Total Synthesis of Pyrrolinitril. II. Synthesis of Ethyl 3-Aryl-5-methyl-2-pyrrolecarboxylate. (I)¹,²

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Ethyl 3-aryl-5-methyl-2-pyrrolecarboxylate (XXIII), a desirable intermediate for chlorination to prepare pyrrolinitril, was derived from ethyl 3-aryl-5-methyl-4-pyrrolecarboxylate (I) by following two routes.

At first, it was undertaken to introduce a second ester group to the 2-position of I before the first ester group at the 4-position of I was eliminated. Then the first ester group was hydrolysed selectively and the resulting carboxyl group was removed by decarboxylation.

Secondly, the ester group of I was eliminated at first, affording 3-aryl-5-methylpyrrole (XIV). Introduction of an ester group to 2-position of XIV was carried out successively by two methods via a cyano group or a carbonyl chloride group.

In the first paper of this series,¹ the preparation of alkyl 3-aryl-5-methyl-4-pyrrolecarboxylates by Knorr’s condensation was reported.

The object of this paper is to describe the conversion of ethyl 3-aryl-5-methyl-4-pyrrolecarboxylate (I), the first key intermediate, into ethyl 3-aryl-5-methyl-2-pyrrolecarboxylate (XXIII), the second key intermediate, by two routes.

In the first attempt, it was undertaken to introduce a second ester group to the 2-position of I before the first ester group on the 4-position of I was eliminated. Then the first ester group was hydrolysed selectively and the resulting carboxyl group was removed by decarboxylation.

Ethyl 2-formyl-3-aryl-5-methyl-4-pyrrolecarboxylates (IIa—c) were derived from ethyl 3-aryl-5-methyl-4-pyrrolecarboxylates (Ia—c) by Vilsmeier reaction.

Oxidation of IIa—c took place difficulty in the usual manner with alkaline oxidation in acetone and gave abnormal products (IVA,b,c) instead of the expected carboxylic acids (III). 1b was also condensed with acetophenone under basic condition to give IVBc. These abnormal products were confirmed to be IV from the NMR spectra, that showed two olefinic protons (CH₂COCH=CH: IVA 6.50; IVc 6.48 ppm, CH₂COCH=CH: IVa 7.15; IVc 7.17 ppm in d₆-acetone).

The formyl compound (IIb) was oxidized with potassium permanganate in poor yield to 3-[3-nitro-4-chlorophenyl]-4-ethoxycarbonyl-5-methyl-2-pyrrolecarboxylic acid (IIIb), which was methylated to methyl 3-[3-nitro-4-chlorophenyl]-4-ethoxycarbonyl-2-pyrrolecarboxylate (XIIb) with diazomethane.

In boiling acetic anhydride, dehydration of ethyl 2-hydroxyiminomethyl-3-aryl-5-methyl-4-pyrrolecarboxylates (Va,b), which were obtained from IIa, b with hydroxylamine, afforded the corresponding ethyl 2-cyano-3-aryl-5-methyl-4-pyrrolecarboxylates (VIa, b) and a by-product, ethyl 1-acetyl-2-cyano-3-aryl-5-methyl-4-pyrrolecarboxylates (VIIa,b). The in-

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The infrared spectrum of this by-product showed no NH absorption band in a 3300 cm⁻¹ region. VIIa, b afforded VIa, b by treatment of 1 mole of alkali. But, when the dehydration was not enough, Va gave another by-product (VIIIa). The infrared spectrum of VIIIa showed the absorption bands in a carbonyl region at 1750 cm⁻¹ and 1710 cm⁻¹, and lacked an absorption due to the nitril. VIIIa was confirmed to be ethyl 2-acetoxyiminomethyl-3-(2-nitro-3-chlorophenyl)-5-methyl-4-pyrrolocarboxylate (VIIIa) from the fact that treatment with boiling acetic anhydride afforded VIa.

In order to obtain IXb via ethyl 2-carbamoino-3-(3-nitro-4-chlorophenyl)-5-methyl-4-pyrrolocarboxylate (IXb), the cyanopyrrole derivative (VIIb) was treated with hydrogen peroxide under a basic condition, but subsequent hydrolysis was not successful under any conditions. 2-Carbamoino-3-(3-nitro-4-chlorophenyl)-5-methyl-4-pyrrolocarboxylic acid (Xb)
was derived from VIb by treatment with concentrated sulfuric acid and afforded 3-(3-nitro-4-chlorophenyl)-5-methylpyrrole-2-carbonitrile (XIXb) under heating. The conversion of XIXb to XXIIIb was described later, but in poor yield.

It is necessary that the cyano group VI should be converted to the alkoxy carbonyl group, because all attempts to obtain the ester derivatives (XI) from the formyl- or cyanopyrroles (II or VI) have been unsuccessful except alcoholysis.

However, alcoholysis of the cyanopyrroles (VIa,b) was difficult in the usual way, owing to their weaker activity than aromatic cyanides.

Hine, et al.\(^4\) reported that the velocity of hydrolysis of the cyano group became more rapid with increasing of the concentration of an undissociated acid. Consequently, the same effect was expected in the alcoholysis as well as hydrolysis with increasing of the concentration of an acid catalyst.

Using ethanol saturated with dry hydrogen chloride at $-50^\circ$, the volume of ethanol increased about two times by hydrogen chloride, the cyano-pyrrole derivatives (VIA,b) afforded XIA,b, expected diethyl 3-aryl-5-methyl-2,4-pyrroledicarboxylate, in good yields. And the 1-acetyl-cyanopyrrole (VIIA,b) also gave XIA,b under the same condition.

Selective hydrolysis of XIA,b by treatment with concentrated sulfuric acid gave 2-ethoxycarbonyl-3-aryl-5-methyl-4-pyrrolocarboxylic acids (XIIA,b), and subsequent decarboxylation of resulting ester-acid afforded ethyl 3-aryl-5-methyl-2-pyrrolocarboxylate (XXIIa,b), the objective compounds in this paper, but in poor yield.

On the other hand, XXIII can be derived from 3-aryl-5-methylpyrrole (XIV) after removing the ester group at 3-position of I, described below as the second route.

The ester group in the $\beta$-position of the pyrrole ring is known to be hydrolyzed with concentrated sulfuric acid through an acylinum ion, but ethyl 3-phenyl-5-methyl-4-pyrrolocarboxylate can not afford the corresponding carboxylic acid.\(^5\)

On the contrary, under the above condition, ethyl 3-nitro-substituted phenyl-5-methyl-4-pyrrolocarboxylates (Ia-c) gave 3-aryl-5-methyl-4-pyrrolocarboxylic acids XIIIa-c in ca. 50% yields, and any additional products could not be isolated. But, when 93% sulfuric acid was employed instead of usual concentrated sulfuric acid, ca. 30% of I could be recovered accompanied with ca. 50% of XIII.

Decarboxylation of XIIIa-c in glycerin or naphthalene gave 3-aryl-5-methylpyrroles (XIVA-c).

Formyl- or acetyl-pyrrole (XVIIA, b or XVa) was derived from XIVa, b by Vilsmeier reaction with phosphorous oxychloride and dimethylformamide or dimethyl acetamide complex. But it was possible that both the 4- or 2-position of XIV could be attacked by those reagents. However, the acetyl compound (XVA) was not identical, as shown by the infrared and the mixture melting point comparison with 3-(2-nitro-3-chlorophenyl)-4-acetyl-5-methylpyrrole (XVIa) prepared from 2'-nitro-3'-chloro-2-aminoacetophenone and acetylacetone\(^5\) and therefore, XVa was proved to be 2-acetyl-3-(2-nitro-3-chlorophenyl)-5-methylpyrrole, and these formyl compounds might similarly be 2-derivative, 3-aryl-5-methyl-2-pyrrolocarboxyaldehyde (XVIIA,b).

These formylpyrroles (XVIIA, b) were converted 2-hydroxyiminomethyl-3-aryl-5-methylpyrroles (XVIIIa, b), one of which was dehydrated to 3-(3-nitro-4-chlorophenyl)-5-methylpyrrole-1-carbonitrile (XIXb). However, alcoholysis of the cyanopyrrole (XIXb) did not afford to ethyl 3-(3-nitro-4-chlorophenyl)-5-methyl-2-pyrrolocarboxylate (XXIIIb) in so good yield as XI described above.

In order to prepared an important intermediate (XXIII) practically by another route, Hoesch reaction was employed to obtain ethyl 3-(2-nitro-3-chlorophenyl)-5-methyl-2-pyrrolooxalate (XXa) from XIVa and ethyl cyanoformate in the presence of zinc chloride, but subsequent decarboxylation was not successful under any conditions.

On the other hand, it was found that XIVa, b was easily allowed to react with phosgene in the presence of an organic base to give 3-aryl-5-methyl-2-pyrrolo carbonyl chloride (XXIa, b) one of which was hydrolyzed to the corresponding carboxylic acid (XXIIa). XXIa, b was also converted in excellent yield to alkyl 3-aryl-5-methyl-2-pyrrolocarboxylate (XXIIIAa,a,a,b) with alcohols. XXIIIAa,b did not show any depression in admixture with an authentic sample prepared from XIIa,b by the first route.

Preparation of pyrrolinitrin from this intermediate will be reported in the following paper.

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Ethyl 2-Formyl-3-(2-nitro-3-chlorophenyl)-5-methyl-4-pyrolecarboxylate (IIa) — To dimethyl formamide (0.3 g), 0.6 g of POCl₃ was added dropwise under cooling, and the mixture was warmed at 60° for 10 min. After cooling, a solution of Ia (0.5 g) in dimethylformamide (5 ml) was added slowly, to this DMF-POCl₃ complex, and stirred at 60° for 1.5 hr.

The reaction mixture was poured into ice-water (30 ml) containing AcONa (4.5 g) and the resulting aqueous solution was heated on a water bath for 0.5 hr. Resulting crystals were filtered, washed with H₂O and recrystallized from benzene as colorless needles (0.4 g), mp 187°. Anal. Calcd. for C₁₅H₁₄O₅N₅Cl: C, 53.50; H, 3.89; N, 8.32. Found: C, 53.24; H, 3.85; N, 8.11. IR (nujol) cm⁻¹: 3410 (NH), 1700 (CHO), 1655 (CO-O-C₂H₅), 1530, 1365 (NO₂).

Ethyl 2-Formyl-3-(2-nitro-4-chlorophenyl)-5-methyl-4-pyrolecarboxylate (IIb) — Ib (0.5 g) was stirred with a mixture of dimethylformamide (0.3 g) and POCl₃ (0.6 g) as described above. The product was recrystallized from AcOEt to give colorless prisms, having mp 185°. Anal. Calcd. for C₁₅H₁₄O₅N₅Cl: C, 53.50; H, 3.89; N, 8.32. Found: C, 53.51; H, 4.02; N, 8.24.

Ethyl 2-Formyl-3-(4-nitrophenyl)-5-methyl-4-pyrolecarboxylate (IIc) — Ic (1.0 g) was treated with a mixture of dimethylformamide (0.5 g) and POCl₃ (0.8 g) as described above. The product was recrystallized from EtOH to give pale yellow needles (1.0 g), mp 184°. Anal. Calcd. for C₁₅H₁₄O₅N₅Cl: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.25; H, 4.60; N, 9.49. IR (nujol) cm⁻¹: 3230 (NH), 1705 (COOC₂H₅), 1640 (CHO), 1515, 1345 (NO₂). NMR (CDCl₃) ppm: 1.12 (3H, triplet, CH₂CH₃), 2.69 (3H, singlet, CH₃), 4.17 (2H, quartet, CH₂CH₃), 7.65, 8.35 (each of them 2H, doublet, arom-CH₂), 9.24 (1H, singlet, CHO).

Ethyl 2-(3-Oxo-1-butenyl)-3-(2-nitro-3-chlorophenyl)-5-methyl-4-pyrolecarboxylate (IVa) — A mixture of Ia (1.2 g), KOH (0.36 g), acetone (80 ml) and H₂O (20 ml) was refluxed for 1.5 hr, condensed in vacuo to ca. 30 ml, and poured into H₂O. The resulting precipitate was collected by filtration, washed with 5% AcOH and recrystallized from EtOH to afford 0.9 g of yellow needles having mp 190—200°. Anal. Calcd. for C₁₅H₁₄O₅N₅Cl: C, 57.37; H, 4.55; N, 7.44. Found: C, 56.98; H, 4.76; N, 7.37. IR (nujol) cm⁻¹: 3300 (NH), 1680 (COOC₂H₅), 1670 (CH₂CO), 1530, 1370 (NO₂). NMR (d₆-acetone) ppm: 0.97 (3H, triplet, COOC₂H₅ CH₃), 2.60 (3H, singlet, CH₂COCH=CH₂), 2.87 (3H, singlet, CH₃), 4.05 (2H, quartet, COOC₂H₅ CH₃), 6.50 (1H, doublet, CH₂COCH=CH₂), 7.07 (1H, doublet, CH₂COCH₂CH₃).

Ethyl 2-(3-Oxo-1-butenyl)-3-(3-nitro-4-chlorophenyl)-5-methyl-4-pyrolecarboxylate (IVb) — IIb (1.8 g), KOH (0.24 g), acetone (30 ml) and H₂O (10 ml) were treated similarly as described above. The recrystallization of EtOH gave 1.9 g of yellow needles (mp 214—215°). Anal. Calcd. for C₁₉H₁₄O₇N₅: C, 57.37; H, 4.55; N, 7.44. Found: C, 57.76; H, 4.55; N, 7.35.

Ethyl 2-(3-Phenyl-3-oxo-1-propenyl)-3-(3-nitro-4-chlorophenyl)-5-methyl-4-pyrolecarboxylate (IVc) — A solution of IIc (0.2 g) and NaOH (0.06 g) in H₂O (0.5 ml) and EtOH (2 ml) was added acetonaphone (0.2 g). The mixture was allowed to stand overnight at room temperature and warmed on a water bath for a few min. After removal of the solvent under reduced pressure, the residue was added H₂O. The resulting precipitate was filtered, washed, dried and recrystallized from EtOH to give yellow prisms (0.32 g, mp 210—211°. Anal. Calcd. for C₁₉H₁₄O₇N₅Cl: C, 62.94; H, 4.34; N, 6.38. Found: C, 62.74; H, 4.35; N, 6.27. IR (nujol) cm⁻¹: 3280 (NH), 1705 (COOC₂H₅), 1665 (C₃H₇CO), 1550, 1340 (NO₂).

Ethyl 2-(3-Oxo-1-butenyl)-3-(3-nitrophenyl)-5-methyl-4-pyrolecarboxylate (IVd) — A solution of IIc (0.5 g) and KHCO₃ (0.45 g) and 2.5 ml of H₂O in 20 ml of acetone was stirred for 6 hr at 27°. The reaction mixture was evaporated in reduced pressure to small volume, and poured into H₂O. The aqueous layer was extracted with AcOEt and the organic layer was washed with H₂O and evaporated in vacuo. The residue was crystallized from EtOH to give 0.22 g of yellow needles (mp 222°. Anal. Calcd. for C₁₉H₁₄O₇N₅Cl: C, 63.15; H, 5.30; N, 8.18. Found: C, 62.88; H, 5.43; N, 7.84. IR (nujol) cm⁻¹: 3280 (NH), 1710 (COOC₂H₅), 1640 (CH₂CO), 1510, 1340 (NO₂). NMR (d₆-acetone) ppm: 1.05 (3H, triplet, CH₂CH₃), 2.50 (3H, singlet, CH₃CO), 2.60 (3H, singlet, CH₃), 4.10 (2H, quartet, CH₂COCH₃), 5.80 (1H, doublet, CH₂COCH₂CH₃), 7.20 (1H, doublet, CH₂COCH₃).

Methyl 3-(3-Nitro-4-chlorophenyl)-4-ethoxy carbonyl-5-methyl-2-pyrolecarboxylate (XIIb) — To a solution of Ib (0.7 g) in dioxane (20 ml) a solution of KMnO₄ (0.27 g) was added with stirring at room temperature until the color of KMnO₄ vanished. After filtration, the filtrate was condensed in vacuo and the residue was poured in 5% H₂SO₄, and the resulting precipitate was collected by filtration. The crude product was dissolved in Na₂CO₃ solution in order to remove undissolved material. The crude carboxylic acid was separated from the solution by acidification, which was treated with CH₃N₂. The methyl ester was recrystallized from benzene-hexane to give pale yellow needles, mp 205—206°. Anal. Calcd. for C₁₉H₁₄O₇N₅: C, 52.39; H, 4.12; N, 7.64. Found: C, 52.60; H, 4.24; N, 7.78. IR (nujol) cm⁻¹: 3400 (NH), 1710, 1678 (COOC₂H₅, COOC₂H₅).

6) All melting points are uncorrected. The infrared spectra were recorded on a Hitachi EPI-S₂. The nuclear magnetic resonance spectra were measured with a Varian A-60 spectrometer using tetramethylsilane as an internal standard.
Ethyl 2-Hydroxyiminomethyl-3-(2-nitro-3-chlorophenyl)-5-methyl-4-pyrolecarboxylate (Va) —— An ethanolic solution of NH₂OH prepared from NH₂OH·HCl (1.54 g) and KOH (1.2 g) in EtOH (20 ml) was added to a solution of IIA (0.2 g) in EtOH (20 ml). The mixture was heated under reflux for 2.5 hr, and evaporated in vacuo. The residue was treated with H₂O and AcOEt. The organic layer was dried, and concentrated. The crystallization from AcOEt—ligroin gave 0.2 g of Va, mp 221—223° (decomp.). The structure was confirmed by dehydrogenation to Vb as described later.

Ethyl 2-Hydroxyiminomethyl-3-(3-nitro-4-chlorophenyl)-5-methyl-4-pyrolecarboxylate (Vb) —— IIB (1.3 g) was treated with NH₂OH as described above to give Vb (0.9 g) as pale yellow needles, mp 189°. Anal. Calcd. for C₁₇H₁₂O₄N₂Cl: C, 51.22; H, 4.01; N, 11.95. Found: C, 51.04; H, 4.21; N, 12.39. IR (nujol) cm⁻¹: 3350 (NH), 3280 (=NOH), 1675 (COOCH₃), 1530, 1345 (NO₂).

Ethyl 2-Cyano-3-(2-nitro-3-chlorophenyl)-5-methyl-4-pyrolecarboxylate (Vla) and Ethyl 1-Acetyl-2-cyano-3-(2-nitro-3-chlorophenyl)-5-methyl-4-pyrolecarboxylate (VIIa) —— i) A mixture of Vb (0.7 g) and Ac₂O (7 ml) was heated under reflux for 30 min. After concentration of the mixture in vacuo, the residue was dissolved in AcOEt. The solution was washed, dried, evaporated, and the residue was crystallized from AcOEt—ligroin as 0.15 g of colorless needles, mp 141—143°. Anal. Calcd. for C₁₇H₈O₃N₂Cl: C, 53.98; H, 3.62; N, 12.59. Found: C, 54.25; H, 3.68; N, 12.50. IR (nujol) cm⁻¹: 3250 (NH), 2200 (CN), 1720, 1680 (COOC₃—H₃), 1535, 1375 (NO₂).

The mother liquor was concentrated and the residue was dissolved in Ac₂O, and the solution was refluxed again for 1.5 hr and evaporated in reduced pressure. The residue was dissolved in CHCl₃ and the solution was chromatographed on silica gel to give 0.3 g of VIIa, mp 106—107°. Anal. Calcd. for C₁₇H₁₀O₄N₂Cl: C, 54.34; H, 3.76; N, 11.18; Cl, 9.44. Found: C, 54.11; H, 3.73; N, 11.12; Cl, 9.63. IR (nujol) cm⁻¹: 3300 (NH), 2200 (CN), 1720 (COOC₃—H₃), 1535, 1375 (NO₂).

ii) A mixture of VIIa (0.1 g) in 5% KOH EtOH was warmed at 50° for 10 min, removed in vacuo, and the residue was dissolved in AcOEt. The organic layer was washed, dried, and concentrated. Recrystallization of the residue from benzene gave colorless needles (0.06 g), which was identified with VIIa by mixed melting point comparison.

iii) A solution of crude VIIa (1.0 g) in Ac₂O (20 ml) was heated under reflux for 3 hr, and evaporated in reduced pressure, and the residue was dissolved in CHCl₃. The CHCl₃ solution was chromatographed on silica gel. The first fraction gave colorless needles (0.5 g, mp 106—107°) after removing the solvent, which was identified with VIIa by mixed melting point comparison. The second fraction gave colorless needles (0.3 g, mp 140—143°), which was identified with VIIa by melting point of admixture.

Ethyl 2-Cyano-3-(3-nitro-4-chlorophenyl)-5-methyl-4-pyrolecarboxylate (Vb) and Ethyl 1-Acetyl-2-cyano-3-(3-nitro-4-chlorophenyl)-5-methyl-4-pyrolecarboxylate (VIIb) —— Vb (1.0 g) was treated with Ac₂O as described above to give Vb (0.8 g) having mp 165° as colorless needles. Anal. Calcd. for C₁₇H₁₀O₃N₂Cl: C, 53.98; H, 3.62; N, 12.59. Found: C, 54.08; H, 3.76; N, 12.47.

The mother liquor was treated as described above to give VIIb (0.1 g), mp 142—143.5°. Anal. Calcd. for C₁₇H₁₀O₄N₂Cl: C, 54.34; H, 3.76; N, 11.18; Cl, 9.44. Found: C, 54.08; H, 3.62; N, 11.18; Cl, 9.64. IR (nujol) cm⁻¹: 2200 (CN), 1750 (COOC₃—H₃), 1710 (CH₂CO). 

Ethyl 2-Acetoxyiminomethyl-3-(2-nitro-3-chlorophenyl)-5-methyl-4-pyrolecarboxylate (VIIia) —— As solution of Va (1.5 g) in AcOH (10 ml) containing Ac₂O (2 ml) was heated at 100° for 5 min and evaporated in reduced pressure. After extraction with AcOEt, the organic layer was washed with H₂O, dried, and evaporated. The fractional crystallization from benzene gave colorless needles (0.3 g), mp 192—193°. Anal. Calcd. for C₁₇H₁₂O₃N₂Cl: C, 51.85; H, 4.10; N, 10.67; O, 24.38. Found: C, 52.15; H, 4.10; N, 10.63; O, 24.47. IR (nujol) cm⁻¹: 3300 (NH), 1755 (CH₂COON—), 1710 (COOC₃—H₃), 1555, 1375 (NO₂).

The mother liquor was concentrated, and the residue was crystallized to form colorless needles (0.3 g, mp 141—143°), which was identified with VIIa by mixed melting point comparison.

Ethyl 2-Carbamino-3-(3-nitro-4-chlorophenyl)-5-methyl-4-pyrolecarboxylate (IXb) —— To a solution of VIB (0.2 g) in 95% EtOH (3 ml) containing one drop of 5% NaOH, 30% H₂O (0.25 ml) was added dropwise under stirring at 40°, and the stirring was continued for 3 hr. The reaction mixture was concentrated in vacuo, and the residue was dissolved in AcOEt, and the solution was washed, dried, and evaporated. The residue was crystallized from H₂O as pale yellow needles, mp 198—199°. Anal. Calcd. for C₁₇H₁₂O₃N₂Cl: C, 51.22; H, 4.01; N, 11.95; Cl, 10.08. Found: C, 51.08; N, 4.03; N, 11.77; Cl, 10.25. IR (nujol) cm⁻¹: 3450 (NH), 3200 (CONH—), 1705 (COOC₃—H₃), 1650 (CONH₃).

Diethyl 3-(2-Nitro-3-chlorophenyl)-5-methyl-4-pyrolecarboxylate (XIA) —— i) from Vla: A mixture of Vla (1.6 g) in 240 ml of EtOH saturated with HCl at —50° was allowed to stand for 3 days at 40° in a sealed tube. The reaction mixture was concentrated in vacuo, and the residue was poured into H₂O (240 ml). The mixture was warmed at 70—80° on a water bath for 1.5 hr. After cooling, the mixture was extracted with AcOEt and the extract was washed, dried, and evaporated in reduced pressure. The residue was crystallized from AcOEt to give colorless needles (0.8 g), mp 158—160°. Anal. Calcd. for C₁₇H₁₄O₃N₂Cl: C, 53.82; H, 4.50; N, 7.35; Cl, 9.31. Found: C, 54.03; H, 4.55; N, 7.40; Cl, 9.30. IR (nujol) cm⁻¹: 3270 (NH), 1705, 1680 (COOC₃—H₃), 1540, 1570 (NO₂).

ii) from VIIa: VIIa (0.3 g) was treated as described above. The product (0.12 g) was identified with XIA prepared from Vla.
Diethyl 3-(3-Nitro-4-chlorophenyl)-5-methyl-2,4-pyrolloedicarboxylate (XIIb) — VIb (0.2 g) gave XIB (0.1 g) as colorless needles, mp 193°. Anal. Calcd. for C_{14}H_{14}O_{5}N_{2}Cl: C, 53.62; H, 4.50; N, 7.35. Found: C, 53.42; H, 4.66; N, 7.48. IR (nujol) cm\(^{-1}\): 3250 (NH), 1710, 1675 (COOC,H\(_4\)), 1530, 1350 (NO\(_2\)).

2-Ethoxy carbonyl-3-(2-nitro-3-chlorophenyl)-5-methyl-4-pyrololecarboxylic Acid (XIIa) — A suspension of XIa (1.2 g) in 2.4 ml of H\(_2\)SO\(_4\) was stirred at 15° for 20 hr. The reaction mixture was poured into 15 g of ice and the resulting precipitate was filtered and added to 10% NaOH solution. After removal of the undissolved material, the basic layer was acidified with 10% H\(_2\)SO\(_4\) under cooling. The resulting precipitate was extracted with AcOEt, and the organic layer was washed with H\(_2\)O, dried and evaporated in vacuo to dryness. Thus obtained crude acid (XIIa) was employed in the next step without further purification.

Ethyl 3-(2-Nitro-3-chlorophenyl)-5-methyl-2-pyrololecarboxylate (XXIIa) — i) From XIa: A mixture of XIa (0.5 g) and 6 ml of glycerin was heated at 250° for 10 min. After cooling, the reaction mixture was poured into ice-water and the resulting precipitate was extracted with benzene. The benzene extract was dried and chromatographed on silica gel. After concentration of the second fraction, the residue was crystallized from benzene as pale yellow needles (0.014 g), mp 223°. Anal. Calcd. for C\(_{14}\)H\(_{13}\)O\(_3\)N\(_2\)Cl: C, 54.46; H, 4.24; N, 9.06. Found: C, 54.46; H, 4.19; N, 8.78. IR (nujol) cm\(^{-1}\): 3300 (NH), 1660 (COOCH\(_3\)), 1530, 1375 (NO\(_2\)). NMR (d\(_2\)-pyridine) ppm: 0.95 (3H, triplet, CH\(_3\)CH\(_3\)), 2.28 (3H, singlet, C\(_3\)H\(_3\)), 4.19 (2H, quartet, CH\(_2\)CH\(_3\)), 6.26 (1H, singlet, 4-position of pyrrole).

ii) From XIVa via XXIa: To a solution of XIVa (0.475 g) and dimethyl aniline (0.242 g) in abs. benzene (20 ml), excess COCl\(_2\) was bubbled at room temperature. The mixture was heated under reflux for 1.5 hr. To the stirring solution of XXIa, dimethyl aniline (0.242 g) and abs. EtOH (1.0 g) were added during 30 min. After removal of excess COCl\(_2\) by bubbling with air, the solution was concentrated. The residue was aciddified with excess 1% HCl and the mixture was extracted with AcOEt. The extract was washed with 1% HCl, water, dried, and evaporated. The resulting colorless needles were washed with a small amount of benzene and recrystallized from benzene. The product was identified with an authentic sample prepared with XXa by mixed melting point comparison.

Methyl-3-(2-Nitro-3-chlorophenyl)-5-methyl-2-pyrololecarboxylate (XXIIIa) — i) From XIVa: To a solution of XIVa (2.0 g) and dimethyl aniline (1.0 g) in abs. benzene (25 ml), a solution of COCl\(_2\) (3.8 g) in abs. benzene (25 ml) was added dropwise with stirring, and then the mixture was heated under reflux for 1 hr.

After cooling, a solution of dimethyl aniline (1.0 g) in abs. MeOH (10 ml) was added dropwise. The stirring was continued for additional 1 hr at room temperature. After removal of excess COCl\(_2\) bubbling with air, the mixture was allowed to stand overnight. The resulting crystals were collected by filtration. The filtrate was washed with 5% NaOH solution, dried, and condensed. The residue was combined with above crystals. Recrystallization from benzene gave colorless needles (2.0 g), mp 198—199°. Anal. Calcd. for C\(_{14}\)H\(_{11}\)O\(_2\)N\(_2\)Cl: C, 52.98; H, 3.76; N, 9.51; Cl, 12.03. Found: C, 52.78; H, 3.88; N, 9.36; Cl, 12.18. IR (nujol) cm\(^{-1}\): 3320 (NH), 1670 (COOCH\(_3\)), 1555, 1375 (NO\(_2\)).

ii) From XXIa: XXIIa (0.5 g) was treated with ethereal solution of excess CH\(_3\)N\(_2\), and the reaction mixture was kept standing overnight, and the solvent was removed. The residue was crystallized from benzene to give 0.4 g of a product as colorless needles, mp 198°. It was identified with an authentic sample described above.

tert-Butyl 3-(2-Nitro-3-chlorophenyl)-5-methyl-2-pyrololecarboxylate (XXIIIb) — XXIa prepared from XIVa (4.8 g) and dimethyl aniline (2.4 g) and COCl\(_2\) as described above was treated with a mixture of dimethylaniline (2.4 g) and abs. tert-ButOH (15 ml). The product was recrystallized from benzene to give 4.9 g of colorless crystals having mp 224—225°. Anal. Calcd. for C\(_{14}\)H\(_{13}\)O\(_2\)N\(_2\)Cl: C, 57.06; H, 5.09; N, 8.32; Cl, 10.53. Found: C, 56.98; H, 5.16; N, 8.32; Cl, 10.62. IR (nujol) cm\(^{-1}\): 3300 (NH), 1665 (COOC,H\(_4\)), 1540, 1370 (NO\(_2\)).

Ethyl 3-(2-Nitro-4-chlorophenyl)-5-methyl-2-pyrololecarboxylate (XXIIIb) — i) From XIB via XIB: XIB (2.0 g) was hydrolyzed similarly as described in XIIa. The crude product was decarboxylated in glycerin as described in XIIa (i). The recrystallization from benzene gave pale yellow needles (0.06 g), mp 167°. Anal. Calcd. for C\(_{14}\)H\(_{13}\)O\(_2\)N\(_2\)Cl: C, 54.46; H, 4.24; N, 9.08. Found: C, 54.72; H, 4.29; N, 9.07. IR (nujol) cm\(^{-1}\): 3300 (NH), 1660 (COOCH\(_3\)), 1530, 1345 (NO\(_2\)).

ii) From XIXb: A solution of XIXb (0.1 g) in EtOH (70 ml) saturated with HCl at -50° was allowed to stand at 40° for 7 days in a sealed tube. After removal of the solvent, the residue was added to 10 ml of hot H\(_2\)O, and the mixture was warmed at 70—80° for 3 hr. The reaction mixture was extracted with benzene, and the benzene layer was chromatographed on a silica-gel column. A small amount of the product was obtained and identified with an authentic sample prepared from XIB by infrared spectrum comparison.

iii) From XIVb via XXIb: A solution of XIVb (0.476 g) described in XXIIIa (i). The product was recrystallized from benzene to give colorless needles (0.3 g, mp 167°). The product was identified with an authentic sample prepared from XIB by comparison of mixed melting point and infrared spectrum.

3-(2-Nitro-3-chlorophenyl)-5-methyl-4-pyrololecarboxylic Acid (XIIIa) — A suspension of Ia (1.0 g) in 93% H\(_2\)SO\(_4\) (20 ml) was stirred for 12 hr at 20°. The solution was poured into 20 g of ice and the precipitate was filtered, and dissolved in KHC\(_2\)O solution. After removal of the undissolved material by filtra-
tion, the precipitate obtained by acidifications gave 0.5 g of XIIIa, mp 215° (decomp.), the infrared spectrum of which showed a band at 1665 cm⁻¹. Its structure was confirmed by decarboxylation to XIVa as described later.

3-[3-Chloro-4-chlorophenyl]-5-methyl-4-pyrrrolecarboxylic Acid (XIIIb)—— A suspension of Ib (1.0 g) in 93% H₂SO₄ (20 ml) was stirred at 40—50° for 30 min. The resulting solution was treated as above to afford XIIIb (0.4 g) mp 214° (decomp.). Anal. Calcd. for C₁₂H₅O₂N₂Cl: C, 51.35; H, 3.23; N, 9.98; Cl, 12.63. Found: C, 51.51; H, 3.23; N, 9.89; Cl, 12.63.

3-[3-Chloro-4-chlorophenyl]-5-methyl-4-pyrrrolecarboxylic Acid (XIIIc)—— A suspension of Ib (1.0 g) in 93% H₂SO₄ (20 ml) was stirred at 35° for 7 hr. The resulting violet solution was poured into ice-water (200 ml), and precipitated crystal was collected by filtration, treated with 5% Na₂CO₃ in order to exclude undissolved materials. Acidification of the filtrate of Na₂CO₃ solution gave XIIIc (0.5 g), the structure of which was confirmed by infrared spectrum, and employed in the next step without further purification. Starting material (0.3 g) could be recovered from above undissolved material by filtration and recrystallization.

When 98% H₂SO₄ was employed instead of 93% H₂SO₄, XIIIc was similarly obtained in the same yield as above, but the starting material could not be recovered in pure form.

3-[2-Chloro-4-chlorophenyl]-5-methylpyrrole (XIVa)——i) A mixture of XIIIa (1.5 g) and 15 g of naphthalene was heated in an oil bath at 200—230° for 0.5 hr. The mixture was dissolved in benzene, then passed through the benzene layer was a silica gel column. The third fraction was collected, evaporated in vacuo, and the residue was crystallized from benzene, 0.6 g of yellow needles (mp 82—83°) were obtained. Anal. Calcd. for C₁₃H₇O₂NCl: C, 55.83; H, 3.83; N, 11.84. Found: C, 56.25; H, 3.96; N, 11.34. IR (nujol) cm⁻¹: 3400 (NH), 1530, 1375 (NO₂).

ii) A suspension of XIIIa (10.0 g) in glycerin (10 ml) was stirred at 200° until the evolution of CO₂ was stopped, and the reaction mixture was poured into ice-water, extracted with benzene. The benzene layer was treated as above. Yellow granules (5.0 g) were obtained mp 82—84°. Anal. Calcd. for C₁₃H₇O₂NCl: C, 55.83; H, 3.83; N, 11.84. Found: C, 55.84; H, 4.05; N, 11.84.

3-[3-Chloro-4-chlorophenyl]-5-methylpyrrole (XIVb)——A mixture of XIIIb (3.0 g) and naphthalene (20 g) was melted by heating in an oil bath. After the evolution of CO₂ was ceased, the reaction mixture was dissolved in benzene. The benzene solution was chromatographed on silicagel. The third fraction was collected and the solvent was removed. Recrystallization of the residue from benzene gave yellow needles (1.5 g) having mp 76°. Anal. Calcd. for C₁₃H₁₁O₂NCl: C, 55.83; H, 3.83; N, 11.84; Cl, 14.98. Found: C, 56.10; H, 3.81; N, 11.74; Cl, 14.98. IR (nujol) cm⁻¹: 3400 (NH), 1530, 1350 (NO₂).

3-[4-Chloro-3-chlorophenyl]-5-methylpyrrole (XIVc)——A mixture of XIIIc (0.5 g) and soda asbesto (0.5 g) was heated under reduced pressure at 150—160° for 40 min in a combustion tube. The sublimed product was collected and purified by re-sublimation to give yellow granules (0.03 g mp 232°). Anal. Calcd. for C₁₃H₁₁O₂N₂: C, 65.33; H, 4.98; N, 13.86. Found: C, 64.97; H, 4.62; N, 13.95. IR (nujol) cm⁻¹: 3350 (NH), 1500, 1315 (NO₂).

3-[2-Chloro-4-chlorophenyl]-5-methyl-2-pyrrrolecarboxaldehyde (XVIIa)—POCl₃ (0.6 g) was added drop-wise to dimethylformamide (0.3 g) under cooling, then the mixture was warmed at 60° for 10 min. A solution of XIVa (0.6 g) in dimethylformamide (3 ml) was added dropwise to the above mixture under cooling, and then the reaction mixture was warmed at 60° for 3 hr, and poured into ice-water (6.0 g) containing 4.5 g of AcONa. The aqueous solution was warmed on a water bath for 30 min, and the isolated crystals were collected by filtration and recrystallized from EtOH to give 0.5 g of colorless prisms mp 228°. Anal. Calcd. for C₁₃H₁₁O₂N₂Cl: C, 54.56; H, 3.41; N, 10.59. Found: C, 54.42; H, 3.45; N, 10.53. IR (nujol) cm⁻¹: 3240 (NH), 1630 (CHO), 1540, 1375 (NO₂).

3-[4-Chloro-3-chlorophenyl]-5-methyl-2-pyrrrolecarboxaldehyde (XVIIb)——XIVb (0.6 g) was treated with a mixture of dimethylformamide and POCl₃ as described above. Recrystallization of the product from AcOEt gave pale yellow needles (0.5 g), mp 192°. Anal. Calcd. for C₁₃H₁₁O₂N₂Cl: C, 54.56; H, 3.41; N, 10.59. Found: C, 54.56; H, 3.32; N, 10.78. IR (nujol) cm⁻¹: 3270 (NH), 1650 (CHO), 1530, 1350 (NO₂).

2-Acetyl-3-(2-nitro-3-chlorophenyl)-5-methylpyrrole (XV)——A solution of XIVa (0.4 g) in dichloromethane (2 ml) was added slowly to a mixture of POCl₃ (0.8 g) and dimethylacetamide (0.4 g), and the reaction mixture was warmed at 60° for 1 hr and poured into ice-water containing AcONa (4.0 g), warmed again for 1 hr. The resulting crystals were collected by filtration and recrystallized from EtOH as yellow needles (0.4 g) having mp 206—207°. Anal. Calcd. for C₁₃H₁₁O₂N₂Cl: C, 56.01; H, 3.94; N, 10.00; Cl, 12.77. Found: C, 56.21; H, 4.15; N, 9.92; Cl, 12.77. IR (nujol) cm⁻¹: 3280 (NH), 1630 (CH₂CO), 1535, 1370 (NO₂).

3-[3-Chloro-4-chlorophenyl]-5-methylpyrrole-2-carbonitrile (XIXa)——i) From XIXb via Xb: A stirring mixture of Xb (200 mg) and 98% H₂SO₄ (0.8 ml) was kept at 15° for 3 hr, and poured into ice-water (20 ml). The precipitate was collected by filtration and treated with 5% NaOH in order to exclude undissolved starting materials. The crude Xb derived from the alkaline filtrate by acidification, was collected by filtration, and dried. A mixture of Xb (0.07 g) and soda asbesto (0.7 g) was heated at 220° under reduced pressure in a combustion tube. Colorless crystals were sublimated, and showed very similar infrared spectra with that of an authentic sample prepared from XVIIIb described below.
ii) From XVIIb via XVIIIb: To a boiling alcoholic solution of NH$_2$OH (excess) described in Va, XVIIb (1.5 g) was added and worked up as usual. 1.0 g of a crude oxime was obtained. A solution of XVIIb (1.0 g) in Ac$_2$O (15 ml) was refluxed for 3 hr, and evaporated in vacuo. The resulting viscous liquid was sublimated under reduced pressure at 200–230$^\circ$ in a sublimation tube to give slight yellow needles (0.6 g) having mp 202$^\circ$ after twice sublimation. Anal. Calcd. for C$_{14}$H$_6$O$_3$N$_2$Cl: C, 55.08; H, 3.08; N, 16.06; Cl, 13.55. Found: C, 54.89; H, 3.29; N, 15.94; Cl, 13.70. IR (nujol) cm$^{-1}$: 3300 (NH), 2200 (CN), 1530, 1345 (NO$_2$).

**Ethyl 3-(2-Nitro-3-chlorophenyl)-5-methyl-2-pyrroleoxalate (XXa)**——To a solution of XIVa (2.0 g) and ethyl cyanoformate (1.8 g) in 50 ml of abs. ether containing 1.8 g of ZnCl$_2$ was passed dry HCl at room temperature for 8 hr, allowed to stand overnight. After removal of the solvent, the residue was washed with ether, and added to 5% HCl. The mixture was warmed on a water bath for 2 hr, and extracted with AcOEt. The extract was washed, dried, and concentrated. Recrystallization of the residue from benzene gave 0.9 g of XXa having mp 182–184$^\circ$. Anal. Calcd. for C$_{13}$H$_5$O$_5$N$_2$Cl: C, 53.50; H, 3.89; N, 8.31; Cl, 10.69. Found: C, 52.70; H, 3.74; N, 8.61; Cl, 10.82.

3-(2-Nitro-3-chlorophenyl)-5-methyl-2-pyrrolecarboxylic Acid (XXIIa)——To a solution of XXIIa prepared from XIVa (0.476 g) and dimethylaniline (0.242 g) and COCl$_2$ as described in XXIIIa (ii), 20 ml of 5% K$_2$CO$_3$ was added with stirring at 0–5$^\circ$, and stirring was continued for 1 hr. After washing the reaction mixture with ether in order to remove undissolved oily material, the aqueous layer was acidified with 10% H$_2$SO$_4$ under ice cooling, extracted with AcOEt. The extracts were washed, dried, and evaporated in reduced pressure, and the residue was crystallized from AcOEt-ligroin to give 0.3 g of colorless prisms (mp 211$^\circ$ decomp.). Anal. Calcd. for C$_{19}$H$_2$O$_5$N$_2$Cl: C, 51.35; H, 3.23; N, 9.98. Found: C, 51.57; H, 3.39; N, 9.64. IR (nujol) cm$^{-1}$: 3380 (NH), 1670 (COOH), 1530, 1370 (NO$_2$).