Synthesis of a Series of Pyrrole-1-acetic Acids as Potential Antiinflammatory Agents

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A series of 3-substituted 2-amino-4,5-dimethylpyrrole-1-acetic acid derivatives were synthesized. The condensation of acetyl methyl carbinol, ethyl glycinate, and the appropriate acetonitrile yielded ethyl 3-substituted 2-amino-4,5-dimethylpyrrole-1-acetate, which was consequently hydrolyzed to produce the corresponding carboxylic acid. The acetamide and trifluoroacetamide series were synthesized by reacting the ethyl 2-aminopyrrole-1-acetates with acetyl chloride or trifluoroacetic anhydride respectively. The corresponding 2-acetamidopyrrole-1-acetic acids were formed by basic hydrolysis of the ethyl esters.

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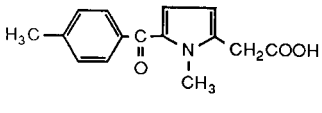
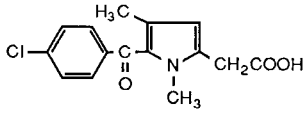
In the search for a more potent nonsteroidal antiinflammatory agent that elicited fewer side effects than compounds currently in use, Carson *el al.* [2] chose to incorporate three chemical features from the potent antiinflammatory agent indomethacin in the synthesis of a series of pyrroleacetic acid derivatives. The three chemical moieties proposed for potent antiinflammatory activity were a carboxyl group, an aromatic ring system, and a carbonyl function which were necessary for optimum binding at the receptor site [3]. Tolmetin (**I**) and zomepirac (**II**) were two of the pyrrole-2-acetic acid derivatives synthesized by Carson *et al.* [2,4] that were marketed for the treatment of inflammation and pain.

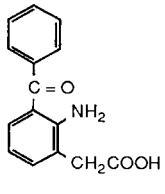


I



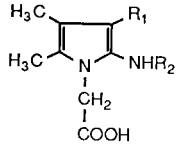
II

Recently, 2-amino-3-benzoylphenylacetic acid (amfenac) (**III**) was shown to exhibit potent antiinflammatory activity [5,6]. Amfenac was one agent, of which only a few compounds have been synthesized, that contain a primary amine and possess potent antiinflammatory action.



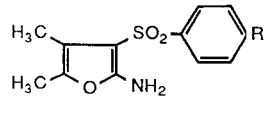
III

The synthesis of a series of pyrrole-1-acetic acid derivatives conforming to general structure **IV** was envisioned utilizing a modification for pyrrole synthesis described by Roth and Eger [7]. Roth and Eger prepared a variety of 1-alkyl-2-amino-3-cyano-4,5-dimethylpyrroles from the condensation of various primary amines, acetyl methyl carbinol, and malononitrile.



IV

The initial synthetic approach involved a direct synthesis of 2-amino-3-arylsulfonyl-4,5-dimethylpyrrole-1-acetic acid. The reaction initially involved condensation of glycine with acetyl methyl carbinol followed by consequent condensation of the appropriate arylsulfonylacetonitrile with the previously formed α-aminoketone. Instead of the desired pyrrole, the direct synthesis approach produced 2-amino-3-arylsulfonyl-4,5-dimethylfurans **Va-b**. Glycine did not enter into the reaction due to insolubility in ethanol/toluene. The reaction was repeated in the absence of glycine to produce the furan in comparable yields.

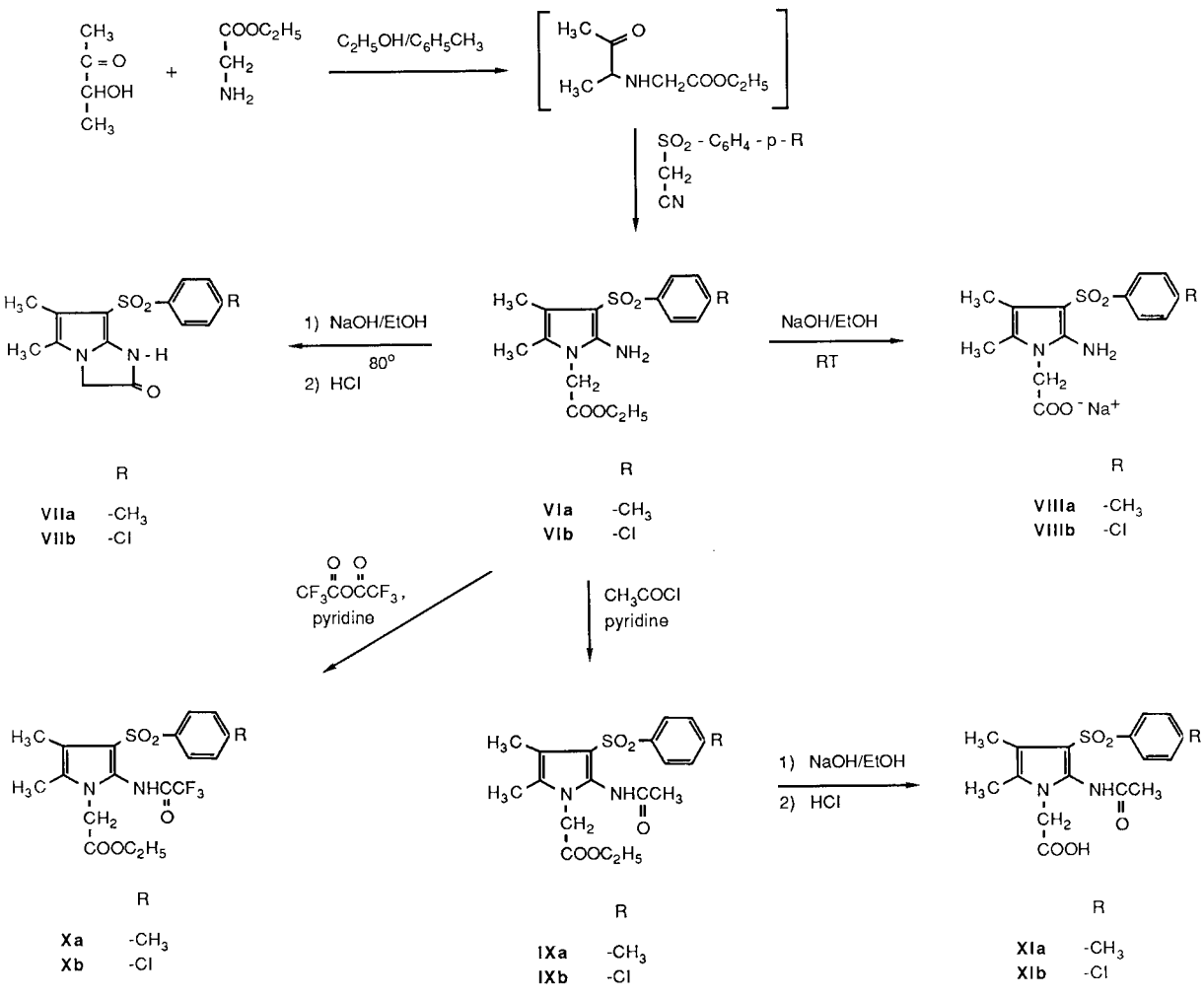


R

Va -CH_3
Vb -Cl

In order to improve the solubility of the primary amine in the reaction, the ethyl ester of glycine was chosen to condense with acetyl methyl carbinol to produce the intermediate α-aminoketone (Scheme I). The intermediate was subsequently reacted *in situ* with the appropriate arylsulfonylacetonitrile to yield ethyl 2-amino-3-arylsulfonyl-4,5-dimethylpyrrole-1-acetates **VIa-b** in good yields.

Scheme I



Formation of the corresponding carboxylic acids from compounds **VIa-b** were anticipated upon suspension in ethanol to which one equivalent of a 1% sodium hydroxide solution was added and heated at 80° for one hour. Upon acidification of the reaction mixture, the major product isolated was 7-arylsulfonyl-5,6-dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazoles **VIIa-b.**

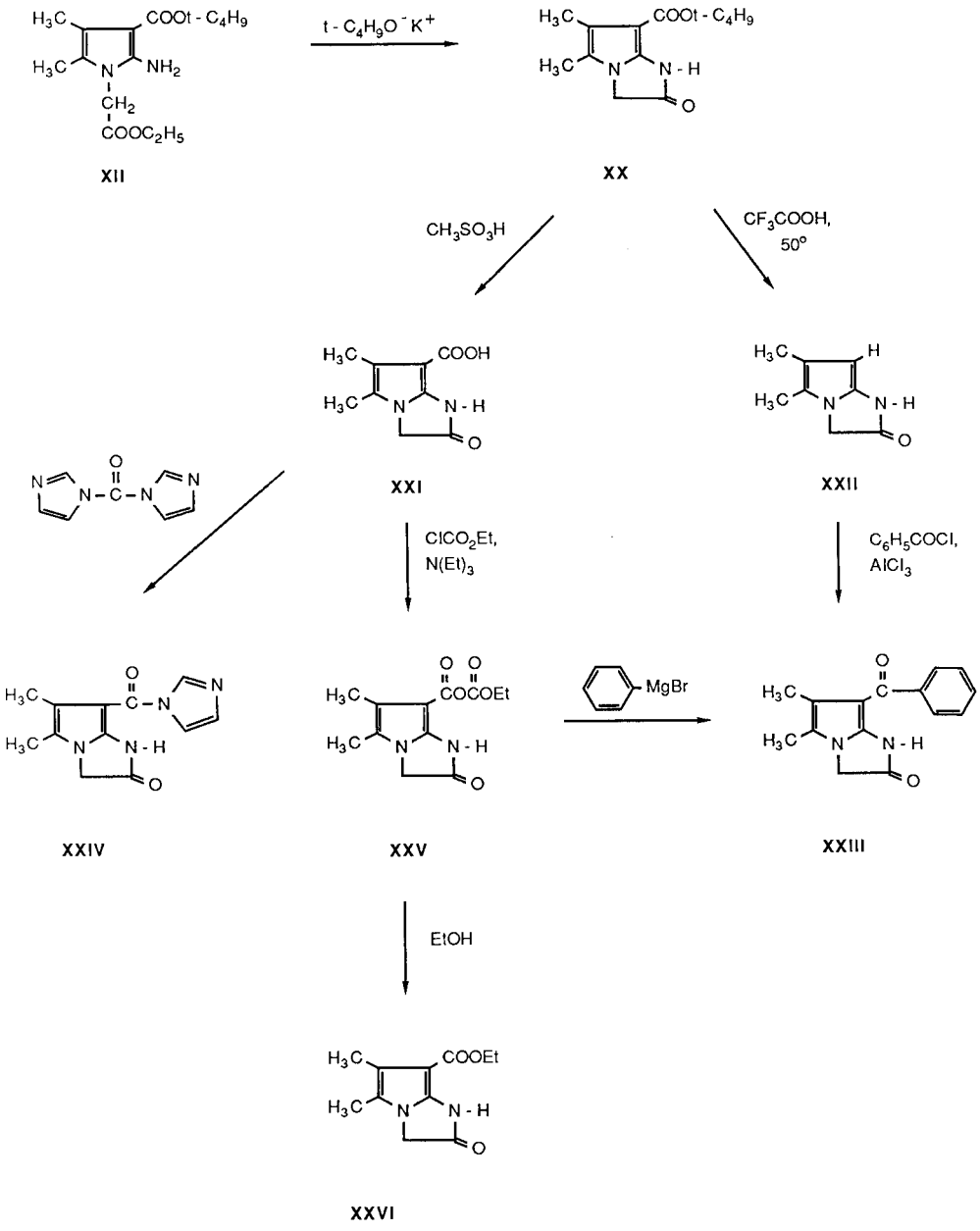
An alternate procedure to prepare the desired carboxylic acids and minimize formation of the pyrrolo[1,2-*a*]-imidazoles would involve isolation of the sodium salt of the carboxylic acids. The ester hydrolysis reaction was performed at room temperature for 24 hours under similar basic reaction conditions. In order to isolate the sodium salt of the carboxylic acid and remove any pyrrolo[1,2-*a*]-imidazole, the *p*H of the solution was adjusted to 8.2 and any pyrrolo[1,2-*a*]imidazole was removed by filtration. The desired products, sodium 2-amino-3-arylsulfonyl-4,5-dimethylpyrrole-1-acetates **VIIIa-b**, were crystallized from water.

Ethyl 2-amino-3-arylsulfonyl-4,5-dimethylpyrrole-1-acetates **VIa-b** were converted to the respective acetamides **IXa-b** by reaction with acetyl chloride in tetrahydrofuran and pyridine. In a similar fashion, the trifluoroacetamides **Xa-b** were synthesized by reacting compounds **VIa-b** with trifluoroacetic anhydride using pyridine as the base.

The acetamides **IXa-b** were consequently treated with one equivalent of sodium hydroxide and acidified at the conclusion of the reaction to yield 2-acetylamino-3-arylsulfonyl-4,5-dimethylpyrrole-1-acetic acids **XIa-b.** Reaction of the trifluoroacetamides under similar conditions produced a variety of compounds presumably due to competition between ester hydrolysis and hydrolysis of the trifluoroacetamide with the possibility of subsequent ring closure to the pyrrolo[1,2-*a*]imidazoles.

The synthesis of ethyl 2-amino-3-(*t*-butoxycarbonyl)-4,5-dimethylpyrrole-1-acetate (**XII**) was achieved from the condensation of acetyl methyl carbinol, ethyl glycinate,

Scheme III



and *t*-butyl cyanoacetate by the procedure previously described (Scheme II) [8]. The compound was characterized as an oil from which several derivatives were synthesized in high yields. The formation of the acetamide **XIII** was performed by dissolving compound **XII** in acetone and pyridine with the consequent addition of acetyl chloride. Alternatively, compound **XII** was reacted with trifluoroacetic anhydride in the presence of pyridine to form the trifluoroacetamide (**XIV**) as illustrated in Scheme II.

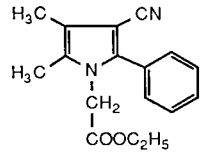
Ethyl 2-acetylamino-3-(*t*-butoxycarbonyl)-4,5-dimethylpyrrole-1-acetate (**XIII**) and ethyl 3-(*t*-butoxycarbonyl)-4,5-dimethyl-2-trifluoroacetylaminopyrrole-1-acetate (**XIV**) upon treatment with methane sulfonic acid resulted in selective hydrolysis of the *t*-butyl ester in the presence of an ethyl ester to produce the corresponding carboxylic acids **XVa-b**.

Under basic conditions, the ethyl ester of compound **XIII** was hydrolyzed to yield another potential antiinflam-

matory agent, 2-acetylamino-3-(*t*-butoxycarbonyl)-4,5-dimethylpyrrole-1-acetic acid (**XVI**).

Due to problems encountered with the hydrolysis of the ethyl esters of the trifluoroacetamides, compound **XIV** was alkylated with methyl iodide in the presence of anhydrous sodium carbonate to produce the tertiary trifluoroacetamide **XVII**. Compound **XVII** was consequently treated with one equivalent of sodium hydroxide to yield 3-(*t*-butoxycarbonyl)-4,5-dimethyl-2-(*N*-trifluoroacetyl-*N*-methyl)aminopyrrole-1-acetic acid (**XVIII**).

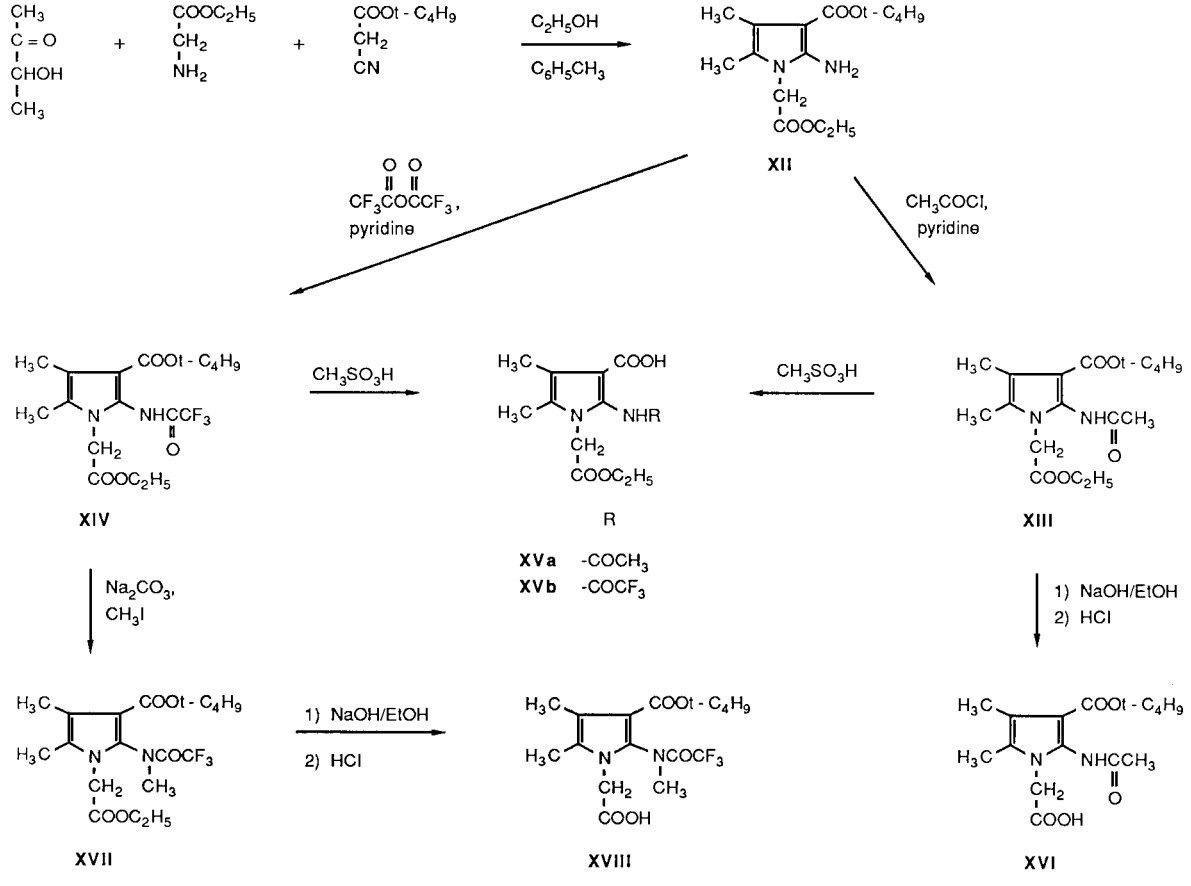
The next analogue to be synthesized was 2-amino-3-benzoyl-4,5-dimethylpyrrole-1-acetic acid. A two step synthesis of the compound was envisioned by first condensing acetyl methyl carbinol, ethyl glycinate, and benzoylacetonitrile to form ethyl 2-amino-3-benzoyl-4,5-dimethylpyrrole-1-acetate followed by ethyl ester hydrolysis to yield the desired carboxylic acid. The initial formation of the pyrrole from the three commercially available products alternatively yielded ethyl 3-cyano-4,5-dimethyl-2-phenylpyrrole-1-acetate (**XIX**).



XIX

An alternate approach to the synthesis of the benzoyl series would involve electrophilic attack of the benzoyl group onto the pyrrole ring. The initial step of the synthesis involves formation of 7-(*t*-butoxycarbonyl)-5,6-dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole (**XX**) by treating compound **XII** *in situ* with potassium *t*-butoxide as illustrated in Scheme III. The formation of the pyrrolo[1,2-*a*]imidazole is a modification of a procedure reported by Sowell *et al.* [9] for the formation of pyrrolo[1,2-*a*]pyrimidines. The formation of 7-carboxy-5,6-dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole (**XXI**) was accomplished by treating the *t*-butyl ester with

Scheme II



methane sulfonic acid. The formation of 5,6-dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole (**XXII**) could be performed by thermally decarboxylating compound **XXI**. An alternate method described by Clezy *et al.* [10] involves treating the *t*-butyl ester **XX** with trifluoroacetic acid at 50° and results in ester hydrolysis and consequent decarboxylation in a one-step process which produces compound **XXII** in high yield.

Scheme III

Compound **XXII** was consequently reacted with benzoyl chloride and anhydrous aluminum chloride as the Lewis acid to undergo electrophilic substitution. The reaction produced two products of which the desired product, 7-benzoyl-5,6-dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrolo-[1,2-*a*]imidazole (**XXIII**), was isolated by chromatography in low yields.

An alternate approach was explored to increase the yield and selectivity for the formation of the 7-benzoylpyrrolo[1,2-*a*]imidazole **XXIII**. The reactivity of carboxylic acids with Grignard reagents usually produce ketones in low yields due to the formation of tertiary alcohols as a competing reaction. In order to increase the selectivity for ketone formation, 7-carboxy-5,6-dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole (**XXI**) was converted to two different intermediates which were shown to form ketones in good yields upon reaction with organomagnesium reagents.

The carboxylic acid **XXI** was reacted with 1,1'-carbonyldiimidazole to form 5,6-dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-7-carboxylic acid, imidazole amide (**XXIV**). The intermediate imidazolide of various carboxylic acids were reported to react with a variety of Grignard reagents to form ketones in high yields [11]. However, after reacting the imidazolide **XXIV** with phenylmagnesium bromide, starting material was isolated.

Utilizing the same carboxylic acid as a precursor to another key intermediate, 5,6-dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-7-ethyl carbonate anhydride (**XXV**) was synthesized by reacting the carboxylic acid with triethylamine and ethyl chloroformate. Although the mixed anhydride was formed in mediocre yields, the reactivity of compound **XXV** with phenylmagnesium bromide to form the 7-benzoylpyrrolo[1,2-*a*]imidazole proceeded readily at -70°.

To illustrate the reactivity of the mixed anhydride toward nucleophiles, compound **XXV** was stirred at room temperature for 15 minutes in ethanol and formed 7-ethoxycarbonyl-5,6-dimethy-2-oxo-2,3-dihydro-1*H*-pyrrolo-[1,2-*a*]imidazole (**XXVI**).

The synthesized compounds were tested against aspirin in the carrageenan pleurisy test. In general, the compounds were shown to exhibit low antiinflammatory activity.

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 specta 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-Amino-3-(*p*-toluenesulfonyl)-4,5-dimethylfuran (**Va**).

General Procedure for Compounds **Va-b**.

A solution of acetyl methyl carbinol (85% aqueous solution) (2.07 g, 0.02 mole), sodium bicarbonate (1.68 g, 0.02 mole), and *p*-toluenesulfonylacetonitrile (3.90 g, 0.02 mole) in 25 ml of ethanol and 10 ml of toluene was refluxed under a Dean-Stark trap with the azeotropic removal of 15 ml of distillate. The solution was refluxed for an additional hour. At the end of the reaction, the inorganic salt was filtered off and the solvent was removed *in vacuo*. The solid residue was suspended in 20 ml of methanol, which was then placed in the freezer. The crude product (3.35 g, 63%) was further recrystallized from 20 ml of methanol to yield a mustard yellow crystal (2.15 g, 64%), mp 130-131°, homogeneous on tlc - ethyl acetate, R_f = 0.85; ir (potassium bromide): 3480, 3340, 1620, 1420, 1280, 1235, 1135, 1060, 800, 700 cm^{-1}; nmr (deuteriochloroform): δ 1.70 (s, 3H, $-CH_3$ at C_4 or C_5), 1.90 (s, 3H, $-CH_3$ at C_4 or C_5), 2.30 (s, 3H, $-CH_3$ of toluene), 5.30 (broad s, 2H, $-NH_2$), 7.05-7.70 (m, 4H, ArH) ppm.

Anal. Calcd. for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28; S, 12.08. Found: C, 58.63; H, 5.77; N, 5.24; S, 12.06.

2-Amino-3-(*p*-chlorophenylsulfonyl)-4,5-dimethylfuran (**Vb**).

The product was crystallized from methanol to yield a pale yellow crystal (2.96 g, 72%), mp 114-115°, homogeneous on tlc - ethyl acetate R_f = 0.96; ir (potassium bromide): 3470, 3340, 1660, 1620, 1420, 1300, 1135, 1060, 750 cm^{-1}; nmr (deuteriochloroform): δ 1.75 (s, 3H, $-CH_3$ at C_4 or C_5), 1.95 (s, 3H, $-CH_3$ at C_4 or C_5), 5.30 (broad s, 2H, $-NH_2$), 7.25-7.75 (m, 4H, ArH) ppm.

Anal. Calcd. for $C_{12}H_{12}ClNO_3S$: C, 50.44; H, 4.23; Cl, 12.41; N, 4.90; S, 11.22. Found: C, 50.48; H, 4.23; Cl, 12.47; N, 4.85; S, 11.24.

Ethyl 2-Amino-3-(*p*-toluenesulfonyl)-4,5-dimethylpyrrole-1-acetate (**VIa**).

General Procedure for Compounds **VIa-b**.

A solution of acetyl methyl carbinol (85% aqueous solution) (2.07 g, 0.02 mole), ethyl glycinate hydrochloride (2.82 g, 0.02 mole), and sodium bicarbonate (1.68 g, 0.02 mole) in 25 ml of ethanol and 10 ml of toluene was refluxed under a Dean-Stark trap with the azeotropic removal of 15 ml of distillate. The solution was refluxed for one hour. The reaction mixture was cooled down to room temperature and *p*-toluenesulfonylacetonitrile (3.90 g, 0.02 mole) was added and the solution was refluxed for an additional hour and a half with the additional removal of 15 ml of distillate. At the end of the reaction, the inorganic salt was filtered off and the solvent removed *in vacuo*. The oil was dissolved in 30 ml of ethanol, then placed in the freezer. The crude product (4.20 g, 60%) was further recrystallized from 100 ml of ethanol to yield a white crystal that turned pale pink with time (3.00 g, 71%), mp 82-83°, homogeneous on tlc - ethyl acetate, R_f = 0.89; ir (potassium bromide): 3420, 3330, 1735, 1610, 1535, 1470, 1290, 1275, 1210, 1120, 1075, 800, 650 cm^{-1}; nmr (deuteriochloroform): δ 1.25 (t, 3H, $-CH_2CH_3$), 1.90 (s, 6H, $-CH_3$ at C_4 and C_5), 2.30 (s, 3H, $-CH_3$ of toluene), 4.20 (q, 2H, $-CH_2CH_3$), 4.35 (s, 2H, methylene of acetic acid), 4.80 (broad s, 2H, $-NH_2$), 7.15-7.75 (m, 4H, ArH) ppm.

Anal. Calcd. for $C_{17}H_{22}N_2O_4S$: C, 58.26; H, 6.33; N, 8.00; S, 9.15. Found: C, 58.35; H, 6.36; N, 7.99; S, 9.21.

Ethyl 2-Amino-3-(*p*-chlorophenylsulfonyl)-4,5-dimethylpyrrole-1-acetate (**VIb**).

The crude product was crystallized from ethanol to yield a white

crystal (4.00 g, 87%), mp 89-90°, homogeneous on tlc - ethyl acetate, R_f = 0.86; ir (potassium bromide): 3430, 3340, 1735, 1620, 1470, 1295, 1220, 1125, 1080, 740 cm^{-1}; nmr (deuteriochloroform): δ 1.25 (t, 3H, $-CH_2CH_3$), 1.90 (s, 6H, $-CH_3$ at C_3 and C_5), 4.20 (q, 2H, $-CH_2CH_3$), 4.40 (s, 2H, methylene of acetic acid), 4.80 (broad s, 2H, $-NH_2$), 7.30-7.85 (m, 4H, ArH) ppm.

Anal. Calcd. for $C_{16}H_{19}ClN_2O_4S$: C, 51.82; H, 5.16; Cl, 9.56; N, 7.56; S, 8.65. Found: C, 51.92; H, 5.17; Cl, 9.61; N, 7.55; S, 8.62.

7-(*p*-Toluenesulfonyl)-5,6-dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]-imidazole (**VIIa**).

General Procedure for Compounds **VIIa-b**.

Ethyl 2-amino-3-(*p*-toluenesulfonyl)-4,5-dimethylpyrrole-1-acetate (1.22 g, 0.0035 mole) was suspended in 10 ml of ethanol and water (6 ml) and stirred in a water bath (~ 80°) until a solution was obtained. One equivalent of a one percent sodium hydroxide solution (14 ml) was added dropwise to the warm solution. The reaction was run at 80° for one hour at which time the solution was cooled to room temperature and filtered. The ethanol was removed *in vacuo* and 10 ml of water added to the solution. The aqueous solution was acidified with 6*N* hydrochloric acid at which time a gum formed. The gum was dissolved in ethanol (10 ml) and placed in the freezer. A beige crystal (0.63 g, 58%) was collected by filtration, air dried and needed no further purification, mp = 265-267°, homogeneous on tlc - ethyl acetate, R_f = 0.72; ir (potassium bromide): 3270, 1750, 1590, 1270, 1115, 1055, 885, 800 cm^{-1}; nmr (DMSO-d_6): δ 1.95 (s, 6H, $-CH_3$ at C_5 and C_6), 2.35 (s, 3H, CH_3 of toluene), 4.45 (s, 2H, N-CH_2), 7.30-7.85 (m, 4H, ArH), 11.40 (broad s, 1H, NH) ppm.

Anal. Calcd. for $C_{15}H_{16}N_2O_3S \cdot 0.25\ H_2O$: C, 58.33; H, 5.38; N, 9.07; S, 10.38. Found: C, 58.46; H, 5.40; N, 9.03; S, 10.40.

7-(*p*-Chlorophenylsulfonyl)-5,6-dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrolo-[1,2-*a*]imidazole (**VIIb**).

The product was crystallized from ethanol to yield peach crystals (0.82 g, 68%), mp 266-268°, homogeneous on tlc - ethyl acetate, R_f = 0.88; ir (potassium bromide): 3200, 1730, 1590, 1300, 1285, 1130, 895, 750 cm^{-1}; nmr (DMSO-d_6): δ 2.00 (s, 6H, $-CH_3$ at C_5 and C_6), 4.45 (s, 2H, N-CH_2), 7.60-7.95 (m, 4H, ArH), 11.40 (broad s, 1H, NH) ppm.

Anal. Calcd. for $C_{14}H_{13}ClN_2O_3S \cdot 0.25\ H_2O$: C, 51.06; H, 4.13; Cl, 10.76; N, 8.50; S, 9.73. Found: C, 51.05; H, 4.13; Cl, 10.71; N, 8.51; S, 9.76.

Sodium 2-Amino-3-(*p*-toluenesulfonyl)-4,5-dimethylpyrrole-1-acetate (**VIIIa**).

General Procedure for Compounds **VIIIa-b**.

A suspension of ethyl 2-amino-3-(*p*-toluenesulfonyl)-4,5-dimethylpyrrole-1-acetate (5.00 g, 0.0143 mole) was suspended in one equivalent of a one percent sodium hydroxide solution (57.1 ml) and stirred at room temperature for 24 hours. The solution was diluted with 100 ml of distilled water and filtered. The filtrate was adjusted to a *p*H of 8.2 with 6*N* hydrochloric acid. Again, the solution was filtered and the water removed *in vacuo*. When 15 ml of water remained, a white flocculent precipitate formed. The aqueous suspension was placed in the refrigerator overnight and a white crystal was collected by filtration and air dried. The sodium salt of 2-amino-3-(*p*-toluenesulfonyl)-4,5-dimethylpyrrole-1-acetic acid (1.95 g, 40%) needed no further purification, mp 195-197°, homogeneous on tlc - ethyl acetate, R_f = 0.0; ir (potassium bromide): 3400, 1650, 1380, 1300, 1275, 1120, 1070, 800 cm^{-1}; nmr (DMSO-d_6): δ 1.90 (s, 6H, $-CH_3$ at C_4 and C_5), 2.35 (s, 3H, $-CH_3$ of toluene), 4.05 (s, 2H, N-CH_2), 5.60 (broad s, 2H, $-NH_2$) 7.25-7.75 (m, 4H, ArH) ppm.

Anal. Calcd. for $C_{15}H_{17}N_2O_4S\ Na \cdot 1.0\ H_2O$: C, 49.72; H, 5.28; N, 7.73; S, 8.85. Found: C, 49.73; H, 5.27; N, 7.70; S, 8.90.

Sodium 2-Amino-3-(*p*-chlorophenylsulfonyl)-4,5-dimethylpyrrole-1-acetate (**VIIIb**).

The sodium salt of 2-amino-3-(*p*-chlorophenylsulfonyl)-4,5-dimethylpyrrole-1-acetic acid was crystallized from water (2.10 g, 43%), mp 98-100°, homogeneous on tlc-ethyl acetate, R_f = 0.0; ir (potassium bromide): 3400, 1650, 1600, 1385, 1300, 1290, 1120, 1075, 750 cm^{-1}; nmr (DMSO-d_6): δ 1.90 (s, 6H, $-CH_3$ at C_4 and C_5), 4.05 (s, 2H, N-CH_2), 5.60 (broad s, 2H, $-NH_2$), 7.50-7.85 (m, 4H, ArH) ppm.

Anal. Calcd. for $C_{14}H_{14}ClN_2O_4SNa \cdot 1.5\ H_2O$: C, 42.92; H, 4.37; Cl, 9.05; N, 7.15; S, 8.18. Found: C, 42.97; H, 4.38; Cl, 9.00; N, 7.12; S, 8.10.

Ethyl 4,5-Dimethyl-3-(*p*-toluenesulfonyl)-2-acetylaminopyrrole-1-acetate (**IXa**).

General Procedure for Compounds **IXa-b**.

A solution of ethyl 2-amino-3-(*p*-toluenesulfonyl)-4,5-dimethylpyrrole-1-acetate (8.00 g, 0.023 mole) and pyridine (1.98 g, 0.025 mole) in 50 ml of dry tetrahydrofuran was placed in an ice bath. Acetyl chloride (2.00 g, 0.025 mole) was added dropwise to the solution and the ice bath was removed. The reaction proceeded for one hour at room temperature. The solvent was then removed *in vacuo*. The residue was dissolved in 20 ml of methanol and placed in the freezer. The precipitate was collected by filtration and air dried to yield a white crystal (6.50 g, 73%) which needed no further purification, mp = 167-169°, homogeneous on tlc - ethyl acetate, R_f = 0.77; ir (potassium bromide): 3300, 2990, 1750, 1660, 1520, 1290, 1120, 1000, 810 cm^{-1}; nmr (deuteriochloroform): δ 1.20 (t, 3H, CH_2CH_3), 2.00 (s, 6H, $-CH_3$ at C_4 and C_5), 2.15 (s, 3H, $NHCOCH_3$), 2.35 (s, 3H, CH_3 of toluene), 4.20 (q, 2H, CH_2CH_3), 4.50 (s, 2H, NCH_2), 7.15-7.80 (m, 4H, ArH), 8.15 (broad s, 1H, NH) ppm.

Anal. Calcd. for $C_{19}H_{24}N_2O_5S$: C, 58.14; H, 6.16; N, 7.14; S, 8.17. Found: C, 58.03; H, 6.16; N, 7.08; S, 8.11.

Ethyl 4,5-Dimethyl-3-(*p*-chlorophenylsulfonyl)-2-acetylaminopyrrole-1-acetate (**IXb**).

The product was crystallized from methanol to yield white crystals (3.13 g, 76%), mp 160-162°, homogeneous on tlc - ethyl acetate, R_f = 0.81; ir (potassium bromide): 3240, 1750, 1300, 1200, 1125, 1070, 740 cm^{-1}; nmr (deuteriochloroform): δ 1.20 (t, 3H, CH_2CH_3), 2.00 (s, 6H, $-CH_3$ at C_4 and C_5), 2.15 (s, 3H, $NHCOCH_3$), 4.20 (q, 2H, CH_2CH_3), 4.45 (s, 2H, N-CH_2), 7.30-7.85 (m, 4H, ArH), 8.30 (broad s, 1H, $NHCOCH_3$) ppm.

Anal. Calcd. for $C_{18}H_{21}ClN_2O_5S$: C, 52.36; H, 5.13; Cl, 8.59; N, 6.79; S, 7.77. Found: C, 52.42; H, 5.15; Cl, 8.65; N, 6.75; S, 7.78.

Ethyl 3-(*p*-Toluenesulfonyl)-4,5-dimethyl-2-trifluoroacetylaminopyrrole-1-acetate (**Xa**).

General Procedure for Compounds **Xa-b**.

A solution of ethyl 2-amino-3-(*p*-toluenesulfonyl)-4,5-dimethylpyrrole-1-acetate (3.85 g, 0.011 mole) in 30 ml of dry tetrahydrofuran was cooled in an ice bath as pyridine (1.00 g, 0.0125 mole) was added. Trifluoroacetic anhydride (2.63 g, 0.0125 mole) was added dropwise to the cooled solution. The ice bath was removed and the solution stirred at room temperature for one hour. The solvent was removed *in vacuo* and the oil dissolved in methanol-water (9:1, 10 ml), then placed in the freezer overnight. The product (3.07 g, 63%) needed no further purification to yield off white crystals, mp 145-146°, homogeneous on tlc - ethyl acetate, R_f = 0.87; ir (potassium bromide): 3230, 3000, 1735, 1430, 1290, 1210, 1145, 1120, 1075, 800 cm^{-1}; nmr (deuteriochloroform): δ 1.20 (t, 3H, CH_2CH_3), 2.05 (s, 6H, $-CH_3$ at C_4 and C_5), 2.35 (s, 3H, CH_3 of toluene), 4.20 (q, 2H, CH_2CH_3), 4.45 (s, 2H, N-CH_2), 7.20-7.75 (m, 4H, ArH), 9.00 (broad s, 1H, $NHCOCF_3$) ppm.

Anal. Calcd. for $C_{19}H_{21}F_3N_2O_5S$: C, 51.11; H, 4.74; N, 6.28; S, 7.18. Found: C, 51.16; H, 4.77; N, 6.25; S, 7.23.

Ethyl 3-(*p*-Chlorophenylsulfonyl)-4,5-dimethyl-2-trifluoroacetylamino-pyrrole-1-acetate (**Xb**).

The product was crystallized from methanol-water to yield light pink crystals, mp 160-161°, homogeneous on tlc - ethyl acetate, R_f = 0.91; ir (potassium bromide): 3240, 3000, 1745, 1580, 1540, 1300, 1150, 1080, 750 cm^{-1}; nmr (deuteriochloroform): δ 1.25 (t, 3H, CH_2CH_3), 2.05 (s, 3H, $-CH_3$ at C_4 or C_5), 2.10 (s, 3H, $-CH_3$ at C_4 or C_5), 4.20 (q, 2H, CH_2CH_3), 4.45 (s, 2H, N-CH_2), 7.35-7.80 (m, 4H, ArH), 8.95 (broad s, 1H, $NHCOCF_3$) ppm.

Anal. Calcd. for $C_{18}H_{18}ClF_3N_2O_5S$: C, 46.31; H, 3.89; Cl, 7.59; N, 6.00; S, 6.87. Found: C, 46.21; H, 3.93; Cl, 7.65; N, 6.00; S, 6.93.

2-Acetylamino-3-(*p*-toluenesulfonyl)-4,5-dimethylpyrrole-1-acetic acid (**XIa**).

General Procedure for Compounds **XIa-b**:

Ethyl 4,5-dimethyl-3-(*p*-toluenesulfonyl)-2-acetylaminopyrrole-1-acetate (3.92 g, 0.01 mole) was suspended in 20 ml of ethanol and water (10 ml) and stirred in a water bath (~ 80°) until a solution was obtained. Next, one equivalent of a one percent sodium hydroxide solution (40 ml) was added dropwise to the warm solution. After one hour at 80°, the solution was cooled to room temperature and filtered. The ethanol was removed *in vacuo* and 10 ml of water was added to the solution. The aqueous solution was acidified with 6*N* hydrochloric acid. A precipitate formed which was collected by filtration, washed with water (2 x 10 ml) and air dried. The white crystals (3.10 g, 85%) needed no further purification, mp = 198-200°, homogeneous on tlc - ethyl acetate, R_f = 0.0; ir (potassium bromide): 3250, 1735, 1640, 1425, 1325, 1270, 1200, 1120, 1075, 800 cm^{-1}; nmr (DMSO-d_6): δ 1.85 (s, 3H, -CH_3 at C_4 or C_5), 1.90 (s, 3H, NHCOCH_3), 2.00 (s, 3H, -CH_3 at C_4 or C_5), 2.30 (s, 3H, CH_3 of toluene), 4.45 (s, 2H, NCH_2), 7.25-7.80 (m, 4H, ArH), 9.60 (broad s, 1H, NH) ppm.

Anal. Calcd. for $C_{17}H_{20}N_2O_5S$: C, 56.03; H, 5.53; N, 7.69; S, 8.80. Found: C, 55.89; H, 5.54; N, 7.64; S, 8.72.

2-Acetylamino-3-(*p*-chlorophenylsulfonyl)-4,5-dimethylpyrrole-1-acetic acid (**XIb**).

The product was crystallized from ethanol and air dried to yield a white crystal (0.69 g, 53%) which needed no further purification, mp 209-210°, homogeneous on tlc - ethyl acetate, R_f = 0.0; ir (potassium bromide): 3320, 1725, 1670, 1540, 1430, 1290, 1120, 1070, 820 cm^{-1}; nmr (DMSO-d_6): δ 1.90 (s, 3H, -CH_3 at C_4 or C_5), 1.95 (s, 3H, NHCOCH_3), 2.00 (s, 3H, -CH_3 at C_4 or C_5), 4.50 (s, 2H, NCH_2), 7.55-7.95 (m, 4H, ArH), 9.75 (broad s, 1H, NH) ppm.

Anal. Calcd. for $C_{16}H_{17}ClN_2O_5S \cdot 1.0\ H_2O$: C, 47.70; H, 4.75; Cl, 8.80; N, 6.96; S, 7.96. Found: C, 47.77; H, 4.75; Cl, 8.89; N, 6.89; S, 7.93.

Ethyl 2-Acetylamino-3-(*t*-butoxycarbonyl)-4,5-dimethylpyrrole-1-acetate (**XIII**).

A solution of ethyl 2-amino-3-(*t*-butoxycarbonyl)-4,5-dimethylpyrrole-1-acetate (74.1 g, 0.25 mole) and pyridine (21.7 g, 0.275 mole) in 150 ml of acetone was stirred in an ice bath. Acetyl chloride (22.0 g, 0.275 mole) was added dropwise to the solution and the ice bath removed. The reaction proceeded for 30 minutes at room temperature. The reaction mixture was poured over 300 g of crushed ice and water and an oil formed. The aqueous phase was extracted with ethyl acetate (200 ml) and the ethyl acetate was dried over anhydrous sodium sulfate. The ethyl acetate was removed *in vacuo* to yield a viscous oil which was recrystallized from methanol-water (1:1, 600 ml). The white crystals (73.4 g, 87%) needed no further purification, mp 69-71°, homogeneous on tlc - ethyl acetate, R_f = 0.78; ir (potassium bromide): 3300, 2990, 1750, 1680, 1550, 1440, 1200, 1110, 770 cm^{-1}; nmr (deuteriochloroform): δ 1.25 (t, 3H, CH_2CH_3), 1.55 (s, 9H, t-C_4H_9), 2.10 (s, 3H, NHCOCH_3), 2.20 (s, 6H, -CH_3 at C_4 and C_5), 4.25 (q, 2H, CH_2CH$_3$), 4.55 (s, 2H, N-CH_2), 8.30 (broad s, 1H, NH) ppm.

Anal. Calcd. for $C_{17}H_{26}N_2O_5 \cdot 0.25\ H_2O$: C, 59.54; H, 7.78; N, 8.17. Found: C, 59.48; H, 7.78; N, 8.14.

Ethyl 3-(*t*-Butoxycarbonyl)-4,5-dimethyl-2-trifluoroacetylaminopyrrole-1-acetate (**XIV**).

Ethyl 2-amino-3-(*t*-butoxycarbonyl)-4,5-dimethylpyrrole-1-acetate was synthesized as previously described. The crude oil (0.25 mole) was dissolved in 200 ml of dry tetrahydrofuran and cooled in an ice bath. Pyridine (20.9 g, 0.265 mole) was added to the cooled solution. Trifluoroacetic anhydride (55.8 g, 0.265 mole) was added dropwise to the solution over the course of a half hour. The ice bath was removed and the solution was stirred at room temperature for one hour. The solvent was removed *in vacuo* and the oil dissolved in methanol-water (10:1, 220 ml), then placed in the freezer overnight. The crude product (10.0 g, 11%) was recrystallized from methanol-water (10:1, 22 ml) to yield a light beige crystal (3.0 g, 28%), mp 82-84°, homogeneous on tlc - ethyl acetate, R_f = 0.90; ir (potassium bromide): 3300, 3000, 1750, 1700, 1560, 1220, 1190, 1120, 1020 cm^{-1}; nmr (deuteriochloroform): δ 1.30 (t, 3H, CH_2CH_3), 1.50 (s, 9H, t-C_4H_9), 2.10 (s, 3H, -CH_3 at C_4 or C_5), 2.15 (s, 3H, -CH_3 at C_4 or C_5), 4.20 (q, 2H, CH_2CH$_3$), 4.50 (s, 2H, N-CH_2), 9.50 (broad s, 1H, NHCOCF_3) ppm.

Anal. Calcd. for $C_{17}H_{23}F_3N_2O_5$: C, 52.04; H, 5.91; N, 7.14. Found: C, 52.00; H, 5.93; N, 7.13.

Ethyl 3-Carboxy-4,5-dimethyl-2-acetylaminopyrrole-1-acetate (**XVa**).

Ethyl 3-(*t*-butoxycarbonyl)-4,5-dimethyl-2-acetylaminopyrrole-1-acetate (33.8 g, 0.1 mole) was placed in a one liter flask and immersed in an ice bath. Slowly, methane sulfonic acid (75.0 g) was added with constant stirring. The mixture was allowed to stir at room temperature for 10 minutes and, then, poured over 300 g of crushed ice to form a gummy semi-solid. The gummy solid was recrystallized twice from ethanol-water (4:1) to yield a beige crystal (24.8 g, 88%) mp 206-207°, homogeneous on tlc-ethyl acetate, R_f = 0.0; ir (potassium bromide): 3300, 3000, 1740, 1660, 1560, 1210, 1130, 950 cm^{-1}; nmr (DMSO-d_6): δ 1.20 (t, 3H, CH_2CH_3), 1.95 (s, 3H, NHCOCH_3), 2.00 (s, 3H, -CH_3 at C_4 or C_5), 2.10 (s, 3H, -CH_3 at C_4 or C_5), 4.10 (q, 2H, CH_2CH$_3$), 4.50 (s, 2H, N-CH_2), 9.30 (broad s, 1H, N*H*COCH$_3$) ppm.

Anal. Calcd. for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43; N, 9.93. Found: C, 55.39; H, 6.48; N, 9.91.

Ethyl 3-Carboxy-4,5-dimethyl-2-trifluoroacetylaminopyrrole-1-acetate (**XVb**).

Ethyl 3-(*t*-butoxycarbonyl)-4,5-dimethyl-2-trifluoroacetylaminopyrrole-1-acetate (2.0 g, 0.005 mole) was place in a 150 ml beaker with methane sulfonic acid (4.0 g) and stirred for approximately 10 minutes at room temperature. At the end of this reaction, the clear brown solution was mixed with 30 grams of crushed ice and stirred about 5 minutes. The insoluble carboxylic acid was collected by filtration, washed with distilled water, and air dried to yield an off-white powder (1.53 g, 91%). The carboxylic acid was recrystallized from diethyl ether to yield a white powder (1.48, 97%), mp 159-160°, homogeneous on tlc - ethyl acetate, R_f = 0.44; ir (potassium bromide): 3280, 3000, 1740, 1670, 1600, 1220, 1030, 940, 920 cm^{-1}; nmr (DMSO-d_6): δ 1.20 (t, 3H, CH_2CH_3), 2.00 (s, 3H, -CH_3 at C_4 or C_5), 2.05 (s, 3H, -CH_3 at C_4 or C_5), 4.05 (q, 2H, CH_2CH$_3$), 4.50 (s, 2H, -N-CH_2), 11.00 (broad s, 1H, NHCOCF_3) ppm.

Anal. Calcd. for $C_{13}H_{15}F_3N_2O_5$: C, 46.43; H, 4.50, N, 8.33. Found: C, 46.38; H, 4.51; N, 8.30.

2-Acetylamino-3-(*t*-butoxycarbonyl)-4,5-dimethylpyrrole-1-acetic acid (**XVI**).

Ethyl 2-acetylamino-3-(*t*-butoxycarbonyl)-4,5-dimethylpyrrole-1-acetate (0.75 g, 0.0022 mole) was suspended in 7 ml of ethanol and water (6 ml) and stirred in a water bath (~ 80°) until a solution was obtained. One equivalent of a one percent sodium hydroxide solution (8.9 ml) was added dropwise to the warm solution. After one hour at 80° the solution was cooled to room temperature and filtered. The ethanol was removed *in vacuo* and 10 ml of water added to the solution. The aqueous solution was acidified with 6*N* hydrochloric acid at which time a gum formed. The aqueous filtrate was decanted and the gum dissolved in 10 ml of ethanol and placed in the freezer. The product was collected by filtration and air dried to yield a white crystal (0.33 g, 48%) which needed no further purification, mp 199-201°, homogeneous on tlc - ethyl acetate, R_f = 0.0; ir (potassium bromide): 3260, 1740, 1650, 1430, 1295, 1200, 1120, 780 cm^{-1}; nmr (DMSO-d_6): δ 1.45 (s, 9H, t-C_4H_9), 2.00 (s, 6H, -CH_3 at C_4 and C_5), 2.10 (s, 3H, NHCOCH$_3$), 4.45 (s, 2H, N-CH_2), 9.40 (broad s, 1H, N*H*COCH$_3$) ppm.

Anal. Calcd. for $C_{15}H_{22}N_2O_5$: C, 58.05; H, 7.15; N, 9.03. Found: C, 57.97; H, 7.21; N, 8.95.

Ethyl 3-(*t*-Butoxycarbonyl)-4,5-dimethyl-2-(*N*-trifluoroacetyl-*N*-methyl)-aminopyrrole-1-acetate (**XVII**).

A mixture of ethyl 3-(*t*-butoxycarbonyl)-4,5-dimethyl-2-trifluoroacetylaminopyrrole-1-acetate (5.0 g, 0.013 mole), anhydrous sodium carbonate (1.49 g, 0.014 mole), and methyl iodide (2.0 g, 0.014 mole) in dry dimethylformamide (14 ml) was stirred at room temperature for 48 hours. The mixture was poured over ice (150 g) to yield a semi-solid. The crude product was recrystallized twice from ethanol-water (9:1, 50 ml) to yield white crystals (2.67 g, 52%), mp 134-135°, homogeneous on tlc - ethyl acetate, R_f = 0.90; ir (potassium bromide): 3000, 1750, 1700, 1400, 1250, 1200, 1050 cm^{-1}; nmr (deuteriochloroform): δ 1.25 (t, 3H, CH_2CH_3), 1.50 (s, 9H, *t*-C_4H_9), 2.05 (s, 3H, -CH_3 at C_4 or C_5), 2.20 (s, 3H, -CH_3 at C_4 or C_5), 3.20 (s, 3H, N-CH_3), 4.25 (q, 2H, CH_2CH_3), 4.45 (s, 2H, N-CH_2) ppm.

Anal. Calcd. for $C_{18}H_{25}F_3N_2O_5$: C, 53.19; H, 6.20; N, 6.89. Found: C, 53.27; H, 6.24; N, 6.88.

3-(*t*-Butoxycarbonyl)-4,5-dimethyl-2-(*N*-trifluoroacetyl-*N*-methyl)aminopyrrole-1-acetic acid (**XVIII**).

Ethyl 3-(*t*-butoxycarbonyl)-4,5-dimethyl-2-(*N*-trifluoroacetyl-*N*-methyl)-aminopyrrole-1-acetate (1.00 g, 2.46 mmoles) was suspended in 10 ml of ethanol and water (2 ml) and stirred in a water bath (~ 80°) until a solution was obtained. One equivalent of a one percent sodium hydroxide solution (9.84 ml) was added dropwise to the warm solution. After one hour at 80°, the solution was cooled to room temperature and filtered. The ethanol was removed *in vacuo* and water (10 ml) added to the solution. The aqueous solution was acidified with 6*N* hydrochloric acid at which time a precipitate formed. The product was collected by filtration, washed with water (2 x 10 ml) and air dried to yield an off white crystal (0.53 g, 54%) which needed no further purification, mp 116-118°, homogeneous on tlc - ethyl acetate, R_f = 0.0; ir (potassium bromide): 3480, 2990, 1710, 1675, 1390, 1245, 1210, 1150, 1050 cm^{-1}; nmr (deuteriochloroform): δ 1.50 (s, 9H, *t*-C_4H_9), 2.10 (s, 3H, -CH_3 at C_4 or C_5), 2.20 (s, 3H, -CH_3 at C_4 or C_5), 3.25 (s, 3H, N-CH_3), 4.50 (s, 2H, N-CH_2), 8.50 (broad s, 1H, COOH) ppm.

Anal. Calcd. for $C_{16}H_{21}F_3N_2O_5 \cdot H_2O$: C, 48.48; H, 5.85; N, 7.07. Found: C, 48.35; H, 5.78; N, 7.02.

Ethyl 3-Cyano-4,5-dimethyl-2-phenylpyrrole-1-acetate (**XIX**).

A solution of acetyl methyl carbinol (85% aqueous solution) (1.03 g, 0.01 mole), ethyl glycinate hydrochloride (2.42 g, 0.01 mole), and sodium bicarbonate (0.84 g, 0.01 mole) in 25 ml of ethanol and 10 ml of toluene was refluxed under a Dean-Stark trap with the azeotropic removal of 15 ml of distillate. The solution was refluxed for one hour. The reaction mixture was cooled down to room temperature and benzoylacetonitrile (1.45 g, 0.01 mole) was added and the solution was refluxed for an additional two hours with the additional removal of 15 ml of distillate. At the end of the reaction, the inorganic salt was filtered off and the solvent removed *in vacuo* to yield a reddish-orange oil; homogeneous on tlc - ethyl acetate, R_f = 0.75; ir (potassium bromide): 2995, 2210, 1745, 1695, 1590, 1445, 1200, 1010, 690 cm^{-1}; nmr (deuteriochloroform): δ 1.25 (t, 3H, CH_2CH_3), 2.05 (s, 6H, -CH_3 at C_4 and C_5), 4.15 (q, 2H, CH_2CH_3), 4.40 (s, 2H, N-CH_2), 7.25 (s, 5H, ArH) ppm.

7-(*t*-Butoxycarbonyl)-5,6-dimethyl-2-oxo-2,3-dihydro-(1*H*)-pyrrolo[1,2-*a*]-imidazole (**XX**).

A solution of acetyl methyl carbinol (85% aqueous solution) (10.37 g, 0.1 mole), ethyl glycinate hydrochloride (14.1 g, 0.1 mole), and sodium bicarbonate (8.4 g, 0.1 mole) in 150 ml of ethanol and 15 ml of toluene was refluxed under a Dean-Stark trap with the azeotropic removal of 30 ml of distillate. The solution was refluxed for an additional hour. The reaction mixture was cooled to room temperature and *t*-butyl cyanoacetate (14.86 g, 0.1 mole) was added and the solution was refluxed for 2 hours with the removal of another 25 ml of distillate. All solvents were removed *in vacuo*. The amber oil was dissolved in 200 ml of toluene, filtered to remove any inorganic salt and brought to reflux under a Dean-Stark trap. The toluene was azeotroped until no water appeared to be present in the distillate. The solution was cooled to room temperature and placed in an ice bath. Then potassium *t*-butoxide (11.2 g, 0.1 mole) was added slowly. The ice bath was removed and the solution stirred in a boiling water bath for 2 hours. The toluene was removed *in vacuo* and the residue was suspended in methanol (80 ml), water (20 ml) and glacial acetic acid (6 ml), then placed in the freezer overnight. The crude product (16.5 g, 66%) was further recrystallized from methanol-water (8.5:1.5) to yield pale yellow crystals (13.8 g, 84%), mp 229-230°, homogeneous on tlc - ethyl acetate, R_f = 0.90; ir (potassium bromide): 3180, 2980, 2930, 1720, 1670, 1600, 1400, 1290, 1110, 770 cm^{-1}; nmr (deuteriochloroform): δ 1.55 (s, 9H, *t*-C_4H_9), 2.05 (s, 3H, -CH_3 at C_5 or C_6), 2.15 (s, 3H, -CH_3 at C_5 or C_6), 4.25 (s, 2H, -CH_2 of imidazole), 8.25 (broad s, 1H, -NH) ppm.

Anal. Calcd. for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.20. Found: C, 62.27; H, 7.30; N, 11.17.

7-Carboxy-5,6-dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole (**XXI**).

7-(*t*-Butoxycarbonyl)-5,6-dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrolo[1,-2-*a*]imidazole (5.0 g, 0.02 mole) was placed in a 150 ml beaker with methane sulfonic acid (10.0 g) and stirred for approximately 10 minutes at room temperature. At the end of this reaction, the clear solution was mixed with 50 grams of crushed ice. The insoluble carboxylic acid was collected by filtration, washed with distilled water and air dried to yield an off white powder (3.83 g, 99%). The carboxylic acid was purified by dissolving in 1*N* sodium hydroxide (20 ml) and reacidification with hydrochloric acid, mp 220-221°, homogeneous on tlc - ethyl acetate, R_f = 0.00; ir (potassium bromide): 3200, 2930, 2600, 1740, 1640, 1590, 1490, 1290, 1130, 940, 850, 715 cm^{-1}; nmr (DMSO-d_6): δ 2.00 (s, 3H, -CH_3 at C_5 or C_6), 2.10 (s, 3H, -CH_3 at C_5 or C_6), 4.35 (s, 2H, -CH_2 of imidazole), 11.10 (broad s, 1H, -NH) ppm.

Anal. Calcd. for $C_9H_{10}N_2O_3$: C, 55.66; H, 5.19; N, 14.43. Found: C, 55.53; H, 5.25; N, 14.41.

5,6-Dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole (**XXII**).

7-(*t*-Butoxycarbonyl)-5,6-dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2,-*a*]-imidazole (12.5 g, 0.05 mole) and trifluoroacetic acid (37.5 g) were stirred in a water bath whose temperature was kept constant between 50-55° for approximately one hour. The majority of the trifluoroacetic acid was removed *in vacuo* and 120 g of ice and water was added to the residue. The solution was adjusted to a *p*H of 9 with 1*N* sodium hydroxide. The precipitate (5.85 g, 78%) was collected by filtration, washed with distilled water and resuspended in methanol: diethyl ether (50 ml: 100 ml) and collected, mp 211-213°, homogeneous on tlc - ethyl acetate, R_f = 0.62; ir (potassium bromide): 3270, 2920, 1725, 1700, 1605, 1450, 1290, 1180, 1110, 870, 740 cm^{-1}; nmr (DMSO-d_6): δ 1.85 (s, 3H, -CH_3 at C_5 or C_6), 1.95 (s, 3H, -CH_3 at C_5 or C_6), 4.20 (s, 2H, -CH_2 of imidazole), 4.90 (s, 1H, -H at C_7), 10.50 (broad s, 1H, -NH) ppm.

Anal. Calcd. for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.66. Found: C, 64.19; H, 6.75; N, 18.54.

7-Benzoyl-5,6-dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole (**XXIII**).

Method A.

5,6-Dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-7-ethyl carbonate anhydride (0.170 g, 0.64 mmole) was dissolved in dry tetrahydrofuran (5 ml) in a dry ice bath under an argon atmosphere. Two equivalents of phenylmagnesium bromide (3*M* solution in diethyl ether) (0.43 ml, 1.3 mmoles) was added dropwise to the above solution. The reaction was run for 0.25 hour in a dry ice bath and 0.3 hours at room temperature. The reaction mixture was again cooled in an ice bath (~ 0°) and four equivalents of 2*N* hydrochloric acid (1.3 ml) was stirred for one hour at room temperature. All solvents were removed *in vacuo* and the residue dissolved in methylene chloride. The organic layer was extracted with distilled water (2 x 10 ml), 2% sodium bicarbonate (10 ml), and brine. The methylene cloride was dried over anhydrous sodium sulfate and removed *in vacuo*. The residue was recrystallized from ethanol-water (3:1, 4 ml) to yield yellow crystals (0.12 g, 74%) which needed no further purification, mp 252-253°, homogeneous on tlc - ethyl acetate, R_f = 0.73; ir (potassium bromide): 3440, 3100, 1770, 1610, 1530, 1400, 1155, 970 cm^{-1}; nmr (DMSO-d_6): δ 2.20 (s, 3H, -CH_3 at C_5 or C_6), 2.35 (s, 3H, -CH_3 at

C_5 or C_6), 4.80 (s, 2H, N-CH_2), 7.80 (s, 5H, ArH), 11.20 (broad s, 1H, NH) ppm.

Anal. Calcd. for $C_{15}H_{14}N_2O_2 \cdot 0.4\ H_2O$: C, 68.89; H, 5.70; N, 10.71. Found: C, 68.95; H, 5.65; N, 10.51.

Method B.

A suspension of 5,6-dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole (1.50 g, 0.01 mole) in dry 1,2-dichloroethane (20 ml) was placed in a dry ice bath while anhydrous aluminum chloride (1.60 g, 0.012 mole) was added slowly. After stirring for 5 minutes, benzoyl chloride (1.69 g, 0.012 mole) was added dropwise and the solution stirred in the dry ice bath for 0.5 hour. The reaction mixture was brought to room temperature and then refluxed for 1.5 hours. At the end of the reaction time, the reaction mixture was cooled in an ice bath and 2*N* hydrochloric acid 15 ml, 0.03 mole) was added slowly and stirred for 1 hour at room temperature. The reaction mixture was filtered, place in a separatory funnel, and more methylene chloride (25 ml) and water (50 ml) was added. The organic layer was extracted with 5% sodium bicarbonate (2 x 50 ml) and brine. The organic layer was dried over anhydrous sodium sulfate and removed *in vacuo*. The resulting residue was triturated with methanol-water (5:1, 30 ml), placed in the freezer, and collected by filtration to yield a mixture of starting material and the desired product. The crude product was purified by chromatography (20% hexanes in ethyl acetate) to give yellow crystals (0.30 g, 12%). The melting point and spectral data were identical to compound **XXIII** obtained under method A.

5,6-Dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-7-carboxylic Acid, Imidazole Amide (**XXIV**).

A suspension of 7-carboxy-5,6-dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrolo-[1,2-*a*]imidazole (1.94 g, 0.01 mole) and 1,1'-carbonyldiimidazole (2.95 g, 0.018 mole) in dry dimethylformamide (15 ml) is heated for 1.5 hours, by the end of which time carbon dioxide evolution had ceased and a solution was obtained. The dimethylformamide solution was poured over crushed ice (200 g) to yield a white crystal (0.75 g, 31%) that was collected by filtration. The product was resuspended in ethanol and recollected with no further purification necessary, mp = 218-220°, homogeneous on tlc - ethyl acetate, R_f = 0.0: ir (potassium bromide): 3440, 3140, 2960, 1730, 1660, 1580, 1400, 1240, 1190, 1170, 920 cm^{-1}; nmr (DMSO-d_6): δ 2.00 (s, 3H, -CH_3 at C_5 or C_6), 2.05 (s, 3H, -CH_3 at C_5 or C_6), 4.40 (s, 2H, N-CH_2), 7.00-8.00 (m, 3H, imidazole H), 10.90 (broad s, 1H, NH) ppm.

Anal. Calcd. for $C_{12}H_{12}N_4O_2 \cdot 0.33\ H_2O$: C, 57.59; H, 5.10; N, 22.39. Found: C, 57.51; H, 5.12; N, 22.36.

5,6-Dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-7-ethyl Carbonate Anhydride (**XXV**).

A suspension of 7-carboxy-5,6-dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrolo-[1,2-*a*]imidazole (1.00 g, 0.0051 mole) and triethylamine (0.625 g, 0.0062 mole) in dry dimethylformamide (5 ml) was brought to 0° in an ice bath. Ethyl chloroformate (0.56 g, 0.0051 mole) was added dropwise to the cold suspension and stirred for 0.5 hours at 0°. The ice bath was removed and the solution stirred for an additional 0.5 hours at room temperature. The dimethylformamide solution was poured over 100 ml of crushed ice and a precipitate formed, which was collected by filtration. The precipitate was dissolved in methylene chloride and extracted with 2% sodium bicarbonate (2 x 10 ml) , 0.1 *N* hydrochloric acid (10 ml) and brine. The methylene chloride was dried over anhydrous sodium sulfate and removed *in vacuo*. The precipitate was suspended in cold ethanol and collected by filtration and air dried to yield a white crystal (0.40 g, 29%) which needed no further purification, mp 146-148°, homogeneous on tlc - ethyl acetate R_f = 0.81; ir (potassium bromide): 3160, 3000, 1790, 1740, 1715, 1590, 1210, 1000, 745 cm^{-1}; nmr (DMSO-d_6): δ 1.25 (t, 3H, CH_2CH_3), 2.00 (s, 6H, -CH_3 at C_5 and C_6), 4.20 (q, 2H, CH_2CH_3), 4.40 (s, 2H, NCH_2), 11.40 (broad s, 1H, NH) ppm.

Anal. Calcd. for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found: C, 54.06; H, 5.34; N, 10.52.

7-Ethoxycarbonyl-5,6-dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole (**XXVI**).

5,6-Dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-7-ethyl carbonate anhydride (0.7 g, 0.0026 mole) was stirred in ethanol (20 ml) for 0.25 hours at room temperature and, then, placed in the freezer overnight. The product was collected by vacuum filtration and air dried to yield a pale yellow crystal (0.58 g, 99%) which needed no further purification, mp 211-213°, homogeneous on tlc - ethyl acetate, R_f = 0.75; ir (potassium bromide): 3260, 2990, 1750, 1700, 1600, 1475, 1110, 760 cm^{-1}; nmr (DMSO-d_6): δ 1.20 (t, 3H, CH_2CH_3), 1.95 (s, 3H, -CH_3 at C_5 or C_6), 2.05 (s, 3H, -CH_3 at C_5 or C_6), 4.10 (q, 2H, CH_2CH_3), 4.35 (s, 2H, N-CH_2), 11.00 (broad s, 1H, NH) ppm.

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.44; H, 6.35; N, 12.61. Found: C, 59.54; H, 6.36; N, 12.57.

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