo-3-methyl-6,7-dihydro-5*H*-indolizin-1-yl]aminomethylene-malonic acid, dimethyl ester (6.8 g) was dissolved in 30 ml of warm Dowtherm A. The solution was then added to 70 ml of refluxing Dowtherm A. The reaction mixture was vigorously refluxed with stirring under argon for 40 minutes. The Dowtherm A was removed *in vacuo* and the residue was triturated with hexanes. A fine light brown solid was collected by filtration and dried. The solid was dissolved in methylene chloride, treated with activated charcoal, and the methylene chloride was removed *in vacuo*. The yellowish brown solid was triturated with ethyl acetate and collected (4.2 g, 71%), mp 250-251°.

The crystals were homogeneous on tlc (in acetone, Rf = 0.82); ir (potassium bromide): 3290, 2960, 1730, 1660, 1580, 1470, 1385, 1340, 1185, 1120, 960, 820, 770, 685 cm⁻¹; nmr (deuteriochloroform): δ 2.2 (m, 3H,

methylene β to carbonyl), 2.6 (t, 2H, methylene α to carbonyl), 2.75 (s, 3H, methyl at 5-position), 3.90 (s, 3H, methyl of ester), 4.00 (t, 2H, methylene α to nitrogen), 8.35 (d, 1H, vinyl proton), 10.50 (d, 1H, NH, at 1-position) ppm.

Anal. Calcd. for C₁₄H₁₄N₂O₄: C, 61.30; H, 5.14; N, 10.22. Found: C, 61.05; H, 5.19; N, 10.17.

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